

# CarboMet

## **Diagnostics and Precision Medicine: Challenges and Opportunities for Glycomics**



Metrology of Carbohydrates for Enabling European Bioindustries

A horizon 2020 coordination and support action (CSA) 2017-2021 funded by the European Commission under FET-OPEN

# Background

CarboMet is a four-year Collaborative Support Action ['CSA'] funded by the EC Horizon 2020 Future and Emerging Technologies initiative. The primary aim of the CSA is to mobilise the European academic and industrial community to identify measurement, data management and metrological challenges that need to be addressed in order to advance and exploit carbohydrate knowledge and applications. The vast majority of proteins in the human body are glycosylated and many of the biomarkers used in clinical diagnostics are glycoproteins. Protein glycosylation offers a new dimension in precision medicine by taking into account the individual variation on the protein/cell surface that is not seen with genomic data. CarboMet has conducted online European-wide stakeholder survey and expert interviews in scientific conferences to identify key topics and the challenges in diagnostics and precision medicine. The data and topics collected will be used to support future funding calls for Horizon Europe. This paper reports on the ethical and technological challenges that were identified with stakeholder engagement and through secondary research to provide a list of recommended areas as high priority research for academic funding and industry investment.

## Executive Summary

Precision medicine has grown rapidly over the last decade with many drug companies investing heavily in the development of targeted drugs for a specific subpopulation of patients. The success of Herceptin® to treat patients with Her2 positive mutations and more recently with immunotherapy drug Keytruda® has accelerated development of patient-specific drugs with high efficacy. Sugars on the surface of cells and complex biomolecules are involved in a myriad of processes, many of which involve cell recognition and communication which is vital in the pathological processes involved in bacterial and viral infection, inflammation and autoimmune disease. This report highlights the value of glycomics in drug discovery, areas which require further development and how it can be integrated into current R&D platforms.

# Introduction

The advent of omics (genomics, transcriptomics, proteomics and metabolomics) has revolutionised the traditional drug discovery process. The tremendous amount of work, often decades of research has been put into the development of the omics platform with the pharmaceutical industry benefiting enormously from this. However, it is becoming increasingly difficult to identify blockbuster drugs with better performance than the current standard which has resulted in higher investment cost reaching 2.6 billion US dollars<sup>1</sup> and with an average timeline of 10-15 years before drug approval. There is an urgent need for innovation to transform the way we identify new drug targets. The human genome project initiated the current wave of precision medicine using genetic information from individuals to identify a sub-population of patients who will benefit the most from a therapeutic intervention. One of the earliest examples is the drug Herceptin® used to treat breast cancer patients who have a specific protein biomarker found in 30% of patients.<sup>2</sup> New developments in this field is gradually leading the pharmaceutical industry from a high throughput discovery process to a more targeted approach by leveraging individual genomic data. The one size fits all approach is no longer being applied in clinical practice and the pharmaceutical industry has realized this and are looking to invest in new technologies that can help differentiate between patient populations. Genetic data has been the gold standard to developing precision medicine, however they do not provide information regarding sugars found on protein and cell surface that are vital in cellular communication and recognition. A newly emerging field of study called 'glycomics' is helping to understand the complex mechanism of glycan synthesis and how it relates to disease progression and can provide a new dimension in the drug discovery process and help companies identify novel therapies in this hyper competitive market.

## What is Glycomics?

Glycans, which are sequences of sugars attached to proteins and lipid are the most structurally diverse biomolecule in the human body. They play a vital role in cell communication, viral and bacterial infection, cancer metastasis and cell growth. The Human Glycome Project (HGP) and GlySign are two European projects with the aim of translating glycan biomarker research into clinical practice.

## Social and Economic Impact

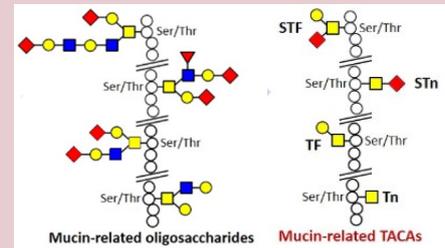
Precision medicine illustrates a model where health care delivery adopts analytics and measurements of individual patients for targeted treatment of diseases. While the benefit of precision medicine has been well documented, development of bespoke treatments, however, raises several ethical dilemmas one of which is the use of human tissue - a common source to identify new targets as they provide information on the aetiology, prevention and treatment of disease. This requires access to thousands of samples from diseased patients and healthy volunteers from what is commonly referred to as biobanks. While donation can be made anonymously, linking the data to various risk factors and individual patients provide the most value and can accelerate the development of a new therapeutic intervention. The new GDPR policy under Article 5 (1)(b) states personal data can be collected for 'specified, explicit and legitimate purposes and not further processed in a manner that is incompatible with those purposes'.<sup>3</sup> It is common for samples from Biobanks to be used in the evaluation of several diseases which at the time of consent might not be apparent. As a result, this can severely delay scientific research and development. A new framework must be implemented with a relaxed ruling while also adhering to patient confidentiality. Perhaps a system where patients can view and give real-time consent if and when data usage changes.

The co-development of companion diagnostics and genetic testing has made the development of precision medicine a costly venture compared to traditional medicine. While the initial investment is substantial, the true value of precision medicine is realized in the long-term with higher drug efficacy and reduced unwanted side-effect lowering hospital admission and related healthcare costs with billions saved over the patients lifetime.<sup>4</sup>

## Case study - Carbohydrates in Cancer

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 important target for the development of cancer vaccine.

The structures shown highlight the differences between normal glycan (structure on the left) and ones which are observed on cancer cells (structure on the right). The differences in the structure can be used in diagnostics and also to develop cancer vaccine by isolating the TACA found only on cancer cell.<sup>5</sup>



**42%**

Number drugs approved in FDA were classed as precision medicine.<sup>7</sup>

Patient population where on average a drug is ineffective.<sup>6</sup>

75% of Cancer Drugs



50% of Arthritis Drugs



40% of Asthma Drugs



## Challenges and Opportunities

Glycosylation is the most common post-translational modification in cells and changes in the glycosylation pattern is invariably linked to various diseases, from rare genetically linked congenital disease of glycosylation (CDG) to prognostic indicators in cancer. Glycosylation also plays a crucial role in regulating protein, stability, folding and function. The complexity of the glycome (repertoire of glycans on cells and tissues) 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.<sup>8</sup> 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.<sup>9</sup>

### How glycomics can be used in drug development

New R&D workflow:



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 acid sugar on the surface.



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



Develop new drugs by elucidating the mechanism of action of proteins/enzymes involved in glycan expression.<sup>9</sup>

CarboMet has identified several areas for development/implementation to realise the immense value of glycomics in diagnostics and precision medicine.



## The Glycome and its role in the human body

The enormous complexity of the glycome in the human body and its function in immunity, cellular communication and disease progression has generated numerous challenges. Some of these are being addressed by the development of analytical tools such as mass spectrometry (a technique used to measure the mass of a molecule which can provide information on the structure). Glycan modification is critical in the function of biological molecules and a complete understanding will be monumental in the development of new drugs.



## Advance Sequencing of Glycans

The incredible diversity of glycans make it extremely difficult to accurately determine its structure. They are among the most complex class of the biomolecules found in the human body since the linkage between the two sugar molecules (glycosidic bond) can have 2 possible spatial configurations and between 4 or 5 possible linkage sites. For example, there is 10 possible combinations between two simple glucose molecule in comparison to only two between two amino acid molecules. New analytical methods are urgently needed to provide information on individual sugar linkages either through a bottom-up or a top-down approach to carbohydrate sequencing. This will provide a powerful new tool to analyse glycan structures in real-time resulting in faster diagnosis and treatment of patients. For example, the genetic disease CDG is caused by subtle differences in the glycan structure where diagnosis at an early stage is critical for the management of the symptoms.



## Bioinformatics and Database including glycan standards

Curation of large multi-centre bioinformatics database for the development of functional glycomics. The database should contain the glycan structure, method of analysis (MIRAGE project), tissue/cell location and prevalence in disease progression. The analysis of glycan structure is complex and requires efficient methods for the production of chemical standards to enable faster and accurate diagnosis. The development of the database will require a collaborative effort between academia, industry and clinics to accelerate the development of diagnostic devices and new therapeutic intervention.

### Key terms

**MIRAGE:** Stands for 'Minimum Information Required for a Glycomics Experiment'. The MIRAGE commission aims to standardise the process of how data is collected and therefore improving the quality of scientific data.

**Companion diagnostics:** This is a medical device used to provide information essential to the safe use of a corresponding drug. The diagnostic test is most often used in companion with biological drugs to determine the applicability of a specific person thus improving efficacy.

**Congenital Disorder of Glycosylation (CDG):** This is one of several rare inborn errors of metabolism in which glycosylation of a variety of tissue proteins and/or lipids is deficient or defective.



## Glycomics

While genomic analysis provides information on the probability of patients developing certain diseases, glycan analysis on the cell surface provides a tremendous amount of data on disease progression and stage. Integrating glycomics with genomic analysis will provide a holistic view on disease development with new insights on biological mechanisms which can be exploited in the discovery of new drugs bringing immense value to the biopharmaceutical and diagnostics industry. Diagnostics can benefit greatly from glycomics research, identifying key therapeutic biomarkers in patients



## Collaborative Business Models

The increased interest and investment in precision medicine has necessitated the development of new diagnostics devices to identify patient subpopulation and new therapeutic targets. Companion diagnostics play a critical role in the success of precision medicine and this requires establishing new collaborative partnership across the whole drug discovery value chain. This means bringing together expertise from immunologists, geneticists, molecular biologists, chemists and even patients as project partners to identify genetic and glycomic biomarkers in the design of new diagnostic tools in parallel to drug discovery and development.

## Conclusions

With many of the global biopharmaceutical companies investing heavily in precision medicine there is a real opportunity for glycomics research to add immense value in the drug discovery process. Sugars play a vital role in the normal maintenance of the human body and divergence from this mean is most often associated with the onset of disease. Exploiting the subtle changes on the surface sugars of cells can provide unique information of disease state and progression which can be used to identify new drug targets. A similar effort is required for glycomics as seen with the human genome project which gave rise to the field of genomics which has been instrumental in the development of precision medicine. Integrating genomic and glycomic data will provide a powerful platform to develop next-generation drugs and diagnostic tools.

## References

1. A. Mullard, *Nat. Rev. Drug Discovery*, 2014, 13, 877.
2. Iqbal, N.; Iqbal, N. *Mol. Biol. Int.*, 2014, 1-9
3. EU GDPR data protection rules 2018: [https://ec.europa.eu/commission/priorities/justice-and-fundamental-rights/data-protection/2018-reform-eu-data-protection-rules\\_en](https://ec.europa.eu/commission/priorities/justice-and-fundamental-rights/data-protection/2018-reform-eu-data-protection-rules_en)
4. Precision Medicine Could Have a Major Impact on Healthcare Outcomes and Costs: <https://hbr.org/sponsored/2018/12/precision-medicine-could-have-a-major-impact-on-healthcare-outcomes-and-costs>
5. Pifferi, C. Design and synthesis of multivalent glycoconjugates for anti-cancer immunotherapy: <http://www.theses.fr/2017GREAV060>
6. The Personalized Medicine Report. Opportunities, Challenges and the Future, 2017: [http://www.personalizedmedicinecoalition.org/Userfiles/PMC-Corporate/file/The\\_PM\\_Report.pdf](http://www.personalizedmedicinecoalition.org/Userfiles/PMC-Corporate/file/The_PM_Report.pdf)
7. Personalized Medicine at the FDA. A progress and outlook: [http://www.personalizedmedicinecoalition.org/Resources/Personalized\\_Medicine\\_at\\_FDA\\_An\\_Annual\\_Research\\_Report](http://www.personalizedmedicinecoalition.org/Resources/Personalized_Medicine_at_FDA_An_Annual_Research_Report)
8. Maverakis, E. et. al. *J. Autoimmune*, 2015, 0, 1-13.
9. Seeling, M.; Bruckner, C.; Nimmerjahn, F. *Nat. Rev. Rheumatol.* 2017, 13, 621-630.