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McGill University Health Centre

HIV Symposium:
Current Therapies and Future Hopes

Friday, September 17th, 2010

8:30 AM to 12:30 PM

Moyse Hall, Arts Building, McGill University

presented by

McGill-CIHR

Drug Development Training Program

Schedule

8:30 - 9:00 — **Coffee/Registration**

9:00 -10:00 — **Dr. Mark A. Wainberg**

HIV-1 Drug Resistance Mutations Can Be Transmitted within Clusters and Do not Impact on Viral Transmission

10:00 -10:15 — **Coffee**

10:15 -11:15 — **Dr. Daria Hazuda**

HIV-1 Integrase Inhibitors: - From the Bench to the Clinic, and Back Again

11:15 –12:15 — **Dr. Dennis Liotta**

The Role of CXCR4 Modulators in Controlling HIV Entry, Inflammation and Certain Types of Cancer.

Dr Mark A. Wainberg

Professor of Medicine and Microbiology and Immunology,
McGill University
Director of the McGill University AIDS Centre
Montreal, QC

HIV-1 Drug Resistance Mutations Can Be Transmitted within Clusters and Do not Impact on Viral Transmission

Mark A. Wainberg, Thomas Toni[1], Michel Roger, David Stephens, Joanne Otis, James Koopman[5]and Bluma G. Brenner.

Introduction. HIV-1 drug-resistance represents a major problem in public health and is a limiting factor in the success of antiviral therapy. We wished to understand whether drug-resistant variants of HIV-1 might be less well sexually transmitted than wild-type viruses to better comprehend the dynamics of clusters involving drug resistance in new transmissions.

Material & Methods. Here, we describe the use of phylogenetic analysis and allele-specific PCR assays (AS-PCR) to provide new insights into HIV transmission dynamics.

Results. K65R adversely affects HIV replication, and this may be one of the reasons that it is found infrequently among individuals who fail antiretroviral therapy. We now show that AS-PCR for K65R in subtype C viruses was able to detect K65R in an additional 4 of 30 samples that had tested negative by bulk sequencing methods. Transmission of K65R, while rare, was also detected in higher numbers by AS-PCR than bulk sequencing, and this was more common among subtype C than subtype B viruses. K65R was never detected as part of a cluster. AS-PCR also

detected M184V more efficiently than bulk sequencing among individuals newly-infected with either subtype B or C viruses. The presence of this mutation faded over time in these persons, as detected by AS-PCR, but at later times than observed with bulk sequencing methods.

In addition, phylogenetic analysis revealed three patterns of HIV spread in MSM population: a) 321 unique dead-end transmissions; b) 84 small clustered events averaging 2.4 ± 0.8 primary HIV infections (PHI)/cluster over 10.9 ± 0.1 month intervals (n=203); and c) large transmission cascades averaging 9.9 ± 1.2 PHI/cluster over 18.8 ± 1.3 month episodic intervals (n=398). Large cluster participants had higher risk contacts (>10 partners, 3 months prior to diagnosis) than the other groups (39% vs. 13%, OR= 4.67, $p<0.001$). Small cluster participants reported higher frequencies of unprotected anal sex than the other two groups (54% vs. 16%, OR=9.3, $p<0.01$). Clustering was also related to viral fitness with less efficient transmission of NRTI mutations than NNRTI mutations in large clusters as compared to the other two groups (3% vs. 8% and 8%, $X^2=10.2$, $p<0.001$ and 18% vs. 10% and 4%, $X^2=37.1$, $p<0.001$, respectively). Clustering was rarely observed in heterosexual transmissions.

Conclusions. The reason that some resistance-associated mutations are not commonly observed in newly-infected subjects is not because they impact on the ability of HIV to be transmitted but rather because they may quickly revert to wild-type in the absence of drug pressure and then be rapidly overgrown by wild-type variants. Clustering of new infections and the growth of established clusters remain important drivers of the HIV epidemic.

Dr Daria Hazuda

Vice President Research
Merck & Co. Inc.
West Point, PA

HIV-1 Integrase Inhibitors: - From the Bench to the Clinic, and Back Again

Although integrase has long been considered promising target for the development of novel antiretroviral agents to treat HIV-1 infection, the complexities of the integration process and technical challenges proved problematic for early drug discovery efforts. After many years, the viability of integrase as a therapeutic target for small molecules has now been validated in vitro as well as in experimental animal model systems of retroviral infection and clinical proof of concept has finally been achieved in HIV-1 infected patients. Insights from the understanding of the basic biology of integration in HIV-1 infection and elucidating the mechanism of action of prototype inhibitors of integrase were both instrumental in the identification and development of compounds that were ultimately suitable for clinical development. This presentation will review the mechanism of action of integrase inhibitors including recent insights from in vitro studies and analysis of drug resistance with an emphasis on implications for future drug discovery efforts on this newest class of antiretoviral agents.

Dr Dennis Liotta

Professor of Organic Chemistry
Emory University,
Atlanta, GA

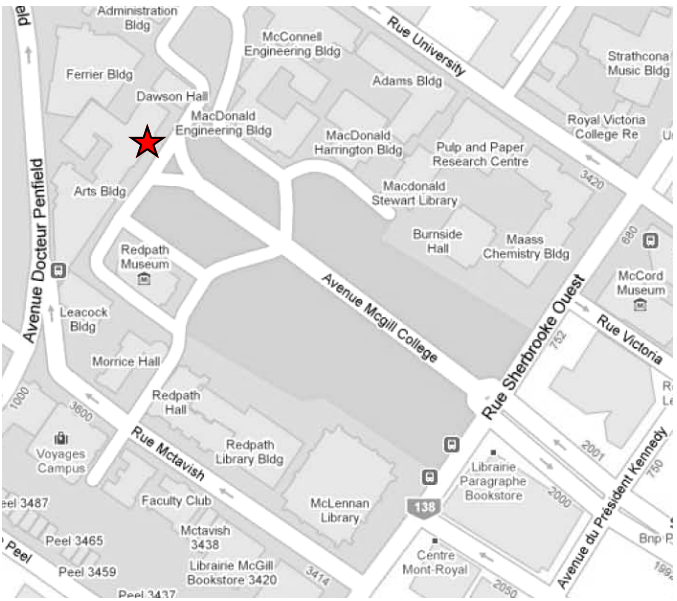
The Role of CXCR4 Modulators in Controlling HIV Entry, Inflammation and Certain Types of Cancer.

The chemokine receptors, CCR5 and CXCR4, are the primary co-receptors responsible for mediating HIV-1 cell entry. Small molecules that antagonize these receptors utilize a fundamentally different approach for controlling viral replication than most other classes of antiretroviral agents in that they act on host cell factors, rather than viral enzymes. While CCR5 modulators that demonstrate clinical efficacy against HIV have now become available, CXCR4 antagonist development is currently at a more nascent stage. Due to the ability of HIV to switch between CCR5 and CXCR4 entry co-receptors, the development of a CXCR4 antagonist is likely critical to prolonging the effectiveness of HIV therapies in patients. In addition, CXCR4 antagonists represent a novel class of drugs that could be used for the treatment of diseases other than HIV/ AIDS. In this presentation I will present some of the opportunities and challenges associated with the development of CXCR4 modulators (antagonists and partial agonists) for treating HIV infection, inflammation and certain types of cancer.

Directions

The symposium will take place in the Moyse Hall of the Faculty of Arts.
From the McGill main entrance on Sherbrooke Street West, go straight along the avenue McGill College. The Faculty of Arts is located at the end of the avenue. Enter through the main entrance of the building. Doors to the Moyse Hall are straight across the lobby.
Registration will take place in the lobby.

Faculty of Arts



McGill-CIHR Drug Development Training Program

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