Creating New Immune Systems for HIV Patients

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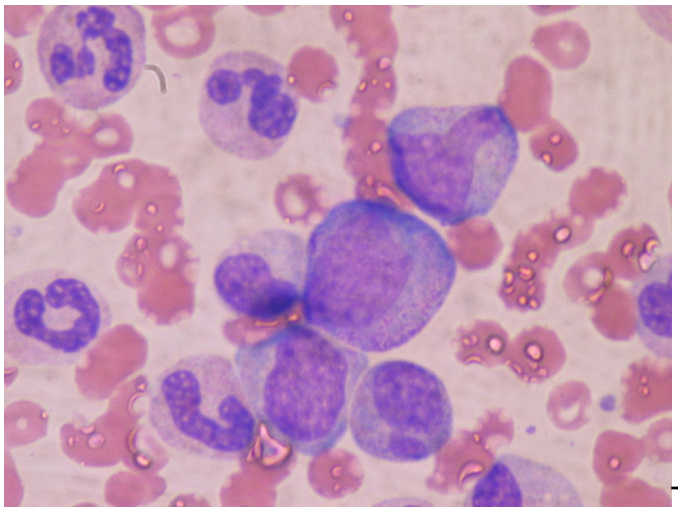 There is good news in attempts to halt HIV by growing, in patients, new immune systems lacking function in a key gene just as the first—and only—cured HIV patient did.

Using blood stem cells possessing a CCR5 gene mutation that blocks CD4 T cell entry of HIV, Calimmune—led by Nobel Laureate David Baltimore—has, for one year, safely begun growing new immune systems in patients.

Calimmune said last week its Data Safety Monitoring Board found the first part of its Phase I trial of four patients so safe, a second half will now launch.

“The approval was to move to the second cohort of our Phase I study,” Baltimore told *Bioscience Technology* via email this week. “I am very glad that we passed through the treatment of the first cohort without serious incident, allowing us to start treatment of the second cohort.”

Another company, Sangamo, plans a similar trial in autumn with City of Hope hospital. “We’re very excited,” City of Hope Department of Virology Chairman John Zaia told *Bioscience Technology*.

Both studies were inspired by the “Berlin Patient,” the first person functionally cured of HIV.

The Berlin Patient

After HIV patient Timothy Brown (aka The Berlin Patient), contracted leukemia in the mid 2000’s, Heidelberg University oncologist Gero Hutter decided to give him a blood stem cell transplant to erase, and replace, his cancer-ridden blood/immune system.

But Hutter had heard a rare few are naturally HIV-immune, possessing a

homozygous (two copy) mutation in the CCR5 gene (CCR5 delta 32), which blocks HIV entry into CD4 T cells. So he acquired donor stem cells homozygous for the mutation. The idea: to erase Brown's cancer-*and*-HIV ridden immune system, and replace it with a cancer-free, HIV-*resistant* immune system.

He gave them to Brown in 2007.

Ever since, Brown's blood has contained no clinically meaningful traces of HIV. He went off his anti-retrovirals. He has been declared by HIV experts worldwide as the first cured [1] HIV patient.

The Calimmune Approach

In response, the team of David Baltimore—a former president of the California Institute of Technology with a Nobel in virology--devised protocols to genetically alter stem cells to possess a similar CCR5 mutation. He and UCLA AIDS Institute director Irvin Chen formed Calimmune around their research. In July 2013, they launched their first trial.

Their approach involves disarming CCR5 [2] in stem cells and CD4 T cells using hairpin RNAs [3] delivered by lentiviral vector.It adds a gene coding for a protein (C46) that inhibits HIV binding.

In the study's first half, four patients received stem cells and CD4 T cells with CCR5 disarmed this way. (The patients had stopped taking anti-retrovirals due to side effects.)

The approach proved safe for a year, according to the internal review board. So more patients can now receive the genetically modified stem cells.

The Sangamo Approach

For months, Sangamo has conducted trials disabling CCR5 in patients' CD4 T

cells—*not* their stem cells. The stem cell approach launching in fall is longer-lasting. Stem cells home to the bone marrow, where they produce all immune cells for the life of the patient. By contrast: "CD4 T cells have to be continually re-infused, being shorter-lived," Zaia told *Bioscience.*

But CD4 T cells are easier to administer. To get new stem cells growing in bone marrow, chemotherapies must wipe out native marrow and create "space," Zaia said. This can be a dangerous period, when old immune cells can reject new cell grafts, and vice versa. By contrast: "CD4's can just be injected into the bloodstream," Zaia said. So Sangamo started with CD4s.

But as noted, stem cells, once settled, can "produce T cells continuously," Zaia said. Hence, the Calimmune and Sangamo stem cell trials. A key difference will be methods to disable CCR5. Sangamo will use zinc finger nucleases where Calimmune uses hairpin RNA .

Still, some researchers wonder if the stem cell graft itself—all gene tweaking aside—plays a role.

Standard Stem Cell Option

Two HIV patients in Sydney, Australia received reduced-intensity conditioning stem-cell transplants for cancer, reported St. Vincent's Hospital at the 20th International AIDS Conference last month. The Berlin patient received harsher conditioning. His transplanted cells also, as noted, possessed two copies of the CCR5 delta32 mutation, where the Australians received normal stem cell grafts, St. Vincent Senior Lecturer Kersten Koelsch told *Bioscience Technology* by email.

Despite the weaker therapy, both Australians have gone three years without detectable HIV. Two types of PCR assays found no HIV RNA in plasma, or HIV DNA in either CD4 T cells, or peripheral blood mononuclear cells.

The Australians remain on anti-retrovirals. But their lack of detectable peripheral blood HIV reserve is interesting, Koelsch told *Bioscience Technology*. It is reminiscent of the Berlin Patient. Anti-retrovirals hold HIV in check for 80 percent of patients—but viral reserves linger anyway.

One of the Australians naturally possesses only one gene copy of the CCR5 mutation. But one copy doesn't halt the disease. And the other patient's CCR5 gene copies were normal.

Can stem cell transplants, on their own, help clear HIV?

"There are several possibilities as to why the [Berlin Patient] transplant was successful," Koelsch said. "One plausible possibility: he received the CCR5 -/- [mutated] donor cells. But it is also possible that other factors, such as [stem cell] graft versus host disease [GvHD], contributed to viral clearance. We have seen a significant reduction of the viral reservoir to undetectable levels in the peripheral blood, together with the change in antibody patterns. So it will be important now to

compare CCR5 -/- recipients [like Brown] with CCR5 +/- or +/+ recipients to see which of the possible mechanisms (CCR5 status of the donor cells, GvHD, conditioning, other) take part in reduction of the reservoir and/or viral clearance. Also, these patients are interesting in regard to the 'hideout' locations of HIV in patients with very low or undetectable virus in peripheral blood."

Earlier, [4] it was widely reported that two high-profile Boston HIV patients, receiving normal stem cell transplants like the Australians', relapsed when weaned off anti-retrovirals.

Still, said Koelsch, the response to the Australian report was "positive, in particular because these patients are currently very rare." There is great interest in finally understanding "the impact of such transplants on the HIV infection, and to investigate in these patients the possible hiding spots for persistent HIV if we can't detect the virus, or the DNA, in peripheral blood. This may then also translate to other patients who haven't received stem cell transplants."

Links:
[1] http://www.nejm.org/doi/full/10.1056/NEJMp1207138
[2] http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0053492
[3] http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2830759/
[4] http://www.nature.com/news/hopes-of-hiv-cure-in-boston-patients-dashed-1.14324