Who Decides on your Health Care?

Dr. Murray Krahn looks beyond the Clinical Trial to the patient

by Sam D’Alfonso

Quick decisions are made at lightening speed, but slow-motion replays reveal a thought process considering context and consequence (e.g. “What will I wear to the office? Will it make me look fat?”). Curiously, in looking at some of the most important health policy decisions made on our behalf, context and consequence are often absent. “Healthcare decision-makers embrace the concept of ‘Evidence Based Medicine’ (EBM),” says Dr. Murray Krahn, F. Norman Hughes Chair in Pharmacoeconomics at the Leslie Dan Faculty of Pharmacy, “by which they mean randomized trials, rather than costs and patients’ values, factors that are also important in health decisions.”

Krahn is Director of the Toronto Health Economics and Technology Assessment (THETA) Collaborative – an interdisciplinary research collaboration based at the Leslie Dan Faculty of Pharmacy. THETA provides advice to the Ontario Ministry of Health and Long-Term Care’s Medical Advisory Secretariat, acting as a source of knowledge creation and information sharing among different health research institutions, and providing training in Health Technology Assessment (HTA), which supports decision-makers in containing costs, maintaining access, and representing Canadians’ values in health care decisions.

“A treatment may work in the ideal conditions of a randomized trial, but ... does it work in the real world?”

An example of a health care area with significant patient-sensitivity is prostate cancer. There are various generic health indexes such as the Quality of Well Being Scale or the Health Utilities Index. “We needed a quality-of-life indicator for prostate cancer patients, who have major preference-sensitivity issues,” says Krahn. “The increase in life-expectancy from treatment is often offset by detrimental quality-of-life side-effects such as sexual, urinary, or bowel dysfunctions. Yet most decision models only take into account physician preferences for treatment.”

Krahn’s own research team developed an assessment tool called PORPUS or Patient-Oriented Prostate Utility Scale. PORPUS is the first prostate cancer-specific, preference-based quality-of-life instrument. As a ten-item patient self-assessment questionnaire, PORPUS expresses a vital factor in health care. Krahn explains: “The general consensus in Health Economics is that societal preference is the same thing as patient preference. PORPUS was developed on the belief that the people who best understand the preferences of patients are the patients themselves.”

PORPUS is a prime example of a decision making approach that integrates the widest possible range of factors in health care decisions – especially the perspective of patients. PORPUS has already been translated into several languages, and a tool for low-literacy populations has also been developed.

Funding provided by the Ontario Ministry of Health and Long-Term Care, the Canadian Institutes of Health Research, National Cancer Institute of Canada, and the Leslie Dan Faculty of Pharmacy (through the F. Norman Hughes Chair).

For more information on Murray Krahn’s research, please visit http://pharmacy.utoronto.ca/graduate/faculty/krahn.jsp

More information on all THETA research projects can be found at www.theta.utoronto.ca
Piecing Things Together

Guri Giaever examines systems to determine gene function

by Amy Brown-Bowers

There’s a molecular biology parable called “Don’t Shoot the Radio” about how molecular biologists would approach figuring out how a radio works.

First they would buy a lot of identical radios and then they would take a gun and shoot each of them in a different spot. Each researcher would take a radio and try to determine if their blown out wire, button or knob was essential to radio functioning.

“This essay is about how, if a biologist was left the task to figure out a radio, they would never be able to accomplish it because you have to look at the system as a whole ... You can study a piece of green wire your entire life and never understand how a radio works,” says Guri Giaever, Canada Research Chair in Chemical Genetics and assistant professor at the Leslie Dan Faculty of Pharmacy and the Terrence Donnelly Centre for Cellular and Biomolecular Research.

“Since the discovery of DNA and cracking the genetic code, people thought that if they could just get to smaller and smaller bits they would understand biology. That’s the reductionism view: ‘If I understand the parts, I’ll understand the whole.’” says Giaever, adding, “More recently it’s become apparent that that’s not going to tell us the answers and that you really need to look at what’s connected to what and how one part affects another part ... We have to figure out how these parts interact and look at them at a systems level rather than at an individual level.”

In Giaever’s HIP-HOP (Haplolnnsuficiency Profiling/Homozygous deletion Profiling) chemical genomics lab, she and her team are using innovative technology to understand gene function and to explore drug action.

In order to accomplish these goals, her team uses yeast as a model system for human cells. Yeast is a good model system because 50% of all yeast genes share a counterpart in our cells.

Using a collection of about 6,000 strains (each of which carries a deletion in a single gene representing the entire cell), they have developed technology that allows them to examine the interaction of all 6,000 different yeast deletion strains under different experimental conditions (typically with or without drugs) at the same time. Gene deletion strains that behave similarly to a known gene can identify similar function, while drugs that behave similarly to a known drug can identify similar mechanisms of action.

While other researchers examine strains one at a time, each in their own test tube, Giaever’s team can drop all 6,000 strains together in a single test tube and, using a molecular chip, report information about how each strain behaves and responds to external stimuli in the context of all the other strains.

In short, Giaever is looking at how all of the parts of the radio interact and work together to impact radio functioning rather than how each part works in isolation.

“So now we’re looking at a systems level because we’re looking at what the relative importance of every gene is in a particular condition all at the same time,” she says. “This allows us to classify gene function.”

As for real world applications, Giaever’s work is contributing to the study and application of pharmacogenomics.

“The idea in pharmacogenomics is that you can have personalized medicine,” Giaever says. By looking at a person’s genetic background and genetic sequence, you can make better decisions about what drugs to administer. For example, in her work she identifies genes important for understanding the variability in drug response, and why some people may be very sensitive to a particular drug while others may not.

Funding provided by the Canada Research Chairs, the Canadian Institutes of Health Research, and the National Human Genome Research Institute.


HIV/AIDS in Africa: Anti-retrovirals are not enough

Key anti-retrovirals are ninety percent in stock, but only seventy percent of patients are using them. Why? Gina Vacarro’s online supplement follows student researchers Victoria Siu and Joti Dhillon to Namibia where they discover the startling complexities of HIV-positive life in Africa. Please visit www.pharmacy.utoronto.ca/about/files/Endeavour_fall08.pdf.
Basics Instinct

by Sam D’Alfonso

In the early 1950s, two molecular biologists at Cambridge University were asked to concentrate their research on the Tobacco Mosaic Virus which had been infecting crops for decades. Despite the official research agenda, geared to the obvious commercial needs of the tobacco industry, the researchers persevered in deciphering the structure of a group of nucleic acids which had been of growing interest to the scientific community since the late nineteenth century. Neither the university nor tobacco growers would have been impressed, but in 1962, these two renegade basic researchers, Francis Crick and James Watson, along with a third colleague, Maurice Wilkins, were awarded the Nobel Prize for their discoveries concerning the structure of DNA.

In the struggle to make wise investment choices with limited research dollars, funders are under pressure to emphasize applied research over basic. This is a worrisome tendency to researchers like Professor David Hampson of the Leslie Dan Faculty of Pharmaceutical Sciences at the University of Toronto. "Don’t misunderstand me, I’m not saying there isn’t an important role for applied research, but the balance between basic and clinical or applied research funding is out of whack," says Hampson. "Time and again history demonstrates that we need a huge volume of basic research to develop intelligent therapeutic strategies. Without it we’ll continue to encounter a high failure rate on clinical trials, which we’re seeing now on a grand scale. This is important because a tremendous amount of money is spent on clinical trials – money that many scientists feel would be better spent on more thorough basic research related to diseases."

Hampson’s laboratory focuses on the interaction between neurotransmitters or drugs and cell signaling proteins called G-Protein Coupled Receptors (GPCRs), which are the largest family of genes in signaling. This is an important area of research because twenty-five to fifty percent of all drugs currently on the market act through GPCRs, making it an area with huge potential commercial applications.

"The main problem is we still don’t know enough about the human body to develop intelligent therapeutic strategies," Hampson explains. "The recent failure of clinical trials of HIV vaccines is the latest example of us still not completely understanding the molecular basis of a disease."

"We need a huge volume of basic research to develop intelligent therapeutic strategies"

This is where research like the work carried out in Hampson’s laboratory comes in. His team works within the GPCR sub-group called Metabotropic Glutamate Receptors (mGluRs). These receptors are major drug targets because they function within the nervous system – signaling cellular processes that affect mood, sensations, memory, or learning. This makes them pivotal to developing new therapies for treatment of stroke, epilepsy, anxiety, Parkinson’s disease, and Fragile X syndrome.

In order to understand the interaction of substances with these receptors, Hampson’s laboratory uses two strategies. The first strategy is to determine the molecular structure and function of a GPCR. Protein mutations selected through computer generated models are formulated. These mutations are then made in the DNA which codes the mutant proteins and is subsequently grown in cell culture. The effects of the mutations reveal new information on the drug binding site within the GPCR that is useful to medicinal chemists.

The second strategy involves genetically manipulating mice to study drug targets in the body. Many drugs, called antagonists, act by blocking a receptor or an enzyme. Through a genetically altered mouse called a “knockout mouse” (so-called because the gene has been deleted from the animal), researchers can produce a mutant mouse that is essentially equivalent to administering the perfect antagonist. This allows a characterization of the phenotype or the behavior of the mouse which mimics a normal mouse given the drug. Although this genetic approach has drawbacks, one of several critical advantages is that the knockout strategy obviates issues related to drug penetration into target organs and cells, which often complicates drug administration studies.

Both strategies pinpoint new possible mechanisms of action on which to base the development of new drugs. "Pharmaceutical companies too often fall into the trap of trying to develop new drugs with the same old mechanism – what we call the ‘me too’ drug strategy," says Hampson. "But if you’re looking for new ways in which a drug can interact with a protein target on a cell, it’s at the basic research level where these new cellular mechanisms are going to be identified."

Funding provided by the Canadian Institutes of Health Research, the Natural Sciences and Engineering Research Council of Canada, and the Fragile X Research Foundation of Canada.

NOTEWORTHY

Professor JACK UETRECHT’s Canada Research Chair in Adverse Drug Reactions was renewed for 7 years. This renewal allows Uetrecht to continue his important research on the mechanisms of idiosyncratic drug reactions. Idiosyncratic drug reactions are adverse reactions to drugs often thought to be drug allergies. In most cases, they are probably immune-mediated and can lead to liver failure, severe rashes, etc.

Professor SHANA KELLEY recently received an award from the Genome Canada technology development competition. Kelley’s project will develop a low-cost electronic chip suitable for analyzing genes that appear to contribute to the progression of breast cancer. It will provide a high-throughput method for screening genes that may help clinicians make treatment decisions. Through this project, Kelley’s laboratory will be developing the electronic chip and then working with collaborators at PMH to screen breast cancer samples and validate the method. The overall objective of the two year project is to develop a device suitable for commercialization.

Associate Professor CHRISTINE ALLEN and Professor RAY REILLY received funding for a joint project from the Ontario Institute for Cancer Research One Millimetre Cancer Challenge program – "Amplified Molecular Imaging of PGFR and Intracellular Regulatory Molecules in Breast Cancer." The One Millimetre Cancer Challenge program is a province-wide initiative to develop new imaging methods to detect small tumours early when they are most treatable. Dr. Reilly is leading the Radionuclide Imaging component of this platform, working in conjunction with Dr. Allen on this project for the next four years.
Breaking Down Walls
Carolyn Cummins combines scientific fields to study metabolic diseases

by Jef Ekins

Nuclear receptors are a class of proteins found within cells that regulate diverse physiological processes. Triggered by the presence of ligands, substances able to bind to and form a complex with a biomolecule to serve a biological process, they can bind directly to DNA and activate the transcription of gene networks. Assistant professor Carolyn Cummins of the Leslie Dan Faculty of Pharmacy is researching these receptors, looking at them from the bottom up and the top down in a unique ‘meet in the middle’ approach.

Cummins’ laboratory could be housed in any number of departments at universities across North America – Physiology, Pharmacology, Molecular Biology, and several others. That she is conducting her innovative research at the Leslie Dan Faculty of Pharmacy, however, is a sign of the merging of scientific disciplines and the expanding scope of pharmacy in recent years.

Combining degrees in Chemistry and Pharmaceutical Chemistry with a Postdoctoral Fellowship focused on nuclear hormone receptors, it seems natural that Cummins would assemble an interdisciplinary laboratory that would bring together diverse branches of science to examine a process from a variety of angles. Supporting her research is a team of five graduate and undergraduate students and a technician whose similarly diverse backgrounds include Cellular and Molecular Biology, Pharmacology, Biomedical Sciences, Physiology and Toxicology.

“The thing I love about this research is that it requires our lab to span so many disciplines. It’s exciting to get to use so many tools in one project to solve a problem.”

Cummins justifies her interdisciplinary approach to scientific exploration by noting that scientific divisions “are now just names – they don’t mean much. The walls have broken down between the different branches of science. You’re not just a traditional molecular biologist anymore – you’re a research scientist.”

Using a state-of-the-art mass spectrometer, Cummins measures endogenous signalling molecules – hormones, cholesterol metabolites, and bile-acids – that activate the nuclear receptors in both live animals and in tissues. Pursuing this from multiple directions simultaneously in a single lab is quite novel and allows Cummins to see how nuclear receptors affect both individual cell lines as well as the animals as a whole, while studying the downstream effects of altering activity in a physiologic context.

In times of physical or mental stress, naturally occurring glucocorticoids tell the liver to provide glucose to the brain to protect the body. When the stress abates and glucose is no longer required by the brain, production halts through a self-regulating process. Occasionally, glucocorticoid-induced hyperglycemia, which occurs when too much glucose is produced for a prolonged period of time, will result. The high glucose levels caused by glucocorticoid-induced hyperglycemia can lead to diabetes.

“All glucocorticoids are derived from cholesterol. It is clear to us now that LXR is involved in this process. But what role does it play? Glucocorticoid research is complicated – it affects metabolic pathways fundamental to every living organism and hard to study in isolation. We are working at making the connections.”

Through looking at science as a whole, and at the connection between individual disciplines, Cummins has been able to assemble a groundbreaking laboratory capable of producing discoveries on a large scale. Her background, interests, and ability to connect scientific practices together to produce a multidisciplinary approach has afforded Cummins a prime seat as science evolves in the new century.

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What does a student gain by traveling to another country and experiencing its culture and state of affairs? For Victoria Siu and Joti Dhillon, recent graduates from the Leslie Dan Faculty of Pharmacy at the University of Toronto, the experience opened their eyes to global healthcare issues and the benefits of cross-discipline collaboration.

Victoria and Joti participated in the 2007 Student Partnership program with the University of Namibia under the auspices of the University of Toronto’s Centre for International Health HIV/AIDS Initiative-Africa program. Their self-initiated project was essentially a ‘needs assessment’ to determine patient adherence to anti-retroviral treatments in Katutura, a suburb of Windhoek, the capital city of Namibia.

“This was the first time pharmacy students would be going to Namibia, and we didn’t know what the role of a pharmacist would be there. We wanted to assess the medication status of the clinic, what they had and what they needed, and we wanted to interview patients and other healthcare professionals,” said Victoria.

Aaron Yarmoshuk, Director of the HIV/AIDS Initiative-Africa program, and Jillian Clare Cohen-Köhler, assistant professor at the Leslie Dan Faculty of Pharmacy, were both there to help bring Victoria and Joti’s project to fruition, although they pass all the credit to the students.

“This project was based on their own initiative, and Victoria really had the tenacity to follow through,” said Yarmoshuk.

This tenacity took Victoria and Joti to Katutura, and a small tuberculosis clinic which had been expanded to include treatment for HIV/AIDS. After visiting patients saw a healthcare professional, or were given prescriptions, Victoria or Joti would interview them with the help of a Nursing student and translator.

The results were mixed. Their assessment of the clinic’s medication stock showed that key anti-retrovirals were ninety percent in stock, which was good. However, they learned through patient interviews that roughly only seventy percent of patients actually knew how to take their medication.

Moreover, other serious challenges often prevented patients from following their medication protocols. As Victoria explained, “These challenges included not having money to return to the clinic via taxi or bus, and other difficult issues such as patients not wanting to bring medication to work where other co-workers could see them because of the stigma attached to their illness.”

“There was another U of T student at the clinic and she studies Gender and Equality. It was helpful having her there because she was able to explain some of the cultural issues, like power relationships between men and women, that might affect adherence to treatment,” said Victoria.

This kind of cross-discipline discussion and collaboration is a key aspect of the Student Partnership program. As Yarmoshuk described, students may be working at different clinics, but they live in one location to promote a sharing of their experience and their expertise.

“We can’t just teach in the classroom, we have to teach in the field so that students get a full experience. I felt that Victoria and Joti were changed by their experience, and that they had a much more mature understanding of the issues,” said Cohen-Köhler.

As for Victoria, she has said that she would love to return and work on other health projects. Two other pharmacy students have since gone to Namibia to continue the work there this past summer, and as Cohen-Köhler said, “it’s about building not only sustainable experiences for students, but sustainable development for a country in need.”

Funding provided by Victoria Siu and Joti Dhillon, with support from the Enhancing the Student Experience Fund at the Leslie Dan Faculty of Pharmacy.