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REDUCING THE COSTS OF BLOCKBUSTER GENE AND CELL THERAPIES IN THE GLOBAL SOUTH

Researchers in low- and middle-income countries are developing their own IP, scaling up local manufacturing, and looking for biomarkers — all in the hope of bringing costs down and getting therapies to people who need them. **By Ben Johnson**

We are living in the age of biology, where new research is translated daily into potential treatments for deadly diseases. Researchers are conducting thousands of clinical trials to assess the efficacy of these first-in-human therapeutics, but alongside excitement, innovation brings costs. These costs are paid by healthcare providers and patients, leaving many blockbuster treatments, from gene therapy and chimeric antigen receptor (CAR)-T cells to immune checkpoint inhibitors, out of reach for most of the world.

"Many patients are suffering in this part of the world, and none of these state-of-the-art technologies are available" says Rahul Purwar, CEO and founder of Mumbai-based ImmunoACT.

It is no surprise then, that scientists in low- and middle-income countries, from India

India's indigenous CAR-T cell therapy was developed at the Indian Institute of Technology Bombay in Mumbai before being spun out to create biotech ImmunoACT.

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to Brazil, are working to reduce costs. They are taking a variety of approaches, including developing their own versions of blockbuster therapies, but regulatory and manufacturing challenges are proving difficult to overcome.

Indigenous CAR-T therapy

Developing local intellectual property (IP) is one step toward bringing innovative therapies to underserved populations. "The only way we can reduce the cost of these high-end technologies is if you own the technology," says Purwar. He founded ImmunoACT on the basis of his research on anti-CD19 CAR-T therapy at the Indian Institute of Technology Bombay. Over the past ten years he and his team have received three patents for a new version of the CAR vector, a proprietary lentiviral gene delivery vehicle, and for the manufacturing processes. (The patents are approved in India and pending in the USA.) "This is, I think, the first example in the country where entire drug development happened in India," says Purwar. His goal is to own all the IP, partly to reduce costs, but also to allow commercialization in other countries. Around 100,000 patients have B cell malignancies each year in India, and so the availability of CAR-T therapies would fulfill a huge need – although no one expects production on this scale for some time.

Purwar is an evangelist for Indian IP. The pharma industry in India is too focused on in-licensing and production of generics, he says. For his CAR-T therapy developed by ImmunoACT, "We did the innovation. We developed our own product, we patented it, and then performed the entire clinical development and commercialization."

ImmunoACT recently completed its phase 2 clinical trials of actalycabtagene autoleucel in 50 patients with B cell malignancies, and the treatment received marketing authorization approval in October 2023. The company will then move on to conduct trials in cancers including myeloma, gastric cancer and brain cancer, as well as for heart attacks, cardiac fibrosis and autoimmune disease. Purwar is closely watching translational research into CRISPR–Cas-mediated CAR-T and allogeneic CAR-T, as the latter could bring down costs substantially.

His low-cost Indian CAR-T therapy is already generating interest across the world. "We will certainly make it affordable and accessible to everybody who can get benefit out of it," says Purwar. He hopes the treatment will cost around US $50,000, a fraction of the current cost – Yescarta (axicabtagene ciloleucel) and Kymriah (tisagenlecleucel) cost $373,000 and $475,000, respectively. Even at this lower cost, 90% of patients in India will still be unable to access treatment, says Purwar, as few patients have health insurance and most pay out-of-pocket expenses. But "at least we have a drug which is affordable to some," he says, "and then my next challenge is how to make it more even affordable."

India is not the only country developing an indigenous version of CAR-T cell therapy. Researchers at Mahidol University in Thailand have developed an anti-CD19 CAR-T therapy, which is licensed to Bangkok-based startup Genepeutic Bio, the first contract development manufacturing company in the country. It says that costs could be as much as 80% lower than existing treatments. Its clinical trials are ongoing, using funding from the Thailand Board of Investment, and it expects approval in Thailand by the end of 2024.

Good manufacturing practice

Cancer is a priority for Indian biotech, as it delivers a good return on investment, says Debojyoti Chakraborty, a scientist at the Council of Scientific & Industrial Research (CSIR) Institute of Genomics and Integrative Biology in New Delhi. But as well as having the world's second highest burden of cancer, India is home to many people with rare diseases – the focus of his research.

Chakraborty developed his own CRISPR–Cas vectors for gene therapy using a naturally occurring Cas9 isolated from the bacteria *Francisella novicida*, rather than the more widely used *Streptococcus pyogenes*. Using his proprietary technology, he has created a gene therapy vector to correct the mutation that causes sickle cell disease; it is in preclinical studies. As in most gene therapies, Chakraborty edits patient-derived cells ex vivo, which requires a bone marrow transplant after myeloablation. He cites two key requirements for bringing this treatment to the clinic: funding from the government of India (initially from CSIR and then from the Ministry of Tribal Affairs) and local manufacturing, including building a good manufacturing practice (GMP) unit at CSIR. Luckily for his project, the number of GMP units shot up in India during the COVID-19 pandemic, when the country produced vaccines for much of the world. This knowhow is crucial in preparing for their upcoming gene therapy clinical trials.

The involvement of the Ministry of Tribal Affairs initially surprised Chakraborty. It does not generally fund medical research, but it is committed to finding a cure for sickle cell disease, one of the biggest problems that tribal communities face. Along with funding, government involvement is helping to connect him with patients, who often live far from New Delhi, in places like Chhattisgarh, a heavily forested state in central India. "The support has been quite remarkable," says Chakraborty; "the entire government machinery seems to be coming together to support this [trial]."

His sickle cell CRISPR–Cas gene therapy is being tested in animal models, but he expects his clinical partners at the All India Institute of Medical Sciences to start recruiting patients from the tribal communities for a small proof-of-concept trial in 2024. After this, he hopes for either technology transfer to a biotech or continued government funding for further trials, as "the government has a lot of healthcare initiatives for poor people." He is also researching new techniques that could cut costs further, including delivering gene therapy in vivo, directly into the bone marrow or via the blood, using lipid nanoparticles. This would avoid the need for myeloablation, ex vivo editing or bone marrow transplant, greatly reducing costs. But this technology remains unproven — for now.

As well as the role of the government, patients are increasingly strong advocates for gene therapy research. "India has a very, very high number of rare disease patients, who now suddenly see that there is an opportunity" to be treated, says Chakraborty, in some cases crowdfunding treatments.

The Albert Einstein Education and Research Center in São Paulo, Brazil, receives tax exemption status from the government to develop health technologies.

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Brazilian gene therapy

In São Paulo, Brazil, Ricardo Weinlich is on a similar mission. He leads gene therapy programs at the non-profit Hospital Israelita Albert Einstein, one of Latin America's top hospitals (where soccer player Pelé, who died in 2022, was treated for colon cancer). Weinlich and his colleagues have developed a proprietary protocol using a CRISPR–Cas9 adeno-associated virus (AAV) vector to replace the faulty sickle cell gene, also using an ex vivo approach. Weinlich's technique is "pretty close to what is being performed in the other labs," he says. However, developing his own IP is essential to reduce the unprecedented costs for gene therapy — Hemgenix (etranacogene dezaparvovec), a treatment for hemophilia from CSL Behring, is the world's most expensive drug, at an eye-popping $3.5 million.

As in India, patients in Brazil have been powerful advocates for making gene therapy available, including suing the public health system, Sistema Único de Saúde (known as SUS). Judges ordered SUS to provide Novartis's Zolgensma (onasemnogene abeparvovec) to several patients with spinal muscular atrophy, at a cost of $1.7 million each, a breathtaking sum for Brazil's public health system. The Brazilian government needs to negotiate with the gene therapy companies to reduce costs, argues Weinlich, rather than waiting for the courts to force treatment.

Weinlich is doing his part to cut costs, and with promising preclinical studies, he is now scaling up manufacturing, with clinical trials starting soon. Rather than commercialization, "The goal is to have a protocol that we can explore here in the public setting to give it with a lower cost to our own population" via SUS, says Weinlich. His funding, along with part of the clinical research at Hospital Israelita Albert Einstein, comes from a tax-exempt program for non-profits offered by the Brazilian government that funds research into new health technologies, including gene therapy.

Abandoned therapies

Indigenous IP is not the only avenue to cut costs. "It's really consumables and reagents that drive the cost" of gene therapy, says Jennifer Adair, who co-leads the Caring Cross Global Gene Therapy Initiative and also holds the Fleischauer Family Endowed Chair in Gene Therapy Translation at the Fred Hutchinson Cancer Research Center in Seattle. Non-profit Caring Cross acquires IP, mostly for lentiviral vectors that have been abandoned by biopharma, which they then provide for clinical trials in low- and middle-income countries. Some of these have proven efficacy from past clinical trials, while others have yet to be tested.

Vector Biomed in Gaithersburg, Maryland, also has a "social mission" to reduce the costs of gene therapy, according to its website. Co-founded by gene therapy pioneer Boro Dropulić, a founder of Lentigen (which developed the vector for the first FDA-approved gene therapy, Kymriah), Vector Biomed's primary goal is to cut through the long manufacturing backlog for viral vectors for cell and gene therapy. It raised $15 million in first-round funding in January 2023, but it will also devote 10% of its manufacturing capacity to medicine for underserved populations, in collaboration with Caring Cross. Vector Biomed is working on alternative envelopes, improved manufacturing processes and other efficiencies to produce higher titers of gene therapy vectors to reduce costs, says Adair, who works closely with the biotech.

In Africa, Cissy Kityo, Executive Director of the Joint Clinical Research Centre in Kampala, Uganda, plans to conduct clinical trials of gene therapies in Uganda using vectors that pharma companies have abandoned, starting with sickle cell disease. She is in discussion with Caring Cross, who have acquired these vectors from Bluebird Bio and Novartis.

Point-of-care manufacturing

Many costs can be cut by keeping it local. For ex vivo gene therapy (including CAR-T cells), patient cells are extracted and cryopreserved before being transported to centralized facilities run by the company providing the treatment, usually in Europe, the United States or China. This incurs high additional costs if the patient happens to be far away, in Brazil, India

or Uganda. Point-of-care manufacturing can change this.

In 2021 Lentigen, which was acquired in 2014 by Miltenyi Biotec out of Bergisch Gladbach in Germany, funded two phase 1 trials of anti-CD19 CAR-T cells in patients with B cell malignancies. What made this trial different was that the CAR-T cells were manufactured on site, in Moscow and in Cleveland. The treatment resulted in high remission rates, at greatly reduced costs.

Biotech startup Immuneel, which has in-licensed CAR-T technology for its phase 2 clinical trial, is also working to reduce costs by point-of-care manufacturing. The Bengaluru, India-based biotech, which was founded in June 2022, counts cancer physician and author Siddhartha Mukherjee among its co-founders, and gene therapy pioneers Bruce Levine and Carl June sit on its scientific advisory board.

The key requirement for point-of-care manufacturing is establishing GMP, says Nelson Hamerschlak, a hematologist at the Hospital Israelita Albert Einstein. Hamerschlak is leading the first phase 1 trial of CAR-T therapy to be approved by the Brazilian regulatory agency, Anvisa (Agência Nacional de Vigilância Sanitária). Hamerschlak and his team use an anti-CD19 CAR-T vector and protocol from Miltenyi-Biotec, but they produce it on-site. At the time of writing, one patient has been treated and is in remission, with a further three having received the home-grown therapy in September 2023.

Low labor costs

Point-of-care manufacturing also takes advantage of one of low- and middle-income countries' greatest assets: the low cost of skilled labor. An analysis from 2022 led by Vikram Mathews, director of Christian Medical College in Vellore, India, found that point-of-care CAR-T cells could be produced in India for $35,107 — one-tenth the price of Yescarta. This analysis, which formed part of preclinical safety testing for a phase 1 clinical trial at the academic health center, used the CliniMACS Prodigy from Miltenyi Biotec, a fully automated closed system. This avoids the need for industrial-grade clean rooms, which are expensive to maintain. Mathews' phase 1 trial in 9 patients is complete, and his team has already treated 20 patients with cancer in a phase 2 trial. He hopes for marketing approval within the next 18 months.

GMP is critical in conducting his clinical trials, says Mathews, whereas workforce costs are key to reducing costs. "While the per capita income may be significantly lower than in a Western country," he says, "the purchasing power parity is actually very high. So the same money goes a long way." The same is true of Brazil, says Weinlich.

Hospitals can cut costs further by using locally manufactured reagents and consumables, from clinical grade culture media and cytokines, to plastic cell culture plates. Pretty much all of these are currently produced in Europe, the USA, or China and so cost more in low- and middle-income countries. With local manufacturing of reagents and consumables, "I'm fairly confident that in a span of two, three years, we could get the cost down to $10,000 to $15,000" for CAR-T cell therapy in India, says Mathews. But his reliance on Miltenyi Biotec for the CAR vector, which was provided free of charge for his clinical trial, brings uncertainty. "If it goes to market, I have no idea what they're going to sell that vector for — if they do sell it," he concedes.

No one doubts that commercial companies have a key role in widening access, but to keep costs down "you have to keep industry in its right place," says Mathews, "so industry produces reagents, but they don't control the entire process."

Scaling up production

Scaling up point-of-care therapy is a challenge. At Christian Medical College, Mathews can treat a maximum of three patients with cancer a month with CAR-T cell therapy, a fraction of what is needed. His vision is for patients to be treated in one of a consortium of hospitals across India, each of which will engineer CAR-T cells. "The scale will force industry to cut costs," he argues.

At ImmunoACT, Purwar has a similar vision of "regional decentralization", in which a few hospitals across the country build GMP units for CAR-T cell therapy. He warns that a completely decentralized, point-of-care approach could mean patients get harmed owing to a lack of quality control. "India is a very large country … every hospital is having different thresholds, different standards" he says.

Kityo also doubts that point-of-care manufacturing of CAR-T or gene therapies is a workable solution for small or medium-sized countries in Africa. Kityo is not only concerned about the costs (which include a large up-front cost for the fully automated closed system and ongoing costs for maintenance), but also because manufacturer Miltenyi Biotec, for instance, requires a third-party distributor in the country to supply the machine and service it. "They placed one in South Africa," says Adair, "but it has not been used to our knowledge in a clinical trial to date." Mobile GMP facilities could be a solution for Africa, says Kityo, with standardized processes and a trained workforce that can provide ex vivo gene therapy across several African countries.

Multiuse resources and redundancy will be critical to keeping costs low, says Kevin Doxzen, André Hoffmann Fellow at the World Economic Forum's Centre for the Fourth Industrial Revolution. One major source of potential funding is PEPFAR, the US President's Emergency Plan for AIDS Relief. With a whopping $6.9 billion budget in 2023, PEPFAR has saved over 25 million lives (although its funding is now under threat). Doxzen argues that when PEPFAR funding is used to build infrastructure for treating HIV, this equipment can also be used for sickle cell disease.

Weinlich agrees that multiuse resources are key to keeping costs low. His gene therapy treatment includes a $5 million price tag for a single batch of the AAV vector to deliver donor DNA. "If we make a joint venture with other hospitals that can use the same approach, then we can split the costs," he argues. For sickle cell disease, there are an order of magnitude more patients in Brazil, India or Africa than in the United States or Europe, which will allow costs to be covered from a much lower price. Costs for certification and validations, including from manufacturers whose products they rely on, could also be shared between different sites within the same country.

Weinlich is also in a partnership with St. Jude Children's Research Hospital in Memphis, Tennessee, where Akshay Sharma is developing a proprietary gene therapy for sickle cell disease based on upregulating fetal hemoglobin. Sharma's clinical trial will start in 2023 in the United States, but once he sees positive results in a few patients, the organization will expand the trial to partner hospitals in Brazil and India. Sharma has high requirements for his partners, who must have experience in bone marrow transplantation, cell therapies, blood banks and a GMP facility. He is in discussions with Weinlich in Brazil and Purwar in India, he says.

Clinical trials will be followed by technology transfer from St. Jude to the partner hospitals in Brazil and India. "We want these therapies to be accessible to people where they need them the most," says Sharma, who argues that gene therapy is especially needed for patients living in remote parts of India, who have little to no access to conventional treatments for sickle cell disease. "You could take this individual from their native place to, let's say, a tertiary care center in Mumbai," he says, "keep them

there for three to six months, do the gene therapy, complete gene therapy there and then send them back."

Biomarkers bring efficiencies

Even blockbuster drugs do not work in all patients. Unlocking the mechanisms of treatment failure could help target therapies to the right patients and avoid wasting expensive therapies on patients who will not respond. Better biomarkers could reduce costs for immune checkpoint inhibitors, says Kenneth Gollob, director of the Center for Research in Immuno-oncology, also at the Hospital Albert Einstein in São Paulo. Anti-PD1 and anti-CTLA-4 therapies are approved by Anvisa, the Brazilian regulator, as a first-line treatment for metastatic non-small-cell lung cancer and for advanced metastatic melanoma. However, as with CAR-T therapies, most patients do not have access via SUS — Merck's Keytruda (pembrolizumab) costs more than $300,000. Gollob and his team have shown that in patients with melanoma, those who express specific chemokines in the blood are more likely to respond to anti-PD1 therapy. He expects response rates in patients with cancer to go up from the 60–65% seen now to over 90% when only patients expressing this biomarker are treated. Happily, such biomarkers can be easily incorporated into the standard flow cytometry diagnostic test for leukemia, which is available in most Brazilian hospitals. "They could be implemented in any SUS health care clinic," he says. What he doesn't know is what price point would lead to provision of immune checkpoint inhibitors by SUS, which are not now available.

Gollob's funding is from British-based pharma GSK, as part of its public–private partnership Trust in Science, match-funded by Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP). Under the terms of their grant, GSK has first refusal on any commercialization. Now that Gollob has identified the biomarkers (research that has not yet been published), he wants to carry out a clinical trial of an anti-PD1 immunotherapy in patients with varying expression of chemokines (ideally with the drug donated by pharma, he says).

Weinlich is also using biomarkers to reduce costs, by improving the efficiency of stem cell transduction, a key part of the gene therapy protocol. Like everyone in the field, he uses a CD34 marker to isolate bone marrow stem cells from patients. But this is not a precise marker for the long-term stem cells that will successfully implant. By his calculations these comprise around 5% of the total $CD34^+$ cell population. If he can find better markers for the long-term stem cells, then he can reduce the amount of vector he needs, cutting costs by up to a factor of 20.

Regulatory challenges

Blockbuster therapies will only be made available in low- and middle-income countries with support from regulators. Such discussions can be challenging, as many regulators have little to no experience with gene and cell therapies or with bone marrow transplantation — a key step in ex vivo gene therapy, including CAR-T cells. When Mathews started his phase 1 trial for anti-CD19 CAR-T cell therapy, his was the first gene therapy trial from an academic center in India. "It took a long time to get regulatory approval because the regulatory framework itself is evolving in countries like India," he says. Purwar agrees that in India "we have a very complex regulatory pathway."

Some reforms have started. Uganda approved its first organ transplant bill in 2022; before this no legal transplants, including bone marrow, were carried out in the East African country. Kityo now has a legal framework to conduct gene therapy clinical trials, although the national drug authority in Uganda has never approved a gene therapy trial before. Caring Cross's Global Gene Therapy Initiative is "doing a lot of training to help them understand it," says Adair.

These researchers conducting clinical trials of blockbuster drugs in Africa, India and Latin America are also benefitting the world, says Adair. Africa in particular has unrivalled genetic diversity. "You want to evaluate [a treatment] in the highest index patient population with the highest genetic diversity," she says, "because that will tell you a therapy that is going to have the best benefit for everyone."

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