Future Trends in Synthetic Biology: What to Expect in Asia

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Abstract

Synthetic biology research and technology translation has garnered increasing interest from the governments and private investors in Asia, where the technology has great potential in driving a sustainable bio-based economy. This Perspective reviews the latest developments and future directions in synthetic biology research and applications, with highlights of important developments from Asia. It also suggests plans for more effective multi-lateral collaborations that promote a sustainable development of the field and mitigate potential biosecurity risks. Through these discussions, stakeholders from different groups, including academia, industry and government, are expectantly better positioned to contribute towards the establishment of innovation and bio-economy hubs in Asia.

Introduction

With more than two decades of development in research and technology translation, synthetic biology is progressively realizing some of the promises in a variety of highly anticipated applications, such as healthcare, food and agriculture, and manufacturing[1,2]. The economic contribution from synthetic biology-enabling or -enabled technologies is growing fast, at a projected compound annual growth rate (CAGR) of 28.8%, expected to reach a market size of US$18.9 billion by 2024[3]. In order to further promote a strong growth of synthetic biology and the broader bio-based economy, at least 50 governments have put forward long-term strategies or groups of policies to invest resources and build talent pools[4]. For instance, the research roadmap by the Engineering Biology Research Consortium (EBRC) delineates a comprehensive set of technical themes and application sectors as a guide for funding agencies and researchers[5]. The UK has also established a bioeconomy strategy to build a collaborative research network, an expert workforce and a supportive business environment to catalyse biotechnology translation[1,6,7].

Although significant research, entrepreneurship, and investment activities in synthetic biology have been highly concentrated in the US and the UK[7], there is also growing interest and determination in developing the bio-based economy in Asia, as witnessed by the increasing investment in research and development[8–10] and policy support at the national level[11–13]. A workshop has been recently convened by stakeholders from academia, industry, and government in Singapore to discuss the status of synthetic biology research – vis-à-vis advancement and bottlenecks – and potential risks and challenges to regulatory bodies. Through the workshop, representatives from different groups achieved better understanding of the technology and consensus regarding multilateral collaborations to effectively advance synthetic biology research and technology translation in Asia.

In this Perspective, we recount the main topics discussed during the workshop and give a review of the latest developments in synthetic biology research and applications, with highlights of noteworthy work from Asia and discussions on collaboration and regulation. First, the current state-of-the-art in synthetic biology research and technology translation is reviewed from the perspectives of enabling technologies, and contextualized within three broad application sectors, respectively. Following that, a summary of the discussions on effective collaborations and regulations to mitigate biosecurity risks is presented. Some of the quotes and recommendations from the workshop are cited in the article, but are not attributed, as the workshop was held under the Chatham House Rule to promote free and open discussions. Collectively, the insights and recommendations from the workshop participants may facilitate a sustained development of synthetic biology research and applications in Asia.

Honing the tools and mining for more resources

Enabling technologies are instrumental in making synthetic biology research possible. These broadly include DNA reading, writing and editing technologies, biomolecular and host engineering technologies, and data science; so important that they are placed at the core of the engineering biology roadmap by the EBRC. Here we review some of the most important developments in these technologies.

(1) DNA reading, writing and editing

The significant reduction in the cost of DNA reading and writing in the last few decades has been the most powerful driving force of synthetic biology development. Since the completion of the Human Genome Project, DNA sequencing technology has advanced rapidly from Sanger sequencing to the more efficient massively parallel sequencing technique, or next-generation sequencing (NGS). With the maturation of NGS between 2007 and 2012, the per-base cost of DNA sequencing was reduced by four orders of magnitude[14]. DNA synthesis, on the other hand, has mostly relied on phosphoramidite-based chemistry. The development of microarray-based platforms has also significantly improved the efficiency and reduced the cost of DNA synthesis[15]. It is estimated that with current state-of-the-art technology, the cost of sequencing a human genome has come down to US$1,000, and that of synthesizing one would be US$6,000[16].

The best manifestation of the advances in DNA technologies is the synthetic yeast genome (Sc2.0) project[17,18], and by further extension, the Human Genome Project – Write[19]. To achieve *de novo* genome assembly of higher complexities, further advancement in DNA reading, writing, and editing is required, for example longer DNA reads, high-fidelity long fragment synthesis and assembly, as well as precision genome editing[16,19]. To this end, multiple emerging technologies and techniques are being developed. For reading, single-molecule sequencing platforms (e.g. Pacific Biosciences and Oxford Nanopore) can extend the read length from the current 300 base-pair limit to an average of 10 kilobases and above[14,20]. For writing, new methods that rely on enzymatic DNA synthesis (e.g. using terminal deoxynucleotidyl transferase) are promising in synthesizing longer oligo fragments of customized sequences[21,22]. In parallel, multiple DNA oligo assembly strategies have been developed to seamlessly assemble large numbers of short oligos into longer DNA fragments[16,23,24]. Last but not least, as a quality control measure as well as functional knock-in/out, precision genome editing tools are essential. Precision base-editing techniques that do not incur double-strand breaks have been demonstrated in both mammalian and plant cells[25–28]. Multiplexed base editing was also achieved with modified CRISPR-Cas systems in *E. coli*[29], as well as in human cells[30], exemplifying the capability of large-scale genome-wide precision editing.

With the continuous evolution of DNA technologies in reading, writing, and editing, we will be better equipped to design, modify and build genomes of any organisms of interest – from engineering disease-resistant crops, gene and cell therapies that can target specific diseases, to extensively recoded and remodeled genomes that incorporate highly customizable gene editing tools. In addition to genome editing and synthesis, the latest DNA technologies also fuel the burgeoning field of DNA data storage, which has the advantage of superior data density and durability[22,31,32].

(2) High-throughput platforms for molecular and host engineering

The advanced DNA technologies have empowered the next layer of engineering, namely biomolecular and host engineering. Within the last two decades, there have been demonstrations of genetic circuits controlled at transcriptional, translational and post-translational levels[33–37]. In addition to new parts and circuits development, there

have been significant efforts in improving the predictability of the engineering process. For instance, genetic elements and system insulators were designed to reduce the context dependency of gene expression[38–41]. There are also data and model-driven design tools[42] to predict design outcomes from individual elements[43,44] to whole systems[45,46]. However, despite progress in design tools, the current status of synthetic biology applications is still largely a trial-and-error process involving "brute force" screening. The development of an engineered enzyme, pathway or whole organism still follows multiple iterations of the design-build-test-learn (DBTL) cycle.

In order to accelerate the DBTL cycle, integrated infrastructure with strong automation and computer-aided design capabilities – biofoundries – were established in multiple research centers around the globe. A global alliance was formed in 2019[47], with 9 members in the Asia region, to promote open source development of both software and hardware, and sharing of protocols, best practices, and standards. The vision is to enable rapid prototyping of engineered biological systems in an agile and reliable manner. In the eminent "10 molecules in 90 days" pressure test taken on by The Foundry at the Broad Institute[48], six of the challenged molecules or their close relatives were successfully produced within the given time constraint. In another study, the biofoundry at the University of Manchester produced 17 potential materials monomers over 85 days[49]. Apart from a demonstration of capabilities, such drills also identified key bottlenecks in further accelerating the engineering process. These include gaps in computer-aided design tools, time needed for DNA synthesis, and complicated analytical methods for product characterization and measurement[48].

"In the near future, workflow for a biological engineer will no longer be limited by the pace of fabrication but instead by their ability to analyze circuit behavior and incorporate the data into the next design cycle."

While academic research continues to improve the efficiency and reliability of the engineering methods and platforms, there are already a few commercial enterprises with business models centered upon developing customized enzymes or microbial hosts, such as Ginkgo Bioworks and Zymergen. Such platform companies not only pioneered the technology translation, but also contributed towards advancing process automation, data curation, and production scale-up[50]. With strong in-house capabilities of discovery, engineering and production, they will be the powerhouses in driving synthetic biology applications in a variety of sectors (to be discussed in later sections).

(3) Data science and machine learning

While the "build" step is empowered by advances in DNA technologies and automated liquid handling, the potential in speeding up the remaining three steps – design, test, and learn – lies in data science and machine learning algorithms. Driven by increasingly efficient and accessible sequencing capabilities, we are generating an explosive amount of data, in the form of genomic/metagenomic and transcriptomic information. When such genetic information is coupled with additional layers of profiling, such as metabolomics and proteomics, they offer powerful tools to understand the intricacy of biological systems, to discover novel enzymes, pathways,

intercellular interactions, and ultimately aid in engineering design[51]. For example, by mining the genome and profiling the transcriptome and metabolome of the UV-resistant animal tardigrades, researchers in Japan were able to identify unique proteins that confer DNA protection against UV radiation[52]. A Chinese group applied comparative genomic and transcriptomic analyses to the resurrection efforts of the plant *Selaginella tamariscina* and revealed genetic mechanisms of drought tolerance in plants[53]. Similar multi-omics approaches also led to the discovery of novel biosynthetic pathways from microbes isolated from Singapore's native environment[54,55], as well as silent secondary metabolites in *Streptomyces* species[56]. Such novel discoveries not only add to our understanding of the biological systems, but also enrich the available molecular tools for synthetic biology research and applications.

With more and more systemic biological data becoming available, the methods for extracting valuable information and enlightening biological designs from such datasets become the next technological challenge; at the same time, this has also created many opportunities for advances in machine learning[57,58]. For example, machine learning algorithms have been developed to predict promoter strength[59] and natural product structures[60,61] from genome sequences, to predict function from molecular structure information[62], to aid the directed evolution of proteins[63,64], to predict base editing outcomes[65], to accelerate metabolic pathway design and optimization[66–68], and to streamline analytical chemistry data processing during the test step of strain engineering[69,70]. These are just a few examples where machine learning has significantly improved the efficiency of otherwise tedious, labor-intensive, or highly unpredictable procedures in engineering biology. Furthermore, combining machine learning with mechanistic systems modelling could enable us to realize the full potential of predictive biology[71]. It is reasonable to expect increasingly valuable applications of machine learning algorithms in advancing the design, test and learning efficiencies.

In order to fully realize the value of the rich biological data source and unleash the power of machine learning, it is essential to standardize the process and control the quality of data acquisition, database curation, as well as to establish protocols for proper sharing (e.g. an extension of the Nagoya protocol to focus on data information sharing[72]). In Japan's Bio-strategy 2019[12], a biological database has been recognized as one of the key pillars for developing the bioeconomy, and accordingly, each industry and social sector needs coordination to generate a comprehensive and coherent data infrastructure. Such initiatives should also be established and widely adopted at the international level to promote the advances of data-driven biological research and engineering.

Unleashing the potential for applications

Among the broad application sectors, we centered our discussions around three major themes: (1) next-generation biomanufacturing, (2) future medicine, and (3) food, agriculture and environmental applications.

(1) Next-generation biomanufacturing

Synthetic biology is driving a manufacturing revolution that explores alternative feedstocks and production processes, and further extends towards the development of products of better performance. In the 2018 BIO industry report, it was estimated that the global economic value of bio-based production, including renewable chemicals and polymers, biofuels, enzymes and materials, reached US$355 billion[73]. Among this immense volume of production activities, the next-generation biomanufacturing driven by synthetic biology has brought in new advantages – the improved efficiency and economic benefits, the potential to produce chemicals and materials of novel properties, and the sustainable "circular" model of production.

"Leverage synthetic biology not to replace existing systems, but to integrate, augment, advance and integrate into existing systems … and to make it better."

The preeminent driving force is the economic benefits of biomanufacturing of natural products and intermediates of high commercial value, such as fragrance, nutrients, and medicine[74]. Conventionally, such molecules are commonly extracted from plants – a costly and tedious procedure. Now with advanced DNA and biofoundry technologies described in previous sections, we are able to "rewire" and "reassemble" identified natural biosynthesis pathways into microbial workhorses to produce (parts of) the desired chemicals in a reliable and "on-demand" manner. In the early years of development, such metabolic engineering endeavors were mainly the focus of academic research, such as those reviewed for engineering microbial production of isoprenoids[75], alkaloids[76], polyketides and non-ribosomal peptides[77]. In more recent years, pathway and/or enzyme optimization have become services provided by platform companies such as Ginkgo Bioworks and Zymergen, which seek to improve the production efficacy of desired molecules for clients. There are also downstream specialists such as Amyris who optimize the scale-up production of commodity molecules[78].

Going beyond what is given by nature, synthetic biologists are also reinventing what can be produced by biological systems. Companies such as Spiber in Japan and Bolt Threads in California have developed fermentation products derived from spider silk protein that are light-weight and possess desirable mechanical properties that cater to different industries. Structural proteins are relatively under-explored for synthetic biology applications. By tapping on the diversity and complexity of such proteins, functional materials that never existed before can be constructed. In addition to exploiting and improving what nature has to offer, there are also studies where an expanded genetic code can incorporate non-canonical amino acids in proteins. With such techniques, we could efficiently expand the structural and functional landscape of proteins for new scientific discoveries and industry applications alike[79].

Last but not least, next-generation biomanufacturing could also accelerate the transformation from the current "linear" economy into a more sustainable "circular" system. In pursuit of a paradigm shift from the petrochemical-reliant industry, synthetic biology researchers and entrepreneurs are exploring alternative renewable feedstocks, as well as output products that are more environmentally friendly. In Taiwan, researchers developed CO^2-based photosynthetic pathways to produce butyrate with the cyanobacteria *Synechococcus elongatus*[80]. Similarly, other metabolic engineering demonstrations sought to improve the production efficiency of

cyanobacteria for a myriad of high-value chemicals[81]. Advances in genetic engineering of microalgae also opened new avenues for photosynthetic production of biofuels and other valuable chemicals in eukaryotic algae[82,83]. In Thailand, part of the national policy on Bio-, Circular and Green Economy encourages waste-to-energy projects, and microbial conversion of biomass waste to alkane and alkene-based fuels is being explored as an exemplified opportunity[84]. The diversification of feedstocks to industrial or agricultural waste and the enhanced utilization of photosynthesis could drive cost reduction from the conventional crop-derived biofuel production.

Challenges faced by researchers and businesses alike include further diversification of the feedstock and synthesizing beyond nature. The well-studied biosynthetic pathways can be exploited for commercial applications, but the real potential of "on-demand" production of any molecules or designer materials will require the integrated advances in sequencing data generation and analytics to identify new biosynthetic pathways. In parallel, it is also recognized that the combination of bio- and conventional chemical synthesis offers versatile solutions to some molecules that present challenging structures, unknown natural synthetic pathways, or are toxic to host cells.

Bottlenecks of technology translation often lie in production scale-up. Projects originating from a research lab or an early-stage startup often lack the resources to carry out pilot scale-up studies. Moreover, the complexity of biological systems and the vast differences of industrial versus small-scale bioreactor conditions often make the outcome of scaled production unpredictable[85]. Further development of predictive models and better integration of modelling with experiments are important in making the scale up process more rational and predictable[86]. More research, and importantly public investment in pilot manufacturing infrastructure[4], is needed for closing the capability gap and reducing risks.

(2) Future medicine

Applications in healthcare have contributed to the majority of synthetic biology translation and commercialization, and unsurprisingly, have attracted the lion's share of investments[87].

Synthetic biology has propelled the advancement of the pharmaceuticals industry through the expansion of therapeutics manufacturing capabilities. Before the advent of recombinant DNA technologies, the majority of pharmaceutical products were limited to small molecules. In 1982, the first commercial synthetic human insulin was produced by engineered *E. coli*[88], replacing the historical standard of extracting it from animals. Ever since, recombinant DNA technologies have fueled the development and manufacturing of more biologics, such as protein and RNA-based therapeutic products. In addition to macromolecules, synthetic biology also revolutionized the manufacturing of some small molecule drugs of high demand, such as the microbial production of artemisinin[89] and cannabinoids[90] to replace the conventional plant source. Going beyond the convention of cell-based biologics manufacturing, pioneering studies using freeze-dried cell-free systems to produce therapeutic molecules in a portable, on-demand manner – from small molecules,

short peptides, to antibody conjugates and vaccines[91,92] – could potentially revolutionize the manufacturing and distribution model of pharmaceuticals.

"Therapeutic products used to be focused on individual molecules – now we are looking at whole organisms for clinical use."

In addition to the manufacturing of molecular therapeutics, synthetic biology also facilitates the development of a new class of cell-based therapies and gene therapies. In 2017, the US Food and Drug Administration (FDA) approved the first chimeric antigen receptor (CAR)-T cell therapy[93], and at the dawn of 2018, the first directly administered viral vector-based gene therapy was also given the green light to market[94]. Such examples of pioneering cell and gene therapies are the harbingers of more therapeutic innovations enabled by synthetic biology. Going beyond gene replacement therapies, which is the mainstream of the current gene therapy technology, the CRISPR-Cas system has been developed into base-editing tools that can bring us closer to precision gene editing for inherited diseases[95]. With respect to cell therapies, CAR-T cells are being enhanced to be safer[96], more versatile[97], and to be sourced and manufactured more robustly[98]. The repertoire of engineered immune cells is also being expanded beyond T-cells to include NK cells[99] and macrophages[100]. In addition to immune cells, engineered bacteria, single species or multi-species consortia, are also being developed for skin, gastrointestinal, and other microbiome-associated diseases[101–104], and notably for systemic metabolic diseases, where the most advanced developments are already in human clinical trials for phenylketonuria[105,106]. Closely related are bacteriophages as highly potent and specific antimicrobials[107]; engineered phages were also developed as modulating agents to enhance the effect of chemotherapy in cancer treatment[108]. It is envisioned that future smart medicine could come in the form of living cells that detect the diseased states and respond with therapeutic accuracy accordingly[109].

In other medical applications apart from therapeutics, synthetic biology has also empowered new methodologies for diagnostics and prophylactics. For *in vitro* diagnostic applications, reaction mixes with nucleic acid sensors based on RNA toehold switch[110,111] or CRISPR-Cas13/Cas12a[112–114] were developed into rapid and sensitive diagnostic tools, with demonstrations in the detection of femto-attomolar level viruses including dengue, zika, and most recently SARS-CoV-2 viruses[115,116]. There are already two companies established in the US to commercialize the technology, as these lyophilized reactions stored on paper-like media have great potential in point-of-care diagnostics in the field or at low-resource regions where manufacturing and cold-chain logistics are hard to access. In addition to *in vitro* diagnostics, novel *in vivo* diagnostics have been developed using live engineered bacteria for the detection, reporting, and even recording of biomarkers associated with pathogen, inflammation and the use of antibiotics[117–120]. New methods for developing vaccines were also demonstrated in the examples of recoding the genome of influenza A virus with multiple premature termination codons[121], and genomic mining for interferon-sensitive mutations in the design of influenza vaccines[122].

All the prior-mentioned emerging medical applications still face different levels of technical challenges before they could be developed into mature products. Moreover, two general challenges facing the newer generation of cell and gene

therapies are regulation and manufacturing. The therapeutics developed from biological systems are inherently more complex than molecular drugs, thus possessing higher uncertainty in safety profiles. The US FDA has drafted clinical trial guidelines for both cellular and gene therapies[123] and live biotherapeutics[124], which facilitate regulatory reviews of such breakthrough new classes of therapeutics. Still, from the experiences of the regulatory bodies in the US, EU and Japan, the evaluation of cell and gene therapies inevitably undertook an adaptive approach, with higher tolerance to risk and uncertainties, but necessitating systemic post-marketing surveillance measures[125]. This requires highly skilled reviewers and well-designed evaluation and surveillance framework, which the regulatory bodies in emerging markets of Asia will need to develop in-house and learn from established systems. Even after the regulatory challenge, the commercial scale manufacturing of cell and gene therapies has proven to be a limiting factor. To circumvent the engineering challenge of a scalable, automated and robust GMP biotherapeutics processing system, strong private-public partnerships will be essential and be most effective in advancing the entire field[126].

(3) Food, agriculture and environmental applications

In addition to medical innovations and next-generation biomanufacturing, synthetic biology is also driving technologies that attempt to solve the many challenges facing the environment and the growing population. The biofuel production from alternative sources discussed in previous sections is already one good example for resolving the mounting energy demand in a sustainable way. Here in this section, we collectively report on the discussions on food, agriculture and other environmental applications.

Significant investment has been put into food and agriculture technologies that could provide solutions to keep up with the pace of the growing global population and climate change. One perpetual theme is centered on boosting the yield of crops or improving the nutrient components in food products. Plant synthetic biology has witnessed progress in genome-editing-enabled precision breeding, which significantly reduces the time needed for selecting desirable traits[127]. Among its wide applications in agriculture, there are three strategies in boosting crop yields, namely increasing carbon fixation efficiency, minimizing plant respiratory CO_2 loss, and establishing nitrogen fixation mechanisms in non-legume crops[128]. On nitrogen fixation, there are genetic engineering methods for crop plants, cereal crops in most studies, to express heterologous nitrogenase genes or to form nodule-like symbiosis similar to legume roots; others seek to engineer bacteria that are naturally associated with cereal crops to carry out nitrogen fixation[129,130]. The California-based startup Pivot Bio has already developed the first microbial-based fertilizer for corn to replace the conventional chemical ones, and it is expected to simultaneously produce better crop yield and avoid chemical pollution to the environment. Additional examples in agri-food applications include the “Golden Rice” project, where rice is engineered to contain provitamin A and is now being distributed in regions with high vitamin A deficiency burdens; yeast-produced human milk oligosaccharides as supplement to formula milk, and various plant-based or cell-based alternative protein products to replace the energy and resource-intensive animal meat.

Synthetic biology research also seeks to reduce the generation, and improve the recyclability, of waste. For example, as an alternative material to the fossil fuel-based conventional plastics, biodegradable polymers can be produced through microbial fermentation[131,132], such as polylactic acid (PLA), polybutylene succinate (PBS) and polyhydroxyalkanoates (PHA). Choi *et al.* summarized key technology advancements in microbial production of a number of PHA monomers, including feedstock, host organisms, enzymes and metabolic pathways[133]. The China-based startup BluePHA, a team of iGEM alumi entrepreneurs, is among a few businesses in Asia venturing commercial production of PHA with microbial fermentation[133]. On the other hand, more efficient breakdown of conventional plastics is another way to fight against the plastics pollution. Since the discovery of the poly(ethylene terephthalate) (PET)-degrading bacterium *Ideonella sakaiensis* and the two key enzymes in 2016[134], there has been many efforts in evolving the enzymes for higher efficiency[135,136]. Apart from plastics pollution, synthetic biologists also seek to reduce and upcycle electronic wastes by exploring heavy metal and rare earth element reclamation and recovery through engineered microbes[137–139].

Many of the research studies on environmental applications, such as alternative fuel, materials, or food production methods, face difficulty in translation into industrial processes or sustainable business models. To compete with the low cost of fossil-fuel-based products, significant technical advancement is necessary – for example, sourcing for cheaper, non-food feedstock that does not take up excessive land use, developing more cost-effective pretreatment methods of lignocellulose and other biomass, and developing consolidated downstream processing technologies that can also exploit high-value byproducts[140,141]. In addition to technology breakthroughs, governments can put forward policy incentives to encourage the adoption of these new technologies, which will be discussed in the following section.

Building a sustainable growth

Currently, there are multiple synthetic biology research centers established, including 9 members of the Global Biofoundry Alliance, in the Asia region. A cross-region organization called the Asian Synthetic Biology Association (ASBA) was also created to promote academic communications, collaborations and technology commercialization. According to BIO industry report, venture investment in therapeutic biotech companies in Asia topped US$2.6 billion in 2019, comparable to that in Europe and about 40% of the number in the US[142]. We do have the “seeds” for synthetic biology research and technology translation, but the next question would be how to cultivate a nurturing soil that supports the development of the “seeds into blossoms”.

Public-private partnerships can play an important role in spurring a sustained development of the field. Long-term government funding is vital in supporting research work towards “grand challenges” at the early stage, for which the risk is too high for industry to stomach[143]. However, in addition to the long-term investment in basic science, it is also important to have an effective mechanism to catalyze technology translation and commercialization, which is often best achieved through private-public partnerships. Gauvreau et al. discussed a “Key Innovation Technologies and Systems (KITS)” model[144] as an ecosystem to propel research and technology deployment, where an integrated operation of research, industry,

entrepreneurship and investment works to achieve sustainability of the ecosystem. In a close working relationship, the research projects in a public institute will be guided by key industry and societal needs, and an effective two-way consultation ensures the products and processes being developed can be turned into viable business models. In addition, the ecosystem has capabilities to establish, and attract start-ups, by having its own investment arms and necessary intellectual property support.

For technologies used for medical and high-value chemical applications, the paths to commercialization are relatively clear; however, applications in the environmental and food sectors can be more challenging, constrained by the status of the market and economics. In such cases, government policies come in as an important lever to trigger the initial exploration of a valid commercialization model. For instance, in Su et al.'s review of biofuel policies in the US, the EU, and China, various policy supports were explored in the studied countries[145]: setting up clear objectives in targeted percentage usage of biofuel in mid-to-long terms; providing financial incentives (subsidies, cost-sharing, tax incentives, public procurement, etc.) to reduce the barrier for the biofuel industry; funding long-term R&D projects to diversify biofuel feedstock, reducing production cost, and study overall emission and general environmental impacts. In parallel, carbon taxing and additional evaluation framework that incorporates negative impacts of fossil fuels in long term also help to "push" the demand for more sustainable alternatives. In another detailed study of the national biofuel policy in India[146], the authors emphasized the many difficulties in achieving the renewable energy targets in the country: apart from the remaining technical challenges, it was also difficult to achieve a coordinated implementation of the biofuel policies at the federal and state levels, accountable long-term stewardship by multiple ministries (e.g. the Ministry of Energy, the Ministry of Agriculture, the Ministry of Finance, among others), and importantly, legal enforcement. Nevertheless, government support in the form of "technology push" and/or "market pull" policies[4] is essential to de-risk technologies for environmental applications, and make them more attractive to industry and investors who will subsequently explore potential sustainable business models. Equally important are frameworks and mechanisms for collaborative governance and performance evaluations[4]. To come up with these policy frameworks, it is important to engage stakeholders from academia, multiple government functions and industry to achieve a common understanding of the objectives, the technology, as well as the market.

> "*Decision makers need to be informed of the technologies to make the right policies*."

Mitigating risks

While we are working hard to advance the technologies, we need to start the discussion of regulations simultaneously. It is a consensus that synthetic biology is a dual-use technology, which not only has the potential to bring benefits to the society, but also has inherent risks of being misused. Entering 2020, the COVID-19 pandemic again reminded us of the importance of biosecurity – when a new pathogen emerges, whether it be a natural, deliberate or accidental cause, it brings catastrophic damage to public health and the economy that has no regard for borders. As the technology to engineer biological systems gets more accessible, the risk of any deliberate or accidental release of a pathogen or an engineered organism

also increases[147]. Moreover, the growing reliance on biological data, especially sequence information, in medical and manufacturing applications makes future bio-based industries prone to "bio-hacking" through data breaches[72].

Risk mitigation measures should adopt a multifaceted approach leveraging technology, regulation, and education. Various biocontainment methods are the first line of barrier preventing accidental release of pathogenic or engineered organisms. These can include physical biocontainment infrastructure design, as well as engineered biological systems (e.g. auxotrophies, kill switches, xenobiological firewalls) that can be multilayered to limit the survival and spread of engineered organisms[148,149]. In addition to biocontainment measures, public policies and institutional oversight are important to prevent potential intentional misuses of synthetic biology. In this regard, a combination of both top-down (from government and funding agencies) and bottom-up (from research groups and research institutes) oversights should be established; at the same time, it is critical to strike a balance in mitigating risks without falling into over-regulation, thus necessitating multi-stakeholder conversations[147,148,150]. Policy makers need to be informed about the technology's risk and benefits to come up with the right policies to mitigate risks effectively. At the same time, synthetic biologists need to listen to public concerns and brainstorm collectively with experts in the fields of public health, cybersecurity, defense and bioethics, on strategies to minimize risk, and measures to identify and counter potential biosecurity events, should they happen. It is recommended to have such conversations early, so that risk assessment and mitigation measures do not fall behind technological advances[148].

In addition to biocontainment and regulations, education is an important way to mitigate risks by raising biosecurity awareness among researchers and the public. In the ethics modules of universities, and the code of conduct trainings for researchers, it is helpful to include the discussions of the dual-use character of synthetic biology[148,151]. A targeted exercise established by the EBRC, the "Malice Analysis" workshops[152], gathers graduate students and researchers in the engineering biology community to practice their abilities to identify potential misuse of synthetic biology research, and to come up with mitigation plans accordingly. In the same vein, appropriately engaging the public on risk-benefit discussions can have the benefits of conveying the message that the researchers and governments have carefully considered the risks of synthetic biology, and preventing potential future backlash in public opinions[148].

Be it promoting technology advancement as a field, or setting up regulations to mitigate risks, regional and global collaborations are essential. Each country may have its specific problems and interests to invest in, such as the issue of tropical infectious diseases facing Southeast Asian countries. As a result, each country may prioritize development of technologies for solving its specific issues, and therefore will also have different levels of risk tolerance associated with applying new technologies[147]. Currently, the standards for biosafety and biosecurity regulations are highly variable even within a single country[153]. Experts are calling for more regional and even global harmonization and collaborations[147,148,153]. For instance, in the face of a novel pathogen, coordinated real-time communication and data sharing across borders will make biosecurity surveillance and response more effective[150]. In order to achieve this, it is important to have researchers and regulators from different

countries align their understanding of the benefits and risks of synthetic biology, and lay out common frameworks for synthetic biology regulations and biosecurity surveillance. One good example is the global harmonization effort by the International Gene Synthesis Consortium, which is establishing a standardized synthetic DNA screening mechanism and working with multiple stakeholders to implement this as a global norm to safeguard against misuses of synthetic DNA[154]. Regional and global forums and working groups provide good opportunities for multilateral strategic planning, and facilitate the establishment of concerted biosecurity surveillance, preparedness and response mechanisms.

> "*Global collaboration requires global harmonization of understanding… and regulation.*"

Conclusion and recommendations

A number of topics of synthetic biology were reviewed in this article, including research advances and technology translation, as well as mechanisms for future investment, growth, and regulations. We summarize some of the key consensuses and recommendations to the field, especially in Asia, through the lens of the workshop in Singapore: this is a collection of opinions from a diverse group of expert practitioners and thought leaders.

- Significant investment and technology advancement in DNA synthesis, computer aided design and process automation, biological data science and machine learning are critical to further enabling synthetic biology research and accelerating the DBTL cycle.
- Biological sequence data are valuable information and central to synthetic biology applications, and their collection, curation and sharing processes should be streamlined and harmonized globally, with robust data security surveillance.
- Applications in various sectors have achieved different levels of commercialization; past experiences encourage early-stage R&D project researchers to have the "end product" in mind, and work closely with industry partners to develop the associated downstream processing, production scale-up, and economic or business models to effectively fulfil unmet needs.
- To facilitate rapid technology translation and deployment, integrated research-development-investment (R&D&I) ecosystem models are worth exploring, where effective private-public partnerships can be established.
- In addition to long-term investment in the development of science and technology, governments should also utilize "push-and-pull" policy instruments to facilitate the adoption of bio-based production, especially when such businesses face daunting competition from fossil fuel-powered industries.
- Synthetic biologists and policy makers should engage multiple stakeholders (public health, data security, defence, economy, and the public) to come up with strategies and regulations for biosecurity surveillance, risk mitigation and effective response mechanisms.
- Regional and global collaboration and standard harmonization are essential in advancing synthetic biology as a field and bolstering biosecurity defence.

With decades of research and key technology advancements, we are witnessing some initial success in technology translation and commercialization of synthetic biology, particularly in next-generation biomanufacturing and medical applications. Additional developments are necessary to realize the full potential of synthetic biology in not only industrial production, but also future smart medicine and environmental applications. We are optimistic that with the prior recommended actions and initiatives, strong collaborative synthetic biology R&D&I clusters can emerge in Asia and contribute to the sustainable growth of the global bioeconomy.

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