COMPUTATIONALLY-GUIDED GLYCOSCIENCE: TOWARD THE RATIONAL DEVELOPMENT OF CARBOHYDRATE-BASED ANTI-VIRAL THERAPEUTICS

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Hemagglutinin (HA) mediates attachment to, and entry of, influenza virus into host cells by binding to sialic acid receptors at the cell surface. Human influenza viruses preferentially bind to sialic acid linked to galactose by a-2,6 linkages; the main type found on the epithelial cells of the human upper respiratory tract. Avian viruses tend to bind to a-2,3 linkages that are found predominantly on avian intestinal epithelium[1]. All influenza A viruses that have infected mammals emerged as some point from avian species[2]. Changes in the amino acid sequence of HA can alter the sialic acid specificity of influenza viruses, with the change of one or two amino acids[3] being sufficient to change the receptor binding specificity and affect interspecies transmission barriers.

Computational methods can be employed both to predict strain specificity, and to potentially to develop carbohydrate-based anti-adhesive (anti-viral) agents.
Here we examine the use of automated docking algorithms (AutoDock)[4] and molecular dynamics simulations with the GLYCAM force field[5] of human and avian receptor – HA complexes[3]. The theoretical methods correctly identify the strain preferences for a variety of H1 hemagglutinins and provide insight into the origin of the affinity differences. Notably molecular clustering is found to be a robust descriptor of strain specificity.

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