The NIH Common Fund Glycoscience Program

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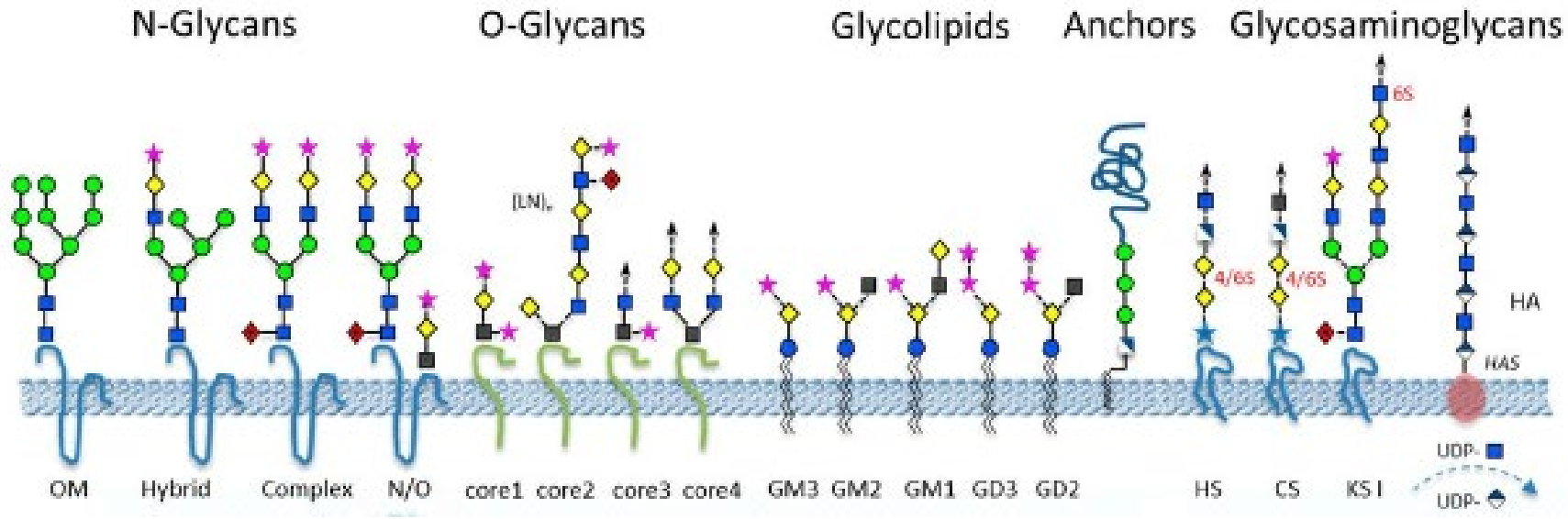
January 25, 2024

National Institutes of Health
Office of Strategic Coordination–The Common Fund

Glycoscience

Glycans:
Information rich, structurally diverse, can themselves be modified, & play key roles in nearly every aspect of human biology and disease.

Major classes of glycan



Science 03 Jan 2014:
Vol. 343, Issue 6166, 1235681

Pragmatic Issues in Glycoscience

Glycoscience a highly specialized field

- Many technical challenges
- Not enough experts to help newcomers

Specialized Expertise, Methods, Instruments

- Cost of capital equipment (NMR, MS)
- Dedicated personnel
- Access

Ambiguity in structure determination

- Glycan microheterogeneity
- Branching
- Isomeric monosaccharides
- Linkage positions, stereochemistry

Lack of:

- Ready access to synthetic oligosaccharides
- Analytical and Computational Tools
- Databases
- High throughput platforms
- Training for non-specialists

The Glycoscience Traffic Jam

2012 Transforming Glycoscience: A Roadmap for the Future

In 2012, NIH commissioned a NASEM study on the field of Glycoscience.

Committee on Assessing the Importance & Impact of Glycomics & Glycosciences
National Research Council, National Academy of Science

The Study Noted:

- *Glycans play central roles in most biological processes*
- *Understudied due to a lack of tools to probe their often-complex structures and properties.*

Identified Priorities:

A roadmap for transforming glycoscience ***from a field dominated by specialists to a widely studied and integrated discipline****, which could lead to a more complete understanding of glycans and help solve key challenges in diverse fields.*

This led to development of the NIH Common Fund Glycoscience program.

https://nap.nationalacademies.org/catalog/13446/transforming-glycoscience-a-roadmap-for-the-future

NIH Common Fund Glycoscience Program

Goal: Create accessible methods and resources to study glycans for use by the broader biomedical research community.

Total Investment: $111M over 7 years

Initiative 1: Facile methods and technologies for **synthesis** of biomedically relevant glycans ($38M)

Initiative 2: Accessible **analytical tools** for structure determination and functional assays ($55M)

Initiative 3: **Informatics tools** for data integration and analysis ($10M)

Initiative 4: Supplements to non-specialists to support **early adoption** of program resources ($5.7M)

Activity Code	# Awards	FY15	FY16	FY17	FY18	FY19	FY20	FY21
Synthesis								
U01	6	■	■	■	■			
	6		■	■	■	■		
	6			■	■	■	■	
Tools								
R21	13	■	■					
	17		■	■				
U01	2	■	■	■				
	3		■	■	■			
	9			■	■	■		
	8				■	■	■	
	7					■	■	■
Informatics								
R34	2	■	■					
U01	1			■	■	■	■	■
Supplements for Early Adoption								
Supplement	7						■	
Supplement	11							■

Common Fund Glycoscience Working Group

Co-Chairs
Jon Lorsch, Director, NIGMS
Martha Somerman, Director, NIDCR

OSC Trio Staff
Ananda Roy
Jessica Smith
Tony Casco
Brionna Hair

Program Coordinators/Project Leaders
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Douglas Sheeley, NIGMS (NIDCR, OSC)
Karl Krueger, NCI
Amanda Melillo, NIDCR (NIGMS, NIDCR)
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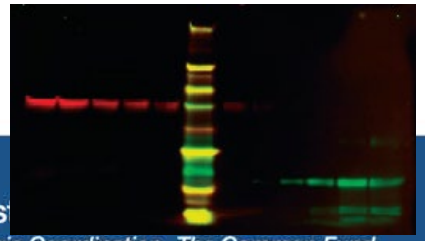
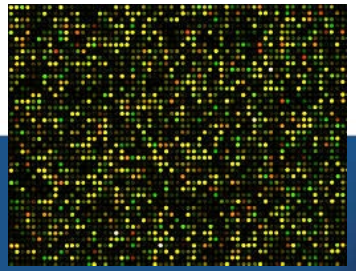
The Glycoscience Program Created an Accessible “Glyco Toolbox”

- New catalytic & chemoenzymatic methods for the synthesis of glycans/ glycan libraries are in place.
- Automation platforms that can be easily adapted by Cores are available.
- Analysis, labeling, and modeling tools/technologies with demonstrated proof-of-concept and public health relevance are being commercialized.
- A unified informatics effort is moving forward to integrate glycoscience with other molecular databases.
- The Human GlycoEnzymes are commercially available.

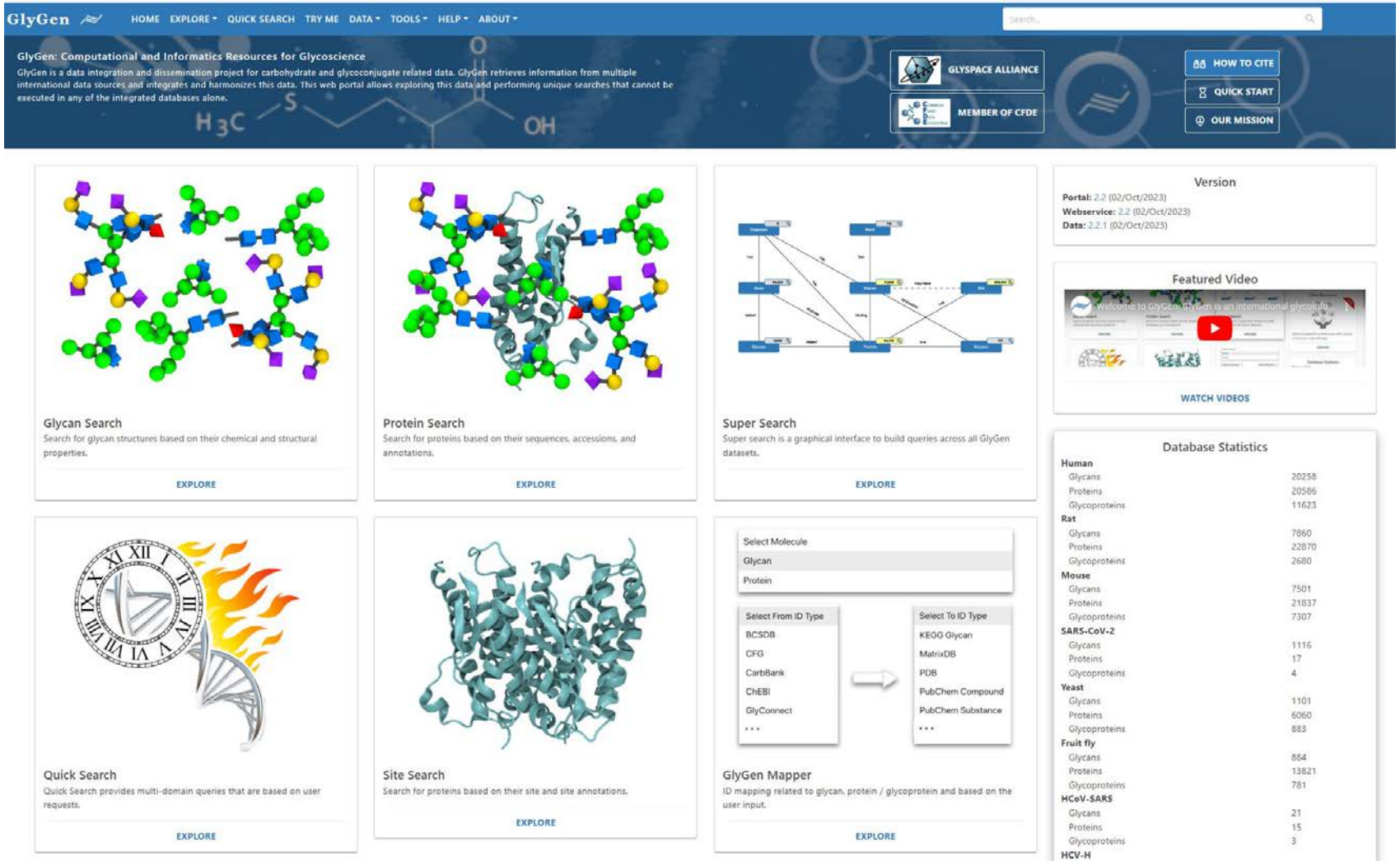




GlyGen

Computational and informatics resources and tools for glycosciences research

- **Training Resources**
- **Integration with protein and glycan databases worldwide**
- **Quick Search:** Multi-domain queries based on user requests
- **Super Search:** GUI to build queries across all GlyGen datasets

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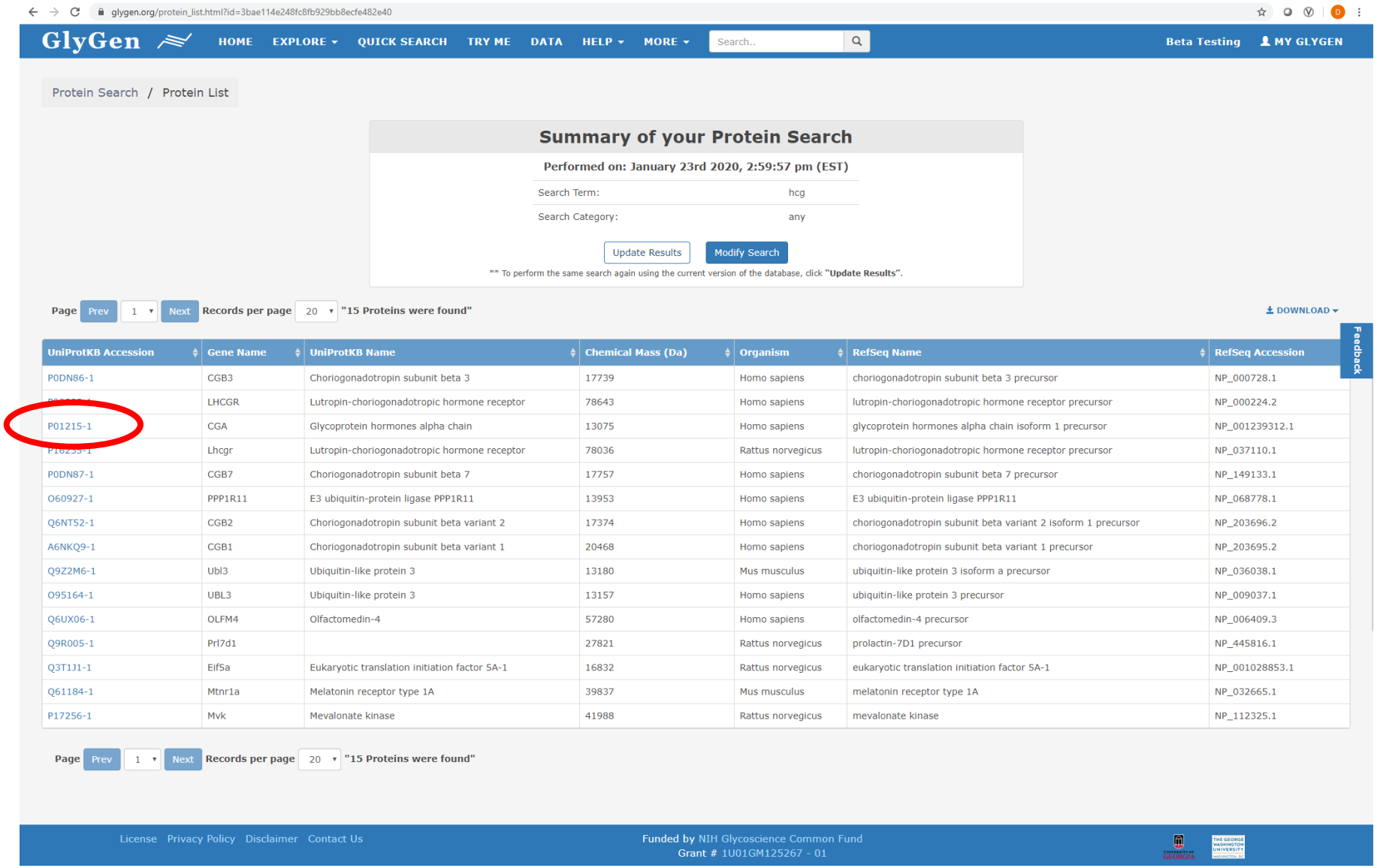
http://www.glygen.org

Protein Search for “hcg” (Human Chorionic Gonadotropin)



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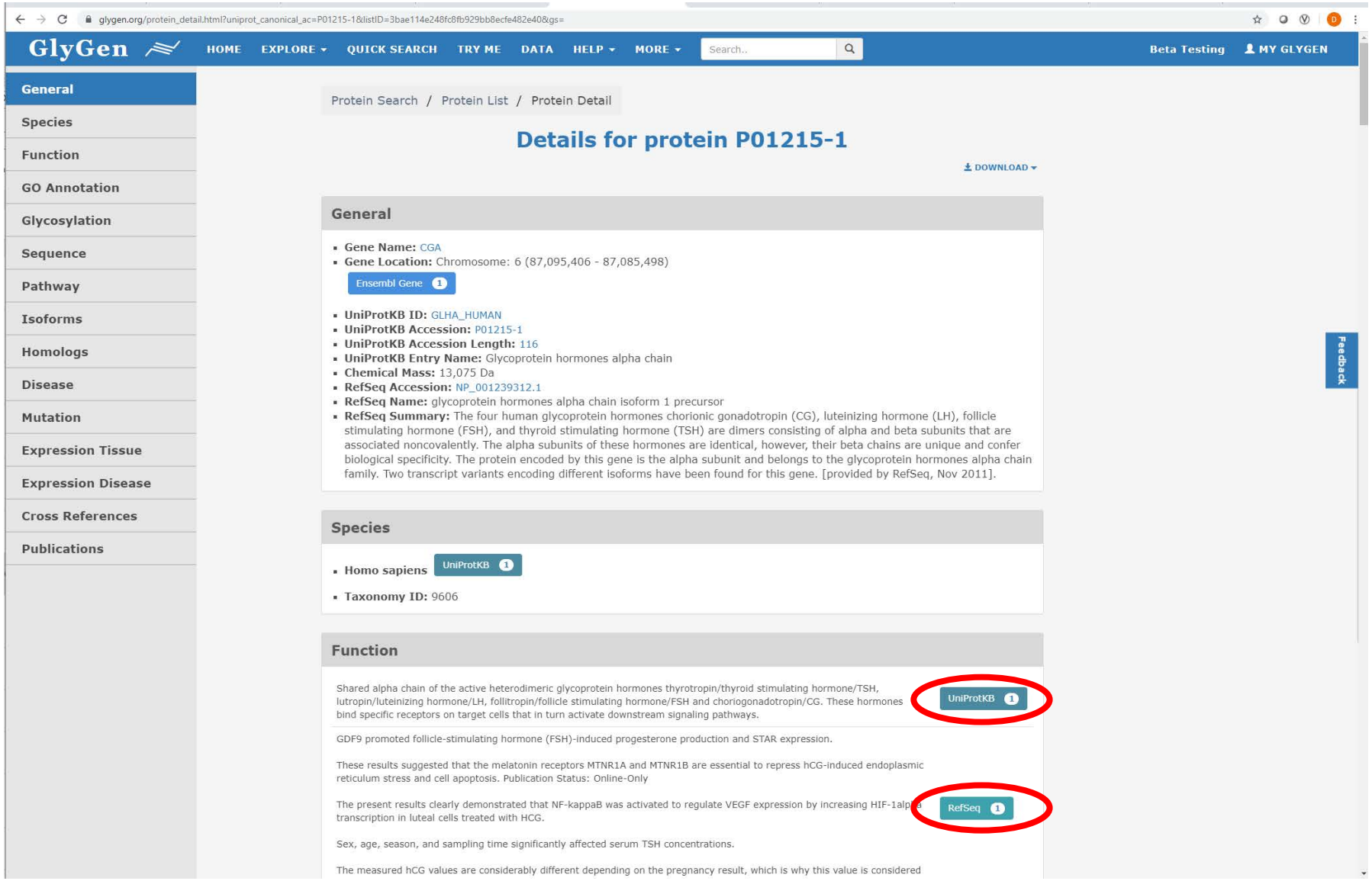
Protein information from UniProt for Glycoprotein Hormone Alpha Chain



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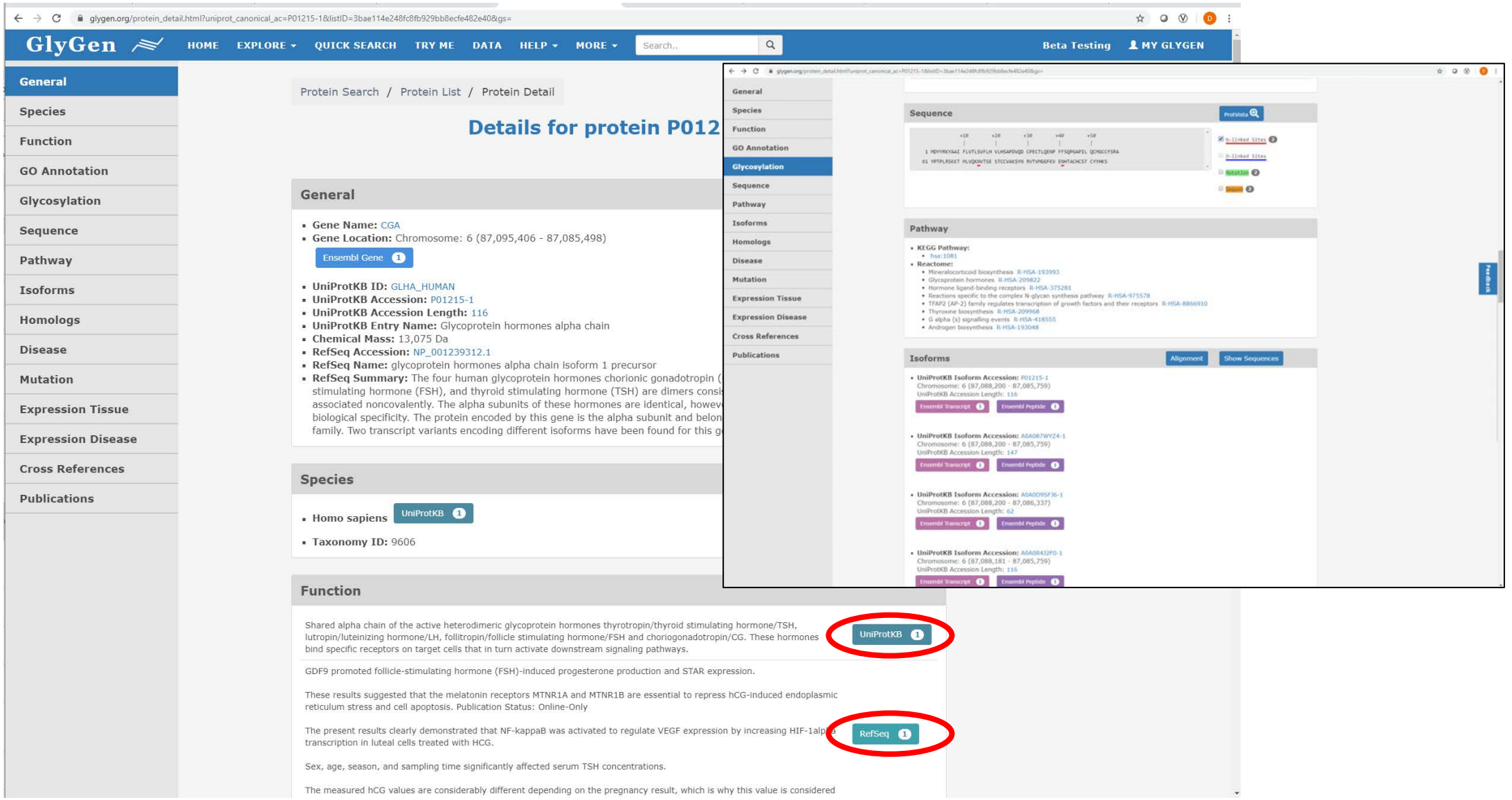

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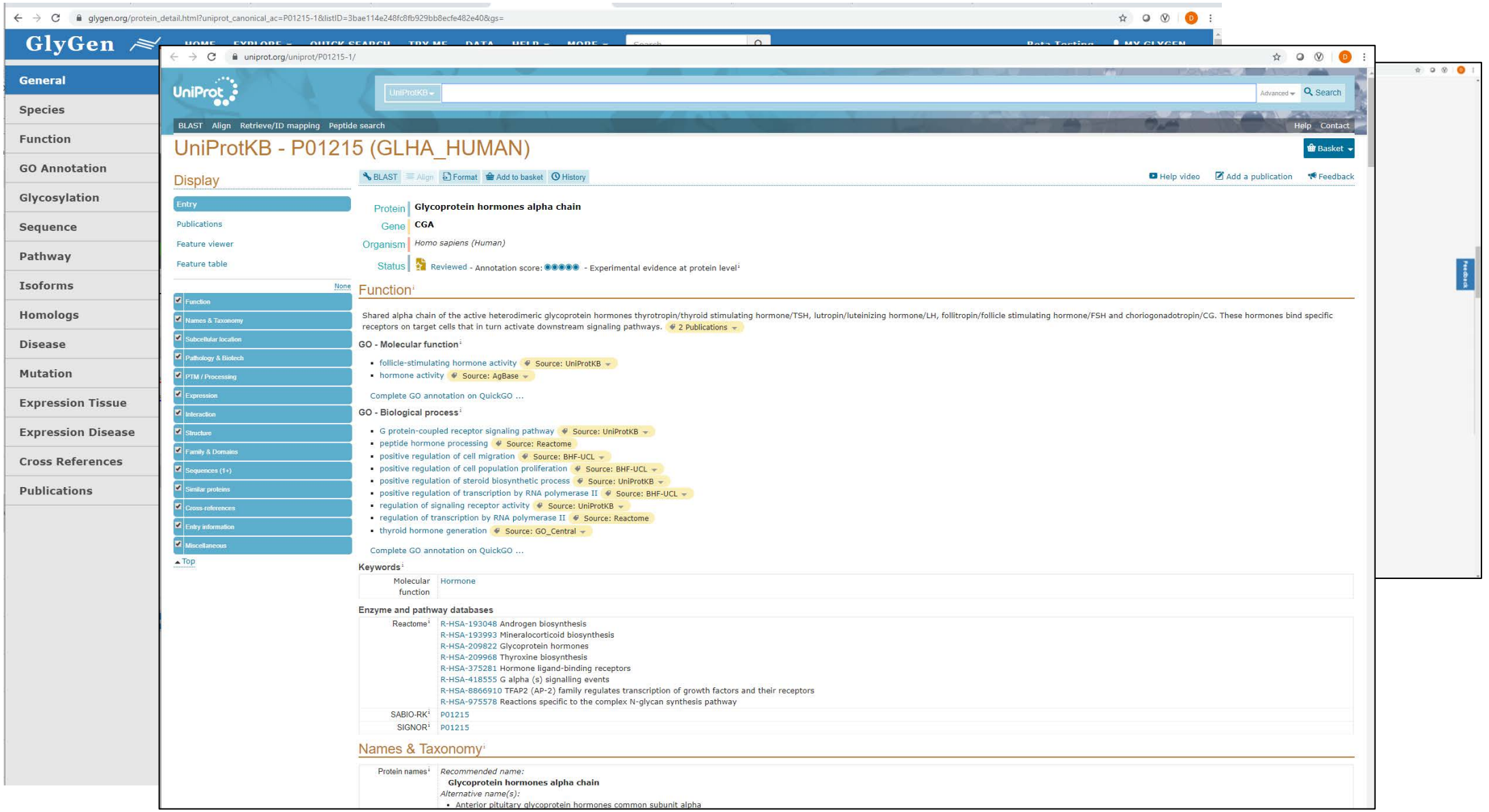
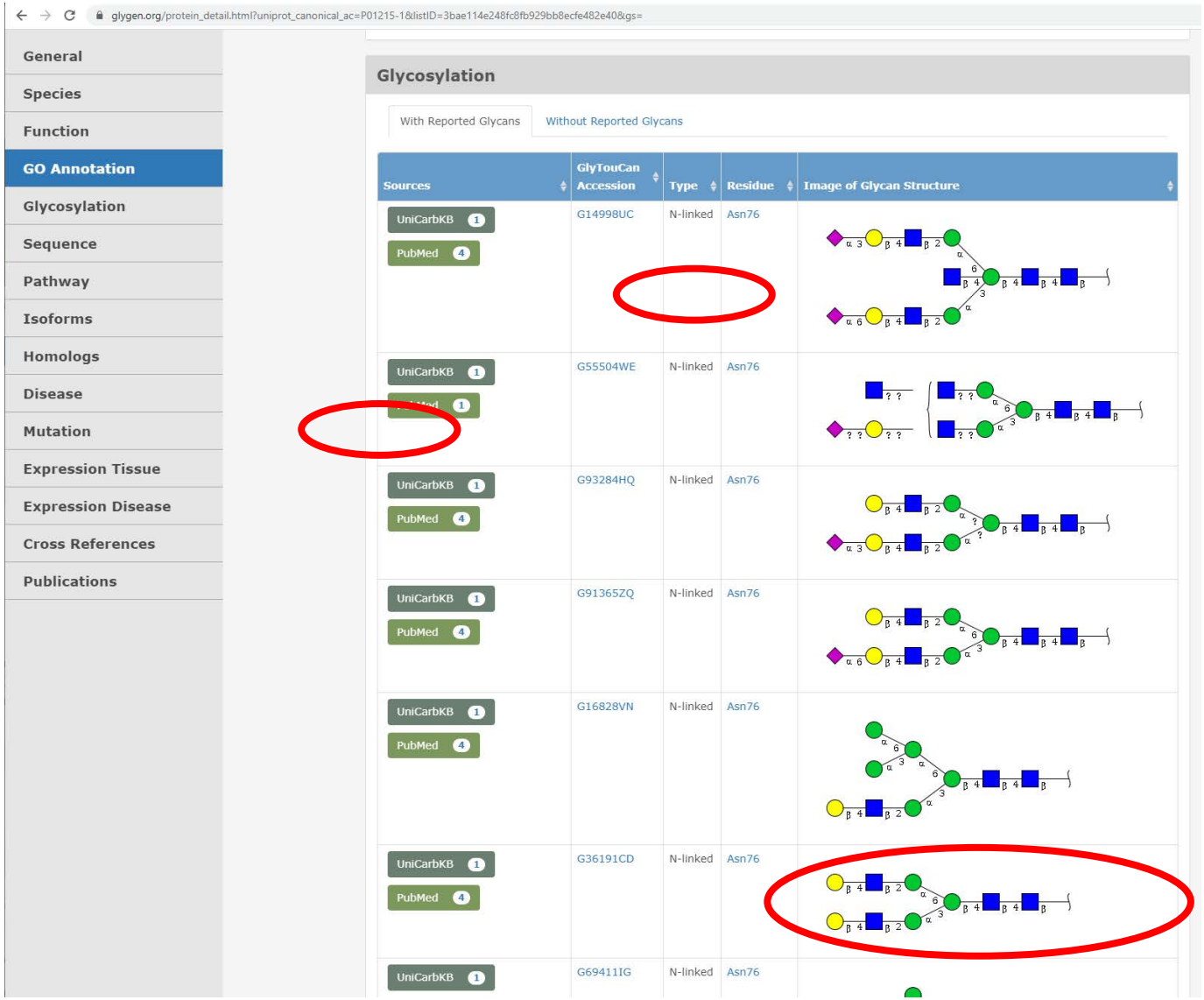


Protein Glycosylation Information: Glycoprotein Hormone Alpha Chain



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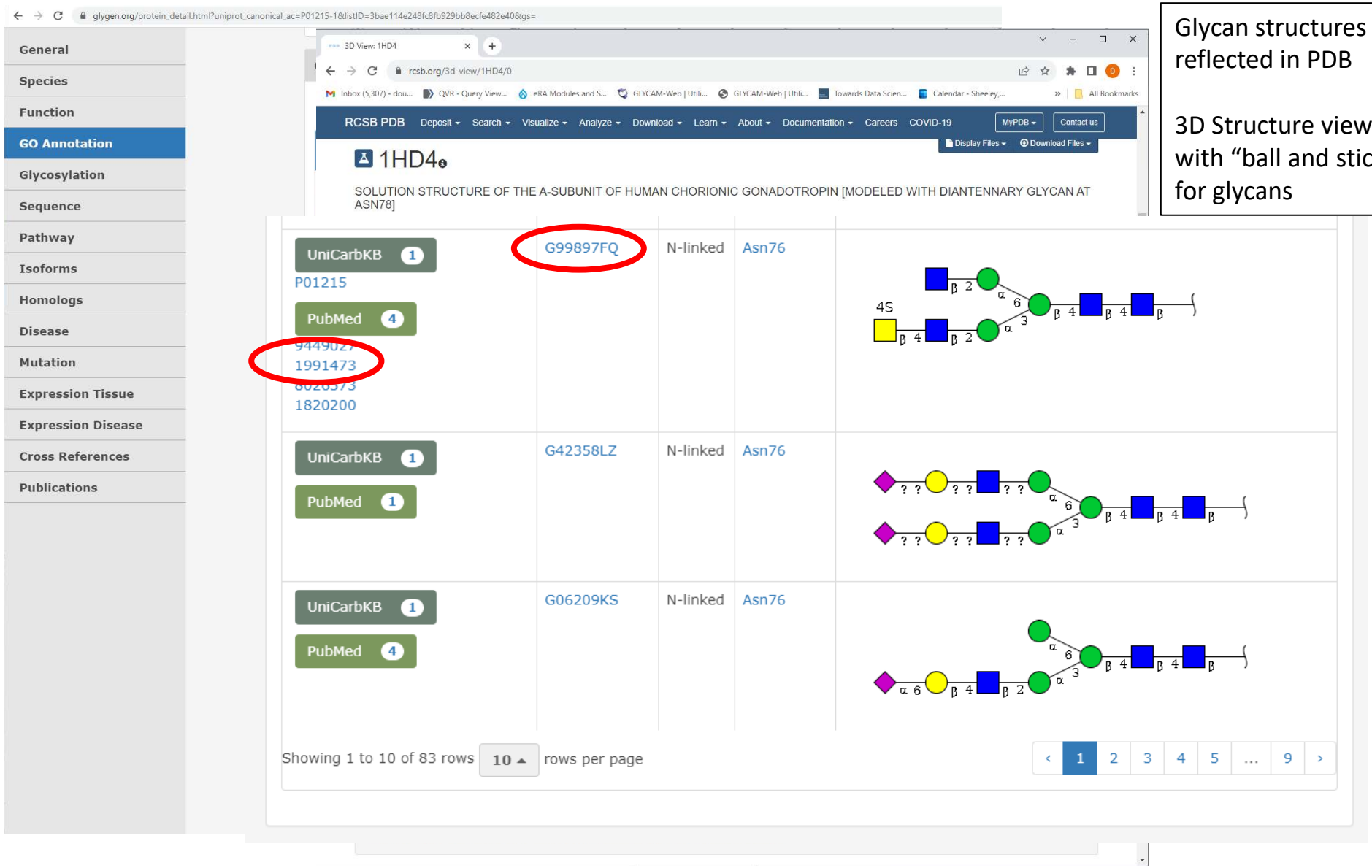
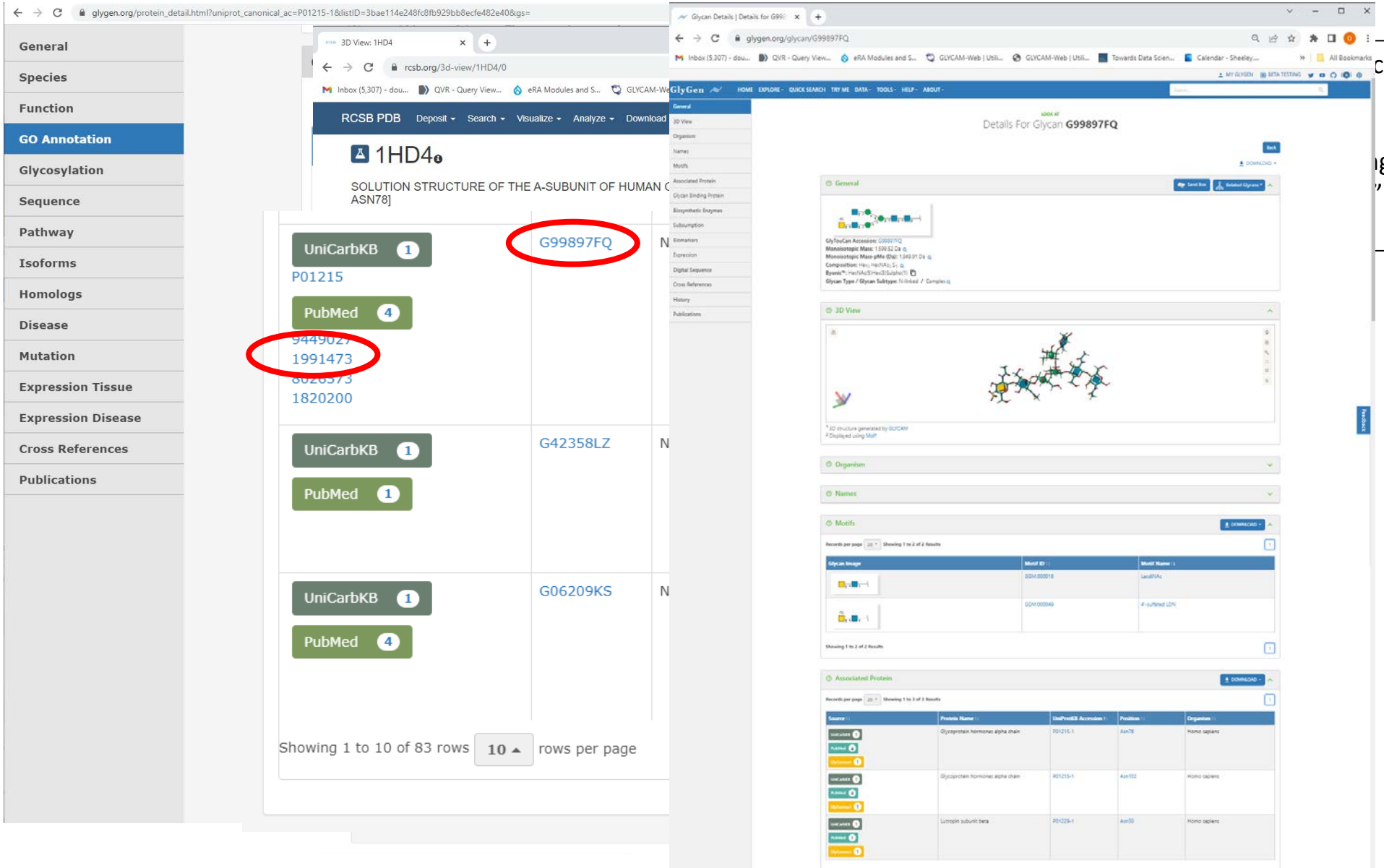


Glycan structures accurately reflected in PDB

3D Structure viewing with “ball and stick” landmarks for glycans

Protein Glycosylation Information: Glycoprotein Hormone Alpha Chain



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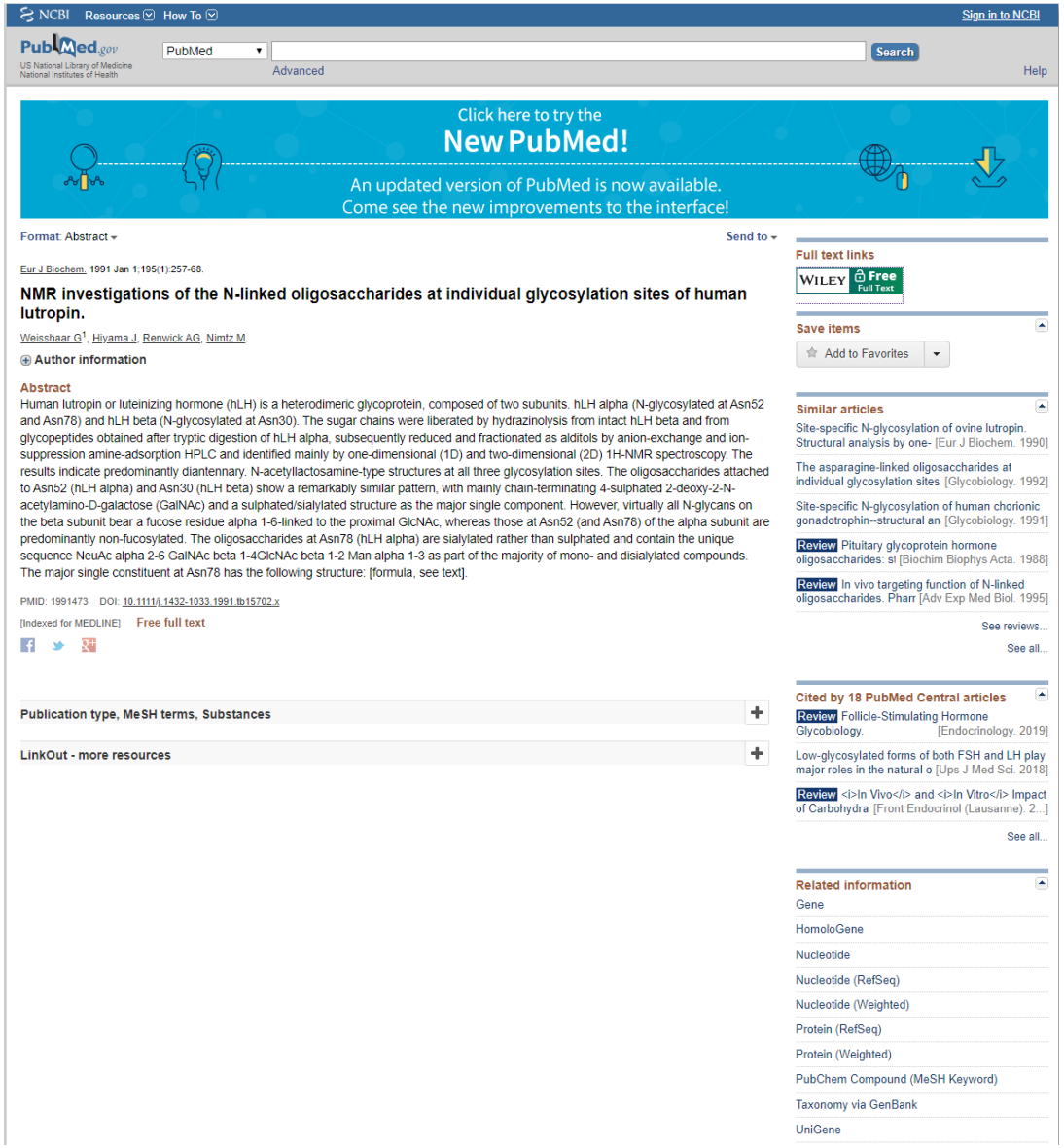
landmarks

Literature reference for identification of the sulfated biantennary glycan



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Weisshaar G[1], Hiyama J, Renwick AG, Nimtz M.

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Abstract

Human lutropin or luteinizing hormone (hLH) is a heterodimeric glycoprotein, composed of two subunits. hLH alpha (N-glycosylated at Asn52 and Asn78) and hLH beta (N-glycosylated at Asn30). The sugar chains were liberated by hydrazinolysis from intact hLH beta and from glycopeptides obtained after tryptic digestion of hLH alpha, subsequently reduced and fractionated as alditols by anion-exchange and ion-suppression amine-adsorption HPLC and identified mainly by one-dimensional (1D) and two-dimensional (2D) 1H-NMR spectroscopy. The results indicate predominantly diantennary. N-acetyllactosamine-type structures at all three glycosylation sites. The oligosaccharides attached to Asn52 (hLH alpha) and Asn30 (hLH beta) show a remarkably similar pattern, with mainly chain-terminating 4-sulphated 2-deoxy-2-N-acetylamino-D-galactose (GalNAc) and a sulphated/sialylated structure as the major single component. However, virtually all N-glycans on the beta subunit bear a fucose residue alpha 1-6-linked to the proximal GlcNAc, whereas those at Asn52 (and Asn78) of the alpha subunit are predominantly non-fucosylated. The oligosaccharides at Asn78 (hLH alpha) are sialylated rather than sulphated and contain the unique sequence NeuAc alpha 2-6 GalNAc beta 1-4GlcNAc beta 1-2 Man alpha 1-3 as part of the majority of mono- and disialylated compounds. The major single constituent at Asn78 has the following structure: [formula, see text].

PMID: 1991473 DOI: 10.1111/j.1432-1033.1991.tb15702.x

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Publication type, MeSH terms, Substances

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Nucleotide (Weighted)

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Protein (Weighted)

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Gerhard WEISSHAAR[1], Jun HIYAMA[1], Alistair G. C. RENWICK[1] and Manfred NIMTZ[2]

[1] Department of Biochemistry, University of Auckland, Auckland, New Zealand
[2] Gesellschaft für Biotechnologische Forschung (GBF), Braunschweig, Federal Republic of Germany

(Received May 21/August 27, 1990) – EJB 90 0580

Human lutropin or luteinizing hormone (hLH) is a heterodimeric glycoprotein, composed of two subunits, hLHα (N-glycosylated at Asn52 and Asn78) and hLHβ (N-glycosylated at Asn30). The sugar chains were liberated by hydrazinolysis from intact hLHβ and from glycopeptides obtained after tryptic digestion of hLHα, subsequently reduced and fractionated as alditols by anion-exchange and ion-suppression amine-adsorption HPLC and identified mainly by one-dimensional (1D) and two-dimensional (2D) ^{1}H-NMR spectroscopy. The results indicate predominantly diantennary, *N*-acetyllactosamine-type structures at all three glycosylation sites. The oligosaccharides attached to Asn52 (hLHα) and Asn30 (hLHβ) show a remarkably similar pattern, with mainly chain-terminating 4-sulphated 2-deoxy-2-*N*-acetylamino-D-galactose (GalNAc) and a sulphated/sialylated structure as the major single component. However, virtually all N-glycans on the β subunit bear a fucose residue α1 – 6-linked to the proximal GlcNAc, whereas those at Asn52 (and Asn78) of the α subunit are predominantly non-fucosylated. The oligosaccharides at Asn78 (hLHα) are sialylated rather than sulphated and contain the unique sequence NcuAcα2-6GalNAcβ1-4GlcNAcβ1-2Manα1-3 as part of the majority of mono- and disialylated compounds. The major single constituent at Asn78 has the following structure:

NcuAcα2-3Galβ1-4GlcNAcβ1-2Manα1
6
Manβ1-4GlcNAcβ1-4GlcNAc-ol.
3
NeuAcα2-6GalNAcβ1-4GlcNAcβ1-2Manα1

hLH is a heterodimeric glycoprotein hormone that consists of two non-covalently associated subunits, both highly cross-linked by disulphide bonds: the α subunit (hLHα) bears N-glycans at positions Asn52 and Asn78, the β subunit (hLHβ) is N-glycosylated at Asn30. The hormone, which is a vital component of the reproductive process, is produced in the anterior pituitary gland and stimulates steroidogenesis in ovary and testis [1 – 3]. The α subunit shares an identical amino acid sequence and carbohydrate attachment sites with the respective α subunits of human follitropin (follicle-stimulating hormone) and thyrotropin (thyroid-stimulating hormone), produced in the same gland, and with that of human chorionic gonadotropin from the placenta; the four closely related hormones differ structurally from each other with regard to their hormone-specific β subunits and the carbohydrate structures attached to both subunits [3 – 7]. Numerous investigations, mostly on human chorionic gonadotropin, suggest that the sugar chains are not required for hormone-receptor binding, but play a critical role in receptor activation via the adenylate-cyclase enzyme system [2, 3, 8 – 10 (and the references cited therein)]. More recently, subunit- and site-specific functions of the carbohydrate moieties have been reported, and the sugar chains on the α subunits, primarily at Asn52, have been found to be more important with respect to hormone assembly, secretion and signal transduction [10 – 13]. Detailed studies of the acidic oligosaccharides in pituitary glycoprotein hormones from three different species [4 – 6] demonstrated that the carbohydrate structures of hLH comprise a highly heterogeneous mixture of almost exclusively diantennary *N*-acetyllactosamine-type N-glycans with the peripheral sequences NeuAcα2-3/6Gal and/or SO_4-4GalNAc; the latter has so far only been found in pituitary glycoproteins (note that the term *N*-acetyllactosamine-type is used throughout the text according to IUPAC nomenclature, although most N-glycans described contain the sequence GalNAcβ1-4GlcNAc rather than Galβ1-4GlcNAc).

For a better assessment of the roles played by carbohydrates in biosynthesis and function of these glycoprotein hormones, knowledge of the detailed oligosaccharide structures at individual glycosylation sites is required. We have recently reported on the distinct site-specific glycosylation of

Correspondence to A. G. C. Renwick, Department of Biochemistry, University of Auckland, Private Bag, Auckland, New Zealand

Abbreviations. COSY, scalar shift-correlated NMR spectroscopy; 1D, one-dimensional; 2D, two-dimensional; FAB-MS, fast-atom-bombardment mass spectrometry; Fuc, L-fucose; GalNAc, 2-deoxy-2-*N*-acetylamino-D-galactose; GlcNAc-ol, N-acetylglucosaminitol; hLH, human lutropin; hLHα,α subunit of hLH; hLHβ,β subunit of hLH.

Enzyme. Trypsin (EC 3.4.21.4).

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Literature reference for identification of the sulfated biantennary glycan

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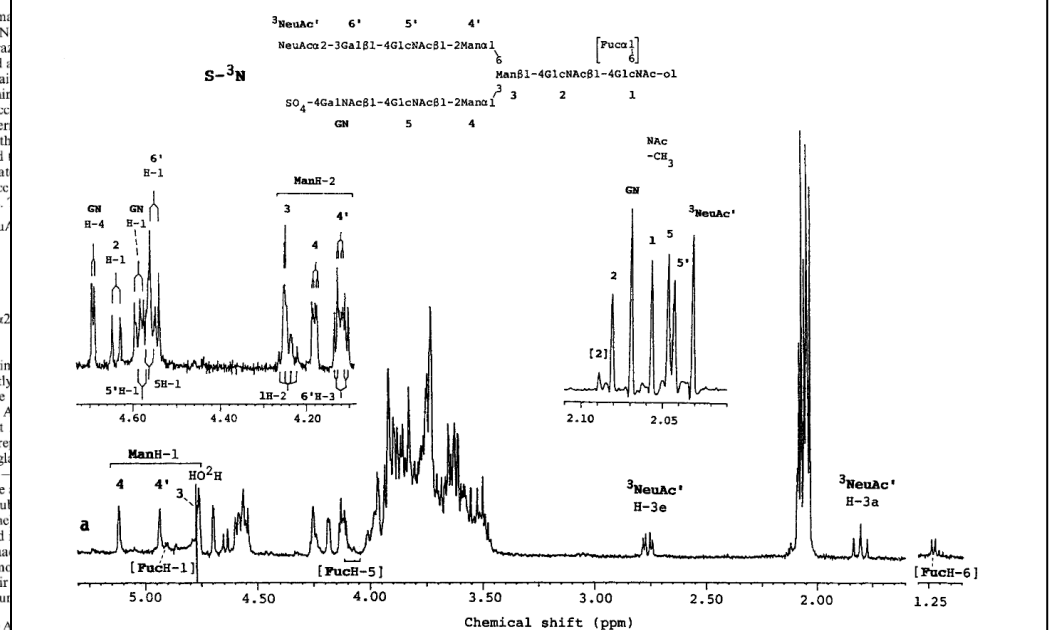
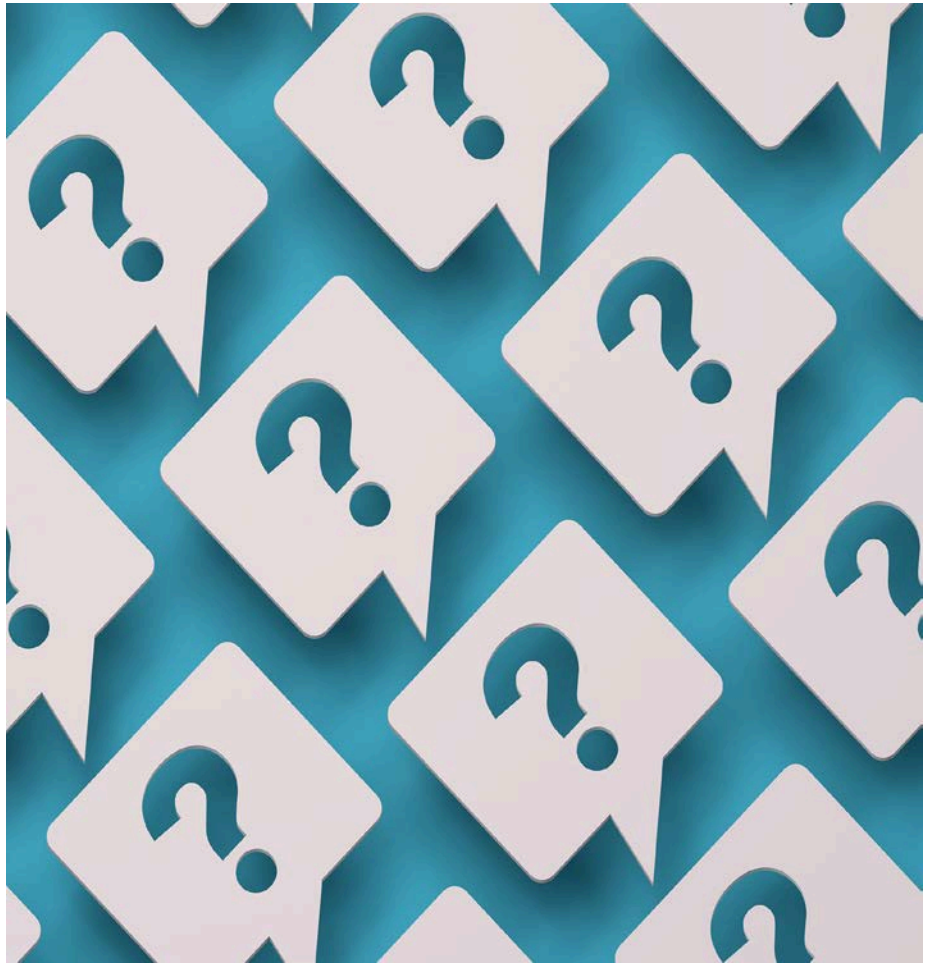


Fig. 4. *400-MHz ^{1}H-NMR spectrum of fraction A_1-4c recorded in ^2H_2O at 298 K.* Labelling of sugar residues refers to structure on top of the figure; assignments in square brackets correspond to the minor fucosylated compound (15%). (a) Resolution-enhanced 1D ^{1}H-NMR spectrum; NAc signals and the spectral region of 4.08 – 4.73 ppm are expanded and the resolution enhanced further. (b) 2D COSY spectrum; **4**H1, **4′**H1, etc. denote diagnonal peaks of Man4 H-1, Man4′ H-1, etc.; **4**H1/H2, **4′**H1/H2, etc. denote cross peaks between Man4 H-1 and H-2, Man4′ H-1 and H-2, etc. The cross peak between Man3 H-1 and H-2 is missing in the spectrum due to the small coupling constant $J_{1,2}$ (< 1 Hz) and a short effective transverse relaxation time T_2* ([31] and the references cited therein)

Glycoscience Program Evaluation

Evaluation Questions



Key Questions

1. What new resources for the glycosciences were developed by the program and how were these resources made available to the community?

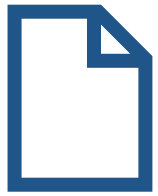
2. How and to what extent are glycoscientists and non-glycoscientists using resources developed by the Glycoscience Program?

3. How has the program facilitated access to resources for the glycosciences?

Evaluation Implementation

- The NIH Office of the Director (OD) requested a summative evaluation of the Glycoscience Program (GSP).
- Ripple Effect worked with the OD and the PP&E Branch to design and implement an evaluation to assess the extent to which the GSP achieved its goals.

Evaluation Methods



Bibliometric Analysis

- GSP catalog of awards and resources
- Publication and bibliometric data
- Corresponding author glycoscientist classification analysis

Qualitative Data

- 20 in-depth interviews
  - Glycoscientists (n=5)
  - Non-specialists (n=15)

Q1. What new resources for the glycosciences were developed by the GSP and how were they made available to the community?

GSP Resources Developed

GSP Resources Dissemination Stratified by the GSP Initiatives

Characteristics	Overall	Synthesis	Tools	Informatics
GSP Resources	56	18	37	1
GSP-Resource Publications	153	81	71	2
Resources with publications	49 (88%)	18 (100%)	30 (81%)	1 (100%)
Publications per resource (range)	0-11	2-11	0-5	n/a
Publications per resource (average)	2.7	4.6	1.9	n/a
Resources with website(s)	21 (38%)	4 (22%)	16 (43%)	1 (100%)
Unique websites	25	5	19	1
Resources with commercialization	15 (27%)	7 (39%)	8 (22%)	0

GSP Resources - Dissemination

How participants learned about GSP and GSP resources

Findings	NS	G
Connections with collaborators and colleagues	12	3
Conferences and meetings	9	4
NIH dissemination	8	3
Webinars and workshops	8	1
Publications	3	3
GSP Website	6	0

Non-specialist n=15, Glycoscientist n=5

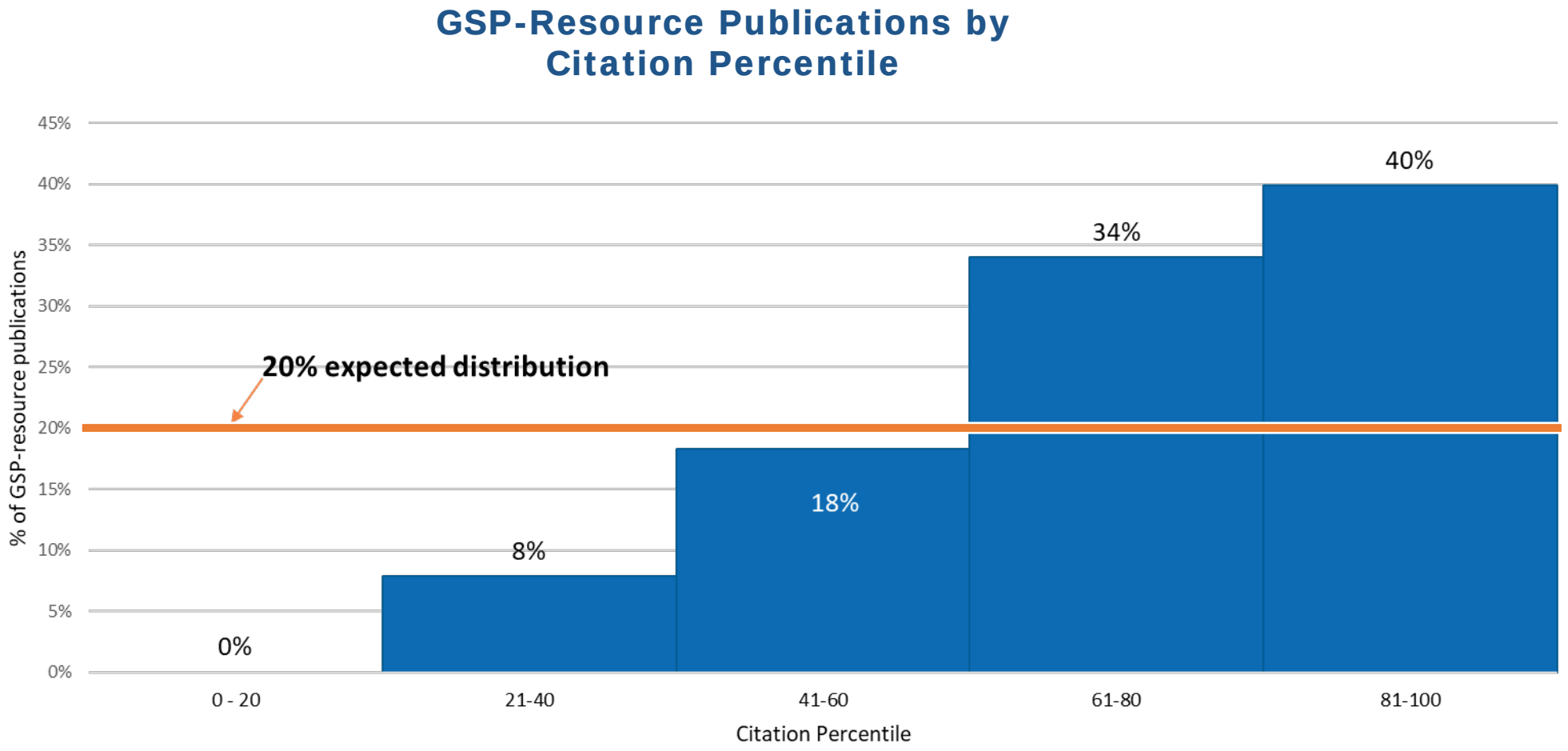
Q2. How and to what extent are glycoscientists and non-specialists using resources developed by the GSP?

Citation of GSP Resources

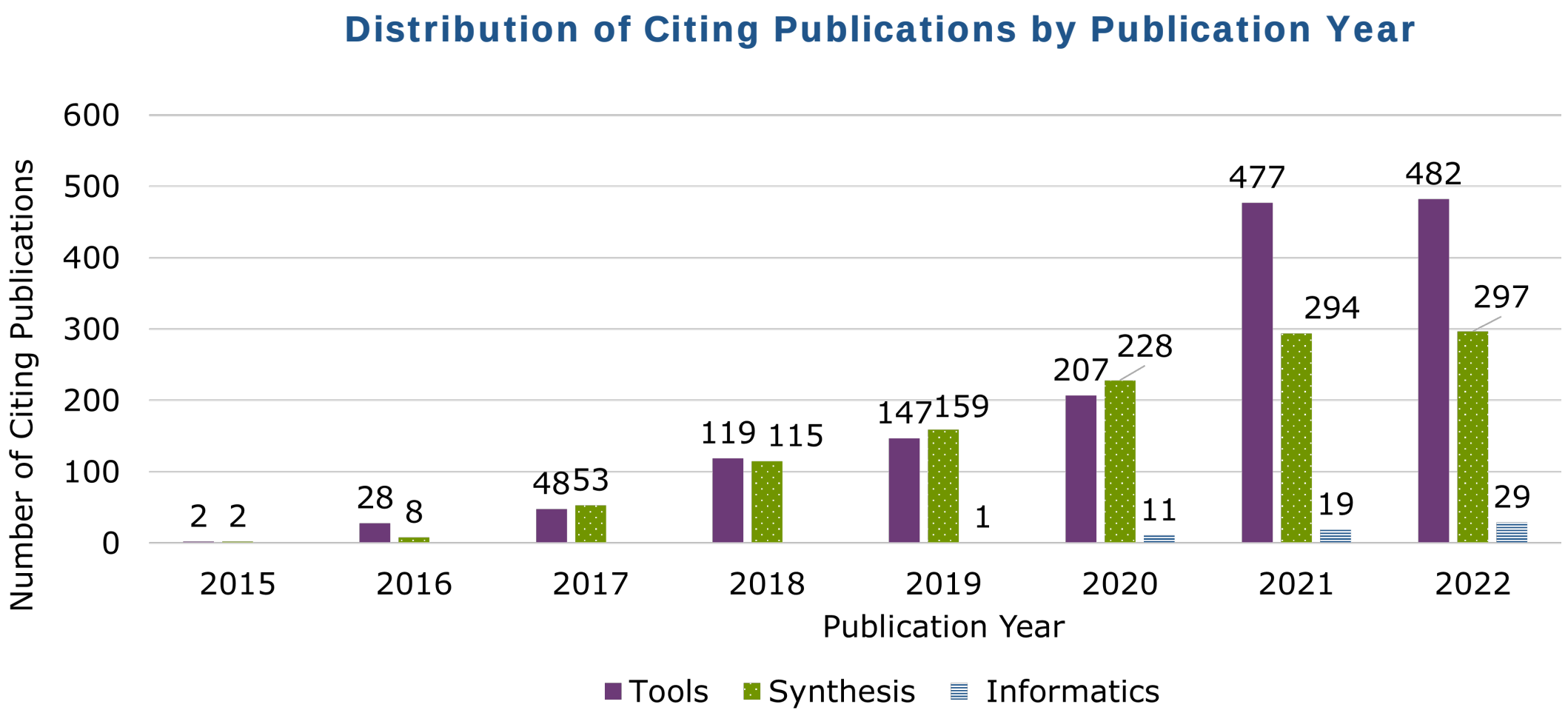
GSP-Resource Citation Metrics by GSP Initiative

Citation Metrics	Overall (n=153)	Synthesis (n=81)	Tools (n=71)	Informatics (n=2)
Total citations	4,361	2,041	2,248	81
Average citations per GSP-resource publication	29	25	32	41
Total citations (self-citations removed)	3,553	1,690	1,816	53
% self-citations	19%	17%	9%	35%
Unique citing publications	2,813	1,232	1,616	66
RCR (median)	1.4	1.2	1.7	4.9
Citation percentile (average)	72	70	73	88
Average citation lag (days)	204	224	206	123

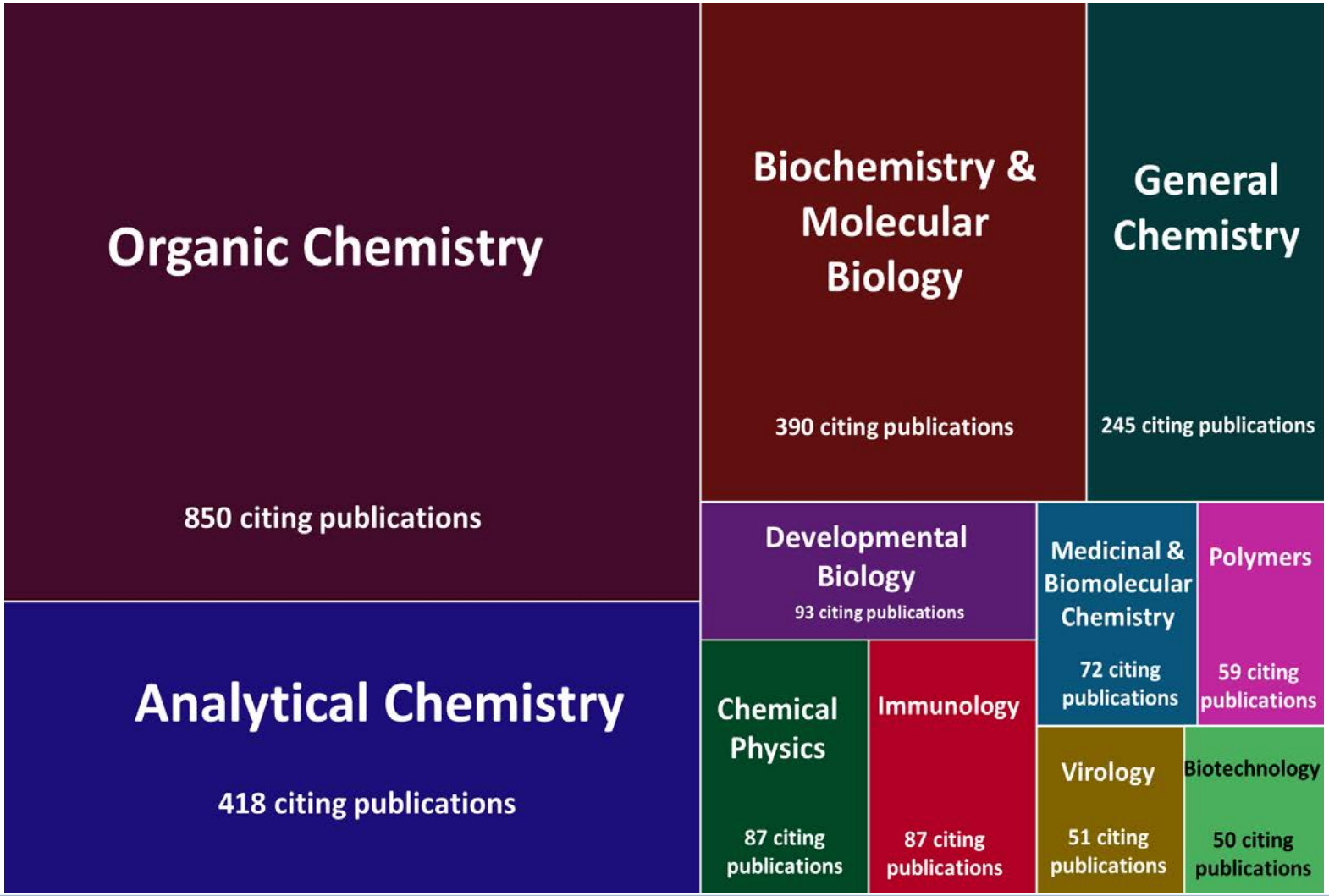
Citation of GSP Resources



Citation of GSP Resources



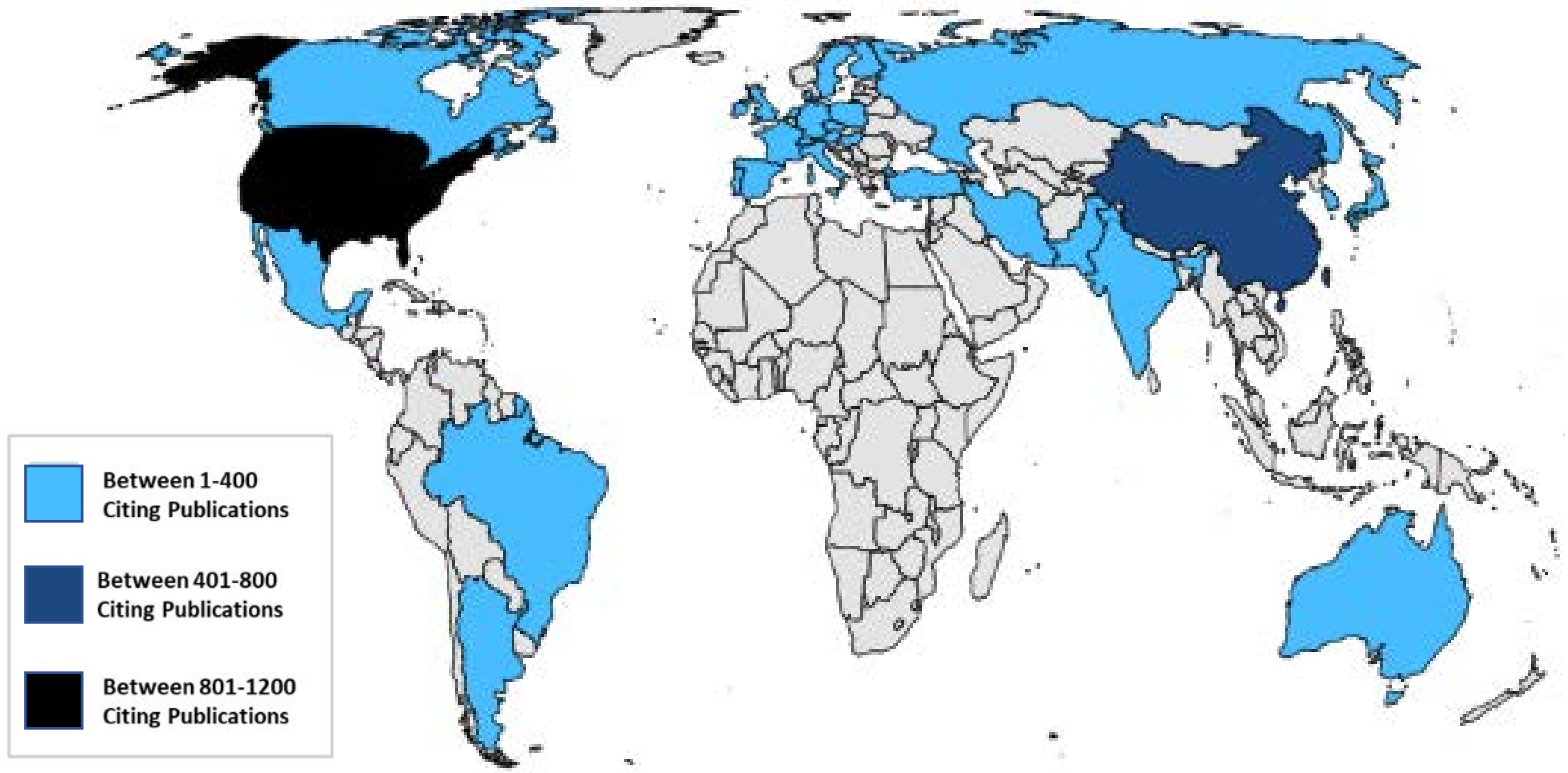
Citation of GSP Resources



Citation of GSP Resources

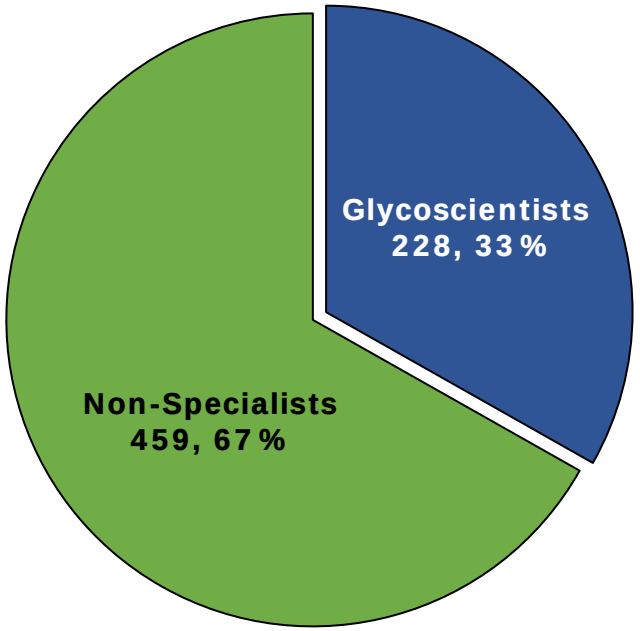
The countries with the most citing authors were:

- United States (33%)
- China (23%)
- Germany (6%)
- United Kingdom (5%)
- Japan (4%)



Citation of GSP Resources

Glycoscientists and Non-Specialists in Sample (n=687)



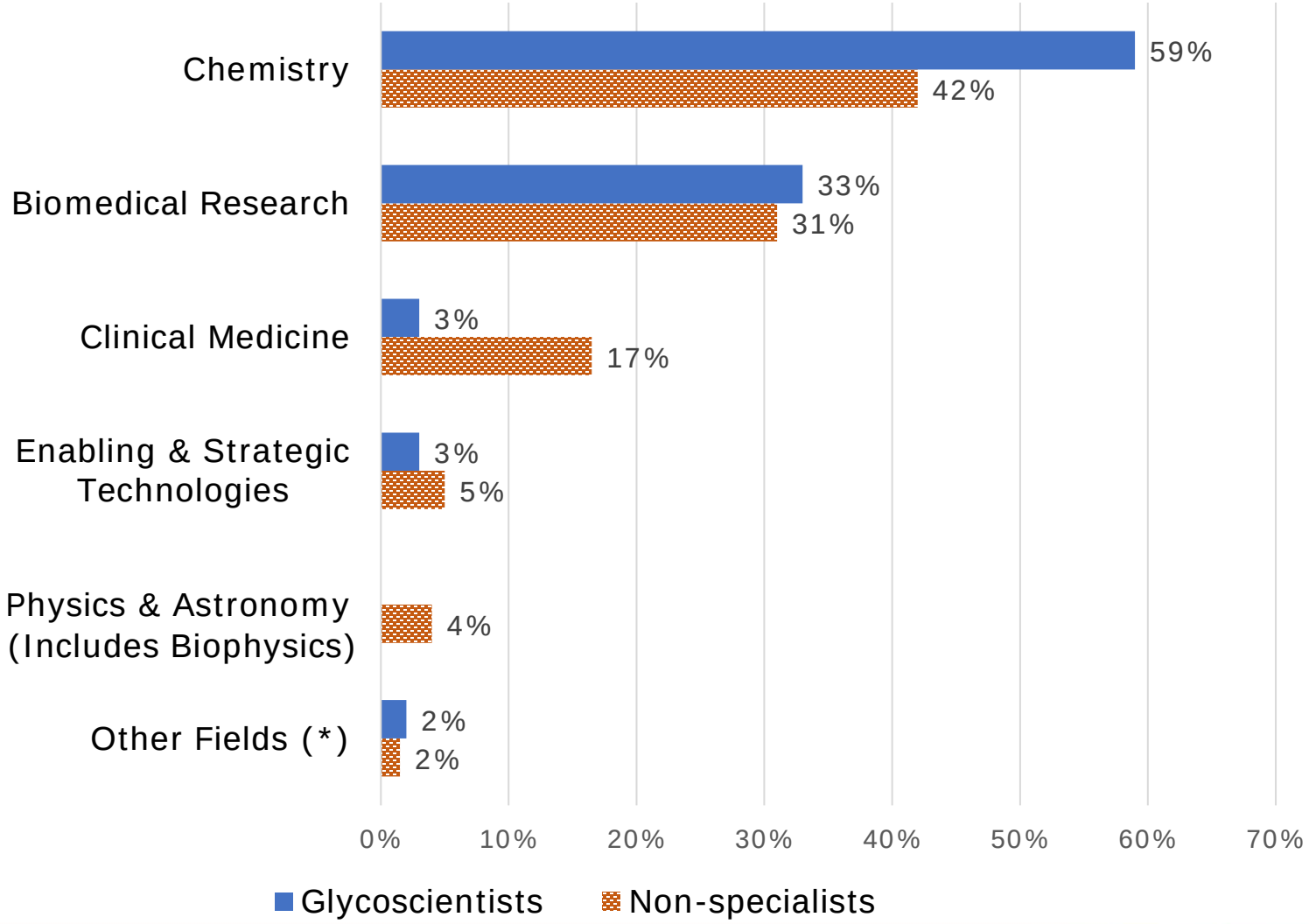
Citation of GSP Resources

GSP Initiatives Cited

GSP Initiative	Glycoscientist Citing Publications (n=620)	Non-Specialist Citing Publications (n=640)
Tools	318 (51%)	404 (63%)
Synthesis	328 (53%)	227 (35%)
Informatics	16 (2%)	21 (3%)

Citation of GSP Resources

Sampled Citing Publications Corresponding Author Classifications



Use of GSP Resources | Interviews

Biochemistry

- Organic Material Science
- Chemical Biology

(n=6)

- ***Use GlyGen to identify enzymes that create glycans of interest***
- ***Cleave glycans from glycoproteins inexpensively and easily using protocol developed by GSP research***

Biology

- Protein Biology
- Microbiology

(n=4)

- ***Identify and bind chemokines using GAGs***
- ***Use GSP-developed products to label amino acids to study cell division***

Immunology

- Immune Engineering
- Gastrointestinal Immunology

(n=4)

- ***Use GSP products to turn bacterial polysaccharides into nanoparticles***
- ***Identify glycan modifications using GSP-developed probes***

Clinical Research

- Pulmonary care
- Nephrology

(n=6)

- ***Examine how glycosylation profiles lead to liver disease***
- ***Conduct omic analyses of kidney biopsies***

Use of GSP Resources

Utility of GSP resources

GSP resource quality

Findings	NS	G
High degree of innovation and quality among GSP resources	14	4
GSP resources are scientifically rigorous	11	4

Non-specialist n=15, Glycoscientist n=5

Both the method development as well as the analytical, the data analysis tools. [Innovation] is what [the GSP is] about. They're really high on that. (Glycoscientist)

One thing that was done that was very nice is that [the probe developer] established collaborations with different scientists who work on different bacteria to show that it's not just E. coli, which is the best studied organism. You could use them for many different bacteria… I thought the development was rigorous and it worked very well. (Non-Specialist)

Use of GSP Resources

Utility of GSP resources

Value added by GSP resources

Findings	NS	G
GSP resources made research possible	11	4
GSP resource shaped research focus	6	1
GSP resources improved glycoscience knowledge among non-specialists	7	0
GSP resources simplified and expedited research	3	4

Non-specialist n=15, Glycoscientist n=5

[The GSP resource is] invaluable, in a way, because there's no other way for us to look at interactions between these different molecules. There are experimental methods, which are very targeted, whereas this, using computational methods, enables you to screen large numbers of molecules. That's really the unique strength. (Non-specialist)

My interactions with the glycobiology community have largely shaped the way my laboratory has gone over the past 10 years. We had a lot of success looking at vascular biology but then we pivoted towards looking more at glycans. And it's fundamentally changed the scope of my lab. (Non-Specialist)

Use of GSP Resources

Utility of GSP resources

Challenges encountered

Findings	NS	G
Scientific limitations of GSP resources	6	2

[The challenge is] the need for still more refined tools. [My research] efforts… have not yet led to the answers that we seek. In this particular example, the [GSP] tools were developed to study mammalian or human-like carbohydrates, and what we study are bacterial carbohydrates… so the translation of the tools to bacterial carbohydrates has not been straightforward, a need still exists. (Glycoscientist)

I had my proteins of interest. We built them into [my collaborator's] assays and he had the expertise to make the molecular glycans that we were testing them against, but how to make that assay work with this new combination required trial and error… We found the best one… but it did take that time and effort to try two other methods that did not work as well. (Non-specialist)

Non-specialist n=15, Glycoscientist n=5

Q3. To what extent was the GSP successful in making glycoscience research resources available to the biomedical research community?

Facilitating access to glycoscience

Accessibility of GSP resources

Facilitating the adoption of GSP resources

Findings	NS	G
Connections and collaborations	6	2

[My collaborators'] willingness to share the materials, and undertake a collaboration, absolutely helped, or we wouldn't have been able to even start. (Glycoscientist)

I think the only thing I would like to tell you is truly the collaborative nature of the people that I work with and how none of this would've been possible. Taking the time to explain something to an immunologist. I think that's a strength. (Non-Specialist)

Non-specialist n=15, Glycoscientist n=5

Facilitating access to glycoscience

Accessibility of GSP resources

Hindering the adoption of GSP resources

Findings	NS	G
User limitations	6	2
Funding limitations	5	0

It's hard to make glycoscience tools for the non-expert… The technical details and the level of familiarity with glycoscience in general is a high bar to start with. Some of the tools when they first started… were really great, if you were already an expert in the field… Some of them are still very niche, and so they're not really applicable to a broad variety of platforms. (Glycoscientist)

It is time consuming to synthesize those probes and takes a lot of money and [my collaborators'] time. We are being very cautious about [using] them in the best way we can and that sometimes can limit how much we can do. (Non-Specialist)

Non-specialist n=15, Glycoscientist n=5

Facilitating access to glycoscience

Impact of GSP resources on field of glycoscience

GSP resource contribution to the field of glycoscience

Findings	NS	G
Provided valuable tools	N/A	4
GSP expanded glycoscience field	N/A	3

[The GSP] creating a variety of different approaches and analysis types is really pushing the field forward and allowing us to measure things that we couldn't measure before. (Glycoscientist)

Probably the biggest overall impact would be enabling more laboratories to engage in the study of glycans that if these tools and approaches weren't available, they would not be pursuing glycans as part of their research. (Glycoscientist)

Non-specialist n=15, Glycoscientist n=5

Facilitating access to glycoscience

Impact of GSP resources on field of glycoscience

Impact of GSP resource on researchers' future funding

Findings	NS	G
Foundation for future funding	13	3

[The resource has] allowed us to have the basic tools and understanding of the tools so that we can elevate the level of the science we're performing… And in fact, I am right now submitting another grant to NIH to use it further. (Non-Specialist)

[The GSP resource] has enabled us to demonstrate expertise in a new tool that we didn't have expertise in before. It's enabled us to establish new and, hopefully, ongoing collaborations that will enable us to submit strong multidisciplinary grant applications. And, obviously, it's also provided us with key preliminary data that we can use to support the scientific premise of future proposals. (Non-specialist)

Non-specialist n=15, Glycoscientist n=5

Analysis Limitations

- Interview findings are representations of stakeholders' perceptions, but they are not generalizable to all stakeholders involved in the GSP.
- Citations were examined as proxies for awareness and utilization of GSP-resource publications
- A subsample of 750 corresponding authors of citing publications were identified for further analysis and classification as glycoscientists or non-specialists. Inferences about the full sample of authors on all citing publications cannot directly be made based on the corresponding author sample.

Key Takeaways

- The GSP resources were described as scientifically rigorous, highly innovative, and high quality by most interview participants.
- GSP resources provided value to interview participants by advancing their research, shaping how they conduct their research, improving their Glycoscience knowledge, and making research easier and faster.
- Glycoscientists perceived that the GSP provided valuable tools to researchers and expanded the field of Glycoscience.
- The GSP-facilitated collaborations were valuable resources for interview participants.
- Factors like going through a learning curve in a new field, technological limitations, and the nicheness of tools hindered the adoption of GSP resources.

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