

THERAPEUTIC PROTEIN HALF-LIFE

●●● Extending *in vivo* half-life of therapeutic proteins – licensing opportunity L-11944

HIGHLIGHTS

Post-translational modifications of therapeutic proteins are commonly made to improve their circulating half-life, thereby enhancing their efficiency. Numerous strategies have been employed towards this end, including covalent modification, 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 blood-stream. However, PEGylation relies on chemical conjugation of PEG chains to free amino groups or engineered cysteine residues on the protein, which can lead to heterogeneous-ly-modified proteins whose activity can be adversely affected.

To address this, the NRC has developed a site-specific, two-step *in vitro* modification process whereby polysialic acid (PSA) is enzymatically added to existing glycans, resulting in proteins with greater stability, solubility and circulating half-life.

TECHNOLOGY TRANSFER

- A commercial exploitation licence for the technology

MARKET APPLICATIONS

- Improve the half-life of therapeutic proteins used to treat a wide range of diseases

A1AT construct	AUC (hr*ng/ml)	t1/2a (hr)	t1/2b (hr)	CL (ml/hr)
A1AT	149.9 ± 47.12	0.44 ± 0.10	5.01 ± 1.47	14.33 ± 4.77
diSA-A1AT	984.3 ± 234.3	0.42 ± 0.031	13.45 ± 1.34	2.11 ± 0.51
PSA-A1AT	2691 ± 303.7	1.12 ± 0.14	27.32 ± 1.29	0.75 ± 0.085

HOW IT WORKS

Many therapeutic proteins are glycosylated during production, both when recovered from human serum and when expressed in cell lines. The terminus of these glycans acts as a handle for further modification. The NRC two-step modification process consists of deploying proprietary enzymes at the N-linked glycan handle to achieve site-specific polysialylation. The technology can be used to modify a variety of glycan structures including bi-, tri-, and tetra-antennary glycans with either -2,3- or -2,6-linked terminal sialic acids.

The NRC has 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. Polysialylation of A1AT was achieved without adversely affecting its function as an elastase inhibitor. In mouse models, the modified A1AT has shown a marked increase in biological half-life with no loss of bioactivity, a shift in elimination route towards the liver, and no observation of abnormal uptake of PSA-modified A1AT in

other organs. The process has been shown to achieve an 18-fold greater bioavailability with PSA-A1AT compared to unmodified A1AT.

BENEFITS

- Improved stability, solubility and circulating half-life of therapeutic proteins
- Lower doses of therapeutic proteins and lower frequency of dosing required

PATENTS

NRC file 11944: Patents issued in Canada, the United States, Japan and Europe.

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