

Background Paper on Glycosciences and Glycomics in the United States

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Carbohydrates (sugars, saccharides, or glycans) are ubiquitous in cells; they can be found on all cell surfaces, in the cytosol and nucleus of eukaryotes, and within the extracellular matrix. DNA itself, the very basis of life, can be considered a complex carbohydrate. Complex carbohydrates or glycans, monosaccharides or oligosaccharides covalently attached to cells or other molecules, are involved in aspects as diverse as cell synthesis, structure, and cell-cell interactions and play critical roles in development and disease. Gaining a comprehensive understanding of the structure and function of all glycans within an organism, glycomics, could be the key to linking gene function to an observed phenotype. In essence, advances in glycomics could be the next step in decoding the molecular make-up of an organism. Originally seen solely as a source of energy for cells with an interesting structural component, carbohydrates may now contribute to solving some of society's most prominent problems.

Background

On March 1, 2010, the National Academies Board on Chemical Sciences and Technology (BCST) and Board on Life Sciences (BLS) sponsored a one-day project initiation meeting focused on scoping a possible National Research Council (NRC) study that would provide an assessment of the glycomics field, including a comparison of similar fields (i.e. genomics and proteomics), applications, and goals for the next ten years. This meeting's participants held expertise in characterization and measurement, data processing and informatics, and application of glycans and glycoproteins, and they represented both academic and governmental sectors. Meeting participants, including program managers at the National Institutes of Health (NIH), the Department of Energy, and the National Science Foundation, expressed considerable interest in a potential NRC study, and provided useful input on the scoping of such a study.

As a result of the above meeting, in September 2010 the National Institutes of Health (NIH) funded a three-month grant to further inform the design of the potential NRC study. In particular, NIH asked the NRC to reach out to researchers and federal program managers to get their sense of the state of glycomics and glycosciences and the challenges facing researchers and funding agencies in advancing this field in order to better understand how to frame such a study, and to summarize this information in a brief background paper. This document represents the results of that outreach. In carrying out this task, NRC staff was assisted by five glycoscience experts¹ who were extremely helpful in efforts to acquire information about the state of glycosciences, its relevant subfields, and practitioners. Information summarized in this background paper was collected via multiple teleconferences between NRC staff, the

¹ A list of the glycoscience experts can be found in Appendix A.

glycoscience experts, federal agency program managers, U.S. researchers, and industry representatives.² This background paper was prepared by NRC staff to inform the design of a potential NRC study by summarizing factual information about the fields of glycoscience and glycomics and the views of those who participated in the discussions about the field's challenges, opportunities, and needs. The paper has not been reviewed and should not be cited, as it does not necessarily reflect the views of the National Research Council or its boards.

Glycomics at a Glance

The central tenet that biological information flows from DNA to RNA to proteins has allowed researchers to gain an understanding of biological organisms at a very fundamental level. Beyond this tenet, proteins translated from mRNA also undergo a number of chemical modifications that carry out different functions in cells. The most abundant post-translational modification is glycosylation, which occurs when mono- or oligosaccharides are covalently attached to other biomolecules such as proteins or lipids (creating macromolecules i.e. glycoproteins, glycolipids, and proteoglycans). However, the term 'glycosylation' is considered by some experts to be misleading due to the fact that it does not take into account multiple possible linkages that may be involved in the glycoprotein or structural diversity of the saccharide. Glycosylation of proteins can actually alter the biological function of the protein; thus, glycans demonstrate a significant influence over biological function. Glycomics is the study of the structure and function of all glycans expressed by cells, tissues, and organisms.

Biologically glycans play significant roles in the development, growth, and function of organisms. Glycans exist on all cell surfaces, cell walls of bacteria, fungi and plants and in the cytosol and nucleus of cells. Glycan structures have been found to be essential mediators in biological processes such as protein folding, cell signaling, fertilization, embryogenesis, neuronal development, hormone activity, and the proliferation of cells and their organization into specific tissues. In addition, protein glycosylation plays a role in pathogen recognition, inflammation, innate immune responses, and the development of autoimmune diseases and cancer. (Varki, et al, 2009)

Glycans exhibit enormous diversity. A glycosylated protein could express different ensembles of glycans when expressed in different cell types. Additionally, a single, well-defined glycosylation site on a fully processed protein can show glycan structural heterogeneity. The range of variations that can exist due to structural diversity of glycan structures, make it challenging to characterize glycans and map them to specific functions and is thought by some to be a barrier to uncovering the glyco-code.

Plant cells are surrounded by a complex polysaccharide-rich primary cell wall. There is emerging evidence that primary cell walls have important roles in the biology of plant cells

² Federal agency program managers, U.S. researchers, and industry representatives who participated in the data gathering teleconferences are collectively referred to as 'discussants' throughout this document. See Appendix B for a list of the discussants who informed this document.

particularly in their development and differentiation. Understanding plant cell wall formation and structure at the molecular level will provide unique opportunities for the development of technologies for the cost effective production of bioenergy from plant biomass.

Microbes are also surrounded by complex polysaccharides or glycoconjugates, which are often critically important for host-pathogen interactions. For example, in the case of pathogenic bacteria, capsular polysaccharides (CPS) and lipopolysaccharides (LPS) can be important virulence factors by impeding phagocytosis, promoting bacterial colonization and persistence on mucosal surfaces and by interfering with leukocyte migration and adhesion. CPS and LPS can be recognized by receptors of the innate immune system leading to the production of cytokines, chemokines and cellular adhesion molecules. With a few exceptions, bacterial polysaccharides can induce an adaptive immune response. Bacterial glycan structures have been employed for the development of vaccines and immune modulators.

The Fields of Glycoscience and Glycomics

Glycoscience and glycomics are truly interdisciplinary fields of research. Chemistry is necessary to understand and interrogate the structure and identify location of glycans. Enzymology is needed to study the glycosyltransferases that are critical in glycan synthesis and glycan/protein interactions that facilitate binding activity between glycans, other molecules, and pathogens. Fundamental biological research is needed to identify biological pathways and glycan function. Research areas related to or encompassed by glycomics or glycoscience include glycobiology, carbohydrate chemistry, synthetic and biosynthetic chemistry, bioinformatics, microbiology, genetics, genomics, proteomics, lipidomics, metabolomics, immunology, reproductive biology, drug development, systems biology, bioenergy and bioproducts, and developmental biology. Most researchers who study glycans consider themselves glycobiologists or carbohydrate chemists.

As research has progressed sub-fields have grown out of glycomics. Proteoglycomics is a systematic study of structure, expression, and function of proteoglycans. (Ly, et al. 2010) This field emerged due to the fact that studying proteoglycans requires a unique approach to understanding proteoglycan structure-function relationships. Glycoproteomics aims to define all of the molecular species (glycoforms) of glycoproteins in a cell or tissue. (Hart and Copeland, 2010) Glycolipidomics focuses on structure-function relationships of glycolipids.

Potential Impacts of Glycoscience and Glycomics

Researchers have determined that glycans play major roles in biological functions and are involved in all phases of life. While genomics and proteomics have produced unparalleled discoveries that have advanced the understanding of biological processes, the picture these present is incomplete. It is thought that ongoing study of carbohydrates in plants, microbes, and animals could lead to the next level of discoveries that may help treat and cure diseases, develop new platforms for energy, and gain a fundamental understanding of life. The following are a few examples of the potential impacts of glycosciences and glycomics based on the discussions with researchers and program managers.

Health

The glycoscience community as a whole recognizes the impact of glycomics in health. Glycans have been shown to play roles in developmental diseases, infectious diseases, and chronic diseases such as cancer and diabetes. Alterations to glycosylation can result in distinctive changes associated with specific disease states. For example, congenital disorders of glycosylation include a group of disorders of abnormal glycosylation of N-linked oligosaccharides caused by a deficiency in 21 different enzymes. (Sparks and Krasnewich, 2005) Genetic mutations disrupting O-glycosylation also have been identified as causes of severe muscular dystrophy. Defective glycosylation is often the result of specific gene mutations resulting in significant phenotype changes.

The prominence of glycans at the cell surface makes them primary targets for infectious diseases and glycans often acts as receptors for pathogens to gain entry into a cell. Thus, using cell-surface glycans as targets could lead to important discoveries in areas such as the diagnosis and prevention of disease. The utility of understanding cell glycans in the development of drugs to prevent infectious disease is evident in the example of flu drugs such as Tamiflu (developed for avian influenza). During early stages of infection, influenza binds to specific glycan receptors. Avian influenza was found to bind to different receptors than normal human influenza viruses. Glycan arrays are used to identify specific binding partners for avian influenza that can then be targeted by developing a structure to attach and block the specific glycan receptor and thus the attachment of flu virus. In addition, oligosaccharides and polysaccharides of bacterial origin are arguably the most cost-effective carbohydrate therapeutics to prevent death and debilitating diseases, as only several micrograms can serve as an effective vaccine.

Carbohydrates are also of great interest to the health and nutrition fields. In today's health conscious society more people are interested in the effects of nutrients on human health. Carbohydrates' roles in signaling and metabolic pathways are of ongoing interest to the nutrition industry.

Energy

One of society's most pressing global issues is energy. The development of effective alternative energy sources around the world, including in the United States, is a major goal. The development of biomass and biofuels as alternative energy sources has been seen as one promising pathway, however many technical challenges exist. One major challenge is understanding the role of glycans in plants. All plants have a structurally complex cell wall of glycans, and the walls undergo many modifications as the plant grows and develops. Despite advanced genomic sequencing technology, the function of most genes involved in cell wall synthesis and modification remains unknown. Another challenge is recalcitrance, a plant's natural resistance to decomposition from microbes and enzymes, which constitutes a major barrier to further development of the biofuels industry. Because glycans are the main components in plant cell walls, advancing the understanding of plant glycans could aid researchers in better understanding and being able to manipulate the cell wall in plant growth and development.

Glycoscience research also may contribute to a number of other questions that remain related to the use of biomass and the development of biofuels for energy and for use of biomass for a diverse array of bioproducts, including the most effective types of crops and the impacts of an increased focus on biomass conversion on food systems, biodiversity, ecosystems, and agriculture.

Industry

Continued development in glycomics research could have significant impacts on a number of industries, including pharmaceuticals, biotechnology, and manufacturing. Glycans can be used as targets for drug therapies and in the development of vaccines and medical diagnostics. A number of biotechnology companies such as GlycoFi, zuChem, and Protaffin have been created based on glycans for the manufacture of food additives, specialty and fine chemicals, vaccines, and biopharmaceuticals. New advances and discoveries in glycomics, might also lead to the development of high-throughput technology for characterization.

A Brief Overview of Glycomics and Glycosciences in the United States

Funding Support

Research support for glycosciences in the United States comes primarily from federal funding agencies. Program managers at many of the funding agencies that support glycosciences research agreed to participate in discussions about the current state and future of glycomics and glycosciences in the United States to help inform the preparation of this background paper. The discussions with program managers at the National Institutes of Health, National Science Foundation (NSF), National Institute of Standards and Technology (NIST), Department of Energy (DOE), and with intramural researchers in the Department of Agriculture's Agricultural Research Service (USDA ARS) highlighted some of the current initiatives supported by these agencies. Brief descriptions of these initiatives based on the discussions are provided below:

- **National Institutes of Health:** Multiple institutes within NIH support research in diverse aspects of glycosciences. For example, the National Cancer Institute has a particular interest in the role of glycosciences in cancer therapeutics development, while the National Institute of Child Health and Development portfolio focuses on the carbohydrate content of human milk and the role of glycans in developmental biology. National Institute of Dental and Craniofacial Research sees its role in supporting glycosciences related to biofilms, oral health and microbes, and National Heart, Lung, and Blood Institute (NHLBI) is interested in glycans' role in mediating biological pathways relevant to heart, lung, and blood diseases and in the development and training of the new generation of glycoscientists. National Center for Research Resources emphasizes technology and methods development. Together, National Institute of General Medical Sciences and NCCR support a significant effort to clone human glycoenzymes and make them available to the research community. In addition

to the efforts of individual institutes, NIH also convenes an intramural Glycobiology Scientific Interest Group and holds a glycosciences seminar series.

- **National Science Foundation:** The NSF Divisions of Chemistry and of Materials Research have not developed program solicitations specifically dedicated to glycosciences, but rather they seek to emphasize proposals driven from interests of the scientific community. Although glycosciences proposals do not currently constitute a large proportion of submissions, the program officers who participated in the teleconferences reported that NSF proposals have included aspects of carbohydrate synthesis and carbohydrate-based biomaterials modifications.
- **National Institute for Standards and Technology:** NIST investments are dedicated to helping advance the infrastructure for glycosciences reference standards and measurement technologies, particularly as they relate to healthcare and to the needs of the biotechnology industry. Programs of relevance to glycosciences include, for example, Measurement Science, Standards and Technology for the Manufacture and Characterization of Biopharmaceuticals, 2009.
- **Department of Energy:** The DOE Office of Biological and Environmental Research (BER) supports three bioenergy research centers while Basic Energy Sciences (BES) invests in energy frontier research centers and many individual programs in plant carbohydrates. DOE glycosciences efforts emphasize plants and non-medical microbes, particularly aspects related to biofuel and bioproduct development such as lignin chemistry and plant cell wall synthesis and deconstruction.
- **U.S. Department of Agriculture:** Intramural researchers with the Agricultural Research Service (ARS) noted that USDA research focuses on the creation of value-added agricultural materials and efforts to improve production and processing. Many of USDA's efforts in glycosciences are focused on bioconversion processes and products. As part of this mission, close interactions with industry are considered essential.

Collaborative Research Initiatives

Because glycans are involved at some level in almost every biological process, a number of integrated and interdisciplinary approaches have been used to advance the glycomics field. Two examples that exemplify the collaborative nature of glycomics research are the Consortium for Functional Glycomics (CFG) and Complex Carbohydrate Research Center (CCRC). CFG is a large research initiative funded by NIH (primarily NIGMS) to “define the paradigms by which protein-carbohydrate interactions mediate cell communication.”

(www.functionalglycomics.org) CFG acts as a clearinghouse for information and as a central hub for many issues related to glycomics. It offers a number of resources and services to the glycomics community including glycomics profiling, carbohydrate compounds and reagents, microarray analysis, mouse phenotyping, glycan array screening, and publicly available databases. All resources are available to investigators free of charge as long as projects are approved for scientific relevance by the CFG's steering committee and investigators agree to

deposit resulting data into CFG databases. It is important to note that CFG has entered its final year of funding.

The Complex Carbohydrate Research Center (CCRC) is a center at the University of Georgia developed to foster interdisciplinary collaboration for carbohydrate research. CCRC receives funding from NIH, NSF, and DOE. The CCRC is comprised of four federally designated centers for carbohydrate research: DOE Center for Plant and Microbial Complex Carbohydrates, NIH/NCRR Research Resource for Integrated Glycotechnology, NIH/NCRR Integrated Technology Resource for Biomedical Glycomics, and an NSF Functional Genomics Center: *A Monoclonal Antibody Toolkit for Functional Genomics of Plant Cell Walls*. (www.ccrc.uga.edu) CCRC is also a major component of the BioEnergy Science Center, one of the three DOE funded BioEnergy Centers. The CCRC is housed in a single building to effectively foster collaboration among its 17 interdisciplinary research groups. Similar to the CFG, CCRC offers a number of services to academic, industrial, and government researchers such as custom synthesis and analysis of carbohydrates as well as information on complex carbohydrates derived from animals, plants, and microorganisms.

Current Education and Training

Several discussants noted that carbohydrate education in the United States appears fragmented (see section on “Possible Areas for Future Study: Challenges, Opportunities, and Needs” for more details). Discussants noted that carbohydrates and glycosciences are generally not emphasized at the undergraduate level and are barely taught in medical schools, despite the increasing recognition of their importance in health and disease. A limited number of research intensive universities (e.g. University of Georgia, Purdue University, etc.) offer specific courses in glycosciences, however many universities incorporate glycosciences primarily in a few lectures in biochemistry courses devoted to metabolic pathways.

The NHLBI at NIH already has recognized a need for additional training and education in glycosciences. As a result, the NHLBI has created the Excellence in Glycomics initiative, which supports collaborative research that could lead to discoveries in new diagnostic and clinical applications. Additionally, NHLBI intends for this program to “create resources and a cadre of “scientifically bilingual” investigators fluent in glycan chemistry and biology that will sustain and advance the application of glycosciences to heart, lung, and blood research.” (www.nhlbi.nih.gov)

American Competitiveness

Another important issue that was raised during the teleconferences is how glycomics efforts in the United States compare to international efforts. Discussants noted that centers of excellence and significant research investments can be found in Europe and Japan. Given the promise of glycomics and its potential impact on health, therapeutics, energy, and agriculture, a further and more detailed analysis of glycomics and glycosciences in the United States would be incomplete without consideration of international standing in today’s global economy.

Possible Areas for Future Study: Challenges, Opportunities, and Needs

A number of challenges, opportunities, and needs for advancing glycosciences and glycomics in the United States were put forward during discussions with glycoscience experts, program managers at federal funding agencies, and U.S. researchers. It is important to note that the points highlighted below reflect the views of the individuals who participated in these discussions and should not be considered consensus findings or recommendations of either the glycosciences community or the National Research Council.

Challenges

Complexity of Glycans

A number of practical reasons why decoding the glycome remain a major challenge, such as carbohydrate synthesis, the structural complexity of carbohydrates and glycoconjugates, and difficulties to uniquely modify or interrogate particular glycoforms.

Synthesis of glycans

Unlike genes and proteins which derive from a more specific template-driven synthesis process, the synthesis of carbohydrates remains significantly more challenging and unpredictable. Carbohydrate synthesis may involve multiple chemical and enzymatic reactions and multiple potential reacting groups, as well as alternate stereochemistry. When chemically synthesizing carbohydrates, controlling the steps of the reactions so that only the desired donor and acceptor groups react and the desired stereochemistry is obtained remain significant obstacles. In addition, glycoproteins commonly exhibit variant glycoforms due to differences during the biosynthesis process or to the actions of enzymes such as glycosyltransferases. Specific ongoing needs highlighted by discussants during the teleconferences included research on chemical and enzymatic synthesis methodologies and in automated glycan synthesis.

Glycan Characterization, Detection and Analysis

The tools used to characterize glycans within an organism, an area that is driven primarily by the application of chemistry-related techniques, were also mentioned as critical components to the field of glycomics. Glycans are difficult to detect and analyze. Unlike compounds such as DNA, they do not absorb UV light well, limiting the application of simple techniques such as UV absorption. The current methods most commonly employed to characterize the glycome include:

- Mass Spectrometry – used to characterize the structures of individual glycans at the cell surface and to define sites of attachment of glycans on proteins.
- Nuclear Magnetic Resonance Spectroscopy – used to study the structure and function of glycan assemblies.
- Lectin and Antibody Arrays – higher throughput techniques (compared to mass spectrometry) used to interrogate the glycome and used to identify glycans used by microbes for infection.
- High performance liquid chromatography – the primary separation technique used for glycans

- Capillary electrophoresis – high-resolution method used to separate glycans
- Glycoarrays – microarrays consisting of carbohydrates, used for high throughput probing of, for example, carbohydrate binding proteins
- Gas Liquid Chromatography-used for glycosyl residue composition and glycosyl residue linkage composition. Capture reagents for specific identification of glycoforms. Development of specific inhibitors for carbohydrate biosynthetic enzymes and carbohydrate binding proteins, to investigate their biological functions. (Varki et al, 2009)

Despite the number of tools available for characterization a number of challenges remain. The sheer number of glycans that exist in an organism presents one significant measurement obstacle. Some estimate that there are more than a million different glycan structures in a mammalian cell's glycome (Hart and Copeland, 2010). Plant and microbial cell walls contain many structurally complex carbohydrates. Only limited high-throughput techniques for rapid characterization of glycans and related glycoforms with a high level of specificity have yet been developed. In addition, many carbohydrate characterization techniques are difficult, costly, and time consuming. In practice, this limits their application to scientists with specialized chemical and biochemical training, highlighting both the need for cross-disciplinary collaborations to advance glycosciences research and a need to continue development of new tools and methodologies.

Relationship of carbohydrate structure to function

Another significant challenge noted during the discussions is improved understanding of the relationship between carbohydrate structure and physical properties and function suggesting that research on this issue remains a fundamental need in the field.

Opportunities

Many of the discussants expressed the opinion that continued research and development in glycosciences has the potential to generate large impacts across multiple fields of biology. The particular opportunities highlighted by individuals varied, but they frequently pointed to emerging applications in human health and in areas such as the development of new bioenergy and bioproduct resources. Selected examples of opportunities that arose during the discussions in the areas of health, applications in bioproducts and energy, and tools are summarized below:

Health

- Biomarker discovery. It is known that cell glycan profiles change with disease states such as cancer and inflammation, although much remains unknown about the mechanisms that control these changes and their physiologic significance. Discussants pointed to the significance of identifying the “glycan signature” of different cell types and of taking advantage of altered glycan patterns for the development of diagnostic biomarkers.
- Development of Biotherapeutics. The role of glycans in infection, in the immune system, and in fundamental cellular processes also opens the door to the development

of new therapeutics, although challenges remain in successfully targeting sugars. For example, it was noted that many microbes make use of carbohydrate ligands as part of the process of cell entry, stimulating interest in the potential development of novel antimicrobial agents (e.g. Tamiflu). Microbial carbohydrates can elicit protective immune responses and therefore provide an important starting point for vaccine development. There is also ongoing interest in the development of monoclonal antibody therapies. The observation that glycosylation profiles are difficult to control during the manufacturing process of therapeutic glycoproteins such as monoclonal antibodies has stimulated collaborations between NIST and FDA, for example, on the development of standards for glycan analysis of therapeutics. It was noted that glycosciences advances of significance to areas such as diagnostics and therapeutics remain areas of great interest to industry.

Applications in Bioproducts and Energy:

- Bioproducts. Discussants observed that plants may serve as economical sources of polysaccharide-based materials, particularly as petroleum resources diminish. Within the biomaterials field, it was also noted that use of polysaccharides for applications such as tissue engineering scaffolds also appears promising.
- Bioenergy. Opportunities in biofuels may arise from improved understanding of plant cell wall synthesis and deconstruction, which could enable more rational modifications of biomass and more efficient conversions of lingo-cellulosics into biofuels.

Tools Development

- Continued developments in existing glycan analysis tools, including developments in mass spectrometry techniques, such as in Ion Mobility mass spectrometry, expansion of available glycan microarrays, expansion of available antibody probes, advances in “shotgun glycomics,” and ongoing developments in glycan analysis and quantification with small sample sizes
- Deposition of data into glycan databases and availability of bioinformatics tools to mine these sources
- Advances in glycan sequencing
- Developments on the expression of modified cell-surface glycoproteins and in chemical tools such as metabolic labeling of glycoproteins.
- Development of tools to monitor the fate of complex carbohydrates in living systems
- Development of selective inhibitors of carbohydrate processing enzymes and carbohydrate binding proteins to selectively interrogate biosynthetic or recognition processes.

Needs

Discussants also mentioned a variety of needs to advance the field and enable it to take advantage of some of the potential opportunities described above. It is important to note that these ideas do not represent the consensus views of the discussants or the NRC—they are

provided as examples of the kind of issues that might be addressed in a future study. Selected examples of needs that arose during the discussions are summarized below:

“Omics” Infrastructure and Positioning Glycomics within the “Omics” Spectrum

Discussants noted that genomics and proteomics were able to make huge leaps forward in research because of the supporting infrastructure that was built around these disciplines. Such infrastructure included techniques for the rapid expansion of nucleic acid material, rapid, automated, and cost-effective nucleic acid sequencing,³ and significant computational advances enabling dynamic simulations of protein and nucleic acid interactions. Widespread access to sequence databases (such as those housed at the National Center for Biotechnology Information) and the expansion of user-friendly commercial kits to purify and characterize genes and proteins have also contributed to the ease with which students and scientists have been able to research genomic and proteomic questions.

Glycomics adds a significant additional layer of complexity beyond genomics and proteomics. Researchers now understand that knowledge of gene and amino acid sequences alone cannot explain many important biological processes, however. As one discussant noted, the “context” provided by post-translational modifications such as glycosylation are critical to decode some of these processes and reach a fuller understanding. Some discussants stated that the field was ready to undertake the characterization of the human glycome despite the complexity of this task. Other participants noted that glycomics might be considered part of the field of metabolomics, another emerging research area. Many of the discussants expressed the view that the time is right to strengthen the enabling infrastructure to allow glycomics to assume its position as one of the “omics” fields and to energize the research community.

Development of Tools, Reagents and Methods

Gaps in tools, reagents, and methods were frequently raised during the discussions. A common theme was the need to develop simplified and cost effective techniques that could be used by non-specialists. It was suggested that the expense and complexity of many of the existing tools limits the ability of the broader biology community to address questions in carbohydrate research. Although the complexity of carbohydrates makes the development of quick and inexpensive methods significantly more difficult, some discussants noted that expansion of the workforce may be limited until tools are developed that will make the field more accessible to both students and other scientists. Some of the specific needs mentioned during the discussions include:

- Fast, simple and affordable methods for separation and structural analysis, particularly for small samples and to achieve high precision.
- Methods to amplify glycans, similar to way PCR amplification of DNA has enabled enormous research advances

³ For example, the Carlson curves show an exponential decrease in the per base cost of DNA synthesis and sequencing over time. Rapid advances in development and access to low cost, high speed DNA synthesis technology have helped to drive the emergence of fields such as synthetic biology.

- Availability of purified reference standards for controls and methods development
- Additional and more widely-available antibodies against carbohydrate targets. The developments of libraries of monoclonal antibodies directed against cell wall polysaccharides was noted a significant recent development.
- Enzymes and enzyme inhibitors tailored for specific applications
- Rapid methods for generating glycoprofiles
- Additional efforts in access and maintenance of carbohydrate databases and standardization of database information

Non-Mammalian Systems

Several discussants noted that research to understand glycosciences in non-mammalian systems, such as in microbes and plants, remains less developed than human glycomics. While mammalian systems have a more limited, although still complicated, repertoire of glycans, plants and bacteria display a much greater range of glycan subunits and linkages. To advance research in non-mammalian systems, discussants noted the need for a wider array of system-specific databases as well as tailored methods and tools. Much also remains unknown about the metabolism of carbohydrates in the complex and variable system of the gut, which affects potential development in areas such as prebiotics and nutrition.

Education

Another theme raised by discussants was a need for more systematic and comprehensive education on carbohydrates, at multiple educational levels, to raise awareness among students and scientists of the fundamental roles played by carbohydrates in almost every aspect of biology, and to stimulate interest in the field. Discussants noted that carbohydrates comprise one of the four fundamental classes of biological molecules (along with nucleic acids, proteins, and lipids) but that this importance has not translated into widespread incorporation into *core* educational curricula. The extent to which carbohydrates are incorporated into courses reportedly varies by school, as do the primary departments in which it is taught. Additional observations by discussants included:

- The interests and research of faculty members influence the carbohydrate topics that are covered
- Traditional departmental divisions may be a barrier to widespread inclusion of a highly cross-disciplinary field like the glycosciences
- Organic chemistry classes frequently focus on petroleum-based hydrocarbons as a starting material, while biochemistry classes often focus heavily on memorization of metabolic pathways. As a result, there may be missed opportunities to incorporate content on carbohydrates or the field may be perceived as boring by students.
- Undergraduates commonly receive only limited exposure to carbohydrates, and the field is also poorly covered by most graduate and medical schools. At least one discussant noted the influence of standardized tests such as the MCAT in affecting course content and suggested this might represent an opportunity to promote greater inclusion of carbohydrate material.

A variety of suggestions were offered to help address some of these points and which could be addressed in more detail in a study, including the creation of on-line courses and educational materials or development of one week hands-on glycosciences training schools like those at CFG and CCRC . It was noted that the glycosciences community might be able to make effective use of existing training support not directed specifically at the glycosciences, such the NSF Integrative Graduate Education and research Traineeship program (IGERT).

Workforce and Funding

Discussants emphasized the interdisciplinary nature of glyco- and carbohydrate sciences, which are situated particularly at the intersection of chemistry and biology. They also noted the need for ongoing communication between the developers of methods, tools, standards, and databases and the users of such tools in both the academic and industrial research communities. Discussants noted that there was currently a “high activation barrier” for many scientists to delve more deeply into glycosciences because current research requires a significant biochemistry background and collaborations with specialized chemists. Although many discussants stressed that significant gaps remained in developing a critical mass of researchers in the field, they also pointed out that many researchers would be interested in studying aspects of glycosciences if they could identify a clearer path forward for how to study these questions and if they had access to more user-friendly tools and methods to do so.

Discussants suggested that there were roles to play for professional societies, journal editors, and scientific meeting organizers to help showcase interesting and important aspects of glycosciences. Review articles, plenary talks, and seminars were all suggested as potential ways to help raise the profile of the field and to highlight the breadth and importance of glycosciences, especially among less specialized scientific audiences.

Several discussants suggested that the lack of new researchers entering glycosciences and the complications and barriers to tackling glycosciences challenges may be having an effect on the portfolio of current glycomics research. While some agencies have attempted to drive submission of proposals by way of detailed requests, other agencies have emphasized funding driven by the interests of the scientific community as reflected through the pool of proposals that are submitted to more broadly-crafted programs. With a limited number of researchers submitting proposals related to glycomics and glycosciences, there may be missed opportunities for agencies to support critical aspects of chemistry and biology needed to advance glycomics and glycosciences.

Drivers in the Glycosciences

Discussants also commented on some of the significant drivers they felt influenced glycosciences development. Many discussants expressed the view that the health implications of glycosciences in areas such as therapeutics and diagnostics are significant drivers in the field, and as a result NIH was viewed as an agency with a major role to play in helping to address challenges and opportunities. Many of the discussants pointed out, however, that glycoscience research extends beyond clinical health. For example, although there has reportedly been less previous interest and funding to support plant glycosciences, more recent interest in

bioproducts and biofuels has expanded these research fields. Several discussants emphasized the current economic climate and budget constraints as centrally significant drivers, particularly given the need to balance glycosciences research with other priorities.

Communication

Discussants pointed out that many glycobio­logists and glycoscientists communicate most frequently within their specialized sub-disciplines, and as a result it may be valuable to foster opportunities for the community as a whole to come together, perhaps to identify common challenges and core priorities across the discipline. Some of the overarching challenges mentioned by discussants included the need to more clearly demonstrate how glycosciences and glycomics fit into the overall puzzle of major biology questions, to better articulate problems in glycosciences that would appeal to biologists, and to explain both what glycosciences can do for society and what major breakthroughs have occurred within glycosciences.

Summary

Some of the overarching themes that emerged from discussions with researchers and program managers are that glycosciences are central to both biology and chemistry, that glycosciences are intimately involved in understanding numerous fundamental cellular and biologic processes, and that an improved understanding of glycosciences could lead to significant impacts in diverse sectors such as health and energy. Many of the discussants expressed support for a study that would bring together experts in relevant scientific disciplines and industry to clearly articulate the major questions and problems in glycosciences and to help set priorities for glycoscience research.

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Appendix A Acknowledgments

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Appendix B

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