Inhibitors of Leucine-rich Repeat Kinase 2 (LRRK2): Progress & Promise for the Treatment of Parkinson's Disease

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Parkinson’s disease (PD)

- Hallmarks of PD include Lewy bodies (LB) and Lewy neurites (LN) composed of alpha-synuclein (α-syn) and progressive loss of dopaminergic (DA) neurons.
- Aggregation of α-syn into filamentous inclusions is a key step in the pathogenesis of Parkinson’s disease.

Spillantini et al. Nature 1997; 388:28
Lippincott et al. Neurology 1999;52:893
Baba et al. AJP 1998; 152:879
LRRK2 plays a pathogenic role in familial PD

- LRRK2 mutations are the most common genetic cause of PD (Berg et al. 2005, Healy et al. 2008)
- Pathogenic mutations in the GTPase, COR, and kinase domains of LRRK2 lead to dominantly inherited late-onset PD (Paisan-Ruiz et al. 2004, Zimbrick et al. 2004)
- G2019S mutation, which increases kinase activity, is the most common mutation
LRRK2 likely plays a key role in sporadic PD

- LRRK2-mediated PD has similar clinical features to idiopathic PD, including α-syn pathology and nigral degeneration.
- Increased LRRK2 protein in brain regions with abundant LB pathology (Cho et al. 2013, Guerreiro et al. 2013).
- LRRK2 genetic ablation protects and overexpression exacerbates α-syn accumulation and downstream neuropathology (Lin et al., 2009, Daher et al. 2012).
- Genetic ablation of LRRK2 or treatment with potent LRRK2 kinase inhibitor protected against DA cell loss caused by viral-mediated overexpression of α-syn (Daher et al. 2014, 2016), or α-syn fibrils (Volpicelli-Daley et al. 2016).

Daher et al. 2014
Volpicelli-Daley et al. 2016
Antisense Technology Uniquely Addresses Challenging Neurological Diseases

- **Broad Distribution**
  e.g. spinal cord, cortical regions and deep brain structures

- **Exquisite Specificity**
  for targeting protein isoforms and genetic variants

- **Currently Undruggable Targets**
  such as toxic and nuclear retained RNAs

- **Multiple Mechanisms**
  e.g. decrease and increase production and splicing modulation
Multiple antisense mechanisms can be employed to modulate target RNA

Bennett et al 2016
Design and benefits of 2\textsuperscript{nd} generation ASOs

- **‘Gapmer’ design** (to activate RNase H)
  - Phosphorothioate backbone
  - DNA in middle
  - Sugar 2’-O-methoxyethyl (MOE) modification at ends
  - 20 bases for high specificity and affinity

- **Benefits of ASOs**
  - Diffusible
  - Dose dependent
  - Stable
  - Reversible
Local CNS delivery of 2\textsuperscript{nd} generation ASOs

- Intrathecal injection in humans, non-human primates, and rats
- Intracerebral ventricular (ICV) injection in mice

Benefits of local delivery:
- Low doses provide broad target suppression throughout the CNS
- Limited exposure to systemic organs
ASOs distribute to many different brain regions in non-human primates following IT injection.

Kordasiewicz et al 2012
ASOs are taken up by neurons and glia following ICV injection in mice
ASOs to LRRK2 as a potential therapy for PD

- ASOs targeting LRRK2 RNA will lower production of total LRRK2 and may be a potential therapy
Conclusions

• ASOs behave in a dose-dependent manner and exhibit long lasting target reduction in the CNS without affecting systemic organs

• Preventive ASO-mediated suppression of endogenous LRRK2 reduces formation of pathological α-syn inclusions and protects mice against α-syn-induced wirehang deficit and DA cell loss in the PFF inoculation mouse model

• Thus, ASO targeting LRRK2 may be of potential therapeutic use for PD
Acknowledgements

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  - Andrew B West
  - Neena John

Knowledge that will change your world
Extra slides
Substantial Progress in Ionis’ Neurological Disease Pipeline
Addressing a Broad Spectrum of Severe Neurological Diseases

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