The Battle for the Brain
Circumventing our natural defense mechanisms to optimize HIV treatment

Reina Bendayan is up against an unlikely foe in her fight to improve the treatment of HIV infection in the brain – the organ’s own natural defense system.

It is widely accepted that HIV infection in the brain presents a significant therapeutic challenge. The blood-brain barrier (BBB) – a tight layer of blood vessel cells separating the central nervous system (CNS) from the rest of the body – prevents potentially harmful toxins from invading brain tissue. Most antiretrovirals, drugs designed to counteract the effects of the HIV virus, are denied entrance at the BBB and cannot reach their intended targets.

If a drug compound is lucky enough to permeate the BBB, it faces another challenge.

Bendayan, an associate professor at the Leslie Dan Faculty of Pharmacy, believes that a select group of transport protein molecules found at the BBB and in glial cells, called P-glycoprotein and multidrug resistance proteins, can significantly impede the treatment of HIV infection in the brain.

These proteins, explains Bendayan, serve as transporters or drug-efflux pumps at the cell surface. "Even if a compound is able to permeate the BBB, these proteins pump the drugs out from the glial cells which are known to be the primary target of HIV infection in the brain," explains Bendayan. "It is yet another mechanism of defense by our system to protect the most vital organ."

Circumventing the brain’s intuitive response is not easy, but the stakes are high – HIV infection in the brain remains one of the major causes of death for people infected with the virus. To counter these transporters, Bendayan employs a variety of techniques in her experiments, including using rodent and human brain tissue to characterize the efflux systems, examining in detail how the transporter proteins are expressed, and surveying brain tissue to determine exactly where these transporters localize.

Bendayan believes that certain drug compounds can act as inhibitors and block the drug efflux tendency of transporter proteins. Identifying and effectively using these inhibitors could result in higher concentrations and improved efficacy of antiretroviral drugs in the brain.

People living with HIV today are more likely to live longer and less likely to develop AIDS thanks primarily to highly active antiretroviral therapy (HAART). Introduced 10 years ago, HAART has proven incredibly beneficial in targeting the virus in the peripheral organs, but the CNS remains vulnerable. "The brain creates a reservoir where the virus can become latent and can eventually re-infect the periphery," explains Bendayan.

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Anna Taddio’s quest to end infant pain

by Amy Brown-Bowers

It doesn’t take fancy equipment to tell that an infant is in pain – flailing limbs and breathless screams are universal indicators – but it has taken years of scientific research to change the way doctors view and treat that pain.

Assistant Professor Anna Taddio is cross-appointed to the Hospital for Sick Children’s neonatal intensive care unit where she sees babies in pain every day. “In my practice, I witness infants in pain. I see their pain and I feel their pain and I want to take it away,” Taddio says.

Pain raises stress levels which tax already fragile infants. Treating pain helps babies heal and develop better, and helps prevent long-term consequences. One of Taddio’s early studies, which examined the long-term effects of infant circumcision without the use of analgesia, showed that untreated pain led to a higher sensitivity to pain four to six months later.

A subsequent study determined that repeated painful procedures done without analgesics can cause babies to anticipate pain and experience pre-procedural anxiety. Her team’s groundbreaking research has led to world-wide changes in analgesic practices in children. For example, analgesics are increasingly used on infants today during procedures such as circumcision and venipuncture.

The death of baby Jeffrey Lawson in 1985 contributed to an about face of the use of analgesics for babies. Today, largely thanks to Taddio’s team, infant pain is viewed much more seriously.

Taddio’s most recent work has examined the use of sucrose as a pain killer for babies during procedures. Amazingly, sucrose has analgesic properties in young infants. Its mechanism of action is believed to involve triggering the release of endogenous processes in our body that enhance free radical formation.

Although results from Wells’ studies in mice cannot be directly applied to humans, they provide a framework for exploring potential human neurodegenerative mechanisms associated with drug exposure or even aging. “Our goal is to facilitate the development of strategies for detecting individuals at higher risk, and therapeutic approaches for minimizing neurodegenerative outcomes.”

Funding provided by the Canadian Institutes of Health Research and the National Institute of Environmental Health Sciences of the National Institutes of Health (US). Study drugs provided by Health Canada and the National Institute on Drug Abuse (US).

The long-term consequences of amphetamine use

by Gina Vaccaro

As recently as 20 years ago, doctors didn’t think that infants felt pain or, that if they did, they would soon forget it and that the dangers of using analgesics on babies far outweighed the benefits of reducing pain during procedures. As such, babies were paralyzed but inadequately anesthetized for surgeries, Taddio says.

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Pharmacy’s research champion
by Maria Saros Leung

To helm a dynamic research portfolio requires a person balance advocacy with high-level administration. Someone who knows first-hand the frustrations and rewards of creating new knowledge, and realizes the incredible infrastructure needed to support this activity.

At the Leslie Dan Faculty of Pharmacy, that person is Robert Macgregor. And in his three years as associate dean of research, he’s had a pivotal role in growing the Faculty’s dynamic research environment.

In 1998, the Faculty embarked on a campaign under the leadership of Dean Wayne Hindmarsh aimed at doubling enrollment in the undergraduate pharmacy program by 2005, and establishing a new facility. Expanding the research enterprise naturally dovetailed with this period of growth.

Macgregor joined the Faculty of Pharmacy at U of T in 1993 after holding careers in both industry and academia. By the time he was appointed to the position of associate dean of research in 2003, he had already implemented several innovations, including helping to nearly triple the number of graduate students, and launching an undergraduate pharmaceutical chemistry program, one of the few offered in Canada.

In 2006, the Faculty moved into its new state-of-the-art building. In anticipation of the significant increase in research space, Macgregor has been busy recruiting from across Canada, the United States and overseas.

The faculty complement has also evolved into research-specific divisions – biomolecular sciences, social and administrative pharmacy, and pharmacy practice. Within these divisions, the Faculty has an enviable mass of expertise in many areas crucial to the understanding and improvement of pharmaco/therapy - toxicology, drug development and delivery, pharmacokinetics, pharmacology, complimentary therapies, pharmacoeconomics, pharmacy education and clinical pharmacy.

It is the cohabitation of the laboratory-based sciences (think cell signalling) with the clinical sciences (think drug transport) with the applied sciences (think interprofessional health teams) that Macgregor believes is the Faculty’s greatest strength moving forward. “There is tremendous potential in having all these researchers, with different backgrounds and views, talking to one another and building collaborations.”

The Lynch pin, of course, is the securing of steady funding. “Research is stochastic. There’s a probability that at any given time someone will make an important discovery. All we can do is ensure that the infrastructure is there to support it.”

“When funds are cut, it is not just the experiments that are lost, we lose the human capital. If we can’t afford to keep grad students, post docs and research assistants, we lose their knowledge. Rebuilding that takes a long time.”

As such, Macgregor is building relationships with stakeholders, including industry, government and peer institutions, to demonstrate the value to society investing in university research brings. Communicating these benefits through vehicles like Endeavour, Macgregor says, is an important component of this advocacy work.

Macgregor remains a scientist at heart, and is cognizant of the challenges facing researchers who must balance demanding teaching and mentoring students, in insecure funding environments. His own work examines how proteins experience changes during inflammation. Levels of proteins increase in the brain, and how drugs work against HIV infection.

Bendayan and the graduate students and post doctoral fellows she supervises have been sharing their findings with the scientific community, including a stop at XVI International AIDS Conference held in Toronto and the prestigious Gordon Conference on Barriers of the CNS held in Tilton, NH. Bendayan also recently headed up the American Association of Pharmaceutical Scientists’ Workshop on Drug Transporters in Bethesda, MD, where she presented her research.

The work is ongoing, as more links need to be made between the blocking of transporter proteins and the impact inflammation has on effective drug transport. Thwarting the brain’s natural armour in order to save lives is not an irony lost on Bendayan. Yet, clearly it is a course worth taking.

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Alternative medicine’s ripple effect
Cross-country study tracks the impact of natural health products

by Gina Vaccaro

hat do a government decision and a social trend have in common? Both, like stones thrown into a pond, have sent converging ripples out into the pharmacy community that could change the practice forever.

In what was a controversial and disputed decision, the federal government made the move to classify natural health products (NHPs) including herbs and other supplements as “drugs” under Canada’s Food and Drugs Act, explains Heather Boon, associate professor and co-director of the Canadian Interdisciplinary Network for Complementary and Alternative Medicine Research (IN-CAM).

At the same time, popularity for complementary and alternative medicine (CAM) and NHPs has blossomed. According to a Health Canada survey, 71 per cent of Canadians regularly take vitamins and minerals, herbal products, homeopathic medicines and the like.

Also providing evidence of the growing demand is a visible retail market reaction. Pharmacies and specialty stores across the country now stock NHPs.

“If pharmacists are supposed to be drug experts, and if we’re going to sell these products, then does this fall under our scope of practice? And, is it fair to hold pharmacists responsible for these products when health food store personnel sell them without any special training?” asks Boon, who is also a pharmacist.

Boon is the lead investigator in a cross-country, multi-partner study pursuing this very question. In the first phase of the study, focus groups were assembled in Vancouver, Edmonton, Toronto and Halifax, and interviews were conducted with pharmacy and consumer leaders.

Because a vast and diverse number of products fall under the CAM umbrella, the focus groups and interview subjects were given three primary examples to discuss: vitamins and minerals, herbal products, and homeopathic medicines. Not enough is known about their safety and efficacy, “There is a very polarized debate in the pharmacy community about the validity of complementary and alternative medicines. Not enough is known about their safety and efficacy.”

This lack of clinical and experimental data would make it hard to have a CAM course curriculum approved by institutions, like universities, that have rigorous evidence-based requirements, says Boon.

And while the community response to her question seems straightforward, the road she must now proceed on may prove a foggy journey.

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Heather Boon

Under Boon’s guidance, the study also aims to draft policy recommendations and submit them to the National Association of Pharmacy Regulatory Authorities (NAPRA). NAPRA promotes the implementation of progressive regulatory programs and standards across the country.

For the average consumer and user of CAM, the study could mean that their local pharmacist would be better able to identify NHPs that could help them, and guide them away from others that might harm.

For the professional pharmacy community the ramifications are not yet known. What is known, however, is that Boon is keenly aware of her responsibility in this time of change: spearheading a comprehensive study that will try to examine all outcomes and then provide a vision for the future.

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