Serum N-glycan Biomarkers Predict Patient Response to Vedolizumab Treatment for Crohn's Disease

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Introduction

Crohn's Disease and Treatment

Vedolizumab is a monoclonal antibody used to treat Crohn's disease (CD). It is a slow-acting therapy, often requiring 6 months before its effects are detectable. A reliable predictor of a patient's response would not only educate the type of treatment a patient should receive, but would also prevent a, consequently, less effective secondary treatment.

Crohn's Disease and Glycans

Glycosylation is a post-translational modification of proteins that impacts their biological activity. Blood serum contains many types of glycoproteins related to immune and inflammatory activities. Changes in glycosylation have been observed in patients suffering from CD, for example, glycan biomarkers can distinguish CD patients from healthy controls. Total serum N-glycan (TSNG) analysis has the potential to predict patient response to vedolizumab. In addition, comparing patients' glycan profiles after treatment may provide insight into the cellular pathways involved in remission, assessed by HBI score.

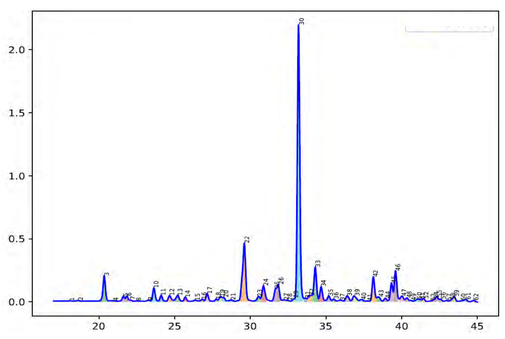
Workflow

Sample Processing

Enzymatic release (PNGase F) of serum glycans

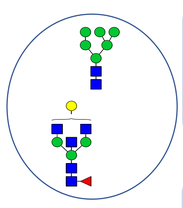
Fluorescently label glycans (Procainamide)

Hydrophilic interaction liquid chromatography with fluorescence detection & mass spectrometry



Data Processing

FA2[r6]BG1

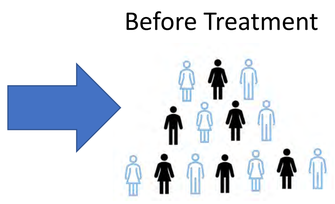


LaCyTools quantifies **direct traits** (individual glycan types)

Group direct traits into **derived traits** (glycans sharing familial similarities) e.g. fucosylation and galactosylation

- 89 direct traits
- 21 derived traits

	Responder	Non-responder
Patients	34	24
Age	41.17 +/ 15.17	43.83 +/ 17.39
Male	16	9
Female	18	15



Statistical Analysis

Traits before and after treatment:

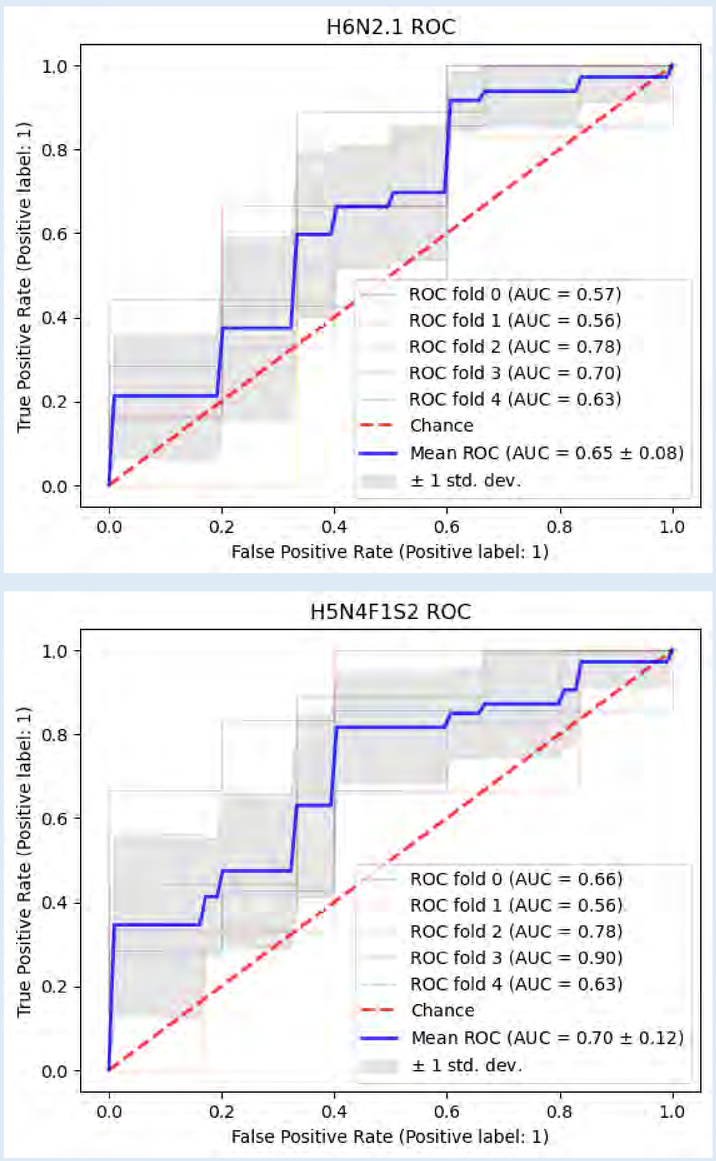
- Univariate analysis
- Logistic regression for response correcting for age and sex with 5-fold cross-validation

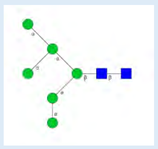
Glycosylation changes

- Univariate analysis comparing before and after treatment

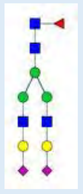
Results

1. Predicting Vedolizumab Response





H6N2 (MAN6) glycan was elevated in responders, prior to treatment, compared to those who failed to respond (p-value 0.041) . This biomarker proved to have moderate predictive capacity (0.65 AUC).



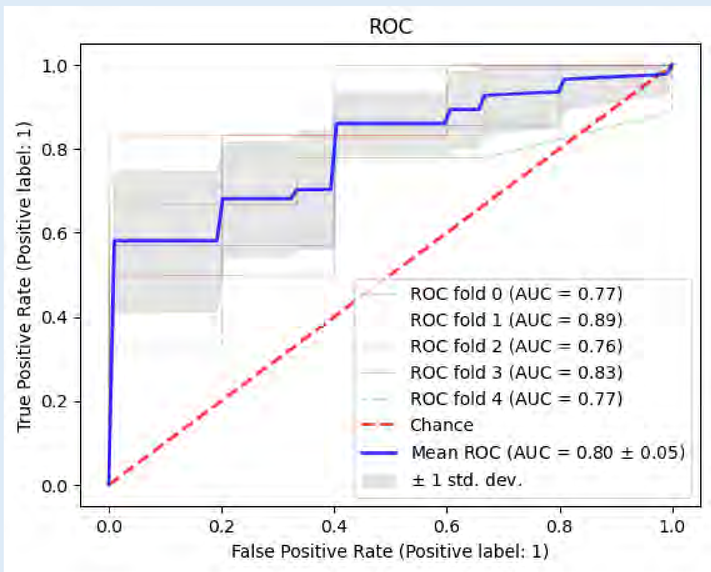
H5N4F1S2 (FA2G2S2) glycan was elevated in responders, prior to treatment, compared to those who failed to respond (p-value 0.010). This biomarker proved to show promise as a predictor of response, with a good predictive capacity (0.70 AUC).

A combination of direct traits did not improve the mode. The clinical marker, F-calprotectin, as a predictor of response is weaker than the glycan biomarkers (AUC 0.43).

2. Markers Confirming Vedolizumab Response

After treatment, traits which significantly differed across response, indicate the varied changes in glycan composition experienced by responders compared to non-responders. The markers of response include:

- **Direct traits:**
  - H6N3, H5N4F1S2, H5N4F1: Higher in responders
- **Derived traits**:
  - A2S0B, A2F0S0B: lower in responders
  - A2S0G, A2FS0G: higher in responders



Random forest model predicting response with 17 significant direct traits after treatment performed 0.8 ±0.05 AUC.

3. Glycosylation Trends

Responders experienced an increase in galactosylation after treatment, with significant difference to non-responders (p-value 0.006); suggesting a decrease in inflammation. Galactosylation levels are known to be lower in IBD patients.

Conclusion & Future Work

- 2 direct traits (2 individual glycans) proved moderate predictors (AUC>0.65) of response
- A combination of traits, both direct and derived, proved to strongly differentiate responders/non-responders after treatment (0.80 AUC)
- Galactosylation levels increased in responders – likely to be due to increased levels of anti-inflammatory IgG antibody
- We intend to replicate analysis with additional treatments and refine the instrumentation used to acquire data

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