Characterization and therapeutic targeting of Parkinson's-related LRRK2

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Propositions related to the present thesis

Stellingen behoorende bij het proefschrift

Characterization and therapeutic targeting of Parkinson's related LRRK2 protein

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1. Several studies have challenged the long-term safety of PD treatment with ATP-competitive LRRK2 kinase inhibitors. Therefore, alternative ways of targeting LRRK2 activity will have a great benefit. — **Chapter 1**

2. While the development of classical kinase inhibitors has benefited from the existence of the natural ATP substrate, there are virtually no small molecule starting points from which allosteric kinase modulators can be built. This renders allosteric kinase inhibitors more challenging to develop. — **Chapter 1**

3. LRRK2 kinase-inhibitory nanobodies do not induce LRRK2 microtubule association -in contrast to ATP-competitive inhibitors - and pave the way toward novel diagnostic and therapeutic strategies for PD. — **Chapter 3**

4. The domain structure of LRRK2 position it among the Receptor Intracellular Protein Kinases (RIPKs) branch of the human kinome. Unlike the other members of RIPK family, there is no identified immune function of LRRK2. — **Chapter 4**

5. An increased odd to develop PD is associated with infections. Although not demonstrating causality, this strengthens the overlooked role of the immune system in the development of PD. — **Chapter 4**

6. Conventional immunostaining has many limitations to detect a dynamic target as LRRK2. GFP-fused nanobodies (chromobodies) are potential substitutes for visualization of endogenous LRRK2, with the possibility to recognize specific conformations of LRRK2. — **Chapter 6**

7. "One who makes no mistakes makes nothing at all." — **Giacomo Casanova**

8. "I would rather have questions that can't be answered than answers that can't be questioned." — **Richard P. Feynman**

9. But how could you live and have no story to tell? — **Fyodor Dostoevsky**

10. "The best way to predict your future is to create it." — **Abraham Lincoln**

11. A man has nothing but what he strives for. " وَأَن لَّيْسَ لِلْإِنسَٰنِ إِلَّا مَا سَعَىٰ "