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Phage Australia: Integrating Australian Phage Banking and Therapeutic Networks and Delivering Solutions for Antimicrobial Resistance

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* This Frontiers program builds on our international leadership in phage therapy, microbiology, clinical and laboratory medicine, genomics, informatics and biotechnology, led by ***Professor Jon Iredell***, Director of the Centre for Infectious Disease and Microbiology at Westmead and expert in phage therapy. He is supported by Deputy Directors ***Associate Professor Ruby Lin*** (Science/ Biotechnology) and Deputy Director (Clinical/ Therapeutics/ Trials), ***Dr Ameneh Khatami***.

PREFACE *The aims of The Medical Research Future Fund are to build long-term investments supporting Australian health and medical research and innovation to improve lives, build the economy and contribute to health system sustainability. Phage Australia was awarded under the MRFF Frontiers Stage 1 scheme. Here we introduce the concept and the establishment phase going into the Stage 2 bid.*

INTRODUCTION Modern medicine has adopted two distinct and complementary approaches to infectious disease control. Vaccination can *prevent* infection – but is only available for a small number of infectious agents. For infections that are not prevented, antimicrobials (mostly antibiotics, with a few antivirals and antifungals) offer the possibility of *treatment*.

Now, however, antibiotics are failing due to growing antimicrobial resistance (AMR) and the R&D pipeline for new antibiotics has all but dried up. As the World Health Organization has warned, this threatens "an end to modern medicine as we know it"[1]. Common infections will once again become untreatable. Cancer treatments and transplants will become increasingly unsafe and even routine operations and procedures will carry high risk of untreatable infection, sepsis, and mortality. By 2050, antibiotic resistant infections are projected to become the leading cause of death worldwide resulting in approximately 10 million deaths annually[2]. The social and economic costs will be enormous.

Inside this issue

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Phage therapy is a last defence against AMR now and a first choice for treatment in the future

Phage therapy offers a third approach to infectious disease control. Phages (also known as bacteriophages) are viruses that prey on bacteria. They remain completely effective against antibiotic resistant bacterial strains, offering a last defence against otherwise untreatable infection.

Phage therapy also brings a number of critical advantages over antibiotic treatment. With careful preparation to remove impurities, they are non-toxic to humans. Unlike antibiotics, each phage is highly precise in the specific bacteria that it targets, meaning that treatment has fewer effects on the healthy bacteria in our bodies. They can be used on their own or in combination with other phages and antibiotics to increase efficacy even more.

Our goal is to establish phage therapy in the Australian (and international) pharmacopoeia

Our primary goal is to establish phage therapy within a framework of approved indications based on clinical trials and a sound understanding of the underlying physiology. Phages will be available for prevention of disease as sole or adjunctive therapy, and as the go-to therapy when antibiotics are inadequate (e.g., in chronic respiratory and medical device infections) or fail completely due to AMR.

We will achieve this through the creation of **Phage Australia**, a national industry ecosystem of genomics and informatics, diagnostics, clinical trials, manufacturing and internationally networked biobanks. Phage Australia will provide both empiric preparations designed by understanding the common pathogens and their phage susceptibilities, and bespoke therapies guided by precision diagnostics. The same diagnostic tools used to make initial therapeutic choices will help us to screen for new phages (i.e., to add to banks) and to monitor therapy. We will work to develop bioinformatics-driven phage optimisation, and to develop phages with new capacities and therapeutic potential.

After 100 years in the shadow of antibiotics, the time for phage therapy has arrived.

New capacities in biotechnology, genomics, laboratory robotics, informatics, and synthetic biology make this the perfect time to bring a hitherto arcane science into the modern pharmacopoeia. Our newly established surveillance and biobanking programs provide ideal complementary infrastructure.

By tapping into the global phage market, projected to reach $1.4 billion by 2026[i], Phage Australia will become a commercially sustainability entity, pioneering and delivering phage therapeutics, and putting Australia at the forefront of the third great revolution in the control of infectious disease.

BACKGROUND

Phages are the most abundant and diverse life form on earth

As their natural predators, phages are found everywhere that bacteria are found. Those that live as obligate parasites ('virulent' phages) are preferred as therapeutic agents and can be sourced from bacterial hotspots such as sewage, hospital wastewater and soil.

Phage therapy offers a solution to the AMR crisis

Phages were first used therapeutically 100 years ago[ii] but fell from favour in most countries with the discovery of antibiotics. Phages prey equally well on drug-sensitive or drug-resistant bacteria and are safer and better tolerated[3]. They can be used in combination with antibiotics or substitute for them when they fail and can even be used to restore the potency of failing antibiotics[4]. They have the same potential scope and global demand as the USD 60 billion antibiotic industry[5].

Phages can treat 'biofilm' infections where antibiotics typically are inadequate

Biofilm infections are common in cystic fibrosis, preventing access to life-saving disease-modifying drugs and lung transplantation. They also commonly destroy prosthetic devices and artificial heart valves[6]. Phages will kill bacteria in biofilms when antibiotics typically cannot[7] and we have shown how powerful phages can be when antibiotics have failed[8-10].

Precision phage therapy avoids the collateral damage of antibiotics.

Traditional antibiotics kill beneficial as well as pathogenic bacteria, disturbing the microbial ecosystem and leaving the patient vulnerable to other pathogens[11]. In contrast, each phage targets specific bacterial strains, preserving the healthy microbiome.

Phages can be used as very precise (bespoke) therapy - guided by diagnostic tests.

Phage susceptibility is usually detected manually, as a 'plaque' of clearing on a lawn of bacteria. We have adapted antimicrobial susceptibility testing methods to allow efficient high-throughput testing of phage susceptibility, including testing phage-phage and phage-antibiotic combinations *in vitro* (not always synergistic, so must be tested[12]). This identifies the phage/s that are most potent.

Combinations or 'cocktails' of phages can be used in urgent cases and for unknown pathogens.

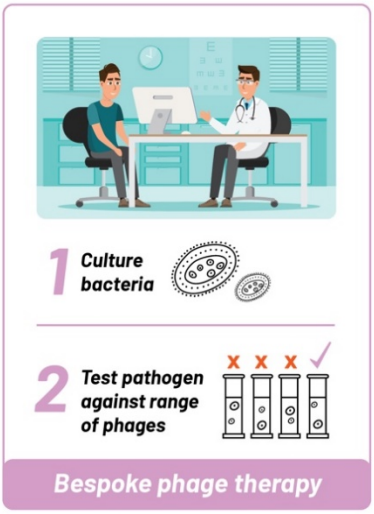
Phage cocktails that target all likely causes of a common infection (e.g., urinary sepsis, pneumonia) can be used as empiric 'off the shelf' therapy. This is most important to avoid delay or when diagnostics are only indicative of a likely infection type (most rapid tests) or are unavailable.

Phage therapy can be administered safely even in the most severely ill.

Our group at Westmead were the first in the world to use intravenous bacteriophages in a systematic trial in severe infection and thus gained new insights into dosing, resistance development, disposition in the host (kinetics of distribution and clearance) and effects on the host immune system. The Westmead trial[iii] generated great interest[iv] and informed the first FDA-approved trial of intravenous phage therapy[v].

Phages can be engineered to improve their potency, range of activity, and shelf life.

'Natural' phages with desirable traits can be created via a process of forced evolution. Modern synthetic biology tools give us additional capacity to redesign these viruses to deliver antibiotics directly to the site of bacterial infection or to carry novel payloads (e.g., CRISPR systems to attack specific antibiotic resistance genes).



Overview of Research Streams

Stream 1: Production

Objectives of Implementation stage:

- An integrated network of phage banks across Australia and internationally
- A system of phage passports to allow the exchange of high value phages
- Treatment grade phages and phage cocktails produced to human clinical standards

Stream 2: Diagnostics

Objectives of Implementation stage:

- NATA-accreditable assays for phage susceptibility testing
- A suite of tests to enable monitoring of phage and bacteria levels and patient response (immune response and microbiome changes) during therapy

Stream 3: Therapeutics

Objectives of Implementation stage:

- A program of compassionate use case-studies to investigate optimal use in specific infections
- Capabilities and infrastructure to enable large-scale clinical trials of phage therapy

Stream 4. Optimisation

Objectives of Implementation stage:

- Genomic analyses that enable rapid matching of phages to bacterial infection, including identification of high-priority characteristics and systematic protocols to select for them
- A web-searchable platform (utilising bioinformatics) to identify and improve properties of naturally occurring phages as therapeutics. This also support stream 3

How the streams work together

The interdependence and complementarity of streams is managed operationally at each node. Streams 1 (APBN) and 3 (APTN) are highly networked by necessity. The supply chain infrastructure required by more centralised production (in Stream 1) leverages APBN and APTN, promoting standardisation and cohesion and drawing from stream 2 (diagnostics) to support the networks. Stream 4 creates efficient workflows in banks (Stream 1), optimises diagnostics (Stream 2) and phages (Stream 3) and integrates data from all three streams to build new IP and identify those strategies which are most successful.

We have set milestones and stage deliverables for the next 12 months. In addition, we have working groups such as 1) Workforce and Skills Development, with the purpose of fit-for-work training in clinical (medical, nursing, pharmacy, biobanking) and scientific (industry and diagnostic microbiology, manufacturing, genomics) aspects of phage therapy and 2) IP, Regulatoy Risks and Commercialisation, with the purpose of generating IP within this network that can be commercialised, thus making this ecosystem sustainable.

The Scientific Advisory Board and Commercial Development Advisory group will provide consult. Industry stakeholders are consulted.

Partners for this MRFF Frontiers are listed (not in particular order): University of Sydney, NSW Ministry of Health, Children's Hospital Westmead, Monash University, Decode BioSciences, Illumina, Cystic Fibrosis Australia, Recombinant Product Facility UNSW, CSIRO, University of Copenhagen, Phage Directory, AGRF, Perkin-Elmer, WIMR, WSLHD, University of Queensland, LyseNTech, South Korea Phage Bank, University of Adelaide, University of Melbourne, University of Flinders, University of Western Australia, Telethon Kids, MTPConnect, ASID, ASAMR, Sciensano, Queen Astrid Military Hospital, Belgium, Armata Pharmaceuticals and Adaptive Phage Therapeutics.

[I] A Credence Industry Market Research Report (October 2018) estimated the global phage market to be US$ 568M in 2017 and forecast a compound annual growth rate of 3.9% between 2018 and 2026. Global Phage Therapy Market 2019 Research report; Industryresearch.biz Press Release Sept 4, 2019; marketwatch.com

[II] On an invisible microbe antagonistic toward dysenteric bacilli: brief note by Mr. F. D'Herelle, presented by Mr. Roux. 1917. Res Microbiol. 2007 Sep;158(7):553-4;

Stone, R. (2002) Bacteriophage therapy. Stalin's forgotten cure. Science 298, 728-731.

[III] ECCMID2019, Amsterdam, June 2019; ASM Microbe San Francisco, 2019

[IV] According to Altmetrics, our Nature Microbiology paper is in the 91st percentile for articles of a similar age in Nature Microbiology and the 98th percentile for all articles of a similar age (17th of Feb 2020)

[V] Voelker, R. (2019) FDA Approves Bacteriophage Trial JAMA. ;321(7):638.

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The Australia Phage Network (#AusPhageNet) consisted of (as of July 2021, we have new members):

- ***Leadership team***

Director: Prof Jonathan R Iredell, Westmead Institute for Medical Research, University Of Sydney, Westmead Hospital
Deputy Director: Assoc Prof Ruby CY Lin (science/biotechnology), Westmead Institute for Medical Research, University of Sydney
Deputy Directory: Dr Ameneh Khatami (clinical/therapeutics/trials), The Children's Hospital at Westmead, University of Sydney

- ***Clinical Node Leaders***

Assoc Prof Steven Tong (Chair of the Australian Society for Infectious Diseases Clinical Research Network)
Prof Deborah Williamson (Director of Microbiology at Royal Melbourne Hospital, Doherty Institute)
Dr Anton Peleg (Alfred Hospital, Monash University)
Dr David Paterson (Royal Brisbane and Womens' Hospital, University of Queensland)
Dr Morgyn Warner (Queen Elizabeth Hospital, Adelaide)
Dr Stephen Stick (Clinical Lead WA Respiratory Health Network)
Dr Chris Heath (Royal Perth Hospital)

- **STREAM Leaders**

Stream 1 convenors:

Assoc Prof Ruby CY Lin (Westmead Institute for Medical Research, University of Sydney)
Prof Jennifer Byrne (University of Sydney, NSW state-wide biobank initiative)

Team members:

Dr Leszek Liszowski (Childrens Medical Research Institute)
Dr Jeremy Barr (Monash University)
Dr Jessica Sacher (Phage Directory)
Dr Shawna McCallin (University of Zurich)
Prof Jon Iredell (Westmead Institute for Medical Research, University of Sydney, Westmead Hospital)
Dr Anthony Kicic (Telethon Kids)
Dr Laura Collie (NSW Health)

Stream 2 convenors:

Prof Deborah Williamson (Director of Microbiology at Royal Melbourne Hospital, Doherty Institute)
Dr Morgyn Warner (Queen Elizabeth Hospital, Adelaide; SA Health)
Prof Jon Iredell (Westmead Institute for Medical Research, University of Sydney, Westmead Hospital)

Team members:

Dr Susan Maddocks (Westmead Hospital, University of Sydney)
Dr Anton Peleg (Alfred Hospital, Monash University)
Dr David Paterson (Royal Brisbane and Womens' Hospital, University of Queensland)
Dr Stephen Stick (Clinical Lead WA Respiratory Health Network)

Stream 3 convenors:

Dr Amene Khatami (The Children's Hospital at Westmead/University of Sydney)
Assoc Prof Steven Tong (Chair of the Australian Society for Infectious Diseases Clinical Research Network)

Team members:

Prof Tom Snelling (University of Sydney)
Prof Bernard Hudson (Royal North Shore Hospital)
Prof Kim Chan (University of Sydney)
Dr Anthony Kicic (Telethon Kids, WA)
Prof Jian Li (Monash University)
Prof Jon Iredell (Westmead Institute for Medical Research, University of Sydney, Westmead Hospital)
Dr Laura Collie (NSW Health)
Dr Julia Warning (NSW Health)

Stream 4 convenors:

Prof Trevor Lithgow (Monash University, Director of the Centre to Impact AMR)
Prof Vitali Sintchenko (University of Sydney, Director CIDM-PH Westmead Hospital, NSW Health Pathology)
Prof Rob Edwards (Flinders University)

Team members:

Dr Leszek Lisowski (Childrens Medical Research Institute)
Prof Ian Paulsen (Macquarie University, Director ARC Centre of Excellence in Synthetic Biology)
Dr Laurence Wilson (CSIRO)
Assoc Prof Denis Bauer (CSIRO)
Prof Deborah Williamson (Royal Melbourne Hospital, Doherty Institute)
Dr Shawna McCallin (University of Zurich)
Prof Paul Groundwater (University of Sydney)
Dr Hien Duong (University of Sydney)
Dr Nouri Ben Zakour (Westmead Institute for Medical Research)
Dr Amith Shetty (NSW Health)
Prof Jon Iredell (Westmead Institute for Medical Research, University Sydney, Westmead Hospital)

- **Scientific Advisory Board**

Chair: Prof Jeremy Chapman (senior physician and academic, member of the Western Sydney Local Health District Board, Professor Emeritus at University of Sydney, and immediate past president of the International Transplant Society)

Board members:

Prof Liz Harry (University of Technology, Sydney)
Mr Graeme Loy (CEO Western Sydney Local Health District)
Prof Scott Bell (University of Queensland)
Prof Chris Cowell (Sydney Childrens Hospital Network)
Prof Dena Lyras (Monash University, President of Australian Society for Microbiology)
Prof Nick Thomson (Sanger Institute, Cambridge University, UK)
Dr Antonio Penna (Director, Office of Health and Medical Research, NSW Government)

- **Commercial Development Advisory Board**

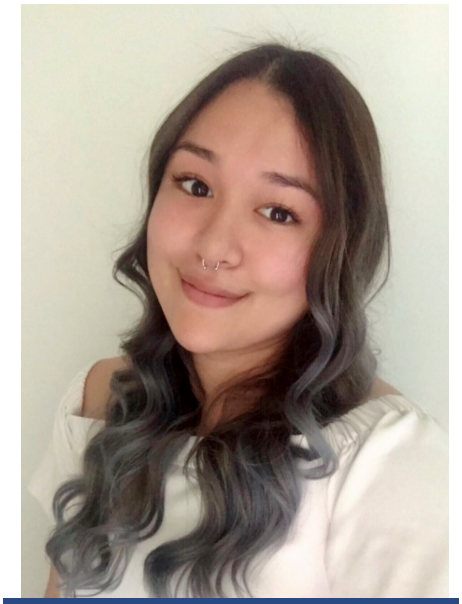
Prof Bruce Robinson (Chair of NHMRC Research Council; Chair of MBS Review Taskforce; Director of Cochlear, MaynePharma, QBiotics; immediate past Dean, Sydney Medical School)
Mr Chris van Niekerk (Executive Director, CVN Pharmaceuticals)
Mr Rick Holliday-Smith (Board Chair of ASX, Cochlear, Snowy Hydro and QBiotics)
Mr Andrew Denver (Board Chair of SpeeDx; Director of Vaxxas, QBiotics)

Staff Profile

Shona Chandra completed her PhD (Science) in veterinary parasitology at the Sydney School of Veterinary Science at the University of Sydney. Her research primarily focused on Australian ticks of medical, veterinary and public health significance, specifically the Australian paralysis tick, *Ixodes holocyclus*, and the brown dog tick, *Rhipicephalus sanguineus* s.l. (now, *Rhipicephalus linnaei*).

Shona's research efforts provided much needed updates for the diversity of ticks in Sydney, and the distribution of brown dog ticks across Australia. In addition, her research enabled the understanding of the microbial diversity of the paralysis tick and other native ticks from various localities across NSW using a metagenomics, 16S rRNA targeted amplicon sequencing approach. Her work on brown dog ticks resulted in the nomination of the 'tropical lineage' of *R. sanguineus* s.l. as *R. linnaei*. Additionally, considering brown dog ticks were first described in Australia in 1896, a retrospective molecular identity study was conducted in collaboration with the CSIRO on museum material of brown dog ticks collected from Australia. Further, Shona conducted a systematic survey utilising morphology and molecular tools to determine the identity of historical and extant brown dog ticks across Australia.

Shona has recently joined the Centre for Infectious Diseases and Microbiology-Public Health (CIDM-PH) as a postdoctoral fellow in pathogen genomics. Drawing on her metagenomics experience and One Health approach, her research will initially focus on determining the longitudinal trends of *Salmonella* Typhimurium and *Streptococcus pneumoniae* infections by combining traditional microbiology with modern, genomic approaches.



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UPCOMING EVENTS

Save the date...

CREID Colloquium
22nd October 2021

MBI Colloquium
17th November 2021

CIDM-PH Colloquium
3rd December 2021

Registrations open soon

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