Thailand Synthetic Biology Ecosystem Assessment and Recommendations

Prepared for

Office of National Higher Education Science Research and Innovation Policy Council (NXPO)

Author

Kent W. Goeking PhD, MBA

Frontis Company

July 29, 2021

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Executive Summary

Synthetic biology is a relatively new field that integrates multiple advanced technologies to enable the ability to engineer the software code of life. This disruptive technology emerged from the established fields of molecular biology, genomics, and genetic engineering by adding systematic approaches for the rational design and rapid development of novel nucleic acid sequences with significantly enhanced precision, predictability, and control. Synthetic biology enables biodevices and biomanufacturing by using cells or cell-free systems. This technology can produce biobased products and capabilities that can sustainably replace many traditional products and solutions in fuels, chemicals, plastics, materials, agriculture, food/cosmetic ingredients, nutraceuticals, pharmaceuticals, vaccines, sensors as well as applications for environmental sustainability and remediation.

One of the key learnings from this report is that the synthetic biology ecosystems studied all accelerate their synthetic biology capabilities by automating and centralizing the Design-Build-Test-Learn (DBTL) engineering cycle. Presently in Thailand, this development cycle is performed manually using equipment and expertise from many different labs or even from other countries with cycle times on the order of months. More advanced ecosystems embed this DBTL principle into a biofoundry cluster of co-located advanced and automated equipment and expertise, where cycle times can be reduced to a single day and the range of variables that can be tested simultaneously is increased exponentially.

Mature synthetic biology ecosystems also consist of many entity segments that work together in a highly coordinated fashion. The universities and research centers are the sources for new intellectual property and cultivate the next wave of talent for the industry. Governments are vital for funding the basic research and facilities necessary and establishing regulatory environments that help overcome traditional barriers to market for synthetic biology companies. Large corporates and investors provide the capital to fuel development and offer exit paths through acquisition or IPO. At the heart of mature synthetic biology ecosystems is the start-up community, either start-ups that spin out of university labs or companies established for a specific problem area that in-license technology from the university and government labs or invent their own. By having a vibrant start-up community, many new ideas can be market tested quickly, allowing the few that survive to gain significant funding and alignment with more considerable corporate interest for substantial scale-up.

The Thailand synthetic biology ecosystem is presently sparse and highly fragmented. Although there are substantial expertise, facilities, and capabilities at the university and government laboratory level, and increasingly at the pilot biomanufacturing level, key infrastructural elements are missing, such as a biofoundry and a precision fermentation contract development and manufacturing organization (CDMO) capability. Further, there is currently insufficient collaboration between the limited skilled resources that do exist. The Thai synthetic biology start-up community is very small and more at the level of genetic engineering than synthetic biology. Thai corporates indicate that they are interested in synthetic biology, but most are taking a “wait and see” approach and using corporate venture capital as a means to monitor the industry without substantial domestic investment into R&D at this point.

Thailand’s current synthetic biology ecosystem is similar to where Singapore was five years ago. Since that time, with the direct support of the Singapore government, a hybrid synthetic biology ecosystem has emerged there with a biofoundry and a consortium at the center rather than the start-up community. Such a hybrid ecosystem approach is also likely to be the most successful for Thailand. Collaboration with Singapore is recommended to develop a robust competitive regional synthetic biology ecosystem capability.

Synthetic biology is a cross-disciplinary field that necessitates skills across many disciplines that are not typically integrated into a single academic program or individual. Synthetic biology requires skills grounded in genetics, molecular biology, systems biology, microbiology, biochemistry, and analytical chemistry. These biological skills need to be applied using quantitative engineering techniques of mathematics, computing, bioinformatics, biostatistics, and advanced computational modeling and simulation. Furthermore, additional skills are required in engineering, robotics, software engineering, artificial intelligence, and machine learning to support high throughput synthetic organism construction and testing. The preferred solution for integrating and developing these cross-disciplinary skills is to fund focused flagship programs where scientists, engineers, and business skills can overlap and synergize.

Therefore, the key recommendations of this report that have emerged from the reviewing both technical literature and over fifty Thailand and international interviews are as follows:

- Thailand should establish a shared, open Synthetic Biology Institute that develops and maintains an integrated biofoundry facility,

- Thailand should solicit and fund Flagship Synthetic Biology Programs that utilizes the Institute’s biofoundry capabilities for accelerated bioproduct development,

- Thailand should promote precision fermentation contract development and manufacturing organization (CDMO) capabilities to leverage emerging scale-up facilities and enable commercial production of high value, low volume bioproducts, and

- Thailand should invest in building an early-stage, consortium-driven, synthetic biology ecosystem similar to and in synergistic collaboration with Singapore and other ASEAN countries.

In summary, Thailand has the essential components to begin the journey towards a viable synthetic biology ecosystem. However, it will require a coordinated effort from the Thai government to initiate such development. The four recommendations are discussed in more depth throughout the various chapters in this report, along with sufficient background material to allow the non-synthetic biology literate reader to appreciate the science, opportunity, and challenges that synthetic biology presents for the Thai economy.

Chapter 1 – Introduction of Core Concepts

This chapter describes the core concepts of synthetic biology and the ecosystem elements required to create vibrant bioproduct development capabilities.

- Synthetic Biology Background
- The DBTL cycle
- Deep Tech Venture Ecosystem Structure

Synthetic Biology Background

Synthetic biology is a rapidly developing field of research that only held its first conference in 2004. It is inherently interdisciplinary bringing together biologists, engineers, chemists, computer scientists, and others to create a new foundation for disruptive biotechnology across a plurality of industrial applications. Synthetic biology represents a transition away from classical biology which focuses on studying natural systems, towards building valuable artifacts out of biological materials that nature either didn't develop through evolution or left underdeveloped for human requirements.

Synthetic biology centers on the design, construction (build), and characterization (testing and learning) of improved or novel biological systems using engineering design principles [1]. It has emerged from the established fields of molecular biology by adding systematic engineering approaches for the rational design and rapid development of novel nucleic acid sequences with significantly enhanced precision, predictability, and control. These synthetic nucleic acid sequences in turn enable biomanufacturing by using cells and cell-free systems as factories which can be scaled up to industrial production volumes. Cells can also be designed to have the ability to turn on and off gene expression through engineered regulatory networks to sense the environment and respond appropriately.

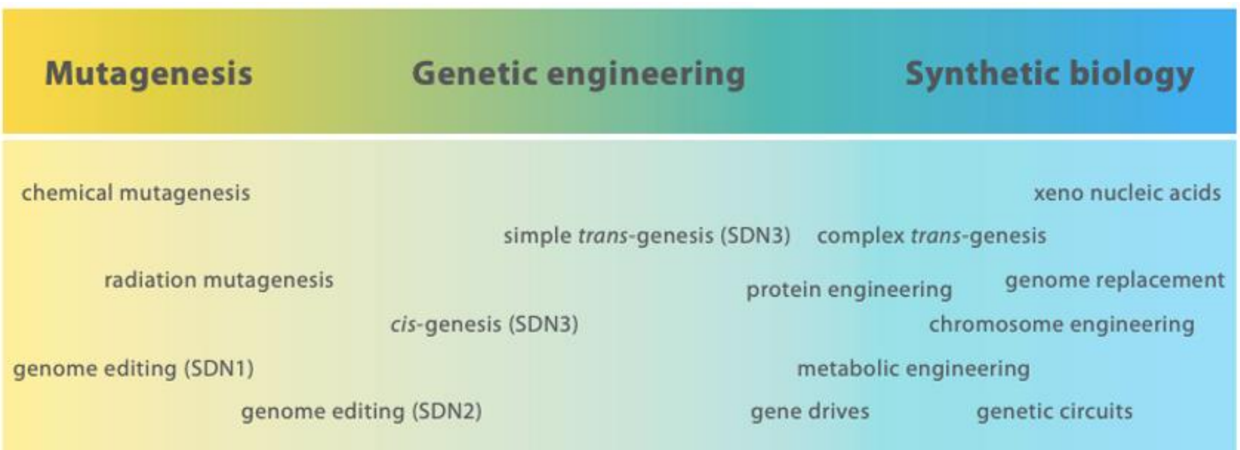

Figure 1.1 - A continuum demonstrating the gradation between Mutagenesis, Genetic engineering, and Synthetic biology (note: SDN refers to site-directed nuclease techniques: SDN-1 involves the unguided deletion or replacement of one or a few nucleotides, SND-2 involves deliberate guided changes to one or a few nucleotides; SND-3 involves inserting a new gene or other genetic elements) [2].

The applications of these new capabilities will have significant disruptive impact on the chemical, environmental, medical, food, agriculture, and materials industries while simultaneously addressing significant societal challenges such as sustainability, climate change, and environmental remediation. Synthetic biology represents one of the most transformative technologies since the advancement of information technology. Today synthetic biology is where the IT revolution was 50 years ago. However, the pace of progress and transformation for synthetic biology will be orders of magnitude faster and equally as profound in its disruption. The US venture capital firm Andreessen Horowitz who famously proclaimed that “Software will eat the world” has recently published a new manifesto proclaiming that now “Biology is eating the world” [3].

Synthetic biology is considered a disruptive technology because of its broad applications and the dramatic drop in the cost of fundamental enabling processes such as DNA/RNA reading and writing (sequencing and synthesis, Figure 1.2). The cost of these processes is falling much faster than Moore's law in microelectronics and results in a non-linear price drop. Such price drops result in a "hockey-stick" type of exponential growth trajectories for synthetic biology industries which will come as a surprise to conventional industry executives who think they have 5-10 years to wait until synthetic biology becomes relevant to their industry.

For example, the simplest living organism known is the bacteria *Mycoplasma genitalium*, has a genome totaling 580kbp (kilobase pairs). Using the latest data from Twist Bioscience a leading DNA synthesis firm, the current retail cost is $.07/bp; it would take $40,600 to synthesize the complete genome compared to the cost of $5.8 million just a decade earlier.

The Genome Project-write is leading the effort to promote high-speed DNA synthesis [4]. The expectation is that a "next-generation" DNA writing technology will do what NextGen sequencing did for DNA reading and completely change the trajectory of cost reduction. Technologies such as enzymic synthesis of DNA are presently at advanced stages of development at several start-ups and promise to produce very long strands of DNA with high precision for a meager cost.

Brief History of Synthetic Biology

The first known reference to the term synthetic biology was published in 1974 by geneticist Wacław Szybalski who commented that “up to now we are working on the descriptive phase of molecular biology... But the real challenge will start when we enter the synthetic phase ... We will then devise new control elements and add these new modules to the existing genomes or build up wholly new genomes.” [5]

The first tools of synthetic biology were proposed in 1978 in response to the Nobel Prize in Physiology or Medicine being awarded for the discovery of restriction enzymes and their application to problems of molecular genetics [6]. Restriction enzymes are DNA cutting enzymes and were forerunners of the Crisper, Zinc-finger, and TALEN technology for gene editing.

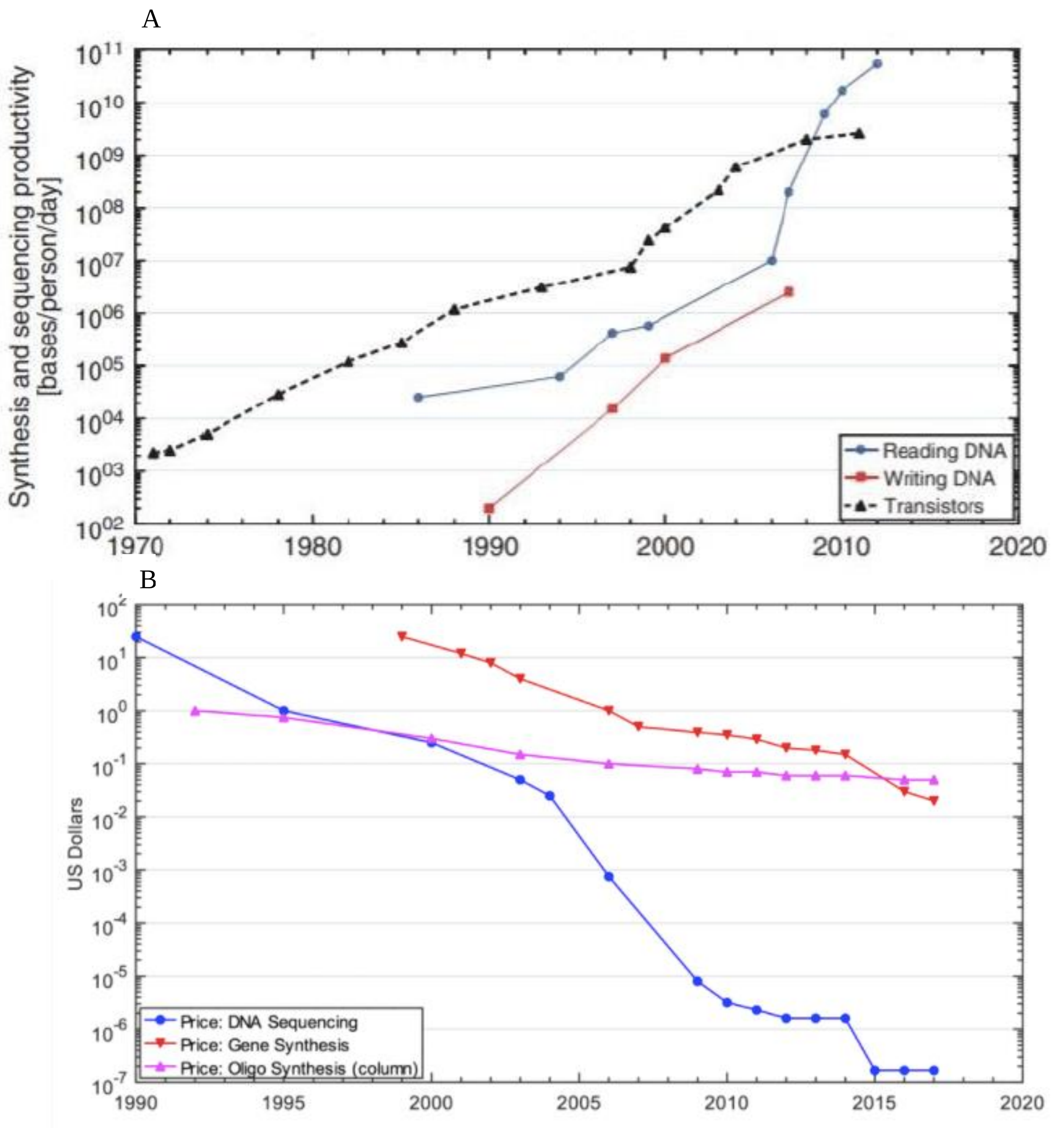

Figure 1.2 - A) Productivity in DNA sequencing and synthesis using commercially available instruments compared with Moore's law (a proxy for IT productivity) B) Price per base of DNA sequencing and synthesis (ca. 2017) [7]

Twenty years later, synthetic biology started to emerge as a coherent field of study with early leadership from Professor Drew Endy at the Department of Bioengineering at Stanford University and Professor Tom Knight at the Massachusetts Institute of Technology (MIT) Computer Science and Artificial Intelligence Laboratory. The early conception of synthetic biology was to treat biological systems as analogous to electronic circuits and components, which required the development of DNA-encoded parts that are modular, behave predictably, and can be used to build more complex systems [8].

The field of synthetic biology has expanded well beyond the electronic circuit metaphor and now includes the precise rewriting of genetic code to create new COVID-19 vaccines and other bioproducts such as the "Impossible Burger" that bleeds synthetic biology "blood" as we can now better discern how biological systems work and make them work for human purposes. Rewriting an entire genome is currently at the frontier of synthetic biology and would allow for designing a minimal living system that would be a more straightforward platform for new device/protein development and less pervious to viral insertions. Examples of this include the Yeast 2.0 project [9] and creating the world's smallest self-replicating synthetic cell from *Mycoplasma genitalium* with only 492 genes, compared to the current workhorse fermentation bacteria *E. coli* which has about 4000 genes [10].

Overview of Synthetic Biology Applications

When people think of biotech and synthetic biology's role in that field, most consider it synonymous with Biopharma applications and, due to the high market potential of new drugs, this has historically been one of the first application areas targeted in Thailand. However, this is only one subset of applications for synthetic biology and one that comes with a high risk/high reward profile that does not easily fit the style of investors and industry in Thailand. Synthetic biology innovations are now driving technological innovation in advanced biofuels, biosensors, diagnostics, food ingredients, cosmetics, specialty chemicals, biomaterials, and other promising application areas.

An early success story is the work done by US start-up Amyris Biotechnologies through the support of the Bill and Melinda Gates Foundation. They sought to produce a potent anti-malaria compound known as artemisinin which is naturally derived from the herb Sweet Wormwood (*A. annua*) that grows in China and SE Asia. The herb is notoriously difficult to cultivate, and the cost of artemisinin extracted from natural sources is typically $900-$1600/kg. A team from Amyris Biotechnologies, the Institute for OneWorld Health, and the University of California Berkeley achieved the complex feat of engineering the metabolic pathway of yeast with 12 new synthetic genetic parts. When inserted into the microorganism, the engineered pathway makes the yeast produce artemisinic acid. A subsequent conventional chemical process is then used to convert artemisinic acid to artemisinin. Synthetic biology produced artemisinin is sold at prices less than 2/3 of the naturally cultivated extract and dropping. The development cost was $53.3m versus the typical pharmaceutical drug development cost of $800m [11].

Another early success story was the development of 1,4-butanediol (BDO), which does not occur naturally. It can be synthesized using a bacterial host (*E. coli*) engineered to utilize a combination of enzymes typically found in separate organisms. BDO is a chemical precursor for the manufacture of plastics, polyurethanes, and elastic fibers [12]. This example demonstrates the power to not only replicate natural metabolic processes, as with artemisinin production, but also the ability to create entirely new biosynthetic pathways that replace chemicals traditionally producible only from petroleum-based feedstocks.

Other examples include the ability to make liquid biofuels for aviation, fragrances from yeast, high-value biomolecules from cultivated crops, antimicrobial drugs, and vaccines. In agriculture, crops can be engineered to be more drought-resistant, increase their photosynthetic conversion efficiency, fix nitrogen, increase the uptake of nutrients without heavy fertilization, and increase resistance to pests and disease.

Synthetic biology can also contribute to environmental health by providing organisms that can sense the environment and respond with enzymes to remediate a potential contamination situation. Synthetic biology revolutionizes biomedicine through the production of new antibiotics, complex biological drugs, biosensors that can detect pre-clinical disease states in the body, and cell engineering such as human cancer immunotherapy to deliver therapeutics directly to the affected tissue. The full scope of the potential for synthetic biology applications is vast and well beyond the scope of this report. Chapter 3 will discuss some applications in more depth that are relevant to the Thai economy.

Synthetic biology is not a panacea for producing all drugs, materials, or chemicals, as it is challenging to get systems based on biology to do things that nature never intended. An example of this is small molecule production of totally synthetic pharmaceutical compounds. If the compound is originally from a botanical or animal source, then there are pathways to produce it, and synthetic biology can appropriate those pathways. But suppose the molecule of interest has never been made, even in minute quantities by natural systems. In that case, it may be complicated to invent new metabolic pathways that are not "natural." It may not be impossible (as is the case of BDO), but a more demanding target than those products that nature has already worked out the basic formulation for production.

Obstacles to success

There is justifiable concern by both the public and government regulators that synthetic biology may expand the risk of biological incidents such as the accidental or deliberate release of dangerous bioagents. This requires strong regulatory processes and ethical guidelines and the development of effective biosecurity countermeasures against these threats. Additionally, consumers may be wary of products that have been produced through genetically modified organisms (GMOs) even if the end product is identical to that already found in nature. This will need to be mitigated through effective science-based communication programs [13].

Although the analogy to electronics is often evoked, the behavior of biological constructs are significantly more complex because they are performed in the context of a cellular environment. There is significant other biologic machinery at work in cells focused on cellular survival, which may interfere with the functioning of the desired engineered metabolic pathway or genetic circuit. One common concern is that the molecule of interest to be produced can become toxic to the host organism, thus self-limiting the productivity of the manufacturing system.

Additionally, unlike the discrete wiring of an electronic circuit, the signaling in a cell is through molecules. An off-target site may interpret that signal intended for another part of the biological system and cause unwanted side effects. Furthermore, living systems tend to mutate over time which can interfere or destroy the desired functionality. These are complications that synthetic biology designers have to compensate for through design redundancies and other techniques.

The DBTL cycle

The key principle behind accelerating synthetic biology is the Design-Build-Test-Learn (DBTL) engineering cycle. This cycle can be performed manually using equipment and expertise from many different labs or even different countries with cycle times typically on the order of months. More advanced labs embed this DBTL principle into a cluster of co-located automated equipment, referred to as a biofoundry, where cycle times and be reduced to a single day, and the range of variables that can be tested simultaneously is very significant.

DBTL Definitions

The DBTL cycle consists of the following components:

- **Design**: using software-enabled approaches to design a starting DNA sequence that can be manipulated and modeled to create predictable new functionality in metabolic pathways for a potential host organism or as a structural DNA construct. A second element is the design phase is the design-of-experiments in order to take full advantage of the parallel high-speed screening capabilities of a well-designed biofoundry and yield optimal datasets for further analysis.

- **Build**: DNA components, either custom designed or taken from a parts library (i.e., Bio-bricks) are assembled and inserted into the host system of choice or cell-free systems. Quality control can be validated by sequencing the resulting assemblies at this stage.

- **Test**: High throughput analytical methods such as automated fluorescence-activated cell sorting (FACS), microtiter plates, high-throughput analytical chemistry are used. The test phase typically generates significant amounts of data for interpretation.

- **Learn**: Due to the large datasets, machine learning approaches are often used at this stage to generate testable hypotheses for what works and why, which can be input into the next cycle of design.

Example of DBTL in action: DARPA's 90 Day Challenge

Between August and November 2016, the United States Defense Advanced Research Projects Agency (DARPA) conducted a "pressure-test" of the synthetic biology DBTL capabilities at the Broad Institute of MIT and Harvard to assess their capability to respond to potential biomanufacturing emergency scenarios. These are scenarios where a critical chemical, pharmaceutical, or material becomes in very short supply due to some disruption in the supply chain. The question asked is, "Can a biomanufactured equivalent be developed in a short time period?"

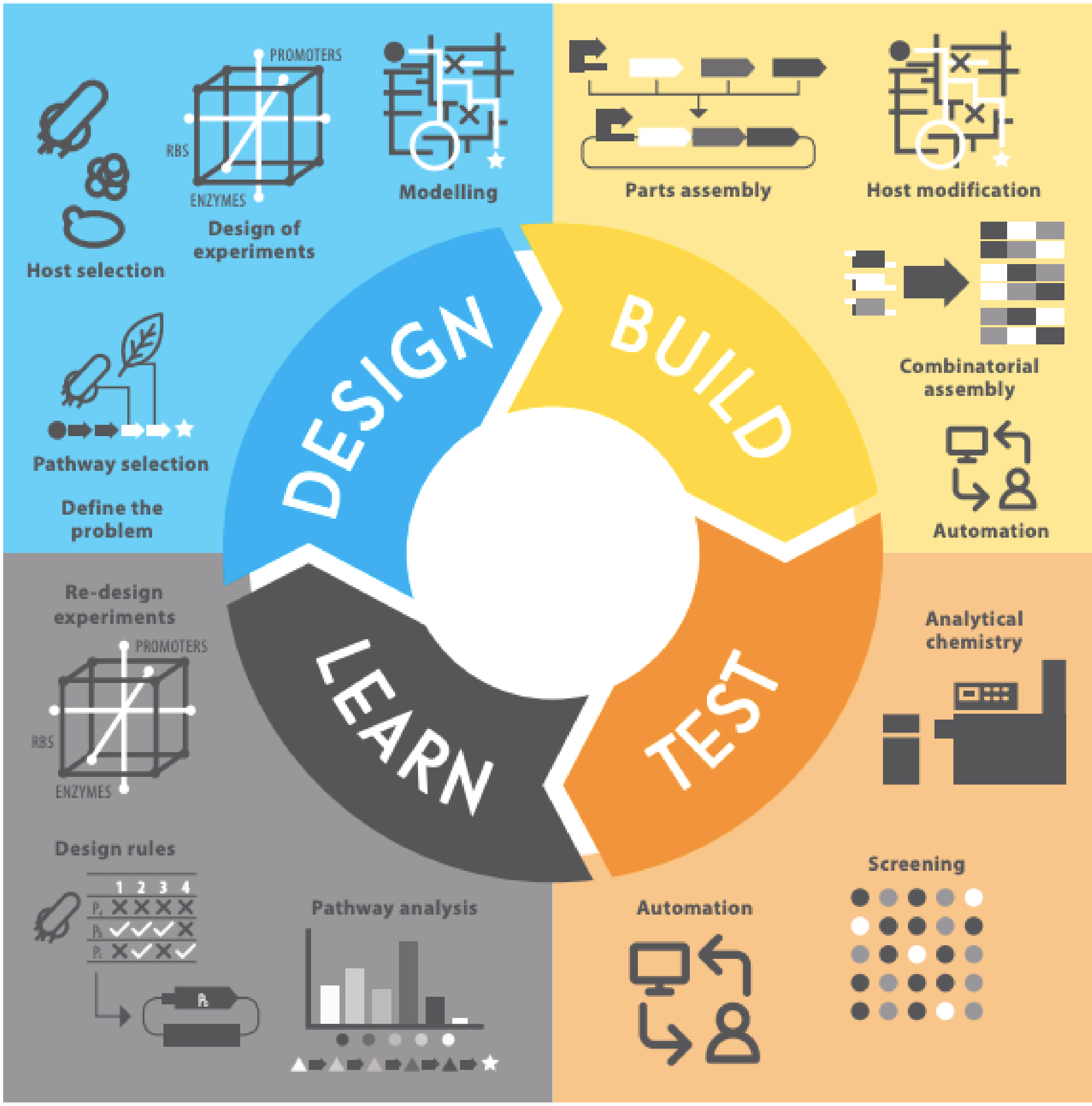

Figure 1.3- A depiction of the DBTL cycle [14].

DARPA picked 10 molecules of interest that had never been produced by synthetic biology before and challenged the biofoundry to design and deliver bioprocesses that could produce these molecules in 90 days or less. Researchers succeeded in creating 6 out of the 10 to specifications and made significant progress on the remaining 4. This rapid development capability has also recently been demonstrated in the real-world case of the development of COVID-19 mRNA vaccines. The utility of such rapid approaches will only accelerate as biofoundries continue to standardize, automate, and utilize artificial intelligence in the future [15].

Synthetic Biology Ecosystem Structure

Deep tech is a term used to describe new technologies that require significant amounts of advanced science and engineering to bring them to realization. Although more challenging to bring deep tech to market, the value is also disproportionally more significant. Deep technologies offer the opportunity for disruptive impact across many industries, opening up new markets, and provide unique solutions to some of the most intractable problems facing society today.

Synthetic biology fits the definition of deep technology and sits at the intersection of biology and engineering. Other deep technologies include quantum computing, blockchain, advanced materials, robotics and drones, artificial intelligence, and photonics.

Characteristics of Deep Tech

The key attributes that characterize a deep technology are:

- Deep tech ventures typically focus on broad problems not specific technology solutions looking for a problem. The general problem itself serves as a compass that allows deep tech ventures to pivot along the way due to unforeseen technology issues that are to be anticipated. For this reason, deep tech ventures should be risk-front-loaded to fail fast if necessary.

- Deep tech ventures primarily focus on physical products (atoms) rather than digital software-type ventures (bits). This is why the DBTL cycle is the engine at the heart of deep tech that propels such ventures towards a viable product solution. The faster the DBTL cycle, the faster novel products can come to market. Deep Tech companies compete on the "rate of learning."

- Deep Tech ventures are heavily convergent, requiring typically two or more advanced technologies, combining elements of three technologies clusters: Matter & Energy, Computing & Cognition, and Sensing & Motion.

- Because of the convergent nature, broad problem applicability, and focus on physical products, deep tech ventures rely heavily on an interconnected ecosystem of critical elements.

- The underlying economics of deep tech often results in exponential value growth as the price of equipment and services drop exponentially. As subsequent DBTL cycles are performed, the original point solution product evolves into a platform solution, attracting increasing amounts of capital due to the enhanced applicability.

- Deep Tech ventures take more time to move from basic science to technology ready for commercialization. This means that the capital requirements for deep tech are much more intensive and typically require a combination of public and private funding.

Deep Tech Ecosystems

As illustrated in figure 1.5, mature deep tech ecosystems consist of many elements that need to work together. The universities and research centers are the sources for new intellectual property and cultivate the next wave of talent for the industry. Governments are vital for funding the basic research necessary and establishing regulatory environments that help overcome traditional barriers to market for deep tech companies. These are foundational elements of the deep tech ecosystem.

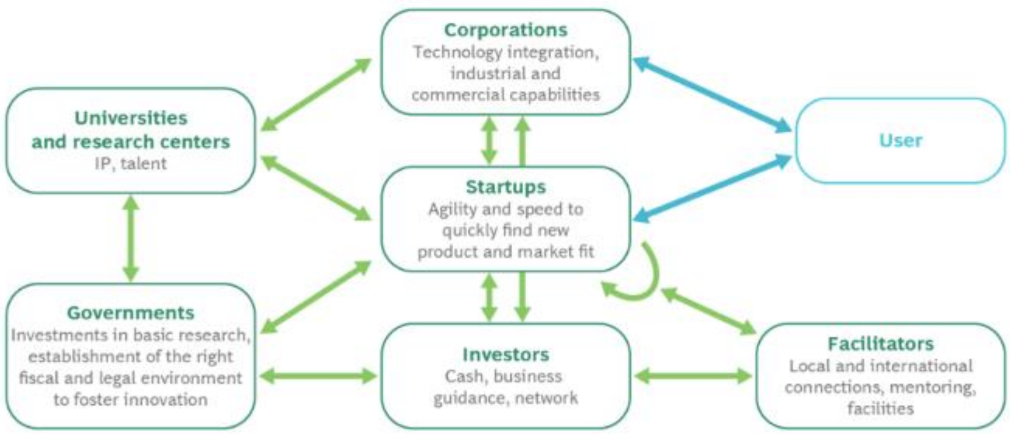

Figure 1.5 - Mature Deep Tech ecosystem structure [16]

The middle three elements are the commercialization engine. At the heart of mature deep tech ecosystems is the start-up community. These can be start-ups that spin out of university labs or companies established for a specific problem area that in-license technology from the university and government labs or invent their own. Start-ups live or die depending on angel, venture capital, and corporate investment. By having a vibrant start-up community, many new ideas can be market tested quickly, allowing the few that survive to gain significant funding and alignment with larger corporate interest for substantial scale-up.

Finally, there is the role of facilitators. These can be incubators, accelerators, or communities such as the SynBioBeta (https://synbiobeta.com/) organization in the US which acts as a synthetic biology community organizer by hosting conferences and communicating to the corporate and finance world the successes of synthetic biology.

As this report will discuss in subsequent chapters, Thailand is currently missing several critical areas of this mature deep tech ecosystem. For example, the start-up community in synthetic biology is very small, and most start-ups are more genetic engineering than synthetic biology in their current product development. Furthermore, corporations are more focused on the low value/high volume end of the value chain and do not typically value synthetic biology as an R&D expense worth investing in. Finally, investors in Thailand are unfamiliar with deep tech technologies and uncomfortable with the long investment times and substantial amounts required to foster start-up success. For these reasons, a revised ecosystem model more appropriate for Thailand in the near term is discussed in the recommendations of chapter 6.

Market Opportunity and Market Value

Synthetic biology is an enabling technology across multiple segments of the global economy include biochemicals, biomedical, agriculture and other application areas as detailed below. A recent McKinsey report [17] estimates that biology could ultimately produce 60% of the physical inputs to the global economy and solve 45% of the world's disease. Between 2010 – 2019 a total of $18 billion has been invested in synthetic biology enterprises.

The global synthetic biology market was valued at USD 22.47 billion in 2018, and is expected to reach USD 145.62 billion by 2024, with an anticipated CAGR of 34.91% during the forecast period. The dominant market segment for synthetic biology (93%) are what are referred to as "enabled products". These are the outputs of synthetic biology processes, as opposed to the genomic inputs (i.e. gene synthesis, gene editing, gene sequencing) or equipment (i.e. DNA sequencers, DNA printers). The various enabled technologies found to be segmented into chemicals, energy and biofuels, agriculture, and other markets [18]

Chemicals are the dominant subsector of enabled products and include important products in the traditional petroleum-refinery value chain: succinic acid, 1,3-propanediol, isobutanol, d-lactic acid and 1,4-butanediol. Energy applications are found to be the second largest market largely due to the persistent US government interest in advancing next-generation biofuels and bio-power, that is supporting continued efforts by companies like Amyris, Solazyme, Qteros, Genencor/DuPont, and Algenol to develop bio-based production platforms, feed stocks, and other products.

Agriculture is the next largest and includes the engineering of complex traits in higher plants but that area has yet to move beyond research activities. The need for mass volumes of bio feedstock with high energy yields, lower input requirements, and greater environmental hardiness, for large scale production of chemicals and fuels, should drive the continued efforts for agricultural synthetic biology.

Synthetic biology is also seen to be massively disruptive in several other markets. For example, the current diagnostics and pharmaceutical applications are centered on improving existing methods to produce on-market drugs production for Merck, Pfizer, Teva, Roche, and DSM.

Chapter 2 – Industries and Applications

The McKinsey study mentioned previously [17] also found that more than half of the potential direct economic impact from biological technologies—applied to nearly 400 use cases in multiple sectors—is outside of healthcare, notably in agriculture and food, materials and energy, and consumer products and services

Thailand can and should participate in this growth market. With the substantial agricultural resources providing economical feedstocks and academic technical expertise, Thailand is well poised for developing industrial processes in areas such as biochemicals and biofuel, agriculture and food, health and medicine, as well as environmental and bioremediation.

Biofuels and Biochemicals

There are three approaches to developing biofuels and biochemicals: 1) high volume/low value molecular equivalents – which have the exact same chemical structure (i.e., ethylene, ethanol, etc.), 2) high volume/low value functional equivalents – which have similar properties but different chemical structures (i.e., bioplastics like PLA, PHA, etc.), and 3) low volume/high value specialty chemicals such as 1,4-butanediol (used to manufacture plastics, elastic fibers, and polyurethanes), caprolactam (primarily used in nylon 6 filament, fiber, and plastics), succinic acid and furan dicarboxylic acid.

Economics of production

The production of biofuels such as ethanol was seen a decade ago as the vehicle that would enable the biochemicals industry to diversify from and expand into replacements for many of the chemicals presently produced by the petrochemical industry. However, the price of oil has significantly declined since the biofuel "boom" was initiated. What made economic sense when oil was \$80-\$100/barrel is no longer viable at present price ranges of \$40-\$60/barrel. For biofuel production to be competitive (without substantial subsidies) the oil price will have to return to over \$100/barrel or through the imposition of carbon taxes or other regulatory pressures to make petrochemical feedstocks less economically viable.

Figure 2.1 – Spot crude oil prices from 2000 - 2020

In addition to pure economic disincentives, there is also a two-fold scaling problem for biofuels. First, oil is refined into fuels using large-scale refineries on the order of 25-50 Mtpa (megaton per annum). In contrast, large-scale fuel ethanol plants produce 1 Mtpa, which increases the capital costs for ethanol significantly when scaling means building more plants, not bigger plants. Secondly, if it were desired to replace the world's fuel production from oil (around 4,000 Mtpa), the energy equivalent amount of ethanol would require 10,000 Mtpa of biomass, or 2.5 times the world's current cereal, corn and sugar production. Finally, ethanol production is already highly efficient, and there is little or no benefit to try and enhance output through synthetic biological approaches.

For the bioproduction of large volume chemicals such as olefins (i.e., ethylene and propylene), the current market price is at about $1/kg but manufacturing them from bioethanol requires 3kg of sugar (approximately $1 in cost) to produce 1 kg of olefins. Thus, feedstock cost alone exceeds that of the oil produced product. Additionally, there is also a scale replacement issue with commodity biochemicals. Replacing the world's olefin production (about 250 Mtpa presently) would require 3x biomass (750 Mtpa) which is equivalent to 20% of the current cereal, corn and sugar production [19].

These cost/scale issues have led to research on 2nd generation ethanol production from feedstocks that do not impact food production, such as lignocellulosic from plant dry matter. This is an active area of research, especially in the US, focusing on plant engineering of bioenergy crops and new enzymes for biomass processing. The critical issue at present is the low yield of usable compounds (sugars and oil) from biomass. Synthetic biology may be the right tool to unlock this potential [20].

Specialty Biochemicals

Flexible precision fermentation bio-refineries at volumes of 20-50 kiloton per annum (ktpa) are the most economical approach for specialty biochemicals. Beyond that size, it is more feasible to scale out (e.g., build more fermenters) than to scale up in volume. This fermenter size gives economic incentive for the production of lower volume, higher value biochemicals such as the flexible precursor chemical farnesene (developed by Amyris) and other products mentioned previously. This scale level is also considered ideal for many life science chemicals and some oxo-chemicals (used in paints, plasticizers, coatings, adhesives, lubricants, etc.) when the value of those products is at least $5-10/kg [21].

In interviews with individuals familiar with the European synthetic biology landscape, they observe that incumbent energy and chemical companies currently "put their head in the sand" and feel that the future will repeat the past and that they are hesitant to invest too soon in next-generation bio-manufacturing. This opinion was echoed by large Thai chemical, feedstock, and energy companies who see synthetic biology as 5-10 years away and only deserving of high-level monitoring at the moment. However, the imperative from industry observers is that the coming synthetic biology disruption will be a more profound transition than anticipated and will happen significantly sooner than expected.

Bioplastics and Biomaterials

The field of bioplastics is very well researched, and Thailand already has significant production capabilities for polylactic acid (PLA) made from starch feedstocks, like cassava, as can be seen at the Corbion production facility in Rayong. Like ethanol production, PLA production is a well-developed fermentation technology, and synthetic biology may not have much to offer in terms of further efficiencies.

Polyhydroxyalkanoates

This section will introduce another class of bioplastics called polyhydroxyalkanoates (PHAs) produced through a bacterial biological fermentation process as an example of alternative bioplastics that offer significant opportunities for synthetic biology enhancement.

PHAs are currently being developed in Thailand by the Fruita Biomed Co., Ltd. The PHAs are made from fruit waste generated from the juice producing process. The PHA plastic is then used for plastic bottle applications for their fruit juice products (parent company Fruita Natural), as well as for medical and cosmetic applications.

PHAs are biopolymers produced by many microorganisms due to metabolic stress caused by exposure to an unbalanced nutritional environment, typically limited nitrogen (most common), phosphorous, or oxygen source combined with an excess carbon source. In such conditions, bacteria can form PHAs as a form of intracellular food storage for periods when the limiting nutrient becomes available again.

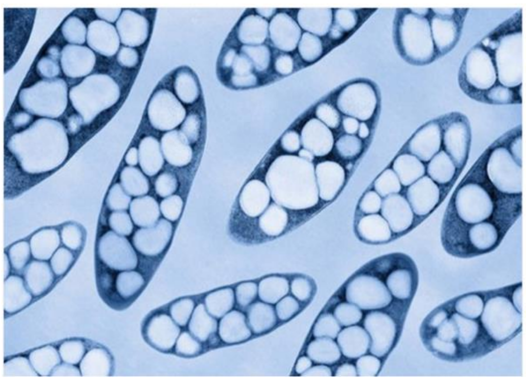

Figure 2.2. Microscopic view of bacteria filled with PHA

Such biopolymers are completely biodegradable to fixated carbon dioxide and water through natural microbiological enzymes (PHA hydrolases and depolymerases). Degradation rates are typically in the order of a few months in sewage to years in seawater without any active intervention. PHAs can substitute for a wide range of petrochemical plastics (polyethylene, polypropylene, etc.) [22]. PHAs have also been proved to be biocompatible and within mammals and are suitable for medical applications as the biopolymer is hydrolyzed very slowly, with after 6 months of implantation in mice, the mass loss was less than 1.6% [23]

Spider silk

Another biomaterial being produced in Thailand as a product of synthetic biology is spider silk by Spyber. Spider silk is stronger than steel, and tougher than Kevlar, but also flexible making it suitable for a large range of applications. In addition to fabrics, synthetic spider silk is being used for to develop structural materials for aircraft, shoes, and cosmetics.

Agriculture and Food

The United Nations estimates that in response to increasing world populations, by 2050, global food production will need to double. However, the limited amount of arable land and changing climate conditions require new solutions for improving agriculture output.

Biotechnology in agriculture has primarily been introduced through genetically modified organisms (GMOs), mainly sold as crop seeds that confer insect or herbicide resistance. The technology used to develop these crops predates synthetic biology but does demonstrate the value of transferring genetic traits to improve agriculture productivity.

Plant based Agriculture

Synthetic biology brings new tools to the table for agriculture, allowing for more complex engineered traits to be introduced to increase water and nutrient use efficiency, pest and disease resistance, photosynthetic efficiency, increased yield, and nutritional enhancements. These will require complex multi-gene constructs.

Nearer to market are synthetic biology modifications that create enhanced metabolic pathways to produce high-value products. An example of this is the modification of oilseed crops such as canola to enhance the production of long-chain omega-3 fatty acids (eicosatetraenoic acid (EPA) and docosahexaenoic acid (DHA)) [24]. In addition to being beneficial for cardiovascular health in humans, it is an essential component of the fishmeal used in fish farming.

Thai companies such as Thai Union are active in testing alternative proteins and omega-3 fatty acids produced through synthetic biology for fish meal. To promote the sustainability of ocean populations of large fish like salmon and tuna and the small fish they feed on such as mackerel and anchovies. The ability to produce proteins and omega-3 fatty acids from microbes for fish farming is a more sustainable way forward for the aquaculture industry.

Other value opportunities for food products include enhancements in digestibility, increased dietary fiber content, reducing or removing allergy-causing compounds (i.e., proteins in milk, eggs, and peanuts) and toxic or unhealthy compounds, and reduced tendency towards browning. Fortifying cereal crops with essential nutrients is another area for synthetic biology applications. For example, the creation of Golden Rice includes the gene for a vitamin A precursor to help prevent blindness in impoverished staple rice-eating populations and increase iron content in rice to combat anemia.

Plant Microbiomes

There are many agriculture challenges for increased productivity through sustainable solutions that are also economical. One opportunity is to enhance what is known as the phytomicrobiome, or the complex collection of microbial communities that provide plant growth-promoting traits. Unfortunately, simply applying such microbes that have been naturally found and isolated has found only limited success. This is because the existing microbial communities are highly resistant to being displaced by new microbes. Therefore, it is important to find new microorganisms that can integrate into existing microbial communities and provide the desired nutrition, fitness, disease control and productivity desired.

Microbiome engineering based on synthetic biology is seen as a potential approach to enable host plants to have the plant growth-promoting traits. Microbes can be selected and engineered to increase their ability to colonize plants, particularly at specific locations such as the roots or leaves. The ability to engineer the genomes of non-model microorganisms allows the utilization of discoveries of new genes that demonstrate improved biocontrol, biofertilization, and biostimulations to be incorporated into species that are already part of the plants phytomicrobiome. [25]

Animal Based Agriculture

Synthetic biology also has potential applications for animal-based agriculture in improved animal welfare, increased productivity, and sustainability of aquaculture systems. However, the regulatory burden surrounding genetically engineered animal lines is significantly higher than that for genetically engineered crops. To date, only one engineered animal line, the AquAdvantage salmon, has gained US FDA approval in 2015 after a 12-year application review process. Near-term genetic enhancements for animals are more likely to be through genetic editing than synthetic biology. Typical applications include increasing the resistance to porcine and avian viruses.

Food Science and Food Ingredients

Another area of synthetic biology application in food science is the further improvements in the way organisms are used to process foods, such as the fermentation processes critical for bread production. The engineering of modified yeast strains has improved rising behavior, increased functional health compound inclusion (i.e., resveratrol), improved flavor and aroma, and improved shelf life. Similar benefits can also be introduced into other fermented products such as beer, wine, yogurts, etc., using synthetic biology.

Natural Extract Replacement

Many start-ups in the US and Europe are developing synthetic biology technologies to produce food ingredients that are otherwise expensive to extract from natural sources. This includes resveratrol, saffron, vanillin, and modified stevia high-intensity sweeteners that do not have the characteristic bitter flavor of conventional extracts. Figure 2.2 below shows the key steps that US firm Codexis developed to convert the primary extract, Stevioside, into the final product called Rebaudioside M (Reb M). Although all four of the forms of the Stevioside molecule are found in the Stevia plant, only the first, Stevioside, is economical for extraction (60% of total extract). The other forms exist in very minute proportions, and the RebM at only 0.01% of the chemical extract.

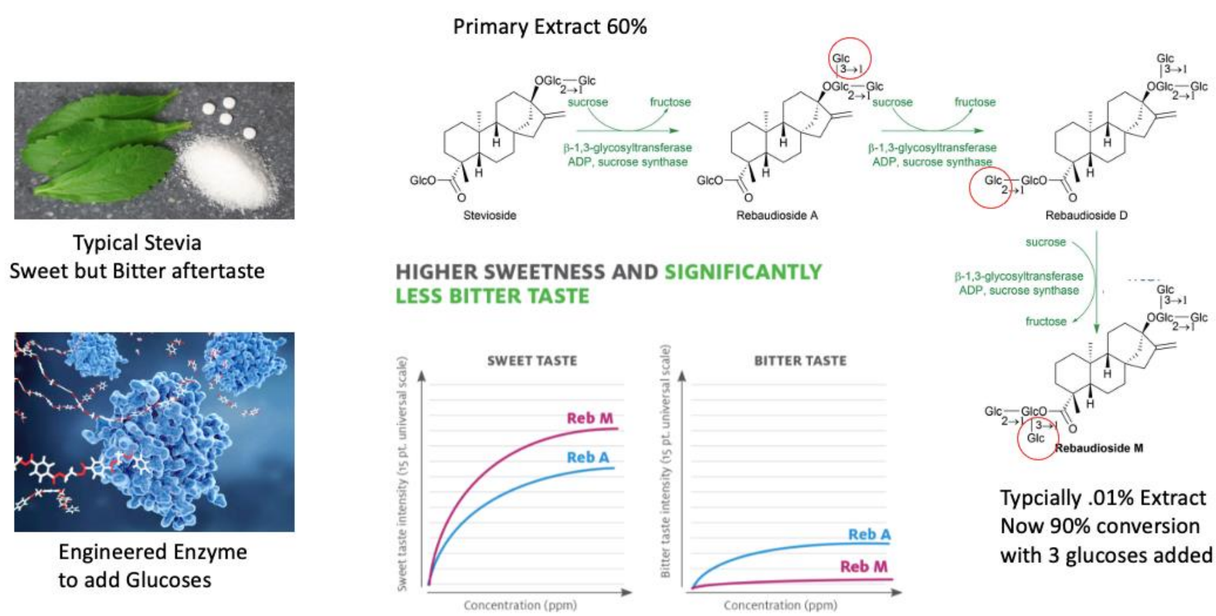

Figure 2.3 – Codexis development path to Reb M version of Stevia sweetener

The synthetic biology development effort consisted of discovering an enzyme that could "decorate" the primary extract with 3 additional glucose molecules. It was known that nature allowed for this metabolic pathway, but the enzyme responsible was unknown. Codexis took the approach to screen thousands of potential enzymes for biobanks until it found one capable of adding glucose, although only very weakly. Once they had a candidate enzyme, they could do protein engineering and go through the DBTL cycle to get to a 90% conversion efficiency.

In Thailand, Bangchak has partnered with sugar producer KSL to form a joint venture called BBGi to develop food ingredients. They will produce the Reb M compound with a proprietary technology developed by US start-up ManusBio. BBGi invested THB 800m in ManusBio and is presently working to scale up a multi-purpose fermentation facility for stevia production and other food ingredients in Thailand under the brand name "WIN Ingredients."

Vanillin, extracted from vanilla beans, is particularly prone to uncertainties in weather conditions and prices subsequently fluctuate significantly. Synthetic vanillin is now 85% of the market, but most of this is produced from petrochemicals or chemically derived from wood pulp. Evolva in Switzerland is now producing vanillin through synthetic biology-enabled fermentation, which customers prefer for its non-chemical manufacturing.

Alternative Proteins

Thai Kyowa Biotechnologies in affiliation with Japan's Kirin Holding, is planning to produce Human Milk Oligosaccharide (HMO) from synthetic biology microbes starting in 2022 in Thailand. Currently, infant formulas contain combinations of sugar and milk derived oligosaccharides that mimic that of natural human milk. The HMOs produced by Thai Kyowa will be a much closer analog to natural human milk and will likely displace earlier food additives in this market.

Another significant market for food ingredients is the production of plant-based meats. In particular, the success of the US start-up "Impossible Foods" is made possible through their synthetic biology production of a protein called leghemoglobin from yeast that is very similar to the iron-containing protein in animals called hemoglobin. The plant-derived protein helps confer the meat flavor, aroma, and cooking characteristics to the plant-based bulk protein that makes up their ground "meat" product. Similarly, there are many US start-up biotechs working on replacing other animal products such as milk and egg whites using synthetic biology.

Opportunities and Concerns

The majority opinion of Thai academics and corporate executives interviewed is that food and agriculture industries are the top opportunity for synthetic biology in Thailand. The focus should be on healthy foods, functional foods, and food as a disease prevention strategy. It is doubtful that much progress can be made with higher-order animals in Thailand, so the focus should be on simple microbial or plant-based systems.

Customers, in particular, want food ingredients that have significant scientific evidence from clinical trials that prove the relevance to Thai phenotypes. Health benefits include immune health, digestive health, stress reduction, and weight management. Customers want food that tastes great, provides good nutrition, is convenient, and comes from sustainable sources. They want to understand the benefit of new food technologies like synthetic biology as to how it is more environmentally friendly, more economical, more nutritional. They also want food safety and shelf-life extension that comes from advanced non-chemical antimicrobial strategies.

One concern is the public and regulatory perception of genetically modifies organisms (GMOs) in the food industry. It is recommended that separate regulations govern animal products versus those produced from microbes or plants. Presently the situation is unclear, and all product categories tend to be treated the same without an appreciation of the differentiated risk and public perception. For example, grocery retailers in Thailand have found little or no impact from declaring that a particular product has GMO elements on the front of the package, as consumers are more accepting than expected. It was also mentioned that NSTDA is currently working on a GMO review process in conjunction with the Thai FDA.

Farmers are also likely to be the first to experience the impacts of global warming. There should be a priority on developing GMO drought-resistant varietals explicitly adapted to the Thai climate and soil conditions. Internationally, there is recognition that agriculture is a crucial industry focus for synthetic biology, particularly in increasing yields.

Interviews with Thai food ingredient industry executives indicate that change in the food industry is happening at an unprecedented rate and food companies need to respond with innovation. Food innovation is about speed, agility, talent, and scale to react to evolving market conditions. This will require high coordination between suppliers, customers, and regulatory agencies.

An example quoted from the COVID experience is that when the demand for hand sanitizer soared in the early days of the pandemic, food companies could respond by transitioning their food-grade GMP facilities to sanitizer production. In contrast, chemical companies with their industrial-grade ethanol could not meet the regulatory requirements.

Health and Medicine

Synthetic biology will significantly impact health and medicine through improved biologics, vaccines, plant-based cell factories, and innovative cancer therapies.

Biologics

Biologics are large complex protein molecules such as hormones or monoclonal antibodies that have been very successful as therapeutics and diagnostics. Unfortunately, such molecules are very expensive to manufacture, and the biopharmaceutical industry is interested in finding new strategies and platforms that can reduce the cost of production. Synthetic biology may offer the opportunity to improve the expression efficiency of genes that have been transferred into the host microorganisms. Traditional recombinant DNA techniques randomly integrate the transgenes into the host chromosome, a "hit-or-miss" approach resulting in highly variable protein expression. A rational approach to choosing the site for insertion can result in high expression levels. In this case, it is not altering the transgene but instead improving the effectiveness of the host organism.

Two Thai companies focus on biosimilars that are typically off-patent complex biologic compounds manufactured locally. Siam Biosciences and Kingen are active in this field and operate as contract development and manufacturing organizations (CDMO). The two primary products produced by Siam Biosciences are Epoetin alfa, which is used to treat anemia, and Filgrastim, which is used to treat low neutrophil count. Both of these biologics are made through recombinant DNA technology. In addition to biosimilars, Siam Biosciences also produces monoclonal antibodies, cosmetics, and vaccines.

At this point, these companies generally do not do their own clone generation and typically go to other countries to license the clones they then use for manufacturing. There is a significant opportunity to utilize synthetic biology strategies to develop new biologics or improve process efficiency through host engineering.

Vaccines

The successful rapid development of the Covid-19 vaccine by multiple companies is a strong indicator that many of the core elements of synthetic biology are now in place. In particular, the mRNA approach is likely to revolutionize vaccinology as candidate mRNA vaccines can be chemically synthesized in a few days. This contrasts with the more complex biotech process involved when producing proteins in cells. Additionally, mRNA simplifies manufacturing significantly, with the same facility being able to manufacture many different RNA solutions for various diseases. One major drawback to mRNA is the relative instability of the lipid nanoparticles that are used to encapsulate it which necessitates the very low storage temperatures.

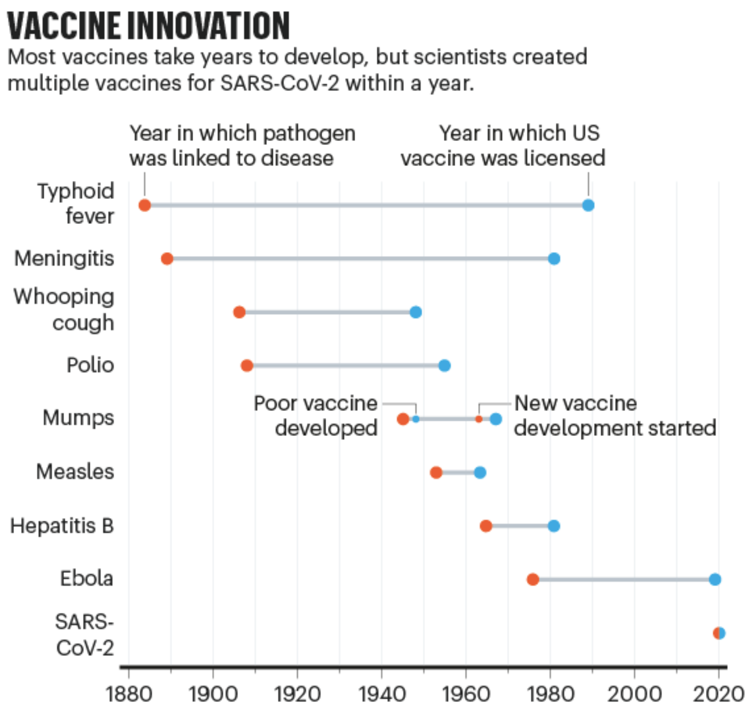

Figure 2.4 Timelines for historical vaccine development compared to Synthetic Biology powered SARS-CoV-2 vaccines.

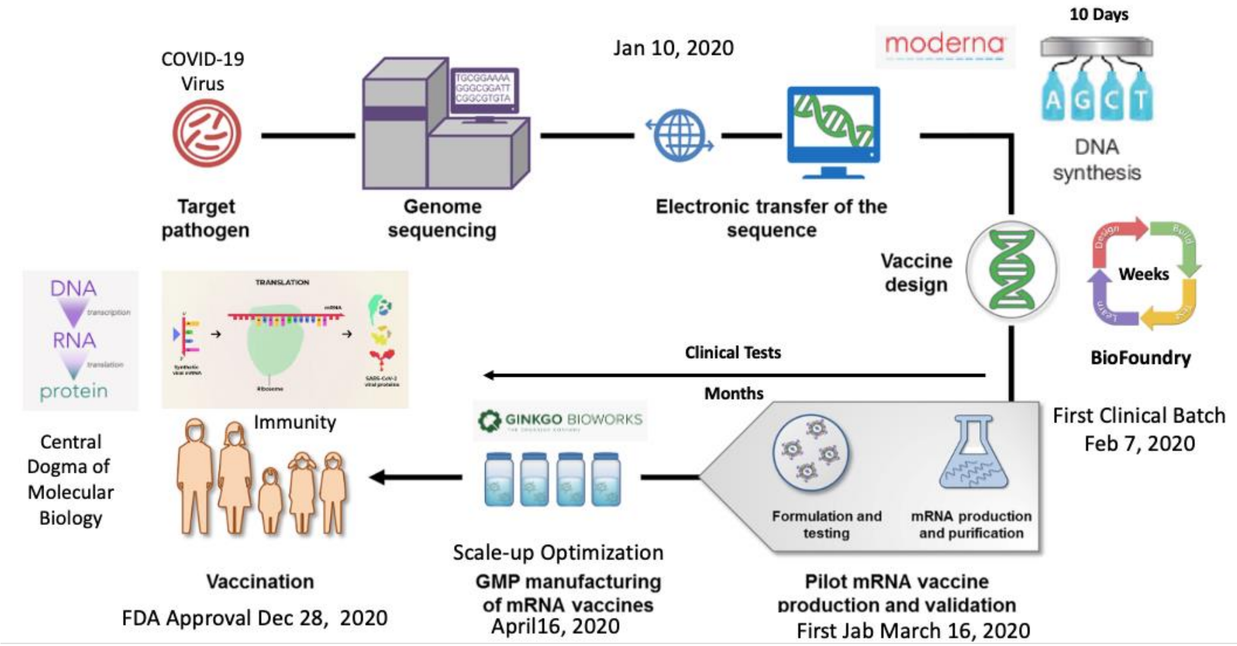

Figure 2.5 Covid-19 mRNA development cycle time

The DNA sequence for COVID-19 was available from China on Jan 10, 2020. From the time it was transmitted electronically, 10 days later, Moderna had successfully synthesized the viral DNA and had begun a DBTL cycle to find the best gene data for a distinctive antigen marker. In less than a month from data receipt, Moderna had an mRNA sequence ready to be put into a vaccine, and the first test in humans began on Feb 7, 2020. The manufacturing scale-up and clinical trials were run in parallel to ensure the vaccine would be both safe and available as soon as possible.

Ginkgo Bioworks, a US-based commercial biorefinery, partnered with Moderna to focus on the DBTL effort for manufacturing scale-up in April of 2020. Eight months later, the US FDA approved the vaccine for use, and manufacturing was scaled, and millions of doses were ready for delivery.

The previous record for vaccine development was for the mumps vaccine in the 1960s, which took about four years. Many believe that the success of vaccine development is going to bring public recognition to the value of synthetic biology for rapid drug development. Presently, Bio-Net in Thailand is working with Australian collaborators to develop and test a DNA version of Covid vaccines.

BioNet, a Thailand vaccine producer has developed their own DNA version of the COVID-19 vaccine, which is now entering Phase 1 clinical trials in Australia. This is a significant development for the Thai biopharma industry as it is advancing vaccine development into the realm of using synthetic biology tools for rapid design and development. As COVID-19 mutates, there will be high demand for continuous rapid adaptation of mRNA or DNA-based vaccines to combat the pandemic.

What is key about this locally developed synthetic biology vaccine is how the technology became to be developed in Thailand. In previous years, BioNet had collaborated in joint research with the Pasteur Institute in France to develop a DNA Zika vaccine. It is at the R&D level where interaction between Thai and French scientist led to the fundamental knowledge transfer that enabled subsequent development of a DNA vaccine against COVID. Typically, Thai companies do not collaborate at the R&D level, only at the production level, where any product IP is already developed and not transferred.

Cell Factories for Medicine production

Synthetic biology can also contribute to medicinal compounds formerly extracted from plants and traditional medicinal herbs. An example of this was described earlier for the antimalarial compound artemisinin, which was previously derived from sweet wormwood, but now produced from yeast.

Thailand has a rich tradition of traditional medicine from indigenous herbs and plants that have been screened for active compounds. There is significant potential to use these medicinal plants as a springboard for improved effective drugs by redesigning the metabolic pathways of yeast or bacteria, which are adapted to fermentation to produce these compounds.

As an alternative to producing such products via bioreactors, it is also possible to engineer plants to produce these compounds in their leaves or stalks. The significant advantage is the ability to utilize photosynthesis as the energy source, and the compounds can be harvested through traditional extraction techniques or eaten directly. Well researched plants like tobacco make good platforms for transgene insertion and offer the possibility of large-scale production at low cost and low maintenance requirements.

In Thailand, a start-up out of Chulalongkorn University called Baiya Phytopharm (https://baiyaphytopharm.com/) is focused on producing biopharmaceuticals, including plant-based vaccines and therapeutic proteins using molecular pharming technology. They make products for cosmetics, like fibroblast growth factor (bFGF) and epidermal growth factor (bEGF), as anti-aging ingredients. They are also in pre-clinical trials to produce SAR-CoV-2 related proteins for potential use in a vaccine and as a rapid Covid-19 test kit.

Biosensors

Biosensors made using synthetic biology can be used for drug discovery, disease diagnosis, and point of care applications. Examples include glucose monitoring, cardiac markers, infectious diseases, coagulation monitoring, pregnancy, and fertility testing, tumor and cancer markers, urinalysis testing, and cholesterol measurement. These new sensors have advantages over existing techniques, including specificity, sensitivity, stability, and cost.

These devices have been demonstrated to detect target chemicals in the body, such as glucose, drugs such as immunosuppressants, and biochemicals indicative of diseases such as α-amylase proteins (produced by acute pancreatitis) and proteins that are indicative of blood clotting and stroke. When a target chemical is recognized, an electric signal is produced an external monitoring device can detect that. Other means of detections, such as fluorescent biosensor reporter molecules, can detect the proteins associated with degenerative brain diseases such as Alzheimer's.

Researchers at Vistec are currently developing fluorophore ligase for protein labeling of beta amyloids in the brain. They are using xeno-proteins produced with amino acids not found in nature. This is an excellent example of the advanced level of synthetic biology research that could benefit significantly from a rapid DBTL bio-foundry capability.

Phage antibiotics

Phages are viruses that specifically target, infect, and kill bacteria. They offer an alternative to conventional antibiotics. Natural phages have been developed as effective antibiotics, including that being utilized by UniFAHS and their product Salmoguard in Thailand, which has isolated phages for attacking salmonella bacteria (http://unifahs.com/).

The technology utilizes a naturally found phage encapsulated to increase shelf-life that can be used to reduce salmonella levels in poultry production and processing when combined with water. Such phages could be modified using synthetic biology to generate other targets and create a platform technology for phage innovation instead of just what nature has already invented.

Cancer Therapies

Cancer immunotherapy is a field that synthetic biology will have a significant impact. In immunotherapy, the strategy is to either use a patient's immune system to attack cancer cells by helping the immune system target the unique markers on the cancer cell surface (antigens) or by engineering immune responses such as immune checkpoint inhibitors.

Synthetic biology is key to the molecules central to the development of Chimeric Antigen Receptor (CAR-T) cell style immunotherapy. The objective is to re-engineer the antibody component that recognizes the antigen into a simpler protein scaffold with better functionality.

In Thailand, the development of CAR-T technology is being undertaken by Genepeutics, which utilizes cleanroom facilities and technologies developed under TCELs leadership. They are focused on developing leukemia-related diseases using gene immunotherapy treatments licensed exclusively from Mahidol. The fundamental value proposition is developing a local capability for immunotherapy rather than relying on other country's ability to produce.

Another approach to cancer therapy that would benefit from synthetic biology is being developed at the Center of Excellence in Systems Biology at Chulalongkorn University. The research focuses on identifying novel antigens, markers unique to a person's cancer, then synthetically producing peptides (short linear chains of amino acids, a protein fragment) that mimic a portion of that antigen to educate the immune system. This personalized cancer vaccine approach requires the rapid design, build, test, and learn cycle if it is to be applied on a larger scale due to the individualized nature of the treatment.

Human Microbiomes

It is increasingly well known that the microbiome in the human gut plays an important role in maintaining and improving human health including regulating metabolism, modulating the immune system, and the production of important neurotransmitters for mental health. Although there are many probiotic and prebiotic solutions on the market presently, synthetic biology offers new and more effective therapeutic probiotics.

Synthetic biology designed probiotics could sense changes in the microenvironment of the gut, including biomarkers of inflammation, or the absence of important signaling molecules, and then respond dynamically with the production of metabolites that can act to correct these imbalances. [26]

In addition to the gut microbiome, the skin microbiome is also a prime target for synthetic biology derived microbial solutions. DARPA has recently funded research into the development of "living medicines" to solve major problems in skin diseases and the ability to reduce the abundance of bacteria on the surface of the skin that secrete compounds that attract mosquitoes. The goal of this project is to displace mosquito attracting microorganisms with functionally equivalent microbes that provide the positive aspects of the skin microbiome without producing the chemicals that attract mosquitoes. It is probable that rates of Malaria, Zika, Dengue, Chikungunya and other mosquito-borne diseases can be reduced. [27]

Environmental and Bioremediation

Engineered cells and proteins can be used to sense various soil and water systems components. Typically, these sensors use an environmentally responsive promoter that controls a reporter gene's expression. An example of a reporter is the gene that produces the luciferase protein, making light and creating a measurable signal. These sensors can be used to assess the amount of bioavailable arsenic, iron, mercury, and other pollutants in lakes, soil, and the ocean.

Detoxification

Engineered microbes and enzymes can also be used to degrade and detoxify a wide range of environmental contaminants such as pesticides, solvents, explosives, and heavy metals. Although natural bacteria have been used in detoxification, synthetic biology promises to improve efficiency and extend the functionality to new contaminants.

One Thai start-up company working in this space is Bio Om Co., Ltd. (https://www.bio-om.com/). They have developed approaches to improve soil productivity with plant growth-promoting rhizobacteria that can also remove toxins in the soil to help farmers convert their soil to organic standards. They also produce enzymes that can effectively remove pesticides from the surface of fruits and vegetables and a pesticide detection assay. Bio Om's solutions are currently unmodified microorganisms and enzymes found in nature, but the application of synthetic biology is seen as a viable next step in product platform development.

Thai Wah Public Company Limited is also investing in research to discover microorganisms that can break down the waste cassava pulp into fertilizer products. They find that conversion of the waste products can release higher bioavailable nitrogen, phosphorous, and potassium back into the soil used to grow cassava. However, efforts to date are focused on naturally occurring microorganisms and no attempt has been made at gene editing for enhancement.

Bioremediation of Waste

Vistec has also spun out a start-up company called Enzmart Biotech to market engineered enzymes and protein markers in Thailand (https://www.enzmart.com/index.php). This is in conjunction with Vistec's C-ROS (Cash Return from ZeroWaste and Segregation of Trash) technology which will convert organic waste from food and agricultural industries, municipalities, communities and households into valuable biofuels and biochemicals (https://www.c-ros.org/en/index.html).

Synthetic biology remediation approaches can also be applied to the recycling of plastics, particularly polyethylene terephthalate (PET). It has recently been reported that an enzyme, found in nature, but significantly enhanced through synthetic biology, can decompose PET into its precursor molecules at elevated temperatures (72C). The enzyme can decompose 90% of a PET sample into component terephthalate acid and ethylene glycol, which can produce new bottles with properties as good as the original. The enzymes also ignore any dye or color applied, such that the recycled plastic will be free from colorants and suitable for being made back into new plastics [28].

Chapter 3 – Technical Capabilities

This chapter provides a high-level overview of the technical capabilities required to enable synthetic biology development. Readers who desire more detail are directed to the document "Engineering Biology – A Research Roadmap for the Next-Generation Bioeconomy" published in 2019 by the US Engineering Biology Research Consortium (EBRC) [29].

Areas of Synthetic Biology Technical Capabilities

The EBRC report defines four major areas of synthetic biology technical capabilities:

1. Gene editing, synthesis, and assembly

2. Biomolecule, pathway, and circuit engineering

3. Host and consortia engineering

4. Data Integration, Modeling and Automation

Individual academic and government labs in Thailand have some of the technical capabilities in these four areas, but there is no facility that has all four capabilities together in an integrated fashion. This is the basic concept of a biofoundry that will be explored in this chapter.

Gene editing, synthesis, and assembly

This area includes the production of single stranded DNA (oligonucleotides) and double-stranded DNA molecules (DNA fragments, genes). These are typically produced using phosphoramidite-based chemistry which is presently capable of only producing short lengths with high accuracy. For the synthesis of 200-nucleotide oligonucleotides the yield of accurately synthesized strands is presently about 35%. Newer phosphoramidite technologies are coming on-line and should yield oligonucleotides thousands of nucleotides long with higher precision., There are also enzymic DNA synthesis approaches in late-stage development that have the potential to extend the length produced with high quality significantly further.

Typically, once the oligonucleotides are manufactured ("printed") they require assembly into multiple DNA fragments (300 to 3000 base pairs long) and subsequently into large genetic systems (10,000 to 1,000,000 base pairs long) using assembly enzymes. After assembly, the DNA is then introduced into cells for clonal separation and replication.

Biomolecule, Pathway, and Circuit Engineering

This area starts with the capability of designing proteins through computational methods which have the predicted three-dimensional shapes and desired functions. Recent breakthroughs in the ability to predict protein folding accurately is accelerating the rate at which functional macromolecules can be designed and produced [30]. Pathway engineering refers to multi-step processes that occurs within a biological cell required to produce the end product. Several precursor steps may be necessary before production of the target biomolecule. Finally, biological circuits can be designed based on previously defined bio-parts that mimic electronic logic and other circuit capabilities.

Host and Consortia Engineering

Once macromolecule sequences, pathways, or circuits have been designed, they need to be put into host systems in order to execute their designed behavior. Traditionally this has occurred in model microbes like *E. coli* (bacteria) and *S. cerevisiae* (yeast), but there are many more possibilities that may hold significant production advantages. For example, using microbes that are photosynthetic like cyanobacteria, opens up the opportunity to utilize non-sugar feedstocks such as methane or lignocellulose. Additionally, using microorganisms that come from extreme environments may allow for higher temperature processing, or extreme pH tolerance etc.

Cell-free systems are another emerging alternative. By eliminating the limitations of all the other cellular machinery required to keep the cell alive while producing the synthetic biology objective, it is possible to increase the concentrations of produced molecules without reaching toxicity limits until much higher levels among other advantages.

Multicellular systems (consortia) are the highest level of complexity for host systems and are considerably less well-developed at this time. These approaches are presently primarily used for reproduction processes where gametes or embryos of plants or animals are edited to achieve characteristics that may be difficult through traditional breeding techniques.

Data Integration, Modeling, and Automation

The need for sophisticated computational capabilities runs throughout the design, build, test, learn methodology. For example, models are needed to predict the interaction of designed synthetic systems with their host organisms. For each stage of the DBTL framework, data and algorithms drive experimental design, interpret assay results and machine learning can then predict process and performance improvements for next-cycle experiments. This is where systems biology and synthetic biology overlap.

All these models and computational systems should be connected through findable, accessible, interoperable, and reusable (FAIR) data and process modeling, so they can be shared with the larger community, and likewise, modeling advancements made elsewhere can easily be incorporated into the local standardized environment.

Synthetic Biology Biofoundry

Many of the technologies mentioned above are available and used individually in biological research by Thai academic, government and commercial laboratories. Some of these capabilities, such as DNA synthesis, are not presently available in country, but can be ordered from suppliers internationally. Additionally, most laboratories in Thailand do not have high levels of automation, with some notable exceptions, so the pace of DBTL cycles is slow, perhaps permitting only a few completed cycles per year. This is due to the manual nature of the way most steps are carried out in Thai labs and the logistics of material transfer. This compares unfavorably to cycle times of days or less for well-constructed biofoundries such as found in the US, UK, EU, China, Japan, Australia and Singapore. Furthermore, since specific capabilities are fragmented across many different labs, true synthetic biology development requires extensive collaboration which is difficult to coordinate for logistical and systemic reasons.

In response to this situation, there is a growing trend for national governments to support the construction of centralized biofoundry facilities that can become a shared resource for that nation's researchers. This section will discuss the fundamental principles of biofoundry operations.

Biofoundry Concept

In order to achieve the goals of building advanced bioeconomy strategies that can produce high value bio-products, especially products derived from waste biomass, there needs to be effective and efficient biofoundries. Most startups, and many large companies, lack the resources or economic incentive for developing the fundamental research and access to sophisticated biologic R&D infrastructure. This is an important role that the public sector can provide. In addition to access to technology, having a centralized biofoundry also promotes the adoption of international standards which leads to enhanced reproducibility, reliability, and ability to collaborate internationally.

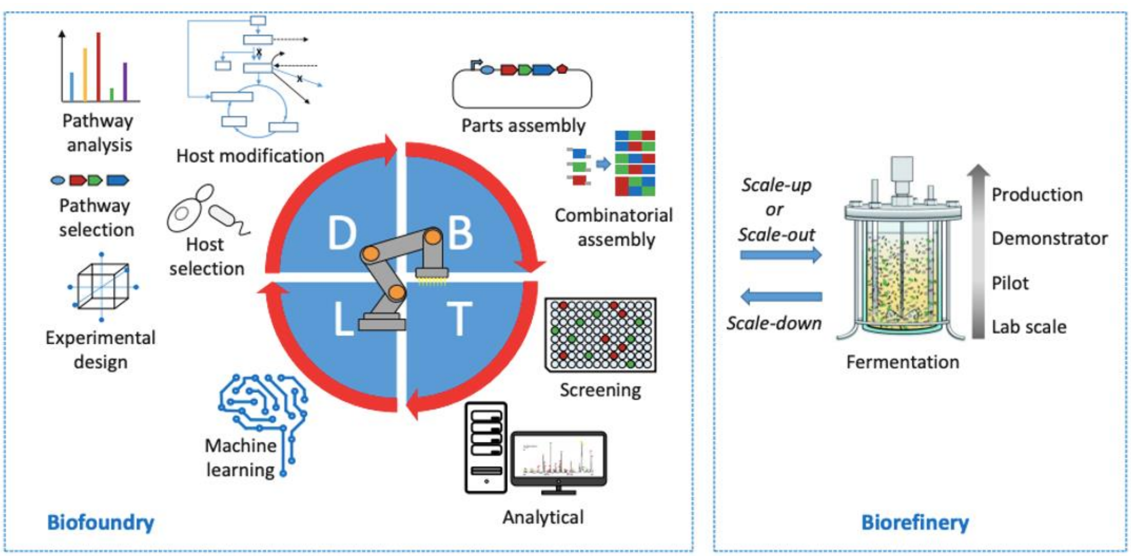

Figure 3.1 Automating the DBTL cycle in the Biofoundry [31]

In particular, the connection between biofoundry DBTL cycle and scale-up to biorefinery needs to be linked. The transition to a biorefinery means changing the bioreactor conditions from liters to hundreds, then thousands of liters which changes many fermentation parameters and significantly affects the outcome of the designed biofoundry organisms and processes. For example, oxygen concentration gradients, changes in pH, shear forces on cells, and even impurities in lower-cost culture media can all impact the product quality as the process is scaled from laboratory, to pilot, to demonstration, to production scale as illustrated in Figure 3.1.

What is required then is an integrated technology platform that encompasses metabolic modeling, high-throughput (HT) pathway and strain construction, quantitative small-scale screening and systems biology, all of which are intimately linked to fermentation and process engineering [32]. As discussed in the next chapter, the biofoundry is a necessary enabler of scale up biorefinery success such as that being designed and built in the EECi facility in Thailand.

By centralizing and integrating the various genetic tools, software, automation required for the DBTL process, a synergy of productivity emerges that allows researchers to innovate at an accelerated pace. There were 16 non-commercial biofoundries globally in 2019, according to the Global Biofoundries Alliance [33].

Figure 3.2 Non-commercial Bio-Foundry global locations of founding members of the Global Biofoundry Alliance with each biofoundry numbered. (1) DOE Agile BioFoundry located across Emeryville, CA, Richland, WA, Golden,CO, Lemont, IL, Los Alamos, NM, Oak Ridge, TN, and Idaho Falls, ID sites; (2) Illinois Biological Foundry for Advanced Biomanufacturing (iBioFAB), University of Illinois at Urbana- Champaign; (3) Concordia Genome Foundry, Concordia University Montreal; (4) DAMP lab, Boston University; (5) Edinburgh Genome Foundry, University of Edinburgh; (6) Earlham Institute, Norwich Research Park; (7) London DNA Foundry, Imperial College London; (8) SYNBIOCHEM, University of Manchester; (9) GeneMill University of Liverpool; (10) Novo Nordisk Foundation Center for Biosustainability, Technical University of Denmark; (11) Frontier Science Center for Synthetic Biology (MOE), Tianjin University; (12) Graduate School of Science, Technology and Innovation, Kobe University; (13) Shenzhen Institute of Synthetic Biology, Shenzhen Institutes of Advanced Technology, Chinese Academy of Sciences; (14) NUS Synthetic Biology for Clinical and Technological Innovation (SynCTI), National University of Singapore; (15) Australian Foundry for Advanced Biomanufacturing (AusFAB), University of Queensland and (16) Australian Genome Foundry, Macquarie University.

Agile Biofoundry Example

In the US, facilities at seven different Department of Energy government laboratories have been combined collectively into a virtual biofoundry capability known as the Agile BioFoundry (depicted as #1 in Figure 3.2). The Agile BioFoundry focuses on developing and distributing publicly available tools, methods, and strains aimed at broadly benefiting the synthetic biology industry. The Agile BioFoundry is a publicly funded effort aimed at delivering technology that will enable industry to either leverage their resources through partnership or adopt their methodologies for developing bioproducts. The Agile BioFoundry is focused primarily on developing biological pathways for producing advanced biofuels and renewable, high-volume chemicals.

Biofoundries can also be constructed and run in the private sector. The most celebrated example of this is Gingko Bioworks which provides biofoundry capabilities as a service. Many larger biotech companies will also have their own internal biofoundry capabilities specialized to their area of interest such as Amyris.

Below is a list the specific technologies and value propositions that have been integrated at the Agile BioFoundry [34]. What is critical is that all laboratories have standardized on a key set of shared technologies to allow interchangeability between collaborating labs.

Design

"We develop bioprocesses for your desired target molecules, as well as the necessary tools to build out pathways in a host organism."

Design Capabilities include:

- DIVA bioCAD

Build

"Our build capabilities include host organism selection for the production of target molecules, methods for biochemical pathway engineering, and genetic transformation to introduce genetic constructs into host organisms for pathway expression."

Build capabilities include:

- Genetic Transformation and Tool Development
- Fungal Genomics, Synthetic Biology and Bioprocess Development
- Droplet Adaptive Laboratory Evolution
- DIVA DNA Sequence Validation
- DIVA DNA Construction

Test

"We help you understand how an engineered pathway behaves in your host organism."

Test capabilities include:

- Targeted Proteomics
- Targeted Metabolomics
- Riboregulators for Precise Control of Gene Expression
- High Throughput Strain Characterization
- Global Metabolomics and Isotopically Labeled Metabolomics for Metabolic Flux Analysis
- FRET Biosensors
- Experiment Data Depot
- Smart Microbial Cell Biosensor Technology
- Microbioreactor Systems and Sampling Platform
- Microfluidic Biocatalyst Optimization

Learn

"We translate your experimental data into predictions for the design of future pathways and processes."

Learn capabilities include:

- Regulatory Modeling
- Pan Genome Analysis
- Metabolic Flux Analysis and 13C Metabolic Flux Analysis
- Machine Learning
- Deep Learning

Scale-Up

"Scale-up is critical for translating your technology to an industrial setting. We incorporate downstream processing steps to identify problems and to provide data for techno-economic and life cycle analyses."

Scale-Up capabilities Include:

- Multiscale Bioreactor Cultivation
- Product Recovery and Purification

Other important capabilities for Synthetic Biology ecosystems

Sequencing and Proteomic facilities

Thailand currently has significant DNA sequencing and proteomic characterization capabilities at national facilities such as the National Omic Center (https://www.nstda.or.th/noc/about-us.html), and in the various universities. Services include Genome Sequencing, Transcriptome Sequencing, RNA-seq, Metagenomics, Gene Expression Analysis, Genotyping by Sequencing, Linkage Analysis, Marker Assisted Selection, Plant Genetic Improvement, and Plant Molecular Biology, etc.

The sequencing facility for the Thailand Genomics program is also set to begin operations by Oct. 2021 at Burapha Univ. Faculty of Pharmacy in Chonburi. Initial volume will be 200 samples/week of whole genome sequencing. Ideally this will also provide sequencing capacity for synthetic biology DBTL in the future.

Biobank and screening facilities

Thailand also has significant repositories of microbial species at national centers such as the Thailand Bioresource Research Center (TBRC) which has over 90,000 microbial strains in their collection, over 5000 yeasts and over 5000 other fungi. Additionally, the Thailand Institute of Scientific and Technological Research (TISTR) has a probiotic bank and microbial center for collecting and preserving strains of useful native and non-native microbes and freshwater microalgae species. TISTR is also the regional Southeast Asia center for the UNESCO World Network of Microbiological Resources Center (MIRCEN). This is addition to collections at major universities, of particular note is the mycology collection at Mae Fah Leung University which houses a novel fungi culture collection of over 10,000 strains, with at least 2000 species that are new to science.

There are also significant high-speed screening capabilities, such as the Mahidol Excellent Center for Drug Discovery (ECDD), the Siriraj Systems pharmacology lab optical microscopy screening capabilities, and enzyme screening capabilities at Vistec. Thailand is well positioned to identify and develop novel organisms for metabolic pathways as well as host chassis development from existing biobanks and screening facilities which would be a valuable input into a biofoundry capability.

Scale Up facilities

Thailand already has some capability in scaling up from laboratory to pilot and demonstration capacities and more facilities are presently being designed and built. These include bioreactors at Vistec (500 l), Biotec (300 l), TISTR (450 l), Mahidol Univ. Dept. of Biology (200 l), and KMUTT.

Of particular note is the scale up facility being designed and constructed as part of the Eastern Economic Corridor of innovation (EECi) Biopolis. This facility will substantially increase the Thailand's capabilities for translation from post biofoundry TRL stages (5-6) through to higher levels (TRL 7-9). The facility is slated to begin initial operations in Q4 2021 with biorefinery operations coming on-line in 2024. The Biopolis facility is designed to support three strategic technology areas:

- Innovative Agriculture and Aquaculture
    - Phenotyping facility/greenhouse to do research on phenomics for trait improvement

- Plant factory for production of high value crops

- Functional Ingredients (Food & Feed, Functional Food/Nutraceuticals)
  - GMP facility to do scale up production for functional ingredients (plants & microbes)
  - Application testbed for nutraceutical, cosmeceutical and pharmaceutical industries

- Chemical & Bioprocess Technology (Biochemical, Biomaterial, Biospecialty)
  - Biorefinery facility to do scale up research & pilot production for market testing
    - Raw materials processing unit – pretreatment, fractionation, transformation
    - Bioconversion unit – fermentation, bioreactor
    - Downstream processing unit – separation, formulation Bio-based material processing unit – master batch technology

Figures 3.3 and 3.4 detail the high-level capabilities planned for the EECi GMP and non-GMP pilot factory capabilities

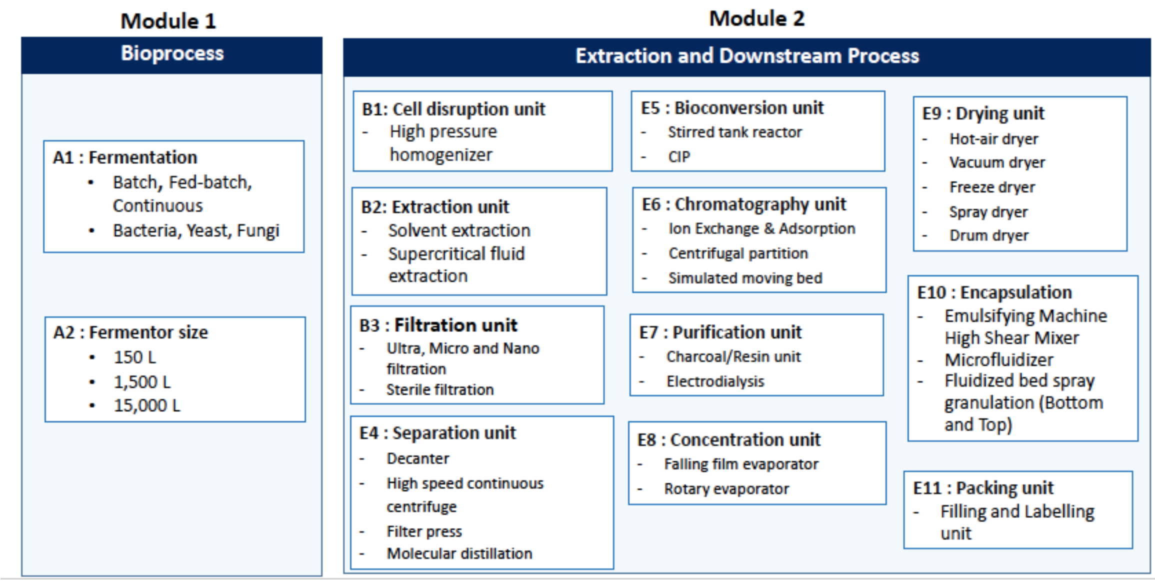

Figure 3.3 EECi GMP biorefinery pilot factory capabilities

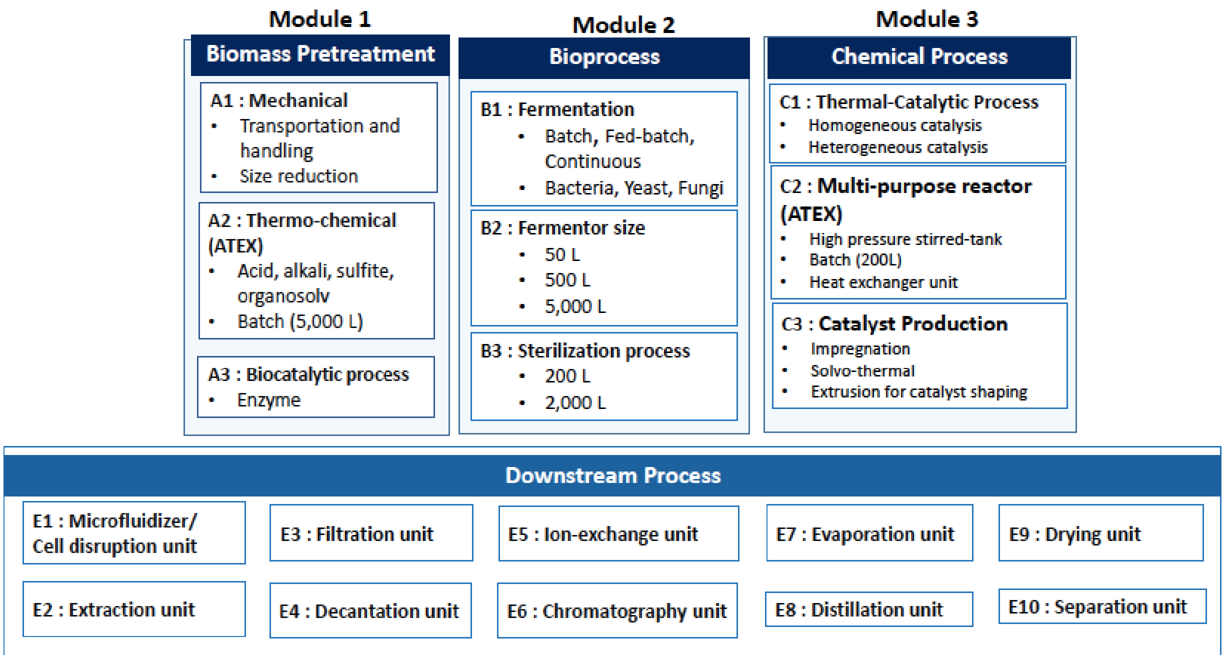

Figure 3.4 EECi Non-GMP biorefinery pilot factory capabilities

Production Facilities

Currently there are no significant contract manufacturing and development organizations (CMDO) for precision fermentation for larger production volumes. For example, the start-up Juiceinnovat8 is currently seeking to produce its product in a facility with 3000-5000 l production capacity but can find none currently available in Thailand. This is a gap that should be targeted, either from a domestic fermentation company, or by attracting an international partner through EEC incentives or similar programs.

Chapter 4 – Comparative Ecosystems

A high-level survey of the synthetic biology ecosystems in the US, UK, and Singapore has been undertaken in order to identify what pertinent gaps may exist in Thailand's current ecosystem. The intent of this report is not to recommend that Thailand replicate or directly compete against these existing ecosystems but rather to use them for gap analysis, collaboration opportunities and identification of potential ecosystem niches that Thailand could serve with a competitive advantage.

United States of America

The concept and origin of synthetic biology can be confidently traced back to the United States biotech community, which emerged in the 1980s following the passage of the Byde-Dole Act which transferred IP ownership from funders (government) to recipients (universities). The US has the most synthetic biology laboratories, the largest number of synthetic biologists, most significant amount of research funding, the most extensive list of publications, and the oldest research centers in this field. It is also the organizational home for two influential synthetic biology events, the Synthetic Biology X.0 conference (the latest SB7.0 was held in Singapore in 2017) and the International Genetically Engineered Machine (iGEM) competition (discussed in Chapter 5).

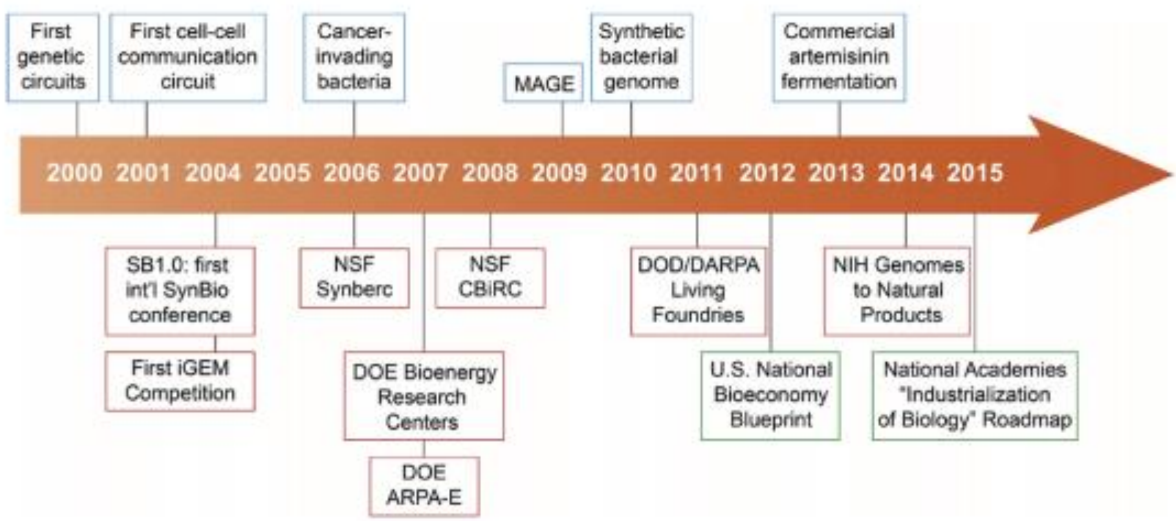

Figure 4.1 Timeline of major US synthetic biology programs through 2015 [31]

US Government Funding

Since 2005, the US government has spent an estimated $140 million per year on synthetic biology [35]. This would equate to over $2 billion though 2020. Funding has been from multiple agencies but without a coordinated government funding mechanism. Some of the most important funders include:

- National Science Foundation (NSF) - Synthetic Biology Engineering Research Center (Synberc) https://www.synberc.org/about.

    - Funded Synberc with $39 million in 2006 for ten years as a multi-institutional research center

    - Key members including
        - Harvard
        - MIT
        - UCSF
        - Stanford
        - Industrial companies

    - Mission
        - To develop the foundational understanding and technologies to build biological components and assemble them into integrated systems to accomplish many particular tasks
        - Develop a network of academic and industry partners focused on synthetic biology
        - Train a new cadre of engineers who will specialize in synthetic biology
        - Engage the public about the opportunities and challenges of engineering biology

    - In 2016, a non-profit, public-private partnership called Engineering Biology Research Consortium (EBRC) was formed to sustain, coordinate and expand foundations developed by SynBERC https://ebrc.org/.

- NSF – Center for Biorenewable Chemicals (CBiRC) http://www.cbirc.iastate.edu.

    - CBiRC was founded in 2008 with funding from the National Science Foundation (NSF), creating an NSF Engineering Research Center (ERC) focused on advanced manufacturing for sustainable biobased chemicals.

    - NSF invested $18.5m in the center over five years, located at Iowa State University.

    - The ERC program creates multi-year, interdisciplinary, multi-institutional centers that join academia, industry, and government in partnership to produce transformational engineered systems. The ERCs also develop engineering graduates adept at innovation and primed for leadership in the global economy.

- Department of Energy (DOE) - Bioenergy Research Centers

    - Committed funding of $750m over ten years since 2007 to better understand the biological mechanisms underlying biofuel production.

    - The goal is to redesign, improve, and develop novel, efficient bioenergy strategies that can be replicated on a mass scale.

    - The three BRC centers are:
        - BioEnergy Science Center (BESC, Oak Ridge, Tennessee) - Focusing on poplar and switchgrass crops and their biomass formation, structure, and recalcitrance.
        - Great Lakes Bioenergy Research Center (GLBRC, Madison, Wisconsin) - Focusing plant fiber breakdown to maximize production of starches and oils.
        - Joint BioEnergy Institute (JBEI, Emeryville, California) - Focusing on microbial synthesis of advanced biofuels.

- DOE - Advanced Research Projects Agency-Energy (ARPA-E)

    - Created in response to the US Congress to "identify the most urgent challenges the US faces in maintaining leadership in key areas of science and technology."

    - ARPA-E funds "high-risk, high-impact" research programs to develop transformational energy technologies. Projects include:
        - synthetic gene circuits to enhance the production of transgenic bioenergy crops
        - Synthetic methylotrophy to liquid fuel
        - Anaerobic bioconversion of methane to ethanol
        - Synthetic biology, protein engineering, and semi-biological photocatalysis to convert methane to n-Butanol

- Department of Defense (DOD) - Defense Advanced Research Projects Administration (DARPA)

    - The living foundries initiative was established to create a revolutionary, biologically based manufacturing platform to provide access to new materials, capabilities, and manufacturing paradigms.

        - Living Foundries – Advanced tools and capabilities for generalizable platforms (ATCG) project:
            - Budget \$35m from 2012 - 2014
            - The goal is to accelerate the biological design-build-test-learn cycle by at least 10X both in time and cost reduction via the development of next-generation tools.

        - Living Foundries - 1000 Molecules project:
            - Budget is \$110m 2015 - present
            - The goal is to demonstrate advances in automation, genome editing, and machine learning to fully integrated, rapid design and prototyping infrastructure that spans design tools, scalable,

automated, and parallelized design fabrication, and high-throughput design evaluation and validation.

- Proof-of-concept strains are being developed for 1,000 distinct molecules and material precursors spanning a wide range of defense-relevant applications, including industrial chemicals, pharmaceuticals, coatings, and adhesives.
- Key participants - UC Berkley, MIT-Broad, Harvard, U of Colorado, U of Illinois at Urbana-Champlain, Amyris and Zymergen.

- National Institutes of Health (NIH)

  - NIH is estimated to have awarded grants for more than $50 million between 2011-2019 for synthetic biology.

    - UCSF Center for Systems & Synthetic Biology
      - Focuses on the principles and architectural features involved in common cellular processing behaviors and using this information to engineer synthetic circuits that can trigger desirable cellular responses to external cues to make them useful in biotechnology and biomedicine.

    - MIT Center for Integrative Synthetic Biology
      - Focuses on exploring the use of synthetic RNA-based circuits to sense and destroy cancerous cells
      - Programming the differentiation of stem cells to generate insulin-producing beta-islet cells for diabetes
      - Engineering approaches to target antibiotic-resistant bacteria

    - Johns Hopkins University School of Medicine Center for Systems Biology of Retrotransposition
      - This program focuses on retrotransposons (mobile elements of the genome) and the study of their mechanism of movement.
      - Studies of synthetic retrotransposons have led to the possibility of redesigning and synthesizing entire eukaryotic chromosomes, such as building a modified yeast genome known as Sc2.0.

    - Stanford Center for Systems Biology and Rockefeller University
      - Genomes-to-Natural products program - applying integrated genomics, synthetic biology, and bioinformatics expertise to develop innovative, high-throughput, and broadly applicable genome-based methods for natural product discovery overcoming technical barriers, and filling knowledge gaps for translation of genetic information into chemical information.

US Start-up Community

The synthetic biology start-up community in the US is the largest globally. There was over $7.8 billion in financing from private, public, and non-dilutive government grants in terms of investment.

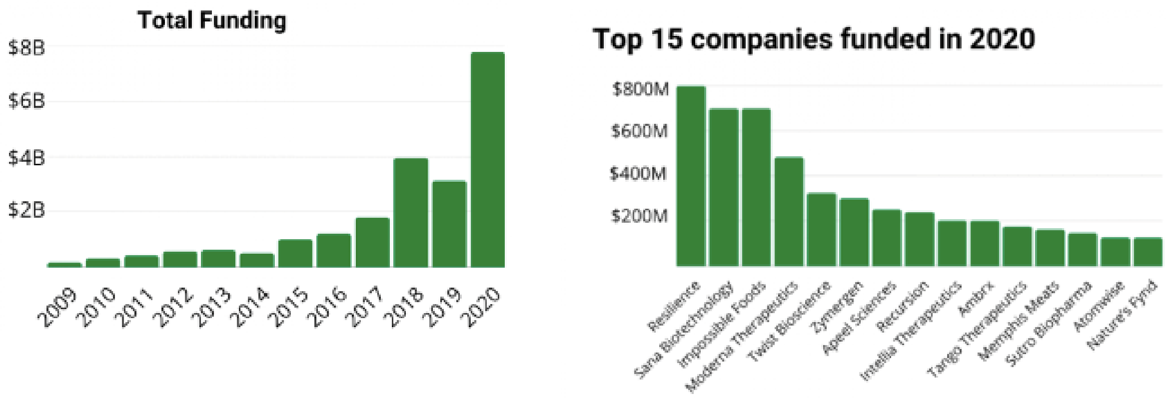

Figure 4.2 – Funding for US Synthetic Biology Start-up community 2009-2020 [36]

In 2016 it was estimated that there were over 190 companies working in synthetic biology across the US. That number is estimated to have doubled since then. Today, several US synthetic biology companies have grown "too big to acquire." These companies are forming the foundation of the synthetic biology industry like Facebook, Apple, Amazon, Netflix, and Google did for the tech sector in the past. Industry futurists predict that in 10-20 years, the top 5 most significant companies in the world will be biology-based.

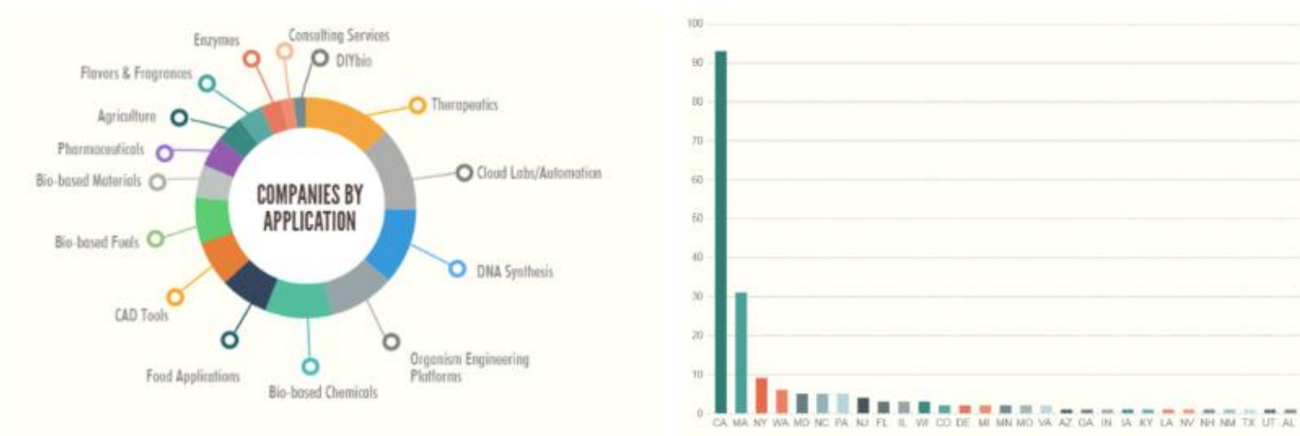

Figure 4.3 Distribution of applications and geography for US synthetic biology start-ups in 2016 [37]

US incubators and accelerators

The US is also home to the most well-funded and experienced start-up incubators and accelerators listed below.

- Indi Bio
- SOSV the Accelerator VC
- Y Combinator
- Onestart
- Singularity University Labs
- Qb3@953
- Illumina Accelerator
- Johnson & Johnson Innovation - JLABS

Key Industry Players in US Synthetic Biology Market

Prominent industry players are also very active in the US through their internal research efforts and collaborations with academia and government programs. They are often the source of corporate venture capital and an acquirer of start-up companies and technologies. Below are some of the most active; note, many of these were synthetic biology start-ups themselves not long ago.

- Thermo Fisher Scientific Inc.
- Twist Bioscience
- Synthetic Genomics, Inc
- Codexis, Inc.
- Agilent Technologies, Inc.
- Cyrus Biotechnology Inc.
- ATUM
- TeselaGen
- Arzeda
- Integrated CAN Technologies, Inc.
- Synthego Corporation
- Creative Enzymes
- New England Biolabs
- Amyris Inc.
- E.I. Du Pong De Nemours and Company
- Genscript USA Inc.
- Integrated DNA Technologies Inc.
- Intrexon Corporation

United Kingdom

The UK is second only to the US regarding the number of publications produced on synthetic biology. There have been significant trans-Atlantic collaborations between several UK universities and MIT in particular, and UK researchers and universities are very active in international competitions and conferences.

Unlike the US, the UK government funding is primarily from the UK Engineering and Physical Sciences Research Council (EPSRC) and the UK Biotechnology and Biological Sciences Research Council (BBSRC) and is more strategically coordinated across consortia and key synthetic biology research centers.

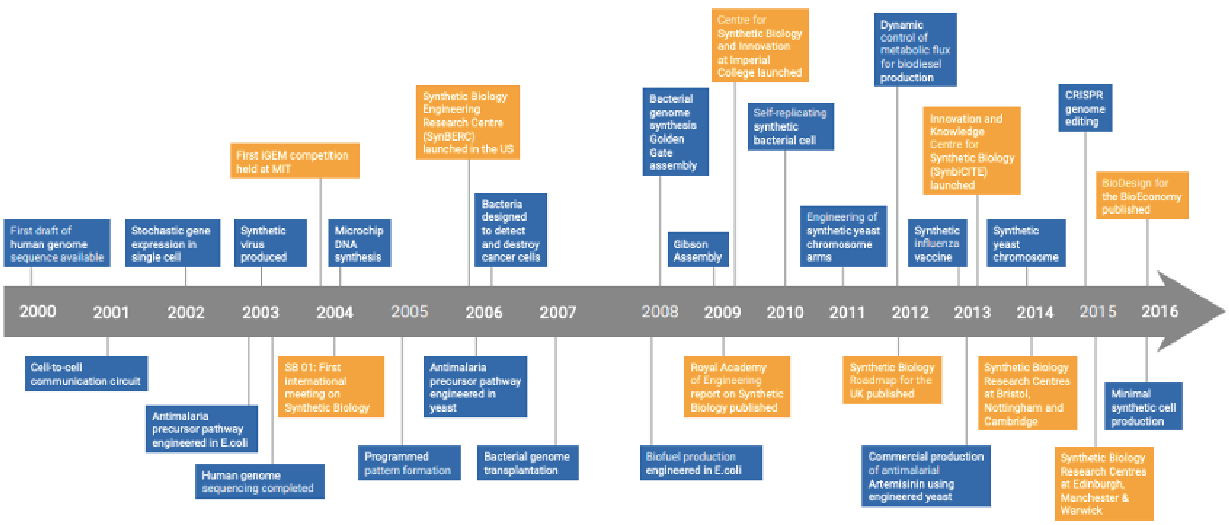

Figure 4.4 Timeline of major UK synthetic biology programs and other synthetic biology milestones through 2016 [38]

UK Consortium - SynbiCITE

Like the Synberc/EBRC in the US, the UK has SynbiCITE (http://www.synbicite.com/) based at Imperial College London. It is intended to be the UK's national industrial center for synthetic biology and is designed to be an effective industrial translation engine, bridging the gap between university-based research and industrial processes to create products and jobs through the industry. It provides a national center of expertise in technology development and commercialization and a nucleating point to benefit the UK economy.

SynbiCITE was established as a synthetic biology accelerator in 2013 with a £28 million commitment from Engineering and Physical Sciences Research Council (EPSRC), Biotechnology and Biological Sciences Research Council (BBSRC), Innovate UK, and its industrial and academic partners.

- The goal of SynbiCITE is to create a globally renowned national resource of interacting partners from academia, industry, and business, which accelerates the commercialization of world-class science and the emerging technologies encompassed by engineering biology into new products, tools, processes, and services.

- Their membership consists of a wide range of academic and industrial partners – including large corporate partners and a network of innovative small to medium-sized companies – collaborating to develop and commercialize synthetic biology research, identify routes to market, and build core skills. Currently, membership consists of 26 Universities, 46 Industry participants, and 26 supporting partners. A complete list of members can be found at http://www.synbicite.com/collaboration/Partners/.

SynbiCITE also organizes an annual synthetic biology conference focused on EU issues and participation known as SynbiTECH https://www.synbitech.com/.

Key UK Synthetic Biology Research Centers

The first synthetic biology research center was established in 2009 at Imperial College. Subsequently, the UK government committed to develop additional centers and initiated a "Synthetic Biology for Growth" program that held two annual competitions in 2013 and 2014 for universities to compete for funding for new centers. At each competition, three new "Synthetic Biology Research Centers (SBRCs)" were awarded with five-year funding commitments. Together with the original center at Imperial College these make up the seven major multidisciplinary synthetic biology hubs across the UK.

Each SBRC has its own cooperative network of research groups and smaller centers. There are over 30 universities that belong to one or another SBRC across the country. This networked environment has brought together the critical mass of diverse researchers necessary for synthetic biology, has inspired individual universities to make significant investments in synthetic biology and has attracted funding from industry and international grants. The seven centers and their missions are listed below.

- Imperial College - Center for Synthetic Biology
  https://www.imperial.ac.uk/synthetic-biology/centre/

  The Centre for Synthetic Biology and Innovation at Imperial College London was the first synthetic biology center to be established and applies a twin-track research strategy to engineering biology to develop platform technologies and applications. Platform technologies include information systems, standards (SBOL and DICOM-SB), characterization protocols (BioParts, devices, and chassis), and DNA assembly. Application areas include biosensors, biocomputing, production therapeutics, cell-based therapies, advanced biofuels, and biomaterials.

- University of Edinburgh – UK Centre for Mammalian Synthetic Biology
  https://www.ed.ac.uk/biology/mammalian-synbio

  UK Centre for Mammalian Synthetic Biology at the University of Edinburgh is building expertise in cell engineering tool generation, whole-cell modeling, computer-assisted design and assembly of DNA, and high-throughput phenotyping to enable synthetic biology in mammalian systems. Applications include tools and technologies for commercial exploitation by the pharmaceutical and drug testing industries, diagnostics, novel therapeutics, protein-based drugs, and regenerative medicine.

- University of Warwick – Integrative Synthetic Biology Centre
  https://www.wisb-uow.co.uk/

  The Warwick integrative Synthetic biology center addresses specific, industrially relevant design challenges across the scales of biological organization; genetic circuits, pathways, cells, and multi-cellular systems, also providing us with a better understanding of some of the critical mechanistic and evolutionary principles underpinning living systems. Application areas include pharmaceuticals, high-value and commodity chemicals, treatments for disease, environmental bioremediation, bioenergy, and food security.

- University of Bristol – BrisSynBio
  https://www.imperial.ac.uk/synthetic-biology/centre/

  BrisSynBio focuses on biomolecular design and assembly using synthetic biology. Including rational design and engineering of nucleic acids, lipids, peptides, and proteins as structural, enzymatic, and regulatory components in new biological and bioinspired systems. Application areas are: producing agrochemicals, pharmaceuticals, and fine chemicals; designing new vaccine platforms; developing products; and establishing new methods to increase wheat yields.

- University of Nottingham – Synthetic Biology Research Centre
  https://sbrc-nottingham.ac.uk/about/about.aspx

  The Synthetic Biology Research Center at the University of Nottingham focuses on microorganisms already able to synthesize fixed-carbon products from single-carbon gases, then applies synthetic biology approaches to engineer-in enhanced chemical products for industrial use. Applications include the sustainable production of chemicals and biofuels. This approach reduces reliance on petrochemicals, reduces climate change, and exploits waste.

- SYNBIOCHEM, University of Manchester
  https://synbiochem.co.uk/facilities/

  Synbiochem – University of Manchester Synthetic Biology Research Centre for fine and specialty chemicals uses predictive synthetic biology to develop faster, more predictable, novel routes to fine and specialty chemicals production (including new products/intermediates for drug development, agrochemicals, flavor/fragrance components, and new materials), and through industrial collaborations, help propel chemicals/natural products production towards "greener' more sustainable manufacturing processes.

- University of Cambridge, The John Innes Centre, and The Earlham Institute
  OpenPlant Synthetic Biology Research Centre
  https://www.openplant.org/

  OpenPlant, a collaboration between the University of Cambridge, the John Innes Center, and The Sainsbury Laboratory in Norwich, accelerates open technologies for plant synthetic biology and applies these to generate novel plant traits. Applications include metabolic engineering for high-value products and foundational work to improve bioenergy sources and enhance photosynthesis and nitrogen fixation.

UK Startups

The UK produced more than 146 synthetic biology start-ups between 2000 and 2016. On average, the number of synthetic biology companies has been doubling every five years, so it is projected that there will be approximately 300 by the end of 2021.

More than half (52%) of new start-ups are tech transfer start-ups from universities, with synthetic biology research centers creating the majority. However, the creation of non-tech transfer start-ups is outpacing traditional tech transfer start-ups, indicating that the innovation ecosystem has become self-sustaining in support of entrepreneurs in the UK.

Below are some statistics on the UK synthetic biology start-up community 2019 [39].

- The number of synthetic biology start-ups is up 28% in the past five years
- 83% of start-ups are technology or IP based
- Top sectors include Health Tech, Tools and Services, Chemicals and Energy
- 37% are at seed funding stage, 26% at venture funding stage
- 15% of start-ups have exited, 4% IPO, 11% acquired
- 33% of recent start-ups have attended an accelerator
- 8% synthetic biology start-up founders are female
- $372m invested in equity finance in 2018
- Average deal $13.7m
- 57% of equity funding went to health tech
- Significant foreign investment – in over 50% of funds raised
- 84% of equity investment was at seed or venture stage
- The average amount of equity taken is 26%
- 82% of synthetic biology start-ups are located in the south of the UK clustered around Oxford, Cambridge, and London Universities

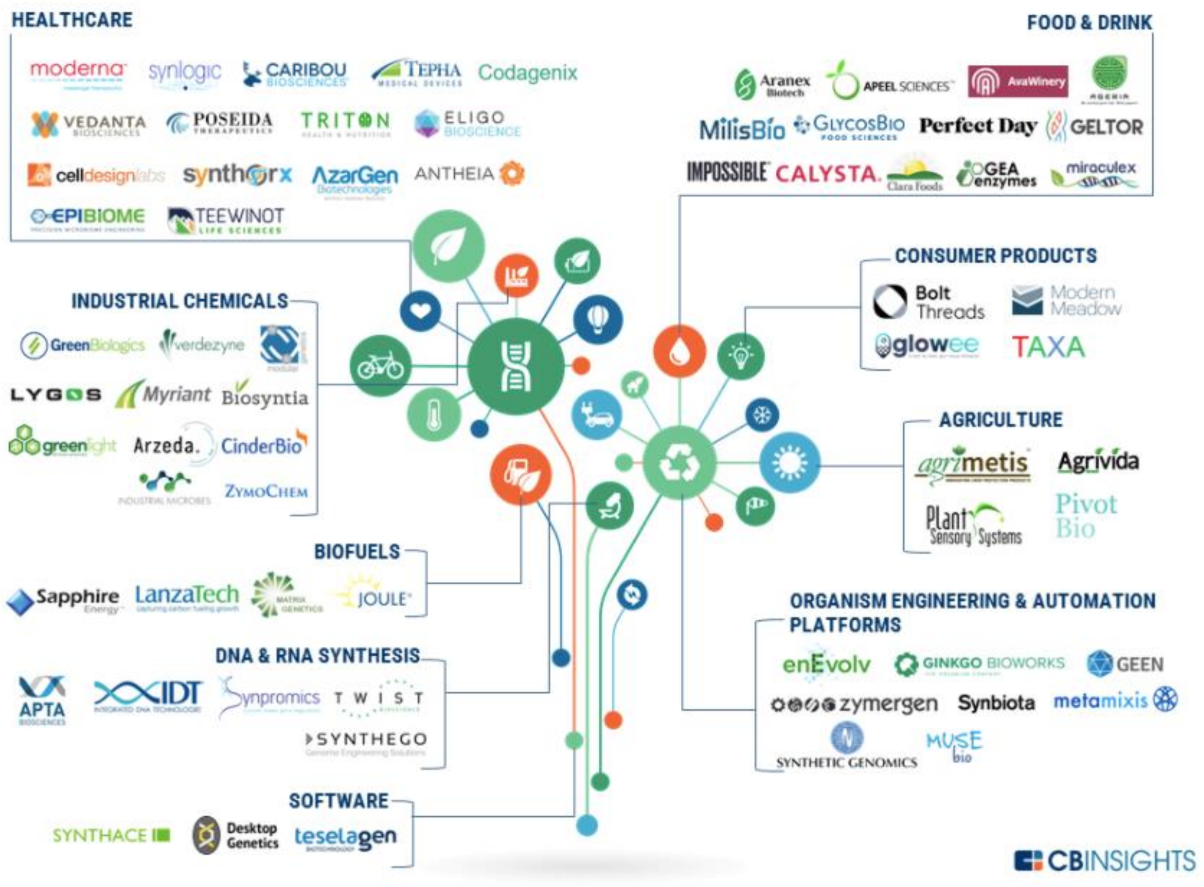

Figure 4.5 Top start-up companies in the UK [40]

Singapore

Government Funding

The Singapore government has injected two waves of funding to enable an active and growing synthetic biology ecosystem. The first set of appropriations occurred in 2014 when the Singapore government formed a national task force focused on synthetic biology. The result was a funding program from the National Research Foundation (NRF), which initially provided funding for six projects, including the SynCTI and SYNERGY projects detailed below.

The NRF launched a second program in 2018 funded at the level of SGD 25m (US $19m) over five years which was awarded to the Temasek Lifesciences Laboratory (TLL). TLL is a non-profit philanthropic research organization focused on the development and physiology of plants, fungi, and animals as a foundation for biotechnology innovation. The TLL synthetic biology programs funded to date focus on three areas:

- Synthetic cannabinoids
- Producing rare fatty acids
- Developing new strains of microorganisms for industrial products

In addition, grants worth up to SGD 500k are available for synthetic biology researchers who collaborate with Chinese peers in collaboration with the National Natural Science Foundation in China.

According to industry observer John Cumbers, CEO of SynBioBeta, "Singapore's biggest edge of the US comes from its educated workforce and its synthetic biology national strategy. The US doesn't have a coordinated research program in synthetic biology like Singapore" [41].

*A*STAR – Agency for Science, Technology, and Research*

A*STAR (formerly known as National Science and Technology Board – NSTB) was established in 1991 and under the Singapore Ministry of Trade and Industry. A*STAR's mission is to support R&D aligned to competitive advantage and national needs for Singapore. The technology domain of Health and Biomedical Sciences (HBMS) is responsible for synthetic biology development in general. The Biopolis hub for biomedical sciences, opened in 2003, consists of scientists and researchers, technical and staff, and industry development commercialization staff. The Biopolis complex also houses other corporate research labs such as Novartis, Danone, Abbot, Procter & Gamble.

Biopolis also plays an essential role as an incubator and accelerator for biotech start-ups. At Biopolis, start-ups have access to facilities designed to incubate, develop, train, and support entrepreneurs. Start-ups also have access to life science labs with facilities and equipment they may not otherwise be able to afford. A*STAR also contributes to the talent flow in the biotech ecosystem by seconding promising researchers to these start-ups.

A*STAR's Singapore Institute of Food and Biotechnology Innovations (SIFBI) has supported two example synthetic biology start-ups in the alternative protein space. Sophie's BioNutrients uses microalgae and patent-pending technologies to develop 100% plant-based & sustainable alternative protein for the food industry and opened its first urban protein production facility in 2020. Shiok Meats is another A*STAR supported start-up that aims to become the first company in the world to bring shrimp grown in a laboratory to market.

Synthetic Biology Clinical and Technological Innovation (SynCTI) center

In 2015, the SynCTI center was established at the National University of Singapore and consisted of a suite of research programs, including a biofoundry capability to accelerate the DBTL cycle (https://syncti.org/). In 2017 SynCTI was the host and local organizer of the 7th International Meeting on Synthetic biology, SB 7.0 (http://sb7.info).

In 2018, Wilmar, one of the world's largest oligo chemical manufacturers from palm oil, established the WIL@NUS corporate laboratory in conjunction with SynCTI. This research center aims to use synthetic biology to convert palm oil industry waste into high-value products using engineered microbes.

Singapore Biofoundry capabilities

The biofoundry facility at SynCTI encompasses high-end robotic tools for protein purification, performing enzyme stability assays, analyzing protein-ligand interaction, and quantitative evaluation of biomolecules with highly sensitive assay platforms. The biofoundry is also used to develop effective scale-up processes by developing and testing optimal parameters required to scale up from pilot fermentation processes to grow and produce microbial and mammalian cells.

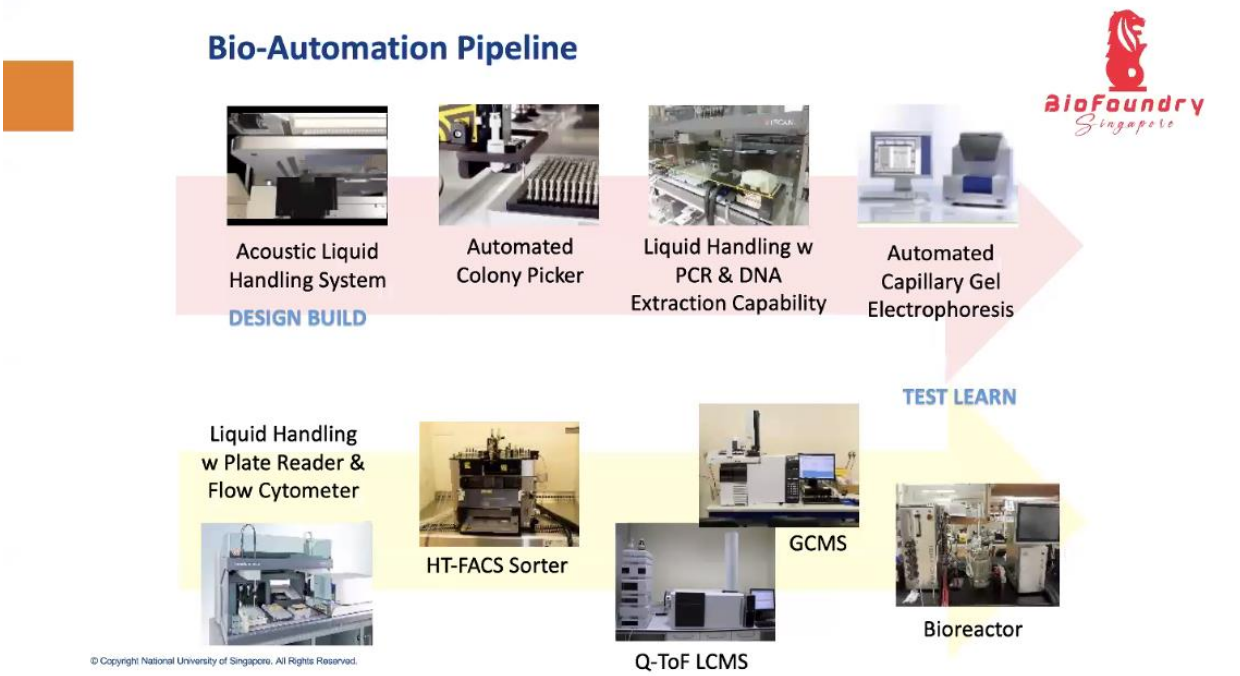

Figure 4.6 Capabilities of Singapore's BioFoundry, located in the Synthetic Biology Clinical and Technological Innovation (SynCTI) center at NUS [42]

SINERGY Consortium

In 2016 the Singapore National Research Foundation provided funding to NUS to establish a synthetic biology consortium named SINERGY to consolidate Singapore's capabilities. The consortium is intended to proactively encourage interaction and co-development between industry, academia, and government research institutes. The goal is to augment human resources development for the bioeconomy and speed up the translation of expertise for industrial biology applications [43]

The consortium consists of the following members presently:

- National University of Singapore
- Nanyang Technological University
- Singapore Institute of Technology

- Ngee Ann Polytechnic
- Singapore Polytechnic
- Republic Polytechnic
- A*STAR – Agency for Science, Technology, and Research
- Agilent Technologies
- Singer Instruments
- Metagenom Bio Life Science
- Olink Proteomics
- Twist Biosciences
- Illumina
- Givaudan
- Bio Basics Inc.
- Engine Biosciences
- Becton Dickinson
- H-GEM
- Huaguang Energy
- AdvanceSyn Synthetic Biology
- Merk
- Nestle
- Wilmar
- ThermoFisher Scientific
- Phidco – Philippine International Development Inc.

In addition, SYNERGY is also affiliated with the following international associations.

- ASBA – Asian Synthetic Biology Association
- Global Biofoundries Alliance
- Synbicite – UK Center for adoption and use of synthetic biology
- BioRoboost – EU standards-setting organization
- EBRC – US Engineering Biology Research Consortium

Comparison to Thailand's Synthetic Biology Ecosystem

In all three countries profiled, the pattern is similar. The national government initiates the building of infrastructure necessary for synthetic biology to be performed. In the US this was done in an uncoordinated fashion according to the agendas of the various funding agencies (DOE, DOD, NSF, NIH), whereas in the UK and Singapore, the funding efforts were more coordinated and directed.

In each case the outcome was the creation of synthetic biology centers, typically housing biofoundry capabilities. This leads to a galvanization of research and technological skills, the building of a community, the attraction of industry, and the education of next generation synthetic biologist.

Subsequently, waves of startups emerge from these ecosystems and start to attract substantially more capital than the original funding. It is estimated that in the US, the government has collectively invested $2.1b over the past 15 years. In the last 10 years alone, the private sector has invested over $21b in startups showing the multiplicative power of the initial government funding.

The key lesson learned by observing these ecosystems, is that government funding that establishes synthetic biology research centers in turn leads to the development of consortia, and finally to the spawning of a vibrant startup community.

Singapore is at a less mature state than the US or UK, and their ecosystem does not yet match that shown in Figure 1.5 which is for a mature deep tech ecosystem, such as present in the US and UK. This mature ecosystem has the startup community as the central engine of growth and innovation. Below is a modified version of the synthetic biology ecosystem that is currently present in Singapore. In this model, a consortium is the central driving organizational element. This model is also likely to be the most appropriate for Thailand to seek to build initially.

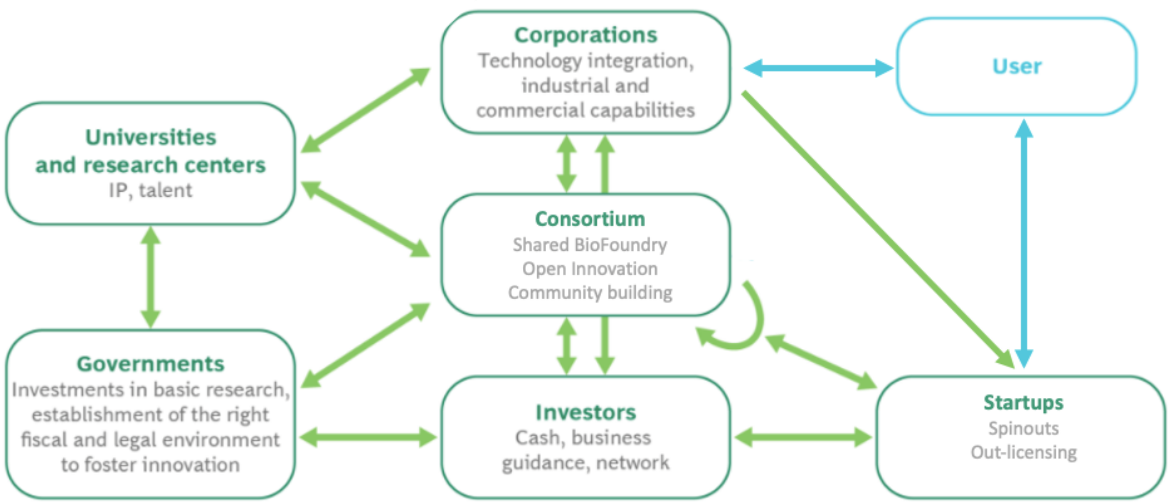

Figure 4.7 – Less mature synthetic biology ecosystem where a consortium takes the central driving force role.

In comparison to the above three ecosystems, Thailand is currently in a less advanced position. Through the interviews it is apparent that even the concepts of synthetic biology are not widely understood, and most often misunderstood to be synonymous with simple genetic engineering. Almost all individuals involved in synthetic biology in Thailand are in academia or government labs.

Thai Corporates in Synthetic Biology

On the corporate side, this investigation only uncovered one company, BioNet, which actually is creating products using the principles of synthetic biology, that being a DNA based COVID-19 vaccine currently in phase 1 trials in Australia. The key to BioNet being able to develop its own synthetic biology derived vaccine had its origins in a previous collaboration between BioNet and the Pasteur Institute in France on Zika DNA vaccines. It was by collaborating at the R&D level that the knowledge and skills to build DNA vaccines was transferred, which could then subsequently be scaled up using BioNet's manufacturing capabilities. This may be a model for other Thai companies to develop technology transfer strategies. This requires having staff and facilities that can contribute to cutting edge international synthetic biology research.

BBGI, which is a joint venture between Bangchak and KSL is also at the forefront of synthetic biology in Thailand. It recently invested THB 800m in a US synthetic biology startup Manusbio whose first product, a synthetic biologically produced stevia sweetener molecule, will be produced in Thailand.

Thai industry in general is not presently very enthusiastic about the potential of synthetic biology. In general, they see it as a far-off potential that they might monitor, but don't expect it to impact their business for 5-10 years. This is particularly true of the petrochemicals industry and large agriculture concerns. There is some corporate venture capital being invested in promising startups, primarily in the US, but very little promise of technology transfer. The model of most large corporates have is to look for a biological product with a TRL level of 7+ that they can partner with and act as a production partner, not involved in the early product development. Additionally, foreign startups will not share their IP, and worry about IP protection in Asia

Synthetic Biology Startups in Thailand

As profiled in chapter 2, there are a few (five found in this investigation) start-ups that have be identified that have the potential to adopt synthetic biology, but at this time all are using naturally found microorganisms for producing their products without significant genetic modification. All of these enterprises could benefit from synthetic biology capabilities and take their initial products as a starting platform for product extensions through genetic modification. However, the barriers of trying to do it themselves without available infrastructure or funding are overwhelming. Most of these start-ups are spun out of universities, typically led by a university researcher who cannot devote full time to these ventures due to their additional teaching and research obligations.

There is one notable exception to this start-up model and that is JuiceInnov8. Instead of being started by a professor, this came from a young entrepreneur, previously involved in digital technologies, looking for something unique in the biological space. The founder teamed up with a university food scientist who was developing a technique to remove sugar from fruit juice using yeast. Unfortunately, JuiceInnov8 was unable to raise significant capital in Thailand and didn't find the support networks sufficient and instead went to the US to participate in incubators and accelerators there. After gaining significant confidence in the product technology and business plan, the choice of whether to grow the company in the US or Thailand was one of stark economics. They calculated that it was five times more expensive to operate in the US, so they returned to Thailand, even given the infrastructure limitations. They are now looking to ramp up to production levels but find it very difficult to produce in Thailand due to the lack of appropriate contract manufacturing facilities.

As described in chapter 3, there are substantial bioreactor facilities available at university and government labs that can support elements of the synthetic biology development, but they are not well integrated and important pieces are missing, such as a biofoundry and larger scale contract production facilities. The production facilities that do exist are targeted to biopharmaceuticals and are too expensive and have requirements that are not necessary for companies wishing to produce food or cosmetic ingredients, or specialty chemicals.

There are few investors in Thailand willing to invest in deep tech, and even fewer willing to invest in biotech type ventures. The issue of long development cycles, and their inability to evaluate risk of biotech ventures increases their hesitancy. The investors interviewed said they would look to a knowledgeable investment lead, likely from the US, to take a stake first before they would follow as secondary partners. That said, it isn't likely that US venture funds would be scouting in Thailand when there is such a rich start-up ecosystem in the US to choose from.

Chapter 6 will discuss some recommended actions that can help progress the Thai synthetic biology ecosystem towards higher levels of capabilities. The Singapore ecosystem serves as a relevant model to learn from, and potentially collaborate with to build a regional capability.

Deep tech investment

The venture capital investors in Thailand are generally not interested in smaller companies, especially during COVID, as they are less willing to take risk and want more certainty with companies that have already been established and have a history of growth. This lack of VC attention is particularly acute for deep tech startups, such as those related to synthetic biology. Instead, the Thai corporate venture groups tend to focus on foreign start-up companies, particularly in the United States, as those companies have access to resources required to grow the business. The effect of this is to leave Thai start-ups devoid of funding and support and reducing Thai corporate engagement to primarily financial investment, or at best toll manufacturing collaboration. US start-ups are very wary of losing control of their IP to Asian partners as it is not possible for them to differentiate between the IP integrity of different Asian nations.

This is evident in the investment philosophies encountered with GC Ventures, Mitr Phol, SCG and PTT. Corporate VC managers report seeing a lot of deep tech deal flow from Singapore, nothing from Thailand. When interviewed, most corporate VC managers are unaware of any Thai synthetic biology startups except for Juiceinnov8 which made an active, largely unsuccessful, attempt to attract domestic Thai corporate VC capital. Instead, Thai corporate VCs are looking at US companies such as Demetrix formed by one of the founders of Amyris, Jay Keasling, focused on the biosynthesis of cannabinoids. Meanwhile there is significant cannabinoid research occurring in Thai university labs that is not receiving significant corporate attention. Similarly, Thai corporates in the aquaculture industry are looking to American startups using synthetic biology to convert carbon dioxide waste streams into high quality proteins and omega 3 fatty acids for more sustainable fishmeal for their fish farming operations.

PTT recently announced the formation of a subsidiary called Innobik LLC that is a channel to invest in international pharmaceutical business in order to develop PTT's capabilities in life science. Their first investment is in Lotus Pharmaceutical, a Taiwanese manufacturer of generic drugs. Innobik has also entered into a joint venture with NR Instant Produce PCL to operate an alternative protein company focused on plant-based proteins. However, neither of these investments indicate an interest in further synthetic biology investment and rely on conventional technology.

Thai corporates would rather participate in the US synthetic biology ecosystem than develop their own products locally, showing their preference for lower risk, high TRL technologies. What local development they do invest in, is typically for low value commodity type biochemical and biofuel type applications. Outside of corporate VC funding, the only other source of venture funding in Thailand are the banks, who want only quick win, not long-term investments.

Chapter 5 – Human Resources

Skills Challenges for Synthetic Biology Ecosystems

Cross-disciplinary skills

Synthetic biology is a cross-disciplinary field that necessitates skills across a wide range of disciplines that are not typically integrated in a single academic program or individual.
The challenge is to develop those trained in the biological sciences to have a more engineering approach, and those trained in the physical sciences to have more biological appreciation. For example, synthetic biology has become a "big data" science, requiring biologist to have skills in handling large datasets and data mining. Likewise, engineers have to develop a solid understanding of modern molecular biology and appreciate the fact that biology has significant complexity and variability and does not lend itself to standardization as easily as physical systems.

Synthetic biology requires skills grounded in genetics, molecular biology, systems biology, microbiology, biochemistry and analytical chemistry. These biological skills need to be applied using engineering quantitative techniques of mathematics, computing, bioinformatics, biostatistics and advanced computational modeling and simulation. Furthermore, to enable the rapid DBTL cycle discussed in previous chapters, additional skills are needed in engineering, robotics, software engineering, artificial intelligence and machine learning in order to support high throughput synthetic organism construction and testing.

If synthetic biology is to move from laboratory to commercial application, there are additional business and production skills required. Synthetic biology entrepreneurs will need skills in management, financing, risk assessment, biosafety and regulatory issues. Scaling beyond the lab to commercial volumes will require further advanced automation, chemical and biochemical engineering knowledge, fluid mechanics and thermodynamics which become very critical as bioreactor volumes increase to production scale.

From the research conducted for this report, it appears that the preferred solution for integrating and developing these cross-disciplinary skills is to form research centers where scientists, engineers, and business skills can overlap and synergize. At the core of these synthetic biology research centers is typically a biofoundry capability that not only enables the rapid DBTL cycle but mandates the intimate collaboration of the myriad skill sets in order to best utilize the potential of such a facility. An extension or separate center focusing on the scale-up issues would likewise bring together other skill sets and perform the same function of collaborative conversion of technologies required for scale-up success.

Fast evolving knowledge base

Synthetic biology is a very fast-growing field and new breakthrough technologies are being developed rapidly at the key research centers in the US, UK, EU, China, Japan, and Singapore. It is important for Thailand to continue to support graduate studies abroad in synthetic biology related fields as it cannot be expected that Thai graduate training programs can be self-sustained at the cutting edge of all aspects of synthetic biology. What was cutting edge five years ago in synthetic biology is largely usurped by new technology now. The only way to keep the Thai academic community current is a continual repatriation of foreign trained synbiologists and engagement with the global synthetic biology community.

Training in Thai universities is also important to maintain the core knowledge and skill infrastructures, but there needs to be more inter-discipline integration. An example of an integrated course taught at the graduate level at MIT is “How to grow (almost) everything” which covers the diverse areas that enable synthetic biology [44].

Synthetic Biology opportunities at undergraduate and secondary levels

There are several international programs that have been developed specifically to engage undergraduate and secondary level students around the concepts and interdisciplinary nature of synthetic biology. Some of these programs, such as iGEM, has already had some Thai student participation, others may serve as models for future development going forward. By encouraging interest at the undergraduate level, there will be both a stronger work force for operations, and a larger number of students interested in advanced studies in fields related to synthetic biology.

iGEM
www.igem.org

The International Genetically Engineered Machine (iGEM) competition was established in 2004 at MIT. The competition has increased in size from 31 students (5 teams) in 2004 to 5,500 students in 2017 (310 teams), which compete and present their work at the annual jamboree. The iGEM competition is run by an independent, not-for-profit organisation dedicated to the advancement of synthetic biology, education, and the development of an open, cooperative community and friendly competition.

The purpose of iGEM is to challenge teams of students from around the world to develop useful tools using synthetic biology and contribute their novel components to the open repositories. Multidisciplinary teams compete to build, design, test and measure their own designs using biological parts and standard molecular biology techniques. Parts that are produced are added to the BioBricks registry and are provided as open source parts to the synthetic biology community.

Competitions like iGEM form an important component towards encouraging young students to pursue careers in the area of synthetic biology. The issue with traditional undergraduate programs that relate to synthetic biology is need for higher levels of interdisciplinary integration. Encouraging broader undergraduate education, as opposed to narrow technical training, will have strong positive effects beyond synthetic biology to other emerging fields which also increasingly require cross-discipline coordination.

Dr. Puey Ounjai, Head of the Center of Nanoimaging at Mahidol, is one of the coordinators of iGEM teams here in Thailand, focused on the high school segment. There has not been much interest at the undergraduate level as students feel they are too busy for such a time-consuming competition. An additional difficulty encountered is that these projects typically require cross lab collaborations and some level of funding which teams either have to raise themselves, or occasionally can leverage existing research budgets. Recently, Thailand had a team from the International Community School (ICS) in Bangkok win a bronze award [45].

BIOMOD
www.biomod.net

BIOMOD is a biomolecular design competition for students created by the Wyss Institute for Biologically Inspired Engineering at Harvard University. It is a similar competition to the iGEMS but smaller in scale and focused on developing self-assembling biological macromolecules (RNA, DNA and proteins) into nanoscale machines (for example using DNA origami) to create molecular robotics and nanoscale therapeutics.

BioMaker Challenge
www.synbio.cam.ac.uk/biomakerchallenge

The BioMaker Challenge is a more recent competition hosted by the University of Cambridge, John Innes Centre or the Earlham Institute. The Challenge encourages interdisciplinary teams to interface synthetic biology approaches with electronics, 3D printing, and instrumentation to develop low-cost sensors and instruments for biology. Teams from the University of Cambridge, John Innes Centre or the Earlham Institute are provided with four months lab support to undertake the projects. There is a focus on developing cheap solutions and open source sharing of information and inventions. It is open only to teams headed by members from University of Cambridge, John Innes Centre or the Earlham Institute, but it is planned that the program will expand beyond the three organisations.

FREAK Lab
https://freaklab.org/

One program developed in Thailand is the Futuristic Research Cluster (FREAK Lab) started in 2017 at King Mongkut University of Technology Thonburi (KMUTT). It is a cross-disciplinary research cluster that converge arts, science, and technology for thinking beyond and exploring the the symbiotic relationship between human and the emerging technologies. An example recent project is "Space TH" in collaboration with MIT Media Lab. This project will launch a small cube containing DNA designed and assembled by Thai students which encodes a popular Thai song. They purpose is to determine if DNA damage received while in space will corrupt the storage of the digitized music. The average age of the team members was 19 [46].

Intellectual Property skills development

There is a need to improve intellectual property strategies in Thailand to assist deep tech development including synthetic biology. In particular, technology transfer professionals need to be very familiar with the Patent Cooperation Treaty (PCT). The PCT allows for an inventor to first file a brief under the PCT which the patent office will review and issue a search report indicating if the invention was novel or previously reported. The cost for this report is typically US$ 5000. The report is accepted by all countries that are signatory to the Paris Accord treaty and provides a green light for submission of patent applications to those individual countries. Vistec is one example of a program taking advantage of the PCT filing process.

There was an example program conducted around the year 2000 in Thailand called the ECAP (European Cooperation Asia Pacific) program that brought European IP experts to Thailand for 2 weeks, trained a number (25-30) of young IP legal staff, then gave them homework and returned 1 year later for assessment. It is estimated that today, half of this class form the Sr. Partners at Thai IP law firms.

Corporate Skills development

The case previously described where BioNet developed sufficient synthetic biology skills to compete in the COVID nucleic acid vaccine development space is a prime example of "learning by doing". In their case, it was the overlap of research collaborators from their own internal corporate lab, with researchers at the premier Pasteur Institute in France. By working together to develop a Zika DNA vaccine, the Thai researchers gained sufficient knowledge that was later translated to the COVID situation.

Traditionally in Thailand, large corporates have looked for technology partners who already have a very advanced technology and are less interested in investing in joint R&D where tech transfer is more likely to occur informally. Opportunities for collaboration between Thai Universities and Thai corporate R&D need to move beyond the ceremonial MOU phase and develop significant contractual collaboration research agreements and commercialized results. If possible, Thai corporates should also seek to collaborate with international R&D groups, both regional, Singapore, Australia, Japan, S. Korea, China, and with premier centers in the US, UK and EU.

Below are two accelerator programs in the UK and the US that are targeted at more corporate and start-up participation in synthetic biology projects.

Bio-start
www.bio-start.uk

Bio-start is an annual not-for-profit competition designed to commercialise the engineering of biology through an accelerator program. It is hosted by SynbiCITE, a synthetic biology commercialisation institute based at Imperial College in London, UK. The competition is a 10-week intensive program that includes mentorship, entrepreneurial training, workshops and access to global networks and opportunities. The competition seeks applications from businesses and researchers in industrial biotechnology, clean technology, agriculture technology, healthcare, or any sector where engineering DNA is an essential component and makes use of synthetic biology. Applicants must demonstrate that they can license the relevant intellectual property and have support from their technology transfer office or employer.

LEAP
www.synbioleap.org/

In the US, a program called “The Synthetic Biology Leadership Excellence Accelerator Program” (LEAP) was established in 2012 envisions catalyzing a next generation of leaders in biotechnology to drive the responsible development of the field. In addition to building a cadre of young professionals taking on leadership roles in the synthetic biology community, LEAP aims to create sustainable tools and mechanisms for engaging a broader range of practitioners in the societal role of biotechnology development.

Chapter 6 – Recommendations

The Thailand synthetic biology ecosystem is presently sparse and highly fragmented. It lacks vital infrastructural elements and has insufficient collaboration between the skilled resources that exist to be self-perpetuating. Thai government investment is recommended to fill value-chain gaps and develop an integrated synthetic biology capability and community. The development paths of other synthetic biology ecosystems reviewed in chapter 4 of this report were all government-led because of recognizing the strategic imperative of maintaining competitiveness in next-generation biologics manufacturing capabilities.

The key recommendations that have emerged from the reviewing both technical literature and over 50 interviews are as follows:

- Thailand should establish a shared, open Synthetic Biology Institute that develops and maintains an integrated biofoundry facility,
- Thailand should solicit and fund Flagship Synthetic Biology Programs that utilize the Institute's biofoundry capabilities for accelerated bioproduct development,
- Thailand should promote precision fermentation contract development and manufacturing organization (CDMO) capabilities to leverage emerging scale-up facilities and enable commercial production of high value, low volume bioproducts, and
- Thailand should invest in building an early-stage, consortium-driven, synthetic biology ecosystem similar to and synergistically collaborating with Singapore and other ASEAN countries.

Synthetic Biology Value Chain

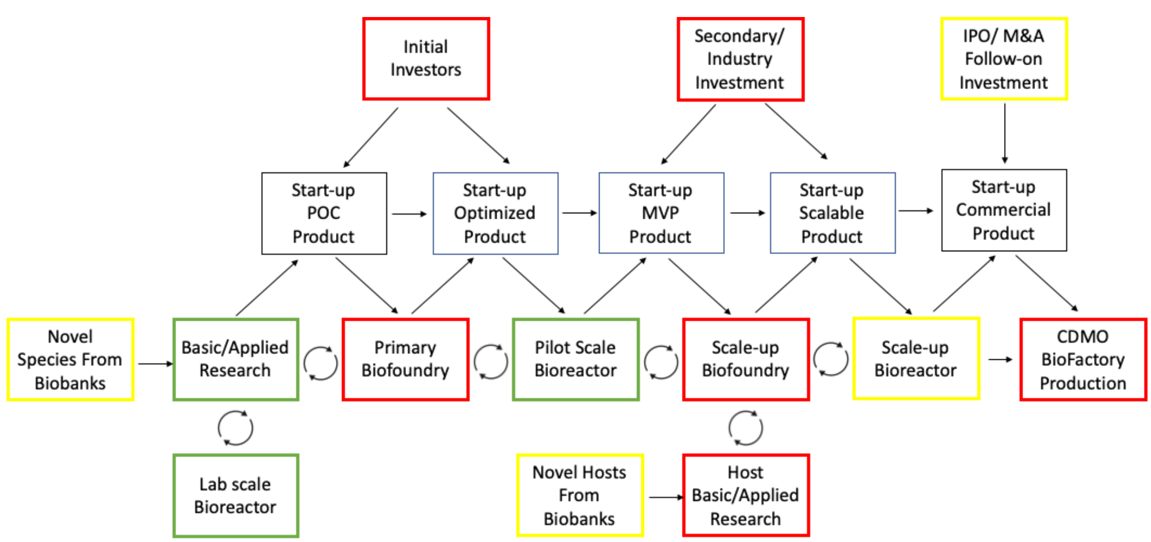

Figure 6.1 Illustration of synthetic biology value chain. Green color represents capabilities that are already present in Thailand, Yellow have some capability, and Red are missing capabilities

Figure 6.1 represents the synthetic biology value chain and the current status of each component in the present Thailand Synthetic Biology ecosystem. In order to advance products from early stages of product development (TRL 1-3) through development (TRL 4-6) and finally into production (TRL 7-9) key capabilities are required.

The process starts with basic and applied research performed at academic, governmental, or industrial research facilities. These capabilities currently exist in Thailand, perhaps not to the same extent as in the US, UK or Singapore, but sufficient for the current stage of synthetic biology development in Thailand. The issues is under-utilization, under-funding, and the independent non-integrated style of research. Many of these laboratories have access to lab scale bioreactors suitable for demonstrating proof of concept synthetic biology capabilities.

One of the inputs into this basic research capability is novel species from biobanks. The biobanks exist in Thailand as documented in Chapter 3, but critically the strains in the banks are missing critical meta-data elements that would allow for selection of potential strains for specific synthetic biology development. For example, a researcher may require a host strain that has resistance to elevated pH, or is known to produce certain secondary metabolites. This information is currently not cataloged and would add significant value to the collections currently housed in biobanks in Thailand. The same is true for later stages of development where robust microbes suitable for scale-up need to be identified. This is also important for intellectual property development, otherwise product developers will have to incur licensing fees for usage of strains developed elsewhere.

Following proof-of-concept product development there is a need for product optimization which is the role of the primary biofoundry. This concept is also discussed in detail in Chapter 3 so won't be described further here. The creation of public biofoundry facilities is possibly the key enabler for the US, UK and Singapore synthetic biology ecosystems. It would be extremely difficult for Thai companies and researchers to compete internationally without access to such a facility domestically.

Following optimization of the synthetic biology organism, the next step is to ramp up production to pilot volumes. This can result in a minimally viable product (MVP) from which start-ups and corporates can begin to assess the market potential of their technology. In order to scale production to commercial volumes it is often required to modify the host organism to be more suitable for larger scale production. This can be done by either modifying the model host used in the POC phase, or migrate the genetic engineering into a new species more adapted to larger scale commercial production. Again, bio-banks could support this migration, but require the characterization of meta-data relevant to scale up challenges.

In addition to biofoundry work for scale-up, facilities such as those being constructed for the EECi facility can be effectively utilized to develop the production process parameters. Finally, once scale up has been developed, there needs to be manufacturing facilities capable of commercial volume production. Presently there is no such contract development and manufacturing organization (CDMO) available in Thailand. This is an opportunity for either a

Thai domestic player, or an international firm to take the lead in synthetic biology manufacturing.

Establish Thailand Synthetic Biology Institute

A synthetic biology institute would serve as the focal point for a national research program in synthetic biology. It would operate as an integrated interdisciplinary platform for research collaborations across academic, corporate, government, and start-up communities in Thailand. It would also act as the entity representing Thailand in international associations such as the Asian Synthetic Biology Association (ASBA) and the Global Biofoundries Alliance.

The primary mission of this synthetic biology institute would be to foster the acceleration of synthetic biology knowledge in Thailand and develop the required integrated and automated DBTL technologies. It would also develop skilled researchers, translational capabilities and drive flagship synthetic biology research programs of strategic relevance to Thailand.

Biofoundry Facility

The biofoundry concept is central to all the synthetic biology ecosystems studied in this report. Nothing comparable to the biofoundries established in the other studied ecosystems currently exists in Thailand, although there are some individual components at discrete university labs. A biofoundry does more than accelerate the DBTL cycle time; it is also critical for developing deeper integration among the multiple disciplines and standardization required to make synthetic biology successful. It is also instrumental in building a sense of a Thai synthetic biology community. Such a biofoundry would also accomplish the following goals.

- Deliver bioproducts at suitable TRL levels for scale-up commercialization using Thailand developed intellectual property,

- Massively increase the solution space that can be examined through automation, high-speed analysis, and machine learning,

- Coordinate and galvanize a diverse group of practitioners around a shared purpose,

- Put Thailand on the world stage as a critical participant in translating high-quality synthetic biology research into commercial reality.

Having a domestic biofoundry capability will also help ensure biosecurity in the advent of future pandemics or regional outbreaks of diseases such as malaria and chikungunya and further extended to livestock diseases like avian, swine flu, or plant pathogen that may significantly impact the Thai agriculture industry. Suppose such a localized disease were to spread throughout Thailand. In that case, Thailand needs to have the independent capability to direct resources to solve its issues and develop its vaccines or other treatments. Additionally, essential economically important precursor chemicals may become in short supply due to international supply chain disruption. Thailand should also have the capability to develop alternative sources for such chemicals needed by Thai industry through available agricultural feedstocks.

Impact on SME and start-up community

A shared biofoundry would also profoundly affect the Thai biotech start-up companies profiled in Chapter 2, enabling them to become genuine synthetic biology companies. For example:

- Baiya Phytoceuticals could develop design/build/test/learn platforms that allow them to deploy and optimize arbitrary protein expression in their plant factory, faster & cheaper than anyone else.

- Bio om could also create their DBTL platforms for assembling customized microbial communities (from natural + synthetic microbes) for various remediation environments.

- UniFAH could take learnings from their Salmoguard product then use the biofoundry to expand and upgrade the capabilities of natural phages they already have in the collection to target other crucial bacterial contamination issues.

- Juiceinnov8 could put together new strains of synthetic yeasts that could remove sugar more efficiently or produce desirable bioproducts by developing novel metabolic pathways in their proprietary yeasts.

- Enzmart Biotech could expand its range of engineered enzymes and protein markers, reducing Thailand's dependence on foreign suppliers of these fundamental life science tools.

The biofoundry capability would shift these start-ups from a limited product set to platform technologies that can address whole categories of problems rather than just specific spot solutions. It offers a bridge over the “valley of death” that start-ups face as they go from TRL 3-4 to TRL 7-8.

Affiliated Academic Synthetic Biology Centers

Similar to the UK, a group of research centers could also be set up at individual universities and government laboratories with unique but complementary technology focus that contribute to the shared biofoundry competency. These could include expertise in surveying biodiversity, identifying new proteins and pathways, biocad design, metabolic modeling, genomic synthesis and editing, high-speed screening, information processing, data warehousing, and machine learning analytical capabilities. Engineering sciences such as control theory, systems engineering, microfluidics, and robotics should also be integrated into the biofoundry to accelerate the DBTL cycle. Systems biology expertise on omics scale data generation and acquisition in genome sequencing, transcriptomics, proteomics, metabolomics, glycomics, and lipidomics are other localized specialization areas that would increase the biofoundry hub's capabilities.

The path to scaling up synthetic biology to commercialization also requires substantial integration of diverse knowledge fields such as the study of transport phenomena, constitutive behaviors (mechanical modeling), convection-reaction diffusion, genome to phenome associations, disease modeling, tissue and organ systems, intracellular communication, chemotaxis, quorum sensing, self-assembly, systems pharmacology, and systems medicine.

The kernel of these centers already exists at several universities and government research facilities; however, they are typically individual labs and not cross-disciplinary collaborations. Each center should integrate two or more complementary but orthogonal disciplines that can significantly contribute to the central biofoundry capability.

Fund Thailand Synthetic Biology Flagship Projects

Having facilities such as a biofoundry or scale-up bioreactors are insufficient to catalyze a synthetic biology ecosystem. These facilities need to be animated with key flagship projects that bring the integrated skills together to create significant value in potential bioproducts in Thailand. It is recommended that a competitive grant program be established that actively encourages cross-institution, cross-disciplinary, cross-industry collaborations that will take early-stage synthetic biology technologies from lab to commercial potential.

Below are examples of flagship projects being undertaken in Singapore and US DOE-centered synthetic biology foundry capabilities.

SynCTI Flagship examples

Singapore's Institute for Synthetic Biology for Clinical and Technological Innovation (SynCTI) has defined three major flagship research programs: Cells by Design, Industrial Biosolutions, and Microbiome Based Solutions.

- The ***Cells by Design*** flagship program has three sub-focus areas: Innovative biosensors, Synthetic Genomics, and Proprietary Microbial strains. Innovative biosensors are microorganisms engineered to detect toxic compounds, metals, and biomolecules. They leverage optogenetics and thermogenetics to allow for light and temperature to control gene expression. Synthetic Genomics refers to organisms with customized chromosomal sequences to further enable engineering capabilities. SynCTI is part of the Synthetic Yeast 2.0 (Sc2.0) consortium. The third sub-focus area is Proprietary Microbial Strains, which isolate, identify and characterize novel microbial strains devoid of IP restrictions. These proprietary strains are being developed as "workhorses" for Singapore's industrial biology exploitation.

- The ***Industrial Biosolutions*** flagship program also has three sub-focus areas: Enzyme Engineering and Biocatalysis, Bioremediation and Biotransformation, and Biologics. Enzyme engineering and Biocatalysis explores and characterizes native enzymes and improves their activities to create novel functionalities. This is done through directed evolution coupled with high-throughput screening, structure characterization, and rational design tools. The bioremediation and Biotransformation sub-focus area seeks to transform waste products and low-value feedstocks into high-value products. In bioremediation, researchers are developing microorganisms that can recover precious metals from electronic waste. For biotransformation, they are focused on the fermentation production of critical intermediate chemicals that are precursors to many pharmaceutical processes. The Biologics sub-focus is developing synthetic alternatives to mammalian cell lines typically used to produce monoclonal antibodies and recombinant production of commercial biologics such as insulin and botox.

- The ***Microbiome-based Solutions*** flagship program has two sub-focus areas: Targeted Microbiome Interventions and Microbial Ecosystems. Researchers are developing live biotherapeutics for microbiome interventions, reprogramming probiotic microbial cells with engineered capabilities to sense and reverse physiological functions associated with disease. They do this by modulating the disease microenvironment. In a similar vein, microbial ecosystem research focuses on identifying key gut microbiome community members which play important roles in regulating glycemic index and diabetes. The second area of focus is monitoring waterway ecosystems to identify the variables responsible for causing outbreaks of specific microbial species.

Agile Biofoundry example (US DOE collective Synthetic Biology labs)

The Agile Biofoundry has a group of projects to develop genetic tools and engineering non-model microbes to convert renewable or waste carbon into fuels and chemicals to replace those currently derived from petroleum. Waste plastic, cellulose, and lignin are potentially cheap feedstocks for the synthesis of these products. Non-model microbes have novel capabilities that are not currently available in traditional production strains, and they aim to understand and leverage these traits for advanced bioproduction.

- The primary objective of these projects will be to generate genetic tools for a range of microorganisms that can serve as host chassis systems for industrial bioprocessing and then apply these tools to engineer organisms for high titer, rate, and yield production of target molecules.

- Examples of organisms include *Clostridium thermocellum*, *Pseudomonas putida, Corynebacterium glutamicum, Megasphaera elsdenii, Clostridium tyrobutyricum*, and novel microbes that consume monomers from various plastics.

- Projects require vector design, gene cloning, synthetic biology, strain construction, physiological characterization, and systems biology ('omics) techniques to investigate microbial physiology and develop bacterial strains for potential use as industrial biocatalysts.

Freedom-to-Operate Host Organisms

One area, in particular, that may be of interest for a Thailand flagship project is the development of proprietary scale-up host organisms. One of Thailand's niche opportunities is to become a preferred location for economical bioproduct scale-up and production. What may be missing are host organisms optimized for scale-up production and are not subject to existing intellectual property licensing requirements.

Thailand has rich biodiversity, and thousands of native microbes and fungi have already been identified, banked, and available to be screened for host potential. By identifying and developing native host strains, Thai start-ups and corporates will be able to scale to production without significant economic impact of royalty payments on the underlying production technology. This is already a synthetic biology strategy that is being pursued in Singapore.

Collaboration with Singapore

Singapore is five years ahead of Thailand in terms of investing and developing synthetic biology capabilities. This should not be seen as a competition but rather a regional opportunity to partner and collaborate for mutual benefit. Singapore has attracted many foreign biotech and pharmaceutical companies to establish their regional HQs and regional R&D facilities. They have built a biofoundry, joined the international community of biofoundries, and even hosted the premier international synthetic biology conference. All this has established Singapore as one of the leading Asian players in the global synthetic biology community.

In conversations with the Singapore synthetic biology consortium (Synergy) leadership, they have expressed a sincere desire to find collaborative synergy between Singapore and Thailand around synthetic biology. Singapore lacks an agriculture sector for significant feedstock production and a significant domestic market for synthetic biology products. Thailand also offers the ability to produce at lower cost and high quality.

It is recommended that while Thailand moves towards building its biofoundry capability, a collaboration and exchange program could be developed where post-doc or other scientific resources could be funded to work in Singapore at SynCTI on research programs of interest to both Thailand and Singapore. By engaging with their biofoundry, Thai researchers will gain first-hand experience in the strengths and weaknesses present in the current Singapore biofoundry configuration. This knowledge will lead to the enhanced design of a Thai biofoundry complementary to Singapore's capabilities and simultaneously next generation in duplicative capabilities. The dipole of a Thai-Singapore synthetic biology relationship would significantly help accelerate acceptance among Thai corporates for more local investment.

Singapore also has a robust venture capital investment community, savvy in deep-tech ventures. Through collaboration, Thai start-ups will gain exposure to these Singapore VCs who can act as the lead investor for venture funding in Thailand. Many investors in Thailand are interested and willing to provide follow-on funding for synthetic biology. Still, they require a lead investor who can evaluate the technology's potential and risk.

Promote Thailand CDMO capabilities

The abundance of feedstock in Thailand and the lower cost of operations also make Thailand an attractive destination for scale-up operations. Start-ups in Thailand require economical scale-up capabilities. Companies from the US, UK, and EU may also find it very economical to produce in Thailand, especially for Asian markets. If Thailand also offered expertise in scale-up technologies, that would significantly benefit production in Thailand and represent resilient Asian supply chains that can scale.

High Value/Low Volume Bioproduct Focus

When the scale-up bioreactor facilities at EECi come online in 2024, Thailand should have multiple candidates ready for scale-up stemming from the previously described flagship programs. The last piece of the synthetic value chain that is missing from the Thailand ecosystem is manufacturing at scale. Although some large corporates may choose to develop their own bioproduct manufacturing capabilities, start-ups and SMEs need a significant need for contract development and manufacturing organizations (CDMO) to partner with them for production.

This CDMO should focus on high-value/low-volume bioproduct manufacturing and be flexible to produce multiple products with fast switchover capabilities. By focusing on the high value/low volume bioproducts, such as specialty chemicals, food ingredients, cosmetic ingredients, and nutraceuticals, start-ups can better attract investment because of the lower capital investment requirements.

Thailand could seek to attract international precision fermentation CDMO or encourage an existing Thai corporate with bioproduct production intent to act as operator/owner of the CDMO. Managing a CDMO and profitably operating it requires high utilization, and a company that already has its own internal bioproduct manufacturing demand can efficiently backfill production volumes when external demand shortages occur.

World-class CDMO Capabilities

A world-class CDMO capability would consist of the following value chain steps:

- *Strain Improvement* – Given the starting strain used for lab level or post biofoundry development, a CDMO would seek to either improve the manufacturability of the given strain through classical mutation or seek to migrate the metabolic engineering into proven industrial strains such as host species custom-designed to be productive at high volumes and tuned to readily available Thailand feedstocks.

- *Fermentation Development* – A CDMO would perform scale-down optimization studies that consider fermentation parameters such as media optimization, cell culture preparation, process conditions (pH, temperature, aeration), oxygen transfer rate, process operation (batch, continuous), stirring speed, foam control, and sterilization.

- *Downstream processing and formulation* – A CDMO would develop the downstream processing such as filtration, centrifugation, drying, evaporation, crystallization, homogenization, electrodialysis, filling/packaging, and dry milling.

- *Scale-up & piloting* – The EECi facility could be used for this step for both GMP and non-GMP bioproduct development.

- *Manufacturing and Regulatory* - Process technology transfer, engineering batch, support regulatory registration, commercial production.

Invest in a Thailand Synthetic Biology Consortium and Ecosystem

As illustrated in Chapter 4, the core of the US/UK synthetic biology ecosystems are four main components: assets, competence, capital, and culture. Leading academic institutions like Stanford, MIT, London College contribute intellectual property, assets, and scientific competence; veterans within the tech industry provide capital and encourage the entrepreneurial-tech-builder culture. Synthetic biology start-up companies can iterate fast, find product-market-fit and scale, making the next generation of deep technology ventures have shorter development cycles and more appealing to VC timeframes forming a virtuous cycle.

In Thailand, a synthetic biology ecosystem will need to be nurtured. Participants need to clearly understand what they bring to the ecosystem and can expect to receive from participation. The fundamental premise must be one of collaboration. One of the critical challenges for deep tech ecosystems is underinvestment due mainly to a lack of understanding about synthetic biology at the larger established companies. Corporates need to clearly understand the technology, investment patterns, market potential, and exit options.

It is in the self-interest of large corporate entities in Thailand to embrace synthetic biology. This new technology is an essential tool for companies struggling to reimagine themselves in the transition from commodity agriculture and petrochemical industry to the emerging bioeconomy. There are many ways that corporates can participate in the synthetic biology ecosystem, through partnerships and joint ventures, collaboration, investment from corporate venture capital, running incubators/accelerators, and M&A offering exits for others. The first step is to accelerate their understanding of a steep biotech learning curve, but not about technology for technology's sake, instead by emphasizing new value opportunities that the technology enables.

Unlike digital technologies, which have disrupted and negated many traditional businesses, synthetic biology is a potential ally that complements the conventional production processes of corporates in Thailand. Large companies can contribute significant market knowledge and customer contacts to start-ups, and start-ups can offer the risk-taking technology development activities lacking in the corporate environment.

Synthetic Biology Innovation Network Orchestration

Once the Thailand Synthetic Biology Institute has been established and gained momentum, the next step is to expand the capabilities into an innovation network along the lines of the Synergy consortium in Singapore, EBRC in the US, and SynbiCITE in the UK. Figure 6.1 illustrates the high-level structure and function of such a network orchestration model.

- A hub firm possesses prominence and power gained through individual attributes and a central position in the network structure. It uses its prominence and power to perform a leadership role in pulling together network members' dispersed resources and capabilities.

- Network orchestration is a set of deliberate, purposeful actions undertaken by the hub firm to create value and extract value from the network.

- Innovation networks thrive as organizational forms when the sources of specific expertise are widely dispersed, and the knowledge base is complex and expanding.

- Innovation arises out of new combinations of existing capabilities.

- Develop Undergraduate and Secondary level Synthetic Biology engagement programs.

- Corporate conferences with international speakers.

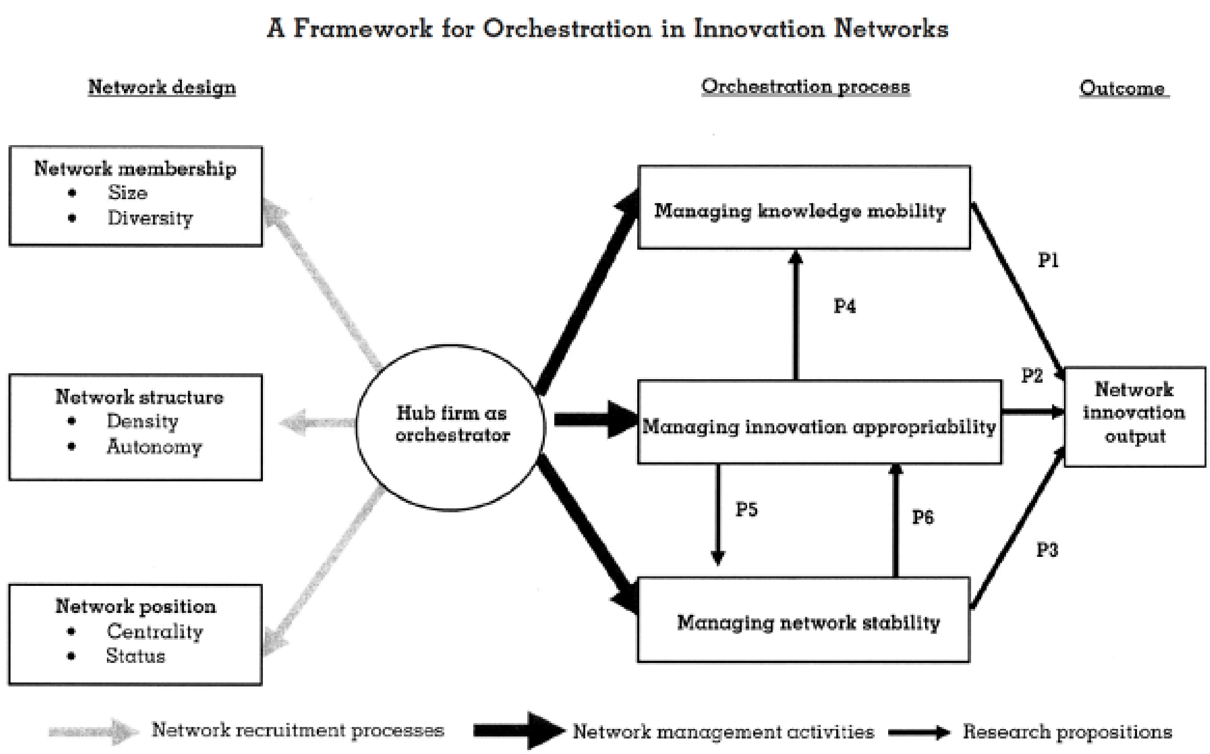

Figure 6.1 R&D Network orchestration model [47]

The critical function of the hub firm is to act as a network orchestrator through the development and execution of processes in three key areas: Knowledge Mobility, Innovation Appropriability, and Network Stability.

Knowledge Mobility

- Knowledge is the chief currency in innovation networks, and minimal innovation will occur if the specialized knowledge of each network member stays mostly locked within its organizational boundaries.

- Knowledge mobility is the ease with which knowledge is shared, acquired, and deployed within the network.

- A hub firm needs to assess the value of relevant knowledge residing at different points in the network and arrange its transfer to other points in the network where it is required.

- Enhancing knowledge mobility requires a hub firm to focus on three specific subprocesses:
    - Enhancing knowledge absorption (e.g., codification, documentation, easy to access repositories)
    - Strengthening network identity (e.g., foster trust and a common identity)
    - Encouraging inter-organizational socialization (e.g., meetings, social events, face-to-face interaction)

Innovation Appropriability

- Appropriability governs an innovator's ability to capture the profits generated by an innovation.

- Innovation may be stimulated or stifled depending on the "appropriability regime" created by the hub firm.

- The potential for unauthorized imitation can be reduced, and appropriability strengthened through instruments such as patents, copyrights, and trademarks.

- Hub firms can ensure equitable distribution of value by focusing on:
    - Developing trust among network members through IP norms and policies
    - Defining procedural justice for settling IP disputes – constitutional contracts (decision rules)
    - Providing tools to help create innovation value (patents, equity joint ventures, etc.)

Network Stability

- As loosely coupled systems, innovation networks may experience unstable linkages among network members.

- Competitive pressures among members can exacerbate the instability, whereby actors may stop collaborating with a hub firm.

- Fostering network stability, including the dynamic ability to allow for network members' entry and exit, is essential for network orchestration.

- The hub firm can increase the network’s dynamic stability by:
    - Enhanced reputation for trustworthiness and market leader
    - Lengthening the shadow of the future – the linkage between current actions and anticipated future-benefits
    - Building multiplexity – creating multiple projects of points of interaction between network actors to reinforce ties that make dissolution more complicated than single-stranded network

Table 1 below summarizes the recommended enablers from this report

Policy Establish a shared, open Synthetic Biology Institute with and integrated biofoundry facility Solicit and fund Flagship Synthetic Biology Programs that are multi-entity, multi-discipline and utilize the Institute's biofoundry capabilities Promote precision fermentation contract development and manufacturing organizations (CDMOs) that includes scale-up R&D Invest in Building a consortium driven, Synthetic Biology ecosystem in synergistic collaboration with Singapore
Regulation Further differentiate between genetically modified organisms that directly enter the food chain and GMOs that are used in the process of manufacturing but do not contribute genetic material to the final product. The product should be regulated, not the process. NXPO should align and engage with the primary international forum deliberating the regulation of synthetic biology, the Convention on Biological Diversity (CBD), along with its subsidiary agreements concerned with the biosafety of living modified organisms (Cartagena Protocol on Biosafety to the CBD), and access and benefit sharing in relation to genetic resources (Nagoya Protocol to the CBD) Similar to the US President's Bioethics Commission recommended approach to synthetic biology regulation the principles of *prudent vigilance* – which balances responsible stewardship of the technology with intellectual freedom for continued investigation – and *regulatory parsimony* – establishing only as much oversight as is necessary to ensure public safety and public benefits from the technology.
Manpower Annual synthetic biology workshop, featuring lectures from international and local researchers, hands-on sessions, and industry engagement Short certification courses in specific synthetic biology sub-topics Strategic workshops between researchers and industry for commercialisation of synthetic biology projects Networking with international synthetic biology consortiums, such as the EBRC (USA), the Flowers Consortium (UK) and the ERASynBio (European Commission) Encouragement of programs such as IGEMs to engage undergraduate and secondary student's interest in pursuing synthetic biology as a career choice
Incentives Financial incentives to start and fund local synthetic biology companies and encourage foreign entrepreneurs to relocate to Thailand to develop their technologies Increase research funding with minimal fluctuations from year to year to enable researchers to embark on longer term more ambitious synthetic biology programs

Table 1 – Summary of recommended enablers – Policy, Regulations, Manpower, and Incentives

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Appendix 1 – Interviews Conducted

Interviews Conducted: (Total = 55)

Thailand Academics:

- Siwanon Jirawatnotai – Associate Professor, Mahidol Univ., Siriraj Hospital
- Somponnat Sampattavanich – Instructor, Mahidol Univ., Siriraj Hospital
- Pakpoom Subsoontorn – Lecturer, Dept. of Biochemistry, Narasuan Univ.
- Pimchai Chaiyen –Dean, School of Biomolecular Science and Eng. , VISTEC
- Chayasith Uttamapinant – Faculty, School of Biomolecular Science and Eng. , VISTEC
- Puey Ounjai – Head, Center of Nanoimaging, Mahidol Univ.
- Trairak Pisitkun – Dir. Center of Excellence in Systems Biology, Chulalongkorn Univ.
- Sarawut Sattayakawee – Lecturer, Naresuan Univ.
- Yuttanant Boonyongmaneerat – Deputy Dir. Metallugy and Mat. Sci Res. Inst., Chulalongkorn Univ.
- Lerson Tanasugarn – Retired Tech Transfer Expert, Chulalongkorn Univ.
- Kevin Hyde, Emeritus Professor, COE in Fungal Diversity, Mae Fah Luang Univ.
- Weasuk Surareungchai – Assoc. Prof, Bioresources and Tech., King Mongkut Univ. of Tech. Thonburi

Thailand Corporates:

- Ketan Trivedi – General Manager, Kerry Group ASEAN,
- Brian Nevin - Sr. Bus. Dev. Director, Kerry Group APAC
- Nattawat Nirdroy – Venture Capitalist at GC Ventures (PTTGC)
- Pravit Prakitsri – COO and New Business Lead – Mitr Phol Group
- Panit Kitsubun – Chief Operating Officer, KinGen Biotech
- Nares Damrongchai – CEO Geneputic Bio, Former CEO TCELs
- John Jiang – Chief Technology Officer, CP Group
- Pornpen Nartpiriyarat – Head of Trading Law and Technical, CP Lotus
- Lalana Thiranusornkij – Open Innovation Leader – Thai Union
- Vitoon Vonghangool – President, Bio-Net
- Suracha Udomsak - Chief Technology Officer, Siam Cement Group
- Tim McCaffrey - Global Business Director, Siam Cement Group
- Yashovardhan Lohia – Head of Global Sustainability, Indorama
- Kittiphong Limsuwannarot – CEO, BBGI Public Company Limited
- Korsak Towantakavanit – Ecosystem and Incubation Manager, BBGI
- Rakchai Rengsomboon – CEO Fruta BioMed and Fruita Natural
- Naruemon Srisuma – VP for Group R&D, Thai Wah

Thailand Consultants/Investors

- Dave Tomsik – AT Biotech Process Engineering
- Mukund Rao – Sr. Advisor to BBGI
- Kulika Weizman – Principal, Creative Ventures and Researcher, BIOTEC
- Tonghathai Kuvanont – Managing Partner, Aimspire

Thailand Start-ups

- Alisa Vangnai – Founder/CEO, Bio om, Professor Dept. Biochemistry, Chulalongkorn Univ.
- Sean Trairatkeyoon – Founder/CEO Juiceinnov8
- Kitiya Vongkamjan – Founder/CEO UniFahs, Asst. Prof Biotechnology Kasetsart Univ.

Thailand Government

- Yatika Somrang – Assistant Mgr EECi
- Thinnakorn Hanchana – Assistant Mgr EECi
- Watcharin Meerod – Sr. Policy Researcher BIOTEC
- Nusara Satproedprai – Research Scientist - Thailand Genomics, Ministry of Public Health, Dept. of Medical Science
- Verawat Champreda – Enzyme Technology Laboratory, BIOTEC
- Porramate Chumyim – Sr. Advisor Food Innopolis
- Sissades Tongsima – NSTDA Biobank

Singapore

- Mathew Chang – Assoc. Prof, Dir Singapore Consortium for Synthetic Biology, NUS
- Mitre Gosker-Kneepkens – Acting Managing Director, Good Food Institute APAC

US

- Andrew Hessel – Chairman Genome Project-write (GP-write)
- Carlos Bustamante – Professor, Biomedical Data Science and Genetics, Stanford
- Jason Anderson – CEO Liberty BioSecurity
- Leah Sanflilippo – Account Mgr. Riffyn Synthetic Biology Software
- Liz Spect – Global R&D lead for Good Food Institute

EU

- Jan Mees – Head of New Business Development CDMO, Lonza
- Massimo Portincaso – Chairman, Hello Tomorrow/Deep Tech Ventures

Australia

- Cameron Begley – CEO, Spiegare BioEconomy Consulting
- Dean Powell – SciTech Specialist, Good Food Institute APAC