Before it Self-destructs

How do you get a cancer cell to destroy its own DNA? Dr. Raymond Reilly describes basic triggers that turn cancer into its own worst enemy.

By Michelle Hampson

It takes years, decades and even generations of accumulated scientific knowledge before applications-based science becomes possible. Dr. Raymond Reilly, a professor at the Leslie Dan Faculty of Pharmacy, conducts research on radiopharmaceuticals and molecular imaging – research that is as applications-based as it gets. The driving forces behind his translational research work are important, basic scientific principles.

Reilly’s lab uses molecular imaging to detect and characterize cancer cells. “It’s important both for deciding on the most appropriate treatment for the patient as well as monitoring that patient for recurrence and progression of the disease,” he explains.

One focus of his work includes Herceptin, a drug used to treat breast cancer cells by targeting the HER-2 receptor. Only about half of the breast cancer patients who have this receptor on their tumour respond to treatment with Herceptin though, and virtually all of those patients become resistant to the drug within one year.

Reilly has linked Herceptin with a radionuclide called indium-111, which emits nanometre-range electrons, Auger electrons discovered in 1925, that are only damaging to the DNA of the cell if the radionuclide decays in close proximity to the cell nucleus. In order for the drug to be particularly effective, Reilly uses knowledge of peptides that contain nuclear localization sequences, known stretches of amino acids, that promote the uptake of proteins into the nuclei of cells.

“So by doing that, we have actually designed a very potent form of Herceptin. In fact, our testing shows that it is at least eight to ten times more effective at killing breast cancer cells than Herceptin itself.”

Moreover, this radio labelled form of the drug is able to kill cells that have become resistant to Herceptin.

Another basic science concept that is critical to Reilly’s work dates back to 1931, when Otto Warburg discovered that cancer cells require a lot more glucose than normal cells. “So we take advantage of that basic science discovery again to use a radiolabelled glucose analog to perform PET scans to detect cancer, but also to monitor response to cancer treatment, because only viable or living cancer cells that are rapidly growing take up fluorodeoxyglucose (FDG),” says Reilly.

By using FDG PET scans, Reilly has been able to differentiate between breast cancer tumours in mice that are responsive or resistant to Herceptin. If this proves true in human patients as well, it could provide a means of determining which individuals would benefit most from treatment with the drug.


Assistant Professor Carolyn Cummins was recently named the Banting and Best Reuben and Helene Dennis Scholar for Diabetes Research. Dr. Cummins also received funding from the Kidney Foundation of Canada to study the role of cholesterol and the nuclear receptor LXR in diabetic nephropathy (kidney disease induced by long-term diabetes). The funding provided by this award and grant will allow Dr. Cummins to continue her research and determine whether LXR activation will provide a novel drug target against the onset or progression of diabetic nephropathy.

The Ontario Institute for Cancer Research recently announced an equity investment in the development of a microchip-based diagnostic system for clinically accepted leukemia biomarkers from Professor Shana Kelley of the Leslie Dan Faculty of Pharmacy and Professor Ted Sargent of the Faculty of Applied Science & Engineering at the University of Toronto. This investment will facilitate testing and refinement of the electronic chip and hand-held device for direct and rapid detection of clinically relevant biomolecules in patient samples.
Communication Breakdown

Dr. Stephane Angers attempts to understand the role cell communication plays in cancer development

By Amy Brown-Bowers

Communication issues are at the root of many modern day problems – relationship distress, car accidents, and political paralysis to name a few. Dr. Stephane Angers, assistant professor and Canada Research Chair in Functional Architecture of Signal Transduction Complexes at the Leslie Dan Faculty of Pharmacy, is researching the role of cell communication issues in the development of cancer.

Much of the work in Angers’ lab centres around signal transduction – communication between and inside cells.

“Cells always analyze the chemical and physical signals present in their environment. Like radio antennas, cells are equipped with different receptor proteins to recognize these signals,” Angers says. “Once the receptors are activated by a cue in their environment, the receptors activate complex networks of communication between proteins inside the cells.”

Simply put, cell receptors pick up on something happening outside of the cell. This kick-starts “signal transduction cascades” of communication inside of the cell that enables them to both “integrate and relay” incoming information and react to what’s happening on the outside, Angers says.

So what exactly does research on cell communication have to do with cancer? The answer is everything.

In cancer, basic cellular communication goes haywire.

“Cells first receive cues from their environment, the receptors are activated by a cue in their environment. Like radio antennas, they pick up on something happening outside. In cancer, signaling pathways controlling cell proliferation. In other words, the normal cell-to-cell communication events instructing cells when they are allowed to proliferate are compromised leading to cell growth in an uncontrolled manner.”

In cancer, basic cellular communication goes haywire.

Foundational scientific research, like that done in Angers’ lab, has recently taken a bit of a back seat to more directly applied cancer research and studies on cancer prevention.

However, contributions from labs like Angers’ clearly demonstrate the essential role of basic science in the advancement of better interventions.

“I feel that it is extremely short sighted to only encourage the applied approach to the detriment of basic research,” Angers notes, adding, “In order to understand what goes wrong during cancer, we need to understand the basic molecular mechanisms ... Only when enough fundamental knowledge is known about a given protein or process is it possible to determine the full impact of a mutation or aberration occurring in cancer cells. Also by identifying and characterizing the proteins involved in these processes, additional strategies and the identification of potential drug targets emerge for therapy.”

Angers points out that while cancer treatments over the last 30 years have not changed very much in that most still rely on a combination of surgery and chemotherapy, neither of which target the root of cancer, he says that there has been a paradigm shift over the last five to eight years towards studying treatments that directly target molecules and proteins at the root of cancers.

“Spectacular results have been obtained ... This is clearly the future of cancer therapies.” Angers says, adding, “The advance of these novel targeted therapies would have been impossible without the last 20 years of cancer research that has allowed the identification of the proteins, mutations, and processes at the root of cancers.”

Funding provided by the Canadian Institutes of Health Research.

Molecular Matchmaking

After graduating from the Pharmaceutical Sciences program at the Leslie Dan Faculty of Pharmacy, Dr. Gregory Poon is now teaching molecules how to behave.

By Amy Brown-Bowers

Striving for maximum gain with minimal pain is hardly new. The drive for more focused targeting of desired results permeates advertising and HR firms, matchmaking and marketing companies, and, by definition, targeted therapy research labs.

For example, most chemotherapy drugs indiscriminately kill both healthy and unhealthy cells, hence the nasty side-effects. But research, like that done in the lab of Dr. Gregory Poon, former graduate student at the Leslie Dan Faculty of Pharmacy and current assistant professor in the Department of Pharmaceutical Sciences at Washington State University, is helping lay the foundation for more targeted drug therapies through the generation of targeted molecules.
Targeted by a Receptor

The search for an elusive delivery system ends at the Leslie Dan Faculty of Pharmacy's door.

By Sam D’Alfonso

“We scoured the world, and found what we were looking for in our own backyard,” says Joseph Elliot, President and CEO of Receptor Therapeutics Inc. Formed in 2008 to find and develop promising cancer therapies in collaboration with pre-clinical development experts, who are rare in Canada, Receptor looked at over 80 new cancer therapies throughout North America, Europe and Asia. They found what they were looking for in the PoLi Drug Delivery System at the Leslie Dan Faculty of Pharmacy, just across the street from their offices at the Medical and Related Sciences (MaRS) building.

PoLi is an injectable gel that provides continual release of chemotherapeutic drugs locally over a period of 21-28 days. This delivery system, the result of research by Drs. Christine Allen and Micheline Piquette-Miller, allows local, intraperitoneal chemotherapy which can improve survival while decreasing systemic toxicities in the treatment of ovarian cancer. “We chose PoLi for its complete biocompatibility,” explains Elliot. “Other gels we found all had a potential for adverse reactions, but the PoLi formulation is safe.” Piquette-Miller adds, “as no formulations have been developed for intraperitoneal drug delivery, clinical trials for such a therapy should be a high priority.” Elliot points out that the biocompatibility of PoLi provides the missing link to the rapid pre-clinical process that will make the clinical trials possible relatively soon.

“PoLi delivers drugs that are already in use with a proven safety record,” he explains.

PoLi’s unique qualities are consistent with the unique factors that created it. “Without Micheline I wouldn’t be doing this,” reveals Allen. Her own background is in chemistry with expertise in the formulation and design of drug delivery systems. “If you go through the literature there are so many papers that are focused on the chemistry of delivery materials or in vitro studies on delivery systems that, unfortunately, go nowhere. What is missing is translation of these systems into something that has impact on therapeutic outcomes in patients,” Allen explains. But combining Allen’s chemistry background and Piquette-Miller’s background in clinical and molecular pharmacology launched PoLi from basic bench research to a licensing partnership with Receptor.

Receptor is working with Allen and Piquette-Miller to prepare PoLi for clinical trials. “To get a drug to humans is a multi-step process in which you have to collect sufficient evidence of safety and product stability,” Piquette-Miller elaborates. “You have to start with in vitro studies of cells before you can even test on animals.”

This multi-step process is difficult, time-consuming, and expensive. Yet Allen and Piquette-Miller have brought PoLi through years of research that produced several patents and the publication of over a dozen research papers examining drug release, toxicity, and efficacy, to the point where they were ready to seek out a licensing partner. Nevertheless, it is the partnership with Receptor that has them discovering an innovative model of collaboration. “Receptor has hired a team of consultants specifically for this product,” explains Allen, adding “all the time and energy is spent on exactly what needs to get done.”

Funding provided by the Canadian Cancer Society, National Cancer Institute of Canada, the Canadian Institutes of Health Research and the Ontario Institute of Cancer Research.

Noteworthy

Professor Shirley X.Y. Wu received funding from the Canadian Institutes of Health Research to study “Targeted nanoparticle carriers for drug combination therapy of breast cancer.” This 3-year grant will allow Dr. Wu to develop and determine the efficacy of nanoparticle carriers containing multiple synergistic cancer drugs with surface molecules specifically binding to tumor blood vessels and cancer cells. Dr. Wu also recently received funding from the Canadian Breast Cancer Research Alliance for a 4-year project entitled “Targeted nanoparticle carriers for drug combination therapy of breast cancer.”

Assistant Professor Suzanne Cadarette received funding from the Canadian Institutes of Health Research for a one year Catalyst Grant in Post Market Drug Safety and Effectiveness. This funding will enable Dr. Cadarette to lay the groundwork for an innovative and collaborative research program that examines the real-world safety and effectiveness of osteoporosis medications and impact of non-osteoporosis medications on fracture risk.

Associate Professor Zubin Austin, Ontario College of Pharmacists Professor in Pharmacy Practice, was recently awarded funding by the Ontario Ministry of Citizenship and Immigration, “How do internationally educated professionals acquire linguistic and cultural competency,” will develop and offer English as a Second Language (ESL) courses for pharmacists to study how professionals learn languages.
“Pharmacy has an important role in managing the disease process and the potential for adverse side-effects of anticancer medications,” De Angelis explains. “Clinical and care for anticancer treatments traditionally focus on simply killing the cancer,” he continues, “but the cost of new agents, the increasing development of agents taken orally and the dependency on patient adherence, plus the impact adverse effects have on patient’s lives, among other reasons compel us to know whether or not a therapy will be toxic to an individual patient.” De Angelis, who lectures at the Leslie Dan Faculty of Pharmacy, fills a consultative role for cancer patients at the Odette Cancer Centre: reviewing issues such as drug interactions, developing clinical services in oncology for pharmacy, and instructing clinical oncology staff on drug-related issues.

The most pressing need is to understand all the interactions between a whole patient and the entire process of cancer therapy. “There is a great deal of research looking at genetic defects in cancer cells and the affect these have on the type and response to therapy,” De Angelis points out, “but little on how a patient’s genetic makeup affects their ability to tolerate the treatments we want to deliver.” Understanding those molecular and genetic pathways can reveal the basis of different toxicities that develop in different patients such as Arthralgias/Myalgias (muscle aches and pain) in breast cancer patients, or our recent grant to study the role of cytokines in pain flares following radiation therapy.” But, De Angelis emphasizes, “genes don’t work in isolation, and we need to understand the interplay of genetic code by bringing different types of data together.”

By extension, cancer therapy doesn’t happen in isolation either. The linear process of targeting a group of malignant cells and dealing with the toxicity fallout is played out against a seemingly asymmetrical backdrop of diverging symptoms, patient preferences and perceptions, and individual risk factors. De Angelis and a team at the Odette Cancer Centre developed the Oncology Symptom Control and Information Resource (OSCIR) program – an electronic database designed to facilitate the assessment, management and tracking of chemotherapy-induced side effects at the bedside.

“The ability to prevent, identify and manage treatment-related side effects with OSCIR, will enable us to develop new side effect prevention and treatment strategies that take into account all the factors playing a role in the disease process and the effect these treatments has on the individual patient,” he explains. “We have the patient front and centre – we want to minimize the impact our treatments have on the patient.”

**Molecular Matching**...continued from page 3

Molecular Matching, said to be the “future truths of Physical Science,” notes Poon, is to be looked for in the face of more obviously applied pursuits, “Basic research is the pipeline to future applications,”

“Unfortunately, there is a tendency in today’s funding climate to emphasize short-term outcomes and marginalize research not seen to produce immediate practical benefits. The results of basic research often take many years to find practical applications. The pressure-sensitive touchscreens on the latest cell phones, for example, make use of principles of quantum tunnelling discovered in the 1920s.

To presume that we have learned all the ‘basics’ would be akin to Michelson’s famous remark in 1894 that ‘the future truths of Physical Science are to be looked for in the sixth place of decimals’ only to be usurped just a few years later by what we know today as quantum mechanics.”

While it may be tempting to split scientific research into two distinct camps – basic versus applied, Poon says that they “are really just two ends of a spectrum.” For example, “basic research is the foundation for devising practical applications; however, it happens also that the solution to a practical problem can inform underlying principles and become new avenues of studying them,” he adds.