

Collaborating for culturally-competent care

Professors Jeffrey Jacobson, Jill Foster, Brian Wigdahl and Irwin Chaiken are global leaders in their field. Here, they give a valuable insight into the pivotal collaborative work they are performing in the ongoing battle against HIV/AIDS



Can you each offer a snapshot of your research background?

BW: Because of my interest in viral infections of the nervous system, in the early to mid-1980s I began working to define the viral and cellular mechanisms involved in the aetiology of HIV-1-induced neurological disease and subsequently on the development of diagnostic tools, treatments and prevention strategies.

IC: I have been involved in the HIV-1 field for the past 16 years, focusing on structure-based mechanism and antagonism of the HIV-1 envelope protein machine normally used by the virus for cell entry and infection.

JJ: I became involved in HIV/AIDS research in response to the clinical challenge of treating a group of patients for whom no effective treatment was in sight.

JF: My first clinical rotation was in the summer of 1982, just as a mysterious new disease referred to as gay-related immune deficiency (GRID) was being diagnosed in Philadelphia among gay men and injection drug users (IDUs). Patients presented with opportunistic illnesses, leading us to suspect it was

caused by a virus, though at that time we had neither a test nor a treatment.

Over the course of your careers, how have attitudes to HIV/AIDS changed?

BW: Because the face of HIV/AIDS has evolved during the course of the pandemic, the disease is now viewed more as another chronic infectious disease that can be managed using an array of increasingly effective therapies. Although many infected individuals now live well beyond the age of 50, with an ever-improving quality of life, the challenges of preventing and curing HIV infection remain.

JJ: The public has become more accepting of HIV-infected patients, and there is less stigma and fear of the disease (although both certainly still exist). Because of the decreased fear of the consequences of HIV/AIDS as a result of effective treatments, the rate of risky behaviour is rising in at-risk populations, particularly men who have sex with other men.

JF: I've seen attitudes within the medical community change from ignorance to fear, to hopelessness to optimism, to complacency. As the initial fear that HIV was going to

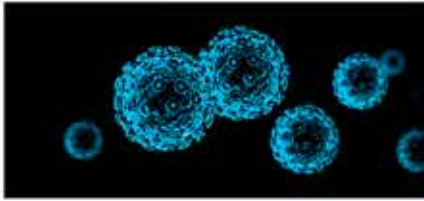
spread beyond the high-risk groups proved unfounded, an HIV medical community evolved to quickly refer patients for specialised care upon diagnosis.

Can you explain the problems that arise with combination antiretroviral therapy (ART), and how you are attempting to combat them?

JJ: ART issues include side effects, cost, and the need for rigid adherence to the regimen over an indefinite period of time. Much of our research effort goes to developing immune-based therapies to improve the immune system's ability to control HIV infection on its own; reducing and perhaps eliminating the need for treatment with anti-HIV drugs; and achieving a so-called 'functional cure'.

BW: Clearly, novel therapies are needed to move us from a state of effective management of chronic HIV disease to an effective cure or elimination of virus from not only infected cells in the peripheral blood but also other compartments including the brain, gut and perhaps other tissue reservoirs. To be able to eradicate the virus, our knowledge concerning all tissues that harbour the virus and the molecular nature of the genome that is retained need further definition.

IC: Overcoming resistance to current drugs and the lack of an effective prevention strategy are driving forces for our current research efforts. In addition, understanding HIV-1 mechanisms and strategies for prevention and treatment could provide clues for dealing with other viral and infectious diseases, and for understanding basic biomolecular mechanisms in healthy cells.



What can be learned from the cases that have emerged in recent years of patients being functionally cured of the disease?

JJ: Recent reports of 'cured' patients have energised the field and lent support to the concept that a cure is perhaps achievable. However, these individual cases arose from unusual circumstances, and do not represent the vast majority of persons infected with HIV.

JF: I agree that functional cures are a double-edged sword. While they are certainly achievable for certain patients under ideal circumstances and with an ideal genetic make-up, they are a distraction from the broad majority of patients for whom this is not currently an option.

BW: Yes, I suspect that we will ultimately find that many patients of this type prove to still be infected; they could therefore be very useful in that continued analysis of these types of patients may help us to further define the nature and location of the viral reservoir.

Research into HIV treatment has evolved remarkably quickly since the virus's appearance around 30 years ago. How do you see this field developing in the coming years?

JJ: The focus will be on prevention, research for a cure, and investigations into the co-infections and non-AIDS complications of HIV disease.

BW: Current pathways of studies focused on treatment may be altered by the development of new technologies opening doors to identification and characterisation of infected cell reservoirs with a specificity and sensitivity not available today.

IC: Inclusion of frontline HIV-1 envelope glycoprotein (Env) spike inactivators and other entry inhibitors in drug cocktails will help to expand the power of combination therapies for infected individuals. Given the urgency to identify prevention strategies, microbicides that can inactivate the virus before cell encounter seem feasible and should be tested.

JF: Without working to relieve the incredible inequity gap present across the world, solutions will be destined to be piecemeal and palliative. Poverty, racism, stigma and hunger fuel all the conditions that lead to the high rates of HIV in the US and globally. Without the political and societal will to ensure a basic standard of living for the most vulnerable, including healthcare as a human right, we are destined to pay the costs brought on by HIV.

Innovation and excellence throughout history

Drexel University College of Medicine is the hub for a thriving partnership of expert organisations devoted to combating HIV/AIDS across diverse populations, both within the US and on a global scale

DREXEL UNIVERSITY COLLEGE of Medicine (DUCOM), Philadelphia, USA, inherited a tradition of more than 150 years of educating and training physicians and research scientists through its evolution, including mergers of the Medical College of Pennsylvania – the successor institution to the first degree-granting medical school for women in the world – and Hahnemann University School of Medicine. Today, through its innovative approach to medical education and translational research its unwavering commitment to patient care, DUCOM continues to accelerate progress in medicine and its extensive history of community involvement endures.

With both a high incidence and prevalence of HIV/AIDS, Philadelphia's overall HIV infection rate of 1.2 per cent is the sixth highest among metropolitan areas in the US and five times the national average. As HIV/AIDS infection expanded, DUCOM was strategic in positioning programmes to maximise impact and funding for a three-pronged front of basic science research, clinical trials and health services research for the delivery of care.

FROM BENCH TO BEDSIDE

DUCOM faculty provide exceptional clinical care to Philadelphia's diverse and often underserved populations of HIV/AIDS patients through a combination of comprehensive healthcare delivery and basic and translational research. Physicians and healthcare professionals from the Division of Infectious Diseases and HIV Medicine in the Department of Medicine; the Department of Pediatrics at the Dorothy Mann Center for Pediatric and Adolescent HIV at St Christopher's Hospital for Children; and

the Partnership Comprehensive Care Practice (PCCP) – the largest HIV patient care center in Philadelphia – help basic scientists to link their discoveries to clinical applications, for a true bench-to-bedside approach.

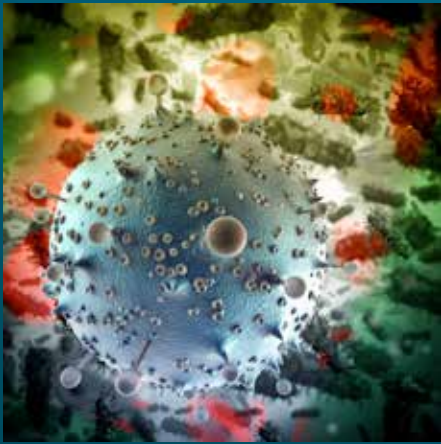
DEDICATED EXPERTS

DUCOM is home to a comprehensive, extensively funded programme of research performed under the oversight of Vice Dean for Research, Dr Kenny Simansky, and includes a substantial portfolio from the National Institutes of Health (NIH). Professors Jeffrey Jacobson, Jill Foster, Brian Wigdahl and Irwin Chaiken are the leaders who, along with their dedicated teams, are responsible for accelerating progress. 30 investigators are engaged in the HIV/AIDS effort in DUCOM, which is further strengthened by collaborations across Drexel University.

THE PROMISE OF GROUNDBREAKING THERAPIES

Jacobson, Professor and Chief of Infectious Diseases and HIV Medicine Division, cares for his patients at Drexel Medicine's PCCP. Jacobson became involved in HIV/AIDS research early in the epidemic in response to the clinical challenge of caring for a group of patients for whom no effective treatment was in sight. He has received NIH funding for a series of studies on improved HIV treatments, immune-based therapies and potential vaccines.

Antiretroviral therapies (ARTs) have been successful at suppressing HIV but do not eradicate it from the body. Jacobson recently led a clinical trial demonstrating that a single dose of a



HIV VIRION

novel therapeutic monoclonal antibody targeting HIV decreased viral loads for at least one to two weeks. He considers the most innovative feature of this therapy to be its long-lasting effect, which exceeds that of currently available drugs. Jacobson and his team believe that developing long-acting injectable anti-HIV therapies that could be administered in a clinical setting and less frequently would greatly increase treatment compliance of at-risk individuals and reduce their infecting others.

Jacobson is also investigating innovative approaches to making the immune system more active against HIV. Inducing the immune system to control the virus on its own without the need for antiviral drugs achieves what has been called a 'functional' cure. Through the national AIDS Clinical Trial Group, Jacobson led an immune system based intervention in which patients whose viral loads had been made undetectable with antiretroviral drugs were exposed to their own virus for short period of time and were asked to stop taking the drugs. This essentially

tricked the immune system into fighting a 'new' infection. The results were encouraging, with about 15-20 per cent of the treated group showing near undetectable viral levels, remaining for at least a year.

In another NIH study, Jacobson's team is using the new tool of monitoring viral set points to explore the idea of taking samples of a patient's virus to create a personalised vaccine. By loading the RNA genetic material of the virus onto active dendritic cells in the lab and transplanting them back into the patient's bloodstream the researchers hope to trigger a stronger, natural immune response, similar to the way vaccines work but with active disease.

"There were many ups and downs and struggles getting patients the care that they needed, helping them deal with the discrimination and stigma," Jacobson reveals. "There were a lot of challenges but also many rewards. To have my career span from my training at the beginning of it all to now is amazing. All of the work has but one goal: finally and forever putting an end to the AIDS epidemic."

EDUCATION AND SUPPORT FOR THE MOST VULNERABLE

Foster, Professor of Pediatrics, Director of the Dorothy Mann Center and Chief of Immunology at DUCOM since 2002, has a particular interest in sexually transmitted diseases, specifically HIV, and has made significant advances in her clinical efforts with children and adolescents. Discussing misconceptions about the disease she explains: "Among youth, especially gay youth, on one hand there is a belief HIV is inevitable and, on the other, it is 'no big deal' because it is easily controlled with one pill once a day". Foster recognises that education and support among this often underserved population is critical: "Youth infected with HIV must negotiate the healthcare system

by themselves to gain testing, seek treatment, and maintain good adherence to medications".

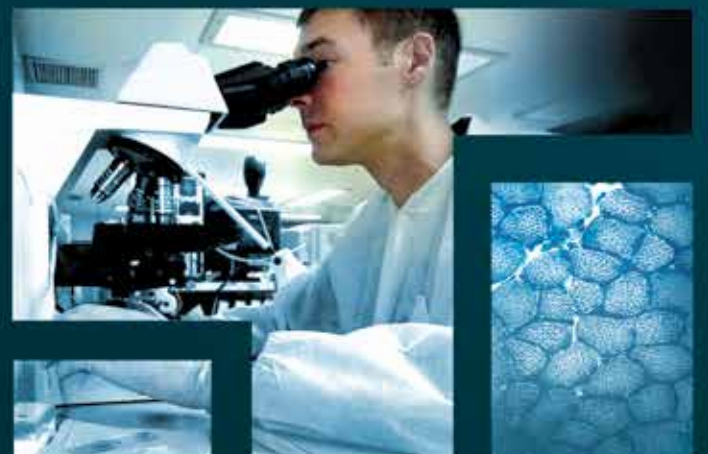
MOLECULAR MECHANISMS INVOLVED IN THE PATHOGENESIS OF HIV

Wigdahl has been interested in HIV since its first appearance in the early 1980s and his leadership was recently acknowledged as the 2013 Pioneer in Neurovirology by the International Society for Neurovirology. For the last 10 years, he has led the Department of Microbiology and Immunology as Professor and Chair. He is responsible for expanding the Department's research enterprise and for building the cross-departmental Institute for Molecular Medicine and Infectious Disease.

The research of Wigdahl and his team is focused on defining the HIV-1 proviral DNA with respect to integration status, epigenetic controls, genetic architecture and specific signature sequences, and signalling pathways that might alter the course of viral expression during infection and therapy. Additional studies focus on determining the impact of chronic substance abuse (in particular cocaine and cannabinoids, two of the most prevalent drugs of abuse in Center City Philadelphia and commonly abused in the Drexel Medicine HIV/AIDS Genetic Analysis Cohort) to define the impact on viral gene expression and disease severity.

HIV-ASSOCIATED NEUROCOGNITIVE DISORDERS (HANDs)

The introduction of highly active antiretroviral therapy (HAART) has netted significantly lower mortality rates, but survivorship also means the HIV population includes older adults who have particular vulnerabilities. Given the significance of this problem, Wigdahl's team has devoted effort to determining the impact of age on long terminal repeat signatures that correlate to HIV-1 clinical parameters including T cell count,





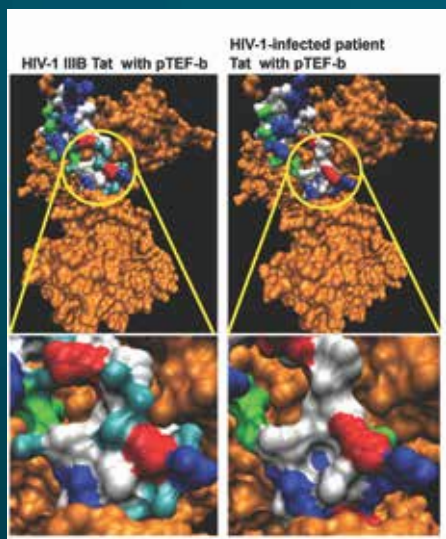
viral load, host clinical factors and host cytokine levels. It is well established that the central nervous system is susceptible to HIV infection and incidence of HANDS increases significantly in older adults. Wigdahl was integral to establishing an interdisciplinary research team providing major new opportunities for both preclinical and clinical investigation of HIV/AIDS-induced cognitive decline and therapeutic options in adult and elderly HIV/AIDS patients. The model shows molecular changes in the HIV virus that are associated with such impairments and offers insight into potential therapeutic interventions.

A NEW APPROACH FOR TREATMENT AND PREVENTION

Chaiken, Professor of Biochemistry and Molecular Biology at DUCOM since 2003, has been at the cutting edge in HIV-1 research for more than 15 years. His expertise in protein complexes and protein machines led his team to investigate different drug design strategies to inhibit HIV.

Inactivating HIV-1 before entry into host cells remains a compelling yet elusive means to prevent viral infection and spread. The HIV-1 cell infection that leads to AIDS pathogenesis is mediated by trimeric envelope glycoprotein (Env) spikes on the virus membrane surface. Env is the only virus-specific protein on the virion surface, and is essential for cell receptor interactions and subsequent virus-cell fusion, whereby the Env spike, especially the most exposed component, gp120, presents an obvious target to attack the virus directly in order to block the molecular recognition steps that lead to host cell infection.

Chaiken and his team are pursuing an entirely novel approach for the treatment and prevention of HIV using a recently revealed class of broadly active peptide triazole inhibitors that bind specifically and with high affinity to HIV-1 gp120, antagonise the interactions of Env with both host cell receptors CD4 and CCR5/CXCR4 co-receptor and cause virus rupture leading to its inactivation before host cell encounter.



Molecular model defining changes in the interaction between the HIV-1 transactivator protein, Tat, and pTEF-b (Cyclin T1 and cdk9) caused by Tat polymorphisms detected in a single patient over a six-month period associated with a decline in neurocognitive performance. The left panel is HIV-1 Tat from the laboratory IIB strain of virus. The right panel is HIV-1 Tat with polymorphisms at two residues that have occurred in conjunction with the patient's transition to neurocognitive impairment.

The binding process leads to structural rearrangements in the spike that allow the membranes of the target cell and HIV virion to fuse together, enabling the contents of the virus to enter the cell.

Chaiken compares this binding process to the springing of a mousetrap, and with the help of collaborators in Drexel's College of Engineering and the School of Biomedical Engineering, Science and Health Systems, he has developed several spike-targeting compounds that trick HIV into springing the mousetrap before it encounters a healthy target cell. These compounds achieve this by imitating the force the HIV virion particle senses when it encounters a healthy cell. As a result, the HIV explodes and is destroyed before it can infect a target cell.

HOPE FOR THE FUTURE

These snapshots of the extensive range of inspired projects undertaken at DUCOM provide an insight into the hugely diverse programme of research, as well as the expert faculty members and dedicated healthcare professionals who are crossing boundaries, opening new avenues and making great progress in research and patient care, providing consistent help and new hope to those affected by HIV/AIDS.

INTELLIGENCE

DUCOM

OBJECTIVES

To conduct basic, clinical and translational research to find new preventive and therapeutic options to improve the care of HIV/AIDS patients.

KEY COLLABORATORS

Drexel University College of Medicine:

Professor Brian Wigdahl

Professor Irwin Chaiken

Professor Jeffrey Jacobson

Professor Jill Foster

FUNDING

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DR KENNY J SIMANSKY received his BA degree in psychology from Queens College, City University of New York (CUNY) in 1972 and his MA (1975) and PhD (1979) in biopsychology from the University of Iowa. In 1982, after completing a postdoctoral fellowship in behavioural neurosciences at the Cornell University College of Medicine, he was appointed Assistant Professor of Pharmacology at the Medical College of Pennsylvania, a predecessor of Drexel University College of Medicine, and achieved the rank of tenured Professor, which he currently holds in the Department of Pharmacology and Physiology. Simansky was funded for 25 years by the NIH for work on the cellular and systems-level mechanisms that regulate food intake and reward.



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