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# Development of anti-HIV double variable domain antibodies that bind both gp120 and gp41 on the envelope protein

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The HIV envelope protein (Env) is the sole virus protein expressed on the surface of virions and infected cells. Consequently, the development of anti-Env antibodies (Abs) for therapeutic applications is the subject of intense investigation. Anti-Env Abs can be used to neutralize cell-free virus and kill HIV-infected cells. After almost two decades with little progress, the introduction of recombinant DNA techniques has lead to a spate of highly effective and broadly reactive neutralizing Abs in the past ten years. HIV Env consists of two, non-covalently linked glycoproteins, the transmembrane anchor gp41, and the receptor-binding surface protein gp120. Neutralizing sites have been identified on both gp120 and gp41. Working with anti-HIV immunotoxins, we have also mapped the targets of these cytoxic agents. Interestingly, there was little correlation between neutralization and cell killing activities. In an effort to increase cytotoxic activity, we have made double variable domain (DVD) Abs that bind to structures on gp120 and gp41 that are the most effective targets for anti-HIV immunotoxins. Neither Ab, alone or in combination, neutralized HIV well. We were initially disappointed that the DVD's offered no improvement in cytotoxicity over a mixture of the two Abs, but then bemused to discover that the DVDs were highly effective at neutralizing HIV infection. Activity was both broad and potent. I will discuss mechanisms whereby two weakly neutralizing Abs become more potent when combined into a single molecule.

## Biography

Seth Pincus has received his MD from New York University. Following a Pediatrics Residency at the University of Utah, he was trained in the Immunology Branch of NCI. His first faculty appointment was at the University of Utah, followed by stints at the NIAID Rocky Mountain Labs at Montana State University where he chaired the Department of Microbiology and from there to his current position in the Departments of Microbiology and Pediatrics, at LSU School of Medicine, New Orleans. He has published over 100 peer-reviewed papers, textbook chapters and invited articles. He has served on or chaired multiple NIH study sections and Editorial Boards.

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