

Innovative Strategies for Imaging Cancers

Dr Frank Wuest



INNOVATIVE STRATEGIES FOR IMAGING CANCERS

Dr Frank Wuest is the Director of the Division of Oncologic Imaging at the University of Alberta, Canada, where he holds the Dianne and Irving Kipnes Chair in Radiopharmaceutical Sciences. His main research interests revolve around the multidisciplinary field of cancer imaging but he is particularly interested in the possibilities of translating techniques developed in the laboratory to clinical settings to enhance patient care. In particular, he focuses on the design, synthesis, and validation of novel molecular probes to optimise the current diagnosis and treatment of cancer.

The aim of Dr Frank Wuest's research at the University of Alberta, Canada, is to dig deeper into the use of molecular imaging techniques to detect cancer. His ultimate goal is to facilitate the translation of novel biomarkers, which have diagnostic and therapeutic potential, from the laboratory to clinic. Biomarkers are defined as characteristics that can be measured from imaging data as indicators of biological processes, including diseases. In addition to his work on cancer imaging, Dr Wuest has also been involved in investigating how cancer cells change to adapt to different conditions, such as low oxygen.

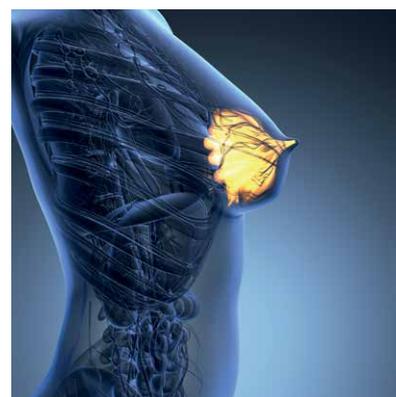
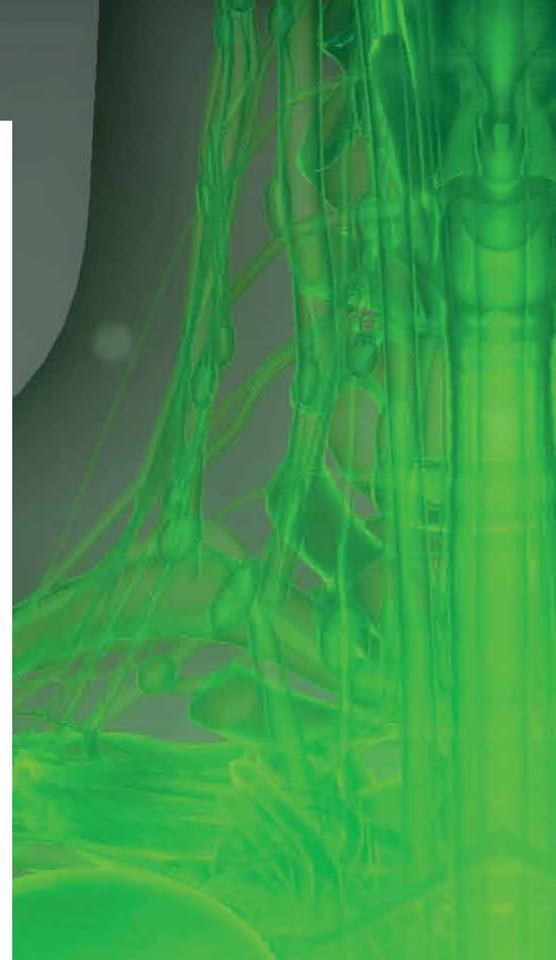
Particular attention is given to the use of novel positron emission tomography (PET) radiopharmaceuticals and pre-clinical PET imaging technology. PET imaging is a technique that can be used to observe metabolic and molecular processes in the body and is often used for diagnosing diseases.

The process works by detecting pairs of gamma rays, which originate from the collision of a positron, emitted by positron emitters, with an electron.

The most common positron-emitting radionuclide is fluorine-18 (^{18}F). Radionuclides like ^{18}F are introduced into the body attached to biologically active molecules called radiotracers, and it is the accumulation of these radiotracers in certain tissues and organs which can be turned into a 3D image to reflect their spatial and temporal biodistribution *in vivo*.

The radiotracer is normally associated with a specific biological process, such as glucose uptake by cells, and can, therefore, be used to infer information about tissue metabolic activity. As Dr Wuest explains, 'The availability of innovative PET radiotracers to visualise and study biochemical processes in living organisms is an important driving force and a key element for the successful application of PET imaging technology in biomedical and clinical research.'

In the 15 years since becoming an independent researcher, Dr Wuest and his group have pioneered the development of novel chemistry techniques for molecular imaging and the validation of novel PET



radiotracers and PET imaging assays that are associated with human pathologies. These assays include the molecular imaging of cancer, metabolic diseases, and neuroreceptors (which are receptor molecules activated by neurotransmitters).

Click Chemistry and COX-2

Part of Dr Wuest's current research is dedicated to the design and validation of probes for molecular imaging of COX-2, which is an important biomarker in cancer and inflammation. His efforts were rewarded by the development of the first successful PET imaging probe ($[^{18}\text{F}]$ pyricoxib) for targeting COX-2 in cancer.

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Leading on from this, Dr Wuest's group has also pioneered the development of fluorescent-labelled probes for the molecular imaging of COX-2 and were the first to use click chemistry for the design of highly specific and potent COX-2 inhibitors. Click chemistry is a class of biocompatible small molecule reactions to generate new compounds. This is often done between a biomolecule and a molecule containing a radionuclide (as for PET imaging). These reactions normally produce rapidly the new molecule in high yield with high specificity. This makes click chemistry ideal for targeting molecules in complicated biological environments, including in living organisms. Dr Wuest's team was among the first to apply click chemistry to the radiolabelling of peptides with ^{18}F .

Even more excitingly, the team used *in situ* click chemistry for the preparation of highly potent and selective COX-2 inhibitors, where the COX-2 binding site was used as a molecular template to generate its own inhibitors. This removed the need for laborious synthesis and screening of a range of compounds, which is the usual approach for drug discovery. The

methods used in the study described above have the potential to be extrapolated for economical and fast screening of other possible drug targets. Dr Wuest's team is currently investigating how the technique could be expanded to detect COX-2 expression at the cellular and whole-body level.

Various ^{18}F -labelled peptides have been designed by Dr Wuest and his collaborators and these molecules can be used as radiotracers to target a wide range of biomarkers associated with cancer and inflammation. The group has also worked with a different short-lived positron emitter, ^{11}C . Together with ^{18}F , the expansion of ^{11}C - and ^{18}F -labelled radiotracers has enabled Dr Wuest's research group to investigate site-specific labelling techniques to incorporate the radionuclide into a specific position of a given molecule. Other, non-standard PET radionuclides have also been investigated in order to determine whether they may be useful for the molecular imaging and therapy of cancer.

Breast Cancer

Breast cancer is the most common cancer affecting women worldwide. As cancer cells proliferate rapidly, there is often limited oxygen available to the cells resulting in changes in molecular processes linked to low oxygen and hexose transport. These hexose transport molecules can be targeted by radiotracers and it has been suggested that low oxygen conditions indicate a poor prognosis for therapy outcomes and survival in patients with breast cancer.

Dr Wuest and his team investigated the expression of these hexose transport molecules in different cancer cells grown in the laboratory under low oxygen conditions. Identification of specific metabolic markers on tumour cells will allow a 'molecular fingerprint' to be established which can subsequently guide the choice of imaging probe used for diagnosing and treating the different forms of breast cancer.



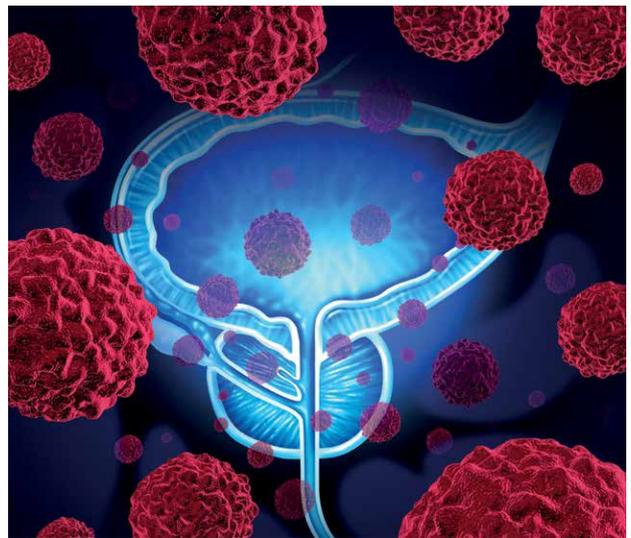
Taking a slightly different approach, Dr Wuest and his team have also recently started to develop a molecular imaging assay for autotaxin, an enzyme also thought to be associated with chronic inflammation, including cancer. This may also have a particular impact on the treatment of breast cancer patients undergoing radiation therapy.

Prostate Cancer

Prostate cancer is the fifth leading cause of cancer-related death in men in Western countries. A molecule called prostate-specific membrane antigen (PSMA) is often increased in prostate cancer. Previously, PET imaging of PSMA with ^{18}F -labelled radiotracers had several limitations, including the amount of time and effort required in producing ^{18}F -labelled PSMA inhibitors.

Using an automated synthesis would remove this limitation – and this is what Dr Wuest and his team set out to do. They were able to simplify the synthesis of clinically important radiotracer [^{18}F]DCFPyL, using a single step radiofluorination procedure in an automated synthesis unit. In addition, [^{18}F]DCFPyL is taken up by tumours and effectively cleared from the body, preventing unnecessary accumulation of the radiotracer in most organs and tissues of the human body. Pre-clinical results confirmed that this molecule is a promising option for targeted molecular imaging of PSMA in prostate cancer.

In addition, work by Dr Wuest and others at the Washington University School of Medicine tested the ‘serve and protect strategy’, which suggests that administering enzymes at the same time as radiolabelled peptides can increase the survival of the peptides, may not be valid for peptides which naturally show metabolic stability in animal models. Other research projects undertaken by Dr Wuest include the development and clinical translation of radiolabelled and metabolically stabilised peptides for molecular imaging and therapy of breast and prostate cancer. In particular, he has already developed a molecule called BBN2 which, when linked to ^{18}F , may be



important for looking at certain types of tumour in breast and prostate cancers.

Ovarian Cancer

The lack of clear symptoms, combined with the high incidence of recurrence, means that ovarian cancer has only a 44.6% five-year survival rate. Cancer antigen 125 (CA125) is a glycoprotein that is overexpressed on the membrane of ovarian cancer cells and may act as a biomarker for ovarian cancer. However, normal levels of the protein can still be associated with the presence of disease. Current assays may be limited in their ability to detect early-stage cancers.

A process called immuno-PET, a version of PET imaging which uses an antibody linked to a radionuclide has shown promise as a strategy that unifies the specificity of antibody binding to a target on the tumour cell with the sensitivity of detection via positron-emitting radionuclides. Dr Wuest and colleagues at MSKCC produced a radiotracer based on an antibody for CA125, which could be used for molecular imaging of the glycoprotein in the body. Furthermore, using a radionuclide to label the antibody for immuno-PET imaging did not compromise the ability of the antibody to bind to its target.

Future Directions

The novel imaging assays that Dr Wuest is involved in designing are vital contributions to cancer care. Specifically, the ‘precision oncology’ concept aims to enhance patient care and outcome through early, more accurate diagnosis and better treatment regimens specifically tailored to each individual patient’s requirements.

Ultimately, the more improvements that can be made to cancer imaging, the better the outcome for the patient. It is this seemingly simple statement that makes the research of Dr Wuest and his colleagues so important for the future of cancer diagnosis and treatment.

Meet the researcher



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Dr Frank Wuest is the Director of the Division of Oncologic Imaging at the University of Alberta, where his research focusses on the use of molecular imaging techniques to assess the potential of novel molecules in the treatment of cancer. He obtained his PhD in Chemistry at the prestigious University of Technology (TUD) Dresden in Germany in 1999, where he also obtained his habilitation in biochemistry in 2006. Between 1999 and 2001, he worked as a postdoctoral fellow with Dr Michael Welch, one of the fathers of radiopharmaceutical sciences, Washington University, School of Medicine (St Louis). Dr Wuest has published over 140 articles to date and he is a Guest Professor at Beijing Normal University in China. He holds the Dianne and Irving Kipnes Chair in Radiopharmaceutical Sciences and is a Senior Scholar of Alberta Innovates – Health Solutions. His research has pioneered the use of novel chemistry for use in molecular imaging and has contributed greatly to the field of oncologic imaging.

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FURTHER READING

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