00:00:02:20 - 00:00:15:11

Martha:

Everything is sort of aligned now in terms of expertise. We have access to the technologies that we need. We're in a good position to actually make this treatment reality.

00:00:15:16 - 00:00:45:06

Katie:

Hello. You are listening to Microbe Talk the podcast by the Microbiology Society. When most people think of viruses, they think of harmful, dangerous microorganisms that invade the body and cause diseases. But the most abundant virus, the bacteriophage, does not harm human cells, but specifically targets and destroys bacteria. As many harmful infections are caused by bacteria, does this make the bacteriophage the enemy of our enemy?

00:00:46:13 - 00:01:09:03

Katie:

I'm Katie, the policy and engagement officer at the Microbiology Society. And in this episode, I speak with Professor Martha Clokie, a microbiologist based at the University of Leicester, to find out more about bacteriophages and their potential applications. We did record this episode on zoom, so there might be a little bit of background noise.

00:01:09:23 - 00:01:31:08

Martha:

So my name is Martha Clokie. I am a professor of microbiology at the University of Leicester, and my work focuses on bacteriophages. So we go right from the fundamental discovery of bacteriophages to characterising them. Looking at them at many different levels. Trying to understand how they work and ultimately trying to develop them as novel antimicrobials.

00:01:31:22 - 00:01:42:21

Katie:

Lovely. Thank you so much for joining us today. And to start off with, please, can you explain for our listeners that don't know, exactly what bacteriophages are and what it is that they do?

00:01:43:11 - 00:02:05:10

Martha:

Sure. So bacteriophages are viruses that kill bacteria. So all bacteria have got these natural enemies and they're very specific, not even to a species sometimes, but even to a strain. So if you take something like E.coli bacteria out of many types, we'll find phages that just infect specific types. So they're just part of the natural microbial world. There's more of them than any other biological entity on the planet. And they've been evolving with bacteria for forever since bacteria existed. And what we're really interested in doing now is actually exploiting the fact that they can target bacteria and studying how they work so we can actually harness them and use them against bacteria that are causing diseases.

00:02:27:03 - 00:02:30:10

Katie:

So how much do we actually know about bacteriophages?

00:02:31:11 - 00:02:58:04

Martha:

Well, we know quite a lot. We know that that there are approximately ten bacteriophages for each bacterial cell on Earth. And we know a lot about certain ones, how they attach, the fact that they inject their DNA, that they take over the transcriptional and the translation machinery of that bacteria. They basically turn bacteria into phage making machines. But what we don't know so much about are the specifics. So I said it's been a very, very long evolutionary arms race, and the different interactions between different bacteriophages are all very different. And the specific sets of interactions that occur are different with the different types of bacteriophages. So we don't know a lot of the details. We know that if we look at genomes of bacteriophages, often we can find ones that we perhaps can only recognise a few genes. So there's a lot of these details to still unravel.

00:03:25:18 - 00:03:33:24

Katie:

So you mentioned earlier that we could harness the power of bacteriophages. How exactly would we do that in a clinical setting?

00:03:35:04 - 00:03:55:03

Martha:

Well, we would be able to use a bacteriophage in a very similar way to the way that we currently use antibiotics. So ultimately, somebody would go into a doctor surgery, somebody in primary care would talk to her and diagnose that they had an infection. They would take a sample. The sample would get sent to a lab. And when we soon as we know what that bacteria is, we could do a test to look at the sensitivity of bacteriophages to make sure we use the right ones. And then the patient could be given a bacteriophage preparation very similar to how they would be given an antibiotic. So perhaps in a pill or a solution that they swallowed as a powder, depending on where the infection is. But it should be perfectly possible to make bacteriophage products quite compatible with standard antibiotic treatments.

00:04:22:18 - 00:04:32:24

Katie:

Can you explain a little bit about why we would we would want to use bacteriophages. What are the benefits of bacteriophage therapy when compared with other treatments?

00:04:33:22 - 00:05:03:24

Martha:

Sure. Yeah. Bacteriophages can be very useful if bacteria are already resistant to antibiotics. We can use bacteriophages very often to re-sensitize those bacteria so that they're then sensitive to the antibiotics again. So we can use bacteriophages to protect current antimicrobials. They also have many other useful properties. One thing is sometimes it's quite difficult to get antibiotics to a particular infected area like a bladder, for example. So if we can just get a few phages to that area, then they will replicate at the site of infection. So unlike other medicines, we have a medicine that's able to amplify where it is needed. So that's another advantage. And very often as well, they can get through biofilms when we have an infection. It's not just individual cells that are at a nice amenable stage to be treated, that they're growing in thick biofilm. And that's difficult for antibiotics to penetrate. So phages can penetrate there as well. So we can use them in many different settings.

00:05:34:08 - 00:05:59:12

Katie:

Professor Clokie was just talking about biofilms. Just to give you a little bit more information, biofilms are communities of microorganisms that stick to each other and surfaces. They're found everywhere, like in the slime on rocks in streams, in washing machines, and in our own bodies. Bacteriophages can target the bacterial cells that make up these biofilms to destroy them.

00:06:00:15 - 00:06:18:02

Martha:

And actually, one of the reasons why they're good is that they will just kill that one bacteria. They won't kill all the other bacteria. So we know very often we have problems with antibiotics because we feel quite groggy afterwards, because our commensal microbiome is being affected. The phages will just destroy the bacteria that we intended it to remove. So it's a very targeted treatment and potentially as well, we could use it to prevent infection even in the first place. So if we think an infection is likely, we could put phages onto a dressing or into a wound to actually prevent infections. So it's a slightly different way of looking at infection control in many ways in the way that we would actually use bacteriophages.

00:06:39:03 - 00:06:59:14

Katie:

The Microbiology Society, with your help, recently responded to a government inquiry on the antimicrobial potential of bacteriophages. We touched on the rich base of bacteriophage research earlier, but this is the first time that phage therapy has been seriously considered at the policy level. So why do you think this is happening now?

00:07:01:02 - 00:07:22:06

Martha:

Well, I think a massive driver is just the sheer problem caused by antimicrobial resistance. We know that in 2019, the most recent figures show that 1.2 million people died from a bacterial infection that was resistant to antibiotics. And this is massive. People talk about AMR becoming a problem in the future. But actually 6 million people have died of COVID. So we've already got in one year we've already got nearly a sixth of these people dying of this number of people dying. Now, it doesn't reach the same kind of headlines because there's many different infections and different parts of the body and different bacteria. But combined, it's already a massive problem. And this is really motivating doctors facing patients, infectious disease doctors who are seeing an increased number of cases of different bacteria becoming resistant in their hospitals. So this is overall acknowledgment that we see

increased disease that we can't treat. And it's not just in humans. We see it as well in animals that we live with and also that we raise for our food. So we're seeing this increased need and that's really driven a revival of this topic. I mean, looking for bacteriophages and using bacteriophages, that technology does predate antibiotics. But what's different now is that we have access to technologies where we can actually develop them as in in a way where in a much more informed way. So we can quite quickly go from isolating bacteriophages, looking at their genomes, and we can use genomic information in all sorts of different ways. We'll be able to make really nice, targeted treatments that will be able to predict from the sequence of the phage whether it's going to be effective in a particular setting. So we have so many more clues at our fingertips now in terms of developing this technology that it's actually a much, much easier time to be able to develop them as a therapy.

00:09:00:18 - 00:09:11:22

Katie:

It sounds like phage therapy is a really exciting and promising option for treating drug resistant infections and reducing the occurrence of AMR. But are there any downsides or risks associated with phage therapy?

00:09:12:18 - 00:09:34:11

Martha:

Well, like with anything there are, of course, there are risks as potential risks of driving bacterial resistance in the same way that bacteria can become resistant to antibiotics, they're going to become resistant to phages. So we need to make sure we do the experiments in advance to minimise that risk. We already know that when we combine phages, the risk is lowered. But we still need to do more research at making sure we have optimal combinations of phages where that risk is minimised potentially. There are also risks of bacteriophages driving immunological responses, so again, we need to be careful about, for example, injecting bacteriophages and making sure we understand the direct risks of using this. But in general, the risk is considered to be very low. So if we look at all of the summaries of all the compassionate studies that have been done and the safety aspects of the clinical trials, the risks are very, very minimal compared to antibiotics, for example.

00:10:15:22 - 00:10:25:15

Katie:

That leads quite nicely into the next question, actually. So how do we use bacteriophage therapy in the UK? Has it ever been used before? Do you know of any examples where it's been used successfully?

00:10:26:16 - 00:11:10:18

Martha:

Yes. Well, there was a very high profile case in Great Ormond Street Hospital where a young girl was given bacteriophages against mycobacterium abscesses. So she had a systemic mycobacterial infection that couldn't be treated, that was resistant to all the antibiotics that the doctors had. Then she heard about bacteriophages and through contacts that her mother had, she went to the hospital and they were able to go through a different network to get to the phage biologist who knows most about mycobacteria bacteriophages and he he's based in Pittsburgh, Graham Hatfull, and he was able to ultimately source bacteriophages that were supplied to her. So that was a quite a high profile case. There have been other cases recently where bacteriophages are being used both in Edinburgh and more recently Tayside to treat diabetic foot ulcers. So ultimately these infections can lead to amputations. So they've been used to successfully treat different patients to prevent amputation. So they're being used in a very, very minor way on a compassionate basis.

00:11:39:11 - 00:11:49:14

Katie:

And finally, I wanted to ask what you think the future looks like for bacteriophage therapy here in the UK. Do you feel optimistic about its potential to treat infections in the future?

00:11:50:16 - 00:12:20:18

Martha:

Yes, I feel very optimistic. I think for the first time we've actually got everything lined up. We've got it. We've got a real interest and motivation. We've got doctors very, very keen to support research programs. You've got a nice set of very talented microbiologists in this country, throughout the country. And here at Leicester we've just been awarded, for example, the first Bacteriophage Research Centre, the University of Leicester supported the centre sites and the Centre for Bacteriophage Research. And we will be in a way leading many of the steps I think that need to happen next, which is to create formal banks of bacteriophages that can act as a starting point. If we have really nice collections of phages now well-characterized with the genomes of phenotypes, that means that people can actually start to look at infections and diseases and still be able to access these phages through the bank and do the studies they need to to develop actual products. These parts of the puzzle still need to come together, so we clearly need more coordinated response. We need the basic science to be resourced. But if you look at just the amount that it's costing, even pneumonia itself at the moment is costing £780 million per year to treat. So and if you look at the total cost of that, AMR, it's vast and I think with with the investment to support the basic research that combined with the other parts, I think we are in a really good position to actually do the

experiments to look at how we would use phages, particularly in combination with other antimicrobials such as antibiotics. Everything is sort of in line in terms of expertise. We have access to the technology that we need. We're in a good position to actually make this treatment reality.

00:13:44:24 - 00:13:56:21

Katie:

Thank you for listening to Microbe Talk. If you enjoyed this episode, please do leave a comment letting us know what you think or tweet about it, tagging us @MicrobioSoc.