

# THE FANTASTIC PHENOMENON OF PHAGES

We talk to **Prof. Andrzej Górski** from the Hirsfeld Institute of Immunology and Experimental Therapy about what is going wrong with antibiotics and whether they might one day be replaced with bacteriophages.



JAKUB OSTALOWSKI

## PHAGE THERAPY

**ACADEMIA: Is your field of study, phage therapy, developing so rapidly because the potential for using antibiotics is slowly being exhausted?**

ANDRZEJ GÓRSKI: The scale of the threat is demonstrated by the fact that the issue of dramatically increasing antimicrobial resistance was recently raised by the UN General Assembly (in September 2016). The UN secretary general compared it to the challenge posed by global warming, whereas the director-general of the WHO added that doctors facing patients will soon have to start saying, “Sorry, there is nothing I can do for you.” In fact, experts believe that we’ve been already brought back to the pre-antibiotic era. In a recently reported case, a female patient had a urinary tract infection caused by *E. coli* resistant to colistin, which is used as a last resort only when other antibiotics fail, especially carbapenems. All this despite the fact that the hopes pinned on antibiotics were so great that the US surgeon general, the country’s top public health official, is reported to have said in the 1960s that it was time to close the book on infectious diseases. Shortly thereafter, the bacteria turned out to be smarter and capable of developing resistance to antibiotics.

**Phage therapy is nothing new, having started in the early twentieth century.**

That’s true, bacteriophages, or “phages” for short, were discovered 100 years ago. In 1915, the British bacteriologist Frederick Twort reported that certain bacteria could be killed by certain viruses. Those findings were confirmed by the Canadian microbiologist Félix d’Hérelle, who soon isolated the first phages and made the first attempts at using them therapeutically. Such therapy was later quite broadly used, also in the United States (where phage preparations were produced by the famous company Eli Lilly) prior to World War II.

**After antibiotics were discovered, however, phage therapy was abandoned in the West in the 1940s. Nevertheless, the research continued in the former Soviet Union, which had limited access to Western scientific achievements. Can the fact that we have a phage therapy center in Poland be explained as a legacy of this?**

Indeed, the facility with the longest traditions in phage therapy is the George Eliava Institute in Tbilisi, Georgia, which was once part of the Soviet Union. Phage therapy started there shortly after World War I. In Poland, we have similar traditions: the first reports of phage therapy come from the 1920s and significant contributions to its development were made by Prof. Ludwik Hirszfild, who studied phages in the State Hygiene Institute in Warsaw and later moved the research to the institute he founded in Wrocław. His studies and therapy were continued by Prof. Stefan Ślopek in the 1970s and 1980s.

**Does antibiotic resistance already pose a major problem?**

As I said, the threat posed by antibiotic resistance is growing dramatically. A expert report commissioned by British Prime Minister David Cameron predicts that if nothing changes, antibiotic resistance will become the number-one cause of death by 2050, followed by cancer. According to estimates, it may kill up to 10 million people as a result of infections caused by such well-known and common pathogens as staphylococci, *Klebsiella*, and *Pseudomonas*.

**Should we blame this on antibiotic overuse?**

Too many antibiotics are used worldwide and such uses are not always justified. Also, antibiotics are administered in huge amounts to farm animals. In addition to antibiotic overuse, advances in the introduction of new antibiotics are too slow, which is yet another factor behind the ongoing crisis. The pharmaceutical industry is withdrawing from efforts to develop new antibiotics, because the expected profits from such drugs are too low compared to the costs of development, as bacteria quickly develop resistance to new medicines.

**So, antibiotics could come to be replaced with bacteriophages. What are they?**

Viruses.

**But viruses are usually thought of as causing disease, not treating them.**

Yes, but the viruses that attack bacteria show no predilection for the cells of mammals, or do not have the molecular mechanisms to cause substantial damage to the functions of these cells. They only infect bacteria and are usually highly specialized, unlike antibiotics. Some phages are so highly specialized that they recognize not only a specific species but even a specific strain of bacteria. Not so long ago, they were even used for the typing of bacterial strains, and such tests can still have certain epidemiological significance. Phage libraries are an important research tool in biomedicine.

**Where can phages be found?**

Phages “feed on” bacteria, so they are found wherever bacteria are present. They are an integral part of the natural environment. If we tested the tea we’re drinking, every milliliter would probably turn out to contain billions of phages. The same holds true for food, soil, even feces. In most cases, therapeutic phages are obtained simply from sewage, often hospital sewage.

**How is that done?**

We put the material where we expect to find phages on a plate with bacteria. After a period of incubation, we can observe the emergence of plaques, or spots where phages have caused the lysis of the bacteria. We then grow the phages found in the plaques in specific strains

**Prof. Andrzej Górski**

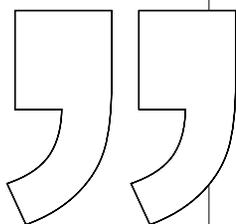
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of bacteria, thus obtaining a phage preparation. Once properly prepared, it can be used as an antibacterial.

**That's done at the Phage Therapy Unit in the PAS Institute of Immunology and Experimental Therapy. Is it the only unit of this type in Europe?**

Yes, even on a global scale. We are the only center of experimental phage therapy that operates according to the most recent ethical, legislative, and administrative requirements in place in the EU countries and in the United States.



Phages trump antibiotics in that they are usually highly specialized, some of them so much so that they only attack one specific strain of bacteria.

**How did the unit come about?**

Phage research was initiated by the founder of the Institute, Prof. Ludwik Hirszfeld, whereas phage therapy was developed by his successor, Prof. Stefan Ślopek. In that period, the Institute produced phage preparations that were given to hospitals, chiefly in Lower Silesia. When Poland joined the EU, we had to adjust to new requirements, including direct contact between the doctor and the patient and the ongoing care and monitoring of patients. When I took over as director of the Institute in 1999, I realized that the only option was to create a separate unit for phage therapy. Formally, it would have been much easier to create a private center, because phage therapy does not fit into the statutory activity of the PAS institutes. In order to continue the mission of Prof. Hirszfeld and his successors, however, we decided to establish such a unit. Obtaining relevant insurance proved to be the most complicated issue. No insurer knew what phages were and the word “viruses” caused fear. In 2005, we finally managed to establish a unit that operated in accordance with all Polish and EU-wide requirements.

We treat patients practically from all over the world and we constantly receive requests for help. Phage therapy is becoming increasingly popular. Experts are pushing for the establishment of similar centers in other countries. There are no regulations that forbid that, and experts predict that the first phage-based products may be registered as drugs and reach pharmacies around 2020.

**Is it possible to produce phage preparations and sell them in pharmacies, just like antibiotics?**

The process poses no major technological challenge. But pharmacies can only sell products that have obtained all the relevant approvals. Clinical trials have to be conducted. We have not managed to do that yet, because we don't have the funds. We have published our findings in recognized journals, such as *Frontiers in Microbiology*. These findings offer strong arguments in favor of the safety of phage therapy, but clinical trials are formally required for registration.

Dr. Robert M. Califf, commissioner of the Food and Drug Administration (FDA) in the United States, suggests that such observational studies could even replace clinical trials in certain cases. I am convinced that sooner or later phages will become part of standard therapy – that's because in the race between bacteria and our civilization, the bacteria are now clearly winning. Maybe such therapy will involve phages, maybe the enzymes they produce to destroy bacteria. I ask the skeptics: as a doctor with nearly 50 years of experience, should I allow a patient with an incurable infection to die, just because phages are not officially registered as drugs yet? After all, we have every reason to believe that such treatment may be effective and, above all, it has no significant side effects. The first principle of the medical profession is *primum non nocere* – “first, do no harm.”

**Why doesn't the Institute conduct clinical trials?**

For a very prosaic reason: we don't have the money. Such trials are usually financed by the pharmaceutical industry, which is, for the time being, not seriously interested in phages. As for EU funds, the EU has so far announced only one project, which was won by a foreign biotech company. Under the current scheme of grants from Poland's National Center for Research and Development (NCBR), it is also very hard to identify such funds, they require collaboration with commercial companies, and the role of scientific institutes in such projects is often reduced to that of a subcontractor. I'm not sure if profits should be a significant criterion for grants meant to improve human health and distributed from public funds. So for the time being, we use phages as an experimental therapy.

**What does that mean?**

If all existing treatment options have failed, then, pursuant to the Medical Profession Act and the Declaration of Helsinki, a doctor has the right to use an experimental therapy, or a therapy whose value has not been ultimately confirmed according to the principles of evidence-based medicine, which means in clinical trials. At the same time, the doctor should have data suggesting that such therapy is safe and may prove effective. The results we have obtained in the Institute and published in international journals undoubtedly provide this basis; they have been presented at various international conferences. We also have an animated scientific exchange with foreign centers.

## PHAGE THERAPY

**What does phage therapy at the Institute look like from the patient's perspective?**

We only consider such treatment options for patients in which existing methods, especially antibiotics, have failed. After isolating bacteria from the material taken from the patient, we check if we have a phage in our bank that could destroy the bacteria. The bank has over 700 phages, so we are very likely to find one that is suitable. Of course, pathogens change, so we constantly try to obtain new phages in order not to fall behind in this race.

**Do you operate as an outpatient facility?**

Yes, we have no inpatient ward, so for now we operate as an outpatient clinic.

**How much does such treatment cost?**

Experimental therapy is not funded by the National Health Fund (NFZ), so it is necessary to cover the cost of the production of bacteriophages, phage typing, and medical consultations. The breakdown of these costs is presented on the Institute's website. Payments are made into the bank account of the Institute.

I receive no remuneration for that, my younger colleagues are paid symbolically. I dare say we work *pro bono publico*.

**What types of infections do you deal with?**

Practically all of the infections with respect to which we have phages. The most common ones include complications following orthopedic surgeries, broken limbs, bone infections caused by staphylococci, complications after hip and knee replacement surgeries. We often deal with infections of the urogenital system. The results are especially encouraging in patients with chronic prostatitis.

**What does a phage bank look like?**

Phages are stored frozen in vials. If necessary, they can be thawed and propagated, as I said before. We produce some of the preparations ourselves. As for other preparations, especially highly purified preparations produced according to Good Manufacturing Practices (GMP), we can order them from Biomed Kraków. However, they are more expensive, which is not without importance, because these costs are borne by patients. At the same time, there is no evidence yet that they are more effective than traditional preparations.

**You've mentioned interactions between phages and the human immune system.**

That's a completely new and fascinating field. We started exploring it around 15 years ago, when we noticed that phages could interact with blood platelets and lymphocytes. In 2005, we published a hypothesis about the protective and potentially immunomodulatory effect of phages found in the gastrointestinal tract

and their translocation from the gastrointestinal tract to other tissues and the possible immunomodulatory significance of that phenomenon. We demonstrated that phages could have anti-inflammatory properties, reducing the production of free radicals (which means that the patients treated with phages often show a dramatic drop in the levels of C-reactive protein, a very sensitive marker of inflammation), as well as the erythrocyte sedimentation rate and the white blood cell count. They can also neutralize endotoxins, which probably play an important role in the pathogenesis of sepsis. In mice, they can cause a decrease in inflammatory infiltration.

This shows that our findings seem to be opening a new avenue for phage research, distinct from their well-known antibacterial properties. Recently, our hypothesis about immunomodulatory role of phages and their translocation received confirmation by two important reports: a) demonstrating their presence outside the human blood and suggesting that indeed translocation is responsible for this phenomenon (Brown-Jaque et al, *Scientific Reports* 2016 doi.10.1038/srep3300); b) suggesting that the beneficial effects of fecal transplantation can be mediated by phages (Ott et al, *Gastroenterology* 2016, listopad).

We treat infections that result from complications after surgeries, urinary tract infections in women and prostatitis in men, including young men.

**In other words, phages not only cure an infection but also reduce the burden it places on the patient.**

Yes. The treatment is the sum of these two properties. Phages not only eliminate bacteria but also have anti-inflammatory properties, which may improve the health of patients to a significant degree.

**It seems that new opportunities are opening up in medicine.**

No scholar is immune to the subjective evaluation of his or her own achievements, and this certainly applies to me, too. But I do hope that our publications and the invitations we receive to deliver lectures at reputable centers abroad confirm the objective value of our work, whereas our patent applications, both granted and filed, confirm their innovative character.

INTERVIEW BY AGNIESZKA KLOCH

