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Letter to Glycoforum

Origins and Evolution of *Essentials of Glycobiology*

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Prologue

"*Whereof what's past is prologue; what's to come, in yours and my discharge.*"

The Tempest (William Shakespeare)

A Google AI Analysis of this quote returned this summary: "*It means that past events have set the stage for what is to come, and the future actions of the speakers will determine their fates. In essence, the past serves as a prelude to the significant events that are about to unfold.*" This article is mostly about the history, origins, and evolution of the textbook *Essentials of Glycobiology*, ending with a brief look to the future, which will be determined by others.

An Award Recognizing all the Editors of "Essentials" In 2021, the Society for Glycobiology (SfG) Board of Directors established the Distinguished Service Award, which was intended to: "*recognize individuals with a sustained record of distinguished service to the Society for Glycobiology and/or the glycobiology community*" (Society for Glycobiology Awards-2024). In 2024 the SfG Board chose to bestow the Award "n*ot to an individual, but rather to a group of distinguished glycobiologists, who have served as Editors of Essentials of Glycobiology* (EoG), a group not officially associated with the Society, but with substantial membership overlap. In so doing, the SfG Board "*recognized the sustained effort and altruistic contributions that drove the creation, production, and enduring impact of a textbook which continues to serve as an invaluable resource for capturing and communicating knowledge in glycobiology*" (Society for Glycobiology Awards-2024). The announcement also noted that editors and authors had chosen not to be financially compensated for their contributions. Proceeds from the book are used to produce the next edition.

Sources of Information and Reuse of Verbatim Text. As executive editor of the EoG editorial group, the present writer was invited to receive the award on behalf of group at the 2024 SfG meeting. The acceptance speech generated an invitation to write an article about the origins and evolution of *Essentials*. Other editors invited to co-author this article chose not to participate. But any detailed history about complex issues written by a single individual is inherently suspect, and prone to unconscious bias. To minimize such a risk, this article extensively quotes verbatim text from multiple sources: the original SfG Award citation (Society for Glycobiology Awards-2024), the Forewords from the First Edition (Stuart Kornfeld) (Kornfeld 1998); Second Edition (Jo McEntyre and David Lipman) (McEntyre and Lipman 2009); Third Edition (Jeffrey Gordon and Lora Hooper) (Gordon and Hooper, 2015); and the Fourth Edition (John Inglis, Rita Sarkar and Stephen Sherry (Inglis et al. 2022)—as well as from websites of the US National Center for Biotechnology Information (NCBI), the Cold Harbor Spring Harbor Laboratory Press and UC San Diego. Some text is also taken from chapters of the book, and from spinoffs of the NCBI pages (see details later). All text that is copied *directly from earlier sources is italicized*. (There is no further use of AI in this review).

Historical Background (includes excerpts from the Preface and Chapter 1 of the Fourth edition of EoG). Until the 1980s, the study of biological systems and disease mechanisms gave equal attention to all major classes of macromolecules: nucleic acids, proteins, lipids, and carbohydrates (glycans). The chemistry and metabolism of glycans were prominent matters of interest in the first part of the 20th century. Although engendering much attention, they were mostly considered as a source of energy, targets for pathogens, or as structural materials. Furthermore, during the molecular biology revolution of the 1970–80s, studies of glycans lagged far behind those of other major classes of molecules. This was in part because of their inherent structural complexity, the difficulty in determining their sequences, and the fact that their biosynthesis could not be directly predicted from a template. By the end of the 1980s, most popular textbooks, monographs and manuals about "Molecular Biology" had a strong emphasis on DNA, RNA, and proteins, with some attention to lipids—but effectively left out glycans, which were poorly understood, far more complex and diverse, and much more difficult to study. The central paradigm driving research in molecular biology thus became that biological information flows from DNA to RNA to proteins. The power of this concept lay in its template-based precision, the ability to manipulate one class of molecules based on knowledge of another, and patterns of sequence homology and relatedness that predict function and reveal evolutionary relationships. With ongoing sequencing of numerous genomes, spectacular gains in understanding the biology and pathology of nucleic acids and proteins have

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occurred. Thus, many scientists now assume that studying just these macromolecules along with lipid bilayers providing compartmentalization will explain the makeup of cells, tissues, organs, physiological systems, and intact organisms. In fact, making a cell requires many small molecule metabolites as well as two other major classes of macromolecules—lipids and glycans—which serve as intermediates in generating energy and as signaling effectors, recognition markers, and structural components. Taken together with the fact that glycans encompass some of the major posttranslational modifications of proteins, we can now perhaps explain how a relatively small number of genes in the typical genome can generate the enormous biological complexities inherent in the development, growth, and functioning of diverse organisms.

The Emergence of "Glycobiology". Beginning in the 1980s, spectacular achievements in studies of nucleic acids and proteins caused most biologists and biomedical scientists to stop paying attention to glycans, and an entire new generation of "Molecular Biologists" learned little about this other major component of all biological systems. The small number of scientists who had continued working primarily on glycans embraced the term "Glycobiology" a neologism coined by Raymond Dwek and colleagues (Rademacher et al. 1988) defined as "*the branch of science concerned with the roles of sugars in biological processes*." A journal of the same name was started by Oxford University Press (Gerald Hart, Founding Editor), and the Society for Complex Carbohydrates renamed itself as the Society for Glycobiology. Meanwhile only a few institutions in the USA had a critical mass of glycoscientists. One such group became locally organized as the UC San Diego Cancer Center Glycobiology Program (Ajit Varki, leader), in collaboration with Hudson Freeze, Minoru and Michiko Fukuda at the La Jolla Cancer Research Foundation (now Sanford Burnham Prebys Institute). The UC San Diego Program then established a Glycotechnology Core Resource (Director, Adriana Manzi), and the 1990s saw the recruitment of Jamey Marth and Jeffrey Esko, increasing the critical mass in the program, which also organized a multiunit chapter on Analysis of Glycoconjugates, in the popular lab manual Current Protocols, with Kaaren Janssen as editor (Varki et al. 2009). A San Diego Glycobiology Symposium (SDGS) suggested by Marth brought together the relatively small number of glycoscientists in California for an Annual gathering. Meanwhile, a graduate-level elective course called "Essentials of Glycobiology" had been taught at UC San Diego for many years. At a 1996 Glyco-Immunology meeting, Hart and Richard Cummings agreed to join forces with some of the UC San Diego scientists to form a Consortium of Glycobiology Editors (CGE) which proposed a book called "Essentials of Glycobiology." Kaaren Janssen introduced the CGE to John Inglis, the Executive Director of CSHL Press, who agreed to the proposal.

The First Edition was published in 1999 (see book jacket and cover in Fig. 1). Writing in the Foreword, the late Stuart Kornfeld (1999) opined that "*The Essentials of Glycobiology could not have appeared at a more opportune time.*" He recalled that "*Glycobiology has its roots in the nineteenth century, when chemists first began to analyze sugars and polysaccharides. Perhaps the first glycoprotein to be studied was the "glycogenous matter" of liver which the famous French physiologist Claude Bernard identified in 1855 as a storage form of glucose . . . . Advances in this area continued at a steady rate during most of this century, including the assembly, processing, and degradation of oligosaccharides and proteoglycans (along with) the . . . identification of numerous families of plant and animal lectins that recognize carbohydrate structures. The surprising finding to emerge is the vast number of enzymes and proteins that are devoted to glycoprotein and glycolipid synthesis and function. The understanding of the biologic roles of glycans has also increased to a great extent, and we now know that these molecules serve multiple functions, ranging from assisting the folding of nascent proteins to determining the trafficking of lymphocytes and granulocytes in the circulation. The important role of glycans is underscored by the growing list of human diseases that are the result of defects in glycan assembly. The challenge for the future is to further define the biologic functions played by glycans. In this regard, recombinant DNA technology has provided another valuable tool . . . the ability to disrupt genes of interest in mice and other organisms. This presents an unparalleled opportunity for the scientist interested in elucidating the biologic roles of sugars . . .*

Essentials of Glycobiology provides an ideal entry into the field. It contains the basic information needed to understand this area along with the most current work at the forefront of the field . . . ."

Limited Recognition by Mainstream Biologists, but Kudos from Nobel Laureates. In keeping with the fact that biological roles and biomedical significance of glycans were getting limited attention compared with DNA, RNA and proteins, citations or reviews of the first edition were rare. In striking contrast every Nobel Laureate, we approached had high praise for the effort, comments which we featured on the back covers (see Fig. 1). This was also true for the next two editions (Figs 2 and 3). The full-length comments of 12 Nobelists can be found on the back covers of the first three editions on the NCBI website, and abbreviated versions appear on the back cover of the fourth edition (Fig. 4).

The Second Edition: In your Hands and Simultaneously Online. Almost 10 years went by before a second edition was produced (see book jacket cover in Fig. 2), with an expanded editorial board, introduction of more color, and publication in print and online simultaneously. This time there was more general attention to the release, including a review by Dwek (2009) which opined that "*the time is definitely right for publication of the second edition of the "Essentials of Glycobiology", for both students and researchers . . . over 50 authors have contributed to this edition, which is reflected in the breadth of the chapter topics . . . the volume benefits from a coherent style with excellent new color illustrations that bring often complex and technical concepts to a readership that may not be familiar with some of the subtleties of glycobiology. Particularly welcome in this latest edition is a more rigorous approach to phylogenetic classification . . . and increased emphasis on nonmammalian glycosylation. . . . and broad, evolutionary consideration of the selective forces that have shaped the incredible diversity of natural glycosylation. . . . the book is rather like a fast-paced tour guide to a famous museum—helpful in pointing out the most important artifacts so that they can be viewed quickly but not providing a full appreciation of why they are so important. On balance, however, the book provides a helpful overview of the important subject of glycobiology and will be a useful reference for students.*"

Accidentally Inventing "Open Access." Another major change occurred regarding the second edition. A retelling of

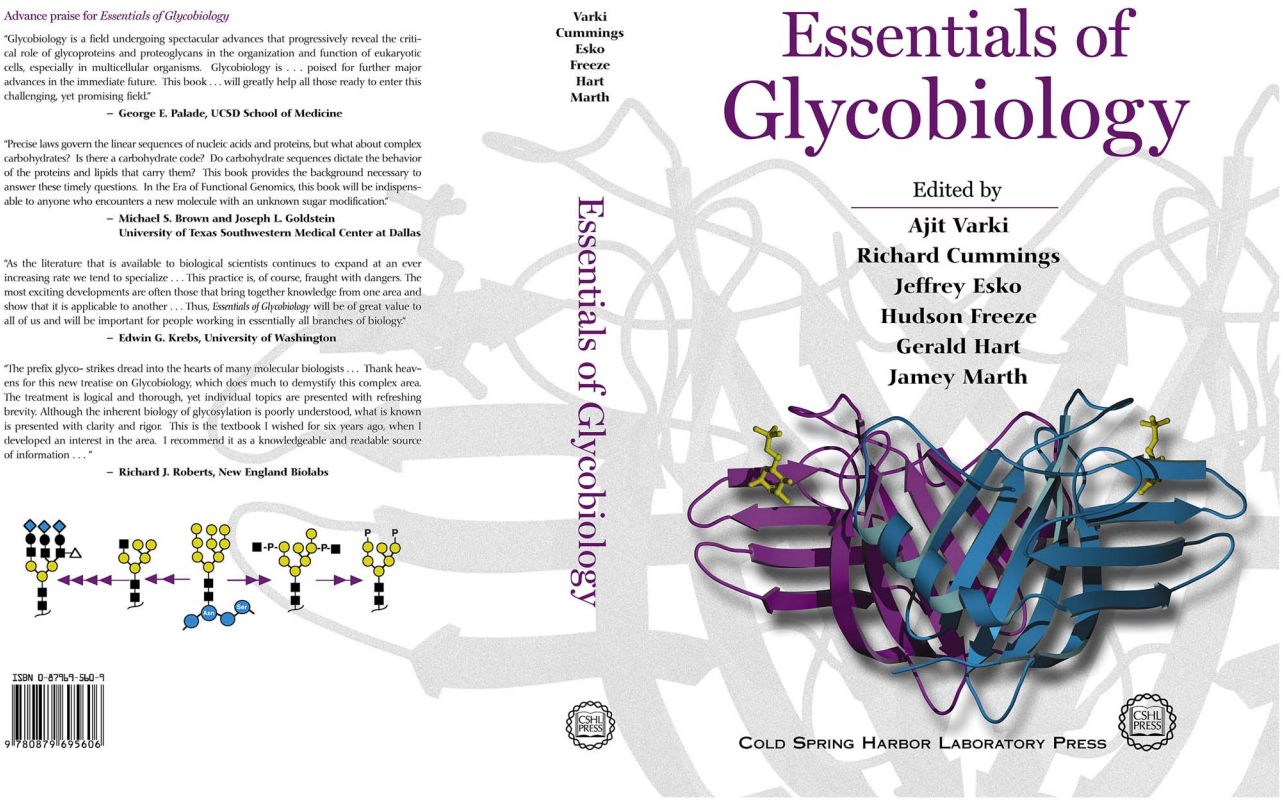

Fig. 1. Jacket and cover artwork: First edition 1999. A ribbon diagram of the bovine cation-dependent Man-6-P receptor (CD-MPR). The two monomers (purple ribbon and blue ribbon) of the dimer as well as the ligant, Man-6-P (gold ball-and-stick model), are shown. (modified, with permission, from Robert, DL, Weix, DJ, Dahms, NM, Kim, JJ. Cell 1998; 93:639–648). Note that the colors used for the symbols on the back cover predated the current SNFG.

the story in a recent UC San Diego news item (Pritchett 2024) stated that "*The decision to share the book freely online for the last two decades occurred almost by happenstance. It was the mid 1990's and the Internet was just getting started when Ajit Varki was serving as editor in chief for the Journal for Clinical Investigation (JCI). Taking advantage of fiscal reserves built up over the years, the executive editor had the idea to offer the journal free online to everyone. It was the first major biomedical journal to be freely available in such an open format (the term "open access" was not coined until more than 10 years later)*, in the Budapest Open Access Initiative (BOAI) in 2002. *Riding on the success of the online journal experiment* (see Savla 2004) *Varki asked David J. Lipman, then director of the National Center for Biotechnology Information (NCBI) if it was possible to similarly share the textbook online for free.*

NCBI accepted a proposal to make the entire book freely available online at NCBI Bookshelf for searching and reading by anyone anywhere in the world with an internet connection—eventually including downloadable slides for each figure."

As Jo McEntyre and David Lipman of NCBI wrote in their Foreword to the Second Edition (McEntyre and Lipman 2009) "*it is not only the science that has changed. The original edition was thought of as a traditional book, to sit on a shelf and be used as a work of reference. However, in late 2002, we at the National Center for Biotechnology Information were approached by the book editors, who expressed an interest in making the book available on the NCBI Bookshelf. This meant that the complete text would be available for searching and browsing* via *the Internet, therefore extending the use of the book to those who might not have access to the hard copy. The publisher of the book, Cold Spring Harbor Laboratory Press, was on board to try the experiment, and so, in early 2003, Essentials of Glycobiology became one of the pioneering textbooks to be distributed electronically.*

In the intervening years, hundreds of people every week have continued to look at Essentials of Glycobiology *online. . . . university libraries all over the world list and link to the electronic book, and major Internet search engines index the content. All of which has extended the reach of this enduringly valuable text.*

Today's freshmen were only nine years old when that first edition came out. This generation of students has grown up with online information as an integral part of the information resources they use—the first port of call for many homework assignments is now an Internet search rather than a trip to the library. Furthermore, knowledge seekers from all walks of life—for example, high-school students or those seeking health-related information on the web—now have the opportunity to use the book. In recognition of the wider audience and changing ways in which students learn, this new edition of Essentials of Glycobiology will be made freely available online simultaneously with the appearance of the printed edition of the book.

This novel approach to textbook publishing is the result of a three-way collaboration between John Inglis and CSHL Press, the NCBI, and the Academic Editors of the book. However, this first is to the enormous credit and vision of . . . the

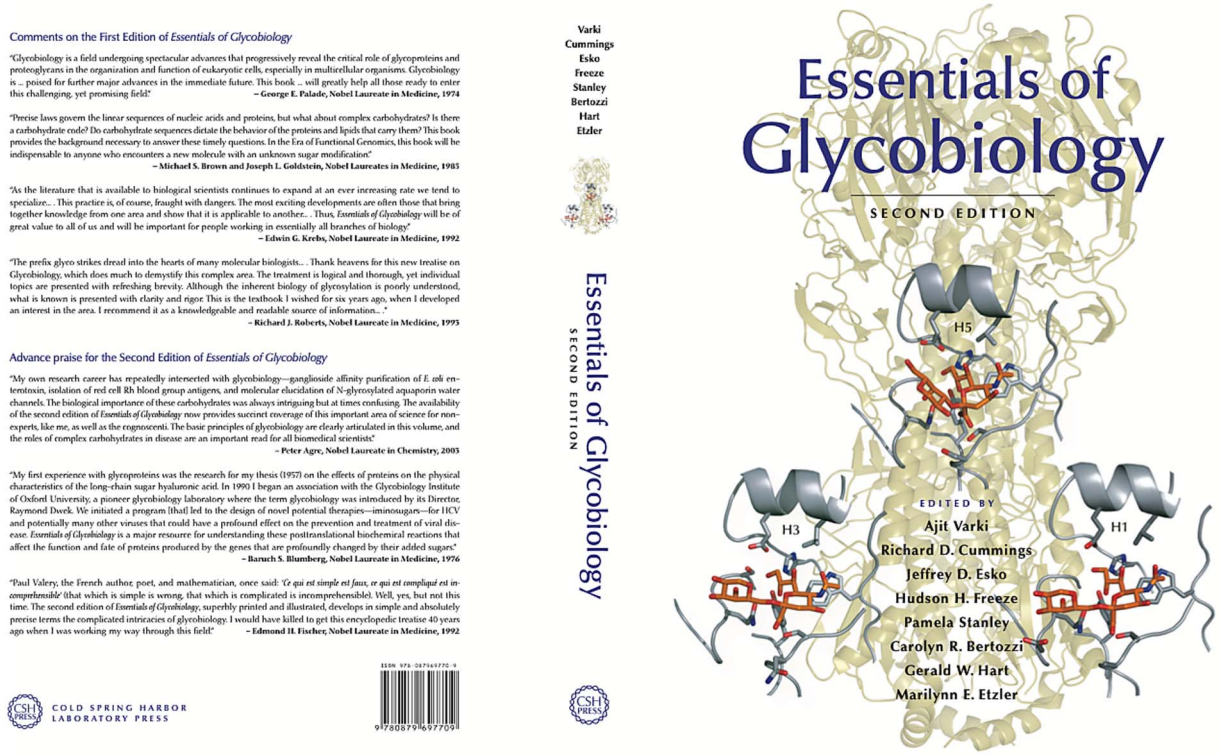

Fig. 2. Cover artwork: Second edition 2009. Influenza a viruses initiate infection by binding to cell-surface sialic acids, via a hemagglutinin molecule (HA). The cover figure background shows a ribbon diagram of the HA structure from the H5N1 influenza strain a/Vietnam/1203/2004 (pdb: 2FKO). The top figure in the foreground shows a sialic acid in an α2–3 linkage to a vicinal galactose, modeled into the receptor binding sites of this H5 "bird flu" strain. An equivalent sialoside in an α2–6 linkage is shown for human H3 hemagglutinin (a/Aichi/2/1968, pdb: 2HMG) and for human H1 hemagglutinin (a/Puerto Rico/8/1934, pdb:1RVZ). The latter strain is derived from the one that caused the great influenza pandemic of 1918. It can be seen that H1 could potentially also accommodate an α2–3 linked sialic acid, explaining at least in part how it jumped directly from birds to humans. (images courtesy of James stevens, Centers for Disease Control and Prevention, Atlanta, Georgia).

editors . . . , who, having labored long and hard to write the book, now seek to maximize its use by all."

Essentials Book Chapters have Assigned PMIDs! Original articles and invited reviews from reputable journals are included in the PubMed resource and recognized by the assignment of a unique PubMed ID. Bookshelf chapters that are individually authored and reviewed at the chapter level, including EoG, were assigned a PMID beginning with the second edition, greatly increasing exposure and a chance of citation (as well as motivation for each author). To date, chapters from the Book have been cited more than 3000 times.

Financial Difficulties. Also critical to the success of this venture were long-term program project grants to the UCSD Glycobiology Research and Training Center (GRTC) and the Department of Cellular and Molecular Medicine from the National Heart, Lung, and Blood Institute (NHLBI). Unlike the case with regular grants, such multiple investigator program projects included a central administration complemented with funds from UC San Diego, which also supported a central editorial office. From the outset the goal was to keep costs as low as possible, and the only income source was a small amount of royalty income from book sales. Making the entire text freely available increased the reach of the book, but potentially reduced sales income. So, it was not clear that that the editors could go forward with the third edition. Given the active involvement of NCBI and the unique nature of the resource, the editors raised the possibility of requesting a small grant from NIH to support the 3rd edition. The NIH Director's office initially responded positively. On the strength of that response, the editors and The Press proceeded with the third edition. However, an NIH administrator later correctly pointed out that the agency could not give out taxpayer money to one group without having a pre-announced open competition. The amount was not huge, but when combined with projected sales of the hard copy version, the uncertainty was almost enough to scuttle the project. Fortunately, an anonymous benefactor came forward with a promise to back up shortfalls as needed, and the plan was back on track. But uncertainties remained about the future. The editors of the CGE (by now registered as a U.S. nonprofit) therefore agreed to do this work purely as a service to the scientific community and will not be accepting any personal income from the book. Rather, we will be assigning any remaining income, after covering production costs, to further the impact of the book in the glycoscience community. Editors of the earlier editions have agreed to forward residual income from that edition toward the same goal.

The Third Edition: Beyond the Usual Suspects (see book jacket cover in Fig. 3).

Major increases in knowledge of glycans made the demand for a new edition arise earlier than before. As headlined in

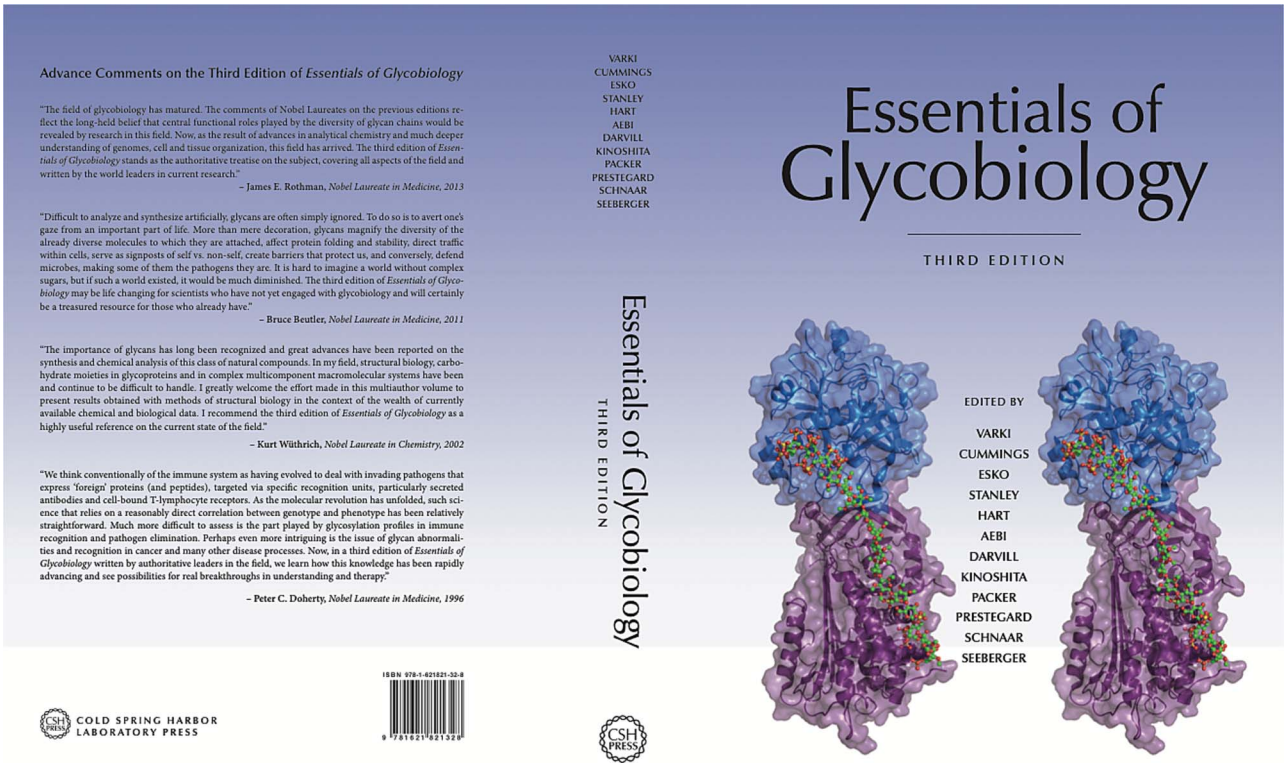

Fig. 3. Cover artwork: Third edition 2017. Stereo view of a crystal structure (1 TB6) of the complex between anti-thrombin (purple), thrombin (blue), and a 16-mer heparin mimetic (SR123781A). The proteins are shown in cartoon with a semitransparent surface, and the oligosaccharide is represented as a ball-and-stick, with carbon in green, oxygen in red, and sulfur in yellow. The oligosaccharide is composed on an antithrombin-specific pentasaccharide based in idraparanux, an uncharged even-saccharide unit linker, and a highly sulfated four residue thrombin-binding unit. Picture courtesy of Jim Huntington, professor of molecular haemostasis, University of Cambridge.

the CSHL Press News item (2017), "*Landmark Glycobiology textbook now available in print and online*." In keeping with the broader reach of the book, the Foreword to this edition was written by Jeffrey Gordon and Lora Hooper (Gordon and Hooper, 2015), experts on topics such as the microbiome, GI mucosal biology etc., who also fully incorporate glycans into their work. They wrote: *Publication of this third edition of Essentials of Glycobiology inspires a look back as well as a look forward. Rarely has a textbook played such a dominant role in defining, reporting, and guiding progress in a field. From a global perspective, the importance of its subject matter is obvious: glycans are the most abundant organic polymers in our biosphere. However, the complexity of these molecules can be intimidating. Glycan biosynthesis occurs in a combinatorial, non-template-driven fashion, in contrast to DNA, RNA, and protein. Glycan biosynthesis and degradation are driven by myriad enzymes, many of whose substrate specificities and kinetic mechanisms remain poorly defined. In addition, glycans perform an immense range of biological functions, serving, for example, as nutrient substrates, as participants in signaling pathways, and as scaffolds for building multicellular "machines." Considering these realities, and the competing allure of many other scientific fields in this rapidly evolving era of genome-driven fundamental and applied science, it is not hard to understand why "glycobiologists" today have become an endangered species. On the other hand, the importance of their field has never been greater. Glycobiology is inherently interdisciplinary and radiates into, as well as being informed and "fertilized" by, so many other areas of biology.*

We all need mentors, and in many ways this textbook has served that function for both nascent and established glycobiologists; it has provoked thinking and provided stewardship as a cogent, consistent, and accessible source of accrued knowledge over its two- (and now three-) edition life span.

This knowledge is also timely as we consider the present and the future. Like many fields, glycobiology has benefited from high-throughput genomics, which has allowed rapid identification of potential glycan-modifying enzymes as well as glycan-binding proteins. This explosion of information is illustrated by the outpouring of microbiome sequencing projects, which are emphasizing how richly endowed microbes are with glycoside hydrolases, polysaccharide lyases, and glycosyltransferases not encoded in the genome of their respective hosts. Moving forward, ongoing analyses of microbial community function will undoubtedly provide new insights into how glycans serve as foundations for nutrient-sharing relationships between primary and secondary consumers in the food webs that sustain these communities. These analyses should also continue to reveal new details about how glycans function as microbial "signposts" recognized and accommodated by the host immune system so that mutually beneficial host–microbial relationships can be established and maintained, whereas in other contexts they are attacked by the immune system or function to cloak pathogens from recognition.

Ongoing improvements in the analytic tools used for characterizing glycan-containing molecules will propel efforts seeking to comprehensively define "glycomes" that comprise all the glycans that can be made by a cell, tissue, or organism as

a function of its differentiation, development, or physiological state. CRISPR-based genome editing tools will provide unprecedented opportunities to precisely manipulate glycan biosynthetic and degradative pathways within cells and thus ascertain the functions of their products. New chemical tools that allow modification of specified glycans in living cells should also facilitate studies of glycan function in different physiological and pathologic contexts. At the same time, improvements in glycan synthetic chemistry are yielding high-diversity libraries that enable the targets of carbohydrate-binding proteins to be determined. These improvements are also allowing specific glycans of interest to be produced in large quantities for a variety of purposes. For these and many other reasons, the readers and editors of this volume face an exciting future for glycobiology and, together, are poised to create that future."

Freely Downloadable Slides of Figures. The efforts of many (especially Editor Richard Cummings) resulted in the generation of figures that were suitable for both teaching and formal lectures. With a few limitations due to copyright issues, the Press and NCBI worked to make these figures as downloadable slides ready for use. There is a convenient page of the UCSD GRTC web site that makes it even easier to find the slides.

The Fourth Edition (see book jacket cover in Fig. 4) was completed during the COVID-19 pandemic, making the choice of the front cover a "no-brainer." Another silver lining was plenty of time to read the hardcover or the online version which were simultaneously published again. We will never know for sure what would have happened without the simultaneous online release, but sales numbers (Table 1) indicate decreasing preference for the paper version (See Table 1.) But this is complicated by the introduction of the freely download able eBook version of the Fourth Edition beginning in September 2022 (2320 downloads, see further details below). Looking at sales/year (see Table 1) may provide a more balanced view of the (not so severe) impact of free online access at NCBI—even harder to be sure about the eBook. Regardless, the persistence of even some hardcopy sales in the face of multiple free electronic versions is consistent with the counterintuitive finding that human minds retain more from hardcopy books than from electronic tablets and pads (Altamura et al. 2025) for reasons possibly involving the book's physical nature, the reduction of cognitive distractions, and the unique way human brains process information from paper versus screens. Of course, the modern human mind completely evolved in Africa >200,000 years, long before the human invention of writing and reading. Regardless, NCBI bookshelf records document >3 million online page views by >1 million unique online users, (see Table 1), affirming that the overall reach of this body of knowledge was much increased by free availability on the Internet.

The Foreword to the Fourth Edition appropriately originated from leaders of three entities that helped to make the project possible: CSHL Press (John Inglis), NHLBI (Rita Sarkar) and NCBI (Stephen Sherry) (Inglis et al. 2022). They wrote: "*The goal of barrier-free access to scholarly information online has preoccupied academic researchers for more than two decades. The debates have focused principally on how to liberate research papers from the constraints of journal subscriptions. But in more recent years, as more journals have become open access, the spotlight has shifted to books, including textbooks, and the challenge of making their content freely available to readers while retaining financial viability. Amid the arguments about paths forward, the 20-year success of Essentials of Glycobiology in achieving the goal is less well-known than it should be. That success is attributable to a unique partnership between two not-for-profit institutions and a consortium of scientist–editors led by the book's executive editor, the indefatigable Ajit Varki.*

The first edition of Essentials of Glycobiology was published in 1999, in the same year that the Director of the National Institutes of Health (NIH), Harold Varmus, proposed creating a freely available archive of all new research manuscripts. The radical "e-BioMed" scheme did not gain traction but pushed by Ajit, then its Editor-in-Chief, The Journal of Clinical Investigation was already making all its articles freely available online at publication. This bold gambit had greatly expanded the readership of the journal's content. Inspired by this success, and as an energetic proselyte for the emerging, cross-disciplinary field of glycobiology, Ajit was eager to give his field the widest possible audience. So, on publication of the textbook, discussion began with its publisher, Cold Spring Harbor Laboratory Press, about ways of making its content freely available. The idea of an open-access book was intriguing to an institution with a 100-year history of innovation in the communication of science.

The National Center for Biotechnology Information (NCBI), a division of the National Library of Medicine at NIH, was led by another entrepreneurial scientist interested in breaking barriers to information flow, David Lipman. Among NCBI's innovations was the creation of Bookshelf, a platform for open distribution of book content. Brokered by Ajit and his colleagues, the Consortium of Glycobiology Editors, who collectively owned the copyright of Essentials in Glycobiology, an agreement was forged between the Laboratory and NCBI that enabled the full text of the book to be discovered, searched, and read online on the Bookshelf, while the print edition remained available for sale through the Press. The risk, seemingly significant at the time, was that the availability of a free, high-quality rendition of the book's content online would limit print sales and prevent the Press from recovering the investment required to create the book.

The online edition of Essentials appeared in 2003, and its usage was substantial, with hundreds of people each week from all over the world continuing to consult it even five years later. The content was discoverable through indexing by major search engines, citations in Wikipedia, listing and linking by libraries, and entries in PubMed. And gratifyingly, interest in the print edition did not appear to waver. So, in 2008, when a second edition of Essentials was ready for publication, another bold decision was taken, to release both the print and Bookshelf editions simultaneously, the first time this had been done with a major textbook. And once again, the gambit paid off, as sales of the print book prospered while usage of the online content was brisk. The same approach was adopted for the third edition in 2017. And now, for this fourth edition, the project continues to evolve, as the freely accessible Bookshelf edition is released simultaneously with both a print edition and an e-book downloadable exclusively from the Press website that can be read easily on a variety of portable devices.

Nearly two decades after the editors, NCBI, and the Press embarked on this joint venture, devotees of glycobiology have

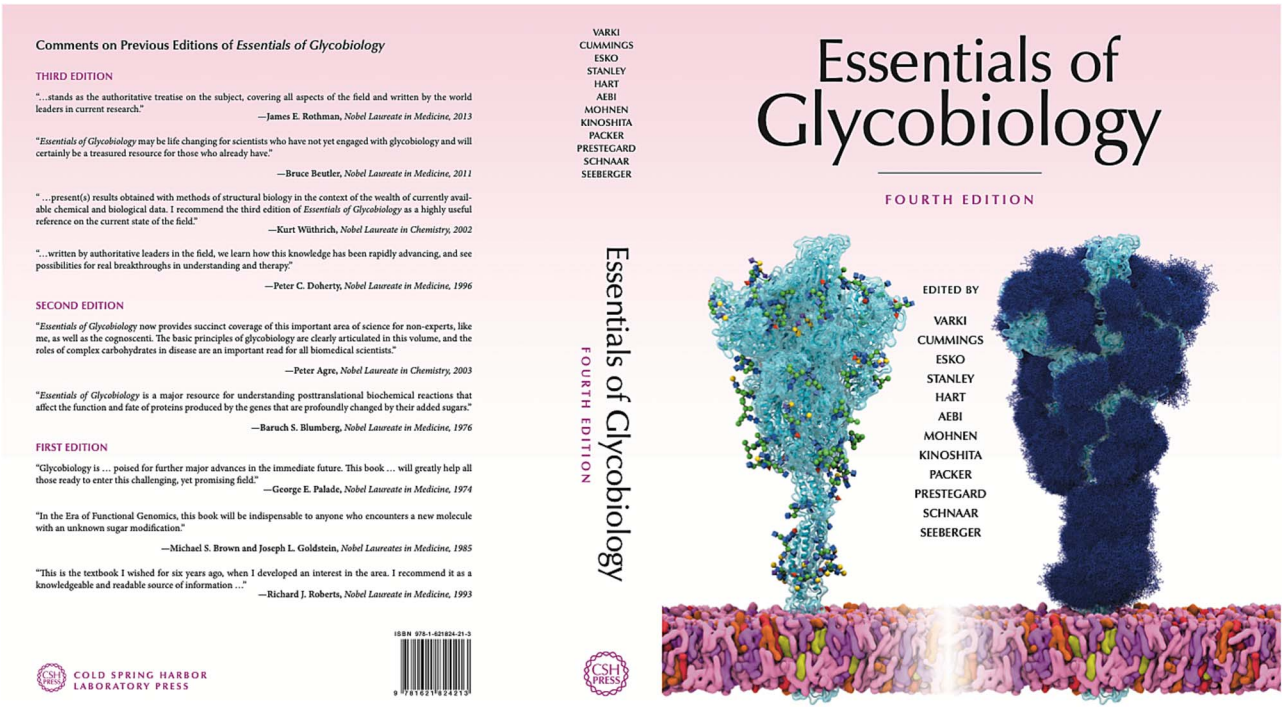

Fig. 4. Cover artwork: Fourth edition 2022. Molecular representation of full-length, fully glycosylated, all-atom model of the SARS-CoV-2 spike protein in the open state, embedded in the viral membrane. The spike model was developed by Casalino et al. (ACS cent sci 6: 1722–1734 [2020]) based on a cryo-EM structure by Wrapp et al, (science 367: 1260–1263 [2020]) and Shajahan et al. (glycobiology 30: 981–988 [2020]). On the left, the full-length SARS-CoV-2 spike in the open state-that is, with one receptor binding domain (RBD) in the "up" conformation-is shown with a cyan transparent surface overlaid on the cartoon representation of secondary structure. Conformation of the spike was selected from molecular dynamics simulations performed by Casalino et al. (ACS cent sci 6:1722–1734 [2020]). N- and O-linked glycans are depicted using the symbol nomenclature for glycans (SNFG), in which blue filled squares are N-acetyl-D-glucosamine (GlcNAc); green circles are D-mannose (man); yellow squares are N-acetyl-D-galactosamine (GalNAc); yellow circles are D-galactose (gal), red triangles are L-fucose (Fuc); and purple filled diamonds are N-acetyl-D-neuraminic acid (Neu5Ac). The lipid bilayer of the viral membrane is depicted with a surface representation, in which the POPC (1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine) is colored pink, POPE (1-palmitoyl-2-oleoyl-sn-glycero-3-phosphoethanolamine) in purple, POPI (1-palmitoyl-2-oleoyl-sn-glycero-3-phosphoinositol) in orange, POPS (1-palmitoyl-2-oleoyl-sn-glycero-3-phosphoserine) in red, and cholesterol in yellow. On the right, the glycan shield (dark-blue bush-like structures) in the spike protein (cyan transparent surface) is shown by overlaying multiple conformations of the N- and O-linked glycans obtained at multiple, interspersed frames along 1 msec of molecular dynamics simulations (Casalino et al. ACS cent sci 6: 1722–1734 [2020]). For each glycan, each conformation sampled along the dynamics is shown with dark-blue sticks. When multiple conformations of each glycan are overlaid, they form a protective bush-like structure providing a visual representation of the extent of protein surface covered over a specific time frame. When the receptor-binding domain (RBD), located in the apical portion of the spike, is in the "up" conformation, it emerges from the glycan shield (as shown in the image with a transparent cyan surface) and becomes available for binding to angiotensin-converting enzyme 2 (ACE2) receptors on the host cell, initiating infection. Artwork designed and created by Lorenzo Casalino in the Amaro laboratory (UC san Diego).

Table 1. Sales and online usage of *essentials of glycobiology* (as of August 2025).

Publication date	Edition	Copies sold	Sales period	Yearly sales[a]	Total online page views	Unique viewers	Pubmed citations
Aug1999–2001	First Edition	2765	3 years	920	NA	NA	NA
Aug 2002–2008	First Edition (Paperback)	1738	6 years	290	208,049	119,158	NA
Oct 2008–2017	Second Edition (Hardcover)	2718	9 years	302	924,193	353,024	2497
Aug 2017–2020	Third Edition (Hardcover)	1460	3 years	486	933,938	318,295	685
May 2020–2025	Fourth Edition (Hardcover)	747	3 years	249	949,873	351,559	347
Sept 2022	Fourth Edition (Free eBook)	2360[b]	NA	NA	NA	NA	NA

NA: Not applicable or not available [a]Numbers rounded off [b]Downloads of the free Fourth Edition

more choices than ever in how they consult and use the content of the latest Essentials. Tastes and information habits have changed greatly during that time—a print edition of such a large book now has much less appeal to readers, despite the elegance of its design and illustrations by Consortium member Rick Cummings and its high production values. But the mission of Essentials has not changed. The Consortium of Glycobiology Editors remains substantially intact but has also recruited a new generation of younger authors who can carry the torch forward in the future. With each edition, they collectively strive to create an up-to-date knowledge resource that will satisfy established investigators but also entice new recruits to the study of the important, diverse, and expanding biology of the glycans. CSHL Press and successive leaders at NCBI remain committed to ensuring that the information the editors have curated reaches the widest possible audience, however and wherever those individuals want to use it. On behalf of our organizations, we congratulate The Consortium

of Glycobiology Editors on creating another remarkable, important, and pioneering contribution to the literature of Glycoscience."

Spinoffs from the Fourth Edition: as the book got bigger, some of the information had to be off-loaded into appendices that the NCBI made available and a few of these emerged as separate spinoffs. The most prominent was Online Appendix 1B. Symbol Nomenclature for Glycans (SNFG), (Varki et al. 2015) which was developed as a collaboration amongst the editors of the book, and a community advisory group. Updates are now managed by Sriram Neelamegam and the SNFG Discussion group (Neelamegham et al. 2019).

The history below is verbatim from the NCBI website (under History of the SNFG). "*Issues regarding nomenclature tend to more controversy than scientific ones, as there is never one correct answer, and some aspects are matters of opinion and taste. In 1978, Kornfeld and colleagues presented a system for symbolic representation of vertebrate glycans, which enjoyed popular use and was eventually adopted and standardized for the first edition of the Essentials of Glycobiology textbook (1999). While this adoption increased usage, the system had limitations and did not use color. Anticipating a second edition, the editors updated the nomenclature and made it available to the community in 2004 before publication. This was widely adopted and disseminated, especially by the NIGMS-funded Consortium for Functional Glycomics (thus sometimes being referred to as the "CFG Nomenclature"). After final publication of the Second Edition in 2009, acceptance by the community remained incomplete, and individual variations began to appear. Anticipating a third edition, a reorganized group of Essentials editors (supported by the NHLBI-funded Programs of Excellence in Glycoscience) further refined and updated the symbol nomenclature, this time reaching beyond vertebrate glycans and considering input from others using related systems. The editors also coordinated with the IUPAC Carbohydrate Nomenclature committee, linked each monosaccharide symbol to the corresponding entry in PubChem at NCBI/NLM, and initiated coordination with other long-term online resources. The system became an online advance Appendix to the Third Edition of Essentials. New symbols were added, but to ensure compatibility with prior publications, no changes were made to symbols in the Second Edition. For this historical reason, chemical features and configurations associated with shapes and colors are internally consistent only for some monosaccharides. For example, many of the nonulosonates do not conform to the stereochemical features otherwise represented in specified columns. Symbol colors are specified in CMYK and RGB settings. Linkages can be shown as in the Second Edition system using IUPAC style, with the originating carbon assumed, and hyphens (not commas) used as an option. The Oxford system of angled monosaccharide linkages with embedded specificity and anomericity can also be used.*

The system is widely accepted in the literature and adopted by many major journals. The efforts of the SNFG represent another step towards mainstreaming glycan bioinformatics. This is a critical step towards completing the description of the molecular and cellular features. of all living systems. Following the initial release in 2015, the SNFG discussion group worked with the NCBI and PubChem to generate periodic SNFG updates. Some key features include downloadable files: Drawing format | Presentation/Slide format.

Each symbol in the main SNFG table (see Fig. 5) represents a specific monosaccharide or class of monosaccharides found in nature. One can hover over a symbol with a pointer to see the monosaccharide name. Clicking on a symbol will link to the corresponding PubChem entry. Symbols can also be copied, with embedded links from the table using right/control-click or highlight-copy (highlight a symbol, then control-c [on pc], or command ⌘-c [on mac]). However, links may not be copied in some browsers. Symbols with embedded PubChem URLs are therefore also available in the presentation/slide. A high-quality SVG object file is also provided. Online Appendix 52A of the book at NCBI lists Organizations and Publications Adopting SNFG, but a systematic effort to make this system universal has not yet been undertaken.

Troubles with Symbol Symmetry, Fucose, and the Revenge of the Red Diamond.

Thus far, this historical summary has been rather dry and factual, suggesting a smooth coordinated process with minor exceptions. In fact, behind the scenes, the present writer and some of the other editors dealt with many small, medium and large issues and outcomes, ranging from the sublime to the ridiculous. Space does not allow full exposition, but the following example is illustrative.

When the use of symbols was started by Kornfeld and colleagues, most were symmetrical, and their appearance did not change with rotation. The exception was the triangle representing 6-deoxyhexoses such as fucose, and complaints from the community emerged. However, a rule of thumb for developing arbitrary scientific nomenclature is to not change from the original assignment unless necessary. As a compromise, note 4 from the main SNFG Table was modified to state that each colored symbol encodes a defined monosaccharide (including D or L) independent of rotation or mirroring. But meanwhile the "focus on fucose" uncovered another problem. Given the high frequency of red-green color blindness, especially in males, it is standard practice not to use both colors in one figure. But somewhere along the way fucose had been colored red. The updated system aimed to use a periodic table approach to different configurations of monosaccharides which would mean that fucose should be yellow (L-Galactose configuration). The attempt to make this change from a red symbol for fucose was met with howls of protest from many, who did not wish to modify their existing personal slide sets. Unlike the case with the symmetry issue, there was no compromise possible, and the symbol for fucose remained red.

Meanwhile the present writer faced a problem with the assignment of colors to sialic acids, type unknown. In general, the SNFG system used white symbols for unknowns, e.g. white circle is a hexose, type unknown (see first row in the table). The problem with applying this approach to sialic acids was that the white diamond had already been taken by the broader category of nonulosonic acids) (Lewis et al. 2023). Thus, final assignment of red color of fucose *was held hostage* until the agreement was made that a red diamond could be *a sialic acid, type unknown*!

A periodic table of monosaccharides. The current SNFG table does not include all the possible monosaccharides. In a recent paper (Cummings 2024), a rationale is given for construction of a more extended periodic table with a selection of 103 monosaccharides, which is largely based on those presented in the KEGG and SNFG websites, and includes room to enlarge as new discoveries are made.

Fourth Edition of *Essentials of Glycobiology*—Appendix 1B: Symbol Nomenclature for Glycans (SNFG)

Symbol Nomenclature for Graphical Representation of Glycans, Glycobiology 25: 1323-1324, 2015. Citation link (PMID 26543186).
Updates to the Symbol Nomenclature for Glycans guidelines, Glycobiology 29:620-624, 2019. Citation link (PMID 31184695).

Table 1. Monosaccharide symbol nomenclature

SHAPE	White (Generic)	Blue	Green	Yellow	Orange	Pink	Purple	Light Blue	Brown	Red
Filled Circle	Hexose	Glc	Man	Gal	Gul	Alt	All	Tal	Ido	
Filled Square	HexNAc	GlcNAc	ManNAc	GalNAc	GulNAc	AltNAc	AllNAc	TalNAc	IdoNAc	
Crossed Square	Hexosamine	GlcN	ManN	GalN	GulN	AltN	AllN	TalN	IdoN	
Divided Diamond	Hexuronate	GlcA	ManA	GalA	GulA	AltA	AllA	TalA	IdoA	
Filled Triangle	Deoxyhexose	Qui	Rha		6dGul	6dAlt		6dTal		Fuc
Divided Triangle	DeoxyhexNAc	QuiNAc	RhaNAc			6dAltNAc		6dTalNAc		FucNAc
Flat Rectangle	Di-deoxyhexose	Oli	Tyv		Abe	Par	Dig	Col		
Filled Star	Pentose		Ara	Lyx	Xyl	Rib				
Filled Diamond	3-deoxy-nonulosonic acids		Kdn				Neu5Ac	Neu5Gc	Neu	Sia
Flat Diamond	3,9-dideoxy-nonulosonic acids		Pse	Leg		Aci		4eLeg		
Flat Hexagon	Unknown	Bac	LDmanHep	Kdo	Dha	DDmanHep	MurNAc	MurNGc	Mur	
Pentagon	Assigned	Api	Fru	Tag	Sor	Psi				

When viewed in presentation/slide-show mode, clicking individual monosaccharide names or symbols will lead to corresponding PubChem page.
Right/Control click to copy a symbol, along with the embedded PubChem URL, which will also remain when pasting into some word-processing applications.

Fig. 5. Summary slide downloaded from the Symbol Nomenclature for Glycans (SNFG) web site. *Each symbol represents a specific monosaccharide or class of monosaccharides found in nature. Hover over the symbol with pointer to see the full monosaccharide name. Click on a symbol to link to the corresponding PubChem entry. Symbols can also be copied with embedded links from the table using right/control-click or highlight-copy (highlight a symbol, then control-c [on pc], or command ⌘-c [on mac]). However links may not copy in some browsers. Symbols with embedded PubChem URLs are therefore also available in the presentation/slide format attachments (see links above the table).* Save the slide as a PDF wherein links are preserved.

The NCBI Glycans Page: The tail wagging the dog? Initial presentation of the SNFG at the NCBI website was not possible because an intermediate page was needed for linking from the main NCBI site. Evan Bolton at PubChem and others interested in searchable glycan databases were able to establish an NCBI Glycans page which states the following: "*Glycans (carbohydrates, sugars, monosaccharides, oligosaccharides and polysaccharides) are widely distributed in nature, in all living life forms. There is much useful glycoscience content at NCBI, including many* publications) *discussing glycans, chemical records containing glycans, macromolecules containing glycans, biosynthetic pathways involving glycans, proteins and genes involved in glycobiology, diseases involving glycans, and books dedicated to glycoscience. This page, as a dedicated glycan information site in NCBI, highlights some useful resources for better integrating the study of glycans into the mainstream of biology, and will be further developed over time, based on interest and usage by the scientific community.*" As with the SNFG page there is The Glycan Informatics Advisory Group (GlyAG).

Status of Related Databases and Resources. In parallel with efforts on the book, many related databases and resources have developed and are summarized in recent papers (Kinoshita et al., 2023; Kim et al. 2025). "*Glycoscience data content in the NCBI Glycans and PubChem provide glycan-related information useful for the glycoscience research-focused, large-scale public chemical database, containing a substantial number of glycoscience resources like GlyTouCan, GlyCosmos, Glycomics@Expasy and GlyGen. PubChem organizes glycan-related information within multiple data collections (i.e., Substance, Compound, Protein, Gene, Pathway, and Taxonomy) and provides various tools and services. GlyCosmos is a portal for glycan-related repositories, including GlyTouCan, GlycoPOST, and UniCarb-DR, as well as for glycan-related data resources that have been integrated from a variety of 'omics databases. Glycoproteins, lectins, pathways, and disease information related to glycans are also accessible from GlyCosmos. The GlySpace Alliance is making efforts to coordinate between these various database and software developers. Glycogenes, glycoproteins, lectins, pathways, and disease information related to glycans are also accessible from GlyCosmos. The GlySpace Alliance is making efforts to coordinate between these various database and software developers.*"

Free Public Access E-book Version. In 2021, the executive editor of the Book was invited to participate in a new venture called the InterVenn Alliance for Translational Glycobiology, which eventually did not go forward, but provided an opportunity for CSHL Press to create a free Public Access E-book edition of the textbook. Excerpts from the press release about this event are reproduced here. *Cold Spring Harbor Laboratory Press (CSHL Press), a publisher of scientific books, journals, and electronic media, today announced a new initiative to broaden access to the expanding science of glycobiology. Supported by an unconditional grant from InterVenn Biosciences, a clinical technology company leveraging glycoproteomics to transform the future of healthcare, the e-Book of Essentials of Glycobiology (Fourth Edition) published by CSHL Press is being made available to readers free of charge, ensuring equitable access for all biologists and translational researchers throughout the world. Essentials of Glycobiology has become the gold standard textbook and key reference work in this field over the past 20 years. The Fourth edition of the book, which was thoroughly revised earlier this year, has an expanded international editorial board and a diverse panel of contributing authors, representing a wide range of expertise in emerging areas. Other key enhancements include a broadened focus on all lineages of life-forms in nature, increased coverage of topics, and in-depth attention to informatics and the exploration of the glycome and the glycoproteome. Most of the figures—many featuring artwork by one of the book's editors, Richard Cummings of Harvard University—are also downloadable for nonprofit and teaching purposes. "The editors of the book are very pleased about the opportunity provided to make the text available as an e-book to all interested audiences," said Dr. Ajit Varki, Distinguished Professor, University of California at San Diego, and Executive Editor of the textbook. "Awareness of the importance of glycobiology and glycoscience among a range of life science and biomedical constituencies still has a long way to go, and free access for all to the e-book represents an important step in raising visibility for the discipline, building on the editors' long-standing commitment to open access* via *the* NCBI/NLM Bookshelf."

"*We are grateful to InterVenn for the support that allowed the distribution of Essentials of Glycobiology as a free, fully featured, downloadable e-book" said Dr. John Inglis, Executive Director at CSHL Press. "This initiative increases the diversity of this valuable content's availability and aligns with the open science goals of CSHL Press."*

Looking Back to the Future. As it happens this article is written close to the 25th anniversary of the first release of the textbook. The time has come for many of the original editors to step away and pass the baton to a new generation. Editors who remain members of the CGE have initiated a search for a new editor in chief of a 5th edition led by Pamela Stanley, current chair of the CGE. The present writer will continue as executive editor of the Fourth Edition but has recused himself from voting in the search process. Meanwhile, both the NCBI (now led by Kim Pruitt, Acting Director) and CSHL Press have indicated an interest in the possibility of continued collaboration going forward.

> "*There is a tide in the affairs of men. Which, taken at the flood, leads on to fortune; Omitted, all the voyage of their life is bound in shallows and in miseries. On such a full sea are we now afloat; And we must take the current when it serves or lose our ventures.*"
> — *Julius Caesar* (William Shakespeare)

Acknowledgments

Space does not allow recognition of numerous individuals who made all this happen over the last 25+ years. As it happens, many of them are named in the preface to the 4th edition https://www.ncbi.nlm.nih.gov/books/NBK579937/. Complete listings of editors and contributing authors can be found at NCBI, for the Second Edition: https://www.ncbi.nlm.nih.gov/books/NBK1902/#contrib.s1; the Third Edition: https://www.ncbi.nlm.nih.gov/books/NBK453093/; and the Fourth Edition: https://www.ncbi.nlm.nih.gov/books/NBK579917/.

The CSHLP Team included Denise Weiss, Kathleen Bubbeo, Inez Sialiano, Carol Brown, Mala Mazzullo, Steve Nussbaum, and Robert Richmond. The Press worked with several NCBI Bookshelf leaders to release online versions of EoG, Initially Jo McEntyre, then Marilu Hoeppner, and currently Stacy Lathrop. Evan Bolton and Jian (Jeff) Zhang at PubChem lead efforts to coordinate with Bookshelf. The SNFG GlycoBook Coordinators at UCSD GRTC over the years include Melanie Nieze, Susan Korosy, Gaylene Eisenach, Tracy Gilstrap, and currently Amanda Cuervo.

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Note added in proof

The Consortium of Glycobiology Editors is pleased to report that Professors Lance Wells and Michael Tiemeyer of the University of Georgia and the Complex Carbohydrate Research Center (CCRC) have agreed to be the co-executive editors of the fifth edition of Essentials of Glycobiology.

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