Medical Xpress

In search of an Alzheimer's cure

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For decades, the field of Alzheimer's research has been dominated by a major hypothesis: that a build-up of beta amyloid (amyloid-β) in the brain causes Alzheimer's disease. However, despite years of research and billions of dollars spent on clinical trials, there is still no cure.

In a paper published in high-profile journal *Acta Neuropathologica*, researchers at the University of Technology Sydney outline evidence to question whether the emphasis on the amyloid hypothesis is preventing the development of alternative – and potentially disruptive – theories in Alzheimer's research.

"Over the last 30 years, the majority of tested therapeutics for Alzheimer's disease have been directed toward removing amyloid-β.

Although we see merit in this strategy, we suggest that disease initiation and progression is more complex than can be accounted for by amyloid-β alone," says Professor of Neuroscience and Director of the UTS Centre for Neuroscience and Regenerative Medicine, Bryce Vissel.

"Alzheimer's disease is a life-changing diagnosis for those living with the condition, their family and friends. We have written this article to encourage research leaders to think outside the box in their attempts to find ways to prevent, halt or reverse the course of the condition."

Prospective new research targets are yet to be fully understood. For example, existing research shows that vascular degeneration, neuroinflammation and synaptic neurodegeneration are all present during the progression of Alzheimer's disease, but their role remains unknown.

The researchers also argue that looking at brain pathology alone is insufficient to understand Alzheimer's, and that a more holistic approach to disease prediction and diagnosis is required – one that considers the unique features of each individual.

"Since amyloid-β and associated pathology is not at all unique to Alzheimer's disease, attempts to construct a mechanism for this condition based solely on it, not unexpectedly, continue to fail," says co-author Emeritus Professor Ian Clark of the Australian National University.

Further, the amyloid hypothesis has its own challenges: for example, many healthy individuals have amyloid-β without Alzheimer's, and there are also significant numbers of people diagnosed with the disease despite having no amyloid-β. What's more, there are at least nine known, modifiable risk factors for Alzheimer's that might not be linked to amyloid-β deposits at all.

Alzheimer's disease is the single leading cause of dementia, which affects up to 50 million people around the world and is a leading cause of death in Australia. The paper is important because it provides a balanced counterpoint to a significant field of research that could affect how we think about the causes and treatments.

"The understanding of Alzheimer's disease causation is incomplete. In this article we have tracked how the modern-day perception of Alzheimer's emerged, we have highlighted where knowledge is lacking and we have suggested new directions for Alzheimer's research to take," says co-author Dr. Gary Morris, a postdoctoral scientist at UTS.

"The most important take-home message is that the understanding of normal brain function and dysfunction has grown enormously in the last few decades. We propose the hypothetical models for Alzheimer's disease causation need to evolve to accommodate these advances. In doing so, new therapeutic strategies will likely emerge."

At its core, Vissel and his team are advocating for what they see as the logical next step in the global fight against Alzheimer's. Their own research is focusing on a range of risk factors and how they combine to cause the disease.

"What's clear is that there are a lot of failing clinical trials, there's desperation around the world to find solutions, so we really have to start thinking in a different way and this paper presents some suggestions for how to do that," says Vissel.

"In this paper, we provide important suggestions for how to go forward to conquer this disease.

"We are confident world efforts will get to a solution."

More information: Gary P. Morris et al. Questions concerning the role of amyloid-β in the definition, aetiology and diagnosis of Alzheimer's disease, *Acta Neuropathologica* (2018). DOI: 10.1007/s00401-018-1918-8