CarboMet

European Commission

Ludger · CellmAbs Biopharmaceuticals · DSM · Glyco@Alps Univ. Grenoble Alpes · GlySign

ayming · Iceni Diagnostics · INNOGLY · Kompuestos™ · bio-shape

GLYCO 2030

A Roadmap for Glycoscience in Europe

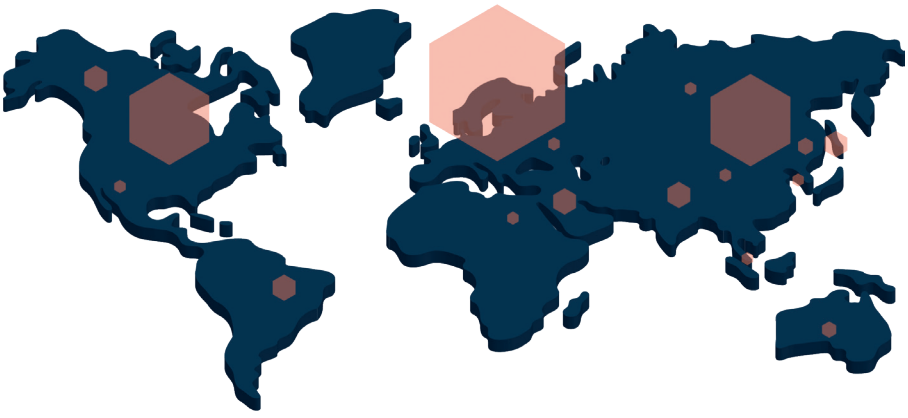
WHAT IS GLYCOSCIENCE?

Glycoscience is the science of carbohydrates, which comprise the most abundant biological molecules and materials on Earth. Glycoscience is recognised worldwide as an area of immense importance in the world economy. It has the potential to solve several of the challenges faced by modern society.
CarboMet is a cross-disciplinary network that has engaged with >350 stakeholders in Europe to identify a number of exciting opportunities which are of great interest to European Society and Bioindustries, in particular the areas of Pharmaceuticals and Personalised Medicine (addressing challenges in health), Food (food security, wellbeing) and Biomaterials (resource efficiency and raw materials) which are presented in this document. Underpinning these opportunities will be a number of emerging glycoscience tools, particularly in measurements and analytics, synthesis and bioinformatics, which will open up glycosciences to a much wider scientific and industrial community and overcome barriers to entry for many commercial applications. This Roadmap is the result of a wide-ranging consultation exercise organised by CarboMet that aims to identify key opportunities and applications in glycoscience in the next 10 years and help inform the broader community, including scientists at all levels, media and policymakers.

INFO | Carbohydrates are a large and important class of biomolecules that have many names: sugars, monosaccharides, polysaccharides and glycans. In living systems, carbohydrates are often chemically linked to proteins, lipids or other metabolites and these are then referred to as glycoconjugates. Therefore, the words "glycoscience" and "glycobiotechnology" are terms encompassing all activities related to science and technology of carbohydrates, respectively. Glycoconjugates reflect Nature in its high complexity and this presents opportunities and challenges to scientists in terms of synthesis and analysis, that have not been fully addressed. Glycoconjugates are responsible for a myriad of complex biological functions affecting the health and well-being of living organisms and the natural environment as a whole both on land and in the sea. Glyco-science and -biotechnology have a unique potential to help solve some of the most significant technological challenges of our times, including the protection of the living environment, promoting human health and well-being and will play an essential part in slowing and even reversing adverse climate change.

THE EUROPEAN GLYCOSCIENCE COMMUNITY

The last decade has seen the growth of the glycoscience network bringing together leading experts to develop a roadmap to drive glycoscience and glycotechnology innovation in Europe. This has previously been facilitated by the European Glycosciences Forum (EGSF) and is currently being led by CarboMet to highlight the achievements of scientific and technological excellence in European glycoscience research. The present document puts forward several areas where some of the most promising technologies can be translated into products in the European and global market.
Glycoscience is becoming an essential part of modern innovative biotechnology. This will provide the European bio-based industries with a strong competitive advantage on a global stage. To fully grasp the opportunities presented in this document, we recommend the formation of a pan-European Glycoscience Group to enact, deliver and advance the areas highlighted in the document.



The European Glycoscience Community is the largest in the World as judged by number of outputs represented by the size of hexagons.
Corolleur, Frederic; Level, Aurelie.; Matt, Mireille.; Perez, Serge. Carbohydr. Polym., 2020, 233, 115833

INTERNATIONAL SUSTAINABILITY GOALS

In 2015, all United Nations Member states adopted a far-reaching policy document for attaining global sustainability – the 2030 agenda for sustainable development.[1] Seventeen ambitious Sustainable Development Goals ('SDGs') have been identified[2] with the target date of 2030 for attaining these goals. Since that date the public awareness of the dangers of climate change has grown enormously and the UN Climate Action

[1] Transforming our world: the 2030 Agenda for Sustainable Development: https://sustainabledevelopment.un.org/post2015/transformingourworld
[2] https://www.un.org/sustainabledevelopment/sustainable-development-goals/

CONTENTS

Summit 2019 endorsed very specific and challenging targets of a 45% decrease in carbon dioxide emissions by 2030, with zero net emissions by 2030.[3] In addition, the importance of scientific research and healthcare in public health has been at the forefront in recent years, improving the quality of life for citizens and supporting the global economy. At a more local level, Horizon Europe ['HEU'], the next European research and innovation framework programme, set to run from the beginning of 2021 to the end of 2027, is adopting a "mission-oriented approach" with a strong emphasis on sustainability aligned with the UN SDGs. The first five Mission Areas have been proposed,[4] namely: **Adaptation to climate change including smart cities, Healthy oceans, seas, coastal and inland waters, Soil health and food**. Each Mission is governed by a Mission Board, comprising "a broad mix of experts from innovation, research, policy making, civil society and practitioner organisations" and has an assembly of high-level experts to "provide an additional pool of ideas, knowledge and expertise that will be actively called upon to contribute to the success of the 5 Missions".

UN SDGs AND INNOVATION IN GLYCOSCIENCE

Significant advances in all aspects of glycoscience is required to accelerate adoption and overcome scientific and technological challenges to achieve UN SDG target by 2030. Glycoscience is central to no less than eight of the 17 SDGs.

UN SDG	Title	Role of Glycoscience
2	Zero Hunger	Nutraceuticals, Prebiotics, Non-meat based diets, Carbohydrate-based fibrous foods, Soil metagenomics, Novel adjuvant materials for agriculture
3	Good Health & Wellbeing	Innovative vaccine design, Growing AMR, Precision medicine and glycomics, Pharmacoglycomics, Role(s) of carbohydrates in the microbiome, Novel carbohydrate-based materials for cosmetics and prosthetics
7	Affordable & Clean Energy	Waste carbohydrate-based bio-feedstock for incineration, Substitute materials for construction and transport having lower energy demands than currently used
9	Industry, Innovation & Infrastructure	Sustainable synthesis of carbohydrates with novel functionalities, Manufacturing high value specialty glycan products having unique functionalities using in vitro synthetic biology
12	Responsible Consumption & Production	Biodegradable and compostable saccharides and glycans for recyclable packaging in a circular economy, Novel textiles, packaging and next-generation display materials
13	Climate Action	Climate change and spread of disease, Climate change and renewable materials to alleviate growing demand for resources
14	Life Below Water	Novel glycans from sea weeds, Novel non-meat based foods, Novel glycans sourced from oceanic archaea, flora and fauna
15	Life on Land	Building healthy soil microbiomes from soil metagenomic analyses, Systemic solutions for the sustainable use of land by balancing carbohydrate production between forestry, agricultural and re-wilded land.

GLYCOSCIENCE IN GLOBAL SUPPLY AND VALUE CHAINS

Responsible Consumption and Production of products and services (UN SDG12) emphasises the need to evaluate and adapt a more sustainable and transparent supply chain, involving stakeholders from suppliers to final consumers.

Supply chains are essentially developed in the value chain terms where innovative and transformative technologies are mapped along the roadmap measuring sustainability, quality and equitable distribution of wealth. Carbohydrates play essential roles in several industries and are directly involved in three distinct value chains:[5]

► Regional biomass based carbohydrates: This is using the raw biomass feedstock such as rice, maize, wood and sugarcane to produce primary molecules such as glucose, cellulose and starch. These can be converted further to produce high-value chemical intermediates.

► Glycomics and healthcare: This value chain encompasses the research tools, diagnostics, biologics and vaccines in the development of new diagnostic therapeutic interventions.

► Non-regional biomass based carbohydrates: This is the direct extraction of high-value sugar products from biomass and used immediately in consumer products.

[3] UN Climate Action Summit 2019: www.un.org/en/climatechange/un-climate-summit-2019.shtml
[4] ec.europa.eu/info/horizon-europe-next-research-and-innovation-framework-programme/mission-oriented-policy-horizon-europe_en
[5] Corolleur, F. et al., Carbohydr. Polym., 2020, 233, 115833

BIOPHARMACEUTICALS

ANTIMICROBIAL RESISTANCE AND VACCINES

Antimicrobial resistance (AMR) is one of the biggest threats to global health and food security today. The improvident use of antibiotics in clinical settings and animal husbandry has been the major cause for the emergence of AMR. It is a concern for both developed and developing countries. The number of deaths due to infections resistant to antibiotics is projected to reach 10 million deaths annually by 2050 – more than cancer. The increased resistance and infection rate equates to healthcare and hospital costs of EUR 1.5 billion per year and will surpass EUR 1 trillion by the year 2050.[6]

INFO | AMR is when micro-organisms such as bacteria, virus and fungi evolve resistance to antibiotics, antivirals and antifungals. This is a natural evolution process which generally occurs over a long time; however, the speed at which AMR is occurring is causing a major threat to the global population. As a result, drugs that were once effective in treating bacterial infection are losing efficacy. This means a simple surgical procedure can result in a life-threatening bacterial infection.

Top 10 global best selling drugs. Biologics (highlighted) which are highly glycosylated have dominated the market for the last decade. The introduction of biosimilars is set to continue this trend.

2008	2013	2020[7]
Lipitor	**Humira**	**Humira**
Seretide	Seretide	**Keytruda**
Plavix	**Enbrel**	Revlimid
Herceptin	**Herceptin**	Eliquis
Enbrel	**Mabthera**	**Opdivo**
Zyprexa	**Remicade**	**Eylea**
Lovenox	**Lovenox**	**Stelara**
Glivec	**Avastin**	Imbruvica
Pantozol	**Lucentis**	Xarelto
Symbicort	Lyrica	Biktarvy

RESEARCH PRIORITIES

It has been more than 30 years since the last class of antibiotics was discovered with many of the 'new' drugs being second and third generation antibiotics without a novel mechanism of action. Even these last resort antibiotics will be inefficient as new resistant strains emerge. The lack of antibiotics has been exacerbated with low ROI for pharmaceutical companies due to high R&D costs and low prices which are not off-set by high volume sales resulting in a diminishing R&D pipeline in the last 30 years.

DEEP UNDERSTANDING OF CELL SURFACE GLYCANS ON MICROBES

Highly targeted and effective carbohydrate-based vaccines can only be developed from a deep understanding of the molecular structure and conformation of the relevant cell surface polysaccharides on bacteria. This will also enable faster and accurate diagnosis for patients.

LARGE SCALE PRODUCTION OF POLYSACCHARIDES

Developing robust chemical and enzymatic synthesis platforms for production of specific oligosaccharide antigen for vaccine development is a priority. Modification of naturally available sugars and the development of rapid automated synthesis of target antigens will accelerate vaccine design and development.

GLYCONCONJUGATE AND ADJUVANT DESIGN

Carbohydrate-based vaccines require a protein carrier to establish and trigger long-term protection (especially in infants, children and in the elderly population). The method to attach sugars to these carriers (also known as conjugation) is often complex (or complicated) and expensive. New methods should allow full control over the modification of the protein with batch to batch consistency.

NEW BUSINESS AND FUNDING MODELS

Cost sharing models for SMEs and incentives for large biopharmaceutical companies are required to facilitate antibiotic discovery. Require new collaborative framework between industry and academia (public private partnerships) to mitigate issues surrounding IP ownership. Open source innovation, collaborative partnership and fast track approval process will persuade public-private investments.

[6] Rappuli, R. et al. Nature, 2017, 552, 165-166.
[7] Nature Biobusiness briefs, Top product forecasts for 2020: https://www-nature-com.manchester.idm.oclc.org/articles/d41573-020-00011-5

GLYCOENGINEERING

Sugars on the surface of cells and biomolecules play a vital role in bacterial and viral infection through cellular communication and adhesion. These sugars also play a crucial role in the stability and efficacy of biopharmaceutical drugs which make them safer and more effective. The process of decorating the surface of biomolecules is called glycosylation and is an integral process in the production of biopharmaceuticals. Current approach to modify glycans has been through either genetic engineering or process optimisation. Both procedures (approaches) are complex, with limited control over glycosylation and a compromise between production yield and degree of glycosylation.

COMPANY INSIGHT | Ludger is a bioscience company specialising in analytics and medical application in glycobiology. They provide glycan analysis services to determine the glycosylation profile on biopharmaceuticals. In addition, the company is involved in medical glycomics R&D. www.ludger.com

CASE STUDY

The rise of biosimilars in the next decade will bring intense competition as many of the top performing biopharmaceuticals in the last 20 years will come off patent. Glycosylation is critical in the development of biosimilars for safety and efficacy and due to the inherent difficulty in controlling glycosylation, glycoengineering will play a vital role in the European biologics market.

INFO | Biologics or biological drugs are medical products produced from living organisms in a complex and highly controlled manufacturing process. The anti-inflammatory drug Humira is one example of a biological drug and is one of the best selling drugs worldwide. A biosimilar is a biologic which is highly similar to the original medicine in terms of safety, purity and efficacy.

RESEARCH PRIORITIES

METABOLIC GLYCOENGINEERING

This is a method to optimise genetic and regulatory processes within cells to increase and/or modify the cells production of certain molecules. This technique exploits the natural promiscuity of glycoenzymes (glycosidases and glycosyltransferases) to incorporate non-natural sugars and/or remove certain sugars involved in disease progression. This technology can be used for imaging tumour cells or in biomarker discovery.[8]

IN VITRO GLYCOENGINEERING

The development of therapeutic proteins independent of fermentation processes provides much greater control on the modification of surface glycans. This requires development of a suite of sugar modifying enzymes called glycosyltransferases through enzyme discovery and engineering. The enzymes should be cheaply available and at kilogram scale in GMP grade.

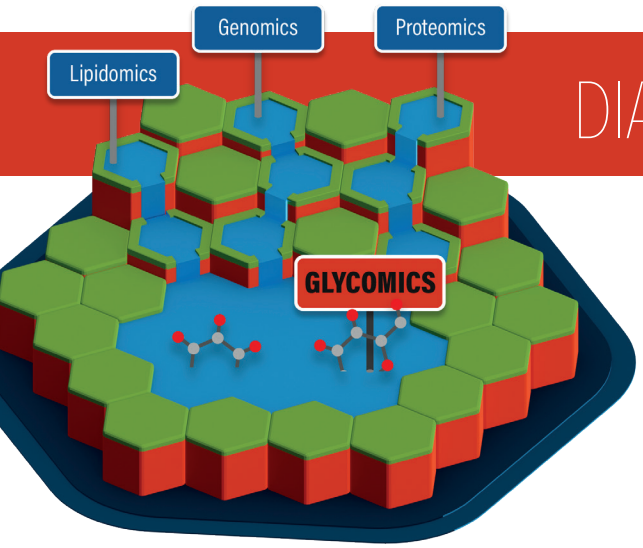
STEM CELLS

The trillions of cells in the human body that make up tissues like skin, blood, liver and nerves are derived from a very important class of cells called stem cells. These cells play a crucial role in the development of an organism but also in the treatment of chronic diseases such as cancer, diabetes and autoimmune diseases. Glycans play an important role in how these cells mature into tissues and organs and also in immune rejection from patients receiving stem cell treatment.[9]

SPECIFIC CHALLENGES

- Isolation and sequencing of cell surface polysaccharides
- Sustainable and rapid synthetic routes to oligosaccharides
- Curation of bacterial structure database to enable faster development of therapies
- Development of biocompatible micro-systems for drug delivery

[8] Yarema, K. J. et al. Nat. Rev. 2019, 3, 605-620.
[9] Varki, A. P. et al. Curr. Opin. Chem. Biol. 2007, 11, 373-380.



DIAGNOSTICS & PRECISION MEDICINE

ROLE OF GLYCANS IN THE HUMAN BODY

All cells and the proteins found in the human body are coated with sugars called glycans. These glycan structures play a crucial role in cellular communication and recognition and are therefore critical in bacterial and viral infection. Besides, numerous diseases are linked to abnormalities in the synthesis of glycans, including genetically determined congenital disorders of glycosylation (CDG) and other common illnesses such as autoimmune and inflammatory disease, neurodegenerative disease and cancer. Glycans are made in a process called glycosylation. It is controlled by numerous genes and utilises >200 enzymes. The process is also affected by environmental factors such as nutrients. Altogether, the involvement of glycans with human disease offers plenty of opportunities for personalised diagnostics, identification of prognostic markers and novel treatment targets.

CASE STUDY | Corona virus

Like influenza and all viruses, coronaviruses which are a group of RNA viruses such as SARS-CoV-2 bind to the highly glycosylated surface of the ACE2 protein on cell surfaces. This host-pathogen interaction mediated by cell-surface glycans provides an entry point for the virus. Notably, the surface of the virus is also decorated with glycans which helps it to avoid detection from the immune system. These glycans also present a pivotal target to develop vaccines against it. Visit page 4 to see how glycans can be used to make carbohydrate-based vaccines.

COMPANY INSIGHT | ICENI Diagnostics is focussed on the development of carbohydrate-based therapeutics and point-of-care diagnostics for infectious disease. The company is developing technology to distinguish between flu and coronavirus. www.icenidiagnostics.com

GLYCOMICS A NEW FRONTIER IN DRUG DISCOVERY

Glycans play a key role in a myriad of biological processes. They are essential in protein folding, interactions and stability, and act as recognition elements facilitating cellular communication. These interactions drive the process of cell signalling, proliferation and differentiation and is central to pathological process of bacterial adhesion, viral infection, inflammation and immune system response. Exploiting these complex interactions will provide new avenues for precision medicine affording a new generation of biopharmaceuticals.

INFO WHAT IS GLYCOMICS | Glycans, which are sequences of sugars attached to proteins and lipid are the most structurally diverse biomolecule in the human body. Collectively known as the Glycome, they play a vital role in cell communication, viral and bacterial infection, cancer metastasis and cell growth. The Human Glycome Project (HGP)[11] and GlySign[12] and Euroglycanomics are ongoing European projects to translate glycan biomarker research into clinical practice. Glycans on the cell surface provide a tremendous amount of data on the development and progression of diseases. Researchers can exploit this vast information in the discovery of new drugs bringing immense value to the biopharmaceutical and diagnostics industry.

CASE STUDY | Cancer vaccine

Cancer cells exhibit different glycosylation patterns from normal healthy cells. These glycans on the surface, also known as tumour-associated carbohydrate antigens (TACA) are an essential target for the development of new interventions. The differences in the structure can be used in diagnostics and also to develop cancer vaccine by targeting the TACA found only on a cancer cell.

COMPANY INSIGHT | CellmAbs focuses on the discovery and development of cutting edge oncology products, aiming to provide the most effective and safe therapeutic and diagnostic solutions to treat cancer patients. The company exploits the differences in glycan antigens between healthy and cancerous cell for a precision approach in cancer treatment. www.cellmabs.com

[10] Liu, Y et. al. 2009, J. Virol. 2009, 84, 12069-12074.
[11] The Human Glycome Project: https://human-glycome.org/
[12] Glycosylation Signatures for Precision Medicine: https://www.glysign.eu/

The complexity of the glycome has made it difficult to analyse and accurately quantify the subtle changes found in different diseases. This diversity also offers an incredible source of new data and access to novel therapeutic biomarkers which would otherwise be difficult to determine through genomic analysis. Glycans with specific sequences play an important role in cell recognition and immunity. For example, alterations in the glycan structure on the surface of immunoglobulin (IgG; an antibody used by the immune system to neutralize pathogen) has been observed in several autoimmune diseases including rheumatoid arthritis.[13] It can also be used as a predictive indicator, for example, IgG variants with altered glycans on the surface can be used as a predictive marker for the onset of disease.[14]

HOW GLYCOMICS CAN BE USED IN DRUG DEVELOPMENT

1. Identification of structural changes of glycans involved in disease progression. This could be where glycans are not fully formed (truncated) or have too many sugars, for example, in cancer there is excess sialic sugar on the surface

2. Genomic analysis to identify expression levels of proteins such as enzyme involved in glycosylation. Identify patients through genetic analysis.

3. Develop new drug by elucidating the mechanism of action of protein/enzymes involved in glycan expression.

CASE STUDY | CONGENITAL DISORDERS OF GLYCOSYLATION (CDG)

Congenital disorders of glycosylation are a genetically and clinically heterogeneous group of >130 diseases caused by defects along glycan modification pathway. While CDG is classed as a rare disease, cases have been reported worldwide with significant impact on the patients quality of life. Currently, mannose and fucose are given as oral supplements as treatment, however, the majority of cases are involved in managing symptoms.

RESEARCH PRIORITIES

MAPPING OF THE HUMAN GLYCOME

Significant investments are required to fully map the human glycome. This requires a concerted effort between public-private institutes and a partnership between several key research infrastructures in Europe.

CLINICIAN ENGAGEMENT

Academics need to work with clinicians and the wider life science sector including, immunologist, clinical biochemists and microbiologists to develop a robust value proposition of research. Scientists must consider the market opportunity, cost-effectiveness and affordability of the therapeutic intervention.

GLYCAN TARGETING DRUGS AND GLYCOMIMETICS

Cell surface sugars are critical in cellular communication and adhesion, for example, viral infections are mediated by surface glycans. Designing drugs to selectively bind to sugar moieties on pathogens is one approach to halt infection. Also, many viruses exploit certain sugars on cells as a gateway to infection, designing these sugar mimics also known as glycomimetic drugs is one approach to trick the pathogen and disrupting the process of viral replication.

CASE STUDY | TAMIFLU MECHANISM OF ACTION

The antiviral drug Oseltamivir sold under the trade name Tamiflu is a glycomimetic drug which mimics the structure of sialic acid. This cell surface-sugar is critical in viral binding. The drug binds strongly to a protein called Neuraminidase (NA) which is used by the virus to cleave sialic acid sugars on the cell surface promoting the release of influenza virus from infected cells and facilitating further infection. By blocking the NA protein, it prevents the release and migration of new viruses and slowing down the infection.

[13] Maverakis, E. et. al., J. Autoimmune, 2015, 0, 1-13.
[14] Nimmerjahn, F. et al., Nat. Rev. Rheumatol. 2017, 13, 621-630.

IMPACT & ENABLING TECHNOLOGY AREAS

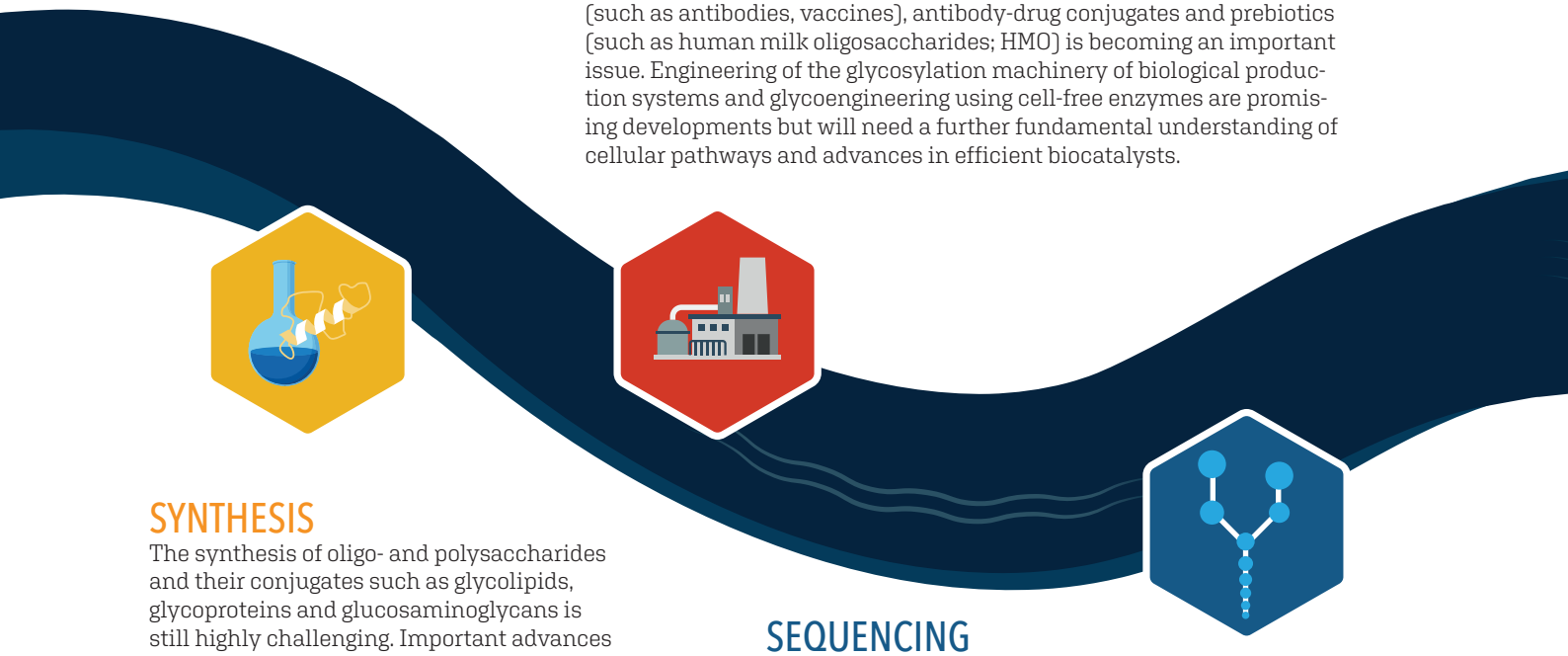
BIOPHARMACEUTICAL
- Rapid analysis and structural characterization of bacteria and viruses.
- Improved bioconjugation technology and adjuvant design.
- Glycoengineering of antibody drugs to lower dose and improve efficacy.
- Cost-effective production of glycan API and antigens for vaccine production.

PRECISION MEDICINE
- Improved point of care diagnostics for clinicians.
- Early identification of glycan biomarkers for autoim mune diseases and cancer.
- Development of glycan targeting drugs.

MICROBIOME
- Sustainable agriculture and food production.
- Improved understanding of link between microbiota and non-communicable diseases.
- Personalised diets and supporting immune system.

SUSTAINABLE MATERIALS
- Production of novel carbohydrate-based materials from waste biomass
- Design new materials based on sequence and func tional properties.
- Bio-compatible scaffolds in regenerative medicine.
- Large scale production to enable commercialization.

SCALABLE MANUFACTURING
With the increased translation of glycoscience into the industry, in particular biopharmaceuticals, scalable manufacturing of glycoconjugates (such as antibodies, vaccines), antibody-drug conjugates and prebiotics (such as human milk oligosaccharides; HMO) is becoming an important issue. Engineering of the glycosylation machinery of biological production systems and glycoengineering using cell-free enzymes are promising developments but will need a further fundamental understanding of cellular pathways and advances in efficient biocatalysts.



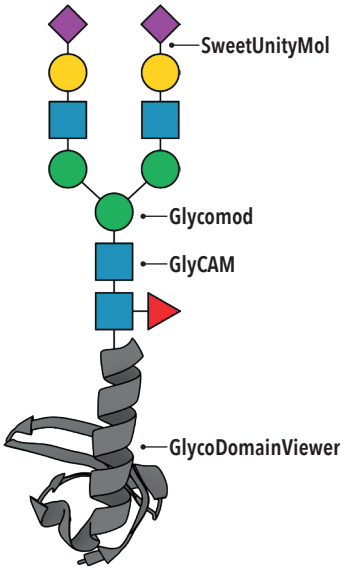
SYNTHESIS
The synthesis of oligo- and polysaccharides and their conjugates such as glycolipids, glycoproteins and glucosaminoglycans is still highly challenging. Important advances have been made in developing robust and selective chemical methods, including solid phase synthesis. At the same time more enzymes have become available as biocatalysts for carbohydrate synthesis, modification and analysis. Particularly attractive are chemo-enzymatic strategies that benefit from both the flexibility of chemical synthesis and the efficiency and selectivity of biocatalysis. For R&D purposes, libraries of glycans and their derivatives should be more easily accessible.

SEQUENCING
Current sequencing methods for carbohydrates are either high-resolution but at the cost of low sensitivity and long timescales (such as NMR) or high throughput, fast and sensitive at the cost/expense of resolution (such as chromatography and MS). Future sequencing strategies will need to combine resolution, sensitivity and throughput. A promising approach being the use of hyphenated MS-methods for carbohydrate sequencing. Development of new methodologies should consider all of the following i) the diversity of natural monosaccharides ii) ring size isomerism iii) Regioisomers iv) Anomeric configurations v) Positional isomerism in glycan structures. AI and machine learning capabilities will provide rapid automated analysis and accelerating R&D in glycoscience.

COMPANY INSIGHT | Bio-Shape is developing new tools and analytical methodology using machine learning to sequence complex carbohydrates. www.bio-shape.com

BIOINFORMATICS TOOLS

The complexity of carbohydrate structure and function in biological system is beyond manual interpretation. Carbohydrates are involved in a myriad of biological processes and have evolved to encode vast amount of information. This requires advanced bioinformatic programs and databases to capture this information.



BIOINFORMATICS DATABASE | GLYCAN AND GLYCOME

Selection of freely accessible databases

- **GlyTouCan** – International glycan repository: https://glytoucan.org
- **GlyConnect** – Curated intact glycoproteins: https://glyconnect.expasy.org
- **CAZy** – Curated families of structurally and catalytically related carbohydrate enzymes: http://www.cazy.org
- **GlycoEpitope** – Curated carbohydrate antigens and glycan epitopes: https://www.glycoepitope.jp/epitopes
- **MatrixDB** – Curated matrix protein-protein and protein-polysaccharide interactions: http://matrixdb.univ-lyon1.fr
- **UniCarb-DB** – Curated glycomics mass spectrometry: https://unicarb-db.expasy.org
- **UniLectin** – Curated structurally classified lectins: https://www.unilectin.eu

Selection of freely accessible tools

- **GlycoMod** – Predicts oligosaccharide structures on proteins: https://web.expasy.org/glycomod
- **GlycoDomainViewer** – Predicts the glycosylated state of proteins: https://glycodomain.glycomics.ku.dk
- **O-Glycologue** – Simulates and predicts glycan biosynthesis: https://glycologue.org
- **GLyCAM** – Predicts the 3D structure of carbohydrates and glycoconjugates: http://glycam.org
- **SweetUnityMol** – Display 3D structures: https://sourceforge.net/projects/unitymol

Selection of freely accessible portals

- **Glyco3D** – 3D structures (saccharides, carbohydrate recognizing proteins): http://glyco3d.cermav.cnrs.fr/home.php
- **Glycomics@ExPASy** – Bioinformatics for glycoscience in Europe: https://www.expasy.org/glycomics
- **GlyCosmos** – Bioinformatics for glycoscience in Asia: https://glycosmos.org
- **GlyGen** – Bioinformatics for glycoscience in the US: https://glygen.org

Please visit www.carbomet.eu/toolbox to find relevant databases and tools by topic.

DATABASES

Large datasets of glycomic measurements are currently being produced including diverse glycan structures and functions, and glycans as biomarkers for diseases such as cancer and diabetes. These are only partially recorded and slowly curated in databases. Existing and future tools are critically needed but their sustainability is far from being ensured.

ROLE OF CARBOHYDRATES IN THE GUT MICROBIOME AND HEALTH

The promotion and maintenance of a healthy relationship with our gut microbiota are increasingly understood to be essential for human health and well-being. The 100 trillion symbiotic microorganisms that reside in the human gut fulfils several vital biological functions and these imbalances in the microbial populations are associated with several inflammations and infections, such as gut disorders e.g. Irritable Bowel Syndrome (IBS), and the Irritable Bowel Diseases (IBD), Ulcerative Colitis, Crohn's disease and non-communicable diseases (e.g. diabetes, cardiovascular diseases and cancers). In Europe, an estimated 2.5 - 3 million people are affected by (IBD) with a direct healthcare cost of more than EUR 4 billion per year.[15]

Carbohydrates play a crucial role in maintaining microbial communities. For example, dietary fibre has a significant influence on overall gut health and carbohydrates are the main modulators of the gut microbiota structure and function.[16] Carbohydrates are also found in the human gut lining and are the first point of contact between the microbiota and the host. Alteration of the carbohydrates in the lining gives rise to several disease profile and are associated to the gut, autoimmune and inflammatory bowel disease. Recent studies suggest intestinal microbiota even affects distant organs and is involved in skin homeostasis.[17]

INFO | Carbohydrate play two crucial functions in the gut. Food derived polysaccharides provide essential nutrients to the gut microbiota. These bacteria consume the sugars to produce chemicals that are beneficial in human health and well-being. Sugars also line the gut lining and mediate the interaction between the microbiota and the host body. Changes in the sugar structure in the lining can lead to infections and disease. Human Milk Oligosaccharide (HMO) has emerged as a promising food ingredient to promote gut health. [18]

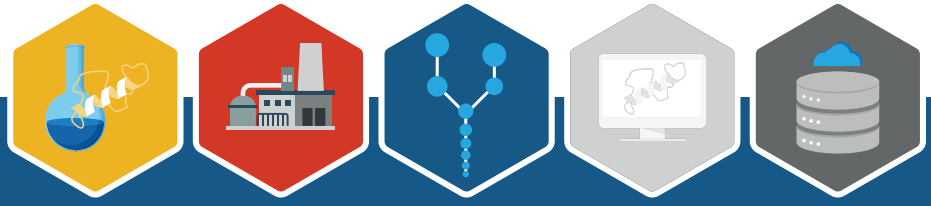
CASE STUDY

Around the end of the 19th century observations indicated that breast-fed infants had higher survival rates than those who were bottle-fed in cases of infection and other diseases. It was later discovered these were a class of compounds called human milk oligosaccharides (HMO). 2'-Fucosyllactose (2'-FL), an oligosaccharide (made up of the 3 sugar units fucose, glucose, and, galactose) is the most abundant HMO in breast milk. While these prebiotics pass through the infants gut undigested, the 'good' bacteria in the intestine consume it to promote immunity, digestion and cognitive health benefits. Recent work has shown HMOs can prevent celiac disease, Crohn's disease and IBS in adults, opening up a whole new market.[18]

COMPANY INSIGHT | In 2015, Glycom a Danish company secured approval from EFSA in Europe and FDA in USA to market HMO as a novel food ingredient for infants.i Glycom was acquired by DSM a global biotechnology company active in Nutrition, Health and Sustainable Living and has developed the largest fermentative HMO production plant in Europe. [19] www.glycom.com; www.dsm.com

The advent of several chronic diseases in the last century can be attributed to a change in diet. Western diets today are typically high-fat, high sugar compared to the relatively low fat, high polysaccharide diets of the past, resulting in the typically modern lower diversity of microbial composition in the gut. This loss of diversity or unbalance, also referred to as 'dysbiosis', has been associated with a number of diseases affecting westernized or "developed" countries. These include neurological diseases (e.g. autism, Parkinson's, Alzheimer's), metabolic diseases (mainly diabetes and obesity), gut diseases (IBD, IBS, Ulcerative Colitis and Crohn's disease, Coeliac disease, liver disease, colon cancer), food allergies or cardiovascular diseases. A comprehensive understanding of the role of carbohydrates in the gut is essential to elucidate the interactions between the human host and gut microbiota in order to exploit these relationships for the benefit of human health. The ageing population and the growing prevalence of non-communicable disease is continuously adding strain to the healthcare system and it is vital to develop new strategies to improve health outcomes and to reduce healthcare costs.

[15] Lakatos et. al., J. Crohn's and Colitis, 2013, 7, 322-337.
[16] Juge, N. et. al., Biochem. J., 2017, 474, 1823-1836.
[17] Ghannoumi, M. A. et al., Front. Microbiol. 2018, 9, 1459.
[18] Juge, N. et. al. Nutrients, 2020, 12, 2808.
[19] EFSA Journal 2015,13, 4184, Safety of 2'O -fucosyllactose as a novel food ingredient pursuant to Regulation (EC) No 258/97



RESEARCH PRIORITIES

ELUCIDATING THE RELATIONSHIP BETWEEN MICROBIOTA AND THE HUMAN GUT

The European glycoscience community is leading the development of new analytical tools and knowledge to understand the mechanisms behind the interactions between our gut, the microbiota and diet. It is essential to integrate and develop glycobiology, glycosynthesis and glycometric approaches to provide mechanistic insights to determine i) How gut microbiota influence human health ii) Identification and validation of novel biomarkers iii) Development of novel microbiome targeted strategies.

CARBOHYDRATE PRODUCTION

The carbohydrates involved in microbiota-host interactions need to be available as validated, high quality pure standards, both for allowing high-throughput analysis and for providing materials as probes for functional studies. While significant advances in carbohydrate synthesis and analysis have been made to produce a range of bespoke carbohydrates, there is an urgent need to be able to produce these on scale, economically and efficiently.

▸ **Synthetic biology:** Fermentative production from microbes/naturally producing microorganism or in genetically modified strains. Require technologies in biomanufacturing with accurate monitoring and purification systems.

▸ **Chemical synthesis:** Require development of new and routine synthetic methodologies for rapid access to sugar building blocks.

▸ **Enzymatic synthesis:** A sustainable approach compared to traditional synthetic approaches. However, a major limitation is the availability of carbohydrate-active enzymes with the required properties and chemical activities. Therefore there is an urgent need to build an arsenal of more glycoenzymes showing an expanded repertoire of chemistries.

NEW METROLOGY AND ANALYTICS

Core to the success of developing new targeted therapies for the microbiome is the development of new standards for measurements and analysis including ISO standards. The subtle differences in surface carbohydrates of bacteria will make classification and identification of 'good' and 'bad' bacteria easier. ISO standards will aid the safe development and production of bespoke carbohydrates for human intervention; through to the safe design of clinical trials and targeted drug design and delivery.

NUTRACEUTICAL AND FOOD SUPPLEMENT

Carbohydrates with high glycaemic-index has often been associated with long-term health risks. The awareness of consumers on the role of carbohydrates in the diet has ensured research and development on new products with significant health benefits.

NEW STRATEGIES TO PROMOTE HEALTH

There is an urgent requirement for academics and industry to engage with consumers to ensure not only that the development of new functional food products is palatable but that consumers are informed on their health benefits and that the needs and expectations are taken into account. Integration of mechanistic knowledge, production and analytics will be essential to developing robust production pipeline and evaluating the health benefits of new products.

CASE STUDY

There is a general perception among consumers to preferentially choose healthy and sustainable food sources. Seaweed polysaccharide has recently emerged as a potential source of functional foods and have been shown to have anticoagulant, anti-inflammatory and anti-oxidant properties.[20] Polysaccharide such as Agar, Alginate, Carrageenan and Fucoidan are found in a variety of food products including desserts, milk and pastries.

SPECIFIC CHALLENGES

▸ New techniques to synthesise and/or isolate novel polysaccharide as nutraceuticals.
▸ Large scale development of human milk oligosaccharides (HMO) and sugar alternatives as functional food ingredients.
▸ Elucidating relationship between intestinal microbiota and antibiotic resistance.
▸ Development of polysaccharides with improved texture and taste profile to support the shift to non-meat based diet.

[20] Mishra, A. et al. Compr. Rev. Food Sci. Food Saf. 2019, 18, 817-831.

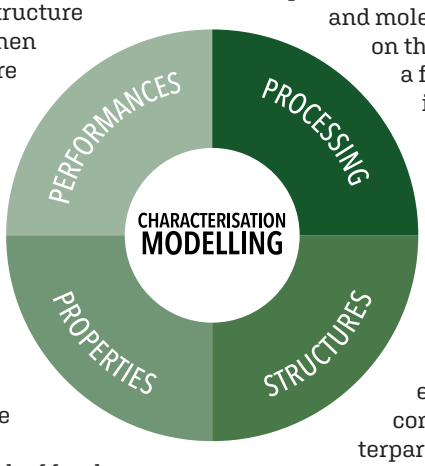
THE CIRCULAR BIO-ECONOMY

The advent of the European bioeconomy first presented in 2012 set out plans to transform the chemical industry in Europe to a more sustainable economy. One of the key underlying principles of the new bioeconomy framework was the utilization of waste resources, in particular food and agricultural waste. On average the EU produces 956 million tonnes of agricultural biomass per annum and a large constituent of this is carbohydrate. The development of bio-inspired sustainable materials from carbohydrates has steadily gained interest from the chemical industry as a strategy to produce new materials with unique properties from waste resources. Natural polysaccharides such as cellulose, hemicellulose, starch, chitin, pectins, and xyloglucan all have properties that make them useful for a variety of applications and their exploitation is crucial to reduce the dependence on fossil fuels and towards the development of the circular economy.

INFO | Materials used in biodegradable films and in next-generation displays[21] is composed of cellulose nanofibers derived from wood and forestry residues.[22] In addition carbohydrate polymers are being used in bio-inks to house viable cells in regenerative medicine.[23]

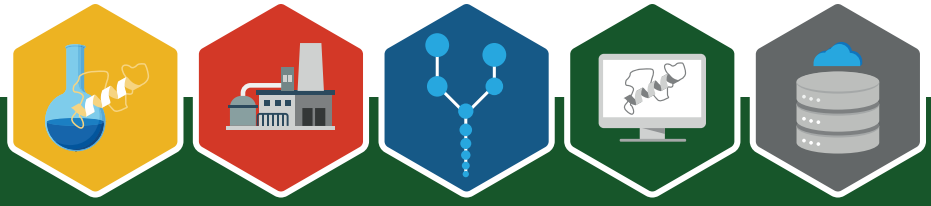
CARBOHYDRATE BASED BIOMATERIALS

Nature has provided an unlimited resource of carbohydrate-based materials and whilst the complexity and diversity of carbohydrates is challenging, this very diversity offers an opportunity to access new chemical and sequence space by tailoring the polysaccharide structure and functional properties for various applications. The inter-relationship between structure and function is perfectly highlighted when comparing cellulose and starch. Both are made of glucose residues but they play different roles in nature. Cellulose provides structural support to plants, whereas starch is primarily used as an energy source. This relationship is a prerequisite to developing a new generation of sustainable biomaterials that can address global challenges in packaging, healthcare, agriculture and consumer care products. Current attempts to establish a comprehensive R&D framework for the development of new biomaterials has been hindered by a lack of funding opportunities for SMEs to support early development (TRL 1 and 2) and the technology that is required to enable accurate measurements and analysis of the materials. To fully exploit the potential of carbohydrate polymers, knowledge sharing from other disciplines such as maths, computer science, physics and engineering is vital with the overall aim to create, transform and enhance existing materials to confer better performance for specific applications. New analytical tools and advances in the physical and biological science will be needed to investigate the relationship between the structure of materials at the atomic and molecular scale and its varying influence on the macroscopic properties. We envisage a future where digitisation is integrated into the R&D workflow and manufacturing processes themselves, with machine-based learning approaches being used to guide the design of new materials.



While the exact delineation of this area (glycomaterials engineering) remains to be established, its overall aim is create novel materials with enhanced property and performance compared to current fossil-derived counterparts. New analytical tools and advances in the physical and biological science will be needed to investigate the relationship between the structure of materials at the atomic and molecular scale and its varying influence on the macroscopic properties. This follows the materials paradigm represented below showing the inter-relation between structure, properties, processing and performance.

[21] LTG ULM GMBH, Bistable ChLCD displays press release: https://www.bmgmis.de/en/products/bistable-chlcd-displays
[22] Futamura cellulose films division: http://www.futamuragroup.com/divisions/cellulose-films/products/cellophane
[23] Xu, F. et. al. Trend Biotechnol. 2016, 34, 746-756.



RESEARCH PRIORITIES

PACKAGING, FILMS AND NEXT-GENERATION DISPLAYS

Agricultural waste has been seen as a major source of valuable feedstocks for carbohydrate based materials. Several research programs and industrial investment has been dedicated to biomass valorization for speciality chemical production. While there have been tremendous achievements and developments in this area over the years, the field still requires further exploration to develop materials with substantially better properties than fossil-based polymers.

COMPANY INSIGHT | Kompuestos is a leading supplier of high-performance material to a range of industries. The company produces biodegradable resins for use in food packaging, catering and agriculture. www.kompuestos.com

PROSTHETICS AND REGENERATIVE MEDICINE

Tissue engineering and regenerative medicine is a rapidly evolving area in healthcare with a projected global market outlook of $16.82 billion by 2023.[24] As a multi-disciplinary field, it also brings with it a set of challenges across both academia and industry. With a high demand for biomimetic scaffold materials, additional investments are required to keep up with developments in this field. Carbohydrate polymers also lack the processing abilities of synthetic polymers and this has largely hindered their application in biomedical science. For example, 3D printing technology can be used in a clinical setting to provide bio-compatible and biodegradable scaffolds for cells providing immense value in regenerative medicine.

CARBOHYDRATES FROM THE OCEAN

The Ocean harbours numerous organisms from which diverse marine polysaccharides with useful physico-chemical and biological properties can be extracted. Compounds such as fucoidan, carrageenan, alginate, and chitosan has been extensively investigated owing to their desirable characteristics, such as biocompatibility, biodegradability, and bioactivity. Alginate and chitosan have shown to be excellent elicitors for plants with the potential to be used as natural pesticides.[25]

FASHION AND TEXTILE

Carbohydrates will play a vital role among the next generation of natural and synthetic textile products. The diversity and abundance of polysaccharides in natural biomass will accelerate development in this area to access new fibres with superior properties in texture and strength with sustainability a key driver for consumers and the environment. For example, textiles in the near future may have certain properties such as self-cleaning (lotus effect), flame retardant and UV blocking.

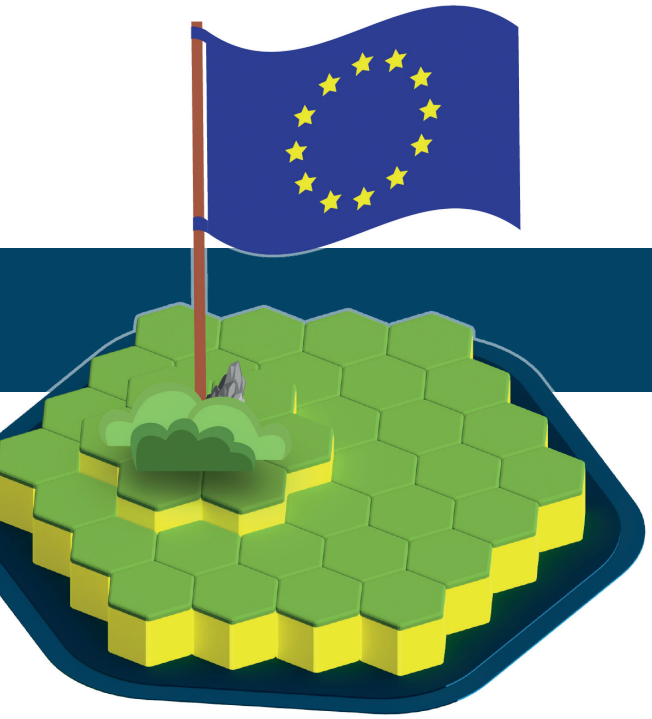
CASE STUDY

Aerogels provide a novel solution to the food and packaging industry which can be produced from biodegradable polysaccharides such as cellulose, hemicellulose, chitosan and alginate. The characteristic porous structure of aerogels opens up several applications including bio-based insulators, water absorbents in packaging and replacement for silica gel encapsulation in food application.[26]

SPECIFIC CHALLENGES

- Improved processing capabilities of carbohydrate-based polymers to obtain desirable microstructure, properties and shape of final product.
- Smart biomaterials that can undergo structural and functional changes upon external stimulation. These materials can be used in 4D bioprinting of artificial tissues and organs.
- Discovery and evolution of enzymes to modify existing carbohydrate polymers.
- Improve dimensional stability of biodegradable films by developing new materials resistant to humidity.
- Large scale sustainable production and application of cellulose nanocrystals.

[24] "Tissue Engineering - Global Market Outlook 2017-2023", Research and Markets, 2017: https://www.researchandmarkets.com/reports/4449999/tissue-engineering-global-market-outlook-2017
[25] El Hadram, A. et. al. Mar. Drugs, 2010, 8, 968-987.
[26] Kikkonen, K. S. et. al. Trends Food Sci. Technol., 2013, 34, 124-136.



ABOUT CarboMet

CarboMet – Metrology of Carbohydrates for Enabling European BioIndustries is a FET-OPEN Coordination and Support Action (CSA) programme with the aim of:

- Establishing a European Glycoscience User Group
- Identify common scientific and technical challenges
- Facilitate the formation of cross-sectorial glycoscience metrology platform
- Establish initiatives to address key challenges in glycoscience

CarboMet has facilitated engagement between key players and stakeholders in each of the 3 enabling technology area and the 4 bioindustry sector through networking in meetings and conferences and by hosting workshops. The programme has published 4 policy papers in biopharmaceuticals, diagnostics and precision medicine, healthy food and the gut microbiome, and sustainable materials. With glycoscience playing critical role in the European economy and in supporting the EU bioeconomy initiative, the CarboMet team has worked closely with policy advisors to ensure glycoscience is included in the new Horizon Europe framework.

FUNDING AND EDUCATION

The field of glycoscience has rapidly expanded in the last decade and is a key focus of many R&D in the field of biopharmaceuticals, diagnostics, food and beverage and developing sustainable materials. Glycoscience plays an integral role in many of worlds economies and industrial processes from developing new vaccines and biotherapeutics to fight cancer and AMR to developing novel solutions in materials. Education and funding is vital to ensure the continued growth and success of glycoscience in Europe. Developing a robust undergraduate and graduate teaching programme as well as coordinating online training workshops, seminars and conferences is crucial to attracting and developing a new generation of glycoscientists. These training programmes should target, technology users, healthcare professionals, scientists, policy advisors and industry professionals to facilitate translational and commercial research in glycoscience.

LIST OF TRAINING COURSES IN GLYCOSCIENCE:

NIBRT - Provides classroom and laboratory courses on the subject of glycobiology and glycoanalytics.
www.nibrt.ie

GlycoPedia - A series of "eChapters" on selected important topics in glycoscience with the intention to promote the field and providing material for educational purposes.
http://www.glycopedia.eu

University of Wageningen VLAG graduate school – Offers annual summer courses with a broad overview of glycoscience.
https://www.wur.nl/en/Education-Programmes/Wageningen-Summer-School.htm

Universidade Nova de Lisboa – The faculty of science and technology provides an online e-learning course in glycobiology and glycochemistry.
https://www.fct.unl.pt/en/education/how-apply

Innogly COST Action – Innovation with Glycans: new frontiers from synthesis to new biological targets is a COST action project with the aim of hosting and financing cross European training schools.
https://innogly.eu/training-schools

Swiss Institute of Bioinformatics – The institute holds several training courses throughout the year including virtual and practical classes in glycoinformatics.
https://innogly.eu/training-schools

ACKNOWLEDGEMENTS

The production of this glycoscience roadmap was made possible thanks to support from the European Commission and the Glycoscience community in Europe. The journey started with a workshop in 2016 called "Metrology of Carbohydrates" which was attended by glycoscientists from industry and academia. Through a series of interactive group discussions the four CarboMet bioindustry sectors emerged along with the three ETAs as areas which showed enormous innovation potential. CarboMet was established to ensure the ideas generated in the workshop was realized through a series of focused workshop in each BIS, publication of policy papers and with the summation of the glycoscience roadmap. The aim of the roadmap is to highlight the challenges and opportunities in European research and innovation and where glycoscience can contribute to the advancement in the four BIS.

CONTRIBUTORS

A complete list of centres of excellence can be found on the CarboMet website: www.carbomet.eu/toolbox

Prof. Sabine Flitsch | University of Manchester (UK)
Prof. Serge Perez | CNRS (FR)
Dr. Claire Doherty | PNO Consultants (UK)
Dr. Rodney Townsend | GnosTek (UK)
Dr. Daniel Spencer | Ludger Ltd (UK)
Prof. Lokesh Joshi | National University of Ireland (IE)
Prof. Anne Imberty | CNRS (FR)
Dr. Paula Domann | LGC (UK)
Prof. Frederique Lisacek | Swiss Insititute of Bioinformatics (CH)
Prof. Peter Seeberger | Max Planck Institute of Colloids and Interfaces (DE)
Prof. Carmen Galan | University of Bristol (UK)
Prof. Antonio Molinaro | University of Naples Federico II (IT)
Prof. Gordan Lauc | Genos (HR)
Dr. Claney Periera | Vaxxilon (DE)
Prof. Boguslaw Szewczyk | University of Gdansk (PL)
Dr. Satish Kumar Devarapu | PreviPharma Consulting GmbH (DE)
Luis Felipe Romero | Dr. von Hauner Children's Hospital, LMU Munich (DE)
Prof. Hermen Overkleeft | Universiteit Leiden (NL)
Dr. Reinhard Schwartz-Albiez | PreviPharma Consulting GmbH (DE)
Prof. Cristina De Castro | University of Naples Federico II (IT)
Prof. Henrik Stålbrand | Lund University (SE)
Dr. Lukasz Rabalski | University of Gdansk (PL)
Dr. Adriana Carvalho-de-Souza | DSM (NL)
Dr. Pascal Salvador | Ayming (FR)
Dr. Noortje de Haan | Leiden University Medical Centre (NL)
Prof. Manfred Wuhrer | Leiden University Medical Centre (NL)
Dr. David Falck | Leiden University Medical Centre (NL)
Dr. Yan Liu | Imperial College (UK)
Prof. Ten Feizi | Imperial College (UK)
Dr. Fabrizio Chiodo | Amsterdam UMC (NL)
Dr. Kai Baldenius | Independent Conultant (DE)
Dr. Niels-Christian Reichardt | CIC BiomaGUNE (ES)
Prof. Pauline Rudd | NIBRT (IE)
Prof. Dirk Lefeber | Radboud University (NL)
Prof. Paula Videira | Universidade nova de Lisboa (PT)
Dr. Gregory Coue | Kompuestos (ES)
Prof. Robert Field | University of Manchester (UK)
Prof. Nathalie Juge | Quadram Institute (UK)
Dr. Jennifer Hendel | Ludger (UK)
Dr. Roberto Adamo | GSK Vaccines
Dr. Angelina Palma | Universidade nova de Lisboa (PT)
Prof. Nico Callewaert | VIB-UGent Center for Medical Biotechnology (BE)
Prof. Johannes Huebner | Dr. von Hauner Children's Hospital, LMU Munich (DE)

Compiled by: Dr Syed Ahmed | Design: www.luminous-lab.com

GLYCOSCIENCE RESEARCH ACTIVITY IN EUROPE

Bioinformatics and Database
Measurements and Analytical
Synthesis of Standards

Please visit www.carbomet.eu/toolbox for a comprehensive list of glycoscience research activity in Europe.

01 | **Swiss Institute of Bioinformatics** | www.sib.swiss
02 | **Department of Structure and Function of Saccharides, Slovak Academy of Science** | www.modlab.chem.sk
03 | **Centre for cooperative research in biomaterials** | www.glycotechnology.net
04 | **CNRS-Cermav** | www.cermav.cnrs.fr
05 | **ETH Zurich, Institute of Microbiology** | https://micro.biol.ethz.ch/
06 | **Oxford Glycobiology Institute** | www.bioch.ox.ac.uk/glycob
07 | **Centre for Proteomics & Metabolomics at LUMC** | https://cpm.lumc.nl/glycomics-and-glycoproteomics
08 | **KTH, Division of Glycoscience** | www.kth.se/che/glykovetenskap/division-of-glycoscience-1.785898
09 | **VIB-UGent Center for Medical Biotechnology** | www.vib.be/labs/nico-callewaert-lab
10 | **Laboratory of Fungal Glycobiology, Polish Academy of Sciences** www.ibb.waw.pl/en/structure/ibb-departments/laboratory-fungal-glycobiology
11 | **Centre for Chemistry and Biochemistry, Universidade de Lisboa** | http://cqb.fc.ul.pt/research/carbohydrate-chemistry
12 | **Max Planck Institute of Colloids and Interfaces** | www.mpikg.mpg.de/en/bs
13 | **Centre for Glycobiology, University of Liverpool** | www.liverpool.ac.uk/integrative-biology/staff/jeremy-turnbull
14 | **Carbohydrate Competence Centre** | www.cccresearch.nl
15 | **Copenhagen Center for Glycomics** | www.glycomics.ku.dk
16 | **Department of Carbohydrates and Cereals** | https://sch.vscht.cz/veda-a-vyzkum
17 | **Norwegian Biopolymer Laboratory, Norwegian University of Science & Technology** www.ntnu.edu/ibt/research/biopol#/view/about
18 | **Department of Organic Chemistry at University of Naples Federico II** https://www.scienzechimiche.unina.it/en_GB/ricerca/la-nostra-ricerca

LIST OF SUPPLIERS FOR GLYCOBIOTECHNOLOGY APPLICATIONS

Carbosynth | www.carbosynth.com
Cyclolab | www.cyclolab.hu
Dextra Laboratories | www.dextrauk.com
Elicityl | www.elicityl-oligotech.com
Glycouniverse | www.glycouniverse.com
Megazyme | www.megazyme.com
Prozomix | www.prozomix.com

www.carbomet.eu

The work reported in this publication has been financially supported by the European Commission Horizon 2020 research framework.
CarboMet is a coordination and support action (CSA) under the Future and Emerging Technologies (FET) Open call
(Grant agreement no. 737395)