Preface

Neurodegenerative disorders represent significant unmet medical needs and major costs to the health care system. In the search for more efficient treatments, immunotherapy targeting abnormal protein aggregates or inflammatory molecules has emerged as one of the most promising therapeutic strategies.

Today immunomodulatory therapies are used to treat multiple sclerosis, and similar concepts are currently being tested for the treatment of Alzheimer's disease. In the latter disorder, pathological forms of the amyloid-β peptide and the tau protein accumulate as plaques and tangles between and inside the brain neurons, respectively. In a pioneering study, immunization against amyloid-β was proven to prevent and reverse pathology in transgenic mice with Alzheimer-like brain pathology. These promising preclinical findings spurred a clinical trial on Alzheimer patients, in which advantageous effects could be observed on both neuropathological and biochemical markers, along with some clinical benefits. Unfortunately, the trial had to be halted due to the development of meningoencephalitis in 6 % of the immunized patients.

In the last decade, there has been a focus on passive immunization with monoclonal antibodies against amyloid-β, which may represent a safer and more reliable approach. Overall, therapeutic antibodies represent one of the fastest growing areas in the pharmaceutical industry for the treatment of cancer, autoimmune disorders, and now also for neurodegenerative disorders. Monoclonal antibodies have appealing drug characteristics such as high target specificity, long half-life, and an ability to reach chemically non-tractable targets.

As for the antibody-based clinical trials for Alzheimer's disease that have been conducted so far, potential treatment effects have been reported in some of the studies whereas other trials have failed to find any obvious beneficial effects. The relative lack of success may be explained by several factors. For example, a certain percentage of the patients included may not have been accurately diagnosed and instead have had a different brain pathology. Moreover, the patients might have been recruited at a too late stage of the disease, when a high degree of brain atrophy and neuronal loss have already been present. Yet another possibility is that the targets have not been optimally chosen. Neither the monomeric, presumably functional, form of the protein nor the ready-formed aggregates seem to possess particularly toxic properties. Instead, the prefibrillar soluble aggregates—oligomers and protofibrils—seem to exert a more toxic effect on cells, and some investigators therefore now regard them as more suitable immunotherapeutic targets.

The successful example of antibody-based treatment for multiple sclerosis and the ongoing efforts to design immunotherapy protocols for Alzheimer's disease are now being followed by a similar development for several other neurodegenerative disorders. Researchers have also begun to explore the possibility of targeting the other pathological proteins that form brain aggregates believed to be central in their respective disease processes. For Parkinson's disease, the α-synuclein protein deposits as intracellular Lewy bodies and Lewy neurites. After administrating vaccine or antibodies against α-synuclein on transgenic Parkinson mouse models, several research groups have shown that the formation of such aggregates and their associated toxicity can be prevented. Such preclinical observations

have also encouraged the development of therapeutics for human use, and the first α-synuclein-based clinical trials are currently underway. Also for Huntington's disease, amyotrophic lateral sclerosis, and prion disorders, such as Creutzfeldt–Jakob disease, initial experiments on cell culture systems and animal models have been successful in reducing the protein pathology that occurs in the respective disorders.

To efficiently battle these diseases, the treatment most likely has to be initiated at an early stage. Thus, along with the development of efficacious drugs, there will be an increasing need for novel ways to diagnose these disorders at a time point when there still has been no or only limited damage to the central nervous system. Thus, there is currently also a focus on designing new diagnostic tests based on more sensitive and specific biomarkers. In general, such biomarkers reflect either the brain deposition of the disease-specific proteins or their presence in cerebrospinal fluid (CSF) and plasma. One example is the ELISA-based assays that can measure decreased levels of amyloid-β 42 along with increased levels of tau and hyperphosphorylated tau in CSF from subjects with Alzheimer's disease. As for imaging, novel magnetic resonance imaging (MRI) and positron emission tomography (PET)-based techniques have emerged that in a better way can visualize the pathological alterations that are known to occur in the degenerating brain. One of the most successful examples is the development of PET ligands that can selectively bind to aggregating amyloid-β and enable imaging of ongoing amyloid deposition in the living brain from an Alzheimer patient. This technique enables not only early diagnosis and a possibility to monitor therapeutic efficacy but also a more accurate recruitment of patients for the clinical trials. In addition, major efforts are underway to design ligands that instead can bind to the other disease-related protein aggregates, such as tau and α-synuclein. Once developed and evaluated, such ligands could enable early detection also of disorders such as frontotemporal dementia and Parkinson's disease.

In this book, we have tried to select a number of topics that will give the reader a thorough understanding of the current status of immunotherapy and diagnostic markers for neurodegenerative disorders. There is an emphasis on the development within the field of Alzheimer's disease, but we also cover a number of other disorders in which most of the activities are still on the preclinical level. In the years to come, we will hopefully witness continued progress in the development of novel immune-based drugs and diagnostic tools for several of these devastating brain diseases.

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