Research Project
By Dr Adekunle Bademosi

Dementia Australia™ Research Foundation

RACE AGAINST DEMENTIA

Understanding the dynamics of tdp-43 aggregation in ftd using advanced imaging tools

What is the focus of the research?

Explore how and why TDP-43 proteins clump in the brains of people living with frontotemporal dementia (FTD). Discover where the protein clumping begins, how the clumps overwhelm the brain's waste-disposal system and start to identify potential drugs that can halt or reverse the clumping of the proteins.

How will this happen?

Stage 1: Use advanced imaging tools to study the TDP-43 proteins before, during and after they clump.

Stage 2: Analyse their tendencies and characterise temporal changes in the mobility at all stages.

Stage 3: Mutate TDP-43 to make it RND-deficient. Tag and track the mutation to assess the impact on nuclear expression patterns.

Stage 4: Characterise and compare the mobility of the proteins to highlight the role of RNA interaction on protein dynamics.

Stage 5: Induce TDP-43 clumping in different ways to observe how the dynamics change over time and see if it stabilises or not.

Stage 6: Test 323 previously identified genetic regulators of TDP-43 and determine their role in its clumping.

Stage 7: Incubate neurons and test them at regular intervals to determine whether autophagy is compromised when TDP-43 clumps.

Stage 8: Investigate whether altering autophagy can prevent the clumps that are associated with FTD.

Why is it important?

Unfortunately, it's difficult to get a true understanding of what has happened inside the brain of someone with FTD without a post-mortem investigation. Once the brain of someone who has lived with FTD is sampled, large clumps of TDP-43 proteins are found. These are toxic.

Dr Bademosi's mentor has already shown that a significant event occurs in mice brains. When TDP-43 proteins are prevented from clumping, there is a level of functional recovery and the lifespans of the mice are extended. This is extremely exciting.

The next step then is finding out why these proteins begin to cluster in the first place, and how these clumps are cleared from neurons. Studying the protein's movements around the clumping event have been attempted in the past, but more work is urgently needed. This research step is extremely important if we are to create some kind of intervention – whether that be a treatment, cure or prevention.

What will this mean for other researchers?

- Knowledge of why and how these proteins clump – and where clumping begins.
- Better understanding of how gene regulators regulate TDP-43.

What is autophagy?

A natural protective mechanism of a cell. It essentially cleans out damaged cells so that the body can generate newer healthier ones. It operates like a waste-disposal centre, even recycling cellular components, and so plays an important role in maintaining the balance.

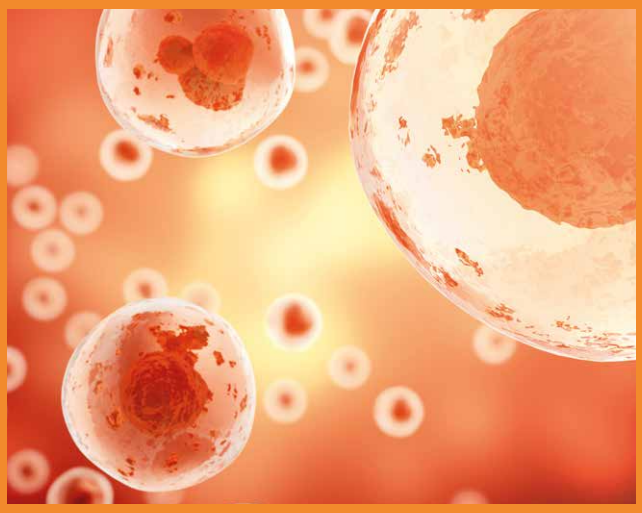
In FTD, autophagy is overwhelmed and results in the continuous accumulation of the TDP-43 protein which forms clumps. Finding a way to modulate it is very important.

What Is FTD?

FTD stands for frontotemporal dementia. A major pathological trait of FTD is the misfolding and clumping of a DNA-binding protein called TDP-43 in the frontal and/or temporal lobes of the brain.

The affected lobes are involved in important things like mood, social behaviour, attention, judgement, planning, self-control, processing sound and understanding what we see. Damage to them can lead to reduced intellectual abilities, changes in personality, emotion and behaviour, difficulty recognising objects and difficulty understanding or expressing language. Protein clumps that occur in people with FTD are toxic and ultimately cause damage to these very important parts of the brain.

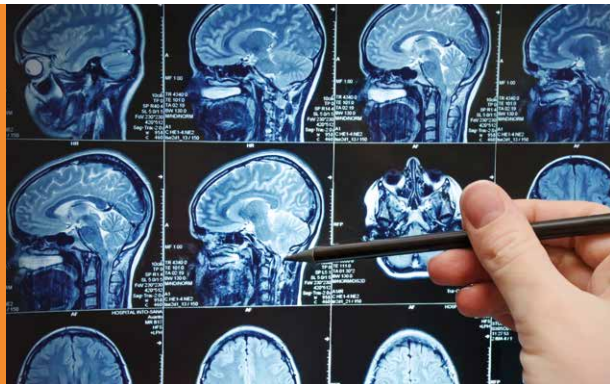
In contrast to Alzheimer's disease, memory is often unaffected in FTD, especially in the early stages.



- An understanding of how the clumps overwhelm the brain's waste disposal-recycle machinery for damaged proteins.
- A map of the dynamics of TDP-43 at high temporal and spatial resolutions.
- Identification of potential new drugs that can halt or reverse the clumping of these proteins.
- The opportunity to screen the effect of new drugs on the protein clumps prior to commencing clinical trials.

What sort of imaging tools will they use?

Dr Bademosi will be using world-class super-resolution single-molecule imaging facilities. This will allow him to perform single particle tracking (SPT), being able to see them with resolutions of up to ten million times that of a standard digital camera!



What will this mean for the future?

- An early diagnostic tool to detect FTD before a person develops any symptoms of the disease.
- New mechanisms for FTD therapy.

“I saw the emotional and financial struggles as well as the hopeless feeling that my family experienced after my grandmother’s dementia diagnosis. Even then, I searched for ways to help her and to stop this disease from taking away my grandma.”

– Dr. Adekunle Bademosi

Who’s undertaking the research?

Dr Adekunle Bademosi, The University of Queensland

Dr Bademosi is a postdoctoral research fellow at Queensland Brain Institute with more than six years’ experience in cellular and molecular neuroscience. He is an experienced postdoctoral researcher with a keen focus on finding practical solutions to complex problems. He holds a PhD and Masters in Neuroscience and is working with Dr Adam Walker, a leading researcher in the field of FTD and a world expert in TDP-43 pathologies.

Dr Bademosi became interested in dementia research after experiencing the condition firsthand in his family. His career goal is to unveil the compromised pathways that induce FTD and to identify potential therapeutics for people living with FTD.

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