Structure-Based Recombination of HIV Neutralizing Antibodies

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HIV/AIDS remains one of the most important current threats to global public health. At least 60 million people have been infected with HIV, of which almost half have died. Although anti-HIV drugs have been effective among the wealthiest populations, a vaccine and/or new methods to prevent infections are drastically needed, especially in underrepresented and marginalized populations in the both the United States and the developing world. Evidence shows that delivery of antibodies, the Y-shaped proteins produced by the immune system to recognize and neutralize foreign objects in our bodies, is a safe and effective strategy used to treat many diseases. We will attempt to make new and improved antibodies that may be used to treat and/or prevent HIV infections. Starting with a novel class of antibodies that effectively neutralizes several strains of HIV using the same mechanism, we will use a synthetic biology approach to break several effective antibodies (parents) into smaller pieces and recombine the pieces from different parents to make a library of mixed antibodies that will be tested for enhanced ability to prevent HIV infection. One may think of each antibody as being a different color, whose structure is an ordered series of beads of a particular shape on a string (for instance, parent 1 could comprise a cube, sphere, pyramid, cone, and cylinder, all in red). We plan to preserve the order of the beads to produce the same shape in all chimeras, but vary the color to make thousands of different colored necklaces (i.e. bead 1 will always be a cube, but it could be blue, red, green, or any color of an available parent antibodies; it will always be followed by a sphere of any available color, etc.). Each shuffled antibody, represented by a necklace of different colored beads, could then be tested for its ability to prevent HIV infection. This method has been proven to work to improve proteins for use in industrial applications.

After successful antibodies have been identified, we will analyze them to determine how the antibodies interact with viral proteins at the atomic level. We will use crystallography, in which we take a mixture of the antibody and the HIV protein that interacts and put it in solution and let it dry slowly, so that it can form an ordered crystal, in the same manner as one might make rock candy. We will then examine the crystal using the x-ray equivalent of a light microscope to look at the position of atoms in our crystals. This analysis will allow us to understand the atomic features that are important and necessary for interactions between antibodies and HIV surface proteins and prevention of HIV infection. Through our studies, we hope to make novel antibodies and uncover new information that can be used to further devise strategies to treat and/or prevent HIV infection.