

EDITORIAL

Clin. Invest. (2013) 3(1), 1–4

Parkinson's disease vaccine: clinical trial challenges when striving for disease modification

Achim Schneeberger^{*1}, Alexandra Kutzelnigg² & Markus Mandler¹



“...efforts are needed to create a clinical (study) environment allowing for rational and effective clinical evaluation of these new drug candidates.”

Progress in understanding the role of alpha-synuclein (aSyn) as a driver of synucleopathies such as Parkinson's disease (PD) led to the development of a novel class of drug candidates characterized by the potential for disease modification. The first member of this new class, the AFFITOPE® Parkinson vaccine candidate PD01A [1] – developed by the Austrian biotechnology company AFFiRiS – has now entered the phase of clinical development (NCT01568099). PD01A is a peptide-carrier conjugate vaccine. Antibodies elicited by PD01A react with aSyn and spare beta-synuclein, a family member not involved in pathology but able to compensate physiological aSyn functions. PD01A demonstrated proof-of-concept in a series of transgenic synucleopathy models. These data, along with favorable preclinical toxicity studies, led AFFiRiS to initiate a Phase I study in early PD patients. The AFFiRiS program is the first ever to treat PD patients with an aSyn-lowering vaccine. Further aSyn-addressing candidates, including monoclonal antibodies and small molecules inhibiting aSyn aggregation, are being developed by other companies; some of them are expected to join PD01A soon in the clinical arena. The challenges that this new drug class faces fundamentally differ from those the currently approved symptomatic drugs had to master. Demonstration of a disease-modifying activity will presumably require identification of patients in early stages of their disease with a high specificity, as well as the availability of biomarkers and clinical end points informing on a change, such as slowing/halting, of the disease process.

Parkinson's disease

PD is the second most common neurodegenerative disorder of the elderly (behind Alzheimer's disease [AD]; currently amounting to approximately 1.2 Mio European, 1.5 Mio US and 2.0 Mio Chinese patients). Until recently, PD was considered a motor disease characterized by akinesia/bradykinesia, rigidity and rest tremor, its non-motor symptoms (neuropsychiatric, gastrointestinal and autonomous symptoms) are now well established [2]. Currently available PD treatments primarily address the disease's motor component. As they deliver symptomatic benefit only, they ultimately lose their activity and fail [3]. Moreover, long-term use is associated with side effects and complications. There are several areas of medical need. First, we lack a disease-modifying agent. Second, measures to combat treatment-induced dyskinesia are limited. Third, there are only a few therapeutic options for non-motor symptoms.

Keywords: disease modification • immunotherapy • Parkinson's disease
• Parkinson's vaccine

¹AFFiRiS AG, Karl-Farkas Gasse 22, A-1030 Vienna, Austria

²Department of Psychiatry & Psychotherapy, Medical University of Vienna, Vienna, Austria

*Author for correspondence:

E-mail: achim.schneeberger@affiris.com

Disease-modification: general remarks & terminology

The term ‘disease-modification’ denotes an intervention that brings about a change in the pathology underlying a given disease. While this could be a disease-aggravating effect, generally the term is meant to characterize a beneficial change, specifically, slowing or even halting the disease process. As a result, the clinical symptoms are expected to stop worsening, improve or disappear. An example would be the treatment of HIV, where highly active antiretroviral therapy (a combination of various antiretroviral drugs) turns down HIV replication, which ultimately leads to restoration of the pool of CD4⁺ T lymphocytes and, thus, amelioration of the acquired immunodeficiency and its consequences (opportunistic infections and certain tumors).

Understanding disease pathology is key

Obviously, rational development of a disease-modifying therapeutic approach primarily requires understanding of the underlying pathology. In the case of PD, there is mounting evidence for a causal and essential pathophysiological role of aSyn. Examples include the demonstration that certain dominantly inherited PD forms are caused by mutations in/duplications of the aSyn gene [4,5]; the observation that aSyn represents the major component of the neuropathological signature lesions in patients (Lewy bodies and Lewy neuritis [6,7]); the genome-wide association study finding that certain aSyn gene variants contain the highest risk for sporadic PD [8]; the demonstration that overexpression of human aSyn recapitulates certain features of the disease in experimental animals [9,10]; and, finally, the fact that clinical symptoms and their progression correlate with the localization and development of aSyn pathology [7].

“The challenges that this new drug class faces fundamentally differ from those the currently approved symptomatic drugs had to master.”

While aSyn appears to be the toxic culprit, downstream events such as mitochondrial dysfunction and oxidative stress are likely to mediate and even modulate its toxicity. Thus, conceptually, two interventional levels may exist: lowering of aSyn levels and blocking the pathological cascade at downstream checkpoints. Theoretically, the former is more appealing as it intervenes before pathology diverges into various toxicity-mediating trajectories.

Intervening early in the disease process

Common sense would predict that the effort of disease modification is most promising, if not solely possible, if one intervenes early, that is, before the occurrence of

‘too extensive’, and thus irreversible, neurodegeneration. This notion is supported by experience gained in the development of disease-modifying drugs for AD. While numerous programs addressing mild-to-moderate patient cohorts failed, there is now first evidence that an immunotherapeutic agent is of clinical benefit in mild as opposed to moderate disease. There is another lesson to be learned from the AD field. This is the need for a high diagnostic specificity – generally, this is more demanding the earlier a diagnosis needs to be established. However, it is a prerequisite for success, as a specific drug can only demonstrate its activity if the study participant to whom it is administered during clinical development does indeed exhibit the pathology in question. AD offers a solution to this as well. Rather than diagnosing AD by exclusion at a stage when the deficit excels a certain threshold, namely that of normal daily functioning, there is a paradigm shift initiated and ongoing. The new diagnostic concept does not refer to severity but, instead, combines disease-specific symptoms with biological markers of the disease [11]. Data gathered by various groups support its validity. They demonstrate that by combining a measure of the episodic memory as a specific symptom with biological disease parameters such as CSF levels of A β and Tau/phospho-Tau or hippocampal atrophy, a diagnosis can be made with high specificity well before the patient reaches the dementia threshold. This led several sponsors to use this type of diagnostic criteria for their clinical studies (e.g., AFFiRiS, Roche, Nutricia) even though full validation has yet to be achieved.

Knowledge of the natural disease course defines trial design & end points

The third premise in the endeavor of developing a disease-modifying vaccine is the knowledge of the natural course of the disease. This relates to changes in both clinical and biological features of the disease. Obviously, the natural course of the disease determines various features of the respective studies such as their duration, design and the end points to be used, as well as statistical methods to be applied. With regard to clinical PD manifestations, there are well-established scales allowing appropriate evaluation and follow-up of motor symptoms. Assessment of non-motor symptoms, for example cognitive constraint, is much less defined. Clinical heterogeneity further complicates matters. A relative lack of information exists at the level of PD biomarkers. Candidates include CSF levels of monomeric and oligomeric aSyn, as well as advanced MRI techniques (e.g., diffusion-weighted imaging). Concerning all of the above aspects, much is still to be defined and learned in PD. To this end, the Michael J Fox Foundation initiated the so-called Parkinson’s

Disease Progression Marker Initiative, the first large research program devoted to unraveling the clinical course of sporadic PD and relating it to measurable biomarkers. Parkinson's Progression Markers Initiative follows the Alzheimer's Disease Neuroimaging Initiative example, which aims at defining the natural course of AD.

The principle evaluation strategy of therapeutic aSyn targeting vaccines

A couple of principles apply to testing of aSyn-lowering agents with regard to their disease-modifying activity. First and foremost, safety needs to be considered. Targeting a self-protein by immunological means bears two principal risks, namely interference with physiological function and autoimmunity [12]. Both are first to be addressed at the level of vaccine design. Tackling pathological forms and aggregations states of the targeted molecule and sparing of precursors/family members with redundant functions are key to the former. A specific issue in PD would be the chaperone function of aSyn within the dopamine-release and -recycling system and the consequences for synaptic integrity. With regard to autoimmunity, vaccines need to avoid both cellular (e.g., activation of target-specific T cells is prevented by short antigenic stretches <8 amino acids) and humoral (crossreactivity of antibodies induced with other human proteins) mechanisms [12]. These safety aspects need to be covered by informed consent and by appropriate safety measures (e.g., evaluation of relevant parameters and/or installation of an independent data safety monitoring board) during and after the study.

Assessing the disease-modifying activity has to demonstrate that the intervention is changing the course of the disease by interfering with its pathology. Theoretically, this could be achieved by evaluation of a single parameter. As such, a parameter does not (yet) exist in PD, the strategy has to be based on assumptions deduced from a disease-modifying effect: it would change the underlying biological process, it would extend to all disease-affected domains, biological and clinical changes would occur in parallel and, finally, would be long lasting. This is straightforward at the conceptual level; however, at the time being is characterized by a relative lack of information on the natural disease course, specifically biological end points reflecting drivers of the disease process, their change over time, their connection with clinical disease manifestations and the timely development (of patterns) of disease symptoms. As a result, development needs to build on a strong 'standalone' rational package and, at the same time, be open to own as well as general progress. To this end, a given program has to build on solid ground starting with evidence for target engagement, measuring

changes of candidate biological markers (including validation efforts) and scales potentially representing all clinical domains affected by the disease. The latter is particularly challenging in PD since non-motor symptoms are only being appropriately appreciated during the last few years and validated scales are largely missing. Moreover, such a program requires connection to basic science and the flexibility to integrate new research findings. Obviously, beyond moving the program on state of the art disease-specific knowledge (and potentially adapting it), ongoing discussions with regulators on aspects such as specific end points, scales describing them and the type of statistical analysis to be applied are expected to facilitate the registration process.

Using defined genetic entities as paradigms might offer a shortcut

Familial PD forms, caused by mutations in the aSyn gene, might offer a solution to all of the limiting factors discussed above. In dominantly inherited synucleopathies, a clear diagnosis can be made years before widespread neurodegeneration is established. Affected individuals represent a (relatively) homogeneous cohort. The clinical course of their disease parallels the one of persons carrying the same mutation (i.e., established disease course). The entities are primarily monogenic. While this would obviate the need for biomarkers, it at the same time offers a unique possibility to work out and establish biological markers reflecting the underlying pathology. Needless to say, such studies impose significant ethical challenges, especially when targeting individuals who carry the mutation but do not yet know their genetic status. Moreover, translation of results from inherited to sporadic disease forms would require parallel pathological processes. Such an approach is currently pursued in the development of disease-modifying AD drugs [13]. This represents a huge effort dealt with by unifying all relevant stakeholders, including patient organizations, academia and sponsors.

Conclusion

Our increasing understanding of the pathology underlying synucleopathies such as PD continues to unravel new targets offering the potential for disease modification. First, ensuing drug candidates, for example, the aSyn-targeting vaccine PD01A, are reaching the phase of clinical development. This marks a landmark of progress in the field with potential for tremendous benefit to patients, healthcare systems and societies as a whole. Now, efforts are needed to create a clinical (study) environment allowing for rational and effective clinical evaluation of these new drug candidates.

Financial & competing interests disclosure

A Schneeberger and M Mandler are employees of AFFiRiS. This work was supported by grants from Austrian Science Promotion Agency, Vienna, Austria and the Michael J Fox Foundation, NY, USA. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References

- Schneeberger A, Mandler M, Mattner F, Schmidt W. Vaccination for Parkinson's disease. *Parkinsonism and Related Disorders* 18(S1), S11–S13 (2012).
- Stern MB, Lang A, Poewe W. Toward a redefinition of Parkinson's disease. *Mov. Disorder* 27(1), 54–60 (2012).
- Rascol O, Lozano A, Stern M, Poewe W. Milestones in Parkinson's disease therapeutics. *Mov. Disorder* 26 (6), 1072–1082 (2011).
- Lansbury PT, Brice A. Genetics of Parkinson's disease and biochemical studies of implicated gene products. *Curr. Opin. Genet. Dev.* 12, 299–296 (2002).
- Singleton AB, Farrer M, Johnson J *et al.* Alpha-Synuclein locus triplication causes Parkinson's disease. *Science* 302, 841 (2003).
- Braak H, Del Tredici K, Rub U, de Vos RA, Jansen Steur DN, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol. Aging* 24, 197–111 (2003).
- Jellinger K. Neuropathology of sporadic Parkinson's disease: evaluation and changes of concepts. *Movement Disorders* 27(1), 8–30 (2012).
- Gasser T. Identifying PD-causing genes and genetic susceptibility factors: current approaches and future prospects. *Prog. Brain Res.* 183, 3–20 (2010).
- Masliyah E, Rockenstein E, Veinbergs I *et al.* Dopaminergic loss and inclusion body formation in alpha-synuclein mice: implications for neurodegenerative disorders. *Science* 287(5456), 1265–1269 (2000).
- Lotharius J, Brundin P. Pathogenesis of Parkinson's disease: dopamine, vesicles and alpha-synuclein. *Nat. Rev. Neurosci.* 3(12), 932–942 (2002).
- Dubois B, Feldman HH, Jacova C *et al.* Revising the definition of Alzheimer's disease: a new lexicon. *Lancet Neurol.* 9(11), 1118–1127 (2010).
- Schneeberger A, Mandler M, Mattner F, Schmidt W. AFFITOME® technology in neurodegenerative disease: the doubling advantage. *Hum. Vacc.* 6, 64–68 (2010).
- Miller G. Stopping Alzheimer's before it starts. *Science* 337, 790–792 (2012).