Targeting the microenvironment of paediatric brain tumours: a new frontier for therapy

INSTITUTE FOR MOLECULAR BIOSCIENCE
If your child was diagnosed with a brain tumour today, where is your hope? Do you hope they survive while suffering considerably with the poor quality of life, or do you give in to the fact that they may peacefully succumb to the disease and not have to endure lifelong consequences?

How are any of these acceptable outcomes today? I want to change the prognosis for children and their families diagnosed with brain tumours, so at least some of these children and families can have hope.

Dr Laura Genovesi
Cure Brain Cancer Foundation Fellow, UQ

Overview

Brain cancer kills more children in Australia each year than any other disease.

Survival rates have barely changed over the last 30 years despite medical advances having achieved far better outcomes for other types of cancer. As an example, nine out of ten children diagnosed with leukaemia will live at least five years beyond their diagnosis, compared to just two out of every ten children with brain cancer.

Efforts to find a breakthrough have been hampered by the very high attrition rate of anticancer treatments in clinical trials. Only five per cent of treatments that show promise in preclinical models continue to perform in clinical trials to the point where they can eventually be used in practice.

One of the most significant reasons for this attrition is due to deficiencies in current preclinical modelling. Researchers need better methods to understand how these treatments are working, when they are administered, but even more importantly, why they are not working if the tumours return.

UQ’s Institute for Molecular Bioscience (IMB) has both the multidisciplinary and internationally recognised expertise to gain pivotal intel to progress new treatments to clinic. If successful, the results will lead to far smarter efforts to discover effective therapies for brain cancer in children.

Unfortunately, brain cancer exploration receives only five per cent of Australian Government cancer research funding. To make a difference for future generations of children, we urgently need philanthropic support.

If we can gain this insight and can target the tumours with additional drug solutions, then we can make an impact on this insidious disease.
We need new treatments that are far less toxic, requiring better preclinical modelling and insights without delay.

Given the devastating rates of survival and the insidious impact faced by survivors throughout their lifetime, clearly there is an urgent need to identify new therapeutic strategies that are more effective and less harmful to developing young brains.

Current preclinical modelling (such as those using mice) plays a central role in the discovery, development, design and delivery of new drug treatments that might demonstrate effectiveness in clinical trials.

However, these models have significant limitations. There is an absence of technology that allows for efficient monitoring within a living organism, and high throughput screening (a critically important process to identify promising compounds, antibodies or genes) of new therapies.

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Additionally, the inability to monitor physiological interactions among tumour cells, and between tumour cells and their microenvironment, in response to a particular therapy means we cannot identify possible resistance mechanisms that drive the recurrence of tumours.

One of the most promising areas anticipated to improve the success rates in drug development is the availability of new preclinical models that better replicate the biology and microenvironmental factors of patients. To further understand medulloblastoma, it is important to build physiologically and mechanically relevant preclinical models to best understand the roles of the microenvironment and complement the current models.

Very few models that capture these aspects of brain tumour biology currently exist, meaning this approach will make a genuine impact by creating new avenues of research across all types of paediatric brain tumours.

Almost all childhood brain cancer survivors have health problems after they finish cancer treatment.

Medulloblastoma, an aggressive and common malignant paediatric brain tumour, is the leading cause of cancer-related deaths in children.

Survival rates for children have stagnated for several decades, and plummet to less than 10 per cent for children where tumours return after treatment.

Those children who do defy the disease to survive, go on to suffer severe side effects due to the intensive, cytotoxic nature of existing ways to treat the tumour on the immature brain.

The damage results in a range of neurocognitive and physical deficits such as difficulties with memory, attention and processing speed that inevitably leads to significant learning delays and academic failure. On top of this, survivors will experience social isolation due to the associated speech impediments and permanent deafness.

Children can also be left with permanent seizures, insomnia, growth abnormalities, hormone deficiencies, and an inability to chew and swallow. Many are no longer capable of independent living.

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We discovered that our son, Max, was sick with brain cancer quite suddenly. It happened almost overnight. He was a healthy, happy everyday ten-year-old boy playing rugby on weekends and suddenly that winter he got sick.

Within a space of only two weeks we went from thinking our beautiful son had some strange virus to discussing life-saving surgery with neurosurgeons. Max ultimately underwent one surgery that was an eight-hour procedure. They were able to debulk the main tumour in the midbrain, remove one tumour entirely from the left side. But none of the others.

If there could be another treatment other than chemotherapy, there are no words to describe how important that is and what a difference that would have made to Max. He underwent 12 months of chemotherapy. Watching a child go through that is something that no one should have to bear – let alone a parent.

MICHELLE TAYLOR
MOTHER OF MAX SHEARER, CHILDHOOD BRAIN CANCER SURVIVOR, BRISBANE, QLD
Our proposed solution

This collaborative research will generate cost-efficient in vivo and ex vivo novel preclinical models to understand the underlying biological response of tumour cells and their microenvironment to novel therapeutics.

Through the collaboration, two new models will be combined with an existing preclinical model to better understand how the tumour behaves with other cell types and their environment. The combination of these models will directly address aspects of paediatric brain tumour biology that cannot be studied in the present models and will advance understanding of how a tumour cell interacts with its surroundings to define the response to therapy.

Better modelling will ensure smarter and more effective clinical trials and significantly reduce the current reliance on toxic substances.

Patient-derived 3D in vitro models of medulloblastoma

Brain matrix is rich in hyaluronic acid (HA), which makes it mechanically soft. Most preclinical in vitro models exist on tissue culture plastic or glass, which is significantly stiffer than actual biology of the brain.

Recent advances in preclinical cancer models have come from the development of relevant 3D models. This project will develop ‘brain mimetic’ 3D models for medulloblastoma by combining HA-functionalised synthetic hydrogels with actual patient cell samples.

Using a combination of live-cell imaging, immunofluorescence, and clinically-relevant therapeutics, we will compare the role of mechanosensitive-signalling in these models with and without treatment to identify what drives tumour growth, invasion and resistance. These models can be adapted for high-throughput drug screens.

Visualising tumour vasculature and drug delivery in zebrafish medulloblastoma models

The research will make use of the zebrafish model to set up a new line of medulloblastoma patient-derived xenografts.

Zebrafish are currently an underutilised model in the paediatric brain tumour field despite clear benefits in live-imaging and gene-editing approaches.

Current brain cancer treatments often fail due to a failure of drug delivery to the brain. Drugs are delivered to the brain via the blood vessels. Brain vessels, however, are extremely specialised and tightly control the compounds that can enter the brain by crossing the vessel wall. This specialised barrier is called the blood-brain barrier.

Utilising the zebrafish model will give the ability to track different tumour types over time, watch them grow, examine the structure of the surrounding blood vasculature and test drug competency to cross the blood-brain barrier in and around the tumour.
Project deliverables and resource requirements

Phase 1
The initial priority of this project is to establish ‘brain mimetic’ 3D models of paediatric brain tumours, to monitor tumour properties such as growth, migration and invasion in different microenvironments. In tangent, the collective will establish zebrafish models of paediatric brain tumours to monitor tumour cell behaviour and blood vessel recruitment to tumours in these models. It is anticipated that the appropriate modelling of more aspects of the brain will alter behaviour of paediatric brain tumour cells. Imperative to these goals is the training of the next generation of innovative cancer scientists and the associated costs for model development.

Phase 2
This is the most innovative phase of the project, drawing on the diverse and unique skills our research team brings to this project in combination. Building on the foundations of Phase 1, the project will use these model systems to test the sensitivity of paediatric brain tumours to new therapies. This will enable monitoring drug sensitivity, tolerance and resistance in the established ‘brain mimetic’ 3D models. It is considered that by modelling the physiologically relevant brain environment, allowing us to monitor the interactions between tumour cells and their surrounding microenvironment, we can understand how these interactions impact drug resistance.

Phase 3
This phase of the project seeks to identify biomarkers of tumour mechanics that regulate drug sensitivity and resistance in established ‘brain mimetic’ 3D models of the tumours. Exploring the effect of drugs targeting the biomarkers in combination with the new therapies will identify whether it is possible to block resistance and improve overall tumour response. It is posited that a more durable tumour response can be achieved using a combination of drugs targeting the mechanics of tumour cells and their surrounding microenvironment. It will also identify components of the brain-associated vasculature that impacts drug sensitivity and resistance to detect methods to overcome the impact of these and better deliver drugs.

Phase 4
The final efforts will translate insights gained across the program of research to our existing preclinical models of paediatric brain tumours to learn whether the new combination of drugs stops resistance and blocks tumour relapse. This phase ensures that insights and learnings gained can be translated to be applied in clinic and ultimately improve patient outcomes.

Featured: Dr Anne Lagendijk in the Institute’s aquarium facility housing zebrafish.
There is nothing that can prepare a parent for the world of childhood cancer treatment. I cannot adequately express the fear, guilt and helplessness that we endured while holding our boy down to be injected with toxic chemicals. The shock of watching your child’s first fistful of hair falling out, the constant gut-wrenching vomiting, the cries of children in outpatients while their central lines were cleaned or blood was taken, the tired scared faces of other parents, the numerous lumbar punctures, MRIs, PET scans, blood transfusions and the constant worrying about the possibility of hearing loss, lung damage, mobility loss or future learning disabilities from radiation was all consuming.

There were numerous other horrible things that my beautiful boy endured during his treatment that cannot be shared. Just know that the treatment was tough, but our brave little man never complained and he behaved with a maturity and positive attitude that was way beyond his years.

BELINDA BRUNOLI
MOTHER OF TOM BRUNOLI, CHILDHOOD BRAIN CANCER SURVIVOR, BRISBANE, QLD
Our expertise

Our interdisciplinary approach is innovative. This project builds on research momentum and the expertise of a group of researchers who have complementary track records in cancer cell biology, mechanobiology, vascular biology and in vivo preclinical cancer models.

It will define an unexplored aspect of brain cancer biology, allowing us to better understand the interplay between tumour cells and their microenvironments, plus the crucial role of mechanical force initiating chemical reactions.

Dr Laura Genovesi (Cancer biology, expert in brain tumours and preclinical mouse modelling)

Dr Genovesi is a Cure Brain Cancer Foundation Research Fellow. Her research program focuses on discovering new therapies targeted to the biology of the tumour that spare the effects on normal brain cells, and stop the growth of medulloblastoma.

Dr Samantha Stehbens (Molecular and cell biology, expert in cell invasion and migration, cell mechanics, bio reporters and imaging)

Dr Stehbens is an ARC Future Fellow in the Division of Cell Biology and Molecular Medicine. Her laboratory focuses on how cancer cell invasion events are synchronised by chemical and mechanical signals during metastasis.

Dr Anne Lagendijk (Vascular biology, expert in imaging, cell mechanics and zebrafish modelling)

Dr Lagendijk is a Group Leader at the Centre for Cardiac and Vascular Biology and her lab investigates how adhesion and cell mechanics are regulated in order to build and maintain a healthy vasculature.

Support where it is most critical for children

The power of this program of research is to better understand the exact basis of tumour recurrence allowing for the development of more effective frontline treatment approaches that combat the tumour. In turn, identifying new agents for clinical trials to be used in combination for children, if realised, this could lead to preventing the recurrence in the first place and determine if tumour vasculature and other aspects of the tumour microenvironment have a significant role in the ability to treat paediatric brain tumours.

Better identifying each patient’s specific treatment needs can ensure better results. This project offers clinicians the vital key to select clinical trial options and treatment pathways that are most conducive to combating the bespoke needs of the tumour. These are knowledge-based decisions that are not presently available to patients and specialists.

The sad reality is that this depth of knowledge is available for adult brain tumour treatment, but this richness of data is not available for children with brain cancer.

This research project can be sparked only with the support of visionary partners who share the passion of these remarkable researchers to enhance existing paediatric brain tumour treatments, and likely many other treatments hampered by the blood-brain barrier. Without creating the fundamental ‘proof points’ of Phase I, the likelihood of the project progressing is significantly decreased.

We invite you to partner with us to realise smarter, more efficient, new solutions to treating what is the biggest killer in people aged under 40, and protect important developing brain cells to enhance children’s lives beyond a despicable battle.

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“Cure Brain Cancer Foundation have proudly partnered with UQ’s researchers, particularly at IMB, from the early genesis of the drive to combat medulloblastoma tumours. We supported Laura with an Innovation Grant in recognition of her determination to identify tangible clinical solutions to translate into better outcomes for families and survivors of brain cancer.”

Beverley Trivett, Director, Cure Brain Cancer Foundation
Enable our life-saving work by partnering with UQ

Life-changing research requires significant funding. With every donation, large or small, you will help our remarkable researchers get closer to disrupting the present treatment of medulloblastoma brain tumours to save little brains across the globe.

Funding Requirements

Phase 1
This phase bears a cost impact of $450,000 in the first year. This is the most critical phase, and unless this section is fully funded from the start, the overall project cannot proceed.

Phase 2
This phase bears a cost impact of $250,000 if it can be executed six months following the initial models being established.

Phase 3
This phase bears a cost impact of $450,000 to be delivered across 12 months.

Phase 4
This phase bears a cost impact of $350,000 to be delivered across 12 months following Phase 3.

Total investment required: $1,500,000

We hope this opportunity is of interest to you and look forward to discussing the potential next steps with you.

Thank you for your consideration.

“...the presentation provided by the Chief Investigator, Laura Genovesi, and her team, closely aligned to Brainchild Foundation’s drive to target research funding towards paediatric brain tumour research. However, it went further in supporting a multifocus approach to the microenvironment of paediatric brain tumours and we feel that this development is unique and should be strongly supported.”

Yvonne Hastings, Secretary, Brainchild Foundation
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