PHAGE FUTURES CONGRESS

Recap of Phage Futures 2019: How do we commercialize phage therapy?

An in-depth look at what was discussed at Phage Futures 2019, in Washington D.C. Written by **Jessica Sacher** and **Jan Zheng**, co-founders of Phage Directory.

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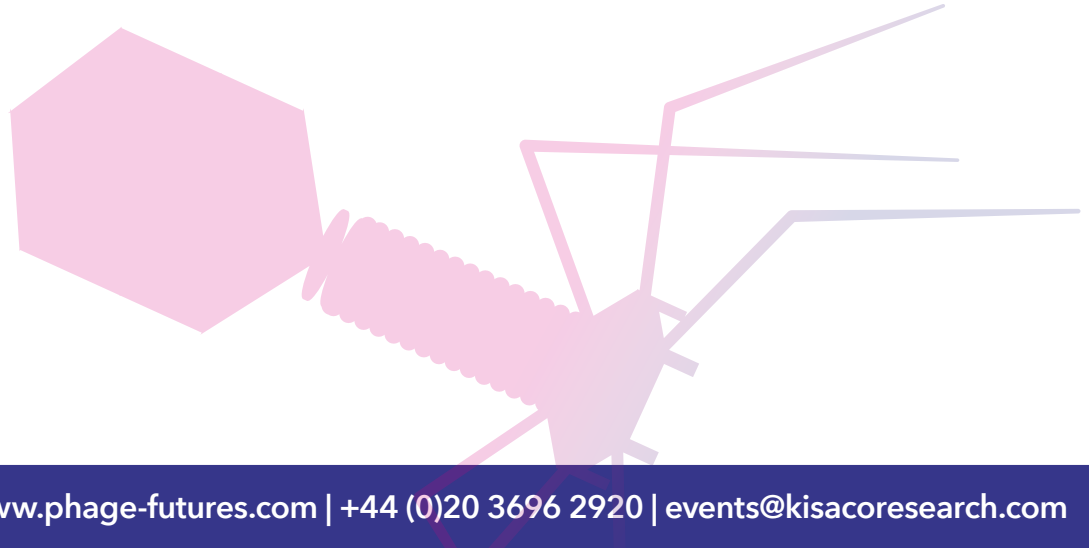
The first annual Phage Futures Congress, hosted by Kisaco Research, was held in Washington, DC from January 29-30, 2019. The event brought in a diverse audience, including representatives of biotech companies that have been in the phage world for some time (like Ampliphi Biosciences) and several that have recently entered the field (like Adaptive Phage Therapeutics, Eligo Bioscience, and Locus Biosciences). Big pharma was represented (Merck, Johnson & Johnson), as were US government agencies such as the FDA and the NIH, and several prominent academic phage researchers were present (such as Dr. Martha Clokie and Dr. Betty Kutter).

This diversity of backgrounds led to two full days of highly engaging presentations and discussions. It appears that the field is filled with passionate, sometimes divergent opinions on how phage commercialization should proceed, but people generally seem ready and willing to learn from one another and move forward.



> "This is a concerted effort to build a phage industry from the ground"

PhagePro
@PhagePro

One-size-fits-all or personalized phage therapy: both strategies have merit

Over the two days, several themes and questions emerged. For instance, there were questions about which route to market is best for phage therapy, ie. whether phage cocktails should be prepared for one-size-fits-all treatment, or whether a personalized approach is preferable. Overall it appears that there will be room for both routes in this field, and that both are plausible and possible. We heard from companies moving forward with each strategy, and the FDA appeared positive and open-minded about both approaches.

Natural vs. synthetically engineered phages: room for both

Similarly, the question of whether to use phages in their natural form vs. engineered/synthetic phages emerged. Representatives of companies like C3J Therapeutics, Locus Biosciences and Eligo Bioscience described their efforts to engineer phages to have different properties, such as higher killing efficacy, altered host ranges, and resistance prevention. On the other hand, strategies used by Ampliphi Biosciences, Adaptive Phage Therapeutics and BiomX to employ natural phages in therapeutic settings were also described.

This dichotomy seemed to be met with similar answers to the one above: essentially, it seems that there will be room for both strategies, and company/investor preference will likely dictate which is used.

Phages for acute infections vs. chronic, microbiome-linked disease: both are being pursued

Another dichotomy discussed was that of phages to treat acute antibiotic resistant infections vs. using them to modify the microbiome to treat chronic disease. Traditionally, phage companies have been aligned towards the former, and this is still a primary strategy of several companies, but this meeting brought up a great deal of discussion on the latter. Locus Biosciences, Eligo Bioscience and BiomX described their strategies of identifying chronic disease-associated bacteria and targeting them with phages. The recently publicized partnerships between the pharma giant Johnson & Johnson and both Locus Biosciences and BiomX suggests that microbiome manipulation might be particularly favorable in the eyes of early investors.

Clinical safety trials: general trust in the safety of phages, now time for clinical efficacy trials

Although there appears to be a consensus that phages are safe, phase I safety trials, where phages are tested on healthy patients, were suggested to be nearly pointless for phages due to the lack of pathogenic bacteria present. This would lead to a lack of phage replication or bacterial lysis, and a lower dose of phage than a real patient would see. Dr. David Harper of Evolution Biotechnologies suggested that phage trials should start at phase 1/2, meaning that safety and efficacy should be evaluated simultaneously from the beginning.

Clinical efficacy trials: a major hurdle to commercialization that has yet to be surmounted for phage therapy

A great deal of discussion centered on clinical efficacy trials, and this emerged as the most important hurdle standing before phage commercialization. It appears that for pharma to invest (which would allow for scale-up of phage therapeutics), they need to see demonstrations of efficacy in clinical trials, and they haven't seen this yet.

There was extensive discussion regarding why most clinical efficacy trials done with phages have been unsuccessful to date. Dr. Shawna McCallin, part of the Nestle phage therapy trial in Bangladesh (2016), led a deep dive into the main reasons for these failures: namely, poor clinical trial design and difficulties manufacturing phages. To illustrate the latter, Dr. Laurent Bretaudeau described the difficulties their team at CleanCells had in manufacturing phages for the 2017 Phagoburn clinical trial. However, it was acknowledged that a great deal of experience has come from these failures, and the open communication about what went wrong was praised by some. There appeared to be optimism that going forward, effective trial design and phage manufacturing could be achieved. In fact, several of the phage biotech companies that were present plan to begin clinical trials as early as 2019.

Toward this end, several groups proclaimed their willingness to collaborate to expedite preclinical and clinical phage development. For example, Dr. Joe Campbell made it clear that NIAID is willing to collaborate with groups who want to test their phages in NIAID's animal models, and encouraged the phage community to get in touch. Greg Merril of Adaptive Phage Therapeutics expressed his company's openness to the idea of partnering with groups in need of phage manufacturing.

Overall, there seems to be a collaborative spirit among the phage community, a willingness to learn from past mistakes, and a shared goal of demonstrating clinical efficacy of phages in the near future.

The FDA is supportive of phage therapy clinical efficacy trials and invites companies to reach out to them early

FDA representatives present at the conference made it clear that they support endeavors to demonstrate clinical efficacy of phage therapeutics, and emphasized the importance of working closely with the FDA when designing clinical trials. They emphasized that phage therapy represents new ground for the FDA, but they appeared open-minded to a variety of approaches for phage development as a biologic drug.

There were questions for the FDA about the extent to which they pay attention to phage regulation in other countries. The response was that the historic data collected from Eastern European phage treatments will not substitute for phage clinical efficacy trials for drugs licensed in the US. Similarly, the recently introduced magistral phage framework in Belgium is on their radar but does not replace their need to see efficacy data collected in controlled clinical trials going forward.

Compassionate phage therapy: enormous potential benefit for individual patients but NOT sustainable or scalable

A big part of the conference revolved around compassionate use of phages. Since the successful treatment of Tom Patterson in 2016, several other US patients have been treated successfully with phage therapy. Tom Patterson himself, along with his wife, Dr. Steffanie Strathdee, who pioneered the phage crowdsourcing that led to his treatment, shared their unique perspectives. Dr. Benjamin Chan of Yale University presented data on 6 patients he has treated with phages since then, all of which appear to have responded very well. Both of these talks were inspiring to many.

Overall, most in attendance seemed to agree that phages can be enormously beneficial for individual patients who can receive phage therapy. However, the consensus was that compassionate phage therapy is not economically viable. Also, in response to perceived confusion in the field, the FDA emphasized that compassionate use is NOT intended as a way to collect human data about a drug prior to clinical trials. Rather, it is intended to treat the individual patient.

> **The primary purpose of expanded access is to provide access to the drugs, and it's not to provide safety or effectiveness data to support drug development**
>
> Dr. Cara Fiore
> FDA

> **It's clear that phage therapeutics can address an unmet need**
>
> Kate Kitsopoulos
> Triangle Insights Group

Making an economic case for phage therapy

Another emphasized concept was the economic case for phage therapeutics. Several speakers, such as Kate Kitsopoulos, a life sciences consultant for Triangle Insights Group, emphasized the importance of choosing a health indication wisely before developing a phage product. Focusing on unmet need (ie. looking at the costs associated with antibiotic resistant infections in a particular patient population) and communicating the associated cost savings a phage therapeutic would provide will help investors, hospitals, and insurance companies see the value in phage therapeutics.

Alternative models for phage commercialization

In addition to the overarching key themes that were repeatedly touched upon, there were also some alternative ideas presented.

Phages in veterinary medicine: a possible way to reduce clinical trial costs, get valuable data, and attract investors

The only human clinical efficacy trial for phages that has been successful to date was an otitis trial in the UK (2009). This trial was done inexpensively and was based upon data obtained from a dog otitis trial done beforehand. Dr. David Harper, who designed and oversaw this trial, emphasized that this strategy worked well and could be repeated. He explained that taking phage therapeutics to market as a treatment for companion animals can be a good way to convince investors to invest in human phage therapy trials. Furthermore, the fact that veterinary clinical trials are less expensive than human clinical trials (and that pet owners are happy to enroll their pets and will pay for products once on the market) makes this industry a logical stepping stone for those interested in commercializing phages.

Phage therapy products for emerging markets

As another first step toward demonstrating efficacy, Dr. Tobi Nagel of the nonprofit Phages for Global Health challenged the phage community to seek opportunities to develop phage therapy products for emerging markets (a subset of developing nations with rapidly advancing economies). Funding may be easier to come by for phage therapeutic development targeting these markets, especially since some of these countries are much harder hit by antibiotic resistance than developed nations.

> **If you prove it right, you can prove it can be done.... If we can get [phage therapy] to market in companion animals, we can potentially convince a lot of people.**
>
> David Harper
> Evolution Biotechnologies

Phage therapy as a way to improve antibiotic stewardship

Instead of using phages to treat infection as a last-line drug, Dr. Carl Balibar of Merck brought up the possibility of using phages as a first-line treatment one day. This would ideally reduce antibiotic use (and thus resistance) overall. However, this would come with new challenges. If phages were marketed to target routine infections, they would have to be priced cheaply and deployed across large populations, and large amounts of real-world data would be required to prove a reduction in antibiotic resistant infections.

Overall impressions

It is clear that the commercialization of phage-based technologies in Western countries is garnering a surge of interest, and there is a strong sense of urgency across the board about getting things right. It seems like there will be many “right” ways going forward, each with their own challenges and trade-offs. Excitingly, several of these strategies are now being seriously explored by biotech companies, the FDA is supportive of their efforts, and pharma is beginning to pay attention.

COMING SOON

PHAGE FUTURES EUROPE

2019 September 25-26th | Belgium

Confirmed Speaker

Dr Ard Struijs from **Erasmus** University Medical Center will be providing a Physician's perspective about administering phage therapy.

Focusing on:

- Magisterial Phage: Who, What and Why?
- Learn from the Belgium early adopters.

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PHAGE FUTURES CONGRESS

2020 January 29-30th | Washington D.C. | USA

Confirmed Speakers

Dr Cara Fiore
Microbiologist
Center for Biologics Evaluation and Research
FDA

Dr Carl Balibar
Principal Scientist
Merck

Dr Biswajit Biswas
Chief, Division of Bacteriophage Science, Biological Defense Research Directorate
US Naval Medical Research Center

Focusing on:

- Developments within phage applications across acute and chronic illnesses
- Regulatory discussions, including clinical trial landscape updates
- Understanding of the animal health phage applications can translate into progressing human phage therapy commercialisation

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About the authors: Phage Directory

Our mission is to accelerate the safe and effective use of phages in medicine and industry around the world. We aim to accomplish this goal by curating phage-related content, advising on phage-related topics and coordinating collaborations within and across disciplines.

For regular updates on phage therapy research, subscribe to their newsletter Capsid & Tail at phage.directory/capsid

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