defeatHIV newsletter

Fall/Winter 2012

Welcome to the first defeatHIV newsletter, a biannual publication of the Delaney Cell and Genome Engineering Initiative. Founded in 2011 and based at the Fred Hutchinson Cancer Research Center in Seattle, WA, defeatHIV is a consortium of scientific investigators and clinicians from both public and private research organizations who are committed to finding a cure for HIV. We are supported through a new program sponsored by the National Institutes of Health and the National Institute of Allergy and Infectious Disease in honor of AIDS activist Martin Delaney. This program, called the Martin Delaney Collaboratory: Towards an HIV-1 cure, focuses on providing support for HIV research strategies that are curative and foster partnerships between public and private research organizations. defeatHIV is one of only three funded Martin Delaney Collaboratories, along with the Collaboratory of AIDS Researchers for Eradication (CARE) based at the University of North Carolina at Chapel Hill, and the Delaney AIDS Research Enterprise (DARE) at the University California, San Francisco.

The success of our mission to pave a way toward an HIV cure depends heavily on our connection with the HIV community. Our intent for this publication is to inform the community about the most current research progress, technologies, and events that evolve from our collaboratory efforts. Future issues will contain the following sections:

- **Focus Point** Discover more about particular areas of scientific discovery within our collaboratory through in-depth feature articles
- **Special Report** Significant breakthroughs are reported when they occur
- **Publications** Learn about the work our collaboratory publishes in academic journals
- **Events** Stay informed about past and future events within the collaboratory

We hope you enjoy this first issue and will look forward to reading about our most current, exciting work in future newsletters and at defeatHIV.org. To become a subscriber, sign up at defeatHIV.org/newsletter. Your feedback and comments are most welcome and can be submitted to: info@defeatHIV.org.

in this issue

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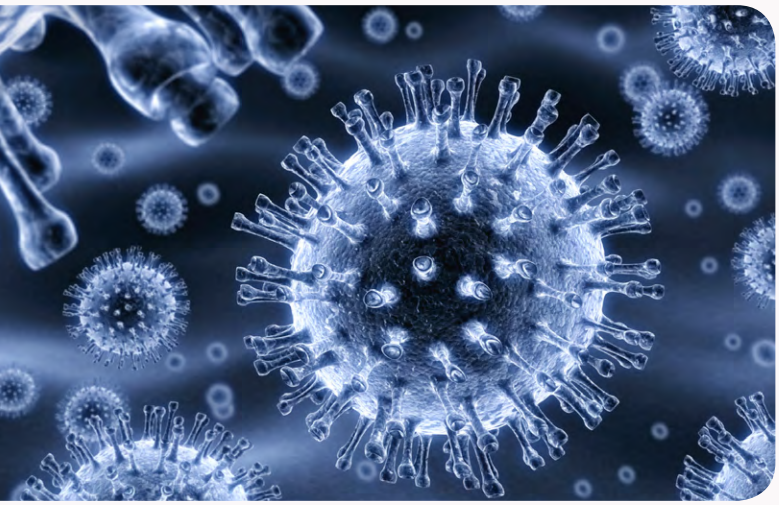
Focus Point | defeatHIV Clinical Studies

Information for patients with HIV infection who are interested in clinical trials

Currently patients with HIV infection have many options for therapy. Most importantly, highly active anti-retroviral therapy (HAART) is used to stop the virus from reproducing itself and from causing harm. In most people, HAART prevents progression of HIV infection and allows people to return to normal life. However, *HAART does not cure HIV infection* because the virus is able to survive in a dormant state (called the latent HIV reservoir). In fact, when HAART is stopped, the HIV virus usually grows back within a couple months, to the same level as in the beginning of the infection.

People living with HIV may develop blood cancers such as leukemia, just as those without HIV develop. HIV infection also may increase a person's susceptibility to developing lymphoma. Whether or not a person has HIV, lymphomas and leukemias are treated the same way, usually with powerful chemotherapy drugs. Sometimes, a hematopoietic cell transplant (HCT) is the best treatment, especially for treatment of a relapse.



In the past, HCT was not recommended for patients living with HIV, because very intensive drugs were given that caused harmful effects to the body and made it easier for the HIV to grow. Since that time there has been progress in several areas that now make it much more likely that HCT will be successful in people living with HIV.

The first is the ability to give HAART after HCT, which helps to keep the HIV under control. Controlling the HIV is very important for patients who need intensive chemotherapy or radiation as part of the HCT, such as patients with lymphoma or advanced leukemia.

The second is the potential for HCT to cure HIV if "HIV-resistant cells" are given back to the patient. We know this is possible because one patient treated in Berlin (known as the "Berlin patient") received cells from a donor who carried a rare, natural mutation that created resistance to HIV. The patient no longer needed HAART after he recovered from the HCT, and the virus did not grow back.

In the past, HCT was not recommended for patients living with HIV. Today, there is a lot of potential for HCT and other cell therapies, such as gene therapy, to help patients living with HIV.

Third, is the development of a new and potentially safer transplant procedure that requires less powerful agents to prepare the body for transplantation. This procedure was developed at the Fred Hutchinson Cancer Research Center and has been studied here and in several other institutions. We have used this procedure successfully in patients with immunodeficiency diseases not caused by HIV and in older cancer patients. Thus far the results have been encouraging and show a lower risk of severe side effects or death resulting from the transplant procedure compared to traditional transplant procedures.

Why are we doing research in HCT and cell therapies for patients with HIV?

There is a lot of potential for HCT and other cell therapies, such as gene therapy, to help patients living with HIV. There also is a need for information about the responses of patients to cell therapies, so that we can make the procedures as safe as possible. And, because of the success of the "Berlin patient", there is a need to understand how HCT was able to get rid of the latent HIV reservoir. We hope that by answering these questions we will learn how to defeatHIV.

What clinical studies are available for patients living with HIV?

Several defeatHIV clinical studies are open for patients living with HIV. The list at right provides a brief outline of each study.

Where can I find more information or eligibility criteria for these clinical studies?

Additional info on these studies, including eligibility criteria, can be found on our website at defeatHIV.org/clinical-studies.

Three clinical trials are currently open and enrolling

Study Protocol ID 1410 | The purpose of the treatment on this study is to replace bone marrow cells with healthy cells donated by a person with a healthy immune system. The new bone marrow or hematopoietic stem cells have the ability to grow into new blood and immune systems. We believe that HAART may give us a new way to help control the HIV and prevent it from infecting the new bone marrow cells. We will monitor the level of HIV in the latent reservoir to determine whether HAART drugs can continue to control or even reduce HIV after hematopoietic stem cell transplantation (HSCT).

Study Protocol ID 2212 | We are performing this study because some patients with HIV also have a serious blood disorder, which needs to be treated with HCT. The study will monitor patients given HCT so that we will learn whether there are serious problems due to the HIV. The purpose of the study is to find out what happens to the latent HIV reservoir in patients who have HIV and who are given HCT for treatment of their leukemia or lymphoma. This study will offer a unique chance to understand the effect of intensive chemo/radiotherapy, and in many cases allogeneic grafts, on clearance of latently infected resting CD4+ cells and reconstitution of HIV-specific immune responses.

Study Protocol ID 2485 | We are performing this study to determine if HIV-positive patients with lymphoma will benefit from autologous peripheral blood stem cell (PBSC) transplant. Patients donate autologous PBSC, which are frozen until later use. Patients are given high-dose chemotherapy to treat lymphoma, and then are given back their own PBSC after receiving chemotherapy - also referred to as conditioning therapy.

Seattle Cancer Care Alliance, where clinical trials are taking place

Focus Point | defeatHIV Team

Meet our team of Investigators and Institutions

Fred Hutchinson Cancer Research Center

Seattle, WA | fhcrc.org

Established in 1975, Fred Hutchinson Cancer Research Center is one of the world's leading cancer research institutes. Its interdisciplinary teams of scientists conduct research throughout the world to advance the prevention, early detection and treatment of cancer and other diseases. Hutchinson Center researchers pioneered bone-marrow transplantation for leukemia and other blood diseases. Recognizing that infectious agents contribute to up to a quarter of the world's cancers, Center researchers also study infectious diseases, including HIV- and AIDS-related malignancies.

Seattle Children's Research Institute

Seattle, WA | seattlechildrens.org/research

Seattle Children's Research Institute is the research arm of Seattle Children's Hospital, which is dedicated to preventing, treating, and eliminating pediatric disease. The research institute has nine major centers, and is internationally recognized for its work in cancer, genetics, immunology, pathology, infectious disease, injury prevention and bioethics.

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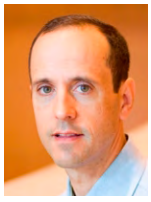

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defeatHIV Team (cont'd)

University of Washington

Seattle, WA | washington.edu

One of the oldest state-supported institutions of higher education on the west coast, The University of Washington was founded in 1861 and is one of the preeminent research universities in the world. Among the UW faculty, there are five winners of Albert Lasker Award for Clinical Medical Research, one winner of the Fields Medal, five winners of the National Medal of Science, nineteen winners of the Presidential Early Career Awards in Science and Engineering, and six Nobel Prize laureates.

Beckman Research Institute of the City of Hope

Duarte, CA | cityofhope.org

Recognized nationwide for its innovative biomedical research, Beckman Research Institute of City of Hope is home to some of the most creative minds in science. With a staff of more than 500, including nearly 100 principal investigators, Beckman Research Institute undertakes fundamental investigations in basic biology and genetics.

Sangamo BioSciences

Richmond, CA | sangamo.com

Sangamo BioSciences is a clinical-stage biopharmaceutical company focused on the research, development and commercialization of engineered DNA-binding proteins as the basis of a novel therapeutic platform to address unmet medical needs. The company is the worldwide leader in the development of proprietary technology enabling specific gene modification and regulation of gene expression.

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Upcoming Events

1st joint Martin Delaney Collaboratory Meeting: "Strategies for an HIV Cure"

November 28-30, 2012

Washington, D.C.

sponsored by the Division of AIDS (DAIDS) at the NIAID, NIH

This meeting will bring together researchers associated with each of the three NIH-funded Martin Delaney Collaboratories, other researchers engaged in HIV cure research, investigators in complementary disciplines, and community members to share scientific results and engage in active discussion about the merits of various HIV cure approaches under investigation. Register now.

Past Events

amfAR "A Cure for HIV/AIDS" Capitol Hill Briefing

June 20, 2012

Capitol Hill, Washington D.C.

sponsored by amfAR, The Foundation for AIDS Research

June 20, 2012 | defeatHIV co-PI Keith Jerome participated in the Capitol Hill Briefing on "A Cure for HIV/AIDS: Recent Advances and New Research Frontiers," sponsored by amfAR, The Foundation for AIDS Research. More than 100 members of Congress, Congressional staff, and leaders from public health, medical, and scientific organizations gathered to discuss the latest scientific advances and strategies commissioned in pursuit of an HIV/AIDS cure. The highlight of the briefing came when Timothy Brown (pictured), also known as the Berlin Patient, spoke from a unique patient perspective – as the first individual to have been functionally cured of HIV.

1st defeatHIV Annual Meeting

May 31, 2012

Fred Hutchinson Cancer Research Center, Seattle, WA

May 31, 2012 | defeatHIV investigators from the Hutchinson Center, University of Washington, Seattle Children's Hospital, City of Hope, Sangamo BioSciences and NIH participated in what was a productive review of the collaboratory's operational and scientific accomplishments in our first year of funding. Also taking part were members of the defeatHIV Scientific Advisory Board, whose comments and feedback on year 1 progress will provide further refinement of our approaches and facilitate achievement of our milestones.

Publications

Recent work from our collaboratory

Towards an HIV cure: a global scientific strategy. Deeks SG, Autran B, Berkhout B, Benkirane M, Cairns S, Chomont N, Chun TW, Churchill M, Mascio MD, Katlama C, Lafeuillade A, Landay A, Lederman M, Lewin SR, Maldarelli F, Margolis D, Markowitz M, Martinez-Picado J, Mullins JI, Mellors J, Moreno S, O'Doherty U, Palmer S, Penicaud MC, Peterlin M, Poli G, Routy JP, Rouzioux C, Silvestri G, Stevenson M, Telenti A, Lint CV, Verdin E, Woolfrey A, Zaia J, and Barre-Sinoussi F. Nat Rev Immunol. 2012 12(8): 607-14. PMID: 22814509

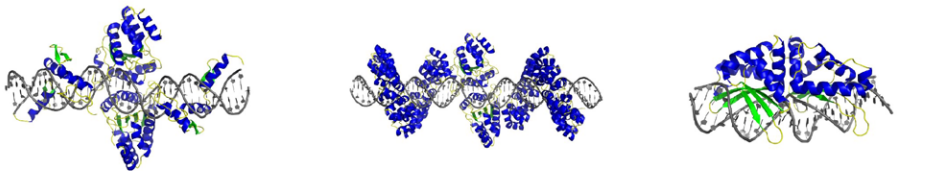
Coupling endonucleases with DNA end-processing enzymes to drive gene disruption. Certo MT, Gwiazda KS, Kuhar R, Sather B, Curinga G, Mandt T, Brault M, Lambert AR, Baxter SK, Jacoby K, Ryu BY, Kiem HP, Gouble A, Paques F, Rawlings DJ, and Scharenberg AM. Nat Methods. 2012 Sep 2; PMID: 22941364

Targeted DNA mutagenesis for the cure of chronic viral infections

Journal of Virology | Sept 2012 | PMID: 22718830

Joshua T. Schiffer, Martine Aubert, Nicholas D. Weber, Esther Mintzer, Daniel Stone, Keith R. Jerome

defeatHIV co-PI Dr. Keith Jerome and his team review the exciting potential of targeted DNA cleavage enzymes and their use in the treatment of chronic viral infections, including HIV, Hepatitis B Virus and Herpes Simplex Virus.



Zinc finger nuclease
2 ORFs
~1.6 kb coding sequence
Leaves 5' overhangs
Relatively simple retargeting
Moderately high specificity
Moderately difficult vectorization/delivery

TAL effector nuclease
2 ORFs
~2.7 kb coding sequence
Leaves 5' overhangs
Very simple retargeting
High specificity
Difficult vectorization/delivery

Homing endonuclease
1 ORFs
~0.8 kb coding sequence
Leaves 3' overhangs
More difficult retargeting
High specificity
Easiest vectorization/delivery

Efficient generation, purification, and expansion of CD34+ hematopoietic progenitor cells from nonhuman primate induced pluripotent stem cells. Gori JL, Chandrasekaran D, Kowalski JP, Adair JE, Beard BC, D'Souza SL, and Kiem HP. Blood. 2012 Aug 16; PMID: 22898598

Optimization and qualification of a multiplex bead array to assess cytokine and chemokine production by vaccine-specific cells. Defawe OD, Fong Y, Vasilyeva E, Pickett M, Carter DK, Gabriel E, Rerks-Ngarm S, Nitayaphan S, Frahm N, McElrath MJ, and De Rosa SC. J Immunol Methods. 2012 Aug 31; 382(1-2): 117-28. PMID: 22626638

Dynamics of envelope evolution in clade C SHIV-infected pig-tailed macaques during disease progression analyzed by ultra-deep pyrosequencing. Tso FY, Tully DC, Gonzalez S, Quince C, Ho O, Polacino P, Ruprecht RM, Hu SL, and Wood C. PLoS One. 2012 7(3): e32827. PMID: 22427893

Is the virulence of HIV changing? A meta-analysis of trends in prognostic markers of HIV disease progression and transmission. Herbeck JT, Muller V, Maust BS, Ledergerber B, Torti C, Di Giambenedetto S, Gras L, Gunthard HF, Jacobson LP, Mullins JI, and Gottlieb GS. Aids. 2012 Jan 14; 26(2): 193-205. PMID: 22089381

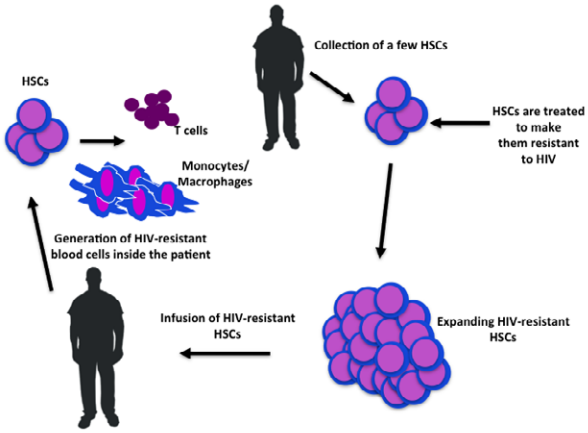
Publications (cont'd)

Hematopoietic-Stem-Cell-Based Gene Therapy for HIV Disease

Cell Stem Cell | Feb 2012 | PMID: 22305563

Hans-Peter Kiem, Keith R. Jerome, Steven G. Deeks, Joseph M. McCune

Investigators from defeatHIV and the Delaney AIDS Research Enterprise (DARE), two of the three NIAID Martin Delaney Collaboratories, partner to review HSC-based gene therapy strategies for HIV disease – demonstrating how scientists in the field are uniting in the fight against HIV.

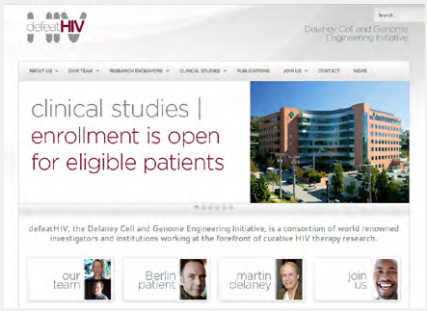


Systemic administration of combinatorial dsiRNAs via nanoparticles efficiently suppresses HIV-1 infection in humanized mice. Zhou J, Neff CP, Liu X, Zhang J, Li H, Smith DD, Swiderski P, Aboellail T, Huang Y, Du Q, Liang Z, Peng L, Akkina R, and Rossi JJ. Mol Ther. 2011 Dec; 19(12): 2228-38. PMID: 21952167

Engineering HIV-resistant human CD4+ T cells with CXCR4-specific zinc-finger nucleases. Wilen CB, Wang J, Tilton JC, Miller JC, Kim KA, Rebar EJ, Sherrill-Mix SA, Patro SC, Secreto AJ, Jordan AP, Lee G, Kahn J, Aye PP, Bunnell BA, Lackner AA, Hoxie JA, Danet-Desnoyers GA, Bushman FD, Riley JL, Gregory PD, June CH, Holmes MC, and Doms RW. PLoS Pathog. 2011 Apr; 7(4): e1002020. PMID: 21533216

Looking Ahead

We hope you enjoyed our first issue of the defeatHIV newsletter. Looking ahead, we are excited about our next Spring/Summer 2013 issue featuring a report on the first joint meeting of NIH-funded Martin Delaney Collaboratories. The Division of AIDS (DAIDS) at the National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH) is sponsoring this scientific meeting focused on the development of innovative strategies to cure HIV infection. The Strategies for an HIV Cure meeting will take place November 28-30 in Washington, DC, bringing together the defeatHIV, CARE and DARE collaboratories to stimulate new ideas for future research projects and develop new scientific collaborations. This is an exciting time for HIV patients, clinicians and researchers alike and we hope you will stay connected with our efforts as we forge a path to an HIV cure!



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