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2018

PHAGES IN BORDEAUX

Domaine du Haut-Carré,
U. Bordeaux
24 & 25 septembre

Monday September the 24th

8h30 **WELCOME**

9h15 **INTRODUCTION**

9h30 **ECOLOGY & EVOLUTION** *@ Agora*

9h30 **Patrick FORTERRE** (40 min+5)
Institut Pasteur, Paris
Drawing viral "trees of life" that raise intriguing evolutionary questions

10h15 **Sylvain GANDON** (15 min+5)
CEFE, CNRS Montpellier
Pathogens drive the evolution of host resistance diversity

10h35 **Marianne DE PAEPE** (15 min+5)
MICALIS, INRA, Jouy-En-Josas
Phage-bacteria coevolution in the mouse gut

10h55 **COFFEE-BREAK**

11h20 **Nicolas GINET** (15 min+5)
Laboratoire de Chimie Bactérienne, UMR7283, Centre National de la Recherche Scientifique UMR7283, AMU
Smuggling of magnetotaxis-related genes by a temperate bacteriophage in *Magnetospirillum magneticum* AMB-1

11h40 **Camille D'HUMIERES** (15 min+5)
Université Paris Diderot - Paris 7 Sorbonne Paris Cité, Paris - Microbial Evolutionary Genomics, Institut Pasteur de Paris
Impact of antibiotics on human gut phageome

12h **Adélaïde RENARD** (15 min+5)
Equipe Bactéries et risque materno-fœtal UMR 1282 Infectiologie et Santé publique, Paris
Functional impact of A-prophage with *Streptococcus agalactiae* adaptation facing Lactobacillus from the vaginal flora.

12h20 **Araiane BIZE** (15 min+5)
Irstea, UR HBAN, 1 rue Pierre-Gilles de Gennes, F-92761 Antony, France.
K-mer approaches provide valuable insight into mobilome evolution in the domain Archaea

12h40 **LUNCH & POSTER SESSION** *@ Badiane Room & Gallery*

14h30 **Astrid WAHL** (15 min+5)
Laboratoire de Chimie Bactérienne, UMR7283, Centre National de la Recherche Scientifique UMR7283, AMU
Control and maintenance of prophages in *Salmonella enterica*

14h50 **Stéphane CHAILLOU** (15 min+5)
Institut MICALIS, INRA, AgroPArisTech, Université Paris-Saclay. Jouy-en-Josas.
Characterization and modelling of phages population structure in smear washed-rind cheese under various environmental ripening conditions.

15h10 **PHAGE-HOST MOLECULAR INTERACTIONS** *@ Agora*

15h10 **Jennyfer MAHONY** (40 min +5)
UCC Cork
"Some like it sweet" – Host recognition by phages of lactic acid bacteria

15h55 **COFFEE-BREAK**

16h30 **Lia MARQUES GODINHO** (15 min+5)
Département de Virologie, Institut de Biologie Intégrative de la Cellule CNRS UMR9198
Function of GroEL during bacteriophage infection of *Bacillus subtilis*

16h50 **Mathieu DE JODE** (15 min+5)
Institut Pasteur Université Sorbonne Paris Cité (USPC)
A single phage protein efficiently disrupts the host physiology by targeting sigma factors

17h10 **Isabelle BERTRAND** (15 min+5)
Laboratoire de Chimie Physique et Microbiologie pour les Matériaux et l'Environnement Centre National de la Recherche Scientifique: UMR7564, Université de Lorraine
Effects of heat and chlorine on the inactivation and physico-chemical properties of bacteriophage MS2

17h30 **Marie-Agnès PETIT** (15 min+5)
MICrobiologie de l'ALImentation au Service de la Santé humaine, Institut National de la Recherche Agronomique : UMR1319, AgroParisTech
Virulent coliphages isolated from 1 year-old children gut microbiota are sub-dominant compared to temperates, but highly infectious

17H50 **END**

20h00 **DINNER** *@ Cité du vin, Bordeaux (access by tram)*

Tuesday September the 25th

8h30 **WELCOME**

9h00 **THERAPY AND BIOTECHNOLOGY APPLICATIONS** *@ Agora*

9h00 **Joana AZEREDO** (40 min+ 5)
University Minho, Braga
Phages/biofilm interaction: strategies to improve phage efficacy against infectious biofilms

9h45 **Martine BOCCARA** (15 min+5)
Institut Langevin, ESPCI Paris, PSL Research University, 1 rue Jussieu, 75005 Paris, France.
Viruses and membranes vesicles produced by denitrifying bacteria

10h05 **Fernando CLAVIJO** (15 min+5)
Laboratoire de Chimie Bactérienne, UMR7283 Centre National de la Recherche Scientifique - Aix Marseille Université; Institut de Recherche en Horticulture et Semences, INRA, UMR1345; Bioline Agrosciences
Assessing phage therapy against the plant pest *Xylella fastidiosa*

10h25 **Pilar GARCIA** (15 min+5)
Instituto de Productos Lácteos de Asturias, IPLA-CSIC. Spain.
Spanish Network of Bacteriophages and Transducter Elements (FAGOMA)

10h45 **COFFEE-BREAK**

11h15 **Gilbert VERBEKEN** (40 min+5)
Hopital de la Reine Astrid, Bruxelles
"Bacteriophage Therapy: Fact or Fiction in Western Medicine"

12h **Raphaëlle DELATTRE** (15 min+5)
Groupe IBBA, unité BMGE, Institut Pasteur/IAME, Inserm, Paris/service d'anesthésie-réanimation Hôpital Beaujon, Clichy
Preliminary studies on pharmacokinetics and pharmacodynamics of virulent bacteriophages treating *Pseudomonas aeruginosa* and *Escherichia coli* lung infections.

12h20 **Frédéric-Antoine Dauchy** (15 min+5)
CHU Pellegrin Bordeaux
Phagothérapie dans les infections ostéo-articulaires

12h40 **LUNCH**

14h30 Assemblée générale

ECOLOGY & EVOLUTION

Drawing viral " trees of life" that raise intriguing evolutionary questions

Patrick Forterre[1,2], Anthony Woo[1], Julien Guglialmini[3], Alexis Criscuolo[3], Violette Da Cunha[1,2] and Morgan Gaia[1].

1 Institut Pasteur, Département de Microbiologie, 25 rue du Docteur Roux, Paris, France.
2 Institut de Biologie Intégrative de la cellule, Département de Microbiologie, Université Paris-Saclay, Orsay, France.
3 Institut Pasteur Center of Bioinformatics, Biostatistics and Integrative Biology, 25 rue du Docteur Roux, Paris, France.

Is it possible to place viruses in universal trees of life? I will briefly discuss this question and its corollaries: are viruses living? What is a virus? How and when viruses originated? My personal view is that viruses are « here, there and everywhere » in the tree of life because they infect all cellular organisms. However, viruses are polyphyletic and cannot be easily traced to their ancestors. Two major lineages of DNA viruses have been defined that are present in the three cellular domains, Archaea, Bacteria and Eukarya: the Adenovirus/PRD1 lineage and the HK97 lineages, both defined by their major capsid proteins and packaging ATPases. I will present our preliminary attempts to decipher the history of these lineages through phylogenetic analyses. We have obtained universal trees of life of the PRD1 and HK97 « super lineages » that are at odd with either the classical Woese's tree of cellular domains or the fashionable (but probably wrong) 2D (eocyte) tree. This raises exciting questions about the role of viruses in the evolution of the three cellular domains. Notably, we have obtained a robust tree of the "Adenovirus/PRD1 sub-lineage" corresponding to the NucleoCytoplasmic Large DNA Viruses (NCLDV). Moreover, NCLDV can be placed in the tree of life based on their RNA polymerases. Our results indicate that NCLDV have co-evolved with proto-eukaryotes, indicating that they can have played a role in the formation of modern eucaryotes.

Type = oral

Les phages gouvernent la dynamique de la diversité de résistance des bactéries

S. Gandon, H. Chabas, E. Ortega Abboud, A. Nicot

CEFE, Montpellier

La diversité de la résistance aux pathogènes dans les populations hôtes peut avoir des effets importants sur les épidémies. Cependant, l'impact des pathogènes sur cette diversité est bien moins étudié. Nous avons développé un système expérimental permettant de suivre l'influence de l'exposition aux phages sur la dynamique démographique et sur la diversité de résistance CRISPR chez les bactéries hôtes. Nous montrons qu'en l'absence de phages, les populations perdent très rapidement la diversité de résistance. L'exposition à une population de phages non diversifiés mène également à une perte de cette diversité à court terme, mais cette diversité est restaurée au bout de quelques jours suite à l'acquisition de nouvelles résistances. L'exposition à une population de phages diversifiés maintient la diversité initiale de résistance et engendre rapidement une différentiation importante entre populations hôtes. Ces résultats illustrent l'impact de la pression de sélection imposée par les phages sur la démographie et l'évolution de leurs hôtes. Ils démontrent aussi que la coévolution antagoniste peut jouer un rôle majeur dans le maintien de la diversité locale et dans la différentiation entre populations.

Type : : poster

Mots-Clés : CRISPR, résistance, diversité

Phage-bacteria coevolution in the mouse gut

Marianne De Paepe, Jeffrey Cornuault, Marie-Agnès Petit, Elisabeth Moncaut

MICALIS Institut national de la recherche agronomique (INRA), UMR1319

Bacteriophages are very numerous in the gut microbiota, but so far there is little proof that they are important determinants of bacterial mortality in this environment. In mouse studies, phage-mediated bacterial mortality in generally limited to a fraction of the susceptible bacteria, suggesting that physiology complicates phage multiplication in the intestine.

We followed in gnotoxenic mice the population dynamics of a dominant gut microbiota species, *Roseburia intestinalis* L1-82, and its phage Shimadzu. Shimadzu is initially a *R. intestinalis* prophage, that systematically evolves towards ultravirulence (the ability to infect a lysogen) in this simplified gut ecosystem, thanks to the acquisition of mutations in the lysis/lysogeny regulatory region. Ultravirulent phages also systematically acquire mutations in their tail fiber, thanks to a diversity-generating retroelement (DGR). In mice, phage infection killed the majority of susceptible bacteria in a few days, leading to the fast selection of resistant bacteria, mainly through new spacer acquisition in a CRISPR array. Intriguingly, the large majority of virions isolated from mouse feces are unable to infect bacteria *in vitro*. In addition, *in vitro,* bacteria infected by phages seem unable to acquire new spacers and become phage resistant, suggesting that different mechanisms are involved *in vitro* and in the mouse gut.

Altogether, these results that for the gut symbiont *R. intestinalis*, both phage infection and bacterial adaptation are more efficient *in vivo,* which suggests that phage are important killer of this bacterium.

Type : : oral

Key-words : microbiote intestinal ; CRISPR ; prophage

Smuggling of magnetotaxis-related genes by a temperate bacteriophage in *Magnetospirillum magneticum* AMB-1

Nicolas Ginet [1,2], Mireille Ansaldi [1,2]

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[2] Aix Marseille Université

Horizontal gene transfers (HGT) enable rapid acquisition and evolution of new abilities coming from other - sometimes distantly related - organisms. Among the various vectors of HGT in bacteria, viruses (or bacteriophages) play a prominent role by transferring genetic material between individuals either by transduction (specialized or generalized) or, in the case of temperate phages, by lysogenization (stable association of the phage genome - then termed prophage - with the host's). Lysogeny may benefit to the host, for instance by raising pathogenicity of vibrio towards humans (cytotoxin CtxAB responsible for cholera is encoded within the genome of the temperate filamentous phage CTX). The prophage is then passively replicated with the bacterial genome until changes in environmental conditions induce its excision and the resuming of the lytic cycle ; alternatively it may be definitively domesticated within the bacterial genome through mutations, deletions or genetic rearrangements. Bacterial magnetotaxis - the ability to navigate along the geomagnetic field lines - is enabled by a series of specific genes shared by magnetotactic bacteria (MTB). These microorganisms form a polyphyletic group and several lines of evidences suggest that HGT events participated to this diversity. We present here evidences that the prophage FRODO found in the genome of the model MTB bacterium *Magnetospirillum magneticum* AMB-1 can excise from its host's genome and form viral particles that transport the magnetotaxis-related genes clustered in the Magnetotactic Islet specifically belonging to this strain.

Type : : oral

Key-words : Prophage ; horizontal gene transfer ; magnetotactic bacteria

Impact of antibiotics on human gut phageome

Camille D'humieres [1, 2, 3, 4, 5], Marie Touchon[4, 5], Sara Dion[3], Erick Denamur [6, 3, 7], Eduardo Rocha [4, 5], Predires Group

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[7] Université Paris Diderot - Paris 7

The microbiota of the human gut sometimes called « the second brain » is a very complex and rich community composed of bacteria, archaea, protozoa, fungi and viruses, coexisting in equilibrium. The study of the dynamics and stability of the human gut microbiota is essential to understand its role in disease, diagnosis, treatment and prevention. Bacteria and their viruses (bacteriophages) are the most important members of this community. In the recent years bacteriophages from gut have started to receive attention, contribution of phages to intestinal microbiota ecology and their effect on human host are just beginning to be highlighted.
In this work, we studied the impact of antibiotics on the human gut phageome. We compared two third generation cephalosporins with distinct pharmacokinetic characteristics, ceftriaxone having higher biliary elimination than cefotaxime. A prospective, monocenter, open, randomized clinical trial in 22 healthy volunteers treated by the intravenous route either with ceftriaxone (1g/24 hours) or cefotaxime (1g/8 hours) for 3 days was performed as part of a project funded by the “Agence Nationale de la Recherche”. This allowed the follow-up of individuals for six months, before, during and after treatment. Preliminary results showed a difference between the two cephalosporins on human phageome diversity. Healthy volunteers treated by ceftriaxone (higher biliary elimination) showed stronger perturbations of their gut phageome than the volunteers treated with cefotaxime, with a drastic decrease of the predominant phage contigs observed just after treatment and a return to the baseline level ten days after treatment. More analyses will be performed to identify the drivers of the observed phageome disruption.

Type : : oral
Thématiques : Ecologie et évolution
Mots-Clés : Instestinal microbiote phageome antibiotic

Functional impact of A-prophage with *Streptococcus agalactiae* adaptation facing Lactobacillus from the vaginal flora.

Adélaïde Renard [1], Pauline Cantin [1], Sandra Dos Santos Borges [2], Marion Lacasse [1], Anne-Sophie Valentin [1], Laurent Mereghetti [1], Roland Quentin [1], Nathalie Van Der Mee-Marquet [1]

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Context*: Streptococcus agalactiae* (GBS) has become since the 1960s the leading cause of neonatal infection in industrialised countries. GBS neonatal infections are mostly associated with the clonal complex CC17. GBS is colonizing the vaginal tract in 1/3 of pregnant women. The CC17-GBS neonatal infections mainly occur during delivery following transmission of GBS to neonates from mothers carrying GBS in their vagina. Vaginal microbiota, dominated by *Lactobacillus crispatus*, prevent vaginal colonization by pathogens, including GBS, and has been suggested playing a protective role against GBS neonatal infection. Using whole genome sequencing of 14 GBS strains representative of the species, we identified 22 prophages clustered into 6 groups A to F. CC17 GBS strains 10avor10o n10e for neonatal infections frequently carry A-prophages inserted near bacterial genes involved in adaptation, stress resistance or virulence, and carrying genes associated to defense systems, adaptive response and putative virulence factor.

Our hypothesis: prophage A may have a positive 10avor10o n GBS adaptation facing Lactobacilli, and thus may 10avor GBS colonization into the vagina and consequent GBS neonatal infections.

Strategy and results: First, we have constructed by deletion or addition of a A-prophage, one couple of isogenic GBS strains differing by their prophage content. Second, we have studied and compared the isogenic strains regarding (1) their growth curves with or without the presence of *Lactobacillus* culture supernatant, and (2) their capacity to form biofilm. Our findings showed significantly different results for prophage-free and lysogenic GBS. We first demonstrated major differences regarding (1) the maximal growth of strains (+15% for the lysogenic strain when compared with the prophage-free strain), (2) the growth rate of strains (in the presence of *Lactobacillus* supernatant, the generation time for the prophage free strain was +43% to +95% compared with the lysogenic strain), and (3) biofilm formation (Biofilm Formation Index twice as important for lysogenic strain when compared with prophage-free GBS).

Conclusion and perspectives. Our data suggest a functional impact of A-prophage carried by GBS strains of CC17. Further investigations are currently performed to investigate the molecular mechanisms associated with the phenotypes observed.

Type : : oral

Key-words : *Streptococcus agalactiae* ; temperate phages.

K-mer approaches provide valuable insight into mobilome evolution in the domain Archaea

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Kmer approaches have greatly developed in recent years, largely driven by the advent of next-generation sequencing. Their speed and automatism, since they are annotation independent, are major advantages. The interest of applying k-mer approaches to study the mobilome is only starting to be explored, with many efforts oriented towards viral metagenomics [1, 2]. We evaluated the potential of applying simple k-mer approaches to understand the evolutionary history of mobile elements by focusing on viruses and plasmids from the domain Archaea, which includes specific and well-defined extrachromosomal element families [3].

We selected more than 590 cell, virus and plasmid genomes, originating from 11 distinct orders of archaeal cells. We subsequently implemented multivariate and statistical analyses to identify the factors underlying the 5-mer composition of mobile element genomes in the domain Archaea.

The mobile element families, the genome GC contents and the phylogenetic position of the host at the taxonomic level of the order were identified as major explanatory factors. Genomes overall grouped according to the host order, except for the haloarchaea, all belonging to the class Halobacteria, which formed a single supergroup. Within each group, cells tended to cluster together while viruses and plasmids tended to cluster according to their own taxonomic family. This was only a general trend as a number of exceptions were observed, with an inhomogeneous level of shuffling across the dataset. The observed pattern likely results from the combined influence of co-evolution and environmental constraints, highly contrasted among those archaea which comprise methanogens and diverse extremophiles.

It confirms the potential of k-mer signal for extrachromosomal contig analysis [1, 2, 4], in particular for their taxonomic assignation. Another application could be the detection of singular evolutionary trajectories by focusing on outliers. Indeed, previously-known and one new case of recent host transfers were efficiently detected during the present study. K-mer approaches rely on a distinct informational content than the more elaborate gene sharing networks and appear as complementary.

References

1, Galiez C et al, *Bioinformatics* 2017, **33**:3113-3114; 2, Iranzo J et al, *Journal of Virology* 2016, **90**:1104311055; 3, Ren J et al, *Microbiome* 2017, **5**(1):69.4, Krawczyk PS et al, *Nucleic Acids Research* 2018:gkx1321-gkx1321.

Control and maintenance of prophages in *Salmonella enterica*

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Thanks to the increasing amount of genomic data, the importance of bacteriophages in horizontal gene transfer (HGT) is largely acknowledged. Bacterial genomes typically harbor multiple defective or functional prophages carrying a wide range of genes that potentially provide new abilities. On one hand, these genetic elements may be selected because they confer a physiological advantage, such as new virulence factors or adaptive traits. On the other hand, uncontrolled expression of prophage genes could be detrimental to the host. Thus, genome evolution by HGT requires a precise equilibrium between the repression and expression of newly acquired genes.
Our goal is to identify general strategies, other than phage repressor based, that are responsible for the maintenance of prophage genes in bacterial genomes. In this context, we have previously shown that the transcription terminator Rho is involved in prophage maintenance in *E. coli* (Menouni et al, 2013). Here, we use *Salmonella enterica* serovar Typhimurium, a primary enteric pathogen, as a model. Usually, *S. enterica* genomes carry 4-5 functional prophages and their genes make up around 30 % of the pool of accessory genes.
To investigate the effect of global regulators on the maintenance of *S. enterica* specific prophages, we designed a targeted approach: the excision level of functional and defective prophages was tested in various mutants of these bacterial regulators by using multiplex and quantitative PCR. Our results show that HNS, a known negative regulator of horizontally acquired genes, negatively controls the excision of Gifsy1 prophage. In contrast to phage lambda or P22, induction of the Gifsy prophage family is not due to repressor cleavage, but rather to its sequestration by an Anti-repressor protein produced when the LexA-dependant SOS-response is activated (Lemire et al, 2011). We show that the Gifsy1-encoded anti-repressor gene *gfoA* is the actual target of HNS and propose the following model: In the absence of HNS, more GfoA anti-repressor protein is produced which then sequesters the GfoR repressor leading to induction of Gisfy1 prophage. We will perform further experiments to clarify if HNS directly regulates *gfoA*. If this is the case, where exactly does HNS bind in comparison to LexA for whom a well conserved binding box is present in the promoter region of *gfoA*?
Understanding how the bacterial host prevents prophage induction will give a clue on the mechanisms involved in cooptation and co-evolution of prophages within their host.

Type : oral

Key-words : HGT, prophages.

Characterization and modelling of phages population structure in smear washed-rind cheese under various environmental ripening conditions.

Eric DUGAT-BONY, Marie-Agnès PETIT, Julien LOSSOUARN and Stéphane CHAILLOU*.

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Génie Microbiologique des procédés et des aliments, INRA, AgroParisTech, Unviversité Paris-saclay, Grignon.

Counting and characterizing phages population and diversity in complex microbial ecosytems is a difficult task. Moreover, phages have highly mosaic genomes and their assembly out of metagenomic sequencing data is still a challenge that is not completely solved. Without the reconstruction of full phage genome sequences it is difficult to assess the bacterial host targeted by the phages present in the ecosystems and thus to assess the role of these viruses in the regulation of the bacterial population.

In the frame of the VIROME ACCESS projet (INRA metaprogram on microbial ecosystem and meta-omics), we have set up a strategy to improve our characterization of phages genomic diversity in complex ecosystems (solid matrix) choosing the rind of smear-type cheese (Epoisses) as a model. We have first improved our viral DNA extraction from these ecosystems by comparing several purification steps and analyzing the yield of viral DNA and the quality of phage genome assembly from shotgun pair-end MiSeq sequencing. Our second strategy was to apply our improved protocol to an experimental design in which ripening conditions were modulated according to two physical parameters (level of oxygen and temperature of ripening). Using factorial central composite design, the structure of bacterial and yeast, whose diversity were characterized by ITS and 16S rDNA V3-V4 amplicon sequencing, were modelled according to these parameters. In parallel, viral DNA were sequenced and the different phages genomes were assembled and characterized for life style (virulent, lysogenic) and their potential bacterial host. The populations of phages were also modelled according the physical parameters applied during the ripening in order to correlate the changes in phages populations to those observed in the bacterial populations.

The possibility to extrapolate our strategy to more complex ecosystems will be discussed.

Type : oral

Prophages and other mobile genetic elements as regulatory switches

Fanny Wegner, Eduardo Rocha

Génomique évolutive des Microbes - Institut Pasteur de Paris, CNRS UMR3525

Active lysogeny is a form of phage-host interaction in which temperate phages are integrated into functional open reading frames. Controlled excision under specific conditions leads to the complete reconstitution of the gene, whilst re-integration of these elements leads to the halt of its expression. This provides a complex regulatory mechanism of bacterial gene expression. Such regulatory switches have been observed in genes relating to competence or sporulation, and can occur with other mobilizable elements beyond phages.

Here, we present the screen of the complete genomes of 363 *Salmonella enterica*and 437 *Escherichia coli* strains for the presence of interrupted genes and the potential of intact or cryptic prophages (as well as other integrative elements) to act as regulatory switches. Our findings indicate that interrupted genes are particularly enriched for functions relating to replication, recombination and repair. We further identify candidates for experimental validation.

Active lysogeny highlights the potential of microbes to co-adapt their mobile genetic elements towards genetic regulation, which is key for pathogenicity or adaptation to new environments.

Type : : poster

Mots-Clés : lysogeny ; coevolution

PHAGE-HOST MOLECULAR INTERACTIONS

Function of GroEL during bacteriophage infection of *Bacillus subtilis*

Lia Marques Godinho [1], Audrey Labarde [1], Eric Jacquet [2], Paulo Tavares [1]

[1] Département de Virologie, Institut de Biologie Intégrative de la Cellule CNRS UMR9198
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Molecular chaperones play an essential role in the folding of nascent chain polypeptides, refolding of misfolded proteins, and other house-keeping and stress-related functions. GroEL is known to play a role in viral infection mediating the folding of capsid proteins during morphogenesis of several Enterobacteriaceae phages.
SPP1 is a lytic bacteriophage infecting the bacterium *Bacillus subtilis*. SPP1 is a dsDNA virus that belongs to the *Siphoviridae* family and acts as a model system for viruses of Gram-positive bacteria. During its infection cycle, SPP1 massively hijacks the host's resources, leading to synthesis of >9 Mbp of viral DNA and 150 000 polypeptide chains to produce 200 virions in 30 minutes, highly challenging the cell.
Our goal in this work was to investigate the dependence of SPP1 on *B. subtilis* GroEL. We constructed an isogenic strain of *B. subtilis* with a knock-down of the essential gene *groEL* taking advantage of an available library of knock-down mutants of *B. subtilis* by CRISPR-Cas9. The infection dynamics of SPP1, as well as SPP1 DNA replication and viral particle assembly were investigated using quantitative PCR and fluorescence microscopy, respectively. Formation of viral particles was the most affected step of the SPP1 infection cycle. Electron microscopy of phage structures found in lysates followed by western blot analysis revealed a defect in phage capsid assembly during infection of the *groEL* knock-down mutant. This knock-down has also a major impact in the infection of *B subtilis* phages phi29 and SPO1. The step(s) of the viral cycle affected is under investigation.

Type : : oral

Mots-Clés : *Bacillus subtilis* ; SPP1 ; chaperonins. groEL

A single phage protein efficiently disrupts the host physiology by targeting sigma factors

Mathieu De Jode, Anne Chevallereau, Laurent Debarbieux

Institut Pasteur Université Sorbonne Paris Cité (USPC)

A bacterial cell infected by a phage becomes a viral factory (or virocell) as most of its resources are dedicated to virions production. To investigate this transformation of the bacteria into a virocell, we are studying the infection of the opportunistic pathogen *Pseudomonas aeruginosa* by the phage PAK_P3. Using a global transcriptomic approach, we found that PAK_P3 alters the transcription of over a thousand host genes and temporally regulates the expression of its own genes. Amongst the early expressed genes, we are now focusing our attention on *gp92*, which is one of the few non-structural genes conserved between *Kpp10virus* and *Pakpunavirus* genera.
We discovered that ectopic expression of *gp92* in *P. aeruginosa* alters cells morphology: they become spherical instead of rod shaped. This change in morphology does not affect cell growth rate nor cell viability. Additional molecular studies revealed that Gp92 possesses an unusual membrane anchoring amino-terminal sequence that is absolutely required for this phenotype. Next, using a bacterial two-hybrid assay we identified the anti-sigma factor MucA and its target the sigma factor AlgU as putative partners of Gp92. Several assays confirmed that expression of *gp92* disrupts the AlgU mediated membrane stress response. Moreover, a mass spectrometry analysis revealed that expression of *gp92* leads to a large modification of the cell proteome, including the overexpression of RpoH and FliA, two other sigma factors. Therefore, the expression of this single phage gene, affecting three sigma factors, alters the regulation of expression of almost 1000 host's genes.
We propose that early expressed proteins like Gp92 allow phages to efficiently disrupt the host cell physiology, and transform a bacterial cell into a viral factory.

Type : : oral

Mots-Clés : phage ; host ; protein ; sigma factors

Effets de la chaleur et du chlore sur l'inactivation et les caractéristiques physico-chimiques du bactériophage MS2

Adrien Brié [1,2], Christophe Gantzer [1], Nicolas Boudaud [2], Isabelle Bertrand [1]

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Les virus entériques pathogènes et les bactériophages sont soumis, en dehors de leur hôte, à de nombreux facteurs conduisant à leur inactivation. Parmi eux, la chaleur et le chlore sont les traitements les plus fréquemment utilisés pour inactiver les virus respectivement dans l'industrie agro-alimentaire et le traitement des eaux. Les effets de la chaleur et du chlore sur les caractéristiques physico-chimiques des particules virales sont encore mal connues. Nos travaux ont été réalisés avec le bactériophage ARN F-spécifique MS2 (10^{14} UFP/mL) utilisé comme modèle des virus entériques pathogènes et notamment des norovirus.

Au cours de l'exposition à la chaleur (60°C pendant 10, 30 et 60 min), l'inactivation a atteint -1 à -2,7 log10 et une diminution de la charge électrostatique négative a été observée. De façon intéressante, une augmentation de l'hydrophobie de surface a été notée uniquement pour les phages ayant conservé leur caractère infectieux. Après exposition à ces conditions, les phages ont tous conservé leur résistance à la RNase. Par contre, l'exposition à une température de 72°C pendant 10 min a conduit à une inactivation massive (-8 log10) avec rupture des capsides d'après les observations de microscopie électronique à transmission confirmées par les tests à la RNase.

L'exposition des phages MS2 à l'hypochlorite de sodium (100 et 200 mg/L, 10 min) a entraîné une inactivation de -1,2 et -3,5 log10, et une faible diminution de la charge électrostatique négative; aucune modification de l'hydrophobie ou de la perméabilité de la capside à la RNase n'a été notée. L'utilisation d'une sonde hydrophobe SYPRO Orange permettant de déterminer le point de rupture des protéines a montré une diminution du Tm de la protéine de capside suggérant sa fragilisation par le chlore.

Lorsque le phage MS2 a été exposé au chlore (100 mg/L, 10 min) puis à la chaleur (55°C ou 60°C, 10 min), une inactivation (-1,9 et -3,2 log10) et une perméabilité de la capside à la RNase supérieures à celles obtenues pour ces deux traitements isolés ont été observées. La modification la plus marquante a été une très forte augmentation de l'hydrophobie de surface uniquement pour les phages MS2 ayant conservé leur caractère infectieux.

Ainsi, les traitements associant ces deux paramètres devraient utiliser le chlore puis la chaleur pour un effet optimal. L'expression de domaines hydrophobes à la surface des capsides au cours des traitements auxquels sont soumis les virus pourrait jouer un rôle important dans la distinction entre virus infectieux et inactivés.

Type : : oral

Mots-Clés : MS2 ; chaleur ; chlore ; inactivation ; hydrophobie

Virulent coliphages isolated from 1 year-old children gut microbiota are sub-dominant compared to temperates, but highly infectious

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A link between one-year old infant gut microbiota and asthma predisposition starts to emerge from several studies. Since bacteriophages constitute an important component
of the gut microbiome, it is of high interest to investigate if they could influence early life microbiota colonization and maturation and whether they play a role in the risk of later asthmatic disease development. To do that, we collaborate within 'Earlyvir' European joint initiative aiming at studying the infant viromes.

Since host prediction from phage sequences still represents a bio-informatics challenge, culturomics might be an interesting alternative to apprehend which species of the microbiota are phage targets. Escherichia coli is one of the first bacterial species to colonize the infant's gut, and still represents 6% of total OTUs at 1 year.
In 24% of the virome samples, coliphages could be directly cultivated on indicator strains.
A collection of 75 purified coliphages was further studied for its host range, over a selection of 90 E. coli strains representative of the cohort. 28% of them were virulent, the remaining ones temperate. Strain response was markedly different in the two phage groups: whereas 93% of the tested strains were sensitive to at leat one virulent phage, only 18% of the strains were sensitive to at least one temperate phage. The host range was also very different in the two groups, with 30% of the virulent phages killing at least 30% of the strains, whereas none of the temperate phages could kill 30% of the strains. We conclude that the virulent fraction has mostly all infective power, and broad host range. In the light of virome sequence analyses, this suggests that not all phages will be equal in terms of impact on the microbiota.

Type : : oral

Mots-Clés : phAPEC8 ; ESSI ; 2 ; VpaE1 ; Stevie ; Gluttony ; T5

Nitric oxide-driven prophage maintenance involves unsuspected activity of NorV(W) reductase

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Bacterial genomes contain large amounts of prophages, either functional or defective. All these prophages contribute to bacterial genome evolution by providing an additional pool of genes that sometimes accommodate new properties to the host, a phenomenon called lysogenic conversion. Prophages usually highjack the host stress response signalisation to resume a lytic cycle when conditions become threatening for the host and therefore for the integrated prophage.
This work shows that nitric oxide serves as a maintenance signal and induces the production of NorV(W) reductase, which in turn prevents prophage induction independently of its usual activity. Surprisingly, nitric oxide, which is a potent nitrosative agent responsible for many cellular damages, does not promote prophage induction but rather maintains and counteracts the SOS-response outcome. Counteracting prophage induction makes particularly sense for enterobacteria when exposed to nitric oxide produced in the gut during inflammation or through their own anaerobic respiration.

Type : : poster

Mots-Clés : Prophages ; Maintien lysogénie ; détoxification du NO ; NorVW ; Répresseur de lyse CI

AppY, a phage-encoded protein central to the bacterial regulatory network

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Bacterial genome diversity is largely due to prophages, which are viral genomes integrated into the ones of bacteria. Most prophage genes are silent, but those that are expressed can provide new properties to their host. In particular, AppY, a transcriptional regulator encoded by the DLP12 prophage in *E. coli* K12, increases the level of RpoS when overproduced. RpoS is the major sigma factor during stationary phase and under many stress conditions in γ-proteobacteria. This factor is highly regulated, in particular *via* changes in protein stability. Indeed, once produced, RpoS is actively degraded by the ClpXP protease. To be recognized as a protease substrate, RpoS interacts with an adaptor protein called RssB, which brings RpoS to the degradation machinery. My recent results show that AppY directly interacts with RssB, the adaptor protein, suggesting a new anti-adaptor function for this protein, considered so far as acting only on transcription. Moreover, it has been suggested that AppY could regulate around 30 genes in the cell. In order to identify these potential AppY targets, we performed RNA-seq experiments. The characterization of some of the targets shows that AppY is involved in resistance to acid stress but also in the inhibition of flagella synthesis and in biofilm formation. Overall, our results suggest a broader role for AppY than previously anticipated. This work brings to light the regulatory pathways existing between genes from bacterial and phage origins as well as the impact of these regulations on bacterial physiology and adaptation to different stress conditions.

Type : : poster

Mots-Clés : stress response ; *E. coli* ; regulation ; lysogeny

Analyse de l'adhésine des phages de type T4 et recherche d'effet synergique entre phages lytiques et bio-molécules antibactériennes

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L'utilisation des bactériophages en thérapie contre les infections bactériennes multirésistantes aux antibiotiques est une alternative prometteuse. Pour cela, la connaissance détaillée des interactions moléculaires entre le phage et son hôte bactérien, déterminant la spécificité, est nécessaire. Le spectre d'hôte d'un phage est majoritairement déterminé par les adhésines phagiques. Leur reconnaissance spécifique des récepteurs situés à la surface bactérienne constitue la première étape de l'adsorption des phages. Chez la majorité des phages lytiques de Type T4, de telles adhésines sont situées à l'extrémité des fibres caudales longues et codées par le gène *38*. L'adhésine gp38 est composée de quatres Segments HyperVariables (HVS) séparés par cinq Motifs Riches en Glycine très conservés (GRM). Cependant, les déterminants de l'adhésine impliqués dans sa spécificité et dans le maintien de sa structure sont encore mal connus.
Ainsi, le rôle des différents composants (HVS et GRM) a été examiné par une analyse comparative de nombreuses adhésines gp38, suivie d'une analyse du spectre d'hôte. Une corrélation a été observée entre motif d'HVS et récepteur bactérien reconnus. Enfin, une modification de la spécificité des adhésines a été obtenue grâce à l'échange d'HVS entre deux phages. Cette analyse apporte de nouveaux éléments sur l'interaction entre le phage et son hôte bactérien, qui pourraient être exploités pour améliorer la thérapie antibactérienne.
Aussi, comme décrit dans de précédents travaux, l'utilisation de l'effet synergique (l'effet PAS) entre phage et antibiotique dans un traitement pourrait s'avérer plus efficace. C'est dans cette perspective que les travaux en cours sont dirigés vers d'autres alternatives thérapeutiques. En effet, certaines molécules antibactériennes comme celle d'huiles essentielles aux pouvoirs antibactériens et permettant un effet synergique avec les phages sont en cours d'exploitation. Pour finir nous avons isolé de nouveaux phages lytiques, recueillis sur deux sites naturels au Maroc, ayant une spécificité pour deux souches bactériennes pathogènes de l'Homme (isolées en milieu hospitalier). Ces isolats phagiques et bactériens constituent des éléments précieux pour enrichir notre banque de bactériophages spécifiques des souches pathogènes rencontrés sur le territoire Marocain. De plus, une étude comparative des interactions moléculaires entre les systèmes hôtes-phages étudiés à Toulouse et ceux isolés au Maroc, suivi d'une détermination de la meilleure molécule provoquant un effet synergique lors de thérapie combinée, pourront amenées des éléments important dans l'utilisation de phages en thérapie ou dans d'autres applications.

Type : : poster
Key-words: T4

Characterization of the long elusive nuclease of bacteriophage T5

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Phage T5 infects *Escherichia coli* and injects its genome in an original two-step mechanism: in the First Step Transfer (FST), only 8% of the phage DNA enters the host cell. The transfer pauses then for several minutes before DNA entry resumes to completion (Second Step Transfer, SST). The FST is accompanied by a very rapid and massive destruction of bacterial DNA (50 % decrease in labeled DNA within 4 min of infection). The identity of the phage T5 DNase has remained elusive for sixty years, as none of the phage proteins encoded on the FST-DNA resemble known nucleases. However, *A1*, a gene carried by FST-DNA, appears to control host DNA degradation as well as the SST. In this study we investigated the role of the 62-kDa protein A1 in DNA degradation *in vitro* and in the bacterial cell.

In the C-terminal half of A1, we identified several motifs that are conserved in a large family of metallophosphatases including the DNA repair and recombination nucleases Mre11/SBcD/gp46. Purified A1 exhibited Mn-dependent DNase activity *in vitro* on ssDNA, but not dsDNA. Using fluorescence microcopy of *E. coli* cells, we observed a rapid decrease in bacterial DNA staining with DAPI upon ectopic expression of *A1*. Moreover, we frequently saw the formation of a focus of fluorescence, suggesting a dramatic reorganization of the bacterial nucleoid. Mutations in putative catalytic amino-acid residues abolished nuclease activity in vitro as well as in vivo. Taken together, our results indicate that A1 is the long elusive early-encoded DNase of phage T5. Future work will aim to understand how the DNase activity of A1, which acts exclusively on ssDNA *in vitro*, facilitates the digestion of genomic double-stranded DNA *in vivo*.

Type : poster

Study of the structure of T5 phage tail tip complex complex using cryo-electron microscopy

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T5 phage is a caudal virus from the Siphoviridae family, which accounts for about 60% of the tailed phages and characterized by a long flexible tail. At its distal end, T5 tail harbours the tail tip complex, which is involved in cell recognition (through the receptor binding protein pb5), cell wall perforation and safe viral DNA channeling to the bacterium cytoplasm.

We aim at obtaining structural information about the tail tip complex, before and after its interaction with the membrane receptor FhuA, as little is known on the mechanisms leading to DNA ejection after binding to the host. Here, we present preliminary work about the structure of T5 tail tip complex, using mainly cryo-electron microscopy (cryo-EM) and single particle analysis.

We produced T5 phage tails from the T5amD20 mutant phage, which has an amber mutation in the major caspid protein gene, allowing the production of fully functional tails. T5 tails were then prepared for cryo-EM (ie. vitrified) and ~ 3200 micrographs were acquired using state of the art Titan Krios electron microscope and K2 Gatan direct electron detector. 10500 individual T5 tail tip particles were obtained from these micrographs and are currently being processed to obtain a high-resolution 3D structure.

This is work in progress and more results will be presented on the poster.

Type : : poster

Mots-Clés : cryo ; electron microscopy ; membrane/pathogen interaction ; T5 phage ; tail tip complex

THERAPY AND BIOTECHNOLOGY APPLICATIONS

Viruses and membrane vesicles produced by denitrifying bacteria

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Excess input of nitrogen from agriculture and water facilities are known to pollute rivers (Xia et al. 2018). To overcome this problem, denitrifying bacteria are currently used in water purification, to transform nitrate into dinitrogen. However denitrification is not performed at maximum yield despite favourable physicochemical conditions. We hypothesize that. bacteriophages could influence denitrification in sewage treatment plants or river as it has been demonstrated for long, in industrial fermentations (de Melo et al. 2018).
To test this hypothesis we studied two denitrifying bacteria isolated from river. We showed the presence in their genome of temperate viruses, which we genetically and morphologically characterized. Using interferometric microscope, we observed in mitomycin-induced phage lysates, the production of a large amount of particles less dense and more heterogeneous in size than phages. We interpreted them as membrane vesicles. Membrane vesicles in addition of being the vehicles of protein and nucleic acids between bacteria have recently been shown to be vehicles for viruses (Tzipilevich et al., 2017). All these observations will be discussed in light of efficiency of denitrification process in sewage treatment plants or river sediment.

Xia X., et al .(2018) The cycle of nitrogen in river systems: sources, transformation, and flux. Environ. Sci.: Processes Impacts, 20, 863–891.
Tzipilevich E, Habusha M, Ben-Yehuda S. (2017) Acquisition of Phage Sensitivity by Bacteria through Exchange of Phage Receptors. Cell. 168(1-2):186-199.
Gonçalves de Melo A., Levesque S., Moineau S. (2018) Phages as friends and enemies in food processing. Current Opinion in Biotechnology 49:185-190

Type: poster

Assessing phage therapy against the plant pest *Xylella fastidiosa*

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Xylella fastidiosa (*Xf*) is a slow growing Gram-negative plant-pathogenic bacterium emerging in Asia and Europe. Long-known in the Americas, this xylem-specialized bacterium is associated with numerous socio-economically important plant diseases. *Xf* is transmitted by xylem feeding insects and belongs to the *Xanthomonadaceae* family. Six different subspecies of *Xf* have been reported so far: *fastidiosa* (*Xff*), *multiplex* (*Xfm*), *pauca* (*Xfp*), *sandyi* (*Xfs*), *tashke* (*Xft*) and *morus* (*Xfmor*). Listed as a quarantine pest in Europe, three subspecies (*Xfp*, *Xfm Xff* and *Xfs*) were recently detected in Europe, probably introduced through commercial exchanges and causing a variety of diseases such as the Leaf Scorch of Olive trees in Italy (Jacques et al. 2016 ; Denancé et al., 2017).
In the absence of efficient and authorized methods to control *Xf*, a major challenge is to develop environmentally friendly biotechnologies to control this plant disease. In this context, we propose the use of bacterial specific viruses, known as bacteriophages, to control *Xf* infections as recently proposed to control destructive bacterial crop diseases. A few phage cocktails became recently available to treat diseases caused by *Xanthomonadaceae* or *Ralstonia solanacearum* (Buttimer et al., 2017).
Different aspects of my work dedicated to phage therapy against *Xf* will be addressed: (i) Using a bioinformatics approach, I first estimated the prophage contents of various *Xf* genomes as they may interfere with efficient phage superinfection, (ii) I will report the isolation of various lytic phages from different environmental sources such as *Xf* infected plants and insect vectors, as well as more generalist sources such as raw sewage influents. To get rid of the difficulties linked to *Xf* culturing, I developed an indirect approach using *X. albilineans* a fast-growing organism and close relative of *Xf* to enrich naturally occurring phages. The characterization of the isolated phages is ongoing, and we are improving *Xf* culture conditions to assay the host range of the isolated phages and test their ability to infect the different subspecies of *Xf.*

Type : oral

Preliminary studies on pharmacokinetics and pharmacodynamics of virulent bacteriophages treating *Pseudomonas aeruginosa* and *Escherichia coli* lung infections

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While the compassionate treatment of antibiotic resistant infections by bacteriophages is becoming more and more frequent in Western countries, data about the dose and the timing required to ensure a successful treatment remain mostly empirical.
Over the past decade we have isolated several virulent bacteriophages that were tested in a murine model of acute pulmonary infection. Here we investigated in mice pharmacokinetics (concentration-time courses in the body resulting from administration of a drug dose) and pharmacodynamics (observed effects resulting from a given drug concentration) of several of these bacteriophages.
First, we record bacteriophage distribution over time into several organs (lungs, spleen, liver, kidneys) and blood compartment after an intranasal or a systemic administration in healthy animals. Second, using our model of acute pneumonia, we observed over time the bio-distribution in the organs and blood compartment of bacteriophages administrated by intranasal or systemic routes. In each organ we compared the relative amount of bacteria and bacteriophages.
Our data provide valuable information on bacteriophages half-life, their elimination route and their ability to reach the bloodstream. In the future, we aim to implement a pharmacokinetics / pharmacodynamics model of pulmonary phage-therapy.

Type: poster

Spanish Network of Bacteriophages and Transducter Elements (FAGOMA)

Pilar García

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The study of bacteriophage biology has delivered and still provides clues to understand multiple biosynthetic and gene regulation processes, due to their relative simplicity in comparison with that of cellular organisms. They have also been a great source of valuable biotechnological tools. Because of this, but also due to the environmental influence of phages by modulating the predominant bacterial microbiota along with their potential applications in infectious therapies and in food safety, research on bacteriophages maintains a constant and steady growth. In this context, the Spanish Network of Bacteriophages and Transducer Elements called “Fagoma” was created in 2011 to join several research groups with a notorious international prestige that work on basic and applied aspects of bacteriophages. Along this time, the Spanish Net has promoted four meetings and several exchanges of students. In addition, the Net has facilitated the common analysis of data obtained by the different groups, the sharing of methodologies and the launch of collaborations as well as the emergence of new ideas that have promoted cooperative work between different laboratories, all of which have contributed to the advance of knowledge. Of note, the current Net is being useful because, at present, the promoting groups have a good knowledge of the interests and methodologies of the different members of the consortium, thus facilitating the synergies associated to collaborative research.

Type : : oral

Mots-Clés : Phage studies, network, Fagoma

Bacteriophage therapy in Western medicine

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For hundreds of millions of years, bacteriophages – the viral parasites of bacteria – protect Earth's biosphere against bacterial overgrowth. Today, bacteriophages could help address the antibiotic resistance crisis that affects all of society. The greatest hurdle to the introduction of bacteriophage therapy in Western medicine is the lack of an appropriate regulatory framework. Belgium is now implementing a pragmatic bacteriophage therapy framework that centers on magisterial bacteriophage preparations. This keynote-talk will discuss regulatory frames and (magisterial) bacteriophage production issues… Inspiration for others, as implemented in Belgium…

Type: oral

Characterization of new bacteriophages for the biocontrol of a plant bacterial pathogen

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Bacterial wilt (Bw) caused by the *Ralstonia solanacearum* species complex (RSSC) is among the most important plant diseases worldwide, severely affecting a high number of crops and ornamental plants. In tropical regions such as the South West Indian Ocean (SWIO), Bw has a major negative impact in local agriculture. Genetic studies of the RSSC have resulted in the hierarchic classification of these bacteria into phylotypes, sequevars and haplotypes; and their worldwide epidemiology has been extensively studied. The difficulties to control Bw are related to high bacterial fitness and genetic diversity, and current intensive agriculture practices. The aims of the present study were to isolate and characterize new bacteriophages (phages) capable of infecting the RSSC, which could be used as a biocontrol tool. Twenty-six phages infecting RSSC were isolated from agricultural samples collected in Reunion Island, in the SWIO. Host range of phages was tested measuring their capacity of replication in 52 RSSC strains, from local or international origin; and 3 bacteria from different but close genera. We demonstrate that all phages preferentially attack the most abundant RSSC variant in the region, sequevar I-31, but harbor a high host range variability. We distinguish specialist and generalist phages regarding their capacity to target the genetic diversity of RSSC, with phages capable of infecting phylotypes still not detected in the Island. Nonetheless, generalist phages restrict their action to RSSC and none of the other bacterial genera are targeted. The studied phages also show differences in their efficiency at decreasing bacterial growth of the most problematic strain of the SWIO (sequevar I-31, haplotype MT035). We find that efficacy and host range in these phages are negatively correlated, with specialist phages being more efficient at controlling the region's RSSC strain than generalist ones. Importantly, we demonstrate this kind of evolutionary trade-off in phages for the first time to our knowledge. All in all, we have partially characterized the first collection of SWIO phages, and advanced the basis for the application of phages as biocontrol measures in the management of Bw. In particular, four phages have the ideal host range and efficacy traits to be considered as candidates for the biocontrol of Bw in the SWIO. We are currently performing molecular analysis and *in vivo* experiments of the isolated phages in order to evaluate their capacity to protect tomato plants from the bacterial disease. The agro-ecological controlled context represented by RSSC affecting tomato greenhouses in Reunion Island provides with a unique opportunity to test phages in a simplified but natural environment.

New Optical Method for detecting and counting biotic nanoparticles

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We have developed an optical microscope for detecting, counting and sizing nanoparticles.
The principle of the detection is based on the interferences produced between an incident incoherent light and the very weak amount of light scattered by the illuminated particle.
Moreover, each detected particle undergoing Brownian motion is tracked over a few frames recorded by the microscope. By coupling the information dealing with both the scattered signal and the spatial diffusion of the particles, one can reach the particles sizes and density.
In the association with Quattrocento, a structure specialized in the creation of innovative companies, the Langevin Institute and PSL have created the Myriade start-up for the detection and characterization of nanoparticles by this innovative method of optical interferometry.
Among these nanoparticles: viruses, vesicles, metal oxides, etc., which opens the way to applications in the fields of medicine, biology and the environment.
The results of some tested nanoparticles will be presented.

Type : : poster

Key-words : Optical microscopie ; Interference ; nanoparticles Counting and Detection ; Brownian motion

IN VITRO AND IN VIVO RESISTANCE TO THE THERAPEUTIC BACTERIOPHAGE 536_P1

GABORIEAU Baptiste, DELATTRE Raphaëlle, DEBARBIEUX Laurent, RICARD Jean-Damien

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Antimicrobial resistance is a major public health problem, especially in patients subjected to a strong antibiotic selective pressure such as those hospitalized in intensive care units and developing ventilator-associated pneumonia. Enterobacteria, including *Escherichia coli*, are a critical priority target for research and development of therapeutic alternatives. Phage therapy is promising but emergence of bacteria becoming resistant to bacteriophages during treatments is under studied.
We isolated and compared bacterial clones of the *E. coli* strain 536 that were selected as resistant to *Myoviridae* virulent bacteriophage 536_P1 from both *in vitro* co-evolution experiments and *in vivo* treatments in a mouse model of pneumonia. The resistance rate, the genetic mutations identified by whole genome sequencing and the impact of these on the fitness and virulence of the strains were studied.
The levels of resistant clones obtained were 23% *in vitro* and 13% *in vivo*. Interestingly, the resistant clones isolated *in vitro* and *in vivo* at early time point display mutations in the same genes involved in the LPS biosynthetic pathway. These mutations lower the fitness of these clones. At late time point *in vivo* the resistant clones carry other mutations in genes involved in the outer capsule biosynthesis.
Therefore, the panel of mutations of bacteriophage-resistant clones obtained *in vivo* is wider than those observed *in vitro*. This may be the result of the combination of multiple mechanisms, probably related to the selective role played by the host environment, including the immune system, on the fitness-cost of bacteriophage-resistant clones. This initial study requires deeper investigations to assess *in vivo* mechanisms of resistance that could account for the failure of phage therapy treatments.

Type : poster

Keywords: *E. coli*; Phage therapy Pneumonia; Resistance

Isolement et caractérisation de phages ciblant *Flavobacterium psychrophilum*, bactérie pathogène des truites d'élevage

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Les pratiques d'élevage intensif exposent la filière truiticole française à divers défis sanitaires parmi lesquels le plus problématique à ce jour est l'émergence de la bactérie *Flavobacterium psychrophilum*, l'agent causal de la maladie du syndrome des alevins de truite arc-en-ciel (Rainbow Trout Fry Syndrom, RTFS). En parallèle aux mesures prophylactiques visant à limiter la propagation de l'agent pathogène, l'utilisation intensive de traitements curatifs antibiotiques entraîne l'émergence de souches antibiorésistantes devenant préoccupante à la fois pour la filière piscicole et pour la santé humaine. La phagothérapie est une approche alternative prometteuse à l'antibiothérapie. Dans ce contexte, nous avons initié une campagne de prélèvement d'échantillons piscicoles (eau ; organes de poissons infectés) afin d'isoler des particules virales lytiques pour *F. psychrophilum*.

L'analyse des échantillons biologiques a permis l'isolement de 20 souches virales. Trois souches lytiques ont été retenues pour leur plus grand potentiel de virulence *in vitro*. La caractérisation morphologique par microscopie électronique de ces bactériophages indique leur appartenance à la famille des *Siphoviridae*. Le séquençage complet de leur génome révèle (i) la proximité de deux flavophages avec un phage précédemment identifié (le phage 6H ; Castillo *et al.*, 2014) et (ii) l'isolement d'un 3e flavophage original. En parallèle, nous avons testé la capacité lytique en coculture de ces trois souches, seules ou en combinaisons. Les résultats obtenus ont permis de définir, *in vitro*, une formulation du cocktail phagique la plus efficace pour limiter le développement de *F. psychrophilum*.

Ces premiers résultats prometteurs incitent à poursuivre l'exploration de la diversité virale régionale pour enrichir notre phagothèque afin (i) d'explorer la diversité génétique des flavophages et dans une perspective de développement, (ii) d'optimiser l'efficacité lytique des cocktails phagiques.

Type : : poster

Key-words : bacteriophages ; flavophages ; *flavobacterium psychrophilum* ; Rainbow Trout Fry Syndrom ; Siphoviridae ; phagotherapy ; aquaculture ; truit ; Aquitaine

Addressing knowledge gaps in the taxonomy of phages of Lactic acid bacteria : phage-host interactions in the underrepresented genera *Oenococcus, Weisella* and non-dairy *Leuconostoc* spp

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Phages infecting lactic acid bacteria have been the focus of significant research attention over the past three decades. Phage infection of dairy starter cultures remains the main cause of fermentation failures in the dairy industry. Owing to their economical importance, dairy phages became the most thoroughly sequenced phage group in the databases. In contrast, our *knowledge of phage* diversity in non-dairy food fermentations is still in its infancy. This is true for the "*Leuconostocaceae*" family, including the members of the *Leuconostoc*, *Oenococcus*, and *Weissella* genera. *Oenococcus oeni* drives the second fermentation of wine, called malolactic fermentation (MLF), which reduces acidity, stabilizes wines and protects it from spoilage. *Weissella cibaria*, *W. confusa, Leuconostoc mesenteroides and L. citreum* have been recently associated with different French sourdough bread, and also with different vegetable fermentations.

In this study, we have collected lytic and temperate phages from food samples and from indigenous strains isolated from sourdough breads and other vegetable fermentations. DNAs have been extracted from 250 phages/prophages. The genetic diversity of phages belonging to different taxonomic groups was further explored. Insights into phage-host interactions provide essential data for the current or future selection, biomass production and inoculation of commercial starters to be used in fermentations and other biotechnological applications.

Type: poster

Survey on prophages infecting lactic acid bacteria *Weissella cibaria* and *W. confusa*

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Lactic Acid Bacteria (LAB) infection by bacteriophages could be responsible for impaired food fermentations. However, there are few studies concerning phages in fermented products other than dairy foodstuffs. *Weissella cibaria* and *W. confusa* belonging to *Leuconostocaceae* family (also including *Leuconostoc*, *Oenococcus* and *Fructobacillus* genera) have been isolated from a wide range of habitats, and are known to be involved in several traditional food fermentations such as starchy, cereal-based, meat and fish products (Fusco et al. 2015). Moreover, strains of these species are recognized to produce copious amounts of oligosaccharides and exopolysaccharides, with special interest as texturizing agents and prebiotics (Bounaix et al. 2010).

No phage has been yet described to infect *W. confusa* and only two phages infecting *W. cibaria* (ϕYS61 from kimchi and ϕ22 from Nham) were currently described, both belonging to the family of *Podoviridae* (Kleppen et al., 2012; Pringsulaka et al., 2011). Besides, several phages infecting *W. cibaria* were isolated from commercial cucumber fermentation (Lu et al., 2012).

The aim of the present study was to investigate the presence of prophages in *W. cibaria* and *W. confusa* strains previously isolated from French sourdoughs (Robert et al., 2009) and from other diverse biotopes. Prophage excision was achieved with mitomycin C induction and led to observe bacterial lysis for all the strains. Unfortunately, no sensitive bacteria could be detected for any of the putative phages excised from the studied strains. Evidence of phage DNA was thus achieved by indirect approach i.e. purification of phage DNA from mitomycin-induced bacterial cultures. Further DNA characterization was achieved by conventional restriction analysis, and repetitive element (Rep)-PCR profile using $(GTG)_5$ primer as a new phage DNA comparative technique.

Overall, the results of this study clearly demonstrate the prevalence and diversity of prophages in the genome of *W. cibaria* and *W. confusa* LAB strains.

Type: poster

Enological environment as a source of a novel Tectivirus

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Acetic acid bacteria (AAB) are ubiquitous, strictly aerobic bacteria occurring in sugary, alcoholic and acidic niches. Members of the group have been reported in a range of food and beverage ecosystems, and play a positive role during the fermentation of vinegar, cocoa bean, kefir, kombucha, and acidic beers (1). In contrast, AAB represent spoilage microorganisms during winemaking, mainly because they are able to produce ethyl alcohol and transform it into acetic acid. The genera *Acetobacter* and *Gluconobacter* are the most important producers of wine spoilage which is legally defined by volatile acidity, largely composed of acetic acid. Detection of AAB is reported at all stages, from the mature grape through vinification to conservation. AAB originate from the leaves of the grapevine and the grapes themselves and fruit flies are considered as a common vector in propagating AAB. Different authors have observed that the less healthy the grapes, the higher the amount of AAB is. Phages infecting AAB have received relatively little attention. This study reports a survey of phages of AAB collected from grapes which resulted in the isolation and sequencing of a novel phage infecting *G. cerinus*, representing a novel member of the family *Tectiviridae*.

Type: poster

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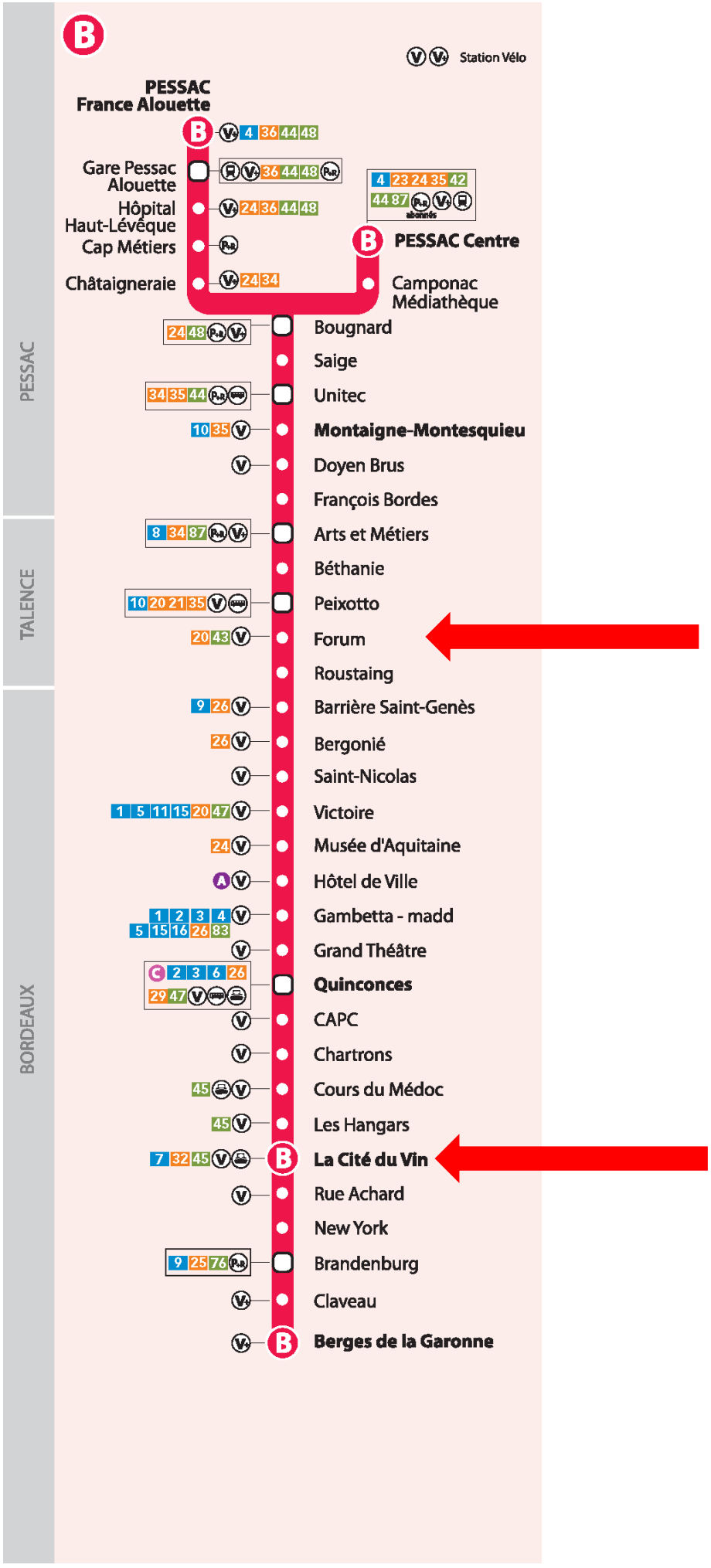
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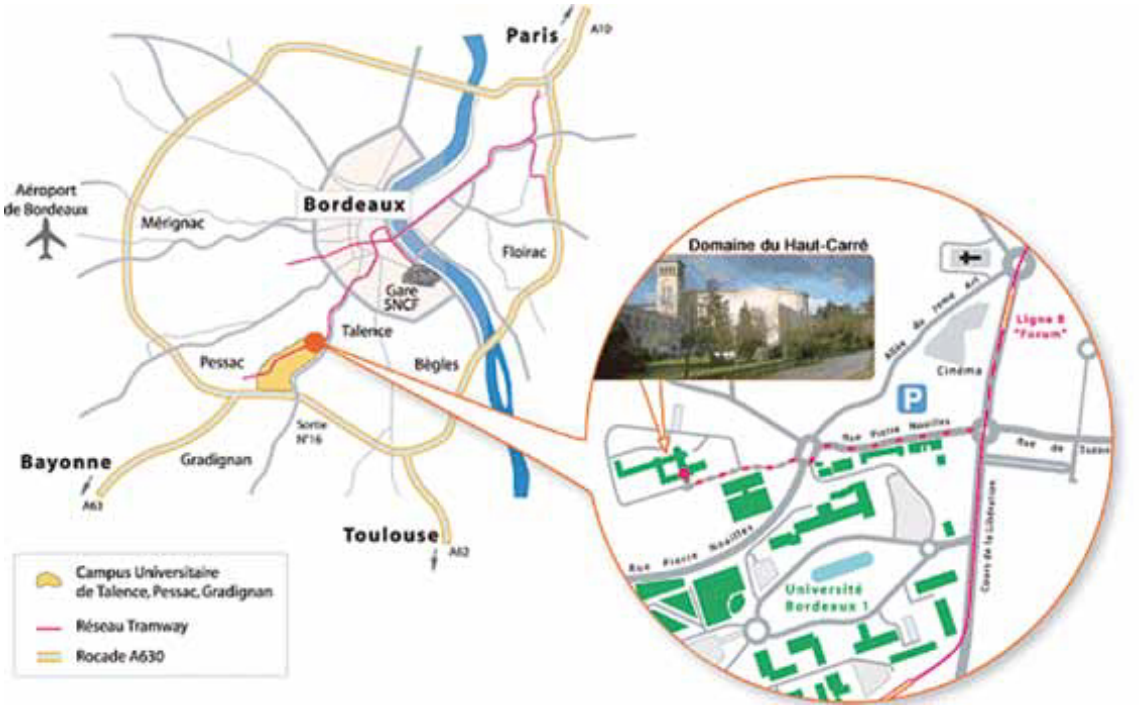
Plan A/Arrêt Forum

Plan B/Arrêt Peixotto

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