Research Project
By Dr Anna Konopka

Dementia Australia™
Research Foundation

Targeting DNA repair process for dementia gene therapies

What is the focus of the research?

Exploring the mechanisms of dementia-related DNA damage and testing a potential treatment to improve the repair process.

Why is it important?

DNA is located inside the cells of every living organism. Genes are small sections of DNA that carry unique genetic information which direct cells to make proteins responsible for human function.

Every day these genes are damaged by thousands of lesions. Being able to repair these DNA lesions is crucial for the maintenance of healthy cells. In most cases, the body has specific mechanisms to carry out these repairs. However, in Alzheimer's disease and frontotemporal dementia, the two most common forms of dementia, this repair process is faulty. As a result, DNA lesions accumulate in the brain. This impairs cellular functions and is thought to cause the cognitive decline that erases memories and devastates families. Unfortunately, we don't know why it occurs.

Both diseases are characterised by a mutation in a protein called TDP-43, which causes it to become toxic. Dr Konopka and others recently discovered that TDP-43 has a role in repairing DNA lesions. This suggests that when it malfunctions, like in dementia, TDP-43 may contribute to the accumulation of DNA lesions. Dr Konopka will investigate a new molecular mechanism that is responsible for the accumulation of DNA lesions in dementia associated with mutated TDP-43. Her team will also test a potential new treatment they hope will improve the DNA repair process.

This project aims to reveal new causes of dementia associated with the mutated TDP-43. With a better understanding of this damage, the mechanism may be able to be repaired. If so, it could lead to a long-awaited dementia treatment.

How will this happen?

Stage 1: express genetically engineered TDP-43 into brain cells from mice to determine its role in the pathology of a DNA-binding enzyme called topoisomerase IIß. Damage to this enzyme leads to DNA damage called double-strand breaks.

Stage 2: use genome profiling technology to identify the specific genes targeted by double-strand breaks associated with the pathological TDP-43.

Stage 3: express enzymes, which remove pathological topoisomerase IIß in neurons delivered from mice brains. This will allow researchers to determine whether enhancing DNA repair is protective against TDP-43 pathology-induced DNA damage.

What will this mean for the future?

- New treatment pathways for Alzheimer's disease and frontotemporal dementia.
- Better understanding of what causes them.
- The potential to develop new gene therapies for dementia.

TDP-43, explained

TDP-43 is a TAR DNA/RNA binding protein. Dr Konopka recently discovered that it has an important role in repairing the most serious type of DNA lesion, the double-strand break, which is the complete severing of both strands. These breaks occur during normal DNA replication and repair, but also after exposure to toxic agents.

Topoisomerase IIß, explained

Topoisomerase IIß is a class of enzymes that maintain the integrity of the DNA double helix by transiently breaking or re-joining the strands during DNA transcription and translation. This prevents the strands from coiling around each other too tightly.

Who's undertaking the research?

Dr Anna Konopka, Flinders University

Dr Konopka is a neuroscientist based at Flinders University, Adelaide. In 2015 she completed her PhD at Nencki Institute of Experimental Biology, a leading neuroscience research unit in Poland, then undertook her first postdoctoral training at Macquarie University, Sydney.

Her research focuses on the role of DNA damage in neurons, with particular interest in the role of DNA damage in neurodegeneration. Dr Konopka's main line of research led to the discovery of a new role of TDP-43 protein in the repair of the most cytotoxic type of DNA damage, double-stranded breaks.

The title of Dr Konopka's project is *Understanding the causes of DNA damage in dementia associated with abnormal TDP-43.*