Beginning

Pandorum's ability to 3D print hu

GAME CHANGER: Arun Chandru, co-founder, Pandorum Technologies

PANDORUM TECHNOLOGIES

LAUNCHED
2013

FOUNDERS
Arun Chandru and Tuhin Bhowmick

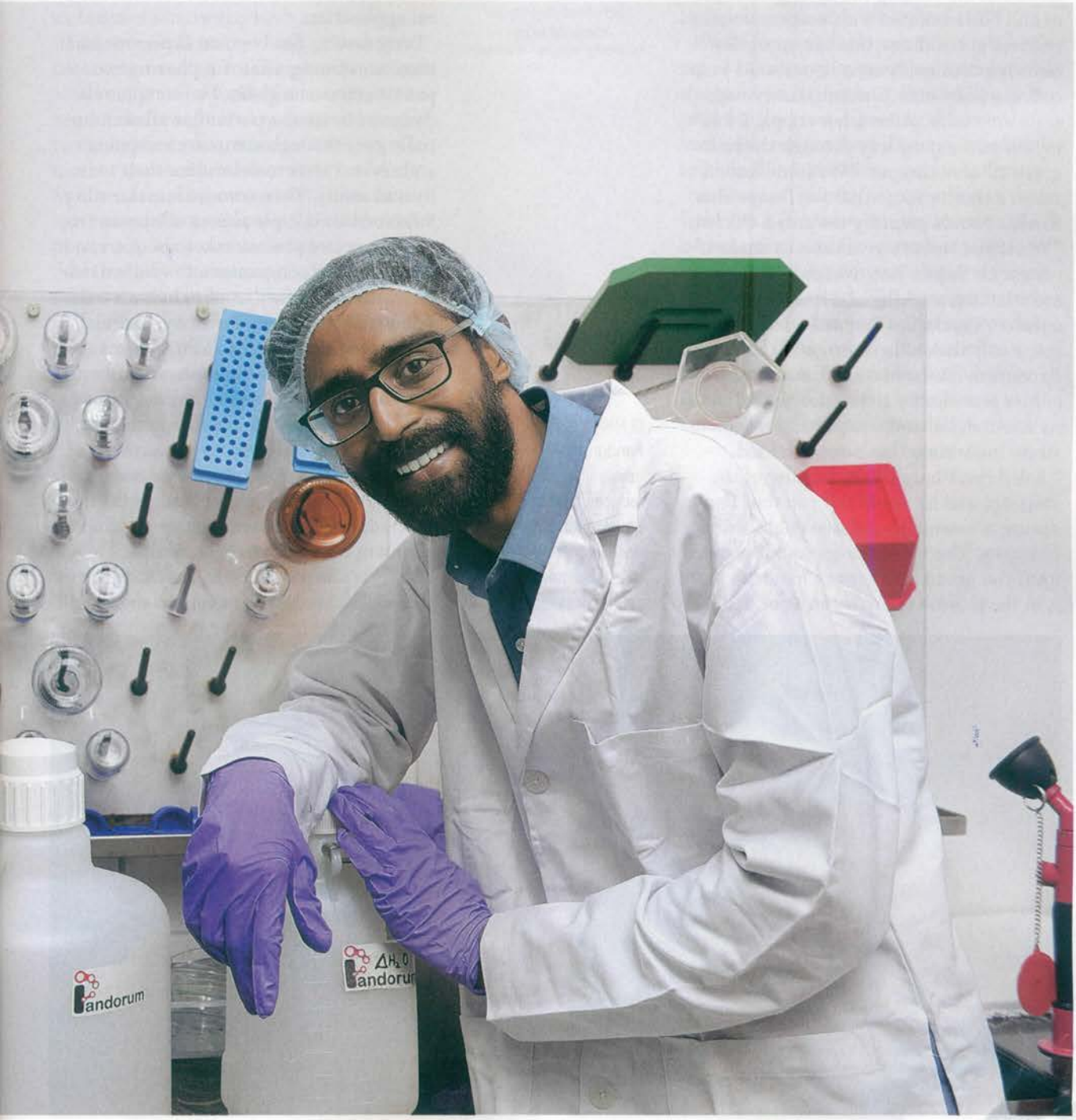
INNOVATION
3D printing of biological tissues

FUNDING
₹230 million

INVESTORS
Sachin Bansal, Binny Bansal, IAN, 500 Startups

# of a new culture

an tissues is a boon for medical research | Shilpa Elizabeth Abraham



DEEPAK G PAWAR

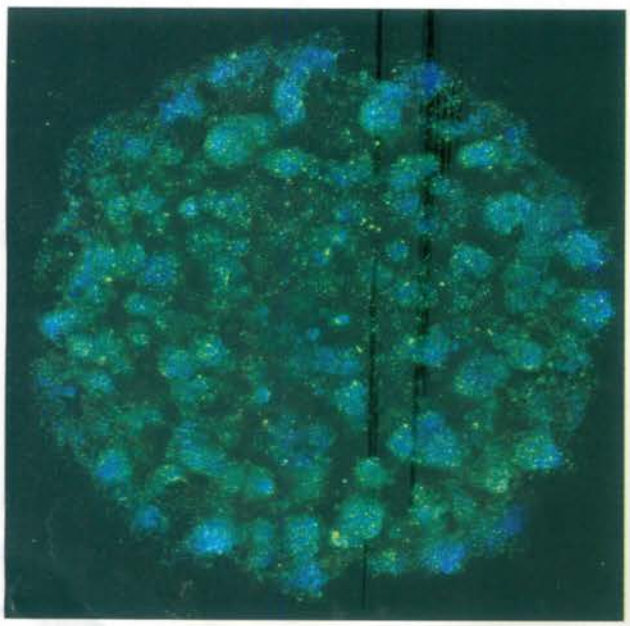
As one enters the quaint and abundantly green campus of the National Centre for Biological Sciences (NCBS) in north Bengaluru, it feels like the clock has slowed down. Among the open green spaces and bushes dotted with academic and residential buildings, one can spot a few birds not commonly seen in cities. As I sip coffee, a baby mantis nonchalantly hops across my table. After a hot cuppa, I find myself making my way through the lush green 20-acre campus. "We could have a taken a shorter route that way," says Siva Sankar Nanda pointing towards a thicket. "Yes, if you want to get bitten by snakes," retorts Dr Vanita Rao. Nanda and Rao are scientists working at a five-year-old incubatee, Pandorum Technologies, inconspicuously tucked in a corner of the NCBS. Pandorum has been using the shared facilities provided by the centre, including its research lab and equipment, to demonstrate innovation that's one of a kind.

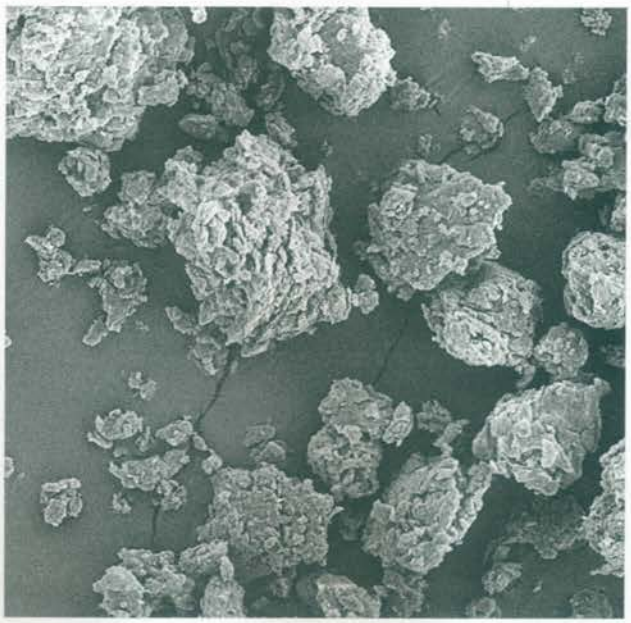
Ask Arun Chandru, co-founder of the start-up, and he would tell you that Pandorum is essentially a tissue engineering company. That might not sound like much until you get to know that Chandru's team is in the process of engineering and 3D printing living and functional biological tissues which can mimic the functions of native human tissues, for the first time in India. The 13-member team has been developing liver tissues and corneal tissues — the former aimed at helping medical research purposes and the latter for clinical application.

Drug testing has been an expensive and time-consuming affair for pharma companies across the globe. The compounds designed to treat a particular ailment initially goes through computer screening and several tests to determine their toxicity and safety. Then comes animal testing followed by multiple phases of human trials. The entire process takes about six to 10 years, costing companies a few billion dollars. However, nine out of 10 human trials fail due to detection of toxicity. "Animal models are not actually close to human models. Also in two-dimensional human cell culture, if you take a liver cell or a cardiac cell and grow it on a flat plate, they lose their functionality within a couple of days. Their morphology is two-dimensional, which means what you don't get is the three-dimensional morphology you find in a human body," Chandru explains.

So, over the past decade, scientists across the world have been working to engineer

IN FOCUS [L-R]: Pandorum's 3D human liver tissue reduces cost of drug development; human decellularised corneas offer a sustainable source of corneal tissue





three-dimensional tissues and organoids which could act as tiny replicas of the biological system inside humans. These can stay alive for a couple of months, thus allowing repeated testing, and fits well into the drug discovery process as pharma companies can use them as a platform for medical research and weed out certain toxicity causing molecules before commencing human trials. While companies such as InSphero in Switzerland and Prellis Biologics and Humacyl in the US are into tissue engineering, what makes Pandorum stand out is its exclusive focus on liver tissues in the pre-clinical space and corneal tissue implantation, which is the first of its kind in the world. "About 40-50% of drugs fail because of hepatotoxicity [liver damage caused due to chemicals]," Chandru points out. "Any new molecule that goes into the body interacts with the liver first. Either it will damage the liver or the liver will damage it. That's why liver is important. Liver tissues don't grow very well in a 2D culture. It hardly grows for four to five days and you have to finish all your tests before that," he adds.

Pandorum currently provides tissues in the format of 96-well plates (eight rows of 12 wells). Each individual well has a small organoid, a small piece of liver tissue of 0.5-1 mm diameter. The drug will be administered in these wells individually, which means that in one plate one can try out 96 experiments. Tuhin Bhowmick, director at Pandorum Technologies, explains, "It will not only reduce cost significantly but is also superior on multiple accounts given that it's derived from human cells and, therefore, has several species specific variations. In the EU and India, animal trials for many tests have been banned recently for ethical reasons. That also opens up a big market for us."

MAJOR BREAKTHROUGH

Pandorum's vision is not just to restrict its work for medical research, but to implant the tissues and organoids in the human body over the long term. A quick skim through some numbers tells us why this could be a game-changer. According to recent statistics, of the 300,000 Indians in need of an organ transplant, only 3% find donors in time. Social stigma, lack of donors, lack of skilled surgeons to handle the complex procedure and the high expenses involved lead to the dismal numbers. "Right now organ donation is the only solution for organ failures. But the world is moving towards bioengineering of tissues and their implantation. We are definitely looking to establish a presence there," says Chandru. They are working with regulatory authorities such as the FDA, EMEA and DGCI.

"Our 96-well plates will not only reduce cost significantly but is also superior since it's derived from human cells

–TUHIN BHOWMICK
Co-founder, Pandorum Technologies

While liver implants can take a while owing to regulatory approvals, Pandorum has started working with LV Prasad Eye Hospital for the bioengineering of corneal tissues and implantation. India is estimated to have about 12 million people suffering from corneal blindness, according to data from the Red Cross. But the number of corneas available for transplantation is as less as 50,000, making the demand-supply ratio highly skewed. "We have been working on this for two years. Our approach is to make a liquid cornea instead of corneal disc," notes Chandru. Intended for partial corneal wounds, the tissue would be a hydrogel kind of formulation which can be applied on the wound. "If you have an injured cornea, our liquid cornea — a suspension of cells with a biopolymer in a liquid form — would be applied to the wounded area. Then it goes inside and solidifies," explains Bhowmick. "These are human-derived cells meant for healing, so once you apply it, they start to divide and regenerate. Gradually, the cornea grows back," he adds.

While InSphero and Humacyl are into tissue engineering, Pandorum stands out for its focus on corneal tissue implantation

According to him, the product is now ready for animal studies and if all goes well, it would probably be the first tissue-engineered product in the country to be implanted inside a patient. "It should be ready over the next couple of years," he hopes. While in terms of the liver tissue development there have been some efforts in the US, UK and Japan, Chandru notes

that the cornea implantation by Pandorum would be first of its kind globally.

During transplantation, the chances of rejection of cornea by the body is high. Dr Vivek Singh, scientist at LV Prasad Eye Institute, points out how the liquid cornea will be a major breakthrough to reduce the problem. "There is big gap between demand and supply of donor cornea and 50% of harvested donor cornea is not fit for transplantation owing to multiple factors. Our strategy is to utilise those corneas for making our liquid cornea," he says.

According to him, it will help reduce the number of post-clinic visits as well as ensure there are no complications post the implant, owing to cellular components and, thus, no immunological complications. While the regulatory framework is evolving, Singh believes it wouldn't be an issue. "We have adequate scientific information on the product — for the biomaterial part from Pandorum. The cellular toxicity and sterility test for the product is done at LV Prasad's GLP facility. However, we still need to go for toxicity and other assay in animals as per the DCGI and other international requirements such as the FDA and European regulations. Then we need to go for pilot clinical trials. I think these regulations are needed to make sure the product meets all safety standards and quality control checks," he says.

"Pandorum was interesting because it is redefining medical research by developing liver and corneal tissues

–SAURABH SRIVASTAVA
Investor, IAN

Liquid cornea will reduce the number of post-clinic visits and ensure there are no immunological complications post the implant

While the benefits of cornea implantation seem to outweigh that of transplantation, the cost factor could still be a challenge, restricting accessibility and subsequent mass adoption. Though the final costs are yet to be estimated, the founders acknowledge this challenge and are thinking of a differentiated cost model. "In developed countries, it can be sold according to the pricing and policies of those countries, but in India it can be sold at reduced costs through collaborations, such as the one we have with LV Prasad and their networks. Kiran Mazumdar-Shaw is on our board and Devi Shetty is always ready to help. Both of them don't hesitate to share their expertise and contacts with us," says Bhowmick, citing the example of Narayana Nethralaya which has brought down the cost of expensive eye surgeries and even performs some for free.

MAKING A DIFFERENCE

Pandorum secured its Series-A funding of ₹230 million earlier this year from a consortium of investors, including Binny Bansal, Sachin Bansal, Indian Angel Network (IAN) and 500 Startups. However, Chandru acknowledges that it was a grant from the Biotechnology Industry Research Assistance Council (BIRAC) that set the ball rolling for the start-up in 2013. Bhowmick and Chandru were pursuing their PhD at IISc, Bengaluru, when they entered a student entrepreneurship competition in 2010 conducted by the Indian government's Department of Biotechnology. The duo won the first prize of ₹500,000 for their proposal to develop a biopolymer for healing wounds. A couple of jury members adviced them to develop the concept into a technology platform instead of limiting it to particular applications. That triggered the idea of Pandorum, and Bhowmick and Chandru went on to register their company in 2011. However, the work gathered momentum when it was extended a helping hand by the BIRAC in 2013. Since then Pandorum has won grants of $100,000 over multiple rounds from it and the start-up got incubated at the NCBS. Meanwhile, the founders stumbled upon the idea of marrying the concept with 3D printing, which ensured extended life for tissues since no chemicals or UV was used in the process of manufacturing. "By FY16 we tried printing our first functional tissue. It was primitive but still quite a feat since we could keep it alive for 40 days. In conventional 2D culture, tissues don't stay alive beyond a few days. With that we started looking outside government grants," remembers Bhowmick. In 2016, Flipkart founders Sachin and Binny Bansal invested in the company in their personal capacity. "We were ready with the proof of concept, but not commercially ready — the phase from there to

raising private funding was challenging," says Chandru.

Saurabh Srivastava, investor, IAN, is among the investors who placed a bet on Pandorum and he explains why. "We were looking at companies solving major challenges in India as well as globally creating huge impact. In healthcare, machine learning and deep tech are changing our ability to do things. Pandorum was very interesting to us because of how they are redefining medical research — by developing liver tissue for drug research and corneal tissue for implantation," he says. While he agrees that it might take longer for him to see some money, Srivastava feels it's okay. "We are looking at the long term. It will take longer for it to see some profit, but we know it will be very valuable in course of time." Chandru seconds this, and adds, "Tissue engineering companies in Europe clock revenue of $10 million-$15 million, while those in the US generate $3 million-$5 million. Yet, these companies are valued over $100 million. This is more like a long-term pipeline thing. So, India is a good place to do [similar tissue engineering] because a lot of outsourcing happens here. Companies such as Jubiliant and Tata Life Sciences do pre-clinical work here."

SETTING MILESTONES

The Pandorum team, which is currently doing commercial validations, is in talks with some pharmaceutical companies for its liver tissue. "As far cornea implants are concerned, we are looking at reaching milestones first. This financial year we expect to file a formal application for Phase 1 trial," says Chandru.

While the founders decline to divulge the expected revenue, they mention that clients would be charged based on the number of plates. Bhowmick estimates to have a revenue of few million dollars by 2020. He notes, "We are not looking at a revenue-focused path before 2020 because there are other challenges to focus on, such as getting clients, regulatory approvals and scaling up. One plate sold by a leading European company costs around €1,500-2,000. We are looking to price it lower while still offering the same features. Our primary focus for now is to work on product approval over the next two years, and scale up the product after that. We are also moving towards automation to do this."

Pandorum plans to form a dedicated business development and finance team and is looking for a space of its own with a state-of-the-art lab. According to the founders, the efforts till date had been more towards R&D, but here on, the focus would be more on manufacturing. While competition could emerge from global as well as Indian companies in the future, the founders believe the segment by itself is in a nascent stage and has enough headroom for multiple players, though the entry barrier remains very high. The presence of foreign companies has only proved to be beneficial in convincing pharma companies that 3D is better than 2D culture.

The presence of foreign players in tissue engineering has proved to be beneficial in convincing pharma companies that 3D is better than 2D

The start-up has its roadmap clear, but its ambitions don't stop with liver and cornea tissues. Pandorum's vision extends to as far as a world of 'homo chippiens,' which the founders believe is not too far. "It's like you have a small piece of liver, a small piece of heart and so on connected to each other on a microfluidic chip, so that's like having a human on a chip. You can pass your drug to the chip and monitor how it gets metabolised, see how it goes through the liver and how the metabolites interact with cardiac tissues, neuro tissues and others. You could make it very patient-specific by taking a sample out of one person and creating a homo chippien, that's his replica, and test it. It's futuristic, but that's where we are going," Chandru exclaims. While the FDA is evaluating the technology, Astra Zeneca is planning to test the 'organ on chip' technology developed by Emulate, a Cambridge-based biotech firm. But these are still early days and as fascinating as it sounds, Chandru, Bhowmick and the team know it's a long way to go.

"50% of harvested corneas are unfit for transplantation. We will utilise Pandorum's technology for liquid corneas

–DR VIVEK SINGH
Scientist, LV Prasad Eye Institute