

## Caractérisation des modifications post-transcriptionnelles des ARN non codants chez Staphylococcus aureus en réponse à divers stress environnementaux : analyse dynamique et fonctionnelle

Laura Antoine

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# UNIVERSITÉ DE STRASBOURG

## ÉCOLE DOCTORALE 414 : Sciences de la vie et de la santé

## Architecture et Réactivité de l'ARN – IBMC Strasbourg

# THÈSE présentée par :

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Caractérisation des modifications post-transcriptionnelles des ARN non codants chez *Staphylococcus aureus* en réponse à divers stress environnementaux : analyse dynamique et fonctionnelle

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A la mémoire de Clément,

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## Résumé de la thèse

## Caractérisation des modifications post-transcriptionnelles des ARN non codants chez Staphylococcus aureus en réponse à divers stress environnementaux : analyse dynamique et fonctionnelle

## Introduction :

Les ARN non codants jouent un rôle essentiel pour la cellule, notamment lors de la traduction. En effet, les ribosomes sont constitués essentiellement d'ARN ribosomiques (ARNr) et les ARN de transfert (ARNt) assurent le décodage des ARN messagers (ARNm). Le processus de traduction des ARNm en protéines peut être régulé par d'autres ARN non codants appelés petits ARN régulateurs (sARN).

Les modifications post-transcriptionnelles influencent la structure de l'ARN et les propriétés chimiques des nucléosides. Les ARNt et les ARNr présentent le plus grand nombre de modifications, qui par conséquent jouent un rôle prépondérant pour leurs fonctions, pour l'efficacité et pour la vitesse de la traduction. Par exemple, la modification en position 34 (la base « wobble ») des ARNt est indispensable tant pour le décodage de différents codons correspondant à un même acide aminé que pour la discrimination de codons proches<sup>1</sup>. Pour les bactéries pathogènes, ces modifications post-transcriptionnelles sont impliquées dans l'adaptation à l'environnement, dans l'expression de gènes de virulence<sup>2</sup> et dans les interactions avec l'hôte lors d'infections. La présence de modification en position 34 des ARNt est liée à la virulence chez *Streptococcus pyogenes*<sup>3</sup>. Par ailleurs, la présence ou l'absence d'une modification sur les ARNr peut conférer une résistance aux antibiotiques ciblant le ribosome<sup>4</sup>.

Dans ce contexte, cette étude a porté sur *Staphylococcus aureus*, une bactérie commensale de l'Homme présente chez 1 individu sur 3 et aussi un pathogène opportuniste responsable d'infections nosocomiales et communautaires <sup>5</sup>. L'émergence de souches multi-résistantes aux antibiotiques est un véritable problème de santé publique, notamment dans le milieu hospitalier. En tant qu'opportuniste, *S. aureus* possède une grande capacité d'adaptation en réponse aux changements environnementaux. Cette capacité lui permet, via la régulation très fine de l'expression des facteurs de virulence, d'être à l'origine de nombreuses infections pouvant être très graves. A ce jour, le rôle des modifications post-transcriptionnelles dans les processus adaptatifs et l'infection par *S. aureus* reste encore inconnu.

A l'aide d'analyses de spectrométrie de masse associées à différentes méthodes de séquençage à haut débit des ARN (RNA-Seq), cette étude consiste à établir une cartographie des modifications post-transcriptionnelles des ARN non codant chez *S. aureus*. Elle vise ensuite à déterminer leurs potentielles variations en fonction de conditions de stress mimant l'environnement durant une infection afin de mieux comprendre leur impact sur la croissance bactérienne, les réponses aux stress et dans la virulence.

#### **Résultats :**

Afin de caractériser les modifications post-transcriptionnelles des ARNt de j'ai mis en place, en S. aureus, collaboration avec Philippe Wolff (UPR 9002, responsable de l'analyse de spectrométrie de masse appliquée aux ARN), une méthode de purification et d'identification par chromatographie liquide couplée à la spectrométrie de masse UPLC-MS/MS (Ultra Performance Liquid Chromatography Tandem Mass Spectrometry)<sup>6,7</sup>. La cartographie réalisée par



**Figure 1.** Modifications cartographiées par différentes méthodes dans les ARNt à gauche et l'ARNr 16S de *S. aureus* à droite

spectrométrie de masse dans les ARNt de S. aureus étant partielle, elle a été complétée et confirmée par différentes méthodes de RNA-Seq telles que le Psi-Seq, le RiboMethSeq et l'Alkaniline-Seq<sup>8</sup>, en collaboration avec le Pr Yuri Motorin et la Dr Virginie Marchand de la plateforme Epitranscriptomique et Séquençage (EpiRNA-Seq) de Nancy. Les données RNA-Seq ont également permis d'obtenir des informations sur les modifications présentes sur les ARNr (Figure 1). Celles détectées dans les ARNt de S. aureus sont très proches de celles caractérisées chez d'autres bactéries à Gram positif tel que Lactococcus lactis<sup>9</sup>. De façon inattendue, mon étude a également révélé des éléments uniques aux ARNt de S. aureus. Précisément, les ARNt de la glycine qui en plus d'être impliqués dans la traduction des protéines, participent également à la formation du pont pentaglycine présent dans la paroi cellulaire des Staphylocoques. Les ARNt responsables du transport de la glycine vers la paroi ont été analysés et ne possèdent pas les modifications spécifiques des ARNt impliqués dans l'incorporation des glycines dans les protéines, specifiquement au niveau de leurs anticodons. De plus, la présence d'une modification dont la masse ne correspond à aucune modification connue à ce jour a pu être détectée en position 37 de l'ARNt de la lysine. Ces résultats ont conduit à un nouveau projet d'étude dans le laboratoire pris en charge par un chercheur postdoctorant afin de déterminer le rôle des modifications (ou leur absence) dans la discrimination des ARNt<sub>Glv</sub>.

Une fois la cartographie établie en condition normale de croissance en laboratoire, différentes conditions de stress mimant ceux rencontrés lors de l'infection et les interactions avec l'hôte (augmentation de la température, privation de nutriments, hypoxie, stress oxydant ou nitrique et présence d'antibiotiques) ont été réalisés. Plusieurs de ces conditions, montrent des variations flagrantes dans le profil de migration des ARNt sur gel de polyacrylamide qui peut résulter de changements dans les modifications (**Figure 2A**). Dans certaines conditions, tel que le stress induit par l'oxyde nitrique (NO), une analyse complète de spectrométrie de masse ainsi que de RNA-Seq de chaque ARNt sera nécessaire pour déterminer si un changement a lieu. Cependant, une condition spécifique qui a montré clairement une variation de migration d'ARNt est le stress oxydant induit par l'addition de méthylviologen entrainant la formation d'espèces réactives de l'oxygène (ROS). La production de ROS est une des défenses principales du système immunitaire contre les infections. Les macrophages produisent des anions superoxydes, du peroxyde d'hydrogène ainsi que des oxydes nitriques en réponse à la phagocytose de bactéries. De plus, ces espèces réactives de l'oxygène et de

l'azote sont impliquées dans l'inflammation et les lésions tissulaires qui sont également hypoxiques<sup>10</sup>. Dans ce contexte, j'ai donc décidé d'étudier l'impact du stress oxydant induit par le méthylviologen sur les modifications des ARNt ainsi que les conséquences qu'une modification différentielle peut avoir sur le processus de traduction.

L'analyse des modifications des ARNt par UPLC-MS/MS montre un clivage par la RNase T1 de l'ARNt<sub>TyrGUA</sub> en 3' de la queuosine en position 34 qui n'a pas lieu en absence de l'agent oxydant (**Figure 2A**). Cet effet suggère que la queuosine, modification complexe et importante impliquée dans le décodage de l'ARNm lors de la traduction, est absente en condition de stress oxydant. L'absence de queuosine dans les bactéries cultivées en en condition de stress oxydant a été confirmée dans les quatre ARNt (ARNt Tyr, His, Asp et Asn) contenant cette modification par électrophorèse d'affinité au boronate et par analyse UPLC-MS/MS des ARNt purifiés. Pour l'électrophorèse d'affinité, des ARN totaux provenant d'une souche de *S. aureus* n'exprimant pas l'enzyme Tgt, responsable du transfert de l'intermédiaire preQ1 sur l'ARNt ont été également utilisés (**Figure 2B**). Grâce à cette méthode, j'ai également montré qu'il était possible de restaurer la présence de queuosine par l'ajout du preQ1 dans le milieu de culture des bactéries soumises au stress oxydant (**Figure 2B**) indiquant une possible inactivation d'une des enzymes impliquées dans la voie de biosynthèse du preQ1 lors du stress.



Figure 2. A. Analyse des ARNt dans différentes conditions de stress environnementaux, à gauche : gel de polyacrylamide (12,5%, 8 M urée) des ARNt de S. aureus cultivés en conditions normales (no stress), à 42°C (augmentation de la température), en milieu MHB (Mueller-Hinton Broth : privation de nutriments) ou stress oxydant (MV : méthylviologen). Les ARN présents dans chaque bande ont été identifiés par UPLC-MS/MS. A droite : chromatogrammes obtenus à partir des bandes encadrées en rouge contenant l'ARNt<sup>Tyr</sup><sub>GUA</sub>, encerclés en rouge les pics correspondants aux anticodons, non clivé par la RNase T1 pour l'ARNt issu de la culture non stressée, clivé pour celui issu de la culture soumise au stress oxydant. Q: queuosine; +: N6-isopentyl Adénosine. B. Electrophorèse d'affinité au boronate, ligne du haut : profil de migration des 4 ARNt contenant la queuosine de la souche WT en condition normale et en condition de stress oxydant et de ces ARNt sans queuosine provenant de la souche n'exprimant pas le gène tqt. Ligne du bas : profil de migrations des ARNt en conditions de stress oxydant et après addition de l'intermédiaire de la queuosine preQ1. C. Volcano plot représentant la transcription différentielle de plusieurs types de gènes tels que les facteurs de virulence, ceux impliqués dans le repliement des protéines et dans les fonctions des ARNt en conditions de stress oxydant. D. Impact de l'absence de queuosine de l'ARNt<sup>IVF</sup> sur la traduction. A gauche : taux de pause des deux codons UAC et UAU de la tyrosine montrant un décodage plus lent du codon UAU en condition de stress oxydant. A droite : diagramme de Venn indiquant les gènes sous exprimés en protéomique pour lesquels le niveau de transcription ne change pas, voire augmente et dont les ARNm sont riches en codons UAU.

Une altération de la queuosine en position 34 implique d'inévitables conséquences au niveau de l'efficacité de la traduction. L'absence de cette modification peut impacter la vitesse et la finesse de la reconnaissance des codons par l'ARNt, ainsi que la fidélité d'incorporation des acides aminés, entrainant la production de protéines anormales. Afin d'étudier les possibles causes et conséquences de l'anomalie de queuosine en position 34, des analyses protéomiques et transcriptomiques ont été réalisées montrant d'importantes variations dans l'expression des gènes marqueurs du stress oxydant mais également de nombreux facteurs de virulence impliqués dans la dissémination et la protection contre le système immunitaire (Figure 2C). Ces résultats sont à corréler avec une analyse de « high resolution ribosome profiling » (hRibo-seq) pour étudier la vitesse de traduction codon par codon. Les résultats préliminaires obtenus, montrent que durant le stress oxydant, les codons UAU nécessitent la présence de la queuosine en 34 de l'ARNt<sup>Tyr</sup> pour être décodés efficacement. En effet, ils présentent une diminution importante de leur vitesse de décodage, tandis que celle des codons UAC ne semble pas être impactée par l'absence de queuosine (Figure 2D). De manière remarquable, l'analyse protéomique en condition de stress oxydant révèle une dérégulation de la traduction pour de nombreux gènes alors que les niveaux d'ARNm demeurent inchangés, voire augmentent. Certains de ces ARNm présentent une composition particulièrement riche en codon UAU. L'analyse de hRiboseg a été répétée en condition de stress oxydant mais aussi en présence de preQ1 pour discriminer plus clairement les effets exclusivement dus à l'absence de queuosine sur les 4 ARNt concernés. Cette étude est actuellement en cours.

## **Conclusions et perspectives :**

La mise en place de L'UPLC-MS/MS en association avec les méthodes de RNA-Seq a permis d'établir les cartographies partielles des modifications présentes dans les ARN non codants de *S. aureus* afin d'étudier leurs variations, en particulier dans les ARNt lors de stress environnementaux mimant les conditions rencontrées lors de l'infection. J'ai ainsi mis en évidence, d'une part une altération de la queuosine des 4 ARNt possédant cette modification en position wobble de l'anticodon et d'autre part étudié l'impact sur la traduction de l'absence de cette modification. L'expérience de hRibo-Seq complète est en cours afin d'élucider la fonction de la queuosine sur le décodage de l'ensemble des codons nécessitant cette modification. Cette étude est réalisée en parallèle avec une analyse de la composition en nucléosides modifiés des ARNt afin de déterminer l'impact du stress oxydant sur les autres modifications post-transcriptionnelles présentes sur les ARNt totaux. Les données d'analyses de RNA-Seq de ribosomes provenant de bactéries soumises au stress oxydant induit par le méthylviologen sont en cours d'analyse. L'étude structurale de l'impact des variations de modifications des ARNt et ARNr sur l'ensemble de la machinerie traductionnelle se déroule en collaboration avec Roberto Bahena, qui est actuellement en première année de thèse.

Pour compléter l'étude de l'épitranscriptome de *S. aureus*, 4 sARN régulateurs (RsaA, C, G et I) ont également été analysés par RNA-Seq. Cependant, les résultats n'ont pas montré la présence de modifications post-transcriptionnelles. Des analyses UPLC-MS/MS seront nécessaires afin de confirmer l'absence de modifications dans ces sARN.

Cette approche que j'ai mise en place pour l'étude des variations des modifications des ARN en réponse au stress oxydant et de leur impact traductionnel, pourra être appliquée à l'adaptation de la bactérie à d'autres conditions environnementales rencontrées lors de l'infection pour lesquelles des profils différents de migration des ARNt ont été observés. Bibliographie : 1. Rozov A, Demeshkina N, Khusainov I, Westhof E, Yusupov M, Yusupova G. Novel base-pairing interactions at the tRNA wobble position crucial for accurate reading of the genetic code. Nat Commun. 2016;7:10457. doi:10.1038/ncomms10457

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## Liste des Abbreviations

Acides nucléiques :

ADN : acide désoxyribonucléique

ARN : acide ribonucléique

ARNm : ARN messager

ARNr : ARN ribosomique

ARNt : ARN de transfert

## <u>Composés chimiques et milieux de</u> <u>cultures</u>

NO : oxyde nitrique

ROS : espèces réactives de l'oxygène

APB : Acide phénylboronique

BHI : Brain heart infusion : infusion cœur cerveau

MV : Méthylviologen

TEA-CI : chlorure de tetraéthyl ammonium.

**Bactéries** 

S. aureus : Staphylococcus aureus

B. subtilis : Bacillus subtilis

L. lactis : Lactococcus lactis

E. coli : Escherichia coli

MRSA : Methicillin Resistant *S. aureus* (résistante à la méthicilline)

## Protéines et facteurs de virulence :

Ahp : Alkyl hydroperoxyde réductase Clf: Clumping factor (facteur d'agglutinement)

Efb : Extracellular fibrinogen binding protéine (protéine de liaison au fibrinogène extracellulaire)

Fnbp :Fibronectinbindingprotein(Protéine de liaison à la fibronectine)

Isd : Iron-Regulated Surface Determinant MSCRAMM : microbial surface components recognizing adhesive matrix molecules (composants de la surface microbienne reconnaissant les molécules adhésives de la matrice)

PSM : Phenol Soluble Modulins Sod : Superoxyde dismutase SpA : Staphylococcal protein A (protéine

staphylococcique A)

TSST : Toxic shock syndrome toxin (toxine du syndrome de choc toxique)

<u>Techniques</u>

LC : chromatographie liquide

MS : Spectrométrie de masse

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## I. Introduction

## 1. Rôle des modifications post-transcriptionnelles chez bactéries pathogènes

Les modifications post-transcriptionnelles des ARN sont impliquées dans de nombreux processus biologiques et sont présentes dans toutes les classes d'ARN. Ces modifications sont constitutives ou modulées en réponse à des processus adaptatifs. Elles remplissent de nombreuses fonctions puisqu'elles peuvent impacter l'appariement des bases, la reconnaissance par les protéines, le décodage ainsi que la structure et la stabilité des ARN. Cependant, leurs rôles dans les adaptations aux stress environnementaux ainsi que durant les infections causées par des bactéries pathogènes commencent juste à être appréciées. Avec le développement de technologies modernes de spectrométrie de masse et de séquençage, des exemples récents de modifications régulant les interactions hôtepathogène ont été étudiés. Ils révèlent comment les modifications des ARN peuvent réguler la réponse immunitaire, la résistance aux antibiotiques, l'expression des gènes de virulence et la persistance bactérienne. Dans la revue suivante, écrite avec l'aide de Roberto Bahena, Stefano Marzi, Pascale Romby, ainsi que 3 étudiants de master, nous illustrons quelquesunes de ces découvertes et soulignons les stratégies utilisées pour caractériser les modifications des ARN et leur potentiel pour de nouvelles applications thérapeutiques. La revue sera soumise à Genes pour le numéro spécial "Functions and Dynamics of RNA Modifications".

# RNA modifications in pathogenic bacteria: Impact on host adaptation and virulence

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## Abstract (200 words max: 138 words):

RNA modifications are involved in numerous biological processes and are present in all classes of RNA. These modifications are constitutive or modulated in response to adaptive processes. RNA modifications play multiple functions since they can impact RNA basepairings, recognition by proteins, decoding, as well as RNA structure and stability. However, their roles in stress, environmental adaptation and during infections caused by pathogenic bacteria have just started to be appreciated. With the development of modern technologies in mass spectrometry and deep sequencing, recent examples of modifications regulating host-pathogen interactions have been demonstrated. They show how RNA modifications can regulate immune responses, antibiotic resistance, expression of virulence genes, and bacterial persistence. Here, we illustrate some of these findings, and highlight the strategies used to characterize RNA modifications, and their potential for new therapeutic applications.

**Keywords:** RNA modifications 1; pathogenic bacteria 2; host-adaptation 3; stress adaptation 4; ribosomal RNA 5; tRNA 6; small non coding RNA 7; mRNA 8;

### 1. Introduction

Bacteria are remarkably versatile organisms, which can survive and grow in numerous environmental niches on the planet. They modulate the expression of their genes to respond and adapt their growth to environmental stress such as temperature and pH shifts, nutrient availability, antimicrobials or dangerous chemical reactive species. This is particularly the case for pathogenic bacteria, which must adapt their metabolism to the host environment and ensure their survival facing the human/animal immune systems and antibiotic therapies. Bacteria can sense the environment directly via the effect that physical and chemical stresses might have on different macromolecules, or via signaling systems, very often two-component systems (TCS), transducing the stress signal from a specific sensor histidine kinase to a corresponding response regulator [1]. The responses are aimed at eliminating the stressor or its effects, at repairing damages or at inducing the escape from the stress, but sometime the external stimuli are signals for switching to programmed life-style changes. They produce profound changes in cell physiology and behaviors, and affect gene expression at transcriptional, post-transcriptional, translational, and post-translational levels. In these processes, an interplay between various TCS, transcriptional protein regulators, and regulatory RNAs orchestrates complex regulatory networks in order to link metabolism adaptation and virulence [2]. Because RNAs, occupy a central position in translation (tRNAs, rRNAs, mRNAs), they actively contribute to these regulatory networks.

In bacteria, the rate of translation is modulated by multiple signals present in mRNAs affecting translation initiation, elongation, termination, and ribosome recycling [3-6]. The mRNA translation initiation signals can be masked or liberated by the binding of proteins or small regulatory RNAs (sRNAs), or by structural rearrangements occurring in response to metabolite binding or to physical cues changes, which also directly affect transcription and RNA folding [7-12]. Besides, codon usage specific for each gene (codon bias) is used in relation to variation of the tRNA pool to fine tune gene expression [13]. Moreover, many studies have emphasized the physiological importance of ribosome heterogeneity to rapid modulation of selective gene expression in response to environmental conditions [14, 15]. These mechanisms are influenced by base or ribose modifications present in RNAs [16] adding another sophisticated layer of regulation. In fact, stresses can alter RNA modification states of various RNA species (i.e., rRNA, tRNA, sRNA and mRNA) with effect on translation rates, on RNA regulatory properties, or on codon recoding.

The number of newly detected modifications enhances at a constant pace [17]. They can be very simple like methylation or deamination, or be more complicated. Some of them require the consecutive action of several modification enzymes and cofactors [18]. These modifications modulate

the chemical and physical properties of the nucleotides and in turn the RNA functions (for a review see [19]). They might change any of the nucleotide interacting edges, which can potentially affect Watson-Crick base-pairing and non-canonical interactions [20]. For example, the A-form RNA helix, favored by C3'-endo sugar pucker, is stabilized by 2'-OH methylation of ribose [21, 22] while dihydrouridine (D) significantly destabilizes the C3'-endo sugar conformation, providing structure flexibility [23]. Interestingly, D is predominantly found in psychrophile bacteria and archaea [23]. Methylation on the bases can influence hydrogen-bonding and stacking interactions [24]. Pseudouridine ( $\Psi$ ) can shift between *syn/anti* conformations with relatively greater ease [25]. The dynamic nature and the regulatory functions of some of these RNA modifications [26] have generated a new field referred to 'epitranscriptomics' [27]. The detection of the bacterial epitranscriptome relies on cutting edge methodologies involving combination of mass spectroscopy (LC/MSMS) and RNAseq based methodologies. Nevertheless, identification of the epitranscriptome of pathogenic bacteria and its modulation upon stress and during the infection process is only in its infancy.

In this review, we illustrate several examples of the involvement of RNA modifications on the expression of virulence genes and in stress responses of different pathogenic bacteria. Even though these studies provide mechanistic explanations for only few cases, they already reveal a multitude of strategies developed by pathogenic bacteria to survive, persist, and fight against host immune defenses based upon the modulation of RNA modifications.

#### 2. Technological advances: Detecting RNA modifications

A prerequisite to analyze the functions of RNA modifications is obviously to be able to detect the modified nucleosides, to quantify them, to map their localization within specific RNA. A detailed description of the available methods is outside the scope of the review. We will give here a summary of the most employed approaches with their limits and advantages (**Table 1**), and details will be found in more specific articles.

Mapping of post-transcriptional RNA modifications using mass spectrometry (MS) existed for over 30 years [28]. The precise measurement of molecular masses (less than 1 Da) provided the possibility to characterize known modified residues in tRNAs using liquid chromatography coupled to mass spectrometry (LC/MSMS). Two complementary MS approaches are routinely used to get a complete repertoire of modified nucleosides obtained either from tRNA extracts in a single experiment [29-31], or from tRNA fragments produced from specific endoribonuclease digestion to determine both the nature of modifications and their location in the tRNA sequence [32, 33]. The analysis of a pure RNA or a class of RNAs hydrolyzed into nucleosides allows precise characterization and quantification of modifications, while oligonucleotide analysis allows precise localization of modified sites on sequence, but no quantification can be achieved. Moreover, the method does not allow complete sequence coverage and the use of RNases with different sequence specificity can increase it. Capillary electrophoresis coupled to MS (CE/MSMS) allows precise analysis of a wide range of molecules (reviewed in [34]), and can also be used for the characterization of tRNA modifications with the two approaches. Because capillary electrophoresis allows analysis of small oligonucleotide fragments, the combination of LC/MSMS and CE/MSMS leads to a better sequence coverage on pure tRNAs [35]. Nevertheless, one of the major limitations of these MS methods is the detection of  $\Psi$ , which is an isomer of uridine and for this reason is a mass-silent modification. The MS analysis of  $\Psi$  can be done because they can be selectively modified by 1-cyclohexyl-(2morpholinoethyl)carbodiimide metho-p-toluene sulfonate (CMCT) [36]. The carbodiimide (CMC) moiety of CMCT modifies the N1 of guanosine, the N3 of uridine, and the N1 and N3 of  $\Psi$ , but alkaline treatment at pH 10.3 easily removes it from them, with the exception of the N3 of  $\Psi$ , therefore producing a detectable mass increment of 252 Da [37]. More recently, pseudouridines have been also detected directly in RNA fragments by pseudo-MS<sup>3</sup> (MS/MS/MS) analysis [38] thanks to the specific signature ion at *m*/z 207.041 for double dehydrated  $\Psi$  [39].

Various high throughput sequencing methods are often used to characterize specific modifications by Reverse Transcriptase (RT) signatures after chemical treatment. These methods do not need to purify the RNA prior to the analysis but they need bioinformatics data treatment and statistical evaluation of errors. NGS-based methods are often not quantitative, have high false-positive rates [40] and require multiple ligation steps and extensive polymerase chain reaction amplification during the library preparation, introducing undesired biases in the sequencing data [41]. Currently, customized protocols must be optimized for each RNA modification type, leading to experimental designs in which the RNA modification type to be studied is chosen beforehand, limiting the ability to characterize the plasticity of the epitranscriptome in a systematic and unbiased manner. A recent review described in details the RNAseq based approaches [42]. We will just mention here the very recent development of single molecule direct RNA sequencing methods developed by Oxford Nanopore Technologies (ONT), which are promising for the analysis of modification landscape on a specific RNA sequence [43-46].

Combination of these highly complementary methods allows a precise localization and characterization of post-transcriptional modifications and their dynamics, a prerequisite to a better understanding of the roles of RNA modification in bacterial adaptation.

	Method	łs	Modifications detected	Quantification	Genome wide	Positional information	Remarks (Pros/Cons)
Structure	X-ra	y Cristallography	All				Difficult to obtain crystals
determination	Cryo Electron Microscopy		modifications	×/√	×	1	Heterogeneous resolution
	Nuclear	Magnetic Resonance					Size limit
	Nucleoside analysis	DMRM [28]	Known modifications	~	~	×	Fragmentation pattern and retention time of modifications must be known
	unurysis	NLS [28]	Various modifications	~	~	×	NLS is less suitable for quantification than DMRM
LC/MSMS		With a reference (SILNAS/CARD/SILCARD) [47, 48]	Known modifications	~	×	V	Relative quantification can be assessed with reference <i>in vitro</i> RNA
	Fragment analysis	Without reference (RNase digests) [33]	Known modifications	×	×	~	Determination of base composition and localization by comparing mass-spectrometry results with expected RNase fragments
	RNA deep-sequencing direct method Nanopore RNA sequencing [51, 52]		A-to-I [49]	~	~		To be accompanied by DNA sequencing to distinguish editing events from SNPs
			Methylations [50]	×	×		Based on RT stops or missincorporations
			m <sup>6</sup> A, m <sup>5</sup> C, A- to-I, Ψ and others	1	1		Based on the use of systematic base-calling 'errors' caused by the presence of RNA modifications. Software is still in development
	Indirect methods: chemical treatments	ICE-Seq [53, 54]	A-to-I				No need of DNA seq
		Bisulfite-Seq [55]	m⁵C	- - -	V		
		Riboxi-Seq [56]					
		RiboMethSeq[57, 58]	νm - ψ				
		Pseudo-Seq[59]					
NGS-based		Ψ-Seq PSI-Sea[60]					
methous		HydraPsi-Seq [61]					
		SLAM-Seq[62]	s <sup>4</sup> U				
		ARM-Seg[63]	m <sup>1</sup> A, m <sup>3</sup> C,	-			
			m <sup>1</sup> G				
			7- 3				
		AlkAniline-Seq[65]	m <sup>°</sup> G, m <sup>°</sup> C, D				
		miCLIP[66]	Methylation	- ↓ ↓	V		
		m <sup>6</sup> A-Seq[67]					
		meRIP-Seq[68]	m <sup>6</sup> A				
	Indirect methods: IP	m <sup>6</sup> A-LAIC-Seq[69]	Nm ac <sup>4</sup> C 5'-NAD cap				
		Nm-Seq / 2OMe- Seq[70]					
		acRIP-Seq[71]					
		NAD capture-Seq[72]					
	Mercury-sulfur affinity[73]		s²U, s⁴U	X?	×	×	APM treatment (Acrylo- aminophenylmercuric chloride)
Affinity gel electrophoresis	Boronate affinity[74]		NAD- or FAD- modified RNAs	√	V	×	APB treatment (Acryloylaminophenyl boronic acid); fast screening (easy and quick); quantification possible as per intensity of bands

Table 1. Summary of main techniques for the detection of RNA modifications.

#### 3. Impact of RNA Modifications on Pathogenic Bacteria Stress Responses and Host Adaptation

### 3.1. rRNA Modifications

The ribosome is a powerful molecular machine and a huge ribonucleoprotein complex (2.3 MDa in bacteria), which performs the crucial task of translating the genetic information into proteins. The ribosome is also a ribozyme with its catalytic centers made by RNAs [75]. To carry out translation, the ribosome needs to balance between speed and accuracy and rRNA base modifications participate to fine tune ribosome structure and function. Indeed, in vitro reconstituted E. coli ribosomes lacking rRNA modifications were severely defective in catalytic activity [76] and the ribosome assembly was also altered (Ofengand's lab). Numerous studies showed that the loss of rRNA modifications perturbs the active site structures [77, 78], and causes altered rates and accuracy of translation [79]. In bacterial ribosomes, there are three major types of rRNA modifications:  $\Psi$ , methylation of the 2'-hydroxyl group of riboses (Nm), and methylation of base (mN) [80]. Even if specific role for several of these modifications was not yet attributed, they confer specific properties to the nucleotides. For instance, they can induce enhanced ( $\Psi$ ) or decreased (D) base stacking, structure rigidity ( $\Psi$  and Nm) or flexibility (mN) to both single- and double-stranded regions with possible altered hydrogen-bonding [25, 81]. These modifications are clustered in highly conserved areas devoted to decoding, peptidyl transfer, binding sites of A- and P- tRNAs, the peptide exit tunnel, and inter-subunit bridges [82, 83](Fig. 1A and 1B).

Bacterial rRNA modifications have been investigated by Mass Spectrometry (MS), Reverse Transcriptase extension (RT), RNAseq, and structure analysis. Several high-resolution structures of 70S ribosomes have been achieved both by cryo-EM and X-ray studies. However, cryo-EM structures can be non-uniform in local resolution and confident assignment of modifications is often possible on their most structurally stable core. Assignment of 35 modifications on bacterial rRNAs was first obtained on the cryo-EM structure of E. coli 70S-EF-Tu-tRNA complex solved at 2.65-2.9 Å resolution [84]. This study provides clues on their roles in fine-tuning ribosome structure and function and in modulating the action of antibiotics. In this structure, the methyl group of nucleosides could be clearly visualized as extra densities, as well as the non-planar dihydrouridine at position 2449 of 23S rRNA, while  $\Psi$ s were identified indirectly by polar residues within hydrogen-bonding distance of the N1 position. Besides, the rRNA modifications were unambiguously identified in the T. thermophilus and E. coli crystal structures at 2.3-2.5-Å resolution, respectively [85, 86]. More recently, sub-stoichiometric modified nucleotides, like m<sup>7</sup>G527 and m<sup>6</sup>A1519 of the 16S rRNA, could be assigned on the structure of E. coli 70S solved at 2 Å resolution, and some antibiotic resistance mechanisms could be proposed [82] (Fig. 1A). In the past three years, cryo-EM analyses of 70S [83] and 50S [87] from S. aureus allowed the placing of 10 rRNA modifications (Fig. 1B).

Because the literature about the functions of rRNA modifications is very rich, we have chosen specific examples in different bacteria, which illustrate the variety of their functional impact. For clarity, we refer to the *E. coli* numbering of the 16S and 23S rRNA sequences. In the decoding region of the small 30S subunit, several modified nucleotides contact tRNA or mRNA, or are close to positions known to be important for translation, contributing to the building of the decoding site. For example, the *E. coli* m<sup>2</sup>G966 contacts the P-site tRNA through stacking with nucleotide at position 34 of the tRNA [88]. Particularly, they stabilize the binding of initiator fMet-tRNA<sup>fMet</sup> to the 30S pre-initiation complex prior to start codon recognition [89]. The correct folding of the 16S rRNA around the initiator tRNA helps to discriminate the initiator tRNA against other tRNAs. In this context, m<sup>2</sup>G966, m<sup>6</sup><sub>2</sub>A1518 and m<sup>6</sup><sub>2</sub>A1519 monitor the characteristic presence of the three consecutive GC pairs of the anticodon stem of the initiator tRNA [90]. In addition, m<sup>4</sup>Cm1402 and m<sup>3</sup>U1498 contact the P-site mRNA codon and play a role in fine-tuning the shape and function of the P-site [82] to increase initiation decoding fidelity [91]. In *S. aureus*, the m<sup>4</sup>Cm1402 modifications are important for infection since *rsmI* and *rsmH* genes encoding the two methylases of C1402 protect *S. aureus* from oxidative stress and restore translational fidelity [92].

On the large ribosomal subunit, *E. coli* Gm2251 and Um2552 are located in the P- and Aloops, respectively, to establish interactions with the CCA end of tRNAs in P- and A- sites. Gm2251 is conserved in all three kingdoms of life [93], whereas Um2552 is present in many bacteria except that in some Bacillus species, like *B. subtilis* and *B. stearothermophilus*, methylation at the neighboring G2553 was observed [94]. Absence of Um2552 modification (*rlmE*-deficient mutant) increases the flexibility of the nucleotides next to it, and induces 50S maturation delay, slower subunit association, and slower translocation rate [95]. Surprisingly, translation with unmethylated U2552 appears to be more accurate suggesting that a certain degree of recoding provided by methylation of this residue is important for cell physiology [96].

The ribosome and more generally the translation apparatus are main targets of antibacterial therapies [97-100]. However, bacteria are continuously evolving resistance mechanisms for antibiotics. Acquisition of additional rRNA modifications is one of the most direct marks of antibiotic resistance. For example, aminoglycosides target the 30S subunit to prevent translocation and A-site tRNA binding, and promotes miscoding (**Fig. 1C**), while macrolides bind to the nascent peptide exit tunnel on the 50S subunit to prevent peptide bond formation and translocation [101, 102] (**Fig. 1D**). Methylation of their rRNA target sites inhibits antibiotics binding [103]. Interestingly, the modification enzymes responsible for the resistance are often inducible and only synthetized when necessary for survival. For example, in *S. aureus* sub-inhibitory concentrations of the macrolide erythromycin (**Fig. 1D**) stall ribosomes on the leader peptide for the methylase (*ermC*) responsible for the dimethylation

of A2058 at the ribosomal peptide exit tunnel of the 50S subunit [104] (Fig. 1D). This pausing induces the transcript to form a structure in which the Shine and Dalgarno sequence for *ermC* is exposed, allowing translation of ermC [104]. ErmC induced-dimethylation of A2058 prevents erythromycin binding (Fig. 1D), but also results in inefficient translation of selected polypeptides [104]. It is interesting to note that, S. aureus strains bearing m<sup>6</sup>2A2058 are not only erythromycin-resistant, but can also better escape host immune system, avoiding recognition by specific Toll-like receptors [105]. Other mechanisms of modifications inducing resistance but compromising bacterial fitness involve methylations of G1405 and A1408 in 16S rRNA, which are required for aminoglycoside resistance in Gram-negative bacteria (Fig. 1C). In fact, these additional modifications interfere with the natural methylation at the neighboring C1407 residue (m<sup>5</sup>C1407) and decrease translation accuracy [106]. Conversely, antibiotic resistance could also arise from the lack of modifications at naturally occurring sites. Indeed, mutation of the ksgA gene encoding methyltransferase, causes a defect of modifications at A1518 and A1519 in the 16S rRNA, and induces kasugamycin resistance [107] accompanied by assembly defects and a cold sensitive phenotype [108]. Similarly, loss of methylation at m<sup>7</sup>G527, which is located near the mRNA decoding site has been shown to confer low-level streptomycin and neomycin resistance [109, 110].

Finally, induction of rRNA modifications has been reported to be a key step in the ribosome reactivation during resuscitation of persistence state [111]. Indeed, antibiotic stresses together with a myriad of other stresses, are sometimes inducing the differentiation of a subpopulation of cells, which become dormant and multi-stress tolerant (persisters) [112]. This transient phenotype, which does not involve genetic changes, can be reverted via different mechanisms to re-activate ribosomes [113-115]. For instance, it has been recently shown by single-cell studies, that in *E. coli* cells resuscitate and ribosome activity is resumed by the action of the RluD enzyme, which is responsible of 23S rRNA pseudouridine (5-ribosyl-uracil) modification at positions 1911, 1915, and 1917 [111].

#### 3.1. tRNA Modifications

tRNAs are key molecules in translational process, their main purpose is to participate to protein synthesis by decoding the mRNA codons into the corresponding amino acids. They contain the largest number of modifications and the widest chemical diversity. Their modifications are known to improve tRNA decoding capacity, to decrease codon sensitivity, and to dictate codon choice and the maintenance of reading frame. Their localization concentrates in two hotspots - the anticodon loop and the tRNA core region, where the D- and T $\Psi$ -loops interact with each other (**Fig. 2**) (reviewed in [116, 117]).

Modifications in the tRNA core are important for the stability of tRNA structure and can contribute to temperature adaptation in thermophilic as well as in psychrophilic organisms [118]. Because they are involved in the tertiary interactions maintaining the L-shape, they are also expected to influence the binding of several proteins to the tRNA (i.e. EF-Tu, aminoacyl-tRNA synthetases, and anticodon modification enzymes) [119-121]. Different mutagenesis studies have demonstrated the role of these modifications in tRNA structure stabilization and their consequences on bacterial physiology during stress adaptation and on pathophysiology. The 2'-O methylation of Gm18, present on several tRNAs and common to all Gram-negative bacteria, is lacking in most Gram-positive species despite the presence of putative *trmH*-like genes. Methylation of the ribose stabilizes G18 in its C3'-endo form increasing its rigidity [122, 123] and promotes Gm18-W55 base pairing (Fig. 2). The 5-methylation of U54 and the isomerization of U55 into  $\Psi$ 55 enhance base stacking and stabilize the tRNA [124-126]. In the mesophilic E. coli, lack of the modification enzymes coded by the genes trmH (Gm18), trmA (m<sup>5</sup>U54) and truB ( $\Psi$ 55), reduces growth rate particularly at high temperature [127]. In the thermophilic T. thermophilus, adaptation to low temperature requires maintaining a sufficient flexibility of tRNAs. In this condition, methylation of the ribose of G18 is prevented but only if  $\Psi$ 55 is present [128]. Moreover, the lack of some of these modifications induces changes in decoding and modulates frameshifting. In the pathogenic bacteria Shigella flexneri,  $\Psi 55$  is linked to the expression of several virulence factors, which are responsible of shigellosis, an intestinal infection causing diarrhea. Deletions of *trmH*, *trmA*, and *truB* genes in *S*. *flexneri* are associated with a reduction of the hemolytic activity and a decrease of the secretion system expression [127]. Furthermore, Gm18 is known to be responsible for TLR-7 dependent suppression of the immune response of dendritic cells, allowing a better tolerance of several enterobacteria by the host immune system [129-131].

The anticodon loop (ASL) is the other hotspot for modifications, which affect the geometry and physicochemical determinants governing the decoding process [132, 133]. The anticodon regions of all tRNAs bind to their cognate mRNA codons on the ribosome with similar affinities, despite diverse codon–anticodon pairings that should exhibit differences in basepairing strengths [134]. The modifications in the tRNA anticodon loop compensate for potential binding differences and ensures uniform affinities of all tRNAs to their cognate codons [135]. Perturbations of these modifications selectively alter the spectrum of proteins during adaptation via rare codon usage and translational frameshifting [136]. Specifically, modifications of nucleotide at position 37 and at the position 34 (wobble) have a strong impact on maintaining the reading frame [136, 137]. Modifications at positions 32 and 38, the first and last nucleotides of the loop, have also important consequences in modulating the affinity for specific codons, by inducing 32-38 basepairing and reducing the size of the loop [138]. This interaction is coordinated with the identity of codons. Strong GC-rich codon–anticodon

interactions are always balanced by a weaker 32-38 pairing and conversely, a weak AU-rich codon-anticodon interaction is coupled with a stronger 32-38 pairing [138]. Several studies have analyzed the link between modifications of anticodon loop residues and gene expression regulation. For example, the introduction of queuosine (Q) in the tRNA<sup>Tyr</sup>GUA, tRNA<sup>Asn</sup>GUU, tRNA<sup>Asp</sup>GUC and tRNA<sup>His</sup>GUG at the wobble position (G34) in Eukaryotes and Bacteria, permits efficient recognition of both NAC and NAU codons. This Q modification allows fine-tuning of translation and has been correlated with low-level translation of Shigella virulence factors, including the main transcriptional regulator VirF [139]. Its efficient translation depends on the presence of Q34 and 2-methylthio-N6isopentenyladenosine (ms<sup>2</sup>i<sup>6</sup>A37) tRNA modifications. Deletion of either tgt (tRNA-guanine transglycosylase, for Q) or miaA (tRNA dimethylallyltransferase, for ms<sup>2</sup>i<sup>6</sup>A) genes leads to a less efficient synthesis of VirF in S. flexneri and reduces its pathogenicity [139]. In E. coli, it has been shown that ms<sup>2</sup>i<sup>6</sup>A is important for translation of RpoS, the general stress response alternative sigma factor, which is particularly rich in UUX-Leu codons over CUX-Leu codons [140]. Similarly, S. flexneri virF contains a high proportion of UUX-Leu codons [141]. Although the mechanism by which Q induces virF translation is not known, it is noticeable that putrescine or a combination of methionine and arginine metabolically related to putrescine, restore VirF expression of S. flexneri tgt mutant [142]. Since polyamine like putrescine can modulate translational fidelity and maintenance of reading frame [143, 144], it is possible that translation misreading of *virF* could occur in absence of Q.

Studies on U34 hypermodifications reveal the central role of wobble U modifications and associated enzymes in bacterial adaptation to environmental conditions and virulence in pathogens. Even if the precise mechanism remains unclear, in the absence of modifications, frameshift occurs resulting in the expression of alternate proteins [136, 145]. Deletion of gidA and mnmE, encoding two enzymes of the 5-methylaminomethyl-2-thiouridine (mnm<sup>5</sup>s<sup>2</sup>U34) modification pathway, was shown to significantly reduce the colonization of Salmonella Typhimurium in liver and spleen, accompanied by decreased invasion of epithelial cells and compromised ability to survive and replicate inside macrophages [146]. This effect can be explained in part by the fact that several colonization genes important for host cell invasion, including the T3SS genes invAEG, spaPQ, and prgHJ were downregulated in the attenuated mutants [147]. In addition, in this strains it has been also observed the repression of several other proteins as the oxidoreductase Ygh, and the thiol peroxidase Tpx, which promote the survival of *S. Typhimurium* under the stressful conditions experienced within host macrophages [148]. The modified nucleotide mnm<sup>5</sup>s<sup>2</sup>U34 is also important for virulence in other bacteria. In Streptococcus species, Gram-positive bacteria responsible for a wide range of infections from skin infection to sepsis, GidA/MnmE modification enzymes are essential for acid stress and high temperature adaptation [149], for pathogenicity [150], reduced ability of adhesion and invasion in epithelial cells, and increased sensitivity to phagocytosis [151]. Transposon mutagenesis in GidA gene is leading to sensitivity to acidic conditions also in Cronobacter sakazakii, an opportunist pathogen causing neonatal meningitis, enterocolitis, septicemia, bloody diarrhea and brain abscesses, decreasing its ability to growth in host digestive system [152]. One of the best-characterized example of host adaptation via the induction of specific tRNA modification at U34 to selectively translate codon-biased mRNAs for persistence genes, has been described for Mycobacterium bovis [153]. When mycobacteria species infect host lungs, they are phagocytized by alveolar macrophages, which are unable to kill and digest them. Consequently, the bacteria multiply and promote the formation of granulomas, which are symptomatic of chronic infections. Human granulomas lacking endothelial and blood vessel are highly hypoxic [154], and mycobacteria enter a quiescent state in which cell replication is halted or slowed [155]. In this condition, DosR, the master regulator of hypoxic bacteriostasis, mediates the expression of approximately 50 genes necessary for dormancy survival [156]. Translation activation of DosR requires shifting from mo<sup>5</sup>U, presents at U34 in tRNA<sup>Thr</sup>UGU in aerobic conditions, to cmo<sup>5</sup>U and mcmo<sup>5</sup>U. This change of modification type, facilitates decoding of ACG codons, particularly abundant in *dosR* transcript [153]. The rationale for this decoding has been described by structural analysis [157]. The presence of cmo<sup>5</sup>U34 induces a classical Watson-Crick base-pairing geometry involving the wobble position, which allows better stacking between U34 and purine 35, and as a consequence increases the stability of the codon-anticodon interaction.

In addition to wobble position, 2'-O-methylations of A, C, and U at position 32 by methyltransferases of the Trm family, have been shown to confer resistance to oxidative stress in *P. aeruginosa*, allowing its survival during infection [158]. Hypomethylation of the 2'-O-ribose moiety at position 32, linked to reduced catalase activity, perturbs codon-anticodon interaction and results in translation insufficiency and transcript misreading [159, 160]. Thiolation of cytidine at position 32 catalyzed by TtcA, a [Fe-S] cluster enzyme, has been shown to play a role in the response to oxidative stress during infections caused by *P aeruginosa* [161].

Finally, modifications of nucleotides in the variable loop have been shown to contribute to host adaptation. For example, m<sup>7</sup>G46 catalyzed by tRNA guanine-N7-methyltransferase (*trmB*) is important for decoding efficiency of tRNA<sup>Asp</sup>GUC and tRNA<sup>Phe</sup>GAA. In *P. aeruginosa*, loss of *trmB* has a strong negative effect on the translation of Phe- and Asp-enriched mRNAs, including those coding for the major peroxide detoxifying enzymes, the catalases KatA and KatB, resulting in oxidative stress-sensitive phenotype [162]. Using tRNA-seq and mass spectrometry performed on *Vibrio cholera* revealed specific modifications in various tRNAs that were not described in *E. coli* tRNAs [163]. These modifications include an acetylated acpU at either position 20 in the D-loop and at positions 46 or 47 in the variable loop. More interestingly, an editing process C-to-  $\Psi$  was for the first time identified at

position 32 of the anticodon loop of tRNA<sup>Tyr</sup>. Although the physiological consequences of these specific features have to be defined, it is tempting to propose that RNA modifications contribute to the speciation of the bacteria and to the adaption of the organism to its specific niches.

#### 3.1. sRNA Modifications

Small trans-acting regulatory RNAs (sRNAs) belong to a very heterogeneous class of RNAs regulating several processes including virulence gene expression, stress adaptation, and quorum sensing [164]. They exert their functions through specific interactions with diverse targets such as mRNAs, sRNAs, tRNA precursors, proteins or even with the ribosome [165]. The sRNAs are very different in length, sequence, structure and regulate gene expression using various mechanisms. So far only few examples of RNA modifications have been reported in bacterial sRNAs [166].

The best examples of regulatory RNAs, where modifications have been identified, are tmRNA and Y RNA, both mimicking the tRNA structure (Fig. 3). The tmRNA together with the small protein B (SmpB) is involved in trans-translation, the major and ubiquitous ribosome rescue system in bacteria [4]. This mechanism is taking place when ribosomes and tRNAs are stalled on problematic and often truncated mRNAs, which can lead to reduced translation [167]. Ribosome halting resulted from i) chemical mRNA damages produced by environmental stresses, ii) rare codons or problematic polypeptide stretches, iii) drugs inducing translational misreading, non-programmed frameshifting, or stop codons readthrough, and from iv) spurious RNase activity or cleavage of the mRNA in the Asite by RelE in response to starvation stress [168-172]. In these situations, trans-translation operates to liberate the ribosome, and simultaneously to degrade the nascent truncated peptide [4]. A vacant ribosomal A-site is the signal recognized by tmRNA/SmpB complex, which is delivered to the ribosome by the translation elongation factor EF-Tu. The tmRNA is characterized by two functional domains embedded into a conserved and complex structure, which are a tRNA-like domain (TLD) specifically aminoacylated with alanine and a mRNA-like domain (MLD) encoding a peptide tag targeting proteolysis [173, 174]. TLD presents a typical tRNA T $\Psi$ -loop with two  $\Psi$ s and one m<sup>5</sup>U [175]. These modifications most probably enhance tRNA structural mimicry and its use in translation as a canonical tRNA (Fig. 3). Most probably that m<sup>5</sup>U54 in tmRNA is introduced by the SAMdependent methyltransferase TrmA as it is for the tRNAs [176]. Although tmRNA has been shown to be essential for the expression of virulence factors during S. Typhimurium infection [177], to our knowledge no studies have been conducted to establish the role of its modifications in bacterial adaptation or infection.

The non-coding Y RNAs are present in both eukaryotes and in several bacteria including some pathogens [178]. Bacterial Y RNA, known as YrlA (Y RNA-like A) RNA, is a modular RNA of variable

length (between 90 and 150 nucleotides) characterized by a large stem involving pairings between nucleotides at the 5' and 3' ends (Fig. 3) and a tRNA-like domain [179]. This domain shows high similarities to the D, T $\Psi$  and acceptor arms of tRNA (Fig. 3). Due to this structure similarity, YrlA is a substrate for two tRNA modification enzymes DusA and TruB, which introduce a dihydrouridine and a  $\Psi$  in the D and T $\Psi$  loops, respectively [180]. The basal stem of YrlA tethers the monomeric ring Rsr protein similar to eukaryotic Ro60 protein, while the effector tRNA-like domain binds the ring-shaped 3' to 5' exoribonuclease polynucleotide phosphorylase (PNPase), forming a double-ringed RNA degradation machine called RYPER [179]. Although the functions and mechanism of RYPER are still under investigation, Rsr and YrlA have been shown to alter PNPase substrate specificity to preferentially direct the degradation of structured RNAs (including rRNAs) [179, 181]. By altering the levels of specific RNA populations, RYPER has been proposed to be involved in stress responses, such as UV irradiation or prolonged stationary phase [182, 183]. In Salmonella enterica, expression of YrlA appears to be confined to certain infection stages [184]. Surprisingly, it was reported that lupus autoimmunity might be triggered and sustained by commensal bacteria expressing Rsr RNPs [185]. Noteworthy, in some bacteria including S. Typhimurium, rsr and Y RNA genes are located within an "RNA repair" operon together with the *rtcA* encoding RNA cyclase and *rtcB* encoding RNA ligase [179], which transcription is activated by tRNA fragments resulting from the SOS response to DNA damage [186]. tRNA fragments also accumulate when tRNAs are hypomodified, such as in  $\Delta truA$ strain where  $\Psi$  at positions 38, 39, and 40 in the anticodon arm of some tRNAs cannot be introduced anymore [187]. Since tRNA fragments are both natural substrates of PNPase and of RtcB religation, it is possible that assembly of RYPER protects them from degradation and that the expression of RtcB could restore tRNAs from halves and translation [186]. Interestingly, in E. coli RtcB re-ligates a 16S rRNA 3' fragment containing the anti-Shine-Dalgarno sequence cleaved by the MazF toxin [188]. This indicates a tight link between RNA modification levels, translation regulation, and RNA metabolism in response to stress.

Another example of sRNA modification in pathogenic bacteria derives from a transcriptomewide profiling of m<sup>6</sup>A distribution in *Pseudomonas aeruginosa*. Methylation sites were found present in two major sRNAs, RsmY and RsmZ [189], which sequester the regulatory protein RsmA to control its activity which is associated with acute and chronic virulence phenotypes [12, 190]. The involvement of these modifications in the regulatory mechanisms of RsmY/Z has not been studied yet.

Recently, one of the best characterized sRNA in *S. aureus*, an opportunistic pathogen causing a large variety of infections, has been shown to contain at its 5'end a peculiar modification which is co-transcriptionally introduced [191]. The expression of RNAIII is under the control of a two-component system, which senses bacterial cell density, to orchestrate the regulation of virulence gene expression

[192, 193]. This dual RNA codes for the cytotoxic δ-hemolysin peptide, while its 5' and 3' UTRs act as antisense RNA to regulate at the post-transcriptional level the expression of virulence genes associated with infectious diseases [193]. Hence, through basepairing interactions with its target mRNAs, it represses several cell wall associated proteins involved in adhesion and tissue colonization, and the transcriptional repressor of toxins Rot while it activates directly or indirectly the synthesis of many secreted proteins and toxins required for infection dissemination. A new RNAseq based approach has been developed to detect the incorporation of NAD, the nicotinamide-adenine dinucleotide, at the 5 ends of RNA transcripts [194]. This study found only few *S. aureus* transcripts containing this 5' cap, including RNAIII. In Gram-negative bacteria, NAD has been reported to have a stabilization effect protecting the RNA from the 5' processing enzyme RppH, which produces monophosphate at the end of RNAs that are substrates of RNase E [194]. In *Bacillus subtilis*, NAD protects RNAs from the exonucleolytic activity of RNase J1/J2 [195]. In *S. aureus*, the presence of NAD in RNAIII does not induce its stabilization nor affects its structure, but it has important consequences on pathophysiology. By a yet unknown mechanism, the NAD modified RNAIII leads to a decreased expression of δ-hemolysin and reduced cytotoxicity [191].

### 3.1. mRNA Modifications

Besides the classical 5'-cap m<sup>7</sup>G modification of eukaryotic mRNAs, other modifications have been described, including the 6-methyladenosine (m<sup>6</sup>A), the 5-methylcytosine (m<sup>5</sup>C), inosine (I) derived from adenine deamination and pseudouridine ( $\Psi$ ). These modifications, which are present within 5'- and 3'-untranslated regions (UTRs) and the coding sequences of mRNAs, contribute to fine tune gene regulation [196-202]. In bacteria, the presence and the roles of mRNA modifications is relatively unexploited in pathogenic bacteria. In bacterial mRNAs, the presence of non-canonical 5' ends has recently been reported for a subset of mRNAs. As described above, co-transcriptionally introduced 5' NAD cap has also been detected in some *E. coli* mRNAs and is thought to modulate mRNA stability and translation efficiency [194, 203]. Recently, NAD cap has been found in mRNAs expressed in *B. subtilis* spores, a dormant state developed in response to different stresses [204]. Its role in these mRNAs remains to be analyzed. Other studies have shown additional types of 5' capping directly incorporated into mRNAs during transcription initiation, which might increase mRNA stability. For example, dinucleoside tetraphosphates, very often Np4A, have been reported in *E. coli* [205]. Interestingly, the incorporation of such dinucleosides depends on their cellular concentration, which increases in some stress conditions such as heat shock [206] and oxidative stress [207].

Bacterial mRNAs can also contain post-transcriptional modifications. In *E.* coli,  $\Psi$ s have been detected in some mRNAs. They can be located at specific codons and as a consequence they alter

translation speed or mRNA decoding [208], and at stop codons to induce nonsense suppression [209, 210]. Ws have been proposed to influence the kinetics of RNase E-directed degradation in Gramnegative bacteria [211]. Another abundant mRNA modification is m<sup>6</sup>A, which has been detected in genes involved in energy metabolism in Gram-negative bacteria, including pathogenic *P. aeruginosa* [189]. Very recently, it has been shown that m<sup>6</sup>A reduces both sense and stop codon reading accuracy [212, 213]. The molecular explanation for this decoding perturbation could be due to the formation of less stable codon-anticodon interactions with cognate tRNAs [212]. Indeed, when compared with unmodified A, m<sup>6</sup>A forms less stable basepairing with uridine (U) and destabilizes local RNA structures and short duplexes [214, 215]. It remains to be studied whether these modifications in mRNAs vary significantly in response to metabolic changes or stress.

Adenosine deamination is most probably the major modification in mRNAs, which can directly influence the activity of the synthesized protein. Adenosine-to-inosine (A-to-I) mRNA editing is catalyzed by the tRNA adenosine deaminase enzyme TadA, which recognizes stem-loop structures resembling the anticodon arm of tRNA<sup>Arg</sup> [216]. Because inosine (I) is recognized as guanosine (G) by the translational machinery, A-to-I editing expands the decoding rules resulting in protein diversification. In *E. coli* and in the two pathogenic bacteria *Klebsiella pneumonia* and *Yersinia enterocolitica*, recoding tyrosine (UAC) to cysteine (UGC) has been reported in mRNAs encoding self-killing toxins like HokB, increasing its toxicity [216]. HokB induces cellular growth arrest in response to starvation as a function of cellular density, via membrane depolarization. By doing so, it was found to mediate antibiotic tolerance leading to persistence [217]. Since bacteria persistence is characterized by the existence of sub-populations of bacteria that are tolerant to an antibiotic treatment with a fitness cost [218], the heterogeneous RNA editing levels of *hokB* mRNA could promote non-genetic cell heterogeneity [219].



**Figure 1.** Natural ribosomal RNA modifications and additionally modification implicated in antibiotic resistance mechanisms as indicated by structural analyses. (A) Cryo-EM structure at 1.98 Å of *E. coli* 70S ribosome (pdb file 7K00). 11 and 24 RNA modifications (red spheres) could be visualized in the 30S (16S rRNA) and 50S (23S rRNA) subunits, respectively [82]. (B) Cryo-EM structure at 3.20 Å of *S. aureus* 70S ribosome (pdb file 6YEF). The limited resolution allowed the visualization of 4 RNA modifications in the 16S rRNA and 6 in 23S rRNA [83]. PTC, Peptidyl Transferase Center on the large 50S subunit. (C) Mechanism of aminoglycoside (Par, paromomycin) resistance induced by methylation of A1408 (pdb file 5ZEJ [220]). The presence of the methyl group directly perturbs antibiotic interaction. (D) Mechanism of macrolide (Ery, erythromycin) resistance induced by dimethylation of A2058 (pdb file 6XHV [221]). The two methyl groups on A2058 prevent the coordination of a water molecule with G2505, which stabilizes erythromycin binding.


Figure 2. Pathogenic bacteria tRNA modifications involved in virulence and stress adaptation. (A) Secondary structure of tRNA. The nucleotides in the loops, where the majority of modifications accumulate, are colored as follow: D loop in green, anticodon loop in pink, variable loop in orange, and T $\Psi$  loop in light blue. The nucleotides for which the modifications are associated with a specific phenotype specified in the figure are in red. (B) Tertiary L-shape structure of tRNA. The 3D model corresponded to the crystal structure of *Saccharomyces cerevisiae* tRNA<sup>Phe</sup>GAA (pdb file 1EHZ [222]). The same color code is used for the secondary (A) and tertiary (B) tRNA structures. The core domain of the tRNA comprises the D-, T $\Psi$ - and variable loops.



**Figure 3.** The structures of tmRNA and Y RNA mimic part of the tRNA structure. (A) The structure of EF-Tu-tRNA<sup>Phe</sup> complex (with GDPNP, GTP analog) from *Thermus aquaticus* (pdb file 1TTT [223]). Each domain of the tRNA is colored: acceptor am in grey, TY-arm in light blue, the variable region in orange, the D-arm in green, and the anticodon-arm in pink. EF-Tu structure is represented in light pink. (B) The structure of the tmRNA fragment in complex with EF-Tu (with GDP and kirromycin antibiotic, in light pink) and SmpB (in light grey) from *Thermus thermophilus* (pdb file 4V8Q [224]). The regions of tmRNA mimicking tRNA are shown with the same color code as for the tRNA. (C) *Salmonella Typhimurium* Y RNA (YrIA, pdb file 6CU1 [225]). The regions of YrIA mimicking tRNA are shown with the same color code as for the tRNA.

## 4. Conclusion and perspectives

The review presented several examples, which unveiled the diversity of functions of RNA modifications in translation and RNA degradation in bacterial pathogens. Because technologies are constantly improving, it is expected that the whole set of modifications will be mapped in RNA molecules as well as their quantifications. This will be the prerequisite to better study their dynamics upon stress or during bacterial infection. Further works correlating the modifications with the characterization of their protein co-factors (referred as writers, readers, and erasers) will be another step necessary to get an in-depth overview of their functions and the physiological consequences on bacterial pathogens. Many questions still remain to be addressed: what is the extent of chemical modifications diversity and complexity among evolutionary distant bacteria? Are there specific classes of bacterial sRNAs and mRNAs that could be modified extensively as it is for tRNAs and rRNAs? What are the consequences of RNA modification defects on bacterial physiology and pathogenesis? Some of the data suggested that some tRNA modifications are species-specific. Hence, it is expected that modifications might contain some metabolites issued from specific metabolic pathways resulting from the bacterial adaption to its ecological niches. Meanwhile during the infection process, the pathogens have to face metabolic burden and should counteract the host defenses mechanisms. It would not be so surprising that some of the modifications might be acquired or disrupted during the infection process with consequences on the bacterial proteome. The functional studies of the modification enzymes might also led to biotechnological applications, to design gene reprogramming or new tools for RNA studies, or to select novel anti-microbial strategies. Many of these studies will require the development of more simple technologies, such as the direct RNA sequencing methodologies, to facilitate the mapping and the discovery of RNA modifications among bacterial species. Although many studies have been done on tRNA and rRNA modifications, we are still far to fully appreciate the impact of modifications on RNA functions. We are only at the beginning of the tip of the iceberg.

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## 2. Staphylococcus aureus

Les Staphylocoques sont des coques à Gram positif commensales de l'Homme, dont plusieurs espèces sont des pathogènes opportunistes. Parmi elles, *Staphylococcus aureus* représente l'espèce la plus virulente, responsable d'un grand nombre d'infections de gravité variable et touchant un large éventail de tissus, allant des infections cutanées bénignes à la pneumonie, l'endocardite, voire la septicémie. *S. aureus* est aussi capable de s'adapter pour persister à la surface et à l'intérieur de tissus humains. Elle est présente sur la peau et dans le nez chez environ 30% de la population (Wertheim *et al.*, 2005). La colonisation de la peau inclus l'implantation de la bactérie à sa surface en tant que constituant du microbiome (Oh *et al.*, 2016). Mais également l'insertion entre les couches de l'épiderme (Nakatsuji *et al.*, 2013), la modulation de la réponse immunitaire et la persistance dans les cellules immunitaires, endothéliales et épithéliales (Soong et al., 2015). Cette internalisation lui permet d'échapper complètement aux défenses immunitaires de celui-ci.

L'émergence de souches multi résistantes aux antibiotiques est une préoccupation majeure de santé publique, particulièrement en milieu hospitalier, les souches MRSA (*S. aureus* résistante à la méthicilline) provoquant des infections nosocomiales graves et difficiles à traiter. La diversité des symptômes cliniques provoqués et les mécanismes de résistance aux traitements dépendent de l'expression de nombreux facteurs de virulence et des voies de réponse au stress.



**Figure 1 : Schéma représentant les étapes de l'infection de** *S. aureus.* La colonisation des tissus amorce l'infection grâce aux adhésines permettant aux bactéries de se fixer sur différents types cellulaires. Au sein des tissus, les bactéries sont confrontées aux défenses immunitaires de l'hôte. Elles doivent donc échapper aux cellules immunitaires, former des colonies et entrer dans une phase de croissance grâce à la formation du biofilm les protégeant des stress environnementaux. Lorsque les colonies sont assez grandes, la phase de dissémination est déclenchée par la production de toxines et exoprotéines (nucléases et protéases) entrainant la rupture du biofilm et conduisant à une infection aiguë ou un choc toxique. En cas de phagocytose, la bactérie est capable de résister au stress généré dans les phagosomes grâce aux systèmes de détoxification et de réparation, elle va ainsi survivre sous forme quiescente. Les flèches annotées « QS » présentent des transitions entre les étapes du cycle d'infection qui sont réalisées sous le contrôle du Quorum Sensing, système à deux composants permettant à la bactérie de détecter la densité cellulaire et moduler l'expression de nombreux facteurs de virulences grâce à l'ARNIII. Cet ARN régulateur permettant simultanément de réprimer les facteurs impliqués dans l'adhérence et la colonisation et activer l'expression des toxines et exoprotéines

Le cycle de l'infection par *S. aureus* est assez précisément établi. A chaque étape du cycle, la bactérie va s'adapter grâce à la production d'un arsenal de facteurs de virulence dont l'expression est coordonnée en fonction de son environnement (**Fig. 1**).

Lors de l'adhérence et l'invasion tissulaire, l'étape initiatrice fondamentale à l'infection, des protéines de la famille des MSCRAMM (microbial surface components recognizing adhesive

matrix molecules) sont produites. Parmi elles, les protéines de liaison à la fibronectine (FnbpA et FnbpB) ou les facteurs de liaisons au fibrinogène, les Clumping factor A et B (ClfA et ClfB) permettent à la bactérie de se fixer sur différents types cellulaires de l'hôte (Eidhin *et al.*, 1998; Heilmann *et al.*, 2004). De plus, la protéine SpA (Staphylococcal protein A) lui permet non seulement de se lier aux immunoglobulines mais également d'échapper aux défenses immunitaires de l'hôte (Falugi *et al.*, 2013).

Afin de se protéger de la phagocytose, *S. aureus* est capable de produire une capsule de polysaccharides (Luong and Lee, 2002). La production de protéases telles que la Staphopain B et l'Aureolysine lui permet de dégrader l'élastine de l'hôte et entrainer la mort des monocytes (Shaw *et al.*, 2004; Smagur *et al.*, 2009; Elmwall *et al.*, 2017). Les CHIPS (chemotaxis inhibitory proteins of *S.aureus*) et Efb (extracellular fibrinogen binding protein) sont également sécrétées afin d'empêcher le recrutement de neutrophiles et l'activation du système du complément (Postma *et al.*, 2004; Rooijakkers *et al.*, 2006).

Pour assurer la prolifération de la bactérie dans les tissus, une structure de protection est produite sous forme de biofilm. Cette structure permet aux cellules de résister aux antibiotiques, d'échapper aux défenses immunitaires de l'hôte et ainsi devenir persistantes en diminuant leur métabolisme. (Arciola *et al.*, 2015; Otto, 2018)

La dissémination de la bactérie est facilitée par la production de toxines et d'exoprotéines (nucléases, lipases et protéases) entrainant la dispersion du biofilm. Ces toxines induisant la lyse des cellules ciblées, telles que les hémolysines (Jarry *et al.*, 2008; Berube and Wardenburg, 2013), les leucocidines (Spaan *et al.*, 2017) et les PSM (phenol soluble modulins) permettent également la propagation de l'infection à d'autres tissus (Periasamy *et al.*, 2012). Elles stimulent la libération de cytokines pro-inflammatoires (IL-18) des kératinocytes et sont indispensables à l'induction de l'inflammation de la peau (Syed *et al.*, 2015). Les cytokines pro-inflammatoires sont importantes pour maintenir les macrophages dans leur rôle de nettoyage des pathogènes avec une production d'oxyde nitrique et d'espèces réactives de l'oxygène importante (Pidwill *et al.*, 2021). Ces toxines sont responsables d'infections aiguës, les entérotoxines par exemple causent des intoxications alimentaires et les TSST-1 (Toxic shock syndrome toxin-1) causent les chocs toxiques Staphylococciques. Il existe une dualité claire entre la production de toxines (infection aiguë) et la tolérance de l'hôte (infection chronique) durant laquelle *S. aureus* évite de stimuler les processus inflammatoires.

L'expression de l'ensemble de ces facteurs de virulence est orchestrée en réponse à de nombreux signaux environnementaux tels que la densité cellulaire, la disponibilité des nutriments ainsi que les stress imposées par les mécanismes de défense de l'hôte. Des systèmes de quorum sensing, codés notamment par le gène *agr* (accessory gene regulator) chez *S. aureus* permettent cette régulation fine de la virulence de la bactérie (Wang and Muir, 2016).

## 3. L'oxydation comme défense contre les pathogènes

La production d'espèces réactives de l'oxygène (ROS) tel que les superoxydes  $(O_2^{-})$  et les peroxydes  $(H_2O_2)$  fait partie de la première ligne de défense mise en place par l'hôte pour lutter contre les bactéries pathogènes. Les ROS sont produits au sein des neutrophiles et des macrophages grâce au complexe de la phagocyte NADPH oxidase (Fang, 2004). Les superoxydes et les peroxydes entrainent la libération d'un atome de fer des metalloenzymes contenant un cluster [4Fe-4S] catalytique, entrainant la destruction du cluster et l'inactivation de l'enzyme (Imlay, 2006). Ces enzymes à cluster [4Fe-4S] sont impliquées dans un grand nombre de mécanismes indispensables pour tous les organismes, notamment les modifications post-transcriptionnelles.



**Figure 2 : Schéma de la formation des radicaux hydroxyles induite par la destruction de centres [4Fe-4S] en présence de peroxyde.** L'ion ferreux libéré va réagir avec le peroxyde produit par les neutrophiles et macrophages entrainant la formation du HO•, encadré en rouge, par une réaction de Fenton.

Les radicaux hydroxyles (HO•) créés par des réactions de Fenton, sont fortement réactifs et interagissent avec toutes les molécules biologiques à proximité en causant des dommages parfois irréversibles. Les molécules les plus spécifiquement touchées sont les acides nucléiques, entrainant des mutations sur l'ADN (Keyer and Imlay, 1996). Les protéines sont également des cibles majeures des ROS, qui peuvent subir des modifications entrainant la formation d'agrégats (Davies, 2005, 2016). Les acides aminés contenant un groupement thiol (méthionine et cystéine) sont particulièrement sensibles à l'oxydation pouvant entrainer l'inactivation des protéines les contenant (Dean *et al.*, 1997; Grimaud *et al.*, 2001).

## 4. S. aureus et son adaptation au stress oxydant

*S. aureus* possède de nombreuses défenses pour s'adapter aux ROS, parmi lesquelles le pigment staphyloxanthine, responsable de sa couleur dorée caractéristique. Présents chez une grande partie des souches de *S. aureus* provenant d'infections humaines, ces pigments caroténoïdes sont connus pour désactiver les singulets d'oxygène. De par leur nombreuses

double-liaisons conjuguées, les caroténoïdes sont des molécules importantes pour la détoxification des ROS. La présence de staphyloxanthine confère ainsi une résistance aux ROS et améliore la survie de la bactérie lors d'infections (Liu *et al.*, 2005).

D'autres systèmes sont également connus pour réduire la concentration de ROS. Les superoxyde dismutases (SOD) sont des metalloenzymes de détoxification des ROS qui catalysent la dismutation du  $O2^-$  en oxygène et  $H_2O_2$ , qui sera ensuite réduit en  $H_2O$  par des catalases ou l'alkyl hydroperoxyde reductase (Clements *et al.*, 1999; Cosgrove *et al.*, 2007). *S. aureus* possède deux gènes codant pour des SOD, *sodA* et *sodM*. L'enzyme SOD majeure SodA dépend strictement du manganèse  $Mn^{2+}$ , tandis que l'enzyme alternative SodM est active lorsqu'elle est chargée en  $Mn^{2+}$  ou en Fe<sup>2+</sup> (Treffon *et al.*, 2020).

L'homéostasie des ions métalliques, plus spécifiquement celle du fer, occupe donc une place importante dans la réponse des bactéries aux conditions oxydantes. De nombreux facteurs liés à l'apport du fer indispensable pour la survie de la cellule, sont mobilisés durant l'infection. Chez l'hôte, les ions Fe<sup>2+</sup> sont séquestrés au sein de complexes moléculaires les rendant très peu disponibles pour les pathogènes qui doivent mettre en place des stratégies afin de pouvoir acquérir le fer nécessaire à leur survie.

Chez *S. aureus*, les protéines du système Isd (Iron-Regulated Surface Determinant) sont des protéines exprimées lors d'un déficit de fer, ces protéines permettent l'utilisation du fer provenant de l'hème de l'hôte. (Clarke *et al.*, 2004; Muryoi *et al.*, 2008). Le système Isd est constitué de 10 protéines, permettant de capter l'hémoglobine et l'haptoglobine avec les recepteurs IsdB et IsdH (Dryla *et al.*, 2003; Torres *et al.*, 2006). L'hème est ensuite transféré à travers la paroi cellulaire via IspA et IspC (Liu *et al.*, 2008; Zhu *et al.*, 2008) vers le transporteur IsdDEF permettant son internalisation dans le cytoplasme. IsdDEF est un abc transporteur dans lequel IsdE est une lipoprotéine se liant à l'hème, IsdD est une ATPase et IsdF est une perméase. Enfin, la porphyrine est dégradée par IsdG ou IsdI qui sont des oxygènases produisant la staphylobiline (Skaar et al., 2004; Reniere et al., 2010). En plus de ce système Isd, la bactérie produit des staphyloferrines A sont codés par les opérons *sfaABCD* (Beasley et al., 2009) et les staphyloferrines B par *sbnABCDEFGHI* (Park et al., 2005; Cheung et al., 2009)

Les systèmes de réparation de l'ADN tels que le système SOS est activé par la protéine RecA, impliquée dans la reconnaissance et la recombinaison de l'ADN simple brin qui est ellemême réprimée par la fixation de la protéine LexA. Lors de dommage sur l'ADN, LexA va être clivé, et permettre l'activation du système SOS (Cirz *et al.*, 2007; Butala *et al.*, 2009). L'opéron *rexBA* fait également partie de la réponse SOS également mis en place par la bactérie afin de survivre aux attaques des ROS produits par les défenses de l'hôte. Les protéines RexAB font partie de la famille des protéines AddAB hélicases-nucléases et sont indispensables pour la survie de la bactérie lors de l'infection. Elles sont impliquées dans la réparation des cassures du double brin (Chang *et al.*, 2006; Ha *et al.*, 2020b).

## 5. Objectifs de la thèse

La cartographie des modifications post-transcriptionnelles dans les ARN non codants de *S. aureus* reste encore peu connue ainsi que leurs implications dans l'adaptation de la bactérie à son environnement, notamment lors de l'infection.

Cette étude a pour but principal dans un premier temps d'établir une cartographie des modifications présentes dans les ARN non codants, plus spécifiquement dans les ARNt de *S. aureus*. Pour cela, une méthode d'analyse permettant de les isoler un à un et de caractériser les modifications présentes doit être mise en place et adaptée aux moyens matériels disponibles ainsi qu'à l'organisme étudié.

Dans un second temps, la cartographie établie pourra permettre une étude dynamique des modifications en adaptation à différentes conditions environnementales rencontrées par la bactérie durant les interactions avec l'hôte, plus spécifiquement les stress rencontrés durant l'infection.

Enfin, l'étude des causes et des conséquences traductionnelles des changements observés pourra être réalisée afin de déterminer le potentiel rôle des modifications posttranscriptionnelles dans l'adaptation aux stress

## II. Résultats :

# Mise en place de la méthode d'analyse des ARN par gel en 2 dimensions et NanoLC-MS/MS

Le chapitre de Methods in molecular biology présente un protocole détaillé pour isoler les ARNt bactériens un a un par gel de polyacrylamide en 2 dimensions ainsi que l'identification des ARNt et la caractérisation des modifications post-trancriptionelles par l'analyse LC-MS/MS. Ce protocole mis en place au sein de l'unité pour l'analyse des ARNt de *E. coli* sera également appliqué sans modifications majeures à cette étude sur les ARNt de *S.aureus*.

# **Chapter 8**

## Mapping of Posttranscriptional tRNA Modifications by Two-Dimensional Gel Electrophoresis Mass Spectrometry

Laura Antoine and Philippe Wolff

## Abstract

RNA modification mapping by mass spectrometry (MS) is based on the use of specific ribonucleases (RNases) that generate short oligonucleotide digestion products which are further separated by nanoliquid chromatography and analyzed by MS and MS/MS. Recent developments in MS instrumentation allow the possibility to deeply explore posttranscriptional modifications. Notably, development of nanoliquid chromatography and nano-electrospray drastically increases the detection sensitivity and allows the identification and sequencing of RNA digested fragments separated and extracted from two-dimensional polyacrylamide gels, as long as the mapping and characterization of ribonucleotide modifications.

Key words 2D Gel isolation, Posttranscriptional tRNA modifications, Nano-LC-MS/MS

## 1 Introduction

RNA modification mapping recently experienced a renewed interest because of the development of new sensitive detection technologies and implication of RNA modifications in the deciphering of gene expression regulation or antibiotic resistance [1, 2]. In this chapter, we provide a detailed protocol for *E. coli* tRNA modification mapping. We present the sequencing by mass spectrometry of two tRNAs, tRNA Ser GCU and tRNA Leu CAG. To obtain the largest sequence coverage, three different nucleotide-specific RNases are used: RNase T1 (cleaves at 3' end of G), RNase A (cleaves at 3' end of U and C), and RNase U2 (cleaves at 3' end of purine but preferably at 3' end of A). The RNA modification mapping and data analysis workflow are shown in Fig. 1. This protocol had been applied successfully to different organisms such as bacteria, archaea, and eukaryotes.

The MS analysis procedure presents several caveats. First, as different tRNAs share similar sequences, it may be difficult to

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Fig. 1 Workflow for posttranscriptional tRNA modifications mapping by two-dimensional gel electrophoresis followed by mass spectrometry analysis. tRNA is separated by 2D gel electrophoresis. Individual tRNA spots are sliced out and in-gel digested by nucleoside-specific RNases. RNase digests are sequenced by LC-MS/MS in order to identify tRNA and to localize modifications

unambiguously attribute such sequences to a single tRNA. Additionally, different sequences can have the same mass (same nucleotide composition) or similar mass (there is a difference of only 1 Da between cytosine and uridine). In those cases, there is often an isotopic pattern overlay, and it can be very difficult to sequence correctly MS/MS spectra. In order to simplify MS/MS analysis and tRNA identification, two-dimensional polyacrylamide gels (2D gels) were used to separate tRNAs (Fig. 2) [3, 4].

After "in-gel RNase digestion," oligonucleotide products (passively eluted from the gel) are separated by nano-ion-pair reversedphase high-performance liquid chromatography (nano-IP-RP-HPLC) [5]. Eluted digests are directly injected in the spectrometer

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Fig. 2 2D polyacrylamide gel (20%) of *E. coli* total tRNA. 10 µg of total tRNA from *E. coli* were loaded; tRNA spots are revealed by ethidium bromide staining. The spots containing tRNA identified by MS/MS sequencing are indicated (black circles) and annotated in the table on the left

via a commercial NanoLockSpray ionization source to provide exact mass measurement. All oligonucleotides are fragmented by collision-induced dissociation (CID) and produce preferential fragments from y and c series for RNA sequencing [6]. Sequencing results are compared to genomic sequence in order to identify tRNA and to map RNA modifications in the sequence.

## 2 Materials

# 2.1 Instruments and Equipment 1. Polyacrylamide gel electrophoresis (PAGE) apparatus for 50 cm glass plates, 1 mm spacers (first dimension). 2. Polyacrylamide gel electrophoresis (PAGE) apparatus for 30 cm glass plates, 1 mm spacers (second dimension). 3. Electrophoresis power supply. 4. UV transilluminator and UV safety glasses. 5. Sterile surgical blades. 6. SpeedVac vacuum concentrator. 7. NanoAcquity UPLC system (Waters, Manchester, UK).

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	<ol> <li>8. Synapt G2-S mass spectrometer equipped with NanoLock- Spray ionization source (Waters, Manchester, UK).</li> <li>9. MassLynx mass spectrometry software with MaxEnt3 module</li> </ol>
	<ul> <li>(Waters, Manchester, UK).</li> <li>10. Acquity UPLC peptide BEH C18 column (130 Å, 1.7 μm, 75 μm × 200 mm) (Waters, Manchester, UK).</li> </ul>
	11. Basic laboratory materials (vortex, thermoblock, etc.)
2.2 Two- Dimensional Gel Electrophoresis	1. Total tRNA from <i>E. coli</i> used in this study was prepared by Gérard Keith (personal gift), but it is also commercially available.
	2. 12.5% Acrylamide/bis-acrylamide (19:1), 8 M urea, 1× Tris- Borat-EDTA (TBE) (first dimension).
	3. 20% Acrylamide/bis-acrylamide (19:1), 4 M urea, 1× TBE (second dimension).
	4. Ethidium bromide (EtBr).
2.3 In-Gel Digestion	1. RNase T1 and A (Thermo Fischer Scientific).
of Separated tRNA	2. RNase U2 was homemade prepared as described [7].
	3. Ammonium acetate 100 mM.
	4. ZIP Tip C18 (Millipore).
2.4 Nano-liquid Chromatography	<ol> <li>Mobile phase A.</li> <li>200 mM Hexafluoropropanol (HFIP).</li> </ol>
	- 7 mM Triethylamine (TEA).
	- 7.5 mM Triethylamine acetate (TEAA) pH 7.5.
	<ul> <li>2. Mobile phase B.</li> <li>– 100% Methanol LC-MS grade.</li> </ul>
3 Methods	
3.1 Two- Dimensional Gel	<ol> <li>Cast the first-dimensional, 12.5% acrylamide/bis-acrylamide, 8 M urea.</li> </ol>
Electrophoresis (See Note 1)	2. Pre-run the gel in $1 \times$ TBE buffer for 30 min at 30 W (constant power).
3.1.1 First Dimension (Denaturing Conditions)	3. Load 10 $\mu$ g per well of <i>E. coli</i> total tRNA in a minimum volume (less than 10 $\mu$ L).

- 4. Run the gel for 7 h at 30 W (constant power).
- 5. Stain the gel with an EtBr solution (10  $\mu$ g/L) for 10 min.

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	<ol> <li>Visualize the bands containing tRNAs under UV light (302 nm). Beware of wearing appropriate protections for handling gel containing EtBr and manipulation under UV light.</li> </ol>
	7. Excise the gel fragments containing tRNAs with a clean razor blade.
3.1.2 Second Dimension (Semi-denaturing Condition)	1. Put the excised gel lanes on the top of the second polyacryl- amide gel, and cast the second-dimensional gel 20% acrylamide/bis-acrylamide, 4 M urea. The excised gel frag- ment from the first electrophoresis should be embedded in the gel.
	2. Run the gel for 24 h at 6 W (constant power).
	3. Stain the gel with an EtBr solution $(10 \ \mu g/L)$ for 10 min.
	4. Using UV transilluminator, excise the spots containing tRNAs (Fig. 2). Beware of wearing appropriate protections for handling gel containing EtBr and manipulation under UV light.
	5. Dry gel spots in Eppendorf tubes under vacuum for 10 min without heating.
3.2 In-Gel RNase Digestion	Rehydrate excised gel fragments with 20 $\mu$ L of RNase T1 (1 U/ $\mu$ L) solution or 20 $\mu$ L of RNase A (0.01 U/ $\mu$ L) solution in 100 mM ammonium acetate (pH is not adjusted), and incubate at 50 °C for 3 h, followed by 12 h at 37 °C. For RNase U2 digestion, rehydrate gel fragments with 50 $\mu$ L of RNase U2 at 0.3 ng $\mu$ L <sup>-1</sup> in 100 mM ammonium acetate (pH is adjusted to 5.3), and incubate at 37 °C for 1 h.
3.3 RNA Digest Product Desalting	1. Prepare ZipTip C18 with 50% acetonitrile in water $(3 \times 10 \ \mu L)$ .
	2. Equilibrate the ZipTip for sample binding with 200 mM ammonium acetate (1 $\times$ 10 $\mu L).$
	3. Bind the digested sample, and wash oligonucleotides with 200 mM ammonium acetate (5 $\times$ 10 $\mu L).$
	4. Elute oligonucleotides with 10 $\mu L$ of 50% acetonitrile in water.
	5. Dry under vacuum for 20 min without heating.
3.4 IC-MS/MS	Nano-LC is performed at a 0.3 uL/min flow rate for 1 h. RNase
3.4.1 Nano-liquid Chromatography	digestion products are eluted using a gradient from 15% to 35% B in 2 min followed by an increase of B to 50% in 20 min and then returning to 15% B in 25 min.

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## Table 1

List of natural and modified nucleotides identified in this study

Name	Short name	Symbol	Nucleotide mass (Da)	[M-H] <sup>_</sup> Np (Da)	[M-H] <sup>_</sup> N > p (Da)	Neutral loss (Da)
Guanosine	G	G	345	362	344	
Cytidine	С	С	305	322	304	
Uridine	U	U	306	323	305	
Adenosine	А	А	329	346	328	
2'-O-Methylguanosine	Gm	#	359	376	358	
1-Methylguanosine	mlG	K	359	376	359	
2'-O-Methylcytidine	Cm	В	319	336	318	
5-Methyluridine	m5U	Т	320	337	319	
Dihydrouridine	D	D	308	325	307	
N6-Threonylcarbamoyladenosine <sup>a</sup>	t6A	6	329	346	328	145

A full list of modified nucleosides is available in the Modomics database (http://modomics.genesilico.pl/modifications/) <sup>a</sup>Due to the neutral loss of threonylcarbamoyl, nucleotide mass fragmentation of t6A corresponds to the mass without modification. This modification occurs exclusively at position 37 in the anticodon loop

3.4.2 Analys	Mass Spectrometry is	All experiments are performed in negative mode. The eluted RNase digests are injected on line into the mass spectrometer via Nano-							
		LockSpray. Capillary voltage is set to 2.6 kV and sample cone to 30 V. Source is heated to 130 °C. For MS, a mass range from 500 to 1500 $(m/z)$ is used, followed by collision-induced dissociation (CID) fragmentation of most intense signals using fast data directed acquisition (FastDDA) mode with a $m/z$ detection range of fragments from 50 to 2000. A collision energy ramp (18–28 V at $m/z$ 500 and 28–38 V at $m/z$ 1500) is applied in the trap collision cell to provide the maximum fragment ions.							
3.5	Data Analysis	All the fragment spectra are manually sequenced (see Note 2).							
		<ol> <li>Deconvolute CID spectra by using MaxEnt3 software (see Note 3).</li> </ol>							
		2. Using Table 1, listing the masses of the most common natural and modified nucleotides, reconstruct the sequence by following the y and/or c series ( <i>see</i> Note 4). Three sequencing examples are shown in Fig. 3. Additionally, Fig. 4 gives a list of all the different masses obtained by nano-LC-MS/MS and the corresponding sequences.							
		3. Note that pseudouridine, an isomer of uridine, is a silent mass and cannot be detected by this method ( <i>see</i> <b>Note 5</b> ).							



**Fig. 3** Typical MS/MS spectra of RNase digested tRNA fragments. Only series y and c have been sequenced. (a) MS/MS sequencing spectrum of CUt6AAG>p after RNase T1 digestion. In the case of t6A modification,

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theoretical	observed					theoretical	observed				
m/z	m/z	z	molecular mass (Da)	sequence	tRNA	m/z	m/z	z	molecular mass (Da)	sequence	tRNA
RNase T1											
878,62	878,63	-2	1758,3	CU6AG>p	Ser GCU	947,11	947,10	-2	1895,2	CUUCAG>p	Leu CAG
946,62	946,62	-2	1894,2	CAUCCG>p	Ser GCU	956,11	956,10	-2	1913,2	CUUCAGp	Leu CAG
955,62	955,62	-2	1912,2	CAUCCGp	Ser GCU	966,12	966,09	-2	1933,2	TUCAAG>p	Leu CAG
1135,15	1135,13	-2	2271,3	UCAAAAG>p	Ser GCU	975,13	975,10	-2	1951,2	TUCAAGp	Leu CAG
1144,16	1144,13	-2	2289,3	UCAAAAGp	Ser GCU	988,14	988,13	-2	1977,3	AADD#G>p	Leu CAG
1240,14	1240,1	-2	2481,2	CUCCCCUG>p	Ser GCU	997,15	997,13	-2	1995,3	AADD#Gp	Leu CAG
1249,15	1249,12	-2	2499,2	CUCCCCUGp	Ser GCU	1252,64	1252,60	-2	2506,2	UCCUUACG>p	Leu CAG
1251,66	1251,63	-2	2504,3	CCUCACCG>p	Ser GCU	1261,65	1261,62	-2	2524,2	UCCUUACGp	Leu CAG
1263,66	1263,64	-2	2528,3	AAUCCCCG>p	Ser GCU	1233,15	1233,11	-3	3701,3	UCCCCCCCCUCG>p	Leu CAG
1272,67	1272,63	-2	2546,3	AAUCCCCGp	Ser GCU	1239,15	1239,10	-3	3719,3	UCCCCCCCCUCGp	Leu CAG
RNase A											
858,11	858,11	-2	1717,2	GGGGTp	Ser GCU	662,09	662,09	-2	1325,2	AGACp	Leu CAG
991,15	991,16	-2	1983,3	AAAAGCp	Ser GCU	1326,18	1326,17	-1	1326,2	AAGUp	Leu CAG
1007,14	1007,15	-2	2015,3	GAAGGCp	Ser GCU	836,12	836,12	-2	1673,2	GGAADp	Leu CAG
1179,66	1179,69	-2	2360,3	GAGAGGCp	Ser GCU	981,13	981,14	-2	1963,3	GGAADD>p	Leu CAG
1417,20	1417,18	-2	2835,4	6AGGGAGUp	Ser GCU	1007,63	1007,64	-2	2016,3	GAAGGUp	Leu CAG
1046,47	1046,49	-3	3141,5	U6AGGGAGUp	Ser GCU	1030,64	1030,64	-2	2062,3	GGGGGTp	Leu CAG
RNase U2											
706,10	706,1	-2	1413,2	CU6A>p	Ser GCU	823,61	823,63	-2	1648,3	ADD#G>p	Leu CAG
807,11	807,11	-2	1615,2	CDGAA>p	Ser GCU	865,60	865,59	-2	1732,2	pGCGAA>p	Leu CAG
915,15	915,15	-2	1831,3	CCGCCA	Ser GCU	927,60	927,60	-2	1856,2	UCCUUA>p	Leu CAG
966,62	966,62	-2	1934,2	GCUGCA>p	Ser GCU	977,63	977,64	-2	1956,3	DD#GDA>p	Leu CAG
1240,14	1240,14	-2	2481,3	CUCCCCUG>p	Ser GCU	1142,16	1142,17	-2	2285,3	ADD#GDA>p	Leu CAG
1388,19	1388,21	-2	2777,4	CU6AGGGA>p	Ser GCU	1147,13	1147,13	-2	2295,3	GKUGUUA>p	Leu CAG
1273,15	1273,16	-3	3821,5	GGCGCUCCCCUG>p	Ser GCU	1425,66	1425,67	-2	2852,3	GUGUCCUUA>p	Leu CAG
				and the second		1479,21	1479,20	-2	2959,4	ADD#GDAGA>p	Leu CAG
						1233,15	1233,17	-3	3701,5	UCCCCCCCCUCG>p	Leu CAG

tRNA Ser GCU

pGGUGAGGUGGCCGAGAGGCDGAAGGCGCUCCCCUGCU8AGGGAGUAUGCGGUCAAAAGCUGCAUCCGGGGTUCGAAU CCCCGCCUCACCGCCA Sequence coverage 77%

pGCGAAGGUGGCGGAADD#GDAGACGCGCUAGCUUCAGKUGUUAGUGUCCUUACGGACGUGGGGGTUCAAGUCCCCC CCCUCGCACCA Sequence coverage 82%

**Fig. 4** List of all digested products experimentally observed for tRNA Ser GCU and Leu CAG, after individual digestion with RNases T1, A, and U2. The MS/MS sequenced products are indicated in red in the full tRNA sequences below the table. Although sequence coverage is close to 100%, some parts of the sequences are still missing. Thus, in the case of uncharacterized tRNA, modifications existing in vivo may be missed

- 4. For methyl groups, it is not possible to localize the group on the base and/or the ribose with this technique (*see* Note 6).
- 5. When a digested tRNA fragment is sequenced, the parent ion and the fragments' masses have to be checked using Mongo Oligo mass calculator (https://mods.rna.albany.edu/mas spec/Mongo-Oligo). A maximum tolerance of 0.05 Da between the measured and calculated mass is routinely tolerated.
- 6. Comparison of the resulting sequences with *E. coli* genomic sequences (http://gtrnadb.ucsc.edu) identifies tRNA (see Note 7).

tRNA Leu CAG

**Fig. 3** (continued) collision-induced dissociation (CID) fragmentation leads to a neutral loss of 145 Da corresponding to the leaving of the threonylcarbamoyl group. \* corresponds to the location of the neutral loss. (b) MS/MS sequencing spectra of GGAADD>p after RNase A digestion. (c) MS/MS sequencing spectra of Gm1GUGUUA>p after RNase A digestion

7. Map modifications on the tRNA sequence. Figure 4 shows a list of all digested tRNA fragments sequenced by MS/MS.

## 4 Notes

- 1. In the first-dimension electrophoresis, tRNAs are completely heat denatured due to the dual action of gel temperature (70 °C) and urea (8 M) and are separated by their length. In the second dimension, urea concentration was decreased to 4 M, and the gel is run at room temperature. Under these conditions, tRNAs are partially refolded, and the separation is based on the partial secondary conformation.
- 2. Software have been developed for interpretation and annotation of MS/MS data (Ariadne [8], RoboOligo [9]), but to obtain unambiguous localization of modifications, manual interpretation of MS/MS spectra is still required.
- 3. Electrospray spectrum produces multiple charged ions. Typically, RNase digest products are two or three times charged. Spectrum deconvolution allows to simplify spectrum reading by transforming multiple charges spectrum (m/z) to mono charge spectrum (mass).
- Generally, the most intense series are y and c. Mongo Oligo online calculator (https://mods.rna.albany.edu/masspec/ Mongo-Oligo) could be helpful to find and/or check ion series.
- 5. Pseudouridine may be specifically derivatized using *N*-cyclohexyl-N'-(2-morpholinoethyl)carbodiimide metho-*p*-toluene-sulfonate (CMCT) in order to be detectable [10].
- 6. LC-MS/MS of digestion products allows the localization of methylation in the correct nucleotide but does not allow the localization on the ribose and/or on the base. Using known tRNA modification sequences, it could be possible to predict the type of methylation. Modomics tRNA database (http://modomics.genesilico.pl/sequences/list/tRNA/) [11] provides a large collection of modified tRNA sequences. Furthermore, based on phylogenetic conservation of modification locations, tRNAmodviz (http://genesilico.pl/trnamodviz/) [12], an online software tool, allows the visualization of modification pattern in tRNAs.
- 7. As with proteomics strategy, RNase digestion generates a set of oligonucleotides, specific to a unique tRNA. tRNA identification is possible by using a genomic tRNA database.

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## 2. Cartographie des modifications post-transcriptionnelles des ARNt de S.aureus

La spectrométrie de masse est un outil puissant pour la caractérisation des modifications post-transcriptionnelles des ARN. La méthode de purification et d'analyse par NanoLC-MS/MS mise en place a ainsi permis d'établir une cartographie partielle des modifications présentes dans 40 ARNt de *S. aureus*. Les modifications spécifiques des bactéries à gram positives telles que le mo<sup>5</sup>U présente notamment dans les ARNt de *B. subtilis* a été localisé en position 34 des ARNt de *S. aureus*. La cartographie des ARNt établie permet l'étude dynamique des modifications des ARNt en réponse aux conditions environnementales rencontrées durant l'infection.

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#### Research paper

Mapping post-transcriptional modifications in *Staphylococcus aureus* tRNAs by nanoLC/MSMS



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#### ABSTRACT

RNA modifications are involved in numerous biological processes. These modifications are constitutive or modulated in response to adaptive processes and can impact RNA base-pairing formation, protein recognition, RNA structure and stability. tRNAs are the most abundantly modified RNA molecules. Analysis of the roles of their modifications in response to stress, environmental changes, and infections caused by pathogens, has fueled new research areas. Nevertheless, the detection of modified nucleotides in RNAs is still a challenging task. We present here a reliable method to identify and localize tRNA modifications, which was applied to the human pathogenic bacteria, Staphyloccocus aureus. The method is based on a separation of tRNA species on a two-dimensional polyacrylamide gel electrophoresis followed by nano liquid chromatography-mass spectrometry. We provided a list of modifications mapped on 25 out of the 40 tRNA species (one isoacceptor for each amino acid). This method can be easily used to monitor the dynamics of tRNA modifications in S. aureus in response to stress adaptation and during infection of the host, a relatively unexplored field.

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#### 1. Introduction

#### 1.1. A brief tour on the roles of tRNA modifications in bacteria

RNA modifications alter the chemical and physical properties of nucleotides and the biological functions of RNA. They are involved in numerous biological processes because they can impact RNA base-pairing formation, the structure of specific RNA motifs, protein recognition, translation and decoding properties, and RNA stability (for a review see Ref. [1]). RNA modifications can be present in many RNA species, but abundant noncoding RNAs such as tRNAs, rRNAs, and spliceosomal RNAs are the most heavily modified ones and depend on the modifications for their biogenesis and function. Today more than 170 modifications have been identified, primarily in tRNAs and rRNAs (http://modomics.genesilico.pl/ modifications/) [2], and numerous RNA-modifying enzymes have

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been characterized [3-8]. The expression and activity of these enzymes can be modulated in response to environmental stresses, adding another layer of complexity in gene regulation. For example, in bacteria, deregulations of modifications in ribosomal RNAs (rRNA) can promote antibiotic resistance [9-11]. In tRNAs, modifications are central for folding, quality control, and efficient and accurate decoding. Also, they control gene expression during stress adaptation [12] and modulate interaction with human host [13].

tRNAs contain the largest number of modifications and the widest chemical diversity [2]. The complexity of tRNA modifications ranges from simple methylations on the base or the ribose to rather complex and large base hypermodifications, the synthesis of which generally depend on a cascade of enzymatic reactions [14]. Modifications have been shown to contribute to the highly conserved L-shaped structure, which is crucial for the interaction with a variety of proteins, the ribosome, and mRNAs. Interestingly, the distribution of the modified nucleotides along the tRNA molecule is conserved across evolution and reflects their two major functions in maintaining the tRNA structure and, ultimately, in decoding. Modified nucleotides concentrate in two hotspots the anticodon loop and the tRNA core region, where the D- and

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LC	Liquid Chromatography	
MS	Mass Spectrometry	
BHI	Brain Heart Infusion	
EtBr	Ethidium Bromide	
TBE	Tris Borate EDTA	
HFIP	Hexafluoro Isopropanol	
TEA	Triethylamine	
TEAA	Triethylamine Acetate	

T<sub>4</sub>-loops interact with each other (reviewed in Refs. [15,16]). tRNA modifications of the core are important for the stability of the tRNA structure. In this context, it was shown that they affect temperature adaptation in thermophilic as well as in psychrophilic organisms [17]. The modifications of the core region are also thought to be important for EF-Tu binding (U to T change at position 54 in the T $\Psi$  loop) [18] and since they are involved in the tertiary interactions maintaining the L-shape, they are expected to influence the binding of several proteins to the tRNA (i.e. aminoacyl tRNA synthetases and anticodon modification enzymes) [19,20], tRNA modifications also facilitate tRNA-mediated transcriptional control through T-box riboswitches to sense intracellular availability of amino acids [21] and participate in quality control of tRNA integrity [22,23]. More recently, it was demonstrated that hypomodification of tRNAs in Vibrio cholerae induces their rapid decay mediated by the degradosome, demonstrating a new quality control mechanism [24].

Their major role in translation is due to their direct or indirect influence on the decoding process and fidelity of translation (i.e., [25]). Because the genetic code is degenerated, the 20 natural amino acids are encoded by 61 triplets that are recognized by 22-46 distinct tRNAs depending on the organism. Therefore, several tRNAs recognize more than one synonymous codon (i.e., the tRNA isoacceptors carry the same amino acid). The first nucleotide at position 34 of the anticodon (wobble base) can potentially form pairs non-complementary in the Watson-Crick sense (for a review see Refs. [26,27]). Detailed structural, physicochemical and kinetic studies of bacterial ribosomes associated with mRNA and aminoacyl-tRNAs have shown that the decoding center of the ribosome imposes specific constraints for the selection of a given codon by its cognate aminoacyl-tRNA by strongly favoring Watson-Crick pairs [25,28-34]. In miscoding induced by GU pairs, these pairs are in a Watson-Crick-like state promoted by tautomerization [27-29]. Interestingly, post-transcriptional modifications of nucleotide 34 can change the physicochemical behavior of the base (frequency of tautomerism), the spatial preference of the nucleotide (syn/anti, puckering of the ribose), the stability of codonanticodon base-pairing and the structure of the anticodon loop itself, all contributing to the fidelity of the decoding process [25,35-40]. A typical example is given by tRNATyr<sub>GUA</sub>, tRNAAsn<sub>GUU</sub>, tRNAAsp<sub>GUC</sub> and tRNAHis<sub>GUG</sub>, which can recognize both NAU and NAC codons, allowing G-C Watson-Crick base-pair with NAC codons and wobble G-U pair with NAU codons. These tRNAs (collectively harboring GUN anticodons), in eukaryotes and bacteria, present the Queuosine (Q) hypermodification on G34 [41]. Recently, Tuorto and colleagues [42] have demonstrated that, in mammals, the presence of Q affected translation speed. In the absence of Q modification, ribosomes pause on NAU codons, while NAC codons are much less affected [42]. Protein aggregation was observed for those genes enriched in NAU codons. This phenomenon seems to be speciesspecific since Q-modification in tRNAs in S. pombe has been

shown to improve translation increasing the decoding speed of Cending codons relative to U-ending codons [43]. Although not yet investigated, such deregulation based on mRNA codon content in response to the tRNA anticodon modification states, might take place in bacteria which display distinct codon usage bias (GtRNAdb [44]). Because tRNA modifications including the anticodon loop modifications can be modulated by various environmental changes, the proteome is expected to vary during adaptation [12]. To date, perturbations of tRNA modifications following physiological stress such as oxidation, temperature, pH, salinity, and nutrient starvation are well established in eukaryotes, but less well studied in bacteria [45,46].

#### 1.2. Roles of tRNA modifications in pathogenic bacteria

During infection, pathogenic bacteria must adapt to the host environment, which is often scarce in nutrients and oxygen, and fastened with toxic metabolites and enzymes. They express virulence genes to interact with host tissues, to compete with the commensal flora, to avoid detection of the bacteria by the host immune system or to fight against it. Thus, pathogenic bacteria rapidly adapt to continuously changing environmental conditions and often regulate virulence gene expression at both the transcriptional and post-transcriptional levels. The analysis of the impact of RNA modifications in pathogenic bacteria during growth adaptation and infection has just started to be appreciated [47]. Recent studies in Gram-negative bacteria, have demonstrated that deletion of genes encoding RNA modification enzymes leaded to infection attenuation in mice, reduced colonization, decreased levels of the pro-inflammatory cytokines, reduced bacterial motility, replication in macrophages, and invasion of epithelial cells ([48] and references therein). For example, the deletion of the tRNA guanine transglycosylase gene (tgt) responsible for Q modifications reduces the translation of VirF, the transcription factor orchestrating Shigella flexneri virulence [49]. Moreover, tRNA modifications in pathogenic bacteria have been shown to modulate interaction with human host [13], or to regulate the expression of genes involved in the protection from oxidative stress, one of the main challenges that pathogenic bacteria must cope with during infection [50]. In mycobacteria, hypoxia modulates tRNA modification state to selectively translate codon-biased mRNAs for persistence genes [51]. In numerous Gram-negative (Escherichia coli, Salmonella enterica, Aeromonas hydrophila, Pseudomonas fluorescens, P. aeruginosa and P. syringae) and some Gram-positive pathogens (Streptococcus pyogenes and S. suis), the GidA/MnmE tRNA modification pathway, which leads to methylation of U34 in different tRNAs, has been implicated in the regulation of bacterial virulence [52]. Even if the precise mechanism remains unclear, an increased frequency of two-base frameshift has been reported [53]. Although these examples illustrate how the dynamic nature of tRNA modifications regulates virulence in various pathogenic bacteria, the roles of RNA modifications in Staphylococcus aureus have not been yet studied.

*S. aureus* is a Gram-positive opportunistic pathogen that is present in a third of the population on skin and in nostrils [54] as commensal bacteria, but is also responsible for a wide range of infections from minor skin abscesses to life-threatening diseases such as septicemia or toxic shock syndrome [55]. *S. aureus* represents a major health problem due to the insurgence of antibiotic multi-resistant strains in the hospital and community settings. Given the importance of tRNA modifications in several aspects of bacterial life, we decided to implement a rapid and easy method for their detection in *S. aureus* tRNAs for which little knowledge existed.

## 1.3. Analysis of tRNA modifications by mass spectrometry approaches

Mapping of post-transcriptional RNA modifications using mass spectrometry (MS) has existed for over 30 years [56]. The ability to get precise measure of molecular masses (less than 1 Da) provided the possibility to characterize modified residues in tRNAs using liquid chromatography coupled to mass spectrometry (LC/MSMS). Two complementary MS approaches have been developed. The first one implies total digest of tRNAs into nucleosides in order to identify the whole repertoire of modified nucleosides in one experiment [57]. The resulting nucleosides are thereby separated by reversed-phase high-performance liquid chromatography (HPLC) [58] and modifications detected using spectroscopy (e.g., UV) or by mass spectrometry [59]. The comparison of the HPLC chromatogram with known standard profiles and the characteristic measured mass-to-charge ratio (m/z) of the ionized nucleosides are contributing to the precise nucleoside identification. Atomic composition is finally obtained via collision induced dissociation (CID) tandem mass spectrometry (MSMS), providing a sensitive method for obtaining a survey of modified nucleosides in the tRNA sample. The second method is based on the generation of tRNA fragments produced from specific endoribonuclease digestion (e.g., RNase T1 cleaves every guanosine at their 3' side). The generated oligonucleotides with known 5' and 3'-nucleotide identity [60] are then separated by HPLC and detected by MS. Fragments along the phosphodiester backbone by CID MSMS can be manually interpreted to localize the modification to a specific nucleotide. Thus, the mass and the sequence of each oligonucleotide is precisely identified by LC/MSMS allowing determination of the nature of each modification and their location in the tRNA sequence [61].

These two complementary methods have provided the first insights into tRNA modification dynamics following various stresses [56,62,63]. For nucleoside analysis, an ensemble of tRNAs can be studied to follow easily the changes of their modification patterns upon growth conditions while the LC/MSMS analysis of oligonucleotides requires purification of specific tRNA prior to digestion. This is usually done by affinity chromatography with a complementary DNA oligonucleotide linked to a solid resin or bead [63]. The recent development of Ultra-Performance LC (nanoLC) permits the careful separation of RNA fragments prior to the mass spectrometry analysis at very slow flow rates (hundreds of nL/min) in a column with a reduced resin diameter (<2 µm). This method requires smaller sample amounts, generates less chromatographic dilution and higher sensitivity. Because it is possible to detect very small amounts of tRNA-derived oligonucleotides, a twodimensional gel electrophoresis (2D-PAGE) can be used to fractionate each tRNA species from bulk RNA extracts.

Here, we describe the use of this method and its application to the analysis of post-transcriptional modifications in *S. aureus* tRNAs. We also provide here for the first time a map of *S. aureus* tRNA modifications present in 26 out of the 40 tRNAs with different sequences, including at least one isoacceptor tRNA for each amino acid. We will also discuss applications to better address the roles of tRNA modifications in the physiopathology of *S. aureus*.

#### 2. Material and methods

#### 2.1. Bacterial growth

S. aureus HG001 strain, a derivative of RN1 (NCT8325) strain with restored rbsU (a positive activator of SigB), was used for tRNA isolation. The strain still contains a mutation at tcaR, a transcriptional regulator involved in teicoplanin susceptibility and biofilm [64]. S. aureus strain was manipulated under a specific hood in a dedicated room for manipulating class II pathogens. Stock culture in glycerol 25%, conserved at -80 °C were plated on a blood-agar Petri dish and grown at 37 °C overnight in Memmert model 100 incubator. One single clone was picked and grown in 2 mL Brain Heart Infusion (BHI from Sigma-Aldrich), incubated at 37 °C with a 180 rpm agitation overnight in a Stuart® orbital incubator S1600C. A preculture (100  $\mu$ L) was added in 10 mL BHI medium (OD<sub>600nm</sub> = 0.05), the bacterial growth was regularly checked until it reached an OD<sub>600nm</sub> = 3 with a Thermospectronic Genesys 20 spectrophotometer (-4 h of culture at 37 °C stirring at 180 rpm).

#### 2.2. Cell lysis and total RNA extraction

Cells were pelleted by centrifugation at 3750 rpm (3000 g) for 15 min at 4 °C in a Beckman Coulter Allegra X12-R centrifuge with a SX4750A rotor. Supernatant was carefully removed and the pellet (200 mg) was resuspended in 1 mL of RNAPro<sup>®</sup> Solution (MP Biomedicals, CA). Cells lysis was performed using a FastPrep®-24 with the 24 × 2 mL holder at 6 m/s speed in 2 mL FastPrep<sup>®</sup> tubes containing 0.1 mm zirconium silicate beads from FastRNA<sup>®</sup> pro blue kit (MP biomedicals, CA).

Total RNA purification followed the procedure described for the FastRNA Pro Blue Kit (MP Biomedicals, CA). RNA was further purified by adding 1/2 volume of chloroform: isoamyl alcohol (19:1), vortexed 10 s before precipitation of the RNA in the aqueous phase obtained by adding 3 vol of cold absolute ethanol (1.2 mL) in 2 mL Eppendorf tubes at -20 °C overnight. RNA was precipitated by centrifugation at 13000 rpm (18000 g) for 15 min at 4 °C using an Eppendorf 5417R centrifuge with a F45-30-11 rotor. The RNA pellet was washed with 500 µL of 80% cold ethanol and dried 20 min under vacuum in a Speed Vac® from Savant, before being resuspended in 200 µL of milliQ water. RNA concentration was determined by measuring absorbance at 260 nm with a Nanodrop ND-1000 spectrophotometer. Total RNA concentration was adjusted to 2 µg/µL. For phenol or chloroform extraction, work has to be done under a fume hood. Eppendorf tubes, tips, and buffers were RNase-free.

#### 2.3. tRNA purification, 1st dimension PAGE

The first dimension gel electrophoresis was performed under denaturing conditions using 15% polyacrylamide gel (15% acrylamide:bisacrylamide 19:1 solution from Roth, 8 M urea, 1 × TBE buffer from Euromedex<sup>®</sup>) (Fig. 1A). Before loading the RNA sample, the gel was pre-run at 900 V for 20 min. One volume of urea-blue solution (urea 8 M, bromophenol blue and xylen cyanol 0.025%) was added to 5  $\mu$ L containing 10  $\mu$ g of total RNA. The sample was heated at 90 °C during 2 min before loading on the gel. After 15 h migration at 500 V at 20 °C, the gel was stained with 0.5  $\mu$ g/mL EtBr solution (from Sigma-Aldrich) by soaking the gel during 5 min, then washed with miliQ water and visualized on a High performance 2UV<sup>™</sup> transilluminator from UVP. The gel slice containing 55 rRNA and tRNAs was cut to perform the second dimension gel.

#### 2.4. Individual tRNA purification, 2nd dimension PAGE

The second dimension was performed under semi-denaturing conditions. The first dimensional gel slice (see § 2.3) was first placed horizontally at the top and between two glass plates ( $20 \times 20$  cm). Then a solution containing 20% polyacrylamide (polyacrylamide-bisacrylamide 19:1), 4 M urea, 1X TBE and 0.06% of ammonium persulfate and TEMED was poured between the plates. Once polymerized, the gel was run at 6 W (200 V) for 24 h at 20 °C using BioRad Protean II xi Cell. The gel was tained with EtBr as described in paragraph § 2.3 before UV visualization (Fig. 1B). Cel

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**Fig. 1. Complete protocol for nanoLC/MSMS analysis of S** *aureus* **tRNAs from isolation to modification mapping.** The five main steps of the protocol are as follow. A. *First-dimension PACE* **Total** RNA was migrated on the first-dimension gel electrophoresis (denaturing 15% PACE with 8 M Urea). The gel slice containing "tRNA-size" (25000–15000 Da) RNA species migrating dose to 55 rRNA, was cut, Arrow 1 indicates the direction of gel migration. The gel slice containing the RNAs is deposited on the top of the second-dimension gel. In parallel, the 21 visible bands (colored by Ethidium Bromide and named from a *t*) were cut individually, digested with RNAs is T1 and analyzed by nanoLC/MSMS to determine which tRNAs are present in each band (see at the end of the legend). *B. Second-dimension PACE*. Separation of the tRNAs from the first-dimension gel slice in the second-dimension gel electrophoresis (semi-denaturing 20% PACE with 4 M Urea). Arrow 2 indicates the direction of migration. After staining, the gel was divided into three large areas to be analyzed by the Gel DoC<sup>M</sup> EZ imager. Here only the middle (left) and bottom (right) parts are reported but the two pieces are coming from the same experiment. No spots were visible on the upper part of the gel (not shown). Each of the legend. *C. RNases in gel digestion.* The spots were subjected to RNase T1 or RNase A digestion, desalted, and used for the liquid chromatography separation of the fragments. *D. nanoLC (Ultra-Performant Liquid Chromatography) and MS* analysis. The RNase derived fragments from each 2D spot are separated on the BEH C18 column with a 300 nL/min flow rate. An example from spot 17 (tRNAval<sub>UACL-2-3</sub>) digested with RNase T1 or RNase A digestication (ESI CD) spectrum obtained for the <sup>5</sup>CCUSUAC = AGp<sup>3</sup> oligonucleotide (*m*/2 = 97.287, triple charged (-3H <sup>1</sup>)) from the *S. aureus* tRNAval<sub>UACL-2-3</sub>. The profile obtained from the MSMS (fragmentation) analysis is shown with its sequence given from its *S* inducetide (sequence in grent, c ion s

pictures were taken with a Gel  $\text{Doc}^{\text{TM}}$  EZ imager with its corresponding 16  $\times$  12 cm UV tray.

2.5. In gel RNase digestion

Gel spots containing tRNAs were excised with a blade scalpel

and dried under vacuum for 10 min (Speed Vac<sup>®</sup>). Digestion of the tRNAs with specific RNase was carried out directly on the gel fragments. The gel spots were incubated with 20 µL of 1U/µL of RNase T1 from Thermo Fisher Scientific (cleavage at G residues) in ammonium acetate 100 mM (pH 6.8) and incubated at 50 °C for 3 h followed by a 37 °C overnight incubation under 300 rpm constant

agitation. Alternatively, 20  $\mu$ L of 0.01 U/ $\mu$ L of RNase A from Thermo Fisher Scientific (cleavages at C and U residues) in ammonium acetate 100 mM were added to the gel spots and the samples were incubated at 60 °C during 3 h, followed by a 37 °C overnight incubation under 300 rpm constant agitation. The samples were stored at -20 °C or immediately desalted, after removal of the gels by centrifugation (10 min, at 18000 g, at 4 °C), using ZipTIP C18 (Millipore) prewet with acetonitrile 50% in milliQ water (3  $\times$  10  $\mu$ L) and 200 mM ammonium acetate (3  $\times$  10  $\mu$ L). The supernatant containing the digested tRNA fragments passively eluted from the gel, was loaded on the column, which was then washed with 200 mM ammonium acetate (7  $\times$  10  $\mu$ L) followed by milliQ water (5  $\times$  10  $\mu$ L). Finally, the fragments were eluted with 10  $\mu$ L of 50% acetonitrile in milliQ water and dried for 25 min under vacuum (Speed Vac\*) (Fig. 1C).

#### 2.6. nanoLC/MSMS of RNA oligonucleotides

The pellet containing the oligonucleotides is resuspended in 3  $\mu$ L of milliQ water. The oligonucleotides were then separated on nanoLC Acquity UPLC peptide BEH C18 column (130 Å, 1.7  $\mu$ m, 75  $\mu$ m  $\times$  200 mm) using a nanoAcquity UPLC system (Waters). The column was pre-equilibrated in Buffer A (200 mM HFIP (Hexa-fluoroisopropanol), 7 mM TEA (Triethylammonium), 7.5 mM TEAA (Triethylammonium acetate, pH 7.5) at a flow rate of 300 nL/min. After loading on the column, the RNase digestion products were eluted using a step gradient with two segments. The first consists of a gradient 15–35% of solution B (100% methanol (MeOH)) for 2 min, followed by the second step where the solution B reaches 50% (during 20 min at the same flow rate). Finally, the MeOH solution is decreased to 15% during 25 min. The column is then re-equilibrated in Buffer A during 20 min (Fig. 1D).

MS and MSMS analysis were performed using a SYNAPT G2-S HDMS from Waters equipped with a NanoLockSpray-ESI source in negative sensitivity mode with a capillary voltage set to 2.6 kV and sample cone to 30 V. Source was heated to 130 °C. For MS analysis, a mass range from 550 to 1500 (m/z) was used followed by Collision Induced Decay (CID) fragmentation of most intense signals with a m/z detection range of fragments from 50 to 2000 with 1s scans (Fig. 1E).

#### 2.7. Data analysis

Chromatograms and spectra were processed using the Masslynx software from Waters (V4.1). CID fragment spectra were deconvoluted by MaxEnt3 tool to convert the *m/z* measured from multicharged ions into singly charged ones. Spectra were then manually sequenced using oligonucleotide fragmentation ion nomenclature [65]. Sequences are deduced by calculating mass difference between consecutive fragment ions singly charged. Typically, the most intense ion series (y and c) were used. Correct manual annotation was checked using MongoOligo online calculator (http://mods.ma.albany.edu/masspec/Mongo-Oligo), with a maximum tolerance of 0.05 Da between the calculated mass and the measured mass for parent and fragment ions. The tRNA genomic sequences were obtained from the HG001 genome [66].

#### 3. Results and discussion

#### 3.1. A global view of S. aureus tRNA modifications

The above protocol is fast and easily implementable. Briefly, the pool of tRNAs extracted from *S. aureus* cultures was isolated by collecting RNA species of sizes smaller than the 5S rRNA (118

nucleotides), which are clearly visible on a denaturing (8 M Urea) 1D gel (Fig. 1A). The tRNA samples were loaded on two different lanes on 1D gel. One lane was used for direct nanoLC/MSMS analysis and the other one was deposited on top of semi-denaturing gel for the second-dimension. The bands from the 1D gel were cut and analyzed by nanoLC/MSMS method to assign each tRNA (Fig. 1A). Several bands contained different RNA species (i.e., band b contains both a 5S fragment and tRNASer<sub>GCU</sub>; and band j contains both tRNAArg<sub>ACG1-2</sub> and tRNAMet<sub>CAU1</sub>). To assign unambiguously fragments to the different tRNAs, we then proceeded to a further purification step using the second-dimension gel electrophoresis under semi-denaturing conditions (4M urea) (Fig. 1B). The 1D bands gave rise to several spots where tRNAs are migrating individually (i.e. band b was resolved into spots 2 and 3 containing 5S rRNA and tRNASerGCU, respectively; and band j was resolved into spots 10 and 12 corresponding to tRNAArgACG1-2 and tRNAMetCAU1, respectively). Each spot was subjected to the in-gel RNase T1 digestion (Fig. 1C) followed by nanoLC/MSMS analysis (Fig. 1D-E), which provided information on the sequences and on the presence of modifications.

Sixty-one tRNA genes are present in S. aureus HG001 [63]. They are transcribed from eleven loci as single genes (tRNASeruGA1, tRNAArgccg, tRNAArgucu and tRNAGInuug3) or organized into seven operons (I to VII, Fig. 2) sometimes together with rRNAs. The number of isoacceptor tRNAs varies between one (Cys, Trp and elongator tRNAMets) to seven (tRNAGly) (Fig. 2). With the exclusion of the non-proteinogenic tRNAGly and the tRNACys, we could determine fragments belonging to 25 different tRNAs (Table 1) representing 46 tRNA genes, at least one isoacceptor for each tRNA. Some isoacceptors have identical sequences and cannot be distinguished in our analysis (the three tRNAAlauGC, the two tRNAArgACG, the three tRNAAsnGUU, the four tRNAAspGUC, two of the three tRNAGlnuug, the two tRNAGlyGCG, the two proteinogenic tRNA-GlyUCC, two of the three non-proteinogenic tRNAGlyUCC, the two tRNAIleGAU, the two tRNALeuUAA, the two tRNAProugg, the three tRNAThruGU and the three tRNAValuAC). For the other tRNAs, we could determine exactly from which gene they were transcribed. Only fourteen tRNAs could not be detected (indicated with blue dots in Fig. 2; tRNAGluUUC2 and tRNAGluUUC3 are identical and therefore counted as single species). Three of them are transcribed from a single gene while the others belong to operons from which other tRNAs were isolated in our analysis. Since the most intense spots on the 2D-gel were all analyzed, it is possible that they are less abundant (less transcribed or more rapidly degraded) and more difficult to be detected. To complete the S. aureus tRNA analysis, it would be necessary to purify them individually using biotinylated oligonucleotides, which could specifically fish them from total RNA extracts [63].

Several modifications were detected on the tRNA fragments (Fig. 3) deriving from the core region (D and  $T\Psi$  stem-loops), the variable region, and the anticodon loop. Modifications at nucleotides in the core region and variable loop include dihydrouridine (D), 1-methyladenosine (m<sup>1</sup>A), 7-methylguanosine (m<sup>7</sup>G), and thymidine (T). A high diversity of modifications was found in the anticodon loop and ten of them concentrate at positions 34 and 37 (Table 1, Fig. 3). Using the present strategy, pseudouridine  $(\Psi)$ cannot be detected since its mass is indistinguishable from that of uridine. In order to trace them, we use N-cyclohexyl-N'-\beta-(4methylmorpholinium) ethylcarbodiimide p-tosylate (CMC) derivatization which modified only  $\Psi$  under alkaline conditions (at pH above 10) [67]. Although such modification can be visualized by mass spectrometry [68,69], we unfortunately lost it during the MSMS fragmentation step preventing the detection of any  $\Psi$ . This technical issue could be solved by the use of acrylonitrile, which is L Antoine et al. / Biochimie 164 (2019) 60-69



Fig. 2. Staphylococcus aureus HG001 tRNA operons organization. The sixty-one genes present in S. aureus HG001 [66] were placed on a circular genome representation using DNAPlotter [96]. The tRNA genes are expressed from eleven loci sometimes as single gene, and more often as operons, which also contain rRNA genes. tRNAs which were not detected in the present study are marked with a blue dot. tRNA genes on the positive and negative strands are represented as long blue and green tracks, respectively. rRNA genes on the positive and negative strands are represented as yellow and pink tracks, respectively. Coding sequences on the positive and negative strands are represented as represented as represented as red and cyan tracks, respectively. Mean centered CC% plot is represented in mustard (above-mean) and violet (below mean).

more resistant to the fragmentation [70].

Table 1 shows the regions that were probed for each analyzed tRNA. Four tRNAs are almost complete (coverage > 70% for the tRNASer<sub>UGA3</sub>, the tRNAPro<sub>UGG1-2</sub>, the tRNALys<sub>UUU2-3</sub> and the tRNAGluUUC1). On average almost 60% of the tRNA sequences were analyzed and, for most of the tRNAs, the core region and the anticodon loop were covered with the exception of tRNALeuUAA1-2 and tRNATrp<sub>CCA</sub>, for which we could not cover any nucleotide of the anticodon loop, and tRNAArgACG1-2 and tRNAGInUUG1-2, for which we could not detect fragments including their anticodons (nucleotides 34-36). In this study, we used RNase T1 and RNase A since they are highly active enzymes able to hydrolyze RNA in the gel. RNase T1 cleaves specifically at guanosines while RNase A cleaves at pyrimidine residues. To enhance the coverage, we tested other RNases. We first used RNase MC1, which cleaves at the 5' of uridine and pseudouridine [71] but no significant gel digestion of the tRNAs could be obtained (data not shown). We finally adapted RNase U2, which cleaves at purines with a slight specificity to adenosine [72], and preliminary data revealed that RNase U2 is able to digest RNAs contained in gel. By using multiple RNases with different base specificity, oligonucleotide fingerprints can be overlapped to provide full sequence coverage and to complete the mapping of tRNA modifications.

Overall, S. aureus tRNA modification types and their localization are similarly found in other Gram-positive bacteria such as Bacillus subtilis [2] and Lactococcus lactis [73] (Fig. S1). S. aureus specific features are discussed thereafter.

#### 3.2. Individual tRNA modification maps

All modifications that were detected in the analyzed *S. aureus* tRNAs are detailed in Table 1. As expected, most of them were localized in the core regions and in the anticodon loops. In general, the modifications were also conserved in many other bacteria.

Our work highlights the possible roles of the modifications at position 34 and 37 in tRNA anticodons for fidelity maintenance, codon selection and discrimination in *S. aureus*. For instance, Q at position 34 of tRNATyr<sub>GUA</sub> was proposed to efficiently discriminate tyrosine codons (UAU and UAC) from stop codon during translation in eukaryotes (review in Ref. [14]) and to increase affinity for UAU codons [42] in bacteria. As expected, we could detect Q34 in tRNATyr<sub>GUA2</sub>, but also in tRNAAsn<sub>GUU1-3</sub>, tRNAAsp<sub>GUC1-4</sub> and tRNAHis<sub>GUG1-2</sub>.

Modification at U34 is regularly found in tRNAs that read split codon-box families where the synonymous A- and G-ending codons encode a different amino acid than the U- and C-ending codons. We detected three major modifications at U34 (Table 1). The mo<sup>5</sup>U (5-methoxyuridine (5)) [74] was present in eight *S. aureus* tRNAs. This modification is only found in Gram-positive bacteria and is believed to enhance translational fidelity by the ribosome [27,39,75]. We found cmnm<sup>5</sup>s<sup>2</sup>U (5-carboxymethylaminomethyl-2-thiouridine (\$)) in the *S. aureus* tRNALy<sub>SUUU2-3</sub>. This hypermodification is ubiquitous in all bacteria and is usually detected in several tRNAs (Ly<sub>SUU</sub>, Gln<sub>UUC</sub>, Glu<sub>UUC</sub>, TrpucA or Leu<sub>UAA</sub>). Finally, mnm<sup>5</sup>s<sup>2</sup>U (5-methylaminomethyl-2-thiouridine (\$)) was observed

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#### Table 1

Characterization of RNA modifications in 26 Staphylococcus aureus tRNAs. Sequences of characterized tRNAs are reported with their respective coverage percentages. In the sequences the color code is as follow: red nucleotides indicate oligonucleotides fragments obtained by RNase T1 digestion, green nucleotides indicate oligonucleotides fragments obtained by RNase A digestion (overlapping sequences are in red) wille black nucleotides represent regions that could not be analyzed. The various regions of the tRNAs are visualized by colors according to the tRNA database http://tma.bioinf.uni-leipzig.de/as follow: sequences highlighted in orange are for the two complementary strands of the anticodon arm; sequences highlighted in green are for the two complementary strands of the D-stem; sequences highlighted in blue are for the two complementary strands of the T-stem; sequences highlighted in light blue are for the two complementary strands of the 3'. Modifications are indicated with symbols described in Fig. 3B.

1D	2D	A.A.	Antloc.		Acc-stern		D-sterr	D-loop	D-sterr		Ac-stem	Ac-loop	Ac-stem	V-region	T-stem	T-loop	T-stem	Acc-stem		CCA C	over, (%	) HG001	Operon
				-1	1	8	10	14	22	26	27	32	39	44	49	53	61	66	73	74			
p/q	20.	Ala	UGC 1-2-3		GGGGGCU	UA	GCUC	AGCUGGGA	GAGC	G	CCUGC	UU <u>5GC</u> AC	GCAGG	AGGUC	AGCGG	UUCGAUC	CCGCU	AGUCUCC	A	CCA	38	00443 01812 01823	= > >
E	10.	Arg	ACG 1-2	÷	ececce	UA	GCUC	AAUDGGAUA	GAGC	G	UUUGA	CU <u>ACG</u> KA	UCAAG	AG7UU	AUGGG	UUCGACU	CCUAU	CEGECEC	G	CCA	38	00441 01814	U V
r.	23,	Asın	GUU 1-2-3	2	UCCACAG	UA	GCUC	AGUGGUA	GAGE	U	AUCGG	CU <u>QUU</u> 6A	CEGAU	CGGUC	GUAGG	UUCGAGU	CEUAC	CUGUGGA	G	CCA	49	00874 01758 02198	fV VII
ï	14.	Asp	GUC 1-2-3-4	10	GGUCUCG	UA	GUGU	AGCGGDDA	ACAC	G	œvec	CUQUCAC	GCAGG	AGAUC	GCGGG	TUCGAUU	CCCGU	CGAGACC	G	CCA	63	00021 01762 01805 01808	- 2 > >
\$	26.	Gln	UUG 1-2	-	UGGGCUA	UA	GCCA	AGCGGUA	AGGC	A	ACGGA	CUUUGAC	UCCGU	CACUC	GUUGG	UUCGAAU	CCAGC	UAGCCCA	G	CCA	27	01.799 02.194	V VII
0	18.	Glu	UUC 1	-	GECUCCU	UG	GUCA	AGCGGDDA	"GAC	A	CEGEE	CUSUCAC	GGCGG	UAAC	ACGGG	TUCGAGU	CCCEU	AGGAGUC	A	CCA	85	00020	1
k	13.	Gly	GCC 1-2	•	GCAGAAG	UA	GUUC	AGCGGUA	GAAU	A	CAACC	UUGCCAA	GOUUG	GGGUC	GCGGG	UUCGAAU	cccen	CUUCUGE	U	CCA	59	00439 01816	H V
r	22.	Gly	UCC 1-2 p	•	eceeeue	UA	GUUU	AAUGGCA	AAAC	С	UCAGC	CU <u>SCC</u> AA	GCUGA	UGUU	GUGGG	UUCGAUU	CCCAU	CACCOGC	U	CCA	61	01,759 02.088	₩ VI
i∕h	9.	His	GUG 1-2	G	GCGGUUG	UG	GUGA	AGUGGDDA	"CAC	A	UCGGA	UUQUGK/GU	UCCGA	CAUUC	GAGGG	TUCGAUC	CCCUU	CAGCCGC	c	CCA	68	01760	v
1	15.	lle	GAU 1-2	-	GGGCCUA	UA	GCUC	AGCUGGDDA	GAGC	G	CACGC	CUGAU6A	GEGUG	AGGUC	GGUGG	UUCGAGU	CCACU	UAGGCCC	A	CCA	53	01.824	V
9	8.	Leu	CAA	÷	GCCGGUG	UG	GCGG	AAUDGGCAG	ACGC	G	CGGGA	CUBAA+A	UCCCG	UUCCACUUGUGGAGU	GUCGG	UUCGACC	CEGAC	CACCOGU	A	CCA	52	01794	v
f	7.	Leu	UAA 1-2	•	GCCGGGG	UG	GCGG	AACDGGCAG	ACGC	A	CAGGA	CUUAAAA	UCCUG	CGGUGAGAGAUCACCGU	ACCGG	TUCGAUU	CCGGU	CCUCGGC	A	CCA	57	00440 01815	U V
e:	6.	Leu	UAG		GCGGGUG	UG	GCGG	AAUDGGCAG	ACGC	A	CUAGA:	CUSAGKA	UCUAG	CGCCUUACGGCGU	GGGGG	TUCGACU	CCCUU	CACCCGC	A	CCA	66	01817	v
$\bar{r}$	24.	Lys	UUU 2-3	÷	GAGCCAU	UA	GCUC	AGUUGGUA	GAGC	A	UCUGA	CU <u>\$/SUU</u> 6/HA	UCAGA	GGGUC	AGAGG	TUCGAAU	ccucu	AUGGCUC	A	CCA	74	01818 02193	V VII
m	16.	Met	CAU II	÷	CGCGGGA	UG	GAGC	AGUUCGGUA	GCUC	G	UCGGG	CUCAUAA	CCCGA.	AGGUC	GGUGG	TUCAAAU	CCGCC	UCCCGCA	A	CCA	44	01763	IV
1	12.	Met	CAU	٠	GECEEUG	UA	GCUC	AGCUGGCDA	GAIGE	G	UACGG	UUMAU=C	CCGUG	AGGUC	GGGGG	TUCGAUC	CCCUC	CACCGCC	A	CCA	65	01811	V
9	21.	Phe	GAA 1	۰.	GGUUCAG	UA	GCUC	AGUUGGUA	GAGE	A	AUGGA	UUGAAKC	UCCAU	GUGUC	GGCAG	UUCGACU	CUGUC	CUGAACC	A	CCA	45	01761	IV
p	19.	Pro	UGG 1-2	۰.	CGGGAAG	UA	GCUC	AGCUUGGUA	GAGC	A	CUUGO	UU <u>SGG</u> KA	CCAAG	GGGmUC	GCAGG	TUCGAAU	CCUGU	CUUCCCG	A	CCA	72	00442 01813	v
b	3.	Ser	GCU	÷	GEAAACG	UA	CUCA	AGUUGGCUGA	"GAG	G	GCCC	CUGCU6A	GOOUG	UAGUCGCGAAAGCGGCGC	GAGGG	TUCGAAU	CCCUC	COUNTCO	G	CCA	66	00873	Ш
c	4.	Ser	UGA 1	5	GGAGGAA	UA	CCCA	AGUCCGGCUGA	AGGG	A	UCGGU	CU5GA+A	ACCGA	CAGGGGCUUAACGGCUCGC	GGGGG	UUCGAAU	CCCUC	UUCCUCC	G	CCA	31	00383	
a	1.	Ser	UGA 3	-	GGAGGAA	UA	CCCA	AGUCCGGCUGA	"666	A	CGGU	CU <u>SGA</u> +A	ACCGA	CAGGGCCUUAACGGGCCGC	GEGEE	TUCGAAU	CCCUE	UUCCUCC	G	CCA	70	01807	V
ŧ	11.	Thr	UGU 1-2-3	-	ecceecc	UA	GCUC	AAUDGGUA	GAGC	A	ACUGA	CU <u>SGU</u> 6A	UCAGU	AGGUU	GGGGG	TUCAAGU	ccucu	Gecceec	A	CCA	34	00437 01803 01819	- v v
\$	25.	Trp	CCA	-	AGGGGCA	UA	GUUC	AACGGUA	GAAU	A	GAGGU	CUCCAAA	ACCUU	UGGU	GUGGG	UUCGAUU	CCUAC	UGECCEU	Ģ	CCA	45	01801	٧
d	5.	Тут	GUA 2	•	GGAGGGG	UA	GCGA	AGUGGCDAA	"CGC	G	GCGGA	CUQUA+A	UCCGC	UCCUUCGGGUUC	GGCAG	UUCGAAU	CUGCC	CCCCUCC	A	CCA	64	02195	VII
n/o	17.	Val	UAC 1-2-3	-	GGAGAAU	UA	GCUC	AGCUGGGA	GAGC	A	UCUGC	CU <u>SAC</u> =A	GCAGA	GGGUC	GGCGG	UUCGAAC	CCGUC	AUUCUCC	A	CCA	54	00436 01820 02196	V

in tRNAGluuuc and tRNALysuuu as shown in several Gram-negative bacteria like Escherichia coli. The hypermodifications (S and \$) at U34 are primarily observed on tRNAs carrying U34 and U35 (Table 1). In fact, these two uridines are essential recognition determinants for the enzyme MnmA, which catalyzes the thiolation at position 2 of U34 [76]. Intriguingly, S. aureus tRNALysUUU2-3 presented both "\$" and "S" modifications at U34 (Fig. S2). Such heterogeneity was also observed at position 37 where t<sup>6</sup>A (N6threonylcarbamoyladenosine (6)) was present on the same fragment presenting S at U34, while an unknown adenosine hypermodification (for a total mass of 530 Da for the nucleotide) was observed for the fragment containing \$34. To estimate the relative abundance of the two different modification patterns of tRNALys<sub>UUU2-3</sub>, the area of the peaks of the two distinct oligonucleotides in the mass chromatogram was determined (Figs. S2E-F). The comparison reveals that the oligonucleotide containing the anticodon with unknown modified adenosine (H) represents 34.6% of the total tRNALys<sub>UUU2-3</sub>. Further analysis will be required to identify this novel modification, to carefully quantify its abundance and to understand the functional consequences of such heterogeneity in tRNALys

The modification contents were also analyzed on the unique elongator tRNAMet<sub>CAU</sub> and one initiator tRNAMet<sub>iCAU</sub> species. The important determinants of the initiator tRNA in all bacteria are the absence of a Watson–Crick base pair between positions 1 and 72 in the acceptor stem and the presence of three conserved consecutive G:C base pairs in the anticodon stem [77]. The peculiarity of the

acceptor stem accounts for the high specificity of the methionyltRNA<sup>fMet</sup> transformylase (FMT) for methionylated tRNAs over other aminoacylated species [78,79], while the anticodon stem-loop is important for IF3 discrimination of non-initiator tRNAs in the 30S translation initiation complex [80-83]. In addition, formylation of the methionine prevents misrecognition of the initiator tRNA by EF-Tu [84,85]. No modification could be detected in the anticodon of the initiator tRNAMet (Table 1). A search in the Modomics database (http://modomics.genesilico.pl [2,86]) shows that the absence of modification in the anticodon is a trait common to other bacterial initiator tRNAs (e.g., Lactococcus lactis and Streptomyces griseus), except that a methylation on the ribose at C32 was observed in Thermus thermophilus and in E. coli. The absence of modification for the initiator tRNA anticodon could be another peculiarity of the translation initiation complex in which decoding is monitored at level of the 30S subunit bound to the initiation factors IF1, IF2 and IF3 [87].

For the elongator tRNAMet<sub>CAU</sub>, we identified a N4-acetylcytidine (M) at position 34 and a N6-methyladenosine (=) at position 37. Modifications at C34 and A37 are present in most of the bacterial elongator tRNAMet and believed to be important to maintain fidelity. For instance, the M34 modification in *E. coli* elongator tRNAMet was shown to prevent misreading of the AUA isoleucine codon [88]. Indeed, the NAU anticodons are particular because besides the tRNAMet, one tRNAIE isoacceptor also carries the anticodon CAU (Fig. 2). In addition, *S. aureus* encode two other tRNAIE isoacceptors with the GAU anticodons. In various



Fig. 3. Atlas of modifications characterized on S. aureus tRNAs. A. The different modifications observed on S. aureus tRNAs are reported on the typical cloverleaf two-dimensional structure of a tRNA. The acceptor stem, the variable region, the D, T $\Psi$  and anticodon loops are indicated. The nucleotide positions where the modifications were found are highlighted by light blue filled circles. B. Table summarizing the modifications with their abbreviations, the tRNAs for which each modification was found and its nucleotide position.

organisms, there are some variations in the tRNAIle content. Indeed, only in some bacteria, some tRNAIle have the UAU anticodons, common also in eukarvotes. Most eukarvotes have two isoacceptor tRNAIle, one with the anticodon IAU (I = inosine), which reads all three isoleucine codons (AUU, AUC and AUA) [89], while the other, with the anticodon  $\Psi A \Psi$ , is thought to read only AUA [90]. In bacteria, tRNAlleGAU reads two of the isoleucine codons (AUU and AUC) and carries a t<sup>6</sup>A modification at position 37, as it is also in S. aureus (Table 1). The other tRNAlleCAU reads the third isoleucine codon AUA and usually carries a lysidine residue (Lysine modified C at position 34). The enzyme TilS, responsible for this modification, is not only essential for the correct recognition of the AUA codon but also for the amino-acid specificity from methionine to isoleucine [91,92]. This modification enzyme is also present in the S. aureus genome suggesting that the lysidine modification is most likely present in tRNAlleCAU to maintain fidelity. Purification of this isoacceptor tRNAlle will be necessary to assert this hypothesis.

A

D

#### 3.3. tRNA modification dynamics under different stress conditions

The protocol presented here can be easily applied to analyze specific stress conditions that might alter the modification state or the nature of modifications in tRNAs. The possibility to probe several tRNAs in one single experiment using 2D-gel isolation procedure, without the need of biotinylated probes to capture (single) tRNA, has removed one of the major bottlenecks for the LC/ MSMS analyses. The recent advances in mass spectrometry technologies and software [93,94] now enable the routine sequence mapping of modifications from much less material than in the past. Prior to modification mapping on individual tRNAs, a complete nucleoside profile of total tRNAs would be complementary to screen for modification changes taking place under specific conditions. The analysis of the dynamics of tRNA modifications upon stress encountered during infection in *S. aureus* might reveal

unexpected strategies developed by the pathogen to survive, persist, and fight against host immune defenses. The increase in the sensitivity of nanoLC/MSMS methodologies and the new development of high throughput RNA sequencing analysis [95] are promising developments amenable to gain a full picture of RNA modifications, opening new areas in the field of RNA regulatory functions in bacteria.

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#### Author contributions

LA conducted the experiments, analyzed the data and wrote the paper; PW developed the MS analysis approach, conducted the preliminary experiments, analyzed the data and wrote the paper; EW designed the research and wrote the paper; PR and SM designed the research, analyzed the data and wrote the paper; All authors have read and approved the manuscript.

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#### Appendix A. Supplementary data

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#### Supplementary file : Figure S1.



**Figure S1.** nanoLC/MSMS analysis of spot n°24 containing Lys-tRNA<sub>UUU2-3</sub> after RNase T1 digestion. *A*. Elution profile of the nanoLC of spot n°24 containing Lys-tRNA<sub>UUU2-3</sub> after T1 digestion. The different fragments are as follow: *a* acceptor stem (sequence <sup>5′</sup>CUACACCA<sup>3′</sup> from position 70 to 76); *b* acceptor stem (sequence <sup>5′</sup>CAUCUGp<sup>3′</sup> from position 25 to 30); *c* acceptor stem (sequence <sup>5′</sup>CCAUUAGp<sup>3′</sup> from position 4 to 10); *d* TΨ loop and stem (sequence <sup>5′</sup>AUCUUUAAUCAG<sup>3′</sup> from position 31 to 42). *B*. MS spectrum of the peak *e* of the nanoLC chromatogram corresponding to the anticodon loop. The two main ions have been selected for further fragmentation. *C*. MSMS spectrum of anticodon loop corresponding to the sequence <sup>5′</sup>ACUSUUA\*AUCAGp<sup>3′</sup> with the 145 Da neutral loos specific of the t6A. A\* is present at position 37, carrying the t6A modification. Measured m/z : 1340,19 (-3H<sup>+</sup>). The specific bonds that fragment most often are the 5′ P-O inter-nucleotide bond. Fragment ions where the charge is retained on the 3′-fragment are denoted as y-type fragment ions {McLuckey, 1992 #79}. *D*. MS/MS spectrum of anticodon loop corresponding to the sequence <sup>5′</sup>ACU\$UUHAUCAGp<sup>3′</sup> without neutral loss. Measured m/z : 1373,50 (-3H<sup>+</sup>).

#### 3. Analyse de RNA-Seq des ARN non codants de S.aureus

Afin de compléter la cartographie des modifications des ARNt (et ARNr), réalisée par NanoLC-MS/MS, des approaches complémentaires basées sur le RNA-Seg ont été combinées (Fig 3.). Les trois techniques qui ont été utilisées permettent de détecter les  $\Psi$ , m<sup>7</sup>G, m<sup>3</sup>C, D et 2'-O methylations. Les analyses RNA-Seq telles que l'HydraPsi-Seq (Marchand et al., 2020), l'AlkAniline-Seq (Marchand et al., 2018) et le RiboMeth-Seq (Marchand et al., 2016; Ayadi et al., 2018) ont été réalisées en collaboration avec le Pr. Yuri Motorin et la Dr. Virginie Marchand de la plateforme Epitranscriptomique et Séquençage (EpiRNA-Seq) de Nancy. Ces analyses ont été réalisées sur les ARNt totaux et sur les ARNr. Les résultats d'HydraPsi-Seq révèlent la présence de pseudouridines en position 13, 32 et 55 des ARNt et également en position 524, 634, 717 et 1282 de l'ARNr 16S. L'AlkAniline-Seq spécifique des m<sup>7</sup>G, m<sup>3</sup>C et D, a confirmé la présence de modifications caractérisées pas NanoLC-MS/MS telles que les dihydrouridines localisées dans la boucle D et le m<sup>7</sup>G en position 46 dans la boucle variable de l'ARNt<sup>Pro</sup>UGG. Cette méthode à également permis la caractérisation d'un m<sup>7</sup>G en 534 de l'ARNr 16S. Le RiboMeth-Seg a confirmé la présence d'un 2'O-méthyl en position 34 de l'ARNt<sup>Leu</sup><sub>CAA</sub> mais a également révélé la présence d'un Gm en position 45 de l'ARNt<sup>Val</sup> UAC ainsi que la présence d'un Cm en position 1411 de l'ARNr 16S.



**Figure 3 :** Modifications cartographiées par différentes méthodes de NanoLC-MS/MS et RNA-Seq dans les ARNt à gauche et l'ARNr 16S de *S. aureus* à droite

#### 4. Réponse au stress oxydant :

Après avoir caractérisé de nombreuses modifications sur des ARNt de *S. aureus*, leur dynamique en réponse à des conditions mimant les stress rencontrés pendant l'infection reste à déterminer. La production par les macrophages et les neutrophiles de ROS générant un stress oxydant est une des lignes de défense du système immunitaire. Tout d'abord, des analyses de transcriptomique différentielle et de protéomique sont réalisées afin de caractériser l'adaptation globale de la bactérie au stress oxydant avant de suivre les changements de modification des ARNt.

L'induction des ROS dans les cultures de S. aureus est réalisée par l'ajout de l'herbicide Méthylviologen (MV ; N,-N'-dimethyl-4,-4'-bipyridinium dichloride ; aussi appelé Paraquat). Le MV est une molécule communément utilisée pour étudier le stress oxydant chez les bactéries et les plantes. La réaction entre le radical du MV et le dioxygène ( $O_2$ ) génère les espèces toxiques : le radical superoxyde ( $O_2^{-1}$ ) et le peroxyde d'hydrogène (Hassan, 1984).

#### i. Analyse transcriptomique et protéomique



**Figure 4 : A)** Volcano plot représentant l'analyse transcriptomique différentielle de cultures de *S.aureus* HG001 soumises à un stress oxydant (**Annexe 1**.). Pyr et Pur représentent les voies de biosynthèse des désoxynucléotides et NR représente la voie de réduction des nitrites et des nitrates. **B)** Extraits du volcano plot.

L'analyse transcriptomique différentielle de cultures de *S. aureus* HG001 cultivées en conditions normales ou soumises au stress oxydant généré par le méthylviologen est réalisée en collaboration avec la plateforme EpiRNA-Seq. Ces résultats montrent une surexpression de gènes codants pour des protéines phagiques et des enzymes de détoxification. De même, des protéines impliquées dans les voies de synthèse des acides nucléiques (purines et surtout pyrimidines), de la réparation de l'ADN ainsi que de la réduction des nitrites et des nitrates sont plus exprimées chez les bactéries stressées (**Fig. 4A.**) La plupart des facteurs de virulence sont sous exprimés, notament *cap8A* impliqués dans la synthèse de la capsule, la staphopain, la triacylglycerol lipase (*lip2*) et les toxines (l'alpha-hemolysin *hly*, la delta-hemolysin *hld* présente dans l'ARNII, les gamma-hemolysins *hlgABC* et les peptides PSM). Tandis que l'hémolysine B, le clumping factor B, la protéine A sont surexprimés en condition oxydante. Le niveau de tRNA semble également légèrement plus faible chez les bactéries

stressées, spécifiquement l'ARNt<sup>Tyr</sup>. Les protéines chaperonnes semblent à l'inverse légèrement plus exprimées durant le stress (**Fig. 4B.**).



**Figure 5 :** Volcano plot représentant l'expression différentielle des protéines de cultures de *S.aureus* HG001 soumises à un stress oxydant (**Annexe 2.**).

Les données de protéomique ont été obtenues par analyse LC-MS/MS d'extraits de protéines totales issues de bactéries HG001 cultivées ou non en présence de MV, cette analyse est réalisée en collaboration avec la plateforme protéomique de l'Esplanade de Strasbourg. Cette analyse montre une activation de l'expression des gènes phagiques ainsi qu'une forte augmentation de l'expression de gènes codant pour des protéines de réponse générale au stress (Dps) ainsi que des sous unités C et F de l'alkyl hydroperoxide reductase (AhpC et AhpF). Plusieurs protéines impliquées dans l'import de fer provenant du milieu (YfiY, YfmC\_2) ou de l'hôte (IsdI) sont également surexprimées lors du stress oxydant. De même, une protéine dont l'expression est influencée par la disponibilité du fer (IsdA) semble légèrement plus présente dans les bactéries stressées. La protéine de réparation de l'ADN RecA ainsi que des protéines impliquées dans le métabolisme des acides nucléiques, plus spécifiquement des pyrimidines sont surexprimées lors du stress oxydant alors que l'expression de la Xanthine phosphoribosyltransferase codée par le gène *xpt* est inhibée (**Fig. 5**.).

#### ii. Dynamique des modifications des ARNt en réponse au stress oxydant

L'effet du stress oxydant sur les ARNt peut être caractérisé en analysant leur migration sur gel de polyacrylamide puis en analysant les modifications présentes par NanoLC-MS/MS. Différentes souches ont été utilisées, la souche de laboratoire HG001 mais aussi la souche clinique USA300 et une souche avec un gène *tgt* inactivé (Fey *et al.*, 2013) et ne présentant pas la queuosine.



**Figure 6 : A)** Profil de migration sur gel (polyacrylamide 12%, 8M urée) des ARNt des souches HG001 (souche contrôle), USA300 (souche clinique) et NE1885 (souche possédant le gène *tgt* inactivé) de *S. aureus*. Les flèches rouges indiquent les positions sur le gel des ARNt connus pour posséder une Q en position 34 et correspondant aux bandes présentant un changement de comportement électrophorétique. **B)** Chromatogrammes obtenus à partir des bandes contenant l'ARNt<sup>Tyr</sup><sub>GUA</sub> issus de *S. aureus* HG001. Encerclés en rouge les pics d'élutions correspondants aux anticodons, non clivé par la RNase T1 pour l'ARNt issus de la culture non stressée, clivé pour celui issus de la culture soumise au stress oxydant. **C)** Northern blot sur gel de polyacrylamide et acide phénylboronique des 4 ARNt contenant une Q34 issus de cultures en présence (MV) ou en absence (ctrl) de stress oxydant.

Les profils électrophorétiques des ARNt issus de la souche de laboratoire HG001 sont similaires à ceux des ARNt de la souche clinique USA300. Les ARNt provenant de cellules soumises à un stress oxydant présentent 3 bandes shiftées correspondantes aux profils de

migration de l'ARNt de la Tyrosine, de l'Histidine ainsi que les ARNt de l'Aspartate et l'Asparagine (Antoine et al., 2019). La souche NE1885 provenant de la Nebraska collection est dérivée de la souche USA300 avec le gène tgt impliqué dans la voie de biosynthèse de la Q inactivé (Fey et al., 2013). Les ARNt extraits de cette souche montrent un profil de migration similaire à ceux issus des souches HG001 et USA300 soumises au stress oxydant (Fig. 6A). L'analyse LC-MS/MS de la bande présentant un changement de migration flagrant provenant de la culture de *S. aureus*, contenant l'ARNt<sup>Tyr</sup> révèle le clivage de l'anticodon par la RNase T1 en 3' de la Q34 de cet ARNt issus de la culture stressée. Ce clivage n'a pas lieu dans l'ARNt<sup>Tyr</sup> issus de la culture non stressée, dû à la présence de la modification, empêchant sa reconnaissance par la RNAse T1 (Fig. 6B). Les gels d'affinité contenant de l'acide phénylboronique (APB) qui interagit spécifiquement avec la queuosine, ralentissent la migration des ARNt modifiés (Igloi and Kössel, 1985). Le Northern blot des gels avec APB montre que les ARNt ne possédant pas de Q34 (NE1885) ont migré plus rapidement que les ARNt issus de cultures non stressées qui contiennent une Q34. La migration des ARNt issus des cultures stressées semble plus rapide, comparable à la migration des ARNt ne contenant pas de Q34 (Fig. 6C).

## iii. Analyse des ARNt contenant la Q34 issus de cultures stressées

Chacun des ARNt contenant une Q34 a été purifié par hybridation avec une sonde d'ADN biotinylée spécifique. L'analyse par LC-MS/MS après digestion avec la RNase U2 révèle la présence d'un G non modifié en position 34 pour 3 des 4 ARNt concernés. Les autres modifications telles que les dihydrouridines dans la boucle D, le m7G dans la boucle variable, la thymidine dans la boucle T $\Psi$  ainsi que les modifications en position 37 de l'anticodon (t<sup>6</sup>A, m<sup>1</sup>G et i<sup>6</sup>A) ne semblent pas impactées par le stress oxydant.

Amino Acid	Anticodon		Acc-stem		D-stem	D-loop	D-stem		Ac-stem	Ac-loop	Ac-stem	V-region	T-stem	T-loop	T-stem	Acc-stem		CCA
Asp	GUC	-	GGUCUCG	UA	GUGU	AGCGGDDA	ACAC	G	CCUGC	CUGUCAC	GCAGG	AGAUC	GCGGG	TUCGGUU	CCCGU	CGAGACC	G	CCA
Asn	GUU	-	UCCACAG	UA	GCUC	AGUGGDA	GAGC	U	AUCGG	CUGUU6A	CCGAU	CG7UC	GUAGG	TUCGAGU	CCUAC	CUGUGGA	G	CCA
His	GUG	G	GCGGCUG	UG	GUGA	AGUGGDDA	AmCAC	A	UCGGA	UUGUGKU	UCCGA	CAUUC	GAGGG	UUCGAUC	CCCUU	CAGCCGC	С	CCA
Tyr	GUA	-	GGAGGGG	UA	GCGA	AGUGGCUAA	ACGC	G	GCGGA	CUGUA+A	UCCGC	UCCUUCGGGUUC	GGCAG	TUCGAAU	CUGCC	CCCCUCC	A	CCA

**Tableau 1**: Séquences des ARNt contenants une Q34 issus d'une culture de *S. aureus* HG001 soumise au stress oxydant. En bleu sont présentés les fragments séquencés par MS/MS après digestion avec la RNase U2.

#### iv. Le précurseur preQ1 restaure la queuosine dans les 4 ARNt contenant la Q34

A partir des données d'analyses de protéomique et de transcriptomique, aucune des 8 enzymes (Fig. 7A) de la voie de synthèse de la queuosine ne présente de changement dans son expression. Cependant, le stress oxydant peut affecter directement l'activité des protéines. Afin de comprendre quelles enzymes sont susceptibles d'être inactivées, les cultures soumises au stress oxydant ont été supplémentées avec le précurseur de la queuosine preQ1. La cinétique d'incorporation de la queuosine a ensuite été vérifiée par électrophorèse d'affinité à l'APB. (Fig. 7B).



**Figure 7 : A)** Voie de biosynthèse de la queuosine (adapté de (Dowling *et al.*, 2016). En rouge sont encadrées les étapes catalysées par des enzymes à cluster [4Fe-4S], en bleu l'étape catalysée par la QueF convertissant lepreQ<sub>0</sub> en preQ<sub>1</sub>. **B)** Northern blot de gels APB des ARNt contenant une Q34 issus de *S.aureus* HG001 cultivées en condition oxydante. A T<sub>0</sub>MV, le stress oxydant est appliqué à la culture et à T<sub>0</sub>preQ<sub>1</sub>, 60min après l'ajout de MV, l'intermédiaire preQ<sub>1</sub> est ajouté au milieu. La culture ctrl est la culture non stressée, sans ajout de preQ<sub>1</sub>, la culture MV est la culture stressée sans ajout de preQ<sub>1</sub>.

Les ARNt issus de cultures stressées présentent des profils de migration semblant indiquer une proportion plus importante d'ARNt ne possédant plus de Q34 au court du stress oxydant. 30 min après l'ajout du précurseur de la queuosine preQ<sub>1</sub>, les ARNt présentent de nouveau un profil électrophorétique similaire à ceux provenant de cellules cultivées en conditions normales. Ce profil se maintient à TpreQ<sub>1</sub>+60 min et suggère une restauration de la voie de biosynthèse de la queuosine.

## III. Discussion

## 1. Mise en place de la méthode et cartographie des modifications

## i. Limites et méthodes complémentaires : le pouvoir de la coopération

La méthode de NanoLC-MS/MS choisie pour cette étude bénéficie d'une grande sensibilité et précision de mesure, permettant de détecter et localiser sur la séquence tous types de modifications connues. Cependant, elle présente plusieurs limites, principalement les informations fragmentaires obtenues ne permettant pas d'établir une cartographie complète des modifications présentes sur l'ensemble des ARNt.

L'utilisation de plusieurs RNases spécifiques permet d'améliorer par recoupement le recouvrement de séquence des ARNt. Cependant, seules les RNases T1 et A sont capables de digérer les ARNt directement à l'intérieur du gel de polyacrylamide. L'utilisation des RNases MC1 ou U2 par exemple, nécessite d'adapter la méthode de purification des ARNt. Pour cela, la purification d'un ARNt spécifique par hybridation avec un oligodésoxynucléotide biotinylé, suivie d'une chromatographie d'affinité peut permettre d'isoler un ARN ciblé qui n'a pas été détecté à la révélation du gel de polyacrylamide en 2D (*cf* § II. 4. iii.). La séparation des fragments d'ARNt digérés peut également être optimisée grâce à l'utilisation de l'électrophorèse capillaire afin de pouvoir détecter les fragments plus courts (Lechner *et al.*, 2020).

La pseudouridine est une modification de masse silencieuse et n'est pas détectable directement par cette méthode. Un traitement chimique au CMCT est possible mais lors des

tests réalisés, les pseudouridines n'ont pas pu être localisées sur les séquences suite au décrochage du groupement CMC lors de la fragmentation. Une altérnative possible est d'utiliser l'acrylonitrile qui semble plus stable en MS/MS (Mengel-Jørgensen and Kirpekar, 2002).

L'analyse par spectrométrie de masse des nucléosides issus de la digestion complète des ARNt suivi de la déphosphorylation des nucléotides fournit la composition globale en modifications des ARNt. Cette méthode ne nécessite pas de séparation ou de purification préalable des ARNt mais ne fournit pas d'informations concernant la position ou la séquence et permet la quantification relative entre différentes conditions des modifications présentes (Helm and Motorin, 2017; Galvanin *et al.*, 2020). Il est également possible comme alternative, d'utiliser l'approche de marquage SIL-IS in vivo en cultivant les bactéries avec du 13C-glucose comme source majeure de carbone pour faciliter la comparaison relative des modifications par LC-MS/MS (Kellner, Ochel, *et al.*, 2014). En dehors de la spectrométrie de masse, les différentes méthodes de RNA-Seq permettent de localiser certaines modifications spécifiques en fonction du traitement appliqué lors de la préparation des librairies. Les analyses quantitatives sont également possibles avec cette méthode.

Les analyses par des méthodes complémentaires permettent de compléter la cartographie des modifications établie et confirmer les résultats obtenus. La combinaison de différentes méthodes citées apporte une caractérisation plus robuste des modifications des ARNt et de la dynamique de celles-ci.

## ii. Cartographie des modifications des ARN non codants de S. aureus

Les données de RNA-Seq (HydraPsi-Seq, AlkAniline-Seq et RiboMethSeq) ont permis de confirmer la présence de modifications sur les ARNt de *S. aureus* et de compléter la carte partielle avec les pseudouridines. Les modifications présentes dans les ARNt de *S. aureus* diffèrent peu des modifications présentes dans d'autres bactéries à gram positif telles que *B. subtilis* ou *L. lactis* pour lesquels des cartographies existent (Vold, 1976; Puri, Wetzel, Saffert, W.Gaston, *et al.*, 2014; de Crécy-Lagard *et al.*, 2020). La cartographie des modifications des

ARNt de *S. aureus* demeure encore partielle. Afin de la compléter, une analyse des nucléosides présents sur les ARNt sera réalisée.

La présence de particularités des ARNt de *S. aureus* a été mise en évidence. Plus précisément, la présence d'ARNt isoaccepteurs de la glycine spécifiques impliqués dans la synthèse de la paroi cellulaire. Ces ARNt interviennent dans la constitution du pont pentapeptide spécifique du peptidoglycane des Staphylocoques via les complexe de proteines FemXAB (facteurs essentiels pour la méthicilline (Giannouli et al., 2009; Rietmeyer et al., 2021) (Fig. 8A). Ces ARNt<sup>Gly</sup>, dits non protéinogéniques, présentent une séquence différente des ARNt<sup>Gly</sup> intervenants dans la traduction (protéinogéniques) et j'ai pu déterminer qu'ils ne possèdent pas la modification 5-méthoxyuridine (mo<sup>5</sup>U) en 34 permettant le décodage des ARNm. Ils présentent également une boucle T particulière avec un G en position 55, L'absence de la Ψ55 peu inflencer la présence d'autres modifications, comme c'est le cas notamment dans l'ARNt<sup>Phe</sup> de Saccharomyces cerevisiae (Barraud et al., 2019). Chacun de ces ARNt<sup>Gly</sup> ont été purifiés et analysé par spectrométrie de masse (Fig. 8B), confirmant l'absence de modifications dans les régions analysées. Une investigation complète est en cours à ce jour au laboratoire pour déterminer le rôle des modifications dans la discrimination de la machinerie traductionnelle et la redirection de ces ARNt vers la voie de biosynthèse correspondante.



**Figure 8 : Séquences des ARNt**<sup>Gly</sup> **de** *S. aureus* adapté de (Giannouli *et al.*, 2009). **A)** P1 et P2 sont les isoaccepteurs protéinogéniques, l'ARNt P2 UCC possède un mo<sup>5</sup>U en position 34 encadré en rouge. Les ARNt NP123 sont des ARNt non protéinogéniques, encadré en rouge la différence de séquence dans la boucle T. **B)** Dû a leur forte identité de séquence, il est difficile de les identifier spécifiquement un par un. NP1 et NP2 sont alors confondu dans nos analyses. Cependant, aucune modification n'a été détectée dans ces ARNt.

La présence d'une modification de masse inconnue a été établie dans l'ARNt de la Lysine (*cf* § II. 3. **Fig. S1**). Cependant, la caractérisation complète afin d'identifier cette nouvelle modification nécessite de plus amples investigations. Il est en effet possible de cultiver les bactéries en présence d'isotopes afin de déteminer la formule brute de la modification (Kellner, Neumann, *et al.*, 2014).

Il n'existe pas de cartographie globale des modifications présentes sur l'ensemble du ribosome de *S. aureus* à ce jour. Seulement 10 modifications ont pu être assignées pas la structure Cryo-EM du ribosome 70S (Golubev *et al.*, 2020). Les données de RNA-Seq des modifications dans les ARNr sont en cours de traitement par Roberto Bahena qui est doctorant au sein de l'équipe. Les résultats obtenus par cette méthode sur les ARNr sont en cours de confirmation par extension d'amorce (Motorin *et al.*, 2007). Pour caractériser certaines régions spécifiques des ARNr, une adaptation de la NanoLC-MS/MS peut être développée (*cf* § V. 3. **Fig. 13**). L'ARNr 16S a été très partiellement analysé par les différentes techniques mises en place (spectrométrie de masse et RNA-Seq), ce qui a permis de localiser

les modifications situées au niveau du site de décodage impliquant des interactions avec les ARNt et l'ARNm.

#### 2. Réponse globale de S. aureus au stress oxydant

La transcriptomique différentielle et les analyses protéomiques ont permis d'établir une représentation globale de l'expression des gènes en condition de stress. Ci-après, Les changements observés seront discutés selon les voies métaboliques impliquées (**Annexe 1**). Il a été mentionné qu'une analyse de transcriptome sur micropuce de la réponse cellulaire de *S. aureus* (NCTC 8325) a déjà été rapportée (Chang *et al.*, 2006). L'étude a été conduite en début de phase exponentielle dans un milieu pauvre, ce qui diffère de notre étude réalisée en milieu riche et plus tard dans la phase de croissance de la bactérie. Cependant, les gènes de la réponse SOS et des mécanismes de réparation de l'ADN ont été retrouvés activés également. D'autres gènes, notamment de nombreux facteurs de virulence pour lesquels nous avons observé des variations significatives, n'ont pas été détectés dans ce rapport.

## i. Système SOS de réparation de l'ADN et gènes phagiques

Parmi les ROS, le radical hydroxyle hautement réactif (HO•) réagit avec l'ADN produisant environ 20 produits majeurs d'oxydation des bases ou des sucres de l'ADN, des clivages du brin, et des crosslinks d'ADN et protéines (Cadet and Wagner, 2013). Les dommages sur l'ADN altèrent la réplication et la transcription, causant la mort cellulaire et peut mener à des mutations. Lorsque la DNA polymérase est bloquée sur une lésion, l'hélicase continue de dérouler l'ADN, générant des régions d'ADN simple brin étendues qui vont être ciblées par les protéines du système SOS (Podlesek and Žgur Bertok, 2020). La réponse SOS entraine l'induction de multiples protéines qui renforcent l'intégrité de l'ADN. Cette réponse inclus également des facteurs qui sont des sources d'erreurs, ils vont permettre d'améliorer la survie et la continuité de la réplication en présence de dommages étendus de l'ADN, mais au prix d'une mutagénèse élevée. Dû à son potentiel mutagène, le système de réponse SOS est sujet à une régulation complexe (Maslowska *et al.*, 2019). L'activation du système SOS de réparation de l'ADN est lié à l'inhibition du répresseur LexA qui va générer l'expression de nombreux gènes, notamment la surexpression de la protéine RecA (Ha *et al.*, 2020b) qui est observé dans nos analyses avec un FoldChange . La protéine RecA est connue pour stimuler l'autoclivage de LexA eu ainsi augmenter l'expression (Bisognano et al., 2004). Nous avons également observé une augmentation de l'expression de *uvrB*, codant pour un facteur requis pendant les étapes précoces de la réparation par excision des nucléotides qui va former un complexe ADN-protéine au niveau du site endommagé permettant l'incision (Gordienko and Rupp, 1997). De plus, de nombreuses protéines impliquées dans la synthèse des purines et des pyrimidines semblent confirmer la mise en place de réparation des acides nucléiques.

L'activation de l'expression de gènes prophagiques suite au stress oxydant était attendue, leur expression étant activée suite au déclenchement du système SOS de réparation de l'ADN (Maiques *et al.*, 2006). Les protéines prophagiques favorisent le transfert horizontal de l'ADN et peuvent entrainer l'acquisition par la bactérie de résistances. Ce transfert génétique entre les bactéries est habituellemnet induit par des stresseurs, comme les antibiotiques (Beaber *et al.*, 2004; Jutkina *et al.*, 2016), les métaux et biocides (Seier-Petersen *et al.*, 2014) et plus généralement par la réponse SOS (Andersson and Hughes, 2014). De plus il a été récemment observé que la diffusion chez *E. coli* de gènes de résistance via la conjugaison et aussi stimulée par le stress oxydant généré par les radiations UV (Chen *et al.*, 2019). Puisque la transduction conditionnée par les bacteriophages est considérée comme un des facteurs principaux des transferts de gènes horizontaux chez les Staphylocoques (Xia and Wolz, 2014; Stanczak-Mrozek *et al.*, 2015), il est possible que chez *S. aureus* le stress oxydant stimule le transfert de gènes via la transduction.

## ii. Détoxification des espèces réactives de l'oxygène

Les protéines AhpCF de détoxification des ROS sont très largement surexprimées, cependant, les analyses protéomiques réalisées n'ont pas montré de surexpression détectable des protéines Sod alors que l'analyse transcriptomique indique une surexpression de *sodM* dont l'expression est activée lors d'un manque de manganèse dans le milieu sans lien avec les conditions oxydantes rencontrées (Karavolos et al., 2003; Garcia et al., 2017). La

catalase KatA est légèrement surexprimée au niveau protéique alors que la transcription reste inchangée, suggérant une régulation au niveau traductionnel de son expression. L'expérience de ribosome profiling à haute résolution pourrait nous permettre de mieux comprendre s'il y a une différence d'efficacité de la traduction du gène *katA*.

## iii. Métabolisme des acides aminés

L'enzyme MetE impliquée dans la biosynthèse *de novo* de la méthionine à partir d'homocystéine ainsi que la sulfite réductase codée par le gène *cysJ* impliqué dans la biosynthèse de la cystéine sont surexprimées. L'expression de la thioredoxine permettant la réduction des thiols dans le cytoplasme est inchangée alors que la protéine régulatrice Spx, nécessaire à son expression est sous exprimée au niveau protéomique malgré une surexpression en transcriptomique.

## iv. Homéostasie du fer

De nombreuses protéines responsables de l'apport du fer sont largement surexprimées, illustrant l'importance vitale de celui-ci pour la survie de la bactérie en conditions oxydantes. Les staphyloferrines et les protéines Isd permettant l'import de celui-ci provenant de son environnement, ou des cellules de l'hôte. Dans un contexte d'infection, la production de ces protéines permettant l'internalisation par la cellule du fer présent dans l'hème ou la transferrine de l'hôte peut permettre à la bactérie de survivre à l'oxydation du Fer induit par les ROS.

## v. La voie de respiration en anaérobie

Les protéines impliquées dans la respiration anaérobie codées par les opérons *narGHWX* et *nasDEF* sont surexprimées au niveau transcriptionnel alors qu'elles sont moins exprimées en protéomique durant le stress oxydant. L'inhibition de l'expression de ses protéines peut s'expliquer par une absence de traduction des ARNm transcrits ou une traduction altérée qui

entrainerait la production de protéines instables et ainsi la dégradation de celles-ci. La surexpression de protéines chaperonnes impliquées dans le repliement semble corroborer la deuxième hypothèse. Cependant, La transcription de ces opérons depend de la présence ou non d'oxygène. En effet, la protéine NreB, qui est codé par l'opéron *narGHWX* et fait partie du régulon NreABC, est une kinase à cluster [4Fe-4S] qui va avoir un rôle de capteur de l'oxygène. En absence de O<sub>2</sub>, le cluster est intact et l'enzyme est active, elle va s'autophosphoryler et transférer le phospore à NreC qui va pouvoir se lier à l'ADN pour activer l'expression des deux opérons le la voie de réduction du nitrate et du nitrite (Fedtke et al., 2002; Nilkens et al., 2014). En présence d'oxygène, le cluster [4Fe-4S] est dégradé et l'enzyme est inactivée. Dans nos conditions expérimentales de stress oxydant, NreC doit être inactive ce qui suggère que la transcription de l'opéron est activée par un autre facteur qui n'est pas caractérisé et qui n'entraine pas la production du protéines fonctionnelles. Ces résultats indiquent qu'il existe un système de régulation plus complexe de l'expression des opérons de la chaine de respiration anaérobie en lien avec le stress oxydant

## vi. L'implication des ARNt et des enzymes de modifications

Les enzymes de modifications des ARNt sont, bien que plus lègérement impactées, également surexprimés en transcriptomique et moins exprimées en protéomique. Les ARNt, plus spécifiquement l'ARNt<sup>Tyr</sup> sont moins exprimés pendant le stress oxydant. Chez E. coli, le stress induit par le H<sub>2</sub>O<sub>2</sub> en milieu minimal entraine une diminution globale de la quantité de ARNt due à leur dégradation et engendrant l'inhibition de l'élongation de la traduction (Zhong et al., 2015). Alors que l'exposition au MV ne touche que l'ARNt<sup>Gly</sup>, altérant le décodage des codons (Leiva et al., 2020). Chez E. coli, l'expression des ARNt peuvent moduler la réponse au stress oxydant. Il est possible que chez *S. aureus*, même si le niveau global d'ARNt n'est pas fortement impacté, des changements au niveau de leurs modifications puissent participer au contrôle traductionnel et à la réponse au stress oxydant.

# vii. La persistance de la bactérie privilégiée au détriment de la dissémination et de l'infection aiguë

Les mécanismes de survie et de réparation des dommages causés par les ROS sont privilégiés durant le stress oxydant au détriment de la production de toxines cytolytiques responsables d'infections aigües telles que les PSM ou les CHIPS. Dans le contexte d'une infection, cela est habituellement observé durant la colonisation des tissus dans lesquels S. aureus établit de nouvelles colonies grâce aux adhésines exprimées telles que la protéine SpA et le clumping factor B. D'un autre côté, le stress oxydant est habituellement rencontré lorsque S. aureus est internalisé dans les neutrophiles et les macrophages. S. aureus a été reconnue comme persistant à l'intérieur des phagocytes ou des cellules endothéliales sur des périodes prolongées (Hamill et al., 1986). Dans ces conditions confinées, le système de quorum sensing Agr devrait normalement augmenter l'expression des toxins et exoprotéines (Carnes et al., 2010). Cependant, chez les bactéries internalisées, il a été démontré que l'inactivation du régulateur Agr empêchant l'expression des facteurs de virulence dépendant du quorum sensing leur permet et persister sous forme de Small Colony Variants (SCV). Ces variants se développent plus lentement mais présentent une plus grande résistance aux antibiotiques, provoquant des infections chroniques (Sendi and Proctor, 2009; Young et al., 2017). Lorsque Les conditions seront plus favorables ou la densité de cellules suffisante, les toxines seront produites afin de disséminer les bactéries et diffuser l'infection (Surewaard et al., 2013; Bojer et al., 2018).

## 3. Modifications des ARNt et stress oxydant

## i. Dynamique des modifications des ARNt durant le stress

En condition de stress oxydant, le profil de migration des ARNt sur gel de polyacrylamide est modifié pour la souche de laboratoire HG001 comme pour la souche clinique de *S.aureus* USA300. La migration des ARNt indique un changement dans l'état de modification de certains ARNt. L'absence de queuosine suggérée par le clivage par la RNAse T1 dans l'ARNt<sup>Tyr</sup>

est confirmée par les profils de migration sur gel d'APB des 4 ARNt concernés. Les ARNt contenant une Q34 migrent à la même vitesse en condition de stress oxydant que les ARNt provenant d'une souche ne possédant pas de queuosine. Les analyses de 3 des ARNt purifiés par chromatographie d'affinité digérés par la RNase U2 montrent la présence de G34 non modifiés pour ces ARNt provenant de cultures stressées.

L'analyse par RNA-Seq en triplicats d'ARNt totaux issus de cultures stressées ou non est à ce jour en cours afin de déterminer si d'autres modifications sont affectées. Les enzymes de modification des ARN, plus spécifiquement les méthyltransférases, font partie des métalloenzymes à centre [4Fe-4S]. La présence de ROS peut donc entrainer leur inactivation et ainsi une diminution des méthylations des ARNt. Cependant aucun résultat obtenu lors de cette étude ne permet de le démontrer. Les 2'OMe présents en position 32 qui sont impliqués dans la réponse au stress oxydant chez *P. aeruginosa* n'ont pas été détectés par NanoLC-MS/MS chez *S. aureus*. De même, les m<sup>7</sup>G en position 46 ont été détectés dans peu d'ARNt, ne permettant pas de réaliser d'analyses sur de potentiels changements lors du stress.

#### ii. Causes de l'absence de queuosine

L'analyse transcriptomique semble montrer une légère surexpression des enzymes impliquées dans la voie de biosynthèse de la queuosine malgré l'absence de celle-ci dans les ARNt. Ces résultats peuvent indiquer la chute de l'activité enzymatique des protéines produites. Les plus susceptibles d'être inactivées sont les enzymes contenant un cluster [4Fe-4S], il y en a 3 impliquées dans la synthèse de la queuosine : QueE, QueG et QueH. La 7-carboxy-7-deazaguanine synthase (QueE) utilise la SAM et catalyse la synthèse du CDG à partir du CPH<sub>4</sub> (**Fig. 7A**, étape 3) (McCarty *et al.*, 2013). *S. aureus* possède deux époxyqueuosine réductases (**Fig. 7**, étape8), QueG utilisant la cobalamine (Dowling *et al.*, 2016) et QueH qui semble être indépendante de la cobalamine (Zallot *et al.*, 2017).

L'ajout d'un intermédiaire de cette voie, le preQ1 permet de restaurer la présence de la queuosine sur les ARNt indiquant une possible inactivation d'une ou plusieurs enzymes en amont de cet intermédiaire. La réduction de l'époxyqueuosine (oQ) ne semble donc pas être

l'étape impactée par la présence des ROS. Comme deux enzymes sont capables de catalyser cette réaction, deux possibilités se présentent : soit les deux clusters ne sont pas sensibles aux ROS, soit leurs activités peuvent se compenser en cas d'inactivation de l'une des deux enzymes. L'enzyme QueE est potentiellement sensible à l'oxydation par les ROS, le fer apical (non coordiné par une cystéine du motif CXXXCXXC) du cluster peut être protégé de l'oxygène s'il est coordiné par un ligand ou à un autre acide aminé situé à proximité.

Cependant, cela ne semble pas être le cas pour QueE, le fer apical des enzymes à SAM doit être accessible pour permettre la coordination du SAM. Par exemple, l'enzyme QueE de *B. subtilis*, proche de celle de celle de *S.aureus* présente un fer très accessible (**Fig. 9**).



**Figure 9.** Comparaison structurelle entre la QueE de *S. aureus* modélisée par homologie est la structure obtenue par rayon X de *B. subtilis* (fichier pdb 5TH5; Bruender et al., 2017). Le motif spécifique pour la coordination du cluster [4Fe-4S] (en orange et jaune) est conservé. Il est composé de 3 résidus cystéine. Chez *B. subtilis*, cys 38 et cys 41 (chez *S. aureus*, cys 37 and cys 40 correspondants) sont assez proches our pouvoir former un pont disulfure si ils sont oxydés. Le 4ème fer du cluster interagit avec l' $\alpha$ -amino et l' $\alpha$ - carboxylate du SAM.

L'enzyme catalysant la synthèse du preQ<sub>1</sub> à partir du preQ<sub>0</sub>, QueF (7-cyano-7-déazaguanine réductase NADPH dépendante) (**Fig. 7**, étape 5) possède une cystéine catalytique en position 57 chez *S. aureus* (**Fig. 10**).



**Figure 10 : Comparaison structurale entre le modèle de QueF de** *S. aureus* **obtenu par homologie avec la structure aux rayons X de QueF de** *B. subtilis* **en état oxydé** (pdb file 5UDG; Mohammad et al., 2017). La Cys 55 de *B. subtilis* (correspondant à la Cys 57 chez *S. aureus*) se lie au substrat preQ<sub>0</sub>, formant un intermédiaire thiomide. Ce résidu catalytique est sensible à l'oxydation et peut former un pont disulfure avec la Cys 99 (Cys 101 chez *S. aureus*). Le preQ<sub>0</sub> ne peut plus se fixer à QueF si la Cys 57 est oxydée, empêchant la formation de la queuosine.

Cette cystéine peut être protégée en conditions oxydantes par la formation d'un pont disulfure avec une deuxième cystéine se situant à proximité (Mohammad et al., 2017). Des analyses de LC-MS/MS ont été réalisées en alkylant les protéines avant la réduction des ponts disulfures mais les cystéines concernées n'ont pas pu être visualisées dû à la trop faible abondance de la protéine d'intérêt. La séparation préalable sur SDS-PAGE n'a pas permis d'éliminer suffisamment les protéines contaminantes. Afin d'enrichir l'échantillon pour l'analyse LC-MS/MS de QueF, il est possible d'exprimer la protéine portant une étiquette (flag-tag) avant purification par chromatographie d'affinité de type coimmunoprécipitation. Après élimination du MV par centrifugation des bactéries, aucune restauration de la queuosine n'a été observée sur gel de polyacrylamide, ce qui semble invalider l'hypothèse de l'inactivation réversible de QueF. De manière identique à preQ<sub>1</sub>, l'ajout du substrat de QueF, preQ<sub>0</sub> au milieu de culture des bactéries cultivées en conditions oxydantes est en cours au laboratoire afin de tenter de restaurer la présence de queuosine.

#### iii. Conséquences traductionnelles de l'absence de Q34

La queuosine est présente en position 34 des ARNt, la position wobble qui est impliquée dans le décodage des ARNm. L'altération de cette modification peut impacter la vitesse et la précision de la traduction des protéines contenant les 4 acides aminés dont l'incorporation dépend des ARNt qui ont perdu la queuosine.

La légère surexpression observée dans l'analyse transcriptomique des gènes de chaperonnes impliquées dans le repliement des protéines peut indiquer un problème d'agrégation des protéines dû à des variations de vitesse de traduction.

Afin d'étudier la vitesse de décodage des ARNm codon par codon, une expérience de ribosome profiling à haute résolution (hRibo-Seq) permet de révéler les sites de pause du ribosome. Un protocole établi pour *E. coli* (Mohammad *et al.*, 2019) a été adapté à l'étude de *S. aureus* au sein du laboratoire. Cette méthode consiste à immobiliser les ribosomes en cours de traduction grâce à la congélation directe des bactéries dans l'azote liquide en présence d'une concentration élevée de sels de magnésium. Après purification des polysomes, les portions d'ARNm qui ne sont pas protégés par la présence du ribosome sont digérées par une RNase spécifique (MNase) permettant de générer des fragments d'ARNm en cours de traduction permet de déterminer d'une par les gènes traduits spécifiquement durant les conditions données mais également d'obtenir un taux d'occupation des ribosomes le long des ARNm.

L'étape de digestion des ARNm est cruciale pour déterminer précisément les codons particuliers pour lesquels la vitesse de décodage est altérée. En effet, la digestion par la RNAse doit générer des fragments de longueur adaptée, correspondant à la position exacte du ribosome et permettant d'assigner un codon spécifique au site de décodage.

L'étude de l'impact des queuosines sur le décodage des ARNm chez les eucaryotes met en évidence des conséquences différentes de l'absence de queuosine sur la vitesse de décodage des codons contenants un C ou un U en 3' dépendant de l'organisme. La queuosine contribuant ainsi à l'harmonisation de la vitesse de la traduction de manière générale (Tuorto *et al.*, 2018; Müller *et al.*, 2019).

Les données préliminaires obtenues durant les tests réalisés au laboratoire semblent indiquer que chez *S. aureus*, spécialement pour l'ARNt<sup>Tyr</sup>, l'absence de Q34, entraine une perte de vitesse de décodage des codons UAU durant le stress oxydant alors que la vitesse de décodage des codons UAC n'est pas impactée (**Fig. 11**).



Preliminary codon pause scores in normal and oxidative stress condition

**Figure 11. Score de pause des codons dans le site A par analyse préliminaire de hRibo-seq** en condition normale (WT, en vert) et stress oxydant (MV, en rouge). Les scores de pauses ont été calculées selon Mohammad *et al.*, 2019. Des variations ont été obsérvées pour les codons synonymes des Cys (C), Asp (D), Gly (G), His (H), Asn (N), Arg (R), Val (V) et Tyr (Y). Les codons Asp (D), Asn (N) et Tyr (Y), et His (H) correspondent aux ARNt contenant une Q34 en condition normale et un G34 en stress oxydant. Parmis eux, les différences les plus importantes sont observées pour l'ARNt<sup>Tyr</sup> qui montre un décodage plus lent pour le codon UAU durant le stress oxydant.

Le protocole utilisé restreint le volume de culture qui peut être utilisé et dans les conditions de notre analyse, réalisée en fin de phase exponentielle (lorsque la traduction est déjà réduite), nous n'avons pas pu obtenir assez de fragments d'ARNm pour réaliser une analyse correcte et complète. Afin d'obtenir suffisamment d'ARNm en cours de traduction, les cellules doivent être en phase exponentielle et contenir un grand nombre de ribosomes matures et actifs. Cela implique pour nous d'induire le stress plus tôt dans la phase de croissance des bactéries et d'arrêter la culture plus tôt car dans les conditions présentées dans cette étude, de nombreux ribosomes se sont révélés être immatures ou inactifs. Un autre aspect qui peut être amélioré pour obtenir une meilleure résolution pour nos expériences de hRibo-seq est le choix de la RNase utilisée pour produire les fragments

d'ARNm protégés par le ribosome. L'utilisation de la MNase ne semble pas adaptée pour cette étude chez *S. aureus*, car la taille des fragments obtenus indique une dégradation non spécifique des extrémités des ARNm protégés par le ribosome. Cette étape de digestion est réalisée avec la RNase I pour les analyses de ribosome profiling chez les eucaryotes, cette procédure a été testées avec succès et sera donc mise en place au sein du laboratoire

Des perturbations dans la vitesse de traduction des protéines peut impacter le repliement de celles-ci et ainsi leur stabilité. Le décodage de certains ARNm, selon leur composition en codons spécifiques, peut donc participer à la régulation de l'expression de certaines protéines au niveau de la traduction. Cette analyse permettra d'étudier l'impact sur la vitesse de décodage de l'absence de la queuosine sur les 4 ARNt concernés et ainsi d'établir le rôle de cette modification dans l'adaptation de la bactérie au stress oxydant.

## **IV.** Conclusions

J'ai participé à la mise en place de la méthode d'UPLC-MS/MS qui, en association avec les méthodes de RNA-Seq, a permis d'établir les cartographies partielles des modifications présentes dans les ARN non codants de *S. aureus*. L'amélioration de cartographie est en cours avec l'utilisation de méthodes complémentaires permettant de la compléter et d'étendre cette analyse à d'autres ARN tels que les ARN régulateurs pour lesquels aucune modification n'a été caractérisée *chez S. aureus* 

Cette cartographie m'a permis d'étudier leurs variations, en particulier dans les ARNt, lors du stress oxydant mimant la production de ROS par les cellules du système immunitaire lors de l'infection. J'ai ainsi pu mettre en évidence une altération de la queuosine des 4 ARNt possédant cette modification en position wobble de l'anticodon. De plus, l'ajout d'un intermédiaire de la voie de biosynthèse restaure la présence de la queuosine, apportant une indication sur la cause possible de l'absence de la modification

Ces résultats ont conduit à la mise en place de la méthode de ribosome profiling à haute résolution et son adaptation pour l'étude de *S.aureus*. Les premières analyses de l'impact sur la traduction de l'absence de cette modification sur les ARNt<sup>Tyr</sup> ont montré des résultats

encourageants. L'expérience de hRibo-Seq complète peut être réalisée afin d'élucider la fonction de la queuosine sur le décodage de l'ensemble des codons nécessitant cette modification. Les cultures contenant du preQ<sub>0</sub> ont été réalisées et peuvent être analysées afin de souligner une potentielle inactivation de l'enzyme QueF lors du stress oxydant.

La cartographie des modifications sur les ARN ribosomiques est en cours de réalisation, les données de RNA-Seq de ribosomes et d'ARNt provenant de bactéries soumises ou non au stress oxydant sont en cours d'analyse. Le projet se poursuit avec l'étude structurale de l'impact des variations des modifications des ARNt et ARNr sur l'ensemble de la machinerie traductionnelle qui est réalisée par Roberto Bahena, qui est actuellement en thèse.

L'analyse des modifications des ARNt<sup>Gly</sup> non protéinogéniques ne possédant pas de modifications a mené à la création d'un nouveau projet de recherche. L'étude structurale des différents isoaccepteurs de la glycine ainsi que de leurs interactions avec la machinerie traductionnelle (EFTU) ou la machinerie responsable du transfert des ARNt vers la paroi cellulaire telles que les protéines Fem (facteurs essentiels pour la résistance à la méthicilline) est en cours avec Hiroki Kanazawa actuellement en contrat post doctoral.

Cette approche mise en place pour l'étude des variations des modifications des ARN en réponse au stress oxydant et de leur impact traductionnel, pourra être appliquée à d'autres conditions environnementales rencontrées lors de l'infection. La combinaison des informations apportées par l'étude de la réponse du pathogène aux différents stress permettra d'améliorer notre compréhension du rôle des modifications durant l'infection.

## V. Matériels et méthodes

## 1. Produits et sondes utilisés

Les produits chimiques et milieux de culture utilisés proviennent de Sigma-Aldrich. Les enzymes utilisées proviennent de ThermoFischer Scientific.

## Sondes utilisées :

	probe for single tRNA purification	probe for Northern blotting					
tRNA <sup>Asp</sup> <sub>GUC</sub>	/5BiosG/GATCTCCTGCGTGACAGGCAGGCGTGTTAACCGCTACAC	GATCTCCTGCGTGACAGGCAGGCGTGTTAACCGCTACAC					
tRNA <sup>Asn</sup> GUU	/5BiosG/GACCGATCGGTTAACAGCCGATAGCTCTACCACTGAGC	GACCGATCGGTTAACAGCCGATAGCTCTACCACTGAGC					
tRNA <sup>His</sup> <sub>GUG</sub>	/5BiosG/GAATGTCGGAACCACAATCCGATGTGTTAACCACTTCAC	GAATGTCGGAACCACAATCCGATGTGTTAACCACTTCAC					
tRNA <sup>Tyr</sup> GUA	/5BiosG/CGAAGGAGCGGATTTACAGTCCGCCGCGTTTAGCCACTTCGC	CGAAGGAGCGGATTTACAGTCCGCCGCGTTTAGCCACTTCGC					
tRNAGly P2	/5Biosg/ATC AGC TTG GAA GGC TGA GGT TTT GCC ATT AAA CTA	/					
tRNAGly NP1+NP2	/5Biosg/TCG TTC CGG GAA GGA ACG TGT TCT AAA AGT TGA ACT A	/					
tRNAGly NP3	/5Biosg/TCA TTC CAG GAA GGA ATG TAT TCT AAG AGT TGA AAT A	/					
rRNA pos	oligonucleotide for rRNA modifications MS analysis						
1202-1241	C GTGTGTAGCCCAAATCATAAGGGGCATGATTGACG						
1395-1440	GGTGTTACAAACTCTCGTGG TGTGACGGGC GGTGTGTACAGACCC						
1497-1542	TCCAGCCGCACCTTCCGATACGGCTACCTTGTTACGACTTCACCCC						

**Tableau 2 :** Oligonucléotides utilisés pour la purification des ARNt, les Northern blot et l'Analyse par NanoLC-MS/MS des modifications de l'ARNr 16S

## 2. Souches bactériennes et conditions de culture

## i. Souches

La souche principalement utilisée pour cette étude est la souche *S. aureus* HG001 de laboratoire, dérivée de la souche NCTC8325 contenant le gène *rsbU* restauré (Herbert *et al.*, 2010). La souche clinique MRSA (methicillin resistant *S.aureus*) *S. aureus* USA300 (Tenover and Goering, 2009) ainsi que la souche NE1885 provenant de la collection Nebraska qui en est dérivée seront également utilisées. La souche NE1885 possède un transposon contenant plusieurs codons stop en position 9 du gène *tgt* entrainant une absence de queuosine (Bose *et al.*, 2013).

## ii. Conditions de culture

Les cultures de bactéries non stressées sont réalisées dans les conditions publiées précédemment (*cf* § II. 2). Brièvement, une préculture sur la nuit est diluée à DO(600nm) = 0,05 dans 20 mL de BHI et est incubée à  $37^{\circ}$ C sous agitation à 180rpm durant 4h jusqu'à une D0(600nm)<sub>finale</sub> = 3.

Les cultures soumises au stress oxydant sont cultivées comme les bactéries non stressées pendant 120 min. A t= 120 min, 10mM final de méthylviologen est ajouté à la culture, les bactéries sont ensuite cultivées dans les conditions de température et d'agitation inchangées pendant 120 min jusqu'à atteindre une DO(600nm)<sub>finale</sub> = 2,5-3.

Pour l'étude de l'effet de l'intermédiaire preQ<sub>1</sub>, le stress est appliqué par l'ajout de méthylviologen au milieu de culture après 90min d'incubation. Après 1h de croissance en condition de stress oxydant, le preQ<sub>1</sub> est ajouté à une concentration finale de 1 $\mu$ M, les cellules sont ensuite incubées dans les mêmes conditions de température et d'agitation.



**Figure 12** : Courbe de croissance des cultures de *S. aureus* HG001 cultivées en condition oxydante dont la queuosine est réstaurée par l'ajout de preQ<sub>1</sub>.

## 3. Analyse par NanoLC-MS/MS de l'ARNr 16S



Denaturing polyacrylamide gel

**Figure 13 : Adaptation de la méthode NanoLC-MS/MS à l'analyse des ARNr.** Brièvement, une partie ciblée de l'ARN est protégée par hybridation d'un oligodésoxynucléotide puis digérée avec la RNAse T1. Le duplexe ARN-ADN est ensuite séparé sur gel de polyacrylamide dénaturant avant une seconde digestion à la RNaseT1 et analyse NanoLC-MS/MS.

L'analyse est réalisée à partir d'ARNt totaux, préparés comme publié précédemment (*cf* § II. 2). 10 µg d'ARN totaux sont dénaturés en présence de l'oligonucléotide (**tableau 2**)dans un tampon cacodylate 10 mM ; 50 mM NaCl ; 25 mM KCl à 90°C pendant 5 min puis renaturés avec l'oligonucléotide d'ADN dans la glace pendant 30 min. L'ARN non protégé est ensuite digéré avec la RNase T1 à 37°C pendant 2h (100 mM Acétate d'ammonium). Les échantillons sont ensuite déposés sur gel de polyacrylamide 10%, 8M urée et migrés dans le TBE pendant 2h à10W constants.

Les ARN sont révélés par bromure d'éthidium, les bandes de gel sont découpées puis les ARN sont digérés en gel et analysés par NanoLC-MS/MS comme publié précédemment ((*cf* § II. 1).

## 4. Analyse transcriptomique

Les triplicats d'ARN totaux sont extraits suivant les protocoles publiés précédemment (cf § II. 2.). Brièvement, les cultures sont centrifugées à 3750 rpm et 4°C pendant 15min puis les cellules sont resuspendues dans 1mL de solution RNA Pro (MP biomedicals) et lysées mécaniquement au fastprep (MP biomedical) 2 fois 40s à vitesse maximale. Les ARN totaux sont extraits au chloroforme, puis précipités à l'éthanol et traités avec 1U de DNase I par  $\mu g$ d'acides nucléigues (estimés par mesure de l'absorbance à 260nm) pendant 45min à 37°C DNase est éliminée sans agitation. La par une nouvelle extraction ลม phénol/chloroforme/alcool isoamylique et les ARN sont précipités à l'éthanol. La concentration et la pureté des acides nucléiques sont mesurées par nanodrop avant la préparation des librairies et séquençage par la plateforme EpiRNA-Seq de Nancy. Les données sont traitées avec Galaxy comme détaillé dans (Lalaouna et al., 2018) pour l'élimination des séquences des adaptateurs, le seuil de qualité, l'alignement sur le génome et le comptage des reads par feature annotée. Pour l'analyse différentielle, Deseq2 est utilisé.

## 5. Analyse protéomique

Les triplicats de protéines totales sont extraits de cellules resuspendues dans le tampon 50 mM Tris pH 8, 50 mM NaCl, 1% triton × 100 et lysée 40s au fastprep. Le dosage des protéines est réalisé par Bradford, les protéines (5 µg) sont précipitées au méthanol contenant 0,1 M d'acétate d'ammonium, puis réduites et alkylées (5 mM DTT, 10 mM iodoacetamide). Les protéines sont ensuite digérées à la trypsine puis les peptides (1µg) sont analysées par NanoLC-MS/MS sur un système NanoLC-2DPlus system couplé à un spectromètre de masse TripleTOF 5600 (ABSciex) (Chicher *et al.*, 2015).

#### 6. Gel d'acide phénylboronique et Northern blot

Les gels de polyacrylamide contenant de l'acide phénylboronique ont été réalisées suivant les protocoles établis (Matuszek and Pan, 2019). Les ARN totaux (2µg) préalablement déacylés sont séparés sur gel de polyacrylamide, 12%, 8M urée, 0,5% APB pendant 3h30 à 13W constant. Les ARN sont ensuite transférés sur membrane de nitrocellulose Hybond N+ (GE Healthcare Life Sciences) par transfert semi-sec pendant 45 min à 10V (Trans-Blot semidry transfert cell, Biorad) et fixés par crosslink UV (Stratalinker 1800, Statagene). Les ARNt sont révélés par hybridation d'une sonde marquée au 32P (**Tableau 2**) et visualisés par autoradiographie.

## 7. Purification des ARNt

Les ARNt sont obtenus à partir d'extraits d'ARN totaux par filtration sur centricons 50 kDa (Amicon Ultra 0,5 mL, Millipore), 20 µg d'ARN total est déposé sur la membrane puis centrifugé 10 min, à 9000 rpm et température ambiante. Le filtrat est immédiatement précipité à -20°C durant la nuit avec 3 volumes d'éthanol contenant 0,1 M d'acétate d'ammonium. Après centrifugation 10 min à 13000 rpm et 4°C, le culot est rincé, séché puis repris dans 50 µL d'eau milliQ. 200 µL de résine streptavidine-sépharose sont préalablement incubée avec 400 µL de sonde spécifique biotinylée (7.5 µM) durant 30min à température ambiante puis rincée avec 400 µL de tampon (10mM Tris, HCl pH 7.5). Les ARNt sont incubés avec la résine streptavidine-sonde en présence de 900 mM de TEA-Cl et 0,1 mM d'EDTA pendant 5 min à 37°C. La résine est ensuite rincée 3 fois avec 400 µL de tampon. L'ARNt hybridé à la sonde est élué par chauffage à 60°C pendant 5 min suivi d'une centrifugation rapide (10 s, 13000 rpm, température ambiante). L'ARNt purifié est ensuite concentré par précipitation à l'éthanol (Yokogawa *et al.*, 2010).

#### 8. Digestion à la RNAse U2 des ARNt purifiés.

La digestion des ARNt à la RNase U2 a été réalisée selon une adaptation de la méthode préalablement publiée (Wolff *et al.*, 2020). Brièvement, 20 ng d'ARNt purifié sont digérés avec 6 ng de RNase U2 produite au laboratoire dans 20 µL d'acétate d'ammonium 100mM à 37°C pendant 2h.

## 9. Modèlisation des structures de QueE et QueF de S. aureus

QueE et QueF *de S. aureus* ont été modélisées par homologie à l'aide du serveur tRosetta (Yang et al., 2020). L'alignement sur les modèles est amélioré par la réalisation d'alignement de séquence multiples (MSA : Multiple Sequence Alignment) utilisant les 1500 séquences disponibles pour chacune des deux protéines. Elles ont toutes deux été estimées comme étant de très haute confiance, avec des TM scores estimés de 0,91 pour QueE et 0,849 pour QueF. Le TM-score est une mesure permettant d'évaluer la similarité topologique des structures de protéines. Les valeurs de TM-score se situent entre 0 et 1, où 1 indique une parfaite correspondance entre deux structures. Les structures utilisées pour modéliser QueE sont les fichiers pdb 5TH5 (*B. subtilis*), 6NHL (*E. coli*), 4NJJ et 4NJH (*Burkholderia multivorans*). Celles utilisées pour modeliser QueF sont les fichiers pdb 4FGC, 4F8B et 5UDG (*B. subtilis*), 3S19 et 3UXJ (*Vibrio cholerae*).

#### 10. Ribosome profiling à haute résolution

Les bactéries sont cultivées comme décrit précédemment. Les cultures (30 mL) sont congelées directement dans l'azote liquide avec le tampon de lyse (20mM Tris, HCl pH8; 150mM MgCl<sub>2</sub>; 100 mM NH<sub>4</sub>Cl; 5 mM CaCl<sub>2</sub>; 0,1% NP40; 0,4%triton X100; 100 U de DNasel/mL de culture). Les billes de cellules congelées sont ensuite lysées au Fastprep 5 x 40s à vitesse maximale en présence de billes en acier. Les lysats sont ensuite décongelés 1 h à température ambiante et directement centrifugés 20 min à 3750 rpm, 4°C. Le surnageant est clarifié par une deuxième centrifugation, à 8000rpm, 4°C pendant 20 min avant d'être déposé sur 4mL de coussin de sucrose (20 mM Tris HCl, pH8 ; 10 mM MgCl<sub>2</sub>; 0.5 M NH<sub>4</sub>Cl ; 0,5 mM EDTA ; 1,1M sucrose), puis ultracentrifugé 45000 rpm, 4°C, 3h30. Le culot est repris dans un tampon de resuspension (20 mM Tris HCl pH8 ; 10 mM MgCl<sub>2</sub>; 5 mM CaCl<sub>2</sub>; 0,1% NP40, 0,4% triton X100 ; 1 mM chloramphénicol) avant la digestion, ici à la MNase : 25 mM CaCl<sub>2</sub> ; 1000U MNase ; incubation à 25°C, 1 h, 1400 rpm. La digestion est arrêtée par l'ajout d'EGTA puis l'échantillon est déposé sur gradient de sucrose (5-50% ; 20 mM Tris, HCL pH7,5 ; 100mM NH<sub>4</sub>Cl ; 10 mM MgCl<sub>2</sub> ; 1mM DTT) et ultracentrifugé à 39000 rpm 4°C pendant 2h46. Les ribosomes 70S sont récupérés, les ARN sont extraits par phénol chaud, précipités puis déposés sur gel de polyacrylamide afin de purifier sur gel les fragments correspondant à une taille d'environ 28 nt et les séquencer. En parallèle, une partie de la culture est gardée pour réaliser l'analyse transcriptomique. Le traitement informatique des données de séquençage est réalisé en collaboration avec Béatrice Chane-Woon-Ming suivant la pipeline développée par Mohammad en 2019 (Mohammad and Buskirk, 2019).

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## Annexes

## Annexe 1 : Tableau de la transcription différentielle durant le stress oxydant

Seuls les adjp<0,05 ont été conservés

	UP regulated genes from the differencial transcriptomic	cs analysis in oxidati	ve stress		
id gene	product	locus_tag_NCTC832	5 gene_NCTC8325	log2FoldChange	padj
HG001_01893 -	single-strand DNA-binding protein, phage	SAOUHSC_02071	The second se	5,424	2,51E-104
HG001_01054 carB	Carbamoyl-phosphate synthase large chain	SAOUHSC_01170	carB	5,412	9,50E-104
HG001_01052 pyrc	Phase protein	SAOUHSC_01168	pyrc	5,305	3 29E-106
HG001 01055 pyrF	Orotidine 5'-phosphate decarboxylase	SAOUHSC 01171	12	5,29	3,09E-126
HG001_01053 carA	Carbamoyl-phosphate synthase small chain	SAOUHSC_01169	1	5,282	6,93E-63
HG001_01903 -	Putative phage protein	SAOUHSC_02081	21	5,257	6,13E-84
HG001_01051 pyrB	Aspartate carbamoyltransferase	SAOUHSC_01166	pyrB	5,174	1,60E-52
HG001_01904 -	Putative phage regulatory protein	SAOUHSC_02083	#1	5,132	1,51E-76
HG001_01895 -	Bacteriophage Mu Gam like protein	SAOUHSC 02003	-	5,120	1.86E-101
HG001 01898 -	Phage protein	SAOUHSC 02076		5,035	5,50E-64
HG001_01902 -	Phage antirepressor protein KilAC domain protein	SAOUHSC_02080		5,024	1,44E-91
HG001_01887 -	Phage protein	SAOUHSC_02065	5	5,004	2,05E-91
HG001_01885 -	Phage protein	SAOUHSC_02063	20	4,979	1,29E-122
HG001_01888 -	Putative phage protein	SAOUHSC_02066	el Solar	4,979	1,64E-111
HG001_01056 pyrE	Drotate prosphoribosyltransferase Phase protein	SADUHSC_01172	pyre	4,966	1,35E-105 3.02E-104
HG001_01889 dnaC 2	Replicative DNA helicase	SAOUHSC 02067		4,923	1.18E-111
HG001_01884 -	Putative phage regulatory protein; Helix-turn-helix domain protein	SAOUHSC_02062	÷.	4,889	3,62E-92
HG001_01883 -	Phage protein; PVL ORF-50-like family protein	SAOUHSC_02061	<b>T</b> .(	4,886	5,90E-94
HG001_01900 -	Phage protein	SAOUHSC_02078	73	4,885	1,40E-93
HG001_01890 -	Phage protein	SAOUHSC_02068	5	4,868	6,99E-99
HG001_02016 -	Phage protein	SAOUHSC_02213		4,855	1 70E 99
HG001_01901 -	Putative phase protein	SAOUHSC 02079		4,833	2.42E-107
HG001 01050 pyrP	Uracil permease	SAOUHSC 01165	23	4,807	5,14E-46
HG001_01875 -	Transcriptional activator RinB (phage)	SAOUHSC_02053	8	4,754	1,21E-118
HG001_01868 -	Putative phage protein	SAOUHSC_02046	#1	4,732	3,62E-66
HG001_01880 -	Putative phage protein	SAOUHSC_02058	*1	4,7	1,30E-90
HG001_01881 -	Phage protein	SAOUHSC_02059	<b>T</b> .(	4,698	4,55E-98
HG001_01876 -	Phage protein	SADUHSC 02048	5	4,694	1,57E-79 8,91E-80
HG001 01882 -	Phage protein	SAOUHSC 02060		4,659	8,31E-112
HG001_01869 -	Phage Mu protein F like protein	SAOUHSC_02047	9	4,631	3,92E-79
HG001_01899 -	Phage protein	SAOUHSC_02077	2 <sup>2</sup>	4,597	2,32E-83
HG001_01873 -	Transcriptional activator, phage-associated	SAOUHSC_02051	20	4,538	9,07E-91
HG001_01878 -	Putative phage protein	SAOUHSC_02056	8	4,536	2,16E-83
HG001_02037 -	Putative phage regulatory protein	SAOUHSC_02234		4,486	4,16E-70
HG001_01874 -	Phage protein	SAOUHSC 02052	*	4,417	5.03E-104
HG001_01383 -	Phage protein	SAOUHSC_01550		4,412	8,41E-68
HG001_02034 -	AntA/AntB antirepressor	SAOUHSC_02229		4,402	3,05E-86
HG001_02036 -	Putative phage regulatory protein	SAOUHSC_02233	2	4,382	3,67E-72
HG001_01877 -	Phage protein	SAOUHSC_02055		4,379	1,19E-87
HG001_02/2/ glpE_3	Thiosultate sulturtransferase GIpE Recipicatory pitrate reductors 1 beta chain	SAOUHSC_03024	-1 	4,351	4,32E-96
HG001_02433 narH HG001_02432 narW	nutative nitrate reductase in beta chain nutative nitrate reductase molybdenum cofactor assembly chaperone NarW	SAOUHSC_02680		4,276	4 39E-52
HG001_01897 -	Phage protein	SAOUHSC_02075	÷.	4,223	3,08E-83
HG001_01866 -	Phage capsid family protein	SAOUHSC_02043	<u>*</u>	4,199	1,95E-57
HG001_02033 -	Phage antirepressor protein KiIAC domain protein	SAOUHSC_02229	<b>T</b> .	4,185	1,60E-83
HG001_01867 -	Putative phage head protein	SAOUHSC_02044	21	4,145	1,63E-61
HG001_01871 -	Phage terminase large subunit	SAOUHSC_02049		4,14	4,87E-53
HG001_01863 -	Phage protein	SADUHSC_02042	8	4,118	9,34E-51
HG001 02023 -	Putative phage protein	SAOUHSC 02219	2	4,043	5.11E-85
HG001_01222 dinB_1	DNA polymerase IV	SAOUHSC_01363	MucB	4,037	1,46E-55
HG001_01858 -	Phage protein	SAOUHSC_02034	•	3,98	5,86E-61
HG001_02031 -	Putative phage protein	SAOUHSC_02227	10 A	3,978	1,83E-46
HG001_02029 -	Phage protein	SAOUHSC_02225	<u>#2</u>	3,977	4,57E-80
HG001_02025 -	Phage protein	SAOUHSC_02221	18 - 1	3,951	6,11E-88
HG001_01801 -	Putative phage protein	SAOUHSC 02214		3,883	2.85E-46
HG001_02028 -	Phage protein	SAOUHSC_02224		3,848	6,04E-45
HG001_01386 -	Phage protein; PVL orf 52-like protein; Phage phi 11 orf23 protein homolog	SAOUHSC_01553		3,847	2,70E-63
HG001_02024 -	Putative phage ssDNA binding protein	SAOUHSC_02220		3,831	7,83E-62
HG001_01860 -	Phage major tail protein 2	SAOUHSC_02036	-	3,821	7,08E-64
HG001_00085 deoD	Purine nucleoside phosphorylase DeoD-type	SAOUHSC_00097	** 	3,814	5,29E-33
HG001_02026 -	Respiratory pitrate reductase 1 alpha chain	SACOHSC_02222	-	3,813	2,0/E-05
HG001 01859 -	Phage protein	SAOUHSC 02035		3,769	1,37E-55
HG001_01862 -	Phage protein	SAOUHSC_02038	-	3,765	3,25E-54
HG001_01872 -	Terminase small subunit	SAOUHSC_02050		3,652	1,14E-36
HG001_00308 -	HTH-type transcriptional regulator	SAOUHSC_00347	1	3,647	5,13E-32
HG001_02027 -	Phage protein	SAOUHSC_02223	1	3,634	5,40E-53
HG001_01057 -	nypotnetical protein; same operon as pyrP-pyrB-pyrC-carA-carB-pyrF-pyrE	5AUUHSC_01173		3,505	8,10E-45

HG001 01200 -	hypothetical protein	SAOUHSC 01334	-	3,4	1,30E-23
HG001_02435 nasF	Uroporphyrinogen-III C-methyltransferase	SAOUHSC_02682		3,396	5,44E-37
HG001_02020 -	Phage protein	SAOUHSC_02217	-	3,323	8,20E-54
HG001_02436 nasE	Assimilatory nitrite reductase [NAD(P)H] small subunit	SAOUHSC_02683	2	3,321	1,65E-29
HG001_01343 -	Ferredoxin	SAOUHSC_01504		3,316	6,98E-40
HG001_01214 parC	DNA topoisomerase 4 subunit A	SAOUHSC_01352	2	3,261	8,08E-45
HG001_02246 aldC_1	Alpha-acetolactate decarboxylase	SAOUHSC_02467	+	3,236	1,69E-21
HG001_02437 nasD	Nitrite reductase [NAD(P)H]	SAOUHSC_02684	8	3,201	1,42E-25
HG001 02431 narX	Nitrate reductase-like protein NarX	SAOUHSC 02678		3,187	3,92E-36
HG001 01911 queE 2	7-carboxy-7-deazaguanine synthase	SAOUHSC 02090	-	3,185	6,19E-61
HG001_01856 -	Phage tail protein	SAOUHSC 02031		3,181	1,69E-41
HG001 01857 -	hypothetical protein	SAOUHSC 02033		3,18	1,86E-38
HG001 01855 -	Prophage endopeptidase tail	SAOUHSC 02030	2	3,152	4,30E-43
HG001 02018 -	hypothetical protein	SAOUHSC 02215	8	3,119	2,24E-22
HG001 02019 dnaC 3	DNA replication protein DnaC	SAOUHSC 02216	2	3,094	7,15E-45
HG001 00086 norB 2	Quinolone resistance protein NorB	SAOUHSC 00099	2	3,013	7,19E-23
HG001 01521 der 3	GTPase Der	SAOUHSC 01700		3.006	2.85E-48
HG001 02629 pvrD	Dihydroorotate dehydrogenase (guinone)	SAOUHSC 02909	2	2,959	6.09E-08
HG001 01213 parE	DNA topoisomerase 4 subunit B	SAOUHSC 01351		2,931	2,91E-45
HG001 00807 argH1	Argininosuccinate lyase 1	SAOUHSC 00898	-	2.89	2.12E-24
HG001 02429 preB	Oxygen sensor histidine kinase NreB	SAOUHSC 02676	-	2.863	7.06112E-32
HG001 02609 isaA	putative transelycosylase IsaA precursor	SAOUHSC 02887		2.863	2.63E-30
HG001 01522 gph 2	Phosphoglycolate phosphatase	SAOUHSC 01701	2	2.849	2.29E-45
HG001 01854 -	hypothetical protein	SADUHSC 02029	8	2 844	3 92F-38
HG001_02014 -	PVI ORE-50-like family protein	SACUHSC 02211		2 814	1 25E-27
HG001_02166_dos	General stress protein 201	SADUHSC 02381		2 778	1.86E-35
HG001_01384 -	hunothetical protein	SAOUHSC 01551	÷.	2,770	2 916-22
HG001_02493	LIDE durate d'animetate	SAOUHSC 02727		2,772	2,510-22
HG001_02015 -	hunsthatical protein	SAOUHSC 022137	÷	2,702	1 416-24
HC001_01530 areF	Shikimata debudeaganasa	5A00H5C_02212		2,70	2 565 43
HG001_01520 afte	Clumping factor B programs	SAOUHSC 02053	-	2,724	5,500-42
HG001_02009 CHB	Nucleare CharD suburit C	SAUUHSC_02903	Č	2,090	0,720-44
HG001_01206 SDCC	Nuclease Socco subunit c	SAUUHSC_01543	3	2,692	2,90E-40
HG001_01518 had0	putative nicounate-nucleotide adenyiyitransferase	SAUCHSC_01097	8	2,659	1,10E-38
HG001_02247 alss	Acetolactate synthase	SAOUHSC_02468		2,641	1,58E-14
HG001_01250 ynes_1	putative ABC transporter ATP-binding protein mes	SAOUHSC_01392	Č.	2,602	3,13E-29
HG001_01519 ynby	KNA-binding protein YnbY	SAOUHSC_01698		2,596	2,07E-30
HG001_02438 shfC (nirR)	Sirohydrochlorin ferrochelatase	SAOUHSC_02685	-	2,585	3,49591E-19
HG001_00937 ythB	Putative cytochrome bd menaquinol oxidase subunit II	SAOUHSC_01032	8	2,584	6,91E-23
HG001_02430 -	hypothetical protein	SAOUHSC_02677	* 22	2,549	5,64788E-26
HG001_00670 nrdF	Ribonucleoside-diphosphate reductase subunit beta	SAOUHSC_00743	nrdF	2,532	5,81E-22
HG001_02428 nreC	Oxygen regulatory protein NreC	SAOUHSC_02675	2	2,512	1,59E-30
HG001_02340 hpxO	FAD-dependent urate hydroxylase	SAOUHSC_02579	÷.	2,511	2,42E-33
HG001_01853 -	hypothetical protein	SAOUHSC_02028		2,508	1,17E-27
HG001_02654 -	anaerobic ribonucleotide reductase-activating protein	SAOUHSC_02941	-	2,491	2,99E-23
HG001_02108 -	putative DEAD-box ATP-dependent RNA helicase	SAOUHSC_02316	*	2,477	6,34E-27
HG001_01682 bioB_1	Biotin synthase	SAOUHSC_01877	-	2,453	3,48E-34
HG001_02013 -	hypothetical protein	SAOUHSC_02210	8	2,441	8,25E-18
HG001_02657 p2d	Precorrin-2 dehydrogenase	SAOUHSC_02945	3	2,411	1,29E-19
HG001_00491 azo1	FMN-dependent NADPH-azoreductase	SAOUHSC_00543	*	2,408	5,19E-17
HG001_02655 nrdD	Anaerobic ribonucleoside-triphosphate reductase	SAOUHSC_02942	-	2,407	8,69E-18
HG001_02154 pyrG	CTP synthase	SAOUHSC_02368	pyrG	2,393	8,99E-22
HG001_01107 rpsB	30S ribosomal protein S2	10 C		2,389	2,03E-27
HG001_02006 -	hypothetical protein	SAOUHSC_02203		2,385	7,01E-22
HG001_00082 sodM	Superoxide dismutase [Mn/Fe] 2	SAOUHSC_00093	2	2,372	1,32E-34
HG001_01850 -	hypothetical protein	SAOUHSC_02025	-	2,354	1,71E-19
HG001_01523 mtnN	5'-methylthioadenosine/S-adenosylhomocysteine nucleosidase	SAOUHSC_01702	2	2,349	3,00E-29
HG001_01517 -	putative nicotinate-nucleotide adenylyltransferase	SAOUHSC_01696	2	2,346	1,82E-24
HG001_01925 cobQ	Cobyric acid synthase	SAOUHSC_02106		2,329	1,16E-29
HG001_01852 -	hypothetical protein	SAOUHSC_02027	*	2,308	6,85E-22
HG001_01092 rplS	50S ribosomal protein L19	SAOUHSC_01211	rplS	2,297	5,73E-24
HG001_02041_xerC_3	Tyrosine recombinase XerC	SAOUHSC 02239	-	2,297	9,53E-19
HG001 02042 hlb 2	Phospholipase C precursor		-	2,281	6,98E-20
HG001_01215 alsT_2	Amino-acid carrier protein AlsT	SAOUHSC 01354	-	2,273	1,10E-25
HG001 00139 ptsG 1	PTS system glucose-specific EIICBA component	SAOUHSC 00155	2	2,27	2,96E-05
HG001 00019 purA	Adenvlosuccinate synthetase	SAOUHSC 00019	1	2,259	4,52562E-15
HG001 01765 hemY	Protoporphyrinogen oxidase	SAOUHSC 01960	2	2,248	1,57E-18
HG001_01766 hemH	Ferrochelatase	SAOUHSC 01961	hemH	2,233	2.42E-24
HG001 01941 -	Trp repressor protein	SAOUHSC 02125	-	2,207	2,38E-13
HG001 01851 -	hypothetical protein	SADUHSC 02026	-	2,195	1,41E-12
HG001 01137 recA	Protein RecA	SADUHSC 01262	recA	2,189	1.32F-20
HG001 01939 pcrA	ATP-dependent DNA helicase PcrA	SAOUHSC 02123	-	2.184	7,32F-27
HG001 02012 -	YopX protein	SADUHSC 02209		2 168	1.58E-10
HG001 00951 vdcV	Inner membrane ABC transporter permease protein YdrV	SAOUHSC 01048	-	2 155	1,25E-14
HG001_02145_prfA	Pentide chain release factor 1	SACUHSC 02359	prfA	2 153	1.46E-22
HG001_02424 parT	putative nitrate transporter NarT	SACUHSC 02671	- Prim	2,133	0.000554699
HG001_00808_are6	Argininosuccinate synthese	SACUHSC 00800	2	2,140	7.776.13
HG001_02005 -	Transcriptional activator RinB	SACUHSC 02202	2	2,134	1.465-00
HG001 01910 verC 3	Tyrosine recombinase XerC	SACILIESC 02020		2,123	6 78F-15
HG001_00512 -	hypothetical protein	SADUHSC 00567		2,121	2 /35-16
	of hearing and hearing	34000130_00307	~	2,106	2,430-10

HG001 00659 recQ 1	ATP-dependent DNA helicase RecQ	SAOUHSC 00730	1.5.1	2,104	4,16E-29
HG001 02008 -	dUTPase	SAOUHSC 02205		2.103	8.88E-15
UC001_02144 ====C	Palance faster alutanias math itrae faster	SACULIES 02250		2,009	0,000 10
H0001_02144 princ	Release factor glocarrine methylcransierase	3A00H3C_02338		2,058	5,520-16
HG001_02009 -	hypothetical protein	SAOUHSC_02206		2,09	9,66E-13
HG001_02004 -	hypothetical protein	-	S # 3	2,09	1,02E-11
HG001 00002 dnaN	DNA polymerase III subunit beta	SAOUHSC 00002	649	2.088	1.57E-20
HG001 02256 tout	tRNA pseudouridina synthese A	SAOLIHSC 02480	truA	2.083	4 316-35
10001_02250 004	united pseudourionite synchrase A	34001130_02480	tion.	2,005	9,510-25
HG001_01957 -	YolD-like protein	SADUHSC_02144	( # )	2,078	2,48E-10
HG001_02123 sceD	putative transglycosylase SceD precursor	SAOUHSC_02333		2,071	1,77E-15
HG001 02003 -	hypothetical protein	SAOUHSC 02200		2.062	4.14E-12
HG001 03007	hypothetical protein	54000050 02204		2.061	2 575 10
H0001_02007 -	hypothetical protein	3A00H3C_02204		2,001	5,520-10
HG001_02658 cysJ	Sulfite reductase [NADPH] flavoprotein alpha-component	SAOUHSC_02947		2,056	7,70E-15
HG001 02411 -	hypothetical protein	SAOUHSC 02656	121	2,046	8,86E-17
HG001_01184_pucH	Thermonuclease precursor	SAOUHSC 01316	121	2 044	5 01E-13
ucool ocore		Shouling poord		2,010	1.045.14
HG001_00878 -	nypotnetical protein	SAUUHSC_00964	0.000	2,018	1,046-14
HG001_00959 typA	GTP-binding protein TypA/BipA	SAOUHSC_01058		2,012	4,82E-20
HG001 00005 gyrB	DNA evrase subunit B	SAOUHSC 00005		2.009	9.48E-24
HC001 01938 linA	DNA	SAOLIUSC 02122	1.001	2.001	7 955.71
H0001_01938 ligh	Diverigase	3A00H3C_02122	0.63	2,001	7,031-21
HG001_00060 spa	Immunoglobulin G-binding protein A precursor	SAOUHSC_00069		1,993	1,52E-17
HG001_02155 rpoE	putative DNA-directed RNA polymerase subunit delta	SAOUHSC_02369	S#3	1,988	1,30E-24
H6001 02253 msl	305 ribosomal protein 59	SADUHSC 02477	rost	1 964	2.69E-16
UC001_01574	Cell share determining protein 35	SACULUEC 01750	. pai	1.00	2,000 20
HG001_01574 mrec	Cell shape-betermining protein Mirec precursor	2400H2C_01129		1,96	2,516-21
HG001_02750 rsmG	Ribosomal RNA small subunit methyltransferase G	SAOUHSC_03051	gidB	1,959	3,77E-16
HG001 01933 gatB 2	Aspartyl/glutamyl-tRNA(Asn/Gln) amidotransferase subunit B	SAOUHSC 02116	gatB	1,941	6,58E-17
HC001 01515 +ult41	dTDP 2 aming 28/205 didease alpha D aluconuranora N8/20N dimethyltransforana	SAOLIUSC 01694		1.04	4 695 22
110001_01313 (VIVI	urbe-stannio-stazeo-urbeoxy-alpha-o-grucopyranose wazen-urneuryitransierase	3A00H3C_01094		1,54	4,301-22
HG001_02090 -	Protein Spr1-like protein	SAOUHSC_02296	( # )	1,936	1,20E-17
HG001_02388 emrB_1	Multidrug export protein EmrB	SAOUHSC_02629	( e)	1,932	6,19E-20
HG001 02751 mpmG	tBNA uridine 5-carboxymethylaminomethyl modification enzyme MnmG	SAOUHSC 03052	Abig	1 927	2 97F-16
UC001_00411	have a the strend events in	CAOLUISC DOACE	Broot	1.035	1.565.30
HG001_00411 -	hypothetical protein	SAUUHSC_00465		1,925	1,566-20
HG001_02010 -	hypothetical protein	SAOUHSC_02207	223	1,919	2,22E-11
HG001 01203 -	hypothetical protein	SAOUHSC 01338		1.913	9.09E-14
HC001 01048 dup 3	Ribecomal Jargo subunit negudo reidino sunthara D	SAOUHSC 01162	IcoA	1.01	0 545 20
H0001_01048 H00_2	Ribosofial large suburit pseudourume synthase o	3A00H3C_01103	ispa	1,51	9,34C-20
HG001_01790 tcyC_1	L-cystine import ATP-binding protein TcyC	SAOUHSC_01990	1.21	1,898	2,77E-15
HG001 01047 IspA	Lipoprotein signal peptidase	SAOUHSC 01162	IspA	1,894	3.62E-15
HG001 01995 -	Phage capsid family protein	SAOLIHSC 02191		1 888	2 26E-10
10001_01555	ringe capital tariny procent	SACONSC_02151		1,000	2,200 10
HG001_01560 apt	Adenine phosphoribosyltransferase	SAOUHSC_01743	( # )	1,886	5,58131E-18
HG001_01791 artQ	Arginine transport system permease protein ArtQ	SAOUHSC 01991	(m)	1,882	1,63E-17
HG001_01479_zouB	High-affinity zinc untake system membrane protein ZnuB	SADUHSC 01656	1.41	1.875	5 45E-17
USOCI DEPT LIND	The second s	Shoulise_01050			1.005.10
HG001_00324 ahpc	Alkyl hydroperoxide reductase subunit L	SAOUHSC_00365	1.5	1,874	1,935-18
HG001_00067 sbnC	Staphyloferrin B synthase	SAOUHSC_00077	223	1,869	5,02E-14
HG001 00008 hutH	Histidine ammonia-lvase	SAOUHSC 00008		1.865	2.86E-15
HC001_01943_purP	Adenulosussinate lussa	SACULIESC 02126	22	1 964	5 40000F 15
H0001_01942 purb	Adenyiosuccinate lyase	3A00H3C_02120	100	1,804	0,422301-13
HG001_00372 mccB	Cystathionine gamma-lyase	SAOUHSC_00422	1.2	1,855	6,45E-15
HG001_02257 ecfT	Energy-coupling factor transporter transmembrane protein EcfT	SAOUHSC_02481	-	1,847	2,29E-16
HG001 01992 -	Phase head-tail joining protein	SAOLIHSC 02188	525	1 846	4 655-09
10001_01002	n hoge need tall joining protein	SACOUNISC_02520		1,040	2,000 10
HG001_02389 emrk	putative mutitorug resistance protein Emrk	SADUHSC_02630	1083	1,843	3,226-19
HG001_01339 -	Glucosaminate ammonia-lyase	SAOUHSC_01499		1,842	1,57E-12
HG001 02120 thiD	Hydroxymethylpyrimidine/phosphomethylpyrimidine kinase	SAOUHSC 02330	1040	1.833	1.31E-13
HC001 03453	humothatical protoin	SAOLUSC 02702		1 022	7 04F 10
H0001_02433 -	nypotietical protein	SACOHSC_02702	100	1,832	2,040-10
HG001_00468 rplA	50S ribosomal protein L1	SAOUHSC_00519	rplA	1,827	6,91E-18
HG001_01070 stp	Serine/threonine phosphatase stp	SAOUHSC 01186	1.70	1,827	1,16E-14
HG001 01573 -	rod shape-determining protein MreD	SAOUHSC 01758	2.2	1 827	1.44E-13
110001_02354		Chourise_02055		1,027	1.075.12
HG001_02754 rpmH	SUS ribosomai protein L34	SAOUHSC_03055	rpmH	1,826	1,878-12
HG001_01849 atl_3	Bifunctional autolysin precursor	SAOUHSC_02023		1,825	4,00E-18
HG001 01571 -	hypothetical protein	SAOUHSC 01756	243	1.817	9,94E-15
HG001 00351 bedM	Tune Literativities ensume EcoKIM protein	SAOLIUSC 00397	0/23	1 913	1 305.14
HG001_00331 HS0M	Type Trestriction enzyme Ecoki wiprotein	3A00H3C_00337		1,015	1,350-14
HG001_01311 ponA	Penicillin-binding protein 1AV1B	SAOUHSC_01467	recu	1,795	7,85E-17
HG001_01461 gcvT	Aminomethyltransferase	SAOUHSC_01634	gcvT	1,793	1,02E-11
HG001 01481 nfp	putative endopuclease 4	SAOUHSC 01658	-	1.788	2.77E-17
UC001 00333 abar	Alled builden and a set of stand and the set of the set	FACULUSE DODEA		1 705	7 455 47
H0001_00323 anpr	Aiky hydroperoxide reductase subdrift P	3A00H3C_00304	223	1,785	7,150-17
HG001_00712 cggR	Central glycolytic genes regulator	SAOUHSC_00794	1.7.0	1,782	2,46E-12
HG001 00363 yciC 1	Putative metal chaperone YciC	SAOUHSC 00410		1,775	2,05E-11
HG001 01691 HE	Riboflavin synthese	SACILIUSC 01888	100	1 773	3 31E-09
UCODI DIISS LED D				1 700	1 405 13
HG001_02156 BitD_2	spermine/spermidine acetyltransferase	SADUHSC_02370	0.00	1,769	1,485-12
HG001_02243 mepM_2	Murein DD-endopeptidase MepM	SAOUHSC_02464		1,768	1,58E-17
HG001 02282 rplV	505 ribosomal protein L22	SAOUHSC 02507	rplV	1.745	2.26E-15
HG001 00409 weft	nutative deoxyribonuclease VcFH	SADUHSC 00463	1	1 742	4 205.15
	Positive bedreated and a			1,743	4,250-15
HG001_01764 ydeN	Putative hydrolase YdeN	SADUHSC_01958		1,741	2,17E-11
HG001_02443 zinT	Metal-binding protein ZinT precursor	SAOUHSC_02690		1,737	8,57E-19
HG001 02022 -	hypothetical protein		<*>	1.734	1.56E-06
HC001_01624	hundhatical protein	CACULUSC 01022	058	4,700	0 000 10
10001_01034 -	nypothetical protein	SAUGHSC_01823	100	1,/23	8,68E-16
HG001_01451 cfiB_2	2-oxoglutarate carboxylase small subunit	SAOUHSC_01623		1,72	2,22E-14
HG001 01934 gatA	Glutamyl-tRNA(Gln) amidotransferase subunit A	SAOUHSC 02117	gatA	1,717	4,02E-11
H6001 01142 kor8	2-oxoglutarate oxidoreductase subunit Kore	SADUHSC 01267	a second	1 716	3 575-00
10001_01142 KOLD	2-oxoBiorarate oxidoreductase suburit Korb	3400H3C_0126/		1,/16	3,320-09
HG001_02352 yifk	putative transport protein Yifk	SAOUHSC_02590		1,709	7,42E-13
HG001_01572 rplU	50S ribosomal protein L21	SAOUHSC_01757	rplU	1,701	4,01E-16
HG001 01382 -	Transcriptional activator RinB	SAOUHSC 01549	0.00	1 701	2.86F-06
HC001_03585 while	Debuteride bieromitensis 2 kudenes 2 methodalatend ACD eventeen Dir C	SACULUSE CODES	1000	1,701	1 336 4 5
HG001_02586 pksG	Polyketide biosynthesis 3-hydroxy-3-methylglutaryl-ACP synthase PksG	SAOUHSC_02860	-	1,698	1,22E-14
HG001_02280 rplP	50S ribosomal protein L16	SAOUHSC_02505	rplP	1,696	3,18E-13

HG001_01848 -	hypothetical protein	SAOUHSC_02022		1,691	1,32E-13
HG001_02446 bdbD	Disulfide bond formation protein D precursor	SAOUHSC_02694		1,689	7,48E-17
HG001_02420 gltT	Proton/sodium-glutamate symport protein	SAOUHSC_02667		1,683	1,47E-12
HG001_02287 rplC	50S ribosomal protein L3	SAOUHSC_02512	rplC	1,68	6,59E-13
HG001 01689 ribH	6%2C7-dimethyl-8-ribityllumazine synthase	SAOUHSC 01886	ribH	1.678	1 28E-09
HG001 02258 ocfA2	Energy coupling factor transporter ATP binding protein EcfA?	SAOLIUSC 02492	chiO	1 674	5 77E 15
HG001_02238 ECIA2	Diference of the state of the s	SACUNIC 02482	COIO	1,0/4	3,770-13
HG001_00475 rpiGB	Ribosome-associated protein L/Ae-like protein	SAUUHSC_00526		1,666	1,596-10
HG001_01846 -	Bacteriophage holin	SAOUHSC_02020	- E	1,665	5,32E-14
HG001 01478 zur	Zinc-specific metallo-regulatory protein	SAOUHSC 01655	*:	1,662	5,53E-11
HG001 01926 murE 2	UDP-N-acetylmuramoyl-L-alanyl-D-glutamate2%2C6-diaminopimelate ligase	SAOUHSC 02107		1.66	3.56E-14
HC001_00252	Turna I restriction modification DNA specificity domain protoin	SAOUHSC 00308		1.66	7 105 12
HG001_00332 -	Type Trestriction modification only specificity domain protein	3A00H3C_00398		1,00	7,196-13
HG001_02284 rplB	50S ribosomal protein L2	SAOUHSC_02509	rpiB	1,654	9,54E-14
HG001_02285 rplW	50S ribosomal protein L23	SAOUHSC_02510	rplW	1,649	7,01E-12
HG001 01831 -	Putative multidrug export ATP-binding/permease protein	SAOUHSC 02003	•	1,646	2,97E-16
HG001 00941 def	Pentide deformulase	SADUHSC 01038	dof	1.644	8 36F-15
HCOOI OISIS ALU I	replace determinase	SAOULIES 01315	der	1,014	4 455 45
H0001_01535 \$100_1	putative protease moo precursor	SAUCHSC_01716	<b>7</b> .2	1,039	4,430-10
HG001_00073 sbnl	L-serine kinase	SAOUHSC_00083	Sec. 1	1,639	9,52E-15
HG001_02283 rpsS	30S ribosomal protein S19	SAOUHSC_02508	rpsS	1,639	1,08E-13
HG001 02286 rpiD	50S ribosomal protein L4	SAOUHSC 02511	rplD	1.638	1.28E-16
HG001 01096 succ	Succinul-CoA ligase [ADB-forming] subunit heta	SADUHSC 01216	SHEE	1 633	1.64E-12
UC001_01030 socc	Constitution for the second state of the secon	SACULIES DIGIS	SUCC	1,033	1,040-12
HG001_00949 potA	spermidine/putrescine import ATP-binding protein PotA	SAUUHSC_01046	-	1,63	1,100-07
HG001_02091 rpsA_2	30S ribosomal protein S1	SAOUHSC_02297		1,626	4,57E-11
HG001_02752 mnmE	tRNA modification GTPase MnmE	SAOUHSC_03053	trmE	1,624	2,36E-10
HG001 01690 ribBA	Riboflavin biosynthesis protein RibBA	SAOUHSC 01887		1.623	4.04E-09
HG001 02635 papD	Aspartate 1-decarboxylase precursor	SAOLIHSC 02916		1.615	2 74E-13
H6001_02033 pailo	Aspartate Precarboxylase precursor	SACONSC_02310	10	1,013	2,740-13
HG001_01337 CMK	Cytidyiate kinase	SAUUHSC_01496	CULK	1,612	3,25E-11
HG001_01338 ansA	putative L-asparaginase	SAOUHSC_01497	#3	1,612	4,47E-10
HG001 01631 ackA	Acetate kinase	SAOUHSC 01820	÷2	1,611	8,50E-08
HG001_01564_tet	Oueuine tRNA-ribosyltransferase	SAOUHSC 01748	tet	1 604	8 50E-13
116001_01504 (gr	Understand de de de la d	SADUNEC 02026	18.	1,004	1,245,10
HG001_02652 glob_2	Hydroxyacyigiutathione hydroiase	SAUUHSC_02936	5	1,602	1,246-10
HG001_01516 rsfS	Ribosomal silencing factor RsfS	SAOUHSC_01695		1,601	1,58E-15
HG001_00936 ythA	Putative cytochrome bd menaquinol oxidase subunit l	SAOUHSC_01031	21	1,599	1,10E-10
HG001 00773 -	hypothetical protein	SAOUHSC 00862	23	1.59	1.85E-12
HG001 01683 mmH 3	Piberomal PNA small subunit methyltransferase H	SAOLUSC 01978		1 590	2 405.07
H0001_01083 TSINH_2	Ribosoniai Rive sinaii subunit metryitransierase n	5ACOHSC_01878		1,303	3,431-07
HG001_00061 sars	HTH-type transcriptional regulator Sars	SAOUHSC_00070	* )	1,586	1,36E-13
HG001_01937 -	CamS sex pheromone cAM373 precursor	SAOUHSC_02121	÷.	1,573	4,16E-12
HG001 00496 folE2	GTP cyclohydrolase FolE2	SAOUHSC 00549	10	1,567	1,60E-14
HG001_00407_metG	MethioninetRNA ligase	SAOUHSC 00461		1 553	1 43E-11
UC001_00467 mill	EQC all an annual matrix 111	SAOLUSC 00518	mille	1 5 4 5	3 055 13
HG001_00467 rpik	SUS ribosomai protein L11	SAUCHSC_00518	<b>FDIK</b>	1,545	3,856-12
HG001_02560 catE_2	Catechol-2%2C3-dioxygenase	SAOUHSC_02828	52	1,542	9,12E-13
HG001_00071 sbnG	Citrate synthase	SAOUHSC_00081		1,542	1,07E-11
HG001 02279 rpmC	50S ribosomal protein L29	SAOUHSC 02504		1.541	8.58E-15
HG001 00697 IN/CA	LbrABC system protein A	SADUUSC 00780	mrA.	1.54	4 126.15
HG001_00037 UNA	Service system protein A	SACONSC_00780	UVIN	1,34	4,120-15
HG001_01735 -	ECOKI restriction-modification system protein Hsds	SAGOHSC_01932		1,538	1,516-11
HG001_00879 -	CAAX amino terminal protease self- immunity	SAOUHSC_00965	*	1,531	1,49E-11
HG001 01158 -	methionine gamma-lyase	SAOUHSC 01284	÷.	1,53	1,45E-11
HG001 00469 -	110 leader			1 525	3 10E-11
HG001 03344	nutative hydrolase	SADULISC DOMES		1 517	A AGE 11
HG001_02244 -	putative nyurolase	5A00H5C_02465	20	1,517	4,400-11
HG001_00068 sbnD	Staphyloferrin B export protein	SAOUHSC_00078	53 C	1,513	6,73E-11
HG001_02109 murF	UDP-N-acetylmuramoyl-tripeptideD-alanyl-D-alanine ligase	SAOUHSC_02317	5. C	1,513	4,28E-10
HG001 02278 rpsQ	30S ribosomal protein S17	SAOUHSC 02503	rpsQ	1,509	1,53E-11
HG001 02423 -	Acid shock protein	SADUHSC 02670	1.000	1 507	4 26E-08
UC001_02423	1D must be shell 2 montanelle 2 de ser alaba D ali san ana selda de ser dava	Shouling parro		1,507	1,200.00
HG001_00497 msnB	ID-myo-inositoi z-acetamioo-z-oeoxy-aipna-D-giucopyranoside deacetylase	SAUUHSC_00550	• :	1,502	1,24E-10
HG001_01499 rpsU	305 ribosomal protein S21	SAOUHSC_01678	rpsU	1,501	4,82E-13
HG001_02255 -	L13_leader	Contract the second second	+	1,496	3,25E-09
HG001 02148 -	hypothetical protein	SAOUHSC 02362	rho	1.484	3.13E-11
HG001 00867 prfC	Pentide chain release factor 3	SADUHSC 00956	nrfC	1 483	3 26E-10
UC001_02430 utml	evitation N escale Areas France View	SAOLUISC DOSSO	price	1,403	7 715 00
HG001_02439 ytmi	putative in-acetyltransferase film	SAUUHSC_02086	Deener	1,482	7,31E-09
HG001_01767 hemE	Uroporphyrinogen decarboxylase	SAOUHSC_01962	hemE	1,478	5,45E-13
HG001_00072 sbnH	2-[(L-alanin-3-ylcarbamoyl)methyl]-2-hydroxybutanedioate decarboxylase	SAOUHSC_00082	<b>1</b> .	1,477	1,97E-12
HG001_00066_sbnB	N-I(2S)-2-amino-2-carboxyethyll-L-elutamate dehydrogenase	SAOUHSC 00076		1 472	9.94E-09
HC001_00365	alaba/hata hudrolase fold eretein	SAOUHSC 00201		1 471	1.676.10
HG001_00263 -	alpha/beta nyurolase lolu protein	SACOHSC_00501		1,471	1,576-10
HG001_02119 thiM	Hydroxyethylthiazole kinase	SAOUHSC_02329	4 C	1,471	1,52E-07
HG001_01844 -	putative sapT prophage toxin	SAOUHSC_02018	÷0	1,468	1,33E-09
HG001 01792 -	Phosphotransferase system%2C EIIC	SAOUHSC 01992	÷3	1,457	1,70E-10
HG001 01994 -	hypothetical protein	SAOUHSC 02190		1 454	1.78F-05
HC001 02201 town	DNA teneirometrica 2	SACULUSC COSE17	2	1 454	2 355 14
HOOOT_OXXAT TODR	Drive topolsoinerase 5	SAUUHSC_02517	<b>7</b> .	1,451	3,33E-11
HG001_01905 immR_1	HTH-type transcriptional regulator ImmR	SAOUHSC_02084	<del>.</del> .	1,451	2,38E-10
HG001_00069 sbnE	L-2,3-diaminopropanoatecitrate ligase	SAOUHSC_00079	21	1,444	3,86E-09
HG001 02288 rpsJ	30S ribosomal protein S10	SAOUHSC 02512a	-	1.443	8,05E-09
HG001_02636_paper	Pantothenate synthetase	SADUHSC 02019	nanC	1.441	2 495-13
ucool_ozoso pane	Channel Marine Synthetidate	SACONSC_02918	Paric	1,441	2,400-12
HG001_01151 glpK	Giycerol kinase	SAUUHSC_01276	gipk	1,438	2,14E-09
HG001_02157 coaW	Type II pantothenate kinase	SAOUHSC_02371	÷.	1,438	9,09E-08
HG001_01071 prkC	Serine/threonine-protein kinase PrkC	SAOUHSC_01187	23	1,431	5,41E-10
HG001 01514 comEA	ComE operon protein 1	SAOUHSC 01693	-	1.43	2.04E-08
HC001 01210	Halliday junction resolvane Rect L	SAOLUSC OTACC	racit	1 420	2 245 00
10001_01510 reco	nonday junction resolvase neco	SAUUHSC_01406	ICCU	1,426	2,340.09
HG001_00811 spsB_1	signal peptidase IB	SAUUHSC_00902	· Avera	1,425	2,71E-08
HG001_02277 rplN	50S ribosomal protein L14	SAOUHSC_02502	rpIN	1,424	1,72E-12
HG001_02682 -	ABC-2 family transporter protein	SAOUHSC 02978	51	1,424	9,24E-12
				1.000.000	

HG001 00819 -	hypothetical protein	SADUHSC D	0910	2	1.422	2 80F-12
HG001_01653_fbc	Estrato, totrabudrofolata ligana	SAOUHSC O	1045		1,410	1 145 00
HG001_01033 HIS	ATD dependent Cla pentage ATD binding submit ClaV	SAOUHICC O	1770	-l-N	1,419	1,140-09
HG001_01591 cibx	AiP-dependent Cip protease AiP-binding subunit Cipx	SAOUHSC_U	1778	cipx	1,418	4,48E-1Z
HG001_00197 tagF	CDP-glycerol:poly(glycerophosphate) glycerophosphotransferase	SAOUHSC_0	0223	•	1,417	2,29E-11
HG001_01635 thil	putative tRNA sulfurtransferase	SAOUHSC_0	1824	5	1,415	1,03E-11
HG001_01482 cshB	DEAD-box ATP-dependent RNA helicase CshB	SAOUHSC_0	1659	5	1,413	2,29E-11
HG001_01736 -	putative type I restriction enzymeP M protein	SAOUHSC_0	1933		1,412	3,19E-09
HG001_01091 trmD	tRNA (guanine-N(1)-)-methyltransferase	SAOUHSC_0	1210	trmD	1,409	2,36E-10
HG001_01645 ptsG_4	PTS system glucose-specific EIICBA component	SAOUHSC_0	1836	-	1,409	2,85E-07
HG001_00950 pot8	Spermidine/putrescine transport system permease protein PotB	SAOUHSC_0	1047	2	1,408	1,02E-06
HG001 02275 rplE	50S ribosomal protein L5	SAOUHSC 0	2500	rplE	1,402	2.21E-11
HG001 00155 azoR	EMN-dependent NADH-azoreductase	SAQUHSC 0	0173		1.402	1.59E-10
HG001 01204 -	hypothetical protein	SAOUHSC 0	1340	-	1.402	1.01E-08
HG001 00517 -	nutative heme perovidase	SADUHSC 0	0573		1 396	2 01E-11
HG001 01993 -	Phase and like head tail connector protein	SAOUHSC O	2180		1 303	0.002756727
HG001_02276 mlV	505 ribosomal protein 174	SAOUHSC 0	2501	rolV.	1 30	1 755-10
HC001_02270 TPIX	Trigger factor	SAOUHSC 0	1770	tia	1,00	0.405.11
HG001_01592 tig	Inger lactor	SAOUHSC_0	2179	LIB	1,307	9,400-11
HG001_01940 pcrb	Heptaprenyigiyceryi prosphate synthase	SAUUHSC_0	2124	3	1,381	3,78E-08
HG001_01085 smc	Chromosome partition protein Smc	SAOUHSC_0	1204		1,379	4,98E-11
HG001_01141 korA	2-oxoglutarate oxidoreductase subunit KorA	SAOUHSC_0	1266	-	1,372	3,35E-06
HG001_01205 sbcD	Nuclease SbcCD subunit D	SAOUHSC_0	1341	-	1,371	2,58E-07
HG001_01561 recJ	Single-stranded-DNA-specific exonuclease RecJ	SAOUHSC_0	1744		1,366	2,90E-12
HG001_00669 nrdE2	Ribonucleoside-diphosphate reductase subunit alpha 2	SAOUHSC_0	0742	nrdl	1,363	7,99E-08
HG001_02011 -	hypothetical protein	SAOUHSC_0	2208	-	1,361	0,000139633
HG001_00871 ktrB_1	Ktr system potassium uptake protein B	SAOUHSC_0	0959	-	1,355	9,75E-10
HG001_01565 queA	S-adenosylmethionine:tRNA ribosyltransferase-isomerase	SAOUHSC_0	1749	Asup	1,35	1,96E-08
HG001 02320 fhuD 2	Iron(3+)-hydroxamate-binding protein FhuD precursor	SAOUHSC 0	2554		1,349	9,45E-11
HG001 01562 secD	Protein translocase subunit SecD	SAOUHSC 0	1746		1.348	9.47E-09
HG001_00658 viiK	nutative ABC transporter ATP-binding protein YiiK	SAOUHSC 0	0729	2	1 344	8.80E-10
HG001_02121_tenA	Putative thiaminase.2	SAOUHSC 0	7331		1 343	3 22E-11
HG001_0202121 tents	Endonuclease MutS2	SAOUHSC O	1000	3	1 241	1 295-10
HG001_000393 Inut32	Levé repressor	SAOUHSC 0	2035		1,341	7.526-11
HG001_02038 IEXA_5	205 siberemal eratain \$14	SAOUHSC_0	2400	and h	1,335	2.055.00
HG001_02274 rpsN1	305 hoosomai protein 314	SAUUHSC_0	2499	rpsite	1,535	2,902-09
HG001_02375 mro	Aldose 1-epimerase precursor	SAUUHSC_U	2014	÷.	1,334	1,27E-08
HG001_01509 lepA	Elongation factor 4	SAUUHSC_0	1688	-	1,332	2,76E-08
HG001_00473 rpoB	DNA-directed RNA polymerase subunit beta	SAOUHSC_0	0524	rpoB	1,33	3,07E-08
HG001_00377 -	hypothetical protein	SAOUHSC_0	0428		1,328	9,56E-10
HG001_02142 ptpB	Low molecular weight protein-tyrosine-phosphatase PtpB	SAOUHSC_0	2356	÷.	1,326	1,37E-06
HG001_00070 sbnF	2-[(L-alanin-3-ylcarbamoyl)methyl]-3-(2-aminoethylcarbamoyl)-2-hydroxypropanoate synt	SAOUHSC_0	0080	-	1,324	5,34E-07
HG001_01997 -	Phage portal protein	SAOUHSC_0	2194	-	1,323	8,17E-05
HG001_01907 -	hypothetical protein	SAOUHSC_0	2086	-	1,322	1,10E-08
HG001_01480 znuC_2	High-affinity zinc uptake system ATP-binding protein ZnuC	SAOUHSC_0	1657		1,32	3,39E-07
HG001_00490 ywpJ_1	Putative phosphatase YwpJ	SAOUHSC_0	0542		1,318	8,39E-08
HG001 01439 -	hypothetical protein	SAOUHSC 0	1610	-	1,317	8,45E-10
HG001 01829 hemL2	Glutamate-1-semialdehvde 2%2C1-aminomutase 2	SAOUHSC 0	2000	-	1.312	1.00E-08
HG001 00790 -	Na+/H+ antiporter family protein	SAQUHSC 0	0880	-	1.308	5.41E-06
HG001_01024_vfnB	Putative HAD-hydrolase YfnB	SAOUHSC 0	1137		1 307	7.96E-09
HG001_01788_trml	<pre>#RNA (outidine(34).7: O)-methyltraneferase</pre>	SAOUHSC /	1099		1 201	1.955-09
HG001_01110 frr	Pibeceme specifing factor	SAOUHSC 0	1000	fee	1,301	2,650-08
HG001_01110 III	Hidden kiese	SAOUHICC O	1230		1,501	0,000-00
HG001_01534 Udk	Undine kinase	SAOUHSC_U	1/15	-	1,298	2,62E-10
HG001_01847 -	hypothetical protein	SAOUHSC_0	2021	-	1,298	6,09E-08
HG001_00001 dnaA	Chromosomal replication initiator protein DnaA	SAOUHSC_0	0001	dnaA	1,297	1,34E-09
HG001_02290 pbuG	Guanine/hypoxanthine permease PbuG	SAOUHSC_0	2516	-	1,288	7,46E-07
HG001_01991 -	hypothetical protein	SAOUHSC_0	2187		1,284	0,001099013
HG001_00801 -	Putative peptidyl-prolyl cis-trans isomerase	SAOUHSC_0	0891	-	1,281	4,59E-10
HG001_00656 kipA_1	Kipl antagonist	SAOUHSC_0	0727	1	1,279	9,23E-10
HG001_01781 liaR	Transcriptional regulatory protein LiaR	SAOUHSC_0	1980		1,277	2,06E-08
HG001_00654 -	hypothetical protein	SAOUHSC_0	0724	-	1,275	1,60E-08
HG001 02753 mpA	Ribonuclease P protein component	SAOUHSC 0	3054	Adu	1,275	5,73E-05
HG001 00499 nagB 1	Glucosamine-6-phosphate deaminase	SAOUHSC 0	0552		1,274	3,52E-10
HG001_01090 rimM	Ribosome maturation factor RimM	SAQUHSC 0	1209	rimM	1,272	2 35E-08
HG001 01996 -	Caudovirus prohead protease	SAOUHSC O	2193	10000	1,269	0.000998902
HG001 00943 pdb4	Puri vate dehvdrogenase E1 component subunit alpha	SAOUHSC O	1040		1.268	8.46F-09
HG001_01089_mmR	205 riboromal protein 516	SAOUHSC O	1208	men	1 765	6 80E-07
HG001_02282 fpi	Isopantenyl-diphosphate delta-isomerase	SAOUHSC 0	2623	(hat	1,263	7 965.00
HG001_01308_opuD_1	Glucine betaine transporter OpuD	SAOUHSC 0	1246		1,205	2 145.05
HG001_01208 0p00_1	busche betalle d'arisporter opub	SAOUHSC_0	1426		1,20	2,140-00
HC001_01200 -	hypothetical protein	SAOUHSC_0	2194		1,259	0.000131300
HG001_01988 -	Codmium9/2C cohalt and sing/bl(s) K(s) antigentee	SAOUHICC C	2184		1,259	0,000131299
HG001_021/4 C2CD_2	caunium/2020 codait and zinc/ri(+)-k(+) antiporter	SAUUHSC_0	2589		1,256	5,80E-08
HG001_02293 gic0_2	putative glucose uptake protein GICU	SAUUHSC_0	2520	-	1,256	2,411-07
HG001_00027 yfkN_1	Infunctional nucleotide phosphoesterase protein YIKN precursor	SAOUHSC_0	0025	÷	1,252	6,87E-07
HG001_00028 rlmH	Ribosomal RNA large subunit methyltransferase H	SAOUHSC_0	0027	-	1,247	2,75E-08
HG001_02143 ywlC_2	Threonylcarbamoyl-AMP synthase	SAOUHSC_0	2357		1,244	1,72E-07
HG001_02642 davT	5-aminovalerate aminotransferase DavT	SAOUHSC_0	2924		1,239	6,63E-06
HG001_01484 trmK	tRNA (adenine(22)-N(1))-methyltransferase	SAOUHSC_0	1661	÷.	1,236	3,25E-09
HG001_02210 -	hypothetical protein	SAOUHSC_0	2425		1,236	6,23E-06
HG001_02272 rplF	50S ribosomal protein L6	SAOUHSC_0	2496	rplF	1,235	2,98E-09
HG001_00137 yecD	Isochorismatase family protein YecD	SAOUHSC_0	0152	•	1,23	2,28E-06
HG001_00498 -	hypothetical protein	SAOUHSC_0	0551	2	1,229	1,89E-06

HG001_00138 ipdC	Indole-3-pyruvate decarboxylase	SAOUHSC_00153	-	1,229	3,85E-06
HG001_00417 prs_1	Ribose-phosphate pyrophosphokinase	SAOUHSC_00472		1,225	1,20E-07
HG001 02273 rpsH	30S ribosomal protein S8	SAOUHSC 02498	rpsH	1.221	4.91E-09
HG001 01146	Thiamine, precursor transporter protein (ThiW)	SACUHSC 01271	10000	1.22	1 935-09
10001_01146 -	manine-precursor transporter protein (mivi)	3A00H3C_01271	-	1,22	1,032-00
HGUO1_UU812 SpSB_2	Signal peptidase IB	SADUHSC_00903		1,22	6,64E-08
HG001_00310 ssb_1	Single-stranded DNA-binding protein ssb	SAOUHSC_00349	£1	1,214	7,79E-08
HG001_01449 -	hypothetical protein	SAOUHSC_01621	nusB	1,207	8,07E-08
HG001 02559 -	Acetyltransferase (GNAT) family protein	SAOUHSC 02827	- C	1,207	3.61E-06
HG001_00299_motE	5. methyltetrahydropteroyftriglutamate, homocycteine methyltransferaer	SACILIESC 00228		1 201	1 505.07
116001_03595 mete	2 hadress 2 methodalateral according 4 methodatera	5400HISC_00000		1,201	3,000,00
HGUDI_02585 mvaA	3-nydroxy-3-metnyigiutaryi-coenzyme A reductase	SAUUHSC_02859	- 53	1,198	2,10E-08
HG001_00944 pdhB	Pyruvate dehydrogenase E1 component subunit beta	SAOUHSC_01041	-	1,197	3,51E-07
HG001_01446 -	Farnesyl diphosphate synthase	SAOUHSC_01618	21	1,193	4,99E-07
HG001 02207 -	Haemolysin-III related	SAOUHSC 02422	22	1.192	6.17E-09
HG001 01452 accB 1	Biotin carboxyl carrier protein of acetyl-CoA carboxylase	SACUHSC 01624	22	1 19	1 70E-08
HC001_02020	In another least tele	EAOUHEC 02226		1.10	E FOF OF
10001_02030 -	hypothetical protein	SACOHSC_02220		1,19	5,522-05
HG001_01906 -	hypothetical protein	SAOUHSC_02085		1,189	1,62E-06
HG001_01109 pyrH	Uridylate kinase	SAOUHSC_01235	pyrH	1,188	7,15E-06
HG001_01712 metK	S-adenosylmethionine synthase	SAOUHSC_01909	÷.	1,187	4,90E-08
HG001_01681_mdtH	Multidrue resistance protein MdtH	SAOUHSC 01876		1.185	1.09E-07
HG001 01122 pbb8	Acetopretyl-CoA reductore	SACUHSC 01257		1 195	2.675-06
UC001_02421	here the third and the	SAOUNISC_02257		1,105	2,070.00
HG001_02421 -	hypothetical protein	SAUUHSC_02668	- 5	1,185	2,63E-05
HG001_02208 -	putative uridylyltransferase	SAOUHSC_02423	-	1,184	1,20E-07
HG001_01990 -	hypothetical protein	SAOUHSC_02186	1	1,179	0,00182997
HG001 01235 femB	Aminoacyltransferase FemB	SAOUHSC 01374	43	1.174	2.25E-07
HG001 02372 JyrA	Lysostaphin resistance protein A	SAOUHSC 02611	20	1 173	9.52E-08
HG001_01080	Protonial in like domain (group 2)	SAOUHSC 02185		1 173	6 385 07
10001_01989 *	bacterial ignice domain (group 2)	SAOOHSC_02185	* :	1,1/2	0,200-07
HG001_01912 -	putative acyl-LoA thioester hydrolase	SADUHSC_02091	#35	1,17	5,82E-08
HG001_00065 sbnA	putative siderophore biosynthesis protein SbnA	SAOUHSC_00075	55	1,17	0,000501837
HG001_01460 gcvPA	putative glycine dehydrogenase (decarboxylating) subunit 1	SAOUHSC_01633		1,168	1,59E-05
HG001_00004_recE	DNA replication and repair protein RecE	SADUHSC 00004	recE	1 166	6.04E-09
HG001_03282_corA	Magnesium transport protein field	SACULIESC 03634	i cer	1,100	7 665 07
HG001_02383 LOFA	Magnesium transport protein CorA	3400H3C_02024	5	1,164	2,000-07
HG001_02203 yixH	Flagellum site-determining protein YixH	SAOUHSC_02417	-	1,161	1,85E-07
HG001_00118 aldA	Putative aldehyde dehydrogenase AldA	SAOUHSC_00132		1,161	1,55E-06
HG001 01692 ribD	Riboflavin biosynthesis protein RibD	SAOUHSC 01889	20	1,16	1,76E-06
HG001 01334 gpsA	Givcerol-3-phosphate dehydrogenase [NAD(P)+]	SAOUHSC 01491	gosA	1.156	3.00E-06
HG001 02118 this	Thiamine phosphate cupthare	SAOUHSC 02228	thiF	1 155	2 195.05
10001_02118 the	manine-prosprate synthase	SAOUHICC 01175	LINE	1,155	2,100-03
HG001_01059 -	hypothetical protein	SADUHSC_01175	#3	1,151	1,08E-07
HG001_01620 accA	Acetyl-coenzyme A carboxylase carboxyl transferase subunit alpha	SAOUHSC_01808		1,151	1,21E-07
HG001_00476 rpsL	305 ribosomal protein 512	SAOUHSC_00527	rpsL	1,15	8,47E-06
HG001 01769 -	Bacterial ABC transporter protein EcsB	SAOUHSC 01966	E.)	1,148	1.95E-06
HG001_00821_cloB_1	Chaperope protein CloB	SACUHSC 00912	28	1 144	5.03E-07
HC001_00021 CIPD_1	humathatian anatain	SAOUHEC_01270		1 142	2,045,08
HG001_01145 -	hypothetical protein	SADUHSC_01270		1,143	2,04E-08
HG001_02607 oatA_2	O-acetyltransferase OatA	SAOUHSC_02885		1,14	3,32E-06
HG001_01447 xseB	Exodeoxyribonuclease 7 small subunit	SAOUHSC_01619	£3	1,139	9,95E-05
HG001 00326 tcvP	L-cystine uptake protein TcvP	SAOUHSC 00367	23	1.134	8,75E-08
HG001 02270 msE	305 ribosomal protein 55	SAOUHSC 02494	rosE	1 133	7.69E-09
HC001_01448 week	Evedeportienusleses 7 Jarge subuelt	EAQUINEC 01630	- poe	1,139	E 00E 00
HG001_01448 XSEA	Exodeoxynbonuclease y large subunit	SAUCHSC_01620	XSEA	1,128	5,092-09
HG001_00641 corC	Magnesium and cobalt efflux protein CorC	SAOUHSC_00711	Same	1,123	4,05E-06
HG001_01639 rpsD	30S ribosomal protein S4	SAOUHSC_01829	rpsD	1,121	1,96E-08
HG001_01095 rnhB	Ribonuclease HII	SAOUHSC_01215	rnhB	1,121	1,30E-06
HG001 02748 -	hypothetical protein	SAOUHSC 03048	-	1,121	6,74E-06
HG001 01636 iscs 2	Cysteine desulturase	SADUHSC 01825		1 121	1 38E-05
HC001_00970	Cerine protoses HirA like protoin	SAOLINSC 00058		1,110	2 525 05
10001_00870 -	serine protease num-nike protein	3A00H3C_00938		1,115	3,322-03
HG001_01843 -	putative phage protein 2 of sapT operon	SAOUHSC_02017	•	1,117	2,82E-06
HG001_01391 -	hypothetical protein	SAOUHSC_01558	*	1,115	0,000846604
HG001_00992 polX	DNA polymerase/3'-5' exonuclease PolX	SAOUHSC_01098	H.	1,111	2,71E-08
HG001 01069 rlmN	putative dual-specificity RNA methyltransferase RImN	SAOUHSC 01185	+ 7	1.111	4.03E-07
HG001_00655 kipt_1	Kinase A inhibitor	SAOUHSC 00726		1 108	1.75E-07
HC001 00438 8-H	ATB dependent also motallegentence Etabl	SACULIEC COMPC		1 101	1 676 07
10001_00428 1151	Arr-dependent zhic metalloprotease rtsh	5MOOFISC_00480	20	1,101	1,371-07
HG001_02526 -	putative lipoprotein precursor	SADUHSC_02789	50	1,098	6,92E-05
HG001_01983 -	hypothetical protein	SAOUHSC_02178		1,098	0,000787174
HG001_02068 -	putative inner membrane protein	SAOUHSC_02272	21	1,097	5,34E-05
HG001 02298 femX	Lipid II:glycine glycyltransferase	SAOUHSC 02527	100	1,096	8,84E-07
HG001 01140 -	Calcineurin-like phosphoestecase	SAOUHSC 01265	22	1 094	4 57E-06
HG001_00434_divic	Coll division protoin DiviC	SACILIUSC 00493		1 097	5 125 06
H0001_00424 divic	cert division protein bivic	3AOOH3C_00482		1,087	5,150-00
HG001_02147 rpmE2	SUS ribosomai protein L31 type B	SAOUHSC_02361	rpmE2	1,086	1,51E-07
HG001_01300 der_1	GTPase Der	SAOUHSC_01455	<ul> <li>•)</li> </ul>	1,085	1,46E-05
HG001_00772 lipA_1	Lipoyl synthase	SAOUHSC_00861	÷	1,081	4,80E-08
HG001_01044 ileS	IsoleucinetRNA ligase	SAOUHSC 01159	ileS	1,079	0,000184868
HG001 02449 tovC 2	L-cystine import ATP-binding protein TcvC	SAOUHSC 02697	2010) TU	1.078	4,12E-06
HG001 01215 2005	Armanaine, tPNA liance	SADULIEC D1/24	arac	1,078	1 615 05
10001_01515 3505	Asparagine - UNVA ligase	5A00HSC_01471	asinc	1,075	1,61E-05
HG001_01413 Int-Tn	Transposase from transposon Tn916	SADUHSC_01582	•	1,071	2,88E-06
HG001_01475 rpmG2_2	505 ribosomal protein L33 2	SAOUHSC_01651	rpmG	1,064	0,000111302
HG001_00399 tmk	Thymidylate kinase	SAOUHSC_00451	tmk	1,061	4,06E-06
HG001 00305 vkuT	putative MscS family protein YkuT	SAOUHSC 00344	1000	1.061	2,21E-05
HG001_00780_patA_1	Pentidoelucan Quacetultransferase	SADLINSC 00870		1.050	3 916.06
HC001_00760 pate_1	Nuclearly and vice writering			1,059	3,610-00
HG001_02749 noc	Nucleoid occlusion protein	SADUHSC_03049	Sec.	1,058	9,40E-07
HG001_01607 coaE	Dephospho-CoA kinase	SAOUHSC_01795	coaE	1,057	1,39E-06
HG001_01953 rutB	Peroxyureidoacrylate/ureidoacrylate amidohydrolase RutB	SAOUHSC_02139	7.1	1,057	1,24E-05

HG001_00474 rpoC	DNA-directed RNA polymerase subunit beta'	SAOUHSC_00525		1,053	3,59E-06
HG001_00311 rpsR	30S ribosomal protein S18	SAOUHSC_00350	rpsR	1,046	1,58E-05
HG001_00146 -	hypothetical protein	SAOUHSC_00163	19 million (19 mil	1,046	6,37E-05
HG001_01536 yhbU_2	putative protease YhbU precursor	SAOUHSC_01717	2	1,044	2,20E-07
HG001_01102 trmFO	MethylenetetrahydrofolatetRNA-(uracil-5-)-methyltransferase TrmFO	SAOUHSC_01223	gid	1,043	3,65E-06
HG001_01715 -	Transposase IS200 like protein	SAOUHSC_01911	2	1,042	1,69E-06
HG001_02039 -	hypothetical protein	SAOUHSC_02237		1,042	4,26E-05
HG001_02630 -	hypothetical protein	SAOUHSC 02910	-	1,042	0,001620305
HG001_02310 -	tRNA-GIn(ttg)			1,04	0,002666821
HG001_01596 rpml	505 ribosomal protein L35	5AOUHSC_01785	rpml	1,037	2,31E-07
HG001_00393 dnaX_1	DNA polymerase III subunit tau	SAOUHSC_00442		1,034	4,83E-07
HG001_02117 yidC	Membrane protein insertase YidC precursor	SAOUHSC_02327		1,034	1,04E-05
HG001_02527 srmB	ATP-dependent RNA helicase SrmB	SAOUHSC_02790	2	1,034	3,15E-05
HG001_01342 -	hypothetical protein	SAOUHSC_01503	2	1,028	7,79E-05
HG001_02315 modA	Molybdate-binding periplasmic protein precursor	SAOUHSC_02549	12	1,024	6,61E-07
HG001 01124 rpsO	30S ribosomal protein S15	SAOUHSC 01250	rpsO	1,024	2,79E-06
HG001_00510 ung	Uracil-DNA glycosylase	SAOUHSC 00564	-	1,024	0,000840362
HG001 01299 vpcP	5'-3' exonuclease	SAOUHSC 01454		1,021	6,35E-05
HG001_01629 ald2	Alanine dehydrogenase 2	SAOUHSC 01818	-	1,02	1,41E-06
HG001_02450 tcyB	L-cystine transport system permease protein TcyB	5AOUHSC 02698	-	1,02	0,000167666
HG001 02481 -	hypothetical protein	SAOUHSC 02733		1.018	4,27E-06
HG001 02306 moaD	Molybdopterin synthase sulfur carrier subunit	SAOUHSC 02538		1,015	6,84E-05
HG001 01049 pvrR	Bifunctional protein PyrR	SAOUHSC 01164	2	1,013	0,000496863
HG001 01144 miaB	(Dimethylallyl)adenosine tRNA methylthiotransferase MiaB	SAOUHSC 01269	2	1,011	6,46E-06
HG001 00675 -	CHY zinc finger	SAOUHSC 00751	12	1,011	6,49E-06
HG001 01097 sucD	Succinvl-CoA ligase (ADP-forming) subunit alpha	SAOUHSC 01218	+	1.007	6,24E-06
HG001 01908 -	hypothetical protein	SAOUHSC 02087		1,006	1,32E-06
HG001 01450 -	hypothetical protein	SAOUHSC 01622	~	1.003	3.84E-06
HG001 01913 pepS	Aminopeptidase PepS	SAOUHSC 02092	-	1.003	1.30E-05
HG001 00771 vfkN 3	Trifunctional nucleotide phosphoesterase protein YfkN precursor	SAOUHSC 00860	-	1.002	1.76E-06
HG001_01566 ruvB	Holliday junction ATP-dependent DNA helicase RuvB	SAOUHSC_01750	ruvB	1,001	2,72E-05

	DOWN regulated genes from the differencial transcri	ptomics analysis in o	xidative stres	s	
id gene	product	locus_tag_NCTC832	25 gene_NCTC83	25 log2FoldChange	padj
HG001_01009 hly	Alpha-hemolysin precursor	SAOUHSC_01121		-4,933	7,31E-95
HG001_00100 cap8A_1	Capsular polysaccharide type 8 biosynthesis protein cap8A	SAOUHSC_00114	2	-4,313	1,48E-50
HG001_00099 adhE	Aldehyde-alcohol dehydrogenase	SAOUHSC_00113	2	-3,985	1,68E-54
HG001_00101 ywqD_1	Tyrosine-protein kinase YwqD	SAOUHSC_00115	-	-3,82	4,93E-46
HG001_01030 ftsL	Cell division protein FtsL	SAOUHSC_01144	5	-3,572	1,09E-52
HG001_02245 -	65 kDa membrane protein precursor			-3,498	7,36E-32
HG001_00102 ywqE_1	Tyrosine-protein phosphatase YwqE	SAOUHSC_00116	-	-3,459	4,35E-38
HG001_00570 psaA	Manganese ABC transporter substrate-binding lipoprotein precursor	SAOUHSC_00634	÷.	-3,302	4,90E-40
HG001_00103 pglF	UDP-N-acetyl-alpha-D-glucosamine C6 dehydratase	SAOUHSC_00117	÷.	-3,2	1,99E-39
HG001_02045 dapE	putative succinyl-diaminopimelate desuccinylase	SAOUHSC_02244	÷.	-3,098	4,16E-35
HG001_00209 bgIA	Aryl-phospho-beta-D-glucosidase BgIA	SAOUHSC_00236	3	-3,079	3,93E-22
HG001_01028 mraZ	Protein MraZ	SAOUHSC_01142	ā.	-3,059	8,47E-48
HG001_00264 lip2	Lipase 2 precursor	SAOUHSC_00300	-	-2,999	3,65E-33
HG001_00206 IrgB	Antiholin-like protein LrgB	SAOUHSC_00233	-	-2,985	5,26E-07
HG001_00358 lpl2	putative lipoprotein precursor	SAOUHSC_00405		-2,962	3,88E-41
HG001_00331 xpt	Xanthine phosphoribosyltransferase	SAOUHSC_00372	-	-2,96	5,87E-31
HG001_00544 adh	Alcohol dehydrogenase	SAOUHSC_00608	adhA	-2,958	9,55E-47
HG001_01680 -	T-box	-	2	-2,95	4,37E-37
HG001_02709 lipA_2	Lipase 1 precursor	SAOUHSC_03006	2	-2,917	2,96E-27
HG001_00571 mntB	Manganese transport system membrane protein MntB	SAOUHSC_00636	2	-2,907	3,21E-40
HG001_02640 ldh2	L-lactate dehydrogenase 2	SAOUHSC_02922	2	-2,845	9,55E-43
HG001_00710 -	RsaH		2	-2,802	6,38E-21
HG001 00104 capD	UDP-glucose 4-epimerase	SAOUHSC 00118		-2,8	1,10E-29
HG001 01029 rsmH 1	Ribosomal RNA small subunit methyltransferase H	SAOUHSC 01143	mraW	-2,787	5,63E-50
HG001 00055 -	Oleate hydratase	SAOUHSC 00061	10000200	-2.771	9.85E-37
HG001 02756 -	RsaG		2	-2.762	2,92E-16
HG001 01172 -	hypothetical protein	SAOUHSC 01303	-	-2.749	2.42E-21
HG001 00318 -	Transelvcosylase associated protein	SAOUHSC 00358	2	-2.721	5.70E-41
HG001 01548 -	hypothetical protein	SAOUHSC 01729		-2.699	4.62E-48
HG001 00359 -	hypothetical protein	SAOUHSC 00406	2	-2 659	1 15E-29
HG001_01297 tdcB	I-threenine dehydratase catabolic TdcB	SAOUHSC 01451	2	-2 654	1.59E-22
HG001_00106 whol	UDP-2%203-diacetamido-2%203-dideoxy-D-plucuropate 2-enimerase	SAQUESC 00120		.2 572	4 155-30
HG001_02103 kdpC	Potassium-transporting ATPace C chain	SAOUHSC 02310		-2.54	1 775-27
HG001_02103 kupc	Streptogramin A acetultransferace	SAOUHSC 00131		2,51	2 765.22
HG001_00105_fcl	GDP-1 fucore synthese	SAOUHSC 00121		2,527	1 105.29
HG001_00927 -	65 kDa membrane protein precursor	3A00H3C_00115	2	-2,525	0.955.29
HG001_00827 +	UTH tree transminimal regulates set	EAOUHEC 01970	*	-2,514	3,035-20
HG001_01684 rot	Hi H-type transcriptional regulator rot	SAOUHSC_01879		-2,499	2,446-25
HG001_02221 -	Transposase DUE domain protein	SAOUHSC_02437	÷	-2,4/7	1,78E-19
HG001_00561 mrpA	Na(+)/H(+) antiporter subunit A	SAOUHSC_00625	-	-2,462	8,59E-28
HG001_01296 stel	Serine/threonine exchanger Stel	SAOUHSC_01450	-	-2,455	1,71E-29
HG001_02181 glm5	Glutaminetructose-6-phosphate aminotransferase [isomerizing]	SAOUHSC_02399		-2,402	3,78E-28
HG001_02105 kdpA	Potassium-transporting ATPase A chain	SAOUHSC_02312	-	-2,4	1,65E-22
HG001_00241 -	hypothetical protein	SAOUHSC_00272	-	-2,382	5,63E-20
HG001_00274 -	PTS system ascorbate-specific transporter subunits IICB	SAOUHSC_00311	*	-2,378	7,71E-22
HG001_02104 kdpB	Potassium-transporting ATPase B chain	SAOUHSC_02311	*	-2,371	3,10E-18
HG001_01630 -	Putative universal stress protein	SAOUHSC_01819		-2,37	2,62E-31
HG001_01610 -	hypothetical protein	SAOUHSC_01798		-2,361	1,04E-22
HG001_02514 ahpD	Alkyl hydroperoxide reductase AhpD	SAOUHSC_02774	÷	-2,352	2,77E-23
HG001_00273 ulaA	Ascorbate-specific permease IIC component UIaA	SAOUHSC_00310	ulaA	-2,348	3,96E-23
HG001_00562 mrpB	Na(+)/H(+) antiporter subunit B	SAOUHSC_00626		-2,342	4,97E-17
HG001_00360 -	hypothetical protein	SAOUHSC_00407		-2,333	8,89E-24
HG001_00556 sarA	Transcriptional regulator SarA	SAOUHSC_00620	2	-2,33	2,30E-20
HG001_02040 -	hypothetical protein	SAOUHSC_02238	10	-2,32	6,72E-25
HG001_02107 kdpE	KDP operon transcriptional regulatory protein KdpE	SAOUHSC_02315		-2,315	2,96E-19
HG001_02677 isaB	Immunodominant staphylococcal antigen B precursor	SAOUHSC_02972		-2,292	2,65E-22
HG001_00899 sspA	Glutamyl endopeptidase precursor	SAOUHSC_00988	-	-2,286	1,08E-22
HG001_00847 -	RsaE	121	-	-2,284	2,58E-06
HG001 01412 -	hypothetical protein	SAOUHSC 01580	-	-2,282	5,01E-24
HG001 00725 -	hypothetical protein	SAOUHSC 00808		-2,258	6,01E-20
HG001 02494 -	hypothetical protein	SAOUHSC 02753	-	-2,239	5.45E-25
HG001 02359 malP	PTS system maltose-specific EIICB component	SAOUHSC 02597		-2,234	2,88E-26
HG001 01744 -	hypothetical protein	SAOUHSC 01945	-	-2,233	2,77E-16
HG001 00120 -	hypothetical protein	SAOUHSC 00134	2	-2.232	4,58E-20
HG001 00108 -	hypothetical protein	SAOUHSC 00122	-	-2.231	3,19E-21
HG001 01075 rpmB	50S ribosomal protein L28	SAQUHSC 01191	rpmB	-2.228	1.21E-23
HG001 02398 -	FtsX-like permease family protein	SAQUHSC 02641	1000	-2.222	1.28F-18
HG001_00564_mnhD1_1	Na(+)/H(+) antiporter subunit D1	SAOUHSC 00628	2	-2 22	1.74F-24
HG001_00275_cmt8	Mannitol-specific cryptic phosphotrapsferase enzyme IIA component	SAOUHSC 00312	8	-2 216	3.56E-20
HG001_00898 cmB	Stanhonain B precureor			-2,210	4 305-17
H6001_02327 -	hypothetical protein	SAOLINC 0367	<u>_</u>	-2,208	3 985-20
HG001_02537 -	Na(4)/H(4) antiporter subunit C	SADUHEC 00677		-2,159	7.065.20
HG001_00363 mrpc	alms	SAUUHSC_00027	2	-2,185	1.025 14
HG001_02182 -	Billio	CADULUCE CORES		-2,182	1,028-14
10001_00724 -	hypothetical protein	SAUUHSC_00806	-	~2,1/5	5,00E-22

HG001_00545 -	hypothetical protein	SAOUHSC_00609		-2,173	0,000132078
IG001_01340 ebpS	Elastin-binding protein EbpS	SAOUHSC_01501		-2,155	3,66E-22
G001_00573 ideR	Iron-dependent repressor IdeR	SAOUHSC_00638	mntR	-2,129	8,63E-19
HG001_00897 sspC	Staphostatin B	SAOUHSC_00986		-2,128	5,00E-17
HG001_02588 clpL	ATP-dependent Clp protease ATP-binding subunit ClpL	SAOUHSC_02862	8	-2,125	2,50E-18
HG001_02057 -	RNAIII	SAOUHSC_02260		-2,116	3,71E-27
HG001_01958 -	hypothetical protein	SAOUHSC_02145	-	-2,11	2,54E-23
HG001_02125 -	hypothetical protein	SAOUHSC_02335	1	-2,099	1,64E-14
HG001_02737 -	hypothetical protein	SAOUHSC_03035		-2,098	1,87E-19
HG001_00248 -	hypothetical protein	SAOUHSC_00280	-	-2,097	4,44E-17
HG001_00482 hchA	Molecular chaperone Hsp31 and glyoxalase 3	SAOUHSC_00533		-2,073	6,43E-21
HG001_01747 -	Thermophilic serine proteinase precursor	SAOUHSC_01949	8	-2,065	1,07E-15
HG001_01772 -	hypothetical protein	SAOUHSC_01969	-	-2,06	5,73E-24
HG001_00889 -	hypothetical protein	SAOUHSC_00977	-	-2,032	1,15E-14
IG001_01064 -	hypothetical protein	SAOUHSC_01180	-	-2,012	9,99E-13
IG001_01978 sak	Staphylokinase precursor	SAOUHSC_02171	-	-2,003	2,33E-19
HG001_02222 -	Alkaline shock protein 23	SAOUHSC_02441		-2,001	9,35E-17
HG001_01237 -	hypothetical protein	SAOUH5C_01376	-	-1,978	1,20E-22
HG001_00316 -	Peptidase propeptide and YPEB domain protein	SAOUHSC_00356		-1,978	1,39E-15
1G001_00046 plc	1-phosphatidylinositol phosphodiesterase precursor	SAOUHSC_00051	-	-1,97	2,79E-21
1G001_02062 agrA	Accessory gene regulator protein A	SAOUHSC_02265	-	-1,967	1,79E-14
1G001_02060 -	Staphylococcal AgrD protein	SAOUHSC_02262	-	-1,962	6,81E-14
HG001_00740 -	hypothetical protein	SAOUHSC_00825	-	-1,942	2,73E-16
HG001_02225 opuD_2	Glycine betaine transporter UpuD	SAOUHSC_02444		-1,94	1,98E-17
4G001_01065 -	IM2 domain protein	SAOUHSC_01181	÷	-1,94	3,89E-16
4G001_00361 -	hypothetical protein	SAOUHSC_00408		-1,936	1,56E-15
1G001_01746 yxiF_2	putative ABC transporter ATP-binding protein YXIF	SAOUHSC_01948		-1,934	4,04E-14
4G001_01298 ald1	Alanine denydrogenase 1	SAOUHSC_01452		-1,927	5,01E-13
1G001_02330 sark	HTH-type transcriptional regulator Sark	SAOUHSC_02566		-1,925	2,59E-13
1G001_02601 Crtiv	Denydrosquaiene desaturase	SAUUHSC_02877	~	-1,921	8,97E-18
1G001_02347 -	RSaUG	-	÷	-1,92	1,068-12
10001_01012 phor	Commo bomolycia component Conservation	SADUHSC 02700	-	-1,919	1,99E-20
4G001_02458 hige	Argining separator	SAOUHSC_02709	-	-1,911	0,49E-19
10001_01445 argn_1	Na(+)/H(+) antiparter subunit E	SADUHSC 00630	-	-1,91	4,000-10
4G001_00363 http:	hyperbasical protein	SAOUHSC_00820		-1,909	3,27E-10
4G001_01495 vbe7	PhoH-like protein	SADUHSC 01673	-	-1,000	1 775-19
4G001_00567 mmG	Na(+)/H(+) antiporter subunit G	SAOUHSC 00632	- -	-1,000	7 485-16
1G001_01955 alkH	Aldehyde dehydrogenase	SAOUHSC 02142	2	-1.887	2 51E-15
16001_01058 -	bypothetical protein	SAOUHSC 00065	÷	-1.881	4.25E-19
IG001_02397 hrtA_2	Putative bemin import ATP-binding protein HrtA	SAOUHSC 02640		-1.876	8 24F-11
16001_01216 elcT	GlcA/glcB genes antiterminator	SADUHSC 01356		-1.871	3 05E-15
HG001 01364 -	hypothetical protein	SAOUHSC 01527	-	-1.871	3.52E-09
IG001 00109 -	hypothetical protein	SAOUHSC 00123		-1.862	9.54E-17
1G001 00227 esxA	Virulence factor EsxA	SAOUHSC 00257	ũ.	-1.858	1.52E-17
1G001 00566 mroF	Na(+)/H(+) antiporter subunit F	SAOUHSC 00632	-	-1.851	2.38E-13
HG001 02365 yehA	putative oxidoreductase YghA	SAOUHSC 02604		-1.849	3.51E-16
4G001 00169 pflB	Formate acetyltransferase	SAOUHSC 00187		-1.839	9.01E-16
HG001_01751 gdmA	Lantibiotic gallidermin precursor	SAOUHSC 01953	-	-1,836	2,24E-13
HG001_02303_sarV	HTH-type transcriptional regulator SarV	SAOUHSC 02532		-1,834	1,02E-10
HG001_02106 kdpD	Sensor protein KdpD	SAOUHSC_02314	-	-1,818	2,02E-16
IG001_00330 -	Purine	1.5.		-1,807	4,69E-05
G001_01032 mraY	Phospho-N-acetylmuramoyl-pentapeptide-transferase	SAOUHSC_01146	mraY	-1,804	2,57E-19
HG001_00902 slyA_2	Transcriptional regulator SIyA	SAOUHSC_00992	-	-1,799	1,23E-11
HG001_00759 -	CsbD-like protein	SAOUHSC_00845	÷	-1,797	8,91E-21
HG001_00560 xerD_2	Tyrosine recombinase XerD	SAOUHSC_00624		-1,786	3,23E-16
IG001_01704 tal	Transaldolase	SAOUHSC_01901	-	-1,785	5,82E-13
IG001_01173 -	hypothetical protein	SAOUHSC_01304	-	-1,783	4,77E-10
HG001_02061 dpi8	Sensor histidine kinase DpiB	SAOUHSC_02264	-	-1,782	1,04E-09
HG001_02223 -	hypothetical protein	SAOUHSC_02442	2	-1,781	3,39E-15
HG001_02059 agrB	Accessory gene regulator protein B	SAOUHSC_02261		-1,78	2,62E-12
HG001_01363 -	hypothetical protein	SAOUHSC_01526	2	-1,779	2,76E-06
HG001_02495 ybbL	putative ABC transporter ATP-binding protein YbbL	SAOUHSC_02754	2	-1,778	5,45E-17
IG001_00414 yabJ	Enamine/imine deaminase	SAOUHSC_00468	2	-1,767	5,40E-18
HG001_00110 -	hypothetical protein	SAOUHSC_00124	-	-1,764	5,05E-13
HG001_01174 -	hypothetical protein	SAOUHSC_01305	-	-1,758	6,40E-08
HG001_02627 -	hypothetical protein	SAOUHSC_02907	-	-1,755	7,58E-07
HG001_01031 pbpB	Penicillin-binding protein 2B	SAOUHSC_01145		-1,753	1,13E-15
HG001_01581 -	T-box		<u>_</u>	-1,751	1,14E-13
HG001_00728 clfA	Clumping factor A precursor	SAOUHSC_00812	-	-1,737	4,36E-13
HG001_00572 znuC_1	High-affinity zinc uptake system ATP-binding protein ZnuC	SAOUHSC_00637	-	-1,736	1,75E-12
HG001_02332 -	hypothetical protein	SAOUHSC_02569	*	-1,731	3,38E-13
HG001_01802 -	tRNA-Tyr(gta)	SAOUHSC_T00057	-	-1,726	8,71E-09
HG001_02112 -	hypothetical protein	SAOUHSC_02320	54 	-1,718	4,31E-13
46001_02195 -	TKNA-Tyr(gta)	SAOUHSC_T00058		-1,709	1,71E-08

HG001_02626 -	hypothetical protein	SAOUHSC_02906	2	-1,707	9,64E-08
HG001_00929 -	hypothetical protein	SAOUHSC_01024	2	-1,703	1,77E-15
HG001_01729 -	hypothetical protein	SAOUHSC_01925		-1,702	7,03E-05
HG001_02379 yhal	Inner membrane protein Yhal	SAOUHSC_02620		-1,699	7,78E-15
HG001_01952 pfbA	Plasmin and fibronectin-binding protein A precursor	SAOUHSC_02138	-	-1,689	1,21E-14
HG001_01544 yrrB	TPR repeat-containing protein YrrB	SAOUHSC_01724	2	-1,689	6,62E-11
HG001_00111 cap5L	putative glycosyl transferase	SAOUHSC_00125		-1,68	1,13E-15
HG001_00174 fadA	3-ketoacyl-CoA thiolase	SAOUHSC_00195	-	-1,676	9,15E-07
HG001_01917 -	hypothetical protein	SAOUHSC_02097	2	-1,675	2,90E-13
HG001_01043 -	T-box		2	-1,666	1,53E-11
HG001_00267 limB_1	Limonene 1%2C2-monooxygenase	SAOUHSC_00304	-	-1,663	5,78E-14
HG001_01287 thyA	Thymidylate synthase	SAOUHSC_01435	thyA	-1,66	1,91E-14
HG001_01361 -	Phage tail protein	SAOUHSC_01524		-1,659	1,82E-09
HG001_02507 nikA	Nickel-binding periplasmic protein precursor	SAOUHSC_02767		-1,658	5,40E-12
HG001_02603 crtQ	4%2C4'-diaponeurosporenoate glycosyltransferase	SAOUHSC_02880		-1,657	9,84E-12
HG001_00329 -	hypothetical protein	SAOUHSC_00371	*	-1,652	2,45E-13
HG001_02697 -	hypothetical protein	SAOUHSC_02994		-1,651	3,15E-14
HG001_00709 -	Epimerase family protein	SAOUHSC_00792	-	-1,651	3,78E-13
HG001_02410 -	FerredoxinNADP reductase	SAOUHSC_02654		-1,649	1,26E-13
HG001_02459 hlgB	Gamma-hemolysin component B precursor	SAOUHSC_02710	*	-1,643	4,60E-15
HG001_00184 ldh1	L-lactate dehydrogenase 1	SAOUHSC_00206		-1,643	4,46E-09
HG001_00625 mgrA	HTH-type transcriptional regulator MgrA	SAOUHSC_00694	-	-1,638	1,53E-12
HG001_00617 -	hypothetical protein	SAOUHSC_00686	1	-1,635	4,47E-12
HG001_02399 hssR	Heme response regulator HssR	SAOUHSC_02643	÷.	-1,63	1,25E-12
HG001_00175 fadN	putative 3-hydroxyacyl-CoA dehydrogenase	SAOUH5C_00196	÷	-1,63	2,14E-06
HG001_01444 recN	DNA repair protein RecN	SAOUHSC_01615	8	-1,619	5,84E-16
HG001_00214 degA	HTH-type transcriptional regulator DegA	SAOUHSC_00242	100	-1,616	4,49E-12
HG001_02093 rsbW	Serine-protein kinase RsbW	SAOUHSC_02299	10	-1,61	8,53E-13
HG001_00503 proP	Proline/betaine transporter	SAOUHSC_00556		-1,608	7,89E-14
HG001_01841 -	hypothetical protein	SAOUHSC_02014		-1,606	3,35E-09
HG001_01731 -	Transposase	SAOUHSC_01928		-1,605	1,71E-11
HG001_00130 psf-1	4'-phosphopantetheinyl transferase psf-1	SAOUHSC_00145		-1,599	1,64E-12
HG001_02545 -	hypothetical protein	SAOUHSC_02812		-1,599	3,25E-12
HG001_01745 -	ABC-2 family transporter protein	SAOUHSC_01947		-1,592	5,42E-10
HG001_02520 -	hypothetical protein	SAOUHSC_02781	5	-1,591	7,96E-13
HG001_01730 -	hypothetical protein	SAOUHSC_01926		-1,589	4,49E-12
HG001_00074 -	hypothetical protein	SAOUHSC_00084		-1,585	3,81E-10
HG001_00741 -	hypothetical protein	SAOUHSC_00826		-1,584	2,66E-11
HG001_01175 -	hypothetical protein	SAOUHSC_01306		-1,58	0,00276172
HG001_02415 sacX	Negative regulator of SacY activity	SAOUHSC_02661	2	-1,573	9,24E-14
HG001_01414 -	hypothetical protein	SAOUHSC_01583	3	-1,562	7,43E-12
HG001_02406 -	putative lipoprotein precursor	SAOUHSC_02650		-1,56	1,91E-11
HG001_01362 -	Glycyl-glycine endopeptidase ALE-1 precursor	SAOUHSC_01525		-1,558	8,74E-16
HG001_00415 spoVG	Putative septation protein SpoVG	SAOUHSC_00469	-	-1,553	3,09E-13
HG001_00678 -	hypothetical protein	SAOUHSC_00754	-	-1,546	6,31E-12
HG001_00738 -	hypothetical protein	SAOUHSC_00823	-	-1,536	1,36E-05
HG001_00303 -	T-box	-	-	-1,514	1,16E-06
HG001_02734 -	hypothetical protein	SAOUHSC_03032	2	-1,513	3,76E-09
HG001_00726 -	hypothetical protein	SAOUHSC_00810	-	-1,51	3,14E-09
HG001_01659 -	hypothetical protein	SAOUHSC_01854	2	-1,506	9,22E-12
HG001_00707 -	tRNA-Arg(ccg)	SAOUHSC_T0005	2	-1,503	0,031150464
HG001_00176 acdA	Acyl-CoA dehydrogenase	SAOUHSC_00197		-1,5	4,39E-06
HG001_02326 ureE	Urease accessory protein UreE	SAOUHSC_02562	ureE	-1,499	8,19E-10
HG001_00663 -	Putative 5'(3')-deoxyribonucleotidase	SAOUHSC_00734	-	-1,495	1,34E-09
HG001_00607 sarX	HTH-type transcriptional regulator SarX	SAOUHSC_00674	1	-1,492	6,69E-10
HG001_01654 acsA_1	Acetyl-coenzyme A synthetase	SAOUHSC_01846	<u>.</u>	-1,488	1,86E-09
HG001_02368 hutU	Urocanate hydratase	SAOUHSC_02607	10 C	-1,484	4,65E-09
HG001_00828 -	hypothetical protein	SAOUHSC_00919	-	-1,48	1,87E-11
HG001_02404 lctP_2	L-lactate permease	SAOUHSC_02648	2	-1,468	2,76E-08
HG001_00690 yvyD	Putative sigma-54 modulation protein	SAOUHSC_00767	14	-1,463	2,90E-11
HG001_02735 nixA	High-affinity nickel-transport protein NixA	SAOUHSC_03033	2	-1,46	2,10E-11
HG001_01927 ftnA	Ferritin	SAOUHSC_02108	÷.	-1,45	7,51E-13
HG001_00528 -	hypothetical protein	SAOUHSC_00586	1	-1,45	9,08E-09
HG001_02367 hutl	Imidazolonepropionase	SAOUHSC_02606		-1,45	1,31E-07
HG001_01428 proC	Pyrroline-5-carboxylate reductase	SAOUHSC_01597	8	-1,448	3,98E-10
HG001_01711 -	hypothetical protein	SAOUHSC_01908	1	-1,447	1,50E-11
HG001_01171 -	hypothetical protein	SAOUHSC_01301		-1,445	0,007144881
HG001_02162 -	hypothetical protein	SAOUHSC_02376	-	-1,444	1,50E-11
HG001_00736 -	hypothetical protein	SAOUHSC_00821		-1,442	2,29E-08
HG001_00047 -	putative lipoprotein precursor	SAOUHSC_00052		-1,441	7,53E-08
HG001_00618 -	Acetyltransferase (GNAT) family protein	SAOUHSC_00687	÷	-1,439	3,28E-08
HG001_01336 rpsA_1	305 ribosomal protein 51	SAOUHSC_01493	rpsA	-1,438	9,56E-13
HG001_01004 -	hypothetical protein	SAOUHSC_01113	-	-1,431	2,16E-08
HG001_00332 pucK	Uric acid permease PucK	SAOUHSC_00373	÷	-1,429	5,92E-06
HG001_02544 ywaC	GTP pyrophosphokinase YwaC	SAOUHSC_02811		-1,424	3,25E-11

HG001_01740 splC	Serine protease SpIC precursor	SAOUHSC_01939	10	-1,419	2,47E-06
HG001_01974 scn_3	Staphylococcal complement inhibitor precursor	SAOUHSC_02167	1.	-1,417	7,20E-08
HG001 00986 -	T-box	-		-1.414	1.11E-09
HG001_02543_zntR	HTH-type transcriptional regulator ZntB	SAQUESC 02810		-1.41	2 68E-13
UCOOL 00121 usell	Inne mechanic protein Verli	SAOULISC 00146		1,100	0.075 1
HGOOT_OUTST YABO	inner memorane protein rago	5A00H5C_00146		-1,409	9,97E-13
HG001_00362 -	hypothetical protein	SAOUHSC_00409		-1,403	4,73E-01
HG001_02172 yhfK	putative sugar epimerase YhfK	SAOUHSC_02387	-	-1,401	4,59E-1(
HG001_01728 -	hypothetical protein	SAOUHSC_01923	Q	-1,401	7,46E-08
HG001 02324 ure8	Urease subunit beta	SAOUHSC 02559	ureB	-1.398	7.41E-03
HG001 01524 -	by notherical protein	SAOUHSC 01704		-1 307	0.004196363
10001_01524	nypotileatai protein	3A00H3C_01704		-1,337	0,00413030.
HG001_02163 pdp	Pyrimidine-nucleoside phosphorylase	SAOUHSC_02377	-	-1,393	1,15E-10
HG001_02094 rsbV	Anti-sigma-B factor antagonist	SAOUHSC_02300	1.4	-1,39	1,11E-1(
HG001_00553 -	hypothetical protein	SAOUHSC_00617	S4	-1,389	1,30E-09
HG001 02418 vdaG	General stress protein 26	SAOUHSC 02665	82	-1.385	3.81E-10
HG001 00126 -	hypothetical protein	SAOUHSC 00141	22	-1 384	3.635-10
10001_00120	hypothesical protein	SACOULISC 00270		1,004	1.000.00
HG001_00247 -	nypothetical protein	SAOUHSC_00279		-1,383	1,05E-08
HG001_01255 dapB	4-hydroxy-tetrahydrodipicolinate reductase	SAOUHSC_01397	G.	-1,381	7,81E-10
HG001_01163 -	hypothetical protein	SAOUHSC_01290	<u>_</u>	-1,38	0,004802171
HG001_01787 nagB_2	Glucosamine-6-phosphate deaminase	SAOUHSC_01987	24	-1,379	4,97E-1
HG001 01611 phoR	Alkaline phosphatase synthesis sensor protein PhoR	SAOUHSC 01799	12 C	-1.376	4.07E-1
HG001 00742 areQ	Argining experter protein ArgO	SAOUHEC 00939	10	1 272	1 215.00
HG001_00743 algo	Arginine exporter protein Argo	SAOUH3C_00828		-1,373	1,210-00
HG001_00634 tetA_2	Tetracycline resistance protein%2C class B	SAOUHSC_00703	28	-1,3/1	5,57E-10
HG001_01256 dapH	2%2C3%2C4%2C5-tetrahydropyridine-2%2C6-dicarboxylate N-acetyltransferase	SAOUHSC_01398	3 C	-1,367	1,20E-09
HG001_00605 -	Inhibitor of apoptosis-promoting Bax1	SAOUHSC_00672	34	-1,365	1,33E-09
HG001 01186 -	hypothetical protein	SAOUHSC 01318	<b>a</b>	-1,365	1.56E-08
HG001 00990 zapA	Cell division protein ZanA	SAOUHSC 01096	-1	-1 262	1.515-01
HGOOL COSSG ZapA	CER division protein zapa	SACOTISC_01030		-1,505	2,510-01
HG001_00835 oppF_1	Oligopeptide transport ATP-binding protein Opp-	SAODHSC_00926		-1,359	2,68E-0.
HG001_02164 deoC2	Deoxyribose-phosphate aldolase 2	SAOUHSC_02379		-1,357	8,55E-13
HG001_02666 -	hypothetical protein		9	-1,356	1,27E-09
HG001 01129 phnF	putative transcriptional regulator PhnF	SAOUHSC 01254	3.9	-1.353	4,60E-09
HG001 02676 aur	Zins metalloproteinase aureolysin precursor	SAOUHSC 02971		-1 249	1 995-0
HGOOL OFFIC	2 inclusioproteinase adreolyski precuisor	3/00/130_023/1	10	-1,345	1,000-01
HG001_00516 -	KSaA	The second second	28. L	-1,346	6,30E-05
HG001_02409 -	Acetyltransferase (GNAT) family protein	SAOUHSC_02653	18	-1,346	0,000139453
HG001_02407 paiA	Protease synthase and sporulation negative regulatory protein PAI 1	SAOUHSC_02651	18	-1,344	4,64E-08
HG001 02363 -	SAM			-1,344	8,59E-08
HG001_00850 vibi	Group 2 truncated hemoglobin Vibl	SAOUHSC 00939		-1 34	1.68E-10
HC001_00801	Asstultanesferres (CNAT) femily protein	SAOUHSC 00030		1,330	2,035,00
H0001_00891 -	Acetyrcransferase (GNAT) family protein	SAUUHSC_00979	2	-1,359	2,036-00
HG001_01660 -	hypothetical protein	SAOUHSC_01855	10	-1,336	1,87E-11
HG001_01192 -	hypothetical protein	SAOUHSC_01324	35	-1,335	6,09E-07
HG001_00170 pflA	Pyruvate formate-lyase-activating enzyme	SAOUHSC_00188		-1,334	8,75E-07
HG001_00249 focA	putative formate transporter 1	SAOUHSC 00281		-1.334	1.31E-09
HG001_00568 abaK_1	Sodium%3C patacrium%3C lithium and ruhidium/H(+) antiporter	SAOUHSC 00633		1 227	2 616 11
10001_00308 III/ak_1	Social 1/22 potassian/22 incliant and rabidianty n(+) and porter	5A00H3C_00033	18	-1,332	3,010-11
HG001_01834 -	nypothetical protein	SAOUHSC_02006	ST	-1,33	2,35E-1.
HG001_00606 melR_1	Melibiose operon regulatory protein	SAOUHSC_00673	÷	-1,329	1,23E-09
HG001_02325 ureC	Urease subunit alpha	SAOUHSC_02561	ureC	-1,329	9,64E-08
HG001 01360 -	Prophage endopeptidase tail	SAOUHSC 01523		-1.324	1.76E-03
HG001 00954 -	hypothetical protein	SAOUHSC 01051		-1 321	1 72E-01
10001_00554	hypothetical protein	SHOULUSC 00018		1.22	7,720,00
HG001_00554 -	nypothetical protein	SAUUHSC_00018	2	-1,32	7,256-01
HG001_00802 yugl_2	General stress protein 13	SAOUHSC_00892		-1,318	4,37E-09
HG001_01223 -	prephenate dehydrogenase	SAOUHSC_01364		-1,317	5,00E-09
HG001 02678 -	hypothetical protein	SAOUHSC 02973	÷.	-1,317	8,46E-09
HG001 02351 ybbH 3	nutative HTH-type transcriptional regulator YbbH	SAOUHSC 02589	3	-1 314	1.04E-07
HC001 00182 hmp	Elsyshementetein	SACULIEC 00204	8	1 212	1 405 01
116001_00183 mmp	havenenoprotein	5400H3C_00204	6	-1,512	1,400-01
HG001_01909 -	hypothetical protein	SAOUHSC_02088	<u> </u>	-1,309	6,86E-O
HG001_00836 dppE	Dipeptide-binding protein DppE precursor	SAOUHSC_00927	-	-1,309	1,00E-05
HG001_02732 yflS	Putative malate transporter YfIS	SAOUHSC_03030	<u>.</u>	-1,306	6,81E-12
HG001 01033 murD	UDP-N-acetylmuramoylalanineD-glutamate ligase	SAOUHSC 01147	murD	-1.306	1.01E-08
HG001 00704 arok 1	Shikimata kinasa	SACULIESC 00787	19662933	-1 305	1 475.00
	Statistics and Statistics First			1,300	4.745.00
HG001_00112 epst	putative sugar transferase EpsL	SAUUHSC_00126		-1,304	4,346-08
HG001_01756 -	tRNA-Ser(gga)	SAOUHSC_T00050	2	-1,294	0,00428682
HG001_00178 ydiF	Acetate CoA-transferase YdiF	SAOUHSC_00199		-1,291	3,53E-05
HG001 00129 grsB	Gramicidin 5 synthase 2	SAOUHSC 00144	<u>8</u>	-1,287	4,56E-08
H6001 01333 hup	DNA-binding protein HU	SAOUHSC 01490	S2	-1.286	1.02F-09
HG001 01971	65 kDa membrane protein precursor	SACUHSC 02160	<u>.</u>	1 204	5 035 00
10001_015/1 -	of Real memoral e protein precursor	SAGONSC_02100	2	-1,284	3,928-00
HG001_02680 manP	PTS system mannose-specific EliBCA component	SAUUHSC_02975		-1,283	8,48E-09
HG001_02719 -	Polysaccharide deacetylase	SAOUHSC_03016	C2	-1,281	9,40E-07
HG001_02600 dapL	LL-diaminopimelate aminotransferase	SAOUHSC_02876	S2	-1,276	3,98E-09
HG001 01164 -	hypothetical protein	SAOUHSC 01292	34	-1,275	0,0157295
HG001 02124 seb 2	Single-stranded DNA-binding protein sch	SAOUHSC 02334		-1 373	2 095.00
HC001_02124 330_2	human and a second a second and a	SACOTISC_02554	10	-1,2/3	2,000-00
10001_01007 -	nypotnetical protein	5MOUNSC_01119		-1,266	4,000-01
HG001_00113 galE	UDP-glucose 4-epimerase	SAOUHSC_00127	19	-1,265	5,66E-09
HG001_01347 -	hypothetical protein	SAOUHSC_01510	5e	-1,264	0,004493515
HG001_01415 -	hypothetical protein	SAOUHSC_01584	36	-1,259	1,47E-06
HG001 01542 -	T-box	1.0	S.	-1,256	4.68E-0
HG001 00529 -	hypothetical protein	SAOUHSC 00597	-	1 354	1 17E 00
10001_00525 -	any particular processing	3400000-000007		-1,234	1,170-00

HG001_01254 dapA         HG001_02331 -           HG001_02331 -         HG001_02354 -           HG001_01759 -         HG001_01759 -           HG001_01759 -         HG001_01759 -           HG001_01255 -         HG001_01255 -           HG001_01255 -         HG001_01556 -           HG001_01556 -         HG001_01556 -           HG001_01655 t;PP         HG001_01242 splA           HG001_02282 -         HG001_02282 -           HG001_02048 -         FHG001_02284 -           HG001_02048 ugtP         HG001_01018 -           HG001_01238 nikE         HG001_0132 -           HG001_0132 -         HG001_0132 -           HG001_0268 gcvH_1         HG001_0268 gcvH_1           HG001_02138 nikE         HG001_0237 1 hutG           HG001_02371 hutG         HG001_0237 1 hutG           HG001_02371 rutG         HG001_0236 -           HG001_0237 ureF         HG001_0237 -           HG001_0235 -         HG001_0235 -           HG001_0235 -         HG001_02	4-hydroxy-tetrahydrodipicolinate synthase nypothetical protein Nickel transport system permease protein NikB RRNA-Gly(tcc) nypothetical protein Nypothetical protein Nypothetical protein F-box Diigopeptide transport ATP-binding protein OppD fhioredoxin-like protein YtpP serine protease SpIA precursor Bacterial Ig-like domain (group 2) Juatative lipoprotein precursor Sacterial Ig-like domain (group 2) Juatative lipoprotein procein OpuCA Processive diacylg/vcerol beta-glucosyltransferase Juatative lipotein Ypothetical protein Ypothetical protein Nypothetical protein S Juatative kinase Nypothetical protein Natative kinase Nypothetical protein Natative kinase inhibitor Jrease accessory protein UreF ron-sulphur cluster biosynthesis Nypothetical protein	SAOUHSC_01396 SAOUHSC_02568 SAOUHSC_02766 SAOUHSC_01986 SAOUHSC_01986 SAOUHSC_01986 SAOUHSC_01980 SAOUHSC_01980 SAOUHSC_01997 SAOUHSC_01992 SAOUHSC_01992 SAOUHSC_01992 SAOUHSC_01993 SAOUHSC_02241 SAOUHSC_02141 SAOUHSC_01131 SAOUHSC_01131 SAOUHSC_011402 SAOUHSC_011402 SAOUHSC_011488 SAOUHSC_011488 SAOUHSC_011488 SAOUHSC_011488 SAOUHSC_01149 SAOUHSC_01672 SAOUHSC_01673 SAOUHSC_02610 SAOUHSC_02610 SAOUHSC_0217 SAOUHSC_02917 SAOUHSC_02149		-1,253 -1,243 -1,234 -1,212 -1,212 -1,212 -1,212 -1,208 -1,208 -1,208 -1,207 -1,207 -1,207 -1,207 -1,192 -1,199 -1,186 -1,186 -1,186 -1,184 -1,182 -1,189 -1,179 -1,179 -1,179 -1,173 -1,173 -1,162 -1,162 -1,158 -1,155	2,90E-08 1,44E-08 1,44E-08 1,41E-05 3,05E-08 2,81E-06 6,49E-06 2,62E-08 1,06E-05 2,34E-05 2,01E-09 0,000610276 2,01E-09 0,000610276 0,12E-06 0,112E-06 0,12E-06 0,000125426 0,000125426 0,000125426 0,000125426 0,000125426 0,000125426 0,000125426 0,000125426 0,000125426 0,00016541 0,0000367906
HG001_02331 -         HG001_02506 nik8_2           HG001_02506 nik8_2         HG001_01759 -           HG001_01756 -         HG001_012354 -           HG001_012354 -         HG001_012354 -           HG001_01255 -         HG001_00353 -           HG001_01556 -         HG001_01655 +           HG001_01655 +         HG001_01665 +           HG001_01665 -         HG001_02248 -           HG001_022489 opuCA         HG001_02248 -           HG001_01238 nikE         HG001_01238 -           HG001_01284 vgtP         HG001_01284 -           HG001_01287 -         HG001_0287 -           HG001_0287 -         HG001_0287 -           HG001_02371 hutG         HG001_02374 -           HG001_02371 hutG         HG001_0237 -           HG001_02371 rutG         HG001_0237 -           HG001_02374 rureF         HG001_0237 -           HG001_02374 rureF         HG001_0237 -           HG001_02374 rureF         HG001_0237 -           HG001_0237 rureF         HG001_0237 -           HG001_02375 -         <	hypothetical protein Nickel transport system permease protein NikB IRNA-Gly(tcc) Nypothetical protein Outiolone resistance protein NorB Nypothetical protein Nypothetical protein T-box Dilgopeptide transport ATP-binding protein OppD Thioredoxin-like protein YtpP ierine protease SpIA precursor Sacterial g-like domain (group 2) Jutative lipoprotein precursor Sacterial g-like domain (group 2) Jutative lipoprotein precursor Jutative lipoprotein precursor Jutative lipoprotein precursor Jutative lipoprotein precursor Jutative levicoldin-like protein OpuCA Processive diacylg/verol beta-glucosyltransferase Jutative levicoldin-like protein 2 precursor Nypothetical protein Vickel import ATP-binding protein NikE Slycine cleavage system H protein Heptaprenyl diphosphate synthase (HEPPP synthase) subunit 1 Indoribonuclease YbeY Spermidine/plutrescine-binding periplasmic protein precursor Jikkimase 'ormimidoylglutamase -lactate permease Nypothetical protein RNA-Asp(gtc) IS Jutative kinase inhibitor Jrease accessory protein UreF on-sulphur cluster biosynthesis Nypothetical protein	SAOUHSC_02568 SAOUHSC_02766 SAOUHSC_01760022 SAOUHSC_01986 SAOUHSC_01980 SAOUHSC_01980 		-1,243 -1,234 -1,225 -1,212 -1,212 -1,212 -1,208 -1,208 -1,208 -1,207 -1,207 -1,207 -1,207 -1,195 -1,199 -1,189 -1,186 -1,186 -1,184 -1,184 -1,182 -1,175 -1,173 -1,162 -1,158 -1,155	1,44E-08 1,11E-05 0,000540677 3,05E-08 2,81E-06 6,49E-06 2,62E-08 2,62E-08 2,01E-09 0,000610276 2,05E-06 1,21E-06 6,11E-07 5,16E-06 1,09E-08 2,83E-06 0,000125426 0,010125426 0,010125426 0,010125426 0,010125426 0,01015541 0,000165510 0,53E-06 5,54E-06 5,54E-06 5,54E-06 5,53E-06 0,000165541 0,000165542 0,00016555 0,00016555 0,00016555 0,00016555 0,00016555 0,0001655 0,0001655 0,000165555 0,00016555 0,000165555 0,00005555 0,0001655
HG001_02506 nikB_2 HG001_01759 - HG001_01786 - HG001_01786 - HG001_02354 - HG001_02354 - HG001_02354 - HG001_01556 - HG001_01556 - HG001_01742 splA HG001_01742 splA HG001_01742 splA HG001_02489 opuCA HG001_02489 opuCA HG001_02489 opuCA HG001_02489 opuCA HG001_02489 opuCA HG001_02489 opuCA HG001_02138 nikE HG001_02138 nikE HG001_01280 - HG001_01280 - HG001_0128 nikE HG001_01280 - HG001_02138 nikE HG001_02183 nikE HG001_02183 nikE HG001_02183 nikE HG001_02184 - HG001_02184 - HG001_02185 - HG001_02371 hutG HG001_02371 hutG HG001_02371 nutG HG001_02371 nutG HG001_02371 nutG HG001_02364 - HG001_02371 nutG HG001_0237 neF HG001_0237 neF HG001_0237 neF HG001_0237 neF HG001_0237 neF HG001_0237 neF HG001_0237 neF	Nickel transport system permease protein NikB RRNA-Glyttcc) hypothetical protein Aunolone resistance protein NorB Aunolone resistance protein NorB hypothetical protein T-box Dilgopeptide transport ATP-binding protein OppD Thioredoxin-like protein YtpP ierine protease SpIA precursor Jacterial [e-like domain (group 2) butative lipoprotein precursor hypothetical protein Carritine transport ATP-binding protein OpuCA Processive diacylg/ycerol beta-glucosyltransferase butative leukocidin-like protein NikE Slycine cleavage system H protein Heptaprenyl diphosphate synthase (HEPPP synthase) subunit 1 indoribonuclease YbeY ipermidine/putrescine-binding periplasmic protein precursor hikimate kinase -lactate permease -lactate permease -lactate permease -lactate permease -lactate protein RNA-Asp(g(c) is butative kinase inhibitor Jrease accessory protein UreF on-sulphur cluster biosynthesis Nachase incenting 	SAOUHSC_02766 SAOUHSC_01986 SAOUHSC_01986 SAOUHSC_01986 SAOUHSC_01995 SAOUHSC_019448 SAOUHSC_019050 		-1,234 -1,225 -1,212 -1,212 -1,218 -1,208 -1,208 -1,208 -1,207 -1,195 -1,195 -1,195 -1,195 -1,186 -1,186 -1,186 -1,184 -1,182 -1,175 -1,173 -1,162 -1,162 -1,155	1,11E-05 0,000340577 3,05E-08 2,81E-06 6,49E-06 2,62E-08 1,06E-05 2,05E-06 1,20E-06 1,00E-05 2,05E-06 1,20E-06 1,00E-08 2,05E-06 1,00E-08 2,83E-06 0,000125426 0,0103125426 0,0103125426 0,0103125426 0,24E-07 2,44E-00 3,67E-08 5,44E-07 2,44E-06 5,54E-06 0,53E-06 0,00038585 0,000116544
HG001_01759 - HG001_01785 - HG001_01786 - HG001_02354 - HG001_02953 - HG001_01295 norB_4 & HG001_01556 - HG001_01855 - HG001_01855 - HG001_01365 - HG001_01365 - HG001_02292 - HG001_02289 cyl_1 & HG001_01280 & HG001_01287 & HG001_02371 hutG & HG001_02371 hutG & HG001_02371 hutG & HG001_00250 & HG001_02372 & HG001_02374 & - HG001_02372 & - HG001_02374 & -	IRNA-Gly(tcc) hypothetical protein optotetical protein popthetical protein popthetical protein r-box Dilgopeptide transport ATP-binding protein OppD Thioredoxin-like protein YtpP ierine protease SpIA precursor Sacterial Ig-like domain (group 2) putative lipoprotein precursor sacterial Ig-like domain (group 2) putative lipoprotein protein OpuCA Processive diacylglycerol beta glucosyltransferase putative leukocidin-like protein 2 precursor hypothetical protein protein protein vickel import ATP-binding protein NikE Slycine cleavage system H protein Heptaprenyl diphosphate synthase (HEPPP synthase) subunit 1 indoribonuclease YbeY ipermidine/putrescine-binding perjalasmic protein precursor shikimate kinase formimidoy/glutamase -lactate permease hypothetical protein RNA-Asp(gtc) is putative kinase inhibitor Jrease accessory protein UreF ron-sulphur cluster biosynthesis hypothetical protein	SAOUHSC_T00022 SAOUHSC_01986 SAOUHSC_01986 SAOUHSC_01986 SAOUHSC_01050 - SAOUHSC_01050 SAOUHSC_01925 SAOUHSC_01942 SAOUHSC_01942 SAOUHSC_02744 SAOUHSC_02744 SAOUHSC_02744 SAOUHSC_02743 SAOUHSC_021313 SAOUHSC_01313 SAOUHSC_013137 SAOUHSC_01409 SAOUHSC_01672 SAOUHSC_01672 SAOUHSC_01672 SAOUHSC_01672 SAOUHSC_02610 SAOUHSC_02610 SAOUHSC_02011 - SAOUHSC_0011 - SAOUHSC_0217 SAOUHSC_0217 SAOUHSC_02139	- - - - - - - - - - - - - - - - - - -	-1,225 -1,212 -1,212 -1,208 -1,208 -1,208 -1,207 -1,207 -1,207 -1,195 -1,192 -1,199 -1,186 -1,186 -1,186 -1,184 -1,182 -1,175 -1,173 -1,173 -1,173 -1,162 -1,155	0,000540677 3,05E-08 2,81E-06 6,49E-06 2,62E-08 2,62E-08 2,01E-09 0,000610276 2,05E-06 1,21E-06 6,11E-07 5,16E-06 1,21E-06 6,11E-07 5,16E-06 1,20E-06 0,000125426 0,0001374835 3,67E-08 5,44E-07 2,41E-08 3,67E-08 5,44E-07 2,41E-08 3,67E-08 5,44E-07 2,41E-08 3,67E-08 5,44E-07 2,41E-08 5,44E-07 2,41E-08 5,44E-07 2,41E-08 5,44E-07 2,41E-08 5,44E-07 2,41E-08 5,44E-07 2,41E-08 5,44E-07 2,41E-08 5,44E-07 2,41E-08 5,44E-07 2,41E-08 5,44E-07 2,41E-08 5,44E-07 2,41E-08 5,44E-07 2,41E-08 5,44E-07 2,41E-08 5,44E-07 2,41E-08 5,44E-07 2,41E-08 5,44E-07 2,41E-08 5,44E-07 2,41E-08 5,44E-07 2,41E-08 5,44E-07 2,44E-08 5,54E-08 5,55E-08
HG001_01786 - HG001_02354 - HG001_02354 - HG001_02354 - HG001_01295 - HG001_01556 - HG001_01655 tpP HG001_01655 tpP HG001_01365 - HG001_01365 - HG001_02489 opuCA (HG001_02489 opuCA (HG001_02484 optP HG001_02484 optP HG001_02484 optP HG001_01238 nikE HG001_01286 gcvH_1 (HG001_0132 - HG001_01325 - HG001_01325 - HG001_01325 - HG001_01325 - HG001_01325 - HG001_01352 - HG001_01352 - HG001_01352 - HG001_01352 - HG001_01355 - HG001_00256 + HG001_00256 + HG001_00256 - HG001_02257 - HG001_02255 - HG001_00255 - HG001_00256 - HG001_00256 - HG001_00256 - HG001_00256 - HG001_00256 - HG001_00256 - HG001_02257 - HG001_00256 - HG0001_00256 - HG0000_00256 - HG0000_00050 + HG00000050 + HG00000050 + HG00000050 + HG000000050 + HG00000000050 + HG000000050 + HG0000000050 + HG0000000050 + HG000	hypothetical protein hypothetical protein Quinolone resistance protein NorB hypothetical protein F-box Dilgopeptide transport ATP-binding protein OppD Thioredoxin-like protein YtpP Serine protease SpIA precursor Jacterial g-like domain (group 2) Juatative likeka protein rgroup 2) Juatative likeka protein precursor hypothetical protein Carnitine transport ATP-binding protein OpuCA Processive diacylglycerol beta-glucosyltransferase Juatative likeka collan-like protein 2 precursor hypothetical protein Ypothetical protein Ypothetical protein Ypothetical protein Sickel import ATP-binding protein NikE Siycine cleavage system H protein Heptaprenyl diphosphate synthase (HEPPP synthase) subunit 1 indoribonuclease YbeY spermidine/putrescine-binding periplasmic protein precursor Jikkimase Formimidoylglutamase -lactate permease hypothetical protein RNA-Asp(gtc) IS Juatatve kinase inhibitor Jrease accessory protein UreF ron-sulphur cluster biosynthesis hypothetical protein	SAOUHSC_01986 SAOUHSC_02592 SAOUHSC_01448 SAOUHSC_01050 		-1,212 -1,212 -1,211 -1,208 -1,208 -1,207 -1,207 -1,207 -1,192 -1,199 -1,189 -1,186 -1,186 -1,184 -1,184 -1,184 -1,182 -1,179 -1,179 -1,179 -1,175 -1,158 -1,155	3,05E-08 2,81E-06 6,49E-06 2,84E-06 2,45E-08 2,45E-08 2,44E-05 2,04E-09 2,04E-09 2,04E-06 1,02E-05 2,04E-09 0,000125426 0,000125426 0,000125426 0,000125426 0,000125426 0,000125426 0,000125426 0,000125426 0,000136541 0,000016541 0,000016541
HG001_02354 -         HG001_01295 norB_4           HG001_01295 norB_4         HG001_01556 -           HG001_01556 -         HG001_01655 typP           HG001_01655 typP         HG001_01656 -           HG001_01655 +         HG001_01365 -           HG001_01365 -         HG001_0242 splA           HG001_0242 splA         HG001_02489 opuCA           HG001_02489 opuCA         HG001_02489 opuCA           HG001_02489 opuCA         HG001_01288 nikE           HG001_01280 rikE         HG001_01283 rikE           HG001_01283 rikE         HG001_01332 -           HG001_01494 ybeY         HG001_00268 gcvH_1           HG001_02371 hutG         HG001_02364 -           HG001_02364 ref         HG001_02264 -           HG001_02371 hutG         HG001_02364 -           HG001_02364 ref         HG001_02364 -           HG001_02364 ref         HG001_02364 -           HG001_02365 -         HG001_02367 ref           HG001_02365 -         HG001_02367 ref           HG001_02365 -         HG001_02365 -           HG001_02365 -         HG001_02365 -           HG001_02365 -         HG001_02365 -           HG001_02745 -         HG001_02745 -	nypothetical protein Quinolone resistance protein NorB hypothetical protein F-box Dilgopeptide transport ATP-binding protein OppD Thioredoxin-like protein YtpP Serine protease SpIA precursor Jacterial [e]ike domain (group 2) Jutative lipoprotein precursor ypothetical protein Zimitine transport ATP-binding protein OpuCA Processive diacylglycerol beta-glucosyltransferase Jutative leukocidin-like protein 2 precursor ypothetical protein Yickel import ATP-binding protein NikE Slycine cleavage system H protein Heptaprenyl diphosphate synthase (HEPPP synthase) subunit 1 indoribonuclease YbeY jpermidine/putrescine-binding periplasmic protein precursor jhikimate kinase -lactate permease -lactate permease -lactate protein RNA-Asp(gtc) IS jutative kinase inhibitor Jrease accessory protein UreF ron-sulphur cluster biosynthesis ypothetical protein	SAOUHSC_02592 SAOUHSC_01448 SAOUHSC_01050 - SAOUHSC_01925 SAOUHSC_01942 SAOUHSC_01528 SAOUHSC_021528 SAOUHSC_02519 SAOUHSC_02519 SAOUHSC_02519 SAOUHSC_02519 SAOUHSC_02541 SAOUHSC_02243 SAOUHSC_01241 SAOUHSC_01402 SAOUHSC_01402 SAOUHSC_01402 SAOUHSC_01672 SAOUHSC_01672 SAOUHSC_01673 SAOUHSC_01605 SAOUHSC_02610 SAOUHSC_020507 SAOUHSC_020501 - SAOUHSC_020501 SAOUHSC_020501		-1,212 -1,211 -1,208 -1,208 -1,207 -1,207 -1,195 -1,195 -1,192 -1,186 -1,186 -1,186 -1,186 -1,184 -1,184 -1,182 -1,179 -1,175 -1,173 -1,162 -1,162 -1,155	2,81E-06 6,49E-06 2,62E-02 2,34E-05 2,05E-06 1,21E-06 6,11E-07 5,16E-06 1,09E-08 2,83E-06 0,000125426 0,000125426 0,000125426 0,0103374835 4,27E-07 2,04E-06 3,22E-06 3,22E-06 3,41E-09 3,47E-07 2,44E-08 5,44E-07 4,45E-08 5,45E-08
HG001_01295 norB_4 HG001_00953 - HG001_01556 - HG001_01556 - HG001_01742 splA S HG001_01742 splA S HG001_01742 splA S HG001_01742 splA S HG001_02292 - HG001_02292 - HG001_02289 opuCA HG001_0248 opuCA HG001_01248 opuCA HG001_01248 norB HG001_01260 - HG001_01260 - HG001_01260 splC HG001_01260 splC HG001_01260 splC HG001_01260 splC HG001_01463 aroK_2 S HG001_01463 aroK_2 S HG001_02637 hutG HG001_02371 hutG HG001_02371 hutG HG001_02371 splC HG001_02237 ureF HG001_0226 - HG001_0226 - HG001_0226 - HG001_0226 - HG001_0226 - HG001_0226 - HG001_0227 ureF HG001_0227 ureF HG001_0227 splC HG001_0227 splC HG001_	Quinolone resistance protein NorB hypothetical protein F-box Dilgopeptide transport ATP-binding protein OppD Thioredoxin-like protein YtpP Serine protease SpIA precursor Bacterial Ig-like domain (group 2) Juative lipoprotein precursor Juative lipoprotein precursor Juative lipoprotein precursor Trocessive diacylghycerol beta-glucosyltransferase Juative leukocidin-like protein 2 precursor Typothetical protein Typothetical protein Juckel import ATP-binding protein NikE Siycine cleavage system H protein Heptaprenyl diphosphate synthase (HEPPP synthase) subunit 1 Indoribonuclease YbeY Spermidine/putrescine-binding perjalasmic protein precursor Sihkimate kinase Formimidoy/glutamase Jactate permease Typothetical protein RNA-Asg(gt) S Juative kinase inhibitor Jrease accessory protein UreF ron-sulphur cluster biosynthesis Nayothetical protein	SAOUHSC_01448 SAOUHSC_01050 		-1,21 -1,208 -1,208 -1,207 -1,207 -1,195 -1,195 -1,192 -1,189 -1,186 -1,184 -1,184 -1,182 -1,182 -1,189 -1,186 -1,184 -1,184 -1,182 -1,175 -1,173 -1,162 -1,155 -1,155	6,49E-06 2,62E-08 1,06E-02 2,01E-09 0,000610276 2,05E-06 1,21E-06 6,11E-07 5,16E-06 1,09E-08 2,83E-06 0,000125426 0,0103125426 0,0103125426 0,0103125426 0,0103125426 0,010325426 0,0105541 0,941E-00 3,67E-08 5,44E-07 2,41E-08 1,45E-06 6,53E-06 0,000165541 0,0001657906
HG001_00953 - HG001_01556 - HG001_01556 - HG001_01556 - HG001_01655 tpP HG001_01655 tpP HG001_01365 - HG001_00248 - pHG001_02292 - HG001_02489 cpUCA (HG001_02484 uptP HG001_02484 uptP HG001_02064 uptP HG001_01238 nikE HG001_01238 nikE HG001_01332 - HG001_01328 - HG001_01328 - HG001_01325 - HG001_00252 potD SHG001_01454 heV hC001_01325 - HG001_00252 potD SHG001_0254 - HG001_00259 lttP_1 HG001_00256 - HG001_00256 - HG001_00256 - HG001_00256 - HG001_00255 - HG001_00255 - HG001_00708 lttP / HG001_00708 lttP / HG001_00708 lttP / HG001_00708 lttP / HG001_00256 - HG0001_00256 - HG00000000000000000000000000000000000	hypothetical protein I-box Dilgopeptide transport ATP-binding protein OppD Thioredoxin-like protein YtpP Serine protease SpIA precursor Bacterial Ig-like domain (group 2) outative lipoprotein precursor hypothetical protein constitue transport ATP-binding protein OpuCA 2 rocessive diacylglycerol beta-glucosyltransferase sutative leukocidin-like protein 2 precursor hypothetical protein typothetical protein hypothetical protein hypothetical protein hypothetical protein hypothetical protein hypothetical protein hypothetical protein hypothetical protein Heptaprenyl diphosphate synthase (HEPPP synthase) subunit 1 indoribonuclease YbeY ipermidine/putrescine-binding periplasmic protein precursor ishikimate kinase formimidoylglutamase -lactate permease hypothetical protein RNA-Asp(gtc) is sutative kinase inhibitor Jrease accessory protein UreF ron-sulphur cluster biosynthesis hypothetical protein	SAOUHSC_01050 	- - - - - - - - - - - - - - - - - - -	-1,208 -1,208 -1,207 -1,207 -1,195 -1,192 -1,199 -1,189 -1,186 -1,186 -1,184 -1,184 -1,184 -1,182 -1,179 -1,179 -1,179 -1,175 -1,173 -1,162 -1,162 -1,155 -1,155	2,62E-08 1,06E-05 2,34E-09 2,04E-09 2,04E-09 2,05E-06 1,24E-06 6,11E-07 5,16E-06 1,09E-08 2,88E-06 0,000125426 0,000325426 0,000325426 0,000325426 0,00035426 3,22E-06 9,41E-09 3,67E-08 5,34E-07 2,44E-08 5,34E-07 2,44E-08 5,54E-06 6,53E-06 0,000385585 0,000165906
HG001_01556 -           HG001_01556 -           HG001_01655 +           HG001_01655 +           HG001_01655 -           HG001_01365 -           HG001_01365 -           HG001_02292 -           HG001_022489 opuCA           HG001_022489 opuCA           HG001_022489 opuCA           HG001_02044 -           HG001_0128 nikE           HG001_0128 nikE           HG001_01238 nikE           HG001_01332 -           HG001_01494 ybeY           HG001_00252 potD           HG001_02371 hutG           HG001_02364 -           HG001_02039 lctP_1           HG001_02364 -           HG001_02371 hutG           HG001_0237 vreF           HG001_0237 vreF           HG001_0227 vreF           HG001_0275 -           HG001_0275 -	Nybolitical protein Flox Dilgopeptide transport ATP-binding protein OppD Thioredoxin-like protein YtpP Serine protease SpIA precursor Bacterial g-like domain (group 2) putative lipoprotein precursor Nypothetical protein Direction protein OpuCA Processive diacylglycerol beta-glucosyltransferase putative leukocidin-like protein 2 precursor Nypothetical protein Nypothetical protein Nypothetical protein Vickel import ATP-binding protein NikE Slycine cleavage system H protein Heptaprenyl diphosphate synthase (HEPPP synthase) subunit 1 indoribonuclease YbeY ipermidine/putrescine-binding periplasmic protein precursor ihikimate kinase -lactate permease -lactate permease Nypothetical protein RNA-Asg(gtc) S mutative kinase inhibitor Jrease accessory protein UreF ron-sulphur cluster biosynthesis Nypothetical protein	SAOUHSC_01930 SAOUHSC_01942 SAOUHSC_01528 SAOUHSC_01528 SAOUHSC_02519 SAOUHSC_02519 SAOUHSC_02519 SAOUHSC_02519 SAOUHSC_02243 SAOUHSC_01241 SAOUHSC_01402 SAOUHSC_01402 SAOUHSC_01402 SAOUHSC_01404 SAOUHSC_01672 SAOUHSC_01672 SAOUHSC_01673 SAOUHSC_02610 SAOUHSC_02610 SAOUHSC_02057 SAOUHSC_02057 SAOUHSC_02057 SAOUHSC_02051		-1,208 -1,208 -1,207 -1,207 -1,195 -1,192 -1,199 -1,186 -1,186 -1,186 -1,186 -1,184 -1,184 -1,182 -1,173 -1,173 -1,173 -1,162 -1,162 -1,155 -1,155 -1,155 -1,155 -1,208	2,062-05 2,342-05 2,342-05 2,052-06 1,212-06 6,112-07 5,162-06 1,095-08 2,835-06 0,000125426 0,010312426 0,013374835 4,272-07 2,042-06 3,222-06 3,242-06 3,242-06 3,242-06 3,242-06 5,3442-07 2,441-08 5,442-07 2,441-08 5,542-06 6,535-06 0,000389585 0,000116541 0,000389585
HG001_01334 oppD_1           HG001_01742 splA           HG001_01742 splA           HG001_01742 splA           HG001_01742 splA           HG001_021742 splA           HG001_02292 -           HG001_02289 opuCA           HG001_02284 opuCA           HG001_02084 ugtP           HG001_01128 nikE           HG001_01288 gcH_1           HG001_01288 gcH_1           HG001_01288 gcH_1           HG001_01494 ybeY           HG001_01494 ybeY           HG001_02371 hutG           HG001_02371 hutG           HG001_02371 rutG           HG001_02371 rutG           HG001_02237 ureF           HG001_0226 -           HG001_0227 ureF           HG001_0227 ureF           HG001_0227 ureF           HG001_0225 -           HG001_0227 ureF           HG001_0227 ureF           HG001_0225 -           HG001_0225 -           HG001_0225 -           HG001_0225 -           HG001_0225 -           HG001_0255 -	Dispeptide transport ATP-binding protein OppD Thioredoxin-like protein YtpP Serine protease SpIA precursor Bacterial [g-like domain (group 2) butative lipoprotein precursor hypothetical protein Carnitine transport ATP-binding protein OpuCA Processive diacy[glycerol beta-glucosyltransferase butative leukocidin-like protein 2 precursor hypothetical protein hypothetical protein hypothetical protein hypothetical protein hypothetical protein hypothetical protein hypothetical sex bey spermidine/putrescine-binding perplasmic protein precursor hikimate kinase formimidoy[glutamase -lactate permease hypothetical protein RNA-Asp(gtc) is butative kinase inhibitor Jrease accessory protein UreF ron-sulphur cluster biosynthesis hypothetical protein	SAOUHSC_00925 SAOUHSC_01860 SAOUHSC_01528 SAOUHSC_01528 SAOUHSC_02519 SAOUHSC_02519 SAOUHSC_02744 SAOUHSC_02744 SAOUHSC_01131 SAOUHSC_01131 SAOUHSC_011377 SAOUHSC_01637 SAOUHSC_01672 SAOUHSC_01672 SAOUHSC_01672 SAOUHSC_01607 SAOUHSC_02610 SAOUHSC_02061 SAOUHSC_02061 SAOUHSC_02061 SAOUHSC_02061 SAOUHSC_02061 SAOUHSC_02061 SAOUHSC_02061 SAOUHSC_02061 SAOUHSC_02061 SAOUHSC_0217 SAOUHSC_0217 SAOUHSC_0217 SAOUHSC_021349		-1,208 -1,207 -1,207 -1,195 -1,195 -1,192 -1,189 -1,186 -1,184 -1,184 -1,184 -1,182 -1,182 -1,179 -1,175 -1,173 -1,162 -1,162 -1,155 -1,155	2,34E-05 2,01E-09 0,000610276 2,05E-06 1,21E-06 6,11E-07 5,16E-08 2,83E-06 0,000125426 0,01037426 4,27E-07 2,04E-06 3,22E-06 9,44E-09 3,67E-08 5,44E-07 2,41E-08 5,44E-07 2,44E-08 5,44E-07 2,44E-08 5,44E-07 2,44E-08 5,44E-07 2,44E-08 5,44E-07 2,44E-08 5,44E-07 2,44E-08 5,44E-07 2,44E-08 5,44E-07 2,44E-08 5,44E-07 2,44E-08 5,44E-07 2,44E-08 5,44E-07 2,44E-08 5,44E-07 2,44E-08 5,44E-07 2,44E-08 5,44E-07 2,44E-08 5,44E-07 2,44E-08 5,44E-07 2,44E-08 5,44E-07 2,44E-08 5,44E-07 2,44E-08 5,555E-08 5,555
HG001_01655 typP HG001_01742 splA HG001_01742 splA HG001_01742 splA HG001_02085 - H HG001_02292 - H HG001_02292 - H HG001_0284 ugtP HG001_02084 ugtP HG001_01018 - H HG001_01288 nikE HG001_01288 nikE HG001_01288 nikE HG001_0268 gcvH_1 HG001_0052 pctP_1 HG001_0052 pctP_1 HG001_0052 fctP_1 HG001_0052 fctP_1 HG001_02371 hutG HG001_02371 hutG HG001_0237 intG HG001_02371 cref HG001_02327 uref HG001_02327 uref HG001_02327 uref HG001_0211 - H HG001_0211 - H HG001_0275 - H	Digoperide transport A Ir-Solitong protein OppU Serine protease SpIA precursor Sacterial Ig-like domain (group 2) outative lipoprotein precursor Typothetical protein Carnitine transport ATP-binding protein OpuCA Processive diacylglycerol beta-glucosyltransferase sutative leukocidin-like protein 2 precursor typothetical protein Vipothetical protein Vipothetical protein Vipothetical protein Vipothetical protein Sivicel import ATP-binding protein NikE Sivicine cleavage system H protein Heptaprenyl diphosphate synthase (HEPPP synthase) subunit 1 indoribonuclease YbeY Sipermidine/plutrescine-binding periplasmic protein precursor Sibikimate kinase Formimidoylglutamase -lactate permease typothetical protein RNA-Asp(gtc) Sis sutative kinase inhibitor Jrease accessory protein UreF ron-sulphur cluster biosynthesis	SAOUHSC_01925 SAOUHSC_01942 SAOUHSC_01942 SAOUHSC_01528 SAOUHSC_02519 SAOUHSC_02744 SAOUHSC_02744 SAOUHSC_02744 SAOUHSC_02744 SAOUHSC_02744 SAOUHSC_02744 SAOUHSC_01131 SAOUHSC_01131 SAOUHSC_011402 SAOUHSC_011488 SAOUHSC_01675 SAOUHSC_01675 SAOUHSC_02610 SAOUHSC_02610 SAOUHSC_02601 SAOUHSC_02601 SAOUHSC_02601 SAOUHSC_02653 SAOUHSC_02563 SAOUHSC_02563 SAOUHSC_021349	- - - - - - - - - - - - - - - - - - -	-1,207 -1,207 -1,195 -1,192 -1,199 -1,186 -1,186 -1,186 -1,186 -1,184 -1,184 -1,184 -1,182 -1,179 -1,179 -1,179 -1,175 -1,162 -1,162 -1,158 -1,155	2,34E-05 2,01E-09 2,005-06 1,21E-06 5,16E-06 1,02F-06 2,05E-06 1,02F-06 2,85E-06 0,000125426 0,000125426 0,000125426 0,000125426 3,22E-06 9,41E-09 3,42F-02 2,04E-06 3,22E-06 9,41E-09 3,42F-02 2,44E-000
HGUD1_U1665 YtPP HGUD1_U1655 + H HGUD1_U1242 splA HGUD1_U0185 - H HGUD1_U2292 - H HGUD1_U2292 - H HGUD1_U22489 opuCA HGUD1_U22489 opuCA HGUD1_U22489 opuCA HGUD1_U2244 - H HGUD1_U2244 - H HGUD1_U1238 nikE HGUD1_U1238 nikE HGUD1_U1238 nikE HGUD1_U1238 nikE HGUD1_U2238 nikE HGUD1_U2237 hUG HGUD1_U2337 hUG HGUD1_U2337 hUG HGUD1_U2345 - H HGUD1_U2325 - H HGUD1_U2325 - H HGUD1_U2255 - H HGUU1_U2255 - H	Inioredoxin-like protein YtpP Serine protease SplA precursor Bacterial Ig-like domain (group 2) Jutative lipoprotein precursor hypothetical protein Carnitine transport ATP-binding protein OpuCA Processive diacylglycerol beta-glucosyltransferase Jutative leukocidin-like protein 2 precursor hypothetical protein Vipothetical protein Vickel import ATP-binding protein NikE Slycine cleavage system H protein Heptaprenyl diphosphate synthase (HEPPP synthase) subunit 1 indoribonuclease YbeY japermidine/putrescine-binding periplasmic protein precursor jihikimate kinase -lactate permease -lactate permease ypothetical protein RNA-Asg(gtc) is jutative kinase inhibitor Jrease accessory protein UreF ron-sulphur cluster biosynthesis ypothetical protein	SAOUHSC_01942 SAOUHSC_01942 SAOUHSC_0053 SAOUHSC_02519 SAOUHSC_02519 SAOUHSC_02519 SAOUHSC_02519 SAOUHSC_02243 SAOUHSC_01241 SAOUHSC_01402 SAOUHSC_01402 SAOUHSC_01404 SAOUHSC_01672 SAOUHSC_01635 SAOUHSC_01635 SAOUHSC_02603 SAOUHSC_02057 SAOUHSC_02017 SAOUHSC_0217 SAOUHSC_0217 SAOUHSC_0217 SAOUHSC_0217		-1,207 -1,207 -1,195 -1,192 -1,189 -1,186 -1,186 -1,186 -1,184 -1,184 -1,184 -1,182 -1,179 -1,179 -1,175 -1,173 -1,162 -1,162 -1,155 -1,155	2,012-03 0,000610276 2,055-06 1,212-06 6,112-07 5,165-06 0,000125426 0,0013374835 4,272-07 2,048-06 3,222-06 3,222-06 3,248-07 2,448-07 2,448-07 2,448-07 2,448-00 2,448-00 0,000389585 0,000016541 0,000389585
HG001_01742 splA         S           HG001_0185 -         H           HG001_02292 -         H           HG001_01018 -         H           HG001_01280 -         H           HG001_01322 -         H           HG001_01494 ybeY         H           HG001_01493 arok_2         S           HG001_01493 arok_2         H           HG001_02371 hutG         H           HG001_02371 hutG         H           HG001_00246 -         H           HG001_00226 -         H           HG001_02262 -         H           HG001_02265 -         H           HG001_00726 clpP         H           HG001_007455 -         H	Serine protease SplA precursor Bacterial Ig-like domain (group 2) Dutative lipoprotein precursor Nypothetical protein Carnitine transport ATP-binding protein OpuCA Processive diacylgkycerol beta-glucosyltransferase Dutative leukocidin-like protein 2 precursor Nypothetical protein Nytochetical protein Nytochetical protein Nikel import ATP-binding protein NikE Silycine cleavage system H protein Heptaprenyl diphosphate synthase (HEPPP synthase) subunit 1 Indoribonuclease YbeY Sipermidine/putrescine-binding periplasmic protein precursor Sihkimate kinase Formimidoy/glutamase -lactate permease Nypothetical protein RNA-Asp(gtc) Sis Dutative kinase inhibitor Jrease accessory protein UreF ron-sulphur cluster biosynthesis Nypothetical protein	SAOUHSC_01942 SAOUHSC_01528 SAOUHSC_02519 SAOUHSC_02519 SAOUHSC_02744 SAOUHSC_02744 SAOUHSC_02743 SAOUHSC_01131 SAOUHSC_011377 SAOUHSC_011402 SAOUHSC_01672 SAOUHSC_01672 SAOUHSC_01672 SAOUHSC_01605 SAOUHSC_02610 SAOUHSC_02603 SAOUHSC_02011 - SAOUHSC_0217 SAOUHSC_02149		-1,207 -1,195 -1,192 -1,199 -1,186 -1,186 -1,184 -1,184 -1,184 -1,182 -1,179 -1,179 -1,179 -1,175 -1,173 -1,162 -1,162 -1,155 -1,155	0,000610276 2,05E-06 1,21E-06 6,11E-07 5,16E-06 1,09E-08 2,83E-06 0,000125426 0,0103125426 0,0103125426 0,0103125426 0,0103125426 9,44E-07 2,04E-06 9,34E-07 2,04E-06 5,34E-07 2,41E-08 1,45E-06 6,53E-06 0,000385858 0,000116540
HG001_01365 -         H           HG001_02392 -         H           HG001_02489 opuCA         H           HG001_01084 uptP         H           HG001_01018 -         H           HG001_01280 -         H           HG001_01288 grWH_1         H           HG001_01332 -         H           HG001_01494 ybeV         H           HG001_01463 arok_Z         S           HG001_02371 hutG         H           HG001_00236 ltP_1         H           HG001_00237 ltrG         H           HG001_02371 kutG         H           HG001_02371 kutG         H           HG001_02374 kutG         H           HG001_024255 -         H           HG001_02455 - <td< td=""><td>Bacterial Ig-like domain (group 2) putative lipoprotein precursor typothetical protein Processive diacylglycerol beta-glucosyltransferase putative leukocilan-like protein 2 precursor typothetical protein typothetical protein typothetical protein typothetical protein leptaprenyl diphosphate synthase (HEPPP synthase) subunit 1 indoribonuclease YbeY spermidine/putrescine-binding periplasmic protein precursor shikimate kinase formimidoylglutamase -lactate permease typothetical protein RNA-Asp(gtc) is sutative kinase inhibitor Jrease accessory protein UreF ron-sulphur cluster biosynthesis typothetical protein</td><td>SAOUHSC_01528 SAOUHSC_02519 SAOUHSC_02744 SAOUHSC_02744 SAOUHSC_02744 SAOUHSC_011311 SAOUHSC_011317 SAOUHSC_011377 SAOUHSC_011377 SAOUHSC_011488 SAOUHSC_01049 SAOUHSC_01049 SAOUHSC_01045 SAOUHSC_01045 SAOUHSC_02603 SAOUHSC_02067 SAOUHSC_02603 SAOUHSC_020917 SAOUHSC_02563 SAOUHSC_021349</td><td>- - - - - - - - - - - - - - - - - - -</td><td>-1,195 -1,192 -1,19 -1,189 -1,186 -1,186 -1,184 -1,184 -1,182 -1,182 -1,179 -1,179 -1,179 -1,175 -1,173 -1,162 -1,162 -1,158 -1,155 -1,155</td><td>2,055-06 1,21E-06 6,11E-07 5,16E-06 1,09E-08 2,88E-06 0,000125426 0,0003125426 0,003374835 4,27E-07 2,04E-06 3,22E-06 9,41E-09 3,45F-08 5,44E-07 2,41E-08 5,44E-07 2,41E-08 5,54E-06 6,53E-06 0,000389585 0,000116541 0,000389585</td></td<>	Bacterial Ig-like domain (group 2) putative lipoprotein precursor typothetical protein Processive diacylglycerol beta-glucosyltransferase putative leukocilan-like protein 2 precursor typothetical protein typothetical protein typothetical protein typothetical protein leptaprenyl diphosphate synthase (HEPPP synthase) subunit 1 indoribonuclease YbeY spermidine/putrescine-binding periplasmic protein precursor shikimate kinase formimidoylglutamase -lactate permease typothetical protein RNA-Asp(gtc) is sutative kinase inhibitor Jrease accessory protein UreF ron-sulphur cluster biosynthesis typothetical protein	SAOUHSC_01528 SAOUHSC_02519 SAOUHSC_02744 SAOUHSC_02744 SAOUHSC_02744 SAOUHSC_011311 SAOUHSC_011317 SAOUHSC_011377 SAOUHSC_011377 SAOUHSC_011488 SAOUHSC_01049 SAOUHSC_01049 SAOUHSC_01045 SAOUHSC_01045 SAOUHSC_02603 SAOUHSC_02067 SAOUHSC_02603 SAOUHSC_020917 SAOUHSC_02563 SAOUHSC_021349	- - - - - - - - - - - - - - - - - - -	-1,195 -1,192 -1,19 -1,189 -1,186 -1,186 -1,184 -1,184 -1,182 -1,182 -1,179 -1,179 -1,179 -1,175 -1,173 -1,162 -1,162 -1,158 -1,155 -1,155	2,055-06 1,21E-06 6,11E-07 5,16E-06 1,09E-08 2,88E-06 0,000125426 0,0003125426 0,003374835 4,27E-07 2,04E-06 3,22E-06 9,41E-09 3,45F-08 5,44E-07 2,41E-08 5,44E-07 2,41E-08 5,54E-06 6,53E-06 0,000389585 0,000116541 0,000389585
HG001_02048 - F HG001_02292 - H HG001_022489 opuCA HG001_02044 - F HG001_02044 - F HG001_01248 nikE HG001_0128 nikE HG001_01238 nikE HG001_01238 nikE HG001_01332 - F HG001_0238 qcvH_1 HG001_01494 ybeY HG001_00252 potD HG001_00395 lctP_1 HG001_02371 hutG HG001_02371 hutG HG001_02364 - F HG001_02364 - F HG001_0237 ureF HG001_02327 ureF HG001_02327 ureF HG001_02325 - F HG001_02625 - F HG001_02745 - F	outative lipoprotein precursor hypothetical protein Carnitine transport ATP-binding protein OpuCA Processive diacylgiycerol beta-glucosyltransferase outative leukocidin-like protein 2 precursor hypothetical protein yipothetical protein Wickel import ATP-binding protein NikE Slycine cleavage system H protein Heptapreryd liphosphate synthase (HEPPP synthase) subunit 1 Endoribonuclease YbeY spermidine/putrescine-binding periplasmic protein precursor Jihikimate kinase lactate permease lactate permease -sloctate protein RNA-Asp(gtc) IS sutative kinase inhibitor Jrease accessory protein UreF ron-sulphur cluster biosynthesis yopothetical protein	SAOUHSC_00053 SAOUHSC_02519 SAOUHSC_02744 SAOUHSC_02744 SAOUHSC_01243 SAOUHSC_01131 SAOUHSC_011377 SAOUHSC_01402 SAOUHSC_01408 SAOUHSC_01488 SAOUHSC_01632 SAOUHSC_01635 SAOUHSC_026610 SAOUHSC_026610 SAOUHSC_02067 SAOUHSC_020611 - SAOUHSC_02053 SAOUHSC_0217 SAOUHSC_02563 SAOUHSC_0217 SAOUHSC_0217	- - - - - - - - - - - - - - - - - - -	-1,192 -1,189 -1,186 -1,186 -1,186 -1,184 -1,184 -1,182 -1,179 -1,175 -1,173 -1,168 -1,162 -1,162 -1,158 -1,155 -1,155	1,21E-06 6,11E-07 5,16E-06 0,000125426 0,000125426 0,000125426 0,0001374835 4,27E-07 2,04E-06 3,22E-06 9,44E-08 5,44E-09 6,53E-06 0,000389585 0,000116541 0,000367906
HG001_02292 - H HG001_02489 opuCA ( HG001_02044 - H HG001_01018 - H HG001_01260 - H HG001_01280 nKK H HG001_01288 gcH_1 ( HG001_01322 - H HG001_01322 - H HG001_01322 - H HG001_01494 ybeY H G001_01494 ybeY H G001_02371 hutG H G001_02371 hutG H G001_02371 hutG H G001_02371 hutG H G001_02371 ntG H G001_02371 ntG H G001_02371 ntG H G001_02371 ntG H HG001_02371 ntG H G001_02371 ntG H G001_02371 ntG H HG001_02371 ntG H G001_02371 ntG H HG001_02371 ntG H HG001_02375 - H	nypothetical protein Carnitine transport ATP-binding protein OpuCA Processive diacylghycerol beta-glucosyltransferase butative leukocidin-like protein 2 precursor hypothetical protein Vickel import ATP-binding protein NikE Slycine cleavage system H protein Heptaprenyl diphosphate synthase (HEPPP synthase) subunit 1 indoribonuclease YbeY sipermidine/putrescine-binding periplasmic protein precursor Shikimate kinase formimidoylglutamase -lactate permease hypothetical protein RNA-Asg(gtc) S putative kinase inhibitor Jrease accessory protein UreF ron-sulphur cluster biosynthesis	SAOUHSC_02219 SAOUHSC_02243 SAOUHSC_00953 SAOUHSC_02243 SAOUHSC_01131 SAOUHSC_01131 SAOUHSC_011377 SAOUHSC_01377 SAOUHSC_01672 SAOUHSC_01672 SAOUHSC_01635 SAOUHSC_02610 SAOUHSC_02603 SAOUHSC_020917 SAOUHSC_021349	- - - - - - - - - - - - - - - - - - -	-1,19 -1,189 -1,186 -1,184 -1,184 -1,182 -1,179 -1,179 -1,175 -1,173 -1,162 -1,162 -1,158 -1,155 -1,155	6,11E-07 5,16E-06 1,09E-08 2,83E-06 0,000125426 0,013374835 4,27E-07 2,04E-06 3,22E-06 9,44E-09 3,67E-08 5,44E-07 2,41E-08 1,45E-06 6,53E-06 0,000389585 0,000016541 0,000389585
HG001_02489 opuCA         HG001_00864 ugtP           HG001_02044 -         HG001_01018 -           HG001_01018 -         HG001_01260 -           HG001_01280 -         HG001_01238 mikE           HG001_01238 nikE         HG001_01332 -           HG001_01494 vbeV         HG001_01493 arok_22           HG001_01463 arok_22         SHG001_02371 hutG           HG001_02371 hutG         HG001_02364 + _           HG001_02364 + _         HG001_02364 -           HG001_02364 -         HG001_02364 -           HG001_02374 ruref         HG001_02327 uref           HG001_02425 -         HG001_0265 -           HG001_02655 -         HG001_0275 -	Carnitine transport ATP-binding protein OpuCA Processive diacylg/vcerol beta-glucosyltransferase putative leukocilan-like protein 2 precursor hypothetical protein vickel import ATP-binding protein NikE Slycine cleavage system H protein Heptaprenyl diphosphate synthase (HEPPP synthase) subunit 1 indoribonuclease YbeY spermidine/putrescine-binding periplasmic protein precursor shikimate kinase Formimidoylglutamase -lactate permease hypothetical protein RNA-Asp(gtc) is sutative kinase inhibitor Jrease accessory protein UreF ron-sulphur cluster biosynthesis hypothetical protein	SAOUHSC_02744 SAOUHSC_02744 SAOUHSC_0253 SAOUHSC_01131 SAOUHSC_01137 SAOUHSC_01377 SAOUHSC_01307 SAOUHSC_01488 SAOUHSC_01488 SAOUHSC_01635 SAOUHSC_02100 SAOUHSC_02100 SAOUHSC_020007 SAOUHSC_020011 - SAOUHSC_02917 SAOUHSC_02563 SAOUHSC_02563 SAOUHSC_01349	- - - - - - - - - - - - - - - - - - -	-1,189 -1,186 -1,186 -1,184 -1,182 -1,179 -1,179 -1,179 -1,175 -1,173 -1,168 -1,162 -1,162 -1,158 -1,155 -1,155 -1,155	5,16E-06 1,09E-08 2,83E-06 0,010125426 0,013374835 4,27E-07 2,04E-06 3,22E-06 9,41E-09 3,67E-08 5,44E-07 2,41E-08 1,45E-06 6,53E-06 0,000389585 0,000116541 0,000367906
HG001_00864 ugtP HG001_02044 ugtP HG001_02044 HG001_0118 - HG001_0128 nikE HG001_01238 nikE HG001_01238 nikE HG001_01332 - HG001_01494 ybeY HG001_01494 ybeY HG001_00952 potD SHG001_02371 hutG HG001_02371 hutG HG001_02364 - HG001_02364 - HG001_02364 - HG001_00221 - HG001_00221 - HG001_00227 ureF HG001_02327 ureF HG001_02327 ureF HG001_02327 ureF HG001_02325 - HG001_02755 - HG001_00785 - HG001	Processive diacylgivcerol beta-glucosyltransferase outative leukocidin-like protein 2 precursor hypothetical protein Nickel import ATP-binding protein NikE Slycine cleavage system H protein Heptapreny diphosphate synthase (HEPPP synthase) subunit 1 Endoribonuclease YbeY ipermidine/putrescine-binding periplasmic protein precursor Shikimate kinase -factate permease -factate permease -lactate permease -sloctate protein RNA-Asp(gtc) is nutative kinase inhibitor Jrease accessory protein UreF ron-sulphur cluster biosynthesis ypothetical protein	SAOUHSC_00953 SAOUHSC_01243 SAOUHSC_01131 SAOUHSC_011402 SAOUHSC_01377 SAOUHSC_01377 SAOUHSC_01377 SAOUHSC_01148 SAOUHSC_01049 SAOUHSC_01049 SAOUHSC_01049 SAOUHSC_02601 SAOUHSC_02601 SAOUHSC_00917 SAOUHSC_02563 SAOUHSC_021349	- - - - - - - - - - - - - - - - - - -	-1,186 -1,186 -1,184 -1,184 -1,182 -1,179 -1,179 -1,175 -1,173 -1,178 -1,162 -1,162 -1,158 -1,155 -1,155	1,09E-08 2,83E-06 0,000125426 0,013374835 4,27E-07 2,04E-06 3,22E-06 9,41E-09 3,67E-08 5,44E-07 2,41E-08 1,45E-06 6,53E-06 0,000389585 0,000116541 0,000367906
HG001_02044 - HG001_01018 - HG001_01260 - HG001_01260 - HG001_01238 nikE HG001_01238 nikE HG001_01332 - HG001_01332 - HG001_01494 ybeY HG001_01494 ybeY HG001_01494 ybeY HG001_02371 hutG HG001_02371 hutG HG001_02376 - HG001_00256 - HG001_00286 - HG001_02327 ureF HG001_0237 ureF HG0	autative leukocidin-like protein 2 precursor iypothetical protein Nickel import ATP-binding protein NikE Slycine cleavage system H protein Heptaprenyl diphosphate synthase (HEPPP synthase) subunit 1 indoribonuclease YbeY sipermidine/putrescine-binding periplasmic protein precursor Shikimate kinase "ormimidoy(glutamase -lactate permease ypothetical protein IRNA-Asp(gtc) S sutative kinase inhibitor Jrease accessory protein UreF ron-sulphur cluster biosynthesis ypothetical protein	SAOUHSC_02243 SAOUHSC_01131 SAOUHSC_011402 SAOUHSC_01377 SAOUHSC_01377 SAOUHSC_01672 SAOUHSC_01672 SAOUHSC_01635 SAOUHSC_02610 SAOUHSC_02603 SAOUHSC_02603 SAOUHSC_0211 - SAOUHSC_0263 SAOUHSC_02563 SAOUHSC_02563 SAOUHSC_01349	- - - - - - - - - - - - - - - - - - -	-1,186 -1,184 -1,182 -1,179 -1,179 -1,175 -1,173 -1,162 -1,162 -1,162 -1,158 -1,155 -1,155	2,83E-06 0,000125426 0,013374835 4,27E-07 2,04E-06 3,22E-06 9,41E-09 3,67E-08 5,44E-07 2,41E-08 1,45E-06 6,53E-06 0,000389585 0,00016541 0,000367906
HG001_01018 - HG001_01260 - HG001_01260 - HG001_01288 gxH=1 HG001_00268 gxH=1 HG001_00352 potD HG001_01332 - HG001_01453 aroK_2 2 HG001_0453 aroK_2 2 HG001_02371 hutG HG001_00059 IcH_1 HG001_0059 IcH_2 HG001_0055 - HG001_02327 ureF HG001_02327 ureF HG001_02327 ureF HG001_02327 ureF HG001_02327 = HG001_02327 ureF HG001_02327 ureF HG001_02327 ureF HG001_02327 ureF HG001_0255 - HG001_0255 - HG001_0255 - HG001_0255 - HG001_0755 - HG001_07555 - HG001_07555 - HG001_07555 - HG001_07555555	hypothetical protein hypothetical protein Nikčel import ATP-binding protein NikE Slycine cleavage system H protein Heptaprenyl diphosphate synthase (HEPPP synthase) subunit 1 findoribonuclease YbeY spermidine/plutrescine-binding periplasmic protein precursor bihkimate kinase Formimidoylglutamase -lactate permease hypothetical protein RNA-Asp(gtc) 35 sutative kinase inhibitor Jrease accessory protein UreF ron-sulphur cluster biosynthesis	SAOUHSC_01131 SAOUHSC_01402 SAOUHSC_01377 SAOUHSC_01377 SAOUHSC_01488 SAOUHSC_01488 SAOUHSC_01635 SAOUHSC_02610 SAOUHSC_02603 SAOUHSC_02603 SAOUHSC_02603 SAOUHSC_00917 SAOUHSC_02563 SAOUHSC_01349	- - - - - - - - - - - - - - - - - - -	-1,184 -1,182 -1,179 -1,179 -1,175 -1,173 -1,168 -1,162 -1,162 -1,158 -1,158 -1,155 -1,155	0,000125426 0,013374835 4,27E-07 2,04E-06 3,22E-06 9,41E-09 3,67E-08 5,44E-07 2,41E-08 1,45E-06 6,53E-06 0,000389585 0,00018541 0,000367906
HG001_01260 - HG001_01238 nikE HG001_01238 nikE HG001_01238 nikE HG001_01332 - HG001_01332 - HG001_01453 aroK_2 SHG001_0052 ptot SHG001_0052 ptot SHG001_0052 ptot SHG001_02371 hutG HG001_02364 - HG001_02364 - HG001_02364 - HG001_02327 ureF HG001_0237 ureF HG001_0235 u	hypothetical protein Nickel import ATP-binding protein NikE Slycine cleavage system H protein Heptaparenyl diphosphate synthase (HEPPP synthase) subunit 1 Endoribonuclease YbeY spermidine/putrescine-binding periplasmic protein precursor Shikimate kinase ormimidoylglutamase -lactate permease -lactate permease -sactate permease S sutative kinase inhibitor Jrease accessory protein UreF ron-sulphur cluster biosynthesis Nypothetical protein	SAOUHSC_01402 SAOUHSC_01377 SAOUHSC_01377 SAOUHSC_01377 SAOUHSC_011672 SAOUHSC_01049 SAOUHSC_01049 SAOUHSC_02610 SAOUHSC_02601 SAOUHSC_02603 SAOUHSC_00917 SAOUHSC_02563 SAOUHSC_01349	- - - - - - - - - - - - - - - - - - -	-1,184 -1,182 -1,179 -1,179 -1,175 -1,173 -1,168 -1,162 -1,158 -1,155 -1,155	0,013374835 4,27E-07 2,04E-06 3,22E-06 9,41E-09 9,47E-08 1,45E-06 6,53E-06 6,53E-06 0,000389585 0,000116541 0,000367906
HG001_01238 nikE HG001_00268 gcH_1 HG001_01332 - HG001_01392 yetD HG001_01494 ybeY HG001_01494 ybeY HG001_02392 petD HG001_02391 hutG HG001_02391 hutG HG001_02394 - HG001_02364 - HG001_02365 - HG001_02255 - HG001_02785 - HG001_07855 - HG001_0785 - HG001_0785 - HG001_0785 -	Nickel import ATP-binding protein NikE Slycine cleavage system H protein Heptaprenyl diphosphate synthase (HEPPP synthase) subunit 1 Endoribonuclease YbeY Spermidine/putrescine-binding periplasmic protein precursor Shikimate kinase ormimidoylglutamase -lactate permease ypothetical protein RNA-Asp(gtc) S putative kinase inhibitor Jrease accessory protein UreF ron-sulphur cluster biosynthesis	SAOUHSC_01377 SAOUHSC_00305 SAOUHSC_01488 SAOUHSC_01672 SAOUHSC_01672 SAOUHSC_02610 SAOUHSC_02603 SAOUHSC_02603 SAOUHSC_020917 SAOUHSC_02563 SAOUHSC_01349	- - - - - - - - - - - - - - - - - - -	-1,182 -1,179 -1,175 -1,175 -1,173 -1,162 -1,162 -1,162 -1,158 -1,155 -1,155	4,27E-07 2,04E-06 3,22E-06 9,41E-09 3,67E-08 5,44E-07 2,41E-08 6,53E-06 0,000389585 0,000116541 0,000367906
HG001_00268 gcvH_1 ( HG001_01332 - H HG001_01494 ybeY H HG001_00952 potD HG001_00952 potD HG001_00952 potD HG001_00371 hutG HG001_002364 - H HG001_00021 - H HG001_002364 - H HG001_01553 - HG001_002826 - H HG001_02827 ureF HG001_02827 her HG001_02825 - H HG001_02785 - H	Slycine cleavage system H protein Heptaprenyl diphosphate synthase (HEPPP synthase) subunit 1 Endoribonuclease YbeY Spermidine/plutrescine-binding periplasmic protein precursor ihikimate kinase Formimidoylglutamase -lactate permease nypothetical protein RNA-Asp(gtc) 35 sutative kinase inhibitor Jrease accessory protein UreF ron-sulphur cluster biosynthesis	SAOUHSC_00305 SAOUHSC_01488 SAOUHSC_01672 SAOUHSC_01635 SAOUHSC_02610 SAOUHSC_02603 SAOUHSC_02603 SAOUHSC_02603 SAOUHSC_00917 SAOUHSC_02563 SAOUHSC_01349	- - - - - - - - - - - - - - - - - - -	-1,179 -1,179 -1,175 -1,173 -1,168 -1,162 -1,162 -1,158 -1,155 -1,155	2,04E-06 3,22E-06 9,41E-09 3,67E-08 5,44E-07 2,41E-08 1,45E-06 6,53E-06 0,000389585 0,000116541 0,000367906
HG001_01332 -         HG001_01434 vbeY           HG001_01454 vbeY         HG001_00952 potD           HG001_01463 arok_Z         S           HG001_02371 hutG         HG001_02371 hutG           HG001_00236 letP_1         HG001_00236 -           HG001_01553 -         HG001_00226 -           HG001_02327 ureF         HG001_02327 ureF           HG001_0211 -         HG001_02265 -           HG001_02655 -         HG001_07455 -	Industry diphosphate synthase (HEPPP synthase) subunit 1 Endoribonuclease YbeY Spermidine/putrescine-binding periplasmic protein precursor ihikimate kinase -lactate permease -lactate permease sypothetical protein RNA-Asp(gtc) 35 sutative kinase inhibitor Jrease accessory protein UreF ron-sulphur cluster biosynthesis wypothetical protein	SAOUHSC_01488 SAOUHSC_01672 SAOUHSC_01635 SAOUHSC_01635 SAOUHSC_02610 SAOUHSC_02601 SAOUHSC_02603 SAOUHSC_00917 SAOUHSC_02563 SAOUHSC_01349	- - - - - - - - - - - -	-1,179 -1,175 -1,173 -1,168 -1,162 -1,162 -1,158 -1,155 -1,155	3,22E-06 9,41E-09 3,67E-08 5,44E-07 2,41E-08 1,45E-06 6,53E-06 0,000389585 0,000116541 0,000367906
HGOD1_01494 ybeY HGO01_01494 ybeY HGO01_00952 potD SHGO01_021455 aroK_2 SHGO01_02371 hutG HGO01_020371 hutG HGO01_022371 hutG HGO01_02364 - HGO01_01553 - HGO01_00826 - HGO01_02827 - HGO01_02327 ureF HGO01_02327 i HGO01_02825 - HGO01_02785 - HGO01_0785	Individuouclease YbeY Spermidine/putrescine-binding periplasmic protein precursor Shikimate kinase -iactate permease -lactate permease wpothetical protein RNA-Asp(gtc) S putative kinase inhibitor Jrease accessory protein UreF ron-sulphur cluster biosynthesis Wpothetical protein	SAOUHSC_01672 SAOUHSC_01049 SAOUHSC_01049 SAOUHSC_02610 SAOUHSC_02603 SAOUHSC_02603 SAOUHSC_00917 SAOUHSC_02563 SAOUHSC_01349	- - - - ureE	-1,175 -1,173 -1,168 -1,162 -1,162 -1,162 -1,155 -1,155 -1,155	9,41E-09 3,67E-08 5,44E-07 2,41E-08 1,45E-06 6,53E-06 0,000389585 0,000116541 0,000367906
HG001_01952 potD           HG001_03952 potD           HG001_02371 hutG           HG001_02371 hutG           HG001_02374 -           HG001_02021 -           HG001_010021 -           HG001_02327 ureF           HG001_0211 -           HG001_02827 ureF           HG001_02625 -           HG001_02655 -           HG001_07455 -	Indontational Constructions of the second se	SAOUHSC_01047 SAOUHSC_01635 SAOUHSC_02610 SAOUHSC_02603 SAOUHSC_02603 SAOUHSC_02603 SAOUHSC_00917 SAOUHSC_02563 SAOUHSC_01349	- - - - ureE	-1,173 -1,168 -1,162 -1,162 -1,162 -1,158 -1,158 -1,155 -1,155	3,67E-08 5,44E-07 2,41E-08 1,45E-06 6,53E-06 0,000389585 0,000116541 0,000367906
HG001_0463 aroK_Z 3 HG001_0463 aroK_Z 4 HG001_02371 hutG 4 HG001_00259 lctP_1 1 HG001_02364 - 1 HG001_01553 - 4 HG001_01553 - 4 HG001_02827 ureF 4 HG001_02827 ureF 4 HG001_02625 - 1 HG001_00708 lctP 4 HG001_01455 - 4	speniniary parescheromong periphasing protein precursor Formimidoylglutamase Formimidoylglutamase -lactate permease nypothetical protein RNA-Asp(gtc) 35 Jutative kinase inhibitor Jrease accessory protein UreF ron-sulphur cluster biosynthesis wpothetical protein	SAOUHSC_01635 SAOUHSC_02610 SAOUHSC_02610 SAOUHSC_02603 SAOUHSC_02603 SAOUHSC_00917 SAOUHSC_02563 SAOUHSC_01349	- - - ureE	-1,173 -1,162 -1,162 -1,162 -1,158 -1,158 -1,155 -1,155	5,44E-07 2,41E-08 1,45E-06 6,53E-06 0,000389585 0,000116541 0,000367906
HG001_02371 hutG HG001_02371 hutG HG001_02371 hutG HG001_00256 - HG001_00226 - HG001_00226 - HG001_02826 - HG001_02827 - HG001_02825 - HG001_02825 - HG001_02785 - HG001_0785 - HG001_07455 - HG001_0455 - HG001_04555 - HG001_04555 - HG001_04555 - HG001_04555 - HG001_04555 - HG001_045555555555555555555555555555555555	onkrimate kinase Forminidoy[glutamase L-lactate permease ypothetical protein ;RNA-Asp(gtc) 5 sutative kinase inhibitor Jrease accessory protein UreF ron-sulphur cluster biosynthesis ypothetical protein	SAOUHSC_01893 SAOUHSC_02610 SAOUHSC_00067 SAOUHSC_02603 SAOUHSC_00917 SAOUHSC_00917 SAOUHSC_01349	- - - ureE	-1,168 -1,162 -1,162 -1,158 -1,158 -1,155 -1,155	2,41E-08 1,45E-06 6,53E-06 0,000389585 0,000116541 0,000367906
HGUD1_U23/1 HutG   HGOD1_U02364 -   HGUD1_U0021 -   HGUD1_U1553 -   HGUD1_U1553 -   HGUU1_U2327 uref   HGUU1_U2327 uref   HGUU1_U211 -   HGUU1_U2625 -   HGUU1_U755 -	orminidovigutamase I-lactate permease Nypothetical protein RNA-Asp(gtc) 35 Jutative kinase inhibitor Jrease accessory protein UreF ron-sulphur cluster biosynthesis Iypothetical protein	SAOUHSC_02610 SAOUHSC_00067 SAOUHSC_02603 SAOUHSC_100011 - SAOUHSC_00917 SAOUHSC_02563 SAOUHSC_01349	- - - ureE	-1,162 -1,162 -1,158 -1,158 -1,155 -1,155	2,41E-08 1,45E-06 6,53E-06 0,000389585 0,000116541 0,000367906
HG001_00059 http_1   HG001_02364 - P HG001_00021 - 1 HG001_00826 - p HG001_02327 ureF   HG001_02237 ureF   HG001_02255 - P HG001_02785 - P	-lactate permease hypothetical protein RNA-Asp(gtc) 35 Jutative kinase inhibitor Jrease accessory protein UreF ron-sulphur cluster biosynthesis hypothetical protein	SAOUHSC_00067 SAOUHSC_02603 SAOUHSC_T00011 - SAOUHSC_00917 SAOUHSC_02563 SAOUHSC_01349	- - - ureE	-1,162 -1,158 -1,158 -1,155 -1,155	1,45E-06 6,53E-06 0,000389585 0,000116541 0,000367906
HG001_02364 -   HG001_00021 -   HG001_00021 -   HG001_01553 -   HG001_01553 -   HG001_02227 ureF   HG001_012217 -   HG001_012121 -   HG001_012625 -   HG001_00708 clpP / HG001_01455 -   HG001_0145 -   HG001_01455 -   HG001_0145 -   HG001_01455 -   HG001_01455 -   HG001_0145 -   HG001_01455 -   HG001_014555 -   HG001_01455 -   HG001_01455 -   HG001_0	nypothetical protein IRNA-Asp(gtc) 55 Jutative kinase inhibitor Jrease accessory protein UreF ron-sulphur cluster biosynthesis Nypothetical protein	SAOUHSC_02603 SAOUHSC_T00011 - SAOUHSC_00917 SAOUHSC_02563 SAOUHSC_01349	- - ureE	-1,158 -1,158 -1,155 -1,155	6,53E-06 0,000389585 0,000116541 0,000367906
HG001_0021 - 1 HG001_01553 - H HG001_00826 - H HG001_02327 ureF U HG001_01211 - H HG001_02625 - H HG001_01455 - H	IRNA-Asp(gtc) 55 Jutative kinase inhibitor Jrease accessory protein UreF ron-sulphur cluster biosynthesis Iypothetical protein	SAOUHSC_T00011 - SAOUHSC_00917 SAOUHSC_02563 SAOUHSC_01349	- - - ureE	-1,158 -1,155 -1,155	0,000389585 0,000116541 0,000367906
HG001_01553 - 6 HG001_00826 - p HG001_02327 ureF I HG001_01211 - I HG001_02625 - I HG001_00708 clpP / HG001_01455 - I	55 Jutative kinase inhibitor Jrease accessory protein UreF ron-sulphur cluster biosynthesis Typothetical protein	- SAOUHSC_00917 SAOUHSC_02563 SAOUHSC_01349	- ureE	-1,155 -1,155	0,000116541 0,000367906
HG001_00826 - F HG001_02327 ureF HG001_02327 ureF HG001_01211 - F HG001_02625 - F HG001_00708 clpP HG001_00708 clpP HG001_01455 - F	outative kinase inhibitor Jrease accessory protein UreF ron-sulphur cluster biosynthesis ypothetical protein	SAOUHSC_00917 SAOUHSC_02563 SAOUHSC_01349	ureE	-1,155	0,000367906
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HG001_01211 - HG001_02625 - HG001_02625 - HG001_00708 clpP HG001_01455 - HG0001_01455 - HG0001_01455 - HG0001_01455 - HG0001_01455 - HG0001_01455 - HG0001_01455 - HG001_01455 - HG0001_01455 - HG0001_00001_0001_00001_0000000000000000	ron-sulphur cluster biosynthesis 1ypothetical protein	SAOUHSC_01349		-1,14	1,55E-06
HG001_02625 - HG001_00708 clpP HG001_01455 - HG001_001_01455 - HG001_01455 - HG0001_001455 - HG0001_0001_0001000000000000000000000000	hypothetical protein	and the second second second second		-1,14	8,82E-06
HG001_00708 clpP //		SAOUHSC 02905	120	-1.139	0.001100864
HG001_01455 -	ATP-dependent Clp protease proteolytic subunit	SAOUHSC 00790	cloP	-1.137	5.17E-08
1000 - 01-00	avaathetical protein	SAOUHSC 01627		-1.136	0.000103352
H6001_01657_ccnA	Catabolite control protein A	SAOUHSC 01850	100	-1.134	4 30E-07
HG001_01757	(BNA-Glu(ttr)	SAOUHSC TOOO19		-1 134	0.006684315
HG001_01737 -	Rive Gio(cc)	SAOUHSC 01007	101	1,134	1 195 05
HG001_01826 perk	reloxide-responsive repressor Perk	SAOUHSC_01997		-1,132	1,180-00
HG001_01694 -	iypotnetical protein	SAOOHSC_01890		-1,13	1,77E-07
HG001_01762 -	RNA-Asp(gtc)	SAOUHSC_T00012	21. <del>4</del> .5	-1,129	0,000404503
HG001_00261 ybbH_2	autative HTH-type transcriptional regulator YbbH	SAOUHSC_00297	+	-1,128	3,10E-07
HG001_01602 -	í-box	SAOUHSC_01789		-1,127	6,79E-07
HG001_00647 -	ectron transfer DM13	SAOUHSC_00717		-1,124	1,27E-05
HG001_01808 - 1	RNA-Asp(gtc)	SAOUHSC_T00014		-1,123	0,000512416
HG001_02197 - 1	RNA-Glu(ttc)	SAOUHSC_T00020		-1,121	0,0067847
HG001_01737 splF	Serine protease SpIF precursor	SAOUHSC_01935	(*);	-1,119	0,000404393
HG001 00706 whiA	Putative sporulation transcription regulator WhiA	SAOUHSC 00789	(+)	-1,115	4,52E-07
HG001 01202 tkt	Fransketolase	SAOUHSC 01337	24.2	-1,114	1,46E-07
HG001 02572 -	hypothetical protein	SAOUHSC 02842	242	-1.113	0.012071358
HG001 01436 pepT 2	Peptidase T	SAOUHSC 01606		-1.112	1.225-06
HG001_01650 prcA	Penicillin-binding protein 1A	SAOUHSC 01840		-1.11	3 485-05
HG001_02252	whether is a protein	SAOUHSC 02501		-1 109	5,402 03
HG001_02333 - 1	(P)(A Children)	5A0UH5C_02331	2.50	1,103	0.000713167
HG001_00459 -	RNA-GIV(gec)	SACUHSC_TOUUZI	-	-1,105	0,000/1216/
HG001_01805 -	RNA-Asp(gtc)	SAOUHSC_100013		-1,102	0,000698607
HG001_00985 -	Jutative TrmH family tRNA/rRNA methyltransferase	SAOUHSC_01091		-1,099	3,49E-07
HG001_02422 sarZ	4TH-type transcriptional regulator SarZ	SAOUHSC_02669	5.50	-1,099	1,11E-05
HG001_01221 -	outative tautomerase	SAOUHSC_01362	1	-1,095	1,27E-06
HG001_00868 -	/ybP-ykoY	5	1.20	-1,095	0,004142821
HG001_01498 -	hypothetical protein	SAOUHSC_01677		-1,093	1,75E-08
HG001_00679 - H	hypothetical protein	SAOUHSC_00755		-1,093	2,12E-07
HG001_01165 -	hypothetical protein	SAOUHSC_01293	0.00	-1,093	0,046553567
HG001 01627 gloB 1	-lydroxyacylglutathione hydrolase	SAOUHSC 01815		-1,089	9,83E-07
HG001_02688 secA 2	Protein translocase subunit SecA	SAOUHSC 02985	azi	-1,086	5,76E-07
HG001 01750 -	hypothetical protein	SAOUHSC 01952		-1.086	2,88E-06
HG001 01453 efc	Elongation factor P	SAOUHSC 01625		-1.084	3.07F-08
HG001_01253 and	Aspartate-semialdehyde dehydrogenase	SAOUHSC 01305	2000 	-1.097	5 105.07
HG001_00025 6cep	Sulfide debudrosenase Iflavosutorbrome al flavonuctale shale autorometer	SACILIEC 00037	0.60	-1,082	1 225.05
HG001_00055 TCCB 5	Annue venyorogenase (navocytochrome c) navoprotein chain precursor	SACUNC CONST	633	-1,082	2,335-05
HG001_00103 - / /	vyrose isomerase-inke rink barrer	SACONSC_00181	100	-1,082	5,258-05
HG001_00502 gph_1	mosphoglycolate phosphatase	SAOUHSC_00555	229.	-1,082	0,000428418
HG001_00806 glpQ1_1 p	sutative glycerophosphoryl diester phosphodiesterase 1	SAOUHSC_00897	3.50	-1,079	7,50E-06
HG001_00994 trxA_2	nioredoxin	SAOUHSC_01100	3	-1,078	9,11E-07
HG001_01249 cvfB	onserved virulence factor B	SAOUHSC_01391		-1,076	1,07E-06
HG001_01426 -	hypothetical protein	SAOUHSC_01595		-1,074	0,013872178

HG001_02574 lipR_2	Putative acetyl-hydrolase LipR precursor	SAOUHSC_02844		-1,07	9,83E-0
HG001_01258 alr2	Alanine racemase 2	SAOUHSC_01400	-	-1,069	1,81E-0
HG001_01824 -	tRNA-Ile(gat)	SAOUHSC_T00028	-	-1,066	0,00232811
HG001_01456 -	hypothetical protein	SAOUHSC_01628	2	-1,064	0,00118503
HG001_00758 metQ_2	Methionine-binding lipoprotein MetQ precursor	SAOUHSC_00844	-	-1,062	0,00010335
HG001_00495 tagE_2	putative poly(glycerol-phosphate) alpha-glucosyltransferase	SAOUHSC_00548	¥	-1,06	2,16E-0
HG001_02647 hmoB	Heme-degrading monooxygenase HmoB	SAOUHSC_02930	2	-1,058	2,79E-0
HG001_02343 -	hypothetical protein	SAOUHSC_02581	2	-1,058	6,24E-0
HG001_02226 -	Zinc-type alcohol dehydrogenase-like protein	SAOUHSC_02445	-	-1,055	1,20E-0
HG001_00114 wbpA	UDP-N-acetyl-D-glucosamine 6-dehydrogenase	SAOUHSC_00128	-	-1,052	8,31E-0
HG001_00321 -	hypothetical protein	SAOUHSC_00362	2	-1,048	1,42E-0
HG001_00694 yfbR	5'-deoxynucleotidase YfbR	SAOUHSC_00774	÷	-1,047	9,13E-0
HG001_01811 -	tRNA-Met(cat)	SAOUHSC_T00041	8	-1,044	0,00297375
HG001_02419 -	hypothetical protein	SAOUHSC_02666	2	-1,042	2,49E-0
HG001_00401 dnaX_2	DNA polymerase III subunit tau	SAOUHSC_00454	2	-1,041	8,09E-0
HG001_01977 -	Bacterial SH3 domain protein	SAOUHSC_02170	÷	-1,04	0,00018003
HG001 00958 -	hypothetical protein	SAOUHSC 01055a	S	-1,038	1,44E-0
HG001 00182 -	hypothetical protein	SAOUHSC_00203	2	-1,038	4,52E-0
HG001 02686 gtf2	Glycosyltransferase-stabilizing protein Gtf2	SAOUHSC 02983	-	-1,036	5,89E-0
HG001_00340 gorB	Quinone oxidoreductase 2	SAOUHSC 00382	w.	-1,035	9,37E-0
HG001 02097 mazE	Antitoxin MazE	SAOUHSC 02304	<b>3</b>	-1,031	4,06E-0
HG001 02604 crtP	Diapolycopene oxygenase	SAOUHSC 02881	*	-1,031	1,94E-0
HG001 00727 -	hypothetical protein	SAOUHSC 00811	-	-1,031	0,00012592
HG001 02530 -	hypothetical protein	SAOUHSC 02794	-	-1,028	0,0022234
HG001 01814 -	tRNA-Arg(acg)	SAOUHSC T0007	*	-1,027	0,00738876
HG001 00626 yciC 2	Putative metal chaperone YciC	SAOUHSC 00695	-	-1,026	3,19E-0
HG001 00357 -	putative lipoprotein precursor	SAOUHSC 00404		-1,025	0,00083145
HG001 00436 -	tRNA-Val(tac)	SAOUHSC T00059	-	-1.025	0,00244388
HG001 01578 comC	Type 4 prepilin-like proteins leader peptide-processing enzyme	SAOUHSC 01764	-	-1,025	0,0300742
HG001 02236 lacR	Lactose phosphotransferase system repressor	SAOUHSC 02456	-	-1.023	4.93E-0
HG001 01820 -	tRNA-Val(tac)	SAOUHSC T00060	-	-1,023	0,00291439
HG001 00621 -	hypothetical protein	SAOUHSC 00690	-	-1.022	2.56E-0
HG001 01366 -	Phage major tail protein	SAOUHSC 01529		-1.022	5.07E-0
HG001 01749 nisC	Nisin biosynthesis protein NisC	SAOUHSC 01951		-1.018	0.00016858
HG001 00443 -	tRNA-Ala(tec)	SAOUHSC T0001	-	-1.018	0.00197790
HG001 01647 htrA	Serine protease Do-like HtrA	SAOUHSC 01838	-	-1.016	5,59E-0
HG001 00520 galK 1	Galactokinase	SAOUHSC 00577	-	-1.016	1.07E-0
HG001 01017 -	hypothetical protein	SAOUHSC 01130	-	-1.015	1,25E-0
HG001 00210 rebM	Demethylrebeccamycin-D-glucose O-methyltransferase	SAOUHSC 00237	-	-1,015	0,00275672
HG001 00437 -	tRNA-Thr(tgt)	SAOUHSC T00053	-	-1.014	0.00517070
HG001 00507 -	hypothetical protein	SAOUHSC 00560	-	-1.014	0,00807065
HG001 00824 ywlC 1	Threonylcarbamoyl-AMP synthase	SAOUHSC 00915	-	-1.01	0,01183502
HG001 01294 ebh 1	Extracellular matrix-binding protein ebh precursor	SAOUHSC 01447	-	-1.009	1.21E-0
HG001 01359 -	hypothetical protein	SAOUHSC 01522	-	-1,008	0,00789153
HG001 01699 -	hypothetical protein	SAOUHSC 01896	-	-1.007	7.34E-0
HG001 02088 -	tRNA-Gly(tcc)	SAOUHSC T00025		-1.005	0,00284785
HG001 00253 hrtA 1	Putative hemin import ATP-binding protein HrtA	SAOUHSC 00287		-1.004	1,03E-0
HG001_01738 splE	Serine protease SplE precursor	SAOUHSC_01936		-1.003	0,01008243
HG001_01251 -	Lysine		-	-1	2,32E-0
and the second state of th	100720-10050000				

## Annexe 2 : Tableau de l'expression différentielle des protéines durant le stress oxydant :

Liste de tous les gènes activés ou inhibés durant le stress oxydant.

UP regulated genes from the differencial proteomics analysis in oxidative stress					
accession description	LogFC (MV/WT)	adjp			
HG001_01897 HG001_01897 gene_NONE hypothetical protein	9,14	1,96E-43			
HG001_01902 HG001_01902 gene_NONE Phage antirepressor protein KilAC domain protein	9,03	5,76E-54			
HG001_00066 HG001_00066  gene_ala   Alanine dehydrogenase	8,63	5,62E-28			
HG001_01894 HG001_01894  gene_NONE   hypothetical protein	7,72	8,10E-24			
HG001_00070 HG001_00070 gene_iucC_2 Aerobactin synthase	7,41	3,27E-19			
HG001_01895 HG001_01895  gene_NONE   Bacteriophage Mu Gam like protein	7,35	2,61E-18			
HG001_01899 HG001_01899 gene_NONE hypothetical protein	7,22	7,52E-17			
HG001_00299 HG001_00299 Igene_metE 5-methyltetrahydropteroyltrigiutamatehomocysteine methyltransterase	7.16	7,63E-12			
HG001_00071 HG001_00071 [gene_gart]5-keto-4-deoxy-D-glucarate aldolase	6,79	1,54E-12			
HG001_01880 HG001_01880 [gene_NONE [hypothetical protein	0,23	1,4/E-08			
HG001_0072 HG01_0072 [gene_dtk]-[gutamy-[gtn acy-carrier protein] decarboxylase	5.01	7,21E-08			
HG001_01293 HG01_012751gene_NUCEEbwoothetical extension	5.91	2 24E-20			
HG001_01857 HG01_01853 [gene_NONE] hypothetical protein	5.68	6.87E-06			
HG001_010059_HG001_00058[gene_incre_1]/vpctraterial.picture.	5.59	1.37E-05			
HG001 01873 HG001 01873 Jene NONE hypothetical protein	5.50	2 76E-05			
HG001 00073 HG001 00073 Jgene NONE Part-like nuclease domain protein	5 50	2.76E-05			
HG001 01900 HG001 01900 Jgene NONE hypothetical protein	5.30	1.17E-04			
HG001 00067 HG001 00067 Jgene jucc 11 Aerobactin synthase	5.19	2.32E-04			
HG001 00218 HG001 00218 gene NONE Penicillin acylase precursor	5.07	4.70E-04			
HG001 01891 HG001 01891 gene NONE hypothetical protein	4,93	9,83E-04			
HG001 01232 HG001 01232 gene trpB Tryptophan synthase beta chain	4,79	2,09E-03			
HG001_01883 HG001_01883  gene_NONE   PVL ORF-50-like family protein	4,44	8,53E-03			
HG001_01866 HG001_01866 gene_NONE Phage capsid family protein	4,23	1,64E-02			
HG001_00064 HG001_00064  gene_yfiY  putative siderophore-binding lipoprotein YfiY precursor	3,99	8,34E-81			
HG001_01859 HG001_01859 gene_NONE Phage protein	3,98	3,18E-02			
HG001_01886 HG001_01886 gene_NONE hypothetical protein	3,98	3,18E-02			
HG001_01884 HG001_01884  gene_NONE   Helix-turn-helix domain protein	3,68	6,59E-02			
HG001_02384 HG001_02384 gene_lcdH L-carnitine dehydrogenase	3,68	6,59E-02			
HG001_00977 HG001_00977  gene_isdB  Iron-regulated surface determinant protein B precursor	3,68	6,59E-02			
HG001_02135 HG001_02135  gene_atpE ATP synthase subunit c	3,30	1,23E-01			
HG001_02215 HG001_02215  gene_NONE Alanine racemase	3,30	1,23E-01			
HG001_00300 HG001_00300  gene_vit Bifunctional homocysteine S-methyltransferase/5,10-methylenetetrahydrofolate reductas	e 3,30	1,23E-01			
HG001_00269 HG001_00269  gene_ymdB O-acetyl-ADP-ribose deacetylase	3,30	1,23E-01			
HG001_01860 HG001_01860  gene_NONE  Phage major tail protein 2	3,30	1,23E-01			
HG001_018// HG001_018// [gene_NONE] hypothetical protein	3,30	1,23E-01			
HG001_02727 HG001_02727 [gene_gipt=3] Iniosurate summtransferase Gipt	3.20	2,44E-09			
HC001_009/3 HC001_009/3 [gang_hc] Soc] [brid-regulated surface determinant protein C precursor	2,19	2,32E-01			
HG001_02305 HG001_02305 [gene_nutr] initiazio legi popionase	2,15	2,325-01			
HG001_02210 HG001_02210 gene_hd2_ch/2/cit/y+ht0/act/y+ht0/hydr0xyysine synthise	2,15	2,32E-01			
HG001_00365 HG001_00365 Jgene_NOVE[hypothetical protein	2.79	2 32E-01			
H6001_00302_H6001_00302]gene_meth(Usstathionine.gamma-synthase/O-acetylhomoserine (thiol)-lyase	279	2 32E-01			
HG001 00065 HG001 00065 Jgene shal butative siderophore biosynthesis protein Sha	2.79	2.32E-01			
HG001_01769_HG001_01769_Leene_NONETBacterial ABC transporter protein EcsB	2.79	2.32E-01			
HG001 01887 HG001 01887 gene NONE hypothetical protein	2,79	2.32E-01			
HG001 01890 HG001 01890 gene NONE hypothetical protein	2.79	2,32E-01			
HG001_01049 HG001_01049 [gene_pyrR]Bifunctional protein PyrR	2,76	4,52E-09			
HG001_02166 HG001_02166 gene_dps General stress protein 20U	2,71	1,02E-27			
HG001_02214 HG001_02214 gene_yfmC_2 Fe(3+)-citrate-binding protein YfmC precursor	2,62	4,81E-52			
HG001_01910 HG001_01910 gene_xerC_2 Tyrosine recombinase XerC	2,45	1,19E-01			
HG001_02629 HG001_02629 gene_pyrD Dihydroorotate dehydrogenase (quinone)	2,33	6,96E-12			
HG001_00586 HG001_00586 gene_yusV_1 putative siderophore transport system ATP-binding protein YusV	2,24	6,82E-02			
HG001_02658 HG001_02658 gene_cysJ Sulfite reductase [NADPH] flavoprotein alpha-component	2,03	1,30E-11			
HG001_00116 HG001_00116  gene_isdl   Heme oxygenase (staphylobilin-producing) 2	2,02	5,34E-05			
HG001_01901 HG001_01901  gene_NONE   hypothetical protein	1,98	4,11E-01			
HGU01_01227 HGU01_01227 [gene_trpE] Anthranilate synthase component 1	1,98	4,11E-01			
HGUUI_UI3/9 HGUUI_UI3/9 [gene_tgs] Folyipolygiutamate synthase	1.98	4,11E-01			
HG001_02000_HC001_02000[gene_h0NE]S-formylgiutathione nydrolase	1,98	4,11E-01			
HG001_012000_HG001_012000[gene_dapt.[Lt-diaminopimerate aminotransferase	1,98	4,11E-01			
HG001_02030_HG001_02039]gene_h03[http://doi.org/window.org/gendse	1.90	4,115-01			
HG001_02025 HG001_02025 Igene_NONE[AntA/AntR antirenressor	1.98	4 11E-01			
HG001_02352_HG001_02352/gene_vifK/putative transport protein VifK	1 98	4.11E-01			
HG001 02409 HG001 02409 gene NONE Acetyltransferase (GNAT) family protein	1.98	4.11E-01			

H6000_10870         H8000_10870			
H600_0098H H600_0098H (apre_u6d) [here oxgenase (tsaphylobilin-producing) 1         198         4.11E-61           H600_01005 (box0_01005) (apre_NONE [hypothetical protein         198         4.11E-61           H600_01203 (box0_012032) (apre_ADONE [hypothetical protein         198         4.11E-61           H600_01203 (box0_012032) (apre_ADONE [hypothetical protein         188         4.11E-61           H600_01203 (box0_012032) (apre_ADONE [hypothetical protein         188         5.26E-62           H600_01203 (box0_012032) (apre_ADONE [hypothetical protein         188         5.26E-62           H600_01203 (box0_012032) (apre_ADOLAN) (hypothetical protein         188         5.26E-62           H600_01203 (box0_012032) (apre_ADOLAN) (hypothetical protein         188         5.26E-62           H600_01203 (box0_01202	HG001_01870 HG001_01870 gene_NONE Phage portal protein, SPP1 Gp6-like	1,98	4,11E-01
H600_10105 H600_10203 [gen_arg F] (Ornithine carbamoyltransferase         198         4,116-01           H600_10200 H600_10203 [gen_arg H1] Proton/sodium/glutamite symport protein         198         4,116-01           H600_10203 [H000_10203 [gen_arg, H1] Proton/sodium/glutamite symport protein         198         4,116-01           H600_1023 H600_10233 [gen_arg, MONE [hypothetical protein         198         4,116-01           H600_10237 [H000_00273 [gen_arg, MONE [hypothetical protein         198         4,116-01           H600_10237 H600_00273 [gen_arg, MONE [hypothetical protein         198         4,116-01           H600_10237 H600_00273 [gen_arg, MONE [hypothetical protein         198         4,116-01           H600_10233 H600_0035 [gen_arg, MONE [hypothetical protein         198         4,116-01           H600_10233 H600_0035 [gen_arg, MONE [hypothetical protein         198         4,116-01           H600_10234 H600_0033 [gen_arg, abp(] [High -fifting hem uptake system protein hdE precursor         198         4,116-01           H600_10232 H600_00333 [gen_arg, abp(] [High -fifting hem uptake system protein hdE precursor         188         5,286-02           H600_10232 H600_00333 [gen_arg, abp[ [Ak] High -fifting hem uptake system protein hdE precursor         188         5,286-02           H600_10232 H600_00333 [gen_arg, abp[ [Ak] High -fifting hem uptake system protein hdE precursor         188         5,286-02           <	HG001_00984 HG001_00984 gene_isdG Heme oxygenase (staphylobilin-producing) 1	1,98	4,11E-01
H6000_01200 H6000_012001 geme_NONE    proportiestical protein         198         4.11E-01           H6000_012021 Meme_NONE    protentiscial protein         198         4.11E-01           H6000_012021 Meme_NONE    protentiscial protein         198         4.11E-01           H6000_012021 Meme_NONE    protentiscial protein         198         4.11E-01           H6000_012071 Heme_NONE    protentiscial protein         198         4.11E-01           H6000_012071 Heme_NONE    protentiscial protein         198         4.11E-01           H6000_012071 Heme_NONE    protentiscial protein         198         4.11E-01           H6000_012073 Hemo_NONE    protentiscial protein         198         4.11E-01           H6000_012073 Hemo_NONE    protentiscial protein         198         4.11E-01           H6000_02073 Hemo_NONE    protentiscial protein         188         4.11E-01           H6000_02073 Hemo_NONE    protentiscial protein         188         526E-02           H6000_0273 Hemo_NONE    protentiscial protein	HG001_01015 HG001_01015  gene_argF Ornithine carbamoyltransferase	1,98	4,11E-01
H6000_2024 M600_202420 Jeac_git1 Protony-odum/gutamate symport protein         198         4,116-01           M6000_1003 Jeac_git2         M6001_20234 Jeac_NONE [hypothetical protein         198         4,116-01           M6000_20273 Jeac_sAVE [hypothetical protein         198         4,116-01           M6000_20273 Jeac_sAVE [hypothetical protein         198         4,116-01           M6000_20273 Jeac_sAVE [hypothetical protein         198         4,116-01           M6000_2023 Jeac_NONE [hypothetical protein         198         4,116-01           M6000_2023 Jeac_sAVE [hypothetical protein bdf precursor         198         4,116-01           M6000_2024 M600_2033 Jeac_sAPC [Ak] Hydroperoade reductase subunit C         192         4,006-77           M6000_2025 H600_2033 Jeac_sAPC [Ak] Hydroperoade reductase subunit A         190         2,996-01           M6000_2025 H600_2025 Jeac_sAPC [Ak] Hydroperoade reductase subunit A         192         4,006-77           M6000_2025 H600_2025 Jeac_sAPC [Ak] Hydroperoade reductase subunit A         1,406-01         1,51         3,366-01           M6000_2025 H600_2025 Jeac_sAPC [Ak] Hydroper	HG001_01200 HG001_01200  gene_NONE  hypothetical protein	1,98	4,11E-01
HEGOD_10193 HEGOD_1033 Jgene_NONE [hypothetical protein         1.88         4.118-01           HEGOD_10224 HEGOD_10223 Jgene_NONE [hypothetical protein         1.88         4.118-01           HEGOD_10224 HEGOD_10223 Jgene_NONE [hypothetical protein         1.88         4.118-01           HEGOD_10223 HEGOD_10225 Jgene_NONE [hypothetical protein         1.88         4.118-01           HEGOD_10223 HEGOD_10225 Jgene_NONE [hypothetical protein         1.88         4.118-01           HEGOD_10223 HEGOD_10225 Jgene_NONE [hydotheck protein         1.88         4.118-01           HEGOD_10223 HEGOD_10223 Jgene_aldC_2] Alpha-acctolactae decarboxylase         1.88         4.118-01           HEGOD_10224 HEGOD_10224 Jgene_aldC_2] Alpha-acctolactae subunit C         1.88         4.118-01           HEGOD_10224 HEGOD_10223 Jgene_aldC_1] Alpha-acctolactae subunit A         1.90         2.996-01           HEGOD_10223 HEGOD_10223 Jgene_abpC1 AlkV Hydroperoxide reductase subunit F         1.88         3.848-51           HEGOD_10223 HEGOD_10223 Jgene_aphC1 AlkV Hydroperoxide reductase subunit F         1.88         3.846-51           HEGOD_10223 HEGOD_10223 Jgene_aphC1 AlkV Hydroperoxide reductase subunit F         1.88         3.846-51           HEGOD_10223 HEGOD_10223 Jgene_aphC1 AlkV Hydroperoxide reductase subunit F         1.88         3.846-51           HEGOD_10223 HEGOD_10223 Jgene_aphC1 AlkV Hydroperoxide reductase subunit C <td< td=""><td>HG001_02420 HG001_02420 gene_gltT Proton/sodium-glutamate symport protein</td><td>1,98</td><td>4,11E-01</td></td<>	HG001_02420 HG001_02420 gene_gltT Proton/sodium-glutamate symport protein	1,98	4,11E-01
H6001_02224 Jence, NONE [IPsotperfamily protein         1,88         4,11E-01           H6001_02231 Jence, NONE [IPsotperfamily protein         1,98         4,11E-01           H6001_00237 Jence, SIANE, JITS marcriptional regulator SIyA         1,98         4,11E-01           H6001_00231 Jence, NONE [IPsotperfamily protein         1,98         4,11E-01           H6001_00235 H6001_00233 Jence, NONE [Insotperfamily protein         1,98         4,11E-01           H6001_0234 H6001_00233 Jence, NONE [Indotterical protein         1,98         4,11E-01           H6001_00234 H6001_00234 Jence, JAC JAJANA sectolacata de decatacosylase         1,98         4,11E-01           H6001_00234 H6001_00234 Jence, JAC JAJANA sectorotal studia subunit A         1,90         2,99E-01           H6001_00234 Jence, JAC JAJANA sectorotal subunit A         1,90         2,99E-01           H6001_00234 Jence, JAJAN JAJANA stangkrasse subunit F         1,86         3,84E-54           H6001_00234 Jence, JAJAN JAJANA stangkrasse subunit F         1,86         3,84E-54           H6001_00237 Jence, DAJO Dapatave transglycosylase StaA precursor         1,87         1,86E-02           H6001_00237 Jence, DAJO Dapatave transglycosylase StaA precursor         1,74         1,46E-01           H6001_00237 Jence, DAJO Dapatave transglycosylase StaA precursor         1,74         1,46E-01           H6001_00237 Jence, DAJO Dapata	HG001_01903 HG001_01903 gene_NONE hypothetical protein	1,98	4,11E-01
H6001_02731 He001_02731 gene_X0NE [IonB superfamily protein         1.88         4.118-01           H6001_00771 Heore, X0NE [Transcriptional regulator SlyA         1.88         4.118-01           H6001_00771 Heore, X0NE [Transcriptional regulator         1.98         4.118-01           H6001_00751 Heore, X0NE [Transcriptional regulator         1.98         4.118-01           H6001_02731 Heoro, X0NE [Transcriptional regulator         1.98         4.118-01           H6001_02731 Heoro, X0NE [Transcriptional regulator         1.98         4.118-01           H6001_02731 Heoro, X0NE [Transcriptional regulator         1.98         4.118-01           H6001_00731 Heoro, X0NE [Add shock protein         1.98         4.118-01           H6001_00731 Heoro, X0NE [Add shock protein         1.92         4.006-77           H6001_00731 Heoro, X0NE [Add shock protein a transcription status subunit C         1.92         4.96-62           H6001_00731 Heoro, Z023 [gene, X0AE [Dutative N-acetytransdress subunit F         1.86         3.46-63           H6001_00731 Heoro, Z023 [gene, X0AE [Dutative N-acetytransdress subunit C         1.74         1.466-61           H6001_00731 Heoro, Z0AE [gene, X0AE [Dutative N-acetytransdress subunit C         1.74         1.466-61           H6001_00732 [gene, X0AE [Dutative N-acetytransdress subunit C         1.74         1.466-61           H6001_2073 [gene, X0AE [Dutative	HG001_02024 HG001_02024  gene_NONE hypothetical protein	1,98	4,11E-01
H6001_00277 H6001_00277 [genc_s]vk_]1 [ranscriptional regulator S]vA         198         4,11E-01           H6001_00273 H6001_00235 [genc_NONE] [rynothtical protein         198         4,11E-01           H6001_00235 H6001_00235 [genc_NONE] [rynothtical protein         198         4,11E-01           H6001_00235 H6001_00235 [genc_NONE] [rynothtic here uptake system protein IsdE precursor         198         4,11E-01           H6001_00234 [efo01_00234 [gencahlc] [Alpha activate subunit A1         190         2,996-01           H6000_00293 [efo01_00236 [gencmAhl [Nei]-(Nei]-operative subunit A1         190         2,996-01           H6000_00293 [efo01_00236 [gencmAhl [Nei]-(Nei]-operative subunit A1         190         2,996-01           H6000_00231 [genc_mAhl [Nei]-(Nei]-operative transglycoxylase IsaA precursor         188         5,206-02           H6000_00233 [gencmAhl [Nei]-(Nei]-operative transglycoxylase ScP precursor         174         1,466-01           H6000_02537 [genc_mAhl [Nei]-(Nei]-operative transglycoxylase ScP precursor         168         1,236-02           H6000_003	HG001_02731 HG001_02731  gene_NONE  DinB superfamily protein	1,98	4,11E-01
H6001_01177 H6001_01177 [gene_NONE] Importing legister         198         4,11E-01           H6001_0223 H6001_0223 [gene_AONE] Transcriptional regulator         198         4,11E-01           H6001_0223 H6001_0223 [gene_AONE] Transcriptional regulator         198         4,11E-01           H6001_0223 H6001_0223 [gene_AONE] Transcriptional regulator         198         4,11E-01           H6001_0023 H6001_00381 [gene_MONE] Transcriptionar regulator         198         4,11E-01           H6001_0023 H6001_00381 [gene_montA] [Na(+)/H(+) antioper subunit A1         190         2,99E-01           H6001_0032 [gene_montA] [Na(+)/H(+) antioper subunit A1         190         2,99E-01           H6001_0032 [gene_montA] [Na(+)/H(+) antioper subunit A1         190         2,99E-01           H6001_0032 H6001_0032 [gene_montA] [Na(+)/H(+) antioperoxide reductase subunit F         186         3,44E-51           H6001_0032 H6001_0032 [gene_montA] [Na(+)/H(+) antioperoxide reductase subunit F         186         3,44E-51           H6001_0032 H6001_0032 [gene_montA] [Hone-regulated sufface determinant protein A precursor         166         1,01E-04           H6001_0037 H6001_00373 [gene_montA] [Hone-regulated sufface determinant protein A precursor         165         1,02E-01           H6001_0037 H6001_00373 [gene_montA] [Hone-regulated sufface determinant protein A precursor         165         1,02E-01           H6001_0037 H6001_00373 [gene_mo	HG001_00277 HG001_00277  gene_slyA_1   Transcriptional regulator SlyA	1,98	4,11E-01
HG001_0025 HG001_00253 Jgene_MONE   Transcriptional regulator         1.98         4, 11E-01           HG001_0253 HG001_00253 Jgene_MONE   Acid shock protein         1.98         4, 11E-01           HG001_0253 HG001_00233 Jgene_MONE   Acid shock protein         1.98         4, 11E-01           HG001_0034 HG001_00324 Jgene_abc[ Aliky hydroperoxide reductase subunit C         1.92         4, 00E-77           HG001_00323 HG001_00323 Jgene_abc[ Aliky hydroperoxide reductase subunit C         1.92         4, 00E-77           HG001_0253 HG001_00323 Jgene_moht[ Nie/H(H) + antigotre subunit A1         1.90         2.98E-02           HG001_0253 Jgene_moht[ Nie/H(H) + antigotre subunit A1         1.98         3, 24E-51           HG001_0253 Jgene_coht[ Digtative transglycosylase ScaD precursor         1.74         1, 46E-01           HG001_0253 Jgene_coht[ Digtative transglycosylase ScaD precursor         1.74         1, 46E-01           HG001_0053 HG001_00523 Jgene_coht[ Digtative transglycosylase ScaD precursor         1.65         1, 23E-01           HG001_0053 HG001_0053 Jgene_coht[ Nighted Schatting Precursor         1.66         1, 23E-01           HG001_0053 HG001_0053 Jgene_mokt[ Nikitel-binding brinding protein MetQ precursor         1.65         1, 23E-01           HG001_0053 HG001_0053 Jgene_mokt[ Nikitel-binding protein Precursor         1.66         1, 23E-01           HG001_0053 HG001_01_013 Jgene_mokt[ Nikitel-binding prote	HG001_01177 HG001_01177  gene_NONE hypothetical protein	1,98	4,11E-01
HG001_0223 HG001_02233 Jgnne_aloC_21 Alpha-actiolactate decarboxylase         198         4,11E-01           HG001_0223 HG001_0223 Jgnne_MOVE [Add shock protein         198         4,11E-01           HG001_0023 HG001_0023 Lgnne_mOVE [Add shock protein         192         4,00E-77           HG001_0023 HG001_0023 Lgnne_mOVE [Add shock protein         192         4,00E-77           HG001_0023 HG001_0023 Hgnne_mOVE [Add shock protein         198         4,11E-01           HG001_0023 HG001_0023 HG001_0023 Hgnne_mAbr [Alpk] hydroperoxide reductase subunit A         198         3,84E-51           HG001_0123 HG001_0122 Hgnne_xOVE [putative N-acetyltransferase         1.74         1,46E-01           HG001_0123 HG001_0123 Hgnne_opAl Copper-exporting P-type ATPase A         1.74         1,46E-01           HG001_0023 HG001_0023 Hgnne_inAbr [Hour regulated surface determinant protein A precursor         1.66         1,01E-04           HG001_0023 HG001_0023 Hgnne_inAbr [Hour regulated surface determinant protein A precursor         1.65         1,23E-01           HG001_0023 HG001_0023 Hgnne_inAbr [Hour twe Ap-C CA thioester hydrolase         1.53         4,35E-01           HG001_0023 HG001_0023 Hgnne_inAbr [Hourtave Ap-C CA thioester hydrolase         1.53         4,35E-01           HG001_0023 Hgnne_inAbr [Hourtave Ap-C CA thioester hydrolase         1.53         4,35E-01           HG001_0023 Hgnne_inAbr [Hourtave Ap-C CA thioester hydrolase	HG001_00525 HG001_00525  gene_NONE Transcriptional regulator	1,98	4,11E-01
HG01_02423 HG01_02423 Igen_NONE  Add shock protein         1.98         4, 11E-01           HG01_0283 HG01_02423 Igen_Side  High-filting heme uptake system protein IsdE precursor         1.92         4, 01E-01           HG01_00324 HG01_00324 Igen_abs[Alby  hydroperoxide reductase subunit C         1.92         4, 00E-71           HG01_02609 HG01_02609 [gen_abs[Alputative transglycoxylase IsaA precursor         1.88         5, 26E-02           HG01_02123 HG001_0212 Jgen_abs[Alputative transglycoxylase SceD precursor         1.74         4, 46E-01           HG001_0232 HG001_0212 Jgen_abs[Alputative transglycoxylase SceD precursor         1.66         1, 01E-04           HG001_0257 HG001_0257 Jgen_coxPl (Pattive h-acetyltransferase         1.74         1, 46E-01           HG001_0057 HG001_0257 Jgen_coxPl (Pattive h-acetyltransferase         1.66         1, 01E-04           HG001_0057 HG001_0057 Jgen_e_, nick  NickeHeinding protein         HC01_Pattive HW/thiaming enerases protein fox transor         1.66         1, 01E-04           HG001_0057 HG001_0057 Jgen_e_, nick  NickeHeinding protein transor         1.65         1, 23E-01           HG001_0257 HG001_0057 Jgen_e_, nick  Juntative HW/thiaming enerases protein transor         1.66         1, 01E-04           HG001_0257 HG001_0257 Jgen_e_, nick  Juntative ABC ransporter solute-holding protein YCQ precursor         1.65         1, 23E-01           HG001_0257 HG001_0257 Jgen_e_, nick  Juntative ABC ransporter solute	HG001_02639 HG001_02639  gene_aldC_2 Alpha-acetolactate decarboxylase	1,98	4,11E-01
H6001_00981 [geneabc] [kijk]-aftinity heme uptake system protein ladit precursor         1.98         4.11E-01           H6001_00234 [geneabc] [kijk] vhipopreroide reductase subunit C         1.90         2.99E-01           H6001_00234 [geneiska] plattive tranglycosylase las A precursor         1.88         5.26E-02           H6001_00234 [Geneiska] plattive tranglycosylase las A precursor         1.86         3.84E-51           H6001_00235 [Geneiska] plattive tranglycosylase SceD precursor         1.74         1.46E-01           H6001_00235 H6001_002357 [geneiNNE] plattive tranglycosylase SceD precursor         1.66         1.53E-02           H6001_00235 H6001_00257 [geneiNNE] plattive tranglycosylase SceD precursor         1.66         1.53E-02           H6001_00257 H6001_00257 [geneiNNE] plattive b-methionine inding pioprotein MetQ precursor         1.65         1.23E-01           H6001_0027 H6001_00257 [geneiNNE] plattive b-methionine inding pioprotein MetQ precursor         1.57         1.48E-02           H6001_0027 H6001_00277 [gene_iNNE] plattive b-methioning protein precursor         1.57         1.48E-02           H6001_0027 [gene_iNNE] plattive the MP thiositer hydrolase         1.53         4.35E-01           H6001_00273 [gene_iNNE] plattive the AC-bodrolase         1.53         4.35E-01           H6001_00273 [gene_iNNE] plattive tary-CoA thoester hydrolase         1.53         4.35E-01           H60	HG001_02423 HG001_02423  gene_NONE Acid shock protein	1,98	4,11E-01
HG01_00324 HG01_00324 Igene_ahbc1 AlkyI hydroperoide reductase subunit C         1.92         4.006-77           HG01_0298 HG00_02039 Igene_mixh2 I Nei/H(+) antipotre subunit A1         1.90         2.996-01           HG01_02032 HG00_02032 Igene_shaP [AlkyI hydroperoide reductase subunit F         1.86         3.846-51           HG01_0212 HG01_02123 Igene_sceD [putative transglycoxylase SceD precursor         1.74         4.366-02           HG001_0257 HG00_02057 Igene_coxPlC putative transglycoxylase SceD precursor         1.66         1.016-04           HG001_0075 HG00_02057 Igene_coxPlC putative N-acetyItransferase         1.74         1.466-01           HG001_0075 HG00_00752 Igene_koxPl I hydroberoide reductase subunit A         1.69         1.538-02           HG001_00757 HG00_00752 Igene_koxPl I hydroberoide reductase subunit R         1.66         1.016-04           HG001_00757 HG00_00752 Igene_koxPl I putative HMP/thiamine permease protein K0E         1.57         1.286-01           HG001_00757 HG00_00757 Igene_koxPl I putative HMP/thiamine permease protein K0E         1.57         1.486-02           HG001_00757 HG00_00757 Igene_koxPl I putative acyl-cox thoseter hydrolase         1.53         4.356-01           HG001_00757 HG00_00757 Igene_koxPl I putative APC cox thoseter hydrolase fish         1.33         4.356-01           HG001_00757 HG00_00757 Igene_koxPl I putative APC cox thoseter hydrolase fish         1.43         3.546-01 <td>HG001_00981 HG001_00981  gene_isdE   High-affinity heme uptake system protein IsdE precursor</td> <td>1,98</td> <td>4,11E-01</td>	HG001_00981 HG001_00981  gene_isdE   High-affinity heme uptake system protein IsdE precursor	1,98	4,11E-01
HG01_00799 HG02_00799 [gene_mhx] hat/h(Hc) antiporter subunit A1         1.90         2.99E-51           HG01_00239 HG02_00233 [gene_mby[ Alkp] hydroperoxide reductase subunit F         1.88         3.84E-51           HG01_00233 HG01_00233 [gene_xbp] Alkp] hydroperoxide reductase subunit F         1.86         3.84E-52           HG01_01235 HG01_01235 [gene_xbp] Alkp] hydroperoxide reductase subunit F         1.86         3.84E-52           HG01_0125 HG01_01255 [gene_xbp] [pattive transglycosylase SceD precusor         1.74         1.46E-01           HG01_00257 HG01_00257 [gene_xbp] [pattive transglycosylase SceD precusor         1.66         1.91E-04           HG01_00978 HG01_00978 [gene_mbx] [pupothetical protein         1.66         1.91E-04           HG01_00977 HG001_00978 [gene_mbx] [Putative D-methionic-binding [pioprotein MetQ precusor         1.66         1.91E-04           HG01_00977 HG001_00978 [gene_mbx] [Putative acyl-CoA thioester hydrolsse         1.53         4.35E-01           HG001_0277 HG001_00578 [gene_wbx] [Putative acyl-CoA thioester hydrolsse         1.53         4.35E-01           HG001_0278 HG001_0278 [Regue_gene_hbx] [Putative acyl-CoA thioester hydrolsse         1.53         4.35E-01           HG001_0278 HG001_0078 [gene_wbx] [Putative acyl-CoA thioester hydrolsse         1.53         4.35E-01           HG001_0074 HG001_00718 [gene_wbx] [Putative acyl-CoA thioester hydrolsse         1.53         4.35E-01	HG001_00324 HG001_00324  gene_ahpC Alkyl hydroperoxide reductase subunit C	1,92	4,00E-77
H6001_02609 H6001_02609 [gene_jsha] hptative transglycosylase isab precursor         1.88         5.26E-02           H6001_02133 H6001_02123 [gene_scP [] hptative transglycosylase SceD precursor         1.74         1.46E-01           H6001_02237 H6001_0257 [gene_soPA [] hptative Nacetyltransferase         1.74         1.46E-01           H6001_0257 H6001_0257 [gene_soPA [] hptative Nacetyltransferase         1.66         1.53E-02           H6001_0257 [kene_topk [] hptative Nacetyltransferase         1.66         1.53E-02           H6001_00375 [kene_topk [] hptative Parethionine-binding lipoprotein MetQ precursor         1.66         1.23E-01           H6001_00375 [kene_topk [] hptative D-methionine-binding lipoprotein MetQ precursor         1.66         1.23E-01           H6001_02507 [kene_topk [] putative AMP (Thaining neprotein NetC         1.57         1.48E-01           H6001_02517 [kene_topk [] putative APC + CoA thicester hydrolase         1.53         4.35E-01           H6001_00574 [kene_wck] [] putative APC - CoA thicester hydrolase         1.48         5.00E-15           H6001_00574 [kene_wck] [] putative APC ransporter solute-binding protein YclQ precursor         1.48         5.00E-15           H6001_00574 [kene_wck] [] putative APC ransporter solute-binding protein YclQ precursor         1.48         5.00E-15           H6001_00278 [kene_wck] [] putative APC ransporter solute-binding protein YclQ precursor         1.48         5.00E-15	HG001_00799 HG001_00799  gene_mnhA1 Na(+)/H(+) antiporter subunit A1	1,90	2,99E-01
HG001_00323 HG0000323 [gene_,scP] putative transglvcos/ses ScD precursor         1.78         3.84E-51           HG001_0123 HG0001225 [gene_,NONE] [putative Nacety/transferase         1.74         1.46E-01           HG001_0125 HG001_00257 [gene_,NONE] [putative Nacety/transferase         1.74         1.46E-01           HG001_00252 HG001_00257 [gene_,NONE] [putative Nacety/transferase         1.74         1.46E-01           HG001_00257 HG001_00257 [gene_,NONE] [putative Acety/transferase         1.65         1.21E-01           HG001_00257 HG001_00257 [gene_,mot.2] [putative Acet determinant protein A precursor         1.65         1.23E-01           HG001_00257 HG001_00257 [gene_,mot.2] [putative acql-CoA thioester hydrolase         1.53         4.35E-01           HG001_00271 HG001_002673 [gene_,wor.2] [putative Acet transporter solute-binding protein YCQ precursor         1.45         3.05E-01           HG001_00273 HG001_002673 [gene_,wor.8] [putative Acet transporter solute-binding protein YCQ precursor         1.45         3.05E-01           HG001_00274 HG001_00268 [gene_,wr.8] [putative Acet Arnsporter solute-binding protein YCQ precursor         1.45         3.05E-01           HG001_00274 [gene_,kr.8] [putative AbD-hydrolase YhB         1.43         3.54E-01           HG001_00278 [gene_,wr.8] [putative AbC transporters solute-binding protein YCQ precursor         1.45         3.05E-01           HG001_00278 [gene_,wr.8] [putative HAD-hydrolase YhB <td< td=""><td>HG001_02609 HG001_02609 gene_isaA putative transglycosylase IsaA precursor</td><td>1,88</td><td>5,26E-02</td></td<>	HG001_02609 HG001_02609 gene_isaA putative transglycosylase IsaA precursor	1,88	5,26E-02
HG001_02123 HG001_02123 [gene_x0NE] putative transplycosylase ScoD precursor         1,74         1,46E-01           HG001_020597 HG001_02597 [gene_x0NE] putative Nacetyltransferase         1,74         1,46E-01           HG001_02597 HG001_02597 [gene_x0NE] hypothetical protein         169         1,53E-02           HG001_00375 HG001_00375 [gene_x0NE] hypothetical protein         169         1,53E-02           HG001_00375 HG001_00375 [gene_x0E] putative MPM (rhinmine permease protein YAGC         157         2,3EE-01           HG001_02507 HG001_02507 [gene_x0E] putative AVC hoises thydrolase         153         4,35E-01           HG001_02573 HG001_02507 [gene_x0E] Putative av/C+OA thioses thydrolase         153         4,35E-01           HG001_02673 HG001_02673 [gene_x0E] Putative av/C+OA thioses thydrolase         153         4,35E-01           HG001_002674 HG001_002678 [gene_x0F] Putative AVC transporter solute-binding protein YdQ precursor         1,44         2,47E-02           HG001_00268 HG001_00268 [gene_x0F] Putative AVC transporter solute-binding protein YdQ precursor         1,44         5,00E-15           HG001_00278 HG001_00278 [gene_x0F] Putative HAVC hydrolase YnB         1,43         3,54E-01           HG001_00278 HG001_00278 [gene_x0F] Putative HAVC hydrolase YnB         1,44         2,47E-02           HG001_00278 HG001_00278 [gene_x0F] Putative HAVC hydrolase YnB         1,44         2,47E-02           HG001_00	HG001_00323 HG001_00323  gene_ahpF Alkyl hydroperoxide reductase subunit F	1,86	3,84E-51
HG001_01025 HG001_01025 [gene_X0NC] putative N-acetyltransferase         1,74         1,46E-01           HG001_02557 HG001_0257 [gene_X0NC] [hypothetical protein         1,69         1,53E-02           HG001_00755 HG001_00753 [gene_x0NC] [hypothetical protein         1,69         1,53E-02           HG001_00757 HG001_00753 [gene_x0NC] [hypothetical protein         1,66         1,01E-04           HG001_00757 HG001_00273 [gene_x0kc] [hutative D-methionine-binding lipoprotein MetQ precursor         1,65         1,23E-01           HG001_0057 HG001_00273 [gene_x0kc] [hutative AC transporter solute-binding protein protein procursor         1,57         1,48E-03           HG001_01512 [gene_X0K0] [putative AC transporter solute-binding protein protein protein Sequence         1,53         4,35E-01           HG001_00267 HG001_00267 [gene_w1K] [butative AC transporter solute-binding protein protein Sequence         1,44         2,47E-02           HG001_00264 HG001_00264 [gene_w1K] [butative AC transporter solute-binding protein protein Sequence         1,43         3,54E-01           HG001_0124 [gene_w1K] [butative AC transporter solute-binding protein protein Sequence         1,39         2,99E-01           HG001_0124 [gene_w1K] [butative AC transporter solute-binding protein protein Sequence         1,33         2,45E-01           HG001_0124 [gene_w1K] [butative AC-02+Ugutative HD-hydrolase KhA         1,39         2,99E-01           HG001_0124 [gene_w1K] [butative AC-02+Ugutativ	HG001_02123 HG001_02123 gene_sceD putative transglycosylase SceD precursor	1,79	4,36E-02
HG001_02597 HG001_02597 Igene_0x0RI (hypothetical protein         1.74         1.46E-01           HG001_00275 HG001_002978 Igene_NXRI (hypothetical protein         1.69         1.53E-02           HG001_00375 HG001_00375 Igene_NXRI (hypothetical protein hand protein AP precursor         1.66         1.01E-04           HG001_00375 HG001_00375 Igene_NXRI [hypothetical protein protein precursor         1.57         2.12E-01           HG001_02507 HG001_02507 Igene_NXRI [hypothetical protein protein precursor         1.53         4.35E-01           HG001_02573 HG001_02673 Igene_arcB [ornithine carbamoyltransferase, catabolic         1.53         4.35E-01           HG001_00573 HG001_02673 Igene_arcB [ornithine carbamoyltransferase, catabolic         1.44         2.47E-02           HG001_00574 HG001_0058 Igene_kynB [kynurenine formamidase         1.44         2.47E-02           HG001_00128 HG001_0028 Igene_kynB [kynurenine formamidase         1.43         3.54E-01           HG001_00128 HG001_00128 Igene_kynB [kynurenine formamidase         1.33         2.99E-01           HG001_00128 HG001_00137 Igene_rg8R [Central gkyckylic genes regulator         1.39         2.99E-01           HG001_00137 HG001_0137 Igene_rg8R [Central gkyckylic genes regulator         1.32         3.80E-06           HG001_0137 HG001_0137 Igene_rg8R [Central gkyckylic genes regulator         1.32         3.80E-06           HG001_0137 HG001_0137 Igene_rg8R [Central gk	HG001_01025 HG001_01025  gene_NONE putative N-acetyltransferase	1,74	1,46E-01
HG001_00752 HG001_00752 [gene_NONE] hypothetical protein         1.531-022         1.531-022           HG001_00757 HG001_00375 [gene_vick] Protein regulated surface determinant protein A precursor         1.66         1.01E-04           HG001_00375 HG001_00375 [gene_vick] Protein Vecl         1.57         2.12E-01           HG001_00375 HG001_00375 [gene_vick] Protative HMP/thiamine permease protein YkoE         1.57         1.48E-02           HG001_01912 [gene_NONE] protative axyl-CoA thioester hydrolase         1.53         4.35E-01           HG001_02677 HG001_02677 [gene_vick] Dutative axyl-CoA thioester hydrolase         1.45         5.00E-15           HG001_00574 HG001_00574 [gene_vick] Dutative axyl-coA thioester hydrolase         1.43         3.54E-01           HG001_00574 HG001_00258 [gene_wirk] Dutative ADC transporter solute-binding protein YdQ precursor         1.43         3.54E-01           HG001_00124 HG001_00128 [gene_xirk] Privative HAD-hydrolase YfnB         1.43         3.54E-01           HG001_00124 HG001_00128 [gene_xirk] Privative HAD-hydrolase YfnB         1.33         2.99E-01           HG001_00174 HG001_00127 [gene_xirk] Cartal glycolytic_genes regulator         1.39         2.99E-01           HG001_00174 HG001_00174 [gene_xirk] Privative HAD-hydrolase YhkB         1.32         3.80E-06           HG001_0174 HG001_00174 [gene_xirk] Privative HAD-hydrolase YhkB         1.43         3.54E-01           HG001_	HG001_02597 HG001_02597 gene_copA Copper-exporting P-type ATPase A	1,74	1,46E-01
HG001_00978         HG001_00978         HG001_00978         HG001_00978         HG001_00978         HG001_00978         HG001_00978         HG001_00977         HG001_00978         HG001_00178	HG001_00752 HG001_00752  gene_NONE hypothetical protein	1,69	1,53E-02
HG001_00375         HG001_00375         Igent_Koll Putative MP/Rthiamine permease protein VkE         1.55         1.23E-01           HG001_02507         HG001_02507         Igen_koll Putative MP/Rthiamine permease protein VkE         1.57         1.48E-02           HG001_02507         HG001_02507         Igen_koll Putative acyl-CoA thioester hydrolase         1.53         4.35E-01           HG001_00574         HG001_00573         Igen_arcs         Igen_arcs         1.44         2.47E-02           HG001_00574         HG001_00573         Igen_arcs         1.44         2.47E-02           HG001_00567         HG001_00569         Igen_arcs         1.44         2.47E-02           HG001_00569         Igen_arcs         1.43         3.54E-01           HG001_00128         Igen_arcs         1.43         3.54E-01           HG001_01218         Igen_arcs         1.39         2.99E-01           HG001_00124         Igen_arcs         1.33         2.99E-01           HG001_00124         Igen_arcs         1.32         3.80E-06           HG001_00147         Igen_arcs         1.32         3.80E-06           HG001_00247         Igen_arcs         1.32         3.80E-06           HG001_00247         Igen_arcs         Igen_arcs         Igen_arcs	HG001_00978 HG001_00978 gene_isdA Iron-regulated surface determinant protein A precursor	1,66	1,01E-04
HG001_00927         HG001_00927         Igene_INk1Nicke1-binding periplasmic protein precursor         1.57         1.48E-01           HG001_02573         HG001_02573         Igene_INk1Nicke1-binding periplasmic protein precursor         1.53         4.35E-01           HG001_02573         HG001_02673         Igene_INk1Nicke1-binding periplasmic protein precursor         1.45         5.00E-15           HG001_00574         HG001_00574         Igene_INK1         Igene_VICL         1.44         2.47E-02           HG001_00298         HG001_00298         Igene_VICL         Igene_VICL         1.43         3.54E-01           HG001_0028         HG001_0028         Igene_VICL         Igene_VICL         Igene_VICL         1.43         3.54E-01           HG001_00186         Igene_VICL         Igene_VICL         Igene_VICL         Igene_VICL         1.39         2.99E-01           HG001_00121         HG001_00172         Igene_CgrB (Central glycolytic genes regulator         1.36         5.99E-05           HG001_02247         HG001_02247         Igene_VICL	HG001_00375 HG001_00375  gene_metQ_1 putative D-methionine-binding lipoprotein MetQ precursor	1,65	1,23E-01
HG001_02507 HG001_02507  gene_nikA Nickel-binding periplasmic protein precursor       1.57       1.48E-02         HG001_01211 HG001_01212  gene_NONE   putative acyl-CA chitoset rehydrolase       1.53       4.35E-01         HG001_02673 HG001_02673  gene_arcB Ornithine carbamoyltransferase, catabolic       1.53       4.35E-01         HG001_00564 HG001_00569 [gene_ursP Durative ABC transporter solute-binding protein YclQ precursor       1.45       5.00E-15         HG001_00298 HG001_00298  gene_kynB Kynurenine formamidase       1.43       3.54E-01         HG001_0124 HG001_0124  gene_grnR] Putative HAD-hydrolase YfnB       1.43       3.54E-01         HG001_00712 HG001_00712  gene_grgR Central glycolytic genes regulator       1.39       2.99E-01         HG001_00712 HG001_00712  gene_grgR Central glycolytic genes regulator       1.36       5.99E-05         HG001_00714 HG001_00747  gene_fblB Coenzyme F4201-glutamate ligase       1.37       2.46E-01         HG001_002247 HG001_02247  gene_glkS Acetolactate synthase       1.38       8.12E-05         HG001_00226 HG001_02246  gene_xik1Cos riboxomal protein 124       1.27       1.38       6.63E-10         HG001_010276 HG001_02276  gene_xik1Cos riboxomal protein YkQ       1.18       4.09E-01         HG001_01119 HG001_01119  gene_xrlGA putative riboxomal protein YkQ       1.18       4.09E-01         HG001_012246 HG001_02246  gene_xik1C_s riboxomal protein YkQ       1.	HG001_00927 HG001_00927 gene_ykoE Putative HMP/thiamine permease protein YkoE	1,57	2,12E-01
HG001_01912       HG001_02573       HG001_02673       HG001_02673       HG001_00674       HG001_00298       HG001_00298       HG001_00298       HG001_00298       HG001_00298       HG001_00298       HG001_00298       HG001_00124       HG001_00747       HG001_00747       HG001_00747       HG001_00747       HG001_00747       HG001_00747       HG001_00747       HG001_0137       Epene_recA       H7420:-Lglutamate ligase       1.37       2.46E-01         HG001_01317       HG001_00247       Igene_recA       H7420:-Lglutamate ligase       1.32       3.80E-06         HG001_02276       HG001_02276       Igene_rpik/LjPutative phosphatase Ymp1       1.28       8.12E-05         HG001_02276       HG001_02276       Igene_rpik/LjSOS ribosomal protein L24       1.27       1.38E-04         HG001_012276       HG001_02276       Igene_rpik/LjPutative phosphatase Ymp1       1.8       4.09E-01         HG001_012276       HG	HG001_02507 HG001_02507  gene_nikA Nickel-binding periplasmic protein precursor	1,57	1,48E-02
HG001_02673 HG001_02673 Jgene_arc8 JOrnithine carbamoythransferase, catabolic       1.53       4.35E-01         HG001_00674 HG001_00676 Jgene_uvr8 JUvrABC system protein B       1.44       2.47E-02         HG001_00298 HG001_00298 Jgene_lym8 JVnraBC system protein B       1.43       3.54E-01         HG001_01024 HG001_01026 Jgene_uvr8 JVnrABC system protein B       1.43       3.54E-01         HG001_01024 HG001_01026 Jgene_urh8 JVnrindine-specific ribonucleoside hydrolase RihA       1.39       2.99E-01         HG001_00712 HG001_00712 Jgene_cggR JCentral glycolytic genes regulator       1.36       5.99E-05         HG001_01247 HG001_00747 Jgene_fbiB JCenzyme F4201-glutamate ligase       1.36       5.99E-05         HG001_02247 HG001_02247 Jgene_alsS JAcetolactate synthase       1.32       3.80E-06         HG001_02247 HG001_02247 Jgene_alsS JAcetolactate synthase       1.22       8.12E-05         HG001_02246 HG001_02247 Jgene_mixJ_1Putative phosphatase YwpJ       1.28       8.12E-05         HG001_02246 HG001_02246 Jgene_mixJ_1Putative phosphatase YwpJ       1.28       8.12E-05         HG001_02246 HG00	HG001_01912 HG001_01912 gene_NONE putative acyl-CoA thioester hydrolase	1,53	4,35E-01
HG001_00574 HG001_00574 Igene_vdCl putative ABC transporter solute-binding protein VdQ precursor       1.45       5.00E-15         HG001_00056 HG001_000298 Igene_kvn8   Kynurenine formamidase       1.43       3.54E-01         HG001_0124 HG001_00124 Igene_vfn8   Putative HAD-hydrolase Yfn8       1.43       3.54E-01         HG001_00712 HG001_00124 Igene_vfn8   Putative HAD-hydrolase Yfn8       1.39       2.99E-01         HG001_00712 HG001_00712 [gene_vgR8   Central glycolytic genes regulator       1.39       2.99E-01         HG001_00747 HG001_00747  gene_ets  Scetolactate synthase       1.36       5.99E-05         HG001_00747 HG001_0137  gene_regR1   Putative phosphatase YwpJ       1.28       8.12E-05         HG001_0276 HG001_02276  gene_rlx150s ribosomal protein L24       1.27       1.38E-06         HG001_02276 HG001_02276  gene_rlx150s ribosomal protein 124       1.22       8.22E-09         HG001_0132 HG001_0226  gene_pym2_1  Putative phosphatase YwpJ       1.28       8.12E-05         HG001_02276 HG001_02276  gene_rlx150s ribosomal protein L24       6.63E-10       1.001       6.63E-10         HG001_0132 Jgene_rym2_1   Putative phosphatase YwpJ       1.28       8.12E-05       1.66       6.63E-10         HG001_0122 Ggene_pym2_1   Putative phosphatase YwpJ       1.22       8.22E-09       1.6001_01232  gene_NONE   Hypothetical protein       1.01       6.63E-10         HG	HG001_02673 HG001_02673  gene_arcB Ornithine carbamoyltransferase, catabolic	1,53	4,35E-01
HG001_00696 HG001_00696 [gene_uvr8] [UvrABC system protein B       1.44       2,47E-02         HG001_00298 HG001_00298 [gene_uvr8] [VurABC system protein B       1.43       3,54E-01         HG001_01024 HG001_01024 [gene_yrh8] Putative HAD-hydrolase YfnB       1.43       3,54E-01         HG001_00186 HG001_00186 [gene_rihA] Pyrimidine-specific ribonucleoside hydrolase RihA       1.39       2,99E-01         HG001_0074 HG001_00747 [gene_fib8] Coenzyme F4201:-glutamate ligase       1.37       2,46E-01         HG001_0137 HG001_00747 [gene_risb] Acetolactate synthase       1.38       5,99E-05         HG001_02247 HG001_02276 [gene_ryk1] S05 ribosomal protein L24       1.28       8,12E-05         HG001_012276 HG001_00276 [gene_pyrC] Dihydroorotase       1.26       6,63E-10         HG001_012246 HG001_002246 [gene_ghdC_1] Alpha-acetolactate decarboxylase       1.28       8,22E-09         HG001_012246 HG001_00230 [gene_fnuD_2] Irotein 124       1.28       8,08E-06         HG001_012246 HG001_00230 [gene_fnuD_2] Irotein YbQ       1.18       4,09E-01         HG001_01023 HG001_0032 [gene_fnuD_2] Irotein YbQ       1.18       4,09E-01         HG001_01032 HG001_0032 [gene_fnuD_2] Iron(3+)-hydroxamate-binding protein FhuD precursor       1.18       4,09E-01         HG001_0032 HG001_0032 [gene_fnuD_2] Iron(3+)-hydroxamate-binding protein FhuD precursor       1.18       4,09E-01         HG001_00491	HG001_00674 HG001_00674  gene_yclQ putative ABC transporter solute-binding protein YclQ precursor	1,45	5,00E-15
HG001_00298 HG001_00298 Igene_lym8 [Kynurenine formamidase       1.43       3,54E-01         HG001_01024 HG001_01024 [gene_lym8 [Putative HAD-hydrolase Yfn8       1.39       2,99E-01         HG001_00712 HG001_00712 [gene_cggR] Central glycolytic genes regulator       1.39       2,99E-01         HG001_00747 HG001_00747 [gene_fbi8] Coenzyme F4201: glutamate ligase       1.36       5,99E-05         HG001_01047 HG001_00747 [gene_rals] Kactolactate synthase       1.32       3,80E-06         HG001_02247 HG001_02247 [gene_als] Kactolactate synthase       1.32       3,80E-06         HG001_02247 HG001_02276 [gene_rplK]50S ribosomal protein L24       1.27       1,38E-04         HG001_02226 HG001_02226 [gene_plK]50S ribosomal protein L24       1.22       8,22E-05         HG001_01052 HG001_0052 [gene_pryC]Dihydroorotase       1.22       8,22E-09         HG001_0119 HG001_0119 [gene_rDGA][putative ribosomal protein FhuD precursor       1.18       2,08E-09         HG001_0119 HG001_00328 [gene_nbvL][hypothetical protein       1.14       4,05E-01         HG001_00491 [gene_rpGA][putative ribosomal protein S12       1.10       2,66E-03         HG001_00491 [gene_rpsL] 30S ribosomal protein S12       1.04       6,61E-06         HG001_00751 HG001_00751 [gene_ryur] Vegatative protein 351       1.03       1,27E-03         HG001_01499 HG001_01499 [gene_ryur] Vegatative protein 352       1.04<	HG001_00696 HG001_00696 gene_uvrB UvrABC system protein B	1,44	2,47E-02
HG001_01024 HG001_01024 [gene_vfn8]Pvtraitive HAD-hydrolase Yfn8       1.43       3,54E-01         HG001_00186 [gene_rihA]Pvtrimidine-specific ribonucleoside hydrolase RihA       1.39       2,99E-01         HG001_00712 HG001_00712 [gene_cggR]Central glycolytic genes regulator       1.37       2,46E-01         HG001_0137 HG001_00747 [gene_fbiB]Coenzyme F420:L-glutamate ligase       1.36       5,99E-05         HG001_02247 HG001_02247 [gene_recA]Protein RecA       1.36       5,99E-05         HG001_02276 HG001_02247 [gene_rym2]_1 Putative phosphatase YwpJ       1.28       8,12E-05         HG001_02276 HG001_02276 [gene_rym2]_1Putative phosphatase YwpJ       1.28       8,12E-05         HG001_01224 HG001_02276 [gene_rym2]_1Putative phosphatase YwpJ       1.22       8,22E-05         HG001_02246 HG001_02246 [gene_aldC_1]Alpha-acetolactate decarboxylase       1.26       6,63E-10         HG001_0132 UHG001_0132 [gene_fhu2_2] Iron(3+)-hydroxamate-binding protein FhuD precursor       1.18       2,08E-09         HG001_0132 HG001_0132 [gene_m2nGA]putative ribosomal protein YkQ       1.18       4,09E-01         HG001_0045 [gene_acol_FMN2_1]S0 ribosomal protein S12       1.10       2,66E-03         HG001_0047 [gene_rysL]30S ribosomal protein S12       1.04       6,61E-06         HG001_0049 HG001_0047 [gene_rysL]30S ribosomal protein S12       1.03       1,27E-03         HG001_0149 HG001_0047 [g	HG001_00298 HG001_00298 gene_kynB Kynurenine formamidase	1,43	3,54E-01
HG001_00186 HG001_00186  gene_rihA  Pyrimidine-specific ribonucleoside hydrolase RihA       1.39       2,99E-01         HG001_00712 HG001_00712  gene_ggR  Central glycolytic genes regulator       1.37       2,46E-01         HG001_00747 HG001_00747  gene_fibl  Coenzyme F420:1-glutamate ligase       1.36       5,99E-05         HG001_0137 HG001_0137  gene_alsS  Acetolactate synthase       1.32       3,80E-06         HG001_02247 HG001_02247  gene_alsS  Acetolactate synthase       1.28       8,12E-05         HG001_02246 HG001_02246  gene_rplX 50S ribosomal protein L24       1.27       1,38E-04         HG001_01052 HG001_02246  gene_rplX 50S ribosomal protein L24       1.26       6,63E-10         HG001_01052 HG001_02230 Igene_htuD_2  lron(3+)-hydroxamate-binding protein FhuD precursor       1.18       2,08E-09         HG001_012320 HG001_00328  gene_rplGA putative ribosomal protein YkQ       1.18       4,09E-01         HG001_00476 Igeno_rpsl_30S ribosomal protein YkQ       1.18       4,09E-01         HG001_00476 Igeno_rpsl_30S ribosomal protein S12       1,10       2,66E-03         HG001_00476 Igene_rpsl_30S ribosomal protein S21       1.03       1,27E-03         HG001_00476 Igene_rpsl_30S ribosomal protein S21       1.03       1,27E-03         HG001_00476 Igene_rpsl_30S ribosomal protein S21       1.03       1,27E-03         HG001_00476 Igene_rpsl_30S ribosomal protein S21	HG001_01024 HG001_01024 gene_yfnB Putative HAD-hydrolase YfnB	1,43	3,54E-01
HG001_00712 HG001_00772 [gene_ccgR] [Central glycolytic genes regulator       1,39       2,96E-01         HG001_00747 HG001_00747 [gene_ftB] [Central glycolytic genes regulator       1,36       5,99E-05         HG001_0137 HG001_0137 [gene_recA] Protein RecA       1,32       3,80E-06         HG001_02247 HG001_02247 [gene_als5] Acetolactate synthase       1,28       8,12E-05         HG001_02276 HG001_02276 [gene_puty_J] [Putative phosphatase YwpJ       1,28       8,12E-05         HG001_012276 HG001_02276 [gene_puty_J] SO ribosomal protein L24       1,27       1,38E-04         HG001_01052 HG001_01052 [gene_puty_J] I/Putative ribosomal protein FhuD precursor       1,18       2,08E-09         HG001_012320 HG001_01052 [gene_puty_J] I/Putative ribosomal protein YlxQ       1,18       4,09E-01         HG001_01119 [gene_rpsL] SO ribosomal protein NIXQ       1,18       4,09E-01         HG001_012320 HG001_00328 [gene_NONE [hypothetical protein       1,13       4,56E-01         HG001_00476 HG001_00476 [gene_rpsL] SO ribosomal protein S12       1,10       2,66E-03         HG001_00476 HG001_00476 [gene_rpsL] SO ribosomal protein S12       1,10       2,66E-03         HG001_00476 HG001_00476 [gene_rpsL] SO ribosomal protein S12       1,01       6,51E-04         HG001_00476 HG001_00476 [gene_rpsL] SO ribosomal protein S12       1,02       2,12E-01         HG001_010471 HG001_00476 [gene_rpsL] SO	HG001_00186 HG001_00186 gene_rihA Pyrimidine-specific ribonucleoside hydrolase RihA	1,39	2,99E-01
HG001_00747 HG001_00747 Jgene_fbiB [Ccenzyme F420:L-glutamate ligase       1,37       2,46E-01         HG001_01137 HG001_01137 Jgene_recA Protein RecA       1,36       5,99E-05         HG001_02247 HG001_0247 Jgene_alsS Acetolactate synthase       1,32       3,80E-06         HG001_00490 HG001_02476 Jgene_ymp_1 Putative phosphatase YwpJ       1,28       8,12E-05         HG001_02246 HG001_02276 Jgene_rplX]50S ribosomal protein L24       1,27       1,38E-04         HG001_0152 HG001_012246 Jgene_aldC_1]Alpha-acetolactate decarboxylase       1,26       6,63E-10         HG001_0152 HG001_012320 Jgene_pyrC Dihydroorotase       1,22       8,22E-09         HG001_01328 HG001_01323 Jgene_rplGA putative ribosomal protein YlxQ       1,18       2,08E-09         HG001_00476 HG001_00328 Jgene_NNE hypothetical protein S12       1,10       2,66E-03         HG001_00476 HG001_00476 Jgene_rpsL]30S ribosomal protein S12       1,05       6,55E-04         HG001_00476 HG001_00479 Jgene_rysUJ30S ribosomal protein S21       1,04       6,61E-06         HG001_02752 HG001_012752 Jgene_mmE]tRNA-dependent NADPH-azereductase       1,02       2,12E-01         HG001_02752 HG001_02752 Jgene_mmE]tRNA modification GTPase MnmE       1,02       2,12E-01         HG001_02752 HG001_02752 Jgene_mmE]tRNA modification GTPase MnmE       1,01       6,28E-01         HG001_02284 HG001_02290 Jgene_idsA]DNA integrity scanning pro	HG001_00712 HG001_00712  gene_cggR Central glycolytic genes regulator	1,39	2,99E-01
HG001_01137 HG001_01137]gene_recA       1.36       5.99E-05         HG001_02247 HG001_02247]gene_als[Acetolactate synthase       1.32       3.80E-06         HG001_00490 HG001_00490 [gene_ywpJ_1] Putative phosphatase YwpJ       1.28       8.12E-05         HG001_02276 HG001_02276 [gene_rplX]50S ribosomal protein L24       1.27       1.38E-04         HG001_0152 HG001_02246 [gene_aldC_1] Alpha-acetolactate decarboxylase       1.26       6.63E-10         HG001_0152 HG001_02320 [gene_pvrC] Dihydroorotase       1.22       8.22E-09         HG001_019 HG001_01052 [gene_pvrC] Dihydroorotase       1.18       2.08E-09         HG001_00328 HG001_00328 [gene_nVDE] hypothetical protein YkQ       1.18       4.09E-01         HG001_00476 HG001_00328 [gene_rpsL] 30S ribosomal protein S12       1.10       2.66E-03         HG001_00476 HG001_00476 [gene_rpsL] 30S ribosomal protein S12       1.04       6.61E-06         HG001_012752 HG001_00476 [gene_rpsL] 30S ribosomal protein S21       1.03       1.72E-03         HG001_02752 HG001_02752 [gene_mmE]tRNA modification GTPase MnmE       1.02       2.12E-01         HG001_0210 HG001_00228 [gene_NONE [hypothetical protein       1.01       6.28E-01         HG001_02252 HG001_02258 [gene_NONE [hypothetical protein       1.01       6.28E-01         HG001_02259 HG001_02258 [gene_NONE [hypothetical protein       1.01       6.28E-01	HG001_00747 HG001_00747  gene_fbi8 Coenzyme F420:L-glutamate ligase	1,37	2,46E-01
HG001_02247   HG001_02247   gene_als5   Acetolactate synthase       1,32       3,80E-66         HG001_00490 HG001_00490   gene_ywpJ_1   Putative phosphatase YwpJ       1,28       8,12E-05         HG001_02276 HG001_02276   gene_nIX   50S ribosomal protein L24       1,27       1,38E-04         HG001_01052 HG001_02246   gene_aldC_1   Alpha-acetolactate decarboxylase       1,22       8,22E-09         HG001_01052 HG001_01052   gene_pyrC   Dihydroorotase       1,18       2,08E-09         HG001_0102320 HG001_00328   gene_fhub_2   Iron(3+)-hydroxamate-binding protein FhuD precursor       1,18       4,09E-01         HG001_00328 HG001_00328   gene_NONE   hypothetical protein       1,13       4,56E-01         HG001_00476 HG001_00347   gene_rpsL   30S ribosomal protein S12       1,10       2,66E-03         HG001_00476 HG001_00476   gene_rpsL   30S ribosomal protein S21       1,03       1,72E-03         HG001_02752 HG001_012752   gene_montE   tRNA rodefication GTPase MnmE       1,04       6,61E-06         HG001_02752 HG001_02752   gene_montE   tRNA modification GTPase MnmE       1,01       6,28E-01         HG001_0211 HG001_00761   gene_wontE   hypothetical protein       1,01       6,28E-01         HG001_02752 HG001_02752   gene_disA  DNA integrity scanning protein DisA       1,01       6,28E-01         HG001_0244 HG001_0244   gene_disA  DNA integrity scanning protein DisA       1,01       6,28E-01	HG001_01137 HG001_01137 gene_recA Protein RecA	1.36	5,99E-05
HG001_00490 HG001_00490  gene_ywpJ_1 Putative phosphatase YwpJ       1.28       8,12E-05         HG001_02276 HG001_02276  gene_ptX]_50S ribosomal protein L24       1.27       1,38E-04         HG001_02246 HG001_02276  gene_ptX]_50S ribosomal protein L24       1.26       6,63E-10         HG001_0152 HG001_0152  gene_ptX]_bydroorotase       1.22       8,22E-09         HG001_0152 HG001_0153  gene_ptX]_bydroorotase       1.18       2,08E-09         HG001_01119 HG001_01119  gene_rplGA putative ribosomal protein YkQ       1,13       4,56E-01         HG001_00328 HG001_00328  gene_NONE  hypothetical protein       1,13       4,56E-01         HG001_00491 HG001_00476  gene_rpsL] 30S ribosomal protein S12       1,00       2,66E-03         HG001_0149 HG001_00476  gene_rpsL] 30S ribosomal protein S21       1,03       1,27E-03         HG001_02752 HG001_02752  gene_mmE1;RNA modification GTPase MnmE       1,02       2,12E-01         HG001_02228 HG001_00228  gene_NONE  hypothetical protein       1,01       6,28E-01         HG001_02752 HG001_02752  gene_mmE1;RNA modification GTPase MnmE       1,02       2,12E-01         HG001_02190  gene_disA DNA integrity scanning protein DisA       1,01       6,28E-01         HG001_02249  G001_0249  gene_NONE  hypothetical protein       1,01       6,28E-01         HG001_0249 HG001_0249  gene_betA Oxgen-dependent choline dehydrogenase       1,01	HG001_02247 HG001_02247 gene_alsS Acetolactate synthase	1,32	3,80E-06
HG001_02276 HG001_02276 [gene_rptX]S05 ribosomal protein L24       1,27       1,38E-04         HG001_02246 HG001_02246 [gene_aldC_1]Alpha-acetolactate decarboxylase       1,26       6,63E-10         HG001_01052 HG001_01052 [gene_prxC]Dihydroorotase       1,22       8,22E-09         HG001_02320 HG001_02320 [gene_fhuD_2]Iron(3+)-hydroxamate-binding protein FhuD precursor       1,18       2,08E-09         HG001_001052 [gene_prxC]Dihydroorotase       1,13       4,56E-01         HG001_00328 HG001_00328 [gene_NONE [hypothetical protein YlxQ       1,13       4,56E-01         HG001_00476 HG001_00476 [gene_rpsL]305 ribosomal protein S12       1,04       6,61E-03         HG001_010476 HG001_00476 [gene_rpsL]305 ribosomal protein S21       1,04       6,61E-03         HG001_010499 HG001_00761 [gene_surl/New etaite protein S21       1,03       1,27E-03         HG001_02752 HG001_02752 [gene_mnmE]tRNA modification GTPase MnmE       1,01       6,28E-01         HG001_0228 HG001_0228 [gene_NONE [hypothetical protein       1,01       6,28E-01         HG001_02752 HG001_02752 [gene_mnmE]tRNA modification GTPase MnmE       1,01       6,28E-01         HG001_02109 [gene_disA]DNA integrity scanning protein DisA       1,01       6,28E-01         HG001_02109 [gene_betA]OXgen-dependent choline dehydrogenase       1,01       6,28E-01         HG001_02249 [G001_02259 [gene_betA]OXgen-dependent choline dehydr	HG001_00490 HG001_00490 gene_ywpJ_1 Putative phosphatase YwpJ	1,28	8,12E-05
HG001_02246 HG001_02246 [gene_aldC_1]Alpha-acetolactate decarboxylase       1,26       6,63E-10         HG001_01052 HG001_01052 [gene_pyrC]Dihydroorotase       1,22       8,22E-09         HG001_02320 HG001_02320 [gene_pyrC]Dihydroorotase       1,18       2,08E-09         HG001_01119 HG001_01119 [gene_rpIGA [putative ribosomal protein YlxQ       1,18       4,09E-01         HG001_00328 HG001_00328 [gene_NONE [hypothetical protein S12       1,10       2,66E-03         HG001_00476 HG001_00476 [gene_rpsL] 30S ribosomal protein S12       1,05       6,55E-04         HG001_01499 HG001_00479 [gene_rysL] 30S ribosomal protein S21       1,04       6,61E-05         HG001_02752 HG001_02752 [gene_nymE] tRNA edgendent NADPH-azoreductase       1,04       6,61E-06         HG001_02752 HG001_02752 [gene_mmE] tRNA modification GTPase MnmE       1,02       2,12E-01         HG001_02109 HG001_02752 [gene_NONE [hypothetical protein       1,01       6,28E-01         HG001_0228 HG001_02728 [gene_NONE [hypothetical protein       1,01       6,28E-01         HG001_02190 HG001_02190 [gene_disA DNA integrity scanning protein DisA       1,01       6,28E-01         HG001_0249 HG001_0249 [gene_betA Oxygen-dependent choline dehydrogenase       1,01       6,28E-01         HG001_0249 HG001_0249 [gene_betA Oxygen-dependent choline dehydrogenase       1,01       6,28E-01         HG001_0249 HG001_0249 [gene_betA Oxy	HG001_02276 HG001_02276 gene_rplX 50S ribosomal protein L24	1,27	1,38E-04
HG001_01052 HG001_01052  gene_pyrC Dihydroorotase       1,22       8,22E-09         HG001_02320 HG001_02320  gene_fhub_2 Iron(3+)-hydroxamate-binding protein FhuD precursor       1,18       2,08E-09         HG001_01119 HG001_012320  gene_rplGA puttive ribosomal protein YlxQ       1,18       4,09E-01         HG001_00328 HG001_00328  gene_roNE hypothetical protein       1,13       4,56E-01         HG001_00476 HG001_00476  gene_rpsL] 30S ribosomal protein S12       1,10       2,66E-03         HG001_00471 HG001_00491  gene_azo1  FMM-dependent NADPH-azoreductase       1,05       6,55E-04         HG001_01499 HG001_01499  gene_rpsL] 30S ribosomal protein S12       1,04       6,61E-06         HG001_02752 HG001_02752  gene_mmE]tRNA-dependent NADPH-azoreductase       1,03       1,72E-03         HG001_02752 HG001_02752  gene_mmE]tRNA modification GTPase MnmE       1,02       2,12E-01         HG001_02228 HG001_02228  gene_NONE hypothetical protein       1,01       6,28E-01         HG001_02190 HG001_02190  gene_disA DNA integrity scanning protein DisA       1,01       6,28E-01         HG001_0249 HG001_02649  gene_betA Oxgen-dependent choline dehydrogenase       1,01       6,28E-01         HG001_0249 HG001_02649  gene_betA Oxgen-dependent choline dehydrogenase       1,01       6,28E-01         HG001_02459 HG001_02649  gene_betA Oxgen-dependent choline dehydrogenase       1,01       6,28E-01	HG001_02246 HG001_02246  gene_aldC_1 Alpha-acetolactate decarboxylase	1,26	6,63E-10
HG001_02320 Igene_fhuD_21 [Iron(3+)-hydroxamate-binding protein FhuD precursor       1,18       2,08E-09         HG001_01119 HG001_01119 [gene_rplGA putative ribosomal protein YlxQ       1,18       4,09E-01         HG001_002328 HG001_00328 [gene_NONE [hypothetical protein       1,13       4,56E-01         HG001_00476 HG001_00476 [gene_rpsL] 30S ribosomal protein S12       1,10       2,66E-03         HG001_00471 HG001_00476 [gene_rpsL] 30S ribosomal protein S12       1,04       6,61E-06         HG001_00761 HG001_00476 [gene_yurY] Vegetative protein 296       1,04       6,61E-06         HG001_02752 HG001_02752 [gene_mmE] tRNA rodification GTPase MnmE       1,02       2,12E-01         HG001_021290 HG001_02752 [gene_monK] tRNA modification GTPase MnmE       1,01       6,28E-01         HG001_02101 [gene_disA DNA integrity scanning protein DisA       1,01       6,28E-01         HG001_0249 HG001_0259 [gene_disA DNA integrity scanning protein DisA       1,01       6,28E-01         HG001_0249 HG001_02649 [gene_betA Cxygen-dependent choline dehydrogenase       1,01       6,28E-01         HG001_02649 HG001_02649 [gene_betA Cxygen-dependent choline dehydrogenase       1,01       6,28E-01         HG001_02649 HG001_02649 [gene_betA Cxygen-dependent choline dehydrogenase       1,01       6,28E-01         HG001_02649 HG001_02649 [gene_betA Cxygen-dependent choline dehydrogenase       1,01       6,28E-01	HG001_01052 HG001_01052 gene_pyrC Dihydroorotase	1,22	8,22E-09
HG001_01119 HG001_01119 Jgene_rpIGA [putative ribosomal protein YIxQ       1,18       4,09E-01         HG001_00328 HG001_00328 Jgene_NONE [hypothetical protein       1,13       4,56E-01         HG001_00476 HG001_00476 [gene_rpsL] 30S ribosomal protein S12       1,10       2,66E-03         HG001_00761 HG001_00476 [gene_rpsL] 30S ribosomal protein S12       1,05       6,55E-04         HG001_00761 HG001_00476 [gene_rpsL] 30S ribosomal protein 296       1,04       6,61E-06         HG001_01499 HG001_01499 [gene_rpsL] 30S ribosomal protein S21       1,03       1,27E-03         HG001_02752 HG001_02752 [gene_mnmE]tRNA modification GTPase MnmE       1,02       2,12E-01         HG001_02190 JG001_02190 [gene_disA]DNA integrity scanning protein DisA       1,01       6,28E-01         HG001_02649 HG001_02049 Igene_betA Oxygen-dependent choline dehydrogenase       1,01       6,28E-01         HG001_02649 HG001_02649 [gene_betA Oxygen-dependent choline dehydrogenase       1,01       6,28E-01         HG001_0279 Igen0_bltD_1[Spermine/spermidine acetyltransferase       1,01       6,28E-01         HG001_02259 Igen0_cefA1[Energy-coupling factor transporter ATP-binding protein EcfA1       1,01       6,28E-01	HG001_02320 HG001_02320 gene_fhuD_2 Iron(3+)-hydroxamate-binding protein FhuD precursor	1,18	2,08E-09
HG001_00328 HG001_00328 [gene_NONE [hypothetical protein       1,13       4,56E-01         HG001_00476 HG001_00476 [gene_rpsL] 30S ribosomal protein S12       1,10       2,66E-03         HG001_00476 HG001_00476 [gene_surl/INN-dependent NADPH-acreductase       1,05       6,55E-04         HG001_00761 HG001_00761 [gene_surl/INN-dependent NADPH-acreductase       1,04       6,61E-05         HG001_00761 HG001_00761 [gene_yurl/IVegetative protein 296       1,03       1,27E-03         HG001_02752 HG001_02752 [gene_mnmE]tRNA modification GTPase MnmE       1,02       2,12E-01         HG001_02228 HG001_02752 [gene_NONE [hypothetical protein       1,01       6,28E-01         HG001_02190 HG001_02190 [gene_disA]DNA integrity scanning protein DisA       1,01       6,28E-01         HG001_02649 HG001_02649 [gene_betA]Oxygen-dependent choline dehydrogenase       1,01       6,28E-01         HG001_0279 HG001_0279 [gene_betA]Oxygen-dependent choline acetyltransferase       1,01       6,28E-01         HG001_02379 HG001_02379 [gene_ecfA1[Energy-coupling factor transporter ATP-binding protein EcfA1       1,01       6,28E-01	HG001_01119 HG001_01119  gene_rpIGA   putative ribosomal protein YIxQ	1,18	4,09E-01
HG001_00476 HG001_00476 [gene_rpst] 305 ribosomal protein 512       1,10       2,66E-03         HG001_00491 [gene_azo1]FMN-dependent NADPH-azoreductase       1,05       6,55E-04         HG001_00761 HG001_00761 [gene_yurY] Vegetative protein 296       1,04       6,61E-05         HG001_01299 HG001_01499 [gene_rpst] 305 ribosomal protein 521       1,03       1,27E-03         HG001_02752 HG001_02752 [gene_mnmE]tRNA modification GTPase MnmE       1,01       6,28E-01         HG001_02228 HG001_02728 [gene_NONE [hypothetical protein       1,01       6,28E-01         HG001_02190 HG001_02190 [gene_disA DNA integrity scanning protein DisA       1,01       6,28E-01         HG001_0249 HG001_02649 [gene_betA Oxygen-dependent choline dehydrogenase       1,01       6,28E-01         HG001_02649 HG001_02649 [gene_betA Oxygen-dependent choline acetyltransferase       1,01       6,28E-01         HG001_02259 HG001_02759 [gene_ecfA1[Energy-coupling factor transporter ATP-binding protein EcfA1       1,01       6,28E-01	HG001_00328 HG001_00328  gene_NONE hypothetical protein	1,13	4,56E-01
HG001_00491 HG001_00491  gene_azo1   FMN-dependent NADPH-azoreductase         1.05         6,55E-04           HG001_00761  gene_yur  Vegetative protein 296         1.04         6,61E-06           HG001_01499 HG001_00761  gene_yur  Vegetative protein 296         1.04         2,12E-01           HG001_02752 HG001_02752  gene_mmmE  tRNA modification GTPase MnmE         1.02         2,12E-01           HG001_02228 HG001_02228  gene_NONE   hypothetical protein         1.01         6,28E-01           HG001_02190 HG001_02290  gene_disA  DNA integrity scanning protein DisA         1.01         6,28E-01           HG001_02449 HG001_02649  gene_betA  Oxygen-dependent choline dehydrogenase         1.01         6,28E-01           HG001_02649 HG001_02649  gene_betA  Oxygen-dependent choline acetyltransferase         1.01         6,28E-01           HG001_02559 HG001_02659  gene_ecfA1 Energy-coupling factor transporter ATP-binding protein EcfA1         1.01         6,28E-01	HG001_00476 HG001_00476  gene_rpsL 30S ribosomal protein S12	1,10	2,66E-03
HG001_00761 HG001_00761 Igene_yur/l Vegetative protein 296       1,04       6,61E-06         HG001_01499 HG001_01499 Jgene_rpsU  30S ribosomal protein S21       1,03       1,27E-03         HG001_02752 HG001_02752 Jgene_mmE  tRNA modification GTPase MnmE       1,02       2,12E-01         HG001_02228 HG001_02228 Jgene_NONE  hypothetical protein       1,01       6,28E-01         HG001_02190 HG001_02190 Jgene_disA DNA integrity scanning protein DisA       1,01       6,28E-01         HG001_02649 HG001_02649 Jgene_betA Oxygen-dependent choline dehydrogenase       1,01       6,28E-01         HG001_00379 HG001_00379 Jgene_bltD_1 Spermine/spermidine acetyltransferase       1,01       6,28E-01         HG001_02259 HG001_02259 Jgene_ecfA1[Energy-coupling factor transporter ATP-binding protein EcfA1       1,01       6,28E-01	HG001_00491 HG001_00491  gene_azo1   FMN-dependent NADPH-azoreductase	1.05	6,55E-04
HG001_01499 HG001_01499 Jgene_rpsUJ 305 ribosomal protein S21         1,03         1,27E-03           HG001_02752 HG001_02752 Jgene_mnmE JtRNA modification GTPase MnmE         1,02         2,12E-01           HG001_02252 HG001_02752 Jgene_mnmE JtRNA modification GTPase MnmE         1,01         6,28E-01           HG001_02190 HG001_02190 Jgene_disA JDNA integrity scanning protein DisA         1,01         6,28E-01           HG001_02649 HG001_00411 Jgene_NONE   hypothetical protein         1,01         6,28E-01           HG001_02649 HG001_02649 Jgene_betA   Oxygen-dependent choline dehydrogenase         1,01         6,28E-01           HG001_00379 HG001_00379 Jgene_bltD_1   Spermine/spermidine acetyltransferase         1,01         6,28E-01           HG001_02259 HG001_02259 Jgene_ecfA1 [Energy-coupling factor transporter ATP-binding protein EcfA1         1,01         6,28E-01	HG001_00761 HG001_00761  gene_yurY Vegetative protein 296	1,04	6,61E-06
HG001_02752         HG001_02752         Igene_mnmE (IRNA modification GTPase MnmE         1,02         2,12E-01           HG001_02228         HG001_02228         Igene_NONE [hypothetical protein         1,01         6,28E-01           HG001_02109         HG001_00100190         Igene_NONE [hypothetical protein         1,01         6,28E-01           HG001_02041         HG001_00411         Igene_NONE [hypothetical protein         1,01         6,28E-01           HG001_02649         HG001_02649         Igene_betA[Oxygen-dependent choline dehydrogenase         1,01         6,28E-01           HG001_00379         HG001_00379         Igene_ecfA1[Energy-coupling factor transporter ATP-binding protein EcfA1         1,01         6,28E-01	HG001_01499 HG001_01499 [gene_rpsU] 305 ribosomal protein S21	1,03	1,27E-03
HGU01_02228         HGU01_02228         1,01         6,28E-01           HG001_02190         HG001_02190         Igene_NONE [hypothetical protein         1,01         6,28E-01           HG001_02190         HG001_00411         HG001_00411         G,28E-01         6,28E-01           HG001_02649         HG001_02649         Igene_betA[Oxygen-dependent choline dehydrogenase         1,01         6,28E-01           HG001_00379         HG001_00379         Igene_betA[Oxygen-dependent choline acetyltransferase         1,01         6,28E-01           HG001_02259         HG001_02259         Igene_ecfA1[Energy-coupling factor transporter ATP-binding protein EcfA1         1,01         6,28E-01	HG001_02/52 HG001_02/52[gene_mnmE]tRNA modification GTPase MnmE	1,02	2,12E-01
HG001_02190 HG001_02190 Jgene_dtsA]DNA integrity scanning protein DisA         1,01         6,28E-01           HG001_00411 HG001_00411 Jgene_NONE [hypothetical protein         1,01         6,28E-01           HG001_02649 HG001_02649 Jgene_betA]Oxygen-dependent choline dehydrogenase         1,01         6,28E-01           HG001_0379 HG001_00379 Jgene_bltD_1]Spermind:spermidine acetyltransferase         1,01         6,28E-01           HG001_02259 Jgene_ecfA1[Energy-coupling factor transporter ATP-binding protein EcfA1         1,01         6,28E-01	HG001_02228 HG001_02228 [gene_NONE] hypothetical protein	1,01	6,28E-01
HG001_00411 Hs001_00411 [gene_NONE [hypothetical protein       1.01       6,28E-01         HG001_02649 HG001_02649 [gene_betA] Oxygen-dependent choline dehydrogenase       1.01       6,28E-01         HG001_00379 HG001_00379 [gene_bltD_1] Spermind/spermidine acetyltransferase       1.01       6,28E-01         HG001_02259 HG001_02259 [gene_ecfA1] [Energy-coupling factor transporter ATP-binding protein EcfA1       1.01       6,28E-01	HG001_02190 HG001_02190[gene_disA]DNA integrity scanning protein DisA	1,01	6,28E-01
HG001_02b49 HG001_02b49 Igene_betA Oxygen-dependent choline dehydrogenase1,016,28E-01HG001_00379 HG001_00379 Igene_bltD_1 Spermine/spermidine acetyltransferase1,016,28E-01HG001_02259 HG001_02259 Igene_ecfA1 Energy-coupling factor transporter ATP-binding protein EcfA11,016,28E-01	HG001_00411 HG001_00411 [gene_NONE   hypothetical protein	1.01	6,28E-01
HG001_003/9 HG001_00259  gene_bit0_1 Spermine/spermidine acetyltransferase       1.01       6,28E-01         HG001_02259 HG001_02259  gene_ecfA1 Energy-coupling factor transporter ATP-binding protein EcfA1       1.01       6,28E-01	HG001_02649 HG001_02649 [gene_betA 0xygen-dependent choline dehydrogenase	1,01	6,28E-01
HGUU1_U2259 HGUU1_U2259 [gene_ectA1]Energy-coupling tactor transporter AIP-binding protein EctA1 6,28E-01 6,28E-01	HGU01_003/9 HGU01_00379 [gene_bltD_1]Spermine/spermidine acetyltransferase	1,01	6,28E-01
	HOUDT_0553 HOUDT_0553 [Bene_ecter1] Fuelds-conbing lactor transporter VIA-pinging blotein FCtV1	1,01	6,28E-01

DOWN regulated genes from the differencial proteomics analysis in oxidative stress				
accession description	LogFC (MV/WT)	adjp		
HG001_00725 HG001_00725  gene_NONE hypothetical protein	-7,12	1,82E-14		
HG001_02120 HG001_02120  gene_thiD   Hydroxymethylpyrimidine/phosphomethylpyrimidine kinase	-5,83	5,64E-06		
HG001_00734 HG001_00734  gene_cspA_1 Cold shock protein CspA	-5,71	4,91E-04		
HG001_00291 HG001_00291  gene_NONE hypothetical protein	-5,56	4,83E-05		
HG001_02681 HG001_02681  gene_yvyl Putative mannose-6-phosphate isomerase Yvyl	-5,40	1,34E-04		
HG001_01211 HG001_01211 gene_NONE   Iron-sulphur cluster biosynthesis	-5,22	3,90E-04		
HG001_00803 HG001_00803 [gene_Noire [inAdH oxidates]	-5,13	0,01E-04		
HG001_01144 HG00_01144 [gene_mide][United][yia]genosite KivA metrykniotransierase Wiab	-5,02	2.09E-03		
HG001_02599 HG001_02594 Jene pac AlPhoshopluromutase	-4 79	3.37E-03		
HG001 01115 HG001 01115 Jeene pol 11DNA polymerase III PolC-type	-4.79	3.37E-03		
HG001_00422_HG001_00422_gene_mazG[Nucleoside triphosphate pyrophosphohydrolase/pyrophosphatase MazG	-4,79	3.37E-03		
HG001_00774 HG001_00774  gene_NONE hypothetical protein	-4,79	3,37E-03		
HG001_01953 HG001_01953  gene_rutB Peroxyureidoacrylate/ureidoacrylate amidohydrolase RutB	-4,66	5,75E-03		
HG001_02343 HG001_02343  gene_NONE hypothetical protein	-4,56	4,13E-08		
HG001_00480 HG001_00480 gene_yxeP_2 putative hydrolase YxeP	-4,51	9,85E-03		
HG001_00923 HG001_00923  gene_purH Bifunctional purine biosynthesis protein PurH	-4,51	9,85E-03		
HG001_00163 HG001_00163  gene_NONE Xylose isomerase-like TIM barrel	-4,51	9,85E-03		
HG001_00223 HG001_00223  gene_NONE hypothetical protein	-4,51	9,85E-03		
HG001_01432 HG001_01432 gene_malL Oligo-1,6-glucosidase	-4,35	1,64E-02		
HG001_00170 HG001_00170  gene_pflA   Pyruvate formate-lyase-activating enzyme	-4,35	1,64E-02		
HG001_01129 HG001_01129 [gene_phnF] putative transcriptional regulator PhnF	-4,35	1,64E-02		
HG001_00317 HG001_00317  gene_NONE   hypothetical protein	-4,17	2,68E-02		
HG001_02452_HG001_02452_Igene_narwiputative initiate reductase molybdenum colactor assembly chaperone warwing the second and the second s	-4,17	2,08E-02		
HG001_0151/1 HG00_0151/1gene_HKNKE1/hpptHister protein	-4,17	2,08E-02		
HG001_00161 HG001_02540 [gene_gint] Figure animaly graduate transporter	-3.96	4.63E-02		
HG001 02150 HG001 02150 Jene vodBHTH-type transcriptional regulator YodB	-3.96	4.63E-02		
HG001 00694 HG001 00694  gene_yfbR 5'-deoxynucleotidase YfbR	-3,96	4,63E-02		
HG001_01034 HG001_01034 [gene_divIB]Cell division protein DivIB	-3,96	4,63E-02		
HG001_01645 HG001_01645  gene_ptsG_4   PTS system glucose-specific EIICBA component	-3,96	4,63E-02		
HG001_02344 HG001_02344  gene_NONE Putative formate dehydrogenase	-3,93	1,23E-21		
HG001_01549 HG001_01549 gene_NONE CsbD-like protein	-3,84	1,17E-04		
HG001_00768 HG001_00768  gene_NONE   Nitronate monooxygenase	-3,72	7,39E-02		
HG001_00999 HG001_00999 gene_murl Glutamate racemase	-3,72	7,39E-02		
HG001_00598 HG001_00598  gene_graR_11 Response regulator protein GraR	-3,72	7,39E-02		
HG001_01028 HG001_01028  gene_mra2  Protein Mra2	-3,72	7,39E-02		
HG001_00180 HG001_00180 [gene_gsiB [Glutathione-binding protein GsiB precursor	-3,72	7,39E-02		
HG001_0142 HG001_01421gene_N0NE1 hypothetical exterior	-3,12	7,39E-02		
HG001_01255 HG001_01255 Jgene_danBl4-hydroxystetrahydrodinicolinate reductase	-3,72	7 30E-02		
HG001_01150 HG001_01150 Jgene_duble diversity in the second	-3.72	7 39E-02		
HG001 02424 HG001 02424 Igene narT I putative nitrate transporter NarT	-3.72	7.39E-02		
HG001 01724 HG001 01724 gene NONE Telomeric repeat-binding factor 2	-3,71	7,39E-02		
HG001_02099 HG001_02099 gene_acp5 Holo-[acyl-carrier-protein] synthase	-3,71	7,39E-02		
HG001_01612 HG001_01612 gene_phoP Alkaline phosphatase synthesis transcriptional regulatory protein PhoP	-3,42	1,23E-01		
HG001_00916 HG001_00916   gene_purC   Phosphoribosylaminoimidazole-succinocarboxamide synthase	-3,42	1,23E-01		
HG001_00826 HG001_00826 gene_NONE putative kinase inhibitor	-3,42	1,23E-01		
HG001_01319 HG001_01319  gene_pimB GDP-mannose-dependent alpha-(1-6)-phosphatidylinositol monomannoside mannosy	-3,42	1,23E-01		
HG001_00724 HG001_00724  gene_NONE hypothetical protein	-3,42	1,23E-01		
HG001_01351 HG001_01351 gene_NONE hypothetical protein	-3,42	1,23E-01		
HG001_00449 HG001_00449  gene_pdxT Glutamine amidotransferase subunit PdxT	-3,42	1,23E-01		
HG001_00/93 HG001_00/93 [gene_mnhG1] Na(+)/H(+) antiporter subunit G1	-3,42	1,23E-01		
HC001_00202_HC001_00202 gene_irgb[Antinoin-like protein LfgB	-3,42	1,23E-01		
HG001_00522_HG001_01537.jgene_NONELPutative_O-methyltransferase/MSMEL_4047	-3,42	1,23E-01		
HG001_02483_HG001_02483.jgene_NONE[LIDP-glucose 4-enimerase	-3.42	1.23E-01		
HG001 01079 HG001 01079 Igene fapR Transcription factor FapR	-3.42	1,23E-01		
HG001 01666 HG001 01666 gene pepA 21 Glutamyl aminopentidase	-3.42	2.68E-05		
HG001_02592 HG001_02592 gene_ydfJ Membrane protein YdfJ	-3,25	6,71E-08		
HG001_00395 HG001_00395  gene_recR   Recombination protein RecR	-3,05	2,00E-01		
HG001_01694 HG001_01694  gene_NONE   hypothetical protein	-3,05	2,00E-01		
HG001_00274 HG001_00274  gene_NONE   PTS system ascorbate-specific transporter subunits IICB	-3,05	2,00E-01		
HG001 01919 HG001 01919  gene vraS  Sensor protein VraS	-3,05	2,00E-01		

HG001_01216 HG001_01216 gene_glcT GlcA/glcB genes antiterminator	-3,05	2,00E-01
HG001_00494 HG001_00494  gene_tagE_1   putative poly(glycerol-phosphate) alpha-glucosyltransferase	-3,05	2,00E-01
HG001_02500 HG001_02500 gene_gltB_2 Glutamate synthase [NADPH] large chain precursor	-3,05	2,00E-01
HG001_00262 HG001_00262  gene_nanE Putative N-acetylmannosamine-6-phosphate 2-epimerase	-3,05	2,00E-01
HG001_01908 HG001_01908  gene_NONE  hypothetical protein	-3,05	2,00E-01
HG001_01164 HG001_01164 [gene_NONE [ hypothetical protein	-3,05	2,00E-01
HG001_02308 HG001_02308 [gene_mobB] Molybdopterin-guanne dinucleotide biosynthesis adapter protein	-3,05	2,00E-01
HG001_01006 HG001_01006 [gene_def1]/reptide deform/sise 1	-3,05	2,00E-01
HG001_01501 HG001_01539[gene_ypt+]5-5 exonuclease	-3,05	2,00E-01
HG001_0724 HG001_0734 Igene NONE[byncation/cation/cation	-3.05	2,00E-01
HG001_00162 HG001_00163 Igene_volve Imponencer protein	-3.05	2,00E-01
HG001_00921 HG001_00921 Ligene_ycj5_chothorhosylformyldycinamidine cyclo-ligase	-3.05	2,00E-01
HG001_02576 HG001_02576 Jgene_NONELbynothetical protein	-3.05	2,00E-01
HG001 02442 HG001 02442 Jene NONElbypothetical protein	-3.05	2 00E-01
HG001 00885 HG001 00885 Igene NONE hypothetical protein	-3.05	2.00E-01
HG001_02634_HG001_02634_Igene_cocE_ICocaine_esterase	-3.05	2.00E-01
HG001_00736 HG001_00736 gene_NONE hypothetical protein	-3.05	2.00E-01
HG001 01470 HG001 01470 gene NONE putative metallo-hydrolase	-3,05	2,00E-01
HG001_01087 HG001_01087 gene_NONE putative DNA-binding protein	-3,05	2,00E-01
HG001_00627 HG001_00627  gene_ydhF Oxidoreductase YdhF	-3,05	2,00E-01
HG001_01674 HG001_01674 gene_rsuA Ribosomal small subunit pseudouridine synthase A	-3,05	2,00E-01
HG001_02126 HG001_02126 gene_fabZ 3-hydroxyacyl-[acyl-carrier-protein] dehydratase FabZ	-3,05	2,00E-01
HG001_01697 HG001_01697 gene_arsC2 Arsenate-mycothiol transferase ArsC2	-3,05	2,00E-01
HG001_02680 HG001_02680 gene_manP PTS system mannose-specific EIIBCA component	-3,04	6,72E-04
HG001_00940 HG001_00940 gene_NONE hypothetical protein	-2,93	2,20E-02
HG001_00541 HG001_00541 gene_mshD_1 Mycothiol acetyltransferase	-2,93	2,20E-02
HG001_00331 HG001_00331 gene_xpt Xanthine phosphoribosyltransferase	-2,84	8,52E-08
HG001_00410 HG001_00410 gene_rsmA Ribosomal RNA small subunit methyltransferase A	-2,81	3,33E-02
HG001_00118 HG001_00118 gene_aldA Putative aldehyde dehydrogenase AldA	-2,81	3,33E-02
HG001_01513 HG001_01513  gene_tadA_2   tRNA-specific adenosine deaminase	-2,77	4,33E-03
HG001_01905 HG001_01905 [gene_immR_1] HTH-type transcriptional regulator immR	-2,69	6,50E-03
HG001_00420 HG001_00420 [gene_mtd] Transcription-repair-coupling factor	-2,67	5,36E-02
HG001_01661 HG001_01661 [gene_murc] UDP-N-acetylmuramate-L-alanine ligase	-2,61	1,00E-02
HG001_00145 HG001_00145 [gene_nsok] (ype-1 restriction enzyme k protein	-2,07	2,90E-04
HG001_02434 HG001_02434 [gene_hat6] kespiratory intrate reductase Laipha chain	-2,50	2 005 01
HG001_02033 HG001_02033 [gene_exa_] LECA repression	-2,55	2,99E-01
H6001_01551 H6001_01551 Jgene_rarAlReplication-associated recombination protein A	-2.55	2,99E-01
HG001_02090_HG001_02090_Igene_NONELProtein SprT-like protein	-2.55	2.99E-01
HG001_02542_HG001_02542_Igene_vdfH1putative HTH-type transcriptional regulator YdfH	-2.55	2.99E-01
HG001 01298 HG001 01298 gene ald1 Alanine dehydrogenase 1	-2,55	2,99E-01
HG001_02487 HG001_02487 gene_opuCC Carnitine transport binding protein OpuCC precursor	-2,55	2,99E-01
HG001_01961 HG001_01961 gene_NONE hypothetical protein	-2,55	2,99E-01
HG001_01132 HG001_01132  gene_phbB Acetoacetyl-CoA reductase	-2,55	2,99E-01
HG001_00406 HG001_00406 gene_rsml Ribosomal RNA small subunit methyltransferase I	-2,55	2,99E-01
HG001_00228 HG001_00228 gene_NONE hypothetical protein	-2,55	2,99E-01
HG001_00029 HG001_00029 gene_NONE hypothetical protein	-2,55	2,99E-01
HG001_01136 HG001_01136 gene_cinA Putative competence-damage inducible protein	-2,55	2,99E-01
HG001_01145 HG001_01145  gene_NONE hypothetical protein	-2,55	2,99E-01
HG001_00914 HG001_00914  gene_purE N5-carboxyaminoimidazole ribonucleotide mutase	-2,55	2,99E-01
HG001_02178 HG001_02178 gene_NONE JSAP domain protein	-2,55	2,99E-01
HG001_00609 HG001_00609 [gene_NONE   hypothetical protein	-2,55	2,99E-01
HG001_02656 HG001_02656 [gene_gtr2]Gi/cosytransferase-stabilizing protein Gtr2	-2,55	2,99E-01
HG001_01551 HG001_01551 [gene_h00ke ] plutative hva internyti haisterase	-2,55	2,992-01
HG001_01563 HG00_00508 [gene_intak_1 source), potession, initiating and rubbidint (http://antipot.et	-2,55	2,99E-01
HG001_01676_HG001_01676_gene_NONE/Ferredoxin-NADP reductase	-2.55	2.99E-01
HG001 00904 HG001 00904 gene vicF putative N-acetv/transferase YicF	-2.55	2,99E-01
HG001 02141 HG001 02141 gene NONE hypothetical protein	-2.55	2,99E-01
HG001 01833 HG001 01833 gene vfhQ putative A/G-specific adenine glycosylase YfhQ	-2.55	2,99E-01
HG001_00767 HG001_00767 gene_tlyC Hemolysin C	-2,55	2,99E-01
HG001_00919 HG001_00919   gene_purL   Phosphoribosylformy glycinamidine synthase 2	-2,55	2,99E-01
HG001_02545 HG001_02545  gene_NONE hypothetical protein	-2,55	2,99E-01
HG001_00175 HG001_00175  gene_fadN   putative 3-hydroxyacyl-CoA dehydrogenase	-2,55	2,99E-01
HG001_00616 HG001_00616  gene_NONE   hypothetical protein	-2,55	2,99E-01

HG001 00746 HG001 00746 gene aroD 3-dehydroquinate dehydratase	-2,55	2,99E-01
HG001_01669 HG001_01669 gene_trmB tRNA (guanine-N(7)-)-methyltransferase	-2,55	2,99E-01
HG001_01543 HG001_01543  gene_recD2   ATP-dependent RecD-like DNA helicase	-2,55	2,99E-01
HG001_00540 HG001_00540 gene_ywqN_2 Putative NAD(P)H-dependent FMN-containing oxidoreductase YwqN	-2,55	2,99E-01
HG001_00185 HG001_00185  gene_ptsG_2   PTS system glucose-specific EIICBA component	-2,55	2,99E-01
HG001_00926 HG001_00926 gene_ykoD_1 Putative HMP/thiamine import ATP-binding protein YkoD	-2,55	2,99E-01
HG001_00633	-2,55	2,99E-01
HG001_00378 HG001_00378 gene_nudC NADH pyrophosphatase	-2,55	2,99E-01
HG001_01664 HG001_01664  gene_NONE hypothetical protein	-2,55	2,99E-01
HG001_00305 HG001_00305 gene_ykuT putative MscS family protein YkuT	-2,55	2,99E-01
HG001_02429 HG001_02429   gene_nreB   Oxygen sensor histidine kinase NreB	-2,55	2,99E-01
HG001_01682 HG001_01682 gene_bioB_1 Biotin synthase	-2,55	2,99E-01
HG001_00811 HG001_00811  gene_spsB_1 Signal peptidase IB	-2,55	2,99E-01
HG001_00377 HG001_00377  gene_NONE  hypothetical protein	-2,55	2,99E-01
HG001_01217 HG001_01217  gene_tqsA Al-2 transport protein TqsA	-2,55	2,99E-01
HG001_01842 HG001_01842 [gene_NONE] putative phage protein 3 of sap1 operon	-2,55	2,99E-01
HG001_02480 HG001_02480 gene_nhaK_2 sodium, potassium, lithium and rubidium/H(+) antiporter	-2,55	2,99E-01
HG001_01040 HG001_01040 gene_NONE YGG1 family protein	-2,55	2,99E-01
HG001_02035 HG001_02035  gene_NONE  hypothetical protein	-2,55	2,99E-01
HG001_00120 HG001_00120 [gene_NONE] hypothetical protein	-2,55	2,99E-01
HG001_0135 HG001_0135 Igene_NONE   Petitase properties and TPEB domain protein	-2,55	2,99E-01
HG001_00125 HG001_00125 [gene_NONE] hypothetical protein	-2,55	2,990-01
HG001_00000 HG001_00000 [gene_opubA] Choine transport A re-binding protein OpubA	-2,43	1.905-02
HG001_01476 HG001_01476]gene_cut[zint-specific interance/eguatory protein	-2,19	1,80E-01
HG001_02183 HG001_02183 Jane mth IPT success many house the full section of the s	-2,15	1.80E-01
HG001_020387 HG001_02105]gene_intra[Trobsystem.htmlmlmlmlmlmlmlmlmlmlmlmlmlmlmlmlmlmlml	-2,18	1,80E-01
HG001_01449 HG001_01449 Jane NONE I by obstratical protein	-2.18	2.04E-07
HG001_00358 HG001_00358 Jame_tothe input the input term precursor	-2.13	1 19E-04
HG001_00579_HG001_00579_Jgene_tagX_Putative_plycosyltransferase_TagX	-2.12	7 39E-02
HG001 01788 HG001 01788 Jene trml ItRNA (cvtidine(34)-2'-O)-methyltransferase	-2.12	7.39E-02
HG001 01495 HG001 01495 gene vbeZlPhoH-like protein	-2.12	7.39E-02
HG001 02433 HG001 02433 Igene narH Respiratory nitrate reductase 1 beta chain	-2.06	2.56E-04
HG001 00018 HG001 00018 gene dnaC 1 Replicative DNA helicase	-2.00	1.08E-01
HG001 00819 HG001 00819 gene NONE hypothetical protein	-1,98	2,47E-01
HG001_01827 HG001_01827  gene_ghrB_2 Glyoxylate/hydroxypyruvate reductase B	-1,98	2,47E-01
HG001_00412 HG001_00412  gene_ispE 4-diphosphocytidyl-2-C-methyl-D-erythritol kinase	-1,98	2,47E-01
HG001_00857 HG001_00857  gene_kefC Glutathione-regulated potassium-efflux system protein KefC	-1,98	2,47E-01
HG001_01091 HG001_01091   gene_trmD   tRNA (guanine-N(1)-)-methyltransferase	-1,98	2,47E-01
HG001_00594 HG001_00594  gene_aes  Acetyl esterase	-1,98	2,47E-01
HG001_00402 HG001_00402 gene_NONE hypothetical protein	-1,98	2,47E-01
HG001_00865 HG001_00865 gene_murE_1 UDP-N-acetylmuramoyl-L-alanyl-D-glutamateL-lysine ligase	-1,94	1,65E-04
HG001_01775 HG001_01775  gene_yhaM 3'-5' exoribonuclease YhaM	-1,88	3,47E-02
HG001_01118 HG001_01118  gene_NONE hypothetical protein	-1,87	1,50E-01
HG001_00576 HG001_00576 gene_tagH_1 Teichoic acids export ATP-binding protein TagH	-1,87	1,50E-01
HG001_01783 HG001_01783  gene_rluD_3   Ribosomal large subunit pseudouridine synthase D	-1,85	1,95E-02
HG001_02693 HG001_02693  gene_sraP Serine-rich adhesin for platelets precursor	-1,83	8,66E-02
HG001_02588 HG001_02588  gene_clpL ATP-dependent Clp protease ATP-binding subunit ClpL	-1,81	8,88E-14
HG001_00849 HG001_00849  gene_NONE hypothetical protein	-1,78	4,42E-01
HG001_01643 HG001_01643  gene_serA D-3-phosphoglycerate dehydrogenase	-1,78	4,42E-01
HG001_00084 HG001_00084 gene_treR_1 Trehalose operon transcriptional repressor	-1,78	4,42E-01
HG001_02238 HG001_02238  gene_NONE   hypothetical protein	-1,78	4,42E-01
HG001_01967 HG001_01967 [gene_ytr8_2] ABC transporter ATP-binding protein Ytr8	-1,78	4,42E-01
HG001_01030 HG001_01030 [gene_ttsL] Cell division protein FtsL	-1,78	4,42E-01
HG001_02183 HG001_02183 [gene_mtr] [Manitol-specific prosphotransferase enzyme IIA component	-1,/8	4,42E-01
HG001_00709 HG001_00709 [gene_NONE] Epimerase ramity protein	-1,78	4,42E-01
HG001_01505 HG001_01505 [gene_type: http://www.hgp.com/districtions/steep states/	-1.70	4,420-01
HG001_02541 HG001_02541 Jøene_vuBTXJulose kinase	-1.78	4,42E-01
HG001_0253 HG001_00653 Jgene_nabBIAminodeoxychorismate synthase component 1	-1.78	4.42E-01
HG001_02304_HG001_02304_lgene_moaAl Cyclic pyranopterin monophosphate synthese	-1.78	4.42E-01
HG001 01158 HG001 01158 gene NONE methioning gamma-lyase	-1.78	4.42E-01
HG001 01520 HG001 01520 gene aroE Shikimate dehvdrogenase	-1.78	4,42E-01
HG001_01642_HG001_01642_gene_NONE_Soluble hydrogenase 42 kDa subunit	-1.78	4,42E-01
HG001 01159 HG001 01159 gene glnR HTH-type transcriptional regulator GlnR	-1.78	4,42E-01
HG001 02258 HG001 02258 gene ecfA2 Energy-coupling factor transporter ATP-binding protein EcfA2	-1,78	4,42E-01

		1.100 0.1
HG001_02521 HG001_02521  gene_NONE   putative lipoprotein precursor	-1,78	4,42E-01
HG001_01654 HG001_01654  gene_acsA_1   Acetyl-coenzyme A synthetase	-1,78	4,42E-01
HG001_00447 HG001_00447  gene_gabR   HTH-type transcriptional regulatory protein GabR	-1,78	4,42E-01
HG001_01944 HG001_01944 gene_NONE Staphostatin A	-1,78	4,42E-01
HG001_01770_HG001_01770[gene_ecsA]ABC-type transporter ATP-binding protein EcsA	-1.78	4.42E-01
HG001_02377_HG001_02377 Jgeng_NONE ABC-2 family transporter protein	-1.78	4 42E-01
	1,70	4,420-01
HG001_00744 HG001_00744 Igene_NONE Involterical protein	-1,78	4,42E-01
HG001_02495 HG001_02495  gene_ybbL putative ABC transporter ATP-binding protein YbbL	-1,78	4,42E-01
HG001_00844 HG001_00844  gene_mecA Adapter protein MecA	-1,78	4,42E-01
HG001_01326 HG001_01326 gene_aroB 3-dehydroquinate synthase	-1,78	4,42E-01
HG001_00052_HG001_00052_lgene_vxeP_1 putative hydrolase YxeP	-1.78	4.42E-01
HG001_02570_HG001_02570.lgene_sdbBLL-serine debudratase_beta chain	-1.78	4.42E-01
UC001_02350 UC001_02350 Jacob and Dire server demandates encodes full and	1.70	4,420 01
Hood _02333 Hood _02333 [gene_mail P is system mailose-specific Elics component	-1,70	4,4201
HG001_00092 HG001_00092  gene_phnD Phosphate-import protein PhnD precursor	-1,78	4,42E-01
HG001_01410 HG001_01410 gene_NONE hypothetical protein	-1,78	4,42E-01
HG001_00522 HG001_00522 gene_galK_2 Galactokinase	-1,78	4,42E-01
HG001 01176 HG001 01176 gene ItaE Low specificity L-threonine aldolase	-1,78	4.42E-01
HG001_01530_HG001_01530_Hgene_accB_21Biotin carboxyl carrier protein of acetyl-CoA carboxylase	-1.78	4 42E-01
HG001_01945_HG001_01945_lgapa_NONE_byrothetical protein	1 70	4.425-01
	-1,70	4,4201
HG001_02485 HG001_02485  gene_norB_5  Quinolone resistance protein NorB	-1,78	4,42E-01
HG001_01037 HG001_01037 gene_NONE Laccase domain protein	-1,78	4,42E-01
HG001_00656 HG001_00656 gene_kipA_1 KipI antagonist	-1,78	4,42E-01
HG001 02422 HG001 02422  gene_sarz HTH-type transcriptional regulator Sarz	-1,78	4.42E-01
HG001_01011 HG001_01011 Jacase_NONE (bypothetical protein	-1.78	4.42E-01
	1.70	4,420 01
Hood _00718 Hood _00718 [gene_None] hypothetical protein	-1,70	4,4201
HG001_00554 HG001_00554  gene_NONE hypothetical protein	-1,78	4,42E-01
HG001_01608 HG001_01608 gene_mutM Formamidopyrimidine-DNA glycosylase	-1,78	4,42E-01
HG001_01095 HG001_01095 gene_rnhB Ribonuclease HII	-1,78	4,42E-01
HG001_00972 HG001_00972  gene_rsmD Ribosomal RNA small subunit methyltransferase D	-1,78	4,42E-01
HG001_02157_HG001_02157.Jgene_coaWIType II pantothepate kinase	-1.78	4 42E-01
HG001_01084 HG001_01084 Japa and Bibourdease 3	1 79	4.425-01
	4.70	4,420-01
HG001_00025 HG001_00025 [gene_yyc1] two-component system tycrG regulatory protein	-1,78	4,42E-01
HG001_01365 HG001_01365  gene_NONE   Bacterial Ig-like domain (group 2)	-1,78	4,42E-01
HG001_01540 HG001_01540 gene_NONE hypothetical protein	-1,78	4,42E-01
HG001_02628 HG001_02628 gene_NONE Fructosamine kinase	-1,78	4,42E-01
HG001_01604 HG001_01604   gene_dnaB  Replication initiation and membrane attachment protein	-1.78	4.42E-01
HG001_00806_HG001_00806.lgene_glo01_1.loutative elycerophosphoryl diester phosphodiesterase 1	-1 78	4.42E-01
VC01_01202 VC01_01202 Jacob NOVE December of oracle system SUC	4 70	4,420 01
Noor_01/01/92 Hoot_01/92 [gene_Nove] Phosphotransierase system, Elic	-1,70	4,420-01
HGU01_02063 HGU01_02063 [gene_ioiC]5-dehydro-2-deoxygluconokinase	-1,78	4,42E-01
HG001_00461 HG001_00461  gene_mrnC   Mini-ribonuclease 3	-1,78	4,42E-01
HG001_00894 HG001_00894 gene_menD 2-succinyl-5-enolpyruvyl-6-hydroxy-3-cyclohexene-1-carboxylate synthase	-1,78	4,42E-01
HG001 00520 HG001 00520 gene galK 1 Galactokinase	-1,78	4,42E-01
HG001_01218_HG001_01218.Jgene_morE_Phosphatidy/glycerol/ysyltransferase	-1.78	4.42E-01
HC001_01526 HC001_01526 Janos_ ubbit_2 Jourtative protector Wbbl productor	1 70	4 435-01
Hood_01201300 Hood_01300 Bene_MIDD_21 participation and the first and th	1.70	4,420-01
HG001_01518 HG001_01518 [gene_nadu] putative nicotinate-nucleotide adenyiyitransterase	-1,78	4,42E-01
HG001_00989 HG001_00989  gene_rnhC Ribonuclease HIII	-1,78	4,42E-01
HG001_00027 HG001_00027  gene_yfkN_1   Trifunctional nucleotide phosphoesterase protein YfkN precursor	-1,78	4,42E-01
HG001_01297 HG001_01297  gene_tdcB L-threonine dehydratase catabolic TdcB	-1,78	4,42E-01
HG001 02611 HG001 02611 gene NONE DNA-binding transcriptional regulator EnvR	-1.78	4.42E-01
HG001_01135_HG001_01135_Jeene_ngsA1CDP-diacyJelycerol-elycerol-3-phosphate 3-phosphatidyItransferase	-1.78	4 42E-01
HG001_02101_HG001_02101[gene_pp_nicer definition protocol program in protocol	1 79	4.425-01
Hood _02101 Hood _02101 gene_Nove pacterial memorial marked domain protein	-1,70	4,422-01
HG001_00564 HG001_00564  gene_mnhD1_1 Na(+)/H(+) antiporter subunit D1	-1,78	4,42E-01
HG001_02616 HG001_02616 gene_NONE hypothetical protein	-1,78	4,42E-01
HG001_00054 HG001_00054  gene_NONE Na+/Pi-cotransporter	-1,78	4,42E-01
HG001_00610 HG001_00610  gene_NONE  hypothetical protein	-1,78	4,42E-01
HG001_01831 HG001_01831   gene_NONE   Putative multidrug export ATP-binding/permease protein	-1.78	4.42E-01
HG001_00780_HG001_00780.gene_patA_1.lPeptidoglycan_0-acetyltrapsferase	-1.78	4 42E-01
LC001_01262_LC001_01262_Lc000_LC001_Lc001_	1.70	4 425 04
Hoost_01202_Hoost_01202 [Belle_Notice Importance in the second se	-1,78	4,420-01
HGUU1_V2383 HGUU1_V2383  gene_corA Magnesium transport protein CorA	-1,78	4,42E-01
HG001_01207 HG001_01207  gene_mscL Large-conductance mechanosensitive channel	-1,78	4,42E-01
HG001_02599 HG001_02599 gene_ldhD_2 D-lactate dehydrogenase	-1,78	4,42E-01
HG001_00247 HG001_00247  gene_NONE hypothetical protein	-1,78	4,42E-01
HG001_01535_HG001_01535_Igene_vhbU_1[putative protease YhbU precursor	-1.78	4.42E-01
HG001_02608_HG001_02608_lagene_NONELAcethyltransforase (GNAT) family protein	-1.79	4 425-01
HC001_02000 HC001_02000 [gene_ht0hc]phcetyfransferae (dhwf) idinify protein	1.70	4,420-01
Leona Leona Leona (Beue agur l'Algendre-sicougi geul/glogeusse	-1,78	4,42E-01
HGU01_U1U32_HGUU1_U1U32  gene_mraY Phospho-N-acetyImuramoyI-pentapeptide-transferase	-1,78	4,42E-01

HG001 02726 HG001 02726 gene NONE Lactonase drp35	-1,78	4,42E-01
HG001 02593 HG001 02593 gene NONE hypothetical protein	-1,78	4,42E-01
HG001_00974 HG001_00974  gene_NONE hypothetical protein	-1,78	4,42E-01
HG001_01480 HG001_01480 gene_znuC_2 High-affinity zinc uptake system ATP-binding protein ZnuC	-1,78	4,42E-01
HG001_00664 HG001_00664  gene_NONE Putative lipid kinase	-1,78	4,42E-01
HG001_00553 HG001_00553  gene_NONE hypothetical protein	-1,77	1,54E-02
HG001_00967 HG001_00967 gene_NONE Cysteine-rich secretory protein family protein	-1,73	3,26E-01
HG001_02489 HG001_02489 gene_opuCA Carnitine transport ATP-binding protein OpuCA	-1,73	3,26E-01
HG001_02115 HG001_02115  gene_cls_2 Cardiolipin synthase	-1,73	3,26E-01
HG001_00668 HG001_00668 gene_nrdl Protein Nrdl	-1,73	3,26E-01
HG001_01063 HG001_01063 gene_prIA Primosomal protein N	-1,73	3,26E-01
HG001_02326 HG001_02326  gene_ureE Urease accessory protein UreE	-1,73	3,26E-01
HG001_02319 HG001_02319  gene_rihB   Pyrimidine-specific ribonucleoside hydrolase RihB	-1,73	3,26E-01
HG001_023/3 HG001_023/3 Igene_rpiA Kibose-5-phosphate isomerase A	-1,73	3,26E-01
HG001_00304 HG001_00304 [gene_spool_(chromosome-partitioning protein spool	-1,73	3,20E-01
HG001_02051_HG001_02051[gene_Noive]hypothetical protein	-1,73	3,20E-01
HG001_00496 HG001_00496 Hgene vid/TIMPACT service member Vig7	1.73	3.26E-01
HG001_00818 HG001_0088[gene_vid4[Sugar hosphatase Vid4	-1.72	2.04E-01
H6001_00205 H6001_00205 Janne NONEIGuconeogenesis factor	-1.72	2.04E-01
HG001 01237 HG001 01237 Jeene NONE hypothetical protein	-1.72	2.04E-01
HG001_00463 HG001_00463 gene_NONE VacP-like NYN domain protein	-1.72	2.04E-01
HG001 02615 HG001 02615 gene azoB NAD(P)H azoreductase	-1,72	2,05E-01
HG001_01085_HG001_01085 gene_smc Chromosome partition protein Smc	-1,72	1,23E-01
HG001_00022 HG001_00022 gene_walR Transcriptional regulatory protein WalR	-1,72	6,91E-02
HG001_01279 HG001_01279  gene_NONE   Acetyltransferase (GNAT) family protein	-1,72	3,76E-02
HG001_00319 HG001_00319 gene_gpmA_1 2,3-bisphosphoglycerate-dependent phosphoglycerate mutase	-1,72	7,06E-02
HG001_02062 HG001_02062  gene_agrA Accessory gene regulator protein A	-1,61	1,65E-01
HG001_01407 HG001_01407  gene_lexA_2   LexA repressor	-1,58	4,11E-03
HG001_01959 HG001_01959 gene_NONE Acyl-coenzyme A:6-aminopenicillanic acid acyl-transferase	-1,56	2,80E-01
HG001_00493 HG001_00493 gene_sdrD Serine-aspartate repeat-containing protein D precursor	-1,53	2,68E-05
HG001_01116 HG001_01116 gene_rimP Ribosome maturation factor RimP	-1,47	7,39E-02
HG001_01939 HG001_01939  gene_pcrA ATP-dependent DNA helicase PcrA	-1,45	5,72E-02
HG001_02527 HG001_02527  gene_srmB ATP-dependent RNA helicase SrmB	-1,45	5,81E-02
HG001_00366 HG001_00366 [gene_NONE]hypothetical protein	-1,44	4,42E-01
HG001_00181 HG001_00181 gene_NONE   hypothetical protein	-1,44	4,42E-01
HG001_02125 HG001_02125 [gene_NONE [hypothetical protein	-1,44	4,42E-01
HG001_01419 HG001_01419 [gene_schp]>egregation and condensation protein B	-1,44	4,42E-01
HG001_01537_HG001_01557_[gene_monk2]httpp://energidob.up/forentidob.up/for	-1,44	4,42E-01
HG001_01000 HG001_01000[gene_gapAz]engtycendeptyce=spinospinate denyurogenase z	1.44	4,42E-01
HG001_01258 HG001_01258 Hgene_cohl Lerobic cohaltoche latase subunit CohT	-1 44	4,42E-01
HG001 01448 HG001 01448 legen xsel Exodexvribonuclease 7 large subunit	-1.44	4.42E-01
H6001 1074 H6001 1074 Jgene this Thiaming pyrophashokinase	-1.38	3.46E-01
HG001 01219 HG001 01219   gene msrA1   Peptide methionine sulfoxide reductase MsrA 1	-1,38	3,46E-01
HG001_00252_HG001_00252_Igene_NONETFtsX-like permease family protein	-1,36	2,83E-01
HG001_02446 HG001_02446  gene_bdbD   Disulfide bond formation protein D precursor	-1,35	2,84E-01
HG001_00359 HG001_00359  gene_NONE hypothetical protein	-1,34	2,18E-01
HG001_01585 HG001_01585 gene_hemB Delta-aminolevulinic acid dehydratase	-1,32	2,99E-02
HG001_00843 HG001_00843  gene_spxA Regulatory protein Spx	-1,29	2,97E-03
HG001_01587 HG001_01587  gene_hemC Porphobilinogen deaminase	-1,27	9,47E-02
HG001_00867 HG001_00867 gene_prfC Peptide chain release factor 3	-1,26	1,23E-01
HG001_02121 HG001_02121 gene_tenA Putative thiaminase-2	-1,25	1,00E-02
HG001_02408 HG001_02408 gene_yhfP Putative quinone oxidoreductase YhfP	-1,23	2,81E-01
HG001_00640 HG001_00640 gene_nagA N-acetylglucosamine-6-phosphate deacetylase	-1,23	2,81E-01
HG001_00641 HG001_00641 gene_corC Magnesium and cobalt efflux protein CorC	-1,23	2,81E-01
HG001_00238 HG001_00238  gene_yezG_1 putative antitoxin YezG	-1,22	7,39E-02
HG001_00782 HG001_00782  gene_NONE DItD central region	-1,22	2,14E-02
HGUUI_UI451 HGUUI_UI451 [gene_ctiB_2]2-oxogiutarate carboxylase small subunit	-1,22	9,25E-02
HOUUT_01333 HOUUT_01333 Houe NONE   YDDK-like protein	-1,21	9,25E-02
HOUUT_01332 HOUUT_01332 [gene_NUNE] Heptaprenyi diphosphate synthase (HEPPP synthase) subunit 1	-1,21	3,44E-01
HG001_02667_HG001_02667_rappe_tuppe_tuppe_transcriptional_ragulater_ShuA	1.21	3,44E-01
HG001_02382_HG001_02382.ligene_siyA_s1 manscriptional regulator SiyA	1 10	5,44E-01 6,82E-02
HG001_02005_HG001_02005_gene_rshillPhosphoserine_phosphatase_Rshill	-1.17	2 06E-01
HG001_02537 HG001_02537 gene_staB UTPelucose-1-phosphateuridvlvtransferase	-1.17	4.42E-01
	Contraction of the second s	(1) (1) (1) (1) (1) (1) (1) (1) (1) (1)

HG001_01950 HG001_01950  gene_pheA P-protein	-1,17	4,42E-01
HG001_00211 HG001_00211  gene_rbsK   Ribokinase	-1,17	4,42E-01
HG001_00699 HG001_00699 gene_lgt  Prolipoprotein diacylglyceryl transferase	-1,17	4,42E-01
HG001_00781 HG001_00781 [gene_dltC [D-alaninepoly(phosphoribitol) ligase subunit 2	-1,17	4,42E-01
HG001_01254 HG001_01254  gene_dapA 4-hydroxy-tetrahydrodipicolinate synthase	-1,17	4,42E-01
HG001_00183 HG001_00183  gene_hmp Flavohemoprotein	-1,17	2,97E-03
HG001_02428 HG001_02428 gene_nreC Oxygen regulatory protein NreC	-1,17	4,42E-01
HG001_00931 HG001_00931 [gene_rim] Ribosomal RNA large subunit methyltransferase I	-1,17	4,42E-01
HG001_02551 HG001_02551 [gene_yxlF_5] putative ABC transporter ATP-binding protein YxlF	-1,17	4,42E-01
HG001_00432 HG001_00432  gene_tol8 Dihydroneopterin aldolase	-1,17	4,42E-01
HG001_01128 HG001_01128  gene_ttsk DNA translocase FtsK	-1,15	2,71E-01
HG001_01280 HG001_01280 gene_NONE   putative CtpA-like serine protease	-1,12	6,45E-02
HG001_00199 HG001_00199 gene_gutB_2 Sorbitol dehydrogenase	-1,12	1,21E-01
HG001_01776 HG001_01776 gene_NONE Leucine-rich repeats of kinetochore protein Cenp-F/LEK1	-1,11	2,34E-04
HG001_01714 HG001_01714  gene_pckA Phosphoenolpyruvate carboxykinase [ATP]	-1,11	9,00E-03
HG001_00679 HG001_00679  gene_NONE hypothetical protein	-1,11	3,31E-01
HG001_01603 HG001_01603  gene_dnal  Primosomal protein Dnal	-1,11	3,34E-01
HG001_01452 HG001_01452  gene_accB_1  Biotin carboxyl carrier protein of acetyl-CoA carboxylase	-1,10	1,48E-01
HG001_02646 HG001_02646  gene_acsA_2   Acetyl-coenzyme A synthetase	-1,10	8,88E-04
HG001_02118 HG001_02118  gene_thiE   Thiamine-phosphate synthase	-1,10	6,13E-02
HG001_00544 HG001_00544  gene_adh Alcohol dehydrogenase	-1,10	2,42E-04
HG001_01624 HG001_01624  gene_nrnA_2   Bifunctional oligoribonuclease and PAP phosphatase NrnA	-1,09	2,59E-01
HG001_00998 HG001_00998  gene_frdB   Fumarate reductase iron-sulfur subunit	-1,08	2,00E-01
HG001_01261 HG001_01261  gene_cspA_2   Cold shock protein CspA	-1,07	2,30E-02
HG001_01031 HG001_01031  gene_pbpB Penicillin-binding protein 2B	-1,07	2,77E-02
HG001_02436 HG001_02436  gene_nasE   Assimilatory nitrite reductase [NAD(P)H] small subunit	-1,07	1,46E-01
HG001_01148 HG001_01148 gene_mutl DNA mismatch repair protein MutL	-1,07	5,82E-01
HG001 02614 HG001 02614 gene NONE Glyoxalase-like domain protein	-1,07	5,82E-01
HG001 01779 HG001 01779 gene NONE hypothetical protein	-1,07	5,82E-01
HG001 02045 HG001 02045 gene dapE putative succinyl-diaminopimelate desuccinylase	-1,07	5,82E-01
HG001_01692 HG001_01692   gene_ribD Riboflavin biosynthesis protein RibD	-1.07	5.82E-01
HG001_01473 HG001_01473   gene_gluP   Rhomboid protease GluP	-1.07	5.82E-01
HG001_00515 HG001_00515   gene_NONE   hypothetical protein	-1.07	5.82E-01
HG001_01539 HG001_01539 Jgene_vrrKJ Putative Holliday junction resolvase	-1.07	5.82E-01
HG001_01058_HG001_01058_lgene_NONE_I3-demethylubiquinone-9_3-methyltransferase	-1.07	5.82E-01
HG001 01197 HG001 01197 Jeene guaClGMP reductase	-1.07	5 82E-01
HG001_00352_HG001_00352_Igene_NONELType L restriction modification DNA specificity domain protein	-1.07	5.82E-01
HG001_03346 HG001_03346 Jene sub8_2 Juosital-1-monophosphatase	-1.07	5.82E-01
HG001_02430 HG001_02430 Jacob NONE Invoctbetical protein	-1.07	5.82E-01
HG001_00551 HG001_00551 Japa NONELCYTH domain protein	-1.07	5.82E-01
HG001_02421 HG001_02421 Jana NONE Invocthetical protein	-1.06	5.82E-01
HG001_022421 HG001_022421 [gene_Hold Childrane SheCD subunit C	-1.06	5,822-01
HG001_00575 HG001_00575 Hg00 tog/Hutesse soco submane c	-1,00	5,822-01
HG001_003745 HG001_00375 [gene_tagA] Futative in-activitient informativitiansierase	-1,00	5,822-01
HG001_02743 HG001_02743 [gene_csptA] cold shock-like protein CsptA	1.06	5,822-01
HC001_00342 HC001_00342 [gene_NOVer] htt domain protein	-1,00	5,62E-01
neoo1_02094 neoo1_02094 [gene_isov] Anti-signa-bialcov antagonist	-1,06	1,05E-01
HG001_002/2 HG001_002/2 [gene_yiki_4] Infunctional nucleotide phosphoesterase protein fikiv precursor	-1,05	4,35E-01
HC001_00245 HC001_00245 Igene_yez0_5 [putative antitoxin Yez0	1,05	4,330-01
ndout_ousoo ndout_ousoo igene_tresi/his system trenaiose-specific tilbu component	-1,05	4,35E-01
nooutay noouutay, igene_yqtt[Putative pyruvate, pnospnate dikinase regulatory protein	-1,05	4,35E-01
Hugot_005/0 Hugot_005/0 [gene_stet_1]N-acetyimuramoyI-L-alanine amidase stet precursor	-1,04	3,19E-01
Huou1_uosa huou1_uuosa (gene_nprk) HPr kinase/phosphorylase	-1,04	1,34E-01
Houri_00728 Houri_00728 [gene_CIA] Clumping Tactor A precursor	-1,02	1,2/E-01
HGU01_U2181 HGU01_U2181 [gene_glm5] Glutaminefructose-6-phosphate aminotransferase [isomerizing]	-1,01	1,75E-04
HG001_02021 HG001_02021 [gene_NONE] hypothetical protein	-1,01	6,59E-02
HG001_01918 HG001_01918 gene_vraR Response regulator protein VraR	-1,01	2,35E-01

Annexe 3 : Tableau de l'expression différentielle selon les voies métaboliques impliquées.

	Pyrimidine deoxyribonucleotides de novo biosyntheis			Diff. Transcri	ptomics MV/ctr	Diff. Proteon	nics MV/ctr	
id	gene	product	locus_tag_NCTC832	25 gene_NCTC8325	log2FoldChan	ge padj	log2FoldChan	ge padj
HG001_01054	carB	Carbamoyl-phosphate synthase large chain	SAOUHSC_01170	carB	5,41	9,50E-104	0,12	7,76E-01
HG001_01052	pyrC	Dihydroorotase	SAOUHSC_01168	pyrC	5,31	1,73E-65	1,22	8,22E-09
HG001_01055	pyrF	Orotidine 5'-phosphate decarboxylase	SAOUHSC_01171	1000	5,29	3,09E-126	0,59	2,47E-01
HG001_01053	carA	Carbamoyl-phosphate synthase small chain	SAOUHSC_01169	*	5,28	6,93E-63	0,67	1,04E-01
HG001_01051	ругВ	Aspartate carbamoyltransferase	SAOUHSC_01166	pyr8	5,17	1,60E-52	0,09	9,09E-01
HG001_01056	pyrE	Orotate phosphoribosyltransferase	SAOUHSC_01172	pyrE	4,97	1,35E-105	0,83	9,18E-02
HG001_01050	pyrP	Uracil permease	SAOUHSC_01165		4,81	5,14E-46	0,90	3,77E-01
HG001_01057	-	hypothetical protein; same operon as pyrP-pyrB-pyrC-carA-carB-p	yrF-pyrESAOUHSC_01173	-	3,51	8,10E-45	ND	ND
HG001_00399	tmk	Thymidylate kinase	SAOUHSC_00451	tmk	1,06	4,06E-06	0,27	8,80E-01
HG001_00669	nrdE2	Ribonucleoside-diphosphate reductase subunit alpha 2	SAOUHSC_00742	nrdl	1,36	7,99E-08	0,40	8,71E-02
HG001_00670	nrdF	Ribonucleoside-diphosphate reductase subunit beta	SAOUHSC_00743	nrdF	2,53	5,81E-22	0,51	2,13E-02
HG001_01049	pyrR	Bifunctional protein PyrR	SAOUHSC_01164		1,01	0,000496863	2,76	4,52E-09
HG001_01109	pyrH	Uridylate kinase	SAOUHSC_01235	pyrH	1,19	7,15E-06	-0,67	2,35E-01
HG001_01337	cmk	Cytidylate kinase	SAOUHSC_01496	cmk	1,61	3,25E-11	-0,10	8,52E-01
HG001_01534	udk	Uridine kinase	SAOUHSC 01715	2000	1,30	2,62E-10	-0,66	6,45E-01
HG001_02154	pyrG	CTP synthase	SAOUHSC_02368	pyrG	2,39	8,99E-22	-0,35	3,37E-01
HG001_02629	pyrD	Dihydroorotate dehydrogenase (quinone)	SAOUHSC_02909	-	2,96	6,09E-08	2,33	6,96E-12

		Purine deoxyribonucleotides de novo biosyntheis			Diff. Transcripte	omics MV/ctr	Diff. Proteon	nics MV/ctr
id	gene	product	locus_tag_NCTC8325 gene_NCTC8	325	log2FoldChange	padj	log2FoldChang	e padj
HG001_00085	deoD	Purine nucleoside phosphorylase DeoD-type	SAOUHSC_00097 -		3,81	5,29E-33	ND	ND
HG001_00019	purA	Adenylosuccinate synthetase	SAOUHSC_00019 -		2,26	4,52562E-15	0,05	9,57E-01
HG001_01560	apt	Adenine phosphoribosyltransferase	SAOUHSC_01743 -		1,89	5,58131E-18	-0,37	7,86E-01
HG001_01942	purB	Adenylosuccinate lyase	SAOUHSC_02126 -		1,86	6,42238E-15	-0,34	2,32E-01
HG001_02655	nrdD	Anaerobic ribonucleoside-triphosphate reductase	SAOUHSC_02942 -		2,41	8,69131E-18	0,27	8,69E-01

	Phage genes		Diff. Transcriptomics MV/ctr		Diff. Proteomics MV/ctr		
id	gene	product	locus_tag_NCTC8325 gene_NCTC8325	log2FoldChange	padj	log2FoldCl	nange padj
HG001_01894		Phage protein	SAOUHSC_02072 -	5,30	3,29E-106	7,72	8,10E-24
HG001_01903	-	Putative phage protein	SAOUHSC_02081 -	5,26	6,13E-84	1,98	4,11E-01
HG001_01904		Putative phage regulatory protein	SAOUHSC_02083 -	5,13	1,51E-76	ND	ND
HG001_01891	4	Putative phage replication protein	SAOUHSC_02069 -	5,13	7,84E-104	4,93	9,83E-04
HG001_01895	2	Bacteriophage Mu Gam like protein	SAOUHSC_02073 -	5,12	1,86E-101	7,35	2,61E-18
HG001_01898		Phage protein	SAOUHSC_02076 -	5,04	5,50E-64	ND	ND
HG001_01902	-	Phage antirepressor protein KiIAC domain protein	SAOUHSC_02080 -	5,02	1,44E-91	9,03	5,76E-54
HG001_01887	(÷	Phage protein	SAOUHSC_02065 -	5,00	2,05E-91	2,79	2,32E-01
HG001_01888		Putative phage protein	SAOUHSC_02066 -	4,98	1,64E-111	ND	ND
HG001_01885	-	Phage protein	SAOUHSC_02063 -	4,98	1,29E-122	ND	ND
HG001_01886	4	Phage protein	SAOUHSC_02064 -	4,94	3,02E-104	3,98	3,18E-02
HG001_01884	54 - C	Putative phage regulatory protein; Helix-turn-helix domain protein	SAOUHSC 02062 -	4,89	3,62E-92	3,68	6,59E-02
HG001_01883	÷	Phage protein; PVL ORF-50-like family protein	SAOUHSC_02061 -	4,89	5,90E-94	4,44	8,53E-03
HG001_01900	+	Phage protein	SAOUHSC_02078 -	4,89	1,40E-93	5,30	1,17E-04
HG001 01890	2	Phage protein	SAOUHSC 02068 -	4,87	6,99E-99	2,79	2,32E-01
HG001 02016		Phage protein	SAOUHSC 02213 -	4,86	5,76E-99	ND	ND
HG001 01896		Phage protein	SAOUHSC 02074 -	4.83	1,20E-88	ND	ND
HG001 01901		Putative phage protein	SAOUHSC 02079 -	4,81	2.42E-107	1.98	4.11E-01
HG001 01875		Transcriptional activator RinB (phage)	SAOUHSC 02053 -	4.75	1.21E-118	ND	ND
HG001 01868		Putative phage protein	SAOUHSC 02046 -	4.73	3.62E-66	ND	ND
HG001 01880		Putative phage protein	SAOUHSC 02058	4.70	1.30E-90	6.23	1.47E-08
HG001 01881		Phage protein	SADUHSC 02059	4.70	4.55E-98	ND	ND
HG001 01870	2	Phage portal protein%2C SPP1 Gp6-like	SAOUHSC 02048 -	4.69	1.57E-79	1.98	4.11E-01
HG001 01876	-	Phage protein	SAOUHSC 02054 -	4.68	8.91E-80	ND	ND
HG001_01882	0	Phage protein	SADUHSC 02060	4.66	8 31E-112	ND	ND
HG001 01869		Phase Mu protein E like protein	SADUHSC 02047	4.63	3.92F-79	ND	ND
HG001_01899	ŝ.	Phage protein	SAOUHSC 02077 -	4.60	2 32E-83	7.22	7.52E-17
H6001 01873		Transcriptional activator, phage associated	SACUHSC 02051	4.54	9.075-91	5 50	2 76E-05
HG001 01878		Putative phage protein	SADUHSC 02056	4.54	2 165-83	ND	ND
HG001_02037		Putative phage protein	SADUHSC 02234	A 49	A 16E-70	ND	ND
HG001 02032	di il	Phage protein	SADUHSC 02228	4.46	4 05E-75	ND	ND
HG001_01874		Phage protein	SADUHSC 02052	4.42	5 03E-104	ND	NO
HG001_01383	0	Phage protein	SADUHSC 01550	4.41	8 415-58	ND	ND
HG001 02034	6	AntA/AntB antirepressor	SADUHSC 02229	4.40	3.055-86	1.98	4 115-01
HG001_02034	2	Putative phage regulation protein	SACULIEC 02225	4.28	3,675-72	ND	ND
HG001_01877		Phage protein	SACUHISC 02055	4.29	1 195-97	3.20	1.735-01
HC001_01807		Phage protein	SACUHSC 02025	4.33	2 095 92	9.14	1,250-01
HC001_01857		Phage protein Disage cancid family protein	SACIUMEC 02073	4,22	1.055 57	4.32	1,500-43
H6001_01800	5	Phage application protein Phage application protein	SACIUSC 02245 -	4,20	1,550-57	ND	1,046-02
HG001_02055	-	Phage antirepressor protein kinkc domain protein	SACUHSC 02029 -	4,15	1,000-05	ND E CO	C PTE OF
HG001_01807	-	Pluative phage head protein	5A00H5C_02044 -	4,15	1,030-01	3,00	0,070-00
H6001_018/1	<i>.</i>	Phage terminase targe solution	SADUHSC_02049 -	4,14	4,676-33	ND	2,227,01
HG001_01865		Phage protein	SACUHSC_02042 -	4,12	9,346-51	2,19	2,325-01
HG001_01863	-	Putative phage protein	SAOUHSC_02040 -	4,07	1,185-55	ND	ND
HG001_02023		Putative phage nuclease	SACOHSC_02219 -	4,04	5,116-85	ND	ND
HG001_01858	S	Phage protein	SAGUHSC_02034 -	3,98	5,865-61	ND	ND
HG001_02031	C.	Putative phage protein	SAUUHSC_02227 -	3,98	1,83E-46	ND	ND
HG001_02029		Phage protein	SAUUHSC_02225 -	3,98	4,57E-80	1,98	4,11E-01
HG001_01861		Putative phage protein	SAOUHSC_02037 -	3,95	1,04E-58	ND	ND
HG001_02025		Phage protein	SAOUHSC_02221 -	3,95	6,11E-88	ND	ND
HG001_02017	*	Putative phage protein	SAOUHSC_02214 -	3,88	2,85E-46	ND	ND
HG001_02028		Phage protein	SAOUHSC_02224 -	3,85	6,04E-45	ND	ND
HG001_01386	.+	Phage protein; PVL orf 52-like protein; Phage phi 11 orf23 protein home	ok SAOUHSC_01553 -	3,85	2,70E-63	ND	ND
HG001_02024	1	Putative phage ssDNA binding protein	SADUHSC_02220 -	3,83	7,83E-62	1,98	4,11E-01
HG001 01860		Phage major tail protein 2	SAOUHSC 02036 -	3.82	7.08E-64	3.30	1.23E-01

HG001_02026 -	Putative phage protein	SAOUHSC_02222 -	3,81	2,07E-65 ND	ND
HG001_01859 -	Phage protein	SAOUHSC_02035 -	3,77	1,37E-55 3,98	3,18E-02
HG001_01862 -	Phage protein	SAOUHSC_02038 -	3,77	3,25E-54 ND	ND
HG001_01872 -	Terminase small subunit	SAOUHSC_02050 -	3,65	1,14E-36 ND	ND
HG001_02027 -	Phage protein	SAOUHSC_02223 -	3,63	5,40E-53 ND	ND
HG001_02020 -	Phage protein	SAOUHSC_02217 -	3,32	8,20E-54 ND	ND

-		DNA repair			Diff. Transcri	ptomics MV/ctr	Diff. Prote	omics MV/ctr
id	gene	product	locus_tag_NCTC832	25 gene_NCTC8325	log2FoldChan	ge padj	log2FoldCha	nge padj
HG001_01889	dnaC_2	Replicative DNA helicase	SAOUHSC_02067	-	4,92	1,18E-111	ND	ND
HG001_01222	dinB_1	DNA polymerase IV	SAOUHSC_01363	Muc8	4,04	1,46E-55	ND	ND
HG001_00018	dnaB	Replicative DNA helicase	SAOUHSC_00018	- ÷	0,51	0,052192362	-2,00	1,08E-01
HG001_00004	recF	DNA replication and repair protein RecF	SAOUHSC_00004	recF	1,17	6,04E-09	ND	ND
HG001_00310	ssb_1	Single-stranded DNA-binding protein ssb	SAOUHSC_00349		1,21	7,79E-08	0,57	2,83E-01
HG001_00510	ung	Uracii-DNA glycosylase	SAOUHSC_00564	2	1,02	0,000840362	-0,66	6,45E-01
HG001_00659	recQ_1	ATP-dependent DNA helicase RecQ	SAOUHSC_00730	14 J	2,10	4,16E-29	ND	ND
HG001_00697	uwrA	UvrABC system protein A	SAOUHSC_00780	uvrA	1,54	4,12E-15	0,27	8,18E-01
HG001_00992	polX	DNA polymerase/3'-5' exonuclease PolX	SAOUHSC_01098		1,11	2,71E-08	-0,37	7,86E-01
HG001_00993	mut52	Endonuclease MutS2	SAOUHSC_01099	12	1,34	1,28E-10	-0,86	3,26E-01
HG001_01095	rnhB	Ribonuclease Hil	SAOUHSC 01215	rnhB	1,12	1,30E-06	-1,78	4,42E-01
HG001_01137	recA	Protein RecA	SAOUHSC_01262	recA	2,19	1,32E-20	1,36	5,99E-05
HG001_01205	sbcD	Nuclease SbcCD subunit D	SAOUHSC_01341		1,37	2,58E-07	ND	ND
HG001_01310	recU	Holliday Junction resolvase RecU	SAOUHSC_01466	recU	1,43	2,34E-09	ND	ND
HG001_01481	nfo	putative endonuclease 4	SAOUHSC_01658		1,79	2,77E-17	-0,20	7,91E-01
HG001_01514	comEA	ComE operan protein 1	SAOUHSC_01693	<del></del>	1,43	2,04E-08	ND	ND
HG001_01561	reci	Single-stranded-DNA-specific exonuclease RecJ	SAOUHSC_01744	-	1,37	2,90E-12	-0,03	9,83E-01
HG001_01566	ruvB	Holliday junction ATP-dependent DNA helicase RuvB	SAOUHSC_01750	ruvB	1,00	2,72E-05	ND	ND
HG001_01938	ligA	DNA ligase	SAOUHSC 02122	-	2,00	7,85E-21	-0,48	2,00E-01
HG001 01939	pcrA	ATP-dependent DNA helicase PcrA	SAOUHSC 02123	*	2.18	7.32E-27	-1,45	5,72E-02

		Nitrate and Nitrite reduction. Porfirines biosisnthesis, anaerobic respiration	atory chain		Diff. Transcri	ptomics MV/ctr	Diff. Proteo	mics MV/ctr
id	gene	product	locus_tag_NCTC83	25 gene_NCTC8325	log2FoldChan	ge padj	log2FoldChan	ge padj
HG001_02438	shfC (nir	R) Sirohydrochlorin ferrochelatase	SAOUHSC 02685	nirB	2,59	3,49591E-19	ND	ND
HG801_02437	nasD	Nitrite reductase [NAD(P)H] large subunit - similar to tRNA U-34 5-methyl	SAOUHSC_02684	nasD	3,20	1,42E-25	-0,35	4,19E-01
HG001_02436	masE	Nitrite reductase [NAD(P)H] small subunit	SAOUHSC_02683	nasE	3,32	1,65E-29	-1,07	1,46E-01
HG001_02435	nasF	Uroporphyrinogen-III C-methyltransferase - similar to queE	SAOUHSC_02682	nasF	3,40	5,44181E-37	0,66	5,51E-01
HG001_02434	narG	Respiratory nitrate reductase 1 alpha chain - molybdopterin (4Fe-4S) clus	SAOUHSC 02681	narG	3,80	2,96E-40	-2,56	1,47E-13
HG001_02433	narH	Respiratory nitrate reductase 1 beta chain - [4Fe-45] cluster	SAOUHSC_02680	narH	4,28	1,58E-52	-2,06	2,56E-04
HG001_02432	narW	Nitrate reductase molybdenum cofactor assembly chaperone	SAOUHSC_02679	nard	4,26	4,39E-51	-4,17	2,68E-02
HG001_02431	narX	Respiratory nitrate reductase subunit gamma	SAOUHSC_02678	nari	3,19	3,92E-36	ND	ND
HG001_02430	nreA	Nitrogen fixation regulatory protein	SAOUHSC_02677	nreA	2,55	5,64788E-26	-1,07	5,82E-01
HG001_02429	nreB	Oxygen sensor two-component histidine kinase [4Fe-45] cluster	SAOUHSC_02676	nreB	2,86	7,06112E-32	-2,55	2,99E-01
HG001_02428	nreC	Oxygen regulatory protein regulator transcription factor of the two comp	SAOUHSC_02675	nreC	2,51	1,59378E-30	-1,17	4,42E-01
HG001_02344	1	Putative formate dehydrogenase	SAOUHSC_02582	fdhA	-0,69	0,002489064	-3,93	1,23E-21
HG001_02343		Putative formate dehydrogenase	SAOUHSC_02581	1	-1,06	6,23554E-05	-4,56	4,13E-08
HG001 02424	narT	putative nitrate transporter NarT	SAOUHSC 02671	-a - 10	2,15	0,000554689	-3,72	7,39E-02

	Regulation of respiratory chain			Diff. Transcript	tomics MV/ctr	Diff. Proteomics MV/ctr		
id	gene	product	locus_tag_NCTC8325 gene_NCTC8325	log2FoldChange	padj	log2FoldChange	padj	
HG001_02428	nreC	Oxygen regulatory protein NreC	SAOUHSC_02675 -	2,51	1,59E-30	-1,17	4,42E-01	
HG001_02059	rex	Redox-sensing transcriptional repressor Rex	SAOUHSC_02273 -	-0,25	0,272186609	0,05	9,53E-01	

		Protein Folding		Diff. Transcri	ptomics MV/ctr	Diff. Proteor	nics MV/ctr
id	gene	product	locus_tag_NCTC8325 gene_NCTC8325	log2FoldChan	ge padj	log2FoldChan	ge padj
HG001_00429	hslO	33 kDa chaperonin	SAOUHSC_00487 hsl0	0,95	8,36E-06	0,01	9,85E-01
HG001_00821	clp8_1	Chaperone protein ClpB	SAOUHSC_00912 -	1,14	5,03E-07	0,09	8,73E-01
HG001_01504	dnal	Chaperone protein Dnal	SAOUHSC_01682 -	0,72	0,000696191	-0,31	5,20E-01
HG001_01506	grpE	Protein GrpE	SAOUHSC_01684 -	0,74	0,00066207	0,23	4,42E-01
HG001_01591	clpX	ATP-dependent Cip protease ATP-binding subunit CipX	SAOUHSC_01778 clpX	1,42	4,48E-12	0,70	4,11E-03
HG001 01592	tig	Trigger factor	SAOUHSC 01779 tig	1.39	9.40E-11	0.90	5.36E-05

		tRNA modification			Diff. Transcri	ptomics MV/ctr	Diff. Proteor	mics MV/ctr
id	gene	product	locus_tag_NCTC832	5 gene_NCTC8325	log2FoldChan	ge padj	log2FoldChan	ge padj
HG001_02727	glpE_3	Thiosulfate sulfurtransferase GIpE	SAOUHSC_03024	+	4,35	4,32E-96	3,20	2,44E-09
HG001_01911	queE_2	7-carboxy-7-deazaguanine synthase	SAOUHSC_02090	-	3,19	6,19E-61	0,93	5,04E-01
HG001_02256	truA	tRNA pseudouridine synthase A	SAOUHSC_02480	truA	2,08	4,31E-25	-0,63	7,17E-01
HG001_02751	mnmG	tRNA uridine 5-carboxymethylaminomethyl modification enzyme MnmG	SAOUHSC_03052	gidA	1,93	2,97E-16	0,65	5,36E-02
HG001_02752	mnmE	tRNA modification GTPase MnmE	SAOUHSC_03053	trmE	1,62	2,36E-10	1,02	2,12E-01
HG001_01564	tgt	Queuine tRNA-ribosyltransferase	SAOUHSC_01748	tgt	1,60	8,50E-13	-0,75	2,61E-01
HG001_01635	thil	putative tRNA sulfurtransferase	SAOUHSC_01824		1,42	1,03E-11	-0,60	4,98E-01
HG001 01091	trmD	tRNA (guanine-N(1)-)-methyltransferase	SAOUHSC 01210	trmD	1,41	2,36E-10	-1,98	2,47E-01
HG001 01565	queA	S-adenosylmethionine:tRNA ribosyltransferase-isomerase	SAOUHSC 01749	queA	1,35	1,96E-08	0,15	9,06E-01
HG001 01788	trmL	tRNA (cytidine(34)-2'-O)-methyltransferase	SAOUHSC 01988		1,30	1,85E-08	-2,12	7,39E-02
HG001_01484	trmK	tRNA (adenine(22)-N(1))-methyltransferase	SAOUHSC_01661		1,24	3,25E-09	0,20	8,25E-01
HG001_01102	trmFO	MethylenetetrahydrofolatetRNA-(uracil-5-)-methyltransferase TrmFO	SAOUHSC_01223	gid	1,04	3,65E-06	0,05	9,33E-01
HG001_01144	mia8	(Dimethylallyl)adenosine tRNA methylthiotransferase MiaB	SAOUHSC 01269		1,01	6,46E-06	-5,02	1,32E-03
HG001 01552	tcdA	tRNA threonylcarbamoyladenosine dehydratase	SAOUHSC 01735	14	0,88	0,000111308	-0,78	3,93E-01
HG001 02072	tsaD	tRNA N6-adenosine threonylcarbamoyltransferase	SAOUHSC_02277	ECD	0,75	0,000378128	-0,87	5,13E-01

HG001_01500	mta8_1	Threonylcarbamoyladenosine tRNA methylthiotransferase Mta8	SAOUHSC_01679	24	0,69	0,001185038	ND		ND
HG001_00404	yfiC	tRNA1(Val) (adenine(37)-N6)-methyltransferase	SAOUHSC_00457	- 4	0,58	0,023934541	ND		ND
HG001_00462	-	Putative TrmH family tRNA/rRNA methyltransferase	SAOUHSC_00513		-0,43	0,074696654	-1	0,51	4,42E-01
HG001_02075	tsaE	tRNA threonylcarbamoyladenosine biosynthesis protein TsaE	SAOUHSC_02280		-0,83	0,016585893	ND		ND
HG001_01122	truB	tRNA pseudouridine synthase B	SAOUHSC_01248	19	-0,90	4,08E-05	0	),44	6,84E-01
HG001_00036	dus_Z	putative tRNA-dihydrouridine synthase	SAOUHSC_00039	17	-0,98	4,87E-06	0	),66	5,51E-01
HG001_00985	-	Putative TrmH family tRNA/rRNA methyltransferase	SAOUHSC_01091		-1,10	3,49E-07	-1	0,04	9,76E-01
HG001_01537	trmR	Putative O-methyltransferase/MSMEI_4947 tRNA 5-hydroxyuridine methy	SAOUHSC_01718	-	0,94	0,004417914		3,42	1,23E-01
HG001_00666	queF	NADPH-dependent 7-cyano-7-deazaguanine reductase	SAOUHSC_00739		0,60	0,00815737	0	),49	4,42E-01
HG001_01789	queG	Epoxyqueuosine reductase	SAOUHSC_01989		0,54	0,030211245	ND		ND
HG001_00496	folE2	GTP cyclohydrolase FolE2	SAOUHSC_00549		1,57	1,60E-14	0	0,50	3,56E-01
HG001_01154	miaA	tRNA dimethylallyltransferase	SAOUHSC_01280	miaA	0,33	0,196377884	0	0,02	9,85E-01
HG001_00650	queD	6-carboxy-5%2C6%2C7%2C8-tetrahydropterin synthase	SAOUHSC_00720	-	-0,10	0,750041318	0	),83	4,42E-01
HG001_00649	queE_1	7-carboxy-7-deazaguanine synthase	SAOUHSC_00719		0,39	0,083379277	ND		ND
HG001_00651	queC	7-cyano-7-deazaguanine synthase	SAOUHSC_00721		0,04	0,872388212	-1	0,28	8,73E-01

	Fermentation			Diff. Transcriptor	nics MV/ctr	Diff. Proteomics MV/ctr	
id	gene	product	locus_tag_NCTC8325 gene_NCTC8325	log2FoldChange p	adj	log2FoldChange	e padj
HG001_02246	aldC_1	Alpha-acetolactate decarboxylase	SAOUHSC_02467 -	3,24	1,69E-21	1,26	6,63E-10

6		Detoxifying enzymes			Diff. Transcri	ptomics MV/ctr	Diff. Proteon	nics MV/ctr
id	gene	product	locus_tag_NCTC83	25 gene_NCTC8325	log2FoldChan	ge padj	log2FoldChang	ge padj
HG001_00082	sodM	Superoxide dismutase [Mn/Fe] 2	SAOUHSC_00093		2,37	1,32E-34	-0,18	7,14E-01
HG001_01477	sodA	Superoxide dismutase [Mn/Fe] 1	SAOUHSC_01653	8	0,47	0,05143839	0,34	3,51E-01
HG001_01194	katA	Catalase	SAOUHSC_01327		-0,499	0,052458991	0,91	3,55E-04
HG001_01633	tpx	putative thiol peroxidase	SAOUH5C_01822	tpx	0,445	0,051341102	0,20	6,15E-01
HG001_00324	ahpC	Alkyl hydroperoxide reductase subunit C	SAOUHSC_00365		1,87	1,93E-18	1,92	4,00E-77
HG001_00323	ahpF	Alkyl hydroperoxide reductase subunit F	SAOUHSC_00364	-	1,79	7,15E-17	1,86	3,84E-51
HG001_02514	ahpD	Alkyl hydroperoxide reductase AhpD	SAOUHSC_02774		-2,35	2,77E-23	-0,67	2,59E-01
HG001_00183	hmp	Flavohemoprotein	SAOUHSC_00204		-1,31	1,40E-05	-1,17	2,97E-03
HG001_02602	crtM	Dehydrosqualene synthase	SAOUHSC_02879	3 <del>1</del>	-1,57	NA	ND	ND
HG001_02601	crtN	Dehydrosqualene desaturase	SAOUHSC_02877	12	-1,92	8,97E-18	-0,66	6,45E-01

		Regulation of detoxifying enzymes		Diff. Transcrip	tomics MV/ctr	Diff. Proteor	nics MV/ctr
id	gene	product	locus_tag_NCTC8325 gene_NCTC8325	log2FoldChang	e padj	log2FoldChan	ge padj
HG001_01826	perR	Peroxide-responsive repressor PerR	SAOUHSC_01997 -	-1.13	1,18E-06	ND	ND
HG001_02092	sigB	RNA polymerase sigma-B factor	SAOUHSC_02298 -	-0,94	5,31E-06	-0,91	2,71E-01
HG001_01423	fur	Ferric uptake regulation protein	SAOUHSC_01592	-0,447	0,080768103	0,53	3,07E-01
HG001_00556	sarA	Transcriptional regulator SarA	SAOUHSC_00620	-2,33	2,305-20	0,31	2,99E-01

		Metal homeostasis			Diff. Transcrip	tomics MV/ctr	Dif	f. Proteon	mics MV/ctr
id	gene	product	locus_tag_NCTC83	25 gene_NCTC8325	log2FoldChang	e padj	log2	FoldChan	ge padj
HG001_00116	isdi	Heme oxygenase (staphylobilin-producing) 2	SAOUHSC_00130	14	-0,663	0,020844767		2,02	5,34E-05
HG001_00981	isdE	High-affinity heme uptake system protein isdE precursor	SAOUHSC_01085	14	-0,86	0,006277875		1,98	4,11E-01
HG001_02320	fhuD_2	Iron(3+)-hydroxamate-binding protein FhuD precursor	SAOUHSC_02554		1,35	9,45E-11		1,18	2,08E-09
HG001_02047	fhuD_1	Iron(3+)-hydroxamate-binding protein FhuD precursor	SAOUHSC_02246		-0,81	0,044043942	ND		ND
HG001_01927	ftnA	Ferritin	SAOUHSC_02108	- 24 - Contract - Cont	-1,45	7,51E-13		0,16	6,45E-01
HG001_00625	mgrA	HTH-type transcriptional regulator MgrA	SAOUHSC_00694	19 (C)	-1,64	1,53E-12		-0,23	7,11E-01
HG001_01527	mntH_2	Divalent metal cation transporter MntH	SAOUHSC_01707	14	-0,88	0,001151062	ND		ND
HG001_00065	sbnA	putative siderophore biosynthesis protein SbnA	SAOUHSC_00075		1,17	0,000501837		2,79	2,32E-01
HG001_00066	≤bnB	N-{{25}-2-amino-2-carboxyethyl}-L-glutamate dehydrogenase	SAOUHSC_00076	12	1,47	9,94E-09		8,63	5,62E-28
HG001_00067	sbnC	Staphyloferrin B synthase	SAOUHSC_00077	34 - C	1,87	5,02E-14		5,19	2,32E-04
HG001_00068	sbnD	Staphyloferrin B export protein	SAOUHSC_00078	14	1,51	6,73E-11	ND		ND
HG001_00069	sbnE	L-2,3-diaminopropanoate-citrate ligase	SAOUHSC_00079		1,44	3,86E-09		5,59	1,37E-05
HG001_00070	sbnF	2-[(L-alanin-3-ylcarbamoyl)methyl]-3-(2-aminoethylcarbamoyl)-2-hydrox	VSACUHSC_00080	12	1,32	5,34E-07		7,41	3,27E-19
HG001_00071	sbnG	Citrate synthase	SAOUHSC_00081	54 C	1,54	1,07E-11		6,79	1,54E-12
HG001 00072	sbnH	2-[[L-alanin-3-ylcarbamoyl]methyl]-2-hydroxybutanedioate decarboxylas	ESAOUHSC 00082		1,48	1,97E-12		6,11	7,21E-08
HG001 00073	sbnl	L-serine kinase	SAOUHSC 00083		1.64	9,52E-15		5,50	2,76E-05
HG001_00573	ideR	Iron-dependent repressor ideR	SAOUHSC_00638	mntR	-2,13	8,63E-19		-0,58	5,48E-01
HG001_00572	mntA	High-affinity zinc uptake system ATP-binding protein ZnuC	SAOUHSC 00637	All sections and a section of the se	-1,74	1,75E-12		0.03	9,71E-01
HG001_00571	mntB	Manganese transport system membrane protein MntB	SAOUHSC 00636	14	-2,91	3,21E-40	ND		ND
HG001 00570	mntC	Manganese ABC transporter substrate-binding lipoprotein precursor	SAOUHSC 00634		-3.30	4.90E-40		0.34	9.47E-02

с. 		Electron transport chain		Diff. Transcri	ptomics MV/ctr	Diff. Proteomi	cs MV/ctr
id	gene	product	locus_tag_NCTC8325 gene_NCTC8325	log2FoldChan	ge padj	log2FoldChange	padj
HG001_01585	hemB	Delta-aminolevulinic acid dehydratase	SAOUHSC 01772 -	0,579	0,019809775	-1,32	2,99E-02

ional regulatory protein WalR ional regulator SIVA	locus_tag_NCTC83 SAOUHSC_00020	25 gene_NCTC8325	log2FoldChang	e padj	log2FoldChang	je padj
ional regulatory protein WalR Ional regulator SivA	SAOUHSC_00020	14	0.202	0.0140770005	and the second se	
ional regulator SIVA	the second se		0,232	0,211077335	-1,72	6,91E-02
	SAOUHSC_02961	<b>2</b> .	0,671	0,007078829	-1,21	3,44E-01
transcriptional regulator SarS	SAOUHSC_00070		1,59	1,36E-13	0,05	9,33E-01
transcriptional regulator SarZ	SAOUHSC_02669	24 - C	-1,10	1,11E-05	-1,78	4,42E-01
transcriptional regulator SarX	SAOUHSC_00674	194 - C.	-1,49	6,69E-10	-0,93	2,86E-01
transcriptional regulator SarV	SAOUHSC_02532	· +	-1,83	1,02E-10	ND	ND
transcriptional regulator SarR	SAOUHSC_02566		-1,93	2,59E-13	-0,71	2,00E-01
ional regulator SarA	SAOUHSC 00620	12 C	-2,33	2,30E-20	0,31	2,99E-01
	Interscriptional regulator Sar2 transcriptional regulator Sar2 transcriptional regulator Sar4 transcriptional regulator Sar4 transcriptional regulator Sar8 ional regulator SarA	Intrascriptional regulator Sar2         SACUHSC_02669           Itanscriptional regulator Sar2         SACUHSC_02669           Itanscriptional regulator Sar3         SACUHSC_02669           Itanscriptional regulator Sar3         SACUHSC_02562           Itanscriptional regulator Sar3         SACUHSC_02562           Itanscriptional regulator Sar3         SACUHSC_02562           Itanscriptional regulator Sar3         SACUHSC_02566           Ional regulator Sar4         SACUHSC_00520	Hanschptonial regulator Sar2     SACUHSC_0269       transcriptional regulator SarX     SACUHSC_0269       transcriptional regulator SarX     SACUHSC_02674       transcriptional regulator SarX     SACUHSC_0252       transcriptional regulator SarA     SACUHSC_0252       transcriptional regulator SarA     SACUHSC_0252       transcriptional regulator SarA     SACUHSC_0256	Hanschpholm regulator Sar2         SAOU SC_0005 -         1,10           transcriptional regulator Sar2         SAOU SC_0069 -         1,20           transcriptional regulator Sar2         SAOU SC_0069 -         1,20           transcriptional regulator Sar2         SAOU SC_0069 -         1,20           transcriptional regulator Sar2         SAOU SC_00674 -         1,49           transcriptional regulator Sar4         SAOU SC_00526 -         1,83           transcriptional regulator SarA         SAOU SC_00520 -         1,93           ional regulator SarA         SAOU SC_00520 -         2,33	Interscriptional regulator Sar2         SAOUHSC_00269         I,10         I,100         I,000         I,000	Interscriptional regulator Sar2         SAOUHSC_00679         I.J.0         I.J.0

E

Diff. Transcriptomics MV/ctr Diff. Proteomics MV/ctr

id	gene	product	locus_tag_NCTC8325 gene_NCTC8325	log2FoldChange padj		log2FoldChange padj	
HG001_00118	aldA	Putative aldehyde dehydrogenase AldA	SAOUHSC_00132 -	1,16	1,55433E-06	-2,81	3,33E-02
HG001_00099	adhE	Aldehyde-alcohol dehydrogenase	SAOUHSC_00113 -	-3,99	1,68476E-54	-1,78	4,42E-01
HG001_00544	adh	Alcohol dehydrogenase	SAOUHSC_00608 adhA	-2,96	9,54629E-47	-1,10	2,42E-04
HG001_01654	acsA_1	Acetyl-coenzyme A synthetase	SAOUHSC_01846 -	-1,49	1,85733E-09	-1,78	4,42E-01
HG001_01955	alkH	Aldehyde dehydrogenase	SAOUHSC_02142 -	-1,89	2,51113E-15	-0,31	4,11E-01

tknA charging			Diff. Transcriptomics MV/ctr		Diff. Proteomics MV/ctr			
id	gene	product	locus_tag_NCTC8325 gene_N		25 log2FoldChange padj		log2FoldChange padj	
HG001_00407	metG	MethioninetRNA ligase	SAOUHSC_00461		1,55	1,42641E-11	-0,10	7,39E-01
HG001_01315	asnS	AsparaginetRNA ligase	SAOUHSC_01471	asnC	1,08	1,60743E-05	-0,32	0,0861312
HG001_01044	ileS	Isoleucine-tRNA ligase	SAOUHSC_01159	ileS	1,08	0,000184868	0,07	0,6020900
HG001_01679	leuS	LeucinetRNA ligase	SAOUHSC_01875	leuS	0,95	0,000494718	0,22	0,1775016
HG001_00434	lysS	LysinetRNA ligase	SAOUHSC_00493	lysS	0,683	0,004966781	0,30	0,0657212
HG001_00547	argS	ArgininetRNA ligase	SAOUHSC_00611	arg\$	0,603	0,007896657	0,12	0,3623763
HG001_01114	proS	ProlinetRNA ligase	SAOUHSC_01240		0,80	0,000847588	-0,23	0,2029304
HG001_00457	gltX	GlutamatetRNA ligase	SAOUHSC_00509	gltX	0,472	0,055358849	-0,02	0,9104106
HG001_01601	thrS	ThreoninetRNA ligase	SAOUHSC_01788	thrS	-0,45	0,061656411	-0,24	0,3307554
HG001_01555	hisS	HistidinetRNA ligase	SAOUHSC_01738	hisS	-0,686	0,011301763	-0,51	0,1148211
HG001_00010	serS	Serine-tRNA ligase	SAOUHSC_00009		-0,80	0,000790321	-0,08	0,6029672
HG001_00842	trpS	TryptophantRNA ligase	SAOUHSC_00933	1	-0,97	8,54628E-05	-0,54	0,0255249


## Laura ANTOINE



## Caractérisation des modifications post-transcriptionnelles des ARN non codants chez *Staphylococcus aureus* en réponse à divers stress environnementaux : analyse dynamique et fonctionnelle

Les modifications post-transcriptionnelles des ARN sont impliquées dans de nombreux processus biologiques. Elles sont constitutives ou modulées en réponse à des processus adaptatifs et remplissent de nombreuses fonctions. La cartographie des modifications dans les ARN du pathogène *S. aureus*, responsable d'un grand nombre d'infections de gravité variable et touchant un large éventail de tissus, reste encore peu connue ainsi que leurs implications dans l'adaptation de la bactérie à son environnement, notamment lors de l'infection.

Cette étude a pour but principal dans un premier temps d'établir une cartographie des modifications présentes dans les ARN non codants, plus spécifiquement dans les ARNt de *S. aureus* puis de révéler la dynamique des modifications en adaptation à différentes conditions environnementales rencontrées par la bactérie lors de l'infection.

Enfin, l'étude des causes ainsi que des conséquences traductionnelles des changements observés pourra être réalisée afin de déterminer le potentiel rôle des modifications post-transcriptionnelles dans l'adaptation aux stress

Mots clés : Modifications post-transcriptionnelles, *Staphylococcus aureus*, adaptation au stress

RNA post-transcriptionnal modifications are involved in numerous biological processes. They are constitutive or modulated in response to adaptive processes and play multiple functions. The mapping of RNA modifications on the pathogen *S. aureus*, responsible for several infections of variable severity and targeting several tissues, is still poorly known, as well as their involvement in the host adaptation processes.

This study aims to produce a first map of modifications that are present on *S. aureus* non coding RNAs, especially *S.aureus* tRNA and to reveal the dynamics of some of these modifications in a stress condition encountered during the infection.

Finally, the mechanisms promoting different modification levels and the impact that these variations might have on the translation processes could be studied.

Keywords : Post-transcriptionnal modifications, *Staphylococcus aureus*, stress adaptation.