Innovation drive seizes Indian biotech

On June 30, India launched a $250-million plan to promote academic entrepreneurship in biopharma and strengthen local manufacturing, the biggest cash injevction into the sector yet. The goal, announced by the government Department of Biotechnology (DBT), is to create "an ecosystem for innovative, indigenous product development" driven by researchers, startups, and small and medium-sized enterprises with equal academia–industry participation, "to make [the] Indian biotech industry globally competitive over the next decade."

The five-year Innovate in India plan, for which India has taken a $125-million loan from the World Bank, will focus on developing new vaccines, biotherapeutics, diagnostics and medical devices.

The cash injection will build on the nation's incipient biotech industry. DBT secretary Krishnaswamy VijayRaghavan says, "The biopharma mission will develop platform technologies in vaccines, drug-discovery and medical technologies in a manner that allows our industry to be truly forward-engineers rather than reverse-engineers."

The Indian biopharma industry is around 10–15 years behind its counterparts in more eveloped countries and faces stiff competition from China and South Korea. "It is time for India to capitalize now on our unique strengths and overcome any hurdles to ensure success in the biopharmaceutical market," India's science minister Harsh Vardhan said during the launch in New Delhi. "The program will help deliver six to ten new products in the next five years, create several dedicated facilities for next-generation skills, and hundreds of jobs in the process."

The Biopharma Mission will be implemented by the Biotechnology Industry Research Assistance Council (BIRAC), a public sector enterprise set up by DBT five years ago to act as an industry–academia interface.

The mission will focus on products that are already at advanced stages of development, and on strengthening biotech clusters and clinical trial networks, says Renu Swarup, senior adviser in DBT and managing director of BIRAC. "Apart from vaccines and biosimilars, the five-year mission will also support development of newer platform technologies for medical devices and diagnostics," she says. "Currently India has only [a] 2.8% share in the global biopharmaceutical market, and the program would elevate this to 5% in [the] next five years."

Most Indian-made biopharma products are import substitutions or cheaper versions of branded drugs, says Govindarajan Padmanabhan, a biochemist at the Indian Institute of Science in Bengaluru, who has chaired all the technical committees of BIRAC since its inception. "The new mission is a major step towards promoting indigenous biotechnology products," he adds.

Vijay Chandru, chairman of Strand Life Sciences in Bengaluru, backs the effort but questions the time constraints. "Five years is pretty compressed time for fresh entrepreneurs to deliver products such as biotherapeutics or new vaccines."

Killugudi Jayaraman *Bangalore*

(ITD) that result in permanently activated FLT3 and are associated with poor outcomes. Less common and considered less risky are activating point mutations in the FLT3 tyrosine kinase domain (TKD). In the Rydapt phase 3 trial, 78% of patients had an FLT3-ITD— and 23% had FLT3-TKD mutations. Within the ITD group, 48% had a low allelic ratio (defined as mutant-to-wild-type allelic ratio of <0.7), and 30% had a high allelic ratio (defined as mutant-to-wild-type allelic ratio of ≥0.7). "The presumption is the high-allelic ratio is more risky, and you will potentially show a greater impact [with Rydapt]" says Daniel Weisdorf, professor of medicine at the University of Minnesota, in Minneapolis. That presumption did not hold, however. "It worked in all of them a little bit," he says.

Rydapt is, nevertheless, "an important product" for front-line therapy, Yver says. Clonal evolution generally occurs in response to the selective pressure exerted during first-line therapy, leading to the emergence of an often highly mutated—and more dangerous—dominant clone at relapse (*Nature* **481**, 506–510, 2012). More potent and specific FLT3 inhibitors, such as Daiichi Sankyo's quizartinib or Tokyo-based Astellas' gilteritinib, both currently in development, could potentially be used in this setting, he says. Gilteritinib has the added advantage of inhibiting the so-called FLT3 F691 'gatekeeper' mutation, which is associated with drug resistance. That could provide a rationale for reserving gilteritinib for treating patients at later stages. "You wait until you see the gatekeeper mutation. You don't want to waste it in the first line [of treatment]," Yver says.

Tübingen, Germany–based Synimmune is revisiting a previously unsuccessful antibody therapy developed by ImClone Systems (now part of Indianapolis-based Eli Lilly). The FLT3-directed monoclonal antibodyIMC-EB10, was abandoned after a phase 1 trial in patients with full-blown AML failed to demonstrate efficacy. "The patient cohort they selected was not the proper one," says Synimmune's founder and CSO Ludger Große-Hovest. The disease burden was simply too heavy for the antibody to work. "We are targeting AML patients with minimal residual disease," he says. What's more, the company is doing so with an Fc-optimized antibody that has enhanced antibody-dependent, cell-mediated cytotoxicity activity. "We get substantially improved tumor cell lysis," says CEO Martin Steiner. The effect is about 1,000-fold greater than that of conventional antibodies. Whether that will translate into a clinical effect will become apparent during 2018. "We would expect to get a first readout about a year from now," says Steiner.

Like many cancers, AML lacks a unique antigen that would differentiate it from healthy tissues, but Große-Hovest contends that FLT3 (also called CD135) is more narrowly expressed than CD33, the target of several antibody and bispecific antibody development programs. Most advanced is a previously approved antibody–drug conjugate, Mylotarg (gemtuzumab ozogamicin), which was first licensed in 2000 to treat CD33-positive AML. Its manufacturer, New York–based Pfizer, withdrew the product following one phase 3 trial that suggested it offered no benefit while it increased the risk of death and toxicities (*Blood* **121**, 4854–4860, 2013). Several subsequent studies with different treatment regimens contradicted these findings, however, prompting its resubmission last year (*Blood* **121**, 4838–4841, 2013). "It's reasonable to think the regulatory agencies are going to reapprove it in some fashion," says Levis.

The risk of unintended toxicities is real. The US Food and Drug Administration (FDA) put trials of two antibody-based AML drugs on hold within the last year: a bispecific antibody JNJ-63709178 (CD3 × CD123), which Johnson & Johnson, of New Brunswick, New Jersey, and Copenhagen-based Genmab, are developing, and vadastuximab talirine, a CD33-directed antibody–drug conjugate in development at Bothell, Washington–based Seattle Genetics. The agency lifted each hold earlier this year, and the trials resumed.

The flow of new targeted agents will soon widen the treatment options for patients but will also pose new questions for clinicians. Establishing the key driver mutations in AML is not a straightforward task; neither is determining optimum treatment choices. "We don't have clinically applicable models yet where you can do rapid molecular profiling, target the right therapy for the right subset and then find out if it works," says Weisdorf. The Beat AML Master Trial, a collaborative effort initiated last year by the Leukemia & Lymphoma Society, of Rye Brook, New York, which involves five cancer centers and four drug development firms, could provide the basis for such a model. In the future, liquid biopsy technologies will allow for more rapid tracking of patients' AML clones and more adaptive treatment decisions, says Yver. "You monitor the tumor as it evolves under pressure, and you adjust the treatment paradigm," he says. Success will be easy to measure. The National Cancer Institute estimates that 10,590 AML patients will die in the US alone this year. A significant reduction in that number would represent real progress.

Cormac Sheridan *Dublin*