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Editorial: Therapeutics for Dementia and Alzheimer's Disease:

New Directions for Precision Medicine.

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Abbreviations:

α7nAChR, α7 nicotinic receptor; Aβ, amyloid-β; ABCA7**,** ATP binding cassette subfamily A member 7; AD, Alzheimer's disease; APOE, Apolipoprotein E; APP, amyloid-β precursor protein; BACE, β-secretase; CMA, chaperone mediated autophagy; IL, interleukin; LATE, Limbic-predominant Age-related TDP-43 Encephalopathy; NLRP3, NOD-like receptor family; PNN,

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perineuronal net; TREM2, Triggering Receptor Expressed in Myeloid cells 2; UPS, ubiquitin proteasome system.

Dementia is an umbrella term of which cognitive impairment is but one of the symptoms. Often mistakenly equated with Alzheimer's disease (AD) in the public, there are many other types of neurodegenerative disease that fall within the same disorder parameters. This misperception largely arises from AD accounting for approximately two thirds of all cases, but there is increasing evidence that, clinically, dementia is a disorder of multiple symptoms that can arise from a dynamic range of neuropathological events. For example, a recently described new entity in dementia called LATE (Limbic-predominant Age-related TDP-43 Encephalopathy (Nelson et al., 2019), has been predicted to account for ~20% of clinical diagnosis for AD. LATE exemplifies the challenges in correlating clinical symptoms with neuropathology and the shifting landscape of dementia diagnoses as this field moves forward.

Progress on recognized therapeutic targets

Cognitive impairment is the key symptom of dementia, despite being only one of the features in neurodegenerative diseases associated with this disorder. As such evaluating cognition is a key readout used by physicians in the initial diagnosis of dementia and AD. However, a concern raised by Barus *et al.* (Barus, Bene, Deguil, Gautier & Bordet, 2019) is that many other factors, including their current medication, may have modulatory effects on cognition and thus a greater awareness of these drug-induced neurocognitive effects is required. Interrogating the different drug targets/mechanisms known to modulate cognitive performance by meta-analysis also led this team from Lille in France to conclude that novel risk factors associated with dementia could be identified through this route.

Whilst new avenues of target opportunity are rapidly developing in dementia it is important to not dismiss the work related to Aβ modulation and the role amyloid-β precursor protein (APP) has in dementia, and particularly AD. There is no doubt that biological knowledge related to Aβ and APP in normal- and patho-physiological conditions has increased dramatically since their identification and it would be erroneous to ignore this information because of disappointing clinical outcomes with drugs for the related secretase targets. Historically, most attention on therapeutics in dementia and AD has focused on the biosynthesis of Aβ from its precursor protein. After the failure of γ-secretase inhibitors, β-secretase (BACE) inhibitors, a chemically demanding drug discovery target, have taken time to reach clinical studies. Meanwhile, understanding of the roles and functions of BACE has expanded dramatically, including the ranges of substrates cleaved by this family of aspartyl proteases. Increasing knowledge of the role of these membrane proteases on additional targets other than APP

processing is now being addressed. Work reported by Neumann *et al.* (Neumann, Machauer & Shimshek, 2019) describes the BACE inhibitor NB-360, a tool compound for use to increase understanding of the physiological functions of BACE-1 and the consequences of its inhibition. In this study they relate the modulation of APP processing to chronic Aβ-related downstream effects with neuroinflammation, neuronal function, and other markers of neurodegeneration. Use of improved robust preclinical procedures that require the same compound to be administered at standardized doses and routes in a range of *in vivo* disease models is hoped to provide a greater understanding of disease onset and progression.

Despite a previously predominant therapeutic focus on modulators of the APP processing, Nalivaeva and Turner (Nalivaeva & Turner, 2019) highlight that Aβ levels in the brain are not only regulated through production but also clearance. This clearance is largely considered to occur through proteolysis by key amyloid degrading enzymes and transport processes requiring proteins such as transthyretin. Even though strategies to elevate expression or activity of these mechanisms still heavily rely on the amyloid cascade hypothesis they do provide alternative therapeutic opportunities in dementia and relate to the overall increased interest in proteostatic clearance pathways that are further mentioned below. Better preclinically characterised tool compounds that modulate cellular Aβ and APP levels may also assist researchers such as Lopez Sanchez *et al.* (Lopez Sanchez, van Wijngaarden & Trounce, 2018) and Cecon *et al.* (Cecon et al., 2019), providing insights into whether it is the loss of protective non-amyloidogenic APP fragments or a gain of Aβ toxic function that is more detrimental in AD. Cellular location also appears to be an important factor in pathogenesis - the link between APP or APP-derived peptides and mitochondrial metabolism remains unclear, despite the mitochondria being a location for APP and Aβ, and energy deficiency a recognized early event in AD progression (Lopez Sanchez, van Wijngaarden & Trounce, 2018). Previously the few dementia-associated therapies aimed at mitochondrial dysfunction have focused on reversing oxidative stress and cell death pathways. Despite the clear contributory effects impaired bioenergetics have in early disease progression and phenotypic outcome, research efforts aimed at boosting bioenergetic function remain to be developed and provide a window of opportunity in drug discovery (Perez Ortiz & Swerdlow, 2019). Continued identification and characterization of binding partners for APP and Aβ also increase the appreciation of the complexity in the pathways related to APP metabolism and their involvement in disease. There are various species of Aβ that are known to act as ligands to neurotransmitter receptors in the brain and Cecon *et al.* (Cecon et al., 2019) highlight the α7 nicotinic

receptor (α7nAChR) as one of these binding partners. As a receptor involved in learning and memory processes, the function of α7nAChR is altered in the course of AD pathology (Bertrand, Lee, Flood, Marger & Donnelly-Roberts, 2015) and provides the basis of a sensitive Aβ screening assay for identifying inhibitors that will specifically target a detrimental effect of oligomeric Aβ accumulation (Cecon et al., 2019).

Recognition of a need for novel therapies

The alternative research areas that have recently gained interest in the community have predominantly been observed and reported upon for many years. However, the advance in capability to evaluate much larger cohorts of patients has provided the necessary impetus to consider these other areas of research more seriously. In turn, this improved capacity has begun to increase the appetite of both academia and industry to work on repurposed or newly discovered therapeutics for diseases linked to dementia. However, the reality of turning more to these new areas of research is that the time it takes to develop such opportunities severely impacts on finding relief to patients suffering from these debilitating diseases in the near future. A realization of the substantial gap between understanding the diverse range of pathological pathways and upcoming therapies in dementia has initiated several campaigns to provide investment and support for translational research in this area. This progress has in part been stimulated by a number of governments from around the world that have a growing appreciation of the substantial impact dementia is increasingly having on society. The outcome is that several international institutes have now been established with the specific aim of assisting the development of novel avenues in therapeutics for dementia.

One field of interest to some of these institutes is in targeting proteostasis to facilitate the clearance of the misfolded proteins associated with neurodegenerative diseases. Newton *et al.* (Newton, Duce & Bayle, 2019) provide an overview of opportunities around small molecule modulation of chaperone activity in order to target degradation either through the ubiquitin proteasome system (UPS) or chaperone mediated autophagy (CMA). Another field gaining interest in dementia for therapeutic targeting is neuroinflammation; a key feature in the progress of AD pathology into the 'cellular phase' (De Strooper & Karran, 2016). While the origin of neuroinflammation in AD is not clear, increased interest (as evident by the number of articles provided to this themed issue) has largely arisen from the identification of several disease risk-associated genes that are highly expressed in microglia (e.g. NOD-like receptor family (NLRP3) inflammasome, the complement system, and Triggering Receptor

Expressed in Myeloid cells 2 (TREM2) (Nizami, Hall-Roberts, Warrier, Cowley & Di Daniel, 2019). Moore *et al.* (Moore, Taylor & Crack, 2018) and Nizami *et al.* (Nizami, Hall-Roberts, Warrier, Cowley & Di Daniel, 2019) review some of these microglial targets, their molecular pathways and highlight novel therapeutic approaches aimed at modulating these targets for AD. Cristiano *et al.* (Cristiano et al., 2019) illustrate that Aβ-induced neuroinflammation may occur through an interleukin-17 (IL-17) pathway, while Herman *et al.* (Herman, Simkovic & Pasinetti, 2019) additionally illustrate the shared immune pathways and neuroanatomical features of AD with major depressive disorder. However, as noted by Saddick and Liddelow (Sadick & Liddelow, 2019), we should not forget astrocytes. Given their integral role in normal neuronal functioning and their involvement in the brain's immune system, any effective therapy directed at an inflammatory target may also have an effect in these cells (Sadick & Liddelow, 2019). Lastly, the known risk factor association of *APOE* as well as other regulators of lipid processes identified in patient GWAS studies (e.g. *Clusterin* and ATP binding cassette subfamily A member 7 (*ABCA7*) has emphasised lipid homeostasis as another area of interest for drug discovery. Despite prior concerns related to undesirable side-effects with agonists of the Liver X and Retinoid X receptors that transcriptionally regulate cholesterol metabolism and inflammation, Fitz *et al.* (Fitz, Nam, Koldamova & Lefterov, 2019) rationalise the development of a second generation therapeutic approach with greater isoform selectivity to these receptors.

Knowledge around possible drug targets that maintain neurons in the physiological condition required for health, and their role in dementia, is at an earlier stage, but is by no means less important at revealing therapies in the future. The perineuronal net (PNN) has increasingly emerged as having a vital role in controlling plasticity, regulating axonal growth and regeneration, as well as memory storage during development and throughout adulthood. This concept has obvious implications in several neurological diseases, including the many forms of dementia. The application of compounds that digest PNNs significantly reduces Aβ burden as well as increase synaptic density. This advance introduces the possibility of modulating the PNN, either through PNN digestion or targeting the interaction of various affiliated molecules to the core components of the PNNs, as starting points for an AD therapy (Duncan, Foster & Kwok, 2019). Ferroptosis is another potential mechanism that could contribute to neurodegeneration in AD (Nikseresht, Bush & Ayton, 2019). As an iron-dependent form of cell death, this novel concept is supported by pathological changes in iron occurring in affected brain regions of AD that correlate with disease outcomes. Tool compounds that

specifically target the mechanisms of ferroptosis have yet to be studied in preclinical models of dementia but early clinical trials with iron chelation therapy have been pursued in AD with encouraging outcomes.

New Directions for Precision Medicine

A more detailed perspective on the historical path trodden to develop treatments and reflection on what can be learnt in the future to obtain truly effective treatments for people living with AD can be obtained from Reynolds (Reynolds, 2019). Clearly, (i) less focus on the traditional amyloid cascade hypothesis, (ii) having a greater depth of understanding disease mechanisms, and (iii) selecting better phenotypically characterised study populations for clinical trials are just a few areas that can increase the chance of success in the future and reinvigorate drug discovery and development. A final important consideration to take into account in developing therapeutics for dementia is drug delivery. There has been a large focus to date on small molecule approaches and immunotherapy, but alternative biological and gene therapy approaches are gaining appeal. Progress here has in part been stimulated by several promising trials in Huntington's and Parkinson's disease, with approaches also emerging in AD (Ittner, Klugmann & Ke, 2019).

The articles in 'Therapeutics for Dementia and Alzheimer's Disease: New Directions for Precision Medicine' provide a glance at the diverse range of topics that continue to be investigated in this rapidly evolving field of research and the overall enthusiasm of researchers, including the authors that have contributed to this special theme. There is real promise that a new dawn in this field of research has risen from recent disappointments in the clinic, and the lessons learned therefrom, and there is reason to be optimistic that subsequent drug discovery and clinic trials will better benefit patients suffering from this debilitating disorder. The articles contained herein will be of interest to academic as well as industry-based researchers and students alike. The editors thank the authors and reviewers for their efforts in enabling this themed issue to cover such a broad range of present-day contemplations in this field.

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