PHAGE FUTURES CONGRESS

Recap of Phage Futures Congress 2020

An in-depth look at what was discussed at Phage Futures 2020, in Washington D.C. Written by **Jessica Sacher** and **Jan Zheng**, co-founders of Phage Directory.

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In attending this year's Phage Futures Congress, we came away with a clear sense of the imminent need for phage therapy.

We heard patient stories (including a first-hand account), learned how Western clinicians are feeling and faring as they treat patients, and heard about the researcher's role in how compassionate phage therapy is currently done.

The most important next steps for the phage therapy field were discussed, including creatively-designed clinical trials, careful consideration of how best to do phage manufacturing, and rational consideration of economic factors behind scale-up of phage therapy. Other topics discussed at length included how artificial intelligence can help us accelerate phage screening, how phage companies should secure IP protection, how phages should be valued, new phage engineering methods, and much more.

Here, we provide a window into what was discussed.

> "Clinical trials are urgently needed to demonstrate phage efficacy, dosing, and more."

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Phage therapy is needed and is helping patients

Ella Balasa gave a phage therapy patient's perspective; she received phage therapy a year ago to treat her chronic Pseudomonas lung infection (she has cystic fibrosis), and believes it is the reason she was able to avoid a double lung transplant in 2019. She believes more patients should have access to phage therapy, that it needs to be an option sooner in life, and is hopeful that when she needs them again, phages will again be available to her. She said since her treatment, the promise of phage therapy has been increasingly catching on among the cystic fibrosis community (30K patients in the US).

Western physicians are increasingly seeing the promise of phages

Dr. Gina Suh, MD at the Mayo Clinic in Rochester, Minnesota, shared her perspective as a physician who treated a patient with phages in 2019. Although never taught about phage therapy in medical school, she took a chance on a patient who requested phage therapy instead of leg amputation. Her patient went from shopping for a wheelchair to walking around and living a normal, infection-free life. Dr. Suh emphasized that the stars really had to align for this patient's treatment to go forward, that it took the patient advocating for himself, and that as physicians, she and her colleagues are eager to see more data on phage therapy efficacy, dosing, duration, indications, mode of administration, antibiotic combination and more in the near future. She considers it important to move away from individual compassionate use toward designing trials that bring this kind of data on a larger scale, because many more patients need this option to be available soon.

Dr. Jon Iredell, MD at the Westmead Institute for Medical Research in Sydney, Australia, discussed the case series his team did with phages, where they treated more than a dozen septic patients with GMP-produced S. aureus phages (supplied by AmpliPhi) and showed no adverse effects. He said since these patients are so critically ill (30-40% mortality), Australian regulators allowed phage therapy even though it was experimental, since it had a track record of safety. Now he too is focused on moving beyond anecdotal and small-scale studies, and advocates for more clinical trials.

Questions from the audience sparked discussion on whether the data from case studies was generally being collected adequately (panel consensus: no, we should be doing better in this area), and whether or not clinical trials should involve antibiotic co-therapies or be tested on their own (panel consensus: this needs to be determined on a case-by-case basis, but phage-antibiotic synergy is so promising that it shouldn't be discounted in favor of showing that phages work independently of antibiotics).

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Missing pre-clinical phage therapy research; support available from NIAID

Although most conversation regarding the next steps for the phage therapy field involves the demand for clinical trials, Joseph Campbell, a program officer at NIAID, highlighted a major gap in preclinical research on phage therapy. To address this gap, he emphasized that NIAID is now funding preclinical phage therapy research, and that it also has a suite of preclinical services available to the phage research and development community. These include in vitro testing of phages against NIAID's large panels of bacteria, animal models (he suggests attempting to replicate human case study results in animals), and more. NIAID also offers support with product development, including GMP manufacturing of phages, regulatory documentation support.

Clinical trials: practicalities and progress

As is at the forefront of most phage therapy conferences these days, there was a general consensus that controlled clinical trials are urgently needed to demonstrate phage efficacy, dosing, and more. There was also acknowledgement that clinical trials with phages are easier said than done.

Nick Conley, Locus Biosciences' Principal Scientist, discussed Locus' progress toward demonstrating efficacy of their CRISPR-enhanced phage product in the clinic. They're currently targeting UTIs, though they noted that long-term, moving toward microbiome indications and away from infectious disease indications will be key for getting to markets large enough for investors. He discussed how Locus recently did what they refer to as a "phase 0" surveillance study, which has helped them gather key data. In this study, they collected patient samples and tested sensitivity of these isolates with their phage cocktail.

A key point was that Locus has been able to skip the GLP toxicology and Phase 1a stage (healthy volunteers/dose escalation trial) based on the in vivo data they've provided to the FDA. This point surprised some members of the audience, and while the representatives of the FDA present could not disclose details, they affirmed that they had seen enough from Locus to make them confident in not requiring this early step to be done. Locus described that they will pursue a "vaccine-like" approach to their phage regulatory pathway, including the potential to modify their cocktail during development, and that the FDA's CBER vaccines division has expressed comfort with this approach.

Other discussion around clinical trials considered the challenges of proving that phage therapy is superior to the standard of care, since standard of care often works so well. On the other hand, for patients where it doesn't work, they're often very sick. Heather Jones, MD, Medical Director at Armata Pharmaceuticals, said for very sick patients, it would be very hard for a clinician to agree to only using phages in accordance with strict trial requirements, without being able to add and change antibiotics on the fly. She said when patients are that sick, it's panic. Antibiotics get swapped out as new doctors come in. Essentially, she said there is no standard of care for these patients. So her recommendation was to start with medically stable patients when looking to demonstrate phage therapy efficacy, such as cystic fibrosis patients with moderate lung disease and chronic pseudomonas infections.

Phage manufacturing

A big focus of the conference was on phage manufacturing. It's clear that this is required for clinical trials, since phages will need to be produced at scale and their quality over time will need to be maintained. Laurent Ciavatti, Business Development and Project Manager at Clean Cells, the company that did the manufacturing of the phages for the PHAGOBURN trial in Europe, gave a detailed account of the issues they faced trying to produce and maintain stability of multiple phages against multiple pathogens at once. His talk constituted a strong warning that before starting a phage therapy clinical trial, manufacturing needs to be given substantial consideration. His main advice: choose a minimal number of phages to produce at a time. Danish Malik, a senior lecturer in chemical engineering at the University of Loughborough, gave a talk on how his lab works as a contract research organization for phage companies, and can help them optimize their phage production and formulation. (Check out an interview with Dr. Malik that we did just prior to the conference for more information: https://phage.directory/capsid/interview-danish-malik). As well, Frenk Smrekar, CEO of JAFRAL, a European contract research and manufacturing organization that specializes in phages, detailed how they can help phage companies all the way from phage isolation to large-scale manufacturing.

Investment into phage therapy

This conference had an interesting session on investment into phage therapy. Michael Higgins, Managing Director of Senior Biopharmaceuticals Equity Research at the investment banking firm Ladenburg Thalmann & Co, talked about how he evaluates phage therapy companies as investments. He talked about how investors tend to compare phages to antibiotics, and how they see antibiotics as something that will keep failing. That said, Higgins noted that this year is a big deal, and that he is impressed by the numerous successful compassionate cases that have stacked up. He's noting the approximately 10 phage companies that have been funded in 2019, and said the interest in phage from the Department of Defense, NIAID, and CARBX is generating interest among some investors. He emphasized that investors look for others putting money in as signals for what to fund. Higgins predicted that in five years we'll hopefully see a lot more public phage companies. Something he highlighted was that investors would look favorably upon something that could be an outpatient treatment, and that seeing phage treatments being reimbursed at $30-40K per patient (and not something low like 3K) is what they're looking for. They want to see companies with $50M annual revenue. He said most investors don't fully appreciate that there's anything unique going on with phage manufacturing yet, but that he can see opportunities for phage manufacturing IP, especially after touring Armata's GMP facility. He also said investors don't appreciate how cheap it is to manufacture phages, how phages can cost less than the vial they're stored in (if manufactured at scale). He also mentioned that anything preventative is harder to sell to investors than therapeutics that treat patients. And he said that investors find it easier to think about respiratory and surgical patients than other patient types, so phage therapy companies covering those indications may fare better.

Phage AI

A topic that came up a lot at this conference was the use of artificial intelligence in the phage field. It's clear that the field values rapid assessment of whether a phage will be useful or not, and algorithms are beginning to be developed that can start making predictions about phage attributes based on phage genome sequence data. Proteon Pharma, a Polish phage company, is creating machine learning tools for phage identification. It's currently a free tool (https://phage.ai), and can tell you whether a phage is lytic or temperate. A key feature is that the tool can be used without the need for a researcher to make their information public; the algorithm can be run privately. Next, they'll be working on a taxonomic classifier and other tools. Also, in making this tool, they had to organize more than 10,000 public phage genomes; these are now free for download on their website. They noted that they are seeking corporate and academic partnerships to keep expanding their dataset and what they can do with it.

Shawna McCallin of Phages4A gave a talk on how her company is developing algorithms that can predict host range of phages. But to train their algorithm, they need substantial amounts of reliable data from phage host range tests. To date, that's not something that's been standardized, so this data is hard to come by. To address this, Phages4A is developing an AI tool called DeepPetri for detecting and quantifying phage lysis based on images of plaque assays. In the near future they'll be rolling out a survey to help demonstrate to the phage community how much variation there is between different researchers as they read the results of their plaque assays.

This part of the conference brought on many audience questions; it's clear that researchers and phage developers alike are interested in, and also reasonably skeptical of, the foreseeable role for AI and machine learning in the phage field. This will be an interesting area to watch.

Protecting intellectual property

Phage IP was a prominent topic at this meeting, with a talk by Michele Wales of Inhouse Patent Counsel and a panel that delved further into this topic. It was made clear that natural phages can't be patented, but they can be if they've got alterations to their sequence. Wales said that a good way to protect against genetic drift of patented phages is to deposit phages with a repository like ATCC when you disclose your patent. For more on phages and IP, check out the interview we did with Michele at https://phage.directory/capsid/interview-michele-wales.

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Financial incentives for phage development

The discussion on phage IP led to a discussion among the audience about government incentives for drug development. Tobi Nagel of Phages for Global Health brought up the precedent that HIV drugs got a push in the US because people were dying, but governments were needed to bring them to African countries. Scott Walker of Merck said Achaeogen, a company that recently released a new antibiotic and subsequently went bankrupt, couldn't even make enough money to do the proper marketing of its new drug once it gained marketing approval. The underlying message was that "getting across the finish line" isn't enough when it comes to drug development, especially when it comes to antimicrobials. There need to be serious considerations about long-term incentives. Walker mentioned that for MDR bacteria, there's no grassroots organization that builds it up, but that a coalition approach might help a lot toward building a case for pull incentives for phage therapy. There was some talk among the audience and the panel about the merits of lobbying for/against policy decisions with implications for phage product development.

Joseph Campbell of NIAID began a conversation about vouchers, where for instance a company selling a new antimicrobial might sell a year of their patent protection to a company selling a cholesterol medicine; cash would flow toward the antimicrobial company, thus acting as a pull incentive. Carrie-Lynn Langlais Furr added that although there aren't currently vouchers for antimicrobials, this system exists for tropical diseases, where you can sell vouchers that give others priority regulatory review (which lets them get to market sooner). She said one voucher was sold for $330 M. However she said currently it's unknown what incentive systems will look like for antimicrobials, and more specifically for phage products, so it's unknown what kind of data will need to be collected to qualify for a voucher. Scott Stibitz of the FDA said that the FDA will need to take a look into this system, and noted that the tropical voucher system is only for vaccines for now.

The US regulatory environment for phage therapy

Things are looking favorable for phage therapy from a regulatory standpoint in the US. At the meeting, Cara Fiore of the FDA reiterated the FDA's commitment to working hand-in-hand with phage companies to improve the chances of phage product market approval. This was also demonstrated through hearing about North Carolina company Locus Biosciences's encouraging dealings with the FDA to date.

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Phages and global health

Another interesting topic given attention at the conference was commercializing phage therapy in a global health setting. Dr. Minmin Yen, CEO of PhagePro, made the case for phages being used preventatively among members of households that contain cholera patients, since the cholera vaccine cannot help these patients fast enough. Her company is working toward an oral phage cocktail and will be testing its efficacy at the icddr,b in Bangladesh.

Dr. Tobi Nagel gave a talk on her nonprofit, Phages for Global Health, which trains researchers in developing countries, who will be hit hardest by antibiotic resistance, to work with phages. Her organization also works toward phage product development, with one current project involving development of Campylobacter phages for agriculture in Kenya. She emphasized the need to work closely with local farmers and other stakeholders, and mentioned that 'agri-veterinarians' are the key people to work with in Kenya on phage product development for agriculture.

Roundtable discussions: stay tuned for a special issue in Mary Ann Liebert's PHAGE journal

The conference included a set of roundtable discussions on topics like sourcing and valuing phages, how the community should be systematically collecting data on phages, clinical considerations, phage diagnostics, and the value of academic-industry partnerships in phage development. Descriptions of the outcomes of these discussions will be covered in an upcoming issue of PHAGE Journal.

Concluding remarks

Although only four months passed between Phage Futures Congress 2020 and the European counterpart of this meeting, the level of conversation at this most recent meeting already gave the feeling of a more mature field. The global conversation is shifting from whether phages work and how to prove it, to scale-up, IP considerations and long-term financial prospects. Companies in the space seem to have a clear idea of what they need to do when it comes to clinical trials, and what's being discussed now is the logistics of phage manufacturing and attracting more substantial investment to the field, both from public and private sources. And importantly, the US FDA continues to demonstrate its commitment to working with developers of phage therapeutics to regulate phage products in a way that makes sense for phages.

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Learn more: check out Phage Futures' social media archives!

Phage Directory provided live coverage of Phage Futures Europe through a custom live feed, which is archived here.

Additionally, the Twitter hashtag #phagefutures was used by many throughout the event (read Tweets from the event here.

Many thanks to Phage Directory's social media assistants Sabrina Green and Ella Balasa, who were integral in providing the event coverage!

About the authors: Phage Directory

Phage Directory provides software and services to make it easier and faster to research and develop phage products. Our mission is to help unlock the untapped potential of phages for phage therapy and biocontrol by empowering people to access, use and build upon the world's phage knowledge.

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