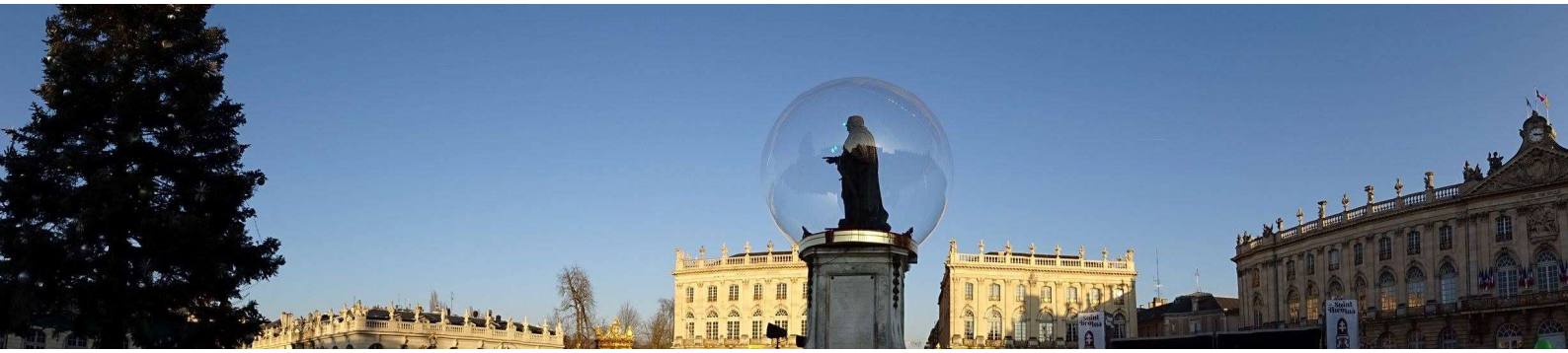

Actino 2024

30-31 mai 2024

Journée des actinobactéries

Nancy

Faculté des Sciences et Technologies

Amphi VG3

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Jeudi 30 mai 2024

13:00 - 13:30	**Accueil des participants**
13:30 - 13:45	**Ouverture**

Interaction / Ecosystème
Modératrice : Hasna BOUBAKRI

13:45 - 14:30	**Conférence invitée :** Genomics-driven discovery of a family of RiPPs that protect Actinobacteria from phage infection - *Helena SHOMAR, Institut Pasteur, Paris*
14:30 - 14:50	Activation of plant immunity by galbonolides promotes rhizosphere colonisation by Streptomyces sp. AgN23 – *Thomas REY, Laboratoire de Recherche en Sciences Végétales, Toulouse*
14:50 - 15:10	Exploration of antibiotics of beehive-associated actinobacteria - *Déborah TELLATIN, Centre d'Ingénierie des Protéines, Liège*
15:10 - 15:30	Lentzea du désert : une actinobactérie qui stimule la croissance des plantes et inhibe des champignons phytopathogènes - *Lorena CARRO, Universidad de Salamanca*
15:30 - 15:50	Prophage induction can facilitate the in vitro dispersal of multicellular bacteria - *Stéphanie BURY-MONE, Institut de Biologie Intégrative de la Cellule, Orsay*
15:50 - 16:30	**Pause café et session posters**

Métabolisme spécialisé / Biologie de synthèse / Biotechnologie
Modératrice : Stéphanie BURY-MONE

16:30 - 17:15	**Conférence invitée :** Scalable discovery of microbial secondary metabolites through synthetic biology - *Vincent LIBIS, U1284 INSERM, Paris*
17:15 - 17:35	Valorisation de la lignocellulose par co-culture fongique-Streptomyces - *Ludovic BESAURY, UMR FARE, Reims*
17:35 - 18:15	Refactoring of the congocidine biosynthetic gene cluster: from gene cassettes to gene cluster - *Hervé LEH, Institut de Biologie Intégrative de la Cellule, Orsay*
17:55 - 18:15	Conséquences de la délétion des voies majeures de biosynthèse de métabolites spécialisés de Streptomyces coelicolor sur le métabolome et le lipidome de cette souche - *Marie-Joelle VIROLLE, Institut de Biologie Intégrative de la Cellule, Orsay*
18:15 - 19:00	**Session posters**
20:30 - 23:00	**Dîner de gala**

Vendredi 31 mai 2024

08:30 - 08:45	**Accueil**
08:45 - 09:00	Présentation du programme interdisciplinaire B4B, I-site LUE - *Stéphane DESOBRY, Université de Lorraine, Nancy*
	Métabolisme spécialisé / Biologie de synthèse / Biotechnologie **Modératrice : Marie Joëlle VIROLLE**
09:00 - 09:20	Streptomyces cavourensis sp. TN638 : Lutte Biologique contre Pythium ultimum, fermentation en milieu semi-solide, purification et caractérisation des biomolécules - *Lotfi MELLOULI, Centre de Biotechnologie de Sfax*
09:20 - 09:40	Development and application of the COMMBAT tool linking environmental signals to the expression control of biosynthetic gene clusters in microorganisms - *Silvia RIBEIRO MONTEIRO, Centre d'Ingénierie des Protéines, Liège*
09:40 - 10:00	Exploiting the inherent promiscuity of the acyl transferase of the stambomycin polyketide synthase for the mutasynthesis of analogs - *Kira WEISSMAN, Ingénierie Moléculaire, Cellulaire et Physiopathologie, Nancy*
10:00 - 10:30	**Pause café et session posters**
	Génomique / Evolution **Modérateur : Jean-Luc PERNODET**
10:30 - 11:15	**Conférence invitée :** Exploration du mobilome des communautés microbiennes au travers des signatures 3D des génomes - *Martial MARBOUTY, Department Genomes & Genetics, Institut Pasteur, Paris*
11:15 - 11:35	Dynamics of Streptomyces genome architecture and genomic island expression - *Stéphanie BURY-MONE, Institut de Biologie Intégrative de la Cellule, Orsay*
11:35 - 11:55	Bridging mismatch repair, double strand breaks repair, and genome plasticity in Streptomyces - *Abbas MOHAMAD-ALI, UMR DynAMic, Nancy*
11:55 - 12:15	Interplay of genome structure and gene regulation in bacteria - *Patrick SOBETZKO, UMR DynAMic, Nancy*
12:15 - 14:00	**Déjeuner**
	Interaction / Ecosystème **Modérateur : Sébastien RIGALI**
14:00 - 14:45	**Conférence invitée :** Modulation of secondary metabolomes upon interspecies interaction between Streptomyces and Bacillus - *Marc ONGENA et Augustin RIGOLET, TERRA teaching and research centre, Gembloux Agro-Bio Tech,Gembloux*
14:45 - 15:05	Study of the molecular dialogue involved in plant-Streptomycetaceae interactions - *Margaux CHEMINAT, Institut de biologie moléculaire des plantes, Strasbourg*
15:05 - 15:25	Couleur et hétérogénéité des fromages à croûte lavée - *Amandine MARTIN, Laboratoire d'Ingénierie des Biomolécules, Nancy*
15:25 - 15:45	Potential functions of AgLTP24, an antimicrobial peptide produced by alder against its bacterial symbiont; Frankia - *Hasna BOUBAKRI, Laboratoire d'Écologie Microbienne, Lyon*
15:45 - 16:00	**Clôture**

Informations pratiques :

- Le diner de jeudi soir se déroulera au restaurant ***Amis*** aux abords de la **place Stanislas** et du **parc de la Pépinière :**

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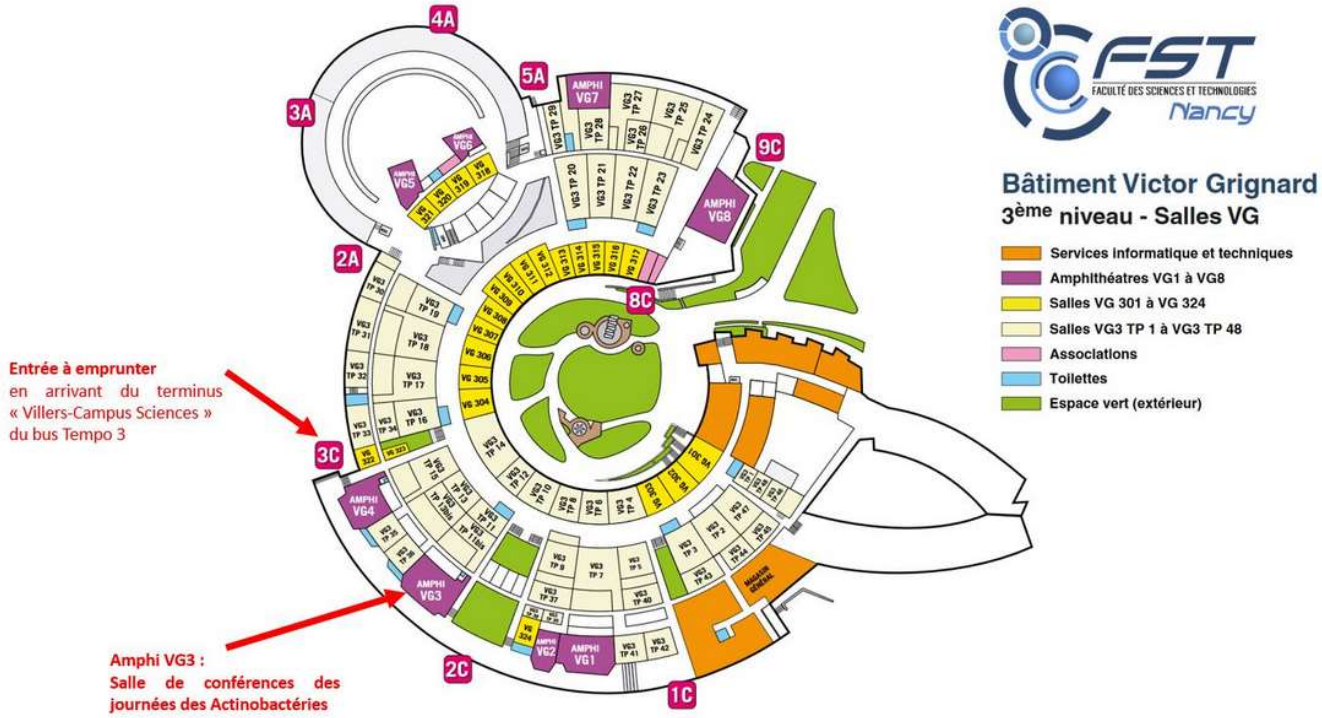

COMMUNICATIONS ORALES

Genomics-driven discovery of a family of RiPPs that protect Actinobacteria from phage infection.

Helena Shomar*†[1]

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Résumé

Bacteria produce a diverse array of natural products, to adapt to changing environments and stress. However, our understanding of the biological functions and ecological roles of the vast majority of these compounds remains limited. Genomic studies have unveiled the untapped metabolic potential of bacteria, with only 3% of natural products being characterized, and millions of molecules yet to be discovered. Recently, it emerged that a few known natural products allow bacteria to resist phage infection, but the prevalence of this defense strategy, called chemical defense, remains unclear. Here we use genomics and synthetic biology to uncover biosynthetic gene clusters that produce unknown natural products involved in anti-phage defense. We found that biosynthetic gene clusters that encode the production of a family of uncharacterized Ribosomally synthesized and post-translationally modified peptides (RiPPs) are often encoded near known anti-phage defense systems. Through heterologous expression in *Streptomyces albus*, we demonstrate experimentally the anti-phage activity of three representatives of this family of defensive RiPPs, present in hundreds of genomes of Actinobacteria. We further demonstrate the role of these defensive RiPPs in a native strain, allowing us to understand the regulation of their production. Finally, we delve into the anti-phage mechanism of action of these compounds. The discovery of defensive RiPPs paves the way for mining bacterial genomes for compounds involved in anti-phage defense, thus opening avenues for the development of new antiviral drugs derived from natural products.

Mots-Clés: Actinobacteria, Phage, anti, phage defense systems, RiPPs

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Activation of plant immunity by galbonolides promotes rhizosphere colonisation by *Streptomyces* sp. AgN23

Clément Nicolle[1], Damien Gayrard[*†2], Alba Noël[‡3], Marion Hortala[1], Aurélien Amiel[2], Sabine Grat[*§1], Aurélie Le Ru[1], Guillaume Marti[1], Jean-Luc Pernodet[3], Sylvie Lautru[3], Bernard Dumas[*1], and Thomas Rey[*1,2]

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Résumé

The rhizosphere, which serves as the primary interface between plant roots and the soil, constitutes an ecological niche for a huge diversity of microbial communities. Currently, there is little knowledge on the nature and the function of the different metabolites released by rhizospheric microbes to facilitate colonization of this highly competitive environment. Here, we demonstrate how the production of galbonolides, a group of polyene macrolides that inhibit plant and fungal Inositol Phosphorylceramide Synthase (IPCS), empowers the rhizospheric *Streptomyces* strain AgN23, to thrive in the rhizosphere by triggering the plant's defence mechanisms. Metabolomic analysis of AgN23-inoculated *Arabidopsis* roots revealed a strong induction in the production of an indole alkaloid, camalexin, which is a major phytoalexin in *Arabidopsis*. By using a plant mutant compromised in camalexin synthesis, we show that camalexin production is necessary for the successful colonization of the rhizosphere by AgN23. Conversely, hindering galbonolides biosynthesis in AgN23 knock-out mutant resulted in loss of inhibition of IPCS, a deficiency in plant defence activation, notably the production of camalexin, and a strongly reduced development of the mutant bacteria in the rhizosphere. Together, our results throw light on the mechanism by which streptomycetes induce the production of a root defence compound to support colonisation of the rhizosphere.

Mots-Clés: Rhizosphere, Galbonolides, Streptomyces, Arabidopsis, Camalexin

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Exploration of antibiotics of beehive-associated actinobacteria

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Résumé

Known as apitherapy, the use of beehive products, has been documented for nutritional and medicinal purposes since ancient times by Egyptians, Greeks, and Romans. In addition to their primary role as nutrients and architectural elements within the hive, bee products, which include pollen, honey, wax, and propolis, also act as effective protectors by keeping their environment free from germs. In addition, a growing number of studies prove that insects (ants, termites, beewolf,...) have selected or host antimicrobial-producing bacterial species in order to preserve their environment from their natural pathogens.
The aim of this project is to characterize the arsenal of antimicrobials of the actinobacterial species isolated from beehives to reveal how these insect-bacteria symbioses maintain colony health. In total, we isolated 221 strains distributed in 55 different phylotypes belonging to 14 actinobacterial genera. Based on phylogenomic analyses, more than 70% of our isolates are representatives of novel species (ANI $<$ 95%), and from 1 to 3 novel genera (ANI $<$ 83%). Some of the isolates possibly belonging to a novel bacterial genus display extreme auxotrophy as they could not grow on all ($>$ 20) carbon sources tested so far. The survival of these strains is most likely guaranteed by cross-feeding as they could only grow at the vicinity of bacteria isolated from the plate where neighboring colonies were originally picked.
The analysis of the reservoir of BGCs of our strain collection suggests that ˜80 % of them are cryptic, i.e. we cannot associate a known natural product to this genetic material. Even more important in terms of novel compound discovery, 60% of the 5,000 BGCs analyzed so far are unique, meaning that this genetic material is exclusively specific to the strains of our collection. Bioactivity assays confirmed that most of the phylotypes produce antimicrobials, some of them being active against bacterial and fungal pathogens, namely *Paenibacillus larvae* and *Ascosphaera apis*, respectively, well-known for causing damages to bees larvae through American foulbrood and Chalkbrood diseases.

Mots-Clés: actinobacteria, beehive, antimicrobial

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Lentzea du désert: une actinobactérie qui stimule la croissance des plantes et inhibe des champignons phytopathogènes

María Blanco[1], Alfonso Sáez-Cornejo[1], Meriem Gasmi[2], Esther Menéndez[1], and Lorena Carro*†[1]

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[2]Laboratoire de Génie microbiologique et applications, Université des Frères Mentouri Constantine – Algérie

Résumé

Les actinobactéries suscitent un intérêt particulier en raison de leur capacité à synthétiser une grande diversité de métabolites secondaires. L'exploration récente de leurs génomes a révélé leur polyvalence métabolique sous plusieurs aspects, notamment dans la production de composés favorisant la croissance des plantes, des nouveaux agents antimicrobiens, ainsi que leurs mécanismes de tolérance à divers stress (Carro et al., 2018). Parmi ces actinobactéries, le genre *Lentzea*, faisant partie de la famille des *Pseudonocardiaceae*, se distingue par son potentiel élevé en tant que producteur de composés bioactifs et d'autres métabolites d'intérêt (Maiti & Mandal, 2022). Certaines espèces de ce genre, récemment décrits au niveau taxonomique, ont été isolées de zones désertiques, arides ou semi-arides, révélant ainsi un potentiel d'utilisation significatif pour atténuer les effets néfastes causés par le changement climatique.
Dans le cadre de cette étude, notre objectif était de caractériser taxonomiquement et fonctionnellement une souche partiellement identifiée comme appartenant au genre *Lentzea*, isolée des zones désertiques du Sahara occidental, en séquençant son génome et en réalisant divers tests pour la promotion de la croissance des plantes, l'inhibition des microorganismes phytopathogènes et de tolérance à différents stress abiotiques. Nous avons effectué une annotation fonctionnelle du génome de cette souche ainsi que des génomes disponibles des souches du genre *Lentzea*. Ces analyses ont révélé la présence de plusieurs gènes impliqués dans la biosynthèse de métabolites secondaires, ainsi que des enzymes ayant la capacité de dégrader les polymères et d'autres bioclusters d'intérêt. De plus, nos résultats ont démontré que cette souche était capable d'inhiber des pathogènes végétaux tels qu'*Acidovorax valerianellae* et le champignon *Leptosphaeria maculans*, ce dernier étant également inhibé *in vitro* et in planta. Ces observations suggèrent que le genre *Lentzea* possède un potentiel sous-exploité en tant que producteur de métabolites secondaires et de composés bioactifs, ainsi qu'en tant que probiotique végétal et agent phytoprotecteur.

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Maiti, P.K., Mandal, S. (2022). Comprehensive genome analysis of *Lentzea* reveals repertoire of polymer-degrading enzymes and bioactive compounds with clinical relevance. Sci Rep 12, 8409.

Mots-Clés: Lentzea, plante, bactérie, désert, antimicrobienne

Prophage induction can facilitate the in vitro dispersal of multicellular bacteria

Hoda Jaffal , Mounia Kortebi , Paulo Tavares , Malika Ouldali , Hervé Leh , Sylvie Lautru , Virginia Lioy , François Lecointe[1], and Stéphanie Bury-Moné[*†2]

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Résumé

Streptomyces are renowned for their prolific production of specialized metabolites with applications in medicine and agriculture. These multicellular bacteria present a sophisticated developmental cycle, and play a key role in soil ecology. Little is known about the impact of *Streptomyces*-phage on bacterial physiology. In this study, we investigated the conditions governing the expression and production of 'Samy', a prophage found in *Streptomyces ambofaciens* ATCC 23877. This siphoprophage is produced simultaneously with the activation of other mobile genetic elements. Remarkably, the presence and production of Samy increases bacterial dispersal under *in vitro* stress conditions. Altogether, this study unveiled a new property of a bacteriophage infection in the context of multicellular aggregate dynamics.

Mots-Clés: Phage, mediated dispersal of multicellular bacteria

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Scalable discovery of microbial secondary metabolites through synthetic biology

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Résumé

Discovery of bioactive secondary metabolites of microbial origin have declined over the past decades, depriving clinical pipelines from a key source of novel lead molecules. Encouragingly, the natural repertoire of microbial secondary metabolites remains vastly underexplored, and recent developments in genome mining technologies offer ways to accelerate the pace of discoveries. Sequencing and bioinformatics allow prioritization of biosynthetic genes predicted to encode new metabolites, and cloning and heterologous expression of such genes can speed up the discovery of therapeutically relevant molecules. Here, a strategy allowing to massively parallelize these processes will be presented. The streamlined interrogation of a large number of biosynthetic genes contained in a strain collection led us to discover several previously uncharacterized natural products, including a novel antibiotic. We will showcase a viable route to scalable natural product discovery through heterologous expression, on the condition of leveraging economies of scales along the process. Finally, we will discuss how this new ability might help shed light on the rules that tightly control the transcriptional activation of biosynthetic genes.

Mots-Clés: Synthetic biology, Heterologous expression, Natural products, Antibiotics, Sequencing

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Valorisation de la lignocellulose par co-culture fongique-*Streptomyces*

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Résumé

La lignocellulose est la biomasse la plus abondante sur Terre, avec environ 181,5 milliards de tonnes produites chaque année. Il peut être utilisé pour la production de produits chimiques, d'énergie et de matériaux et représente une ressource renouvelable prometteuse pour la bioéconomie. La lignocellulose est un matériau complexe composé principalement de trois fractions : la cellulose (40-50%), l'hémicellulose (25-30%) et la lignine (15-20%). En raison de la composition chimique hétérogène et de la récalcitrance structurelle pour la conversion biologique, le développement d'un procédé de conversion de la lignocellulose reste un enjeu majeur. La lignocellulose dans l'environnement est presque totalement dégradée du fait de la synergie de multiples partenaires microbiens alors qu'*in vitro* elle atteint près de 50%.
L'utilisation de co-cultures microbiennes synthétiques présente ainsi de nombreux avantages (capacité de prévenir une carence nutritionnelle due à la diversité des voies métaboliques présentes, la capacité d'échanger des métabolites au sein de la communauté) et a été mise en œuvre afin de mimer les processus naturels et de répartir les différentes fonctions exercées vers des populations spécifiques et optimisées. Dans ce contexte, des souches bactériennes (*Streptomyces*) et fongiques (*Aspergillus*, *Trichoderma* et *Phanerochaete*) capables de déconstruire séparément les parois cellulaires végétales lignocellulosiques ont été co-cultivées ensemble. Ces genres microbiens possèdent un large arsenal enzymatique codant pour des enzymes lignocellulolytiques (Carbohydrate Active enZymes) et ces micro-organismes sont également reconnus par leurs capacités à produire un large panel de produits naturels. Dans ce contexte, l'utilisation de biomasses lignocellulosiques, abondamment disponibles et peu onéreuses constitue un intérêt pour la production microbienne de métabolites par ces approches de co-cultures mais également pour l'élicitation de voies de métabolites secondaires silencieuses causé soit par la composition hétérogène de la lignocellulose soit par les interactions entre les 2 types de μorganismes également.

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Des approches de génomiques comparatives des différentes souches microbiennes ont permis de montrer un contenu métabolique et lignocellulolytique plus important et plus diversifié *in silico*. Les expériences *in vitro* ont été menées en mesurant l'efficacité de la dégradation du son de blé par quantification de différentes activités enzymatiques lignocellulolytiques produites par les microorganismes et également en analysant les différents métabolites produits au cours de la croissance microbienne sur le son de blé en mono et co-culture. Des analyses transcriptomiques par Dual RNA-Seq chez différents co-cultures fongiques avec *Streptomyces avermitilis* sur différents subtras lignocellulosqiues ont permis de démontrer une surexpression de transcrits impliqués dans les voies métaboliques associées à l'utilisation du carbone et la production de métabolites secondaires. Plus généralement, les résultats obtenus dans cette étude sont prometteurs et ont démontré : 1) une mise en place facile des co-cultures de micro-organismes différents de 2 domaines du vivant, 2) une surexpression de plusieurs activités enzymatiques lignocellulolytiques, 3) une élicitation de certains gènes de cluster biosynthétiques spécifiques observés uniquement dans l'expérience de co-culture, 4) une plus grande diversité de métabolites secondaires produits par les μorganismes lors d'une croissance sur lignocellulose au lieu de glucose, 5) une diaphonie microbienne spécifique et une interaction observée au niveau de l'espèce entre les *Streptomyces* et les champignons menant à une production spécifique d'enzyme lignocellulolytique et de métabolite secondaire (en fonction du partenaire microbien mais également de la biomasse lignocellulosiques). Ces résultats démontrent que les co-cultures représentent des approches stratégiques pour la production de molécules d'intérêt et pour la valorisation de la lignocellulose.

Mots-Clés: Lignocellulose, co, culture, dual RNA, seq, lignocellulolytic activities: Streptomyces

Refactoring of the congocidine biosynthetic gene cluster: from gene cassettes to gene cluster

Céline Aubry, Laetitia Caraty-Philippe , Hervé Leh*† , Jean-Luc Pernodet, and Sylvie Lautru‡

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Résumé

Pathway refactoring is a synthetic biology approach that consists in rewriting DNA sequence containing all the genetic information necessary for the expression and functioning of a metabolic pathway in heterologous or native host. It is often used to decouple gene expression from its native complex regulation, which, in the field of specialized metabolism, allows the expression of silent biosynthetic gene clusters. It can also be used to optimize the production yield of a metabolite or as a first step towards the generation analogs by combinatorial biosynthesis. We refactored the biosynthetic gene cluster (BGC) of the pyrrolamide congocidine (*cgc*). We constructed 11 basic gene cassettes, designed to constitute functional units, to express the 21 of 22 genes of the *cgc* cluster. The gene coding for the transcriptional activator was omitted and for each of the basic gene cassettes, a synthetic promoter was used. The functionality of every cassette was verified through a combination of genetic complementation of mutant strains, HPLC analyses and bioassays. The gene cassettes were then assembled on two compatible integrative plasmids. Both constructs were introduced in the *Streptomyces lividans* TK23 heterologous host. Culture supernatant analysis of the resulting strain showed the production of congocidine, yet at lower levels (roughly a fourth) than those observed for the native cluster in the same host. To determine whether differences in gene transcription could explain at least in part the difference in congocidine production, we compared the transcription of 12 *cgc* genes in the strains expressing either the native or the refactored congocidine BGC. Our results shows that the relative strength of the synthetic promoters we used in our study differs from the one reported in the literature and that a same promoter can yield different transcription levels, possibly due to the stability of the mRNA and the genetic context of the gene/operon. Altogether, this study illustrates some of the potential pitfalls that synthetic biologists may encounter when refactoring gene clusters.

Mots-Clés: congocidine, biosynthetic gene cluster, gene cassettes, refactoring, synthetic biology

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Conséquences de la délétion des voies majeures de biosynthèse de métabolites spécialisés de *Streptomyces coelicolor* sur le métabolome et le lipidome de cette souche.

Marie-Joelle Virolle*[1]

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Résumé

Des souches chassis dérivées de *S. coelicolor* délétées pour une ou plusieurs des principales voies de biosynthèse de métabolites spécialisés (CPK, CDA, RED et ACT) ont été construites par le groupe du Dr MJ Bibb (JIC, UK) dans le but d'augmenter la disponibilité en précurseurs afin d'améliorer la production de métabolites spécialisés issus de voies de biosynthèse hétérologue de métabolites spécialisés provenant de différentes espèces de *Streptomyces.* Nous avons utilisé ces souches afin de déterminer l'impact de la délétion de ces voies de biosynthèse sur le lipidome et le métabolome de ces souches.
Nos études ont révélé que, de manière inattendue, les souches délétées pour les clusters RED et CDA qui dirigent la biosynthèse d'antibiotiques de type peptidique, avaient un contenu en triacylglycérol (TAG) plus élevé et un contenu en acides aminés (AA) plus faible que la souche d'origine. Par contre, le contenu en TAG des souches délétées pour les clusters CPK et ACT qui dirigent la biosynthèse d'antibiotiques de type polycétide, était similaire à celle de la souche d'origine, alors que le contenu en acides aminés de ces souches était plus élevé que celui de la souche d'origine.

L'explication la plus simple de ces résultats inattendus est que chez les souches délétées pour les clusters RED et CDA, le surplus en acides aminés lié à l'absence de la biosynthèse de RED (Pro, Glycine, Ser) et CDA (Asp, Asn, Gly, Hydrophénylgly, Glu, Méthylglu, Ser, Thr et Trp) était dégradés en acétylCoA stocké sous forme d'acides gras dans les TAG. Par contre, le contenu élevé en AA de la souche délétée pour le cluster ACT suggérait que la disponibilité plus élevée d'acétylCoA résultant de la délétion de ce cluster était métabolisée par le cycle de Krebs, entraînant la biosynthèse d'acides aminés.

L'impact important qu'a eu la délétion des clusters dirigeant la biosynthèse de ces métabolites spécialisés sur le métabolome et le lipidome de *S. coelicolor* suggère, qu'outre leur impact lié à leur bio-activité dont on sait peu de choses, l'utilisation de précurseurs issus du métabolisme primaire pour la biosynthèse de ces métabolites spécialisés pourrait avoir un rôle négatif dans le contrôle de la croissance de la bactérie du fait de la réduction de la disponibilité de ces précurseurs. En effet, la production de ces métabolites spécialisés coïncide généralement

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avec des phases de ralentissement ou d'arrêt de la croissance.
Enfin, ces études ont confirmé la corrélation existant entre un contenu élevé en TAG et une faible production d'antibiotiques (et inversement) révélée par certaines de nos études précédentes. En effet, quand l'acétylCoA est stocké sous forme d'acides gras dans les TAG, il ne peut être utilisé pour soutenir l'activation du métabolisme oxydatif qui génère du stress oxydant, un déclencheur majeur de la biosynthèse de nombreux antibiotiques chez différentes espèces de *Streptomyces*.

Mots-Clés: Streptomyces, chassis strain, antibiotic biosynthetic cluster, heterologous expression.

Streptomyces cavourensis sp. TN638 : Lutte Biologique contre *Pythium ultimum*, fermentation en milieu semi-solide, purification et caractérisation des biomolécules

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Résumé

La bactérie filamenteuse TN638, nouvellement isolée et sélectionnée pour ses activités antimicrobiennes, notamment contre le phytopathogène *Pythium ultimum* (*P. ultimum*) agent causal de la pourriture aqueuse de la pomme de terre, a été identifiée comme étant une nouvelle bactérie actinomycète du genre *Streptomyces*, appelée *Streptomyces cavourensis* sp. TN638.

In vitro, le surnageant bioactif de la souche sp. TN638 inhibe le développement mycélien et la germination des oospores de *Pythium ultimum*. *In vivo*, la perte de poids des tubercules de pomme de terre infectés par *P. ultimum* et non traités par le surnageant bioactif de sp. TN638 est de 75%. Pour l'étude préventive (tubercules infectés par le phytopathogène et traités par le surnageant bioactif) la perte de poids n'est que de 15%.

La purification, *via* plusieurs techniques chromatographiques, de l'extrait bioactif d'une culture en milieu semi-solide de la souche de *Streptomyces cavourensis* sp. TN638, a permis l'obtention de sept biomolécules pures (M1-M7). Par le *biais* de plusieurs techniques spectroscopiques, (M1-M7) ont été caractérisées chimiquement. Il s'agit de trois dérivés de dikétopipérazines ; M1 : Cyclo- (Leu-Pro), M2 : Cyclo-(Val-Pro) et M3 : Cyclo-(Phe-Pro) et de quatre Macrotetrolides ; M4 : Nonactine, M5 : Monactine, M6 : Dinactine et M7 : Trinactine.

Mots-Clés: Streptomyces cavourensis sp. TN638, lutte biologique, Pythium ultimum, fermentation semi, solide, purification et caractérisation

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Development and application of the COMMBAT tool linking environmental signals to the expression control of biosynthetic gene clusters in microorganisms

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Résumé

It is nowadays commonly accepted that known microbial natural products only constitute a small fraction of bioactive compounds in the microbial world. Many of them are not produced under laboratory conditions and a main challenge is to identify the molecular mechanisms involved in the transcriptional control of the biosynthetic gene clusters (BGCs). What are the environmental cues that trigger the specialized metabolism of bacteria and with which molecular mechanisms these molecules transmit the message to the bacterial developmental program? To answer these questions, bioinformatic tools are being developed and applied to unveil new signaling pathways of known or cryptic specialized metabolisms.

The main objective is to contribute to setting up an automated methodology for fast, reliable, and exhaustive identification of BGCs – either cryptic or associated with known natural products – whose expression responds to a specific environmental cue. The methodology named COMMBAT (COnditions for Microbial Metabolite Biosynthesis Activated Transcription), is based on the detection of *cis*-acting elements bound by a transcription factor of interest in BGCs. The methodology is divided into four main steps: 1) Creation/Selection of a position weight matrix (PWM) of a transcription factor's *cis*-acting elements; 2) Selection of BGCs to analyze (either BGCs that were identified from downloaded genome sequences or known BGCs from the MIBiG database); 3) Scan of the BGCs with the PWM created at step 1; 4) Analysis of the output generated at step 3 to identify BGCs (either known or cryptic) that would reliably respond to a specific environmental signal.

The COMMBAT tool can have several applications. It can identify the regulator of a known or unknown BGC and the tool can also be used to predict the extent to which a regulation pathway is conserved amongst several species. In addition, the tool will calculate a COMMBAT score that considers the relative position of the binding site to the gene and the gene kind. This score will determine how likely the found binding site of a regulator is going to control the production of the BGC's metabolites. Furthermore, an online version of the COMMBAT tool is in development and a demonstration of this online tool will be made during the presentation.

Mots-Clés: Bioinformatics, Bacteriology, Signaling pathways, Biosynthetic gene clusters

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Exploiting the inherent promiscuity of the acyl transferase of the stambomycin polyketide synthase for the mutasynthesis of analogs

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Résumé

The polyketide specialized metabolites of bacteria are attractive targets for generating analogues, with the aim of improving their pharmaceutical properties. Here, we aimed to produce C-26 derivatives of the giant anti-cancer stambomycin macrolides using a mutasynthesis approach, as this position has been shown previously to directly impact bioactivity. For this, we leveraged the intrinsically broad specificity of the acyl transferase domain (AT12) of the modular polyketide synthase (PKS), which is responsible for the alkyl branching functionality at this position. Feeding of a panel of synthetic and commercially available dicarboxylic acid 'mutasynthons' to an engineered strain of *Streptomyces ambofaciens* (Sa) deficient in synthesis of the native alpha-carboxyacyl-CoA extender units, resulted in six novel stambomycins as judged by LC-HRMS and NMR. Notably, the highest product yields were observed for substrates which were only poorly accepted when AT12 was transplanted into a different PKS module, demonstrating the critical role played by domain context in the overall functioning of PKS proteins. We also demonstrate the superiority of this mutasynthesis approach relative to the alternative precursor-directed strategy, in which monoacid building blocks are supplied to the wild type strain. Finally, we identify a malonyl-CoA synthetase, MatB_Sa, with specificity distinct from previously identified promiscuous enzymes, making it a useful addition to a mutasynthesis toolbox for generating atypical, CoA activated extender units. Overall, this works confirms the interest of biosynthetic pathways which combine a dedicated route to extender unit synthesis and a broad specificity AT domain for producing derivatives of fully-elaborated complex polyketides.

Mots-Clés: Mutasynthesis, PKS, acyl, transferase, stambomycin, *Streptomyces ambofaciens*

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Exploration du mobilome des communautés microbiennes au travers des signatures 3D des génomes

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Résumé

Les communautés microbiennes, composées de bactéries, d'archées, d'eucaryotes et de virus, sont vitales et omniprésentes dans les écosystèmes de la Terre. Avec un nombre de particules estimé à 1031, les virus sont non seulement les entités génomiques les plus nombreuses dans ces habitats, mais aussi un réservoir substantiel de diversité génétique. En tant que prédateurs mais aussi agents de transfert horizontal de gènes, les virus influencent considérablement les processus d'évolution. Les progrès récents des technologies de séquençage ont facilité l'exploration des génomes viraux dans les échantillons environnementaux, élargissant ainsi notre connaissance de la biodiversité virale. Cependant, l'assemblage précis de génomes viraux complets à partir de ces séquences reste un défi c omplexe qui nuit à la précision des études ciblant la diversité et la fonctionnalité des virus. En outre, l'absence d'associations distinctes entre les hôtes et les virus au sein de ces communautés réduit considérablement notre compréhension de leur dynamique et de leur impact. La technique de MetaHiC utilisent l'ADN comme biomarqueur pour délimiter les interactions génomiques, ce qui permet de mieux comprendre l'organisation des écosystèmes d'espèces mixtes. Nous avons développé MetaTOR, un algorithme basé sur ces données, pour reconstruire méticuleusement les génomes viraux et identifier les hôtes correspondants en analysant les données Hi-C. Nous avons mis en œuvre cette méthodologie sur une gamme complète de génomes viraux et d'hôtes. En appliquant cette méthodologie à un large éventail de données publiques et inédites, nous avons compilé un vaste catalogue de plus de 6.000 génomes viraux assemblés couvrant plusieurs phylums. Ces travaux ont mis en évidence un réseau complexe d'interactions entre les hôtes et les virus, dévoilant des caractéristiques inédites de diverses familles virales, notamment les Crassvirales et les Megaviricetes.

Mots-Clés: virus, communauté, dynamique, interactions

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Dynamics of *Streptomyces* genome architecture and genomic island expression

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Résumé

Streptomyces are characterized by a large linear chromosome divided into a central region harboring cores genes and two extremities enriched in poorly conserved sequences including genomic islands (GIs) encoding notably specialized metabolite biosynthetic gene clusters (SMBGCs) or prophages. The majority of these GIs remain transcriptionally silent over growth under lab conditions. We previously demonstrated in *Streptomyces ambofaciens* ATCC 23877 that this genetic compartmentalization correlates with chromosome architecture and gene expression during vegetative growth: The distal ribosomal RNA (*rrn*) operons delimit a highly structured and expressed region termed 'central compartment', presenting structural features distinct from those of the terminal compartments which are almost transcriptionally quiescent. This architecture is dynamic during cell growth. We thus further explored the link between chromosome architecture dynamics and GI expression. First, we analyzed chromosome dynamics in a stress condition associated with prophage and other mobile genetic elements activation. Second, we explored the impact of relocating an SMBGC from the terminal to the central compartments. Altogether, these results highlights the extent of chromosome architecture dynamics and its links with GI expression and *Streptomyces* physiology.

Mots-Clés: Chromosome architecture, Genomic islands, Spatial compartmentalization, Phage, SMBGC, Transcription

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Bridging mismatch repair, double strand breaks repair, and genome plasticity in *Streptomyces*

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Résumé

The dynamic nature and frequent genomic rearrangements observed in *Streptomyces* genomes potentially enhance their rapid evolution and adaptability. These bacteria harbor a linear chromosome with a central region shared across the genus and variable chromosomal ends, which exhibit higher susceptibility to recombination compared to the central region (Lorenzi et al., 2021). Recent studies highlight the crucial role of double-strand break (DSB) repair mechanisms in shaping *Streptomyces* genomes (Hoff et al., 2018). Repair processes, involving homologous or non-homologous recombination, may lead to genome rearrangements. Our research focuses on the EndoMS/NucS endonuclease, identified as a potential source of endogenous DSBs, and recently implicated in a non-canonical mismatch repair (MMR) process in archaea and actinobacteria (Cebrián-Sastre et al., 2021). Our first aim is to elucidate whether NucS activity stimulates recombination in *Streptomyces*. Genetic analyses have demonstrated NucS's involvement in MMR, as indicated by hypermutability and marked colonial phenotypes in NucS-deficient mutants. Biochemical assays have revealed NucS's cooperation with the β-clamp to efficiently cleave G/T, G/G and T/T mismatched DNA, generating DSBs. These observations align with the transition-shifted mutational spectrum observed in NucS-deficient mutants, highlighting NucS's preference for correcting G/T mismatches occurring during replication (Dagva et al., 2024). Interestingly, our data unveil a crescent-shaped distribution of the transition frequency from the replication origin towards the chromosomal ends, supporting the hypothesis on a possible link between NucS-mediated DSBs and *Streptomyces* genome evolution.
We are currently exploring the correlation between NucS and genetic exchange among *Streptomyces* strains through conjugational assays, exploring how different *nucS* alleles influence species barriers and conjugative recombination efficiency. Furthermore, we aim to elucidate the mechanism of DSB repair achieved by NucS, employing affinity purification mass spectrometry (AP-MS) to identify partner proteins involved in DSB repair pathways. These investigations aim to unravel the connections between MMR, DSB repair, and genome plasticity in *Streptomyces*. As crucial sources of biomolecules for medicine and biotechnology, understanding the rapid evolution of *Streptomyces* genomes provides avenues to diversify their specialized metabolism (Bury-Moné et al., 2024).

Mots-Clés: DNA recombination, evolution, Mismatch Repair, NucS

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Interplay of genome structure and gene regulation in bacteria.

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Résumé

Absolute gene position and its local neighborhood plays a significant role in the formation of gene regulation patterns. In particular, the impact of gene copy numbers linked to replication processes as well as DNA supercoiling levels will be discussed. These fundamental and potential early mechanisms of regulation are, by their nature, observed throughout the bacterial kingdom.

Mots-Clés: genome architecture, DNA supercoiling, gene regulation

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Modulation of secondary metabolomes upon interspecies interaction between *Streptomyces* and *Bacillus*

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Résumé

In this work, we explored the interactions between the biocontrol rhizobacterial species *Bacillus velezensis* and several *Streptomyces* isolates including the model soil species *S. coelicolor* and *S. venezuelae* but also natural strains collected from cave representing another harsh environment. The objective was to assess whether the specialized metabolome (the pattern of secreted soluble secondary metabolites) of both *Bacillus* and *Streptomyces* could undergo unsuspected changes upon interaction in contact-independent settings. We detected many new features among the products secreted by *Streptomyces* in response to *B. velezensis*. For most of them, further investigations are required to determine their structures and bioactivities but we could identify likely novel variants of avilamycins that could be particularly interesting given the veterinary and potential pharmaceutical outcomes of this type of antibiotic. Likewise, some components of the secondary metabolome of *B. velezensis* are induced and/or modified upon interaction including the polyketide macrolactin, the siderophore bacillibactin and the cyclic lipopeptides (CLPs) surfactin, iturin and fengycin. Our data revealed that these *Bacillus* CLPs are actually promptly degraded by *Streptomyces*. The enzymatic degradation is associated with the release of free fatty or amino acids that are used as nutritional sources by *S. venezuelae* to sustain growth, thereby reflecting a foraging strategy to support fitness in oligotrophic environments such as soil. However, CLPs are precious metabolites retaining key ecological functions and we will discuss how their breakdown may affect the establishment and competitiveness of *B. velezensis* in the rhizosphere niche.

Mots-Clés: Streptomyces, Bacillus, interspecies interactions, secondary metabolome

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Study of the molecular dialogue involved in plant-Streptomycetaceae interactions

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Résumé

It is now established that plants shape the structure of their microbiota through genetic or physiological control. We wondered whether modulating plant terpenoid profiles could help to remodel the microbiota. In a first study, we used a mutant of *Arabidopsis thaliana* called *chs5/dxs1*, carrying a weak allele of the gene coding for 1-deoxy-D-xylulose-5-phosphate synthase (DXS1), a key enzyme in the biogenesis of plastid isoprenoids. This mutant shows a reduction in carotenoids and xanthophylls, and an imbalance in phenylpropanoids and lipids compared with the wild type. We demonstrated that bacteria of the genus *Actinacidiphila* (*Streptomycetaceae*) were more abundant in the microbiota of the wild type than in that of the mutant. We used a non-targeted proteomic approach to identify the proteins involved in the *Arabidopsis-Actinacidiphila* interaction. Our results revealed that the metabolic status of *A. thaliana* was crucial for the specific recruitment of *Actinacidiphila* to the microbiota, leading to a modulation of the Arabidopsis proteome. In a second study, we demonstrated that *Streptomyces* spp. are less abundant in the roots of a wild-type barley (cv. Bowman) than in the roots of a mutant plant deficient in the signaling process mediated by brassinosteroids, a class of terpenic phytohormones. Using omics approaches (metabolomics and proteomics), we are currently characterizing the molecular processes involved in the interaction between barley and *Streptomyces* isolates that have plant growth promotion and biocontrol capacities.

Mots-Clés: Plant bacteria interactions, Plant Growth Promoting Bacteria, terpenoids, isoprenoids

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Couleur et hétérogénéité des fromages à croûte lavée

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Résumé

L'apparence des fromages est un critère important dans le choix des consommateurs et dépend de paramètres technologiques et des flores d'affinage utilisées lors de leur fabrication. La couleur des fromages à croûte lavée est liée au développement d'une flore de surface complexe, associant une grande diversité de bactéries et de levures qui vont synthétiser des pigments responsables d'une coloration rouge-orangée. L'objectif des travaux réalisés est de mieux comprendre l'évolution de la couleur des fromages à croûte lavée ainsi que la relation entre le microbiote et la couleur. L'évolution de la couleur de la surface de trente-trois fromages de différents lieux de production a été analysée. Des photos ont été prises pendant deux mois à intervalles réguliers, avant et après la Date Limite d'Utilisation Optimale. La couleur de chaque pixel des images a été analysée dans l'espace colorimétrique CIELAB. L'analyse des variables de la couleur révèle une grande variabilité de couleur entre les fromages. Une approche de clustering a permis de montrer que trois familles peuvent être distinguées sur les critères de variance et de moyenne des variables CIELAB. Ces groupes se distinguent notamment par des moyennes et des hétérogénéités de luminances, des angles de teintes moyens ainsi que par des moyennes et des hétérogénéités d'intensité de couleur différentes. Une analyse de la structure des communautés par metabarcoding a montré que le microbiote se compose de 4 genres majoritaires : *Glutamicibacter*, *Psychrobacter*, *Halomonas* et *Vagococcus*. *Glutamicibacter*, Actinobactérie la plus majoritaire, représente jusqu'à 60 % de l'abondance relative retrouvée. Les analyses montrent que la variabilité de la couleur est liée à la communauté de microorganismes présents, suggérant un lien entre hétérogénéité de communauté et couleur.

Mots-Clés: fromage à croûte lavée, hétérogénéité, analyse d'images, microbiote

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Potential functions of AgLTP24, an antimicrobial peptide produced by alder against its bacterial symbiont *Frankia*

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Résumé

Frankia is an actinobacterium able to make symbiosis with over 230 species of dicotyledonous plants, in particular the black alder (*Alnus glutinosa*). Recognition between the two partners initiates a symbiotic programme at root level, leading to the formation of a new organ, the nodule, dedicated to trophic exchanges. Within this nodule, *Frankia* fixes atmospheric nitrogen inside specialized cells named as diazovesicles, thereby supplying nitrogen compounds to the plant, which in return transfers carbon compounds derived from its photosynthetic activity. The recognition, entry and maintenance of the bacterium in the nodule require fine coordination on the part of both partners, but the molecular mechanisms involved are still poorly understood, given that genetic engineering modifications of the *Frankia* and the host plant have yet to be developed. To decipher these mechanisms, transcriptomic approaches have been developed in this project and have enabled the identification of numerous genes over-expressed by the plant during the early step of symbiosis leading to the bacterial recognition (*1*).
The most overexpressed gene is a gene encoding an antimicrobial peptide classified in the 'lipid transfer protein' family and named here AgLTP24. This study highlights the potential role of AgLTP24 by combining in planta immunohistochemistry and physiological/molecular analysis of this peptide in *Frankia* cultures under *in vitro* conditions. It is particularly interesting to note that at sub-inhibitory concentrations, AgLTP24 positively modulates nitrogen fixation and could therefore play a potential role in trophic interactions with the plant (*2*).

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Mots-Clés: Frankia, Symbiosis, antimicrobial peptide, infection, nitrogen fixation

*Intervenant

POSTERS

Characterization of bacterial strains isolated from barley

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Résumé

Plant roots are in interaction with several organisms including plant growth promoting (PGP) bacteria or bacteria that inhibit phytopathogens, an activity defined as biocontrol (1). Plants select those bacteria in part via their root exudates (2) that contain a wealth of metabolites, particularly terpenoids. We hypothesized that brassinosteroids (BRs), a class of terpenic phytohormones could be involved in bacterial selection in barley. Using a metabarcoding approach, we compared the microbiota of the barley Wild-Type (WT) and of a mutant plant named BW312. This mutant is deficient in the signaling process mediated by BRs, which is causing an increased production of BRs and a semi-dwarf growth phenotype (3). We demonstrated that OTU affiliated to the *Streptomyces* genus are more abundant in roots of the mutant than in roots of the WT plant. In parallel, we isolated several *Streptomyces* from barley, among them *Streptomyces* sp. GPA1 belonging to a new species and phylogenetically closed to the bacteria highlighted in the metabarcoding approach. The genome of GPA1 and two others *Streptomyces* belonging to a new species, GPAT2 and GPN2, was sequenced and explored. We analyzed the biocontrol and PGP capacities of those bacteria on the wild-type plants. We demonstrated that GPA1, GPAT2 and GPN2 inhibit the growth of two microorganisms which affect barley seeds germination: *Pseudomonas* sp. MRN1 and a fungus of the *Fusarium* genus. We have observed that GPA1 colonizes and enhances plant roots length. GPA1 can also use root exudates for its growth and for the formation of biofilm, suggesting that root exudates may be involved in GPA1 selection by the plant. Other omics approaches (metabolomics and proteomics) are optimized in order to characterize the molecular processes involved in the interaction between GPA1/GPAT2/GPN2 and WT barley.
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Mots-Clés: Barley, Streptomyces, PGPR, Biocontrôle, Fusarium, Pseudomonas

*Intervenant

Transcription factors WblE and MtrA, do they co-control transcription at target *dnaA* promoter in *Streptomyces venezuelae* NRRL B-65442?

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Résumé

Streptomyces have a complex multiphasic life cycle. The transition from multicellular to unicellular phase is carried through a highly controlled process including sporulation and the formation of specialised aerial structures. This transition is mainly regulated by a well conserved transcription factor family in the *Actinomycetota* phylum, the WhiB-like proteins (Wbl). Among the members of this iron-sulphur cluster carrying protein family, WblE has been demonstrated to be essential and to target promoters of genes involved in protein synthesis, secondary metabolism and development (e.g. *bldA, adpA*, *bldD* and *dnaA*). This makes WblE a prime candidate as a regulator of DNA replication in *Streptomyces venezuelae* NRRL B-65442. MtrA, the cognate response regulator from the two-component system MtrAB, coordinates chloramphenicol production and sporulation in *S. venezuelae* NRRL B-65442. In this study, we analysed the interplay between WblE and MtrA regulator at one of their common targets, *dnaA* promoter. Combining surface plasmon resonance and ReDCaT (Reusable DNA Capture Technology) chip technology, and bacterial two-hybrid analyses, we studied the possibility that MtrA inhibits the binding of WblE to its target sequences in the *dnaA* promoter region. Altogether these results illustrate the complex regulatory networks that surround replication regulation during the *Streptomyces* development cycle.

Mots-Clés: Specialised metabolism regulation, Transcription factors, ReDCaT Surface Plasmon Resonance, Two, hybrid system, Transcription initiation regulation

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Identification of molecules eliciting signaling pathways to specialized metabolite biosynthesis in actinomycetes

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Résumé

Abstract

The production of microbial secondary/specialized metabolites is strictly controlled in time and space and most biosynthetic gene clusters (BGCs) remain transcriptionally silent as their environmental elicitor is not present under laboratory conditions. The combination of our PREDetector/COMMBAT bioinformatic tools (see Silvia Ribeiro Monteiro presentation) and the AURTHO approach (Anderssen et al., 2022), allows us to identify the transcription factors (TFs) that control the expression of many BGCs in Streptomyces species and other actinomycetes. For many of these examples, the last step of the signaling pathway (TF-BGC) is known, but the environmental elicitor transported or sensed that will target these TFs remains unidentified. In this project we aim at unveiling the molecules and their associated TFs that witness appropriate conditions for triggering the expression of both known and cryptic BGCs. By combining in silico approaches we will predict a series of candidate elicitors – with a special focus on carbon sources – whose identity and role will be further confirmed by TF-ligand-DNA interactions and proteomic approaches. Once the environmental trigger is known, the selected microorganisms will be grown in culture conditions with and without their predicted elicitor, and the production of their associated molecule will be assessed by comparative metabolomics and mass spectrometry imaging. Our poster presents the whole strategy of our project and the preliminary results.

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Mots-Clés: Secondary metabolites, carbon sources, transcription factor, biosynthetic gene clusters, Actinomycetes

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Development of vectors for the efficient *E. coli* - *Streptomyces* intergeneric conjugation

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Résumé

One of the most commonly used methods to perform genetic manipulation in *Streptomyces* is intergeneric conjugation using *E. coli*. A key element in this method is the helper plasmid encoding the conjugation machinery allowing gene transfer from *E. coli* to *Streptomyces*. The pMATING plasmid, developed by the group of V. de Lorenzo, is a synthetic modular plasmid based on RP4 and designed to be transferred by conjugation within complex microbiomes (1). This 23Kb plasmid is composed of the MATING module containing the genes encoding the machinery of DNA transfer, a module for *E. coli* replication (ori RK2), a module for antibiotic resistance (kanamycin resistance gene) and two copies of the transfer origin (OriT) (figure 1A in the attached file). Our project aims to adapt this vector for *E. coli* - *Streptomyces* conjugation by preventing its own transfer in *Streptomyces*. Initial modifications included the deletion of one copy of the OriT and the replacement of the kanamycin resistance cassette by an ampicillin resistance one, yielding pOSV874 (Figure 1B in the attached file). The transfer of pSET152 into *S. lividans* TK23 by conjugation using *E. coli* ET12567 bearing either pUZ8002, pUZ8003 (2) and pOSV874 were then conducted. We observed similar conjugation efficiency when using pOSV874 or pUZ8003. However, pUZ8002 was 10-fold more efficient than the former two. Further experiments are currently in progress to remove the second copy of OriT in pOSV874.

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Mots-Clés: pMATING vector, E. coli – Streptomyces conjugation, Intergeneric conjugation

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Refactoring of the congocidine biosynthetic gene cluster: from gene cassettes to gene cluster

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Résumé

Pathway refactoring is a synthetic biology approach that consists in rewriting DNA sequence containing all the genetic information necessary for the expression and functioning of a metabolic pathway in heterologous or native host. It is often used to decouple gene expression from its native complex regulation, which, in the field of specialized metabolism, allows the expression of naturally silent biosynthetic gene clusters. It can also be used to optimize the production yield of a metabolite or as a first step towards the generation non natural-natural analogs by combinatorial biosynthesis. We refactored the biosynthetic gene cluster (BGC) of the pyrrolamide congocidine (*cgc*) from S. ambofaciens. We constructed 11 basic gene cassettes, designed to constitute functional units, to express the 21 of 22 genes of the *cgc* cluster. The gene coding the transcriptional activator was omitted and for each of the basic gene cassettes, a synthetic promoter was used. The functionality of each cassette was individually verified through a combination of genetic complementation of mutant strains, HPLC analyses and bioassays. The gene cassettes were then assembled on two compatible integrative plasmids. Both constructs were introduced in the *Streptomyces lividans* TK23 heterologous host. Culture supernatant analysis of the resulting strain showed the production of congocidine, yet at lower levels (roughly a fourth) than those observed for the native cluster in the same host. To determine whether differences in gene transcription could explain at least in part the difference in congocidine production, we compared the transcription of 12 *cgc* genes in the strains expressing either the native or the refactored congocidine BGC. Our results shows that the relative strength of the synthetic promoters we used in our study differs from the one reported in the literature and that a same promoter can yield different transcription levels, possibly due to the stability of the mRNA and the genetic context of the gene/operon. Altogether, this study illustrates some of the potential pitfalls that synthetic biologists may encounter when refactoring gene clusters.

Mots-Clés: refcatoring, congocidin cluster

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From the prediction of biosynthetic gene clusters in a diversity of *Frankia* genomes to first steps in biological screening.

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Résumé

Frankia has largely investigated for its beneficial function as nitrogen fixing plant in the root nodules of angiosperm plant host named "actinorhizal plants". The existing *Frankia* symbiotic strains have been characterized as belonging to three phylogenetic clusters: cluster 1 comprises *Alnus*-infective and *Casuarina*-infective strains; cluster 2, Rosaceae/Cucurbitales/Ceanothus-infective strains; and cluster 3, Elaeagnaceae/Rhamnaceae/Gymnostoma-infective strains. Most of them are also able to survive as free-living soil bacteria suggesting the importance of this genus to produce biosynthetic gene cluster (BGC) to survive to environmental changing conditions.
Since the first three genomes, which were sequenced in 2007 and explored to reveal the presence of 25 to 31 BCG (*1*)? very few of them lead to compound structure elucidation and/or biological function identification. Indeed, we found a type II Polyketide Frankiamicin (*2*), fungicidal macrolide named Frankiamide (*3*), and the metallophore Frankobactin (*4*). Since then, more than 50 genomes have been sequenced and numerous *Frankia* have been isolated from plant nodules. In the collection of the 'Actinorhizal Symbiosis' team, more than 80 strains of *Frankia* were used, and around twenty of which have had their genome sequenced. We have used this diversity of genomic data to initiate a recently developed project combining BCG prediction using antiSMASH and biological screening. For the functional screening, two methods will be combined. The first is an OSMAC-type approach, which consists of growing *Frankia* in different culture media and screening certain biological activities. For the second, the BGCs predicted by antiSMASH are currently being screened for transcription factor binding sites in order to identify the culture conditions required for the production of known and cryptic natural products from our collection of strains. Ultimately, we hope to identify new *Frankia* functional BCG, decipher how they are transcriptionally regulated and then characterize the structures of these compounds.

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Mots-Clés: Frankia, Symbiosis, BCG, OSMAC, transcription factor

Functional diversification of *Streptomyces* through horizontal gene transfer

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Résumé

Streptomyces are ubiquitous spore-forming and filamentous soil bacteria found in plant root microbiota. They are characterized by a large linear chromosome and are mainly known for producing numerous specialized metabolites with varied ecological roles, such as antibiotics, antifungals, antioxidants and enzymes. In the laboratory, we have *Strepto-myces* belonging to the same population, i.e. strains of the same species co-isolated from the same habitat (here, soil grains from the rhizosphere of a beech tree). Analysis of their genomes showed that, despite their taxonomic and ecological proximity, these strains were not clonal but possessed numerous variable genes and functions (e.g. different production of specialized metabolites). This variability is attributable to intense gene transfer (HGT) over very short timescales. The HGT is a major evolutionary force in bacteria, enabling them to adapt rapidly to environmental changes. This work aims to understand the impact of HGTs on the functional diversification of a *Streptomyces* population, notably through their biosynthetic gene clusters (BGCs). We have already confirmed that entire BGCs can be transferred by HGT between strains in the laboratory population. In order to mimic these evolutionary processes over longer timescales, experimental evolution experiments will be carried out by replicating strains from the population over several generations. Genetic and metabolic impacts on evolved strains will be compared with ancestral strains using genomics and metabolomics techniques.

Mots-Clés: Evolution, Metabolomics, Gene transfer, Functional Diversification

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