Variable Viruses. The Past, Present, and Future of Bacteriophage Research (23.-24.02.2023, University College Dublin)

Hybrid event:

Physical Location: University Club, University College Dublin, Dublin 4 (invitation only)

Free Virtual Attendance: https://us02web.zoom.us/webinar/register/WN_KKjMaFiMQVCU7YSYylXufA

Abstract:

Co-discovered in 1917, bacteriophages have helped transform human knowledge of the microbial cosmos. In laboratories, clinics, and the field, phages have been used to map and manipulate bacterial genomes, chart global microbial diversity, and diagnose and treat bacterial infections in humans, plants, and animals. After experiencing repeated booms and busts as therapeutics, diagnostics, and typing tools, the current crisis of antimicrobial resistance (AMR), advances in genomic sequencing, and growing interest in phages' role in shaping wider microbial ecologies has led to a resurgence of interest and investment in phage research and applications. Meanwhile, a growing body of social sciences research is casting new light on the complex webs of knowledge and material exchange connecting the various schools of phage research. *Variable Viruses* is a two-day workshop that brings together international experts from across the biomedical humanities and sciences to reflect on the evolution, current state, and future directions of bacteriophage research. Interdisciplinary panels will assess the complex biological and social history of human-phage interactions, the relationship between basic and translational research, and the regulatory, ethical, and structural challenges of harnessing bacteriophages.

Day One (23.02.2023)

Registration (8:30-8:50)

Welcome (8:50-9:00) – Claas Kirchhelle and Charlotte Brives

Panel One: Phages In The Lab: Molecular Biology & Evolution (9:00-10:55) (Chair: Charlotte Brives)

William Summers (Yale University, USA) – How phages became respectable: 1940-1950

From its beginning in 1917 bacteriophage research took two main pathways: what are phages, and what can we do with them? While phage might be "useful," to attack infections, their biological nature and mode of action were initially unknown and remained contentious for several decades. The problem of the nature of phage was initially confusing for two main reasons: their small size precluded any clear visualization of any morphology that might belie their nature. Was phage a molecule, something like the enzymes lysozyme and pepsin that could digest other biological materials? Was it a tiny, "ultramicroscopic" lethal microbe with its own metabolism? Until about 1940, "authoritative" opinion favored the former interpretation; the "bacteriophage phenomenon" represented an autocatalytic enzyme-like substance. The other difficulty was that "authoritative" opinion held that bacteria were fundamentally different from other life forms, no visible nucleus, no sexual reproduction, maybe even no "genes." D'Herelle and his iconoclastic followers thought differently: phages were simply "filterable viruses" that infected bacteria. Convincing evidence started to accumulate in about 1940 that vindicated d'Herelle and illuminated the biological nature of phage as legitimate biological entities and models for many of the most basic life processes common to all cells

Neeraja Sankaran (National Centre for Biological Sciences, Bangalore, India): From plaques to pocks and still smaller plaques: Bacteriophage as the basis of quantitative virology

This paper presents two episodes from the history of experimental virology that exemplify the integral role of bacteriophages in making animal virology a quantitative science. In the 1930s, the Australian

biologist Macfarlane Burnet —who had begun his research career working on bacteriophages—drew on this background to devise techniques for growing and quantifying influenza viruses on the membranes of fertilized chick eggs. His work led directly to development of methods for producing antibodies needed for the large-scale production of vaccines against influenza. Nearly two decades later, at Caltech, Renato Dulbecco, an exponent of the American Phage Group, transferred his phage-gained knowledge and skills to developing *in vitro* techniques for assaying animal viruses, obviating the need for live animal hosts. This advance was the first step in making animal virology quantitative, which in turn opened up investigations which led, among other things, to understanding aspects of viral multiplication, genetics and the mechanisms of cancer causation.

Rémy Froissart (CNRS/ MIVEGEC, Montpellier, France): Bacterial regrowth in phage therapy : evolutionary training increases host-range and virulence (but not always!)

The efficacy of phage therapy depends not only on the ability of bacteriophages to infect pathogenic bacteria but also to inhibit their growth over time. However, regrowth is often observed due to either emergence of resistant genotypes or due to other processes. In order to increase host-range and fitness, we first performed in vitro evolutionary training of one isolated and purified bacteriophages (five independent lineages) by performing 6 to 8 consecutive passages against 8 not co-evolving bacterial genotypes of Salmonella enterica serotype Tenessee. While the ancestral bacteriophage was able to infect 3 out of 8 bacterial genotypes, evolved populations expanded their host range (8/8 infected bacterial genotypes). Moreover, bacterial growth inhibition of adapted bacteriophage populations was maintained without appearance of resistant bacteria for more than 20 hours despite a 3-4 log dilution of the bacteriophages. We will present comparison of the population sequencing of both ancestral & adapted bacteriophages. On the other hand, in the process of modeling E.coli (REL 10K)– T7 population dynamic during kill curve, we observed successive waves over time in the bacterial population (closed system). We demonstrated that the cycling was not due to emergence of resistant genotypes and frequency dependent selection (Red Queen) and we propose particular interactions between T7 and its host to explain our results. For the sake of successful phage therapy, our results demonstrate the importance of in vitro evolutionary training taking into account the diversity of bacteria isolated in situ prior to the use of therapeutic bacteriophages.

Blanca Perez-Sepulveda (University of Liverpool, Liverpool, UK): A different toolbox: phages with activity against multidrug-resistant invasive *Salmonella*

New lineages of invasive non-typhoidal *Salmonella* (iNTS) are responsible for about 77,000 deaths each year worldwide due to bloodstream infection, mostly in sub-Saharan Africa. Because these novel iNTS lineages target immunocompromised individuals and are multidrug-resistant, they represent a dangerous public health problem. We isolated and characterised a pool of 32 iNTS phages isolated from water samples collected from different locations in the UK and Malawi. Individual plaques with different morphologies were repeatedly purified by plaque assay, and phage DNA was extracted and sequenced. The isolated phages were further characterised based on morphology, host range, genome structure, and phylogenetic analysis, and classified into three major geographically distributed clusters. This study represents the first exploration of the potential for phages to target *Salmonella* responsible for bloodstream infections. This phage collection has the potential for wider applications and could have utility against multidrug-resistant iNTS infections in clinical and food preparation settings.

Coffee/ Tea/ Biscuits (10:55-11:05)

Panel Two: Phages & Biosocial Environments (11:05-13:00) (Chair: Frédéric Laurent)

Claas Kirchhelle (UCD, Dublin, Ireland): Connecting the dots – bacteriophage-typing and global bacteriological surveillance.

Bacteriophage-typing (using standardised sets of bacteriophages to differentiate between bacteria at the species and strain level) transformed knowledge of microbial environments. Between the 1930s and 2000, key public health laboratories around the world used carefully maintained collections of bacteriophages to map microbial diversity while simultaneously acting as hubs for research on phage therapy, clinical diagnostics, and microbiology. Focusing on typing for enteric pathogens, this presentation builds on the extensive bacteriophage-typing archives of Institut Pasteur, the UK's former Public Health Laboratory Service, and India's National Institute of Cholera and Enteric Diseases to trace the rise, global expansion, and transformation of phage-based networks. It reconstructs the technology's importance for the development of Cold War infection control policies, shows how

(post)colonial geopolitics distorted research infrastructures, and traces lasting impacts for current research.

Senjuti Saha (Child Health Research Foundation, Dhaka, Bangladesh) (virtual) Old tools, new applications: use of environmental bacteriophages for typhoid surveillance and evaluating vaccine impact

Typhoid-conjugate vaccines provide an opportunity to reduce the burden of typhoid, caused by *Salmonella* Typhi, in endemic areas. As policymakers design vaccination strategies, accurate and high-resolution data on disease burden is crucial. However, traditional blood culture-based surveillance is resource-intensive, prohibiting sustainable implementation. *Salmonella* Typhi is a water-borne pathogen, and we tested the potential of Typhi-specific bacteriophage surveillance in surface water bodies as a low-cost tool to identify *Salmonella* Typhi reservoirs in the environment. Water samples were collected and tested for the presence of *Salmonella* Typhi bacteriophages at two sites in Bangladesh: urban capital city, Dhaka, and a rural district, Mirzapur. *Salmonella* Typhi-specific bacteriophages were detected in 66 of 211 (31%) samples in Dhaka, in comparison to 3 of 92 (3%) samples from Mirzapur. During the same time, 4,620 blood cultures in Dhaka yielded 215 (5%) culture-confirmed typhoid cases, and 3,788 blood cultures in Mirzapur yielded 2 (0.05%) cases. This indicates a strong positive correlation between the presence of Typhi-specific phages in the environment and the burden of typhoid. We are rolling out a national bacteriophage surveillance study to assist policy decisions on impact of typhoid control strategies.

Tristan Nolan (UCD, Dublin, Ireland): Bacteriophages as a reservoir of antimicrobial resistance genes and tool in monitoring water quality.

Bacteriophages are the most abundant biological entity in the biosphere and therefore have a dynamic role in our environment. Bacteriophages can act as a reservoir for AMR and a tool to track faecal pollution. Bacteriophages can obtain and transfer AMR genes via transduction. In addition, bacteriophages are ubiquitous in sewage, prompting their use as a surrogate to track sewage contamination in aquatic environments. In recent years, they have been proposed as alternative faecal indicators that may be more suitable as a proxy for human-specific enteric viral pathogens in the aquatic environment, such as crAssphage and MS2 bacteriophages. To date, bacteriophages have been overlooked in the context of the environmental resistome, where the focus has been on culture-specific microbes or molecular analysis of bacteria. Targeting bacteria alone can lead to significant underestimations of the levels of AMR in these ecological niches. Our studies aimed to assess the dynamic role of bacteriophages in aquatic environments. We investigated the role of bacteriophages in harbouring AMR genes which confer resistance to beta-lactams, sulphonamides, tetracyclines and fluoroquinolones classes of antimicrobials and, as a result, their contribution to the levels of environmental resistance in the riverine systems. All AMR genes were detected in rivers and bathing waters (n=292). The River Liffey and Dodder profiles were similar, as both had the lowest levels of AMR genes in bacteriophages at their sources. The Rives Liffey and Dodder had 14.25% and 3% of samples positive for AMR genes in bacteriophages. With an increase in downstream agricultural peaking in urban sampling points, the River Liffey and Dodder see an increase in positivity for AMR genes in bacteriophage- with 52% and 42.25% positive in urban areas in the Rivers Liffey and Dodder, respectively. Furthermore, we evaluated the performance of bacteriophages as faecal indicators in different aquatic environments. Mathematical models were used to assess the impact of hydrodynamic properties on the spatial concentration of faecal indicators after a simulated sewage discharge in different aquatic environments. Our results showed bacterial faecal indicators decayed faster than viral indicators in aquatic environments. In addition, we demonstrated that the new crAss_2 molecular marker performed equally well as the existing microbial source tracking (MST) Bacteroidales – associated human marker HF183. We determined that including more stable viral markers, such as somatic coliphages, F-specific bacteriophages and crAssphage, will improve the reliability of water quality modelling and minimise the risk of waterborne illnesses from faecal contamination.

Rijul Kochhar (MIT/Harvard/Michigan, Boston/ Michigan, USA) (virtual): Faith, Filth, Phage: cosmotechnical histories of the bacteriophage in post-antibiotic worlds

The confluence (sangam) of India's two major rivers, the Ganga and the Yamuna, is located in the city of Allahabad. Ritualistic dips in these river waters are revered for their believed curative power against infections, and salvation from the karmic cycles of birth and rebirth. The sacred and geographic propensities of the rivers have mythic valences in multiple religious traditions. Yet the connection of these river waters with curativeness also has a base in historical microbiology: near here, the British

bacteriologist Ernest Hanbury Hankin, in 1896, first described the 'bactericidal action of the waters of the Jamuna and Ganges rivers on Cholera microbes', predating the discovery of bacterial viruses (now known as bacteriophages) by at least two decades. Bacteriophages are "bacteria-eating" viruses—found abundantly in nature, and used extensively in genetics research—that once functioned as a Cold War-era tool for controlling bacterial infections in the former Soviet Union. Delving deeper into the bacteriophage's cultural history, and pursuing the record of Allahabad's purificatory waters in sacred writings and folklore as well as later elaboration in the work of Hankin, this presentation traces an epistemology of time that connects the mythic to the post- Hankin modern scientific. In asking how imaginations of the waters' antibacterial properties continue to be articulated through idioms of faith, filth and the phage, the talk explores how the bacteriophage virus comes to be spoken about within secular and sacred epistemes of infection and riverine pollution, among contemporary historians, biologists and doctors, and in the city's museums. At the same time, it traces the phage in histories arcing from the ancient religious literature, to colonial disease control efforts, to today, where bacteriophages are being conceived as a potential response to the crisis of planetary antimicrobial resistance (AMR). Considered together, these ethnographic instances illustrate extant struggles over forms of life comprising faith, evidentiary veracity, and world-making experience. Allahabad presents a 'cosmotechnics' where faith, filth and phage are inextricably intertwined, generating complex triangulations between natural ecologies, cultural practices, and scientific imaginations. Cosmotechnics, therefore, opens up novel avenues to reimagine the phage as a protean object, one that occupies partial and multiple spaces within historico-mytho-scientific arenas of the contemporary world.

Lunch (UCD Club) 13:00-14:00

Panel Three: Bacteriophages As Therapeutics – Booms, Busts & Continuities (14:00-15:55) (Chair: Frédéric Vagneron)

Dmitriy Myelnikov (Cambridge University, Cambridge, UK): Revisiting the history of bacteriophage therapy in Stalin-era Georgia and Ukraine

Until its recent revival, bacteriophage therapy was largely abandoned in most post-WWII medical contexts, with the notable exception of the Soviet Union and a few Eastern Block countries. In the USSR, bacteriophage therapy and research were institutionalised due to the high-profile collaboration between Felix d'Herelle and Giorgi Eliava and the latter's successful campaigning for state investment, but its success was cemented by the military uses during the invasion of Finland (the Winter War of 1939–40) and World War II. Within the sprawling landscape of Soviet microbiology, the relative periphery of research institutions in Tbilisi, Kyiv and Kharkiv allowed them to pursue more experimental treatments and research programmes; at the same time, key players were executed in the Stalin purges and their memory remained silenced until the 1970s at the earliest. While many Russian scientists suffered during the Great Terror of 1937–38, the Ukrainian and Georgian cases raise distinct issues – those of language, power struggles over local scientific infrastructure, and accusations of nationalism threatening the Soviet project. In this talk, I aim to revisit the Stalin-era history of bacteriophage therapy to bring centre stage the colonial relationships between the metropole and the other Soviet republics, and to reflect on the many links between the Soviet military strategy, state violence and antibacterials.

Miriam F. Lipton ((Oregon State University/ Science History Institute, Corvallis/ Philadelphia, USA): It's all in the (Microscopic) Details: Soviet Bacteriophage Therapy After Stalin

During the post-Stalin era of the Soviet Union researchers developed and administered bacteriophage therapies. Unfortunately, continuity between this long tradition and current work being done outside of the former Soviet Bloc has been lost. Through a close examination of bacteriophage therapy in the post-Stalin years, with a particular focus on the Russian Republic, I hope to bridge this informational gap. Through my recent acquisition of hard-to-access Russian language Soviet scientific publications, in this talk I will provide an example of the breadth of Soviet scholarship on bacteriophage therapy in the first ten years after Stalin's death in an effort to help revitalize this relevant history.

Angus Buckling (University of Exeter, Exeter, UK): The importance of (co)evolution in phage therapy

Bacteria-phage interactions often result in very rapid evolution of bacteria resistance and (sometimes) phage infectivity, which can great alter the outcome of phage therapy. Here, I will briefly outline the problems associated with rapid evolution, but equally how it can potentially be exploited to improve phage therapies.

Claire le Hénaff (University of Bordeaux, France): Bacteriophages in wine production.

Interactions between phages and bacteria have been explored in several natural environments, which include the human body, marine environments, and soil. The gained knowledge on the influence of phage dynamics in microbiomes is now used to disentangle the role of phages during winemaking. Understanding the complexity of the phage-host interactions may be of interest for the future of the wine industry, to better control the essential malolactic fermentation step and/or offer environmentally friendly tools to limit spoilers and improve the sustainability aspects all along the production chain. The topic may also open large windows onto plant biostimulation and biocontrol, which are key levers for the sustainable development of viticulture. A large number of microorganisms can modulate the plant physiology throughout its life cycle, keeping the grapevine holobiont healthy or not. As an example, phages have been successfully implemented in planta in Texas, USA, to control *Xylella fastidiosa*, the causal agent of Pierce's Disease of grapevines.

Coffee/ Tea/ Mini Pastries (15:55-16:15)

Panel Four: Phage infrastructures – Culture Collections & Phage Banks (16:15-18:00) (Chair: Claas Kirchhelle)

Frédéric Vagneron (University of Strasbourg, Strasbourg, France) - TBA

Ana Filipa Moreira Martins (DSMZ, Braunschweig, Germany) (virtual)- Bioresource Centers and phage research - EVREA-Phage as a forward-looking DSMZ project

The main mission of the Leibniz Institute DSMZ as a scientific Bioresource Centre is the conservation and supply of a broad diversity of microbial resources, keeping them safe, authentic and viable for current and future applications. Since 2005, the DSMZ is an ISO:9001-certified BRC including the phage collection established by late 1980's. Declining therapeutic options for otherwise common infections let phages regain attraction making them also subjects of research at the DSMZ where projects bear great potential investigating phage diversity, various aspects of phage-host interaction and ultimately their potential for therapeutic applications. The DSMZ phage group is currently involved in publicly funded translational research projects: Phage4Cure, PhagoFlow, IDEAL-EC and EVREA-Phage, the last two under DZIF support. The most recent EVREA-Phage project aims at isolating and selecting synergistically acting phages as an effective treatment strategy in controlling and eradicating MDR Enterococcus faecium, a growing challenge within healthcare associated settings. Animal models demonstrating phage efficacy are highly regarded, upgraded by innovative in vitro gut model standing as an integrated step towards translational requirements. While remarkable scientific progress is currently recorded in the field of phage biology and application, further research is necessary to better understand phage action in vitro and in vivo.

Frédéric Laurent (Hospices Civils de Lyon, France): Phage collections and Phage therapy

The aim of the PHAGEinLYON program is globally to promote the development of the use of phage therapy in France and more specifically, through the PHAG-ONE national research project to implement a national platform for the public non-profit production of therapeutic phages to treat multi-resistant and/or chronic bacterial infections. It includes phage discovery, phage training, phage production, and phage purification for the purposes of providing hospital preparations of therapeutic phage having all authorizations from French National Agency for Medicines and Health Products Safety (ANSM) for human use. For the development of such productions, it is crucial (i) to have access to collections of clinical strains representative of species targeted to be able to select the most relevant phages for the targeted clinical use, (ii) to build and collections of - natural phages based on phage discovery approaches (isolation, purification, selection) using environmental sampling; -trained/engineered phages with enhanced lytic activity or extended spectrum activity; -therapeutic phages ready-to-be used after manufacturing pharmaceutical process including purification, formulation, fill and finish, and CQs. All these processes must follow all the requirements of pharmaceutical production edited by European health authorities including traceability of staff, manipulations, GMP or GMP-like products etc. The way the development of this public production and the implementation of this public establishment for therapeutic phage production has been and is managed will be presented.

Martha Clokie (University of Leicester): 'UK phage therapy infrastructure; the role of the Leicester Centre for Phage Research'

The University of Leicester's recently established Centre for Phage Research has six phage-focussed academic staff members alongside structural biologists, biochemists, bioinformaticians, microbiologists and medical practitioners who work synergistically to determine how phages interact with relevant microbes in relevant disease contexts. We have amassed, sequenced and studied large collections of phages that target clinically relevant pathogens. Many of these phage sets have been well characterised in terms of their host range, virulence, and ability to kill their target host in physiologically representative models. We are extending our work to encompass more key pathogens and also studying our existing phage sets at higher resolution. Ultimately the Centre for Phage Research will carry out the necessary work to help underpin the translation of phage research and in doing so supply well characterised phages to be developed for use in UK patients.

Conference Dinner **(7:15pm – bar reservation from 6:45pm) - Roly's Bistro**

Day 2 (24.02.2023)

Panel Five: Bacteriophages As Therapeutics – Translational Science (8:30-10:25) (Chair: Paul Turner)

Laurent Debarbieux (Institut Pasteur, Paris, France) - Experimental evidences supporting pulmonary phage therapy

Bacteriophages infect and kill bacteria very efficiently in laboratory conditions. In the environment, the abundance of bacteriophages also supports an efficient bacterial killing. However, this efficiency never reached a broad application of bacteriophages for treating bacterial infections in human. Over the past decade, using an acute murine pneumonia model, we obtained a large set of experimental evidences supporting the benefit of using bacteriophages to treat bacterial infections. Along these studies, we also highlighted our limited understanding of the mechanisms involved in this in vivo efficacy. In particular, we found that the immune response was acting synergistically with bacteriophages to provide a full rescue while neither bacteriophages nor immune response alone was sufficient. Moving towards a closer mechanism for the synergy, we recently investigated the role of specific immune cells and found unexpected outcomes that will be discussed in the perspective of future clinical applications.

Martin Witzenrath (Charité Hospital, Berlin, Germany) – Bacteriophages to treat lung infections

Bacterial lung infections cause high morbidity and mortality worldwide. The burden of antimicrobial resistance is increasing. Whether bacteriophages may represent an alternative to antibiotics for the treatment of respiratory infections, or not, remains elusive. We used a bacteriophage lysin, a specific bacteriophage, and a customized bacteriophage cocktail to treat pneumonia caused by *Streptococcus pneumoniae, Acinetobacter baumannii, and Pseudomonas aeruginosa*, respectively, in mice. Treatment efficacy and potential side effects were evaluated. Further, treatment of bacterial infection in human lung tissue was investigated ex vivo. To gain key insights into interactions between phages and bacterial biofilms, we studied the impact of three lytic phage combinations on P. aeruginosa static biofilms. While in general, bacteriophage therapy of lung infections may be feasible, our results point at numerous hurdles that may need to be overcome. In a currently planned clinical trial (Phage4Cure), which focuses on the treatment of P. aeruginosa infection in bronchiectasis, we are trying to consider these challenges.

Joana Azeredo (Universidade do Minho, Braga, Portugal), Bacteriophages are powerful weapons against infectious biofilms but need a little help

Phage therapy to combat difficult-to-treat biofilm infections is gaining an increasing popularity due to growing number of successful clinical cases. The chronic nature of biofilm-related infections is ideal for a personalized phage therapy modality, providing a treatment time buffer that allows the proper development and preparation of personalized therapeutic phage cocktails. However, biofilms are challenging for therapeutic phages, mainly due to the protection offered by the biofilm matrix and resistance mechanisms. Therefore, in vitro data and clinical reports suggest that the association of phages with other chemical/mechanical treatments may be beneficial to increase the efficacy of phage therapy against biofilm infections. Here I will present the major challenges imposed by biofilms to phage

attack as well as the strategies that can be used to counteract biofilm defences and improve the antibiofilm efficacy of phages.

Koichi Kameda (Institut Francilien Recherche Innovation Societe/ CSH, Paris/Delhi, France/ India): Pharmaceutical R&D and equity

In this presentation, I will discuss examples of “alternative” pharmaceutical R&D, in particular cases where equity has guided the development of health goods, such as the public production of vaccines and diagnostics in Brazil. By discussing ways of pharmaceutical production that are different from the traditional and market-driven model I aim to advance a reflection on a model of bacteriophage production that better addresses societal concerns related to the fight against AMR and social justice.

Coffee/ Tea/ Biscuits (10:25-10:45)

Panel Six: Bacteriophages As Therapeutics – Hopes & Hurdles (10:45-12:40) (Chair: Laurent Debarbieux)

Joint presentation: Jean-Paul Pirnay (Queen Astrid Military Hospital, Brussels, Belgium); Grégory Resch (University of Lausanne, Lausanne, Switzerland); Tristan Ferry (Hospices Civils de Lyon, Lyon, France) (30mn): National academic programs as an immediate strategy for a quick and successfully implementation of phage therapy at the clinic.

Tristan Ferry, Jean-Paul Pirnay and Grégory Resch, three established phage therapy scientists in respectively France, Belgium and Switzerland will present their visions for the development of national phage therapy programs in the academic setting. Pros and cons will be presented and the example of a successful and unique European collaboration for the personalized treatment of a pandrug-resistant spinal Pseudomonas aeruginosa infection will be highlighted.

Paul Turner (Yale University, New Haven, USA): Leveraging evolutionary trade-offs in development of phage therapy (20mn)

One possible strategy to combat the antibiotic resistance crisis is a renewed approach to ‘phage therapy,’ where these administered viruses not only kill the target bacteria, but also predictably select for phage resistance that reduces virulence and/or increases antibiotic sensitivity (evolutionary trade-offs). By utilizing virulence factors as receptor binding sites, the phages exert selection for bacteria to evolve phage resistance by modifying (or losing) the virulence factor, potentially reducing bacterial pathogenicity. This talk presents examples of phages that kill target bacteria while selecting for phage resistance that coincides with useful clinical traits, and compare in vitro data to phenotypic, genetic and metagenomics analyses of microbes isolated longitudinally from patient samples before, during and after emergency phage therapy treatments.

Charlotte Brives (CNRS, Bordeaux): Facing antibiotic resistance, a political ecology of microbes (20 mn)

For the past five years, as an anthropologist of science and health, I have been observing the development of phage therapy in France after more than a hundred years of existence. From laboratory practices to patients' stories, through the maze of regulations on drugs and health products, clinical trials and the place of bacteriophage viruses in different ecosystems, I have tried to understand, together with biologists, physicians, patients' associations and regulatory agencies, how and under what conditions phages could become allies in the fight against bacterial resistance to antibiotics in human health. The result of this work is a book in which I outline the contours of a medicine that already exists, discreetly attentive to the ecological dimension of infections, in which phages would have their place, as well as the conditions of possibility of such a practice of infectiology. In particular, I show how it is impossible to think about the development of phages in human health without taking into consideration the way in which antibiotics have profoundly transformed not only medicine and pharmacy in the second half of the 20th century, but more globally all ways of life and societies on Earth, in a direct or indirect way. Antibiotics, chemical molecules presented as miraclculous, have been and still are mass-produced and consumed, in human health but even more so in the agro-industry. They have become, through their multiple and often unfortunate uses, a real pharmakon: as much a remedy as a poison. It is important not to make the same mistakes with phages. Phage therapy, therefore, can only provide a lasting, albeit partial, response to the problems posed by antibiotic resistance if it is invented on a

radically different basis from that of antibiotic therapy. It could then make it possible to treat infections caused by resistant bacteria while preserving the efficacy of available and future antibiotics as well as non-pathogenic bacteria whose importance for human health is constantly being demonstrated by studies on the microbiota. Initiatives are already underway, which this network has allowed me to explore.

Working Lunch (12:40-13:30)

Panel Seven: Where next for Phage Research? (13:30-14:50) (Chair: Jean-Paul Pirnay)

Sylvain Moineau (Université Laval, Quebec, Canada) (virtual): Where next for phage research? (20mn)

It is well-recognized that phages can influence the balance of microbial ecosystems, including our microbiota. Phages will continue to be excellent viral models applicable to various research areas, including as surrogates in aerovirology studies related to the ongoing pandemic. Phages can also be both friends and foes. Friends since they suppress pathogenic bacteria. Phages will most certainly be further leveraged in industrial and medical applications as biocontrol agents. Foes because they can destroy bacteria that play key roles in fermentation and biotechnology processes. Understanding their biology, ecology and evolution is still of utmost importance to develop new defence strategies to control them in biotechnology processes and to optimize their antibacterial activity in food safety and public health. Finally, the last decade has seen a heightened awareness of the value of collections of viruses for the conservation of genetic resources and biodiversity. Long-term support will be essential to maintain these infrastructures.

Sabrina Green (Lab of Gene Technology, KU Leuven, Leuven, Belgium), Phage therapy from Texas to Belgium—is the personalized approach effective? (20mn)

The emergence of antibiotic resistance is undermining modern medicine. The problem is compounded by the inherent adaptability of bacteria in the face of intense selective pressures. Phages are viruses that infect bacteria. They are diverse, evolvable, and have been proposed as a possible solution for this crisis. Our group developed a center called TAILOR in Houston, Texas which facilitated the treatment of 12 patient cases treated with phage therapy (PT) and concomitant antibiotics for infections which varied caused by the pathogens *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Pseudomonas aeruginosa, Enterobacter cloacae, Klebsiella aerogenes and Escherichia coli*. All patients were successfully treated with intravenous (IV) personalized PT and antibiotics without major adverse effects. Among these patient cases, PT resulted in 4/12 cases of bacterial eradication. Of the infections not eradicated with PT (3/12) patients improved clinically. For some cases it could not be determined whether PT was a success or not (3/12). However, for patients with negative outcomes (2/12)—without clinical improvement or bacterial eradication we suggest that phage pharmacodynamics and immunological parameters contributed to PT failure. Phage are safe and can offer an alternative for difficult-to-treat infections. Among improvements needed to develop effective treatments is to work with more experienced groups in PT like groups in the country of Belgium which has facilitated the treatment of 100+ patients using standardized methods developed or used by people from the Eliava Institute in Georgia which has a long-standing phage therapy center.

Funder/ Industry Perspectives on Phage Therapy (7 minute pitches):

Helmut Kessmann (INCATE, Basel, Switzerland) (virtual)

Ed Buurman (CARB-X, Boston, USA),

Jakob Krause-Haaber (SNIPR-Biome, Copenhagen)

Closing Remarks (14:50-15:00) – Claas Kirchhelle/ Charlotte Brives