With increasing life expectancy, neurodegenerative diseases represent a mounting burden and thus an ever more significant challenge for society, accompanied by increasing costs for health care systems. It is already foreseeable that, due to the genetic and abiotic risk factors, targeted personalized treatment of patients will be necessary. Therefore, it is essential to identify novel pharmaceutical compounds and to unveil the (individual) mechanisms provoking neurodegenerative diseases. A common feature of these diseases is the damage to nerve cells and thus the loss of cognitive, motor, or sensory abilities. Although the underlying mechanisms are yet elusive, accumulating evidence suggests fundamental involvement of oxidative stress (ROS, reactive oxygen species) and inflammation. Thus, anti-inflammatory and anti-oxidant substances could, if used in time, significantly influence the onset or course of the diseases. The FDA approved in June 2021 the first antibody targeting the neurotoxic Aβ peptide (Aduhelm, Aducanumab) for some cases of Alzheimer’s disease under the condition that future studies should prove its beneficial effect. Other monoclonal antibodies such as lecanemab or Donanemab are trailing behind in the pipeline. Even if these therapeutic antibodies would finally demonstrate efficacy in treatment of this type of dementia, they still suffer from side effects (Amyloid Related Imaging Abnormalities, ARIAs) and comparably expensive production methods. Facing the still growing number of patients, this will elicit tremendous demands towards the health systems in economical means: around 55 million people worldwide have dementia and this number is thought to increase to 139 million in 2050 as reported by the WHO. Small molecules would at least come along with low production costs and two avenues for identification of novel drugs are conceivable: drug-repurposing and initial screens from not yet fully developed biological sources. Despite the extensive work that has been conducted in the latter field, only a small proportion of natural existing anti-oxidative and anti-inflammatory compounds has been analyzed in the context of neurodegenerative diseases, yet. The immense reservoir of biological compounds generated in bacteria and fungi seems almost inexhaustible and waits for its exploitation concerning its use in prophylaxis or treatment of neurodegenerative diseases. Since high through put screenings have been developed for cell-line-based assays, we need far more sophisticated readout systems to evaluate the potential of candidates derived from natural sources, their synthetic derivatives or even complex mixtures of these compounds. To exploit this potential completely and to overcome the limitations of investigations based only on cell lines, we need to combine primary neuronal cell culture models with functional approaches, ex-vivo experiments based on brain slices or complex tissues up to simple model organisms such as i.e. C. elegans. At the end, the compounds will have to be investigated concerning their systemic effects in an animal model of the disease itself.

In this issue of Biological Chemistry we highlight different aspects in drug development for neurodegenerative diseases, ranging from novel identified drugs, new molecular targets and patho-mechanisms to different screening methods. Thereby, we hope to encourage other scientists to use new tracks, or to look for unusual sources of potential therapeutics, be it the role of formylpeptidyl receptors, the impact of fungal derivatives or natural anti-inflammatory compounds.

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