Research Project
By Dr Karissa Barthelson

Dementia Australia Research Foundation

RACE AGAINST DEMENTIA

Adult- and childhood-onset dementias: Related causes and related solutions

What is the focus of the research?

To assess the similarities between Alzheimer's disease and a common form of childhood dementia called Sanfilippo syndrome to see whether treatments that target their shared pathologies could be therapeutic in both conditions.

How will this happen?

Stage 1: Use both in vivo and in vitro testing (on

zebrafish and mice/human cells respectively) to compare the pH of the endolysosomal pathway in Sanfilippo syndrome and Alzheimer's disease to see if acidification is impaired similarly in both.

Stage 2: Compare the changes in iron homeostasis in Sanfilippo syndrome and Alzheimer's disease to discover if improper acidification of the endolysosomal pathway results in an intracellular iron imbalance.

Stage 3: Use compounds that restore lysosomal acidification and iron homeostasis to try to 'rescue' molecular and behavioural traits in Sanfilippo syndrome and Alzheimer's disease.

Stage 4: Use a maze to test the spatial working memory of the Alzheimer's and Sanfilippo fish, and whether the compounds can rescue the observed memory changes.

Stage 5: Choose the most promising candidate from the zebrafish experiments to test in mouse models to see if the results replicate, and determine whether iron- or acidification-based therapeutic strategies could alleviate molecular and behavioural changes in Alzheimer's disease.

Why is it important?

Childhood Onset Dementia is not well enough understood. Some children develop symptoms as babies, but others do not experience these until they become teenagers. Children with Childhood Onset Dementia experience similar symptoms to that of an adult with Alzheimer's disease – memory loss, confusion, issues with sleep, concentration and speech. Like with Alzheimer's disease, each child's experience with Childhood Onset Dementia is different, which can be frustrating for the child, terrifying for the parents and difficult to navigate. Most difficult to cope with of all, perhaps, is that Childhood Onset Dementia is progressive. This means parents watch their children lose the ability to play, talk, write, and even walk. They watch their children's brains unlearn all the vital skills they have helped them to learn - how to read, toilet, eat and eventually live.

Despite this being an incurable and fatal disease, new research pathways are giving hope for the future. Given there is much overlap in the brain

Don't Only Old People Get Alzheimer's Disease?

The short answer is no. There are more than 27,000 Australians with Younger Onset Dementia. This affects people under the age of 65. Childhood Onset Dementia (often called Childhood Alzheimer's) also affects one in 2,800 Australian babies. There are approximately 70 rare genetic disorders that can cause this fatal disorder.

What is the Endolysosomal Pathway?

Endolysosomes support important cargo molecules with normal cellular function including immune responses and homeostasis. It is thought that any abnormality or dysregulation in this might contribute to the development of Alzheimer's disease through iron dyshomeostasis and neuronal dysfunction. If this is true, a therapeutic intervention based on acidification or restorative iron could help people with Alzheimer's disease and Childhood Onset Dementia.

Why Zebrafish?

Whilst mice are often used to model Alzheimer's disease, the small size of their litters provides inadequate biological replication for this project. The impact of gender on their brain makeup can also obscure the effects of mutant genotype. In contrast, zebrafish, who are also able to inherit Alzheimer's-like genomes, show negligible gender effect on their brains and are able to generate very large families (~100 siblings!). These siblings have a variety of genotypes and can be raised together in a single tank which reduces genetic and environmental variation. Their optically transparent larvae also make them an ideal model species for iron staining dye.

What's the Difference Between In Vivo and In Vitro?

In vitro testing is research performed in a laboratory setting, often in petri dishes or test tubes. Testing microorganisms or cells in this way allows scientists to study a larger number of subjects in a controlled environment.

However, in some research it is vital to factor in the conditions inside a living organism. In these cases, in vivo testing can be done inside a whole living organism. With this, researchers can replicate human diseases in animals or better evaluate the safety and effectiveness or drug candidates in human trials.

and behavioural changes between Alzheimer's disease and childhood dementias, Dr Barthelson believes the disease-associated mechanisms may also be similar. Whereas Alzheimer's disease is complex and difficult to wholly capture in animal models, the genetic bases of childhood dementias are much better defined. More reliable animal models – like zebrafish – also exist for childhood dementias which will help research to uncover the next clue to finding durable solutions to both.

What will this mean for people with dementia?

- Important information about the links between Alzheimer's disease and Childhood Onset Dementia.
- Potential innovative solutions and treatment pathways to alleviate behavioural changes of people with dementia.

What will this mean for the future?

- A better understanding of if and how the endolysosomal system can be targeted for new therapeutic strategies in both Alzheimer's disease and Sanfilippo syndrome.

Who's undertaking the research?

Dr Karissa Barthelson, Flinders University

Dr Barthelson is a researcher in the School of Biological Sciences at Flinders University. Her doctoral research has been recognised by multiple awards, including the Harold Woolhouse prize and the Postgraduate All Round Achievement Award from The University of Adelaide, as well as the D.G. Catcheside Prize from the Genetics Society of AustralAsia. She is working to establish a zebrafish facility at Flinders University to help expand work with models of Alzheimer's disease and Childhood Onset Dementia.

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