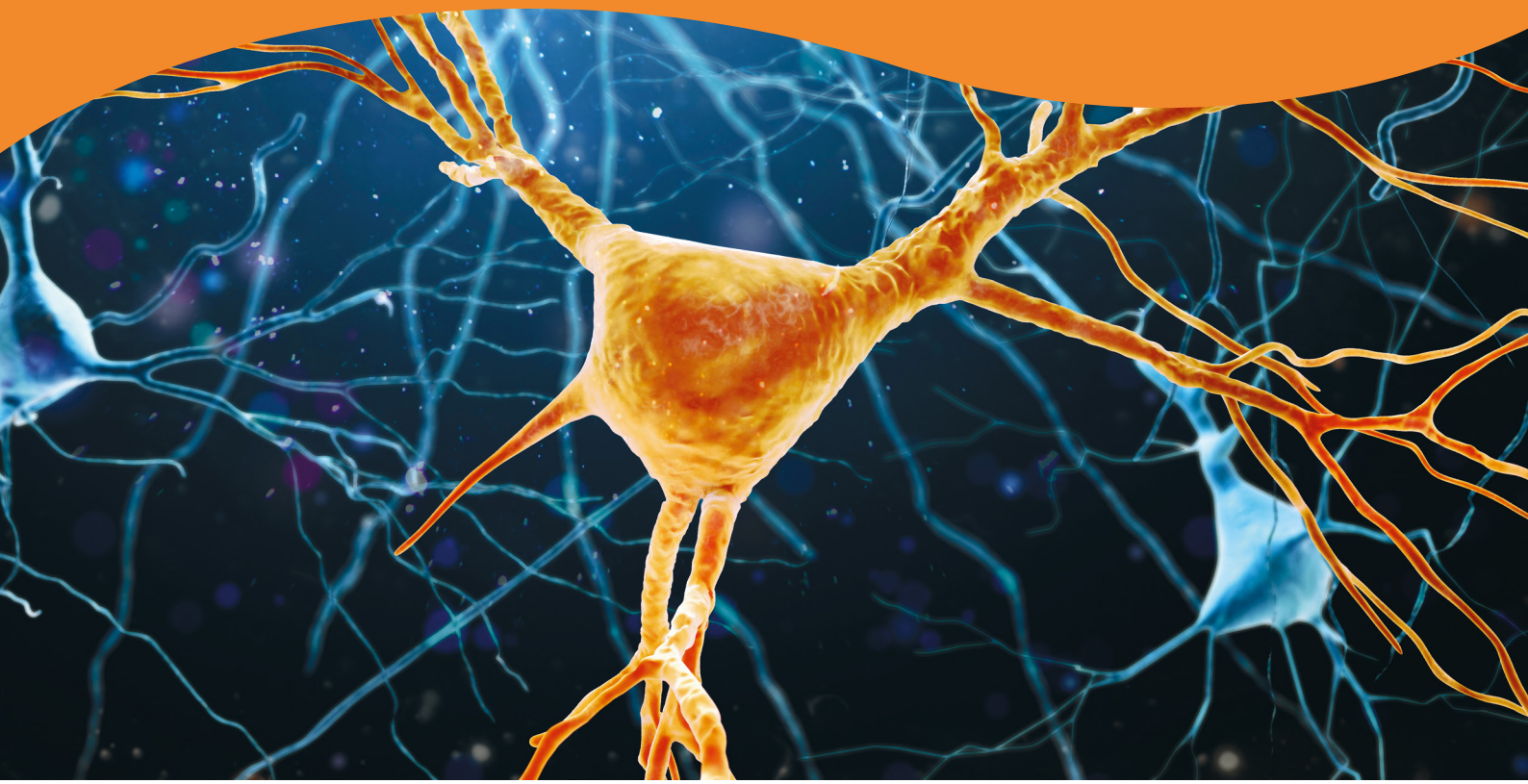
Research Project
By Dr Sonam Parakh

Dementia Australia™
Research Foundation



Targeting malfunctioning brain proteins to prevent frontotemporal dementia

What is the focus of the research?

To investigate the impact that faulty proteins in brain cells have on frontotemporal dementia (FTD) and determine whether a nuclear regulator called nucleoredoxin can prevent this malfunction.

What is nucleoredoxin?

An important chaperone in the nucleus that helps proteins fold correctly. It can prevent them from misfolding, and can also rearrange their disulphide bonds to help them form properly.

Because the misfolding of proteins is linked to FTD, Dr Parakh and her team are hopeful that better understanding NRX may lead to the discovery of a prevention or treatment for FTD.

Nuclear chaperones like NRX have never been examined as potential targets for therapeutic intervention in FTD before, but several studies have suggested they may have a role to play in neurodegeneration. Dr Parakh and her team are hoping that role may be protection against FTD.

Why is it important?

Dementia is a devastating disease that affects not only the person diagnosed, but the people around them. There are more than 100 forms of dementia and there is still no cure.

Where some forms of dementia are more common in older people, frontotemporal dementia can affect anybody. It's typically diagnosed in people at a younger age, with symptoms beginning in their fifties, sixties, or sometimes younger.

This younger onset means that families suffer unique challenges, as the person diagnosed is often still of working age and may have dependents and families relying on their income, provision, guidance and support. Finding a cure or effective treatment for frontotemporal dementia could be life-changing for countless Australians.

Researchers now know that the nucleus (cell brain) is critical in the initiation of disease. It is the master regulator of all cellular functions. Dysfunction in this compartment is being increasingly linked to frontotemporal dementia.

However, the health of proteins inside the nucleus of people with frontotemporal dementia hasn't been studied. Proteins fold into structures that help with cell growth. This folding is regularly challenged by stresses from inside and outside the cell. When proteins malfunction, they misfold, become toxic and start to aggregate. This misfolding and aggregation of a DNA-binding protein called TDP-43 is a pathological hallmark of frontotemporal dementia.

Dr Parakh's innovative project aims to identify how and why misfolded TDP-43 forms in the nucleus of neurons and why they accumulate in a non-conventional location (cytoplasm) of people with frontotemporal dementia. She will also identify new ways to prevent that from happening.

Her team previously discovered that a specific protein, called nucleoredoxin (NRX), prevents proteins from misfolding and aggregating in the nucleus. It also protects against several other similar events linked to frontotemporal dementia. Dr Parakh is now taking the critical next step and investigating if nucleoredoxin can be used to develop new treatments for frontotemporal dementia.

Frontotemporal dementia, explained

This type of dementia occurs when there is progressive damage to the frontal and/or temporal lobes of the brain. The affected lobes are involved in 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. In contrast to Alzheimer's disease, memory is often unaffected in frontotemporal dementia, especially in the early stages.

How will this happen?

Stage 1: measure protein folding with a small-molecule sensor called a fluorogenic probe.

Stage 2: cause mutations in cell nuclei, then test how nuclear mechanisms fail and cause protein misfolding. This will help the researchers understand how FTD-associated mutations cause protein misfolding.

Stage 3: validate stage 2 findings and examine the distribution of NRX in cortical and hippocampal neurons and test for abnormalities in the affected neurons in FTD tissues.

Stage 4: test whether NRX can restore the conventional nuclear localisation of proteins using specific nuclear/cytoplasmic reporter.

Stage 5: cause mutations in neuronal cells, then treat them with dye to measure the health of proteins inside. Determine the role of NRX against protein misfolding in the nucleus. This will determine if FTD-associated mutations make nuclei more susceptible to misfolding.

Stage 6: deplete NRX to test if protein dysfunction occurs.

Stage 7: test whether NRX is directly controlling the health of proteins in the cell nuclei that are expressing FTD-associated mutations.

What will this mean for dementia researchers?

- A potential new therapeutic target for FTD that could assist with developing a treatment.
- Greater understanding of the mechanisms of FTD.
- Knowledge of the key mechanisms that induce nuclear proteostasis stress.
- An understanding of the protective qualities of NRX.
- A better understanding of how specific protein misfolds are involved in neurodegeneration.
- Answers as to whether disruption to the nucleus facilitates neurodegeneration in FTD.

Why hasn't this been studied before?

Little is known about protein misfolding in the nucleus and consequently, the role of nuclear proteostasis (protein homeostasis) has remained unexplored in FTD. This is partly due to unsuitable tools.

A tool called NTPAN-MI has recently been invented to specifically detect nuclear protein misfolding - and therefore nuclear proteostasis. NTPAN-MI stains the nucleus of cells that have disrupted nuclear proteostasis. Dr Parakh plans to use NTPAN-MI to help fill the gaps in knowledge of nuclear proteostasis in frontotemporal dementia.

> **Protein dysfunction in the nucleus of neurons is an important but unexplored process that we believe is central to frontotemporal dementia.**
>
> **– Dr. Sonam Parakh**

Who's undertaking the research?

Dr Sonam Parakh, Macquarie University

Dr Parakh is a postdoctoral researcher in the Department of Biomedical Sciences at Macquarie University's Centre for Motor Neuron Disease Research. She received a Bachelor of Biotechnology at Bangalore University, a Masters in Biotechnology and Bioinformatics at La Trobe University, and a PhD in Neuroscience from Macquarie University.

Dr Parakh's work focuses on characterising and identifying the molecular origins of frontotemporal dementia, motor neuron disease and amyotrophic lateral sclerosis, to develop future therapeutic targets.

The title of Dr Parakh's project is *Defining the role of nuclear proteostasis in the pathogenesis of frontotemporal dementia.*