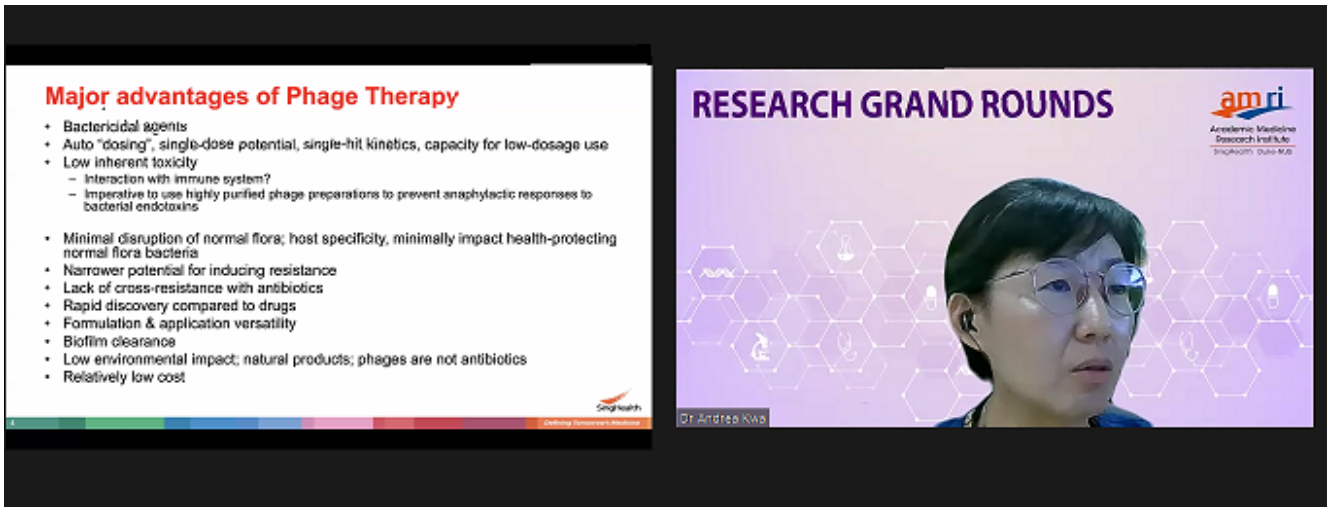
Research e-Bulletin

# Bacteriophages as a Therapeutic Agent – From Dumps to Trumps?

*In our fourth Research Grand Rounds (RGR) for 2023 held on 19 July, participants gained insights on non-traditional antibacterial therapeutics and innovative approaches to effectively treat difficult-to-treat infections and eradicate biofilms. Our speakers, Dr Andrea Kwa (Deputy Director (Research), Pharmacy, Singapore General Hospital) and Dr Wilfried Moreira (Principal Investigator and Senior Research Fellow, Singapore Centre for Environmental Life Sciences Engineering, National University of Singapore) also discussed on phage therapy.*

Bacteriophage therapy is gaining significant renewed interest after several high-profile clinical successes where patients with untreatable bacterial infections made successful recoveries upon receiving customised phage cocktails.




In the opening presentation "Implementation of Bacteriophage Therapy for the Treatment of Refractory Resistant Infections" by Dr Andrea Kwa, she addressed the significant burden of Antimicrobial Resistance (AMR) in the region and the alarming decrease in the antibiotic pipeline. She also highlighted the rising number of case reports on Phage therapy over the past five years, showcasing its success in individual cases.

Dr Kwa then discussed the significant advantages of phage therapy, notably their evolutionary potential. The clinical implications for this are that phages can be developed and trained to overcome resistant bacteria; new phage therapeutic targets could be procured in a fraction of the time required for novel

drug development.

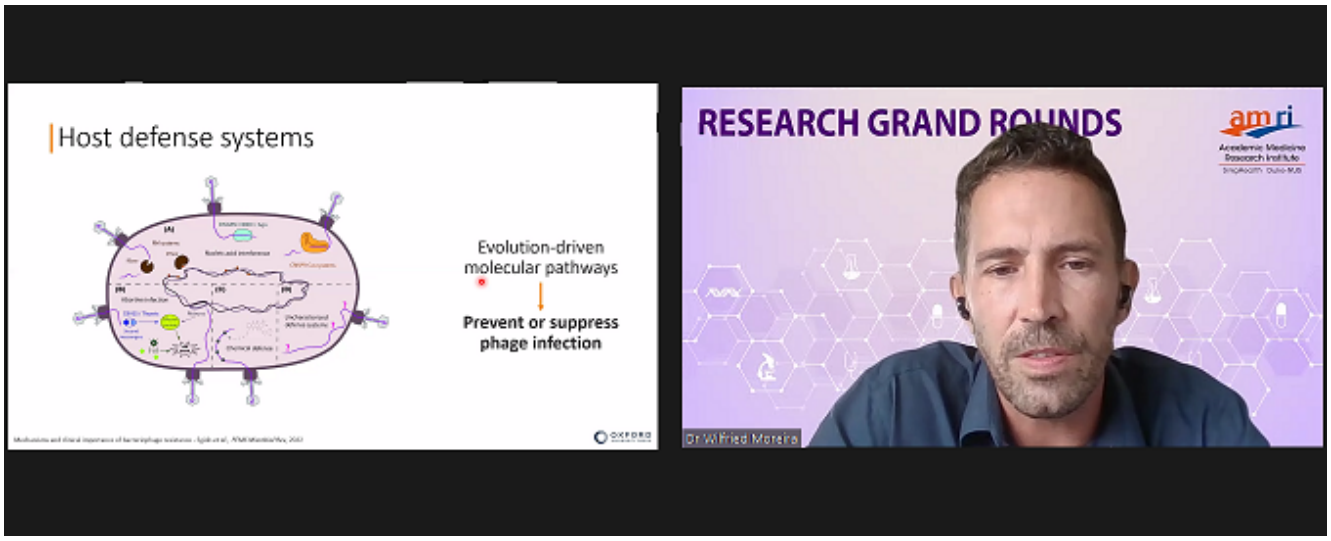
However, it is essential to note that not all phages are suitable for use as therapeutics. Good therapeutic phages should possess two key characteristics: they need to demonstrate efficacy (having the potential to eradicate the offending pathogen) and does not modify the host genome. These attributes can be reasonably ensured by ensuring that phages are obligately lytic, stable under typical storage conditions and temperatures, and subjected to thorough efficacy and safety studies. Ideally, their genomes should be fully sequenced to confirm the absence of undesirable genes that may promote lysogeny, or further resistance of the bacteria.

Dr Kwa further elaborated on how phages work to kill bacteria and how this process can lead to the modification of bacterial properties through evolution. When exposed to phage therapy, bacteria may undergo changes in response, leading to the development of phage resistance. Interestingly, during this process, some bacterial strains may become more susceptible to antibiotics.

She presented a Gantt chart outlining the timeline from request to administration, and expounded on the processes of phage identification, production, purification, and formulation. Similar processes are adopted at various international phage centres including the center for Innovative Phage Applications and Therapeutics (IPATH), UC San Diego, and the Tailored Antibacterials and Innovative Laboratories for phage (Φ ) Research (TAILΦR), Baylor College of Medicine. She also emphasized the importance of phage susceptibility testing.

Next, Dr Kwa emphasized the importance of personalized or customized phage-antibiotic treatment. There is now in vitro data to demonstrate that phage therapy alone is unlikely to be effective, especially for the treatment of drug resistant infections. However, they have observed that select phages, when combined with antibiotics, demonstrate an enhanced ability. Utilising phage and antibiotic as combination therapy can be beneficial in treating extreme drug resistant infections, providing a promising approach to address this growing problem of antimicrobial resistance, when treatment options are limited.

In her concluding remarks, Dr Kwa presented a roadmap that outlines the different processes involved and the stakeholders participating in the phage therapy journey. This roadmap serves as a comprehensive guide to navigate the complexities and collaborations necessary for successful phage therapy implementation.




Next, Dr Wilfried Moreira began by explaining that bacteriophage resistance is the result of co-evolution between bacteriophages and their hosts, much like antibiotic resistance.

During his presentation, Dr Moreira presented an overview of phage therapy and emphasised the importance of understanding phage resistance *in vitro*-and during clinical treatment. He explained that phages can be employed as antimicrobials, and bacteria have ways to develop resistance to phages. Hence by comprehending resistance mechanisms, researchers can design more effective antimicrobials, and this understanding can, in turn, inform and advance phage therapy strategies.

Dr Moreira then elaborated on the three categories of mechanisms of resistance to bacteriophages. The first category, host receptor adaptations, involves random mutations or phenotypical variations that decrease phage absorption by the host. The second category, host defense systems, includes molecular pathways that either prevent or suppress phage infection within the host. The third category, phage-derived phage defense systems, comprises phage-encoded molecular pathways that compete with other phages, ultimately benefiting the host bacteria. These diverse mechanisms of resistance play a significant role in the intricate relationship between bacteriophages and their bacterial hosts.

In response to resistance, phages have the capability to evolve and overcome bacterial defenses. Dr. Moreira further shared case studies of phage therapy, delving into the safety, outcomes, and resistance observed in these cases. He emphasised the importance of comprehending resistance *in vitro*, noting that some resistant mutants exhibited altered biofilm formation. Understanding these dynamics is crucial for advancing our knowledge of phage therapy and its potential in combating bacterial infections.

He also elaborated on the complex interaction between phages and biofilms, explaining how phages are well-equipped to target and attack biofilms, and they can be engineered to effectively disperse them. In conclusion, he shared several key takeaways from phage therapy and biofilms, emphasizing their potential to assist in the treatment of biofilm-related infections. Notably, phage therapy has shown positive clinical outcomes and a good safety profile. However, he highlighted the need for follow-up studies concerning bacterial load and resistance monitoring, as well as symptoms tracking. While *in vivo* studies of phage therapy for biofilms remain relatively limited, underscoring the importance of conducting more comprehensive research is key. Additionally, the establishment of standardized treatment protocols and evaluations is crucial to optimize the efficacy and reproducibility of phage therapy for biofilms.

Finally, Dr Moreira stressed the importance of the collaborative nature of phage biology and phage therapy research and the need for a collective effort and carefully elaborated framework to make phage therapy a reality in Singapore.

During the Q&A segment, the attendees actively and enthusiastically participated, posing a wide range of questions related to the practical implementation of bacteriophage therapy and the issue of bacterial resistance to bacteriophages. The engaging discussion provided valuable insights and delved deeper into the understanding of phage therapy.


Dr Jasmine Chung facilitated the Q&A session, with several key takeaways:

- Compared to the regulatory framework for drug development, implementing phage therapy may be a relatively less expensive process to identify new therapeutic targets to treat drug resistant infections. Phages are ubiquitous in the environment; they have anti-bacterial properties, which could be leveraged as antibiotic adjuncts to treat refractory / resistant infections. Phages have to be well-characterised with proven phage-antibiotic efficacy demonstrated *in vivo*, pass robust quality assurance and quality control standards, prior to regulatory approval for clinical use, these processes are time-consuming and are potentially barriers to the implementation of phage therapy (which are often required emergently).
- Although individual phages are highly specific, there is a range of phages that could be isolated from the environment to target a range of pathogens, such as methicillin-resistant *Staphylococcus aureus* (MRSA), Vancomycin resistant Enterococci (VRE), drug resistant gram-negative bacteria, phages against other pathogens such as nontuberculous mycobacteria (NTM) have also been identified. However, NTM phages are harder to find and develop (genetic engineering techniques may need to be employed). Because NTM are slow growers, the process of hunting and matching phages for NTM will take considerably longer time from the lab's perspective.
- Phage directories have been established to allow global sharing of phage expertise. When requests are made for a global phage hunt, specialized phage laboratories with potential suitable phages for clinical use will still need to receive the bacterial samples to conduct screening tests to determine phage efficacy prior to the release of the phage product for production and purification. These steps add to the overall time required before phage can be used as a therapeutic product.
- Because phage hunting is a time-consuming, having a targeted approach and establishing a bank of therapeutic phages against commonly encountered pathogens is crucial to shorten the process of identifying appropriate phages for clinical use, expediting the treatment process. This will bring phage therapy a lot closer from bench to bedside.

We would like to thank Dr Kwa, Dr Moreira and Dr Chung for sharing their perspectives on Bacteriophages as a Therapeutic Agent. If you have further enquiries or are interested to collaborate with our presenters, feel free to write to:

- Dr Andrea Kwa (andrea.kwa.l.h@sgh.com.sg), or
- Dr Wilfried Moreira (wilfried.moreira@nus.edu.sg), or
- Dr Jasmine Chung (jasmine.chung.s.m@singhealth.com.sg).

**About Research Grand Rounds (RGR)**

Held every two months over lunchtime, RGR showcases the achievements of researchers from the SingHealth Duke-NUS Academic Medical Centre (AMC), serving as a knowledge exchange and community engagement platform.

**About Academic Medicine Research Institute (AMRI)**

The SingHealth Duke-NUS Academic Medical Centre (AMC) is driven by 3 key pillars: clinical delivery, education and research; with the aim to discover new treatments and enhanced diagnostic tools to improve care for our patients. As one of the largest academic healthcare cluster in Singapore, basic scientists and clinical researchers within the AMC work together to address disease areas that most affect our population. Academic Medicine Research Institute (AMRI) is the AMC's one-stop research enabler that provides support in administration and scientific techniques to the research community in the AMC. These research support functions reside within SingHealth and its member institutions, and Duke-NUS Medical School.

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