

Séminaire de Microbiologie de Strasbourg

jeudi 28 mars 2019

Collège Doctoral Européen

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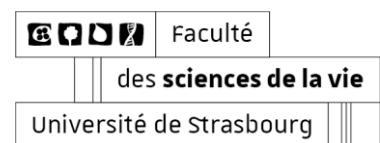
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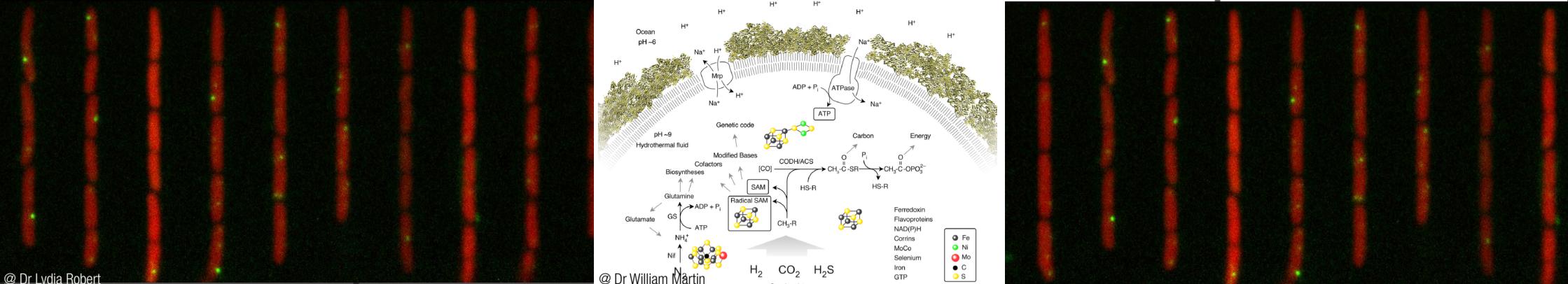
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Pr. LETT Marie-Claire, Laboratoire de Génétique Moléculaire, Génomique, Microbiologie GMGM, UMR 7156, Strasbourg



Séminaire de microbiologie de Strasbourg

Jeudi 28 mars 2019

Journée de rencontres entre chercheurs séniors, juniors, doctorants, masters travaillant dans le domaine de la bactériologie, la mycologie, la parasitologie et la virologie.

Deux conférences plénières :

9h

The last universal common ancestor: in search of microbe n°1

Dr William MARTIN - *Institute of Molecular Evolution, Heinrich-Heine-Universität Düsseldorf, Germany*

13h45

Mutation dynamics and fitness effects at the single cell level

Dr Lydia ROBERT- *Sorbonne Université, Laboratoire Jean Perrin, Paris*

Date limite de soumission d'un résumé (oral/poster) : 1^{er} mars 2019

Nombre de places limité à 120 personnes



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jeudi 28 mars 2019

Collège Doctoral Européen

Programme

8h30 Accueil

8h55 Introduction

Dr. Françoise BRINGEL Laboratoire de Génétique Moléculaire, Génomique, Microbiologie, Strasbourg

9h00 Conférence plénière

The last universal common ancestor: in search of microbe n°1

Dr. William MARTIN - Institute of Molecular Evolution, Heinrich-Heine-Universität Düsseldorf, Germany

Présentation du conférencier: Prof. Joseph MORAN, ISIS UMR7006

Modérateurs : **Dr. Renaud CHOLLET**, Merck

Dr. Anne FRIEDRICH, Laboratoire de Génétique Moléculaire, Génomique, Microbiologie, Strasbourg

10h00 Communication orale

Survey of phenotypic expressivity at a species-wide scale using CRISPR-Cas9

Sabrina BIBI-TRIKI CNRS, Génétique Moléculaire, Génomique, Microbiologie Strasbourg

10h20 Présentation des sponsors

10H35 Pause-café

11h05 Communications orales

RsaC sRNA modulates the oxidative stress response during manganese starvation in Staphylococcus aureus

David LALAOUNA, Jessica Baude, ZongFu Wu, Arnaud Tomasini, Stefano Marzi, François Vandenesch, Pascale Romby, Isabelle Caldelari and Karen Moreau UNISTRA CNRS, Architecture et Réactivité de l'ARN, UPR 9002, Strasbourg

La lugdulysine : un facteur de virulence potentiel et découverte d'un nouveau mécanisme de maturation enzymatique

K. PROLA, Levy N., Argémi X., Strub J.M., Keller D., Cianferani S., Ruff M., Prévost G. UNISTRA, CHRU de Strasbourg, FMTS, EA 7290 Virulence Bactérienne Précoce.

11h45 Présentation "flash" des posters en 3 minutes

12H30 Cocktail déjeunatoire offert par nos sponsors

13h00 Session posters

13h45 Conférence plénière

Mutation dynamics and fitness effects at the single cell level

Dr. Lydia ROBERT Sorbonne Université, Laboratoire Jean Perrin, Paris

Présentation de la conférencière : **Dr. Françoise BRINGEL** GMGM, Strasbourg

Modérateurs : **Dr. Antoine GRILLON**, IPPTS

Dr. Lysiane FOUGY, Aérial

14h45 Communications orales

Towards searching for novel dehalogenases in environmental samples by ultrahigh-throughput screening

Emilie GEERSENS, Vuilleumier Stéphane and Ryckelynck Michaël. Institut de Biologie Moléculaire et Cellulaire (IBMC) Strasbourg

Phosphatidic acid as a limiting host metabolite for the proliferation of the microsporidium Tubulinosema ratisbonensis in Drosophila flies

Adrien Franchet, **Gaëtan CARAVELLO**, Sebastian Niehus, Gaëtan Caravello, and Dominique Ferrandon Université de Strasbourg, CNRS, M3I UPR 9022, Strasbourg

15h45 Pause-café et session poster

16h15 Communications orales

Réseau d'interactions des protéines impliquées dans l'acquisition du fer par le sidérophore pyoverdine chez Pseudomonas aeruginosa.

Anne Bonneau, Béatrice Roche and Isabelle Schalk

UMR7242, ESBS, Université de Strasbourg, CNRS, Bld Sébastien Brant, F-67412 Illkirch

Étude des bases moléculaires pour la vectorisation d'antibiotiques permettant de contourner la faible perméabilité des membranes de Pseudomonas aeruginosa.

Q. PERRAUD, V. Gasser, P. Cantero, N. Zill, E. Baco, F. Hoegy, G. L. A. Mislin, L. Ehret-Sabatier, I. J. Schalk, UNISTRA CNRS UMR 7242, Illkirch

Fine-tuning of predictive microbiology models through microlocal characterization of foods by Nuclear Magnetic Resonance (NMR).

R. Recht, L. Fougy, V. Stahl, **E. HAMON** Aerial, Illkirch

17H15 Vote de la meilleure communication orale- **Prix MERCK**

Vote du meilleur poster- Prix CASDEN

Remise des prix

Dr. Renaud CHOLLET Merck, Mosheim

Dr. Valérie GEOFFROY Biotechnologie et Signalisation Cellulaire, UMR 7242, Illkirch

17h30 CONCLUSIONS

Prof. Ermano CANDOLFI Institut de Parasitologie et de Pathologie Tropicale de Strasbourg, Strasbourg

Prof. Ph. ANDRE Laboratoire de Biophotonique et Pharmacologie, Illkirch

LISTE DES POSTERS

1. Regulation of IL-17A expression during Toxoplasma gondii infection?
Faïza FAHMI-BITTICH, Julie Brunet, Alexander W. Pfaff and Ermanno Candolfi
Institut de Parasitologie et de Pathologie Tropicale – EA 7292, Strasbourg
2. Spontaneous fermentation of sauerkraut: characterization of bacterial ecosystem linked to physico-chemical changes
Lysiane FOUGY, Hezard B., Desmonts M-H. Aerial, ILLkirch
3. Importance des voies d'import du fer dans la résistance aux antibiotiques
Gwenaelle GRAULIER, I. Schalk, P. Fechter
CNRS UMR7242 Biotechnologie et signalisation cellulaire, ESBS, ILLKIRCH
4. Intracellular localizations of PvdS ECF sigma factor in Pseudomonas aeruginosa
Léa HAAS, Isabelle Schalk, Julien Godet
Laboratoire de Biophotonique et Pharmacologie, UNISTRA CNRS 7021, ILLkirch
5. Membrane aminoacyl-tRNA synthetases and signaling pathways
Marine HEMMERLE, H. Becker UNISTRA CNRS, Génétique Moléculaire, Génomique, Microbiologie Strasbourg
6. Bacterial alteration of asbestos cement wastes
Agathe JAOUEN, S. David, V. A. Geoffroy CNRS UMR7242 Biotechnologie et signalisation cellulaire, ESBS, ILLKIRCH
7. Triple element isotope fractionation of chloromethane from bacterial degradation by two different pathways
Jing LUO, Jaime D Barnes, S Christoph Hartmann, Thierry Nadalig, Frank Keppler, Stéphane Vuilleumier UNISTRA CNRS, Génétique Moléculaire, Génomique, Microbiologie Strasbourg
8. Staphylococcus aureus Panton-Valentine Leukocidin causes an alternative NETosis in human neutrophils presenting histone 3 citrullination on NETs
Viola MAZZOLENI, Gaëlle Zimmermann-Meisse, Daniel Keller, Gilles Prévost UNISTRA VBP EA7290, Fédération de Médecine Translationnelle de Strasbourg, Institut de Bactériologie, Strasbourg
9. Characterization of the interactions between icaR mRNA and regulatory RNAs in Staphylococcus aureus
Noémie MERCIER, Eva Renard, Stefano Marzi, Pascale Romby, Alejandro Toledo-Arana, Isabelle Caldelari UNISTRA CNRS, Architecture et Réactivité de l'ARN, UPR9002, Strasbourg
10. Modes of action of antibiotics against multi-drug resistant pathogens
Eva RENARD, Emma Schenckbecher, Eric Ennifar, Gilles Prevost, Daniel Keller UNISTRA Structure et dynamique des machines biomoléculaires, laboratoire "Architecture et Réactivité de l'ARN", IBMC, Strasbourg

11. Effet des bactéries associées à l'orge dans le métabolisme des terpénoïdes

Loïc WAECKERLE, Chloé Groh, Florence Arsène-Ploetze, Hubert Schaller CNRS IBMC, Strasbourg

12. Bacterial adaptation to the utilization of chloromethane

Louis-François MEY, Yousra Louhichi, Stéphane Vuilleumier, Françoise BRINGEL
CNRS Laboratoire de Génétique Moléculaire, Génomique et Microbiologie

13. Ingénierie de la voie de biosynthèse du siderophore chez *Pseudomonas* pour la production de pyoverdine fonctionnalisée

Sébastien MATHIEU, Coraline RIGOUIN
CNRS UMR7242 Biotechnologie et signalisation cellulaire, ESBS, ILLKIRCH

14. Antibacterial Potential of the Arab Mineral Pharmacopeia

Joshua MALSA, Anne FOSTER, Catherine VONTHRON, Elora AUBERT,
Véronique PITCHON, Isabelle SCHALK, and Pierre FECHTER
CNRS UMR7242 Biotechnologie et signalisation cellulaire, ESBS, ILLKIRCH.

15. Impact of the zinc finger motifs in HIV-1 Gag on the specific selection of genomic RNA and its trafficking to the plasma membrane.

Emmanuel Boutant, Jeremy Bonzi, Halina Anton, **Maaz Bin Nasim**, Raphael Cathagne, Eléonore Réal, Philippe Carl, Pascal Didier, Jean-Christophe Paillart, Roland Marquet, Yves Mély, Hugues de Rocquigny, Serena Bernacchi.

**RESUMES
DES
COMMUNICATIONS ORALES**

The last universal common ancestor: In search of Microbe No. 1.

Prof. Dr. William Martin
Institute of Molecular Evolution
Heinrich-Heine-Universität Düsseldorf, Germany

The concept of a last universal common ancestor of all cells (LUCA) is central to the study of early evolution and life's origin, yet information about how and where LUCA lived is lacking. We investigated all clusters and phylogenetic trees for 6.1 million protein coding genes from sequenced prokaryotic genomes in order to reconstruct the microbial ecology of LUCA. Among 286,514 protein clusters, we identified 355 protein families (~0.1%) that trace to LUCA by phylogenetic criteria. Because these proteins are not universally distributed, they can shed light on LUCA's physiology. Their functions, properties, and prosthetic groups depict LUCA as anaerobic, CO₂-fixing, H₂-dependent with a Wood-Ljungdahl (WL) pathway, N₂-fixing, and thermophilic. LUCA's biochemistry was replete with FeS clusters and radical reaction mechanisms. Its cofactors reveal dependence upon transition metals, flavins, S-adenosyl methionine (SAM), coenzyme A, ferredoxin, molybdopterin, corrins, and selenium. Its genetic code required nucleoside modifications and SAM-dependent methylations. The 355 phylogenies identify clostridia and methanogens, whose modern lifestyles resemble LUCA's, as basal among their respective domains. LUCA inhabited a geochemically active environment rich in H₂, CO₂, and iron. The data support the view that the first organic molecules — and life — arose from CO₂ in a hydrothermal setting. As reconstructed from genes, LUCA was half-alive.

Survey of phenotypic expressivity at a species-wide scale using CRISPR-Cas9

Sabrina Bibi-Triki, Téo Fournier and Joseph Schacherer

Université de Strasbourg, CNRS, GMGM UMR 7156, F-67000 Strasbourg, France

Elucidating the underlying rules that govern the phenotypic diversity observed in natural populations is an old but still unaccomplished goal in biology. Many genetic variants are known to have an impact on the phenotypic variation. However, a mutation can exhibit variable expressivity meaning that individuals who have this same mutation may express the phenotype to different degrees. The key to a better understanding of the genotype-phenotype relationship could benefit from a comprehensive view of expressivity cases within large populations. In this context, yeast and more precisely *Saccharomyces cerevisiae* is a powerful model system. Indeed, more than 50 rare genetic variants have been identified as involved in a given phenotypic variation. Taking advantage of these variants, we assessed the level of phenotypic expressivity of some of these genetic variants across a large population of *S. cerevisiae* isolates coming from a vast array of ecological and geographical origins. More specifically, we used the CRISPR-based editing methodology to introduce the selected genetic variants in a hundred *S. cerevisiae* genetic backgrounds. Using these CRISPR-engineered isolates, we determined the level of phenotypic expressivity of the different genetic variants tested. This allowed us to determine the complexity and degree to which phenotypic variation depends on genetic background. It also lays the foundation to dissect the genetic basis of the phenotypic expression variation.

RsaC sRNA modulates the oxidative stress response during manganese starvation in *Staphylococcus aureus*

**David Lalaouna, Jessica Baude, ZongFu Wu, Arnaud Tomasini, Stefano Marzi,
François Vandenesch, Pascale Romby, Isabelle Caldelari and Karen Moreau**

*Université de Strasbourg, CNRS, Architecture et Réactivité de l'ARN, UPR9002,
Strasbourg, France*

The human pathogen *Staphylococcus aureus* produces numerous small regulatory RNAs (sRNAs) for which functions are still poorly understood. Here, we focused on an atypical sRNA called RsaC. Its length varies between different isolates due to the presence of repeated sequences at the 5' end, ranging up to 1,116 nt in HG001 strain. The 3' part of RsaC is highly conserved and contains C-rich sequences, which are characterized as regulatory motifs in other staphylococcal sRNAs. Using MS2-affinity purification coupled with RNA sequencing (MAPS) and quantitative differential proteomics, we identified *sodA* mRNA as a main target of RsaC sRNA. SodA is a Mn-dependent superoxide dismutase involved in oxidative stress response. We demonstrated that in presence of RsaC, *S. aureus* cells were less resistant to oxidative stress, in relation with lower activity of SodA enzyme. Remarkably, *rsaC* gene is co-transcribed with the major manganese ABC transporter MntABC and, consequently, RsaC is mainly produced in response to Mn starvation. This 3'UTR-derived sRNA is released from *mntABC*-RsaC precursor after cleavage by RNase III which presumably recognizes a duplex formed by RsaC and its antisens RNA. By negatively regulating non-essential Mn-containing enzymes such as SodA, RsaC reduces the needs for Mn. SodM, an alternative Sod enzyme using either Mn or Fe as co-factor, replaces SodA to response to oxidative stress. Thus, RsaC may counteract the sequestration of Mn by the host organism, strategy used to limit the virulence of *S. aureus*.

La lugdulysine : un facteur de virulence potentiel et découverte d'un nouveau mécanisme de maturation enzymatique

Prola K.¹, Levy N.², Argémi X.¹, Strub J.M.³, Keller D.¹, Cianferani S.³, Ruff M.², Prévost G.¹,

1. Université de Strasbourg, CHRU de Strasbourg, FMTS, EA 7290 : Virulence Bactérienne Précoce

2. Institut de Génétique, Biologie Moléculaire et Cellulaire

3. Laboratoire de Spectrométrie de Masse Bio-Organique, IPHC, UMR 7178

L'amélioration de l'identification bactérienne des staphylocoques à coagulase négative (CoNS) (1) a permis de mettre en évidence la pathogénicité de *Staphylococcus lugdunensis*. Malgré sa sensibilité aux antibiotiques, ce CoNS peut causer des infections chroniques variées telles que des endocardites ou des infections ostéo-articulaires avec une virulence comparable à son homologue, *Staphylococcus aureus*. L'étude clinique prospective VISLISI (2) collectant 81 souches de *Staphylococcus lugdunensis* a permis de révéler et d'identifier la sécrétion d'un potentiel facteur de virulence. En effet, les études statistiques ont démontré la corrélation entre la survenue d'infections ostéo-articulaires et la détection d'une activité protéolytique due à cette enzyme, la lugdulysine.

Cette zinc métallopeptidase est synthétisée, puis sécrétée sous la forme d'un précurseur inactif contenant un propeptide de 64 aa, localisé dans le domaine N terminal de la lugdulysine. Sous sa forme active, la lugdulysine possède une activité optimale en présence de Ca²⁺ à 55°C et à pH 6.0. Nous avons montré que la lugdulysine est principalement active sur les peptides et les protéines peu structurées. La structure tri-dimensionnelle de la lugdulysine a été déterminée à l'IGBMC à une résolution de 1.8 Å par cristallographie aux rayons X. L'analyse de cette structure a révélé la présence de trois sites de fixation du calcium et a permis de confirmer la présence dans le site actif d'un atome de zinc coordonné par le motif (²⁴¹H_E²⁴⁵H + ²⁶⁸E). De plus, 22 acides aminés du propeptide, normalement éliminés lors de la maturation de l'enzyme, interagissent étroitement avec le domaine mature. Ces interactions sont probablement importantes dans la maturation et l'activité enzymatique puisque deux mutations (G299S et S412F), localisées au niveau du site d'interactions avec le propeptide résiduel, et les mutations E242Q et Y315F dans le site actif enzymatique, empêchent toutes la maturation de la pro-lugdulysine en enzyme mature.

- 1) Argemi, X., Riegel, P., Lavigne, T., Lefebvre, N., Grandpré, N., Hansmann, Y., Jaulhac, B., Prévost, G., and Schramm, F.** (2015). Implementation of MALDI-TOF MS in routine clinical laboratories improves identification of coagulase negative staphylococci and reveals the pathogenic role of *Staphylococcus lugdunensis*. *J. Clin. Microbiol.* JCM.00177-15.
- 2) Argemi, X., Prévost, G., Riegel, P., Keller, D., Meyer, N., Baldeyrou, M., Douiri, N., Lefebvre, N., Meghit, K., Ronde Oustau, C., et al.** (2017). VISLISI trial, a prospective clinical study allowing identification of a new metalloprotease and putative virulence factor from *Staphylococcus lugdunensis*. *Clin. Microbiol. Infect.* 23, 334.e1-334.e8.

Mutation dynamics and fitness effects at the single cell level

Lydia ROBERT

Sorbonne Université, Laboratoire Jean Perrin, Paris

Mutations are the source of genetic variation upon which natural selection acts and therefore the driving force of evolution. In order to understand the generation of diversity among life forms, from the variety of Galapagos finches to the spread of antibiotic resistant bacterial strains, as well as the diversity between cells in an organism, such as in cancer evolution, we need a quantitative characterization of the dynamics of mutation accumulation as well as their effects on fitness. Although commonly divided, according to their fitness effects, into three categories, good, bad and neutral, in reality mutations show a distribution of fitness effects (DFE), from strongly deleterious to highly beneficial. This distribution is an important quantity in evolutionary biology but is difficult to measure experimentally. In previous studies on microorganisms, the quality of DFE estimation was often limited either by a small sample of mutations and/or by a sampling bias due to the effect of natural selection, which purges strongly deleterious mutations. In studies involving higher organisms, the low number of individuals that can usually be monitored limits the precision of DFE estimation. In addition, the dynamics of the mutation accumulation process has never been experimentally revealed, due to the lack of appropriate tools.

Using a microfluidic setup we followed the growth of thousands of individual *Escherichia coli* cells for hundreds of generation as they accumulate mutations. Individual cells grow in separate microchannels, thus avoiding any selection bias and therefore producing an unbiased sample of tens of thousands of mutations. Lethal and strongly deleterious mutations can also be detected as they appear, in contrast to previous studies. This high-throughput data allowed a quantitative characterization of the DFE. Using a fluorescent reporter of nascent mutations based on the expression of fluorescent Mismatch Repair protein MutL, allowing detecting nascent mutations as fluorescent foci in the cells, we also follow directly the dynamics of the mutation accumulation process in single cells.

Towards searching for novel dehalogenases in environmental samples by ultrahigh-throughput screening

Geersens Emilie, Vuilleumier Stéphane and Ryckelynck Michaël

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Key words: Dehalogenation, enzymes, droplet-based microfluidics, single cell

The microbial biosphere represents a huge reservoir of enzymes with a wide palette of activities. Dehalogenase biocatalysts involved in cleavage of carbon-halogen bonds, in particular, are of great interest for many biotechnological and bioremediation applications. However, the diversity of enzymes in the biosphere remains largely unexplored due to several limitations such as the difficulty to cultivate the large majority of microorganisms in the laboratory. On the other hand, metagenomic sequence analyses performed directly on environmental samples only allow to identify enzyme-coding-genes that are already known.

Indeed, despite the large diversity of halogenated compounds found in nature, only a small number of dehalogenase families, and furthermore most often of limited substrate range, have been discovered and characterized to date. The goal of my PhD project is to develop and apply a new single-cell resolution ultrahigh-throughput functional screening pipeline using droplet-based microfluidics. This pipeline will serve to directly screen environmental samples and metagenomic gene libraries using fluorescence-based detection of dehalogenation reactions. As a first proof of concept, the pipeline was set up using a purified enzyme (DhlA) active with the well-known halogenated contaminant 1,2-dichloroethane, and with the same dehalogenase expressed in a model bacterium (*E. coli*).

Phosphatidic acid as a limiting host metabolite for the proliferation of the microsporidium *Tubulinosema ratisbonensis* in *Drosophila* flies

Adrien Franchet*, Sebastian Niehus, Gaëtan Caravello, and Dominique Ferrandon[®]

Université de Strasbourg, CNRS, M3I UPR 9022, F-67000 Strasbourg, France

* Present address: The Francis Crick Institute, London, UK

Microsporidia are located at the base of the fungal evolutionary tree. They are obligate intracellular parasites and harness host metabolism to fuel their growth and proliferation. However, how the infestation of cells impacts the whole organism and how the organism contributes to parasite proliferation remain poorly understood. Here, we have developed a *Tubulinosema ratisbonensis* systemic infection model in the genetically-amenable *Drosophila melanogaster* host in which parasite spores obtained in a mammalian cell culture infection system are injected into adult flies. The parasites proliferate within flies and ultimately kill their hosts. As commonly observed for microsporidia infecting insects, *T. ratisbonensis* preferentially grows in the fat body and ultimately depletes the host metabolic stores. We find that supplementing the fly diet with yeast does not benefit the host but the parasite, which increases its proliferation. Unexpectedly, fatty acids and not carbohydrates nor amino-acids are the critical components responsible for this phenomenon. Our genetic dissection of host lipid metabolism identifies a crucial compound hijacked by *T. ratisbonensis*: phosphatidic acid. We propose that phosphatidic acid is a limiting precursor for the synthesis of the parasite membranes and hence of its proliferation.

Réseau d'interactions des protéines impliquées dans l'acquisition du fer par le sidérophore pyoverdine chez *P. aeruginosa*.

Anne Bonneau, Béatrice Roche and Isabelle Schalk

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Pseudomonas aeruginosa est un pathogène opportuniste responsable d'infections chez les malades immunodéprimés. Lors d'infections, *P. aeruginosa* sécrète de nombreux facteurs de virulence dont la pyoverdine (PWD), un sidérophore produit par la bactérie pour acquérir le fer (un nutriment essentiel à la croissance bactérienne). La fonction de la PWD est de chélater le fer ferrique dans l'environnement de la bactérie et de le ramener dans la cellule bactérienne via un mécanisme impliquant diverses protéines. Dans ce processus, le complexe PWD-Fe est reconnu dans un premier temps à la surface bactérienne par un transporteur TonB-dépendant, FpvA, permettant l'import au travers de la membrane externe (1). Dans le périplasme, le complexe PWD-Fe interagit avec deux protéines périplasmiques, FpvC et FpvF qui vont participer au mécanisme de dissociation du fer de la PWD (2). Cette réaction de dissociation implique d'une part une réduction du fer par la réductase de membrane interne FpvG et d'autre part un transfert du fer du sidérophore vers la protéine périplasmique FpvC (3-4). Le fer est ensuite transloqué vers le cytoplasme bactérien par le transporteur ABC FpvDE et l'apo-PWD est recyclée vers le milieu extracellulaire par la pompe à efflux PvdRT-OpmQ (5). Des études de dissociation du complexe PWD-Fe ont montré que l'activité optimale de la réductase FpvG nécessite trois autres protéines, FpvH, FpvJ et FpvK, dont les rôles biologiques restent indéterminés (3).

L'objet de ce travail a été de caractériser par double hybride bactérien et des approches d'immuno-précipitations, le réseau d'interaction protéique impliqué dans le mécanisme de dissociation du fer de la PWD. Les différentes interactions mises en évidence nous permettent de proposer l'existence d'un complexe multi-protéique faisant intervenir les deux protéines membranaires FpvG et FpvH ainsi que trois protéines périplasmiques FpvJ, FpvF et FpvC.

1. **Poole, K., Neshat, S. & Heinrichs, D.** (1991) Pyoverdine-mediated iron transport in *Pseudomonas aeruginosa*: involvement of a high-molecular mass outer membrane protein. *FEMS Microbiol Lett* **1**:1-5
2. **Brillet, K., Ruffenach, F., Adams, H., Journet, L., Gasser, V., Hoegy, F., Guillon, L., Hannauer, M., Page, A., & Schalk, I.** (2012) An ABC transporter with two periplasmic binding proteins involved in iron acquisition in *Pseudomonas aeruginosa*. *ACS Chem Biol* **7**: 2036-45
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Étude des bases moléculaires pour la vectorisation d'antibiotiques permettant de contourner la faible perméabilité des membranes de *Pseudomonas aeruginosa*

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Les souches multirésistantes de *Pseudomonas aeruginosa* représentent une menace pour la santé des patients atteints de mucoviscidose. Comme de nombreuses bactéries, *P. aeruginosa* utilise des sidérophores, petites molécules organiques facilitant l'acquisition du fer, un nutriment essentiel à la croissance bactérienne et limitant au cours d'une infection. Une approche innovante pour surmonter la faible perméabilité des membranes de *P. aeruginosa* aux antibiotiques est de détourner les voies d'acquisition du fer sidérophore-dépendantes pour promouvoir l'import d'antibiotiques par une approche de Cheval de Troie. La stratégie consiste à attacher des antibiotiques incapables de traverser la paroi bactérienne de *P. aeruginosa* de manière covalente aux sidérophores. Ainsi, le pathogène en acquérant le fer via le ou les sidérophore(s), incorporera également l'antibiotique lié. Au laboratoire, nous nous intéressons plus particulièrement à des chélateurs du fer de type catéchol pour transporter des antibiotiques dans *P. aeruginosa*. Nous avons cherché à identifier les différentes protéines et mécanismes moléculaires impliqués dans l'import du fer par des vecteurs catéchols et leur conjugués sidérophore-antibiotiques correspondant chez *P. aeruginosa*.

Nous avons employé une approche de protéomique *label-free* développée dans le but de pouvoir analyser des échantillons complexes contenant à la fois des bactéries et des cellules humaines. Les protéines différentielles impliquées dans l'acquisition du fer ont ensuite été étudiées par qRT-PCR.

Cette approche nous a permis de déterminer que des composés de type catéchol liés au linézolide sont capable de traverser la membrane externe de *P. aeruginosa* sur un modèle d'infection de cellules épithéliales, d'induire l'expression des gènes de la voie du sidérophore entérobactine et réprimer des gènes impliqués dans la biosynthèse et le transport des deux sidérophores naturellement produit par *P. aeruginosa*.

Fine-tuning of predictive microbiology models through microlocal characterization of foods by Nuclear Magnetic Resonance (NMR)

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Numerous mathematical models have been proposed to describe bacterial population behaviors in foods. These models generally depict the growth kinetics of particular bacterial strains based on their cardinal values. Recently, these traditional/macroenvironmental approaches have been complemented for a food-borne pathogen *Listeria monocytogenes* by an individual-based modelling (IBM) focusing only on a few cells and their surrounding microenvironment. It takes into account the single-cell growth probability according to key physicochemical parameters of the food matrix and its storage temperature¹.

In this context, there is an increasingly prominent issue to accurately characterize the physicochemical properties of foodstuffs. While robust methods are usually used to individually investigate pH, water activity (a_w), as well as NaCl, organic acid and total phenol concentrations, one sample per analysis and per parameter is required. Besides for pH and a_w , there are few devices for microlocal scale analysis².

This work describes an NMR-based multiparametric approach to characterize the microenvironment of foods. It shows how NMR can simultaneously measure the physicochemical parameters of interest for predictive microbiology purposes using a single 10-mg sample. The approach was designed and validated on four food matrices: a smear soft cheese, cooked peeled shrimps, smoked salmon and smoked ham. This proof of concept and application opens new doors for the improvement and fine-tuning of predictive microbiology models through systematic spatial characterization of foodstuffs at microlocal scale. It also paves the way to new practices in food safety management.

¹Augustin et al. *Food Microbiology*, 2015, 45, 205-215.

²Ferrier et al. *Appl. Env. Micro*, 2013, 79, 5870-5881

**RESUMES
DES
COMMUNICATIONS PAR AFFICHE**

Regulation of IL-17A expression during *Toxoplasma gondii* infection

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Toxoplasmosis is caused by the obligate intracellular protozoan; *T. gondii* which is capable of modulating different signaling pathways of the host cell in order to multiply and to escape the immune response. However, severe clinical forms like ocular toxoplasmosis are explained by an excessive inflammatory response. The inflammatory cytokine IL-17A has been identified as a marker of disease severity. South American patients have more severe forms of ocular toxoplasmosis than European patients, due to the existence of more virulent *T. gondii* strains in South America. This difference in the virulence of the strains leads to markedly different cytokine profiles. However, the mechanisms of IL-17A regulation *in vitro* are still unknown.

During this work, we have shown that the regulation of the *IL-17A* promoter in infected cells varies according to cell type and parasite strain. This strain-dependent regulation is ruled by the polymorphic protein ROP16. Furthermore, the UHRF1 transcription factor is overexpressed in cells infected with *T. gondii* via the action of parasite proteins as ROP16. It has been shown *in vitro* that UHRF1 binds to the *IL-17A* gene promoter and modulates its activity during Toxoplasma infection, but the mechanisms of action are still unknown. In addition, we have shown that the activation of the *IL-17A* promoter can be controlled by epigenetic modulation that may involve histone modifications, among other, by acetylation or methylation. These phenomena could be due to the recruitment of epigenetic enzymes such as HDACs, DNMTs and G9a via UHRF1.

Spontaneous fermentation of sauerkraut: characterization of bacterial ecosystem linked to physico-chemical changes

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To produce sauerkraut, cabbage leaves, previously cut into strips, are salted and placed under anaerobic conditions in containers, so that the natural lactic fermentation can start. Described in literature, the spontaneous fermentation occurs in three different phases of pH lowering and a succession of species of *Leuconostoc*, *Lactobacillus* and *Pediococcus* manages these phases. The quality of sauerkraut obtained in this way depends on the substrate, the production environment, but above all on the natural bacterial population. Currently, there is little information on the bacterial ecosystems of cabbage and sauerkraut. To achieve a better control of product quality, it is necessary to determine the diversity of the bacterial population in cabbage and its dynamics during the fermentation in relation to physico-chemical changes.

Throughout the fermentation, 54 samples were taken (6 fermentation stages*9 replicates). The physico-chemical monitoring of fermentation was carried out by measuring pH, titratable acidity, lactic acid and acetic acid levels, glucose and fructose concentrations. To characterize the bacterial diversity, the 16S rDNA of 29 samples (4 fermentation stages) was amplified for Illumina Hiseq sequencing. Reads were then clustered into Operational Taxonomic Units (OTU). Abundance of bacterial species was quantified by qPCR.

The 29 samples provided 1,221,090 bacterial 16S rRNA sequences, which were analyzed and clustered into 111 OTUs. The bacterial diversity of salted cabbage was mainly composed of *Proteobacteria* species such as *Pectobacterium carotovorum*, *Pantoea agglomerans* or even *Acinetobacter rhizosphaerae*. At the beginning of fermentation, *Leuconostoc mesenteroides* was dominant and remain during the two first stages of fermentation. Combined to this *Leuconostoc* species, other bacteria, such as *Lactobacillus curvatus* or *Leuconostoc fallax*, were predominant and certainly contributed to the fermentation process. At the end of the fermentation, changes in bacterial diversity were observed. *Pediococcus parvulus* and *Lactobacillus plantarum* were predominant whereas they were subdominant at the beginning of fermentation.

The development of lactic acid bacteria, leading to the acidification of products, makes sauerkraut unfavourable to the development of *Proteobacteria* and more specifically *Enterobacteria*.

Importance des voies d'import du fer dans la résistance aux antibiotiques

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Pseudomonas aeruginosa est une bactérie pathogène opportuniste causant notamment de graves infections pulmonaires chez les personnes atteintes de mucoviscidose. Malgré les traitements antibiotiques préventifs ou curatifs, une grande proportion de malades développe des infections chroniques. Au cours de ces infections chroniques, *P. aeruginosa* évolue pour s'adapter à son environnement, échapper plus facilement au système immunitaire et mieux résister aux antibiotiques. Parmi les différents mécanismes d'adaptations, apparaissent souvent des mutations dans les gènes impliquées dans l'import du fer.

Pour se développer, *P. aeruginosa*, comme la plupart des organismes, a absolument besoin de fer. Cependant, il s'agit un élément très peu biodisponible, car il précipite à pH physiologique, et il l'est encore moins en contexte infectieux dû notamment à la présence de chélateurs de fer produits par l'hôte. Pour obtenir le fer dont elles ont besoin, les bactéries synthétisent des sidérophores, petites molécules sécrétées dans le milieu extérieur où elles vont lier le fer avant d'être re-importées dans les bactéries. *P. aeruginosa* produit deux sidérophores : la pyoverdine (PWD) et la pyochéline. La synthèse de PWD fait intervenir une machinerie complexe, qui est sous le contrôle d'un facteur de transcription, *pvdS*. Ce régulateur contrôle non seulement l'expression des gènes permettant la synthèse de PWD, mais également l'expression de nombreux autres gènes impliqués dans la virulence de la bactérie. Nous étudions également l'implication de ce facteur de transcription dans la résistance aux antibiotiques.

La délétion de ce gène, ou d'autres gènes de ces voies d'import du fer, ne modifie que peu les concentrations minimales inhibitrices (MIC) vis-à-vis de plusieurs familles d'antibiotiques. Par contre, des expériences de co-culture sur plusieurs jours entre souche sauvage et mutantes des voies d'import du fer ont montré qu'une souche mutante pour *pvdS* semble prendre le dessus en présence d'antibiotique. L'objectif sera à présent de comprendre quels avantages apporte la délétion de ce gène, favorisant une meilleure résistance aux antibiotiques.

Intracellular localizations of PvdS ECF sigma factor in *Pseudomonas aeruginosa*

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In *Pseudomonas aeruginosa*, as in most bacterial species, the expression of genes is tightly controlled by a repertoire of transcriptional regulators, particularly the so-called sigma factors. Sigma factors are an essential component of RNA polymerase and determine promoter selectivity. The extra cytoplasmic function (ECF) sigma factors are small regulatory proteins that are quite divergent in sequence relative to most other sigma factors. ECF sigma factors provide a means of regulating gene expression in response to various extracellular changes.

PvdS is an ECF sigma factor implicated in iron regulation and is responsible for the biosynthesis of pyoverdine. PvdS is also involved in the control of the expression of at least two other virulence factors: exotoxin A, an endoprotease.

In order to better understand how the expression PvdS is regulated, its localizations have been studied both in iron-rich and iron-deprived conditions by 3D-single-molecule localization microscopy. Our preliminary data provide a cellular mapping of PvdS with an accuracy that has never been achieved before.

Membrane aminoacyl-tRNA synthetases and signaling pathways

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Aminoacyl-tRNA synthetases are the family of ubiquitous enzymes essentially known for their primary role which is to form aminoacyl-tRNA for protein synthesis. However, recent studies have demonstrated their involvement in many other cellular processes including apoptosis and autophagy^{1,2}.

In the yeast *Saccharomyces cerevisiae* the methionyl-tRNA synthetase (MRS) and the glutamyl-tRNA synthetase (ERS) are found in a complex together with the Arc1 protein. Inside this complex the Arc1 protein acts as a cytosolic anchor and an aminoacylation cofactor for the two aaRS. The formation of this complex is regulated by the metabolic status of the cell. Indeed, the diauxic shift that occurs when the cell switches from fermentation to respiration, leads to the transcriptional repression of the *ARC1* gene and the release of the two aaRS, which then relocate into the nucleus (for MRS) and the mitochondria (for ERS)³.

Even if Arc1 was described as exclusively cytosolic, studies have shown that it interacts with lipids such as phosphoinositides⁴. Arc1 could thus bind to membranes and may trigger the relocalization of the entire complex at the surface of membranes.

The interaction of Arc1 with phosphoinositids and membrane fractions was confirmed by our lab using subcellular fractionation, vacuole purification experiments and a new microscopy tool developed by our team. My work now focuses on the lipid-binding strategy of the AME components and the vacuolar localization of the entire pool of cytosolic aminoacyl-tRNA synthetases in the yeast *Saccharomyces cerevisiae*. In the future, we will study how, when and why cytosolic aminoacyl-tRNA synthetases relocate at the vacuole surface.

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Bacterial alteration of asbestos cement waste

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Asbestos are naturally occurring minerals composed of fibrous silicates. Their ability to resist heat, fire, tension, electric and chemical aggressions and their low cost made them good candidates for the building industry. As a result, intensive utilisation of asbestos started in 1930 for the fabrication of rope packings, heatinsulating boards and fiber cement.

Fiber cement is a building and construction material, used mainly in roofing and facade products because of its strength and durability. However, due to environmental and health risks of asbestos, many countries decided to ban these products during the 80s.

Asbestos containing waste is usually disposed of in controlled landfills, but this practice does not definitively eliminate the problem related with asbestos fiber release and conflicts with movements in support of sustainable land use and recycling. Another way to take charge of the waste consist of extreme heating able to convert it into non toxic-glass, this process is called vitrification. However, it requires huge amounts of energy and is very expensive.

Recent studies have shown that biological degradation of asbestos by micro-organisms could be a possible alternative to treating the waste. Previous experiments in the laboratory highlighted a bacterial degradation of asbestos waste by a *Pseudomonas* strain. These bacteria are able to sequester iron with siderophores called pyoverdine, which makes asbestos compounds less toxic to humans. However, these studies were focused on flocking waste, and it remains undetermined if a bacterial degradation could be possible on fiber cement. If this technic is successful, biological degradation would be a cheaper way than vitrification and a more sustainable way than storage.

Triple element isotope fractionation of chloromethane from bacterial degradation by two different pathways

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Chloromethane (CH_3Cl) is responsible for a significant part of stratospheric ozone destruction by halogenated compounds, and has detrimental impacts on human health¹. Microorganisms may play important roles in both production and degradation of CH_3Cl ². Previous research showed that *Leisingera methylohalidivorans* MB2 grows with CH_3Cl using a different enzyme than CmuAB from the only pathway for CH_3Cl degradation pathway characterized so far³. Stable isotope fractionation is a valuable tool for characterization of modes and extent of contaminant degradation⁴. Here, we investigated triple element (chlorine, carbon and hydrogen) isotopic fractionation patterns of CH_3Cl during growth of the chloromethane-degrading strain MB2 lacking *cmu* genes, as compared to that observed for *cmu* pathway strain CM4. Isotope fractionation of chlorine was substantial, and very similar for the two strains, unlike previously reported hydrogen fractionation³. Our analysis provides new and useful data to help constrain the global budget of CH_3Cl in the biosphere, and will contribute to help define the still elusive chloromethane utilisation pathway of *Leisingera methylohalidivorans* MB2, currently under investigation in our laboratory.

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***Staphylococcus aureus* Panton-Valentine Leukocidin
Causes an alternative NETosis in human neutrophils
presenting histone 3 citrullination on NETs**

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Staphylococcus aureus is a major cause of nosocomial and community infections being able to produce various virulence factors such as Panton-Valentine Leucocidin (PVL), one of several bi-component toxins (BCTs). In particular, PVL targets C5aR-expressing cells, thus activating mainly human leukocytes such as neutrophils, amongst other targets.

Here, we demonstrate that PVL, in the presence of 1mM of $[Ca^{2+}]_{ext.}$, causes human neutrophil extracellular trap (NETosis) process in vitro, presenting a parallel increased level of autophagy and ending up with the ejection of chromatin fibers, decorated with neutrophil elastase (NE). Nevertheless, unlike phorbol 12-myristate 13-acetate (PMA), a NETosis inducer used as positive control, PVL NETosis is independent of NADPH oxidase for the production of reactive oxygen species (ROS), rather involving mitochondria, xanthine oxidase (XO) and myeloperoxidase (MPO). Surprisingly, the nuclear factor kappa (NF- κ B) does not seem to be involved in this process, while a small conductance channel (SK) is necessary for the PVL NETosis.

Moreover, kinases are differently activated compared to PMA and only PVL presents citrullinated histone 3 (citH3) on NETs.

These results suggest that PVL provokes a non-classical form of NETosis, an *ad hoc* modified type of this immune response, rather than rapid membrane pore formation.

Characterization of The Interactions Between *icaR* mRNA and Regulatory RNAs in *Staphylococcus aureus*

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Staphylococcus aureus is an opportunist pathogen, which produces surface proteins involved in host adhesion or biofilm, and toxins to invade its host. Their expression varies upon stress and environmental conditions and is tightly regulated by transcription factors, two components systems and regulatory sRNAs. In *S. aureus*, biofilms are mainly composed of the exopolysaccharides β -1,6 N-acetylglucosamine (PNAG). The *icaADBC* operon encoding enzymes needed in the synthesis of PNAG is transcriptionally inhibited by the regulatory protein IcarR. As published, the 3' UTR of the mRNA *icaR* repressed its own translation by an anti-sens mechanism. Recently, the host laboratory identified a sRNA named RsaI binding to *icaR* mRNA and indirectly inducing biofilm formation. The aim of the project is then to identify the factors allowing *icaR* translation to counteract RsaI and to study their effect on biofilm synthesis. To this end, RNAs interacting with *icaR* mRNA are identified *in vivo* by MS2 affinity purification coupled with RNA-Sequencing (MAPS). Electrophoretic Mobility Shift Assay (EMSA) will validate the RNA-RNA hybrids and their functional effect on IcarR will be established by western blot or gene fusions.

Previous MAPS experiences showed that two sRNAs, RsaA and RsaE, bind *icaR* mRNA in accordance with *in silico* predictions. My task will be to confirm the role of RsaA and RsaE in biofilm regulation. In summary, I will decipher the role of *icaR* integrating both transcriptional regulatory networks and sRNA mediated post-transcriptional regulatory signals to control biofilm formation in *S. aureus*. Moreover preliminary results demonstrate that RsaA binds the 3' end of *icaA*, which adds another layer of potential regulation.

Modes of action of antibiotics against multi-drug resistant pathogens

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The study of drug-target interactions always been a key step to design and produce more effective antibiotics in order to tackle the emergence of resistance in bacteria responsible for nosocomial infections. Almost half of all antibiotics target the bacterial ribosome.

Structural aspects of ribosome/antibiotics interactions have been investigated⁽¹⁾, but kinetic and thermodynamic data, yet essential for a complete understanding of mechanism of action, are still sparse. Isothermal Titration Calorimetry (ITC) is a true in-solution and label-free approach that directly provides all thermodynamic parameters of an interaction⁽²⁾.

Here we use ITC to gain insights into the interaction between macrolides, aminoglycosides and oxazolidinones or new compounds and the ribosome from diverse pathogens (*Pseudomonas aeruginosa*, *Klebsiella* spp., *Enterococcus* spp., *Acinetobacter* spp.). Our data will be completed with structural studies by Cryo-EM of theses complexes, in order to obtain an integrative view of modes of action of antibiotics against bacterial ribosomes.

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Effet des bactéries associées à l'orge dans le métabolisme des terpénoïdes

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Les communautés de micro-organismes constituant des microbiotes peuvent avoir des effets bénéfiques pour leurs hôtes. Si les microbiotes sont relativement bien étudiés chez les animaux, les aspects fonctionnels des microbiotes végétaux sont encore peu connus. Parmi ces aspects, les interactions métaboliques, impliquant l'échange de métabolites, peuvent jouer divers rôles notamment dans la croissance et la résistance aux stress biotiques ou abiotiques. En particulier, l'équipe étudie le rôle d'hormones d'origine terpénoïde, les brassinostéroïdes, dans les interactions orge-bactéries. Pour cela, nous avons considéré trois génotypes d'orge brassicole : le sauvage, un variant *bri1* porteur d'un allèle faible du gène codant le récepteur des brassinostéroïdes¹, et un mutant suppresseur de *bri1*. L'ADN présent dans la phyllosphère, les racines et la rhizosphère des plantules de ces trois génotypes a été extrait et purifié. Après amplification du gène codant l'ARN 16S bactérien, un inventaire du microbiote a pu être réalisé. En comparant les microbiotes de chaque génotype, nous avons identifié les genres bactériens dont la présence semble être affectée par une modification de la réponse aux brassinostéroïdes. Pour étudier l'effet de ces bactéries sur la croissance de la plante, nous avons isolé certaines souches du microbiote d'orge et développé un système de culture axénique de ces orges en hydroponie afin d'y inoculer une souche choisie. Cette étude nous permettra d'identifier les bactéries à effet positif sur la germination ou la croissance de l'orge, ou contribuant à une meilleure résistance aux stress abiotique ou biotique.

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Bacterial adaptation to the utilization of chloromethane

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Chloromethane (CH_3Cl , CM) is the most abundant volatile halocarbon in the atmosphere. Its photolysis by UV radiation contributes up to 16% of the ozone layer destruction by halogenated compounds. This toxic gas mainly produced naturally, can be degraded biotically by methylotrophic bacteria. Methylotrophs are microorganisms that can use one-carbon compounds as carbon and energy source. Among them, *Methylo rubrum extorquens* strain CM4 is a well-studied facultative methylotroph that can use CM, methanol and other multi-carbon compounds (such as succinate) to grow. Most CM-degrading strains harbour a set of genes (*cmuACB fmdB paaE hutI metF2 purU folD*), conserved in clusters, and including all known essential genes for CM growth of the *cmu* pathway, the only pathway for CM degradation characterized so far¹. The *cmu* genes are found associated with mobile elements in a multitude of bacterial taxa suggesting that their acquisition via Horizontal Gene Transfer (HGT)². Transfer of this gene set cloned on a plasmid to *Methylo rubrum* strains of known genome sequence, lacking *cmu* genes and unable to grow on CM, resulted in only poor growth with CM³. This suggests that acquisition of *cmu* pathway genes by HGT was not sufficient for efficient CM utilisation, and required additional post-transfer adaptations that have not been yet characterized.

In order to identify the key functions and determinants allowing growth on CM, an experimental evolution approach was initiated. Transconjugants of *Methylo rubrum* strains AM1, DM4 and PA1 harbouring cloned plasmid-borne *cmu* genes are currently cultivated for many generations on CM in the presence of succinate provided in growth-limiting amounts. Variants capable of efficiently utilizing CM for growth will be selected and isolated. Genome sequencing of evolved variants will be used to identify beneficial mutations. This *in labo* evolution strategy was already used successfully to identify genes required in adaptive growth with dichloromethane (CH_2Cl_2)⁴.

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Ingénierie de la voie de biosynthèse du siderophore chez *Pseudomonas* pour la production de pyoverdine fonctionnalisée

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Les sidérophores sont des métabolites secondaires qui permettent aux bactéries de subvenir à leur besoin en fer en cas de carence. En biotechnologie, ils sont utilisés (i) comme biocapteurs puisqu'ils ont la capacité de chélater les métaux ; (ii) pour promouvoir la croissance de plantes agricoles, (iii) dans de nouvelles stratégies thérapeutiques contre les infections bactériennes. Toutes ces applications sont facilitées par une production importante de sidérophore, et certaines nécessitent de conjuguer le sidérophore à une autre molécule. Dans ce contexte, mon stage comporte deux objectifs : (i) concevoir une souche châssis pour une production facilitée d'un sidérophore, la Pyoverdine, à partir de deux souches de *Pseudomonas* (*P. aeruginosa* PAO1 et *P. putida* KT2440) ; (ii) fonctionnaliser *in vivo* la Pyoverdine, par ingénierie enzymatique, pour faciliter la conjugaison du sidérophore à d'autres molécules.

- (i) Pour la souche châssis, l'objectif est de lever la régulation par le Fer (qui inhibe l'expression de la voie de biosynthèse en milieu riche). Pour cela, nous cherchons à substituer le promoteur natif du gène de l'activateur transcriptionnel PvdS par un promoteur inducible (*araCP_{BAD}*) ou constitutif (Pc) chez les deux souches.
- (ii) Concernant le second objectif, il s'agit de modifier par ingénierie enzymatique la voie de biosynthèse de la Pyoverdine chez *P. putida* KT2440, pour pouvoir incorporer un acide aminé non naturel très réactif dans la Pyoverdine, la Propargylglycine.

La souche de *P. aeruginosa* PAO1 exprimant *pvdS* sous contrôle du promoteur *P_{BAD}* est capable de produire la Pyoverdine dans un milieu de culture riche, de façon indépendante de la concentration en Fer et dépendante de la concentration en Arabinose.

Antibacterial Potential of the Arab Mineral Pharmacopeia

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Metals have been used for centuries to fight bacteria, but their use fall down due to the discovery of antibiotics, and to their toxicity. Nevertheless, the development of multi-drug resistant bacteria leads to reconsider the antibacterial properties of metals. A collaboration between historians, chemists and biologists allowed to investigate the Middle Ages Arab pharmacopeia, which was the golden age of the Arabic medicine. More than 100 remedies have been retrieved, revealing that most of those against cutaneous infections contained metals. Some of these remedies will be reproduced and separated in different fractions containing herbal extracts, metals or a combination of both.

The purposes of this studies will be to investigate the potential antibacterial activity of these different fractions, their effect on the bacterial phenotypes and to start studies on their mechanisms of action.

The minimum inhibitory concentration (MIC) of these fractions will be evaluated. For that, pathogenic microorganisms will be grown in 96 well plates containing decreasing concentration of herbal extract, metals, fractions or a combination between metals and fractions. The results will allow to identify the fractions with antibacterial activities. The effect of these active fractions on the phenotype of pathogenic bacteria (*Pseudomonas aeruginosa*) will be studied through a proteomic approach. The results will be confirmed at the mRNA level by qRT-PCR. Then, some of the genes whose expression varied in the proteomic analysis will be deleted. Their function, their involvement in the effect of the remedies will be tested by comparing the effect of the active fractions on the mutants versus the wild-type strain. With this approach we hope to find new combinations of molecules and metals that could help to fight the multi-drug resistance of bacteria.

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Impact of the zinc finger motifs in HIV-1 Gag on the specific selection of genomic RNA and its trafficking to the plasma membrane.

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Assembly of human immune deficiency virus-1 (HIV-1) is a highly regulated process which includes the selection and packaging of host cellular and viral components to produce infectious virion. The viral protein Gag orchestrates the assembly process¹. Indeed, Gag selects the gRNA from the bulk of cellular and spliced/unspliced HIV-1 RNAs by specifically interacting with the packaging signal (Psi) which consists of four stem loops (SL1-4) located in the 5' end of genomic RNA. As the cellular trafficking of the viral RiboNucleoProtein remains yet to be precisely defined, we investigated the role of the zinc fingers in NC domain in cells to better understand the Gag mediated-specific selection of gRNA, and its trafficking to the PM. More in detail, we compared the interactions of the wild-type Gag precursor, several NC mutants and a non-myristoyled version of Gag, that cannot interact with the PM (GagG2A) with gRNA by combining bio-imaging approaches based on fluorescence such as confocal microscopy, PALM-STORM (*Photo-Activated Localization Microscopy* and *Stochastic Optical Reconstruction Microscopy*), microinjection assays, FRET-FLIM (Fluorescence Resonance Energy Transfer- Fluorescence Lifetime Imaging Microscopy), and RISC (Raster Image Correlation Spectroscopy). Our data showed that Gag interacts with viral RNAs in the cytoplasm, and at the PM as well, where they co-localize. Importantly we found that this interaction is driven by ZF motifs in the NC domain, and one ZF is sufficient to ensure the gRNA recruitment in the cytosol and its trafficking to the assembly sites at PM. Besides, the two ZF motifs displayed a similar role. Finally, the substitution of the Glycine at the N-terminus prevented as expected the co-localization with the gRNA at the PM, but did not impair the specific recruitment of gRNA. Taken together, our data clearly show that the discriminants for the specific Gag-gRNA selection exclusively reside in the ZF motifs in the NC domain.

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