EXPERT INTERVIEW

# The role of biomarkers in drug discovery for neurodegenerative disease

There's a need to propel and reinvigorate the current state of drug discovery pipeline in tackling pressing neurodegenerative disorders such as Alzheimer's disease (AD), Lewy body dementia, Parkinson's disease, frontotemporal dementia (FTD), and other diseases that cause dementia.

Dr. Brigid Ryan, a neuroscientist at the Centre for Brain Research at the University of Auckland, investigates neurodegenerative disease by taking a multidisciplinary approach in defining early biomarkers of dementia.

She has been studying microRNAs (miRNA) in brain function since her PhD days, exploring their role in memory, and is currently an Auckland Medical Research Foundation post-doctoral research fellow in the Human Brain Plasticity and Neurodegenerative Diseases Research Group, led by Professor Maurice Curtis. Her focus is on the potential utility of dysregulated plasma miRNA profiles as biomarkers in neurodegenerative disorders like AD, with a focus on inherited frontotemporal dementia.

We had the privilege of speaking with Dr. Ryan regarding her ongoing research and its powerful implication in aiding neurodegenerative drug pipelines, delving into her perspectives on this exciting field of biomarker discovery.

## Meet the scientist

**Dr. Brigid Ryan,** *Research Fellow, New Zealand Genetic Frontotemporal Dementia Study*

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**RV** **Your recent publication explored plasma miRNAs that were altered in a mouse model of tauopathy, a classical feature in neurodegeneration. In a nutshell, how does this work fit into your larger research identifying potential early biomarkers of dementia?**

**BR** The work with the mouse model was being done in parallel with the work with the human cohort [from a longitudinal study of early biomarkers, prior to clinical symptoms, in genetic FTD families] – And the idea really was to identify some interesting miRNAs from that mouse model and then see if they are also of interest in the human – [We need to now] validate that they might actually have utility in the human study – So the human study is longitudinal, and we've been running it for four years now, so it will be in the next six months that we're starting to do all the sequencing for plasma miRNAs from the human study, so that's going to be really exciting to see what we come up with.

**RV** **Your research highlights the value of identifying relevant biomarkers before clinical symptoms appear, where this idea of timing could play a critical role in assessing the real therapeutic possibility of drugs. Can you describe this idea further?**

**BR** My assumption is that as soon as that happens [where early, even preclinical biomarkers are validated], then pharma would be very much interested in [neuroscience drugs] again. We could show there is some potential, and that the issue wasn't with the mechanisms behind the potential treatments, the issue was with the timepoint that we were treating.

**RV** **Can you explain more about the timeline?**

**BR** Essentially, the previous clinical trials that have happened in all of the work that pharma has done have been intervening with somebody [who] already has dementia. What I think now, which is fairly uncontroversial, is that some of these treatments that have already been trialed have failed at their later timepoint. But if we were able to give those same treatments to people either in the very early stage of Alzheimer's disease, for example at the MCI [mild cognitive impairment] stage or preclinically, then those treatments have the potential to work.

And the physiological mechanisms and the physiological rationale for those treatments might not necessarily be incorrect. It's just that we're treating too late in the disease course and by that time the cells are really too badly damaged for any sort of rescue of that neurodegenerative fix to happen.

When you look at the current clinical trials that are happening – the newer treatments, compared to the treatments that were started a few years ago – you can see a shift towards including patient groups that are at that earlier timepoint in the disease. Some of the pharma companies are interested in looking at these preclinical groups that they are identifying, for example, people with significant mutations that will cause the person to develop Alzheimer's or FTD in the future but they don't have any clinical symptoms currently. And they are trialing those drugs at the really early timepoint. I think a lot of people in the field would agree that it's quite a promising area for potential drug treatments.

**RV** **Your work looks at miRNA biomarkers and not necessarily causative genetic mutations. How does this play into your overall aim?**

**BR** One way to identify those people preclinically is if they have a genetic mutation. But what I'm really interested in is whether we can identify preclinical dementia in larger cohorts of people... If we could identify biomarkers that allow us to find people who have sporadic, preclinical dementia [not necessarily of an inherited genetic origin] and if we're confident that they're in that preclinical phase, not because of a mutation but because of a sporadic form of the disease.

If we could do that, then that would give us access to a much bigger patient cohort for testing those treatments and would allow us to implement potential treatments in a much larger group of people.

**RV** **So it sounds like the goal would be developing biomarker profiles that would be relevant to a larger population than just those with associated genetic disease-associated mutations as the biomarker. Is that what you had in mind as well using plasma/blood as your sample type to profile?**

**BR** The goal for the work that we're trying to do is to develop a biomarker that could be used in a population-based screening test, so the dream is that we really get to a level where we could have, for example, a blood test for everyone in the population and identify people who are at risk of developing dementia in 10 or 20 years' time, and that's just not feasible with imaging or CSF, so the blood test is the goal in terms of lack of invasiveness and just cost and ability to do it in a population-based way. If we could do that, then that would give us access to a much bigger patient cohort for testing those treatments and would allow us to implement potential treatments in a much larger group of people.

And I think that's definitely where the field's heading for whatever application you're thinking about. So for example, if you're looking at pharma needing a biomarker to determine whether the drug that they're trialing is working, it's obviously always going to be preferable to be doing it with a blood test rather than having to do multiple lumbar punctures or MRI.

**RV** **How do you think your research relates to other areas of neurodegenerative research?**

**BR** The most obvious similarity across all of the neurodegenerative diseases is that it's protein aggregation which is eventually causing the cell damage. What's important is which part of the brain, which cell types are affected. And so, in terms of those similarities that you see across patients, as the disease progresses, these aggregates spread to more and more parts of the brain.

If the cell death is happening in the same cells in the same part of the brain, you will still get the same symptoms. In that way, I think there are some interesting similarities across the different neurodegenerative disorders, which potentially could be treated in a similar way if the treatment focused on the protein aggregation.

And for all neurodegenerative diseases, there's a huge focus on biomarkers and there's a huge focus on preclinical biomarkers, and I think that everything I've said about Alzheimer's applies to other neurodegenerative diseases as well. Personally, I'm biased because I'm really interested in the FTD field, but I think there's some really exciting work happening in terms of the clinical trials in that field, especially the tau-based therapies, which are currently being trialed in both sporadic and genetic forms of FTD, and I think that's really promising.

## More about the scientist

**Dr. Brigid Ryan, Research Fellow**

Brigid leads the New Zealand Genetic Frontotemporal Dementia Study (FTDGeNZ), a multidisciplinary longitudinal observational study of a large family cohort with a genetic mutation that causes FTD. The FTDGeNZ team of neuroscientists and clinical researchers are proud to be part of the international effort to contribute to dementia research by studying genetic FTD cohorts.

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