Biocon's target factory

Thomas X Neenan, Robert E Burrier & Sunghoon Kim

South Korea's 8-year effort to create an integrated platform for novel target and lead development provides an academic drug discovery model for other emerging economies.

Innovative drug discovery and development remains a profound, decades-long challenge even in established US biotech centers such as Boston and San Francisco. In many other places in the world, key facets of the drug discovery ecosystem are often missing or suboptimal. South Korea is no different. Although it has a growing biotech-services and biosimilar sector, robust companies capable of sustaining innovative therapeutic development programs remain rare. The challenge of building a national infrastructure or companies with critical mass capable of carrying out novel target discovery and lead development prompted the South Korean government to create the Medicinal Bioconvergence Research Center (Biocon) in 2010.

In this article, we describe the center's inception, outline its main principles and strategy, provide a status update on its pipeline of products, and discuss how its principles may be relevant in other regions lacking similar requisite expertise and resources for innovative drug discovery and development.

South Korea's biopharmaceutical sector

South Korea has shown spectacular growth and development over the past half century to become an economic powerhouse. By 2015, sustained double-digit export growth had helped to make Korea the sixth-largest exporter and 11th-largest economy in the world (OECD economic surveys, Korea 2016). Although the Korean economy's traditional industrial mainstays have been automobile manufacturing, shipbuilding and information technology, powerhouse companies in those sectors, such as Samsung (Seoul) and LG (Seoul), have increasingly been diversifying and turning their attention to the biopharmaceutical sector. This transition has been driven in part by the South Korean government's desire for rapidly growing, high-value industries. Additionally, as drug-discovery technologies become increasingly dependent on highly sophisticated engineering and instrumentation, large, centrally controlled Korean conglomerates have both the interest and resources to support fundamental discoveries in innovative biology and chemistry, even though they may not yet have launched intensive drug discovery projects at a global level.

Despite the relatively small size of South Korea's population (51 million), the country is the 13th largest pharmaceutical market in the world and the third largest in Asia. South Korea has several factors that offer the possibility of success and sustained growth on the global biotech stage, including a highly regarded domestic healthcare system and a world-class clinical trial infrastructure. Furthermore, a low fertility rate is expected to increase the percentage of South Korea's over age 65 population from 13.1% in 2015 to 15.8% by 2020. This aging population will expand demand for pharmaceuticals in areas such as heart disease, obesity, cancer and diabetes. For example, an estimated 8.7% of the Korean adult population has diabetes, and 22% of all deaths are caused by heart disease.

As a final demographic factor, South Korea has a high-technology culture in which scientific education is highly regarded, an essential factor in a workforce capable of delivering cutting-edge biomedical research to match other areas of technological development in the country. Sixty-nine percent of the Korean population between the ages of 25 and 34 are college and post-college graduates, ranking Korea first among Organisation for Economic Cooperation and Development (OECD; Paris) countries. In Korea, the number of colleges per 10,000 people is 0.072, a level approaching that of the United States and Japan (0.146 and 0.098, respectively). In particular, over 30% of the total biotech workers (2,342) are PhDs[1].

The Korean domestic pharmaceutical and biotech market remains relatively small from the perspective of global big pharma and is often seen as secondary to the larger Asian markets of China, Japan and, increasingly, India. The Korean government has therefore steadily increased its investment in biotech and pharmaceuticals to ensure that the country shares in the global expansion of the biopharmaceutical industry. Korean regulatory reform and streamlining by the Ministry of Food and Drug Safety (Osong; formerly known as the Korea Food & Drug Administration) have moved in parallel. In 2014, the Ministry of Food and Drug Safety joined the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S), an agreement guaranteeing that South Korea's Good Manufacturing Practices align with international standards. Other recent developments include the introduction of the review of English language protocols for phase 1 clinical trials and the establishment of regulatory reciprocity with other countries, such as Brazil and Saudi Arabia. This allows drugs approved in South Korea to be marketed in these other jurisdictions without additional clinical testing or administrative review.

Historically, Korean companies have been discouraged from developing innovative drugs for both commercial and cultural reasons. First, the tendency of Korean consumers to self-diagnose and prescribe has created a market for over-the-counter generic drugs and

Thomas X. Neenan, Robert E. Burrier and Sunghoon Kim are at the Medicinal Bioconvergence Research Center (Biocon), Seoul, South Korea, and Sunghoon Kim is in the Department of Molecular Medicine and Biopharmaceutical Sciences, Graduate School of Convergence Science and Technology and College of Pharmacy, Seoul National University, Seoul, South Korea.
e-mail: sungkim@biocon.snu.ac.kr

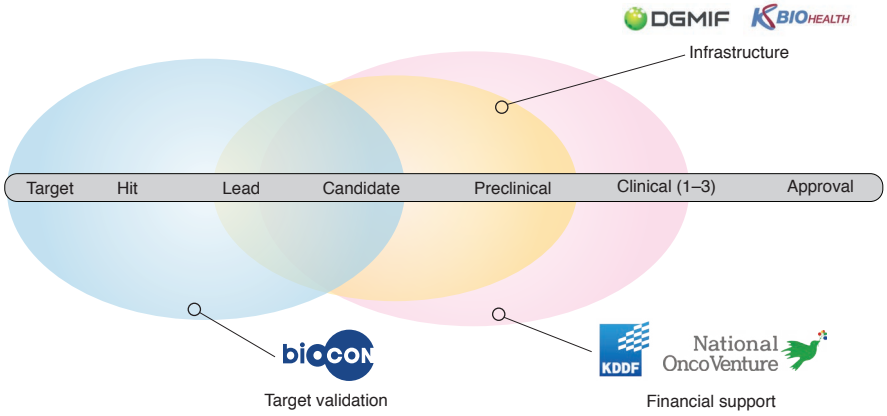

Figure 1 Biocon in the context of other Korea's national programs to facilitate drug discovery. DGMIF (Daegu Gyeongbuk Medical Innovation Foundation) and KBio (New Drug Development Center) are national infrastructures, helping candidate identification and development. KDDF (Korea Drug Development Fund) and NOV (National OncoVenture) select and financially support new drug discovery projects from lead to clinical phase. Biocon focuses on target and early lead development, capabilities that are missing in other national programs as well as in industry. There is some degree of overlap among these national programs to facilitate collaboration.

traditional Asian medicines rather than high-priced, physician-prescribed branded drugs. Second, many Korean companies have little experience and expertise, not only for developing programs around novel biological targets, but also with the process of liaising with global regulators and marketing channels. Third, there is a shortage of globally experienced senior management to run R&D-intensive companies in Korea. Finally, the domestic market has provided insufficient commercial incentive for companies to take on the higher attrition risks of novel drug development.

For these reasons, the Korean biopharma sector has, for many decades, focused more on 'me-too' products and development of biosimilars mainly targeting domestic markets. Novel discoveries of potential global interest have typically been out-licensed early to multinational companies wherever possible.

Recent changes in Korean biopharma

Increasingly, biotech companies in South Korea are coming of age, bolstered by innovative investment programs from the government and by the recent international success of a small number of Korean industry flagship companies. Several Korean firms have set up US branch offices and laboratories to get real-time access to the global biotech ecosystem. In addition, several large contract manufacturing companies have entered the market in Korea to supply pharmaceutical finished products under contract to global pharmaceutical companies.

Although young biotech startups in Korea suffer from pressure for short-term revenue generation and from limited sources of capital, the environment is rapidly changing as the environment shifts to a more US-type VC-driven model. Indeed, South Korea is increasingly seen as an interesting place for trans-border biotech startups, which can capitalize on a favorable regulatory environment, high-quality research and access to highly skilled graduates.

Building on these strengths, the government has also been proactive in directly investing in individuals and institutions that show commercial potential in the biotech space. In fact, commercial applications within academic research laboratories are now seen as an increasingly important means to complement and sustain Korean government funding.

Over the past decade, numerous public initiatives have been launched to bolster biotech innovation, providing non-dilutive funding, dedicated facilities and expertise to support translation of molecules through development. This approach is notably different from that in the United States, where the government provides seed funding for startups via Small Business Innovation Research and Small Business Technology Transfer programs, but the heavy lifting of taking drug candidates forward through development is largely taken on by the private sector.

Korean programs of particular note include the DGMIF (Daegu Gyeongbuk Medical Innovation Foundation; Daegu) and KBIO (the Korea New Drug Development Center; Osong). These two organizations, founded in 2009, offer infrastructure and technical support for drug candidate development (**Fig. 1**). In addition, the Korea Drug Development Fund (KDDF; Seoul), founded with a budget of ~$800 million in 2011, have supported a total of 134 projects in different stages of clinical development. Similarly, National OncoVenture (NOV; Goyang), founded the same year by the Korean Ministry of Health & Welfare, is supporting 12 oncology programs. Both KDDF and NOV offer financial and strategic support to both industry and academic programs that pass their selection criteria.

Challenges and motivation for Biocon

Notwithstanding these advantages, the establishment of a fully integrated, innovative drug discovery and development industry in Korea faces several challenges. It remains clear that the academic sector in Korea has an important role to play in the development of a strong and vibrant R&D-intensive biotech sector. However, the country is still short of experience and successes in translating original academic discoveries to first-in-class drug development. Academic career progression is still focused primarily on publications rather than translation. Successful integration of academic research into the pharmaceutical economy requires the ability to fund and start new companies that can mature and add value to early academic research, as well as develop business relationships with existing large companies. Furthermore, South Korean corporate culture has not demonstrated the requisite combination of development and fund-raising experience vital to the viability of young startup biotech companies. The funding ecosystem is short of highly experienced venture capitalists, university technology transfer officers, and entrepreneurially minded scientists. The country devoted ~$3 billion of grants to the biotech sector in 2016, with an average grant providing ~$150,000 over 3.3 years. However, the investment ratio of private to public financing is much lower in biotech (0.82) than in sectors such as information technology (5.4) or nanotechnology (9.9). Moreover, the investment culture in South Korea favors operational productivity (i.e., output easily measured by units produced), rather than R&D-intensive innovation with long timelines in which opportunities are hard to financially quantify, which is often the case for life science ventures focused around new target biology. For this reason, many interesting early discoveries and inventions with great potential for novel drug discovery are not effectively pursued beyond academic publication and basic patent filing in academic laboratories.

Taken together, these factors prompted the Korean government to fund the formation of such organizations as Biocon not only to provide a bridge between basic research and downstream development, but also to address

the continuing need to spur drug development efforts around novel drug targets in Korean biotech.

Defining a mission

Biocon was initiated in 2010 by the Korean Ministry of Science and Information and Communication Technology (MSIT; Gwacheon) as part of its Global Frontier Project, and one of us (S.K.)—a member of the faculty at Seoul National University (SNU)—was assigned as director of the project through a competitive, multi-level review process (see **Box 1** and **Fig. 2**). SNU therefore provided a logical home for the project's headquarters, together with a core research group and an administration office.

Biocon was given an expected budget of ~$100 million to be spent over a period of 9 years—compatible with the timelines for entry to lead identification in an innovative drug discovery program. Although the entire project was subject to an annual review process for performance and direction, Biocon leadership was given autonomy (within the framework of the original request for proposals) not only to direct the project's focus but also to reallocate resources and to search for additional academic and industrial collaborators to join the project. This aspect of the program was innovative in that it allowed very rapid decision making based on progress by individual research groups. Furthermore, this provided Biocon's leadership the freedom to rapidly reallocate resources to individual projects on the basis of changing scientific and commercial realities. The close partnership between the government and the project enabled rapid decisions on infrastructure and scientific direction while allowing the researchers to maintain focus on their ongoing drug discovery programs.

A key element of Biocon's infrastructure development was the question of intellectual property (IP). In the highly collaborative world of drug discovery, lack of IP ownership clarity can become a stumbling block for efficient research across a consortium. The Global Frontier structure addressed this concern early by making Biocon an independent foundation that can hold and leverage IP, as well as by building IP into contracts with outside research partners. Additionally, the process allowed the director to act as single point of contact when commercial discussions are initiated with potential outside partners, who are often discouraged by the necessarily amorphous nature of many multi-investigator projects. In the case of Biocon, an early emphasis was placed on attracting globally experienced business development expertise in house to both facilitate communications with outside commercial partners and manage realistic expectations.

A strong research focus

To find its niche in the drug discovery process, Biocon reviewed domestic screening centers, such as the Korea Chemical Bank (Daejon) and Institut Pasteur Korea (Seongnam); and international centers, such as the Scripps Research Institute (Jupiter, FL) and the Experimental Therapeutics Center, A*Star (Singapore). Acknowledging that these centers are well equipped and experienced, we elected to devote our resources to other directions. We also chose to avoid offering services that could already be provided by contract research organizations.

To both provide the project with a unique focus and build on Biocon's internal expertise—the center's founding investigators were predominantly professors and researchers from public institutions—Biocon decided to concentrate on roles that could be best fulfilled by the academic sector. This suggested a focus on identification, validation and delivery of novel targets for downstream development.

The biopharma industry generally recognizes that novel target discovery is often best performed in academic labs, whereas such labs tend to lack the relevant expertise in validating druggable targets and taking lead compounds

Box 1 Biocon: genesis of a target factory

In 2010, MSIT launched the Global Frontier Project, an initiative targeted at solving global challenges in major R&D areas across several technology areas of long-term interest to the Korean government, including biotech. As of 2017, MSIT had launched 10 programs (the original plan was for 15). The ultimate objective was to achieve success in multiple programs at a level that would constitute globally competitive research efforts. The process used to choose projects is outlined in **Figure 7**.

As the first step in project selection, an Open Global Frontier Forum was established to solicit suggestions for potential research areas on which the Global Frontier Project could focus. In total, the MSIT received 136 suggestions, which were then reviewed by a scientific committee (103 experts from diverse fields); a subsequent in-depth 'promotion committee' finally distilled the suggestions down to a shortlist of 7 prioritized areas. Specialists in each of these 7 areas were then recruited to a planning committee that then worked to further develop the proposals from a scientific perspective and in line with MSIT's common philosophical '4G' code (global, ground-breaking, group and green). Transparency of the process was ensured by public disclosure of all the participating committee members. Subsequently, MSIT publicly announced the final 7 topics, providing a month for feedback and to solicit applications from qualified individuals interested in directing these efforts.

The selection process for project directors was conducted in two oral competitions, first within a field of projects (for example, drug discovery) and then between the projects of different fields (for example, drug discovery versus virtual reality).

Together with four other competing proposals in drug discovery, Biocon's project was assessed by a review committee consisting of top-level scientists as well as nonscientific experts in other area. Biocon then had to compete with six other projects of different fields, and finally was selected as one of the three projects to start in 2010. (The two other projects selected were on bioenergy and virtual reality.)

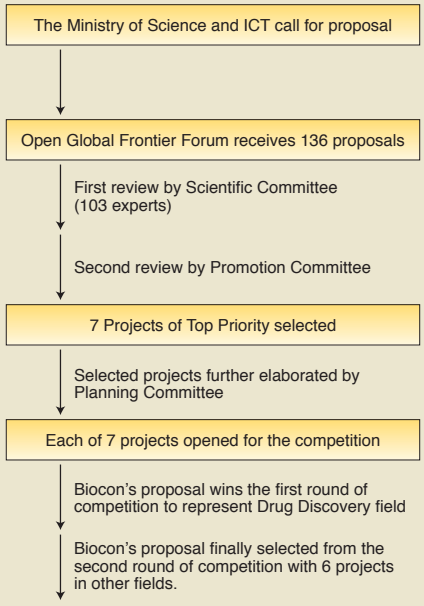

Figure 2 Selection process for the Global Frontier Project and Biocon. Biocon was the winner for biotech, one of several technology areas targeted by the Korean government initiative aimed at addressing global challenges in major R&D fields.

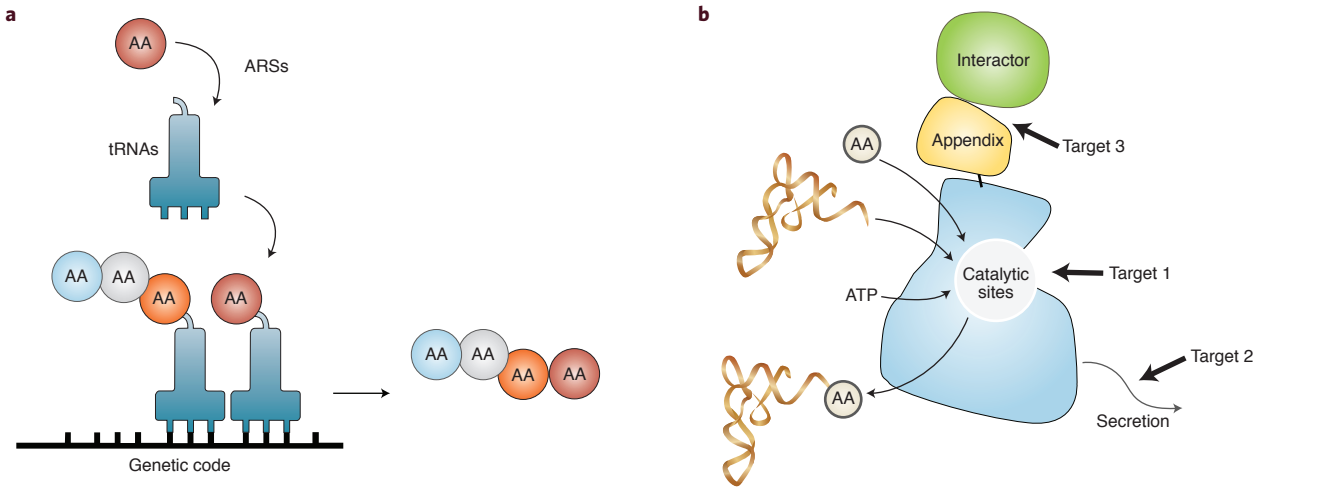

Figure 3 The promise of ARSs as therapeutic targets. For decades, drug researchers have overlooked ARSs, mainly because of their common nature as protein synthesis enzymes. However, the field has recently grown in unexpected and explosive ways, and it has become clear that newly discovered activities and disease-associated behaviors of ARSs (mutations, variant formation, interaction and secretion, etc.) not only have wide-ranging applications but also offer diverse opportunities for innovation and product development. The Biocon team had deep experience in the field and was convinced from the onset that the field offered a vast horizon of untapped biology with great therapeutic potential. (**a**) ARSs consume ATP to activate their substrate amino acids (AA) and link them to the acceptor ends of their cognate tRNAs for protein synthesis. (**b**) Multiple routes to developing new therapeutics from different biological activities of ARSs. One route is to develop chemicals that can specifically inhibit or modulate the catalytic activities of ARSs[7–9] (Target 1). Chemicals specifically inhibiting pathogenic ARSs have been clinically used as anti-infectives for decades[10–12]. Targeting the catalytic sites of human ARSs might require additional drug design for maximum therapeutic benefit. A novel chemical specifically targeting human prolyl-tRNA synthetase (Daewoong Pharmaceuticals; Seoul) showed safety and promising efficacy against cardiac fibrosis[13]. A second route is to exploit the unique extracellular activities of many ARSs that are known to be secreted under specific conditions (Target 2)[14–16]. For instance, systemic administration of purified glycyl-tRNA synthetase and tryptophanyl-tRNA synthetase showed potent immune stimulatory activities against cancer[14] and bacterial infection[15], respectively, suggesting that full-size or active fragments could be used as novel biologics. Alternatively, targeting the pathologically secreted ARSs with specific antibodies could yield drugs. A third route is to exploit the ability of ARSs to mediate diverse signaling pathways via specific protein–protein interactions (Target 3)[17–20]. "Appendix" indicates extended non-catalytic domains that are often involved in the interactions with other cellular factors.

further into clinical development. Biocon aimed to fill this gap in South Korea and to establish a 'target factory' that assembles the comprehensive data required for well-validated targets. Within the expected budget size and timeline, Biocon focused efforts on projects from a specific and related target space, rather than a basket of fashionable but mutually unrelated targets. In this way, Biocon believed that high-quality coherent datasets could be generated, accumulating a deep domain knowledge in the focused target space.

With a potential 9-year lifespan and support to carry programs to the level of lead discovery, Biocon has had the luxury of focusing on a big idea. Rather than chasing popular drug targets, such as kinases and various membrane proteins, we elected to launch a major program exploring new functions and biomedical applications of human aminoacyl-tRNA synthetases (ARSs), an area relatively unexplored in drug development. Although ARSs are essential enzymes, covalently matching the corresponding amino acids and tRNAs for protein synthesis (**Fig. 3a**), they have not been seriously investigated by the drug development community, and they thus represent a very large and hitherto unexplored target space. Biocon is exploring multiple routes from the biology of ARSs to find new drug targets and therapeutic agents (**Fig. 3b**). The research goal has been to develop a strong core of both science and technology, focusing on deep biology and medicine of ARSs that would provide a portfolio of programs spanning a variety of unmet clinical opportunities.

Building infrastructure and collaborative teams

To maintain coherency and communications among the projects, a strong core research group was established that coordinated all projects with the participating academic and industrial partners, grouped into four key functions: target identification, drug design, drug screening and disease modeling (**Fig. 4**). The core group, housed at SNU, currently consists of 11 PhDs, 14 technicians, 25 graduate students (11 doctorate and 14 masters), with 8 administrative/technical positions.

In any given year of the program, Biocon works with ~40 external research labs in South Korea in different fields, affiliated with major universities, institutions and hospitals. The core research group also seeks to run collaborative projects with international collaborators (particularly in the United States, European Union, China, Japan, Singapore and Israel). In general, the core group is in charge of fundamental discoveries in target biology, and it integrates and validates the diverse datasets obtained from the four specialist groups. Tight and frequent communication between the project managers in the core and external groups is essential. Both internal and external communications are facilitated by Korea's advanced information technology structure, allowing real-time web-based global interactions. The core group also interfaces with a TRADE (Translation and Development) group made up of experts in business development and commercialization dedicated to linking the project discoveries to downstream development via partnering or spin-out companies. Projects are in constant flux, fulfilling the needs of the programs for external expertise and constantly being replenished by new external collaborators through a 'real-time open program' process that solicits new expertise anytime during the fiscal year to immediately add needed capabilities critical to individual project success.

From a structural and strategic perspective, Biocon has certain unique characteristics. First, to validate targets from the molecular to the clinical level, Biocon has a fully integrated yet flexible team structure, allowing expansion or contraction of various collaborative groups as

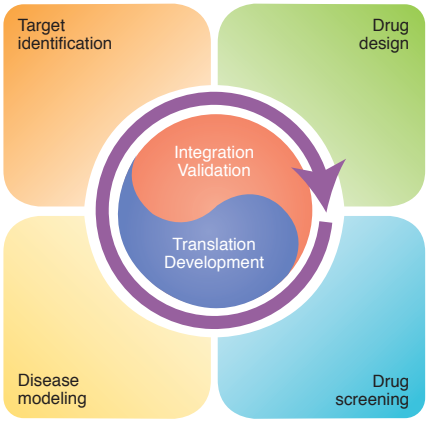

Figure 4 Biocon's team structure is functionally divided between core and external specialist groups. The core group selects the targets of focus and integrates and validates the data incorporated from the specialist groups. The core group also works closely with our Translation and Development (TRADE) group for further downstream development. External teams are grouped to target identification (genomics, proteomics, bioinformatics, structural biology and molecular and cell biology), drug design (medicinal chemistry, antibody and peptide engineering), drug screening (nanotechnology, microfluidics, three-dimensional (3D) cell culture and *in vivo* imaging technologies) and disease models (genetically modified or patient-derived orthotopic mouse, zebrafish and fly models and pathological analysis of human specimens).

needed. This approach is best summarized as "letting the science pick the researchers rather than letting the researchers pick the science." Second, the core group integrates, coordinates and directs the activities of consortium members, allowing a rich diversity of talent and expertise to be brought to bear in a focused way. Third, Biocon focuses on a specific target space to obtain in-depth understanding of the target actions while retaining flexibility in the specific disease indications and therapeutic modality (small molecule, antibody, etc.). Fourth, Biocon also pays careful attention to innovative technologies (including engineering, nanotechnology and information technologies) that might impact the research focus and facilitate target and lead validation, and seeks to run this technological track in parallel with the science track for drug discovery.

The target validation process

The vision of Biocon includes discovery of fundamental insights into the ARS enzyme family that can then be shuttled through a series of biological, chemical, mechanistic and efficacy steps. Specific programs are targeted toward different ARSs, with a project leader running each project in an entrepreneurial way. Resource needs are communicated to the core management team, which evaluates them in light of the overall Biocon mission. Missing skill sets or resources are added to programs as needed, usually by seeking proposals from external academic or commercial sources.

Contracts with commercial sources are structured to preserve all IP for Biocon. External academic relationships usually involve some IP sharing (based on the Korean government's guidelines), whereas IP in commercialization relationships can be held both by Biocon and the participating institutions or companies. Conversely, contributions from academic or commercial groups can be terminated if the needs of a particular program change. Changes are generally made on an annual basis. As with any complex set of discovery programs, projects tend to ebb and flow over time, but experience has shown a portfolio that 6 or 7 projects can be sustained in parallel.

The scientific objective for each project is to map out a new target landscape by adhering to the principle of publishing mature discoveries in academic journals, together with patent filings. Generally, initial discoveries of target biology are disclosed with proof-of-concept lead molecules if available. The output of each effort is, ideally, a validated target package comprising a well-understood target function and structure, highly sensitive assays and potential biomarkers, and target-specific hits or leads, together with some early efficacy and toxicology data (**Fig. 5**). The overarching goal is to explore this neglected area of biology in an effort both to apply Biocon's focused and integrated approach to drug discovery and to develop a series of well-validated targets that can be commercialized, either through direct partnering to a large pharmaceutical company or through the formation of, or licensing to, startups.

Ultimately, Biocon hopes to leverage successes in the ARS arena to establish research platforms for other target spaces that can be validated in a similar manner. Biocon is also keen to carry one or more of the project's assets to an initial regulatory filing, both for value creation and for clinical proof of concept.

Progress and outputs

Progress in cutting-edge science is rarely linear, with no simple way to evaluate the economic value and academic excellence of a research organization. The challenge for the Korean government and for Biocon was how to both establish a sustainable target discovery platform and also prioritize the scientific originality needed for innovative drug discovery—all in a country where innovative drug discovery is the exception rather than the rule. This duality is seemingly contradictory because sustainability requires predictable revenue generation whereas scientific originality generally requires continued investment. Nonetheless, Biocon has pursued both tasks as much as possible by publishing scientific discoveries and technological inventions with concomitant patent filing whenever possible.

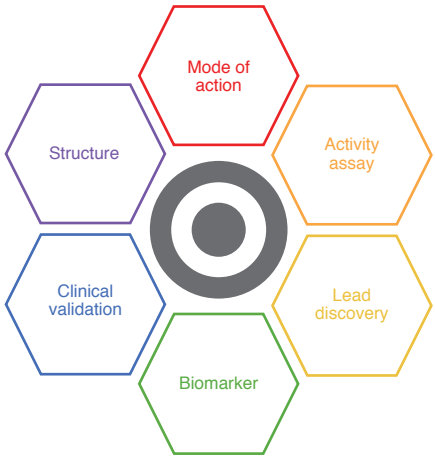

Figure 5 Biocon's six key criteria for target validation. Those include the knowledge of action mechanism, target structure determination, assay design, clinical validation, lead identification and biomarker identification. Biocon runs multiple coherent approaches to meet these criteria for target validation.

Out of 262 research articles that have been published by Biocon principal investigators over the past 7 years, 46 articles directly relate to ARSs, many of which have contributed to the development of the therapeutic and diagnostic pipelines. Notably, although Biocon continues to focus on interests of target discovery and development, it has also (primarily through program necessity) invented several new technologies. Given the strong engineering capabilities of Korean academic collaborators and access to the Korean technology ecosystem, these efforts have led to the commercialization in Korea of several new devices and instruments. Representative examples in the two tracks are listed in chronological order in **Figure 6**.

The Korean government's original goal with the first round of funding over 9 years was to generate a portfolio of nine innovative therapeutic and diagnostic pipelines, at least one of which would be ready for clinical development, with others spread over different stages—from hit discovery to lead optimization. To date, Biocon, either alone or through the collaboration with external partners, has generated one drug candidate (for fibrosis) that is completing

preclinical development; three candidates (for alopecia, inflammation and renal cancer) are entering pre-clinical development; and two leads (for colon cancer and neural disorders) are being further optimized, together with one further promising screening program (**Fig. 7**, top). In the diagnostic space, two programs have been licensed, one to a major pharmaceutical company and the other to a startup (for sepsis and bile ductal or pancreatic cancer, respectively); two novel cancer markers are also under clinical validation (**Fig. 7**, middle).

In Biocon's technological track, a cell-penetrating antibody[2] approach, a three-dimensional cell culture and scanning platform[3] and intravital microscopy technologies[4] have contributed to the formation of three project-specific companies. Additionally, new technologies for extracellular vesicle and nanoparticle separation[5] and for specific protein modifications[6] are under validation and further optimization (**Fig. 7**, bottom). To date, 21 licenses have been granted to existing pharma, biotech and startup companies.

On the basis of these data and many newly emerging therapeutic leads and technologies from the project, Biocon's performance has consistently been highly ranked by the annual review committees formed by the Korean government. This process occurs in two parts: first external reviewers (consisting of academicians, industry researchers, patent lawyers and company executives) are invited by Biocon to assess its pipeline; second, the Korean government recruits a second committee that provides an additional layer of oversight.

Expecting that the government support will end in 2019, Biocon is continuing its efforts to ensure the sustainability of both the target and technological pipelines through the spinoff of startups, out-licensing, codevelopment and connection to other government programs (**Fig. 1**). Through the combination of these efforts, Biocon is expected to shape a sustainable research ecosystem with its R&D and financial allies, continuing its role as a 'target factory' both for the growing Korean market and, more importantly, as a partner in the global biotech ecosystem

Closing remarks

The Biocon model provides a new model for integrated drug development, particularly focusing on the early discovery phase that has rarely been conducted in an organized way. We propose it to be especially relevant in countries that lack several of the ingredients for a vibrant biotech ecosystem. Such ingredients include a base of sophisticated investors who understand the timelines and capitalization needs of innovative life science ventures; faculty and academic institutions capable of efficient technology transfer, translation and startup creation (rather than focused simply on publishing papers); and an industrial base familiar with innovative drug development that can provide seasoned management to run new ventures.

However, the Biocon model is only likely to be replicated in economies where, despite these limitations, there is an appreciation of both the financial investment but, more importantly, the time needed to nurture a biotechnology ecosystem. Rapidly emerging economies are often driven to produce low-value, high-volume products, in part driven by the need to employ large numbers of less educated people. There is a rush therefore toward product quantity over self-sustaining quality. Patience and continuous investment in education and institutions are required to build a complex biotechnology landscape. Additionally, an openness to the outside world in terms of scientific cooperation, freedom to travel and regulatory flexibility are key to being able to participate in what is truly a global ecosystem. Without these, it is unlikely that, even with great talent, the Biocon model could flourish elsewhere.

Several factors were key to Biocon's success. First, the Korean government understood and accepted that long timelines and considerable financial support were required for the center to succeed. It also allowed Biocon's leadership a high level of autonomy, key to ensuring flexible and rapid decision-making.

Second, the project was and is subject to a rigorous annual review process for both qualitative and quantitative milestones. This allows project performance to be constantly evaluated and milestones moved according to needs.

Third, Biocon has proven the power of a systematic and multidisciplinary effort converging on a target of focus (for example, ARSs in the current stage). In principle, the process, once established, can be universally applied to any type of target analysis.

Finally, Biocon has shown that strong, centralized but flexible management is key

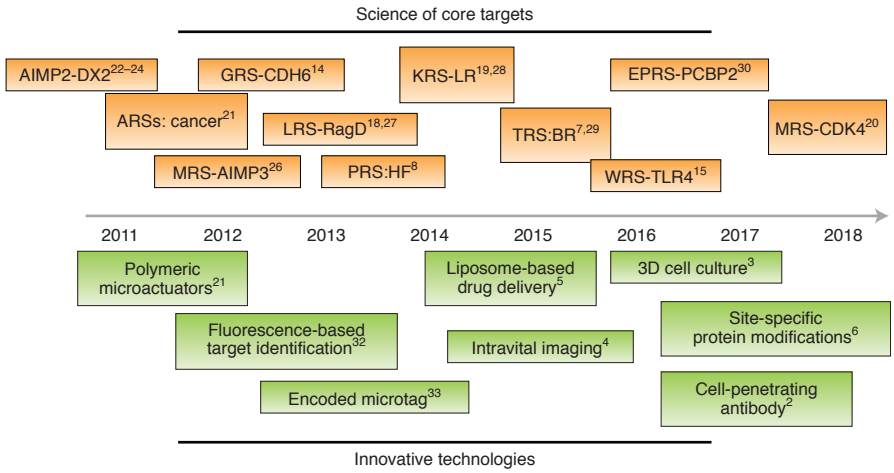

Figure 6 Representative discoveries in the core target biology (focusing on ARS biology) and innovative technologies applicable to the processes of drug discovery are shown. In the research of core targets, the potential association of ARSs with various cancers was systematically analyzed[21]. AIMP2-DX2 is an oncogenic variant of a tumor suppressor, AIMP2[22–24], that is associated with multiple ARSs as a complex[25]. Methionyl-tRNA synthetase (MRS) makes a tight interaction with a tumor suppressor, AIMP3 to control translational initiation within the multi-tRNA synthetase complex (MSC)[26]. Upon dissociation from the MSC, MRS can interact with CDK4 to control CDK4 stability[20]. Glycyl-tRNA synthetase (GRS) is secreted to kill tumor cells via its interaction with CDH6 (K-cadherin)[14]. Leucyl-tRNA synthetase (LRS) controls the mTORC1 pathway in a leucine-dependent manner via RagD[18,27] and lysyl-tRNA synthetase (KRS) promotes cell migration via the 67-kDa laminin receptor on the cell surface[19,28]. Halofuginone (HF)[8] and borrelidin[7,29] specifically inhibit the catalytic activities of prolyl-tRNA synthetase (PRS) and threonyl-tRNA synthetase (TRS), respectively. Glutamyl-prolyl-tRNA synthetase (EPRS) and tryptophanyl-tRNA synthetase (WRS) defend against viral and bacterial infection through interactions with PCBP2[30] and TLR4-MD2[15], respectively. Therapeutic potential of these targets has been explored at Biocon. In Biocon's technological track, innovative technologies were devised for use in drug discovery, including polymeric microactuators for efficient drug screening[31], fluorescence-based target identification[32], lithographically encoded microtags[33], liposome technology for target discovery[5], intravital real-time microscopy[4], 3D cell analysis[3] and a cell-penetrating antibody modality[2]. A novel method for site-specific protein modifications has also been recently reported[6]. Many of these discoveries and technologies have been either out-licensed to existing companies or were integral IP for new startups.

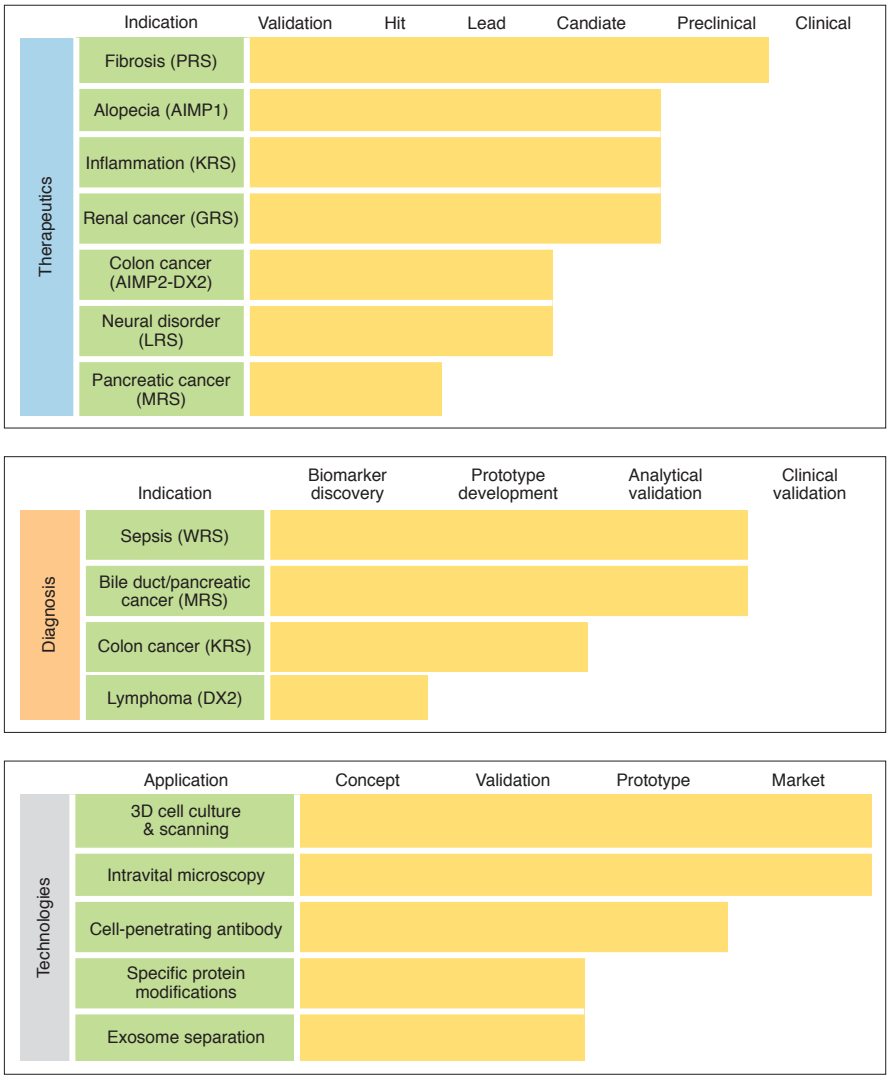

Figure 7 Biocon's therapeutic, diagnostic and technological pipelines. For therapeutics, the unique pathophysiological activities of different ARSs have been explored to build the current pipelines. For diagnostic applications, specific secretion and cytological characteristics of different ARSs have been validated as biomarkers for the indicated diseases.

to coherent and sustained output from collaborative target discovery research that often generates diverse, scattered results. The project has developed a structure that leverages the academic expertise of participating principal investigators but encapsulates a vision that supersedes personal academic agendas and ensures effective collaboration and a focus on the larger goal. The core management team sets long-term, clear but sustainable objectives, allowing the evolution of fluid yet modular teams that can efficiently execute the research goals. This thinking is in line with Biocon's working philosophy of "letting the science pick the researchers rather than letting the researchers pick the science." Long-term projects have a natural rhythm of resource growth and contraction, depending on the stage of evolution. We believe that allowing project teams to dynamically expand and contract is a key to successful outcomes. The project has run with a turnover of 3 or 4 teams per year (10–15% of the total participating teams).

Biocon has been constructed as a flexible network of scientists, both academic and commercial, around a large but relatively unexplored area of science. The project concentrates on fundamental understanding of the underlying biology of the ARS field, but with a keen eye on the potential development of therapeutic products.

Although the center has focused on ARSs as a target area, the approach attempts to be nondogmatic, seeking the best in people and institutions throughout Korea and across a global network. In addition, the project attempts to be inclusive in acknowledging the contributions of all stakeholders and respectful of the trust and financial support of the Korean government. Filled with deep rooted commitment for new biology and the curiosity that drives fundamental science, Biocon hopes to be a good example of purpose-driven, organized basic research that forms a benchmark for other organizations.

ACKNOWLEDGEMENTS

This work was supported by a Global Frontier Project grant (NRF-M3A6A4-2010-0029785).

COMPETING INTERESTS

The authors declare no competing interests.

1. Organisation for Economic Co-operation and Development. *OECD Education at a Glance* 2014 (OECD Publishing, 2014).
2. Shin, S.M. *et al. Nat. Commun.* **8**, 15090 (2017).
3. Park, M.C. *et al. Cancer Res.* **76**, 1044–1054 (2016).
4. Choe, K. *et al. J. Clin. Invest.* **125**, 4042–4052 (2015).
5. Lee, J. *et al. Nano Lett.* **15**, 2938–2944 (2015).
6. Yang, A. *et al. Science* **354**, 623–626 (2016).
7. Fang, P. *et al. Nat. Commun.* **6**, 6402 (2015).
8. Zhou, H., Sun, L., Yang, X.L. & Schimmel, P. *Nature* **494**, 121–124 (2013).
9. Son, J. *et al. Acta Crystallogr. D Biol. Crystallogr.* **69**, 2136–2145 (2013).
10. Schimmel, P., Tao, J. & Hill, J. *FASEB J.* **12**, 1599–1609 (1998).
11. Rock, F.L. *et al. Science* **316**, 1759–1761 (2007).
12. Novoa, E.M. *et al. Proc. Natl. Acad. Sci. USA* **111**, E5508–E5517 (2014).
13. Park, J.S. *et al. Circulation* **136**, A24036 (2017).
14. Park, M.C. *et al. Proc. Natl. Acad. Sci. USA* **109**, E640–E647 (2012).
15. Ahn, Y.H. *et al. Nat. Microbiol.* **2**, 16191 (2016).
16. Kim, S.B. *et al. J. Cell Biol.* **216**, 2201–2216 (2017).
17. Ko, Y.G. *et al. J. Biol. Chem.* **276**, 6030–6036 (2001).
18. Han, J.M. *et al. Cell* **149**, 410–424 (2012).
19. Kim, D.G. *et al. FASEB J.* **26**, 4142–4159 (2012).
20. Kwon, N.H. *et al. ACS Pharmacol. Transl. Sci.* https://doi.org/10.1021/acsptsci.8b00001 (2018).
21. Kim, S., You, S. & Hwang, D. *Nat. Rev. Cancer* **11**, 708–718 (2011).
22. Choi, J.W. *et al. PLoS Genet.* **7**, e1001351 (2011).
23. Choi, J.W. *et al. J. Mol. Cell Biol.* **4**, 164–173 (2012).
24. Lee, H.S. *et al. Biochem. J.* **454**, 411–416 (2013).
25. Park, S.G., Ewalt, K.L. & Kim, S. *Trends Biochem. Sci.* **30**, 569–574 (2005).
26. Kang, T. *et al. J. Mol. Biol.* **423**, 475–481 (2012).
27. Kim, J.H. *et al. Nat. Commun.* **8**, 732 (2017).
28. Kim, D.G. *et al. Nat. Chem. Biol.* **10**, 29–34 (2014).
29. Jeong, S.J. *et al. Exp. Mol. Med.* **50**, e424 (2018).
30. Lee, E.Y. *et al. Nat. Immunol.* **17**, 1252–1262 (2016).
31. Kim, J. *et al. Nat. Mater.* **10**, 747–752 (2011).
32. Park, J., Oh, S. & Park, S.B. *Angew. Chem. Int. Ed. Engl.* **51**, 5447–5451 (2012).
33. Han, S. *et al. Adv. Mater.* **24**, 5924–5929 (2012).