First-in-class selective nanomolar inhibitors of galectin-8 N-terminal domain

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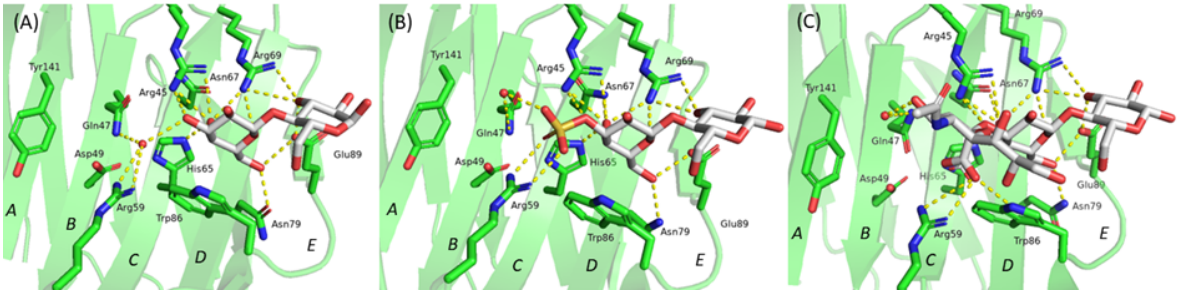
Galectins are found throughout the body and exhibit a variety of functions.[1] Among galectins, galectin-8, is nearly universal in both healthy tissues and tumours, and is found both intracellularly and extracellularly. Intracellularly, damaged and potentially pathogen-infected vesicles can be targeted for antibacterial autophagy by galectin-8 as a function of the immune system.[2] Extracellularly, carbohydrate recognition by galectin-8 modulates cell growth, death, and adhesion to influence lymphangiogenesis and tumour survival and metastasis.[3] In 2020 Cagnoni et al. stated: ˝The impact of specific galectin-8 CRD–glycan interactions in the biological functions of the full-length lectin is still a matter of controversy˝. [4] In order to allow advanced studies of these galectin-8-associated biological functions, potent and selective galectin-8 inhibitors are needed and exactly these were the overarching aim of our work.

Ligand selectivity among galectins has ever been a challenging objective. As we will present in this work, intrinsic differences between galectin binding sites allow a fine tuning of ligand selectivity and potency (Figure). Starting from our recently published series of benzimidazole-galactosides [5], we have designed a series of 2-substituted galactosides that exert sub-micromolar affinities for galectin-8 for the first time, while retaining promising selectivity versus related galectins. These selective compounds facilitate the study of galectin-8 biology and may have pharmaceutical relevance in the wide range of galectin-8 associated pathologies.



3D structure of Gal-8N in complex with A) lactose (PDB 3AP4); B) lactose 3'-sulfate (PDB 3AP6); C) 2,3'-sialyllactose (PDB 3AP7). A-E denote subsites.

This project has received funding from the European Union's Horizon 2020 under the Marie Skłodowska-Curie grant agreer No 765581. The authors kindly thank Barbro Kahl Knutson for FP assay.

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