# BIG MOLECULES FIGHT BRAIN CANCER

## University of Queensland researchers are working with a team of experts to develop the next generation of imaging and treatment tools

Twenty-first century science is exciting, powerful and big. Today's 'Big Science' pulls together the best minds and the latest technologies to tackle what The University of Queensland (UQ) scientist Andrew Whittaker describes as "hugely complex problems".

Professor Whittaker is a Professorial Fellow and Group Leader at UQ's Australian Institute for Bioengineering and Nanotechnology (AIBN). A polymer chemist, he builds and manipulates large molecules for applications in nanotechnology and health.

Right now, Professor Whittaker is collaborating with an impressive range of scientists and clinicians on a Big Science project initiated by Stephen Rose, a clinical imaging expert with CSIRO and UQ.

Their collaboration, the Glioma Project, began about five years ago when Associate Professor Rose was talking with Professor Whittaker about the limits of existing diagnostic imaging technology. Professor Rose expressed frustration that the technology is frustratingly inadequate when it comes to diagnosing a lethal form of brain cancer, glioblastoma.

Very simply, glioblastoma -- also known as glioblastoma multiforme and grade IV astrocytoma -- is a particularly aggressive, treatment-resistant tumour which forms in glial cells, the connective tissue of the central nervous system which includes the spinal cord and brain.

The survival rate is low, with glioblastoma patients living on average only 1-2 years. "Despite the lower incidence of the disease it kills as many people in Australia as melanoma," says Dr Simon Puttick, a Research Fellow in Molecular Imaging and the newest member of Professor Whittaker's AIBN group.

Worse, brain cancer kills more children and people aged under 40 in Australia than any other cancer, according to the not-for-profit Cure Brain Cancer Foundation.

Randal Bishop knows this terrible statistic well. The deadly disease took the life of his 17 year-old daughter Shaynae in July 2009. The tragedy inspired him to launch the inaugural Bridge2Bridge (B2B) charity cycle ride, under the auspices of the Foundation. Contributions from the upcoming B2B charity cycle ride in NSW will support the Glioma Project's work.

It's important to note that project partners seek to improve both diagnosis and treatment for glioblastoma. "It's a step-by-step process of identifying enabling technology and seeing if we can get the experts in those fields and engage stakeholders," says Professor Whittaker.

The team now includes experts in a range of disciplines -- medical research, oncology, physics and biology – from across UQ, the CSIRO, Queensland Health, the Clive Berghofer Queensland Institute for Medical Research and Genesis Cancer Care.

With funding from the National Health & Medical Research Council and the Cure Brain Cancer Foundation, the Glioma Project has taken several big steps, beginning with the limitations of imaging technology.

According to Professor Rose, the critical problem there is that techniques such Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET) can't provide detailed information about the activity of the tumour, especially its boundaries, or 'margins'. As well, glioblastomas may invade healthy tissue, far from the original tumour.

Without this precise information the effectiveness of surgery is reduced. It also makes it difficult to plan and monitor follow-up treatment with radio- or chemotherapy. This is a situation the Glioma Project team want to change -- and large biomolecules they've developed could be the key.

The idea is to create designer molecules to carry novel biomaterials, or agents, capable of increasing the sensitivity of diagnostic imaging. The molecules could also deliver therapeutic agents, able to kill tumour cells without harming healthy tissue.

As Professor Whittaker suggests, "There's no point in imaging unless we can move the therapy forward."

To help crank up the sensitivity of the imaging technology, Glioma Project members at QIMR Berghofer, Professor Andrew Boyd and Doctors Bryan Day and Brett Stringer, have identified a target on the tumour's cells. It serves as a 'receptor' for novel imaging agents created by the group. Known as EphA2, the receptor -- a large molecule called a protein -- sits on the surface of normal and cancer cells.

It's like a "cellular GPS," Dr Puttick explains. "It helps cells know what to do and where to go". When a cell becomes cancerous it will have more EphA2 receptors than the surrounding tissue. Such "over-expression" makes EphA2 a good target for molecules bearing the new imaging agents.

Target in sight, Dr Puttick – "I'm the hands-on chemist doing the experiments" – is in the lab creating transporters for the agents. A range of approaches has been identified and tested. One the most promising is based on proteins created by Professor Boyd's team and refined by AIBN bioengineering scientist Associate Professor Stephen Mahler. The group is now working with a number of such protein ferries.

The next step is to load the ferries with an "imaging agent sensitive enough and bright enough to mark the tumour", says Professor Whittaker.

Results are “extremely promising”, he notes, especially for PET scans which are proving more sensitive than MRI scans with glioblastoma. Professor Whittaker adds: “Now we need something in there [the ferry] to destroy the tumour cells.”

That “something” is a radioactive substance designed to emit high-energy killer particles. Even better, imaging agents can be used alongside the treatment agents, enabling oncologists to ensure the radioactive substances target only disease tissue.

But as Dr Puttick notes, in the case of new medical products and procedures, input from the end users – doctors and surgeons -- is needed to put the effort into a real-world context.

“Scientific success is only part of the equation, the solution must be applicable and affordable in current clinical practice,” he says, “. To that end he acts as the project’s “intermediary”, ensuring all the players meet regularly.

Specifically, Genesis Cancer Care radiation oncologist Dr Michael Fay, Dr Paul Thomas, Assistant Director of the Queensland PET Service, Royal Brisbane and Women's Hospital, and medical specialist and UQ Executive Dean Professor Nick Fisk provide clinical expertise.

Rounding out the team are AIBN polymer chemist Dr Kristofer Thurecht, along with cancer biologists Dr Brett Stringer and Dr Bryan Day from QIMR Berghofer Medical Research Institute. Professor Andrew Boyd heads the Berghofer’s Brain Cancer Research Unit and was also a co-founder of the Glioma Project.

All up, the group has succeeded in creating advanced biological tools to image and treat brains affected by glioblastoma, and has even tested them with animals. “We’re ready to go to early human trials but need the funding,” says Professor Whittaker, who attributes the rapid progress to the “open-minded collaboration” between the group’s partners.

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Chief Investigators on the NHMRC are, in order:

- A/Prof Stephen Rose, Principal Research Fellow at the Centre for Medical Diagnostic Technologies in Queensland (MedTeQ), Centre for Magnetic Resonance (CMR), University of Queensland and head of the Imaging Research Laboratory.
- Professor Andrew Boyd, Professor of Experimental Haematology, Queensland Institute of Medical Research.
- Prof Andrew Whittaker, Professorial Fellow and Group Leader Australian Institute for Bioengineering and Nanotechnology (AIBN), The University of Queensland
- Dr Paul Thomas, Assistant Director of the Queensland PET Service, Royal Brisbane and Women's Hospital
- Dr Mike Fay, Royal Brisbane and Women's Hospital
- Professor Nick Fisk, Executive Dean Faculty of Health Sciences The University of Queensland.