

Advanced diagnostics and therapeutics for Alzheimer's disease

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VALORISATION

Alzheimer's disease (AD) is the leading cause of dementia worldwide. Over 46 million people suffer from dementia, with AD accounting for 60-80% of the cases and this number is expected to double every twenty years [1]. This means that about every 3 seconds, a new case of dementia will be diagnosed worldwide. By 2050, over 130 million people are expected to suffer from dementia, of which around 90 million will have AD.

The societal burden of AD is especially high, since not only the patient who has the dementia is affected, but also family and friends, and society as a whole by providing care and loss of productivity. In general, dementia patients require more intensive care than patients from other diseases, and the costs for dementia are higher than the combined costs for cancer, heart disease and stroke [2]. In addition, cognitive impairment, a symptom of dementia, is the strongest prediction for transition of elderly people to a care home [3].

In terms of economic value, the global cost of dementia exceeds 800 billion US\$, which accounts for over 1% of global gross domestic product (GDP). A minority of these costs (20%) is attributable to direct medical care costs, possible because very few treatment options are available [1]. Direct social care (home, nursing) and informal care costs each attribute 40% to the costs. Informal care costs are costs made by unpaid informal care givers (such as relatives) who are for example unable to work during this time.

Despite the fact that the societal cost of AD is substantial higher than those of stroke, heart disease and cancer, research funding into AD is less than in these disease [4]. It is therefore imperative that both fundamental and applied research funding is increased to prevent an economical disaster in the coming decades. The problem is further aggravated by the fact that there is no cure for the disease available. In addition, the exact disease process remains vague and also diagnosis of AD is not straightforward [5].

The thesis contains both a therapeutic and a diagnostic component that offers direct possibilities for valorization. First we will discuss possible valorization options from a therapeutic point of view, while subsequently we will discuss diagnostic options suggested in this thesis.

7.1. THERAPEUTIC OPPORTUNITIES

At the moment, 5 different drugs are approved for AD. Every year, about 1 billion dollars are spent on these drugs in the USA alone [6]. While these drugs provide some symptomatic relief for patients, they do not tackle the underlying cause of AD, and as such, they lose their effectiveness over time.

In this thesis, immunotherapy against amyloid was investigated as a possible treatment option. Anti-A β treatment has been tested in over 25 000 patients in various clinical trials (Chapter 2). Although cost estimates are not available, these trials are likely to represent a huge investment on the part of pharmaceutical companies. Furthermore, there is a large societal costs and effort required both on the patient and caregiver side. Knowledge obtained in this thesis helps to improve future immunotherapy trials and possible increase the success rate of anti-A β strategies, if these strategies are further pursued in the future.

Despite the fact that immunotherapy trials have failed so far, we show that preventive treatment might be a viable option for the treatment of AD. One key question remains

of course whether it will be possible to identify patients early enough. A big problem is that amyloid pathology starts about 15-20 years before the onset of cognitive problems [7]. It remains thus to be seen how it would be possible to select patients for possible treatment, or if treatment starting in the state of Mild Cognitive Impairment (MCI) is sufficient to obtain a disease modifying effect.

Our results show that there might be valorization opportunities in custom antibody formats and effector mechanisms. In this thesis, an antibody with full effector mechanisms (Fc γ -receptor binding and complement activation) was compared with an antibody with no effector mechanisms. A possible valorization opportunity would be to investigate antibodies with partial effector mechanisms (eg. only complement activation or only Fc γ -receptor binding) and see which mechanisms is the most important for an efficient and safe therapy. This specific modification could then be patented. Additionally, it might also be worthwhile to investigate different, more exotic antibody formats, such as bispecific antibodies to increase brain penetration and increase the effective dose in the brain.

7.2. DIAGNOSTIC OPPORTUNITIES

While AD can only be diagnosed with certainty post-mortem, a number of options are currently available for early diagnosis of the disease. As discussed in Chapter 1 of these thesis, diagnostic tools currently in common use are cognitive tests and CSF measurements. A β and tau measurements in CSF are now routinely being used as part of the neurological examination in patients with cognitive impairments. However, besides these measures, also imaging biomarkers are being routinely used. One advantage over imaging techniques is that they also provide additional spatial information as to where pathology is spreading and about the severity of the pathology. While structural Magnetic Resonance Imaging (MRI) is routinely used for diagnosis, the use of Positron Emission Tomography (PET) to image amyloid is now finding routine use.

One of the disadvantages of current amyloid PET tracers is that they are only able to image fibrillar A β deposits (plaques). However, recent experimental data suggests that it is actually the oligomeric A β species which are more toxic. It would therefore be of great diagnostic and scientific value if different A β species could be imaged. This thesis proves in pre-clinical studies that this might be feasible.

The use of monoclonal antibodies radiolabeled with ^{89}Zr is routinely applied in the clinic for imaging of tumors [8]. Despite the fact that radiation dose is always a concern with PET imaging, the technology has proven safe in humans. We, and very recently also others, have shown that antibodies can be used for imaging amyloid in the brain *in vivo* [9, 10]. This opens opportunities to try this technology in humans. Since both the use of ^{89}Zr and some of the antibodies we tested have already passed clinical trials, and proven safe, amyloid immuno-PET could be tried very fast in humans. This could provide valuable new insights in amyloid pathology in patients. *In vivo* imaging using this technique in mice suffers from several drawbacks, such as the high bone uptake of ^{89}Zr [11]. In humans, this problem would not occur, and the technique would therefore benefit from a higher signal-to-noise ratio.

Besides applications for diagnosis and fundamental science, immuno-PET also offers the possibility to use monoclonal antibodies as a theranostic tool. Since several

antibodies are still in clinical trial, this would provide a valuable addition to current clinical trials. A theranostic is a drug that is a diagnostic tool and a therapeutic drug at the same time. By using the same antibody that is used for therapy for imaging pathology, target engagement can be shown on an individual patient basis. This will allow to screen patients before inclusion in clinical trials, possibly increasing success of the trial and preventing people with non-AD dementia from being included in the trial. Furthermore, therapy effects could be monitored over time.

Finally, the fact that immuno-PET can be used for $A\beta$ imaging, as we show in this thesis, might also mean that immuno-PET can be used to target other proteins in the CNS. Applications for immuno-PET might therefore include also other proteinopathies such as Parkinson's disease, for which no tracers are available for the moment. Monoclonal antibodies against α -synuclein could be radiolabeled and used to confirm Parkinson's disease. Other possible disease could be for instance Prion disease, but also in AD there are still possible targets left. Besides $A\beta$, also tau might prove a valuable target to image with immuno-PET, and currently there are only few tau tracers available, and these are still in early development. A possible caveat is that tau is intracellular, and it remains an open question whether antibodies will be able to bind then. However, results from a study using tau antibodies for *in vivo* imaging system (IVIS) imaging, shows that this might not be such a big issue [12].

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