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FOR IMMEDIATE RELEASE
November 10, 2008

NEW HOPE FOR HIV TREATMENT: CELLS EXHAUSTED FROM FIGHTING HIV INFECTION CAN BE REVITALIZED

Researchers at the University of Toronto and the University of California, San Francisco, have revealed new hope for HIV treatment with the discovery of a way to ‘rescue’ immune cells that are exhausted from fighting off HIV infection.

The team lead by Drs. Mario Ostrowski, of the University of Toronto’s Faculty of Medicine, and Douglas Nixon, of the Division of Experimental Medicine at the University of California, San Francisco, has discovered that a molecule called Tim-3 is present at high levels on poorly functional immune system cells which are ‘exhausted’ from fighting HIV infection. The researchers found that blocking the activity of Tim-3 on these cells improved their function and allowed them to rejoin the battle against HIV.

“In the typical course of HIV infection, an initial burst of very high levels of the HIV virus is brought partially under control by the infected person’s immune system, specifically by an immune system cell called a CD8+ killer T cell. In the majority of cases without antiretroviral drug treatment, the immune system is eventually overwhelmed and progression to AIDS occurs,” said co-principal author Brad Jones, a PhD candidate in Immunology at the University of Toronto.

Progression to AIDS is associated with a breakdown in those CD8+ T immune system cells. In a typical viral infection, those cells rapidly multiply, kill off virus-infected cells and stimulate other cells in the immune system. But over time, in the battle to fight off HIV infection these CD8+T cells become less functional and enter into a state known as ‘exhaustion.’ “The mechanisms that lead to this exhausted state are not well known,” said Jones. “We felt that if we could understand these mechanisms then we may be able to intervene and re-energize the immune system.” The research team theorized that this exhausted state may result from the Tim-3 molecule sending a signal to shut down CD8+ T cells in HIV-infected individuals.

The researchers observed that Tim-3 expression on T cells, in particular the CD8+ T cells, associated remarkably strongly with clinical parameters of HIV disease progression in a diverse group of HIV-infected individuals. “From these results we predicted that the Tim-3 pathway might be manipulated to potentially confer clinical benefit and serve as a promising new target for clinical intervention to decrease the severity of HIV infection,” said co-principal author Lishomwa Ndhlovu, MD, PhD in the Division of Experimental Medicine, University of California, San Francisco.

“To test this, we produced a molecule capable of blocking the Tim-3 signal and studied the effect that this had on CD8+ T cell function in vitro,” said Mario Ostrowski, MD, Associate Professor in the Department of Immunology, University of Toronto. “We observed that blocking the Tim-3 pathway rescued those cells and restored their ability to fight off infection.”

This discovery, published in the November 24th issue of the *Journal of Experimental Medicine* opens up the possibility of new therapies aimed at blocking the Tim-3 signal and reinvigorating the immune system’s natural ability to battle infection.

(more)

“We still do not know how the virus triggers Tim-3 or if this is restricted to HIV infection,” said Dr. Ndhlovu, “but our findings may provide a new direction to vaccines and therapies that will potentially reverse these dysfunctional cells and allow them to control HIV-1 replication.”

“Our hope is this will enable those infected with HIV to turn the tide in the long battle between the immune system and HIV. Future studies which block Tim-3 signaling in animal models of chronic viral infection will help to evaluate the therapeutic potential of this approach,” said Jones.

Co-authors include Brad Jones, Mario Ostrowski, Prameet Sheth, Jessica Wong, Bahareh Vali, Feng Yun Yue, Malathy Satkunarajah, Gabor Gyenes, Martin Hyrcza, Rupert Kaul, and James Rini from the University of Toronto; Lishomwa Ndhlovu, Douglas Nixon, Aashish Jha, Brian Long, Marc Schweneker, Joan Chapman, and Joseph McCune at the Division of Experimental Medicine at UCSF; Jason Barbour, Gerald Spotts, and Frederick Hecht from the HIV/AIDS Division of the Department of Medicine at UCSF; Colin Kovacs, Aref Sassi, Mona Loutfy, Roberta Halpenny, and Desmond Persad at the Maple Leaf Medical Clinic, and Tae-Wook Chun of the National Institute of Allergy and Infectious Diseases, National Institutes of Health.

The research was supported by funds from the Canadian Institutes for Health Research (CIHR), UCSF Gladstone Institute of Virology & Immunology Center for AIDS Research (P30 AI027763), the UCSF AIDS Biology Program of the AIDS Research Institute (ARI), and the National Institutes of Health (AI60379, AI68498, AI64520, and AI066917) and the Cancer Research Institute.

The Faculty of Medicine at the University of Toronto is home to Canada’s pre-eminent medical school. Founded in 1843, the Faculty of Medicine catapulted onto the world stage with Sir Frederick Banting and Charles Best’s discovery of insulin in the 1920s. Today, the Faculty of Medicine ranks among the top institutions in the world, with 10 fully affiliated hospitals and 15 community-affiliated sites.

Established in 1827, the University of Toronto is Canada’s largest and most influential university with almost 12,000 faculty and staff working at three campuses and 10 academic hospitals in the Toronto region. Our world-leading scholars teach more than 60,000 students in 841 distinct undergraduate programs as well as 520 graduate and 42 professional programs. According to Thomson ISI data, U of T faculty also publishes more research than any other publicly funded university in North America. And with over 400,000 alumni in more than 130 countries around the world, U of T is truly global in reach and impact.

The University of California, San Francisco (UCSF), Division of Experimental Medicine, the Gladstone Institute of Virology and Immunology and the UCSF Positive Health Program are affiliated with the AIDS Research Institute (ARI) at UCSF. UCSF ARI houses hundreds of scientists and dozens of programs throughout UCSF and affiliated labs and institutions, making ARI one of the largest AIDS research entities in the world.

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