How can subtleties of noncovalent binding be used to target “undruggable” glycans?

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The National Institutes of Health recognizes “undruggable targets” as validated therapeutic targets that remain outside of the reach of pharmacological regulation. Cell-surface glycans play a role in nearly every human disease, but there is only one approved therapy that operate by inhibiting binding to these molecules, and are thus amongst the most important undrugabble targets. Researchers have long-envisioned molecules that inhibit specific cell-surface glycans, but similarities in structures between glycan overexpressed in disease and those involved in normal biological processes make developing therapies based on glycan binding particularly challenging. Here, we show how incorporating biomimetic binding modes common to glycan binding proteins into synthetic carbohydrate receptors (SCRs) can overcome this challenge. With these flexible SCRs, binding selectivity can be manipulated to distinguish between glucose and mannose. The resulting SCRs have potent activity against flaviviruses, including Zika, whose mode of action involves interrupting binding between cell proteins and glycans on the viral envelope. To further investigate how multivalency and cooperativity are involved in this antiviral activity, we have developed a new printer to prepare glycan microarrays so we can explore binding in a more biologically relevant environment. These studies lead us to reevaluate and redefine the concepts of affinity and selectivity in the unique context of glycan binding.