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Treatment concept successfully translated into human patients

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Keywords

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We are living in exciting times. Neuroscience has greatly prospered in the last decades, which allowed us to develop more and more precise concepts at molecular, cellular, and network levels of how the brain functions and responds to injuries or diseases [1]. The opportunities brought about by innovative methods and tools open fascinating perspectives for neuroscientists. Besides the unique satisfaction associated with unraveling the brain's mysteries, a proper understanding of physiological and pathophysiological processes should enable us to take measures to enhance brain health and alleviate the consequences of brain diseases. *Exploration of Neuroscience* takes up this banner, providing a platform for excellent experimental and clinical works, which cut edges and exceed borders, for a broad readership [1].

In the inauguration issue of *Exploration of Neuroscience*, the neuropathologist and neurologist Professor Kurt A. Jellinger [2] provided his very personal view of the current state of neuropathology, with a focus on Alzheimer's and other age-related diseases. Born in 1931, Professor Jellinger has been a Full Professor of Neuropathology at the University of Vienna School of Medicine since 1973, Director of the Department of Neurology, Lainz Hospital Vienna since 1976, and Director of the Ludwig Boltzmann Institute of Clinical Neurobiology Vienna since 1977 until his retirement. He is well known to the neuroscience community as the Chief Editor of the leading neuroscience journal *Acta Neuropathologica*, which he was responsible for from 1976 to 2004. I still vividly remember communicating with him within this journal my first own papers as the first author as a young postdoctoral fellow. Prof. Jellinger carried out this role with a lot of personal dedication as a man of vision, a characteristic he has maintained until today.

Presenting a review of the history of neuropathology and the evolution of research methods including immunohistochemistry, proteomics, genetics, and brain imaging since the 19th century, Professor Jellinger [2] provided a succinct overview of the understanding of the spectrum neurodegenerative diseases, including Alzheimer's pathologies, tauopathies, and α-synucleinopathies, which we have today. Professor Jellinger [2] outlined recently introduced diagnostic entities, such as limbic-predominant

age-related TAR DNA-binding protein 43 (TDP-43) encephalopathy (LATE), which he critically discussed regarding the influence of associated age-related comorbidities, including coexistent Alzheimer's pathology, which to a considerable degree explain heterogeneities in disease manifestations and outcomes. Professor Jellinger [2] subsequently evaluated neuroimmunological diseases, brain cancers, cerebrovascular diseases, and neuromuscular diseases in an analogous way, again with very similar findings. He described that research technologies have provided essential information about disease pathogenesis and development, enabled diagnostic accuracy, and identified therapeutic targets in various neurology subspecialties, although in several disease areas, specifically in neurodegenerative diseases or stroke, these discoveries have not led to the identification of disease-blocking or disease-delaying treatments until now [2]. He concluded that joint efforts of neuropathologists, clinical and other neuroscientists will be necessary to overcome the challenges of disease-modifying treatments in the future.

It may be a freak of nature that Biogen Inc. and Eisai, two leading biotechnology companies, announced on September 27, 2022 the results of the randomized placebo-controlled double-blind phase III Clarity AD multicenter trial that lecanemab (10 mg/kg biweekly; development code: BAN2401), an anti-β-amyloid (Aβ) protofibril antibody, exhibited disease-modifying effects in the most prevalent neurodegenerative disorder, that is, in patients suffering from Alzheimer's disease (AD) [3]. In a cohort of 1,795 patients with mild AD or mild cognitive impairment (MCI) and confirmed presence of Alzheimer's pathology in the brain, lecanemab significantly improved the primary endpoint [Clinical Dementia Rating-Sum of Boxes (CDR-SB); a global cognitive and functional scale] and key secondary endpoints with highly statistically significant results. In the intent-to-treat (ITT) analysis, lecanemab reduced clinical decline on the CDR-SB compared with placebo at 18 months by 27% [4]. This improvement is noteworthy. These data have been published on November 29, 2022 in the *New England Journal of Medicine*. The two companies currently discuss this data with regulatory authorities in the U.S., E.U., and Japan with the aim of marketing authorization. Following previous study failures in the Alzheimer's field, which included other immunotherapies, β- and γ-secretase inhibitors, and neuroprotectants, this is the first successful phase III trial showing efficacy of a disease-modifying treatment in neurodegenerative disease. In July 2021, another immunotherapy, aducanumab, which had also been developed by Biogen Inc. and Eisai, had been approved by the U.S. Federal Drug Administration for the treatment of patients with mild AD or MCI [5]. Unlike lecanemab, aducanumab exhibited very modest disease-modifying effects, which had not been detected in predefined endpoints [6], but only in posthoc analyses [7] of two randomized placebo-controlled phase III trials. For this reason, many experts were sceptical about the effects of aducanumab in patients with AD.

What do we learn from the Clarity AD trial? Considering the size of the trial and the apparently potent effects of lecanemab, the Clarity AD trial is a major advancement in the treatment of patients with AD, which represents the most prevalent form of dementia, for which hitherto no causative treatments existed. In view of repeated failures of Aβ targeting treatments including immunotherapies to induce functional improvements in randomized controlled clinical trials, the Aβ concept had been questioned [8], and several researchers claimed that different targets were needed to improve clinical outcomes in this field. Considering the high age and associated vascular risk factors and diseases of Alzheimer's patients, there had been doubts if it would at all become possible to develop efficacious treatments in this patient group. From this perspective, the Clarity AD trial provides the proof-of-concept that it is possible to ameliorate clinical outcomes in age-related diseases using treatment concepts obtained in experimental model systems. Thus, the Clarity AD trial also is an incentive for researchers working in other disease areas, such as stroke or Parkinson's disease, in which no causative treatments exist. The Clarity AD trial also is a motivation for authors of *Exploration of Neuroscience*. We should aim not only at elucidating disease processes but actively strive to influence them. The successful completion of this task requires joint efforts of neuroscientists from different research areas, including molecular neurobiologists, translational neuroscientists, neuropathologists, and clinicians, as correctly pointed out by Professor Jellinger [2]. We will further pursue this path.

Abbreviations

AD: Alzheimer's disease

Aβ: β-amyloid

Declarations

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The author contributed solely to the work.

Conflicts of interest

The author declares that there are no conflicts of interest.

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