Experimental report for ESRF Expt. MX-1706, proposer Clemens Grimm, University of Wuerzburg, Beamline BM14U

Overview

Galectin-1, a prominent member of animal lectins, is overexpressed in malignant tissues and involved in numerous types of cancer.[1, 2, 3] The protein exhibits characteristic carbohydrate-recognition domains on opposite sites of the homodimeric structure and interacts selectively with β-galactosides (like lactose and *N*-Acetyllactosamine) of glycoconjugates on cell surfaces. These interactions introduce biomolecular processes as cell proliferation, apoptosis and tumor progression.

The binding constants of natural carbohydrates are low and range in the micromolar.[4, 5] This fact demonstrates the urgent need for the identification and development of highly affine and selective ligands. Our work presents a rational approach for the design of novel Galectin-1 ligands and aims at introducing binding partners as potential lead structures for therapeutical drug development. To realize this intent we had performed two rounds of rational drug design (compare proposals MX 1495 and MX 1555) during which we extended a natural *N*-Acetyllactosamine anchor with a growing artificial bioorthogonal function using the Sharpless-Huisgen-Meldal "click reaction".[6,7]

Here, in the third design round, we address two charged groups at the periphery of the carbohydrate binding cleft.

Evaluation and results

In this third round of rational ligand design we tried to address two charged groups (Asp26 and Asp125) in more distant vicinity of the Gal1 carbohydrate binding cleft. Therefore, a set of potentially suitable guanidine and amino derivatives of NB169 were soaked with the Gal1 crystals. While no binding was detected for the guanidino derivatives, the amino derivative JB60 showed weak, albeit significant density for the ligand in a structure solved at 1.3Å resolution (Fig. 1B). The intended salt bridge to Asp125 could be observed as predicted. Occupancy refinement suggests that one fourth of the ligand binding sites within the soaked crystal is unoccupied, which might be the main reason for the observed relatively weak but distinct ligand density.

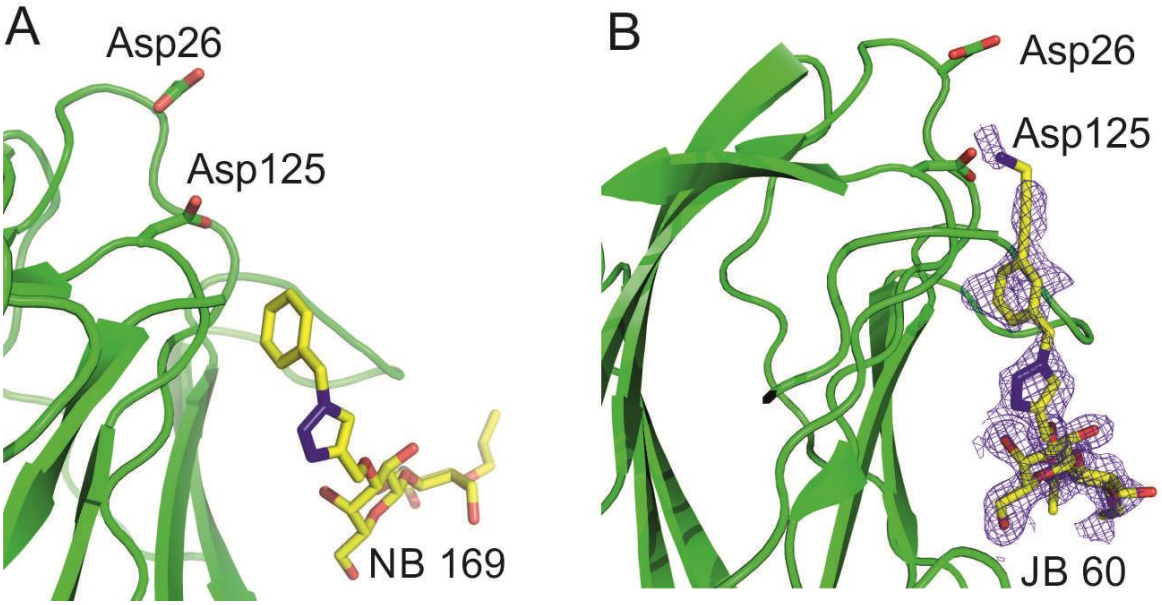

Fig. 1: (A) Ligand NB169 from design round 2 bound to Gal1. (B) Ligand JB60 from design round 3 bound to Gal1. A salt bridge from the terminal amino group of JB60 is formed to residue Asp125 as intended. The 2Fobs-Fcalc density is shown on 0.5σ level for the ligand.

References

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