

Phage Research

13 July 2004 | News



Gangagen

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Research

In India, it is rare to come across companies that break the mould of conventional research and get into challenging and relatively unknown fields. Gangagen is one such.

Gangagen owes its existence to Dr J Ramachandran, a renowned molecular biologist, who happened to watch a BBC documentary in 2000 on phages. The programme discussed how phages (or bacteriophages), which are viruses that kill bacteria, are used to treat bacterial infections with a huge degree of success in Russia. Despite Dr Ramachandran's wide and varied experience in research on antibiotics and bacterial infection, phages were totally new to him. This set his mind racing on the possibilities for breakthrough research on phages. Having dealt with bacterial infections in the pharma research industry, he was suddenly hopeful that the solution lay in phages.

An Idea that Paid Off

Enthused by the bright prospects, Dr Ramachandran acted swiftly by starting a company called Gangagen Biotechnologies Pvt Ltd. He floated the idea to Bangalore-based ICF Ventures, which pooled an initial investment of \$2 million. He roped in molecular biologists Dr Sriram Padmanabhan and Bharati Sriram, who left their lucrative jobs to answer the calling of innovative research. The company kicked off operations in September 2000 by renting 800 sq. ft space, infrastructure and people at Bangalore Genei. Their first job was to create a comprehensive "library" of infectious bacterial samples and phages

from hospitals in Bangalore, Vellore and Hyderabad.

According to Dr Ramachandran, phages are easy to find and the best samples can be obtained in the unlikeliest of places, from river waters to temple ponds to even sewage.

Globally, there are a handful of phage research companies, scattered across countries like the US, Canada, Russia, Georgia and Israel. To make headway and create a niche for the company, Dr Ramachandran went for an out-of-the box approach. It was a known fact that once a phage attacks a bacterial cell it synthesizes its own proteins, multiplies prolifically, kills the host and bursts out of the host cell in a process called lysis. Although the bacterial cell would be destroyed in the process, there is a potential harm from the release of dangerous endotoxins and the body's own immune system, which could respond by producing antibodies.

This, Dr Ramachandran thought could be prevented if the phages could somehow be contained within the host cell after killing the bacterium. He filed a patent for this concept and Dr Padmanabhan and his team started work to bring about this process.

The team succeeded. Phages encoded two proteins-holins and endolysin, for causing cell lysis. What the Gangagen scientists did was to introduce a recombinant gene that was deficient in endolysin protein. The result: the genetically modified phage gets rid of the bacteria and at the same time is restricted within the host cell. The body in turn eliminates the bacteria harmlessly. " We are the only company in the world to hold IP on this technology and it has given us a competitive edge that cannot be bettered by others," said Dr Padmanabhan, who heads the molecular biology division. Dr Ramachandran filed the full patent application in August 2002. Another patent followed for whole cell vaccines that contain phage-filled cells. "Experiments on animals have shown that these phages have countered infection effectively," said Dr Goda Krishna, business and operations manager, Gangagen, Bangalore.

"We Need a Novel Alternative to Antibiotic Drugs."

-Dr J Ramachandran, founder and president of Gangagen Inc.

image not found or type unknown biotechnology and pharmaceutical industry, who has served earlier as head, R&D, Astra Zeneca, Bangalore. He was also president of Astra Biochemicals Pvt Ltd and of the merged entity AstraZeneca India. He is credited with discovering and developing new therapies for tackling tuberculosis and antibiotic resistant infection. He has also been associated with leading US biotech companies like Neurex and Genentech in California.

With such a formidable research record, it seems only natural that he made the natural progression to a new path-breaking area-phage therapy. He shares his thoughts on the exciting research opportunity that phage research offers.

How do you think phage research has evolved over the years and where does Gangagen figure on the map?

In the 1960s scientists looked at phages only as a model and didn't concentrate on the therapeutic aspects. The phage DNA model was the hottest topic of research. This faded in the 1970s and 1980s. In the last decade, there has been a revival in phages because of the problem of antibiotic resistance.

Phage therapy is almost 100 years old. What Gangagen is doing is developing technology to improve the quality of phage therapy. We are the only company to develop IP in this area. We have several top-notch researchers and phage biologists on our board. Some of them include Dr Ryland Young, an expert on molecular biology of phage lysis, Dr Sankar Adhya, a renowned scientist who's done considerable work on model phage lambda and Dr Carl Merill, a scientist at the National Institute of Health.

At what stage of development is the company right now?

It will take a while before we bring out our product. R&D takes a long time. We will be conducting clinical trials in two phases, which will take another three-four years. After that, our product has to be approved by regulatory authorities. I cannot hazard a guess about how long that could take.

We will file the product in the US first. Six months after that, we will also file it internationally. We would like to license our product to interested pharmaceutical and biotechnology companies. Our phage product will cover around 80 percent of pathogens and will be for topical use.

What prompted you to start work in this new field? How would you explain the different research areas of Gangagen in India and Canada?

Over the years, there has been an overuse and misuse of antibiotics. Since many bacteria are getting resistant to antibiotics, there is a dire need for some novel drug. The therapeutic values of phages have been neglected for some time. It is a very exciting area.

We have a diffused approach at Gangagen, which helps us to concentrate on specific areas of research. In India, our focus is on human uses of phages. We believe that a developing country like ours is in the greatest need of such therapy since most deaths here are from bacterial infections than say heart disease. Also, since phages were discovered more than 100 years ago in the Ganges, we thought it was apt to focus on human applications.

The company's Canadian counterpart, Gangagen Life Sciences, does research on the veterinary and environmental applications. Canada is a country where they are proactive on environmental policies. They faced a lot of problems due to the pathogen E coli0157, which spreads from animal manure to humans. By using phages, we are trying to eliminate the pathogen in animals, plants and the environment.

How expensive is phage research?

Phage research involves more of microbiology and molecular biology and not expensive chemistry. We estimate a two- to three-fold cost savings compared to the R&D of antibiotic drugs.

What is the investment that has gone into the company?

Initially, ICF, which is based in Bangalore, pitched in with a seed fund of in \$2 million in 2000. We had a second round of funding from angel investors who ploughed in another \$2 million in 2002. Right now, we are in talks with VCs who can fund around \$3-5 million to help with our expansion plans in Bangalore.

Modus Operandi

Gangagen Inc. is US-based and has two subsidiaries. Gangagen Biotechnologies Pvt Ltd (GBPL), based in Bangalore, focuses on human applications, while Gangagen Life Sciences Inc. (GLSI), based out of Ottawa, Canada, works on veterinary and environmental applications of phages.

GLSI is headed by Michel Cretien, a renowned medical scientist. This division works on developing phages to get rid of bacterial infection in animals, plants and the environment.

The bacterial contamination of manure that causes ground water pollution is a serious issue in Canada. The problem assumed serious proportions in 2000 when several people died after drinking contaminated water in Canada. Treating meat infected with bacteria is another issue. Several countries may make it mandatory for meat manufacturers to ensure that their product is free from contamination. GLSI is trying to introduce phages that could be given to cattle before slaughter to pre-empt any possible dangerous infection in meat thereafter.

The Indian division is currently looking at human topical applications. However, it will take around four years before the product would see the light of day. The first phase of clinical trials on the product will get underway by the end of the year. This will be followed by more trials, safety and efficacy tests in humans and getting the product approved by regulatory authorities. "Some researchers tell us that it is unethical to make them wait for so long to get a good product like this," quips Dr Goda Krishna.

Future Direction

GBPL's research threw up a very useful by-product, a diagnostic kit to detect bacterial infection. While the regular kits available in the market fail to detect contamination soon enough, Gangagen's kit could detect the bacterial load based on phage activity immediately. This is faster and more cost-effective, according to Bharati Sriram, who heads the diagnostics group. The company, which is yet to file a patent on the kit, thinks that this could find application in medical diagnostics, food processing and soft drink manufacturing companies.

The company has mapped out the sequence of research to follow from here on. Next in line are phage research to treat oral infections, urinary tract infections and ultimately tuberculosis and cholera. "We believe that phages can also attack dormant Mycobacterium tuberculosis bacteria. So the possibilities are enormous." Around six more patents are in the offing.

To strengthen its research activities, the company is in talks with VCs to raise more funds to expand the Bangalore base, especially the pharmacology and fermentation divisions.

Dr Padmanabhan best describes the Gangagen experience. " We look forward to come to work everyday. This concept is a gold mine."

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