A Regulation Proposal for the Approval and Implementation of Novel Phage Therapies in Medical Settings

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Summary
The OhioState 2021 iGEM team is proposing a genetically engineered phage therapy solution to treating sepsis. This solution targets the harmful endotoxin, lipid A, that is left untreated when typical antibiotic medication is administered to treat Sepsis. Without addressing the endotoxin, the patient's organs can still go into failure.

The lack of regulations surrounding phage therapy prevents the use of this treatment. The Coordinated Updated Framework from 2017 outlines the current regulatory standing for biotechnology products, but phage therapy is not included in this document. Additionally, the FDA does not outline the criteria that phage therapies need to meet to move to a clinical trial phase. As such, there should be a regulation added that considers the use of synthetic biological phage therapy solutions to treat diseases.

Background
Sepsis is a life-threatening complication due to an overreaction of the immune system to a bacterial infection in the blood. There are about:

- 1.7 million cases in the United States each year
- 270,000 Americans dying from sepsis each year

And 1 in 3 patients who died in a hospital died from a sepsis infection, making sepsis one of the leading causes of death in the hospital setting (1).

Antibiotics are the typical medication prescribed for a bacterial infection. Many target the bacterial cell wall, which in turn leads to the bacteria lysing, or breaking apart. Lipopolysaccharide (LPS) is a membrane protein in gram-negative bacteria and is made of three different components: an O-antigen, core oligosaccharide, and, most importantly, lipid A.

Lipid A is the component of the LPS that results in the toxicity of gram-negative bacteria. After cell lysis, the LPS, and therefore lipid A, is released into the body. The immune system takes action by causing a cytokine storm, which is an over-release of cytokines. A cytokine is a protein that signals for the immune cells to travel to a certain area in the body. Too many cytokines cause a cytokine storm, which can lead to organ damage and eventually death due to an overabundance of immune cells.

Solution

Phage therapy is an effective way to prevent a cytokine storm while still resolving a septic infection. Phage are viruses that infect and kill bacteria by lysing. The Ohio State iGEM team is

developing a new treatment for sepsis where the natural ability of phage to infect a specific bacteria will be leveraged to lead to the transcribing of proteins that bind to lipid A.

The first step to this involved researching modifiers that could detoxify LPS, namely binding to the lipid A portion of LPS or stopping its release all together. To prevent the phage from immediately lysing the bacteria, it was decided that it would be best to use a FraR repressor alongside a pFraB promoter, which represses phage toxicity genes so that they do not lyse the bacteria. To clarify, here is an outline of how this circuit will function:

Since the phage requires the bacteria as a host to produce in, it would be a disadvantage for lipid A proteins to be produced because anti-lipid A proteins will be toxic to the bacteria. The phage needs to be produced to be used as a therapeutic for treatment in humans, and the way to produce them is by growing them in a bacterial host. The genetic circuit to produce these results will contain two promoters. These promoters are pR and pFraB, which are located upstream of the anti-lipid A protein genes. The pR promoter functions to encourage overexpression of the anti-lipid A proteins, while the pFraB promoter will allow for the production of the phage in the lab setting. When the FraR repressor binds to the pFraB promoter, the anti-lipid A protein cannot be produced. Since the anti-lipid A protein needs to be produced when the phage therapy is used in humans, FraR will not be used outside of the lab. The sole purpose of the FraR is to allow the phage to be produced.

We put each of the modifiers in a separate FraR circuit to test the efficiency. By using these circuits and putting them into a phage, the release of lipid A can be prevented while still using phage to kill the bacteria.

Due to the properties of engineered phage, a new piece of legislation should be designed that allows this phage therapy to be considered as a treatment for sepsis. Currently, there is no outline on the steps needed for phage therapy to be approved in a given setting. There is limited implementation of phage therapy, and implementation has only been approved by the FDA in emergency situations (5). As of now, there is only one phage therapy being tested in a clinical trial, which is attributed to the lack of regulations surrounding this area (2). Less regulations for approving phage therapy leads researchers and doctors to stray away from implementing this technique for treating bacterial infections. A database that contains phage permitted for treatment by the FDA should be used so that phage therapy can be implemented as a treatment in a clinical setting.

The Cost of Sepsis

Sepsis accounts for around 24 billion dollars of annual healthcare spending in the USA. This is the largest spending amount for any one ailment (4), and it is disproportionately high considering that sepsis cases account for only 3.6% of hospital stays in the USA (3). One of the largest reasons for the disproportionately high cost of sepsis treatment is the amount of time sepsis patients spend in the hospital. Sepsis patients spend 75% longer in the hospital than most other conditions (4). It is also important to point out that there is a strong correlation between the severity of a sepsis case and the cost of treatment. Additionally, as severity and treatment prices increase, so does mortality rate. As noticable in the following figure, sepsis has a large cost to our society.

Severity of Sepsis Case	Average Cost	Average Length of Stay	Mortality Rate
Average	$18,023		12.5%
Mild Sepsis without Organ Dysfunction	$16,324	4.5 Days	5.6%
Severe Sepsis	$24,638	6.5 Days	14.9%
Septic Shock	$38,298	16.5 Days	34.2%

Overall, the amount of money poured into sepsis treatment, along with the high mortality rate, and the lack of innovation in treatment options shows that current sepsis treatment is ineffective and inefficient. The aim of this proposal is to introduce a new treatment for sepsis that lowers the sepsis mortality rate and cheapens the cost of sepsis treatment. Current sepsis treatment is a very individual process, and not a one size fits all, upscale-able treatment. This phage therapy is much more universal than the current sepsis treatment, making it cheaper and easier to scale.

Ethical Implications

Phage therapy, in itself, requires no more ethical consideration than any other experimental new drug. If anything, ethical considerations favor the development of phage therapy if it is considered that scientists have a moral obligation to provide a solution to combat emerging health issues, like antibiotic resistance. The traditional ethical considerations for experimental drugs that apply to this phage therapy are as follows: ethical testing and informed consent, patent rights, proper implementation, and equal access based on socioeconomic status (2).

Ethical testing and informed consent are the largest consideration for the near future of our project. There is a moral obligation to consider the lives and free wills of patients who volunteer for trials of this therapy. This is ensured through complete transparency and sharing as much knowledge as possible. Proper experimental design and strict regulation, both internal and

external, are also key in ensuring ethical human testing. In general, the purpose of human trials is not to heal the test subjects, but rather to gather data on the drug/therapy. This is something that should also be emphasized to patients before signing off on joining the trial.

If the point of patenting is reached, it should be used only to ensure that proper accreditation for the discovery is given and ensure that further research can be published without fear of the idea being stolen (2). This does not give permission to charge unreasonably high costs for this therapy.

Proper implementation is important when considering the rapid evolution that bacteria can produce. If phage therapy is not used carefully, then the problem of phage therapy resistance will develop, similar to how overuse of antibiotics has led to antibiotic resistance. That means it is important that each researcher plays a part in ensuring that the therapy does not encounter resistance issues, such as by only using the therapy when it is the only option to treat a patient.

Lastly, equal access to the therapy should be ensured, regardless of socioeconomic status. This relates to the ethical implication of patent rights, as access to capital should not be a determining factor for optimum medical treatment. It is on the researchers and doctors to ensure that is the case. The optimal situation to solve this problem is to create a process for wide scale distribution. If that is not possible, it is important to ensure that what phage can be produced are only used in dire straits and that monetary incentive plays no part in the decision of who has access to the therapy. At some point, that burden falls on the hospital systems to ethically administer the therapy, but each researcher should also do their best to promote ethical administration of the product.

Works Cited

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