Chapter 3: Research

Research Highlights

Over the last academic year, our faculty and students continued to push the boundaries of biomedical engineering research. Here are several highlights of their work.

New delivery strategies needed for more nanoparticle cancer drugs to reach their target

Targeting cancer cells for destruction while leaving healthy cells alone has been the promise of the field of cancer nanomedicine. But a new meta-analysis of 117 published papers led by Professor Warren Chan and post-doctoral fellow Stefan Wilhelm found that less than one per cent of designer nanoparticles reached their intended tumour target—and that figure hasn’t changed much over the last 10 years.

Their analysis showed that altering the nanoparticles to target cancer cells made little difference in net delivery efficiency. The majority of nanoparticles end up in the liver, spleen and kidneys, since the job of these organs is to clear foreign substances and toxins from the blood. This suggests researchers may have to control the interaction with these organs to prevent nanoparticles from being filtered out of the blood before they reach the target tumour.

One strategy Chan and Wilhelm pursued involved engineering nanoparticles that could dynamically respond to conditions in the body by altering their surfaces or other properties. This strategy may help the particles to avoid being removed by filtering organs, but have the optimal properties needed to enter tumours.

They also argued that a new systemic and coordinated long-term strategy is needed to increase nanoparticle delivery efficiency and that researchers will need to understand much more about the interaction between nanoparticles and the body’s various organs than they do today. To this end, Chan’s lab is also developing techniques to visualize these interactions across whole organs using 3D optical microscopy. This particular work, titled “Three-dimensional optical mapping of nanoparticle in intact tissues,” was published on April 21, 2016, in the journal ACS Nano.

The full results of their review, titled “Analysis of nanoparticle delivery to tumours,” were published in Nature Reviews Materials on April 26, 2016.

Novel treatment for overactive bladder receives clinical trial funding

An overactive bladder (OAB) is a condition that affects 18 per cent of Canadian adults and up to 500 million people worldwide. OAB involves a frequent and sudden urge to urinate, and it is particularly prevalent among people over 65 and more frequently diagnosed in women.

Professor Paul Yoo received funding to co-lead a clinical trial to test a novel treatment for OAB that targets the saphenous nerve, a peripheral nerve in the leg. Funding for the trial, announced on June 24, 2016, was provided by AGE-WELL and is co-led with Dr. Sasha John, a research associate at Baycrest. The team is collaborating with Dr. Magdy Hassouna at Toronto Western
Hospital on a pilot clinical trial involving 30 patients who are seeking relief from their OAB symptoms. The trial marks the first time the saphenous nerve has been targeted for OAB electrical stimulation therapy.

Yoo and his team recently showed in pre-clinical studies that electrical stimulation of the saphenous nerve inhibited the bladder in a similar fashion to that achieved by tibial nerve stimulation, an emerging therapy available to people with OAB. The new nerve stimulation target may provide better treatment due to the use of lower amplitude electrical pulses than tibial nerve stimulation, which would make it more comfortable for people with OAB. Also, the saphenous nerve does not activate foot muscles, like the tibial nerve does, which could make it a very versatile neural target for treating patients.

The investigators have multiple approved and pending patents on the technologies being explored by this project and have been approached by several industrial partners interested in this novel therapy for OAB. If successful, the new therapy could markedly improve independence and quality of life for those affected by OAB.

Rapid gene expression panel predicts effectiveness of treatments for leukemia patients

The standard treatment for patients diagnosed with acute myeloid leukemia (AML) is intensive chemotherapy, but patients vary widely in their response. Currently, it is difficult to predict who will do well with chemotherapy from those that would do better with novel therapies offered by clinical trials.

A team led by Stanley Ng, a senior PhD candidate in Professor Peter Zandstra’s lab, developed a new, rapid gene expression test. This test could help clinicians determine the best management for patients with AML by making it possible to accurately predict a patient’s response to chemotherapy within one to two days of diagnosis. The test is the result of a collaboration between the University of Toronto’s Faculties of Applied Science and Engineering and Medicine, the Princess Margaret Cancer Centre in Toronto, and leukemia clinics in France, Germany and the Netherlands.

In AML, leukemia stem cells (LSCs) are often resistant to standard chemotherapy. To develop the predictive test, Ng analyzed data produced by his collaborators, Drs. Jean Wang and John Dick at Princess Margaret, on genes more strongly expressed in LSCs. He identified 17 genes whose expression levels can be used to calculate a numerical risk score called LSC17 for each patient.

Ng then linked LSC17 scores with patient outcomes by gathering gene expression and clinical data from more than 900 AML patients treated at Princess Margaret and across Europe. His analysis revealed that patients with low LSC17 scores responded well to standard chemotherapy and survived longer than those with high scores. Princess Margaret is validating the test and plans to use it in a prospective clinical trial in several Ontario hospitals.

The work is described in a study, titled “A 17-gene stemness score for rapid determination of risk in acute leukaemia,” published on December 15, 2016, in the journal Nature.
Exploring ways to stimulate damaged muscle to fix itself

If a patient suffers a debilitating muscle injury, a tissue graft often offers the best hope to restore lost function. Surgeons will replace the damaged muscle with healthy muscle from another part of the patient’s body or from a donor. However, the success of this procedure can be limited by the availability of grafts and the tendency for the new tissue to die before it incorporates into the patient’s body.

University Professor Michael Sefton and Professor Penney Gilbert are leading a multidisciplinary team that is taking a different approach, which could revolutionize how doctors treat skeletal muscle injuries. The researchers are exploring ways muscle stem cells can be stimulated to repair injured or damaged tissue, a process known as endogenous repair, instead of replacing injured tissue.

The team is one of 19 Medicine by Design-funded projects, announced on July 25, 2017, to accelerate discoveries in regenerative medicine and move them from the lab to patients more quickly.

To get muscle tissue to fix itself, the researchers are testing whether a novel biomaterial scaffold can coax stem cells that are present in the muscle to spring into action to heal traumatic injuries. If successful, the team’s approach could shorten recovery, reduce pain and restore function sooner in patients around the world who suffer skeletal muscle injuries in car accidents, natural disasters and wars.

Sefton and Gilbert’s project brings together about 20 researchers from diverse fields, including clinicians, scientists and engineers who are experts in tissue engineering, stem cell biology and medicine.

Do physical stresses turn genes in muscle stem cells on and off?

Professor Penney Gilbert has been awarded a $1.4-million grant from the Human Frontier Science Program (HFSP) to lead a new, international collaboration to study how physical stress triggers the expression of genes in muscle stem cells.

While scientists have already uncovered many of the secrets that explain how and when genes are turned on and off, most of them involve ‘chemical cascades’ of signaling molecules and cell receptors. Many these methods can take a long time to achieve the final result.

But Gilbert and her colleagues want to test the idea that under certain circumstances, physical forces—as opposed to chemical changes—could cause certain genes to become activated or deactivated.

The project, announced on March 27, 2017, enables Gilbert to combine her expertise in muscle stem cells with advanced methods in biophysics from Professor Timo Betz at the University of Münster in Germany and molecular imaging techniques developed by Professor Xavier Darzacq at the University of California, Berkeley. Together, the team will comprehensively examine the ways in which muscle stem cells transmit the physical stresses they experience into changes in their DNA and gene expression.

The results of the study could provide scientists with new, non-chemical strategies for turning genes on and off in muscle stem cells and possibly other types of cells. And, these findings could in turn help treat genetic diseases or other conditions caused when genes fail to turn on and off in the right place or at the right time.
Mending broken hearts—engineering a tiny tissue patch that could be injected rather than implanted

Repairing heart tissue destroyed by a heart attack or other medical conditions with regenerative cells or tissues usually requires invasive open-heart surgery. But Professor Milica Radisic and Miles Montgomery, a PhD candidate in Radisic’s lab, have developed a tiny patch of heart tissue with its own blood vessels that could be injected, rather than implanted.

After many attempts, Montgomery successfully designed a heart-repair patch with shape memory that unfolds into a bandage-like structure as it emerges from an injection needle. The injected patch unfolds to nearly the same size as a patch implanted by more invasive methods and the heart cells survive the procedure well. The researchers also showed that injecting the patch into rat hearts can improve cardiac function after a heart attack.

Radisic and her team are collaborating with researchers at the Hospital for Sick Children to assess the long-term stability of the patches and whether the improved cardiac function is maintained. The injectable patch could enable surgeons to use minimally-invasive techniques, which reduce recovery time, scarring and other risks. If the procedure could be performed successfully in human patients, it would significantly improve quality of life.

The researchers have applied for patents on the invention and are exploring whether the patch could be used in other organs, such as the liver.


Transplanting healthy pancreatic cells under the skin to advance type 1 diabetes treatment

Researchers from University Professor Michael Sefton’s lab have demonstrated that the space under our skin might be an optimal location to treat type 1 diabetes (T1D).

PhD candidate Alexander Vlahos led a project that involved transplanting healthy pancreatic cells under the skin—an accessible and less hostile site—to produce insulin for blood glucose regulation. Once successfully implanted, these cells can then produce insulin to help regulate blood glucose levels. However, one challenge of using skin is that it has relatively few blood vessels.

Vlahos injected healthy pancreatic islets under the skin with a network support of blood vessels and found that normal blood sugar levels could be restored within 21 days, provided blood vessels are injected at the same time.

The next phase of their research will involve engineering the blood vessel network first with the hope that fewer islets will be required. This strategy would allow more of the cells to survive and function within the host, reducing the need for multiple donors per patient.

Vlahos’ study, titled “Modular tissue engineering for the vascularization of subcutaneously transplanted pancreatic islets,” was published on August 16, 2017 in the journal Proceedings of the National Academy of Sciences (PNAS).

Earlier results of this work provided the basis for a $1.1-million research grant from international diabetes foundation JDRF to support a three-year study on this topic. The grant was announced on October 12, 2016.
Research Funding

In 2016-2017, IBBME attracted $7.8 million in research funding.

This high-level of support from multiple funding agencies is a continued testament of our faculty’s strength in biomedical and clinical engineering research. It will help us advance our collaborations and multidisciplinary work with our partners and continue to grow our world-class academic programs for our students.

Figure 3.1a Total Research Funding

<table>
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<tr>
<th>Academic Year</th>
<th>Federal</th>
<th>Ontario</th>
<th>Other</th>
<th>Number of grants</th>
<th>Total PIs</th>
<th>Average per PI</th>
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<td>2012-2013</td>
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1) Federal figures represent all sources of national government funding, including the Canada Foundation for Innovation (CFI), Canada Research Chairs (CRC) program, Canadian Institutes of Health Research (CIHR), Natural Sciences & Engineering Research Council of Canada (NSERC), and the Networks of Centres of Excellence of Canada (NCE).

2) Ontario figures represent all sources of provincial funding, including the Ministry of Research & Innovation and the Ontario Centres of Excellence.

3) Other sources of research funding include corporate partnerships, foundations support, hospital research partnerships, internal University grants, professional organizations, and research partnerships with peer institutions.

4) Total number of grants administered through IBBME.

5) Total number of core and cross-appointed faculty members who administered their research grants through IBBME.

6) Average funding per PI calculated by the total annual funding divided by the number of faculty members who administered their research grants through IBBME during the academic year.
Figure 3.1b Federal Research Funding by Source, 2016-2017

Total federal research funding: **$5,103,294**