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Phage therapy gains ground due to antibiotic resistance

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As a global debate rages on the future of antibiotics due to the presence of yet another â€œsuper bugâ€?, NDM-1 resisting all known antibiotic treatments, the health community is seriously looking at alternate options

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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 pencillin in the 1920s. The super convenience of penicillin and other antibiotics relegated phages to the background. 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 worldwide. GangaGen is ready to start the human trials of the world's first â€œsuperbugâ€? killer, ed from phages.

StaphTAME, a novel biological drug, using a genetically-modified protein, developed from bacteriophages (the viruses that kill bacteria) by a small Bangalore-based biotech company, GangaGen Biotechnologies, is all set for human clinical trials in India and the US.

â€œStaphTAME is a recombinant protein that kills the superbug MRSA (Methicillin Resistant Staphylococcus Aureaus) and all staph bacteria rapidly in minutes by a novel mechanism,â€? disclosed GangaGen founder and well-known molecular

biologist, Dr Janakiraman Ramachandran, who has been toiling in the labs for the last decade after retiring as the head of its R&D at AstraZeneca in Bangalore. GangaGen was founded in 2000 with a `9.36 crore ($2 mn) funding from ICF Ventures.

MRSA is currently the most serious hospital-acquired infection and as it does not respond to treatments with almost all the known and most powerful antibiotics, it has been termed a â€œsuperbugâ€? out of human control. In fact, because of the untamed nature of the â€œsuperbug,â€? experts have been predicting that the era of antibiotics is over. An alternate method to control harmful bacteria is urgently required. The New Delhi metallo-beta-lactamase (NDM-1) â€œsuperbugâ€? now a cause of concern in the global medical fraternity is one of MRSA strains.

StaphTAME is the world's first therapeutic protein developed from bacteriophages to reach the human clinical trials stage. So far, bacteriophage therapy has been used only for treatments after the bacterial infections sets in. â€œAll preclinical development of StaphTAME has been completed and a successful pre-IND meeting with the US regulator, Food and Drug Administration (FDA) has been concluded,â€? Dr Ramachandran shared from the US, as he is preparing for the product's clinical trials in the US and in India.

StaphTAME, also called the P128 protein, was developed by researchers at GangaGen's Bangalore (India) and Ottawa (Canada) facilities, based on a key protein from bacteriophage. When the phage, the virus that kills bacteria, first interacts with a bacterial cell, they damage the cell wall in order to insert their genetic material.
â€œGangaGen has identified the active portion of the phage molecule that causes this damage, and coupled it with another protein sequence that allows binding to the surface of Staphylococcus,â€? explained Dr Bharati Sriram, a senior researcher at GangaGen. GangaGen has already filed both composition of matter and use patents for StaphTAME and is now vigorously pursuing worldwide patent protection for the product.

The P128 protein has been tested against over 200 global strains of S. aureus, more than half of which are methicillin-resistant, and has proved capable of killing all of them, revealed Dr Bharati. Some of the strains used include a panel of 30 New York/New Jersey strains representing 3,000 isolates, 56 Japanese isolates, 119 Indian isolates and eight Canadian isolates.

But is this â€œwonder drugâ€? going to be available soon? For this to happen, the fledgling startup urgently needs funds to speed up the clinical trials. Few million dollars are required to conclude the trials faster. â€œThe main hurdle is lack of adequate financing to complete the clinical trials quickly,â€? Dr Ramachandran confessed.
GangaGen, after the meeting with the USFDA in March 2010, has prepared StaphTAME formulation for intra-nasal use. The company has also scaled up manufacturing efforts to support clinical studies. The phase I & II studies will include safety, dosing, and preliminary efficacy testing.

GangaGen is clearly the world leader in developing such a â€œsuperbugâ€? killer product from phages. Exponential Therapies, which has been developing a similar product since 1994 closed the research program in 2005. Another US-based company, Phage Therapeutics in Seattle, Washington, too had started to develop a product against MRSA in 1997 but wound up in 2003.

Will NMD-1 be the â€œantibiotics killerâ€??

About 82 years ago, Alexander Fleming discovered antibiotics and penicillin became a wonder drug in the next few decades. In the six decades following, medical researchers have developed a wide range of antibiotics that treat several infectious diseases. However, in the last two decades, scientists and commentators have started to write premature obituaries of antibiotics. In fact, the latest headlines in newspapers based on the NMD-1 reports have a common theme: â€œIs it the end of antibiotics?â€?

But is it really so?
What is happening today seems to be an exact replica of the events more than 16 years ago. In March 1994, the venerable Newsweek magazine ran a report, â€œThe End of Antibiotics?â€? by Sharon Begley. The reference was to the discussions at the annual meeting of the Association of Advancement of Science in San Francisco that concluded in February 1994. Microbiologist Alexander Tomasz of Rockefeller University warned, â€œmany common bacteria are evolving resistance to more and more antibiotics.â€?

The data for 1992 indicated that resistant infections killed 19,000 patients in hospitals in the US that year and contributed to the death of 58,000 more outside. In 2005, more than two million people in the US were affected by infections and 90,000 of them died. In the UK, there were 3,00,000 infected patients with 5,000 deaths, according to information compiled by science writer, Thomas Hausler in his book, 'Viruses vs Superbugs'.

Even after 16 years, antibiotics continue to thrive even though more resistance has been reported regularly. Will the August

2010 obituary on antibiotics also be another such premature exercise?

Majority of the hospital infections are caused by the Staphylococcus aureus bacteria. Dr Tomasz has found that 70 percentof the known 3,000 strains of this bacteria found all over the world belonged to just five strains. What this means is that it doesn't matter where the bacteria was found first. These tiny microbes have always had a way in spreading themselves to all parts of our planet. So blaming a particular city, hospital, or country does not help the cause of finding a quick cure.
Phage therapy i.e., using viruses that kill harmful bacteria, one of the most promising cures around the corner.

It is certainly not the end of antibiotics. And NMD-1 will not be the â€œantibiotics killerâ€? anyway.

Why phage therapy is not already a treatment of choice?
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 quite 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.

Narayanan Suresh and Jahanara Parveen"GangaGen's StaphTAME is ready to tame superbugs"

Image not found or type unknown 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 BioSpectrum, GangaGen's founder, Dr 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.

Q What are the current areas of research at GangaGen?
GangaGen has developed a highly proprietary product called StaphTAME (also known as P 128) for the control of the superbug Methicillin Resistant Staphylococcus Aureus (MRSA), 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 US Food and Drug Administration (FDA) has been concluded. GangaGen is preparing to conduct clinical trials of StaphTAME later this year, both in the US and in India. StaphTAME is a recombinant protein that kills MRSA and all Staph bacteria very 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 emerge as a secondary infection following antibiotic treatment, and is rivaling MRSA as a hospital-acquired infection in the UK.

Q 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 that 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, US, was 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.

Q In spite of its vast potential, why has the phage technology/therapy failed to win the right recognition in India, and also in other countries?

It is really unfortunate that phage therapy has not reached its potential in spite of the remarkable success it demonstrated in the first half of the last century, both in Europe and 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 less 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 and 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 late 1920s, 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 pharmaceutical companies did not pursue phage therapy is the perceived lack of patent protection for naturally occurring phages.

In the context of debate on the presence of superbugs and predictions of the end of antibiotics, what role can phage therapy play to restrict 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 the US FDA standards. GangaGen is preparing to rectify this by conducting the phase I/II/III trials with StaphTAME.

Q What are the significant breakthroughs achieved by phage therapy in recent years?

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.

Q What hurdles do you anticipate in the path of phage therapy solutions?

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

Narayanan Suresh and Jahanara Parveen in Bangalore