Refining personalised cancer medicine

In pursuit of improved cancer treatments, Assistant Professor Catherine Coolens is employing a broad and distinguished array of approaches, encompassing disciplines from basic engineering and physics to clinical translation and radiation oncology.

What stimulated your interest in cancer diagnosis and treatment technology, and how has this led you to your current research?

I grew up in a family of business executives so when I started talking about astrophysics and medicine, it was met with healthy scepticism and confusion, but nevertheless strong support. During university I gradually became more and more interested in the medical applications of physics and interactions of radiation with DNA and cells. Radiation oncology is probably one of the most technically challenging and interesting fields in medicine, and when I was offered a doctoral position at The University of London, days after my grandfather was diagnosed with lung cancer, it seemed the choice had come full circle. Over the last few years I have been very focused on the development and validation of functional imaging techniques to non-invasively assess how a tumour is behaving and growing, and using that information to evaluate the efficacy of radiation treatment.

How do you balance your clinical and academic responsibilities? Are the lines between the two ever blurred?

Working in an applied field can also make it quite challenging to balance these responsibilities, mainly because purely clinical and academic research have traditionally been rooted in two different modus operandi. Clinical responsibilities typically require faster decision making and, although significant planning is involved in commissioning new technology and treatment approaches, the patient’s needs come first so your daily schedule is much more unpredictable. On the other hand, academic responsibilities and traditional research goals are inherently more long-term, as ideas often need to percolate. Finding the time in a busy schedule to write grant proposals and get back into your train of thought can be difficult, and time management is essential. One of the reasons I joined the Princess Margaret Cancer Centre at University Health Network (UHN) is the organisational recognition that good quality research and development will ultimately advance clinical care, making the research translation here very successful and interesting indeed.

Why is there such a need for personalised cancer treatment? Can you outline the advantages of careful measurements or markers of the patient’s genetic, proteomic and physiological state?

Dr Robert Buckman, who was a tremendous medical oncologist and a very funny humanist, always said: “Cancer is not a word, but a sentence”. We have come a long way in treating cancer thanks to improved technology and population-based knowledge gathering, but this can only take you so far. It has long been known from laboratory experiments that people have different sensitivities to radiation, as well as from population studies following Hiroshima, Nagasaki and Chernobyl. In addition, it is becoming increasingly clear that every tumour environment is different. Therefore, having improved prognostic and/or predictive information on individual tumour behaviour and genetic makeup that can better discriminate which type of treatment will be most beneficial for a particular patient is essential in improving outcomes, as well as taking cancer from a potentially life threatening disease to a cure, or chronically manageable disease. These personalised measurements are likely to consist of complementary genetic and molecular profiling as well as functional imaging, since tumour biology can be sampled invasively over time but only imaging can provide simultaneous geometric information.

Have there been many challenges or setbacks during your research career, and what role do you foresee your studies playing in future diagnosis and treatment technologies for cancer patients?

There are always challenges or it wouldn’t be research, but I have found that staying rooted in the clinically relevant questions has helped me to focus on how to best overcome them. In terms of the future of my research, I would hope that validating our pioneering functional imaging methodologies will make for faster, easier and non-invasive methods that can help guide patients’ treatments in a more informed, personalised and human way.

Clearly, your role is both exciting and altruistic. However it is also challenging. Other than your education and experience, what do you attribute your accomplishments to?

I have lived in other big cities such as London, Boston and San Francisco, and one of the reasons I accepted a position at the Princess Margaret Cancer Centre – in addition to the fantastic team and reputation – is the diversity and work-life balance that both the programme and Toronto offer. I’ve always believed in the ‘healthy mind, healthy body’ philosophy. I take time to practise mixed martial arts, yoga, music and spend time with my family. Toronto has spectacular restaurants, excellent nightlife and numerous offerings in arts, culture and events that celebrate personal diversity, which I happily participate in. This provides me with enjoyable ‘downtime’ away from the office which makes me more focused professionally.

How does collaboration contribute to the realisation of your research aims?

I very much enjoy collaborating with scientists from different disciplines, and the University of Toronto and UHN provide ample opportunity for these types of multidisciplinary interactions. The best ideas often come from being challenged to substantiate your work, and doing so amongst different disciplines brings out that extra level of effort in the attempt to speak a common language. For example, over the past five years, I have collaborated with institutions in the US, Netherlands, UK, Norway, Spain, France, Germany and Australia. Some of my closest collaborators are radiation oncologists running the clinical trials needed to answer the important questions. The availability of clinical data to work on new techniques is really an iterative process that benefits all of us in translating innovation from the bench to the bedside.
The ways in which cancer is detected, diagnosed and treated are currently on the brink of major change. Increasingly, clinicians and researchers are seeking to take a more precise, personalised approach, involving the gathering of highly specific biomarkers from each patient. These biological markers not only shed light on the complex mechanisms by which cancers develop and spread, but are also expected to unlock the door to the identification, design and administration of optimal treatment combinations for individual patients, boosting cancer control and reducing unnecessary toxicity.

Before this pioneering approach can become widespread, however, a lot of work remains to be done to improve the precision and accuracy with which biomarkers can be measured. Without the necessary detailed biomarker information, both the quality of cancer care and the medical community’s wider understanding of these biological measurements will continue to suffer. In response, a series of groundbreaking studies are currently underway at the University of Toronto (UofT), Canada, and affiliated University Health Network (UHN). The multidisciplinary projects, encompassing basic engineering, physics, clinical translation research and development and clinical radiation oncology, are already making significant headway in their attempts to develop and deploy image-based biomarkers for personalised cancer medicine.

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Establishing validity

The researchers at UofT and UHN have been focusing their efforts on establishing the clinical applicability of new uses for dynamic contrast-enhanced computed tomography (DCE CT), an advanced imaging technology underpinned by the intravenous injection of a contrast agent that makes blood-flow visible to regular CT scanning devices. By harvesting images that elucidate the speed and direction of the flow of blood through tissue, it becomes possible to both model and calculate the permeability of tumour microvasculature. Given this information, researchers are able to ascertain how effectively specific drug molecules can deliver therapy to the desired location.

Dr Catherine Coolens, Assistant Professor at the Institute of Biomaterials and Biomedical Engineering and Radiation Oncology at UofT and radiation physicist at Princess Margaret Cancer Centre – part of the UHN – explains that the technology itself is not new: “DCE CT has long been used to highlight areas of concern and to better visualise tumours, but mainly as a qualitative test; we are trying to use this information quantitatively as the basis for evaluating a response to treatment”. The researchers are aware that tumour volume is not necessarily a good indicator of treatment efficacy, especially early on in the process, so if DCE CT demonstrates that a tumour is showing a reduced capacity to grow, and this can be measured early on during treatment, then clinicians could adapt their treatment plan accordingly if this change was not seen. In order for this approach to become clinically commonplace, however, the process would need to be properly validated and standardised. Currently, this cannot happen in patients due to the impossibility of knowing the so-called ‘ground truth’, leading Coolens and her colleagues to trial an innovative solution.

Phantom simulation framework

In addition to the validation of measurements, appropriate tracer kinetic modelling and analysis methods are required for the quantitative use of DCE CT to be successfully incorporated into radiation treatment response and assessment. To bridge this gap, Coolens and her fellow researchers have established a cutting-edge phantom simulation framework capable of using biopolymers and tissue printing to accurately represent perfusion of the lungs, liver and cardiovascular system. At a basic level, the dynamic flow phantom effectively simulates the injection of a contrast agent into the bloodstream, controlling the exchange of the agent into the simulated extravascular interstitial space. ‘Depending on the operating settings, one can create different contrast enhancement curves that are reproducible and predictable, allowing quality assurance and the investigation of other variables such as the choice of kinetic model, type of contrast..."
agent and imaging technique,” elaborates Coolens, underlining that the flexibility of this technique is perhaps its strongest attribute.

Having strived to develop a quality assurance framework capable of delivering testing and analytic tools that can be of use to clinicians and researchers throughout Ontario, the work of Coolens and her collaborators is paying off as the research community is coming on board. Indeed, the pressing need for standardisation of the team’s advanced imaging techniques is being acknowledged, and requests have already come in for clinical trials from all over North America into the newly set up QIPCM office supported by both the TECHNA Institute – led by Dr David Jaffray – and the Ontario Institute of Cancer Research. Ultimately, it is only through the type of validated and standardised technology which Coolens and her colleagues are developing that oncologists, radiologists and other clinicians will be able to introduce these innovative therapeutic methods into their programmes of care and treatment management.

OUTPERFORMING CONVENTIONAL METHODS

A vital part of the research at UofT has lain in assessing whether the innovative 4D DCE CT is more accurate in measuring tumour perfusion than traditional region-of-interest approaches. Through the study of preliminary evaluations of metastatic brain cancers, Coolens and her colleagues have successfully gleaned that the availability of true volumetric DCE CT data opens up a fresh approach to analysing the relevant kinetic problem. The novel technology being developed has allowed the researchers a method of temporal dynamic analysis that was particularly salient in the examination of extremely small metastases. This investigation is very much ongoing: “I am currently writing up the results of a study which demonstrates that the dynamic and automated method throws up some interesting and promising results with regards to liver tumours, even in the presence of breathing-induced deformable motion,” Coolens elucidates. Subsequently, the team has extended its approach in order to design software capable of considering

DCE-MRI as well as PET data, opening up new avenues for exploring the various imaging techniques currently available. For example, once the contrast enhancement measurements are complete, the kinetic analysis methods between imaging techniques are very similar, therefore a common platform for automated voxel-based analysis is highly relevant.

INTERSTITIAL FLUID PRESSURE

Alongside this research, the team at UofT and UHN is also planning investigations into the potential of interstitial fluid pressure (IFP) as an important biomarker, particularly in cervical cancer. Led by Coolens’ colleague Dr Michael Milosevic, the investigators are analysing the elevation of IFP in solid malignant tumours as a direct result of vascular abnormalities. High IFP has already been shown to have links with a range of critical processes including changes in gene expression, accelerations in tumour proliferation, development of metastases and resistance to radiation treatment. In addition, Milosevic’s group has succeeded in showing that it can also serve as a strong adverse predictor of survival following radiation treatment, and can be used to identify those individuals most likely to benefit from concurrent cisplatin chemotherapy.

Whilst IFP has great potential value as a biomarker for the improvement of personalised cancer treatment, at present it is only measurable using invasive needle-based techniques. As a result, Coolens, Milosevic and their colleagues are striving to develop a project that capitalises on current knowledge regarding tumour hypoxia and microenvironmental research; biophysical modelling of transport within tumours; and cutting-edge imaging techniques in order to design and develop a consistent, minimally invasive magnetic resonance approach to measuring IFP. If successful, this would enable the widespread adoption of IFP measurement in clinical practice and across a range of forms of cancer, leading the way for new personalised treatments that could ultimately improve the quality of care, reduce the invasiveness of therapy and significantly boost survival rates.