

## **StaphTAME is Ready to Tame Superbugs**

**GangaGen Biotechnologies is close to getting the world's first phage-based product ready to tame the deadly bacteria strains stalking patients around the world. J. Ramachandran talks about the breakthrough product.**

**By Narayanan Suresh and Jahanara Parveen**

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As a global debate rages on the future of antibiotics due to the presence of yet another "superbug," NDM-1 resisting all known antibiotic treatments, the health community is seriously looking at alternate options. One of the most promising alternative appears to be the use of bacteriophages, the viruses that kill bacteria, which was used extensively in many parts of the world prior to the discovery of the wonder antibiotic Penicillin in the 1920s. The super convenience of penicillin and other antibiotics relegated phages to the background. In this gloomy scenario, there is hope. GangaGen Biotechnologies, founded by a renowned molecular biologist from AstraZeneca 10 years ago to relentlessly pursue phage research, is close to getting the world's first phage-based product ready to tame the deadly bacteria strains stalking patients around the world. GangaGen is ready to start the human trials of the world's first "superbug" killer, StaphTAME, a genetically-modified protein developed from phages. In an exclusive interview to Narayanan Suresh and Jahanara Parveen of *Technology Review India*, GangaGen's founder, J. Ramachandran, talks about his breakthrough product, his passionate search to find a "superbug" killer, and the help he needs from the global society to complete his dream of a "harmful bacteria-free" world. Excerpts:



**J. Ramachandran**

**Credit: Courtesy of GangaGen**

### **What are the current areas of research at GangaGen?**

GangaGen has developed a highly proprietary product called StaphTAME (also known as P128) for the control of the superbug MRSA (Methicillin Resistant Staphylococcus Aureus) which is currently the most serious hospital-acquired infection. All preclinical development of StaphTAME has been completed and a successful pre-IND meeting with the U.S. FDA has been concluded. GangaGen is preparing to conduct clinical trials of StaphTAME later this year both in the U.S. and in India. StaphTAME is a recombinant protein that kills MRSA and all Staph bacteria rapidly (in minutes) by a novel mechanism.

*Pseudomonas aeruginosa* is the most antibiotic-resistant pathogen after MRSA and is the source of major infection in burns and wounds. GangaGen is developing a proprietary product for the control of *Pseudomonas aeruginosa* that is currently undergoing preclinical development. GangaGen hopes to advance this product into clinical trials next year.

GangaGen's research team is also engaged in the discovery and development of phage-based products for the control of other pathogens including *Clostridium difficile*, which often emerges as a secondary infection following antibiotic treatment and is rivaling MRSA as a hospital-acquired infection in the UK.

### **Is there enough innovation/ research happening in the area of phage therapy globally? Which are the other companies working in this area?**

GangaGen is a pioneer in developing innovative products based on phages. Many of the phage companies around the world did not pursue innovation but rather focused on the production of natural phages which have some limitations. Release of endotoxins from the pathogens killed by phages, immune response to the phage and potential for acquiring toxic genes from a pathogen and transferring it to the beneficial bacteria present in the patient, are some of the problems in the use of naturally occurring whole phages. GangaGen developed the proprietary "Lysis-deficient Phages" to circumvent these problems through genetic engineering of the natural phages. Lysis-deficient phages kill the pathogens as effectively as the natural phages but due to the deletion of the "endolysin" gene, do not release phage or endotoxins and do not have the opportunity to transfer toxic genes. Two patents on the Lysis-deficient phages were issued to GangaGen by the US Patent Office in 2005. This accomplishment of GangaGen was described in an article in *BioSpectrum* in July 2004. Phage Therapeutics in Seattle, Washington, in the U.S. started in 1997 to develop natural phage against MRSA but closed down in 2003. Exponential Therapies, the oldest phage company started in 1994 but closed the phage program in 2005. There are several small companies developing natural phage for agricultural use and animal health in various stages of development.

### **Inspite of its vast potential, why has this technology/therapy failed to win the right recognition in India and in other countries?**

It is really unfortunate that phage therapy has not reached its potential in spite of the remarkable success demonstrated in the first half of the last century both in Europe and in India.

Felix d'Herelle, the French Canadian scientist who demonstrated the efficacy of phage for the control of Shigella infection in the World War I years in France, came to India in 1927, and showed that cholera could be effectively controlled with phage. Impressed by this, Morison, the director of King Edward VII Pasteur Institute in Assam tried phage therapy in villages in Assam that had cholera epidemics every year. Nowgong, the village that used phage treatment had fewer than 10 deaths due to cholera, whereas Habibganj that did not

use phage had over 300 deaths. This study was published in the *Transactions of the Royal Society for Tropical Medicine and Hygiene* in London in 1935 and is described on the GangaGen website.

The reason that phage therapy did not emerge as the treatment of choice for infection are manifold. In order to use phage as a therapy, the pathogen causing the infection must be properly diagnosed so that the appropriate phage can be used. Phages are highly specific and a given phage such as the cholera phage will kill only cholera bacteria but not others. Diagnosis is not easy even now, and in the early part of the past century, it was extremely difficult. When Penicillin was discovered in the 1930s, physicians in the Western world abandoned phage and embraced antibiotics since they had broad spectrum activity. Penicillin could be used to treat many infections. In fact, it is the overuse and misuse of antibiotics over the last six decades that led to the emergence of robust antibiotic-resistant pathogens like MRSA. The second major reason why pharma companies did not pursue phage therapy is the perceived lack of patent protection for naturally occurring phages.

**In the context of debate about the presence of superbugs and predictions of the end of antibiotics, is bacteriophage therapy ready to take its place? What role can phage therapy play to kill/treat the superbug/superbug infections?**

Lysis-deficient Phage and phage-based products like StaphTAME can play a very important role in controlling the superbugs as they have been shown to effectively kill these antibiotic-resistant pathogens in the laboratory as well as in animal models. What stands in the way of phage products is the lack of proper placebo controlled double blind clinical trials according to U.S. FDA standards. GangaGen is preparing to remedy this by conducting the Phase I/II/III trials with StaphTAME.

**What the significant breakthroughs achieved by the phage therapy in recent years globally and in India?**

Apart from the results achieved by GangaGen, a company in the UK has reported that middle ear infection could be treated successfully with phage against *Pseudomonas* bacteria.

**What hurdles do you foresee in the path of phage therapy solutions?**

The main hurdle is lack of adequate financing to complete the clinical trials quickly.