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â??In five years, India will have a well-established bacteriophage infrastructureâ?•

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Atif Khan, Scientist, Water and Steam Chemistry Division, Biofouling and Biofilm Processes Section, Bhabha Atomic Research Centre, Kalpakkam, is a dedicated researcher on bacteriophages. Tapping his knowledge on how bacteriophage is explored in India was a revelation. Several factual and evidence-based information was shared by him with BioSpectrum India.



How is research in India contributing to the development of novel bacteriophage-based technologies, such as phage engineering or phage cocktails?

In India, the public is unaware of the irrational use of antibiotics, which is leading to the development of antibiotic resistance. This infection is leading to the death of the patient due to non-availability of any alternative treatment regime. In such an instance, bacteriophage treatment proves to be economical and takes lesser time and acts without any side effects.

The engineered phages are such that the same phage can kill multiple types of bacteria leading to a broad range of application. Similarly, phage cocktail contains multiple types of phages against a target bacterium having different target killing mechanism and when they are used in therapy, there are very high chances that bacterial pathogen in the patient will be killed. Application of phage cocktails is mostly preferred in any case of phage therapy. This is because multiple phages in the formulation do not allow bacteria to develop resistance against them due to their varied mechanism of action. Engineered phages are used in case when the bacteriophages against the target organism is not available or difficult to be found in the environmental samples. In such cases, phages are engineered to identify a completely different host by modifying their tail fibres that are used by phages for host cell recognition.

What is the current market size of bacteriophage-based products and therapies in India, and how is it projected to grow in the coming years?

India is at a nascent stage of bacteriophage-based products. Currently, we are focussing on the treatment of human patients suffering from antibiotic resistant infections. In this area, researchers like us are making the phage bank having fully characterized phages that can be used for phage therapy. Coming to industrial applications, CIBA in Chennai has developed phages for controlling Vibrio in prawn farming, Dr. Palani from University of Madras is consistently working on phages for agricultural applications. Proteon Pharmaceuticals, a Polish Company, is settling up its plant in Nashik, Maharashtra whose phage formulations are found to be very effective in combating agricultural and poultry pathogens. Overall, it can be said that India will have the phage infrastructure built up in the coming 5-8 years.

Bacteriophages have shown significant promise in tackling Antimicrobial Resistance (AMR) due to their ability to target and kill specific bacterial strains. Please elaborate on this statement and also share some examples from India-based success stories of AMR tackling phages and also add a note on its effectiveness compared to traditional antibiotics?

Owing to the irrational use of antibiotics, the bacteria is continuously developing AMR and the Pharma companies are not coming up with any new antibiotics which can tackle the growing problem of AMR. If we get a new antibiotic today, it will take 7-8 years for this antibiotic to come into the market. However, when this new antibiotic comes into human use, the bacteria already possessing a robust system of developing AMR, will develop resistance to this new antibiotic within 10 days. On the

other hand, bacteriophages are highly specific for their host and they are highly abundant in the ecosystem (100 million different phages in our ecosystem). So, in case if any phage fails in the phage therapy, isolation and characterization of another phage from environment will take a maximum of two weeks which is much lesser than that of antibiotics.

Compared to traditional antibiotics, phages are better with respect to-

*Auto dosing property (phages can multiply when they find their host while antibiotics cannot). This result in lesser dosage of phages compared to the requirement of multiple doses of antibiotics.

*Phages can effectively cross blood brain and blood-testis barrier where most of the molecules are not allowed to pass through.

*Phages can be effectively cleared by the human immune system without producing any allergic response.

*Phages being specific to their host does not disturb the normal gut microbiota while antibiotics are broad range and kill the gut bacteria leading to stomach upset and diarrhoea.

Are there any unique indigenous bacteriophage strains or resources in India that offer a competitive advantage or research opportunities?

As said in an interview by Dr. Mzia Kutateladze (Director, Eliava Institute of Bacteriophages, Tbilisi, Georgia), India is the richest source of bacteriophages compared to any other country. If you like to talk about the competitive advantage, the opportunity lies in the phages of the bacterial host which rarely cause any diseases (*Staphylococcus similans*). In case of multidrug resistant S. similans infection, most of the labs and their surrounding environment will not have phages for this host. India could be a country where the phages can be found in a system like local sewage. I have one such experience, where a CF patient in Switzerland had P. aeruginosa infection and needed phage therapy. Many labs tested their phages and found that the bacteria was resistant to 140 phages. I asked the concerned doctor and he sent me the host. Interestingly, I have isolated a lytic phage for that host from a sewage sample in my locality. If you see the Indian Phage diversity in this way, India has a very bright future in bacteriophage research opportunities.

What is the regulatory landscape for bacteriophage-based therapies and products in India, and how is it evolving to accommodate this emerging field?

Currently, India is moving towards the use of phages for treatment of MDR infection. Recently, a meeting was held between ICMR officials and phage researchers like Dr Ramesh N, Dr Sanjay Chhibber and Dr Vinod Kumar C.S. which concluded to pace up the research for bacteriophages in India by opening the centres for bacteriophage research. As pointed out by Dr. C. Sheela Sasikumar from SS Clini Research LLP, we have to start working on developing the protocols for phage therapy from regulatory point of view rather than just doing the basic research and clinical trials. Presenting an organized data to regulatory authorities will have very high chances of getting the approval of practicing phage therapy in India. However, in the current scenario, the key regulatory aspects are not finalized for Indian perspective due to non-availability of sufficient data but it will be set up in the coming years.

What are the challenges and limitations of using bacteriophages in India, such as issues related to production, purification, stability, and delivery methods?

The major limitation of using bacteriophages in India is its awareness in public domain. Once the doctor will say that it is a virus, a majority of population will not prefer it because of the impression created by COVID-19. However, if the people are made aware of the advantages of using bacteriophages, the next hurdle comes in the production. There are no Indian pharma companies working on phages and no one dare to work on them due to its less popularity in India. If the large scale production is taken up by any pharma companies in future, the problems on purification, stability and delivery methods can be easily solved as a lot of work has been done at the lab scale by Phage Australia which can be extrapolated in the Indian environment.

Can you share some information on the ongoing clinical trials or research projects related to bacteriophages in India, and what are their objectives and outcomes?

Some Indian phage researchers like Prof. Vinod Kumar C.S. has done clinical trials on the efficacy of phages for treatment of infections. Similarly, Prof. Gopal Nath has successfully used bacteriophages for controlling the bacterial infections on the human burn wounds. Other researchers like Prof. Urmi Bajpai and Prof. Vikas Jain are doing their research on using bacteriophages against Mycobacterium for controlling Tuberculosis.

Some important ongoing research projects in India are undergoing in:

Dr Ramesh N. lab for development of phage bank for treatment of MDR infection in humans.

Dr Hiren Joshi's Lab, for development of phage bank for treatment of MDR infection in humans and developing cocktail of marine phages for controlling biofouling in marine industries.

Dr Taruna Anand's lab is working developing phage formulations for controlling bacterial infections in animal husbandries.

The overall objectives of these projects will be to replace the use of antibiotics or biocides currently used in these systems with bacteriophages to control the emerging MDR pathogens. In coming years, there are higher chances that a number of industries will start using bacteriophages in place of antibiotics or use antibiotics along with phages to increase the phage efficacy.

What is the level of public awareness and acceptance of bacteriophages as an alternative to antibiotics in India, and are there any public health campaigns promoting their use?

Going back to 1927, during the emergence of Asiatic cholera epidemic in Punjab, India, Dr. Felix d'Herelle (researcher who discovered bacteriophages in 1917) demonstrated the potential of phage therapy by treating 74 severely ill patients. Astonishingly, the phage therapy group exhibited only a 6% mortality rate, compared to the 63% mortality rate in the control group (Can J Infect Dis Med Microbiol. 2007 Jan; 18(1): 15–18.doi: 10.1155/2007/365761). In today's India, people will accept a treatment when they will get a positive result when they are left with no hope. This condition is happening today in India when antibiotics stop working in patients with MDR infections. Phage therapy is still not popular in India but because of Pranav Johri's efforts, he successfully treated nearly 70 patients with MDR infections and gave some boost to the name of phage therapy as an alternative to antibiotics.

As of now there are no campaigns specifically for promoting the use of bacteriophages but Dr Ramesh is doing a campaign on safe use of antibiotics (Indian Initiative for Management of Antibiotic Resistance).

What are the funding and investment trends in the Indian bacteriophage sector, and are there any notable collaborations between academia, industry, and government agencies?

In the past 4 years, bacteriophage research gained limelight when Dr. Stephanie Strathdee treated her husband with phages suffering from MDR infections (description in her book: A Perfect Predator). In research sector, ICMR is now focussed on developing an alternative to antibiotics and phages are one of the best options. Water and Steam Chemistry Division at BARC, Kalpakkam has started their working on bacteriophages and getting funds to develop phage bank and formulations for treatment of MDR infections. Similarly, Proteon Pharmaceuticals from Slovenia have started their plant in India and they have multiple phage-based products like BAFADOR and BAFACOL for controlling target bacterial infections in poultry and fishery industries. Coming to the startups, Dr. Yatee Gupta and his team in New Delhi are working on developing phage formulation for aquaculture (www.phagefinders.com).

How do Indian researchers and companies compare internationally in terms of bacteriophage research and development?

India is the land where the first activity of lytic bacteriophages was observed and deployed for treatment of Cholera in the Punjab region of India. However, due to poor infrastructure of Indian science during pre-independence, further research was not able to carry out on bacteriophages and antibiotics took over. In the current scenario, Indian bacteriophage research has gone to the next level of bacteriophage isolation and characterization, clinical trials and treatment of treatment of MDR

infections. Prof. Gopal Nath from BHU was able to treat a 6 year old burn infection within 1 month using bacteriophages and the infection did not recurred. Coming to the basic research, Prof. Vikas Jain from IISER Bhopal has developed expertise in cloning the endolysin gene derived from phages for its application in antibacterial and antibiofilm applications.

What intellectual property and patent trends are associated with bacteriophage-related innovations in India?

Bacteriophage research being in the nascent stage in India, patents are coming out from different labs completely based on bacteriophages. Prof. Sanjay Chhibber from Punjab University has filed a patent on evaluation of different delivery strategies for therapeutic applications of *Klebsiella pneumoniae* phages in burn wound model. Similarly, Dr. Ramesh N. from VIT, Vellore has filed patent on Stabilization of Lyophilized Caudovirales Bacteriophages. There are many other patents coming out from different phage laboratories in India leading to development of bacteriophage innovations. India being a rich land of bacteriophage diversity, many more patents are expected to come in future.

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