5.3 Can phages be used to fight bacteria in Food and Medicine?

Slide 1: In this section we will discuss whether or not phages can be used to fight bacteria in two different fields: food and medicine. As has been mentioned in the previous sections, bacteriophages have the ability to recognize their host very specifically and lyse it with high efficiency. Now the question rises whether or not we can use these abilities in practice.

Slide 2: First we will talk about the use of bacteriophages in Food. More specifically we will discuss this topic by means of an example concerning the battle against the food pathogen *Listeria monocytogenes.* In the next part, we will talk about the use of phages as medicinal products and the different ways of how phage therapy preparations can be made.

Slide 3: *L. monocytogenes* is a Gram positive, rod shaped bacterium (as is visible on the picture) This bacterium is able to survive in different environments like for example the soil. The bacteria are responsible for the disease Listeriosis, which can be lethal and has a mortality of up to 30%. This figure is rather high and illustrated the importance of finding strategies to fight this bacterium. The main route of infection is by contaminated food. This can be vegetables, fruits, meat, milk etc that contain the bacterium. While infecting, the majority of *Listeria* bacteria are discovered by the immune system. However, the possibility that not all the bacteria are eradicated by the body exists and these bacteria will enter the host cells. Here, they are safe against antibodies and other circulating immune factors.

Slide 4: Because this pathogen has a mortality ranging from 20 to 30%, the urge to find solutions is quite high. One way to tackle *Listeria* is by using bacteriophages to disinfect food before it is sold to the customer. The Food and Drug Administration (or FDA) from the US has found that these phages are Generally reconsidered as safe meaning that they have obtained the so-called GRAS-status, This means that they are considered to be safe to use. Furthermore, the United States Department of Agriculture has approved the use of phages as processing aid. This means that the viruses can be used during the processing of food like for example to decontaminate meat. In 2010, the Ministry of Health from the Netherlands also approved phages to be used as processing aids.

Finally, the European Food Safety Authority or EFSA has found the phages to be safe. Nowadays, the phage preparations are being sold by the company Micreos under the name Listex.

Slide 5: In the next part of this section, we will talk about the application of phages in medicine. As soon as d' Herelle discovered the potential of phages to kill entire populations of bacteria, he saw the possibility to treat bacterial infections in humans which was up until that moment impossible. In 1919 he created his first phage cocktails to treat bacterial dysentery. Afterwards He started a commercial lab with as main activity the production of phage cocktails called L'Oréal. However, during the second world war, broad-spectrum antibiotics were discovered that drove phage therapy into the background, especially in the Western World. In Eastern Europe and Russia, phage therapy remained quite popular until the 1970ties and is still performed nowadays. In Western Europe and the US, the use of phages is very rare and can only be performed under the so-called "compassionate use" framework that is based on article 37 from the Declaration of Helsinki which allows phage therapy as an alternative treatment method when no other treatments are available and the patients live is at risk. Now more then ever, it is important that new strategies to fight multidrug resistant bacteria are found. And one possibility is the use of phages.

Slide 6: When looking more closely to phage therapy, there are two different ways of how phage cocktails can be designed. One way is called the "Prêt-à-porter approach". In this Prêt-à-porter approach there are 4 different steps before the phage cocktails can be sold to the customer. These steps are similar to the discovery and testing of regular drugs. In the first step, a general cocktail is created that allows to treat bacterial infections caused by the most occurring strains of bacteria. Once this cocktail is composed, it is produced and vigorously tested. Different rounds of testing are performed: pre-clinical trials with animal tests and three clinical trials in humans to assure the safety of the phage cocktail. These procedures take a long time and a lot of money before they are completed. Finally, the generalized phage cocktail can be marketed and sold to the patients.

Slide 7: This Pret-a-porter approach has the hurdle that phages are considered as medicinal products according to the European law and the FDA. In detail, the

law considers every product that claims to have properties for treatment, a medicinal product. Another problem of the pret-a-porter approach is that it takes a long time and a lot of money before the cocktail can be sold to the customer. Moreover, there is no patient specific approach since there is a generalized phage cocktail. In other words, patients cannot be treated according to their specific needs. Another big disadvantage is that a generalized cocktail is more sensitive to resistance development of the bacteria compared to a patient-tailored cocktail.

Slide 8: The other approach to design phage cocktails is patient specific and is called the sur-mesure approach. Here, a phage cocktail is prepared according to the patient's needs. First, the bacteria that cause the infection are brought in culture and different phages from a library are tested to kill the patient's bacteria. These phages are combined in a cocktail. This cocktail is further processed according protocols that specifically describe how it should be made to ensure the patient's safety. Next, it can be used to treat the patient. When resistance to the tailored phage cocktail is observed, a new cocktail can be created the same way as before.

Slide 9: This approach is rather fast and cost efficient compared to the pret-a-porter approach from before. More specifically, due to the use of specific protocols to make the cocktail, no extra trials are needed to ensure the patients safety. Another advantage is that this approach is patient specific. There is however need for a new legislative framework since this kind of treatment can only be performed under the Declaration of Helsinki which allows to perform an alternative treatment when no other treatments are available when the patient's live is at stake.

Slide 10: In Belgium, the situation is slightly changed since the authorities have decided to consider quality-controlled phage preparations as the ones described in the sur-mesure approach, as magistral preparations. This means that medicinal doctors, together with pharmacists, can ask for a specific phage cocktail to treat a patient. This allows to treat individual patients outside the compassionate framework of the Declaration of Helsinki. This approval by the Belgian Authorities could be the first step in implementing phage therapy in modern medicine.

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