ASIA

The new biotech frontier?

Biotechnology Can Transform India into a Global Innovation Hub

Kiran Mazumdar-Shaw

India's biotechnology industry has, over the past few decades, built a robust portfolio of products and services based on a strong platform of technological capabilities. The country has emerged as the world's largest vaccine producer, an insulin manufacturer with global scale, and the largest supplier of genetically modified cotton globally. India is also one of the world's most attractive destinations for life sciences research, with about 800 companies currently valued at over $10 billion and a sustained growth of about 20% compound annual growth rate over the past decade. With a favorable business environment, the biotechnology industry could generate revenues of $100 billion by 2025.

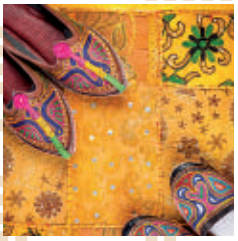
India is now ranked among the top 12 biotechnology destinations in the world and second in Asia. Already a biotechnology hot spot, India also has what it takes to become a global biotechnology innovation hub. Its competitive edge lies in its large, qualified, English-speaking scientific talent pool, production costs that are roughly a third of that in the West, a network of distinguished research laboratories and state-of-the-art pharmaceutical labs, global-scale manufacturing facilities, and biodiversity.

In fact, biotechnology can be a powerful enabler for transformational socioeconomic change as it can spur not only economic growth and provide much-needed jobs but also ensure that we find answers to modern challenges in health care, energy, food security, and environmental sustainability. This transformative innovation combines new technologies, new methods, and new knowledge that can lead to an inclusive and enlightened economy that ensures a better quality of life for all of India.

India's biopharmaceutical companies have achieved global reputations by helping to increase access to drugs like insulin, erythropoietin, monoclonal antibodies, and other recombinant proteins that offer lifesaving therapies for a host of diseases from diabetes to renal disorders to autoimmune disorders to cancer. Companies like Shantha Biotechnics and Bharat Biotech have pioneered a vaccine revolution, and today two out of every three children in the world are immunized with a vaccine made in India.

The biopharmaceuticals segment, which accounts for nearly two-thirds of Indian biotechnology industry revenue, offers a huge prospect for growth. Given its global manufacturing scale and biology, process development, and engineering skills, India can tap the estimated $250 billion to $300 billion global biopharmaceutical opportunities and emulate its earlier success with affordable chemistry-based generic drugs.

Going forward, biosimilars, biomedical devices, genomics, bioinformatics and 3D bioprinting, synthetic biology, gene editing using clustered regularly interspaced short palindromic repeats (CRISPR) technology, contract research services, and agricultural biotechnology offer new growth opportunities for the industry.



Biosimilars

The unfolding biosimilars opportunity in emerging markets in the near term and developed markets long term will give Indian biopharmaceutical players the next big bolus of growth. From $1.3 billion in 2013, the biosimilars market is expected to reach nearly $24 billion in 2019.

India is well poised to play a significant role in the biosimilars area where companies like Biocon, Dr. Reddy's Laboratories, Intas Pharmaceuticals, Zydus Cadila, and others are developing high-quality biosimilars to provide affordable access to complex biologics.

Indian patients have had access to some of the biosimilars, such as recombinant human insulin, insulin analogs, and filgrastim since the early 2000s; more recently, complex antibodies such as trastuzumab, rituximab, and adalimumab have also been introduced. This early experience with developing biosimilars will pave the way for Indian players to capitalize on this unfolding global opportunity. India's experience with chemistry-based generics could also allow Indian biosimilars players to offer affordable cutting-edge biotherapeutics to patients and health care systems around the world.

Kiran Mazumdar-Shaw, Chair and Managing Director, Biocon Limited

Biomedical devices

The government's recent decision to allow 100% foreign direct investment (FDI) in medical devices through the automatic route has opened an opportunity for manufacturing world-class biomedical devices in India. Relaxation of the FDI regime has also made it attractive for overseas players to leverage India's cost advantage to tap the $400-billion medical device market globally.

With India's medical device market projected to grow from its current $5 billion in sales to $50 billion by 2025, the country offers the industry a huge opportunity for growth and expansion.

Genomics, bioinformatics, and 3D bioprinting

As technological advancement has brought down the cost of genome sequencing, genomics and big data analytics are other emerging opportunities. Already, genome sequencing is being combined with molecular diagnostics, imaging, and data analytics to decipher the cellular structure of malignant tumors and tailor treatment regimens. Given their technological prowess, Indian companies like Strand Life Sciences are leveraging the potential of bioinformatics through big data to find answers to the challenges in translational medical research. Some, like Ganit Labs, are successfully bringing down the cost and time required for sequencing, analyzing, and interpreting genome data. India has the potential to emerge as the key provider of high-end analytics based on genomics-related big data.

There is tremendous growth potential in the area of biomarkers and companion diagnostics. This area is the future of new medicine; it will personalize therapy and optimize the benefits of biotech drugs. A new range of advanced yet affordable health care monitoring devices is being developed by Indian companies like XCyton Diagnostics, and Bigtec Labs.

Pandorum Technologies, a Bangalore-based tissue-engineering start-up, recently made India's first artificial human liver tissue with the help of 3D printing technology. This is a significant milestone that showcases the tremendous potential of 3D printing technology to develop organs and save lives.

The biopharmaceuticals segment, which accounts for nearly two-thirds of Indian biotechnology industry revenue, offers a huge prospect for growth

Synthetic biology

Synthetic biology is gaining global prominence in developing new diagnostics, novel vaccines and drugs, and a number of value-added nutritional and food ingredients. Indian researchers' recent success in sequencing the genome of the medicinal plant tulsi (*Ocimum tenuiflorum*) has opened opportunities for using synthetic biology techniques to synthesize the plant's bioactive compounds for use in treating human diseases.

Gene editing

CRISPR–Cas gene splicing allows scientists to edit genomes with precision, efficiency, and flexibility, and to do so cheaply, quickly, and accurately. In a country like India, such a tool holds tremendous potential for treating and eliminating a number of genetic diseases specific to the country's population. This technique can be used to genetically alter mosquitoes and limit the spread of mosquito-borne diseases like malaria, dengue, and chikungunya. Similarly, it can also be used to create hardier indigenous varieties of plants that are resistant to certain diseases and pests.

Contract research services

Indian biotechnological companies are also well positioned to offer contract research services to multinational corporations, which increasingly outsource R&D work to third-party service providers. Indian players are well positioned to tap the $67-billion global contract research-service opportunity for discovery and development services.

Agricultural biotechnology

Agricultural biotechnology can be leveraged to usher in a second green revolution with unprecedented opportunities to ensure food security for both India and the world. India has only 2.3 percent of the world's land area but must ensure food security for 17.5 percent of the world's population. Biotechnology offers scientific techniques that optimize the use of available resources without placing additional demands on land or water to boost yields—which is just what India needs. These solutions, which can easily be scaled across the country, can also improve the quality of the produce with disease-free and nutritionally enhanced crop varieties.

Indian farmers who opted for genetically modified Bt cotton* are reaping the early benefits of agricultural biotechnology through increased crop yields. Bt cotton has made India the largest cotton producer in the world and converted the country from a net importer to a net exporter of this important cash crop. Over 90% of the country's cotton-growing areas today grow Bt cotton, which has doubled cotton yields over the last decade.

Apart from genetically modified crops, agricultural biotechnology is leveraging molecular markers in crop breeding for the selective propagation of genes that improve yields and resist disease. Micropropagation is another area where biotechnology is helping to produce pathogen-free plants and address soil-imbalance issues.

* Pest-resistant cotton engineered with a gene from the bacteria *Bacillus thurengiensis* to produce a toxin that kills bollworms

India's experience with chemistry-based generics could allow Indian biosimilars players to offer affordable cutting-edge biotherapeutics to patients and health care systems around the world

Beyond cultivation, biotechnology also provides value-added economic opportunities in the area of biopesticides and biofertilizers, which have the potential to help farmers reap more profit from their crops.

The way ahead

The Indian government's "Make in India" initiative, which aims to transform the country into an attractive cost-effective global manufacturing hub, has identified biotechnology as a thrust area. The government has also unveiled the National Biotechnology Development Strategy (NBDS) to provide a strategic road map for creating an optimal ecosystem that encourages innovation in biotechnology. Some of the sector's immediate needs—access to capital, quality infrastructure, and high-end talent—are likely to be eased with the implementation of this road map. NBDS, therefore, will set the biotechnology agenda for the country and help its evolution as a biotechnology hub and preferred destination for innovation.

India needs to unleash the power of biotechnology to promote socioeconomic progress by transforming agriculture, health care, energy, and the environment. This will lead to the dawn of a new economic era that can aptly be called a "bioeconomy." This new era will offer India the opportunity to emerge as a leading bioeconomic power and also drive inclusive growth. ■

About the author

Kiran Mazumdar-Shaw, a pioneering biotech entrepreneur, is the Chair and Managing Director of Biocon Limited, Asia's leading biopharmaceuticals enterprise. Named among *TIME* magazine's 100 most influential people, she is recognized as a global thought leader for biotechnology. Under her stewardship, Biocon has evolved from an industrial enzymes company to a fully integrated, innovation-led, emerging global biopharmaceutical enterprise committed to reduce therapy costs of chronic conditions like diabetes, cancer, and autoimmune diseases. Ms Mazumdar-Shaw is an Independent Member of the Board of Infosys, a global leader in consulting, technology and outsourcing solutions. She is also the Chair of the Board of Governors of the Indian Institute of Management, Bangalore.

Is Japan the New Frontier for the Biopharmaceutical Industry?

Dr. Sei Murakami and the Japan Affiliate BIO CoP

In 2014, Japan joined the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S), two international instruments between countries and pharmaceutical inspection authorities, which provide together an active and constructive co-operation in the field of good manufacturing practice (GMP). PIC/S's mission is "to lead the international development, implementation and maintenance of harmonised GMP standards and quality systems of inspectorates in the field of medicinal products."[13] Japanese regulatory authorities applied for PIC/S membership in March 2012, and Japan became the 45th PIC/S participating authority as of 1 July 2014.[1]

Japan's participation in PIC/S not only enables its international GMP harmonization but will also provide more opportunity to extend its biotechnology and biopharmaceutical innovations globally. In this article, we introduce and examine recent biopharmaceutical industry achievements, and review Japanese focus on biologicals, regenerative medicine, and manufacturing technology.

Biologicals

Japan's long history with fermentation technology began centuries ago with the discovery of fermented foods. Today it includes microbial pharmaceutical production and clinical monoclonal antibody with continuous innovation. The following are examples of current Japanese pharmaceutical manufacturers' proprietary technologies.

Kyowa Hakko Kirin Co., Ltd.

Eliminating fucose from sugar chains on an antibody enhances antibody-dependent cellular cytotoxicity (the critical factor in antitumor activity) by up to a hundredfold both *in vitro* and *in vivo*. Kyowa Hakko Kogyo Co., Ltd., (now Kyowa Hakko Kirin Co., Ltd.) developed this technology and named it POTELLIGENT Technology. Several POTELLIGENT monoclonal antibodies are currently in ongoing clinical trials.

Kyowa also developed COMPLEGENT Technology, which enhances complement-dependent cytotoxicity (CDC), a major mechanism of action in an antibody. By introducing portions of IgG3 into corresponding regions of IgG1, COMPLEGENT Technology significantly enhances CDC activity beyond that of either IgG1 or IgG3 alone, while retaining the desirable features of IgG1.

Kyowa has licensed both POTELLIGENT and COMPLEGENT technologies to biopharmaceutical companies around the world through BioWa, Inc.[2]

Chugai Pharmaceutical Co., Ltd.

Recycling antibodies are engineered so that a single antibody molecule can bind to an antigen multiple times. It targets previously untargetable antigens, and achieves a product profile that could not be realized with a conventional antibody.

Sweeping antibodies are recycling antibodies that has been further engineered to bind to FcRn at neutral pH. A sweeping antibody can be administered in smaller doses with longer-dosing intervals than can be achieved by conventional antibodies.

Bispecific antibodies (BiAbs) have two different binding sites—two different heavy chains and two different light chains—that can respectively bind to two different antigens. Chugai's large-scale BiAb manufacturing technology has produced ACE910, a bispecific antibody granted breakthrough therapy designation by the US Food and Drug Administration in

Kobe GMP manufacturing site.

2015. ACE910 will be investigated for the prophylactic treatment of hemophilia A.[3]

Ono Pharmaceutical Co., Ltd.

Opdivo (nivolumab), codeveloped by Ono and Bristol-Myers Squibb, is the world's first immune checkpoint inhibitor blocking the PD-1/PD-1 ligand pathway, proven to extend overall survival in patients with advanced non-small cell lung cancer previously treated with chemotherapy. It received regulatory approval in Japan for the indication of unresectable melanoma in July 2014, and currently has regulatory approval in more than 40 countries.[4]

Regenerative medicine

With the invention of induced pluripotent stem cells (iPS cells), Japanese industry, government, and academia have put monumental efforts into the application and development of regenerative medicine.

iPS cells

iPS cells are immature cells that can develop into any type of body tissue. The method of making iPS cells was established by Professor Yamanaka Shinya at Kyoto University.5 He and Sir John Gurdon were awarded the 2012 Nobel Prize in Physiology or Medicine for the discovery that mature cells can be reprogrammed to become pluripotent. The Center for iPS Cell Research and Application (CiRA) was established at Kyoto University in April 2010 to serve as a global leader in iPS cell research, conduct basic and applied research of iPS cells with the goal of developing new regenerative medicine, and train future leading scientists and promote research collaboration with Kyoto University's Institute for Integrated Cell-Material Sciences, Graduate School of Medicine, and University Hospital. Advanced goals include producing clinical-grade iPS cells, preparing for clinical studies on Parkinson's disease and blood diseases, and developing iPS-cell-based personalized medicine for intractable diseases such as Alzheimer's disease.[6]

CiRA and Takeda Pharmaceutical Company Limited formed the Takeda-CiRA Joint Program for iPS Cell Applications (T-CiRA) in April 2015.[7] The program combines CiRA's expertise in iPS cells with Takeda's expertise in drug development. The center will conduct research to develop clinical applications for iPS cells and innovative iPS-cell-based medicines, including treatments for heart failure, diabetes mellitus, neuropsychiatric disorders, cancer, and intractable muscle diseases.

Regenerative Medicine Promotion Act

The Japanese Diet (parliament) enacted the Regenerative Medicine Promotion Act on 10 May 2013.[8] The act is a comprehensive promotion of policies on regenerative medicine from R&D to implementation.

The Act on the Safety of Regenerative Medicine, which came into force on 25 November 2014, established standards for institutions providing regenerative medicine and cell culturing, as well as processing facilities for medical treatment and clinical research. The act enables medical institutions to outsource cell culturing and processing. It also specifies three categories of regenerative medicines and stipulates necessary procedures for each category:

- Class I are high-risk, such as those not previously used in humans (ES and iPS cells, for example)
- Class II are medium risk, such as those currently in use (somatic stem cells, for example)
- Class III are low risk (such as the processing of somatic cells)

Based on these risk levels, procedures for submission of plans, standards of cell culturing and processing facilities, and licensing procedures for regenerative medicine are required.

Another piece of legislation affecting marketing of regenerative medicine is the Revised Pharmaceutical Affairs Act, which came into effect on 25 November 2014. This act established an approval and licensing system for regenerative medical products that accommodates the early implementation of regenerative medicine. It also adopted post-marketing safety measures, such as obtaining informed consent from patients on the use of the product and the recording and storing of information on treated patients.

With these acts, the swift and smooth implementation of safe regenerative medicine, as well as the delivery of various products as early as possible, is expected.

Manufacturing Technology

Recent advancements in biopharmaceutical manufacturing are enormous. The following are instances of R&D activities in biopharmaceutical manufacturing in Japan.

Manufacturing Technology Association of Biologics

In 2013, the R&D partnership Manufacturing Technology Association of Biologics was established to develop key technologies for the discovery and manufacture of pharmaceuticals for next-generation treatments and diagnoses. The project was sponsored by Japan's Ministry of Economy, Trade, and Industry. In 2015, the Japan Agency for Medical Research and Development (AMED) joined the project. Over 40 MAB research results were presented at the 67th Annual Meeting of the Society for Biotechnology in Japan in 2015.[9]

In Japan the single-use systems market is constantly growing

In 2015, with the support of Kobe University and many other organizations, MAB completed construction of the Kobe GMP manufacturing site at the Integrated Research Center of Kobe University (Figure 1). Among facility's purposes are application of developed technologies and products into actual GMP-conformed manufacture, the accumulation of novel process data for establishing process platforms, and manufacturing operations education.

Single-use systems

In Japan, the single-use systems market is constantly growing. To ensure the quality of biologics manufactured in single-use systems, an appropriate risk assessment and a stable supply of biologics are necessary. Risk control strategies based on the risk assessment—including selection of appropriate single-use components and qualification of the single-use system—are important.

Although the number of Japanese single-use manufacturers is still limited, many novel technologies and products are emerging. Japanese pharmaceutical manufacturers, together with engineering firms, members of academia, regulatory authorities, and Japanese/global single-use suppliers, have discussed the risks of single-use systems and established control strategies to assure the quality of biologics. These results were published in a white paper entitled "Approaches to Quality Risk Management When Using Single-Use Systems in the Manufacture of Biologics" in 2015.[10] This study will be useful in promoting the development of biologics as well as in ensuring their safety, quality, and stable supply.

Conclusion

What drives this intense Japanese pharmaceutical R&D effort?

In Japan, the number of people aged 65 and over became the highest in the world in 2005,[11] and reached 33 million in 2014, its highest point to date. This pushed the percentage of the population aged 65 and over to 26 percent. By 2060, one in 2.5 people is expected to be 65 or older, and one in four will be 75 or older. Although Japan has successfully established advanced technologies and systems to address these problems, still more are required. These demographics will further drive the development of pharmaceuticals in "Japan as a forerunner of finding answers for emerging issues."[12] ■

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The next 10 years should be a golden age for the Chinese biologics industry

China: the Next Frontier for Biologics

Dr. Chris Chen and Dr. Sheng Yin

Led by development of monoclonal antibodies (mAbs), the biologics industry has witnessed phenomenal growth in the past 20 years. The emergence of mAbs has produced significant breakthroughs in the treatment of cancer and autoimmune diseases. In 2015, seven of the top 10 best-selling drugs were biologics, including six mAbs.[1] Recently approved immuno-oncology mAbs such as Keytruda (pembrolizumab) and Opdivo (nivolumab) and an exciting immuno-oncology pipeline are set to drive the growth of antibody therapeutics in the years to come.

In 2014, the mAb industry accounted for $68 billion in global pharmaceutical sales. By contrast, total mAb sales in China were merely $0.9 billion, despite over 40% average growth during the past 5 years.[2] MAb treatments for autoimmune diseases accounted for 20% of global biologics sales, but only 4% in China.[3] In China, expensive treatments—including mAbs—are usually paid by patients out-of-pocket, so affordability is a major challenge in adopting these new medicines.

China's outdated regulatory system, designed mainly for small-molecule generics, has not been able to provide the necessary support for innovative products from either domestic companies or multinational corporations. It is estimated that new products are typically launched in China 5–9 years later than in the United States. Approximately 30% of US-approved cancer treatments, for example, are not yet available in China. Availability of these novel treatments poses another significant challenge for the Chinese pharmaceutical industry.

As China is the largest developing country with a dramatically aging population, the need for new medicines to treat cancer and other diseases is becoming urgent. Regulators, the pharmaceutical industry, and policy makers are working together to address both affordability and availability of these new medicines—especially mAbs.

CFDA guidelines

Dr. Chris Chen

The first wave of changes came from recent top-down regulatory reforms. In March 2015 the China Food and Drug Administration (CFDA) published its first guidance on the development and evaluation of biosimilars, which is much welcomed and puts an end to many discussions and debates over whether biosimilar standards in China should be consistent with global guidelines. It is anticipated that biosimilar companies in China will now adapt quickly to develop biosimilars to global regulatory standards. Thus, select companies in China may play expanding roles in the development and introduction of biosimilars to the global drug market.

Besides issuing the biosimilars guideline, the CFDA also implemented major reforms to drive innovation. In February 2016, the agency announced comprehensive overhauls and stated that it would give fast-track status to innovative products that fill the gap of unmet medical or clinical needs in the country. Equally important, the agency plans to significantly reduce Investigational New Drug (IND) application review time. This is expected to reduce IND review for oncology products from 18–24 months to 2 months, and closely align CFDA review process with other global regulatory agencies. These reforms will generate great excitement from the Chinese biotech industry to develop both biosimilar and innovative biologics.

To address the affordability of biologics with no or expired patents, a cluster of domestic companies are focused on the development of biosimilars. Due to limited resources in talent, good manufacturing practice, manufac-



turing to global regulatory standards, and financial support, as well as the lack of return in the near-term, Chinese companies naturally selected biosimilar investments that generate potentially higher returns with lower risk.

Booming biopharmaceuticals

Per Reuters' reports, China now boasts the second-highest number of biosimilars in development after the United States. As of April 2016, it is estimated that 27 companies are developing a biosimilar to Humira (adalimumab). Alphamab, a Suzhou, China–based biologics drug company, claimed to have 28 biosimilar programs in development (the most in China), followed by Qilu Pharmaceuticals with 10 programs.[4] Many of these companies are collaborating with global contract research organizations (CROs) to gain access to high-producing cell lines and deep process knowledge to leverage the CROs' integrated talent, technology platforms, and research and manufacturing facilities, in addition to minimizing upfront financial investment (Table A).

This biosimilar development is a direct reflection of China's booming biopharmaceutical industry. China-based biosimilar developers are expected to compete fiercely with global companies to drive down treatment cost; this will somewhat address the affordability challenge in China. If history can repeat itself, current development of mAb biosimilars could mimic biosimilar erythropoietin (EPO) and human growth hormone (HGH) development in China in the 1990s, where more than 20 companies had products on the market and pricing was driven down by over 60%. As a result, the Western EPO and HGH innovator companies gave up the Chinese market to these domestic companies and today, after continued intense competitive pressures, four or five local companies now dominate the Chinese market for these drugs.

There are also three biosimilar versions of Enbrel (etanercept) approved in the Chinese market, which are priced at 30%–50% of the originator product. The domestically manufactured etanercept generated approximately $113 million sales in 2014, accounting for approximately 62% of Chinese market share. This suggests that with a sound biosimilar strategy both Chinese biosimilar developers and foreign companies aiming for the Chinese biosimilar market can be successful and at the same time help drive down health care costs in China (Table B).

Strategic pillars

Since 2012, the Chinese government has named the biopharmaceutical industry as one of seven "strategic and pillar industries." The government created mega research grants with an average $1 billion per year to support of technology platform development that will spur pharmaceutical innovation. The class of anti-programmed cell death protein 1, (anti-PD-1) mAbs and antibody-drug conjugates (ADCs) were listed as separate megaprojects.

As a result, there are already five companies with novel anti-PD-1 mAbs filed with the CFDA for clinical trial approval or in Phase I trials. In December 2015, China's very first anti-PD-1 antibody by Shanghai Junshi Biosciences was approved for clinical trials by the CFDA, almost at the same time as Bristol-Meyers Squibb's anti-PD-1 mAb Opdivo. Throughout China an additional 15 anti-PD-1 or anti-programmed death-ligand 1 (anti-PDL-1) programs are in preclinical development. It is hoped that this strong support for both local innovation in China and global innovation worldwide will gradually address China's availability challenge by bringing in novel biologics to treat diseases in patients who need them most (Table C).

Table A: Biosimilars in development by Chinese companies[5]

Name	Brand Name	Chinese Biosimilar Development Projects
Adalimumab	Humira	27
Bevacizumab	Avastin	18
Etanercept	Enbrel	15
Infliximab	Remicade	13
Rituximab	Rituxan	25
Trastuzumab	Herceptin	24

Table B: 2014 Tumor necrosis factor blocker sales in China[6]

Brand Name	Biosimilar	Company	2014 Sales
Etanercept	Yisaipu Qiangke	3S Bio (CPGJ) Shanghai Celgen	$113 million
Enbrel	Etanercept	Pfizer	~$10 million
Remicade	Infliximab	Janssen	~$50 million
Humira	Adalimumab	Abbvie	~$10 million

China now boasts the second-highest number of biosimilars in development after the United States

One of the reasons the market space in biosimilars and anti-PD-1 mAbs is so crowded is that the Chinese pharmaceutical market is still fragmented by the types of drug bidding and insurance plans provided by each province. It is possible that any company could have a strong hold in one or several provinces. In addition, a local Chinese biologics company only needs to receive approximately 15%–20% market share to be profitable, due to the lower cost basis and lower margin expectations. This crowdedness will not disappear until the Chinese pharmaceutical market consolidates and several dominant companies emerge.

Golden age

With innovation in great demand, Chinese companies are also looking abroad to beef up their biologics pipelines quickly—and to some extent more cost-effectively. Table D outlines recent cross-border deals focusing on innovative biologics. Most companies are sourcing innovation from the United States, Europe and South Korea. In particular, there are several interesting and complementary collaborations between Korean and Chinese companies. Korean companies tend to invest more in research and early discovery, while Chinese companies consider development and manufacturing as their core expertise. A number of cross-border biosimilar deals were also recently announced. This trend is expected to continue at an even faster pace as companies continue to invest in biologics in China.

Table C: Anti-PD-1 mAbs pending IND approval or in clinical trials[7]

Official Name	Sponsor	Status
Nivulomab	Bristol-Myers Squibb	Phase I clinical trial
Pembrolizumab	Merck Sharp & Dohme	Clinical trial application filed
Humanized PD-1 mAb	Junshi	Phase I clinical trial
Humanized PD-1 mAb	Hengrui	Phase I clinical trial
Humanized PD-1 mAb	BeiGene	IND filed
PD-1 mAb	Genor	IND filed
Fully human PD-1 mAb	Gloria	IND filed

Besides sourcing innovation abroad, local innovations are bubbling, and several collaborations with US companies have been announced, as well: Innovent–Eli Lilly and Hengrui–Incyte partnerships are centered on anti-PD-1 mAb assets available from Chinese companies. Interestingly, a third such partnership between Merck Sharp & Dohme and Akeso Bio also

Table D: International collaboration in innovative biologics[8]

Licensee	Licensor	Licensor Region	Product
Simcere	Apexigen	USA	VEGF mAb
3S Bio	Alteogen	Korea	HER2 ADC ALT-P7
Zhejiang Medicine	Ambrx	USA	HER2 site-specific ADC (ARX-788)
Eddingpharm	Prima BioMed	EU	LAG-3-Fc fusion protein
3S Bio	PharmAbcine	Korea	Tanibirumab
Chemo Wanbang Biopharma	Genexine	Korea	EPO-HyFc (GX-E2)
Jinghua	Kadmon	USA	Fully human PDL-1 and VEGFR2 mAbs
3S Bio	Alteogen	Korea	HER2 ADC ALT-P7
Beike Biotech	Altor Bioscienes	USA	Immunotherapy
Galaxy Bio	Oncoimmune	USA	Immuno-oncology portfolio including CTLA4 mAb
Zai Lab Ltd	UCB	EU	Undisclosed first-in-class autoimmune program
CANbridge	APOGENIX GmbH	EU	CD95R Fc fusion protein
Tasgen	Genexine	Korea	A portfolio of five products
CANbridge	Aveo	USA	HER3 mAb
Shutaishen	InflaRx	EU	Novel infectious disease target

Table E: Chinese companies' biologics out-licensure or codevelopment partnerships[9]

Licensee	Licensor	Product
Eli Lilly and Company	Innovent	Anti-PD1 mAb and bispecifics involving anti-PD1 mAb
Incyte	Hengrui	Anti-PD1 mAb
Merck Sharp & Dohme	Akeso Bio	Immuno-oncology mAb

focused on another immuno-oncology asset. All three innovations were originally derived from global CROs, indicating strong global CRO–biologics company partnerships in China (Table E).

Although there will be plenty of challenges, the next 10 years should be a golden age for the Chinese biologics industry, both in terms of innovative biologics and biosimilar mAbs. With investment pouring in, the regulatory process bottleneck expected to disappear, and private insurance emerging to pay for expensive biologics, entrepreneurship in China is poised to become wildly successful. This, in turn, could trigger even more excitement for the biologics industry. It is not surprising that IMS Health predicts that China could be the world's second-largest biologics market by 2020.[3]

China *is* the next great frontier of the biologics industry! ■

China's biosimilar development is a direct reflection of its booming biopharmaceutical industry

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