THE SYNTHESIS OF MULTIVALENT GLYCOMIMETICS FOR THE IMPROVED TREATMENT OF GLIOBLASTOMA MULTIFORME

Lucy A. R. Spicer[a], M. Piazzoni[b], F. Milanesi[c], O. Francesconi[c], L. Russo[b], S. Sattin[a]

[a] University of Milan, Dipartimento di Chimica, via Golgi, 19, 20133, Milano, Italy
lucy.spicer@unimi.it
[b] University of Milan-Bicocca, Dipartimento di Medicina e Chirurgia, Via Raoul Follereau, 3, 20854 Vedano al Lambro (MB), Italy
[c] University of Florence, Dipartimento di Chimica 'Ugo Schiff' (DICUS), Via della Lastruccia, 3, 50019 Sesto Fiorentino (FI), Italy

Glioblastoma Multiforme (GBM) is a fatal form of malignant brain tumour that is complicated to treat due to its heterogeneity and therapy resistance [1]. The standard treatment is to surgically remove as much of the tumour as safely possible and place a chemotherapy directly into the resection site; undoubtedly an invasive and potentially damaging procedure. Activation of complement system (CS) following brain injury is a major contributor to secondary brain damage [2]. Studies have shown that inhibition of Mannose Binding Lectin (MBL), an activator of the CS, can reduce the loss of sensorimotor capabilities after traumatic brain injury or stroke [3]. This project seeks to improve treatment outcomes by taking advantage of this cerebral protective effect, via the formulation of biodegradable chemotherapeutic hydrogels with MBL inhibitors. To prepare the hydrogels, the multivalent pseudo-dimannoside MBL inhibitor (Fig. 1-A) was synthesised at half gram scale, alongside a new generation of potentially more stable glycomimetic inhibitors (Fig.1-B) [4]. Their tetravalent scaffold linked to a pseudodisaccharide is believed to be a key factor in affinity for the MBL's oligomeric binding site (Fig 1-C). The goal of this work is to reduce treatment-related complications of GBM tumour removal and establish MBL's potential as a therapeutic target to minimize surgical brain damage.

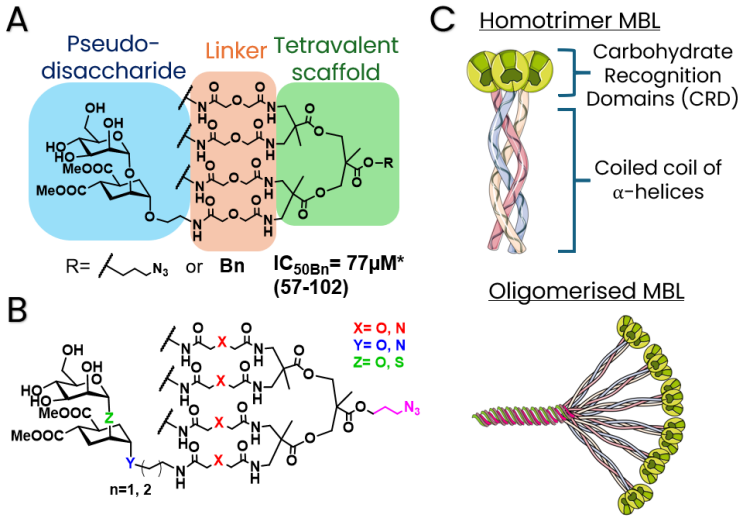

Figure 1. A: Structure of the tetravalent psedo-dimannoside inhibitor with its building block approach. *Inhibition of murine MBL-C binding to Man-BSA immobilised on a SPR sensor.[4] **B**: Novel inhibitors which will contain various combinations of heteroatoms applicable due to its interchangable synthetic route. **C**: Diagram of the MBL in it's monomeric (homotrimer) and oligomerised forms.

References:
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