Synthetic glycopeptide selected by directed evolution in complex with anti-HIV-1 Fab 2G12

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IgG 2G12 is an anti-HIV-1 broadly neutralizing antibody that recognizes a high-mannose patch of glycans on the envelope protein gp120. Discovered in 1998, 2G12 was one of the first anti-HIV-1 broadly neutralizing antibodies to be isolated. 2G12 is very unusual in that it binds to a purely carbohydrate epitope, with no protein contacts. 2G12 is also the only known IgG that has evolved so that its Fab regions are domain swapped by their V_H domains. The resulting IgG is linear, rather than the normal Y-shape, and has two closely spaced antigen binding sites as well as potential binding sites at the V_H-V_H' interface, allowing for high avidity recognition of multiple high-mannose glycans. Here we describe work to develop novel, synthetic glycopeptide antigens by a combination of directed evolution and click chemistry, and the crystal structure for a synthetic glycopeptide in complex with the Fab fragment from 2G12.