Structure of human CENP-A-H4-HJURP Complex

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MS.16.1


Engineering immunity against HIV-1 using designed antibody constructs

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Despite decades of effort, no current vaccine elicits neutralizing antibodies at concentrations blocking HIV-1 infection. In addition to structural features of HIV's envelope spike that facilitate antibody evasion, we proposed that the low density and limited lateral mobility of HIV spikes impedes bivalent binding by antibodies via inter-spike cross-linking [1]. In addition, molecular modeling suggested that bivalent binding within a single trimeric spike (intra-spike cross-linking) is also unlikely for antibodies directed against most protein epitopes. The resulting predominantly monovalent binding minimizes avidity and thereby high affinity binding and potent neutralization, thus expanding the range of HIV mutations permitting antibody evasion. In this talk, I will review our efforts to create high avidity anti-HIV antibodies at concentrations blocking HIV-1 infection. In addition to structural features of HIV’s envelope spike that facilitate antibody evasion, we proposed that the low density and limited lateral mobility of HIV spikes impedes bivalent binding by antibodies via inter-spike cross-linking [1]. In addition, molecular modeling suggested that bivalent binding within a single trimeric spike (intra-spike cross-linking) is also unlikely for antibodies directed against most protein epitopes. The resulting predominantly monovalent binding minimizes avidity and thereby high affinity binding and potent neutralization, thus expanding the range of HIV mutations permitting antibody evasion.

MS.16.2


The multiple personalities of transthyretin

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The human plasma protein transthyretin (TTR) is a soluble protein that functions as transport protein for thyroxin. At certain conditions however the normally tetrameric protein dissociates and forms structurally less defined monomeric or dimeric species that are prone to aggregate and form fibrils/amyloids leading to disease—familial amyloidotic polyneuropathy (FAP, type I). One of our aims is to characterize in detail the structural changes in the TTR protein that lead to amyloid formation and disease [1,2].

To prevent transthyretin fibril formation, one rather successful approach is to stabilize the native state structure, thereby reducing the protein’s ability to form the misfolded intermediate structures needed to form fibrils [3]. Even though a number of stabilizing compounds have been found [4,5], it is still desirable to find new and more structurally diverse scaffolds, and for those reasons we have initiated a fragment-based lead generation campaign [6] using human transthyretin as target protein. In this presentation, we will review our experiences and some of the results observed.

MS.16.3


Structural biology and medicinal chemistry in neglected diseases of poverty

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Parasitic diseases are a major global cause of illness, morbidity, long-term disability, and death, with severe medical and psychological...