28AB-ISMS30 **Structural Basis to Dissect the Binding Affinity and Specificity of Human Galectin Inhibitors**

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Human galectins serve as appealing targets in cancer immunotherapy and fibrotic diseases. We report herein the binding interactions of three thio-digalactoside (TDG) derivatives with human galectins-1, -3 and -7 by X-ray crystallography, isothermal titration calorimetry and ^{19}F NMR spectroscopy. There are five subsites (A–E) in the carbohydrate recognition domain of galectins. The arene-arginine interactions were confirmed for the first time at subsite E. In addition to the interactions contributed by sugar residues at subsites C and D, the substituent of TDG derivatives was found to preferentially bind to subsite B of galectin-3, whereas the same group was in favor of subsite E of galectins-1 and -7. The observed dual binding modes not only demonstrate how the potency can be improved from K_i values of μM to nM, but also offer useful insight to develop selective inhibitors for individual galectins.