# DECODING THE MOLECULAR BASIS OF THE SPECIFICITY OF AN ANTI-STN ANTIBODY

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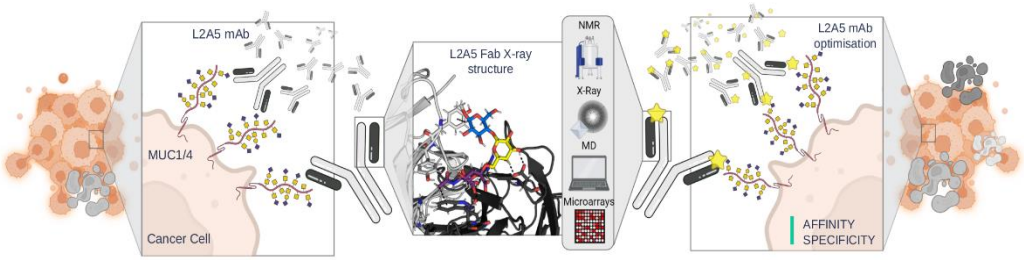


The mucin O-glycan sialyl Tn antigen is a cancer exposed truncated O-glycan, linked to Ser or Thr residues. It has been related with different types of cancers, such as breast, colorectal, and bladder cancer, often leading to a high risk of metastasis and poor prognosis. Anti-glycans antibodies (Abs) with high specificity and affinity have been developed for diagnostic and therapeutic purposes. However, these Abs are challenging to generate and have limited effectiveness, resulting in low titers and short protection durations. For these reasons, experimental structural insights are needed to study anti-glycan Ab specificities. In this study, through a multidisciplinary approach, we combined X-ray crystallography, NMR spectroscopy, computational methods, glycan/glycopeptide microarrays, and biophysical techniques, to thoroughly investigate the L2A5 sTn recognition mode [1], a novel preclinical anti-sTn Ab [1]. The X-Ray data, in line with the NMR experiments, demonstrate that the L2A5 fragment antigen-binding (Fab) specifically binds to core sTn moieties, with a similar binding pose for the sTn linked to Ser or Thr. The Neu5Ac establishes key interactions with the receptor and the GalNAc moiety provides additional contacts. Furthermore, L2A5 exhibits specificity toward cancer-related MUC1 and MUC4 mucin-derived sTn glycopeptides, contributing to its selective targeting against tumor cells. This newfound knowledge holds promise for the rational improvement and potential application of this anti-sTn Ab in diagnosis and targeted therapy against sTn expressing cancers, improving patient care.

**References:**

1. Soares CO, Laugieri ME, et al *JACS Au.* **2024,** *16, 225-236*.