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► **To cite this version:**

Frédéric Corolleur, Aurélie Level, Mireille Matt, Serge Perez. Innovation potentials triggered by glycoscience research. Carbohydrate Polymers, 2020, 233 (Online Early), pp.1-14. 10.1016/j.carbpol.2020.115833 . hal-02454363

HAL Id: hal-02454363

<https://hal.science/hal-02454363v1>

Submitted on 21 Jul 2022

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1 Innovation potentials triggered by glycoscience research results

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10

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

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

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

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

26

27 **1 Introduction**

28 For centuries, humankind has exploited the characteristics of carbohydrates extracted from
29 nature (e.g., sugar cane, wood, fiber, plant extracts, etc.), which has provided an unlimited
30 resource of carbohydrate-based materials. Cellulose is a major component of wood, as well as
31 of cotton and other textile fibers such as linen, hemp, and jute (ramie). For this reason,
32 cellulose has always played an essential role in the life of humans, and its applications could
33 even constitute a landmark in the understanding of human evolution. The use of
34 polysaccharides and carbohydrates during ancient times was considered as energy giving. The
35 two main subspecies of rice were domesticated roughly 10,000-14,000 years ago. Rice has fed
36 more people over a longer period of time than any other crop. The first cereal grains were
37 domesticated about 8,000 years ago by ancient farming communities in the Fertile Crescent
38 region. These tribes started to grow and develop wheat for bread and many types of plants that
39 are carbohydrate-rich. Maize was domesticated in Meso-America, in the area that is now
40 Mexico. Because it was nutritious, easy to store and carry, adapted to diverse growing
41 conditions, and provided food and fuel, maize became a staple food for most American and
42 Caribbean cultures. However, it is only at the beginning of the 19th century that the isolation
43 and description of cellulose, starch, pectin, and chitin took place, and initiated the science of
44 carbohydrate polymers. Carbohydrate studies focused on the elucidation of the structure and
45 chemical modifications of monosaccharides and small oligosaccharides. One, among the
46 various focuses of these investigations, dealt with fermentation processes and the role of
47 carbohydrates in cellular metabolism. Afterwards, research in the fields of chemistry and
48 biology has begun to examine carbohydrate structures and their biological functions (Horton,

49 2008). The discovery that a large proportion of biological information is encoded in
50 carbohydrate structures has become a central concept in glycobiology (Rudd, Karlsson, Khoo,
51 & Packer, 2015). Now, glycoscience is an interdisciplinary field involving biochemistry,
52 polymer chemistry, material science engineering, physiology, developmental biology,
53 microbiology, medicine, and ecology. The exploration by glycoscientists of the
54 physicochemical and biological functions of carbohydrates sustains a vibrant field of research
55 worldwide (Figure 1). Carbohydrates are not restricted to food and nutrition applications; they
56 are also used for the production of bio-based chemical products (surfactants, solvents), new
57 bio-based composite materials, biopolymers, new drugs, and new vaccines.



58
59 Figure 1: Worldwide scientific interests and outcomes in glycoscience over the period 2014-
60 2019. The scientific publications covering the field of polysaccharides are displayed in blue;
61 those related to glycomics are displayed in red. The size of the circle is proportional to the
62 number of articles published by researchers within a given zone. (see Supplemental Materials
63 for details of the analysis)

64
65

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

70 The article is organized as follows. In section 2, we highlight the two socio-economic
71 concepts (innovation niches and industry value chain) used to carry on our analysis. Section 3
72 presents the regional biomass (sucrose, starch, wood, etc.) value chain, which exploits the
73 physicochemical properties of carbohydrates. Section 4 explores the glycomics value chain
74 based on the biological functions of carbohydrates. In Section 5, we analyze the non-regional
75 biomass (microbial, pectin, guar, chitin, etc.) value chain that exploits both properties. Section
76 6 discusses the results and concludes.

77 **2 Socio-economic conceptual background**

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

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

96 2.1 Emergent strategic niches based on glycoscience

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

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

112 In the present article, we analyze three aspects of strategic niche creation (Schot, 2008). First,
113 we consider emergence since the technologies we focus on are at a very early stage and are

114 often far from the market. We demonstrate the central role played by glycoscience in this
115 emergence phase. Second, we consider niche emergence as a process in which newcomers
116 and outsiders challenge the incumbents, but also in which incumbent firms and policymakers
117 from neighboring regimes can be significant at this stage (Turnheim and Geels, 2019; Penna
118 & Geels, 2015). Third, we consider the creation of strategic niches at different points in the
119 industry value chain.

120 2.2 Industry value-chain

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

125 The sustainability transition towards a bioeconomy is hampered by difficulties in efficiently
126 producing bio-based products due to the absence of well-established value chains (Carraresi,
127 Berg, & Bröring, 2018). The bioeconomy value chains suffer from information asymmetries,
128 market power along the chain, risk-sharing, and stabilization of supply and demand (Viaggi,
129 2018). A growing number of separability points and a lack of cross-chain connections and
130 interactions between the consumers and the various supply-sides hamper their functioning.

131 In this article, we use the concept of industry value chain as a rough representation of the flux
132 of glyco-molecules and the actors involved along the chains. We conceptualize three industry
133 value chains based on two-step reasoning. First, the physicochemical vs the biological
134 properties of carbohydrates induces to distinguish respectively between biomass-extracted
135 carbohydrates and glycomics (cf. section 4). Second, among the biomass-extracted
136 carbohydrates, we distinguish between the regional (cf. section 3) and the non-regional (cf.
137 section 5) biomass. Regional biomass (sugar and starch plants, fiber plants, wood) is bulky,

138 making it difficult and costly to transport. To reduce these transportation costs, agro-
139 industries (starch producers, sugar manufacturers, pulp and paper firms) often locate close to
140 the biomass source. Non-regional biomass encompasses microbial biomass, botanical biomass
141 (plant cell walls, legume seeds, shrubs, roots), microalgae, and animal and human origins.
142 This non-regional biomass contains carbohydrates exploited for their physicochemical and
143 biological properties –which will be referred to as dual properties throughout this article.
144 Compared to regional biomass, transportation of non-regional biomass is neither difficult nor
145 costly.

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

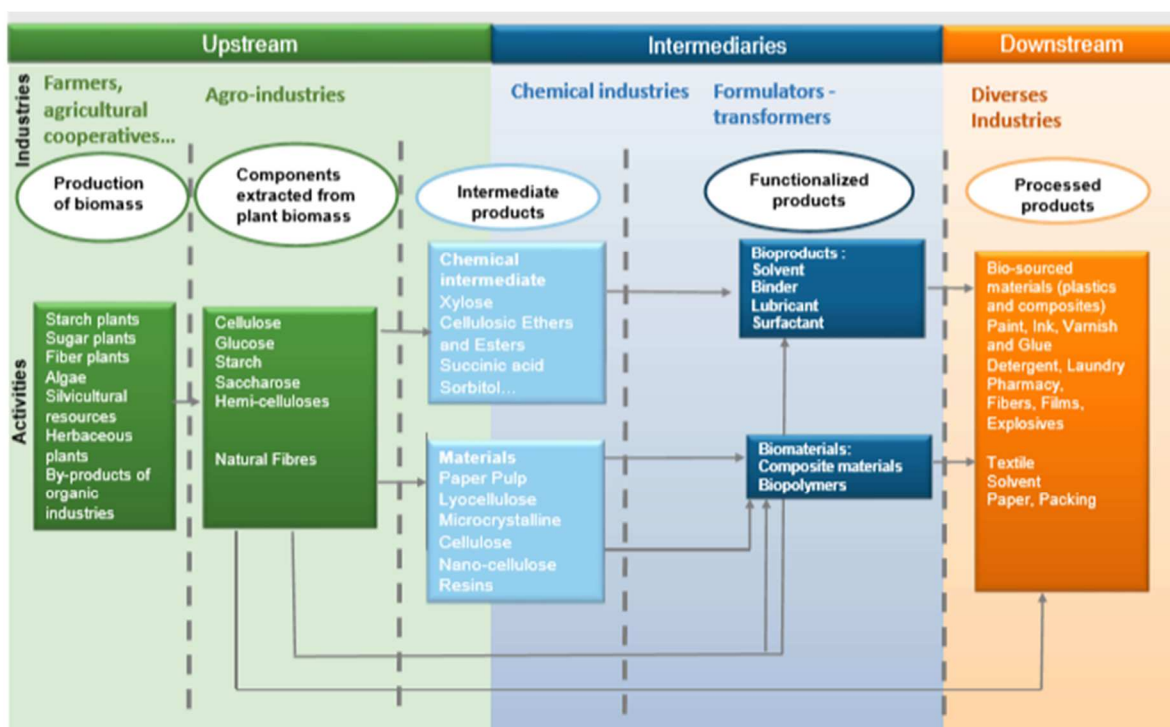
149 The purpose of this study is to dissect the three value chains processes and analyze the
150 features that they have in common. Hence, this study will not detail the complex value chain
151 for every single biomass or glycomics, nor to give precise figures in terms of volume or
152 revenues concerning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

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

157 **3 The regional biomass value chain: from biomass-based** 158 **carbohydrate to bio-products**

159 The regional biomass value chain starts with biomass production (e.g. rice, maize, sugarcane,
160 wood, algae) (cf. Figure 2). Using the biomass feedstock, the agro-industries extract primary
161 molecules (e.g. glucose, cellulose, starch, etc.) or fibres. These primary molecules can be
162 broken down further into intermediate chemical products (e.g. direct polymers and gums such

163 as xylitol, succinic acid, sugar acids, esters) and materials (e.g., paper pulp, microcrystalline
 164 cellulose, nanocellulose). We include these intermediary biochemical products and
 165 biomaterials in the upstream part of the value chain in which agro-industry is the main actor
 166 (section 3.1.). These intermediate products are sold mainly to the chemical industry and
 167 formulators-transformers, which use them to produce bio-products (bio-based solvent, binder,
 168 lubricants, etc.) and biomaterials (biopolymers, composite materials) (section 3.2.). Processed
 169 end-products are produced by diverse industries (section 3.3)



170

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

172 3.1 The upstream stage: extracting sugars from biomass to produce intermediate bio-
 173 chemicals and bio-products

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

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

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

199 Hemicellulose extraction is essential (Chirat, 2017) since it is resulting in new sugar markets
200 (e.g., xylose, mannose, arabinose). Xylitol produced from xylose, could satisfy some of the
201 demand for a less polluting and less energy-consuming food additive production process

202 compared to sulphuric acid hydrolysis. The main issues related to xylitol derived from
203 hemicelluloses are the production process and its scaling up.

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

209 **The nanocellulose niche**

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

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

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

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

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

242 tons/day. Celluforce (Canada) has a broad portfolio of patents, collaborates with a wide range
243 of research institutes and is co-developing new applications with end-users. In 2015,
244 Celluforce and Schlumberger joined forces to explore using CNC in the oil and gas sector. In
245 2019, the Canadian firm will restart its production of CNC following its production facility
246 upgrading.

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

252 Box 1: The nanocellulose niche

253 The main difficulty in the upstream stage of the regional biomass value chain is related to the
254 ability of the biorefineries to supply economically viable intermediary products in appropriate
255 quantities and quality, to the chemical industry and the chemical formulators (intermediary
256 actors). Biorefineries can produce a large number and many types of biochemicals, but only in
257 small volumes. To satisfy the demand from the chemical/formulator industries, biorefineries
258 have had to introduce quality standards. In 2017, the Bio-Based Industries Consortium listed
259 224 biorefineries in Europe. Most are pilot or demonstration plants, with only a few full-scale
260 plants. Pilot and demonstration biorefineries provide a bridge between basic knowledge and
261 technological breakthroughs on the one hand and industrial applications and commercial
262 adoption on the other (Hellsmark, Frishammar, Söderholm, & Ylinenpää, 2016). Pilot and
263 demonstration biorefineries provide opportunities to develop open innovation strategies and to
264 build networks of multidisciplinary stakeholders (e.g., the Bazancourt-Pomacle biorefinery is
265 the result of a collaboration among companies, farmers and research centres, (Marion et al.,
266 2017)). The articulation and subsequent convergence of these actors' vision, learning,
267 experimentation, and the building of relational networks, will be required to overcome the
268 various technological barriers, identify demand and allow the emergence of radical
269 innovation. Successful experiments will attract new actors and allow these technological
270 niches to grow and develop over time (Lopolito, Morone, & Sisto, 2011).

271 3.2 Intermediary stage: producing bio-based chemical products and bio-based
272 materials

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

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

290 The bio-sourced material sector faces the same dilemma as the chemical industry: substitution
291 of petrol-sourced products by glyco-products with identical or similar technical properties
292 (drop-in innovations) vs development of glyco-based products with new functionalities (non-
293 drop-in innovation). Technological and market uncertainties are lower for the drop-in
294 innovation path. Volume sales are potentially significant, but the price and performance

295 competition with petrol-sourced products is fierce, generally at the disadvantage of the bio-
296 products. The non-drop-in innovation path is characterized by higher technological and
297 market uncertainties, and preferably a low volume but higher value. One challenge is the
298 existence of a willingness to pay a Green Premium for the innovation (Carus et al, 2014).
299 Companies are progressively exploring this latter path. However, an issue related to
300 glycochemical and polysaccharides is the high number of steps involved in their production
301 compared to those of petrochemical goods.

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

305 3.3 Downstream stage: few existing applications constrained by the demand-side

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

314 While lack of demand imposes a limitation on the development of applications, the supply-
315 side is also subject to certain constraints. Many innovation projects are still at the research or
316 demonstration stage or have yet to identify a promising market. Manufacturers find it difficult
317 to adopt new bio-based molecules and develop new technologies because: (i) if the bio-
318 product is a substitute, it must cost less or perform better than the equivalent petrol-sourced

319 product; (ii) there needs to be apparent demand for the bio-product with new functionalities;
320 (iii) the production process needs development and scaling-up. An example of a product with
321 new functionalities is hydrophobic paper, produced on a commercial scale and available in the
322 market (see Box 2).

323

324 **The hydrophobic paper niche based on chromatogeny**

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

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

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

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

346 Box 2: The hydrophobic paper niche based on chromatogeny

347 Many research and innovation projects, combining the front-end results of glycoscience and
348 industrial competence, have led to high expectations. These expectations induce the actors to
349 allocate resources and effort and engage in technological development, which results in a
350 niche. For instance, polysaccharides could find promising application in advanced
351 microelectronics. An EU project has led to the design of bio-sourced copolymers with
352 controlled architectures, based on glucose, sucrose or cyclodextrin, which can be used to
353 produce ultra-thin films for nanometric lithography uses ('Des matériaux écolos bien sucrés',

354 2019). Some Japanese microelectronics firms are interested in these resins, which allow the
355 storage of more data on a particular surface than do their petrol-sourced counterparts.

356 **4 The glycomics value chain and the role of glycoscience**

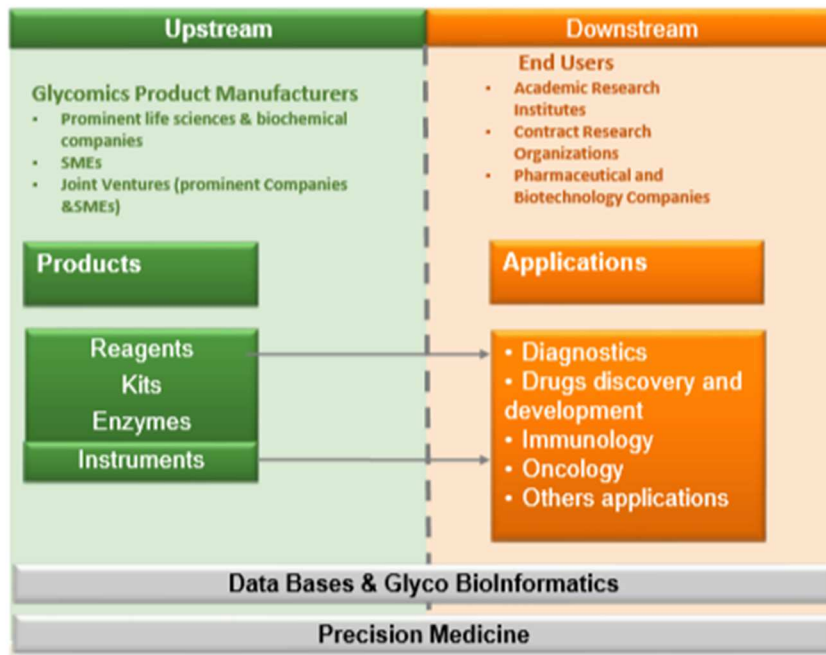
357 The glycomics value chain encompasses reagents and research tools (kits and instruments),
358 diagnostics, therapeutic drugs (new ones, bio-betters and biosimilars) and glycoconjugate
359 vaccines (Figure 3). Since 2000, the pharmaceutical industry has been threatened by an
360 innovation deficit and a patent cliff. The patent cliff refers to the immediate decline in
361 revenue following the expiry of a patent and the entry of generics or biosimilars.
362 Pharmaceutical firms are exploiting various strategies to meet these challenges. They range
363 from incremental strategies, such as drug repositioning, to radical strategies such as precision
364 medicine. Precision medicine is an approach for disease treatment and prevention that takes
365 into account variability in genes, environment, as well as stages of the disease and
366 nutritional/environmental exposures for each person. Glycans are essential modulators of
367 numerous biological processes that determine person-to-person differences in their
368 susceptibility to response to drug treatment or common complex diseases. Glycomics can
369 significantly complement the genomics and proteomics tools that are already being evaluated
370 for developing personalised medicines. This approach allows doctors and researchers to
371 predict more accurately, which treatment and prevention strategies for a particular disease will
372 work in which groups of people. Synthetic carbohydrate-based diagnostics, therapeutics and
373 vaccines contribute to these strategies (Almeida & Kolarich, 2016; Jin et al., 2019; Lauc,
374 2016).

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Figure 3: Organisation of the glycomics value chain.

388 4.1 Upstream

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

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

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

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

424 drug and the production process. Inevitably, any manufacturing process changes are subject to
425 regulation. In the case of biologics, the bio-manufacturers had to obtain approval for both the
426 drug and the production process.

427 **The Automated Glycan Assembly (AGA) niche**

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

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

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

445 Box 3: The Automated Glycan Assembly (AGA) niche

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

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

465 4.2 Downstream

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

479 with the ability to stratify the population-based on individual genetic predispositions to
480 respond to drug treatments (i.e., precision medicine).

481 Glyco-based precision medicine diagnostics are at an early stage. It is expected that the
482 regulatory authorities will approve glycan-based biomarkers for application as diagnostic,
483 prognostic, predictive or therapeutic biomarkers in the short-run (Almeida & Kolarich, 2016).

484 The growth prospects are better for therapy selection diagnostics and safety, sensitivity and
485 resistance markers related to drugs already in the market, than for companion diagnostics
486 (McKinsey&Company, 2013). The top four diagnostic companies account for
487 approximately 70% of global sales. Start-ups are commercialising tests to facilitate the
488 development by medical doctors of individual effective precision healthcare strategies (see
489 Box 4). The development of precision medicine is dependent on scientific and technological
490 advances. It is also posing policy, regulatory (related to approval of the companion diagnostic
491 test, reimbursement mechanisms and pricing) and ethical issues (informed consent processes,
492 privacy and confidentiality, inequality of access) (Stern, Alexander, & Chandra, 2017).
493 Collaborative networks and alliances are common strategies in the biopharmaceutical
494 industry. However, the links between new drug development and diagnostic development
495 firms are scarce.

496 **The Glycan Age niche**

497 Age-related diseases are a significant cause of death. Evaluating the effect of any intervention
498 (drug, diet prescription) that influences ageing requires a reference point. Discovery of robust
499 and accurate biomarkers of ageing is the current holy grail for ageing research (Krištić et al.,
500 2014).

501 N-Glycans are a complex class of oligosaccharides, their structure is heterogeneous and it
502 includes a conserved core region substituted with other sugars in a not stoichiometric fashion
503 (Stanley, N. Taniguchi & M. Aebi, 2017). Serum N-glycan profiling has identified glycan
504 biomarkers associated with the ageing process. Most Immunoglobulins G (IgG) glycans fall
505 into the category of N-Glycans and represent up to 80% of the total serum immunoglobulins
506 in humans. The IgG glycosylation appears to be highly regulated - both during homeostasis
507 and in cases of its disturbance, disease and infection. This differential IgG glycosylation is
508 known to modulate IgG effector functioning and to be involved in the development and
509 progression of diseases; it seems to be both a predisposition and a functional mechanism
510 involved in disease pathology. Both genes and the environment influence the composition of

511 the IGg glycome, making it an excellent biomarker of an individual's general state of health.
512 Every individual in the world has a specific glycosylation pattern, which, while reflecting the
513 general state of health at a given time, changes as a function of health and lifestyle.
514 Glycanage Ltd, a start-up created in 2016, has commercialized a test (GlycanAge®) that
515 provides a fast and personalized estimate of the individual's biological age (a measure of how
516 well the body is performing relative to its chronological age), using high-end technology for
517 the analysis of IGg glycans. IGg glycosylation analysis is performed on a small blood sample
518 using liquid chromatography. Other small firms have proposed alternative technological
519 solutions (e.g., Zymo Research, USA - Life Length, Spain).

520 Box 4: The Glycan Age niche

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

530 Given the costs and the demand conditions in the vaccines market, only a few suppliers will
531 be able to supply each vaccine type. The firms involved are subject to high fixed costs,
532 complicated and time-consuming production processes, price-sensitive demand and dynamic
533 competition over quality. Five multinational corporations (GlaxoSmithKline, Merck,
534 Novartis, Pfizer, Sanofi) account for 80% of the global vaccine market. Historically, these
535 firms were the leading innovators, but more recently, small biotech and emerging-market
536 players are responsible for the majority of the new vaccines. Given the forecast reduction in
537 the costs related to developing glycoconjugate vaccines using AGA (Pardo-Vargas et al.,
538 2018), Glycan Expression Technology and Protein Glycan Coupling Technology, this should
539 allow simplified manufacturing processes for the production of glycoconjugate vaccines.
540 Speedy and practical research on such accessible, economic vaccines depends on the

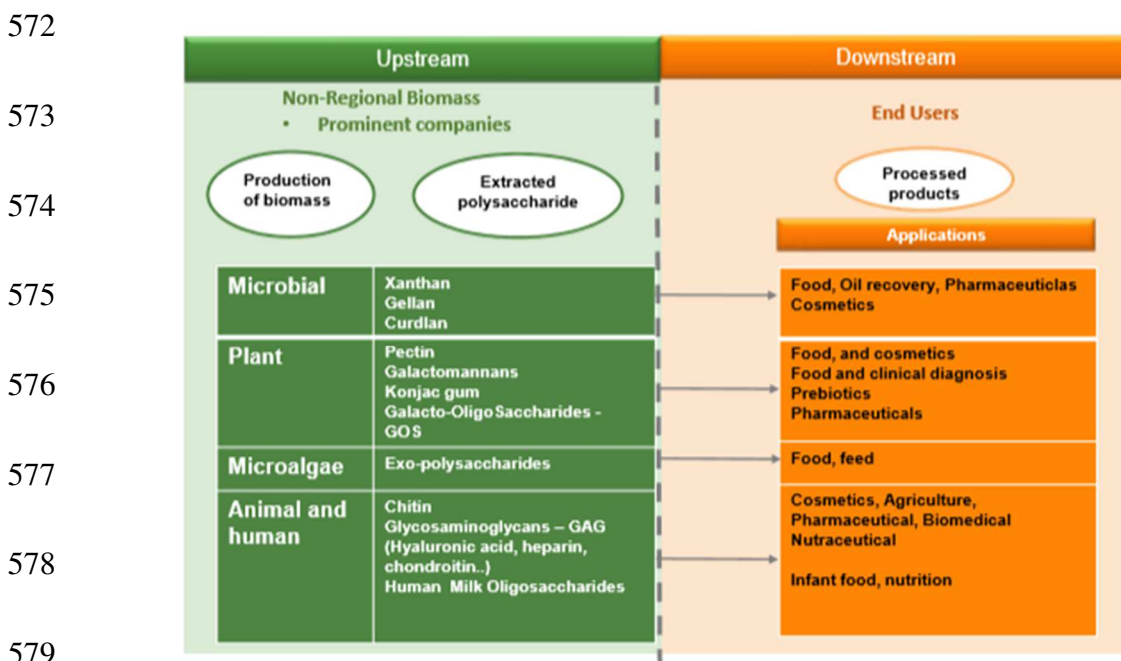
541 availability of quick, accurate and reliable measurement capabilities, which do not adequately
542 exist at present, rendering, for example, the previous glycoconjugate generally approaches too
543 expensive for veterinary applications, especially for livestock farming.

544 Glycosylation engineering is a determinant of the therapeutic efficacy of protein drugs and
545 vaccine success. A biosimilar must demonstrate appropriate glycosylation qualities to obtain
546 regulatory approval. Glycosylation engineering is opening up business opportunities for
547 Contract Research Organizations (CRO) and Contract Manufacturing Organizations (CMO).
548 The constraints imposed by price competition (from generics and biosimilars) and decreasing
549 R&D productivity, is prompting pharmaceuticals companies to partner with CROs and CMOs
550 to gain access to specialized technologies. Both CROs and CMOs have undergone significant
551 consolidation in recent years. Established biologics firms have been developing internal
552 glycoengineering expertise (e.g. Amgen), while less well-established companies have
553 acquired glycosylation solutions and promising developments via mergers and acquisitions
554 (e.g. Roche's acquisition of Glycart in 2005, Merck's acquisition of GlycoFi in 2006, and
555 AstraZeneca's acquisition of MedImmune in 2007). In 2015, only three suppliers (Boehringer
556 Ingelheim, Lonza and Samsung) were involved in large-volume mammalian cell-culture
557 production based on six or more 12kL bioreactor lines. The entry barriers to CMOs are lower
558 for those operating on smaller scales (up to 3kL), for small volumes of biopharmaceuticals,
559 such as those needed for clinical supply, or for small-volume commercial production (e.g.,
560 biologics for niche indications) (Gennari, Loesch, Santagostino, Otto, & Mc Kinsey & Co,
561 2017).

562 **5 The non-regional biomass value chain with dual properties**

563 The non-regional biomass value chain (cf. Figure 4) is relatively simple. It includes two
564 significant steps: extraction of polysaccharides from various types of biomass (the upstream
565 stage), and the downstream industrial application stage (mainly in food and beverages,

566 pharmaceuticals and cosmetics). Recognition of the biological importance of glycans and
 567 their conjugates is shedding new light on non-regional biomass-based polysaccharides, used
 568 mainly for their physicochemical properties. The controlled deconstruction of complex
 569 polysaccharide architectures, combined with the fine analytical characterization of the
 570 resulting structural motifs, could help the identification of new embedded biological
 571 functions.



580 Figure 4: Organisation of the non-regional biomass value chain

581 5.1 Upstream stage: extracting various polysaccharides with dual properties

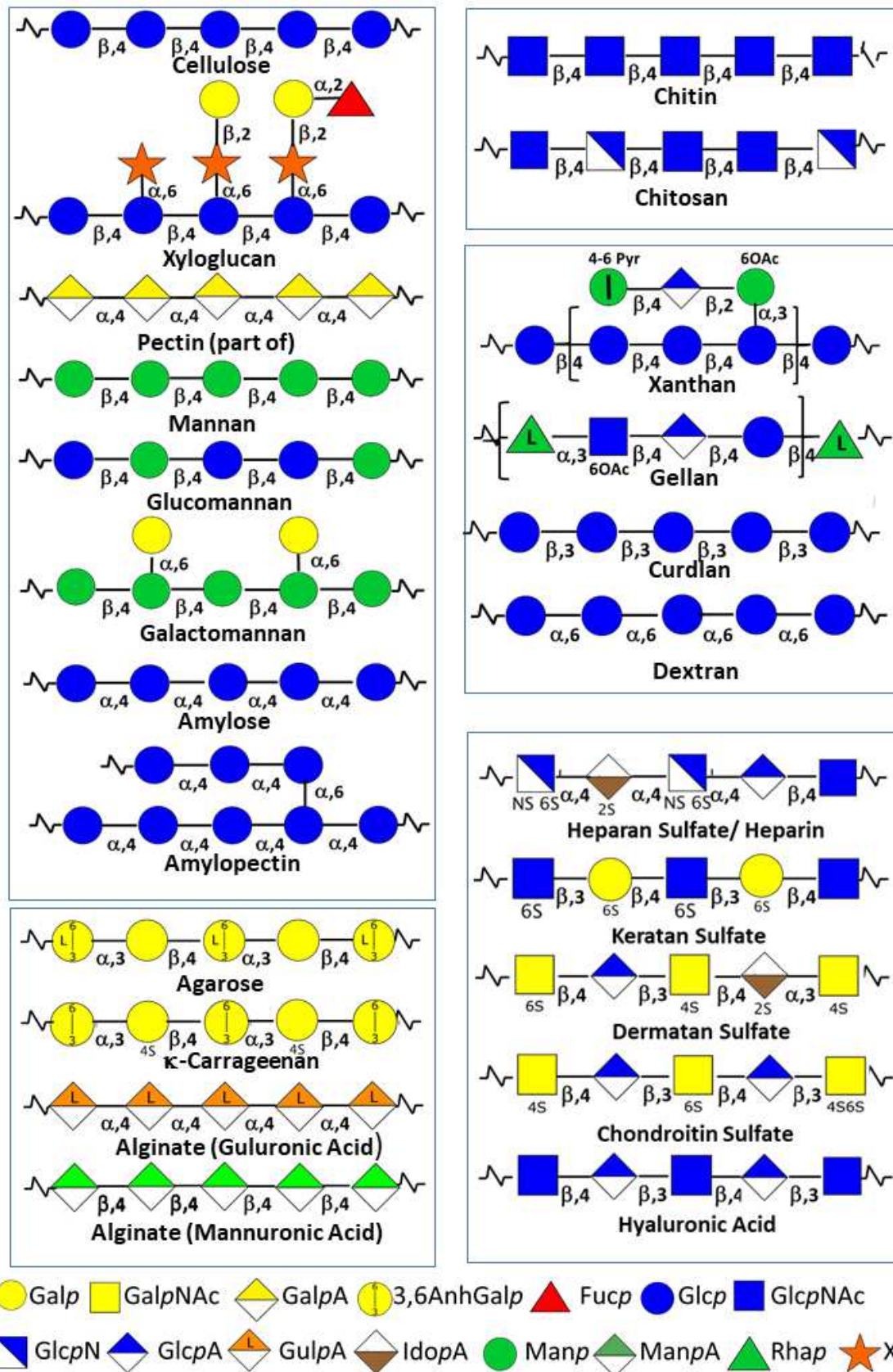
582 The upstream step involves several families (microbial, botanical, microalgae, animal, and
 583 human) of non-regional biomass, each producing specific types of polysaccharides with
 584 physicochemical and biological interesting properties (Dimitriu, 2004). The schematic
 585 representations of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

587 5.1.1 Microbial biomass

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

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

601



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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).

607 5.1.2 Botanical biomass

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

625 Galactomannans are polysaccharides that are present in and are extracted from various
626 legume seeds (guar, carob, fenugreek, cassiata, dhaincha) and full-grown perennial trees
627 and shrubs (Mathur, 2017). Galactomannans extracted from trees and shrubs have no
628 commercial applications as such, but legume-based galactomannans are produced
629 commercially. They are excellent thickeners used as a food additive, dietary fibers, and clinical
630 nutrition ([Kontogiorgos, 2019](#)). Each galactomannan has specific molecular properties and is

631 not easily replaceable in specific applications. The main producers are in the US and include
632 Cargill and Sigma Aldrich Manufacturing.

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

637 **Elicitor niche**

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

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

658 Box 5: Elicitor niche

659 5.1.3 Microalgae

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

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

683 5.1.4 Polysaccharides from animal and human sources

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

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

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

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

713 Galactooligosaccharides (GOS) are produced by enzymatic conversion of lactose using
714 galactosidases; they are of interest for their potential health benefits. GOS are prebiotics: "A

715 substrate that is selectively utilized by host microorganisms conferring a health benefit”
716 (Gibson et al., 2017). The top four manufacturers account for the major industry share. R&D
717 investment and new product development will be key to meeting increased demand.

718 Human milk oligosaccharides (HMOs) are a family of structurally diverse unconjugated
719 glycans, unique to human breast milk, although not digestible by human infants (Kunz et al.,
720 2000). HMOs act as prebiotics, helping to establish commensal bacteria, enhance memory and
721 brain development, and act as anti-adhesives to prevent the attachment of microbial pathogens
722 to mucosal surfaces (L. Bode, 2012; Heger et al., 2019). Due to their complex and diverse
723 structure, their extraction and synthesis are difficult. New techniques, such as extracting HMO
724 from cow milk, chemical or enzymatic synthesis, and microbial production, are currently
725 being explored by the leading players (see Box 6). Production of HMO is expensive, and the
726 HMO market will need considerable investments in the coming decades

727 5.2 Downstream stage: various applications with high innovation potential in the 728 health sector

729 5.2.1. Microbial biomass

730 Research activity is focused on pre-treatments, fermentation, and downstream processing
731 techniques to develop economically viable new biopolymers based on microbial
732 polysaccharides for large-scale innovative applications. The gelling properties of microbial
733 polysaccharides are exploited mainly by the food sector, although xanthan and gellan are used
734 also by the pharmaceutical and cosmetics industries. Xanthan gum is associated with a wide
735 range of drugs designed to extend the contact time of active ingredients and slow drug release
736 in tablets. Modified xanthan gum is being investigated as a promising scaffold for tissue
737 engineering. In the cosmetics industry, xanthan gum is used to prepare water gels. Xanthan is
738 used in oil recovery and mineral ore processing. In the US and Europe, xanthan has been

739 approved as a food additive and, generally, is recognized as safe for pharmaceutical
740 applications. The use of gellan gum has the potential for application in the field of tissue
741 engineering, mainly as a material for cartilage reconstruction. Some recent research suggests
742 that due to its biocompatibility and non-toxic properties, gellan gum could be used to produce
743 novel wound dressings designed to inhibit postsurgical adhesion and prevent scar formation
744 (Osmałek, Froelich, & Tasarek, 2014). Gellan gum has received legislative approval in the
745 US, Canada, Europe, Latin America, and Asia for use in food, cosmetics, pharmaceutical, and
746 non-food products. The US FDA has approved the use of curdlan as a food additive.

747

748 5.2.2. Botanical biomass

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

763

764 5.2.3. Micro Algae

765 Except for microalgae produced by the energy sector, most microalgae are considered a
766 valuable source of biomolecules for various applications, mainly in health food segment
767 (75% of the production volume in Europe over the past decades; Enzing et al., 2014), but also
768 in cosmetics (anti-ageing creams) and chemistry (biodegradable plastics). In Europe,
769 microalgae used for human nutrition are required to pass strict homologation procedures.
770 Only two species have been authorized: *Chlorella sp.* and *Spirulina sp.* (Enzing et al.,
771 2014).

772 5.2.4. Polysaccharides from animal and human sources.

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

783 **Human Milk Oligosaccharides (HMO) niche**

784 Human milk oligosaccharides (HMOs) are complex sugars found in human breastmilk, which
785 assist in early-life immune programming and protection against infectious diseases. HMOs
786 are a structurally and biologically diverse group of complex indigestible oligosaccharides.
787 More than 200 different oligosaccharides have been identified, varying in composition from 3
788 to 22 monosaccharide units. The quantities and structures of these HMOs differ among
789 women. The structures of the most common oligosaccharides contain neutral fucosylated
790 molecules. The research underlines the importance of human milk as an early-life influence

791 on the development of a healthy immune system. HMOs play many different roles in both
792 infants and adult digestive health. Additional protection might be achieved through
793 modifications of the gut microbiota composition and metabolism, to regulate intestinal
794 immunological aberrancies and maintain gut integrity. However, we need a better scientific
795 understanding of these mechanisms. Production of HMOs by synthetic methods is challenging
796 due to renown problems in carbohydrate synthetic chemistry; namely, the different hydroxyl
797 functions have similar reactivity hampering the achievement in good yields of products with
798 the desired stereo- and regioselectivity. Accordingly, the synthetic approach requires high
799 R&D and production investments, and the costs associated are the bottlenecks of the
800 innovation in this area.

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

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

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

822

823 Box 6: HMO niche

824 **6 Discussion and conclusion**

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

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

829 - The definition of glycoeconomy and related policy issues.

830 6.1 Glyco-based strategic niches and their impact on value chain structuration

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

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

846 The innovations considered in this article constitute opportunities to develop complementary
847 value chains or cross-chain connections. The functional food value chain, based on HMOs, is
848 an emerging value chain that is not a replacement for either the food or the pharmaceutical
849 value chains but instead is located between them (Carraresi et al., 2018). In cross-chain
850 connections, the existing value chain is neither substituted nor complemented, but new links
851 are being created between individual stages. The same applies to the nanocellulose value
852 chain, where we observe the emergence of new networks between lignocellulosic
853 biorefineries and different types of end-users (consumer goods producers, technology

854 providers, pharmaceutical companies, etc.). The most advanced glycosciences research will
855 induce future cross-linkages between the three value chains: for instance, nanocrystals and
856 nano-fibrils of cellulose. Such novel materials produced in the regional biomass value chain
857 could be used as templates for the development of innovative medical treatments based on the
858 grafting of bio-active anti-cancer, anti-microbial molecules (glycomics value chain).

859 6.2 Towards the definition of glycoeconomy and policy issues

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

878 *eco-efficient and competitive carbohydrate-based goods and services.*” This definition
879 combines a science-based innovation perspective, a niche-based perspective, and a functional
880 substitution perspective.

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

897 The glycoeconomy is an emerging economy characterized by pilots, demonstrators, few
898 commercial-scale production facilities, and niche market phase. At this stage, the policy mix
899 should be designed to build industrial capacity and establish favorable conditions for
900 experimentation and the diffusion of radical innovations (Hellsmark, Frishammar, Söderholm,
901 & Ylinenpää, 2016). For the more embryonic technologies (e.g., algae biorefineries),
902 policy and specific innovation programs should be developed to promote collaboration

903 between academia and industry and provide funding to allow scaling up of pilot plants.
904 Demand-side innovation policies should be implemented to develop new markets (e.g., public
905 procurement, tax incentives, and awareness-raising campaigns).

906

907 **Acknowledgement**

908 The authors would like to thank all the researchers of Glyco@Alps for their fruitful insights to
909 this article. [Appreciation is extended to the reviewers of this article for their sound and](#)
910 [relevant comments and suggestions.](#)

911 **Funding**

912 This work was supported by the Cross-Disciplinary Program Glyco@Alps, within the
913 framework “Investissement d’Avenir” program [ANR-15IDEX-02].

914

915

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