When the unpredictable happens
Jack Utrecht’s research restores trust in our medication

A diverse idiosyncratic drug reactions can be described as an unpredictable negative reaction by an individual to a drug. They can affect any organ but the skin, liver, and bone marrow are the most common targets. While these unexpected reactions occur in a small percentage of patients taking a drug, given the number of medications that take medication and the number of different medications available, the total number of patients affected can be large.

“Not only is this a significant therapeutic problem, but it can also lead to restrictions on the use of a drug and contribute to the uncertainty of drug development,” says Jack Utrecht, a professor at the Leslie Dan Faculty of Pharmacy and the Canada Research Chair in Adverse Drug Reactions.

Understanding these reactions could make drug therapy safer by predicting which patients are at increased risk of adverse reactions.

Utrecht is sensitive to the real and painful trauma felt by patients who experience adverse idiosyncratic reactions. Understanding these reactions, he says, could help to make drug therapy safer by designing safer drugs and predicting which patients are at increased risk of adverse reactions.

To that end, Utrecht is attempting to discover the mechanisms that can cause idiosyncratic reactions; an investigation he describes as difficult and requiring a broad spectrum of talents.

“The more you study biomedicine the more you realize how complex a field it is, requiring knowledge of chemistry, immunology, and histology, among others.”

In wading through this complexity, and possessing the aforementioned talents, Utrecht has made several key observations to guide his research. One of these principle observations is that idiosyncratic reactions appear due to chemically reactive metabolites of the drug rather than to the drug itself. The hypothesis is that the drug chemically bonds with proteins in a cell, causing cell stress and initiating an immune system reaction. Watching for markers of cell stress may help to better predict which drug candidates are likely to cause adverse reactions.

“Most idiosyncratic reactions appear to be mediated by the human immune system, which makes it difficult to accu-
The ethics of pandemic planning

Alison Thompson

By Maria Saros Leung

In the event of a pandemic, health care leaders and governments can expect to be faced with a host of tough decisions. Who gets priority if a vaccine is in short supply? At what level of risk should health care practitioners be exposed? And how should restrictive measures, such as quarantines, be used?

Alison Thompson, an assistant professor at the Leslie Dan Faculty of Pharmacy, says that these ethically fraught decisions should be grounded in values.

Thompson is building on her work as a post-doctoral researcher at the Centre for Research on Inner City Health at St. Michael’s Hospital in Toronto. She was part of a team based at U of T’s acclaimed Joint Centre for Bioethics that developed an ethical framework for the decision-making process required during an influenza pandemic.

The framework, which was informed by the SARS crisis in 2003, consists of 10 values which guide decision-making. For example, one value states that health care practitioners’ duty to provide care is not absolute; and they may have to weigh this duty against competing obligations to their own health, family or friends.

“A classic public health strategy... is social distancing, but when you have people living together, that’s not really an option”

To that end, she’s examining pandemic planning in the shelter system and how it affects marginalized groups, specifically the homeless and under-housed. “A classic public health strategy for managing communicable diseases is social distancing, but when you have people living together, that’s not really an option,” says Thompson. “People who are marginalized in society tend to have limited access to the health care system and often bear the brunt of these conditions. We have to pay special attention to these groups in emergency preparedness planning.”

Her appointment to the Faculty of Pharmacy has positioned Thompson to also explore the role of the pharmacists in pandemic planning, and how pharmaceutical companies can respond to pandemics. “I’m interested in if we can make private parties serve the public good and alternative ways of meeting the public need.”

Making the medicine go down with a little bit of....glass?

Ping Lee breaks down the body’s own barriers to health

by Gina Vaccaro

Advances in technology used to synthesize pharmaceutical compounds yields thousands of new candidate molecules in the time it would have previously taken to synthesize one. While this is good news for drug development, there are ramifications to developing compounds so rapidly.

“In the new era of drug discovery, one of the undesirable results is that many compounds which look promising when being synthesized in the laboratory, turn out to be insoluble,” explains a leading researcher in the field, Ping L. Lee, a professor at the Leslie Dan Faculty of Pharmacy and the GlaxoSmithKline Chair in Pharmaceutics and Drug Delivery.

Solubility is a measure of how well a compound dissolves in water. Low solubility means that less of the drug dissolves, therefore less is accessible for the body to process. This lack of biological availability in turn causes the compound to be far less effective than it could be.

Lee and his team are currently researching ways to improve the bioavailability of several poorly soluble drugs, including a class called new chemical entities or NCEs, and to design programmable delivery systems that will release the drug when and where it is needed.

“Patients, who previously had to take several daily doses of a drug... could instead take one dose.”

Lee says, “One of the methods we are trying is to convert the drug into an amorphous state.”

Converting the drug into an amorphous, or non-crystalline state, can dramatically increase its solubility. There are distinct challenges to doing this, because while using an amorphous form improves solubility, this form also renders the drug thermodynamically unstable. Changes in temperature during storage could promote crystallization of the drug, consequently making it less bioavailable.

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Micronutrients to the rescue?

Peter O'Brien searches for a solution to our diet dilemma

By Sam D'Alfonso

What you eat could be killing your cells. This is a scary reality that Peter O'Brien, professor emeritus at the Leslie Dan Faculty of Pharmacy, believes can be mitigated by micronutrients. According to O'Brien, our cells are in combat with our entire lifestyle, and sometimes it's our cell's that lose out.

“Recent studies have demonstrated a strong correlation between diet with high levels of fat, refined carbohydrates, meat, and cooked foods, and the increased exposure to toxins that cause disorders like insulin resistance, diabetes, Alzheimer’s, and even some cancers,” he explains.

Endogenous toxins, created by our natural metabolic process are the culprit. It all goes wrong when our ability to detoxify our systems becomes overloaded; a result of an imbalance between what the cells want and what we choose to eat. O’Brien’s research team is targeting a cytotoxic axis of evil: oxidative stress, fructose, and polyunsaturated fatty acids. He has observed that it’s the synergy between these that can be lethal to cells, particularly if micronutrients or vitamins are not adequate to cope with the excesses of our chosen diet.

“Japan is a perfect example of the change in health issues of a population moving towards North American living standards and lifestyle within a generation. Post-World War II, Japa- nese mortality rates for colon cancer, ischemic heart disease and cerebral infarction were among the lowest in the world but had increased almost ten-fold by the 1990s.”

For O’Brien, the solution lies in understanding how enhancing certain micronutrients may be used to boost the cell’s ability to counteract the toxic effects of a Western diet.

O’Brien’s latest research in micronutrients is an interesting new twist in a long and distinguished career in pharmacometrics. His work with industry and government has been recognized with The McNeil-Janssen-Ortho Award, in recognition of a significant contribution to pharmaceutical research at the national and international level. He is also the recipient of an Honored Life Membership conferred by the Association of Faculties of Pharmacy of Canada.

Research has shown that they significantly reduce the mobility of the entrapped drug until it is released in the body.

“Not only are we looking to engineer a polymer that enhances solubility, but this polymer could also be a way of controlling the rate of drug release.”

Developments in drug delivery systems can have a big impact on our health care system. Highly soluble and well-absorbed compounds with an accurately controlled rate of delivery make for effective drugs. This translates into a host of benefits for not only the health care system as a whole, but for the individual patient.

Patients, who previously had to take several daily doses of a drug due to its short activity duration, could instead take one dose that elicits the desired therapeutic results for an extended period. A reduced dose frequency also increases the likelihood of patient compliance, resulting in more effective health care spending.

According to Lee, the solution to such a quagmire is to molecularly disperse the drug in another material, specifically a polymer. The polymer would retard the thermodynamic transition of the drug, act as a buffer between the molecules of the drug to prevent it from crystallizing, and be pharmaceutically appropriate.

“Much of our research is in finding the ideal polymers to use. Glass-like polymers are good candidates for this purpose,” explains Lee.

This search for the proper material is, for Lee, a particularly fascinating aspect of his research. Research conducted thus far shows that polymers which behave like rubber at room temperature are unlikely contenders. Glassy hydrophobic polymers (polymers which behave like, and in fact resemble, glass) at room temperature seem to possess the ideal properties required.

Making Medicine cont’d from page 2

NOTEWORTHY

CAROLYN CUMMINS joined the Leslie Dan Faculty of Pharmacy as an assistant professor in September 2007. She recently completed a Howard Hughes Medical Institute postdoctoral fellowship with David Mangelsdorf at the University of Texas Southwestern Medical Center in Dallas, Texas. Currently, Cummins is interested in understanding the mechanisms of nuclear receptor activation and function in metabolic diseases such as diabetes and obesity.

ALISON THOMPSON (see page 2) was appointed an assistant professor to the Leslie Dan Faculty of Pharmacy. Anna Taddio has accepted a full-time position at the faculty in the pharmacy practice division. Taddio’s research examines the ethics of pandemic planning and pandemic planning in the shelter system.

Formerly of the Hospital for Sick Children and until recently cross-appointed to the Leslie Dan Faculty of Pharmacy, ANNA TADDIO has completed a full-time position at the faculty in the pharmacy practice division. Anna’s research examines the prevention and management of pain in newborn infants.

ZUBIN AUSTIN (see page 4) is among the recipients of the inaugural Leadership in Faculty Teaching (LIFT) Award from the Ontario Ministry of Training, Colleges, and Universities. The award is designed to recognize and encourage teaching excellence at Ontario’s colleges and universities. Austin, who holds the Ontario College of Pharmacists Professorship in Pharmacy Practice, received his LIFT award for being “at the forefront of lifelong learning initiatives that harness community and cross-cultural learning opportunities.”
Health care human resources

Zubin Austin is teaching professionals how to rely on each other

by Amy Brown-Bowers

TV commercials that aired this summer announcing the launch of MedsCheck are a sign of exciting and timely changes in the Canadian health care system for pharmacists, says Zubin Austin, assistant professor at the Leslie Dan Faculty of Pharmacy.

The program entitles people in Ontario, taking three medications or more, to a yearly 30-minute consultation with their pharmacist.

“It’s the leading edge of what I hope and expect are going to be some significant changes in the way pharmacists are utilized in health care,” says Austin, who is also the Ontario College of Pharmacists Professor in Pharmacy Practice.

“Programs like MedsCheck provide pharmacists with the option to actually use their clinical knowledge in a practical and concrete way, improve the quality of care... (and) contribute to improving the efficiency of the health care system as a whole.”

Austin is at the forefront of research into optimizing human resources in Canadian health care to improve patient care and the overall efficiency of the system. Part of the solution is a changing role for pharmacists, says the recipient of Ontario’s inaugural Leadership in Faculty Teaching award this year.

“The health system is relying more and more on medication... it’s not only just the frequency with which people are using medications and seeing multiple physicians, but it’s also the reliance that the health care system places on medication to improve the quality of people’s health,” Austin says.

Unleashing pharmacists’ extensive knowledge and training in medication therapy makes good sense.

“I think it accurately reflects a more appropriate division of labour. Pharmacists’ education and training is focused on medication in a way that no other health care professional’s is,” Austin says.

He sees this changing role of pharmacists as part of a shift towards a model of greater collaboration.

“I think there’s broad recognition that the expertise required to manage an individual patient is far more than one individual health care professional can provide,” he says.

Austin spent years witnessing communication breakdowns in health care while working as a pharmacist in a hospital setting. “I had a lot of frustration seeing how the health care system operated in an uncoordinated manner, and seeing how much that affected efficiency, effectiveness, and cost effectiveness,” he says. “The system hasn’t set itself up to allow for effective communication and collaboration.”

Better and more effective use of resources is what Austin is working to achieve through spearheading research and pilot programs.

He is project lead in creating a 10-week orientation program for internationally-educated health professionals at the Leslie Dan Faculty of Pharmacy. The program, to be launched in five cities across Canada in January, will help internationally-educated pharmacists, nurses, physiotherapists, occupational therapists, medical laboratory technicians and medical radiation technicians adapt to working within the Canadian health care system.

In 2001, Austin established the International Pharmacy Graduate program at the Faculty, a bridging program that helps internationally-educated pharmacists transition their skills to Canadian standards.

“The work I’m involved with addresses the human resource side of the cost equation in health care and tries to prepare individuals whether they’re pharmacists, non-pharmacists, internationally-educated or not. I’m trying to prepare health care professionals for their role and in that way improve the efficiency and effectiveness of the health care system.”