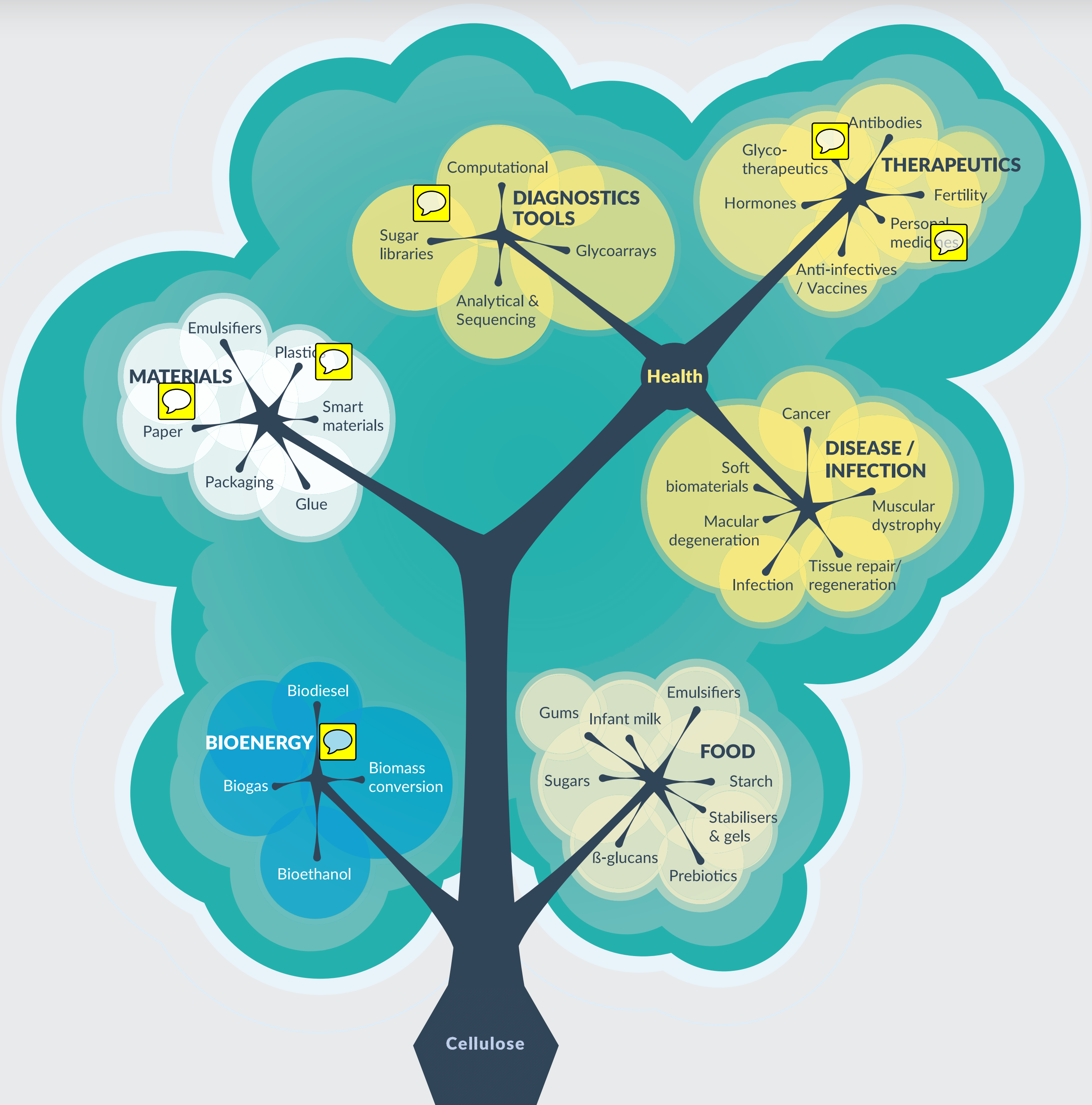
A roadmap for
Glycoscience in Europe



What is glycoscience?

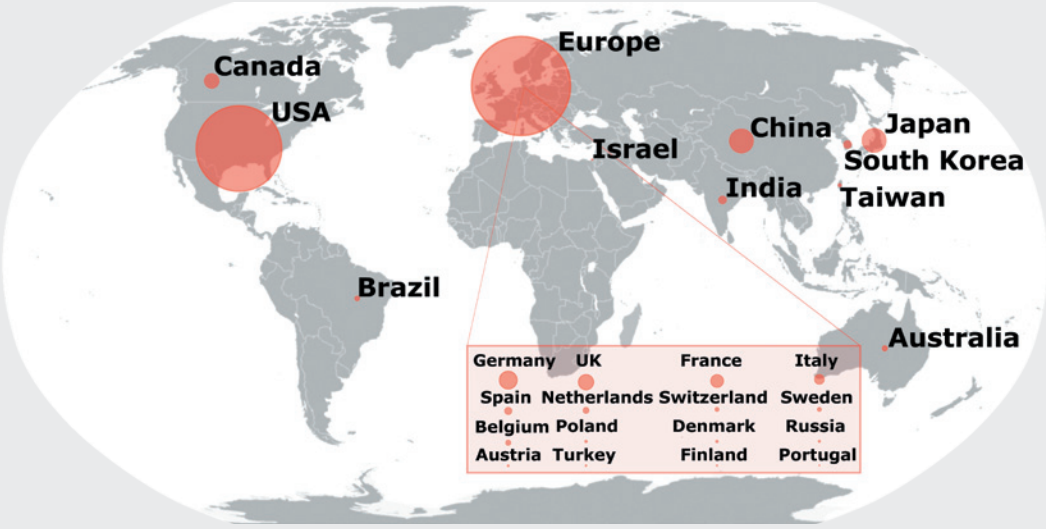
Glycoscience is the science and technology of carbohydrates, which are the most abundant biological molecules on Earth and make up part of the biology of all living organisms. Glycoscience is recognised worldwide as an emerging area with the potential for radically new biotechnological applications to solve several of the challenges faced by modern society.

We see a number of exciting opportunities which are of great interest to European Society and Bioindustries, in particular in the areas of **Pharmaceuticals and Personalised Medicine** (addressing challenges in health), **Food** (food security, wellbeing) and **Biomaterials** (resource efficiency and raw materials). Underpinning these opportunities will be a number of emerging **Glycoscience Tools**, particularly in synthesis, analysis, bioinformatics and modelling, which will open up glycosciences to a much wider scientific and industrial community and overcome barriers to entry for commercial applications. Importantly, full exploitation will only be possible, if the broader community is educated in the opportunities brought by the emerging field of glycoscience, through cooperation with the media and policy makers, as well as **Education and Training** for students and scientists at all levels.

The **European Glycosciences Forum (EGSF)** has brought together a group of European experts to consider how the recent leading achievements of glycoscience and glycotechnology in Europe can be driven forward. This paper summarises highlights and achievements of scientific and technological excellence and puts forward a number of areas where some of the most promising opportunities for translation into products on the European market have been identified. Glycoscience is becoming an essential part of modern innovative biotechnology and having access to state-of-the-art knowledge and technologies in glycoscience will provide the European bio-based industries with a strong competitive advantage on a worldwide stage leading to long-term job creation and sustainability. However, our goals will be slow to achieve with the current fragmented landscape of national centres and short-term projects. To take full advantage of the opportunities presented by glycoscience, we recommend the establishment of an **Integrated European Roadmap for Glycobiotechnology** with the aim of setting up a number of transnational long-term public-private partnerships.

EGSF Chair: Professor Sabine Flitsch (UK)
EGSF Vice Chair: Professor Serge Perez (France)

The publication output of European R&D glycoscientists is the highest in the world. The size of the circles represents the relative proportion of glycoscience papers published. The 25 top performing countries are depicted.



This data was produced by carrying out a Web of Science literature search on 20th January 2015 using the following search terms: *glyco*, *glyco**genom*, *glycom* and *glyco**proteom* during 2010-2015 giving a total of 1,557,961 results. The EU produced 34.6% of the total search results versus the USA (30%), which had the 2nd highest country output [1].

How can glycoscience benefit Society and drive the Bioeconomy?

Carbohydrates are produced from sunlight and carbon dioxide by plants, algae and some photosynthetic bacteria. Created by photosynthesis, carbohydrates provide the largest renewable biomass on Earth and are the economically **viable and sustainable alternative to fossil resources** for energy and raw materials. Carbohydrates are the biomass that helps reduce carbon footprints and thus allowing the European Bioeconomy to **achieve economic growth without damage to the environment**.

During the dynamic process of glycosylation, the simple carbohydrates from photosynthesis are converted to complex carbohydrates, glycoconjugates or glycans which are an integral part of cell biology, and are present on the cell surface and the macromolecules contained within. Glycosylation influences the function of these molecules, playing an **essential role in health and disease**. This includes the development of innate and adaptive immunity, the growth and spread of cancer, responses to bacterial and viral infections, and the development of diseases such as diabetes. Understanding and exploiting glycoscience and glycomics has become an essential part of modern molecular medicine.

Contents

Glossary

Carbohydrates are also known as **sugars**, **saccharides** and **glycans**.
Glycoconjugates are biomolecules such as proteins, lipids or metabolites linked to glycans.
Glycoscience and **Glycobiotechnology** encompass all activities related to the science and technology of carbohydrates, repectively.
Glycomics studies the structure and function of carbohydrates in cells, tissue and organisms.

Carbohydrates such as starches have an essential role as a food source for animals and humans, and modern agrochemical biotechnologies are working to improve production yields of carbohydrates to ensure the **stability of the food supply chain**.

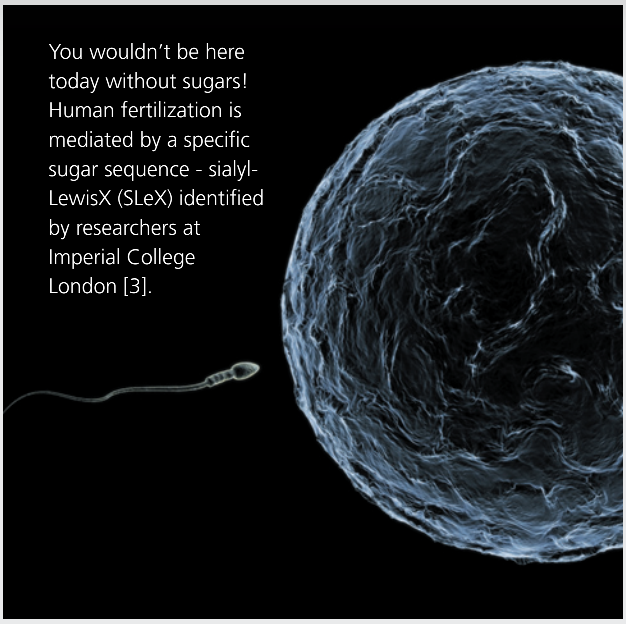
There is an increasing understanding that specific glycans can improve health and prevent disease. Carbohydrate polymers (oligo- and polyfructans, beta-glucans) can have a beneficial effect on human gut microbiota, and human milk oligosaccharides can help to improve long-term health. Glycans are also providing drug development targets and new druggable chemical entities.

European glycoscientists have been at the forefront of developing the novel tools needed for fast and reliable synthesis and analysis of glycans including chemical, enzymatic or microbial synthesis, high-throughput automated analysis, development of glycan microarrays and the establishment of databases and modelling tools to enable advances in glycobiotechnology.

This has been recognised by the European community leading to the establishment of networks such as the EGSF to address the need for cross-disciplinary integrated approaches and interactions with large international glycoscience networks, such as those established in the US, Japan or Canada [1]. At the same time there are a growing number of national glycoscience centres, large FP7 and H2020 funded research and training programmes, COST programmes and training schools in Europe [see page 15]. In 2012 the US National Research Council on behalf of all the National Academies published 'Transforming Glycoscience: A Roadmap for the Future' [1] in consultation with the international scientific community. This extensive review of the state-of-the-art highlighted the strength of glycoscience in many European countries.

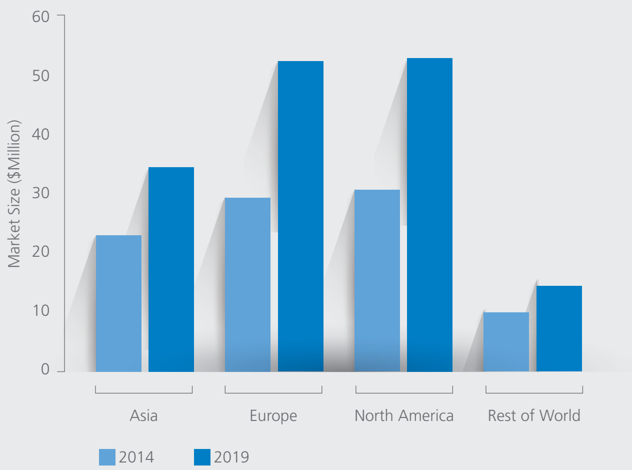
We see a number of exciting opportunities which are of great interest to European Bioindustries, such as:

- Developing cost-effective processes for using **carbohydrate-based feedstocks** to produce existing and novel materials with low carbon footprint, reducing reliance on fossil raw materials.
- Reducing healthcare costs by using carbohydrate-based biomarkers to develop more effective disease **diagnoses** and better targeted/personalised **medicines**.
- Developing new vaccines, antimicrobials, anticancer drugs and diabetes treatments, and creating more efficient and cost-effective production processes, by building on and underpinning the recent successes of **biopharmaceuticals**.
- Understanding more about glycans in **foods** (such as milk oligosaccharides, soluble fibre, sweeteners) and their health benefits; learning how they can contribute to prevention of disease and overall wellbeing especially in infants and in old age, for example through their interaction with the gut microbiota; and improving large scale production processes.



The glycomics R&D market includes enzymes, instruments, kits, and reagents used in research and development. Glycomics is used in diagnostics, drug discovery research, immunology, oncology, and many other applications. The rapidly increasing global glycomics market (expected $930 million by 2019 from $510 million in 2014) is driven by investment in R&D from government and industry worldwide. This strong investment is expected to drive current and future product development in glycoscience in areas such as Medicine, Biomaterials and Food [2].

Glycomics R&D market sizes by geographical segment [2].



1. Walt et al. (2012) Transforming Glycoscience: A Roadmap for the Future, National Academies Press, Washington, D.C.

2. Glycobiology/Glycomics Market By Product [Enzymes (Glycosyltransferase, Neuraminidase, Glycosidase), Instruments (HPLC, Mass Spectrometry, MALDI-TOF), Kits, and Reagents], Application (Immunology, Oncology), End User Global Forecast to 2019, Markets and Markets

3. Pang et al. (2011) Science, 333, 1761 DOI: 10.1126/science.1207438

Pharmaceuticals

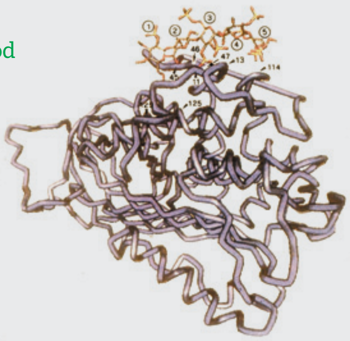
The role of glycoscience in pharmaceuticals

The number of therapeutics based on glycans, glycan targets and glycosylated products is rapidly increasing. Examples including heparin, cyclodextrin, carbohydrate-based vaccines, and glycosylated natural products such as the antimicrobial vancomycin have been on the market for a long time. More recent examples include Tamiflu and Relenza, which were developed to treat the influenza virus. With the advent of biopharmaceuticals such as human erythropoietin and therapeutic antibodies, glycoconjugates will continue to increase their major market share.

Therapeutic glycoproteins: an important group of biopharmaceuticals

Approximately 40% of all approved therapeutic proteins and eight of the top ten selling biologics of 2010 [1] (generating over $35 billion in annual sales) contain N-linked oligosaccharides. Hence an understanding of the glycosylation of biologics is of paramount importance for the biopharmaceutical sector. The challenges in the development and production stages are to create a defined and targeted glycan profile, resulting in better *in vivo* product characteristics and increased biotherapeutic efficacy. Glycoengineering of host cell lines and process optimization to achieve higher efficacy and tight quality control of glycoprotein production will be paramount for current and future biologics.

Heparin, a polysaccharide (1-5) that interacts with antithrombin (grey) in blood used to regulate clotting. European researchers are investigating heparin for the treatment of other diseases including cancer, inflammatory conditions, malaria, and amyloid diseases. With thanks to Prof Ulf Lindahl



Glycoengineering

The Novo Nordisk Foundation with assets from Novo Nordisk and Novozymes recently funded The Center for Biosustainability with a total of €150M of which approximately €35M is devoted to engineering the Chinese hamster ovary (CHO) cell line for improved production of therapeutics including genetic engineering of glycosylation capacities.

Tools

Glycosylated biopharmaceuticals such as glycoproteins provide particular challenges in terms of production and analysis for quality control (ICH guideline Q6B). Glycoproteins are generally produced via fermentation in cell lines. Whereas the sequences of the proteins are constant, the patterns of glycosylation on the molecule can be variable and may depend on the production conditions. This variability can influence the efficacy and safety of the resulting therapeutics.

There is a particular demand for tools that can address the following challenges:

- Working with patterns of glycosylation on recombinant glycoproteins to manage safety and efficacy.
- Changing the glycome of cells, in particular stem cells, to improve engraftment after transplantation or change their capacity for immune response.
- High throughput analysis to provide benchmarking for drug supply chain security and the development of novel glyco-drugs.
- Creating assays for glycan-mediated function such as targeting, or changing the molecule's half-life through glycosylation.

Addressing these challenges would be of great benefit to major European industries including biotech, pharma and biosimilar industries and instrument manufacturers, as well as the healthcare sector. Patients will also benefit through development of biopharmaceuticals that are lower cost, safer and more effective.

Opportunities for trans-European collaborative projects

Biopharmaceuticals are generally expressed in plant or animal cell lines, or in microorganisms. A better understanding of the glycosylation processes in these expression systems would be of great benefit to the pharma and biotech industries [2].

As an example, there are around 500 genes involved in glycosylation in the cell. Knowledge about the way in which these interact allows glycosylation to be controlled. Glycoengineered cell lines are now available and high throughput analysis allows the products from these to be thoroughly characterised. This results in a much more homogenous product which may be more effective and will be easier to manage from a regulatory point of view. However, the development of more precision glycoproteomics tools are also required.

Top 10 best-selling drugs in Europe 2008–2013

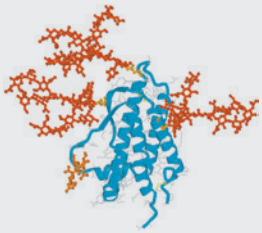
Biologicals now dominate the top 10 list of best-selling medicines in Europe, with eight of the top 10 best-selling drugs now being biological (highlighted in green) [1].

	2008	2013
1	Lipitor (high cholesterol)	Humira (arthritis)
2	Seretide (asthma)	Seretide (asthma)
3	Plavix (blood clotting)	Enbrel (autoimmune diseases)
4	Herceptin (breast cancer)	Herceptin (breast cancer)
5	Enbrel (autoimmune diseases)	Mabthera (leukaemia)
6	Zyprexa (schizophrenia and bipolar disorder)	Remicade (arthritis)
7	Lovenox (deep vein thrombosis)	Lovenox (deep vein thrombosis)
8	Glivec (cancer)	Avastin (cancer)
9	Pantozol (stomach acid)	Lucentis (age-related macular degeneration)
10	Symbicort (asthma and COPD)	Lyrica (epilepsy)

Drug discovery and development represents a significant portion of the global R&D glycomics market, some 36.63% in 2014. This segment is poised to reach $353.29 million by 2019 from $187.69 million in 2014 [4].

Erythropoietin (EPO)

Perhaps one of the most well known examples of a biopharmaceutical is erythropoietin, also known as EPO. EPO is a glycoprotein with approximately 40% of its weight due to glycosylation [3]. Advances in recombinant DNA technology techniques have allowed the production of recombinant EPO for therapeutic use in treating anaemia, first approved by the FDA in 1989. Glycoscience has since played a major role in bringing improved EPO variants with modified glycosylation to the market. One such product Aranesp® from Amgen has been found to have a significantly longer half-life in the body after injection providing improved therapy. It is anticipated that worldwide sales of EPO therapeutic products will continue to grow as even more effective variants for anaemia treatment are found.



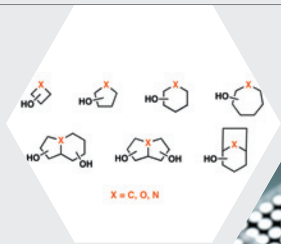
Human erythropoietin - a glycoprotein. The glycans (red) are linked to the protein (blue) via individual amino acids (orange) that make up the protein polypeptide chain. With thanks to Professor Pauline Rudd.

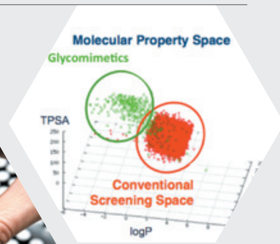
National Institute for Bioprocessing Research & Training (NIBRT), Dublin

NIBRT is a world-class institute that provides research and training solutions for the bioprocessing industry. NIBRT houses the Glycobiology group headed by Professor Pauline Rudd, which performs research, analysis and training focused towards the needs of the Biopharmaceutical Industry.

Glycomimetics

Glycomimetics are small organic molecules derived from sugars. They have been shown to have activity both *in vitro* and *in vivo* with good safety profiles. They have very favourable attributes as drug molecules including water solubility, absorption, blood brain barrier penetration, chemical and biological stability, and oral bioavailability. This class of compounds provides the scientist with access to new polar chemical space for the development of therapeutics.





1. 'Biologicals dominate Europe's best sellers' IMS Health, MIDAS, MAT June 2013

2. Shi and Goudar (2014) Biotechnology and Bioengineering, 111 (10) 1907 DOI: 10.1002/bit.25318

3. Bunn H.F. (2013) Cold Spring Harbour Perspectives in Medicine 3:a011619 DOI: 10.1101/cshperspect.a011619

4. Glycobiology/Glycomics Market By Product [Enzymes (Glycosyltransferase, Neuraminidase, Glycosidase), Instruments (HPLC, Mass Spectrometry, MALDI-TOF), Kits, and Reagents], Application (Immunology, Oncology), End User Global Forecast to 2019, Markets and Markets

Personalised Medicines

The role of glycoscience in personalised medicine

All cells, including human cells, have carbohydrates on their surface, in a covering known as the glycocalyx. This coating of glycolipids and glycoproteins controls a variety of fundamental biological processes, for example helping sperm to recognize eggs during fertilization, determining blood groups, or enabling the body to identify diseased cells or infectious agents. The carbohydrates of the glycocalyx are produced through highly complex biosynthetic pathways controlled by both genes and the environment. The makeup of the glycocalyx is therefore highly sensitive to genetic mutations, changes in gene activation or silencing, or environmental factors such as diet, alcohol consumption or smoking. This makes the glycocalyx a useful target for personalized medicine, including finding new biomarkers for diseases such as cancer, and for patient stratification in clinical trials.

Glycobiomarkers and disease intervention targets

Glycobiomarkers have potential in a number of diseases:

Infectious diseases:
Carbohydrates mediate many host-pathogen interactions, for example the flu virus recognises its host by binding to a particular sugar (sialic acid) on the cell surface. This sugar can be used as a target in diagnostics and therapeutics, such as Tamiflu or Relenza

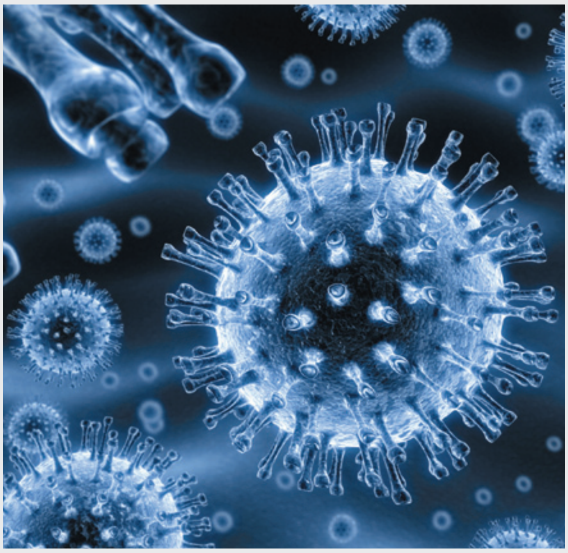
Cancer:
Cell surface glycans on cancer cells are a rich source for biomarkers, and may be involved in metastasis

Diabetes and associated diseases:
Glycosylation and glycation on cell surfaces can cause problems in diabetes, and have potential as biomarkers

Immune diseases:
Glycans act as targets for antibodies, which are also glycosylated proteins

Why are Pandemic Seasonal and Bird Flu viruses different?

Many viruses attach to human cell surface sugars. Professor Ten Feizi's research group at Imperial College London have used carbohydrate microarrays to understand this process and have uncovered how seasonal, pandemic 2009 swine flu and bird flu viruses differ in their cell surface recognition. [1]



The flu virus

Glycan databases and standards

Researchers seeking to understand the biochemical structure-function relationships of carbohydrates require detailed descriptions of the assay conditions and the experimental results. While these are currently insufficiently reported in the literature, as glycoscience research advances, there will be increasing amounts of emerging scientific data.

To manage the data, and to make the information accessible to the wider scientific community, publicly available databases and modelling tools have been developed for use in glycoscience. There are a number of challenges involved, however – finding a permanent home for these bioinformatics tools, and establishing standards to ensure the quality and consistency of the data (see textbox on MIRAGE). The MIRAGE project "Minimum Information Required for A Glycomics Experiment" is working to establish guidelines for data presentation from glycomics research in a variety of outputs including reporting experiments in scientific journals through to online database entries [2].

Challenges and opportunities in personalised medicine

As personalised medicine advances, there will be many opportunities to develop lower-cost and better targeted products for the diagnostics market such as: on-/in-body sensors; nanotechnology-based sensors for use in the field; theranostics; companion diagnostics.

An understanding of pharmacoglycomics and the opportunity to monitor human glycomes beyond blood group antigens will be an increasingly important aspect in personalised medicine and regenerative medicine.

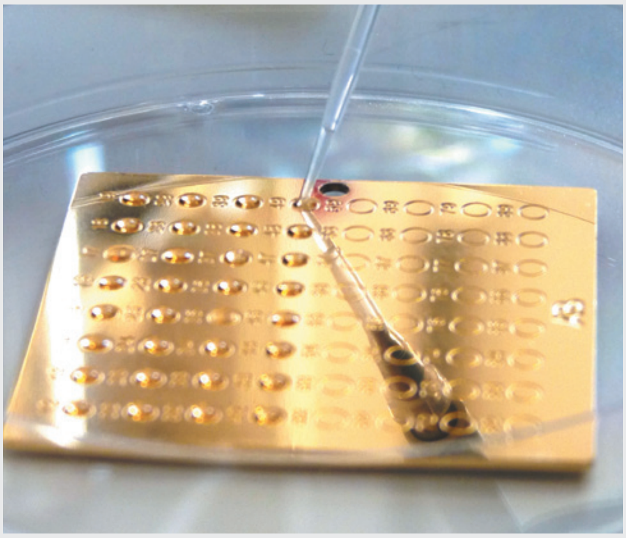
Development of fast and effective diagnostic tools for the detection of pathogens and for monitoring of health and disease will greatly benefit society by both reducing human suffering and cutting healthcare costs. The tools will also allow governments and healthcare providers to put preventative measures into place, for example vaccination programs in infectious disease outbreaks, or targeted interventions for diseases such as cancer or diabetes.

These new opportunities will be of great benefit to pharmaceutical, biotechnology and diagnostic companies and to the healthcare systems.

Studying glycan interactions to find biomarkers for disease

Glycans decorate cell surfaces in the form of glycoconjugates, where glycans are bound via proteins, 'glycoproteins' or lipids, 'glycolipids' to make up the glycocalyx. The glycocalyx can be mimicked in the laboratory using carbohydrate arrays where glycans are displayed on the surfaces of microarrays. Such 'glycoarrays' have been used to identify biomolecular interactions involved in signalling on cell surfaces [3].

Glycobiomarkers have enormous potential for use in diagnostics and personalised medicine. In the the EU project GlycoBioM - 'Tools for the Detection of Novel Glyco-biomarkers' [4] high-throughput screening technologies have been used to identify new glycan biomarkers for a range of diseases. For example, the team have discovered a novel biomarker for maturity-onset diabetes of the young (MODY) [5].



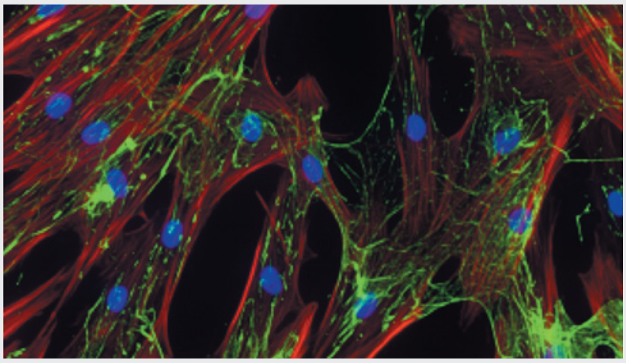
Glycan array technologies have become an important tool to study carbohydrate-protein interactions [6]

Glycans in stem cells and regenerative medicine

European scientists have carried out significant research into the role of glycans in stem cells and the application of glycan-based technology for regenerative medicine and tissue engineering, such as materials for organ replacement and patient-specific testing of therapeutics.

Glycans on the surface of cells re-organise as cells differentiate, producing tissue- and cell-type specific glycans, which determine stem cell fate. Glycans have also been found to be key molecules that direct cell behaviour making them excellent markers of stem cells, offering attractive targets for the specific delivery of therapeutics or toxins for cancer treatment or as tools to manipulate stem cell differentiation *in vitro*.

Stem cell therapies also have potential for treating Congenital Diseases of Glycosylation (CDGs) – hereditary diseases with impaired glycosylation processes, some of which are lethal.



Stem cells display a characteristic pattern of sugars (shown here in green) that direct their behaviour and can be used to target them *in vivo*. Image shows bone marrow-derived mesenchymal stem cells. Nuclei in blue, actin cytoskeleton in red and heparan sulphate glycosaminoglycans in green. With thanks to Dr Catherine Merry.

1. Liu et al. (2009) J. Virol. 84, 12069-12074 DOI: 10.1128/JVI.01639-10

2. http://www.beilstein-institut.de/en/projects/mirage

3. Park et al. (2013) Chem Soc Rev., 42, 4310-4326 DOI: 10.1039/C2CS35401B

4. http://glycobiom.eu

5. Thanabalasingham et al. (2013) Diabetes, 62(4), 1329-37. DOI: 10.2337/db12-0880

6. Both et al. (2014) Nature Chemistry 6, 65–74 doi:10.1038/nchem.1817

Enabling Technologies

Tools

The last 10 years has seen great advances in development of tools for glycan analysis. Examples include:

- Commercially-available LC/MS instrumentation and workflows
- Glycan arrays for the identification of carbohydrate-binding proteins
- Commercially-available anti-carbohydrate antibodies
- Virtual screening of carbohydrate specificity
- Diagnostic imaging using labelled carbohydrates in cells and whole organisms
- 2D electrophoresis
- Lectin blotting
- Blood group screening
- Contrast agents
- Nanoparticles
- Glucose biosensors
- High-throughput genomic sequencing of genes involved in carbohydrate biosynthesis
- Novel synthetic methods for the production of glycan standards

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A number of online databases and tools have been developed by European researchers and are now open access and valuable resource for the worldwide glycoscience community:

CASPER - an online tool for calculating NMR chemical shifts of oligo- and polysaccharides
http://www.casper.organ.su.se/casper/

CAZY – Carbohydrate Active Enzymes - describes the families of structurally-related catalytic and carbohydrate binding modules (or functional domains) of enzymes that degrade, modify or create glycosidic bonds
http://www.cazy.org

Glycan Library – a list of approximately 830 lipid-linked sequence-defined glycan probes derived from diverse natural sources or chemically synthesised
https://glycosciences.med.ic.ac.uk/glycanLibraryIndex.html

GlycoBase 3.2 – a database of over 650 N- and O- linked glycan structures HPLC, UPLC, exoglycosidase sequencing and mass spectrometry (MALDI-MS, ESI-MS, ESI-MS/MS, LC-MS, LC-ESI-MS/MS) data
https://glycobase.nibrt.ie/glycobase/show_nibrt.action

Glyco3D – a portal of 3D structures of mono, di, oligo and polysaccharides and carbohydrate recognizing proteins (lectin, monoclonal antibodies, glycosyltransferases and glycosaminoglycan binding proteins:
http://www.glyco3d.cermav.cnrs.fr

Glycan Builder – a software library and set of tools to allow for the rapid drawing of glycan structures with support for all of the most common symbolic notation formats
http://www.unicarbkb.org/builder

GlycoDomainViewer – an online resource to study site glycosylation with respect to protein context and conservation
http://glycodomain.glycomics.ku.dk

GlyMAP – an online resource mapping out the variational landscape of glyco-active enzymes
http://glymap.glycomics.ku.dk

GlycoMod – an online tool to predict oligosaccharide structures on proteins from experimentally determined masses
http://web.expasy.org/glycomod/

GlycoMiner/GlycoPattern – software tools designed to detect, characterize and perform relative quantitation of N-glycopeptides based on LC-MS runs
http://www.szki.ttk.mta.hu/ms/glycominer/

Glycosciences.de – a collection of databases and bioinformatics tools for glycobiology and glycomics
http://glycosciences.de/index.php

MonosaccharideDB – a comprehensive reference source for monosaccharide notation http://www.monosaccharidedb.org/start.action

NetOGlyc – next generation prediction of O-glycosylation sites on proteins
http://cbs.dtu.dk/services/NetOGlyc/

SugarBind – a database of known carbohydrate sequences to which pathogenic organisms (bacteria, toxins and viruses) specifically adhere
http://sugarbind.expasy.org

SweetUnityMol – software to display 3-D structures of carbohydrates, polysaccharides and glycoconjugates
http://sourceforge.net/projects/unitymol/files/

UniCarbKB – online information storage and search platform for glycomics and glycobiology research
http://www.unicarbkb.org

UniProtKB – the universal protein sequence database with information on glycosylated proteins
http://www.uniprot.org/

The GlycanBuilder software was developed as part of the EUROCarbDB project.

It provides the scientific community with an intuitive, interactive glycan drawing tool that is internationally used to present carbohydrates in different notation formats [1, 2].

Mass spectrometry is regarded as a gold standard glycomics technique and is expected to account for the largest share of the global glycomics instruments market - poised to reach $67.49 million by 2019 from $36.25 million in 2014 [6].

European glycoscientists are leading MIRAGE - a global effort to improve the quality of glycomics data in the literature.

The MIRAGE project "Minimum Information Required for A Glycomics Experiment" is funded and co-ordinated by the Beilstein Institute and is a global effort with representatives from Europe (UK, Germany, Ireland, Sweden) working together with counterparts from the USA, Australia, and Taiwan. Since 2011, the group has been working to establish guidelines for data presentation from glycomics research in a variety of outputs including reporting experiments in scientific journals through to online database entries [3]. It is expected that consistent reporting will allow clear communication of the wide range of glycoscience research efforts for the benefit of the broader scientific community. The MIRAGE working group reports the progress of its work at the Beilstein Glyco-Bioinformatics Symposia and in scientific journals.

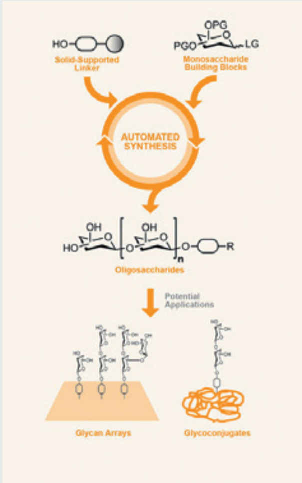
The MIRAGE project is an excellent example of how collaboration between European laboratories and beyond can make significant advances in glycoscience that would be impossible in single research centres or laboratories. [4]

European glycoscientists are at the forefront of developing novel tools for glycan synthesis

The glycan structures found in nature can be made in the laboratory using organic chemistry methods starting from and using carbohydrates. Termed 'Glycomimetics', as well as leads for drug development these can be used as chemical probes (to inhibit or stimulate activity) which are useful for understanding lectins and carbohydrate processing enzymes, to identify inhibitors/(ant)agonists/ligands, as biomarkers, or as diagnostic agents with huge potential in the development of novel vaccines, diagnostics and therapeutics against infectious diseases for application in health and medicine. Some bioactive oligosaccharides can be produced in large-scale quantities at low cost by bacterial fermentation.

Another approach to the synthesis of glycans is to use solid supports enabling the assembly of sugar building blocks into glycans, in a similar way to the programmable synthesisers that have long been used to produce DNA and amino acid sequences.

Research pioneered by Professor Peter Seeberger, (Director of the Max-Planck Institute for Colloids and Surfaces in Potsdam) [5] in this area has led to the first automated solid –phase carbohydrate synthesiser to be built which is currently being trialled by researchers at the University of Leiden and a second machine will be installed at the University of York in 2015.



Training and education in glycosciences

Glycoscience is still an emerging technology, and so it will be important to educate the users of the technologies, which will include patients, healthcare professionals, scientists and policymakers, with coordinated programmes of online training as well as seminars, meetings and conferences. A number of very popular summer workshops exist already, but this activity needs to be expanded to audiences outside the specialist glycoscience community.

Training in Glycoscience is available in a number of formats:

European Training Course on Carbohydrates - A four day course that takes place every two years at Wageningen University. This broad course in glycosciences combines general introductions in the field of polysaccharides and glycoproteins. http://www.vlaggraduateschool.nl/glycosciences/

Glycobiology & Glycochemistry e-learning course - A series of youtube videos and downloadable powerpoint presentations sponsored by the EGSF. http://www.egsf.org/resourcecentre/links/

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

GlycoTRIC – Glycobiology Training, Research and Infrastructure Centre - A two week summer course that takes place annually at Imperial College London to promote interdisciplinary study of the functions of sugars in biology and their roles in human health. http://www3.imperial.ac.uk/glycotric

NIBRT - Provides classroom and laboratory courses on the subject of glycobiology and glycoanalytics, allowing students to gain a broad overview of the concepts, strategies and techniques that are used in research and biopharmaceutical analytical Glycoscience. www.nibrt.ie or training@nibrt.ie

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Food and Nutrition

Glycobiology, food and health

Sugars are important components of everyday foods and an understanding of polysaccharide production in plants is important for food security and production, including crop protection.

The role of carbohydrates in foods as a way to improve health and prevent disease is increasingly discussed. As an example, prebiotic and antimicrobial oligosaccharides and polysaccharides have potential to treat and prevent infections, but further research is needed. As knowledge on the role of gut microbiota in health and functioning of humans and animals is vastly growing, the impact of food on the gut microbiota should be considered and the respective processes thoroughly studied.

Germination of barley.
With thanks to Professor Rob Field.

There are a number of areas of opportunity:

Production of human milk oligosaccharides to promote infant health

Human milk oligosaccharides (HMOs) make up to 10% of solids in human milk, and provide many benefits in infant development and resistance to infection. Adding HMOs to formula milk could have potential to improve infant health, but HMOs are notoriously complex and challenging to produce and purify. There is therefore a need for alternative approaches, such as biotechnology routes including chemoenzymatic methods [1].

Milk Formula accounted for the largest share of the Overall Western Europe baby food and pediatric nutrition market – i.e. 44.48% – of Western Europe Baby Food & Pediatric Nutrition Market at $3,449.1M in 2012. The segment is expected to reach $3,977.7 M in 2017 [2]

Production of natural sweeteners

Sugar-based sweeteners are important components of food products. With the rise of obesity and diabetes in the world, there is a need to find lower calorie alternatives to sucrose, and these could be produced through biotechnology. A number of natural sweeteners, for example stevia, are carbohydrate-based. Larger-scale and lower-cost production through biotechnology could be an opportunity for the bioeconomy to provide society with healthier food.

Europe accounts for intense sweetener sales of €218M – an estimated 23% of the global market, with the region's largest markets in the UK, France and Germany [3].

High intensity sweeteners & sugar substitutes

Due to rising rates of obesity and its associated diseases including diabetes, a number of alternatives to table sugar (sucrose) have been found and marketed for use as low-calorie alternatives for sweetening and enhancing the flavor of foods. High-intensity sweeteners are regulated as food additives [8]. Carbohydrate-based examples of sweeteners include sucralose (600 times sweeter than sucrose), steviol glycosides (>200 times sweeter than sucrose), Luo Han Guo fruit extracts (100 times sweeter than sucrose) as well as sugar substitutes such as sugar alcohols (includes xylitol often found in chewing gum) (>25% sweeter than sucrose) [8].

Did you know?

One litre of mature human milk contains about 5–15 g of free oligosaccharides, which is similar to the amount of protein present depending on the lactation period [7].

Prebiotics to promote health

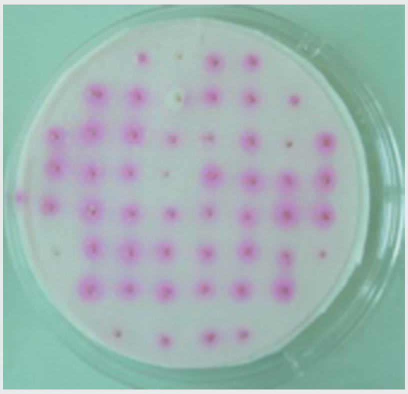
Promoting a healthy gut microflora is increasingly understood to be important for infant and adult health and healthy aging, as well as preventing allergies, infection, immune disease and chronic disease. Prebiotics, usually carbohydrates such as galacto-oligosaccharides (GOS) prepared from cow milk lactose and fructo-oligosaccharides (FOS) prepared from plant inulins, support the growth of the gastrointestinal microflora, changing its composition or activity, and can improve wellbeing and health.

The challenges are to identify prebiotic carbohydrates, study their interaction with the gut microbiota, and produce and purify them in sufficient quantities for the food industries either from natural sources (plants) or by enzymatic synthesis using sugar-polymerizing enzymes and cheap sugars such as sucrose or lactose as the substrate. Such applications would need a much better understanding of the metabolic capabilities and functions of the gut microbiota.

Maintaining a healthy gut flora using human milk oligosaccharides in infancy, and soluble fibre later in life, could be a cost-effective way to improve and maintain the health of our society.

The understanding of a healthy diet will need to go hand in hand with dialogues with regulatory bodies, education, public information, and marketing. Understanding the impact of food on human health would also have potential in veterinary markets.

By 2015, the European market for prebiotics in foods and beverages will reach €767 million [4].



Colorimetric detection of the hydrolysis activity of various CGTase mutants – an enzyme used for modifying starch. With thanks to Centre de Researches sur les Macromolécules Végétales (Cermav), CNRS.

Beneficiaries and end-users

Better understanding in this area will help to develop a more healthy society and facilitate considerable savings in healthcare costs. In addition, development of healthy food additives and substitutes is of great interest to the European food industries, drinks industries, and animal feed industries.

Beta-glucans – natural polysaccharides that are beneficial for health

Beta-glucans are natural glucose polysaccharides that are found in many food sources including oats and other cereals, yeast and mushrooms and have been shown to be beneficial for health.

Beta-glucans have been shown to have cholesterol lowering properties and therefore can play an important role in reducing the risk of coronary heart disease. In 1991, the FDA approved the health claim and recommended a minimum of 3g per day. It has since been shown that increased consumption of beta-glucans leads to a corresponding decrease in the risk of coronary heart disease.

Beta-glucans have also been found to have a beneficial impact on the immune system. They can bind to white blood cells and activate them leading to increased anti-tumour and antimicrobial activity. This understanding will help the pharmaceutical and health industries design new treatments and drugs based on beta-glucans [5,6].

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Materials and Biorenewables

Polysaccharides for sustainable materials

The development of sustainable biorenewables will facilitate the move from our dependence on hydrocarbons towards a sustainable biobased chemicals industry with a lower carbon footprint. For example, cellulose, hemicellulose, starch, chitin, xyloglucan and other polysaccharides are all natural products and are often found in biological waste streams. They can be produced in plants that can be grown on low value or marginal land or even by bioremediation.

Glycobiotechnology will have an important role in supporting the development of sustainable processes for the bioconversion and bioengineering of carbohydrates, to create tailor-made carbohydrate polymers with unique properties and for novel applications. There are many opportunities for innovation in the use of plant-derived oligo- and polysaccharides as performance chemicals, for example by modifying their polarity or functionality.

The self-organization of polysaccharides into dynamic and hierarchical supramolecular structures is a key characteristic of both plant (for example starch) and mammalian (for example hyaluronic acid) polysaccharides. Soft structures made of flexible polysaccharides are fundamental to the extracellular matrix and the nuclear pore permeability barrier.

As in plants and mammals, polysaccharides are also present in bacteria and marine organisms such as algae. Investigations into polysaccharide biosynthesis in these organisms will no doubt reveal a range of useful enzymes for the production of biobased materials due to the vast diversity of microorganisms and their metabolic potential. These microbial enzymes can be used to convert carbohydrates on an industrial scale, and carbohydrate polymers with unique properties could be tailor-made.

These biorenewable materials have potential to replace petrochemical-derived soluble polymers for a variety of applications, including: Dispersants: pigment dispersion in paints; highly concentrated filler dispersions for paper; improved performance of detergents; cement dispersions fluidizing concrete for construction of high-rise buildings; Rheology modifier: increasing or decreasing viscosity for applications as diverse as shampoo formulation or enhanced oil recovery; Flocculants: contaminated water treatment.

Emerging tools

The synthesis and selective modification of polysaccharides is highly challenging. At production scale, 'glycoenzymes' that can catalyse the selective synthesis and modification of polysaccharides remain the most cost-effective and environmentally-friendly route. As more and more genomes are sequenced, novel glycoenzymes, particularly from microorganisms that use polysaccharides as feedstock, are now widely accessible and will transform glycobiotechnology.

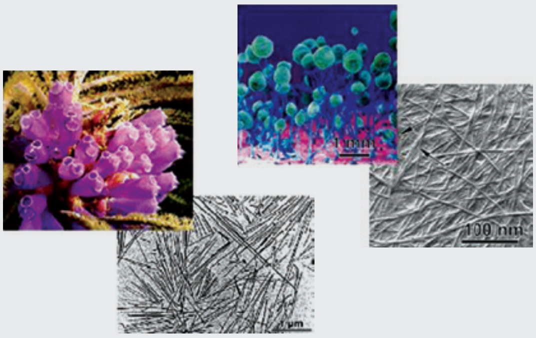
Analytical methods based on nuclear magnetic resonance spectroscopy and mass spectrometry, together with atomic force microscopy, and optical tweezers are now used hand-in-hand with theoretical tools to analyse structures. New instrumentation is required to accompany the overarching concepts which are at the interface between physics and biology, to support the generation of highly-defined innovative biobased materials.

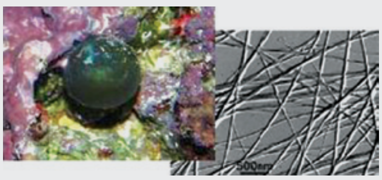
Challenges and opportunities

Surprisingly little is known about polysaccharide biosynthesis and a complete understanding of the enzymes involved will help create improved production processes and novel biomaterials. For example, understanding the biosynthesis of cellulose [1], or learning more about the physical interactions within cell walls in order to overcome the barrier of cell wall degradation. Such key questions that could be addressed by large transnational and interdisciplinary European-based projects, the success of which will be of great benefit to the European bioeconomy.

Building on past successes, the use of enzymes in biotechnology in combination with chemical synthesis is expected to increase to create new high-value/low volume and low-value/high volume materials.

As the next generation of advanced biorefineries are designed, it will be important to develop high-value carbohydrate-derived product streams of biomimetic and smart materials alongside with biodiesel and bioethanol to exploit the full commercial potential of biomass. Potential products include novel barrier coatings and membranes, natural emulsifiers, superabsorbers, fillers for wound healing, gelling agents and soft biomaterials for food science and biomedicine (e.g. tissue engineering) bioplastics, replacements for bisphenol A for (plastics), and drug delivery agents.





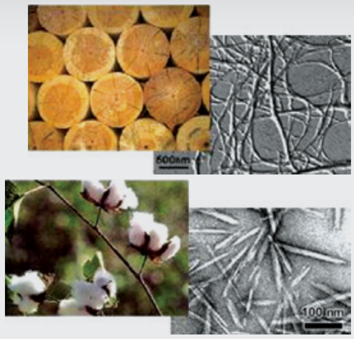
Images taken from reference 4.

Estimates conclude that a shift to biological raw materials and biological processing methods could save up to 2.5 billion tons of CO_2 equivalent per year by 2030, increasing markets for bio-based raw materials and new consumer products several-fold [6].

End-users

Major beneficiaries will include a wide and diverse range of companies involved in the bioeconomy of Europe:

- Chemical industries
- Energy companies developing advanced biorefineries
- Medical device companies for novel biomaterials
- Membrane companies
- Biotechnology companies
- Healthcare sector
- Food ingredients
- Packaging
- Biodegradable materials (e.g. for nappies)
- Cosmetic companies



A spotlight on cellulose-based biopolymers

Cellulose is the most abundant natural polymer on earth. It is a linear, homo-polymer made up of glucose sub-units. Predominantly found in plants, cellulose is a crucial component of cell walls providing backbone and giving structure to plants. It is insoluble in water and biodegradable and it is a combination of all these properties that have made cellulose attractive for commercial exploitation as a biobased polymer.

The earliest examples of cellulose-based materials include cellophane (regenerated cellulose), nitrocellulose (cellulose treated with nitric acid) and celluloid (a mixture of nitrocellulose and camphor), which were discovered and developed in the late 19th and early 20th centuries.

Since then, various modifications of the –OH groups on the surface of cellulose has led to a wider range of cellulose materials being made available. These cellulose derivatives are mainly cellulose esters and cellulose ethers which have various properties that has enabled their use in a wide range of applications from plastics in coatings, inks, gelling and thickening agents, adhesive and binders and more.

As well as chemical modification of cellulose, the polymer can be broken down into smaller fragments for example into nanocellulose, which has been reported as a useful reinforcing agent in composite materials termed 'nanocomposites' [2].

These modifications of cellulose are mostly carried out using traditional chemical methods, however, enzymes are increasingly being used in a more sustainable approach to the production of cellulose-based biopolymers, as well as other sugar-based polymers including starch. A greater understanding of the production of cellulose in plants would allow even more possibilities for cellulose-based biopolymers.

Cellulose and Starch - natural examples of how the structure of a polysaccharide can affect its properties and uses

Cellulose and starch are both naturally occurring homo-polymers of glucose. However, both polysaccharides have different structures and have different roles in nature.

In cellulose, the glucose sub-units are linked in straight chains via β-1-4 linkages and provides structure to plants. In starch, the glucose sub-units are found in two forms; amylose (straight chains of glucose linked with α 1-4 linkages) and amylopectin (branched chains of glucose with α 1-4 linkages and α 1-6 linkages) and is used as an energy store [3, 4].

We encounter cellulose in our everyday lives in the form of cotton, paper and wood products. Europe has a strong history in the paper and pulp industry with some of the largest producers in the world located in northern Europe where they can take advantage of the ready supplies of the wood required produced in the Scandinavian forests. However, with more and more print moving online, the demand for paper products is dwindling. Technologically, the processing of wood for pulp and paper may not differ much from that required to process biomass into sustainable materials and chemicals. This pre-existing infrastructure will play a vital role in bringing newly developed sustainable products to market in Europe and beyond.

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The European Science Foundation (ESF) is an independent, non-governmental organisation, the members of which are 66 national funding agencies, research performing agencies and academies from 29 countries.

The strength of ESF lies in its influential membership and in its ability to bring together the different domains of European science in order to meet the challenges of the future.

Since its establishment in 1974, ESF, which has its headquarters in Strasbourg with offices in Brussels and Ostend, has assembled a host of organisations that span all disciplines of science, to create a common platform for cross-border cooperation in Europe.

ESF is dedicated to promoting collaboration in scientific research and in funding of research and science policy across Europe. Through its activities and instruments, ESF has made major contributions to science in a global context. ESF covers the following scientific domains:

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About IBCarb

IBCarb – Glycoscience Tools for Biotechnology and Bioenergy is a BBSRC funded Network in Industrial Biotechnology & Bioenergy. IBCarb will support UK glycoscientists to develop cutting edge technology in synthesis, biology and analysis of carbohydrates and bring these technologies to the market and provide innovative manufacturing processes. Glycoscience has clear strategic relevance to both industrial biotechnology and bioenergy and IBCarb with its focus on natural carbohydrates is ideally placed to contribute to many aspects of the Industrial Biotechnology and Bioenergy agenda, moving away from dependence on hydrocarbons to develop sustainable biotechnologies and reduce green house gas emissions and ensuring both energy and food security.

IBCarb activities are organized around 5 themes:

- Tools
- Renewables (Materials, Chemicals & Energy)
- Food
- Health
- Societal Impact

www.ibcarb.com

Please reference as – Flitsch et al. (2015) A roadmap for Glycoscience in Europe - a joint EGSF/IBCarb publication.
For more information about this White Paper please contact ibcarb@manchester.ac.uk

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Glycoscience Research Activity in Europe

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