

SFU Associate Professor and BC-CfE Scientific Associate Dr. Mark Brockman

How the power of T-Cells may lead to an HIV cure

Dr. Mark Brockman, a BC Centre for Excellence in HIV/AIDS (BC-CfE) Scientific Associate, recently presented at St. Paul's Hospital as part of the BC-CfE's Forefront Lecture series on the potential of using host T cells to eliminate the HIV viral reservoir.

One of the principal challenges in achieving long-term ART-free HIV remission or a cure is the existence of a viral reservoir which resides within host cells as little as a day or two following infection. This resilient array of proviruses evolves and diversifies over time in the absence of antiretroviral therapy equipping them to evade host immune response. If an individual achieves viral suppression and is taken off antiretroviral therapy, the virus is thus capable of 'rebounding' using this viral reservoir to propagate and recirculate in an individual's blood.

Current HIV cure research is focused on 'blunting' this viral rebound or finding a sterilization cure, where the reservoir would be completely eliminated.

One approach Brockman discussed, referred to as 'Kick and Kill', is being investigated by HIV researchers. These compounds trigger and shock proviruses, which make up the reservoir, to appear in plasma where they can be targeted and eliminated by host immune cells and antiretroviral therapy. However, latency reversal agents (LRAs) alone do not seem to reduce the size of this reservoir; another arm of therapeutics is required to complement their effects.

Brockman explained a huge focus of his laboratory's research is the use of host immune response to eliminate viral reservoirs following the use of LRAs - specifically, by exploiting CD8 killer T cells.

CD8 T cells play an important role in control of HIV in the acute phase of the infection, where they can suppress viral levels in the blood. However, after a month or so, HIV has adapted sufficiently to overcome host immune responses where the infection reaches a steady state and the virus cannot be eliminated.

As a component of the adaptive immune system, CD8 T cells recognize pathogen-derived peptides presented by human leukocyte antigens (HLA) on the surface of infected cells. They then mount a tailored immune response that attempts to eliminate the infection.

Research shows there are thousands of genetic variants (or alleles) of HLA among the population. The HLA alleles expressed by an individual determine which HIV peptides are presented to CD8 T cells, with some HLA alleles being better equipped to mount a strong CD8 T cell response to infection.

Brockman explained that in addition to the scale of HLA variation among the population, there is also genetic variability in the HIV peptides presented to T cells. The virus rapidly mutates these sequences to further mask itself from T cells and their response.

HIV peptides bound to HLA are recognized by specific T cell receptors expressed on the immune cells. Millions of T cell receptor variations are present within an individual, reflecting the enormous genetic diversity present within the immune system. Only a small number of T cell receptors respond to a particular peptide/HLA combination, and the exact contribution of T cell receptor variation to the immune response to HIV is still not well understood by researchers.

Brockman and his research team are attempting to deconstruct this highly diverse process in an effort to

exploit it for development of an effective HIV cure. Collaborating with researchers in South Africa, they are investigating the impact of HLA and T cell receptor variation on an individual's response to HIV infection. In collaboration with researchers at the CDC in China, they are using advanced crystallography techniques to better understand the structure and dynamics of HLA-peptide-receptor interactions.

By getting a better understanding of the mechanisms used by T cell receptors to recognize HIV infection, we can improve our ability to develop vaccines and therapies that overcome the challenge of HIV diversity.

In addition to his studies, Brockman discussed a number of strategies that are being investigated by others to enhance host immune responses to HIV. These include selectively expanding antiviral T cells outside the body and re-administering them to patients; and gene therapy, where T cell receptors are engineered in the laboratory and the altered receptors are then inserted into an individual's T cells.

A less invasive approach using soluble bi-specific molecules, such as HIV-specific antibodies or T cell receptors, could also be used to re-direct CD8 T cells to sites of viral infection. In many respects, this approach could be the safest as it doesn't require manipulation of an individual's immune system.

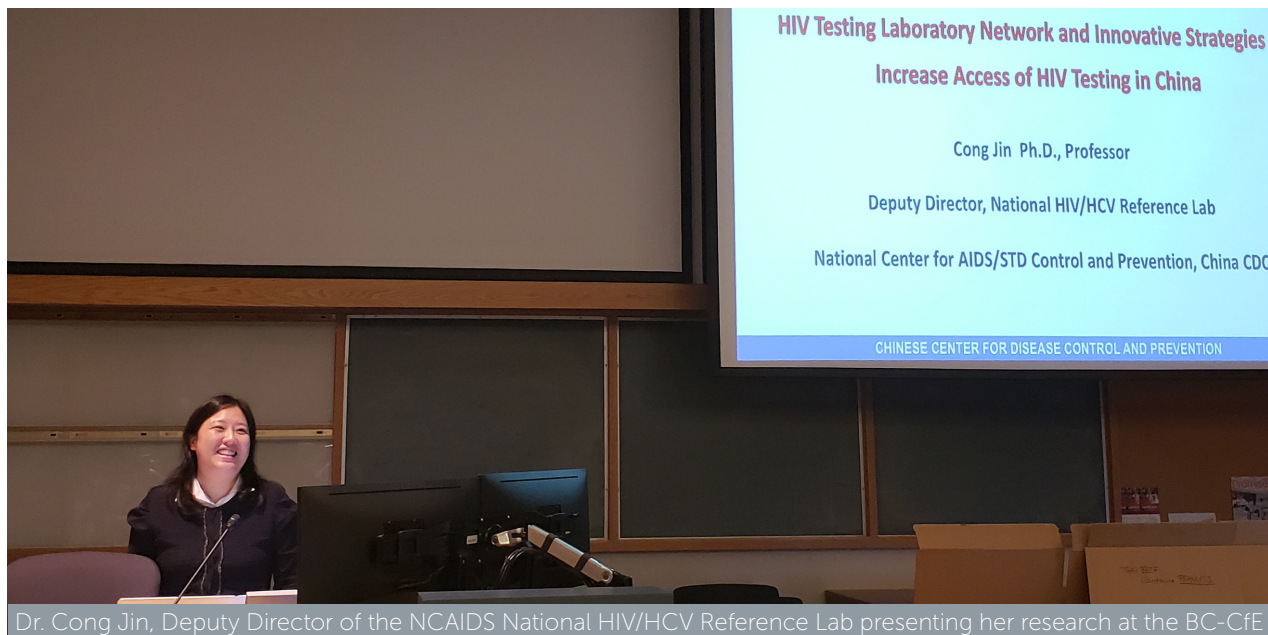
Investigating potential cures for HIV is a significant focus of the BC-CfE's laboratory program. While **Treatment as Prevention**® strategies are being applied widely in BC to ensure early and efficient diagnosis of HIV, cure research is also essential to explore in tandem with clinical efforts if we are to fully eliminate HIV as a public health threat.

» "We are dedicated to working with scientific collaborators, clinician-researchers and community partners to advance our goal of developing a safe, effective and scalable cure for HIV. Based on the BC-CfE's pioneering solutions such as Treatment as Prevention® and HAART at the height of the AIDS pandemic, we are well positioned nationally and globally to advance HIV cure research."

— Dr. Zabrina Brumby, BC-CfE Laboratory Director



China installs HIV test kits in university vending machines to increase diagnoses among students



Dr. Cong Jin, Deputy Director of the NCAIDS National HIV/HCV Reference Lab presenting her research at the BC-CfE

As part of the BC-CfE Forefront Lecture series, we welcomed Dr. Cong Jin, a virologist who is currently Deputy Director of the National HIV/HCV Reference Lab in the National Center for AIDS/STD Control and Prevention (NCAIDS) in China. Dr. Jin presented to a rapt audience of scientists and clinicians on the HIV testing laboratory network in China and the innovative strategies the country is developing to increase testing. This includes installing HIV testing kits in university vending machines.

In 2018 alone, over 240 million HIV tests were conducted in China. Despite significantly increasing the volume of tests, HIV detection rates have not increased accordingly in some regions over the past decade. Dr. Jin spoke about some innovative steps the NCAIDS has taken in the face of this public health threat to increase testing efficiency and help more people learn about their HIV status, thus narrowing the gap towards the first goal of the 90-90-90 targets.

Speaking about the need for the vending machine pilot project, Dr. Jin explained it was precipitated by two main factors, "China has experienced an upsurge in HIV infection rates among younger populations- this is thought to be linked to limited pre-college sex education and an increase in sexual openness."

Dr. Jin explained how self-sampling HIV testing using university vending machines as a vehicle allows the students to collect urine samples at home. Students use a self-sampling kit which includes a special capped tube filled with a sponge as well as an instruction card which is then mailed to an accredited HIV testing laboratory. Results can be checked on a web platform or mobile app using the unique code printed on each self-sampling kit. Students can then link to further medical support and health care if needed.

"Up to May of 2019, 10 provinces had taken part in this project. We have received over 5,000 urine samples, with 67 of these testing positive for HIV. Not only are we

raising awareness of the importance of testing and of the virus itself, this approach has other advantages- it is simple, convenient, protects confidentiality and provides linkages to professional supports," Dr. Jin explained.

The NCAIDS also led pilot studies into the effectiveness of self-testing among the general population. As of August 2019, the first self-testing product, which uses urine samples, was approved on the Chinese market. Instead of testing in a health care setting, people can now get tested for HIV and get their results from home. They conducted two pilot studies - one where the kits were distributed through pharmacies, and the other which involved selling the kits online. From a study among men who have sex with men population, which ran from November to December 2017, over 27,000 kits were sold online. This indicated to the NCAIDS that there is a genuine need for more flexible testing options for those living in China.

"China is a huge country geographically, which in itself presents many challenges when it comes to ensuring there is ready access to testing and treatment for HIV," said Dr. Julio Montaner, Executive Director and Physician-in-Chief of the BC-CfE. "For **Treatment as Prevention**[®] to be successful, it is essential to not only ensure adequate testing rates, but also immediate access to treatment for people living with HIV. I understand the challenges and constraints within the system in China at present which the NCAIDS is currently working through and we sincerely commend them for these innovative efforts."

Exploring the availability of self-testing has been added to China's National HIV Strategic Plan (2016-2020) and the NCAIDS formally issued national self-testing guidelines on October 2019 to provide a framework for expansion of these services throughout the country.

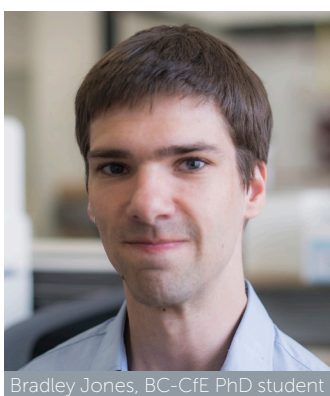
For upcoming BC-CfE Forefront Lectures, visit <https://education.cfenet.ubc.ca/calendar-of-events/>.

PUBLICATION

Recent BC-CfE publication adds to HIV cure knowledge

One of the key focus areas for the BC-CfE laboratory program is the pursuit of an effective, safe and scalable cure for HIV. While current treatments are highly effective and prevent viral transmission if taken correctly, copies of HIV persist in the body for an individual's lifetime following infection. These copies are called "the HIV reservoir". One of the biggest challenges HIV cure researchers must solve is how to eliminate these persistent HIV copies, which are genetically diverse and resilient to current treatments.

Recently, a BC-CfE paper was published which adds to existing evidence on the genetic diversity of the HIV reservoir. Lead author Bradley Jones, a PhD student at the BC-CfE, wrote the paper entitled '*Genetic diversity, compartmentalization and age of HIV proviruses persisting in CD4+ T cell subsets during long-term combination antiretroviral therapy*'



Bradley Jones, BC-CfE PhD student

which was published in the *Journal of Virology* this year. The research sought to better understand the genetics and diversity of HIV copies that persist within host CD4+ T cells in individuals receiving antiretroviral treatment over 10-20 years. The researchers used molecular evolutionary techniques to characterize the age, genetic diversity and distinctiveness of persisting HIV copies in different CD4+ T cell subsets.

The researchers found that each study participant had a unique "landscape" of persisting HIV populations, and that, there was no evidence to suggest that any particular CD4+ T cell subset harboured the longest-persisting, most genetically diverse HIV reservoir. This research highlights that a personalized

medicine approach may be required if and when an effective HIV cure strategy is developed. The researchers are grateful to the participants, without whom this study would not have been possible.

RECOGNITION

Congratulations to BC-CfE researcher Hanwei Sudderuddin!



Congratulations to Hanwei Sudderuddin, a research assistant with the BC-CfE laboratory program, who was first author on a paper entitled '*Longitudinal within-host evolution of HIV Nef-mediated CD4, HLA and SERINC5 downregulation activity: a case study*'. The research study was published in the scientific journal *Retrovirology*. HIV mutates rapidly, even in an individual person. Sudderuddin isolated 50 HIV sequences from a single person over a more than 10-year period and tracked the genetic and functional evolution of a key HIV protein called Nef. Studies such as these help us understand the limits to HIV's adaptability.

LECTURES & EVENTS

Forefront Lecture - Research Methods Series

Title: *What's a quasi-experiment? And why should I care?*

Speaker: Dr. Michael Law

Thursday, February 13, 2020, 12-1PM

Hurlburt Auditorium, Providence Level 2, St. Paul's Hospital

HIV Care Rounds

Title: *Management of Opioid Use Disorder in Individuals living with HIV*

Speaker: Dr. Aida Sadr

Wednesday, February 26, 2020, 12-1PM

Conference Room 6, Providence Level 1, St. Paul's Hospital

For more information, contact us at Education@cfenet.ubc.ca or visit our website at <http://education.cfenet.ubc.ca>

BC Centre for Excellence in HIV/AIDS

- > Improve the health of British Columbians with HIV through comprehensive research and treatment programs;
- > Develop cost-effective research and therapeutic protocols;
- > Provide educational support programs to health-care professionals;
- > Monitor the impact of HIV/AIDS on B.C. and conduct analyses of the effectiveness of HIV-related programs.

Physician Drug Hotline
1.800.665.7677

St. Paul's Hospital Pharmacy Hotline
1.888.511.6222

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How you want to be treated.



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