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Genetic and clinical pharmacology studies in GBA1-associated Parkinson's disease

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CHAPTER 9

Discussion

This thesis describes a series of studies related to GBA-PD and development of a novel pharmacotherapeutic intervention. As one of the most common neurodegenerative diseases worldwide, Parkinson's disease is vigorously being researched, to better understand and consequently better treat this debilitating progressive affliction. Despite the fact that this disease was first described already more than 200 years ago by James Parkinson, no disease-modifying treatment is yet available. This also explains why all new clues regarding the pathogenesis will be turned upside down and inside out, to explore any possibility to design a disease-modifying treatment targeting this factor of the pathogenesis. One such example is the *GBA1* gene, which is considered one of the most promising targets currently known for a new disease modifying therapy for PD. The chapters in this thesis describe studies that have contributed to exploration of this therapeutic target and will hopefully support future research to be more effective.

Apart from the novel results yielded by the various studies, described in the respective chapters, there are several overarching lessons that need to be taken into account in future studies. These include methodological and physiological challenges, which one needs to be aware of, because these can be relevant for the design, execution, and interpretation of a drug trial involving GCase as the target. Methodological challenges were present in most papers of this thesis.

A serendipitous methodological finding hugely impacted the results of the *GBA1* screening (**Chapter 3**). The *GBA1* gene is susceptible to an imbalanced amplification of alleles, which initially resulted in a large number of false-negative results which was corrected by changing the type of polymerase used. Sequencing of the *GBA1* gene was already known for its risk of false-positive results due to the nearby pseudogene, but we have shown that false-negative results should be considered as well. This could also explain conflicting results in existing literature. Additionally, it is another confirmation that sequencing of the *GBA1* gene can only reliably be performed using dedicated conditions, and not with coarser techniques like GWAS and imputation without validating this first.

In accordance with this first lesson, care was taken in selecting international cohorts that allow a valid comparison of our *GBA1* screening results (**Chapter 2**). Many papers only screened for 'the most common' variants in

the *GBA1* gene which is primarily based on studies performed in the Ashkenazi Jewish population who have a remarkably high incidence of certain *GBA1* mutations. Several papers, including our own, have shown the existence of population-specific variants, underscoring the relevance of performing full-gene screenings in populations of sufficient size. Preferably, costs for full-gene sequencing are reduced so this can be standard practice in the future.

Because *GBA1* variants behave as risk-factors with limited penetration, they require a less straight-forward type of counseling than in case of an autosomal dominant or recessive disorder. Since *GBA1* variants lack therapeutic consequences, there is little experience in informing patients on the potential relevance of *GBA1* variants. Our large-scale *GBA1* screening therefore underscored the need to develop documentation to guide clinicians in this process (**Chapter 4**).

Implementation of novel biomarkers is challenging since there is no reference to guide expectations. The LTI-291 trials were the first to determine various glycosphingolipids in plasma, PBMCs and CSF (**Chapter 7 and 8**). The findings of these trials yielded an unexpected increase in GluCer levels, requiring an adaptation of the hypothesis of how these biomarkers should be interpreted. We hypothesize that lowering of the intralysosomal sources may have led to an increase in total intracellular (including extralysosomal) presence of GCase substrates. Alternatively, the findings may reflect a chance finding.

Lastly, another serendipitous finding was the significant impact of cell types for certain biomarkers related to GCase activity (**Chapter 6**). Peripheral blood mononuclear cells (PBMCs) consist of monocytes and lymphocytes and are a valuable and easily accessible source to determine biomarkers in a cell-based environment. Inherent to the isolation methodology, there will be a varying amount of granulocyte contamination, rendering PBMC isolation susceptible to collecting at least three different cell types. This issue may be solved by more costly procedures that subtype PBMCs. Knowledge of the relevance of these different cell types for a biomarker determination is therefore essential to adequately interpret PBMC based data.

Several reasons underlie the challenge in proving efficacy of a novel disease-modifying treatment for neurodegenerative diseases like Parkinson's disease. First, the inherent typically slow progression of neurodegenerative

diseases, and the relatively large day-to-day variability of measurements assessing disease progression (like the MDS-UPDRS in PD). Both issues hamper the detection of a disease modifying effect and require adequate powering of studies and a long follow-up. Development and use of biomarkers in early stages of drug development may contribute to the decision-making on whether to proceed with such large trials. Use of wearables or measurements at home (either using video, or tasks on computers or tablets etc.) will hopefully reduce variability associated with snapshot measurements of less frequent in-hospital clinical assessments. Efforts to allow a more reliable estimate of the progression rate should be pursued but are complicated given the non-linear progression of PD. Additionally, only using fixed baseline characteristics (like a gene variant) may introduce noise if dynamic characteristics (like age and duration of disease) are not considered.

The development of a successful trial requires an effective recruitment strategy highlighting the need of adequate communication and collaboration. An excellent example is the *GBA1* screening (**Chapter 2**), which was a collaborative effort of ten medical centres, local patient groups and the national patient association, which was essential for successfully finding 40 GBA-PD patients for the first-in-patient trial of LTI-291 (**Chapter 8**). In just three months, the genetic screening evolved from a first idea into a fully approved protocol with a first reach-out to patients. In the course of months, ten movement disorders neurologists sent letters to the PD patients from their center, informing them about the study. Every patient that applied, received an information letter. Every patient that signed, received a saliva tube. All in all, tens of thousands of letters were sent (our corporate outgoing mail had to be upgraded...) to achieve a successful screening of the *GBA1* gene in 3402 patients over a period of less than one year - a large operation associated with a relatively minor effort for collaborators and patients. Unanticipated, this project gave rise to the earlier discussed serendipitous finding (**Chapter 3**), but also to new international collaborations, both published (**Chapter 5**, New Zealand/Australia) and still unpublished (*GBA1* and *LRP10* interaction, Italy; *GBA1* intron variant, United Kingdom).

In the future, treatment of Parkinson's disease may be based on a profile of genetic and/or biological markers that guide the development of a

personalized approach. Certain glycosphingolipid levels and GCase activity may contribute to such a profile which may also include other potential drug targets, involving endosomal, mitochondrial and cellular trafficking functioning, inflammation or alpha-synuclein subtypes. Involvement of different biological pathways may vary between patients and therefore determine the personalized content of a cocktail of drugs targeting different pathways. This may lead to new dilemmas, e.g. biological profiles frequently do not provide a clear (black and white) cut-off as to when to treat or not. Considering the unmet need of a disease-modifying treatment in PD, every patient would likely want to try all of these drugs, however small the benefit might be, assuming it has a favorable safety profile. Which will make it a matter of costs.

This highlights another topic of public debate, which is drug development in general, its costs, pricing of new drugs and maximizing profit (e.g. by making creative use of patents). It is justified to make profit for drug discovery and development. But it is difficult to determine what is reasonable and what is excessive. Because it pertains to medical needs of humans, there is an additional moral pressure. Most people engage in research because they are interested in the science and want to help others, but unfortunately there are also examples of abuse of this medical need for (excessive) profits. Increasing transparency of the full drug development process, and reducing defensive bureaucratic obligations, could stimulate a fair healthcare and reimbursement process. Additionally, drug studies should be performed by transparent and professional organizations, where employees receive a reasonable wage, with a clearly defined maximum, for like a medical specialty, running clinical trials is a specialization on its own. Only by such in-depth knowledge of the drug development process, can e.g. trial design pitfalls be prevented and can redundant bureaucratic requests be identified and omitted.

In conclusion, this thesis is a collection of studies that together form another tiny, yet necessary, step toward a better care for a growing patient population. This goal can only be achieved through the continuous dedicated efforts of researchers, patients and other caregivers.