Mechanistic early phase clinical pharmacology studies with disease-modifying drugs for neurodegenerative disorders

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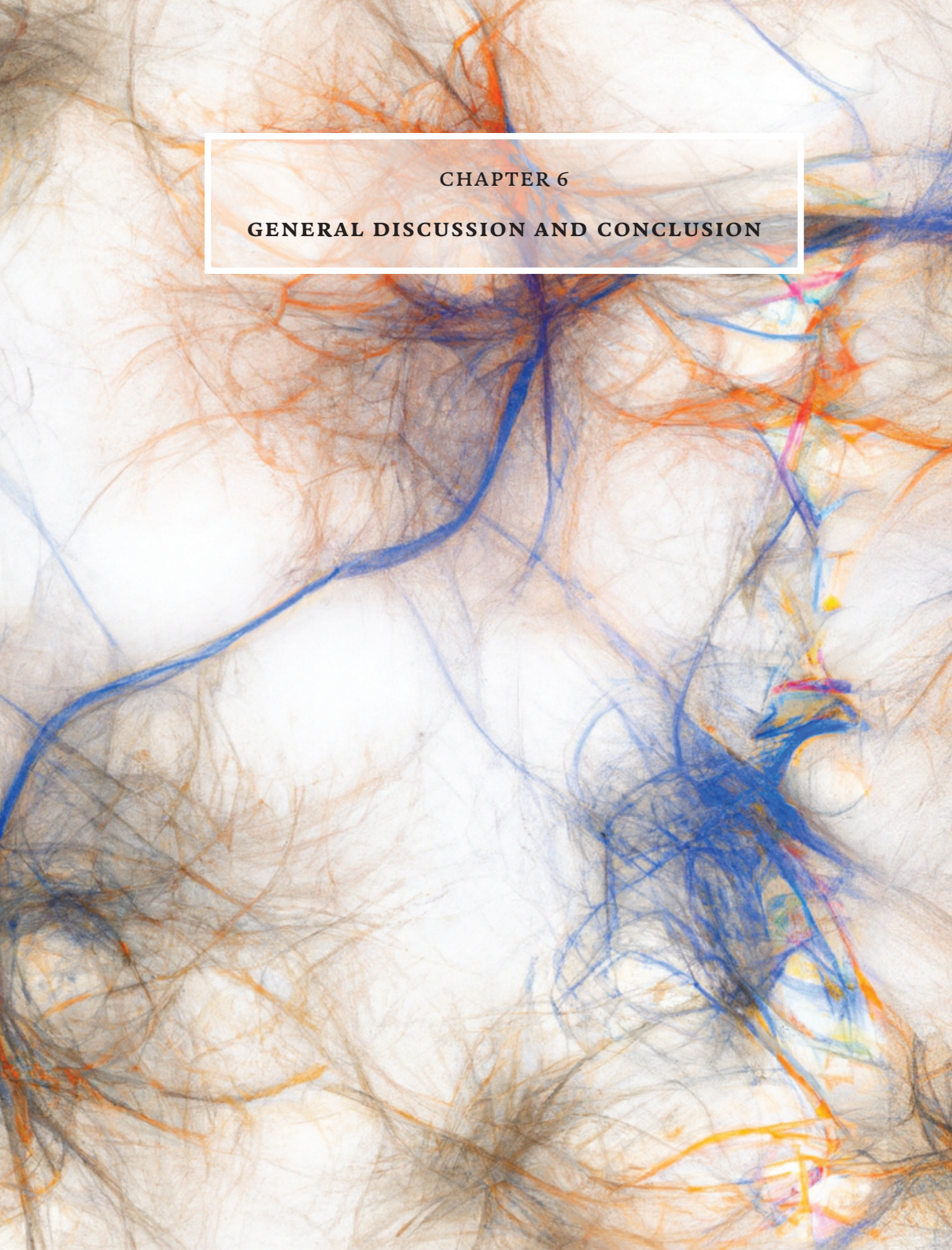

CHAPTER 6

GENERAL DISCUSSION AND CONCLUSION

We are now at the forefront of a paradigm shift in the treatment of neurodegenerative disorders, driven by advances in our understanding of neurodegenerative disease mechanisms, identification of specific mutations and novel drug targets, and advances in drug development techniques over the past decades. In some ways, the advances we may expect to see in the field of neurodegeneration over the next decades could very well mimic the revolution in understanding and treatment of cancer that we have witnessed over the last four decades. The oncology revolution began with the discovery of tumor specific oncogenes and blood serum biomarkers that could be used as surrogate endpoints in clinical trials in the 1980's,[1–3] and rapidly triggered an exponential increase in identification of oncogenes that in turn led to the development of an expanding arsenal of increasingly specific targeted therapies with monoclonal antibodies, check-point inhibitors, and recently patient-personalized chimeric antigen receptor (CAR) T-CELL therapies, greatly enhancing oncology patient's chances of survival.

Since 2010, the number of identified associated genetic mutations linked to Alzheimer's disease, Parkinson's disease, and ALS has expanded from less than 10 for each indication to over 75 for AD, over 200 for PD, and over 30 for ALS today.[4–6] This has undoubtedly contributed to a rapid expanse of the pipeline of potential disease-modifying treatments for these indications, which currently holds 119 compounds for AD, 52 compounds for PD, and over 100 compounds for ALS.[7–9] The extent of this pipeline is hopeful to patients and those that carry genetic risk-factors for developing these disorders. But at the same time, this broad pipeline also offers a challenge for drug-developers and clinical trial investigators. For example, in 2022 there were over 7,900 participant slots to be filled in active phase 2 and phase 3 ALS trials alone,[9] which is higher than the total number of people being diagnosed with ALS in the United States each year (~6,000). This highlights that careful consideration is needed for how to strategically use limited resources – including funds, clinical research capacity, and participants – to focus late-stage clinical investigation towards those compounds that present the highest chance of maximum clinical benefit and overall drug-development success.

This thesis discusses one way to support such strategic drug development decisions in the field of neurodegenerative diseases, by using (pharmacodynamic) biomarkers to demonstrate proof-of-mechanism in early phase clinical pharmacology studies (*Chapter 2*). When utilized in early clinical development, these biomarkers can help select the best drug candidates, their anticipated effective dose levels, optimize trial designs, guide decisions to move forward into late-stage development, and/or terminate unsuccessful compounds early to facilitate optimal use of scarce resources. Moreover, there is a strong ethical argument to be made; to only initiate trials with compounds that have a demonstrated reasonable chance of efficacy in patients suffering from these debilitating and progressive diseases.

In addition, many of the potential disease-modifying treatments in development for neurodegenerative disorders target completely new pharmacologic targets (first-in-class). This makes these compounds and their clinical development different, with larger uncertainty (as reflected in a high development-failure rate), compared to non-first-in-class compounds for relatively well-understood therapeutic areas. The use of pharmacological biomarkers in early-stage clinical development therefore also helps link the dose-response curve in humans to the pre-clinical data, which is essential to uncover the relationship between the minimally pharmacologically active dose and a safe therapeutic dose in humans.

The importance of uncovering this relation between the pharmacologically active dose and a safe therapeutic dose is highlighted in *Chapter 3*, that describes the early clinical development trajectory of the RIPK1 inhibitor SAR443060 (DNL747). Although the exact level of RIPK1-inhibition that would be required for potential clinical efficacy in human AD and ALS is still under investigation, recent reports suggest that inhibition levels of >95% may be required.[10] That level of inhibition is significantly higher than the median 66% to 82% of RIPK1-inhibition that was achieved with 50 mg BID SAR443060 at trough concentrations in PBMCs of ALS and AD patients, respectively. Higher dose levels of SAR443060 (up to 400 mg BID) did lead to median RIPK1-inhibition of >95% in PBMCs in healthy subjects, but these higher dose levels were not deemed safe for chronic dosing in patients due to serious thrombocytopenia and anemia findings in long-term toxicity studies in monkeys at these higher dose levels. Consequently, SAR443060 development was discontinued. However, as other (non-CNS-penetrant) RIPK1-inhibitors have achieved higher levels of RIPK1-inhibition with dosing periods of up to 84 days,[11] the dose limiting toxicities observed are most likely compound specific and not common to RIPK1-pathway inhibition. This led to the decision to further pursue RIPK1-inhibition with SAR443820 (DNL788), a CNS-penetrant back-up compound for SAR443060, as a potential disease-modifying treatment strategy for ALS in the HIMALAYA study that is currently enrolling.[12] These insights and the subsequent strategic drug-development decisions would not have been possible without the use of phosphorylation of RIPK1 in PBMCs as a target engagement biomarker in SAR443060's early clinical development program. Or worse, without these target engagement insights, late-stage RIPK1-inhibi-

tion trials could have been initiated with inadequate SAR443060 dose-levels, potentially eventually leading to a discontinuation of the pursuit of RIPK1-inhibition as a potential treatment strategy for AD and ALS for a lack of clinically efficacy of potentially inadequate dose levels.

One important challenge, however, that remains for the further development of CNS-penetrant RIPK1-inhibitors for neurodegenerative diseases is that direct measurement of RIPK1-inhibition levels in CNS-tissue (the actual target site) is not possible as of today. While preclinical data suggests that peripheral RIPK1-inhibiton demonstrates similarities with brain RIPK1-inhibition,[13] and SAR443060 unbound-plasma and CSF drug concentrations were similar, these are still only surrogate markers for the pharmacologic situation in the target astrocytes and microglia in the CNS. Moreover, it has been demonstrated that lumbar CSF drug concentration may not always be an accurate surrogate of brain extracellular fluid drug concentrations, particularly in CNS diseases, and that systems approaches accounting for multiple levels of CNS complexity may be needed to better predict brain pharmacokinetics.[14]

Chapters 4 and *5* demonstrate the benefits of expanding an early-phase biomarker strategy beyond target-engagement biomarkers alone. For the development of LRRK2-inhibitor BIIB122 (DNL151) as potential targeted disease-modifying treatment for Parkinson's disease patients with a LRRK2 mutation, besides peripheral and central target engagement biomarkers (whole blood pS935 and CSF tLRRK2), also down-stream kinase substrate (PBMC pRAB10) and lysosomal functioning (urine BMP) were used to explore the compound dose-response curve. This combination of biomarkers offers an even stronger pharmacologic proof-of-mechanism, as it not only demonstrates that the compound affects its direct target, but it also helps explore the dose response curve of downstream pathway effects that do not necessarily correlate linearly with the level of target engagement (as demonstrated by the differences in dose-response curves for the biomarkers in *Figure 3* and *4* in *Chapter 5*). These additional biomarker insights helped to define the anticipated optimal therapeutic dose level of BIIB122 (225 mg oral tablets QD) for further clinical evaluation in the recently initiated phase 3 LIGHTHOUSE study in PD patients carrying a LRRK2 mutation.[15]

This study will need to tell us if LRRK2-inhibition ultimately provides clinical benefit in the form of slowing Parkinson's disease progression. Because, despite the promising LRRK2 pathway biomarker readouts for BIIB122, that piece of the puzzle still remains to be confirmed in humans. However, if LRRK2-inhition can provide therapeutic benefit, then based on the data-rich early-stage clinical development program, BIIB122 is optimally positioned to be successful.

Another benefit of the biomarker-intense development program for BIIB122 is that it provided confirmation that LRRK2 kinase activity also appears to be elevated in PD patients without a LRRK2 mutation, tough to a lesser extent than in those carrying a LRRK2-mutation (*Chapter 4*). This provides a strong rationale for the recent initiation of the phase 2B LUMA study investigating the clinical effects of LRRK2 inhibitor BIIB122 in PD patients *without* a LRRK2 mutation.

What these pharmacological biomarkers can't tell us, however, is the optimal timing for initiating disease-modifying treatment. The LUMA study will be enrolling early-stage (H&Y stages 1 and 2) PD patients, but it could still turn out that we may need to treat even earlier (e.g. already prior to symptom onset) to achieve meaningful long-term disease-modification. This ultimately would require identification and validation of prognostic biomarkers and screening programs for those at risk (which, from an ethical perspective, should only be initiated if an effective treatment is available).

The biomarker strategy for the early-stage development of LRRK2 inhibitor BIIB122 proved to be very valuable in the clinical development of this compound. However, it may not always be possible to use such extensive biomarker characterization for every novel compound, simply because of technical (assay) limitations, incomplete understanding of newly unraveled disease pathways, high within-subject variability in candidate biomarkers hindering reliable interpretation of results, and/or time and money constraints. Nonetheless, the RIPK1 and LRRK2 examples provided in this thesis do suggest that we should always strive to include a pharmacodynamic biomarker in early-stage development of potentially disease-modifying compounds for neurodegenerative disorders.

What challenges still lie ahead

Although there has been great progress in linking subpopulations with neurodegenerative disorders to specific genetic mutations, in many other cases molecular defects underlying the disease have not yet been identified. Without a better understanding of these disease processes and the underlying key molecular defects, it remains difficult to develop effective targeted therapies aimed at disease-modification. And based on the high clinical development failure rate we have seen to date for compounds targeting general pathological processes, such as amyloid-β in AD or α-synuclein in PD, targeted therapies may eventually be our best shot at significantly slowing down disease-progression. Which brings us back to the comparison to the field of oncology, where the discovery of very specific molecular defects in different types of cancer has led to highly effective drugs specifically targeting these

defects. And a similar trend is now visible in the neurodegenerative space, with distinct targeted treatments being developed for e.g. PD patients with a LRRK2 versus a GBA mutation, or ALS patients with a SOD1 versus C9ORF72 mutation.

Another remaining challenge in drug development for neurodegenerative disorders lies in the translational animal models, that are not as advanced, or predictive of human clinical efficacy, as in other therapeutic areas. This is not surprising, since these models are human-engineered to reproduce the initial proteinopathy and/or make use of specific genetic mutations, and therefore may not be able to fully mimic entire sequence of pathophysiologic events that occur in human disease as long as our molecular understanding of these diseases remains incomplete.[16] Some limitations of animal models may not be easily overcome, such as the short life-span of rodents that may lead to incomplete development of pathological hallmarks and/or neurodegeneration. On the other hand, advances in genome editing and our expanding understanding of neurodegenerative disease mechanisms will undoubtedly help improve and validate new preclinical models. This increased disease-understanding will also help better understand the utility and limitations of various animal models, so that the best-fitting and most-predictive models (and treatment-timing) can be selected for the preclinical development of each specific compound for each specific disease subtype.[16]

Finally, the uncertainty around the timing of the molecular onset of the disease and best time for intervention, the large heterogeneity in disease-progression between patients, and the lack of validated biomarkers for the rate of disease-progression all make it difficult to precisely evaluate clinically relevant responses to novel compounds without the use of very large and lengthy trials. To overcome this challenge the neurodegenerative disorders research community is exploring innovative clinical trial design approaches, including platform and adaptive designs to maximize the statistical power of trials and minimize the duration and overall number of patients required for these trials.[17,18]

Additionally, efforts are being undertaken in developing risk-based inclusion criteria for trials to reduce participant-exclusion rates and improve generalizability of trial results.[19]

Future outlook

With an increasing understanding of disease mechanisms and a drug development pipeline fuller than ever, it is an exciting time for the neurodegenerative field. This is perhaps best illustrated by the recent readouts of the phase 3 lecanemab (a soluble amyloid-β protofibrils antibody) study in early AD, that demonstrated a reduction of markers of amyloid in early Alzheimer's disease and resulted in moderately slower decline on measures of cognition and function than placebo at 18 months.[20]

The consistency of all endpoints in this trial being in the same direction suggests that the amyloid hypothesis may hold true after all, and that anti-amyloid-β therapies could slow down progression of AD.

On the other hand, lecanemab was only able to slow the rate of cognitive decline by 27% at 18 months. This could suggest that the administered lecanemab dose may have been too low (only 0.1-0.3% of the administered IV dose of lecanemab is recovered in CSF[21]), or that intervening at the stage of early AD is already too late. However, it could also indicate that targeting amyloid-β alone may not be enough to achieve meaningful disease-modification. In fact, given that there are more people at risk of developing neurodegenerative disorders, e.g. due to the presence of disease-related genetic mutations, than there are people that actually develop disease symptoms, it is not unlikely that development of these conditions may require simultaneous activation of more than one pathogenic pathway, and that certain cellular defense mechanisms fail concomitantly.[22]

This could imply that to achieve clinically meaningful disease-modification it may eventually require a combination of drugs targeting multiple affected disease pathways in parallel. And, similar to the field of oncology, we may eventually need a combination of genetic screening and prognostic biomarkers to be able to define the optimal combination of disease-modifying drugs for each individual patient.

In the end disease-modifying treatments are only expected to be able to slow down disease progression and not to lead to reversal of disease. In this aspect the neurodegenerative field is very different from oncology. Where in oncology the goal is to eliminate tumor cells, in neurodegeneration the goal is to protect from neuronal cell death. This fight has proven to be even more challenging so far, especially given the fact that neurons have very limited capacity to regenerate and disease symptoms only present when a majority of neurons has already been lost. At this moment it is too early to tell if we will ever be able to cure neurodegenerative disorders. However, based on neuron's limited capacity to regenerate, a cure may eventually only be possible via prophylactic gene therapy for people at risk and/or via neuro-regenerative cell therapies.

While such a potential cure may sound like a faraway future, the preparations for its development are actually already happening today with new disease mechanisms being unraveled, new genetic mutations being identified and dozens of potential disease-modifying therapies entering early clinical development. Each of these discoveries will expand our understanding and bring us one step closer to a cure for these debilitating diseases. In fact, the pace at which these developments are evolving is an indication that we are heading into a phase of exponential growth. Disease-modifying treatments sounded like a faraway future not too long ago, but today we are testing them in the clinic. In data-rich mechanistic early-phase studies these disease-modifying treatments help us further understand and validate disease mechanism and potential treatment options. And as we have seen in other areas of research, when knowledge starts to expand exponentially, this will attract more resources and innovation starts taking place at an unprecedented speed. And soon a paradigm can shift.

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