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TOWARDS THE NEW BIOECONOMY: BIO-MANUFACTURING AS A STRATEGIC ECONOMIC DEVELOPMENT INITIATIVE FOR QUEBEC

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Towards the new bioeconomy: Bio-manufacturing as a strategic economic development initiative for Quebec*

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Abstract

Globally, the bioeconomy can be defined as the domain of the economy based on products, services and processes derived from biological resources. In this regard, synthetic biology refers to the characteristics of a field derived from biology that has developed over the past thirty years thanks to advances in applied genetics and bioengineering. Some predict that the future economy will primarily be a bioeconomy based on these emerging techniques, which are consistent with the decarbonization of our economy. We first describe the international reality of the "Bio Revolution" and then aim to assess Quebec's position. Next, we present some government policies following a top-down approach from different jurisdictions. A case study of a Montreal-based company allows us to highlight the problems it faced in attracting the financial capital needed for its growth. Another critical issue in the field is the scalability of production processes. We explore this issue further in agritech, a high potential sector but whose realization faces several socio-economic challenges. This analysis serves as a backdrop to our recommendations to develop a roadmap for government support for synthetic biology.

Globalement, la bioéconomie peut être définie comme le domaine de l'économie basée sur les produits, services et processus dérivés des ressources biologiques. À cet égard, la biologie de synthèse réfère aux caractéristiques d'un domaine dérivé de la biologie qui s'est développé au cours des trente dernières années grâce aux progrès de la génétique appliquée et de la bio-ingénierie. Certains prédisent que l'économie future sera principalement une bioéconomie basée sur ces techniques émergentes, lesquelles sont cohérentes avec la décarbonisation de notre économie. Nous décrivons d'abord la réalité internationale de la « Révolution Bio » et tentons d'évaluer la position du Québec. Par la suite, nous présentons des politiques de soutien à la bioéconomie de diverses juridictions. Une étude de cas d'une entreprise de Montréal nous permet de mettre en évidence les problèmes auxquels elle a dû faire face pour attirer le capital financier

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nécessaire à sa croissance. Outre le financement, un autre enjeu critique dans le domaine est la montée en charge (scalability en anglais) des processus de transformation. Nous explorons davantage cet enjeu en agro-technologie, secteur à haut potentiel mais dont la réalisation comporte plusieurs défis socio-économiques. Cette analyse sert de toile de fond à nos recommandations qui portent sur l'élaboration d'une feuille de route pour le soutien gouvernemental à la biologie de synthèse.

Keywords: Bioeconomy; biomanufacturing; innovation; agritech; capital / Bioéconomie; biofabrication; innovation; agro-technologie; capital

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Executive Summary

The bio-economy can be characterized as that portion of the economy based on products, services and processes derived from biological resources. Synthetic biology refers to features of the derivation that have evolved in the last thirty years due to advances in applied genetics and bio-engineering. Some predict that the future economy will be primarily a bio-economy based on these emerging techniques.

Quebecers are very conscious of the environmental challenges that they and the world currently face. It is widely accepted that we need to move away from the carbon-based economy -- within the next generation if possible. This objective ultimately requires changes in personal behaviour and a re-orientation of current consumption values. But it will be difficult to embrace wholeheartedly these objectives in economic isolation without a shared social sense of trajectory to the new economy. We also need measures of progress along the trajectory.

This Report suggests that advances in theoretical synthetic biology along with efficiency gains in bio-engineering can serve to provide some technical elements in the move away from the carbon-based economy. In all, the potential of the bio-economy strikes the right notes. It is circular by definition; it is environmentally friendly by definition; and given the current resources of the planet, it could support sustainable development for the world's entire population.

The Report is organized in six Parts. These should be viewed as a vector starting from the international reality of the Bio Revolution (Part A) and the current reality in Quebec (Part B). We then move to a presentation of top-down government policy in different jurisdictions in Part C. Part D traces the development of a Montreal-based company to highlight the problems it faced in attracting the financial capital to move from being a promising local start up to attracting international attention. We view this very particular section as the core of the Report: it illustrates how the new cost structure discussed above works in practice and describes in practice the challenges of scalability. This problem is addressed directly in the following section. Part E deals with the extraordinary global promise of agri-tech and contrasts this promise with a review of serious concerns regarding its socio-economic impact. These issues are of particular relevance to Quebec and to our

partners. With this Part, the Report has come full circle. We then offer in Part F some recommendations for the development of a roadmap for government support of synthetic biology.

In organizing these recommendations, we rely on the framework elaborated in a previous Report for the Ministry of Finance *Appui gouvernemental à l'innovation: Proposition de cadre intégré* where we found it useful to look through the lens of the capital required for successful commercialization of fundamental research.

Capital throughout our Report takes various forms: Intellectual Capital (research support), Financial Capital (funding to support product development), Infrastructure Capital (existing support provided by the relevant ecosystem), Human Capital (required human resources both technical and managerial) and Social Capital (broad support required for the acceptance of a particular innovation). Successful commercialization requires the imaginative interplay of capital in these five forms. It is our opinion that the requisite capital allotted in Quebec along these lines is lacking. The role of government policy is to establish the conditions to foster this interplay.

Accordingly, our recommendations are organized along these five capital components. Specific details can be found in Part of the Report. Here we present the context and sketch the proposals.

Recommendation I: Investing in Social Capital

It strikes us that a broader social engagement regarding the development of the bio-economy is needed. It would be too ambitious and probably ineffective to attempt to do so immediately on a broad scale involving the public at large. A segmented approach seems more reasonable. At the outset, may we suggest that the Government establish a Leadership Council to develop policy recommendations regarding the bio-economy. The composition of the Council could reflect relevant stakeholders from different economic sectors, the academic sector, and the government sector. Some international representation would make good sense. A natural Chair for the Council would be Québec's Chief Scientific Officer.

Recommendation II: Investing in Intellectual Capital

We find that researchers in synthetic biology and bio-engineering are dispersed across the Province and that their activities appeared uncoordinated. The model that emerges is one in which an individual senior researcher leads a research laboratory which involves students and technicians. We consider that a pan-university umbrella group is needed to co-ordinate research and activities relating to the bio-economy. The multi-disciplinary character of the bio-economy could be reflected in its composition. Dedicated research funds should be made available to support the initiatives of this group.

Recommendation III: Investing in Infrastructure Capital

Even at this nascent stage of the development of the bio-economy, it would be useful to invest some funds in infrastructure, particularly to nurture start-ups, as a means of evaluating the potential for growth of synthetic biology in Québec. The issue of scaling up to market along the production chain should be addressed sooner rather than later. Moreover, an analysis of the economic rationale for establishing a mid-size bio-refinery in Quebec should be performed.

Recommendation IV: Investing in financial capital

The people we interviewed in the venture capital sector indicate that, in Quebec and for that matter, in the rest of Canada as well, the development of start-up companies must, for the time being, be supported by the government. For enterprises that have reached a more advanced stage of development, support modalities led by the private sector but with government support should be considered. We present some modalities in this regard.

Recommendation V: Investing in Human Capital

The new bio-economy reality entails workforce transformation and the development of new trans-disciplinary skills. It is creating additional opportunities in automation and software engineering, chemical and materials engineering, skilled labour manufacturing and new roles in product integration. All the World Economic Forum recommendations (Part C Section 7.2) are relevant and should be seriously considered. Furthermore, studies should be mandated to anticipate future workforce needs and allocate resources (human as well as material) accordingly across the CEGEP and University networks.

Recommendation VI: Demand-side support for the new bio-economy

The Government itself can participate in the transition to the low-carbon economy in different ways. It can actively monitor its own carbon footprint. It can as well participate in the development of the bio-economy via its purchasing power.

Mandate and organization of the Report

As its title indicates, this Report concerns a very particular and novel industrial sector. The aim of the paper is to (i) highlight the importance of the area broadly described as bio manufacturing or, more precisely, as synthetic biology. As well, the Report (ii) contributes in a preliminary way towards the policy development of an innovation strategy for Quebec in this industry by underscoring the challenges faced in the development of such a policy.

Although our work has been supported by several private-sector partners (Agropur, La Fondation Molson, Saputo) and has involved the participation of Concordia University, the Report's conclusions and recommendations—it must be emphasized at the outset-- are our own.

The primary factor that animates the Report can be stated bluntly: Quebec is currently ignoring a critical techno-scientific area that will support important socio-economic advances in the upcoming decades. Indeed, one interlocutor observed that we are simply *missing the boat* and risk finding ourselves with a severe development deficit in an industrial area that will come to dominate economic growth in the 21st century.

One daunting reality facing policy makers is that bio manufacturing is one component in what has been the exponential development of a panoply of new bio-based technologies. The recent emergence of biology-based scientific and industrial expertise in the last fifty years amounts to what McKinsey has described provocatively as the *Bio Revolution* in their survey of the field. Indeed, the scientific reality does justify this dramatic turn of phrase with a story line that begins with the biochemical analysis of the gene in the 1950s and continues with many extraordinary chapters including recent developments that have produced the life-saving Covid vaccines.

Recent advances have enabled significant cost reductions in transformative engineering techniques such as DNA synthesis and sequencing. With increasing economies of scale, the opportunity to deploy innovative biomanufacturing solutions has become a practical reality. Moreover, these solutions are emerging as increasingly relevant approaches to solving current socio-economic challenges surrounding environmental deprivation and sustainability. As this Report will describe, venture capital markets in the US have responded positively and aggressively to this bio revolution.

Capital markets have responded due in part to due the emergence of a more favorable development cost perspective. Until recently, cost considerations restricted biomanufacturing development to either high-cost/low volume goods such as pharmaceuticals or low-cost/high- volume commodities such as bioethanol production. Improvements in biomanufacturing techniques are currently altering this value equation for products that span much broader segments of the economy. Indeed, the cost of goods so derived can be reduced while their quality control improved. Personal care, nutrition, materials are all affected by new production techniques.

The orientation of the Report reflects this emerging economic reality. We do not consider directly the economic and social potential of the development and manufacture of pharmaceutical products in Quebec. Government intervention at this level—as for example the recent announcement by *Moderna* that it will be investing in manufacturing facilities in Montréal—is beyond the scope of this Report. Of course, this investment is welcome under the right conditions. The analysis of these conditions is not our concern. Rather in this particular instance, our focus is more generic and concerns more the development of human capital required to support this investment as well as others in the area.

Given the favorable cost structure, it is the economic potential surrounding the development and engineering of new products within the Quebec economy that is the primary concern of the Report. In this regard, scale and scalability are particularly relevant in new product development. A considerable amount of scientific insight and engineering ingenuity and dollars may go towards the development of a few grams of an exciting product. But the process must be scaled up through increasing levels to validate quality maintenance and commercial viability. This challenge faced by a start-up in going through these steps has been termed the *valley of death*.

A separate section of the Report is reserved for a discussion of the potential impact of synthetic biology on agriculture. *Promise, but problems* encapsulate potential applications, particularly in the development of alternative proteins. If any progress is to be made in this area, the Government must play an active role in managing the social context for non-traditional agricultural development.

To the best of our knowledge, Quebec does not have a general strategic policy to assess and, where possible, to direct and to successfully contribute to these developments in the bio-economy and the development of bioengineering capacity in the province. In sum, there appears to be a policy vacuum in this area. As part of this project, we have interviewed various players in academia, industry and finance relating to bio manufacturing (Part B of the Report). The area is marked by haphazard development. These issues cannot be resolved in a vacuum, and it is clear that the Government should provide direction and co-ordination at different levels and in different forms. Such input is a necessary condition for any future development of this industry.

There is also one theme that frequently appears in the literature we have reviewed on the development and promise of synthetic biology and its applications. Its evolution will create the need for entirely new skill sets in the workforce. This point is stressed by the experts interviewed in this Report and needs to be addressed directly in Quebec's education and training policies.

In sum, our Report makes the case for the development of a Quebec roadmap for government support of synthetic biology as an important instrument for future economic growth and increased employment.

Toward this end, we build upon the framework elaborated in our previous Report *Appui gouvernemental à l'innovation: Proposition de cadre intégré* where we adapt a supply-demand framework to analyze government support of innovation that is ultimately oriented to the goal of commercialization. By its nature, bio-manufacturing resides closer to the commercialization end of the innovation process. We did interview various researchers to gain their impressions of the front-end research context and support, but our concerns have been always practical. Here we have found it useful to look through the lens of the capital required for successful commercialization in this area.

Capital in our Report takes various forms: Intellectual Capital (research support), Financial Capital (dollars to support product development), Infrastructure Capital (existing support provided by the relevant ecosystem), Human Capital (required human resources both technical and managerial) and Social Capital (broad support required for the acceptance of the particular innovation). Successful commercialization requires the imaginative interplay of capital in these five forms. It is our opinion that the requisite capital allotted in Quebec along these lines is lacking. The role of government policy is to establish the conditions to foster this interplay.

What is truly needed in our opinion is a series of a series of in-depth reports devoted to these capital challenges. This Report can only hint at or allude to the issues that need be addressed. Time and resources considerations precluded us from being comprehensive in this regard. Accordingly, the Report provides what should be viewed as contextual snapshots of these issues. These snapshots are intended to be, as the name conveys, suggestive and stylized, not detailed and comprehensive.

Accordingly, the style of the Report may seem unusual in its sketch-like format. In our opinion, a comprehensive bibliography would only distract from the capital policy considerations discussed above. On the other hand, the science underpinning the bio-revolution is not widely understood or appreciated, and we have attemted to provide (as briefly as possible) some relevant background in the three technical Annexes. We hope that these will contribute to the understanding of certain aspects of the biology. All in all, we are offering impressions that point to the need for more detailed and thorough analysis.

The Report is organized in six Parts. These should be viewed as a vector starting from the international reality of the Bio Revolution (Part A) and the current reality in Quebec (Part B). We then move to a presentation of top-down government policy in different jurisdictions in Part C. Part D traces the development of a Montreal-based company to highlight the problems it faced in attracting the financial capital to move from being a promising local start up to attracting international attention. We view this very particular section as the core of the Report: it illustrates how the new cost structure discussed above works in practice and describes in practice the challenges of scale-ability. This problem is addressed directly in the following section. Part E deals with the extraordinary global promise of agri-tech on the one hand and contrasts this promise with a review of serious concerns regarding its socio-economic impact. These issues are of particular relevance to

Quebec and to our partners. With this Part, the Report has come full circle. Part F offers some recommendations for the development of a roadmap for government support of synthetic biology. In keeping with our methodology these recommendations are organized according to the capital support that would be required for the development of the bio-economy in Quebec.

TOWARDS THE NEW BIOECONOMY: BIO-MANUFACTURING AS A STRATEGIC ECONOMIC DEVELOPMENT INITIATIVE FOR QUEBEC

Tables and Figures

Part A

The Commercial Potential of Synthetic Biology

> This part of the Report provides an overview of recent developents in synthetic biology, as well as giving some indication of the considerable amount of financial capital that has supported these developments.

The bio-economy can be simply characterized as that portion of the economy based on products, services and processes derived from biological resources. Synthetic biology refers to features of the derivation that have evolved in the last thirty years due to advances in applied genetics and bio-engineering; some definitions (that are important for regulatory purposes) are reviewed in the Appendix to this Part of the Report. Some predict that the future economy will be primarily a bio-economy based on these emerging techniques. According to the McKinsey Global Institute, "as much as 60% of the physical inputs to the global economy could in principle be produced biologically." We review the features of the McKinsey report entitled *The Bio Revolution* in Section 1 that follows.

Section 2 deals with the growth in private-sector financing that has supported the development of products and services in the bio-economy. Capital markets have responded in part due in part to due the emergence of more favorable development costs. Until recently, cost considerations restricted biomanufacturing development to either high-cost/low volume goods such as pharmaceuticals or low-cost/high- volume commodities such as bioethanol production. Improvements in biomanufacturing techniques are currently altering this value equation for products that span much broader segments of the economy. Indeed, the cost of goods so derived can be reduced while their quality control improved. Personal care, nutrition, materials are all affected by new production techniques.

The orientation of the Report reflects this particular aspect of the emerging economic reality. Accordingly, we do not consider directly the economic and social potential of the development and manufacture of pharmaceutical products in Quebec.

Section 1 The Bio Revolution

The McKinsey Report with this title covers a lot of ground. In what follows we look at three aspects of the new bio-economy: its context, its impact and issues in commercialization.

Context

According to the recent McKinsey analysis of *The Bio Revolution*, there are four broad scientific facets of the Revolution:

Biomolecules

Mapping engineering intercellular molecules.

Biosystems

Mapping and engineering cells, tissues and organs.

Biomachine interfaces

Connecting nervous systems of living organisms to machines.

Biocomputing

Using cells and cellular components for computation.

Table 1 – The Scope of Bio innovation

Bio innovation is occurring in four key arenas.

	Biomolecules	Biosystems	Biomachine interfaces	Biocomputing
Definitions				
Mapping	Cellular processes and functions via measuring intracellular molecules (eg, DNA, RNA, proteins) in the study of omics	Complex biological organizations and processes, and interactions between cells	The structure and function of nervous systems of living organisms	Intracellular pathways or networks of cells to return outputs based on specific conditions (for computation)
Engineering[1]	Intracellular molecules (eg, via genome editing)	Cells, tissues, and organs, including stem cell technologies and transplantation	Hybrid systems that connect nervous systems of living organisms to machines	Cells and cellular components for computational processes (storing, retrieving, processing data)
Examples	Gene therapy for monogenic diseases	Cultured meat grown in a lab	Neuroprosthetics for motor control (implant or external headset) of human or robotic limb	Data storage in strands of DNA

Source: McKinsey Global Instittue. 2020. The Bio Revolution: Innovations transforming economies, societies, and our lives. Exhibit 1, p. 3.

Corresponding to these scientific and engineering advances, innovative products and applications are emerging in various sectors; notably:

- Human health. Advances in this area have certainly proven their value over the last two years. A new wave of innovation includes therapies to prevent and treat disease as well as improvements to drug development.
- Agriculture, aquaculture and food. Innovations in this sector improve the quality and productivity of agricultural production and the development of alternative proteins that will alleviate the pressure on the environment related from traditional livestock and seafood.
- Consumer products and services. The number of personalized biologically-based products and services is increasing, as well as innovative approaches to well-being and fitness.
- Materials, chemical, and energy will be made in ways that will transform traditional industries. Applications include innovations related to the production of material, improved and novel fermentation processes and advances in biofuels.

Social Consequence of the New Bio-economy are impactful

The McKinsey Report estimates that as much as 60% of the physical inputs to the global economy could be produced biologically. Currently, one third of these inputs are biological materials (wood, cotton etc). The remaining two thirds are not biological materials (plastics, aviation fuels). These could in principle be produced using innovative biological processes or replaced with substitutes using bio innovations. Nylon is currently being made using genetically engineered microorganisms instead of petrochemicals. Three important and far-reaching consequences of the biological capability:

- Biological means could be used to produce a large share of the global economy's physical materials. Fermentation is now being used to create fabrics (leather from mushroom roots). The fabric minimizes shedding during washing *and* reduces the flow of microplastics to the ocean.

- Increased precision in production enables the customization of products to individual needs. Personalized, precision medicine could be tailored to the individual's genome.
- The interface between biological systems and computers in the form of bio-machines is leading to progress in treatments and diagnostic technology.

McKinsey has compiled a library of 400 « use cases » that are scientifically feasible and likely to be commercially viable by 2050 with an estimated economic impact of $2 - $4 trillion dollars with more than half the impact outside of healthcare in food, energy, materials and consumer products.

Issues in Commercialization

There are three broad stages in the passage from lab to adoption: scientific research, commercialization and diffusion. These are affected by the following factors. The first is a necessary condition:

- Investment in scientific research.

The remaining factors play a role in commercialization and diffusion:

- A new product must compete with an existing product not only on cost but on offering better quality and reliability.
- Is the business context suitable for the changing landscape?
- Are appropriate delivery and marketing strategies in place?
- Does the regulatory framework support the arrival of new bio-based products?

Section 2 Investments in Biotech

Pharma-focused biotechnology is not the focus of this report. However, the label 'biotechnology' also encompasses other applications that rely on bio-manufacturing. Hence, the development of biotech over the past few decades captures successes in pharma as well as in other sectors and can serve as a template for the future potential of bio-manufacturing. As other applications gain traction, more granular data will become available in the future.

Taking a wide span perspective, 2020 stands out as one of the best years on record for biotechnology financing worldwide. Stock market indices remained on the rise until December. Initial public offerings (IPOs) had a banner year, with more than 73 life sciences companies collectively raising more than $22 billion. Thirty-three special editions tied to biotech specific purpose acquisition companies (SPACs) — IPO shell companies that offer private biotechs an alternative to going public without the expensive traditional IPO — have raised the colossal sum of $6.3 billion. Private fundraising also exploded, with fund inflows up 37% year-on-year, and private equity firms like Blackstone Life Sciences continued to expand into venture finance.

In the next sections we will successively present: the financing mechanisms used by bio-manufacturing companies; a summary financial portrait of public companies in bio-manufacturing.

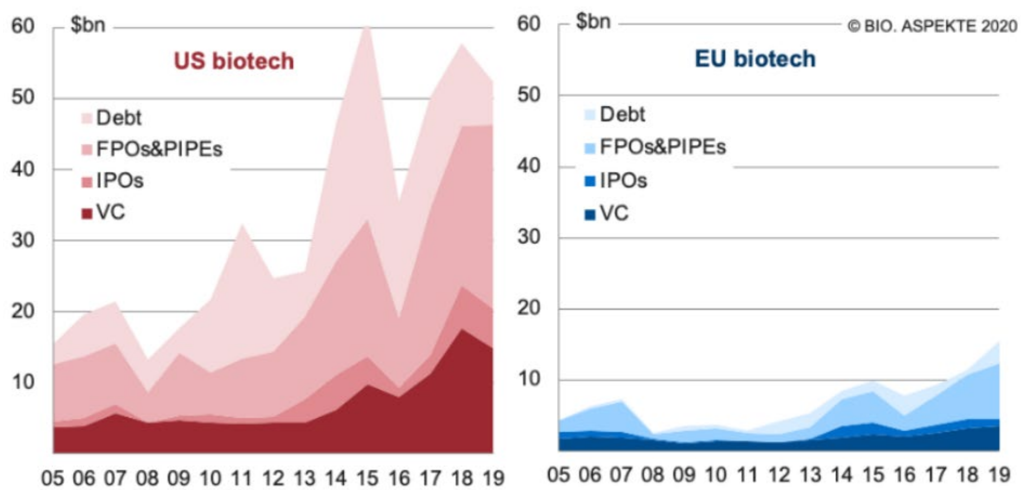
2.1 Financing mechanisms

All developments of US bio-manufacturing companies and their products have been strongly supported by early successes and favorable financing conditions, e.g. specialized risk taking and investors, attractive peer groups on stock markets as well than a favorable regulatory environment. In particular, the opportunity to go public and locate subsequent funding as a publicly traded company with a defined enterprise value has supported this thriving industry.

In Europe, on the other hand, there is no comparable funding climate for biotechnology, although the money is basically available. There is less risk taking combined with almost non-existent biotech success stories. In the United States, a handful of early stage companies have managed to reap the low-hanging fruits of new modern biotechnologies. This led them to become well-funded success stories that were able to grow based on their own revenue and new developments.

The impact of these favorable financing conditions is illustrated in the Figure: biotechnology financing in the United States is about 5 times higher than in Europe. This does not mean that there is better science in the United States than in Europe, but a better translation of efforts into business and innovation, supported by a funding ecosystem. Moreover, the industry in Europe started about 15 years later, which means that a fair comparison should actually include different time periods. With this, the years 2005 in the United States and 2019 in Europe must be compared due to the same amount of funding of around 15 billion dollars.

Figure 1 – Financing Sources for Biotechnology

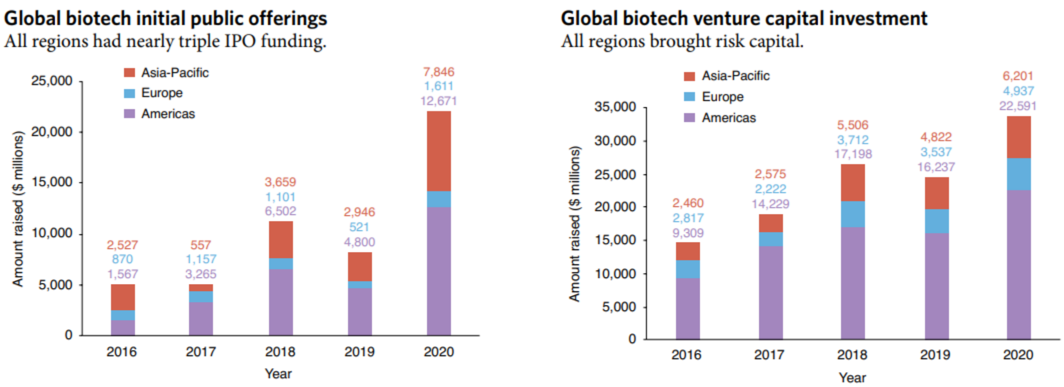


Source: Data taken from EY Global Biotechnology Report 2017

In 2019, venture capital (VC) and follow-on public company (IPO) offerings reached an all-time high and total equity financing volume surpassed the benchmark of $10 billion. There were 4 venture capital rounds above $100 million which increased the total amount of venture capital; in addition, 9 venture capital rounds reached more than $50 million. This may signal that the financial situation is stabilizing at a higher level than in previous years.

The current COVID-19 pandemic is mobilizing additional public and private funds for companies active in vaccine or drug development. Between 2019 and 2020, all investments in IPOs and VCs increased from $33 billion to nearly $56 billion, an increase of more than 70%. In addition, there is a significant increase in the number of IPOs and the number of VC financing rounds in 2020 in all regions of the world.

Figure 2 – Financing of Biotechnology



Number of IPOs

	2016	2017	2018	2019	2020
Asia-Pacific	18	13	28	40	44
Europe	23	26	16	8	14
Americas	25	33	56	46	73

Source: BCIQ BioCentury Online Intelligence

Number of rounds

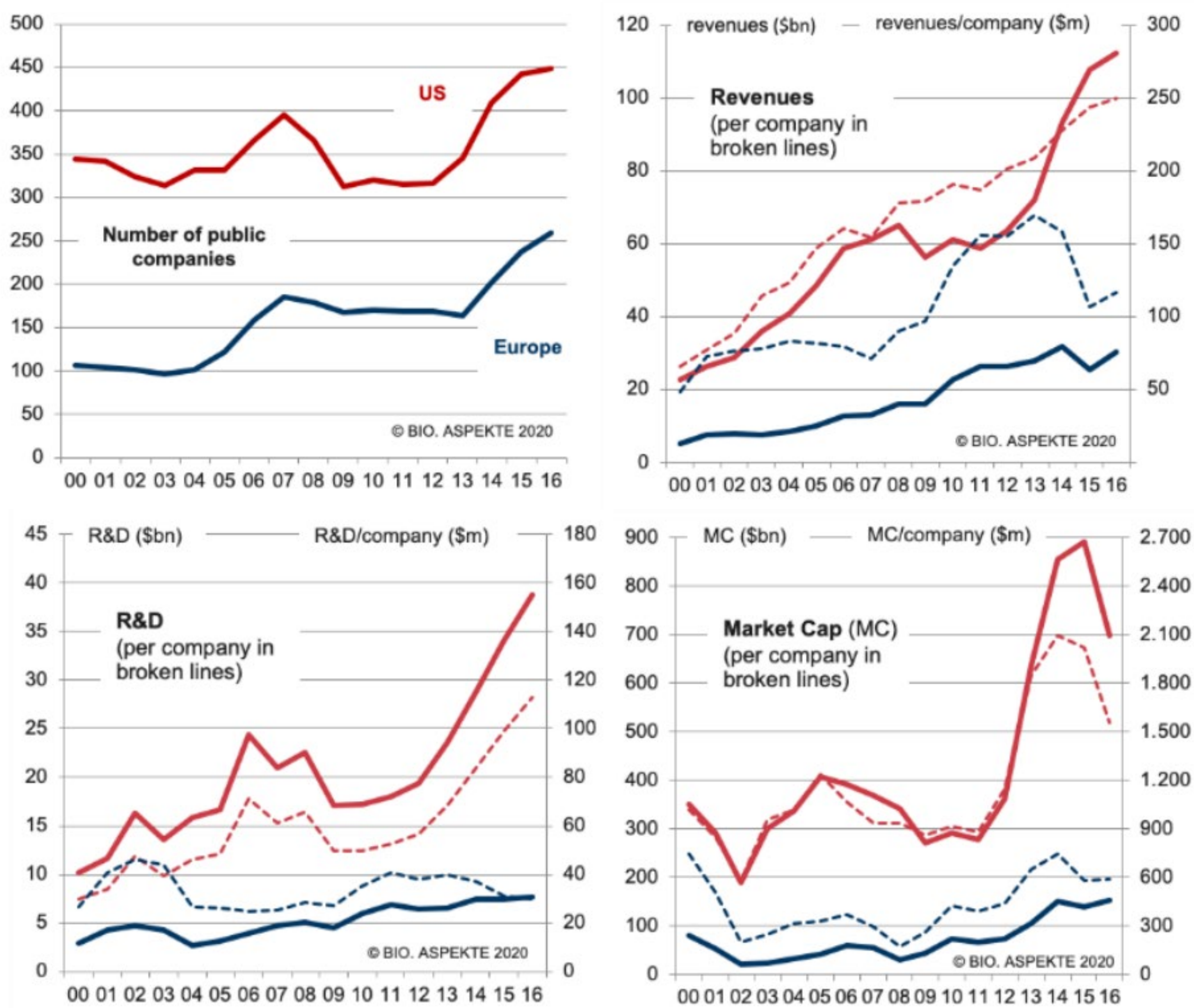
	2016	2017	2018	2019	2020
Asia-Pacific	70	82	104	109	112
Europe	195	182	171	176	178
Americas	428	492	501	411	442

Source: BCIQ BioCentury Online Intelligence

2.2 Financial portrait of bio-manufacturing companies

Due to a number of positive conditions, the US biotechnology industry has experienced steady growth in terms of the number of companies, sometimes interrupted by setbacks due to general economic crises. Mainly in the 1990s, the European biotech industry caught up very quickly with the number of biotech companies. However, as measured by the number of public biotechnology companies – which are often better financed – Europe consistently lags behind the US. Public companies are the driving force of the US biotechnology industry. They represent about 90% of all income and about ¾ of all employees in the industry.

Figure 3 – Comparison of the U.S. and European Biotech Sectors



Source: WifOR Institute (2020) Measuring the Economic Footprint of the Biotechnology Industry in Europe

The Figure shows selected metrics – number of public companies, revenue, research and development (R&D) spending, and market capitalization – for the European and US public biotech markets. To account for the higher number of public biotechnology companies in the United States, the analysis includes the calculation of parameters by company. Unfortunately, the underlying data for the measures is only available up to 2016.

As noticed in the previous figure the number of companies in Europe and in the United States increases at the same rate. After a stagnation in the number of public companies between 2008 and 2013, there has been an increase in the number of companies in recent years. Despite this increase, the average revenues per airline in Europe (broken blue) are down, unlike the average revenues of American airlines (broken red). The same observation can be made for company expenditure on R&D.

In 2020 the biotechnology market was around 500 billion dollars. In 2027, it is estimated that the global market will reach a total value of 950 billion, representing an annualized growth of 9.2%. The market will be dominated by the United States in America and by Germany in Europe.

Appendix Part A

What is Synthetic Biology?

Synthetic biology refers mainly to a biotechnology research field seeking to facilitate or accelerate the creation, or "synthesis", of new biological parts, systems and devices, or to redefine biological systems that already exist in nature. It is a multidisciplinary field that spans several areas of biology and engineering, particularly biotechnology, molecular engineering, biophysics, genetic engineering, metabolic engineering, chemical engineering, and electrical and computer engineering[1].

At an international level, the definition of synthetic biology is not standardized and widely agreed upon, but is formulated in different ways depending on study committees or other scientists. Appendix III of the report entitled *Opinion on Synthetic Biology I*[2] and submitted to the European Commission in 2014 presents a list of 23 definitions, showing some of the varying nuances and degrees of precision that may exist among them. For instance:

- British public body *UK Research and Innovation* focuses on the engineering aspects in its 2012 definition, mentioning the "design" and "engineering" of new biological parts and systems, or the redesign of existing systems: "*Synthetic biology is the design and engineering of biologically based parts, novel devices and systems as well as the redesign of existing, natural biological systems*." Public policies launched thereafter in the United Kingdom referred to this definition.
- The definition given in the United States by the Presidential Commission for the Study of Bioethical Issues, and outlined in their 2011 report to Congress, more explicitly mentions the roles of DNA manipulation and computer science in creating new biochemical systems or organisms: *"Synthetic biology is the name given to an emerging field of research that combines elements of biology, engineering, genetics, chemistry, and computer science. The diverse but related endeavors that fall under its*

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[1] https://en.wikipedia.org/wiki/Synthetic_biology

[2] https://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_044.pdf

umbrella rely on chemically synthesized DNA, along with standardized and automatable processes, to create new biochemical systems or organisms with novel or enhanced characteristics."

Finally, the French Ministry for Higher Education and Research provides a more technical definition: "Synthetic biology is defined by the intentional design of artificial biological systems, by coupling mathematical modeling and biomolecular methods. Its emergence is based on the analytical power of molecular biology (-omics) and on the predictive and explanatory models that integrate the results (systems biology), as well as on the drastic fall in the costs of scientific calculation and of reading and writing DNA." [translation][3].

This emerging technology covers many areas of application, particularly in health, pharmaceuticals and vaccines, energy and food. The sector is structured between, on the one hand, gene foundries that synthesize genes and their compositions and, on the other hand, synthetic biotechnology companies that develop microorganisms from these synthesized genes to design products through metabolic engineering[4].

[3] https://cache.media.enseignementsup-recherche.gouv.fr/file/Rapport_Biologie_de_synthese/58/5/L2_BIOLOGIE_DESYNTHeSE_version_finale_web2_202585.pdf

[4] Id.

Part B

Bio-manufacturing: A View from the Field

> In this Part of the Report we move from a global perspective to place Quebec at centere stage. In short, we ask a variety of actors: where does Quebec stand relative to the global changes in biotech innovation? We learn that there appears a need for increased capital support in all its dimensions if Quebec is to participate in the economic benefits of this evolving sector.

The macro-economic and sectoral data currently available do not allow us to have a detailed reading of the relative importance of bio-manufacturing in Quebec, particularly in the agri-tech sector. Consequently, our analytical approach relies heavily on interviews conducted with different actors involved in three distinct but nevertheless interrelated poles of interest:

- Industrial pole, which includes leaders of major agri-food processors, entrepreneurs and investors;
- Research-teaching pole, which includes in particular teacher-researchers with activities focused on bio-manufacturing or agri-tech or related to these fields as well as a manager;
- Pole of innovation transfer and support centers, which notably includes institutes or technology transfer centers oriented towards the food industry. These institutes and centers work in partnership with companies (industrial pole) and research and educational institutions (teaching-research pole).

The profiles of the people interviewed are presented in the table at the end of Section 3. We used a so-called 'snowball' approach for the selection of these people: from initial contacts with our partners, we asked them to identify people who could shed additional light on our research problem, And so on. A certain saturation level in the comments was quickly reached; namely where the observations and findings put forward by the interviewees were similar.

In what follows, the presentation of our analysis of the comments made by the interviewees is carried out in two stages. First, in a format structured around the pole to which the interviewees belong, we initially report their observations and comments without imposing an analysis filter. Then, in a second step, we make a synthesis of the comments made by trying to cross-check the findings, the aim being to identify areas of convergence. In addition, where appropriate or possible, we validate claims made by interviewees with independent facts or information. From this analysis, we infer five success factors, which we designate as so many forms of capital, necessary for the development of a bio-manufacturing sector in Quebec.

Section 3 Three Sectorial Views on the Quebec Bio Economy

3.1 Industrial Sector

Inside the industrial hub, we met leaders of large agri-food companies as well as entrepreneurs and venture capitalists. Almost all of the people interviewed have a scientific profile (engineering or science), despite the fact that they hold management or investment positions.

Quebec has several large companies focused on agri-food, which are or will possibly be affected by innovations in bio-manufacturing. In addition, there is a tradition in Quebec in bio-manufacturing, essentially in terms of the fermentation process: we are thinking here of the manufacture of cheese, yeasts and beer.

Our perception of the comments of the people interviewed in the industrial pole is that there is a great variance among them regarding the appreciation of bio-manufacturing and its potential beyond traditional applications. On the one hand, within established companies targeting consumer markets, innovations in bio-manufacturing as well as prospects for the development of bio-manufacturing processes are very focused and relatively peripheral to the strategic priorities of management. The need for these companies to invest in order to maintain their gains in their traditional markets or to develop related markets may explain this state of affairs. In addition, over the years, Quebec has developed an ecosystem focused on animal proteins where the immediate interests of the main stakeholders are quite distant from the development of bio-manufacturing. This situation contrasts with what can be observed in other contexts. Thus, the case of Tyson was cited to us as an example. American multinational and world leader in animal processing (beef, chicken, pork), Tyson Foods now defines itself as the *Protein Leader.* The strategy put forward by the company is to *Sustainably Feed the World with the Fastest Growing Protein Brands*[5]. This strategic repositioning is accompanied by investments in the development of alternative protein sources, supported by a research and development budget and a venture capital fund. Although still relatively modest within the company, alternative sources of protein are at the heart of its strategy.

By contrast, the message received from entrepreneurs and venture capital investors is that bio-manufacturing allows spectacular advances in the transformation process, in sustainable development and in value creation. Thus, venture capital investors with an international network of contacts tell us that the economic potential of bio-manufacturing is attracting the attention of political leaders at the highest levels in certain countries. Similarly, the entrepreneurs we met testified that the development of a bio-manufacturing sector makes it possible to take advantage of several advantages held by Quebec; in particular, access to clean electricity and water, which is essential for fermentation processes. In addition, the presence of a decentralized network of universities and colleges provides access to researchers and a recruitment pool throughout the province.

An issue raised for the development of the bio-manufacturing industrial cluster, particularly with regard to plant-based protein products, is the current trend for producers to imitate traditional products; eg, burgers without beef. croquettes without chicken, etc. Although this choice may alleviate consumer apprehensions, it imposes many constraints on producers in terms of texture, flavor or color, which require the addition of many ingredients. However, varieties of ingredients can also intimidate consumers. Also, imitating existing products reduces the options for developing new products. Thus, 'snack' type products are relatively easier to develop than 'steak' type products. The contribution of multi-functional expertise (scientific but also culinary and marketing) therefore appears

[5] https://www.tysonfoods.com/who-we-are/our-story/purpose-values

to be essential to decouple vegetable protein from animal protein with regard to its appearance and consumption.

3.2 Research/Teaching Sector

Our interviews in the academic world were conducted with experienced professor-researchers holding industrial research chairs or heads of research centers within their university. Although all interested in issues affecting to varying degrees bio-manufacturing and agri-tech, they come from different university departments: engineering, agricultural sciences, management and biology. This diversity in terms of skills and expertise profiles is a good illustration of one of the challenges linked to the development of a bio-manufacturing sector in agri-tech, namely the need to adopt a multidisciplinary perspective.

Another particularity of the professor-researchers we met is the fact that all have experience in an industrial environment, the nature of this experience varying according to the profiles. In the unanimous opinion of these professor-researchers, experience in business is essential to the development of a dynamic research program that brings scientific and economic benefits. In fact, the identification of relevant research topics as well as obtaining funding from companies for carrying out research projects rely on a researcher's ability to understand the issues facing the sector, in terms of market demand and production management. In other words, companies will be more inclined to finance projects whose commercial benefits are more easily identifiable. However, the marketing of a product based on research implies knowledge of the transformation processes that experience in industry makes it possible to acquire.

In addition to facilitating the funding of research, this close collaboration between university researchers and companies also makes it possible to develop the expertise of the students and researchers involved in the projects as well as their career potential in industry. In fact, having contributed to the implementation and completion of research projects with potentially commercial significance, these students and researchers have acquired skills and competencies that make them particularly interesting for employers. In this regard, the professors-researchers interviewed agree in stating that their students do not encounter any difficulties in finding work.

3.3 Innovation Transfer Sector

Quebec has developed an infrastructure network to support innovation in bio-manufacturing within companies. Thus, in the dairy sector, Novalait is supported by producers and processors with a view to investing in research. Based on funding obtained from producers and processors, the organization acts as an intermediary between them and research centers and teams, in addition to ensuring the dissemination of innovations within the sector. On an annual basis, the funds collected by Novalait total nearly $800,000, but their research impact is estimated at more than $3 million due to the leverage effects induced by various government programs and the contributions of the partners involved. However, the scope of the organization covers the entire dairy chain and is not focused on bio-manufacturing.

Another organization related to bio-manufacturing is the CREBIQ (Consortium for Research and Innovations in Industrial Bioprocesses in Quebec). Created in 2008, CREBIQ finances innovation projects in three sectors, namely 1) industrial bioproducts (bioenergy, bio-sourced chemistry, bio-sourced materials, 2) the environment and 3) bio-food. CREBIQ funds projects with proof of concept (pilot) up to a maximum of $1.5 million per project. However, there is a leverage effect through the use of other government programs, provincial or federal. According to the information gathered, over the years, CREBIQ has financed more than 325 projects worth $130 million against a total investment of $65 million. However, it is clear that the projects funded are relatively small, which limits their impact in terms of advances in bio-manufacturing.

A third organizational model aimed at supporting innovation consists of college technology transfer centers (CCTT), which are found throughout Quebec. One of these CCTTs particularly targets the agri-food sector, namely CINTECH Agroalimentaire, which is attached to the CEGEP de St-Hyacinthe. Its business partners are found among the major agri-food groups in Quebec. Its field of action is agro-food processing (meat, dairy products, etc.) with the priority of promoting co-products emanating from processing processes. Recently, this CCTT has identified the bio-manufacturing of plant proteins as a field to be developed, with priority given to plant-based plant proteins. This choice is explained in particular by the possibilities offered by plant-based vegetable proteins in terms of strengthening the circular economy. Support for innovation for the bio-manufacturing of plant proteins from fermentation processes or cells is not yet envisaged, as the demand is not there.

However, according to some interviewees, Quebec and Canada as a whole are out of step with the leaders elsewhere in the world in the development of plant proteins, regardless of the bio-manufacturing process. Consumption habits, the need to accelerate the transfer of knowledge between research centers and industry and the willingness of consumers to try new sources of protein, all condition progress in the bio-manufacturing of vegetable proteins.

Section 4 Bio-manufacturing: A Matter of Capital

In our opinion, the perspectives outlined in the previous section relate to two questions or themes. On the one hand, from their point of view, what are the keys to success in the development of a strong bio-economy focused on agri-food? On the other hand, according to their knowledge of the environment and the context, what is their assessment of the current position of Quebec in terms of the bio-economy, all focused mainly on agri-food (or agritech)?

Essentially, it emerges that the development of a strong bio-economy relies on the optimal combination of five forms of capital, which are in close interaction and must therefore be seen in an integrated way:

- Infrastructure capital
- Human capital
- Research capital
- Financial capital
- Social capital

4.1 Infrastructure capital

Infrastructure capital refers to production facilities such as production workshops, equipment, bioreactors, fermentation tanks, etc.

The main challenge in bio-fabrication is scalability, i.e. the ability to reproduce, in increasingly higher volumes, the results obtained in the laboratory. Any product or solution development process in bio-manufacturing will therefore be based on a series of steps to ensure that ultimately, large-scale production can be achieved and ensured in a safe manner while respecting all control criteria. The corollary of this imperative for scalability in bio-manufacturing is the need for researchers, developers and entrepreneurs to have access to a range of facilities of differentiated capacity.

In this regard, several respondents mentioned that there are facilities (fermentation tanks/bioreactors) throughout the province, which are sufficient for experimentation.

However, according to them, there are no facilities for product development and pre-marketing.

In fact, according to some, Quebec's ability to scale up bio-manufacturing is limited. For example, it would seem that even having access to laboratory space is an issue. Also, the availability of bioreactors/fermentation tanks in a few locations across the province is referred to as a “sprinkling” in comparison to other jurisdictions. There is no 'bio-hub' with large capacities such as can be found in France or in other European countries[6]. In fact, we were told that more than one team of researcher-entrepreneurs had to go and develop in Europe, since Quebec does not offer any levels in terms of scalability other than fermentation tanks with limited capacity which, although useful for experiments cannot accompany a ramp-up approach with a view to pre-marketing.

Although there is a biotechnology center located in Montreal (NRC) with in theory a significant capacity, its use in a pre-commercial development perspective has presented several challenges. The center does not have a storage silo, is not designed with a continuous supply in mind and poses problems in terms of drying. According to respondents, while the center is technically adequate, its usefulness for product development is limited in its current form. Some participants refer to an INRS project to acquire larger scale bio-fermentation facilities as a step in the right direction. However, compared to the facilities available in Europe, there is still a significant difference in scale.

In this regard, one respondent explicitly replies that the absence of a major industrial player with a significant bio-fermentation capacity is probably a necessary condition for the development of a dynamic ecosystem of bio-manufacturing entrepreneurship. Indeed, in addition to the possibility of using these facilities to validate the ramp-up of a bio-manufacturing process, such players contribute to the development of the intellectual and human capital necessary for growth.

[6] The BioHub © project was launched in 2006 by chemical group Roquette and supported by agency BPI France (formerly Industrial Intervention Agency). The program aimed to develop new foundations or intermediate bases for plant-based chemistry in France and the European Union. Subsequently, the program was joined by several other partners such as BASF and ARKEMA.
https://www.usinenouvelle.com/article/roquette-cloture-le-programme-biohub-avec-succes.N1185292

A participant put forward an example to illustrate the limited scalability that prevails in Quebec. In recent years, products from distillation have been popular with consumers. This popularity has seen the revival of the distillation industry, which once flourished in Quebec. According to the latest information, the Quebec union of micro-distilleries had nearly 50 members offering more than 200 products[7]. However, according to our respondent, only three of these distilleries have the capacity to produce their own alcohol: the other micro-distilleries source their alcohol from outside Quebec.

Within large agri-food groups, which have large-scale production facilities, the recovery of by-products through bio-manufacturing processes is envisaged but does not seem to be a strategic priority. Indeed, there are several pitfalls in this process. For example, the implementation of bio-manufacturing facilities focused on the valorization of by-products requires significant investments in a context where the priorities are rather the maintenance of market shares for traditional products as well as the maintenance of the financial health. In addition, the marketing of products from bio-manufacturing requires familiarity with new markets, often quite different from traditional markets, as well as requiring different expertise.

4.2 Human capital

One participant summed up the human capital challenge that Quebec faces in the development of biomanufacturing: "To produce, you need engineers who understand biology". However, according to several respondents, this expertise is rare in Quebec and has even withered over time. More generally, the scarcity of resources and graduates with expertise and knowledge in the field is a recurring theme among our respondents.

From a perspective of developing the bio-economy and bio-manufacturing, Quebec faces several challenges in terms of human capital. First, at the college and university level, professors with expertise in the field are relatively few and scattered across several institutions. If there are centers of excellence, they appear to us to be based on a single

[7] https://www.newswire.ca/fr/news-releases/distilleries-du-quebec-la-nouvelle-reference-sur-l-industrie-de-la-distillation-au-quebec-801502666.html

individual, who has no immediate successor. In this regard, it is clear that cutting-edge research is based on collaboration with industry, which is favored by the researchers' possession of industrial experience. However, the trend within universities is rather oriented towards hiring professor-researchers without industrial experience. Second, there are no specialized or bio-manufacturing-oriented programs. Some agricultural programs may be similar to it but do not have the same purpose. The absence of dedicated programs leads some researchers to tell us that they are facing a shortage of students to carry out projects. Third, the lack of specialized venture capital funds and the fragmentation of the sector means that the pool of available skills is limited. For a successful company moving towards the commercialization phase, there is a shortage of production and marketing managers at all levels. One participant told us that he had to call on consultants from Boston to complete a project.

More generally, as mentioned by one respondent, the lack of critical mass in the bio-economy sector in Quebec implies that the human capital found here is limited and lacks depth.

4.3 Research capital and know-how

Intellectual capital is based on the presence of innovation and research infrastructures, both fundamental and applied. From the point of view of research, as mentioned above, expertise in Quebec rests on a few individuals dispersed in different institutions. More generally, the emerging observation is that the bio-economy or bio-manufacturing are intrinsically multi-disciplinary, which poses a challenge in the structures of universities where silos are predominant. To date, only McGill University has a bioengineering department within its faculty of engineering. However, several major international research institutions (e.g., Stanford, MIT, Imperial College) have such a department. Several other institutions have also created departments of bio-medical engineering (eg, Toronto). These departments are associated with undergraduate, graduate and postgraduate programs that train graduates with the knowledge and skills to help scale-up companies in biomanufacturing. In this regard, some respondents mention to us the need to develop programs in computational biology in order to combine biology and informatics in the development of bio-manufacturing. However, a few respondents told us about the administrative difficulties they encountered within their universities in carrying out initiatives involving more than one department or faculty.

4.4 Financial capital

An observation shared by several respondents is the weak presence if not the absence of venture capital in bio-manufacturing, regardless of the sub-sector and particularly in bio-manufacturing oriented towards agri-tech in Quebec and even in Canada. This assertion is confirmed by the latest figures published by the venture capital sector via Réseau Capital[8]. The information and communications technology (ICT) sector attracts the majority of capital from venture capitalists and conducts the majority of venture capital investments. Thus, for the first nine months of 2021, nearly 80% of venture capital in Quebec was invested in ICT (information and communication technologies). The life sciences, cleantech and agri-food sectors share the rest, but it should be noted that the bio-economy dimension of these three sectors is relatively small; official data does not contain pertinent details. For comparison, it is estimated that in the United States, the agritech sector alone raised over US$5 billion in capital in 2020 in over 400 deals, with 28 companies raising over US$100 million each[9].

According to some participants, the lack of presence of venture capital oriented towards the bio-economy can be explained by several factors. First, investments in the bio-economy require longer time horizons, especially in biotechnology, than other sectors usually supported by venture capital. Second, there are no venture capital funds specializing in the bio-economy (all sub-sectors combined) in Canada. There is therefore no local expertise in the field: it resides in American funds that invest here. Third, the required capital reaches significant levels especially in the pre-commercialization and commercialization phases. The number of American companies having raised more than $100 million in venture capital in 2020 is an illustration of this.

[8] https://reseaucapital.com/wp-content/uploads/2021/11/en-quebec-t3-2021.pdf

[9] https://www.croplife.com/management/agtech-venture-capital-roundup-an-overview-of-startup-funding-in-2020-and-what-to-expect-in-2021/

4.5 Social capital

Our interviews also show that beyond the technological or financial aspects, the success of a bioeconomy sector (biotechnology or biomanufacturing) depends on its social acceptability, which has several facets.

On the one hand, the acceptability by the surrounding community of research and production facilities is considered by many to be a critical issue. For several stakeholders, the designations of biotechnology, biomanufacturing or synthetic biology have a negative connotation or at the very least bear risks that are difficult to envisage (health, environmental, etc.). In this respect, the proximity of dense residential sectors is perceived as being unfavorable to the growth and development of large-scale facilities. In these circumstances, the support of municipal authorities is also seen as an essential asset.

On the other hand, the consumption of products from biomanufacturing also involves an issue of social acceptability. The example of genetically modified organisms (GMOs) is often cited as illustrating what not to do due to the negative reaction that this expression generates in several quarters (e.g. European Union). In addition, the nutritional aspects of food products from biomanufacturing are subjects of debate in specialized circles. Indeed, making their texture, flavor and appearance compatible with the tastes of the population may require the addition of potentially harmful additives from a nutritional point of view (e.g., salt, dyes). In addition, from a protein point of view, the properties of foods from biomanufacturing processes (plant-based or cell-based) are not necessarily equivalent to those from foods from traditional agriculture[10].

Some participants point out that, from a sustainable development perspective, the bio-economy sector has several advantages due to its limited carbon footprint and its economical use of resources. From this point of view, the production of protein foods on a large scale constitutes a possible partial solution to the challenges of global warming, which results in part from our diet of animal proteins from high-intensity farming. On the other hand, according to one participant, sustainable development also encompasses the health and well-being of individuals and according to him, the nutritional properties of

[10] See, for example: https://truthunmuted.org/dont-be-fooled-lab-grown-meat-is-a-disaster-in-the-making/

foods produced by agritech processes undermine their potential benefit in terms of the environment. As an alternative to the production of food from agritech, our participant highlights the merits of regenerative agriculture, which ultimately aims to produce food with quality nutritional properties while respecting the environment[11]. Large agri-food groups have also begun to invest in such a strategy, such as General Mills and Nestlé.[12,13]

4.6 Synthesis

A participant well summarized the keys to success in biomanufacturing which, according to him, are based on the following elements:

- Facilities or good production management practices are applied (physical capital/human capital);
- Competent and experienced staff (human capital);
- From science for the scaling up of biomaterials to biomanufacturing
- (eg, 1 liter to 100 liters to 1000 liters) (intellectual capital);
- Sufficient capital (financial capital);
- Support from the community (eg, municipal authorities) (social capital).

These keys to success dovetail well with the five types of capital that emerged from our interviews. Moreover, these keys to success or the five types of capital make it clear that to be effective, any government action will have to be holistic and encompass all these dimensions. According to a participant, given the diversity of sectors and fields underlying the bio-economy, and the scale of the capital required to have an impact, it seems important to adopt a niche positioning oriented towards targeted and strategic investments.

[11] For more information, see: https://regenerationinternational.org/why-regenerative-agriculture/

[12] https://www.generalmills.com/en/Responsibility/Sustainability/Regenerative-agriculture

[13] https://www.nestle.com/media/pressreleases/allpressreleases/support-transition-regenerative-food-system

Apendix Part B
List of People Interviewed

Position	Sector
Vice-president R&D	Food company
Vice-president Innovation	Food company
Senior Director Innovation	Food company
Professor-researcher with industry experience	Faculty of Engineering
Professor-researcher with industry experience	Faculty of Science
Professor-researcher with industry experience	Faculty of Management
Professor-researcher with industry experience	Faculty of Agriculture
Researcher and entrepreneur	Genomics and biotechnology
Partner	Venture capital firm
Partner	Venture capital firm
Director General	Center for Industrial Research & Innovation
Director General	Center for Innovation and Sector Transfer
President and CEO	Research Support Institute
Investor	Biomanufacturing company
Investor (angel investor)	Biomanufacturing company
Director	Center for Innovation and Sector Transfer

Part C

Top-Down: International Policy

> This part of the Report deals with specific policy initiatives that have been adopted in different jurisdictions. A suggested model for Quebec that could follow the UK experience is presented in Section 5. The following two sections have an international focus: in the former, we survey common elements across varios countries. The final section summarizes the resulst of an internstion symposium on biomanufacturing held under the aegis of the World Economic Forum.

In the United States, the field of synthetic biology received sudden and significant congressional attention in May 2010 when Craig Venter, a biotechnologist and synthetic genomics entrepreneur, reported having succeeded in activating in a living bacterial cell a synthetic genome created from chemical components and capable of self-replication. Following this announcement, President Barack Obama ordered the establishment of the Presidential Commission made up of a panel of scientists and responsible in particular for identifying the appropriate ethical limits to maximize the public benefits and minimize the risks of synthetic biology. This commission submitted to the President the report *New Directions: The Ethics of Synthetic Biology and Emerging Technologies* in December 2010, in which it recommends, among other things, that the government regularly reassess the risks and other ethical issues as the science of synthetic biology progresses.

In short, the synthetic biology revoltion was underway in the United States. Other countries were forced as a consequence to play catch-up and have made impressive strategic strides in attempting to establish the new bio-economy over the last decade. One of the earliest and most comprehensive strategic plans was undertaken by the UK in 2011. As the country's Roadmap provides a template for similar initiatives, we describe in detail in this Section the details of the detail of the Roadmap and its implementation.

Initiatives with similar objectives have acknowledged the importance of the bio-economy and have framed plans to point their economies in this direction. Section 6 surveys international efforts in a report compiled by *International Advisory Council on Global Bio-economy.* It provides a useful international overview of core strategies aimed at furthering the development of the bio-economy.

The World Economic Forum recently invited leaders to address the steps that need to be taken at this junction in the development of the bio-economy. Their call for action comprises two components: scaling partnerships and workforce compensation. This material is covered in Section 7.

Section 5 Roadmap for the Development of Synthetic Biology in the UK

In 2011, the UK Government commissioned a review of significant strengths and opportunities within the country's academic base. The aim was the development of policy that would address the *valley of death* between scientific discoveries and commercial development. Among the eight various possibilities considered, synthetic biology was selected because of the country's legacy and success in biotechnological commercialization, as well as the potential for substantial growth in different product and service markets.

The construction of a Synthetic Biology Roadmap was entrusted to an independent group consisting of representatives from industry, academia, along with observers from relevant government departments. The group was chaired by an industrialist with experience in the commercialization of scientific research. Five main recommendations were proposed: (i) invest in a number of multidisciplinary centres; (ii) build a skilled country-wide synthetic biology community; (iii) invest to accelerate technology to market; (iv) assume an international role; (v) establish a leadership council to monitor, assess and stimulate developments in policy regarding synthetic biology and to provide an overarching co-ordinating function spanning research initiatives and commercial translation.

Significant funds were reserved to achieve these objectives. Six *Synthetic Biology Research Centers* were established (in biomedicine, biochemical, DNA plant registry, biopharma, engineering of biochemical products, bio systems design and engineering). These were university based across six institutions. As well, there was strategic capital investment to support DNA research capabilities with the ultimate objective of creating jobs and driving economic growth. Finally, further investments were made to enhance doctoral training on the one hand (at three universities) and support start up companies on the other (a dedicated fund was established to be managed by a private-sector company).

The Roadmap underscored the importance of the availability of an expert workforce in supporting the development of an emergent field. It acknowledged the need to steer training from the underpinning sciences to broader, technical multidisciplinary skills. The development of entrepreneurial skills particularly in post-doctoral research was also stressed.

The infrastructure initiatives were implemented by 2016. At this time some 50 start-ups and larger companies were actively engaged in synthetic biology in the UK. Following the recommendations of the Leadership Council that had determined that sufficient progress had been achieved, the Government moved to second stage of development with the announcement of *The UK Synthetic Biology Strategic Plan* This document presented a refreshed focus on commercialization with explicit strategic objectives: to accelerate industrialization, accelerate commercialization, build an expert workforce, enhance value via international partnerships. The Plan did not demarcate specific fields of applications in synthetic biology. Rather it pointed to key applications and market opportunities such as in medicines and healthcare, biofuels.

The UK roadmap for synthetic biology and its subsequent development in the strategic plan can be viewed as a model or template for government support for the commercial development of an emerging, potentially transformative scientific domain. It combines supply-side support in the form of the establishment of research centers across the university system and demand-side concern for market sensitivity. Capital is provided in the four forms analyzed in this Report. Research Capital at the university level is extensive, as is Infrastructure Capital in the various technical centers established by the program. There is a manifest concern for the development of skills or Human Capital. The Leadership Council in various documents has emphasized the development of sustainable, environmentally sensitive technology with appropriate governance initiatives and the creation of technical standards responding to social expectations; i.e., Social Capital.

It is difficult to assess at this point whether this investment has led to success commensurate with its objectives. We consider two different evaluations. The first is a self assessment offered by the Leadership Council in 2020 in the document *Synthetic Biology UK: A Decade of Rapid Progress*; the second considers market investment in UK firms in the area over the five years.

The survey of the technical accomplishments and commercial development of firms in the UK synthetic biology universe appears impressive. In 2019 there were over 150 start-ups and more established firms in field comprising health care, agri-tech and biomaterials and bio-chemicals. The document presents specific companies and their products. A network of bio-foundries has been developed in the UK. A group of companies are addressing social challenges such as developing products to remove micropollutants from treated water, generation low carbon fuel options, and the development of low carbon jet fuel. Non-breeding mosquitos have engineered to arrest the development of tropical diseases. On the research side, seven synthetic biology research centers are in operation; there are five innovation clusters. Over 1000 postgraduates have trained over the previous five years; the start-ups employ some 2000 staff. A variety on international linkages have been established including extensive collaboration with Singapore's National University.

The Leadership Council Report provides some financial impact figures. Private investment in start-ups has grown from $50 million to almost $4 billion in 2018, an annual increase of 35%. There have a number of successful exits in the form of IPOs and acquisitions. The ratio of private to public funding exceeded 10:1 by 2016.

Section 6 Global Bio-economy Policy Report

In 2021 the *International Advisory Council on Global Bio-economy* prepared a comprehensive surveying policy and policy changes for all 60 or so countries that had and were developing policy during the past decade. The study focuses in particular of the 19 dedicated and macroregional policy strategies. The focus is the engagement of government actors in the bio-economy broadly construed. Indeed, it is a policy issue as to what exactly comprises the bio-economy or a policy strategy for the bio-economy. Our Report is more narrowly directed to issues in bioengineering. None the less, the Report is instructive in surveying a wide range of policy orientations which can be readily adapted to our preoccupations.

Comprehensive approaches for promoting innovation towards economic growth comprise a wide-variety of strategies. The methodology adopted in this particular study posed a number of questions to various countries to illuminate their goals in promoting the bio-economy organized as to whether they addressed the supply side or demand side of the economy. The supply side measures involve capacity building and education, infrastructure development, and supporting commercialization; on the demand side, measures relate to general awareness building and information campaigns, alongside market promotion policies using lead buyers and tax policies. Other questions probed the extent of regulatory measures and issues related to good governance.

As this methodological approach dovetails nicely with our own, we find the study particularly useful. We are less concerned about which country adopted what policy that with the nature of the supply-side and demand-side measures that would aid in formulating the components of a Quebec appropriate framework for the support of bioengineering in the province. We survey the study's findings in this section under the headings *Core Elements of Policy Strategies* and *Specific Policy Proposals*.

Core Elements of Policy Strategies

- A range of bio-economy strategies seek to address global societal changes, particularly for shifting to a low-carbon economy and contributing to achieving the objectives of the Paris Accord.

- Sustainable development is also a policy preoccupation. Governments link their support of the bio-economy to promoting a sustainable economy. Interesting German policy acknowledges that not all sustainable objective goals can be achieved simultaneously and must of necessity weigh challenges, opportunities and trade-offs. In general, sustainability is construed to involve both an economic and social dimension. Japan for example highlights the social dimension, a discussion that calls for changes in behaviour values.
- An economic agenda is at the forefront of strategy discussion with the bio-economy viewed as an integral component of the renewal of certain industries, Latvia's strategy has focused on arresting the decline in agricultural employment with n emphasis on new technology and skills.
- The Covid pandemic has highlighted the importance of the bio-economy in developing new measures to combat disease and improve human health.
- An important trend in policy discussion is the heightened role of the importance of the circular economy.
- There is considerable emphasis on technological convergence; bio-digitalization is seen as a path to the development of innovative sustainable products and applications.

Specific Policy Proposals

We first look at the supply-side proposals.

- Policy strategies highlight the importance of promoting links between fundamental and applied research, and supporting multidisciplinary research alliances. Countries underline the need for increased private R & D in the form of industry lead consortia.
- Strategies look to strengthen international networking.
- *Cluster development* is often referred to. The promotion of public-private partnerships is viewed as highly relevant.
- Germany underscores the need to provide space for experimentation.

- Safe innovation has been stressed by Japan and Germany: harmonization of digital data, efficient data management systems, and the development and use of standards.
- Start-up support is widely seen as a tool to promote bioeconomic innovation.
- There is increasing recognition that the funding of high-risk investment is not well supported, Venture capital and investment funds for bio-based start-ups are promoted in France.
- Regarding infrastructure investments: there has been large-scale bio-refinery development across the European community.

Demand-side initiatives include:

- A specific approach that allows innovation and sustainable products to compete with existing ones has been widely adopted via public procurement policies.
- The need to raise public awareness of the importance for bio-economic strategies is generally acknowledged. In Germany, science communication and open dialogue formats have become increasingly popular.

The coordination of the broad range of bio-economy actors and their different interests poses a considerable challenge. The importance of policy coherence and effectiveness in strategic policies has grown particularly significant given the complexity of transformations associated with developments in the bio-economy. Some countries have established dedicated bio-economy advisory councils to monitor overall policy and to assess the success of various policy initiatives.

Section 7 World Economic Forum: Accelerating the Biomanufacturing Revolution

The transition to a mature bio-economy faces fundamental economic hurdles. Until recently, cost considerations restricted biomanufacturing development to either high-cost/low volume goods such as pharmaceuticals or low-cost/high- volume commodities such as bioethanol production. Improvements in biomanufacturing techniques are currently altering this value equation for products that span much broader segments of the economy. Indeed, the cost of goods so derived can be reduced while their quality control improved. Personal care, nutrition, materials are all affected by new production techniques. As we have noted elsewhere in the Report biological applications suggest promising approaches to solving major and imminent environmental challenges.

In this context, the World Economic Form brought together in 2021 leaders from business, academia and government to identify opportunities where biomanufacturing could enhance innovation and economic development. This group identified two key strategies needed to attain these objectives: scaling partnerships and growth of a skilled workforce.

7.1 Scaling Partnerships and investment to accelerate commercial biomanufacturing

Strategic partnerships can be used to accelerate the development and ultimate adoption of biomanufacturing approaches. One focus is to establish platform companies.

- *Cell development toolkits*. Platform companies leverage economies of scale in a particular technology system to serve different applications. On this approach, software applications are developed from a basic toolkit on a common platform. The software is decoupled from the application. Cell development kits lower the barrier to developing new biomanufacturing applications. Such platform companies enable broader access to the bio-economy by offering significant cost savings and reduce development timelines *Ginko Bioworks* is one such example.
- Pioneers in product development (say, a class of molecules) may not be best suited to direct the downstream process to bring to market a finished product from the molecule. A partnership with a company experienced in bringing products to market is needed.
- Many potential biomanufacturing applications must balance the high cost of producing small volumes until a market is established to support scaled-up

production. Carrying the costs of development and manufacturing scale maybe overly capital intensive for technology pioneers. Contract manufacturing companies can offer large-scale solutions.

- Public-private programmes, such as biomanufacturing cooperatives where organizations co-invest and co-design, could help technology pioneers co-invest and co-design.

Scaling partnerships offers an opportunity to expand the biomanufacturing ecosystem and aggregate expertise and technologies to increase the success rate of commercial biomanufacturing. Investment in the creation of advanced, collaborative spaces will break down the barrier to the commercialization of new biomanufacturing applications.

7.2 Workforce Transformation

The biomanufacturing revolution is changing the traditional hierarchy of the biotechnology workforce. The development and deployment of a biomanufacturing process from upstream biological engineering, through manufacturing and ending with product integration and marketing require a wide and diverse set of interdisciplinary, cross functional skills. In this regard, the World Economic Forum offers various observations:

- The new ecosystem will require a postgraduate-trained workforce to fill upstream bioengineering roles.
- Biomanufacturing is creating additional opportunities in automation and software engineering, chemical and materials engineering, skilled labour manufacturing and new roles in product integration.
- Biomanufacturing requires the development of a cyan-collar manufacturing jobs, characterized as the intersection between sustainable green technologies and traditional blue-collar manufacturing. These jobs are accessible with an undergraduate degree.
- The growth of these cyan-collared jobs is particularly relevant in rural areas. Many low-cost feedstocks for common biomanufacturing applications are grown close to

fermentation facilities with the concomitant opportunity to expand skilled jobs outside the city.

- Automation and digitalization are standard skill sets. The new technologies will enable the development of targeted certificate programmes.
- But it remains clear that technical innovation will still be driven by PhD-level scientists and academia.
- There will be a new class of entrepreneurs developing apps on biological platforms that must have the relevant “business” skills to design and implement with biology.

The reality is that the biomanufacturing workforce of the future will share many of the skills shared across the broader STEM community. This community can only benefit with the opportunity for greater workforce mobility.

Part D

Bottom Up: The Challenge of Getting to Market

> We shift gears in this Part of the Report in moving in Section 8 from a consideration of broad sectoral public policy to develop an appreciation of the actual challenges faced by a small commercial start-up. The following section describes the important issue of scalability at the heart of the biomanufacturing process.

Start-ups that develop new products using synthetic biology generally face similar problems notwithstanding the extreme dissimilarity of their products. From a scientific perspective, each company has had to isolate and engineer different technical pathways in order to end with a product that could potentially be refined for commercialization. As well, the companies have had to face similar hurdles in their organizational development. These shared obstacles we have isolated as particular capital challenges—Financial, Infrastructure and Human-- that need to be surmounted if the company is to survive.

To illustrate this dynamic, we interviewed at length Shoham Mookerjee of *Hyasynth Bio*, a Montreal start-up that is now attracting serious attention in the form of a significant capital infusion due to arrive later in 2022. The development of this company is instructive from a policy perspective; Section 8 recaps details of the interview.

As we have seen illustrated in the interview with Hyasynth Bio, the *valley of death* in the development of bio products, vividly describes the challenge of scaling from very small production to an adequate level in order to establish some further support for the technical feasibility of the product and to take a first step towards the market. We have also interviewed Xavier Hervé of District 3, an incubator supported by Concordia University, to learn further about this challenge. He has a very specific proposal for Québec to bridge the *valley of death* that we describe in Section 9.

Section 8 The Development of Hyasynth Bio in Montreal

Currently housed in labs at UQAM, this company is the brainchild of four young scientists who met in an MA programme directed by Vincent Martin at Concordia University. They wanted to turn the academic work they were learning into a practical vehicle that would be financially viable and have social benefit.

In a first step, they outlined on paper several ideas and development plans. These were submitted to an accelerator fund in Ireland where they presented their ideas. One was accepted and in 2015 Hyasynth received $30 000 in start-up capital from an Irish Venture Capital fund (in return for an equity stake in the company).

The business of *Hyasynth Bio* is the production of cannabinoids, the active compounds of cannabis. These chemicals are normally produced by plants. In synthetic biology, a fermentation process is developed to produce CBD, the active molecule in cannabis. The molecule can then be used in healthcare products (pills, oils) to deal with a variety of ailments including anxiety, pain and cardiovascular disease. The process bypasses the considerable and unsustainable agriculture infrastructure required to produced cannabis in large quantities (along with the natural resources such as water to support this infrastructure; it admits more controlled, less seasonal production; finally, from a government perspective, it can be more easily regulated with less possibility of diversion to the black market.

However, the engineering framework for synthetic production is daunting. The process is fermentation based; see Appendix B for a layman's account. The idea is to develop a yeast strain that produces CBD. Here genes are found from other contexts that do the job (which DNA sequences work best?); these are pasted into yeast and a production process can be launched. The involves several pathways whereby a molecule of interest is produced at each step, ultimately feeding into the final step that yields the desired CBD molecule. The use and discovery of the "best" enzymes to activate and efficiently direct the processes was the challenge. Here *Hyasynth* made advances that the company was able to patent. These patents (in all, three pathways were discovered and patented) effectively created a barrier to entry for competitors in this field which, not surprisingly, has attracted considerable attention.

The time line for these discoveries has been quick. From a paper start in 2015, the first patent was filed in 2017. But a new enzyme was needed for the final production stage (the plant-based cannabis enzyme didn't work well); this was found in 2019, and patents filed. Production could begin; *Hyasynth* was on the map!

What did production actually entail in practice at this point in 2021? Six one-liter fermenters each produce a small quantity of CBD in a week. Current overheads at Hyasynth vary from $220,000 to $600,000. a month; as is described below, another source of funds had been found in the interim. The first valley of death for the young company has been crossed.

In January 2022, *Hyasynth* began to outsource fermentation operations to a private company in Wisconsin at the larger capacity of 250 liters. Two runs (at $400k) have been booked with monthly CBD per gram production costs falling by a factor of 200 with a more significant level of production. Some potential customers who have signed a letter of intent will buy several grams from this output for testing and evaluation.

Capital has been required to pursue these steps. By 2017, the initial investment from the Irish VC firm had been fully used. At this point a $1 million capital infusion from *Anges Quebec* enabled the hiring of two employees. The next year a new investor became involved (OGI) whose CEO had a pharmaceutical background and understood the importance of finding the right enzymes in cannabis fermentation. OGI's capital involvement was $10 million spread over 3 years from 2018-2021 and involved tight scrutiny of Hyasynth's with meetings scheduled at frequent intervals. "The company would have been more successful if this investment had been located earlier." Hyasynth is currently closing a deal (up to $20 million) with US strategic investors. Through this development, the ultimate goal is to make the company profitable and then see what emerges as the most interesting final stage(s) in its development.

To survive this initial period, the company has needed space and personnel. From a rent-free primitive space at Concordia, *Hyasynth* moved to unused facilities at UQAM where it has paid an annual $45 sq. ft. rate for 3500 sq ft. Once the new investment is secured the plan is move to dedicated laboratory-oriented facilities in Laval; here the sq. ft. cost will be much higher for a larger space.

The complexity of the fermentation process entailed the creation of three groups within the company: (i) yeast engineers to optimize sugar flow; (ii) enzyme engineers to promote molecular transformations; (iii) process engineers to oversee the fermentation process. Six people were involved in the early stages, then thirty people hired in 2019, generally chemical engineers with a specialization in biochemistry who chose to work in fermentation. Ideally, young people with skills in applied biology were sought.

Mr. Mookerjee emphasized that it was difficult to hire talent from the US innovation hubs in Boston and San Francisco due to salary issues and a sense of restricted career potential working in an environment with a smallecosystem in engineering biology. Although there is considerable demand for fermentation infrastructure, the availability of human capital, above all in chemical and mechanical engineering, will be a problem if the development of such facilities is to be achieved.

Addendum Given the nature of the company's output, it was necessary for *Hyasynth* to obtain a Dealer Licence under the Narcotic Control Regulations of Health Canada. From the outset, the company has needed to make several presentations to Health Canada describing how cannabis can be made with yeast and not involve plant harvesting.

Section 9 The Valley of Death

When we visited Hyasynth Bio, the co-founder displayed the fruits of five years of scientific labour and millions of dollars involving dozens of scientists and technicians in the very concrete form of six one-liter cannisters of liquid from which the desired product could be extracted by filtration. Maybe a gram's worth! But it was a quality gram that was attracting some attention.

Defined by the United States Government Accountability Office, Manufacturing Readiness Levels (MRLs) are precisely defined quantitative measures that are used to assess the maturity of new product or technology from a manufacturing perspective. MRLs provide decision makers at all levels with objective metrics to evaluate the development maturity of the proposed product as well as the attendant risks that must be faced in bringing the product to market. The MRL components include the availability of the feedstock to be transformed, production capacity, the supporting pool of talent with the relevant skills, and the appropriate infrastructure required for certification, and the validation of market demand.

MRLs are about scale. One-thousand-liter production is viewed as the entry level for serious investor participation. The scaling imperative passes by a factor of ten from one liter to a hundred liters to thousand and then ten thousand before reaching market demand levels scaled at around several 100,000 liters and beyond. MRL assessments are relevant all along this exponential scaling chain.

The reality is that proof of even the 1000-liter fermentation benchmark cannot be established in Quebec. MRL validation cannot be established here. The danger is that, as a consequence, innovators may be forced to leave the Province taking with them potential economic value and jobs.

District 3's Xavier Hervé argues that Quebec requires a mid-size biorefinery. On his analysis, it is the missing link that is required in the Province to enable new technology developed here to become commercially viable. Without it, innovation initiatives cannot progress along the scaling chain. With it, Hrvé argues, it enables an economic ecosystem that is critical for the prosperity of Quebec.

The elements of his argument can be summarized along the capital lines we have been pursuing:

- Research capital in the Quebec University system has been strong with world-class results;
- Human Capital is present given the training students receive in the CEGEP system and the quite accessible University system;
- The Universities provide dynamic for a for social debate and contribute to Social Capital;
- Infrastructure Capital resides in the formidable array of fermentation experts engaged at Lallemand, Agropur, Saputo and Molson;
- Recent policies have addressed the need for seed financing and stressed the importance of entrepreneurship. There has emerged in the Province a well-developed start-up system.

The argument concludes that the Government in partnership with industry and investors ahould collaborate to supply the mid-size bio-refinery, the missing link in the development of industrial biotechnology in Québec.

We certainly agree that a local bio-refining capacity could play an important role in the development of the bio-economy. A business plan analyzing the costs and potential revenues of such a refinery would in effect be a diagnostic of the current state of the bio-economy in the Province and would reveal its strengths and weaknesses. Indeed, the allocation of funds for such a study is one of the Recommendations of this Report given in Section 12.

Appendix Part D

The Magic of Fermentation

Fermentation is a natural biochemical process that decomposes organic matter, such as glucose, in an oxygen-deprived environment through the action of microorganisms – yeasts, bacteria and/or fungi. In this process, organic matter is ingested by these microorganisms that then generate acid, gas or alcohol molecules. Yeasts are single-celled fungi that are able to activate the fermentation process, and enzymes issued by these microorganisms are catalysts[14].

There are various types of fermentation, mainly ethanol fermentation, lactic fermentation to make foods based on milk, also on meat or fish, and acetic fermentation used in the production of vinegar. Fermentation has many applications in traditional human nutrition, and is an integral part of the production of many foods and beverages. Food fermentation consists of the transformation of sugars and other carbohydrates into alcohol on the one hand, or into preservative organic acids and carbon dioxide on the other hand.

In the first case, alcohol production is obtained when juices from fruits are made into wine, when cereals (malted barley) are brewed into beer, and when starchy foods such as potatoes are fermented and then distilled to produce spirits. In the second case, the production of organic acids is used to preserve and flavour vegetables and dairy products, and the generation of carbon dioxide is used to leaven bread[15].

The biotransformation process of organic matter produced by bacteria, fungi and other microorganisms also allows for improvements in the digestibility and nutritional value of foods[16].

[14] https://ensaia.univ-lorraine.fr/sites/ensaia.univ-lorraine.fr/files/users/telechargements/rapport_final_fermentation2.pdf

[15] https://en.wikipedia.org/wiki/Fermentation_in_food_processing

[16] https://en.wikipedia.org/wiki/Fermentation

Precision fermentation (synthetic biology)

In contrast to natural fermentation, precision fermentation refers to a technology based on a process in which microorganisms act as tiny cell factories and are directed to produce molecules with specific characteristics. The target molecule can be a protein, a lipid, a flavour compound, a fragrance, an enzyme, or some other class of molecule. "Directions" are given to these microorganisms by genetic engineering when developing the microbial strain. Here, strain discovery and development require massive datasets in terms of microorganism specimens and genomic data[17].

After being engineered, the microorganisms are cultivated in fermenters and fed with essential nutrients to ensure their growth. Once the required density is reached, the desired product is recovered and purified into a functional product. When the optimal culture process is found, the fermenter capacity can be scaled up sometimes to several thousand liters[18].

Precision fermentation is a technology of synthetic biology that has been developed for several decades and used in the elaboration of pharmaceutical products such as insulin or vitamins[19]. In food, its techniques are used in the manufacturing process of alternative proteins, especially microorganism-based substitutes. Eggs and dairy products, including ice cream and cheese, are examples of food that can be generated through precision fermentation[20].

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[17] https://gfi.org/science/the-science-of-fermentation/ & https://www.shiru.com/post/what-is-precision-fermentation

[18] https://www.shiru.com/post/what-is-precision-fermentation & https://www.forbes.com/sites/errolschweizer/2022/03/02/what-should-consumers-be-asking-about-precision-fermentation/?sh=2472e85c27b0

[19] https://perfectday.com/myths-vs-facts/

[20] Southey, F. (2022, 27 Janvier). What's next in alternative protein? 7 trends on the up in 2022. Food Navigator. https://www.foodnavigator.com/Article/2022/01/27/What-s-next-in-alternative-protein-7-trends-on-the-up-in-2022

Part E

Synthetic Biology and Agricuture: Promising but Problematic

> The debate surrounding genetically modified organisms has crowded out discussion about the potential benefits of synthetic biology in the realm of agriculture. In the Part of the Report we review the approaches adopted in the field of protein transformation and trace its progress towards alleviating the world protein deficit. Section 11 discussess the importance for a wider appreciation of the social implications of the protein transformation.

The transformative possibilities of synthetic biology in agriculture are extensive. The field could emerge as the primary tool in resolving the challenges of sustaining and expanding the global food supply. Here issues of economic and environmental feasibility are paramount.

In this section, we focus on emerging development in finding protein alternatives to meat. The material presented rests heavily on a 2020 study by the Boston Consulting Group entitled *Food for Thought: The Protein Transformation.*

There are three types of alternative proteins: plant based, microorganism based and animal cell based. The production of protein passes through similar steps that are described in Section 9. Venture capital funding from 2015 to 2020 alone totaled more than $4 billion with $3 billion going to plant-based alternatives, followed by $730 million in microorganisms and $15 million in animal-cell based proteins.

The transformative possibilities of synthetic biology in agriculture are extensive. The field could emerge as the primary tool in resolving the challenges of sustaining and expanding the global food supply. Here issues of economic and environmental feasibility are paramount. The potential applications are illustrated in the following Table.

Table 2 – Applications in the Agrifood Sec

Applications of synthetic biology in the agrifood sector.

Area of application		Host	Traits/product	Examples
Agriculture	Crop improvement	Plant	Productivity increase	Improved carbon fixation in crops.
		Plant	Production of novel substance or increased content of existing substance	Nutraceuticals such as carotenoid; Increased content of lignocellulose, oil, soluble sugar as bioenergy.
		Plant	Reduced need for inputs into agriculture	Engineered crops with reduced demands for inputs such as pesticide, water and nitrogen.
		Plant	New ways of self-incompatible crop breeding	Diploid potato breeding.
		Microbe	Biofertilizer or biopesticide production	Provide biofertilizer or biopesticide through plant-microbe interaction.
	Pest/crop disease control	Microbe	Biosensors	Pathogen detection in plants and soil.
		Microbe	Bio-insecticides	Fusion protein toxic to certain insects.
		Microbe	Synthetic microbe killing specific pests	Synthetic virus/fungus targeting and killing specific pests
		Insect	Sterile pests with synthetic gene drive system	Synthetic gene drive for sex-ratio distortion of certain pest group
	Environmental enhancement	Microbe	Biosensors	Pollutant test such as heavy metal.
		Microbe	Bioremediation	Bioremediation of metal, radionuclides and other substances.
		Microbe	Tackling soil erosion	Engineered bacteria for promoting root growth and protecting the soil from erosion.
		Microbe	Biofuels	Production of cellulosic ethanol, diesel, etc.
	Livestock management	Microbe	Biosensor and biotherapeutics	Whole cell-mediated health monitoring and disease treatment
		Microbe	Function of facilitating feed processing	Engineered microbe or enzyme for feed processing.
		Animals	Animal breeding	Breeding of new lines depending on synthetic gene drive, genome editing, synthesised genes, etc.
Food	Food products	Microbe, plant	Novel foods	Casein for milk production from yeast; Egg white from yeast.
		Microbe, plant	Food additives	Colorant and flavours (vanillin, raspberry ketone, Stevia et al.); nutraceuticals (vitamins, carotenoid et al.).
	Food processing	Microbe	Improved fermentation process	Higher fermentation efficiency or better flavour products.
	Food safety diagnosis	Microbe	Biosensors	Food toxin, pathogen, parasite or other substance detection.
	Food waste processing	Microbe	Waste degradation and useful substance extraction	Engineered microbe for phosphorus recovery from food waste.
	Food packaging	Microbe	Material production	Biodegradable material such as biopolymer.

Shan, J. et al, 2019, Synthetic biology applied in the agrifood sector: Public perceptions, 2 attitudes and implications for future studies, Trends in Food Science & Technology (Vol 91).

In perusing this list of applications, we can hardly object to their value and relevance with key social and environmental concerns addressed head on. In their survey in 2019, McKinsey estimated that the annual impact synthetic biology applications in agriculture and food could range from $0.8 trillion to $1.2 trillion in the next 10 to 20 years. In this section, we focus on emerging developments in alternative proteins.

10.1 The Protein Transformation

The reality is that the world has a taste for animal-based protein. In 2020, world consumption of meat, seafood, dairy and eggs amounts to 75 kilograms per person or 575 million metric tons. These numbers are increasing, particularly in developing markets. Yet social concerns are growing more pronounced: concern for the environmental cost of producing all this meat, concern for the treatment of animals and concern for human health as a consequence of consuming large amounts of conventional protein.

In 2020, 13 million metric tons of alternative proteins, or about 2% of the animal protein market, were consumed globally. There is some interest in alternatives, but greater consumption of alternatives rests to a large extent with their achieving parity with animal proteins along three dimensions: taste, texture, and price. It must be observed that alternative proteins are hardly a bargain.

There are three types of alternative proteins: plant based, microorganism based and animal cell based. The production of protein passes through similar steps:

Table 3 – Value Chain in the Development of Vegetable Proteins

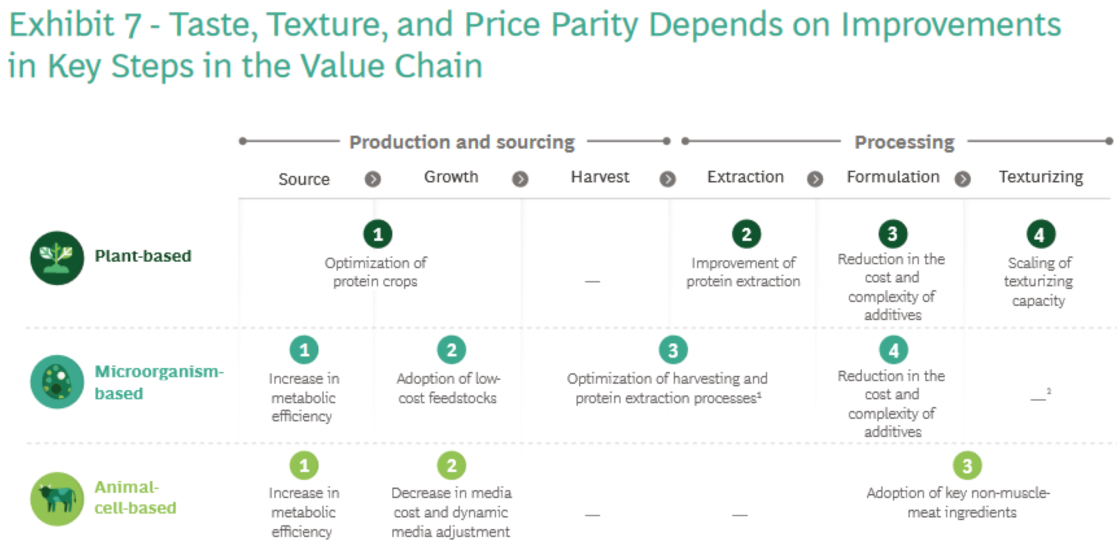

Exhibit 7 - Taste, Texture, and Price Parity Depends on Improvements in Key Steps in the Value Chain

	Production and sourcing			Processing		
	Source	Growth	Harvest	Extraction	Formulation	Texturizing
Plant-based	1 Optimization of protein crops		—	2 Improvement of protein extraction	3 Reduction in the cost and complexity of additives	4 Scaling of texturizing capacity
Microorganism-based	1 Increase in metabolic efficiency	2 Adoption of low-cost feedstocks	3 Optimization of harvesting and protein extraction processes[1]		4 Reduction in the cost and complexity of additives	—[2]
Animal-cell-based	1 Increase in metabolic efficiency	2 Decrease in media cost and dynamic media adjustment	—	—	3 Adoption of key non-muscle-meat ingredients	

Source : *Boston Consulting Group (2020) Food for Thought: The Protein Transformation, p. 17.*

We find it useful to go into greater detail in presenting these processes, as the directions for improvement effectively demarcate market opportunities for new companies in the area.

- *Plant based*

  Inputs such as soybeans and yellow beans are mixed with additives for taste. Different extrusion techniques lead to different textures. Products such as Beyond Meat's various meat alternatives and Impossible Food's ground beef have achieved a semblance of parity.

  Directions for improvement: (i) new varieties of soybeans and yellow beans with increased protein content that are more suitable for human consumption need to be developed to reduce the cost per kilogram of the finished product; (ii) the process of extracting protein from crops needs to be scaled up. In this context, the sale of extraction by-products such as soybean oil can lessen the cost of extraction; (iii) improved natural flavoring is desirable; (iv) improved texturing or extraction processes.

- *Microorganism based*

  Protein is produced by growing bacteria, yeasts, algae or fungi in a carbohydrate rich environment through fermentation. The fermentation process is more sustainable than the production of plant-based protein. Microorganisms hold the promise of making realistic substitutes for eggs. They can also play a role in improving the taste and texture of plant-based protein.

  Directions for improvement: (i) improving the metabolic efficiency by which microorganisms convert the feedstock; (ii) finding less expensive feedstocks; (ii) different steps (centrifugation, filtration and drying) are required to obtain the protein extract and decreasing costs via more efficient extraction is a field open to technological improvement; (iv) additives must be developed to reach taste and texture parity.

- *Animal cell based*

  The protein products are cultured directly from (a few) animal cells in bioreactors fed by nutrient-rich media. A test restaurant for SuperMeats's cultured chicken has opened in Israel.

  Directions for improvement: (i) improve the sped and output of the culturing process; (ii) reduce the costs of the media from pharmaceutical quality to farm quality; (iii) find techniques/ingredients (eg, fat) to induce the cells to form fibers and meat-like fat (the goal would be unsaturated fat!).

We conclude by observing that investment capital is currently focused on companies that are integrated along the value chain that can integrate solutions to particular technical solutions. These firms are best able to deal with specific problems such as improvements described above in the metabolic processes or addressing challenges in improving flavoring or texture. These solutions must then be incorporated into large-scale industrialized platforms that require specific engineering capacities.

Venture capital funding from 2015 to 2020 alone totaled more than $4 billion with $3 billion going to plant-based alternatives, followed by $730 million in microorganisms and $15 million in animal-cell based proteins.

Section 11 The Need for Social Engagement

Biological processes are self-replicating, self-sustaining and do not respect jurisdictional boundaries. Innovation in this area brings in its wake profound and unique risks. Different values within one's one culture may make it difficult to forge consensus, including many life and death issue. International regulation, particularly in agriculture, will be difficult to formulate. Finally, low barriers to entry open the door to potential misuse.

11.1 The move to alternative proteins will impact farmers as an economic sector

As the major producers of animal-based proteins, the world's farmers have a major role to play in any transition to alternative proteins. The potential disruptive impact of a significant re-alignment of consumer consumption is evident. Even in a modest growth of alternatives will require a reorientation of farm output towards produce that is more oriented to human consumption. Significant capital investments will be required and need to be supported by long-term contracts and price guarantees.

11.2 Social acceptance cannot be taken for granted

The main lines of the developments in synthetic biology relating to agriculture are certainly daunting:

- *Biosynthesis of high-value plant metabolites*
  The utility of plants as the source of high-value compounds is undermined by their dependence on arable land and water. Transplantation of multigene pathways to foreign microbes (bacteria) offer a potentially economically viable alternative approach.
- *Opportunities for plant-based agriculture*
  One target for improvement is nitrogen fixation. Nitrogen is expensive to produce and environmentally consequential using some 1% of total annual energy expenditure. Efforts are underway to introduce direct nitrogen fixation in to higher plants with the goal of reducing global fertilizer use by one third.

- *Engineering of genetic circuitry*

  The introduction of biosensors has a potentially transformative impact. The development of "smart plants" will enable to adjust appropriately to their environment.
- *Gene editing and gene drives*

  A potential example of this technology is to clear animals of antibiotic resistance. Another application for gene drives to eradicate pest species.

Few people would question the benefits of developing a bio-economy to combat the significant challenges of our times. However, public resistance to GM technology in some parts of the world is undoubtedly a harbinger of future controversies relating to developments in synthetic biology.

Multiple risk issues have been raised in relation to human health, environmental, socioeconomic and ethical impacts of synthetic biology applied in the agri-food sector. Novel foods are certainly linked to public concerns about their long-term impact on public health. Such concern is the subject of ongoing debate. Moreover, open source platforms make it easier to access sophisticated biological agents by people working outside research institutes, a reality that makes bio-error a threat to daily living. Novel applications will have impact on existing supply chains and entail socioeconomic risk for some sectors. Ethical concerns arise in worries about 'tampering with nature' or 'playing God.'

This tension between benefits and worry regarding innovations in agri-tech or more generally in synthetic biology presents a quandary for the advocates of synthetic biology. The solution can only be found in early, effective and ongoing communication with regard to each application. A Quebec technology roadmap should not simply be concerned simply about research and economic development. There is a decided need to establish trust in this development and instill confidence that the developments are in the broader social interest.

Appendix Part E

Plant-based vs. Cell-based Meat

Plant-based meat

Plant-based meat, or meat alternative, refers to products made from plant ingredients to serve as a replacement for traditional animal-based products. Alternatives can be made for meat, seafood, as well as milk, eggs and dairy products[21]. Inputs used for the production of these substitutes generally include soybeans, wheat, cereals, peas and other plants, also specific bacteria and fungi[22].

These products seek to create the same sensory experience and nutritional composition as traditional meat. Though plants don't have muscle tissue, they are made up of proteins, fats, vitamins, minerals and water, like animal meat. Plant meat exploits this biochemical similarity between plants and animals looking for analog replacements. The aim is to replicate a piece of meat that looks, smells and tastes like animal meat. In general, ground and minced meat, because of their simpler texture, are easier to reproduce than larger cuts such as chicken breasts or pork chops.

Broadly speaking, the production process typically involves three primary stages. It starts with the cultivation of crops to obtain the raw material, followed by a processing stage of these crops to eliminate the useless parts of the plant and obtain the proteins, fats and fibers that will constitute the vegetable meat. The last step consists in a final mixture of ingredients and a manufacturing process create a muscular texture that is similar to meat[23].

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[21] https://gfi.org/science/the-science-of-plant-based-meat/

[22] https://fr.wikipedia.org/wiki/Substitut_de_viande

[23] https://gfi.org/science/the-science-of-plant-based-meat/

Cell-based meat

Cell-based, or cultivated meat, is a “replicated” meat product made from *in vitro* culture of living animal cells[24]. Production process is mainly based on tissue engineering techniques, using cells that can self-renew and differentiate as starting inputs[25].

The growing of animal cells in a controlled environment along with shaping techniques aim to create a product that replicates the taste and texture of pieces such as chicken breast or ground beef.

A McKinsey & Company article gives a description of the process as follows[26]:

- Animal cell lines are first purchased or developed and then preserved in cells bank.
- When producing a batch, needed cells are thawed in small shake flasks and then placed in bioreactors or "cultivators"[27].
- The cells grow in these bioreactors in nutrient-rich media; as they grow in volume and density, they are progressively directed to larger bioreactors so that they can reach the desired density.
- When this density is reached, the cells are harvested in a centrifugation process during which the cells are separated from the media.
- Depending on the end product, the meat cells can be mixed with other additives to achieve the desired texture before being shaped and packaged for storage and distribution.

[24] https://gfi.org/science/the-science-of-cultivated-meat/

[25] https://en.wikipedia.org/wiki/Cultured_meat

[26] Brennan, T., Katz, J., Quint, Y., et Spencer, B. (2021, 16 Juin). Cultivated meat: Out of the lab, into the frying pan. *McKinsey & Company*, Figure 1. https://www.mckinsey.com/industries/agriculture/our-insights/cultivated-meat-out-of-the-lab-into-the-frying-pan

[27] https://gfi.org/science/the-science-of-cultivated-meat/

Part F

Supporting the Bio-economy in Quebec: A Capital Matter

This part of the Report ties the various threads of the previous disussion into a series of policy proposals. The focus id on the requisite capital investments needed to support the development of a biomanufacturing sector in Québec.

This Report has provided various snapshots of the bio-economy in Quebec and in international jurisdictions. The overall picture that emerges is that recent advances in bio-engineering have led us to a threshold opening onto new production processes. These will impact the world economy in profound ways. Yet it is difficult to predict how this transformation will evolve. A certain amount of prudence is required. We do not want to be grasping for phantom benefits. On the other hand, changes in economic orientation in matters as complex as those surrounding the new bio-technologies require considerable planning. A good number of countries are engaged is strategic policy to help launch the bio-economy. There appears to us to be an urgent need for this preliminary work in Quebec if we are to play some role and benefit accordingly in the development of the new economy on our own terms.

In what follows we describe various elements that could find their way into a planning process. Our suggestions are not prescriptive. We are reacting as economic observers not as actors in the strategic deliberations. To underscore this perspective, we have labelled the following section (in an apt French phrase) as *Pistes de reflection*. It effectively presents what we think are the capital requirements that need to be invested to advance the potential of synthetic biology in Quebec.

Section 12 Capital Recommendations

12.1 The Promise of the Bio-economy

Quebecers are very conscious of the environmental challenges that they and the world currently face. It is widely accepted that we need to move away from the carbon-based economy -- within the next generation if possible. This objective ultimately requires changes in personal behaviour and a re-orientation of current consumption values. But it will be difficult to embrace wholeheartedly these objectives in economic isolation without a shared social sense of trajectory to the new economy. We also need measures of progress along the trajectory.

This Report has suggested that advances in theoretical synthetic biology along with efficiency gains in bio-engineering can serve to provide some technical elements in the move away from the carbon-based economy. In all, the potential of the bio-economy strikes the right notes. It is circular by definition; it is environmentally friendly by definition; and given the current resources of the planet, it could support sustainable development for the world's entire population.

None the less, the new bio-economy represents transformative change. As we have seen in responses to the covid crisis, resistance to suggested change in even very modest form can take different unproductive avenues. As well, some developments in applied biology are intrusive and can be legitimately viewed as problematic, even worrisome. Such change, moreover, will undoubtedly impact some economic sectors more than others and provoke resistance. For us, the primary recommendation in such a context of transformative change is for the Government to invest in what we call social capital.

We have suggested throughout this Report that there are capital deficiencies that seriously constrain the development of a bio-economy in Quebec. The development of strategies for addressing these capital deficiencies strikes us a primary and immediate concern if Quebec is to participate in this economy. Accordingly, we have organized our recommendations along the five capital concepts that we have been considering throughout the Report.

12.2 Specific Recommendations

Recommendation I: Investing in Social Capital

Context It strikes us that a broader social engagement regarding the development of the bio-economy is needed. It would be too ambitious and probably ineffective to attempt to do so immediately on a broad scale involving the public at large. A segmented approach seems more reasonable. At the outset, may we suggest that the Government

Establish a Leadership Council on the new bio-economy

The composition of the council could reflect relevant stakeholders from different economic sectors, the academic sector, and the government sector. Some international representation would make good sense. A natural Chair for the Council would be Québec's Chief Scientific Officer.

I.1 The Leadership Council could mandate different reports on the bio-economy surveying the terrain covered by this Report in a deeper, more comprehensive manner. These would include an inventory of the existing resources (people and companies) in the public and private sectors that play or could play some role in the bio-economy. A segmentation analysis of the bio-economy should be undertaken to see which general initiatives best suit the Province.

I.2 A primary concern of the Leadership Council should revolve around the implications of the bio-economy for the Agricultural Sector; see Part E of the Report.

I.3 The Council should develop metrics to measure the extent of the bio-economy and to measure the impact of investments undertaken by the private and public sectors.

1.4 The Council could also serve as an observatory of global trends in the bio-economy. This observatory function would focus on research developments, product innovations as well as the evolution of government policies and strategies in countries showing leadership in the bio-economy.

In some sense, the recommendations that follow could all fall under the aegis of the Leadership Council. But they are presented as stand-alone suggestions that could be implemented independently of the existence of the Council.

Recommendation II: Investing in Intellectual Capital

Context We find that researchers in synthetic biology and bioengineering are dispersed across the Province and that their activities appeared uncoordinated. The model that emerges is one in which an individual senior researcher leads a research laboratory which involves students and technicians. Since the laboratory revolves around the senior researcher, his or her departure would most likely lead to its disappearance and the dispersion of the collective knowhow that it represents. In short, there is considerable key-person risk in these endeavours.

II.1 A pan-university umbrella group is needed to co-ordinate research and activities relating to the bio-economy. The multi-disciplinary character of the bio-economy should be reflected in its composition. Dedicated research funds should be made available to support the initiatives of this group.

II.2 The umbrella group should have the means to support doctoral and post-doctoral training.

II.3 A priority for this group would be to establish links between researchers and with the private sector.

II.4 The group could also perform an inventory of existing research and teaching resources within the province (e.g., laboratories, human resources, programs) with the view of identifying unused capacities as well as gaps that undermine future developments in the area (see recommendation III below).

Recommendation III: Investing in Infrastructure Capital

Context Even at this nascent stage of the development of the bio-economy, it would be useful to invest some funds in infrastructure, particularly to nurture start-ups, as a means of evaluating the potential for growth of synthetic biology in Québec. The issue of scaling up to market along the production chain should be addressed sooner rather than later: is there sufficient economic rationale for establishing a mid-size bio-refinery in Quebec?

III.1 There should be resources directed toward the development of lab space as well as funds allocated for start-ups and early-stage companies.

III.2 A business model that would outline the financing needs and potential revenues of a mid-size bio-refinery located within Quebec should be developed. To what extent is government support of this project essential? What is the appropriate role for government in such an endeavour?

Recommendation IV: Investing in financial capital

Context The people we interviewed in the venture capital sector indicate that, in Quebec and for that matter, in the rest of Canada as well, the development of start-up companies must, for the time being, be supported by the government. For enterprises that have reached a more advanced stage of development, support modalities led by the private sector but with government support should be considered. We present some modalities in this regard.

IV.1 The establishment of an investment fund or funds with time horizons of approximately three years specifically targeting promising young companies in the bio-economy in the development phases surrounding the emergence of the proof of concept. The financing of these funds would be governmental (eg, Investissement Québec) but their management would be assumed by dedicated specialized teams;

IV.2 The establishment of a fund of funds focused on the bio-economy in which the State, via Investissement Québec, would play the role of limited partner would partner with other players from the private sector. This fund of funds would invest in specialized funds, in Quebec and elsewhere, to support companies that have reached the commercialization or pre-commercialization phases. The Government investment would be at risk until the other partners achieved a target rate of return. Once this target rate of return is reached, the Government would obtain a return corresponding to its capital outlay. Such a vehicle would reduce risk for investors and direct capital to the sector.

Recommendation V: Investing in Human Capital

Context The new bio-economy reality entails workforce transformation and the development of new trans-disciplinary skills. It is creating additional opportunities in automation and software engineering, chemical and materials engineering, skilled labour manufacturing and new roles in product integration. All the World Economic Forum recommendations (Part C Section 7.2) are relevant and should be seriously considered.

V.1 Studies should be mandated to anticipate future workforce needs and allocate resources (human as well as material) accordingly across the CEGEP and University networks;

V.2 Given the importance of integrating know-how and knowledge (knowledge) in synthetic biology, whether at university or in business, cooperative-type programs or internships should be set up in CEGEPs. and universities. Although such programs already exist in certain universities and certain disciplines, their establishment in a systematic way for courses relating to the bio-economy seems essential to us. In addition, where possible, an international perspective should be considered and funded;

V.3 Funding could be provided to the setting up and early development of dedicated education and professional development programs for future managers in the emerging bio-economy. The intended target audience for such programs would be individuals with prior industry experience (in the bio-economy or in related sectors) and a science or engineering background.

Recommendation VI: Demand-side support for the new bio-economy

Context The Government itself can participate in the transition to the low-carbon economy in different ways. It can actively monitor its own carbon footprint. It can as well participate in the development of the bio-economy via its purchasing power.

VI.1 The Government could adopt specific public procurement policies that allows bio innovation and sustainable products to compete with existing ones. In other words, for some procurement programs, a portion of the budget should be allocated for purchases of a more innovative nature. Such an approach would require some adaptation in the specifications for goods to be purchased as well as different relative weighting between price and specifications.

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