Secondary N-Glycan Remodeling of Therapeutic Proteins: α(2-6) Sialyltransferase

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Abstract

Sialylation plays important roles in the development and function of biotherapeutic proteins; in particular it can have a large impact on product stability, efficacy and pharmacokinetics. An α(2-6) linkage-specific sialyltransferase (ST) was used to increase sialylation of Galß1-4GlcNAc units on Enbrel® and Rituxan® *in vitro*. The activity of ST was examined *via* a timecourse, and N-glycan analysis was performed to determine the level of hypersialylation achieved at each time point. N-glycan samples were prepared using ProZyme's GlykoPrep® Rapid N-Glycan Sample Preparation with 2-AB and APTS; analysis was performed using a Waters ACQUITY UPLC®-FLR system and Beckman Coulter® PA 800 *plus*-LIF system. Additionally, linkage specificity was confirmed by treatment of the hypersialylated glycans with Sialidase A™ and Sialidase S™ exoglycosidases.

Introduction

With an increasing number of innovator biotherapeutics losing patent protection, the development of biosimilar therapeutic proteins is of increasing interest. A key step in proving biosimilarity is ensuring proper N-glycosylation. Specifically, the presence or absence of sialic acid can dramatically affect the pharmacokinetics of a protein, as well as its immunogenicity. Differences in glycosylation can also give rise to significant changes in a drug's efficacy[1]. In addition, N-glycosylation is a sensitive indicator of product quality and consistency, since it is highly dependant on the bioprocessing environment. It is therefore essential that N-glycosylation be targeted and controlled at the optimal level.

Once the optimal profile has been established, cell-culture conditions are not always adequate to achieve the targeted profile with the high protein expression levels needed for commercialization. This makes clear the importance of early screening for the desired glycosylation profile. However, modifying cell-culture conditions can go only so far; other approaches are needed to produce multiple versions of the glycosylated samples, so that differences in N-glycosylation may be evaluated for corresponding effects on drug efficacy. Exoglycosidases have been used to modify glycosylation profiles, and the modified glycoproteins have been evaluated in bioassays and animal studies. Most recently, transferases have been used to remodel proteins, but have only been available as research tools.

Methods

Sialyltransferase reaction: Reaction of Enbrel or Rituxan with the α(2-6) linkage-specific sialyltransferase ST6Gal-1 Sialyltransferase (ST) was performed in solution for 2, 6, 24, 48 and 72 hours at 37°C. The reaction mix consisted of 50 µg of Enbrel or Rituxan, 30 µg ST and 150 µg CMP-NANA, in 25 m*M* KH_2PO_4/100 m*M* KCl buffer, pH 7.2.

Sialidase digestions: Select samples of Enbrel or Rituxan were pre-treated with Sialidase A (37°C, overnight) and then purified on AssayMAP PA50 Cartridges before ST treatment.

Preparation and analysis of N-glycans: Enbrel and Rituxan were purified using AssayMAP PA50 Cartridges. N-glycan samples were prepared using GlykoPrep Rapid N-Glycan Sample Preparation with 2-AB (product code GP96NG-AB) and APTS (GP96NG-APTS, developmental). UPLC analysis was performed with a Waters ACQUITY UPLC (H-class) with a fluorescence detector (330/420 λ); 1 µl of 2-AB glycan in aqueous solution was injected onto a Waters ACQUITY UPLC BEH glycan column (1.7 µm, 2.1 x 100 mm) at 60°C . The separation method consists of an 8-minute gradient with a total run time of 10 minutes. CE analysis was performed with a Beckman Coulter (BC) PA 800 *plus* Pharmaceutical Analysis System equipped with LIF detection (488/520 λ). Injections were 2 psi for 10 seconds with a separation time of 20 minutes. The method uses N-CHO capillary (BC) with an effective length of 50 cm, Carbohydrate Separation Buffer (BC). Contact ProZyme for method details.

Linkage Analysis: After the ST reaction, the 2-AB-labeled Enbrel and Rituxan N-glycans were digested with Sialidase A or Sialidase S: 2 µl of Sialidase A or Sialidase S + 6 µl of 500 mM ammonium acetate pH 5.5 + 22 µl of 2-AB-glycan (equivalent to the amount released from 22 µg of glycoprotein) were incubated at 37°C for 1 hour. N-glycans were cleaned up using GlykoPrep CU Cartridges, eluted in 25 µl water and analyzed on the UPLC.

Sialic acid quantitation: Quantitation was performed on samples after a 24-hour ST incubation. Glycoprotein was bound to an AssayMAP PA50 cartridge, washed, and then eluted. From 50 µg protein in the ST reaction, 1 µg of Enbrel or 4 µg of Rituxan was used for the analysis. Sialic acid was quantitated using the Rapid Sialic Acid Quantification Kit (product code GS300).

Identification of the sialic acid species: The sialic-acid species were identified by derivitization of released sialic acids with DMB using the Signal™ DMB Labeling Kit (product code GKK-407). The DMB-labeled glycans were separated on a Waters ACQUITY UPLC C18 column (1.7 µm, 2.1 x 50 mm) with a run time of 6 minutes.

Results & Discussion

Sample preparation and analysis: The GlykoPrep kit coupled with fast UPLC-FLR or CE-LIF methods enabled rapid, accurate and precise evaluation of N-glycan profiles for a large number of samples. GlykoPrep has been used to determine time of harvest in smaller bioreactors, and can enable close monitoring in a bioprocessing setting[2].

Samples: Enbrel (etanercept) is a fusion protein composed of the Fc domain of human IgG and the p75 tumor necrosis factor receptor (TNFR). The N-glycan profile of Enbrel primarily contains a mixture of biantennary sialylated and non-sialylated glycans. The majority of the Fc-domain N-glycans are fucosylated and non-sialylated (predominantly G0F and G1F), while the majority of the TNFR N-glycans are sialylated (predominantly A1, A1F, A2, A2F). Rituxan (rituximab) contains neutral, biantennary oligosaccharides with core fucose as well as high-mannose N-glycans and trace amounts of sialylated species.

ST timecourse: Figure 1/Table 1 shows Enbrel N-glycan profiles from ST reactions over a timecourse (2 - 72 hours). At 2 hours, much of the reaction was already completed; G2, G2F and G1F[3] were converted to sialylated species. For Rituxan (Figure 2/Table 2), G2F decreased from 9.4% to 1% and G1F[3] decreased from 8.9% to less than 1%. In both proteins, G1F[6], peak 3, did not change appreciably during the timecourse. The G1F[6] isomer does not appear to be well-sialylated in any of the reactions, which may be a result of the specificity of the enzyme, and is in agreement with the observation that the ST acts on the α(1-6) Mannose arm more slowly than the α(1-3) Mannose arm[3,4].

As the reaction was nearly completed by 2 hours in the UPLC timecourse, we performed a 2 hour reaction with APTS-labeled N-glycans for CE analysis. For Enbrel (Figure 3/Table 3), G2F disappeared, the G1F[3]/G2 peak decreased from 7.7% to 0.6%, and the A1F (2-3) peak decreased from 17% to 2.7%. For Rituxan (Figure 4/Table 4), G2F decreased from 8.5% to 1%, G1F[3] decreased from 9.8% to 1.7%, and A1F (2-3) disappeared. As with the 2-AB-labeled N-glycans, G1F[6] is not well sialylated.

Degree of sialylation: 2-AB-labeled N-glycans were evaluated in terms of potential for sialylation; *i.e.*, incomplete (galactose present/sialic acid absent, as in G1F, G2F A1, A1F) or complete (galactose present/sialic acid present, as in G1FS1, A2, A2F) (Table 5b). For Enbrel, 83% of available sites were sialylated at 2 hours, with no change at 48 hours. For Rituxan, 59% of sites were fully sialylated at 2 and 48 hours. Of the N-glycans that had the potential to be sialylated (but remained un-sialylated), the G1F[6] isoform comprised 2/3 of those left unsialylated, suggesting a limitation of the ST. Therefore, modification with a galactosyl transferase to a fully galactosylated form could result in a dramatic increase toward complete di-sialylation.

Sialidase digestion before ST remodeling: Therapeutic glycoproteins are manufactured using a variety of cell types and processes, not all of which result in a fully humanized glycosylation profile. Even after cell-culture optimization, secondary N-glycan remodeling may be desirable. As an example, pretreatment of Enbrel with Sialidase A to remove all the α(2-3) sialic acid linkages before the sialyltransferase reaction creates a different glycosylation profile, with only α(2-6) sialic acid linkages (Figure 5).

Linkage analysis by sialidase digestion: After the sialyltransferase reaction, the 2-AB-labeled samples were digested with Sialidase A, which cleaves all non-reducing terminal sialic acids, and Sialidase S, which cleaves only α(2-3)-linked sialic acids. Enbrel originally had α(2-3) sialic acid linkages, as confirmed by digestion with Sialidase S (Figure 6a). After remodeling with ST, the glycans were only partially cleaved by Sialidase S, as they were a mixture of sialic acid linkages (Figure 6b). The majority of Rituxan N-glycans were α(2-3) sialic acid linkages, and, as expected, before remodeling with ST, the same Rituxan N-glycans were cleaved by both Sialidase A and Sialidase S (a). Glycans added during remodeling were cleaved by Sialidase A, but not Sialidase S (Figure 7b).

Sialic acid profiling: Sialic acid species were identified by DMB labeling with the Signal DMB Labeling Kit and comparison against a standard; results indicated that the sialic acid species present were only Neu5Ac (data not shown).

Sialic Acid Quantitation: Enbrel was found to contain 120 pmol of sialic acid per µg of glycoprotein. Addition of ST resulted in a 14% increase in sialylation (Figure 8/Table 6). This closely matched the sialylation change of the N-glycan profile at the 24-hour timepoint, which showed a 15% increase in sialylation upon ST treatment (Table 5a). For Rituxan, the amount of sialylation was below the limit of detection (40 pmol). The N-glycan profile indicated very minor amounts of sialylation on Rituxan with approximately a 14-fold increase in sialylation after addition of ST.

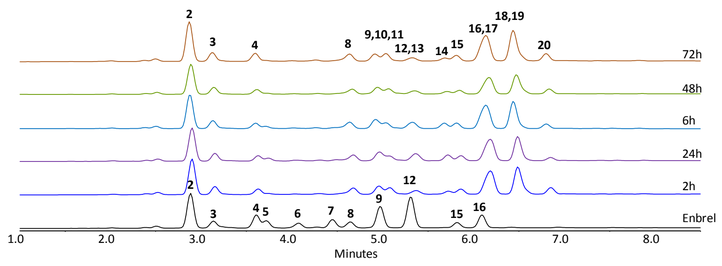


Figure 1 – Timecourse of ST Reaction on Enbrel® UPLC® profile of 2-AB-labeled Enbrel N-glycans after incubation with ST for times noted. Peak numbers correspond to N-glycans in Legend 1.

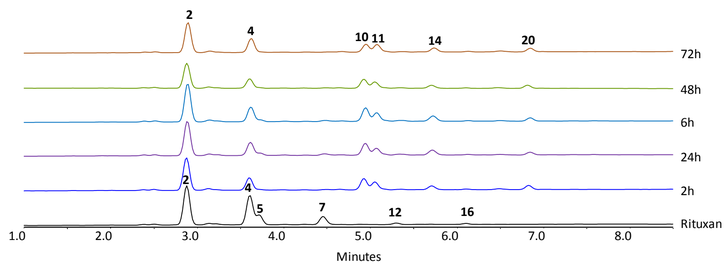


Figure 2 – Timecourse of ST Reaction on Rituxan® UPLC® profile of 2-AB-labeled Rituxan N-glycans after incubation with ST for times noted. Peak numbers correspond to N-glycans in Legend 1.

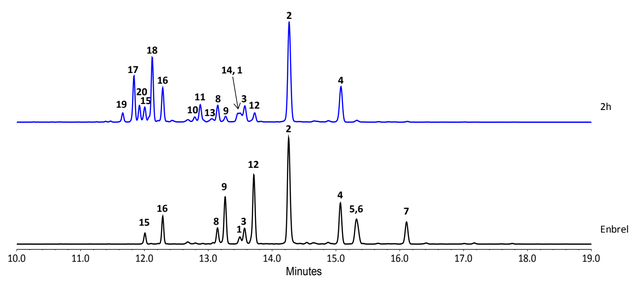


Figure 3 – Timecourse of ST Reaction on APTS-labeled Enbrel® CE profile of Enbrel N-glycans after incubation with ST for 2h. Peak numbers correspond to N-glycans in Legend 1.

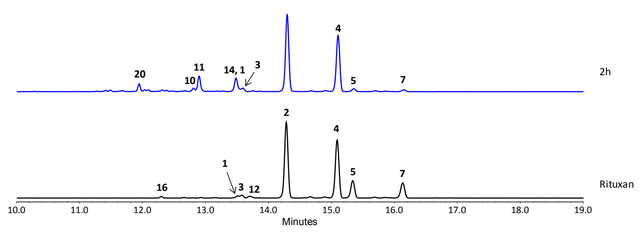


Figure 4 – Timecourse of ST Reaction on APTS-labeled Rituxan® CE profile of Rituxan N-glycans after incubation with ST for 2h. Peak numbers correspond to N-glycans in Legend 1.

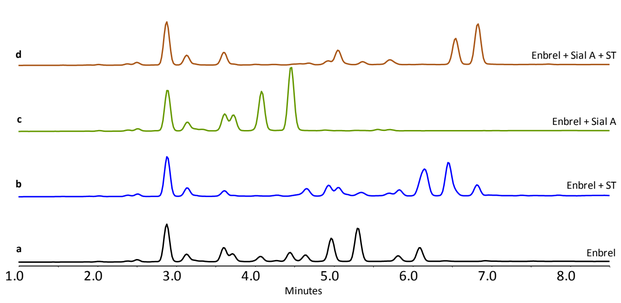
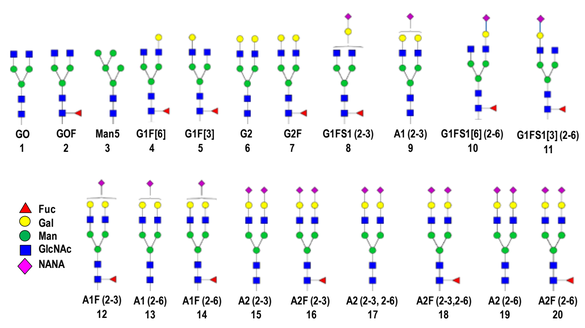


Figure 5 – Modification of Enbrel® by Sialidase A Digestion Before Treatment with ST UPLC® profile of N-glycans of a) Enbrel; b) after modification with ST for 24 hours; c) digestion with Sialidase A; d) digestion with Sialidase A followed by ST reaction for 24 hours.



Legend 1 - N-Glycan Structures, Peak ID Numbers and Notations Peak ID numbers identify the associated structure on the N-Glycan

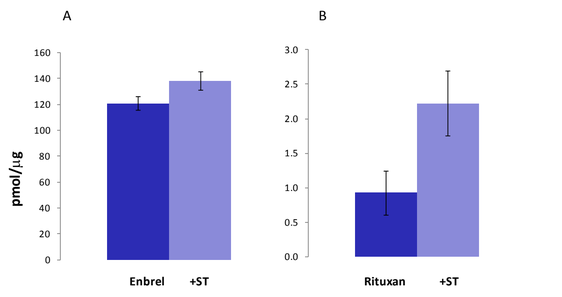


Figure 8 – Quantitation by Rapid Sialic Acid Quantitation Kit
Amount of sialic acid per µg protein of Enbrel® (A) and Rituxan® (B)

Table 1 – 2-AB-Enbrel® N-Glycan Relative Abundance and Reproducibility Over ST Timecourse

2-AB-Enbrel	% Peak Area	Std Dev	%CV
G0	1.3	0.04	3%
G0F	20.6	0.40	2%
Man5	5.2	0.26	5%
G1F[6]	8.1	0.11	1%
G1F[3]	4.4	0.19	4%
G2	3.4	0.08	2%
G1S1 (2-3)	0.6	0.09	15%
G2F	5.5	0.03	0%
G1FS1 (2-3)	3.9	0.03	1%
A1 (2-3)	13.9	0.15	1%
A1F (2-3)	20.0	0.08	0%
A2 (2-3)	3.5	0.07	2%
A2F (2-3)	8.2	0.15	2%

2-AB-Enbrel + ST	2h			6h			24h			48h			72h		
	% Peak Area	Std Dev	%CV	% Peak Area	Std Dev	%CV	% Peak Area	Std Dev	%CV	% Peak Area	Std Dev	%CV	% Peak Area	Std Dev	%CV
G0	1.4	0.02	1%	1.4	0.07	5%	1.4	0.03	2%	1.4	0.05	4%	1.4	0.03	2%
G0F	20.8	0.21	1%	20.6	0.60	3%	20.2	0.77	4%	21.4	0.51	2%	21.0	0.27	1%
Man5	5.2	0.16	3%	5.2	0.28	5%	5.3	0.11	2%	5.3	0.21	4%	5.2	0.07	1%
G1F[6]	3.7	0.03	1%	3.6	0.09	2%	3.5	0.24	7%	3.7	0.16	4%	5.2	0.03	0%
G1F[3]	0.7	0.04	6%	1.9	0.11	6%	1.4	0.01	1%	0.7	0.06	9%			
G1FS1 (2-3)	5.3	0.04	1%	4.7	0.08	2%	5.1	0.35	7%	5.3	0.17	3%	5.2	0.04	1%
G1FS1[6] (2-6) & A1 (2-3)	5.5	0.03	1%	7.1	0.25	3%	6.3	0.29	5%	6.1	0.32	5%	4.4	0.11	2%
G1FS1[3] (2-6)	4.7	0.15	3%	3.0	0.09	3%	3.7	0.22	6%	4.6	0.17	4%	4.8	0.08	2%
A1F (2-3) & A1 (2-6)	2.9	0.08	3%	5.6	0.10	2%	4.7	0.16	3%	3.0	0.36	12%	2.5	0.12	5%
A1F (2-6)	2.1	0.04	2%	3.8	0.07	2%	3.4	0.24	7%	2.1	0.28	14%	1.8	0.04	2%
A2 (2-3)	3.3	0.03	1%	3.4	0.10	3%	3.3	0.02	1%	3.3	0.11	3%	3.4	0.09	3%
A2 (2-3, 2-6) & A2F (2-3)	19.6	0.22	1%	18.5	0.13	1%	19.3	0.46	2%	18.8	0.96	5%	19.8	0.08	0%
A2F (2-3, 2-6) & A2 (2-6)	19.1	0.14	1%	16.2	0.17	1%	17.7	0.29	2%	18.5	1.00	5%	19.7	0.07	0%
A2F (2-6)	4.1	0.09	2%	2.0	0.02	1%	2.7	0.07	2%	4.1	0.04	1%	4.2	0.04	1%

Table 2 – 2-AB-Rituxan® N-Glycan Relative Abundance and Reproducibility Over ST Timecourse

2-AB-Rituxan	% Peak Area	Std Dev	%CV
G0F-GlcNAc	0.8	0.04	4%
G0	1.0	0.07	7%
G0F	40.8	0.77	2%
Man5	1.7	0.06	4%
G1F[6]	32.3	0.56	2%
G1F[3]	8.9	0.84	9%
G2F	9.4	0.13	1%
A1F (2-3)	1.8	0.09	5%
A2F (2-3)	1.1	0.08	8%

2-AB-Rituxan + ST	2h			6h			24h			48h			72h		
	% Peak Area	Std Dev	%CV	% Peak Area	Std Dev	%CV	% Peak Area	Std Dev	%CV	% Peak Area	Std Dev	%CV	% Peak Area	Std Dev	%CV
G0F-GlcNAc	1.0	0.16	16%	0.9	0.24	27%	0.9	0.04	4%	0.9	0.06	7%	0.8	0.04	5%
G0	1.2	0.07	6%	1.1	0.08	7%	1.2	0.09	8%	1.2	0.25	21%	1.2	0.02	2%
G0F	37.9	0.94	2%	37.0	1.32	4%	37.9	0.93	2%	36.4	0.63	2%	36.8	0.56	2%
Man5	2.4	0.56	23%	2.2	0.34	16%	2.1	0.11	5%	2.8	0.14	5%	2.3	0.35	15%
G1F[6]	15.4	0.33	2%	15.5	0.36	2%	15.3	0.30	2%	15.7	0.32	2%	18.5	0.24	1%
G1F[3]				2.1	0.31	14%	1.5	0.15	10%						
G2F	1.0	0.12	12%	2.2	0.03	1%	1.7	0.03	2%	1.1	0.09	8%	0.8	0.06	8%
G1S1 (2-6)	1.2	0.05	4%	0.8	0.01	1%	0.9	0.05	6%	1.2	0.08	7%	1.2	0.20	17%
G1FS1 [6] (2-6)	13.7	1.09	8%	14.1	0.19	1%	14.1	0.38	3%	14.2	0.29	2%	10.7	0.21	2%
G1FS1 [3] (2-6)	10.6	0.19	2%	8.6	0.35	4%	9.7	0.47	5%	10.5	0.26	2%	11.0	0.11	1%
A1F (2-3)	1.1	0.18	16%	1.7	0.35	21%	1.6	0.05	3%	1.3	0.05	3%	1.0	0.12	12%
A1F (2-6)	5.4	0.29	5%	6.6	0.18	3%	6.4	0.11	2%	5.6	0.18	3%	6.0	0.42	7%
A2F (2-3)	1.1	0.26	24%	1.0	0.20	21%	0.7	0.38	53%	1.1	0.12	12%	1.0	0.17	18%
A2 (2-6)	2.0	0.63	31%	1.1	0.47	44%	0.9	0.08	9%	1.7	0.03	1%	2.1	0.33	16%
A2F (2-6)	4.9	0.11	2%	3.1	0.18	6%	3.5	0.27	8%	5.2	0.28	5%	4.7	0.15	3%

Table 3 – APTS-Enbrel® N-Glycan Relative Abundance and Reproducibility on CE

APTS-Enbrel	% Peak Area	Std Dev	%CV
A2 (2-3)	2.8	0.34	12%
A2F (2-3)	6.8	0.49	7%
G1FS1 (2-3)	4.3	0.15	3%
A1 (2-3)	11.5	0.37	3%
NGA2	1.8	0.05	3%
Man5	3.8	0.14	4%
A1F (2-3)	17.0	0.79	5%
NGA2F	25.3	1.42	6%
G1F [6]	9.3	0.28	3%
G1F [3] & NA2	7.7	0.13	2%
NA2F	5.1	0.02	0%

APTS-Enbrel + ST (2h)	% Peak Area	Std Dev	%CV
A2 (2-6)	2.0	0.05	2%
A2 (2-3, 2-6)	9.8	0.11	1%
A2F (2,6)	3.4	0.09	3%
A2 (2-3)	3.4	0.02	0%
A2F (2-3, 2-6)	14.0	0.15	1%
A2F (2-3)	7.7	0.05	1%
G1FS1[6] (2-6)	1.3	0.03	2%
G1FS1[3] (2-6)	4.1	0.04	1%
A1 (2-6)	1.3	0.02	2%
G1FS1 (2-3)	3.7	0.04	1%
A1 (2-3)	1.7	0.11	7%
A1F (2-6)	1.8	0.06	4%
NGA2	2.1	0.01	1%
Man5	4.0	0.04	1%
A1F (2-3)	2.7	0.29	11%
NGA2F	23.8	0.10	0%
G1F [6]	8.2	0.07	1%
G1F [3] & NA2	0.6	0.07	11%

Table 4 – APTS-Rituxan® N-Glycan Relative Abundance and Reproducibility on CE

APTS-Rituxan	% Peak Area	Std Dev	%CV
A2F (2-3)	1.0	0.07	7%
NGA2	1.3	0.10	8%
Man5	1.6	0.11	7%
A1F (2-3)	1.3	0.03	3%
NGA2F	41.6	0.24	1%
G1F [6]	31.8	0.34	1%
G1F [3]	9.8	0.19	2%
NA2F	8.5	0.19	2%

APTS-Rituxan + ST (2h)	% Peak Area	Std Dev	%CV
A2F (2-6)	3.2	0.47	15%
A2F (2-3)	1.0	0.05	5%
G1FS1 [6] (2-6)	1.6	0.13	8%
G1FS1 [3] (2-6)	7.1	0.24	3%
A1F (2-6) & NGA2	7.1	0.15	2%
Man5	1.7	0.01	1%
NGA2F	38.7	0.99	3%
G1F [6]	27.7	0.63	2%
G1F [3]	1.7	0.20	12%
NA2F	1.1	0.11	10%

A

Enbrel	2h	6h	24h	48h	72h
51	66	66	66	65	65

Rituxan	2h	6h	24h	48h	72h
3	40	38	39	41	39

B

Enbrel	2h			48h	
23	83			83	

Rituxan	2h			48h	
2	59			59	

Table 5 – Overview of Sialylation (A) % Sialylation: Total amount of N-glycans from Enbrel® and Rituxan® that are sialylated after incubation with ST. (B) % of Sialylation, Excluding Glycans That Are Not Substrates for ST: Degree of sialylation as measured against the occupancy of potential sialylation sites.

	Avg pmol/µg	%CV	% Increase in Sialylation
Enbrel	120.9	4%	
+ ST	138.2	5%	14%
Rituxan	0.9*	34%	
+ ST	2.2	21%	144%

Table 6 – Quantitation by Rapid Sialic Acid Quantitation Kit Amount of sialic acid per µg protein of Enbrel® and Rituxan®. *The Rituxan sample was outside of the linear range of the assay.

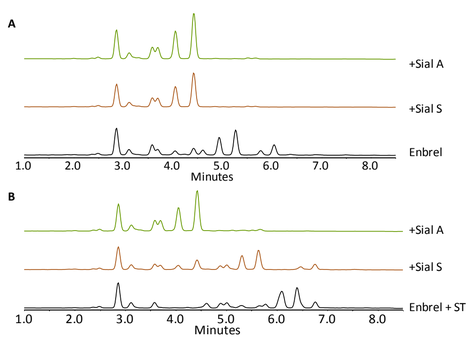


Figure 6 – Linkage Analysis of Enbrel® Digestion of Enbrel (A) and Enbrel® incubated with ST (B) with the exo-glycosidases Sialidase A and Sialidase S, UPLC® profiles. Sialidase A releases all non-reducing terminal branched and unbranched sialic acids. Sialidase S releases α(2-3) linked sialic acids.

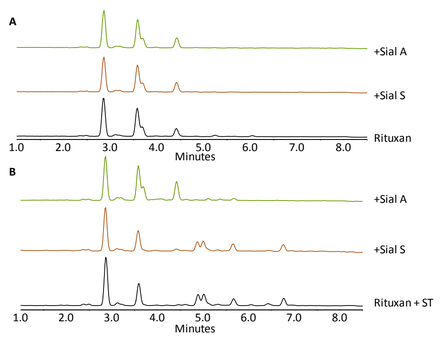


Figure 7 – Linkage Analysis of Rituxan® Digestion of Rituxan (A) and Rituxan incubated with ST (B) with the exo-glycosidases Sialidase A and Sialidase S, UPLC® profiles.

Conclusions

- GlykoPrep sample preparation coupled to fast UPLC-FLR detection and CE-LIF enabled accurate and precise confirmation of N-glycan profiling before and after enzymatic modifications.
- ST is effective in altering the glycosylation profile of therapeutic proteins such as Enbrel and Rituxan. In only 2 hours, ST delivers a high level of completely sialylated N-glycans (83% for Enbrel; 59% for Rituxan), allowing for modifications of the N-glycan profile while minimizing bioprocessing time.
- Degree of modification can further be controlled by exoglycosidase digest before the ST reaction.
- Given that ST has less effect on the G1F[6] isomer, addition of a galactosyl transferase could dramatically increase sialylation.
- Use of secondary modeling in bioprocessing could allow maximal protein yield while ensuring optimal N-glycosylation profiles.
- Roche Custom Biotech, a division of Roche Diagnostics, is introducing a line of animal-origin free transferase enzymes suitable for bioprocessing applications. ProZyme in partnership with Roche is commercializing the associated research tools to support research and development. Large-scale and GMP-grade versions of the transferase enzymes can be obtained directly from Roche Custom Biotech for use in manufacturing and biopharmaceutical production.

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