Neurodegenerative diseases

AETIONOMY

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Reclassifying neurodegenerative diseases to enable drug development – time to change course?

Introduction

Neurodegenerative diseases are a growing global challenge as medical advances ensures more individuals live longer. By 2020 there will be > 40 million individuals in the world with Alzheimer's disease (AD) and by 2040 without the development of truly disease modifying drugs this will be > 80 million. Similar trends are also seen for Parkinson's disease. The annual treatment and social care of individuals with Neurodegenerative diseases is estimated to be > 1 trillion dollars by 2050 making it one of the most important socioeconomic challenges of this century. Discovering and developing disease modifying drugs i.e. those that prevent progression of the disease has been very challenging with many programs failing. November 2016 saw another phase 3 failure with Lilly's solanezumab failing at the final stages of development. Is this the end of the amyloid hypothesis or a case of too little, too late and too broad.

The Amyloid Hypothesis

Alzheimer's disease is a chronic neurodegenerative disease, originally described by Alois Alzheimer (1906), causing progressive memory impairment (dementia). It usually presents in the seventh and eighth decade of

life but earlier onset is not uncommon. The cause(s) of AD are not fully understood but the presence of amyloid (protein) plaques was demonstrated in after histopathological examination of the brains of patients 1911. The amyloid hypothesis was originally defined in 1991 with AD showed deposits of amyloid in affected brain regions. Since this time the disease has been thought of as being a disease of amyloidosis. There was always the question of whether these were pathological lesions causing the dementia or just the downstream consequences – the aftermath but not the storm. Subsequent genetic studies revealed that in familial AD the affected genes were often part of the amyloid cascade either increasing production or reducing the clearance of amyloid. It was not just any amyloid that was thought to be the pathological cause of this devastating disease but the 42 amino acid truncated peptide. Just 42 amino acids but enough to cause the disease. It therefore seemed reasonable that drugs targeting the amyloid cascade would be of beneficial effects to patients with early AD.

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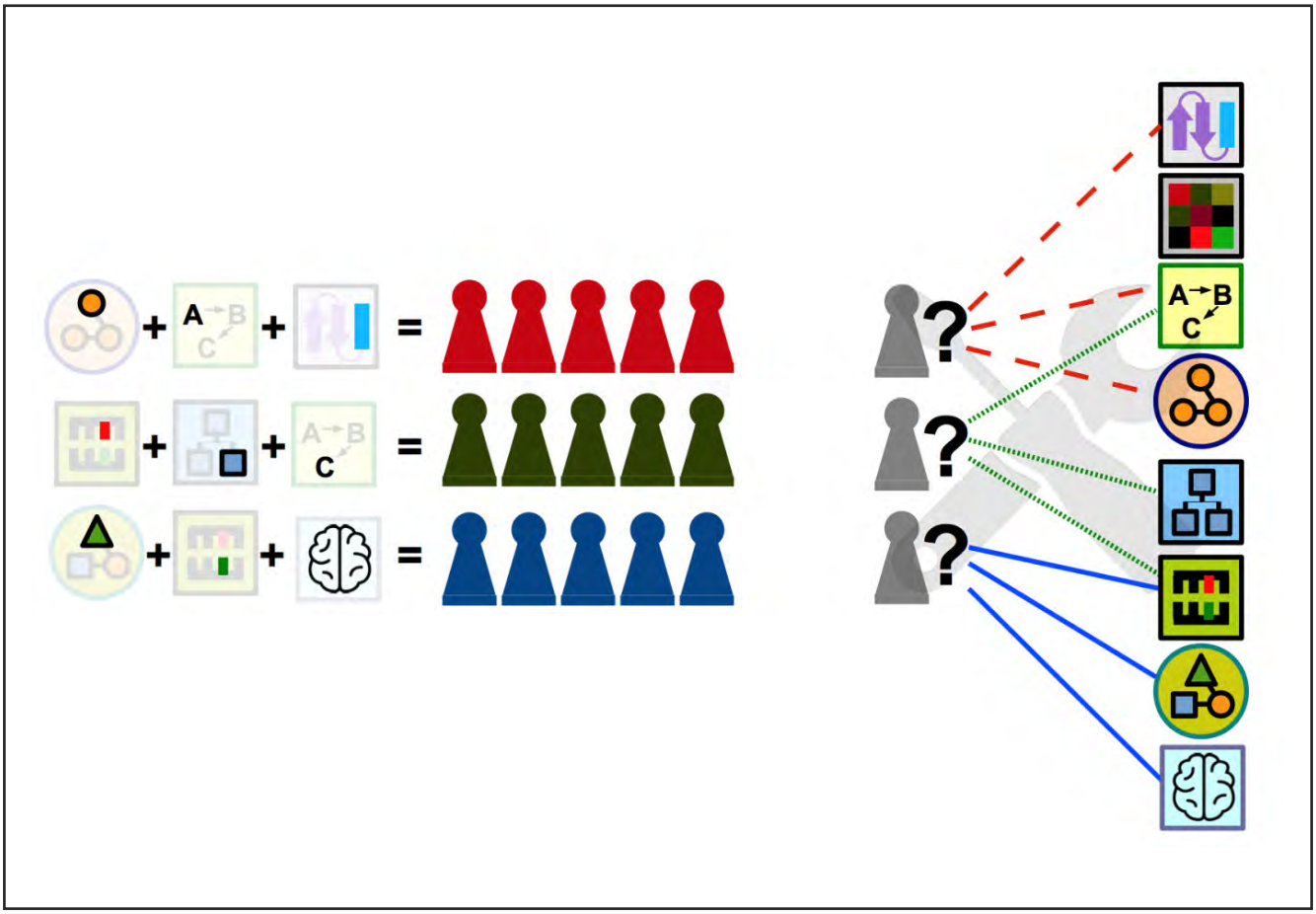
Amyloid therapies

Multiple potential therapies targeting amyloid processing have been developed and studied with several are still in drug development. These therapies all have demonstrated an ability to reduce amyloid load in preclinical models but this has so far not translated into benefit to humans. Amyloid is undoubtedly associated with AD and its presence has been a core part of the diagnosis either in a post mortem diagnosis or more recently detected through imaging techniques. However the amount of amyloid does not correlate with disease severity and many subjects have significant amyloid deposits but no symptoms. Despite these anomalies the majority of current potential therapies have been targeting this mechanism. The community eagerly awaits the results of a clinical trial using Biogen's aducanumab as the most promising agent so far but given the failure of other admittedly less potent molecules targeting amyloid deposition many are pessimistic of a good result.

The failure of these therapies to date could be because the amyloid hypothesis is flawed and despite the association, amyloid is a downstream consequence of the disease process and not pathogenic in its own right. However the presence of familial forms of the disease caused by genes involved in amyloid processing make this unlikely e.g. the presinilin 1 gene is part of a protein complex which degrades amyloid creating the pathological 42 amino acid peptide. It is much more likely that for most individuals amyloid is not the sole cause and additional pathological mechanisms are involved. Indeed we now know that the Tau protein is one of these additional mechanisms. It is therefore time to start focussing on some of these other mechanisms to tease apart the causes of AD that we can target with new therapies. Amyloid deposition is one of the early mechanisms of the disease and takes place many years before the memory impairment and it is likely that the only way to impact the disease through this mechanism is to treat individuals 10-20 years before they were going to get AD and remember not everyone with amyloid plaques gets AD. Therefore we need to look for mechanisms which are important in later stages of the disease process and / or can still be successfully modified once the very early symptoms appear. AETIONOMY is a consortium with the sole purpose of identifying these other mechanisms involved in AD and reclassifying neurodegenerative disease using these discriminatory mechanisms which will help us develop new treatments.

At AETIONOMY we have been taking the totality of research in AD and using our knowledgebase integrating this information into a common framework to search for these other mechanisms. By looking for these other mechanisms we hope to find sub-populations of patients which can be treated by targeting the



cause in them which is present with the amyloid plaques. Success will result in a new way to classify AD beyond just the presence of memory problems and plaques. Success will also result in new mechanisms to target and precision medicines for AD.

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AETIONOMY is an Innovative Medicine Initiative (IMI) funded consortium established to develop an initial mechanistic based classification of neurodegenerative diseases with an initial focus on Alzheimer's and Parkinson's disease. This public private partnership is co led by Duncan McHale from UCB and Martin Hofman-Apitius from SCAI Fraunhofer. The premise behind the project is that although large sums have been invested in research in neurodegeneration and a lot of data generated the co-ordination and integration of this data across the community has been less well addressed.

The consortium has brought together experts in informatics, computing, engineering, mathematical modelling of disease, neuroscience and clinical neurology from leading academic centres as well as neuroscience, informatics and neurology drug development experts from the EFPIA Industry partners.

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The project therefore is not focusing on generating more data but on bringing together all accessible data, curating it to ensure consistency and putting it into a knowledgebase which can be mined and used for disease modelling. Once finalised the knowledge-

base will be available for both researchers to access as well as being a curated and harmonised repository for the storage of future research datasets.

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The AETIONOMY researchers will use this database to identify sub-groups of patients with different molecular causes and will use this to develop a new taxonomy of disease.

The Need to Truly Share Data

The biomedical community has already spent over 10 billion in research into the causes and treatments for neurodegenerative diseases. This has led to a high quality evidence base but a lack of real progress for patients. One contributing factor is the fact that these projects often focus on individual technologies e.g. genetics or hypotheses e.g. the amyloid hypothesis in Alzheimer's disease. AETIONOMY therefore decided that rather than generate another set of data it would look to create a framework where the currently available data could be brought together harmonised and stored so that researchers could look across 100s of millions of euros of research and develop new hypotheses.

The knowledgebase is now built and based in Germany and Luxembourg. It is currently being populated using data from publically available datasets, partner data sets including EFPIA company clinical trial datasets and datasets from collaborators. We are now reaching out to the whole Neurodegeneration Research community and asking for them to share their data do that we can integrate together all of the high quality science that has already been performed and enable drug discovery and developments for the millions of current and future sufferers of this disease. This call to share data is being driven at the highest levels at was a key recommendation of the OECD meetings on meeting the Alzheimer's disease challenge and was christened "unleashing the power of Big Data for Alzheimer's Disease and Dementia Research". A failure to share data will result in duplicating research or wasting resources on areas that have not been validated and delaying getting treatments to patients.

The Future

The future will include a new way to classify neurodegenerative diseases based on the causes of the disease in each individual. We will have screening programs to identify patients at risk of developing neurodegenerative diseases and we will start treatment before symptoms occur. However before we get to this nirvana we must come together and share the data that is being generated across large numbers of publically and privately funded research programs to deliver on our common goal of discovering and developing treatments for neurodegenerative conditions.

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