The VIRUS that heals

VIRUSES are dangerous organisms. Shortly after invading another life form, they take over the host's survival kit and begin to make copies of themselves. A virus does not eat, drink, excrete, travel or make merry. All it does is reproduce, in a frenzy that is unmatched in the living world.

Bacteria are dangerous too, but they are not as focussed as viruses. They eat and produce waste, apart from reproducing. Bacteria are also clever. They know how to evade the antibiotic missiles we launch at them.

Some viruses, called phages, attack bacteria. Phages multiply inside the bacteria, burst open the cell and invade other bacteria. One phage can become a million within an hour of infection. Phages also know a trick or two about bacterial behaviour. It's difficult for bacteria to defend against a phage attack.

Phages are the most numerous organisms on earth; their total weight is more than the weight of all the elephants in the world. They are also the primary reason why bacteria haven't taken total control of the planet. What can we learn from these crafty creatures?

J.Ramachandran was fascinated by the BBC documentary on 10 April 2000. It was the *Horizon* series that he loved to watch, and the presenter was talking about the wonderful things phages could do for us if we knew how to tame them. Ramachandran had had a distinguished career as a drug researcher in some of the leading companies in the world. He had led research on antibacterials at Astra Zeneca in Bangalore. But he knew next to nothing about phages.

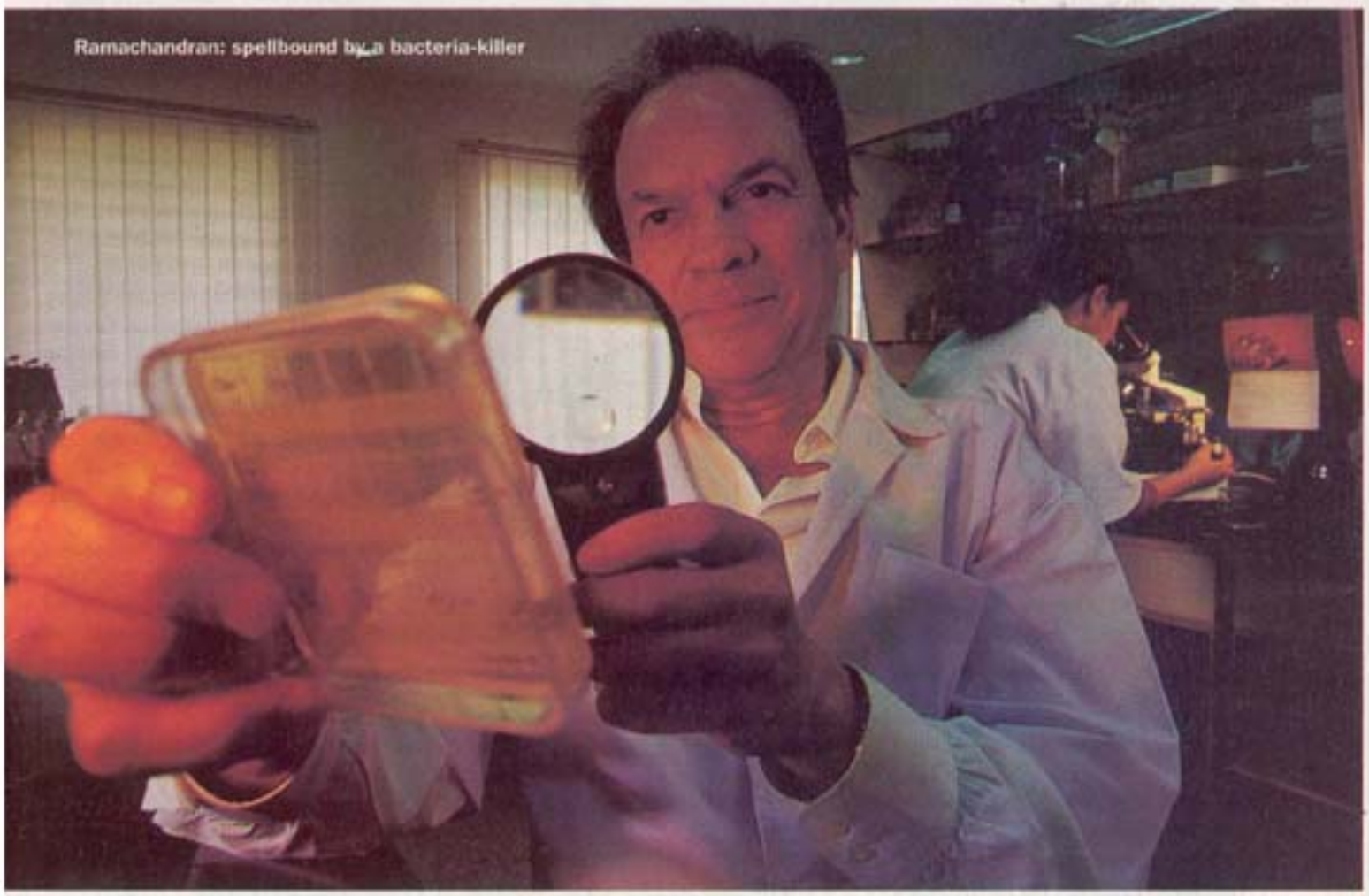
The documentary showed an institute at Tbilisi in Georgia. This institute was the only one in the world that had continued research on phages, which were used there to cure fatal wounds, among other diseases. Antibiotic resistance plagued the Soviet hospitals, like in other places in the world. "From my work at Astra Zeneca I knew that we were waging a losing battle against bacteria," he says. "But phages seemed an effective way to tackle the problem."

Ramachandran was then in California. Halfway across the globe, in Hyderabad, Sriram Padmanabhan was watching the same show on BBC. Sriram had kick-started Dr. Reddy's biotechnology programme, but was itching to move on to other things. "The documentary was an eye-opener," Sriram says. "I told my wife Bharathi (also a scientist at Dr. Reddy's) that this was the topic to work on."

Sriram didn't know that Ramachandran (his former boss at Astra Zeneca) had also watched the programme, or that their paths would cross soon. He forgot about the documentary after a while, while Ramachandran decided to educate himself about phages. Ramachandran learned that phages were first discovered in the Ganges, way back in

There aren't too many companies that put their money on viruses. But this one has — and it could well be on its way to global leadership.

by P. Hari


Ramachandran: spellbound by a bacteria-killer

1896. Ramachandran started a company in Bangalore to investigate phage therapy and called it GangaGen Biotechnologies, as a gentle reminder to the world as to where it all started.

GangaGen rented a place at Bangalore Genei. Meanwhile, news of the firm reached venture capital firms. Ramachandran got a call from ICF Ventures in the city. After just two meetings, its officials told him they wanted to invest $2 million in GangaGen. "They did not even ask me for a business plan," says Ramachandran, "and said they invested in people, not in business plans."

Ramachandran's credentials had impressed ICF Ventures. He had taught at the University of California in San Fransisco and worked in Genentech, the world's leading biotech company, where he did pioneering research on human insulin receptors. He then moved on to Astra Zeneca (after a few hops), where he set up the Bangalore R&D centre from scratch. "It was a dream to back someone like Ram," says ICF managing director Vijay Angadi.

Ramachandran sat in the Stanford University library for weeks to read about phages. He learned that phages were used for treating cholera as early as in the 1920s in Punjab. Recently Georgian doctors successfully used phages to treat wound infections that did not respond to antibiotics. Phages were safe as they attacked only bacteria. Phage therapy seemed promising, but for some scientific and business challenges.

The first barrier was our own immune system. A phage is an intruder and will be treated as such; the human body will develop antibodies to the phages. The second problem was the 'lysis' of the bacteria. The phage reproduces rapidly inside the bacteria and comes out in large numbers, scattering bacterial toxins in the process. The third issue was related to business. Phages were known for a long time and no one knew how to get patents on old knowledge. "One reason why pharmaceutical companies ignored phages was that they could not get patents," says Ramachandran.

Yet it was absolutely vital for him to get some patents for the firm's survival.

SRIRAM, who remembered the BBC documentary as soon as he got a call from Ramachandran, needed no persuasion to work on phages. His wife and he joined GangaGen on 30 September 2001, and were greeted by an excited Ramachandran. "Let's sign a non-disclosure agreement first," said his former boss. Ramachandran had filed a provisional patent application three days ago, but it was just an idea. Patent offices would give GangaGen a year to work out the details; Sriram had his job cut out.

By then GangaGen had become a US firm, GangaGen Inc, which fully owned the Bangalore firm. The Bangalore firm had exclusive rights to sell its products in Asia-Pacific. The new lab in the city would be ready in February 2002. Sriram and his wife had eight months after that to ensure the idea worked.

Ramachandran had made one sig-

Photographs: RAMAS PRASAD

The soul of GangaGen: (L to R) Scientists M. Jayasheela, Bharathi, Goda Krishna and Sriram

nificant observation during his research. The bacterium is killed as soon as the phage penetrates its wall. Lysis is necessary for the phage to come out, but is not important as far as the death of the organism is concerned. Could the lysis be stopped and the phages trapped inside the bacterium? The body's immune system would clear the dead bacteria. It was an ingenious idea, but there was no guarantee it would work.

Sriram and Bharathi located the phage gene responsible for lysis. They then inserted a piece of DNA into this gene to stop it from functioning. This genetically-engineered phage would enter a bacterium, multiply and then remain inside. There was a double benefit. The bacterial toxins would not scatter and the body would not develop antibodies to the phages. But it would develop antibodies to the dead bacteria and clear them from the body. Sriram proved these results; Ramachandran filed the full patent application in August 2002.

The US Patent Office has now published this application and another one seeking to use the phage-filled bacteria as a vaccine (the dead bacteria will generate an immune response). The patent applications make sweeping claims: anyone using this process on any phage will have to pay royalties to GangaGen. The patents, when granted, will open up an area that no company has explored: to use the phage as a vaccine. It is almost like discovering a blockbuster, except that the product is actually a process.

ICF invested $2 million in June 2001. The lab was up by early 2002. Ramachandran began expanding his team. He got his friend David Martin on the board of directors. Martin had worked at Genentech and had worked on two multibillion-dollar blockbusters, the human growth hormone and tissue plasminogen activator. He was later president of Chiron Therapeutics, a top-notch biotech firm. Martin took over as CEO of GangaGen last month.

The next to join the board was Ryland Young, an expert on phage lysis. Young is now executive director of research at GanagaGen Inc. Two more leading phage researchers joined. Shankar Adhya, a member of the US National Academy of Sciences, and Carl Merril, a scientist at a National Institute of Health lab. Adhya and Merril together hold the only significant patents on phages.

GangaGen Inc started a subsidiary in Ottawa, Canada and got Michel Cretien, a well-known medical scientist and brother of Canada's prime minister, to head it. GangaGen has another close associate: James Watson, Nobel laureate, who discovered the DNA double helix. Watson may join the board soon. GangaGen has a team that would be the dream of any phage therapy firm in the world.

IN mid 2002 GangaGen got $2 million more from angel investors at a 50% higher valuation. Ramachandran is now looking for more money at higher valuations. GangaGen's patents will be the milestones for investors. Its first product, for tackling infection in vegetables, will go for field trials next month in Canada. Products for humans will follow.

Bacterial contamination in manure is a big problem in the US and Canada. Infected manure pollutes ground water. In 2000, contaminated water in Ontario made 2,000 people ill and killed seven people. Another problem is infected meat. Canada may make it mandatory for all firms that sell meat to establish that their product is free from dangerous bacteria.

Treating manure using GangaGen's proprietary phages may help reduce ground water contamination. Canada produces 750 million tonnes of manure. At $1 for treating one tonne, GangaGen could make $75 million if it gets 10% of this market. Treating cattle with phages two weeks before slaughter can reduce infections in meat. GangaGen's next product will be for the meat industry.

The third product may be an ointment for treating infections on wounds and burns. Bacteria like pseudomonas and staphylococcus that infect wounds are notoriously resistant to antibiotics, but not to phages. GangaGen would later go the whole hog and develop products to treat any kind of infection, including serious ones like tuberculosis.

GangaGen is in a new field and has little competition. There are a few companies practising phage therapy, but none have significant intellectual property or a team like GangaGen's. Yet there are challenges, not the least of which is the regulatory regime. Few regulators in the world have dealt with viruses as a drug. Yet if phage therapy picks up, GangaGen is set to become a leader. ■