

NRC Institute for Biological Sciences (NRC-IBS)

Polysialylation of Proteins for Improved Bioavailability

The Business Opportunity

The post-translational modification of therapeutic proteins is commonly used to improve their circulating half-life, thereby enhancing their efficiency. Numerous strategies have been employed towards this end, including covalent modification of the proteins, such as through PEGylation - the chemical addition of chains of polyethylene glycol (PEG) to therapeutic proteins – which improves protein stability and solubility, prevents proteolytic degradation, and reduces the clearance rate from the bloodstream. However, PEGylation of proteins relies on chemical conjugation of PEG chains to free amino groups or engineered Cysteine residues on the protein, which can lead to heterogeneously-modified proteins whose activity, can be adversely affected.

The chemical addition of polysialic acid (PSA) to proteins represents an alternative means of improving the circulating half-life of proteins. Its biodegradability and non-immunogenicity reduces adverse effects on the patient, but current technology still requires chemical addition to proteins, leading to undesirable heterogeneous modification.

The Technology

NRC-IBS has developed a site-specific, two-step in vitro enzymatic modification process to homogeneously “PSA modify” proteins with existing N-linked glycans. The process uses our patented polysialyltransferases, and results in proteins with greater stability, solubility and circulating half-life. We have demonstrated the ability of this system to modify three glycoproteins with varying N-linked glycan compositions: including the human therapeutic proteins alpha-1-antitrypsin (A1AT) and factor IX, as well as bovine fetuin.

In mouse models, the modified A1AT has shown a marked increase in biological half-life of the protein with no loss of bio-activity, a shift in elimination route towards the liver, and no observation of abnormal uptake of PSA

modified A1AT in other organs.

Further, with this approach we can:

- Modify a variety of glycan structures including bi-, tri-, and tetra-antennary glycans with either α -2,3- or α -2,6-linked terminal sialic acids.
- PSA modify A1AT without adversely affecting its function as an elastase inhibitor.
- Achieve an 18-fold greater bioavailability (area under the curve) with PSA-A1AT compared to unmodified A1AT.

Patent Position

US Patents 7,211,657 and 7,169,914 granted in 2007 - NUCLEIC ACIDS ENCODING SIALYLTRANSFERASES FROM CAMPYLOBACTER JEJUNI.

Patent Pending – ENGINEERED (TRUNCATED) VERSIONS OF POLYSIALYLTRANSFERASES WITH ENHANCED ENZYMATICAL PROPERTIES - NRC IBS case 11944 (Japan, US, Canada, China, Europe)

The Market

PSA modification, like PEGylation, is part of the \$118B Protein Engineering market, which has grown at a rate of 12% over the past 5 years. A1AT and Factor IX are just two examples of a number of therapeutic proteins amenable to modification, their current worldwide sales exceeds \$5 billion per year.

Technology Transfer Possibilities

This technology is available for non-exclusive licensing.

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