



SCIENCE FOR THE BENEFIT OF HUMANITY

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# Novel and Potent Broadly Neutralizing Antibodies For HIV Therapy

## Technology Summary

Researchers around the world have attempted to design and develop effective vaccines and therapies for HIV infection with little to no success for over twenty-five years. The main impediment to this effort is the rapid mutation of HIV, resulting in the evasion of the immune system and antibody response. The current mode of therapy is a combination of anti-retroviral agents, which is successful in controlling HIV infection but it is burdensome due to the requirement for daily intake, side effects and resistance to the drugs. There is still a need for HIV therapies that are complementary and able to address the rapid mutation rate of HIV.

Scientists at The Rockefeller University in collaboration with investigators at The California Institute for Technology have identified and characterized neutralizing antibodies present in HIV-infected individuals whose immune response is able to control the virus and prevent disease progression. These individuals have high levels of antibodies that inhibit HIV proliferation so that the virus cannot infect new cells. Recently, this team of esteemed scientists showed that a specific combination of five potent neutralizing antibodies targeting the HIV surface protein gp120 effectively suppressed viral replication in humanized mice for sixty days following treatment due to the increased half-life of the antibodies (see Klein, et al 2012, *Nature*). This antibody cocktail and other combinations could be a potent mode of HIV therapy either in addition to or in place of current therapeutic agents. It is also possible that the HIV neutralizing antibodies could be administered to prevent HIV infection.

## **RU 1024 (CIT 5943) & RU 1079 (CIT 6220): Novel classes of broadly neutralizing antibodies against HIV.**

Our scientists have discovered a class of agonistic CD4-binding site (CD4bs) antibodies that mimic the binding of host CD4 by HIV's gp120 core protein and a class of antibodies that bind various carbohydrate epitopes in gp120. These antibodies show broad and potent neutralizing activity individually, but a specific combination of five antibodies controls viral load in humanized mice well after the cessation of therapy.

**Patent Information:** Patent applications US-2014-0328862 and PCT application WO2014/063059 are pending.

## **References:**

<http://newswire.rockefeller.edu/2012/11/06/potent-antibodies-neutralize-hiv-and-could-offer-new-therapy-study-finds/>

Klein, *et al.* 2012. HIV therapy by a combination of broadly neutralizing antibodies in humanized mice. *Nature*, doi: 10.1038/nature11604.

Scheid, *et al.* 2011. Sequence and structural convergence of broad and potent HIV antibodies that mimic CD4 binding. *Science*, 333:1633-1637.

Mouquet *et al.*, 2012. Complex-type N-glycan recognition by potent broadly neutralizing HIV antibodies. *Proc. Natl. Acad. Sci.*, doi: **10.1073/pnas.1217207109**

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**The Rockefeller University also has the following intellectual property in the field of HIV neutralizing antibodies:**

**RU 1182 (CIT 6795): Broadly neutralizing HIV antibodies and their epitopes**

Our scientists have identified a novel antibody called 8ANC195, which binds an epitope spanning multiple subunits of the HIV glycoprotein envelope. This interaction is complementary to other HIV neutralizing antibodies previously identified, therefore this antibody could be an ideal component in therapeutic antibody cocktails for effectively treating HIV.

Patent information: PCT patent application WO2015/117008 pending.

Reference: Scharf, et al., 2014. Antibody 8ANC195 reveals a site of broad vulnerability on the HIV-1 envelope spike. **Cell Reports**, 7:785-95.

**RU 1204: Broadly neutralizing HIV antibodies and latency activators**

Latent reservoirs of HIV-1 in cells are refractory to anti-retroviral therapies and remain a major barrier in curing HIV-1. Our investigators have found that a combination of neutralizing antibodies that bind Fc receptors and viral inducers that act by independent mechanisms of action are effective at reducing viral rebound in vivo as tested in a humanized mouse model.

Patent information: U.S. patent application pending

Reference: Halper-Stromberg, et al. 2014. Broadly neutralizing antibodies and viral inducers decrease rebound from HIV-1 latent reservoirs in humanized mice. *Cell*, 158:1-11.

**RU 1045 (CIT 5930): Improved anti-HIV antibodies by rational structure-based design.**

Our scientists have determined the structure of a potent anti-HIV antibody alone and in complex with the HIV-1 spike protein gp120. With this information, they designed an antibody with a G54W substitution and other mutations to confer hydrophobic properties at that position in antibodies against the CD4-binding site on gp120. This single substitution increases contact with the gp120 bridging sheet resulting in an improvement in breadth and potency by an order of magnitude, which should significantly improve clinical utility of these antibodies.

Patent Information: Patent applications US 2012-0288502 A1 WO2013016468 A3 are pending

References: Diskin, *et al.*, 2011. Increasing the potency and breadth of an HIV antibody by using structure-based rational design. *Science*, 334:1289-93.

**RU 1097 (CIT 6235): PVL antibody variants resistant to HIV escape**

PVL antibodies are a class of potent anti-CD4 binding site antibodies that target HIV. Studies show, however, that when PVL antibodies are used to treat HIV infections in vivo, escape mutants emerge. Our scientists have used rational structure-based design to engineer PVL antibodies with specific site mutations that confer resistance to HIV escape. Specific antibodies have been isolated and characterized from HIV-infected human donors, and then changes made to specific antibodies based on rational structure-based design. Antibodies of interest were then tested for neutralizing activity against virus panels and humanized mouse models.

Patent Information: Patent applications US 2013-0209454 A1, WO2013090644 A3, WO 2013192589 A1, and US2014017234 (A1) are pending.

**RU 1216 (CIT 7002): Engineered anti-HIV-1 reagents that achieve potent and broad neutralization activity by intra-spike crosslinking.**

Antibodies developed during HIV-1 infection lose efficacy as the virus mutates its envelope spike. HIV-1 uses its small spike number to impede bivalent binding of IgGs through inter-spike cross-linking, thus hindering avidity, potent neutralization, and expanding the range of mutations permitting antibody evasion. Our scientists engineered antibody-based molecules capable of avid binding through intra-spike cross-linking. Bivalent binding resulted in synergy (>100-fold average increased potency) and shed light on dynamic states of the HIV-1 envelope protein. These results support the hypothesis that low spike densities facilitate antibody evasion and demonstrate that intra-spike cross-linking lowers the concentration of antibodies required for neutralization by up to 2.5 orders of magnitude.

Patent information: U.S. patent application pending

Reference: Galmidi, et al. 2015. Intra spike crosslinking overcomes antibody evasion by HIV-1. *Cell*, 160:433-446.