Innovation potentials triggered by glycoscience research

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Abstract: Glycoscience is an interdisciplinary field, which leads to different industrial applications derived from physicochemical and/or biological properties of carbohydrates.

This study aims to evaluate how glycoscience may act as a driving force to make research innovative and sustainable in industrial and/or commercial areas. To this end, we rationalized the two main properties of carbohydrate molecules into three main value chains. The regional biomass (sugar, starch, wood) value-chain exploits the physicochemical properties of carbohydrates; the glycomics explores the biological functions of carbohydrates and the non-regional biomass (microbial, pectin, chitin) value-chain exploits the two properties.

Each value-chain harbors one or more niches prone to or at an emerging stage of development, and all these niches share a techno-scientific push approach aimed at developing high value-added products with new functionalities, new bioactive glycans, and new enabling technologies that will lead to new applications and possible novel therapies and diagnostics tools.

Keywords: carbohydrate polymers, glycomics, biomass, value-chains, innovation niches, bioeconomy

1 Introduction

For centuries, humankind has exploited the characteristics of carbohydrates extracted from nature (e.g., sugar cane, wood, fiber, plant extracts, etc.), which has provided an unlimited resource of carbohydrate-based materials. Cellulose is a major component of wood, as well as of cotton and other textile fibers such as linen, hemp, and jute (ramie). For this reason, cellulose has always played an essential role in the life of humans, and its applications could even constitute a landmark in the understanding of human evolution. The use of polysaccharides and carbohydrates during ancient times was considered as energy giving. The two main subspecies of rice were domesticated roughly 10,000-14,000 years ago. Rice has fed more people over a longer period of time than any other crop. The first cereal grains were domesticated about 8,000 years ago by ancient farming communities in the Fertile Crescent region. These tribes started to grow and develop wheat for bread and many types of plants that are carbohydrate-rich. Maize was domesticated in Meso-America, in the area that is now Mexico. Because it was nutritious, easy to store and carry, adapted to diverse growing conditions, and provided food and fuel, maize became a staple food for most American and Caribbean cultures. However, it is only at the beginning of the 19th century that the isolation and description of cellulose, starch, pectin, and chitin took place, and initiated the science of carbohydrate polymers. Carbohydrate studies focused on the elucidation of the structure and chemical modifications of monosaccharides and small oligosaccharides. One, among the various focuses of these investigations, dealt with fermentation processes and the role of carbohydrates in cellular metabolism. Afterwards, research in the fields of chemistry and biology has begun to examine carbohydrate structures and their biological functions (Horton, 2008). The discovery that a large proportion of biological information is encoded in carbohydrate structures has become a central concept in glycobiology (Rudd, Karlsson, Khoo, & Packer, 2015). Now, glycoscience is an interdisciplinary field involving biochemistry, polymer chemistry, material science engineering, physiology, developmental biology, microbiology, medicine, and ecology. The exploration by glycoscientists of the physicochemical and biological functions of carbohydrates sustains a vibrant field of research worldwide (Figure 1). Carbohydrates are not restricted to food and nutrition applications; they are also used for the production of bio-based chemical products (surfactants, solvents), new bio-based composite materials, biopolymers, new drugs, and new vaccines.

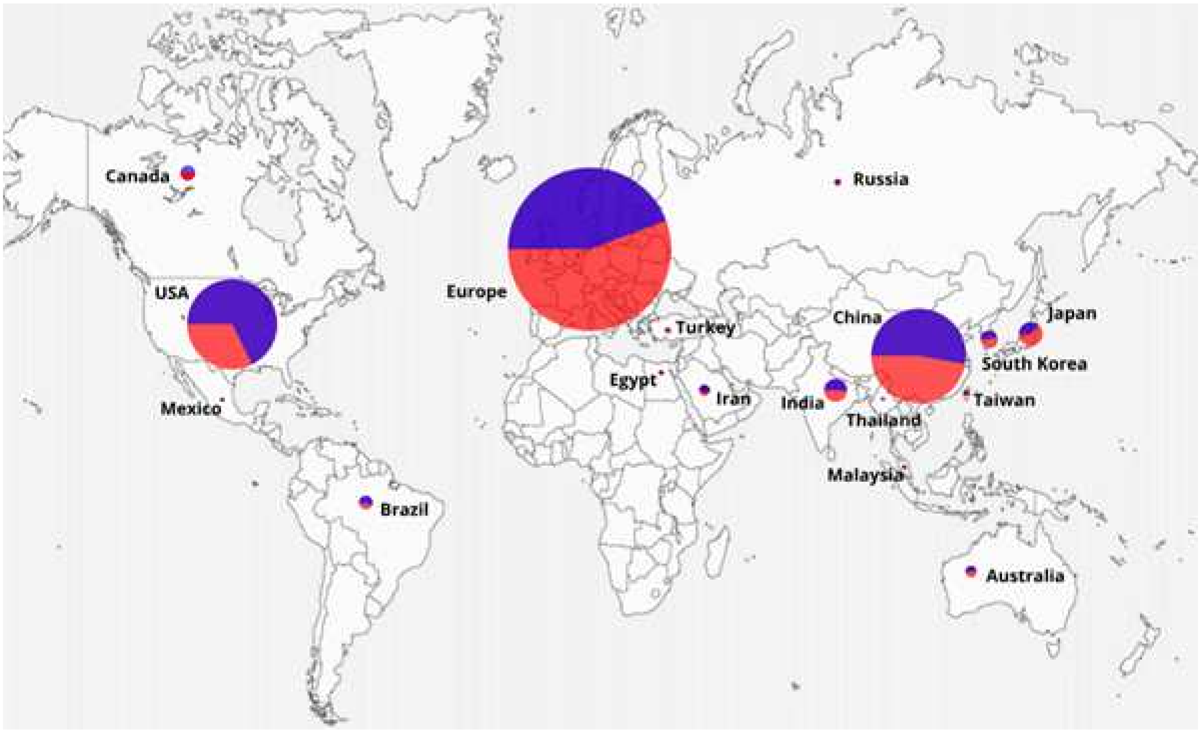


Figure 1: Worldwide scientific interests and outcomes in glycoscience over the period 2014-2019. The scientific publications covering the field of polysaccharides are displayed in blue; those related to glycomics are displayed in red. The size of the circle is proportional to the number of articles published by researchers within a given zone. (see Supplemental Materials for details of the analysis)

The present study focuses on carbohydrate-based innovations and, therefore, excludes lignin, protein, oil, and intermediate molecules. The aim is to highlight the role of glycoscience as a potential driver of radical innovations developed in protected niches to help various mature industries to shift to new sustainable, innovative systems.

The article is organized as follows. In section 2, we highlight the two socio-economic concepts (innovation niches and industry value chain) used to carry on our analysis. Section 3 presents the regional biomass (sucrose, starch, wood, etc.) value chain, which exploits the physicochemical properties of carbohydrates. Section 4 explores the glycomics value chain based on the biological functions of carbohydrates. In Section 5, we analyze the non-regional biomass (microbial, pectin, guar, chitin, etc.) value chain that exploits both properties. Section 6 discusses the results and concludes.

2 Socio-economic conceptual background

The current societal challenges (climate change, poverty, health insecurity, natural resource scarcity, loss of biodiversity) are due to unsustainable consumption and production patterns (Köhler et al. 2019). These global problems require radical shifts to new socio-technical systems. Socio-technical systems consist of technologies, markets, user practices, cultural meanings, infrastructures, standards, policies, industry structures, and supply and distribution chains. These shifts, called “sustainability transitions,” are nonlinear and systemic processes that call for radical research and innovation, more sustainable modes of production and consumption and, new social change, and policy systems. Many examples of “sustainable innovations” such as biorefineries, bioproducts, low energy buildings, local food supply are currently developed. However, these experimentations are deeply rooted around fossil-based products and power plants and intensive agricultural systems all locked-in path-dependent technological trajectories.

We analyze the role of glycoscience as a potential source of innovative solutions that could trigger the phasing-out of the fossil-based economy to shift to a bioeconomy. In our approach, glycoscience is also central for the transition from the blockbuster model towards the Precision Medicine model. Given the systemic issue of sustainability transitions, the socio-economic background of this paper focuses on two broad concepts: the Strategic Niche Management (cf. 2.1) and the industrial Value Chain (cf. 2.2).

2.1 Emergent strategic niches based on glycoscience

The concept of niches is used in innovation studies in different ways (Coles et al. 2018). One common meaning is linked to the size of the market. For instance, small new technology-based firms provide specialist technologies in niche markets and are in search of a stable small market. In this paper, the concept of niche corresponds to emergent strategic niches or protected innovation areas formed to phase-out a current locked-in technological trajectory.

New strategic niches are the sources of path-breaking innovations. Radical niche-innovations deviate from dominant trajectories in terms of their technology, markets, regulations, and modes of production and consumption. Niches are ‘protected spaces’ (Raven, 2006) that shelter these radical innovations from the mainstream socio-economic pressures (selection rules and modes, regulation, consumption, and production practices). Protection allows for experimentation, for example, in pilot and demonstration projects, to co-develop new technologies and their associated markets. In the emerging phase of a niche, there is not necessarily a well-defined market, but several actors commit resources and efforts because they have high expectations about the economic, social, and sustainable potentials of the technology.

In the present article, we analyze three aspects of strategic niche creation (Schot, 2008). First, we consider emergence since the technologies we focus on are at a very early stage and are often far from the market. We demonstrate the central role played by glycoscience in this emergence phase. Second, we consider niche emergence as a process in which newcomers and outsiders challenge the incumbents, but also in which incumbent firms and policymakers from neighboring regimes can be significant at this stage (Turnheim and Geels, 2019; Penna & Geels, 2015). Third, we consider the creation of strategic niches at different points in the industry value chain.

2.2 Industry value-chain

An industry value chain is a representation of all the value-creating activities involved in producing goods and services within the industry, starting with the raw materials and ending with the product delivered to the final consumer. The notion of value chain refers to the industrial organization and potential development and opportunities.

The sustainability transition towards a bioeconomy is hampered by difficulties in efficiently producing bio-based products due to the absence of well-established value chains (Carraresi, Berg, & Bröring, 2018). The bioeconomy value chains suffer from information asymmetries, market power along the chain, risk-sharing, and stabilization of supply and demand (Viaggi, 2018). A growing number of separability points and a lack of cross-chain connections and interactions between the consumers and the various supply-sides hamper their functioning.

In this article, we use the concept of industry value chain as a rough representation of the flux of glyco-molecules and the actors involved along the chains. We conceptualize three industry value chains based on two-step reasoning. First, the physicochemical vs the biological properties of carbohydrates induces to distinguish respectively between biomass-extracted carbohydrates and glycomics (cf. section 4). Second, among the biomass-extracted carbohydrates, we distinguish between the regional (cf. section 3) and the non-regional (cf. section 5) biomass. Regional biomass (sugar and starch plants, fiber plants, wood) is bulky, making it difficult and costly to transport. To reduce these transportation costs, agro-industries (starch producers, sugar manufacturers, pulp and paper firms) often locate close to the biomass source. Non-regional biomass encompasses microbial biomass, botanical biomass (plant cell walls, legume seeds, shrubs, roots), microalgae, and animal and human origins. This non-regional biomass contains carbohydrates exploited for their physicochemical and biological properties –which will be referred to as dual properties throughout this article. Compared to regional biomass, transportation of non-regional biomass is neither difficult nor costly.

The three value chains are representative of the glycoeconomy and allow us to identify the innovation potential of glycoscience. We give a comprehensive view about the main biomasses in use along with the related polysaccharides and on the glycomics.

The purpose of this study is to dissect the three value chains processes and analyze the features that they have in common. Hence, this study will not detail the complex value chain for every single biomass or glycomics, nor to give precise figures in terms of volume or revenues concerning the numerous segmented markets. For analytical reasons, this article is not exhaustive in terms of intermediary molecules and potential applications.

Our data are from sectoral reports, scientific journals, and interviews with scientists and representatives of industries and institutions (see Supplemental Material for more details about the qualitative method used to develop this interdisciplinary article).

3 The regional biomass value chain: from biomass-based carbohydrate to bio-products

The regional biomass value chain starts with biomass production (e.g. rice, maize, sugarcane, wood, algae) (cf. Figure 2). Using the biomass feedstock, the agro-industries extract primary molecules (e.g. glucose, cellulose, starch, etc.) or fibres. These primary molecules can be broken down further into intermediate chemical products (e.g. direct polymers and gums such as xylitol, succinic acid, sugar acids, esters) and materials (e.g., paper pulp, microcrystalline cellulose, nanocellulose). We include these intermediary biochemical products and biomaterials in the upstream part of the value chain in which agro-industry is the main actor (section 3.1.). These intermediate products are sold mainly to the chemical industry and formulators-transformers, which use them to produce bio-products (bio-based solvent, binder, lubricants, etc.) and biomaterials (biopolymers, composite materials) (section 3.2.). Processed end-products are produced by diverse industries (section 3.3)

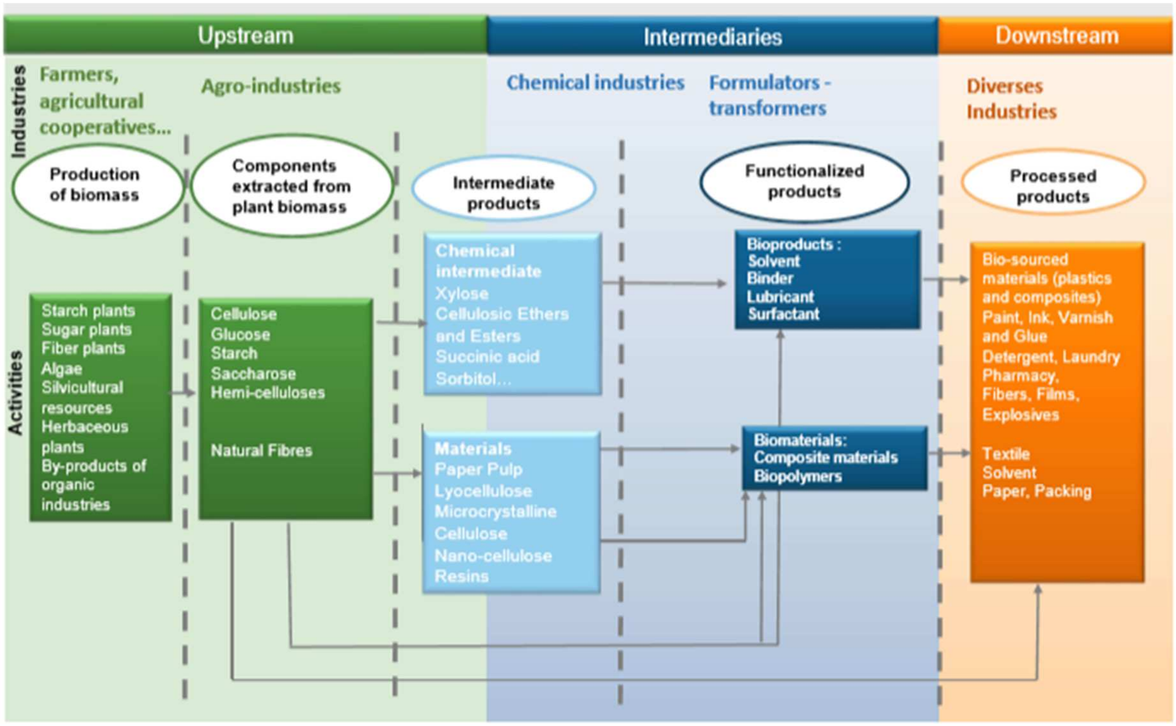


Figure 2: the regional biomass value chain (source: Werpy & Petersen, 2004)

3.1 The upstream stage: extracting sugars from biomass to produce intermediate bio-chemicals and bio-products

Regional biomass value chain is organized around biorefineries, which, since 2000, have attracted increasing attention from industry, policymakers and academics (Hassan et al. 2019). Bio-refineries are an integral part of a future sustainable bioeconomy.

The first generation bio-refineries were organized around the starch and sugar industries, two mature and concentrated industries, with a value chain structure, historically focused on animal feed and human food production. In most cases, the leaders (e.g. Cargill, Roquette Frères, Beneo-Remy) have added biorefinery units to their initial production processes, to develop new intermediary products (e.g. sorbitol, maltitol, mannitol, etc.) for the food and non-food sectors. This diversification to produce intermediary molecules from biomass has been based on incremental innovation. These biorefineries can adapt and respond to customer demand related to both volume and product diversification.

The second-generation biorefineries are integrated lignocellulosic plants, which are based on non-edible biomass (e.g., wood, agricultural straw, dedicated cultures and bio-based wastes) (OECD, 2018). They are used to produce a new generation of glyco-based chemicals. Historically, the paper industry used lignocellulosic biomass to produce pulp. Some pulp and paper companies have reorganized and invested heavily in modifying their production means. The innovation strategies in this mature industry are constrained by the production processes used, and most pulp and paper firms aim at incremental rather than radical innovations (Novotny & Laestadius, 2014). Kraft and bisulphite processes are better suited than mechanical processes to integrate lignocellulosic biorefineries and offer more potential for radical change. The integration of lignocellulosic biorefineries has allowed pulp and paper firms to move to the production of intermediate goods with higher value-added such as speciality cellulose, nanocellulose and cellulose derivatives. The versatility of nanocellulose is making it one of the most exciting new niche materials (cf. Box 1) in the forest bioeconomy (Stern et al., 2018).

Hemicellulose extraction is essential (Chirat, 2017) since it is resulting in new sugar markets (e.g., xylose, mannose, arabinose). Xylitol produced from xylose, could satisfy some of the demand for a less polluting and less energy-consuming food additive production process compared to sulphuric acid hydrolysis. The main issues related to xylitol derived from hemicelluloses are the production process and its scaling up.

Algae biorefineries are in their infancy: the expectations but also the technological challenges are enormous. The economic viability of using algae as a biorefinery feedstock remains unclear and depends on the potential for the co-production of biofuels and biochemicals (Konda, Singh, Simmons, & Klein-Marcuschamer, 2015). The seaweed industry is small and mature and there are opportunities for diversification.

The nanocellulose niche

Nanocellulose refers to Cellulose Nanocrystal (CNC), Cellulose Nanofibres (CNF) or microfibrillated or bacterial nanocellulose. Nanocellulose is obtained from native fibres using acid hydrolysis, which gives rise to highly crystalline and rigid nanoparticles that are shorter than the nanofibrils obtained from homogenization, microfluidization or grinding methods. The resulting material is CNC. CNF is a material that is composed of nanosized cellulose fibrils. Typical fibril widths are between 5 and 20 nanometers and include a wide range of lengths, typically several micrometres. The fibrils are isolated from any cellulose-containing source, including wood-based fibres, via high-pressure, high temperature and high-velocity impact homogenization, grinding or microfluidization.

Since early 2000, techno-scientific activities in this area worldwide have increased hugely. The number of scientific articles increased by 1,450% between 2004 and 2016, and the number of patents increased by 592% (Billet & Fromental, 2017). The numbers of nationally-funded and European Framework funded R&D projects have shown a similar positive trend. The leading academic players come from Europe (Finland, France, Sweden), Japan, China and the US. The high expectations derive mainly from the increasing concern over the environment, growing demand for renewable, recyclable, and biodegradable products, interest in nanotechnology and a declining paper market.

Potential applications of nanocellulose are mainly in paper and paperboard, textiles, paints and coatings, medicines and pharmaceuticals, cement, oil and gas, composites and plastics. Suppliers and end-users are patenting nanocellulose related products.

The leading manufacturers of Microfibrils (MFC) and Cellulose Nanofibrils (CNF) are Borregaard (Norway), Daicel (Japan), Engineered Fibers Technology, LLC (USA), Kruger (Canada), Nippon Paper (Japan) and Stora Enso (Finland). In 2016, CNF production was around 8.7 tons/day mainly from pilot plants. In 2016, Borregaard constructed the world's first commercial-scale production facility to produce Exilva MFC. The Exilva project received funding from the Bio Based Industries Joint Undertaking and involved partners along the entire value chain, including public research institutes and end-users (Unilever, Chimar). This European niche successfully transformed a pilot plant into a flagship plant and aims at producing adhesives, coating, agricultural chemicals, personal care and construction applications.

The main CNC actors are Blue Goose Biorefinery, Celluforce (Canada), Forest Products Laboratory (USA) and Meloda Ltd (Israel) In 2016, CNC production was estimated to be 1.5

tons/day. Celluforce (Canada) has a broad portfolio of patents, collaborates with a wide range of research institutes and is co-developing new applications with end-users. In 2015, Celluforce and Schlumberger joined forces to explore using CNC in the oil and gas sector. In 2019, the Canadian firm will restart its production of CNC following its production facility upgrading.

The main barriers in these emerging niches are related to the absence of clearly expressed demand from end-users, the predominance of pilot plants and very few commercial-scale production facilities capable of supplying large quantities of nanocellulose, and the huge investments needed to develop both applications and supply. Public and private actors continue to invest huge resources in development of applications.

Box 1: The nanocellulose niche

The main difficulty in the upstream stage of the regional biomass value chain is related to the ability of the biorefineries to supply economically viable intermediary products in appropriate quantities and quality, to the chemical industry and the chemical formulators (intermediary actors). Biorefineries can produce a large number and many types of biochemicals, but only in small volumes. To satisfy the demand from the chemical/formulator industries, biorefineries have had to introduce quality standards. In 2017, the Bio-Based Industries Consortium listed 224 biorefineries in Europe. Most are pilot or demonstration plants, with only a few full-scale plants. Pilot and demonstration biorefineries provide a bridge between basic knowledge and technological breakthroughs on the one hand and industrial applications and commercial adoption on the other (Hellsmark, Frishammar, Söderholm, & Ylinenpää, 2016). Pilot and demonstration biorefineries provide opportunities to develop open innovation strategies and to build networks of multidisciplinary stakeholders (e.g., the Bazancourt-Pomacle biorefinery is the result of a collaboration among companies, farmers and research centres, (Marion et al., 2017)). The articulation and subsequent convergence of these actors' vision, learning, experimentation, and the building of relational networks, will be required to overcome the various technological barriers, identify demand and allow the emergence of radical innovation. Successful experiments will attract new actors and allow these technological niches to grow and develop over time (Lopolito, Morone, & Sisto, 2011).

3.2 Intermediary stage: producing bio-based chemical products and bio-based materials

The type of biobased intermediary products (xylitol, sorbitol, nanocellulose, resins, …) produced from biomass is diverse and depends on the bioresources and production processes used. These intermediate products are sold mainly to the chemical industry and formulators-transformers (e.g., Lenzing, DSM, Solvay, Sigma-Aldrich, Unilever), which use them to produce bio-products (bio-based solvent, binder, lubricants, etc.) and biomaterials (biopolymers, composite materials).

Although the chemical industry has changed to produce bio-based chemical products, it continues to rely heavily on the production of petrochemical-based products. It is R&D intensive, mature and concentrated with capital intensive and large-scale production processes. These production processes are well established and based on catalysis. The chemical industry is beginning to replace petrol-based products with bio-sourced products to increase its competitiveness (Philp, Ritchie, & Allan, 2013) and is under pressure to deliver environmentally friendly products. The purity of the intermediate bio-molecules and biomaterials and the reduced environmental impact of their incorporation in production processes are important issues for the chemical/formulator industry. High levels of purity are needed to avoid contamination in biocatalytic processes and glycosciences research is aimed at developing sustainable cracking techniques to extract purer molecules.

The bio-sourced material sector faces the same dilemma as the chemical industry: substitution of petrol-sourced products by glyco-products with identical or similar technical properties (drop-in innovations) vs development of glyco-based products with new functionalities (non-drop-in innovation). Technological and market uncertainties are lower for the drop-in innovation path. Volume sales are potentially significant, but the price and performance competition with petrol-sourced products is fierce, generally at the disadvantage of the bio-products. The non-drop-in innovation path is characterized by higher technological and market uncertainties, and preferably a low volume but higher value. One challenge is the existence of a willingness to pay a Green Premium for the innovation (Carus et al, 2014). Companies are progressively exploring this latter path. However, an issue related to glycochemical and polysaccharides is the high number of steps involved in their production compared to those of petrochemical goods.

Finally, the market distortion created by the considerable policy support for using biomass to produce bioenergy could be a barrier to innovation and the development of a market for the new bio/glyco-chemicals (Philp et al., 2013).

3.3 Downstream stage: few existing applications constrained by the demand-side

Various sectors, such as automobile, textile, pharmaceutical, cosmetics, paint, agro-food and packaging, are potential users and developers of biomass-based carbohydrate products. The few products that have been commercialized include bio-plastic bags, paints, detergents and paper. Few of applications are available on the market due to lack of a clear and articulated demand. Consumers lack knowledge about the potential quality and sustainability of these innovative products. Creating a new market involves a high degree of uncertainty and high marketing costs to promote novelty (Viaggi, 2018). Demand-side innovation policies would be required to develop new markets.

While lack of demand imposes a limitation on the development of applications, the supply-side is also subject to certain constraints. Many innovation projects are still at the research or demonstration stage or have yet to identify a promising market. Manufacturers find it difficult to adopt new bio-based molecules and develop new technologies because: (i) if the bio-product is a substitute, it must cost less or perform better than the equivalent petrol-sourced product; (ii) there needs to be apparent demand for the bio-product with new functionalities; (iii) the production process needs development and scaling-up. An example of a product with new functionalities is hydrophobic paper, produced on a commercial scale and available in the market (see Box 2).

The hydrophobic paper niche based on chromatogeny

The search for a green chemical process to improve the functionality of commodities, such as paper and board, resulted in a breakthrough innovation principle called chromatogeny. Chromatogeny uses a solvent-free chemical pathway for the molecular grafting process and brings hydrophobicity to hydrophilic reactive substrates. Chromatogeny makes paper and 3D-cellulosic objects both strongly hydrophobic, recyclable and biodegradable. The aim is to improve the water-resistance of cellulosic-based materials. The main markets of these waterproof papers include, among others the health and medical sectors, and construction, filters, hydrophobic fibres for composites.

The experimental requirements of chromatogeny are compatible with industrial implementation. Following the award of the first patent in 1997 (granted to Centre Technique du Papier - CTP, Grenoble), it has taken 18 years to achieve full-scale production of the first commercial machine for the production of hydrophobic paper. The creation of this niche was enabled by the involvement of CTP, Korea (Technical Centers, paper manufacturing companies), a US engineering subsidiary and the Korean government.

Several difficulties were encountered: (i) identification of value; (ii) identification of the right industry partner or an appropriate size and with a culture of innovation; (iii) identification of proper R&D, sales, marketing and production personnel; and (iv) defining the upscaling scenario.

Starting in 2017, TK Polymer has been producing silicon less chromatogeny treated paper, which is easy to recycle, and plastic-free chromatogeny treated packaging and biodegradable and recyclable papers.

Box 2: The hydrophobic paper niche based on chromatogeny

Many research and innovation projects, combining the front-end results of glycoscience and industrial competence, have led to high expectations. These expectations induce the actors to allocate resources and effort and engage in technological development, which results in a niche. For instance, polysaccharides could find promising application in advanced microelectronics. An EU project has led to the design of bio-sourced copolymers with controlled architectures, based on glucose, sucrose or cyclodextrin, which can be used to produce ultra-thin films for nanometric lithography uses (‘Des matériaux écolos bien sucrés’, 2019). Some Japanese microelectronics firms are interested in these resins, which allow the storage of more data on a particular surface than do their petrol-sourced counterparts.

4 The glycomics value chain and the role of glycoscience

The glycomics value chain encompasses reagents and research tools (kits and instruments), diagnostics, therapeutic drugs (new ones, bio-betters and biosimilars) and glycoconjugate vaccines (Figure 3). Since 2000, the pharmaceutical industry has been threatened by an innovation deficit and a patent cliff. The patent cliff refers to the immediate decline in revenue following the expiry of a patent and the entry of generics or biosimilars. Pharmaceutical firms are exploiting various strategies to meet these challenges. They range from incremental strategies, such as drug repositioning, to radical strategies such as precision medicine. Precision medicine is an approach for disease treatment and prevention that takes into account variability in genes, environment, as well as stages of the disease and nutritional/environmental exposures for each person. Glycans are essential modulators of numerous biological processes that determine person-to-person differences in their susceptibility to response to drug treatment or common complex diseases. Glycomics can significantly complement the genomics and proteomics tools that are already being evaluated for developing personalised medicines. This approach allows doctors and researchers to predict more accurately, which treatment and prevention strategies for a particular disease will work in which groups of people. Synthetic carbohydrate-based diagnostics, therapeutics and vaccines contribute to these strategies (Almeida & Kolarich, 2016; Jin et al., 2019; Lauc, 2016).

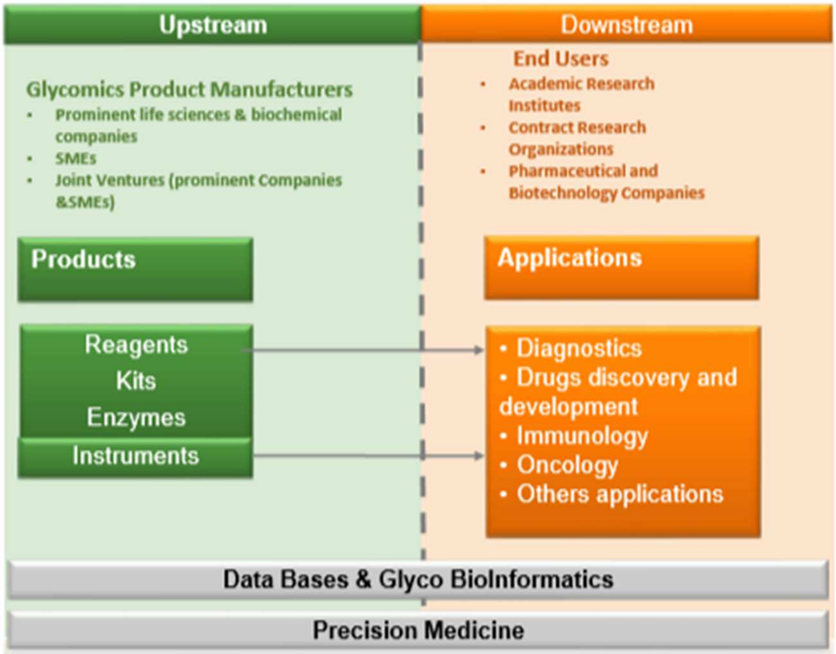


Figure 3: Organisation of the glycomics value chain.

4.1 Upstream

The number and variety of the reagents needed for research and product development, such as antibodies, monosaccharides, oligosaccharides, glycoproteins, enzymes and lectins involved in the glycan recognition, biosynthesis and degradation pathways, are growing. Reagent suppliers have developed different glycan expression systems (glycosidically-linked monosaccharides) and glycoconjugates (glycoprotein, glycolipid, proteoglycan). They have begun to explore new alternatives: i) fermentation process, chemical synthesis, enzymatic synthesis, combined integrated approach and Automated Glycan Assembly (AGA) for glycan production systems (Pardo-Vargas, Delbianco, & Seeberger, 2018); ii) mammalian cells (e.g., CHO and HEK 293), yeast, plant and insect cells (Clausen, Wandall, Steentoft, Stanley, & Schnaar, 2015) as the most frequent biological platforms for glycoconjugates. Reagent firms provide kits for glycan extraction, labelling, purification and release (e.g. the New England

Biolabs product portfolio includes a wide range of glycomics enzymes, kits and reagents). Instrumentation suppliers have developed a variety of techniques and instruments to analyse glycans and glycoproteins, the most often used being HPLC, mass spectrometers, MALDI-TOF and array (glycan and lectin) systems. None of them, on their own, can define all aspects of the glycome. Developments are needed to guarantee higher throughput for quantitative structural characterization of all class of glycans, and with generic methods.

The reagents, kits and instrumentation segments are highly concentrated, with around six firms accounting for two-thirds of their respective markets (Grand View Research, 2018). This concentration is increasing because of merger activity (e.g. in 2018, Agilent Technologies acquired Prozyme). New entrant companies are facing high barriers to entry (e.g. high levels of capital investment, regulation complexity). They more easily penetrate niche market segments, such as glycan and lectin arrays.

The increased use of glycoproteins (monoclonal antibodies) is challenging current production capacity and costs (mammalian cell lines are more expensive and less efficient than yeast and *Escherichia coli)*. By allowing non-specialists to rapidly and easily access to oligonucleotides and oligopeptides, automated synthesis and sequencing methods have been essential in the advancing genomics and proteomics. In contrast, the development of glycoscience has been impeded by the complexity of the chemical synthesis of carbohydrates. Researchers have endeavoured to develop a comparable automated system to synthesise oligosaccharides. Among the parallel efforts on new production alternatives derived from universities and developed by spinoffs, the Automated Glycan Assembly (AGA) has been developed. (see Box 3) Biopharmaceutical firms need to be sure about the efficacy of these different technologies because any change in the manufacturing process is subject to regulations. For instance and in the case of biologics, the bio-manufacturers has to obtain approval for both the drug and the production process. Inevitably, any manufacturing process changes are subject to regulation. In the case of biologics, the bio-manufacturers had to obtain approval for both the drug and the production process.

The Automated Glycan Assembly (AGA) niche

Since AGA was introduced in 2001, by P. Seeberger and colleagues at the Max Planck Institute of Colloids and Interfaces, the synthetic glycan process has received systematic improvements (Pardo-Vargas et al., 2018). In 2013, a spinoff, GlycoUniverse (Berlin), was set up to commercialize Glyconeer 2.1™, the first fully automated oligosaccharide synthesizer.

Its prohibitive costs have had the effect of limiting AGA technology to microarray applications and carbohydrates in small quantities. Combining Glyconeer with standardized purifications and quality-control techniques has eased access to synthetic glycans. Activotec Ltd (Cambridge, UK) commercialized an automated oligosaccharide synthesizer, which was sold first by GlycoUniverse in 2014. Collaborations involving users of Glyconeer have been established in Europe (notably within the H2020 funded Glycovax project) and internationally. The Glyconeer technology provides rapid access to glycans for use as the basis for carbohydrate-based vaccines (Vaxxilon AG, GSK Vaccines) and diagnostics. A companion diagnostic is a device used as a companion to a specific medicinal product to determine its safety and efficacy to one particular person.

A first synthetic glycan vaccine candidate against the particularly deadly hospital-acquired infection, Klebsiella pneumonia, was announced and disclosed (Seeberger et al., 2017).

Box 3: The Automated Glycan Assembly (AGA) niche

This value chain relies on the accumulated knowledge on glycan structures, distribution, etc., and now benefits of the inclusion of this information in many glyco-related databases. The consolidation of databases is in progress due to the overcome of some related technical challenges. Analysis of the structures of individual glycans, their distribution on cells and tissues, their relations to each other and their interaction with proteins and lipids, produce a huge volume of data, high-performance computing, and comprehensive information search and data extraction. A growing number of academic and commercial organizations is working on integrating disparate types of data, from various tools and instruments, and are developing new online searchable and bioinformatics platforms. Some examples of these databases include GlycoCosmos (https://glycosmos.org/), Glyco3D (Perez et al., 2017), GlycoStore

(Zhao et al., 2018), Kegg Glycan (https://www.genome.jp›kegg›glycan) and UniCarb (https://unicarb-db.expasy.org). These improvements are easing data interpretation for less experienced glycoscientists. New developments are emerging where software applications based on machine learning trained on both experimental and computational data will allow the transition of glycoanalytics to high-throughput use and faster detection of novel drug-diseases relationships and will facilitate the implementation of precision medicine. Free access to data online are re-shaping scientific and industrial practices. The challenge by firms in a sustained open innovation system is how to deal with the apparent contradictions related to contributing to and exploiting open data, and protecting their business (Price, 2015).

4.2 Downstream

Biologics are driving pharmaceuticals market growth. Most of the biotherapeutic products under development or recently approved are glycoproteins. The large pharmaceutical companies, traditionally, have focused on blockbusters that target significant population diseases. However, the patent cliff, price competition from generics and biosimilars and declining R&D productivity are challenging this blockbuster model. Firms can increase their profits by introducing design differences to delivery devices or container closure systems, or developing bio-betters, or new drugs that build on successfully approved biologics and provide improved potency, half-life, safety, immunogenicity and efficacy. Many pharmaceutical companies opt for a drug-repurposing strategy (i.e., proposing novel therapeutic indications for already approved, discontinued or archived drugs). In all these cases, glycoengineering is essential expertise for drug development (Beck et al., 2015). A more radical option is the development of niche-buster innovations. A growing number of new drug approvals are related to the treatment of rare diseases and/or companion diagnostics with the ability to stratify the population-based on individual genetic predispositions to respond to drug treatments (i.e., precision medicine).

Glyco-based precision medicine diagnostics are at an early stage. It is expected that the regulatory authorities will approve glycan-based biomarkers for application as diagnostic, prognostic, predictive or therapeutic biomarkers in the short-run (Almeida & Kolarich, 2016). The growth prospects are better for therapy selection diagnostics and safety, sensitivity and resistance markers related to drugs already in the market, than for companion diagnostics (McKinsey&Company, 2013). The top four diagnostic companies account for approximatively 70% of global sales. Start-ups are commercialising tests to facilitate the development by medical doctors of individual effective precision healthcare strategies (see Box 4). The development of precision medicine is dependent on scientific and technological advances. It is also posing policy, regulatory (related to approval of the companion diagnostic test, reimbursement mechanisms and pricing) and ethical issues (informed consent processes, privacy and confidentiality, inequality of access) (Stern, Alexander, & Chandra, 2017). Collaborative networks and alliances are common strategies in the biopharmaceutical industry. However, the links between new drug development and diagnostic development firms are scarce.

The Glycan Age niche

Age-related diseases are a significant cause of death. Evaluating the effect of any intervention (drug, diet prescription) that influences ageing requires a reference point. Discovery of robust and accurate biomarkers of ageing is the current holy grail for ageing research (Krištić et al., 2014).

N-Glycans are a complex class of oligosaccharides, their structure is heterogeneous and it includes a conserved core region substituted with other sugars in a not stoichiometric fashion (Stanley, N. Taniguchi & M. Aebi, 2017). Serum N-glycan profiling has identified glycan biomarkers associated with the ageing process. Most Immunoglobulins G (IGg) glycans fall into the category of N-Glycans and represent up to 80% of the total serum immunoglobulins in humans. The IgG glycosylation appears to be highly regulated - both during homeostasis and in cases of its disturbance, disease and infection. This differential IgG glycosylation is known to modulate IgG effector functioning and to be involved in the development and progression of diseases; it seems to be both a predisposition and a functional mechanism involved in disease pathology. Both genes and the environment influence the composition of the IGg glycome, making it an excellent biomarker of an individual's general state of health. Every individual in the world has a specific glycosylation pattern, which, while reflecting the general state of health at a given time, changes as a function of health and lifestyle.

Glycanage Ltd, a start-up created in 2016, has commercialized a test (GlycanAge®) that provides a fast and personalized estimate of the individual's biological age (a measure of how well the body is performing relative to its chronological age), using high-end technology for the analysis of IGg glycans. IGg glycosylation analysis is performed on a small blood sample using liquid chromatography. Other small firms have proposed alternative technological solutions (e.g., Zymo Research, USA - Life Length, Spain).

Box 4: The Glycan Age niche

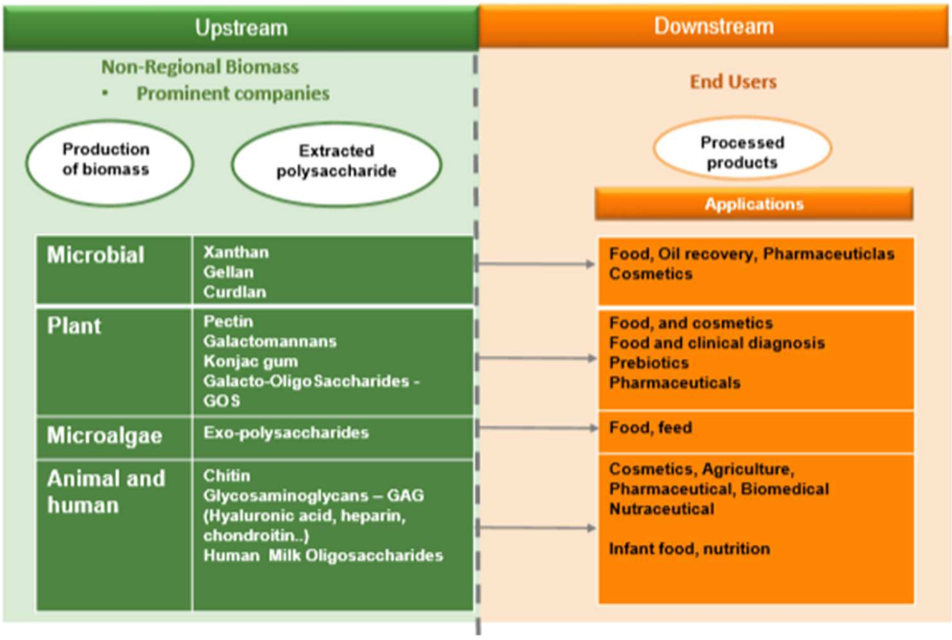
Glycans are also used as vaccine components. Bacterial cell surface polysaccharides are crucial mediators in the host-pathogen recognition process involved in immunization mechanisms and, therefore, are critical targets for vaccine design. The first polysaccharide vaccines were approved in the 1970s and were followed, in the 1980s, by conjugate vaccines (glycans coupled to proteins). Conjugate vaccines confer more effective and longer-lasting immune protection than polysaccharide vaccines. There are several carbohydrate-based cancer vaccines at different stages of development (Jin et al., 2019). Polysaccharide-based compounds and formulations constitute potential vaccine adjuvant candidates (e.g., inulin, chitosan) (Sun et al., 2018).

Given the costs and the demand conditions in the vaccines market, only a few suppliers will be able to supply each vaccine type. The firms involved are subject to high fixed costs, complicated and time-consuming production processes, price-sensitive demand and dynamic competition over quality. Five multinational corporations (GlaxoSmithKline, Merck, Novartis, Pfizer, Sanofi) account for 80% of the global vaccine market. Historically, these firms were the leading innovators, but more recently, small biotech and emerging-market players are responsible for the majority of the new vaccines. Given the forecast reduction in the costs related to developing glycoconjugate vaccines using AGA (Pardo-Vargas et al., 2018), Glycan Expression Technology and Protein Glycan Coupling Technology, this should allow simplified manufacturing processes for the production of glycoconjugate vaccines. Speedy and practical research on such accessible, economic vaccines depends on the availability of quick, accurate and reliable measurement capabilities, which do not adequately exist at present, rendering, for example, the previous glycoconjugate generally approaches too expensive for veterinary applications, especially for livestock farming.

Glycosylation engineering is a determinant of the therapeutic efficacy of protein drugs and vaccine success. A biosimilar must demonstrate appropriate glycosylation qualities to obtain regulatory approval. Glycosylation engineering is opening up business opportunities for Contract Research Organizations (CRO) and Contract Manufacturing Organizations (CMO). The constraints imposed by price competition (from generics and biosimilars) and decreasing R&D productivity, is prompting pharmaceuticals companies to partner with CROs and CMOs to gain access to specialized technologies. Both CROs and CMOs have undergone significant consolidation in recent years. Established biologics firms have been developing internal glycoengineering expertise (e.g. Amgen), while less well-established companies have acquired glycosylation solutions and promising developments via mergers and acquisitions (e.g. Roche's acquisition of Glycart in 2005, Merck's acquisition of GlycoFi in 2006, and AstraZeneca's acquisition of MedImmune in 2007). In 2015, only three suppliers (Boehringer Ingelheim, Lonza and Samsung) were involved in large-volume mammalian cell-culture production based on six or more 12kL bioreactor lines. The entry barriers to CMOs are lower for those operating on smaller scales (up to 3kL), for small volumes of biopharmaceuticals, such as those needed for clinical supply, or for small-volume commercial production (e.g., biologics for niche indications) (Gennari, Loesch, Santagostino, Otto, & Mc Kinsey & Co, 2017).

5 The non-regional biomass value chain with dual properties

The non-regional biomass value chain (cf. Figure 4) is relatively simple. It includes two significant steps: extraction of polysaccharides from various types of biomass (the upstream stage), and the downstream industrial application stage (mainly in food and beverages, pharmaceuticals and cosmetics). Recognition of the biological importance of glycans and their conjugates is shedding new light on non-regional biomass-based polysaccharides, used mainly for their physicochemical properties. The controlled deconstruction of complex polysaccharide architectures, combined with the fine analytical characterization of the resulting structural motifs, could help the identification of new embedded biological functions.



<u>Figure 4</u>: Organisation of the non-regional biomass value chain

5.1 Upstream stage: extracting various polysaccharides with dual properties

The upstream step involves several families (microbial, botanical, microalgae, animal, and human) of non-regional biomass, each producing specific types of polysaccharides with physicochemical and biological interesting properties (Dimitriu, 2004). The schematic representations of the structures of the polysaccharides described in this study are displayed in Figure 5.

5.1.1 Microbial biomass

Micro-organisms produce several polysaccharides (xanthan, gellan, curdlan, pullulan, glucan, etc.), which are speciality hydrocolloids and have valuable viscoelastic (rheological) properties. Compared to polysaccharides derived from plants and microalgae, the commercial success of many microbial polysaccharides has been limited; exceptions are curdlan, xanthan, and gellan (Michaud, 2018). Some microbial polysaccharides have specific biological properties, such as elicitors (see Box 5), antiparasitic, anticoagulants, or antimicrobial agents, and find applications in the pharmaceutical and cosmetics industries.

A major scientific challenge is developing new microbial polysaccharides, such as bacterial hyaluronic acid and glucuronan, with fundamental biological properties, which might induce niche development of interesting medical applications (cell therapy, tissue engineering). Another issue for scientists is improving the knowledge of these new polysaccharides, reducing their production and extraction costs and characterizing their structures and rheological and biological properties.

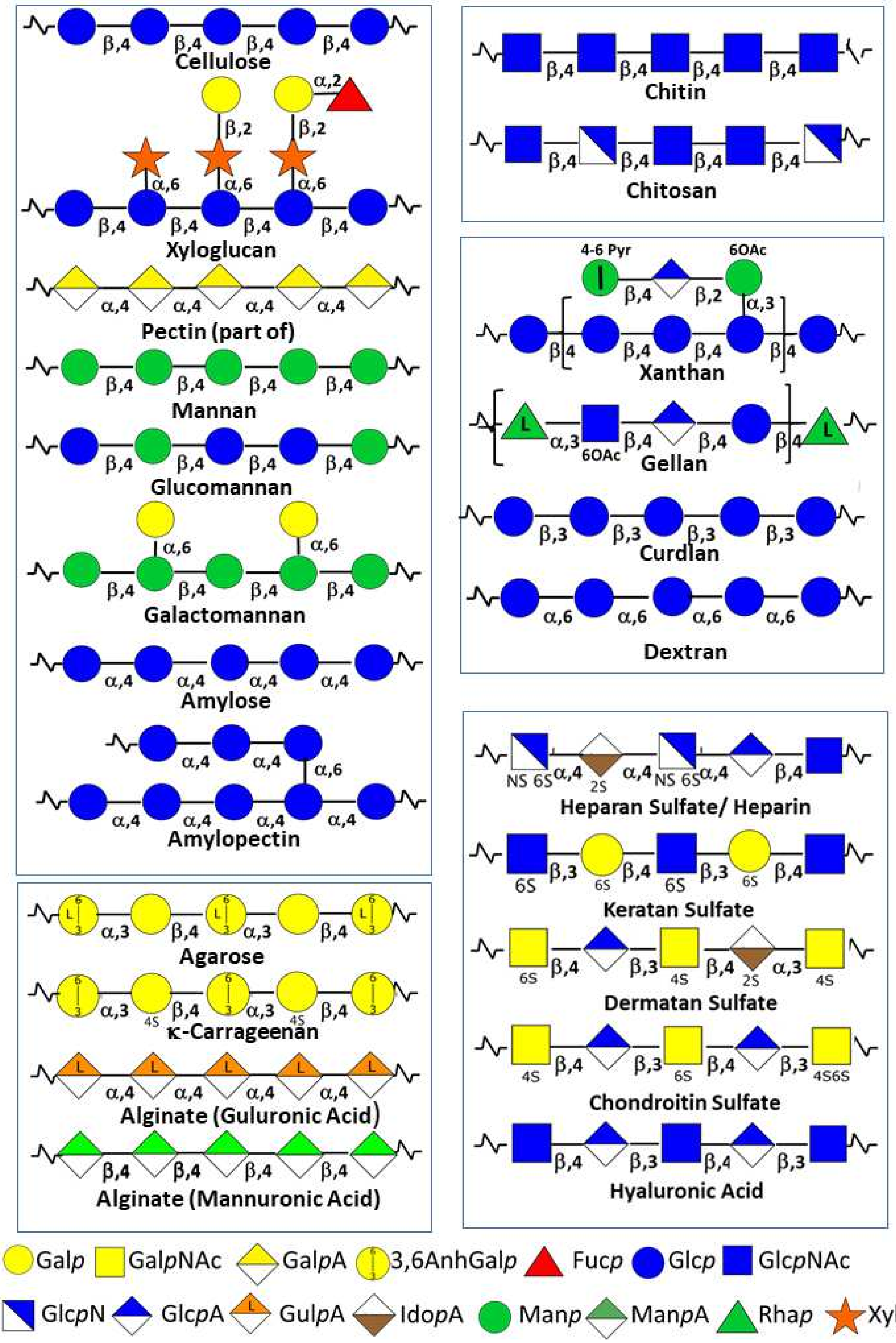


Figure 5: the structures of the polysaccharides described in this article. The pictorial representation used to compose the picture uses the universally accepted symbols for monosaccharides under the so-called "Symbol Nomenclature for Glycans" https://testpubchem.ncbi.nlm.nih.gov/glycans/snfg.html , (Varki et al., 2017).

5.1.2 Botanical biomass

Botanical biomass includes families of polysaccharides such as starch, pectin, galactomannan, konjac gum. Pectin, extracted mainly from apple pomace and dried citrus peel, two by-products of fruit-juice production, has thickening, stabilizing and gelling as well as immune-stimulating and eliciting properties (see Box 5) (Lara-Espinoz et al., 2018). The pectin market is mature and has no ~~clear~~ unconditional market leader. The structure and location of the industry are changing, but constrained by the need for substantial capital investment and large-scale sources of raw material. In spite of hundreds of papers proposing new raw materials and modern extraction methods, pectins are still extracted with hot acids from apple or citrus by few producers (Cargill, Givaudan, CPKelco, Danisco, Hebstreith). Both large**,** experienced and international players and small-scale regional actors are investing in R&D to develop new and better products, based on healthy and organic raw materials**.** Extracting pectin from the fruit is a complex process; the producers are working on the development of new extraction technologies and other valuable ingredients. Biorefineries using clean microwave-based technology are showing promising economic and technical performance. In response to this fast-growing market, several research institutes are innovating in methods to extract pectin from sugar beet, sunflower, coffee bean, chickpea and opuntia waste (Ciriminna, Chavarría-Hernández, Inés Rodríguez Hernández, & Pagliaro, 2015).

Galactomannans are polysaccharides that are present in and are extracted from various legume seeds (guar, carob, fenugreek, cassiatora, dhaincha) and full-grown perennial trees and shrubs (Mathur, 2017). Galactomannans extracted from trees and shrubs have no commercial applications as such, but legume-based galactomannans are produced commercially. They are excellent thickener used as a food additive, dietary fibers, and clinical nutrition (Kontogiorgos, 2019). Each galactomannan has specific molecular properties and is not easily replaceable in specific applications. The main producers are in the US and include Cargill and Sigma Aldrich Manufacturing.

The glucomannan konjac gum is obtained from the root of the konjac plant, which is cultivated in China, Taiwan, and Japan. It is synergistic with k-carrageenan and xanthan gum, which form thermo-reversible elastic gels. Its main applications are as thickeners, stabilizers, gelling agents and film forms.

Elicitor niche

Plant resistance is based on the ability of the plant to perceive microorganisms and induce an immune response to stop their invasion. This ability relies on the perception of eliciting molecules released during the plant/pathogen interaction. Fragments of pectin (or elicitors) may be released after damage or pathogen-encoded cell wall degrading enzymes, which induce the innate immune response. The hemicellulose components include xyloglucan oligosaccharides, which are the main constituents of the hemicellulose contained in the cell wall of dicotyledonous plants. Enzymatic extraction and purification (from apple pomace) produce well-characterized xyloglucan oligosaccharides. Studies show that these oligosaccharides trigger immune responses and enhance resistance to pathogens in different plant species, especially grapevines (Claverie et al, 2018).

Elicityl, a start-up based on an academic patent, is commercializing an oligosaccharide from this same family; it is providing similar enhancement of grapevine resistance to spring frosts. These bio-stimulants used in both fertilization and elicitation and in plant protection, are adding to the armory of agricultural inputs compatible with sustainable development. The authors did not find any data on the market size for elicitors. In Europe, the bio-stimulant market is estimated by the European Biostimulant Industry Council to be around 500 million euros, with nearly 3 million hectares treated. The bio-stimulant market is evolving. Initially, it was confined to SMEs; agri-food companies keen to develop specific technologies and plant protection companies that want to expand their product portfolios, are beginning to acquire these SMEs.

Box 5: Elicitor niche

5.1.3 Microalgae

Microalgae are microscopic algae found in freshwater and marine systems. They consist of a heterogeneous group of microorganisms, capable of self-nourishment using inorganic materials as their nutrient source, and growth and development using light as their energy source. They can potentially produce large amounts of a large variety of exopolysaccharides, which makes them attractive for new commercial applications (Delattre, Pierre, Laroche, &

Michaud, 2016). Recent progress in the production of microalgae in photobioreactors could reduce the cost of industrial products and prompt further studies about the structure of the polysaccharides produced. So far, this information is lacking or fragmentary due to the lack of reproducibility of culture conditions, the origin of the strains, and the complexity of analysis. World production of microalgae is concentrated on a dozen microalgae species: *Arthrospira, Chlorella, Dunaliella salina, Aphanizomenon flosaquae , Haematococcus pluvialis , Crypthecodinium cohnii, Shizochytrium sp, Spirulina maxima.* The production is dominated by large US, Asian, and European companies and SMEs. Commercialization of polysaccharide production from microalgae could increase if their rheological and biological properties were fully characterized, and their average price was compatible with the costs of hydrocolloids (in the case of a low-value market) and biological reagents (in the case of a high-value market). Microalgae harvesting and recovery techniques are demanding in terms of cost, energy, and time. Well-established firms are investing heavily in R&D to develop more economically efficient production processes**.** The main technological challenges and barriers to entry are represented by the ability to scale up production, reduce production costs, and achieve stable and reliable operations. Capital investments, legislation, access to finance for SMEs, intellectual property rights issues and limited public knowledge are additional significant barriers.

5.1.4 Polysaccharides from animal and human sources

Animal and human sources include families of polysaccharides such as chitin/chitosan, glycosaminoglycans (GAG) galactooligosaccharide, (GOS), and human milk oligosaccharide (HMO).

Chitin is a long-chain polymer of N-acetylglucosamine, and an essential component of fungi cell walls, the exoskeletons of crustaceans and insects, radulae of molluscs, cephalopod beaks and fish scales. It is the second most synthesized polymer by living organisms after cellulose.

The extraction of chitin and modifications to prepare chitosan involves stepwise chemical methods. Chitin and chitosan have remarkable physico-chemical and biological qualities (biocompatibility, anti-thrombogenic and hemostatic properties, cicatrizant, anticholesterolemic, antimicrobial, antioxidant, antitumor chelation agent, biodegradable, high humidity absorption) (Rinaudo & Perez, 2019).

Glycosaminoglycan (GAG - hyaluronic acid, heparin, chondroitin, dermatan and keratan) polysaccharides are essential components of connective tissue. GAG chains, except hyaluronic acid, are covalently bonded to a core protein, and the whole molecule takes the name of proteoglycan. GAGs are involved in a variety of extracellular and intracellular functions. Hyaluronic acid helps to protect the body's joints by increasing synovial liquid viscosity and cartilage elasticity. In the skin, it fills the intercellular spaces and improves hydration. It is the only GAG produced biotechnologically, relying on microbial fermentation. Heparin has strong anticoagulant properties and is extracted from porcine intestines. In 2016, due to its large pig population, China was the biggest supplier of heparin. Chondroitin and dermatan, are extracted from the bovine or porcine trachea and shark cartilage. They help cartilage hydration and contribute to bone flexibility and elasticity; they are produced mainly in Asia. The absence of a risk-free and steady source of chondroitin is hampering the market growth and satisfaction of growing nutraceutical and medical demand (Badri, Williams, Linhardt, & Koffas, 2018). Commercially extracted GAGs from animal sources are not a sustainable option due to the limited availability of animal tissues, scaling-up problems, their adverse impact on the environment, and quality control issues. The main scientific challenge is to move to non-animal GAG production methods: chemo-enzymatic synthesis of synthetic heparin, chondroitin synthase, etc.

Galactooligosaccharides (GOS) are produced by enzymatic conversion of lactose using galactosidases; they are of interest for their potential health benefits. GOS are prebiotics: "A substrate that is selectively utilized by host microorganisms conferring a health benefit" (Gibson et al., 2017). The top four manufacturers account for the major industry share. R&D investment and new product development will be key to meeting increased demand.

Human milk oligosaccharides (HMOs) are a family of structurally diverse unconjugated glycans, unique to human breast milk, although not digestible by human infants (Kunz et al., 2000). HMOs act as prebiotics, helping to establish commensal bacteria, enhance memory and brain development, and act as anti-adhesives to prevent the attachment of microbial pathogens to mucosal surfaces (L. Bode, 2012; Heger et al., 2019). Due to their complex and diverse structure, their extraction and synthesis are difficult. New techniques, such as extracting HMO from cow milk, chemical or enzymatic synthesis, and microbial production, are currently being explored by the leading players (see Box 6). Production of HMO is expensive, and the HMO market will need considerable investments in the coming decades

5.2 Downstream stage: various applications with high innovation potential in the health sector

5.2.1. Microbial biomass

Research activity is focused on pre-treatments, fermentation, and downstream processing techniques to develop economically viable new biopolymers based on microbial polysaccharides for large-scale innovative applications. The gelling properties of microbial polysaccharides are exploited mainly by the food sector, although xanthan and gellan are used also by the pharmaceutical and cosmetics industries. Xanthan gum is associated with a wide range of drugs designed to extend the contact time of active ingredients and slow drug release in tablets. Modified xanthan gum is being investigated as a promising scaffold for tissue engineering. In the cosmetics industry, xanthan gum is used to prepare water gels. Xanthan is used in oil recovery and mineral ore processing. In the US and Europe, xanthan has been approved as a food additive and, generally, is recognized as safe for pharmaceutical applications. The use of gellan gum has the potential for application in the field of tissue engineering, mainly as a material for cartilage reconstruction. Some recent research suggests that due to its biocompatibility and non-toxic properties, gellan gum could be used to produce novel wound dressings designed to inhibit postsurgical adhesion and prevent scar formation (Osmałek, Froelich, & Tasarek, 2014). Gellan gum has received legislative approval in the US, Canada, Europe, Latin America, and Asia for use in food, cosmetics, pharmaceutical, and non-food products. The US FDA has approved the use of curdlan as a food additive.

5.2.2. Botanical biomass

The polysaccharides obtained from botanical biomass (pectin, galactomannans, and konjac gum) are used mainly as additives in the food and beverage industry. Clinical uses of galactomannans include the diagnosis of certain diseases such as aspergillosis infections in humans. Demand for pectin from the pharmaceuticals and cosmetics sectors has increased significantly, thanks to its bioactive hydrocolloid functions. In medicine, pectin is used in wound-healing preparations, colostomy devices and to reduce blood cholesterol levels (Ciriminna et al., 2015), and is used as a therapeutic agent for cancer, heavy metal toxicity, fibrotic diseases, and chronic inflammation. Food Additive laws regulate the composition and use of pectin. It is generally regarded as a safe additive by several government food agencies. Similar to natural polymers and chemically modified natural polymers, pectins are exempt from REACH (The Registration, Evaluation, Authorization, and Restriction of Chemicals) registration, although the substances used to modify the pectins chemically and which are chemically bound within the final polymer, are not. Carob, guar, tara and fenugreek gums are recognized as safe and edible food additives.

5.2.3. Micro Algae

Except for microalgae produced by the energy sector, most microalgae are considered a valuable source of biomolecules for various applications, mainly in health food segment (75% of the production volume in Europe over the past decades; Enzing et al., 2014), but also in cosmetics (anti-ageing creams) and chemistry (biodegradable plastics). In Europe, microalgae used for human nutrition are required to pass strict homologation procedures. Only two species have been authorized: *Chlorella sp.* and *Spirulina sp.* (Enzing et al., 2014).

5.2.4. Polysaccharides from animal and human sources.

Among the polysaccharides found in animal and human**,** chitin and chitosan are used in cosmetics (skin creams, shampoo, lacquers, varnishes), agriculture (control of pre- and post-harvest diseases), environment (bioremediation and decontamination), and the textile, building, packaging and civil engineering sectors. Their pharmaceutical and biomedical applications focus on tissue engineering, artificial kidney membrane, wound healing and dressing, artificial skin, bone damage, articular cartilage, liver pathologies and nerve regeneration (Islam, Bhuiyan, & Islam, 2017). The main applications of hyaluronic acid are as derma fillers (cosmetics), osteoarthritis, ophthalmics (cataracts, glaucomas, age-related macular degeneration, dry eye) and vesicoureteral reflux. As for glycans from the human source, a typical example is given for HMOs. This is discussed in box 6.

Human Milk Oligosaccharides (HMO) niche

Human milk oligosaccharides (HMOs) are complex sugars found in human breastmilk, which assist in early-life immune programming and protection against infectious diseases. HMOs are a structurally and biologically diverse group of complex indigestible oligosaccharides. More than 200 different oligosaccharides have been identified, varying in composition from 3 to 22 monosaccharide units. The quantities and structures of these HMOs differ among women. The structures of the most common oligosaccharides contain neutral fucosylated molecules. The research underlines the importance of human milk as an early-life influence on the development of a healthy immune system. HMOs play many different roles in both infants and adult digestive health. Additional protection might be achieved through modifications of the gut microbiota composition and metabolism, to regulate intestinal immunological aberrancies and maintain gut integrity. However, we need a better scientific understanding of these mechanisms. Production of HMOs by synthetic methods is challenging due to renown problems in carbohydrate synthetic chemistry; namely, the different hydroxyl functions have similar reactivity hampering the achievement in good yields of products with the desired stereo- and regioselectivity. Accordingly, the synthetic approach requires high R&D and production investments, and the costs associated are the bottlenecks of the innovation in this area.

Elicityl (F), Inbiose (B), Glycom (DK), Jennewein Biotechnologie (D), ZuChem (US), Medolac Laboratories (US), Glycosyn LLC, DuPont (health & nutrition) and BASF are the main players in the global HMO market where competition is intensifying due to the increased number of market entrants. The global HMO market is expected to overgrow in the coming decade. The antimicrobial protection and prebiotic functions of HMOs make them useful and practical food and beverage ingredients for infants and medical/therapeutic cases, which are the most rapidly growing segments.

The many partnerships between large and small biotech firms exemplify the innovation dynamics in this niche. In 2016, Inbiose and DuPont Nutrition & Health began collaborating on fucosyllactose for human nutrition. 2’fucosyllactose (2’FL) received EU Novel Food approval and the US FDA entered no objections to GRAS. In May 2019, BASF and Glycosyn signed a partnership agreement for the development and commercialization of novel HMOs for use in dietary supplements, functional nutrition and medical food. DuPont and BASF are producing the most current version of HMO, which consists of the 2’FL sugar. They sell to consumer manufacturers. They aim to research the production of more of the HMO varieties found in breast milk.

Following 20 years of research, in 2016, Abbott was first to introduce HMOs in infant formula, for sale in the US baby nutrition market. This formula is now available in 15 or more countries. In 2017, Nestlé incorporated HMOs in its infant formula, available in over 35 countries. Nestlé has entered into a long-term HMO collaboration with Glycom and owns shares in the company.

Box 6: HMO niche

6 Discussion and conclusion

This study provides an analysis of the three glycan-related value chains, namely the regional, the glycomic and the non-regional value chains. Our results lead to a discussion centred around two main topics:

- Glyco-based niches and their impacts on the value chain structuration

- The definition of glycoeconomy and related policy issues.

6.1 Glyco-based strategic niches and their impact on value chain structuration

The innovation niches are characterized by a techno-scientific push approach, focused primarily on R & D in complex carbohydrates, enabling technologies and production processes. In some niches (nanocellulose and elicitors), unstructured demand, regulation constraints, or societal acceptance, could hamper their development – especially for nanocellulose applications. However, elicitors are compatible with sustainable agriculture strategies, such as chemical pesticides-free husbandry. One of the main limitations, which applies to all the niches discussed in this paper, is the scaling-up of the production processes. Massive investments will be needed to develop commercial-scale production facilities and ensure the subsequent economic viability of the firms.

The so-called 'stretch' character of innovations refers to the pioneer opportunities related to options that deviate from the existing regime. The niches discussed here are aimed at developing high value-added products with new functionalities, new bioactive glycans, and new enabling technologies in the fields of synthesis, analysis, bioinformatics, and modelling that will lead to new applications and possible novel therapies and diagnostics not enabled by the non-glycan regime.

The innovations considered in this article constitute opportunities to develop complementary value chains or cross-chain connections. The functional food value chain, based on HMOs, is an emerging value chain that is not a replacement for either the food or the pharmaceutical value chains but instead is located between them (Carraresi et al., 2018). In cross-chain connections, the existing value chain is neither substituted nor complemented, but new links are being created between individual stages. The same applies to the nanocellulose value chain, where we observe the emergence of new networks between lignocellulosic biorefineries and different types of end-users (consumer goods producers, technology providers, pharmaceutical companies, etc.). The most advanced glycosciences research will induce future cross-linkages between the three value chains: for instance, nanocrystals and nano-fibrils of cellulose. Such novel materials produced in the regional biomass value chain could be used as templates for the development of innovative medical treatments based on the grafting of bio-active anti-cancer, anti-microbial molecules (glycomics value chain).

6.2 Towards the definition of glycoeconomy and policy issues

The "bioeconomy" concept can be interpreted in various ways and involves multiple approaches and subsequent policy strategies. It can be understood, first, as the economic opportunity offered by the biotechnology revolution (genomics, proteomics, glycomics, bioinformatics, etc.), in which scientific advances in biotechnologies will generate radical innovations and paradigmatic changes. They will concern pharmacy, medicine, agronomy, and chemistry (Vivien, Nieddu, Befort, Debrefamp; Giampietro, 2019). The Organisation for Economic Co-operation and Development (OECD) generally supports this perspective. Second, bioeconomy can be understood as the economic opportunity offered by the transformation of biomass into biofuels, biopolymers, and biochemicals. In this resource substitution perspective, biorefineries use biomass to produce the same platform molecules as produced by the petrochemical industry (Vivien et al., 2019). A third interpretation of the bioeconomy encompasses a policy goal aimed at achieving a "sustainable bioeconomy" by transforming current socio-technical systems. The policy mix involved in making this transition supports the creation of niches to create new products (chemicals and materials) that substitute existing products or functions (biodegradable, longer lifecycle, better performance such as bio-based polyethylene replacing fossil-based plastics) (Vivien et al., 2019). Based on these definitions and the three value chains described in this article, we propose a definition of the concept of glycoeconomy: "*Transforming glycosciences knowledge into new, sustainable,* *eco-efficient and competitive carbohydrate-based goods and services."* This definition combines a science-based innovation perspective, a niche-based perspective, and a functional substitution perspective.

The diffusion of niche products requires that suppliers and end-users develop a shared vision and jointly influence policy goals and directions. Policy coordination between the regional, national, and supra-national levels, and between innovation and sectoral policies should be improved. For glycosciences applications that affect multiple sectors, a range of policy instruments should be considered, including chemical regulations, Common Agricultural Policy, waste regulation, bioenergy, import tariff regimes, etc. The implementation of REACH in Europe in 2007, has been one of the main drivers of the change towards green chemistry and sustainable chemical industry (REACH, 1907/2006/EC). It includes certain exemptions for bio-based chemical products. The lengthy and expensive process of obtaining approval for new chemicals is problematic for new entrants, especially small firms not familiar with the conditions of REACH. Specific problems might arise for firms that use biowaste as a resource for bioproduct development; this places them at the interface between waste legislation and REACH (Luit, Waaijers-van der Loop, & Heugens, 2017). There is a need to balance policy actions related to bioenergy/biofuels and bio-based materials (especially chemicals and plastics) to support the development of the latter (i.e., efficient policy support, better access to biomass in terms of price and quantity) (Philp et al., 2013).

The glycoeconomy is an emerging economy characterized by pilots, demonstrators, few commercial-scale production facilities, and niche market phase. At this stage, the policy mix should be designed to build industrial capacity and establish favorable conditions for experimentation and the diffusion of radical innovations (Hellsmark, Frishammar, Söderholm, & Ylinenpää, 2016). For the more embryonic technologies (e.g., algae biorefineries), policy and specific innovation programs should be developed to promote collaboration between academia and industry and provide funding to allow scaling up of pilot plants. Demand-side innovation policies should be implemented to develop new markets (e.g., public procurement, tax incentives, and awareness-raising campaigns).

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