ETPrime

How Bugworks did a cancer pivot and scaled a digital drug-discovery model to fight deadly diseases

Recovering from several setbacks, a bunch of scientists got together to work on deep-science projects that could help develop new antibiotics. Seeded at the now-defunct AstraZeneca R&D centre at Bengaluru a decade ago, the venture has since worked with 19 partners across the globe.

(From left) V Balasubramanian, Shahul Hameed, Anand Anandkumar, and Santanu Datta of Bugworks; courtesy of Bugworks

Anand Anandkumar and Taher Abbasi walked into the AstraZeneca R&D centre in 2007, hoping to sell their computing platform to the multinational pharma company. They had founded the startup Cellworks in Bengaluru, specialising in computational approaches to cancer therapy.

AstraZeneca had expanded its R&D centre in Bengaluru in 2003 to focus on infectious diseases.

Anandkumar and Abbasi had no idea about what AstraZeneca really did in Bengaluru. They presumed that the company would be developing drugs for cancer. But during their presentation they discovered that AstraZeneca R&D in Bengaluru had no use for any product on cancer.

However, the company's management was impressed by the Cellworks technology and proposed to work together on infectious diseases. "We were so desperate to sell our computing platform to them that we decided to work on infectious diseases," says Anandkumar.

In those days, AstraZeneca was struggling with a scientific problem: the different competitive environments in a cell for drugs against bacteria and for metabolic diseases. Drugs compete with other molecules in the cell for binding to a target. After a drug blocks a target for a while, the original substrate molecule builds up in the cell and starts reducing the drug's effectiveness.

This does not matter for metabolic diseases such as diabetes, as scientists do not look for 100% efficacy for the drug. But it is a deal-breaker for antibiotics because scientists are looking to eliminate the invader bacteria from the body.

Tweaking a model

To be effective, an antibiotic has to work in a non-competitive environment. "We were thinking about this problem when Anand and Taher came to us with their presentation," says TS Balganesh, head of AstraZeneca R&D in 2009.

Cellworks was then developing software to simulate biological networks, to see the ripple effects of a drug through a molecular network in the cell. Balganesh immediately recognised the value of this approach in simulating bacterial metabolic networks. And through that recognition, he seeded one of India's most promising startups.

By then, most big drug companies had given up on antibiotics as being too complicated to develop. Pharma companies had screened millions of compounds for efficacy against bacteria, using very advanced technology, but with disastrous results. No new class of antibiotics had been discovered since 1962.

After a long battle with the legal team in the UK, AstraZeneca in Bengaluru managed to give Cellworks a USD50,000 project to build simulation of the metabolic network of a bacterium. The scientists had not bothered to wait for legal clearance.

Like all cells, bacterial cells also have complex metabolic networks — like a criss-crossing system of roads in a city — that are essential to its survival. "We were looking for the best road to block to kill the bacteria," says Santanu Datta, who was then the principal scientist of AstraZeneca R&D. "Often the best road is not the highway."

However, at that time, AstraZeneca as a company did not have much faith in the computer modelling idea. So Datta left and Cellworks picked him up. It was not long before AstraZeneca saw the utility of the computational approach of Cellworks in tackling tuberculosis.

Drug companies have over the years developed 18 drugs for this dreaded infectious disease. None

of them works in isolation, and the normal practice is to give four drugs in combination. If these drugs are to be tested in combination in six doses, clinicians have to perform 3.9 million experiments to get the right combination at the right dose. So, doctors use intuition to decide the four best drugs for a patient. Cellworks thought it could decide using computation.

Datta roped in V Balasubramanian from AstraZeneca to jointly apply for a grant from Welcome Trust. Balasubramanian had developed a TB model as part of his PhD thesis at the University of Wisconsin, and it was being used around the world for drug testing. He had also developed the testing facilities at AstraZeneca.

Welcome Trust gave the team — Cellworks and AstraZeneca — USD1 million. This project identified two combinations that were never tried anywhere in the world as the best form of therapy.

One door shuts, another opens

By the time the project ended, the AstraZeneca R&D centre had closed down. The company had decided to get out of infectious diseases. At the same time, there were rumblings within Cellworks. The company board decided not to work on bacterial platforms and focus on oncology instead. So Anandkumar and Datta had to form their own company to continue their work on antibacterial drugs. And they had the entire scientific staff of AstraZeneca to choose from.

Soon enough, Anandkumar and Datta got some senior scientists from AstraZeneca to join them. They set up a company in 2014. Balasubramanian readily joined the new firm, christened Bugworks.

It got space at the incubator Centre for Cellular and Molecular Platforms (C-Camp) in Bengaluru, adjacent to the campuses of the National Centre for Biological Sciences and the Institute of Stem Cell Science and Regenerative Medicine.

Not only did Bugworks have one of the best intellectual environments in the world, it also had access to advanced equipment at C-Camp.

Next, it needed money.

During this period, Anandkumar and Datta had met Jawahar Gopal, one of the owners of furniture company Featherlite. They invited him to dinner at Anandkumar’s home one day, primarily to explain to him the problems of antimicrobial resistance and the complexities of drug discovery. At the end of the dinner, Gopal gave them a cheque of INR1 crore. “I had taken the cheque with me but did not tell them in advance,” says Gopal. “I loved their passion for science.”

Things fell rapidly into place after that. Bugworks got repeated grants from the Department of Biotechnology, totalling INR2 crore. By 2017, it had a drug candidate with a novel mechanism of action, hitting two key bacterial enzymes at once. It got USD2 million from Carb-X, a Boston-based organisation that funds drug antibiotic discovery and development. Subsequently, the company raised USD11 million in equity funding.

Making an impact on a global scale

"Bugworks had a platform technology, a candidate with novel action, and a truly global development model," says Kiran Mysore, venture partner at Utec, a Japanese venture-capital firm that invested in Bugworks.

Seven people who joined from AstraZeneca form the core of the scientific team. Balasubramanian is now the president of the company. Another dozen people from the defunct AstraZeneca R&D centre work with the company in various capacities. "They are doing some very deep science," says S Ramaswamy, professor at the Institute of Stem Cell Science and Regenerative Medicine.

Many powerful antibiotics have failed in the last few decades because the bacteria have a mechanism, called the efflux pump, that flushes out drugs before they can do their jobs. The platform technology of network modelling that Bugworks had developed has now morphed into a complex set-up that is used to avoid the efflux pump.

Bugworks has collaborated here with Satoshi Murakami of Tokyo Institute of Technology, one of the recognised experts on the efflux pump. It has worked with 19 partners around the world, all specialists in areas critical to drug development. At the moment, its team is working with William Hope of the University of Liverpool for modelling the correct dosages.

Today, all the drug candidates from Bugworks can avoid the efflux pump. "The efflux pump is relevant to a lot of other areas that have nothing to do with bacteria," says Ramaswamy. One area is cancer, to find a way of stopping the efflux pump of human cells from throwing out the cancer drug.

Bugworks has now applied to Carb-X, a Boston-based organisation that funds antibiotic research worldwide, for another grant for another molecule. Last month, the AMR Industry Alliance, an association of global pharmaceutical companies, elected the company as a board member.

The only other biotech startup on this board is Entasis Therapeutics, based in Boston, another AstraZeneca spin-off.