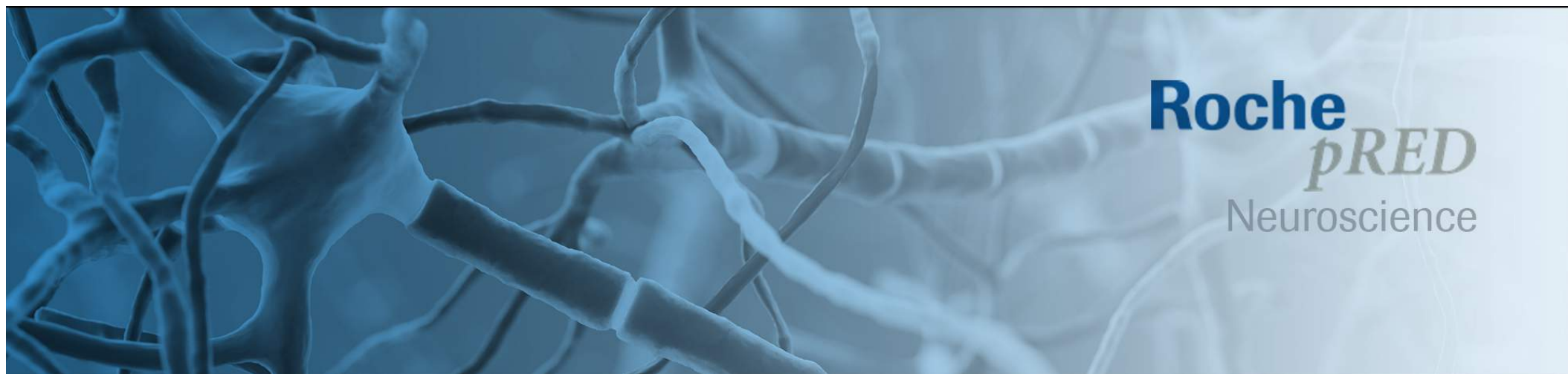


RG7935 / PRX002

A mAb targeting α -synuclein for disease modification in Parkinson's disease: from preclinical models to first in humans

***11th GEdPD Meeting and 3rd International Parkinson's Disease Symposium
Luxembourg, Oct 6-8, 2016***

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Principal Scientist, Neuroscience Discovery*



Disclosure

- Roche and Prothena entered into a worldwide collaboration to develop and commercialize antibodies that target alpha-synuclein (aSyn) for the treatment of Parkinson's disease.
- The humanized monoclonal anti-aSyn mAb RG7935 / PRX002 is currently in Phase 1 clinical trials.
- Today's presented data were generated by Prothena.

In memoriam Dale B. Schenk, PhD

Innovative scientist and inspirational leader



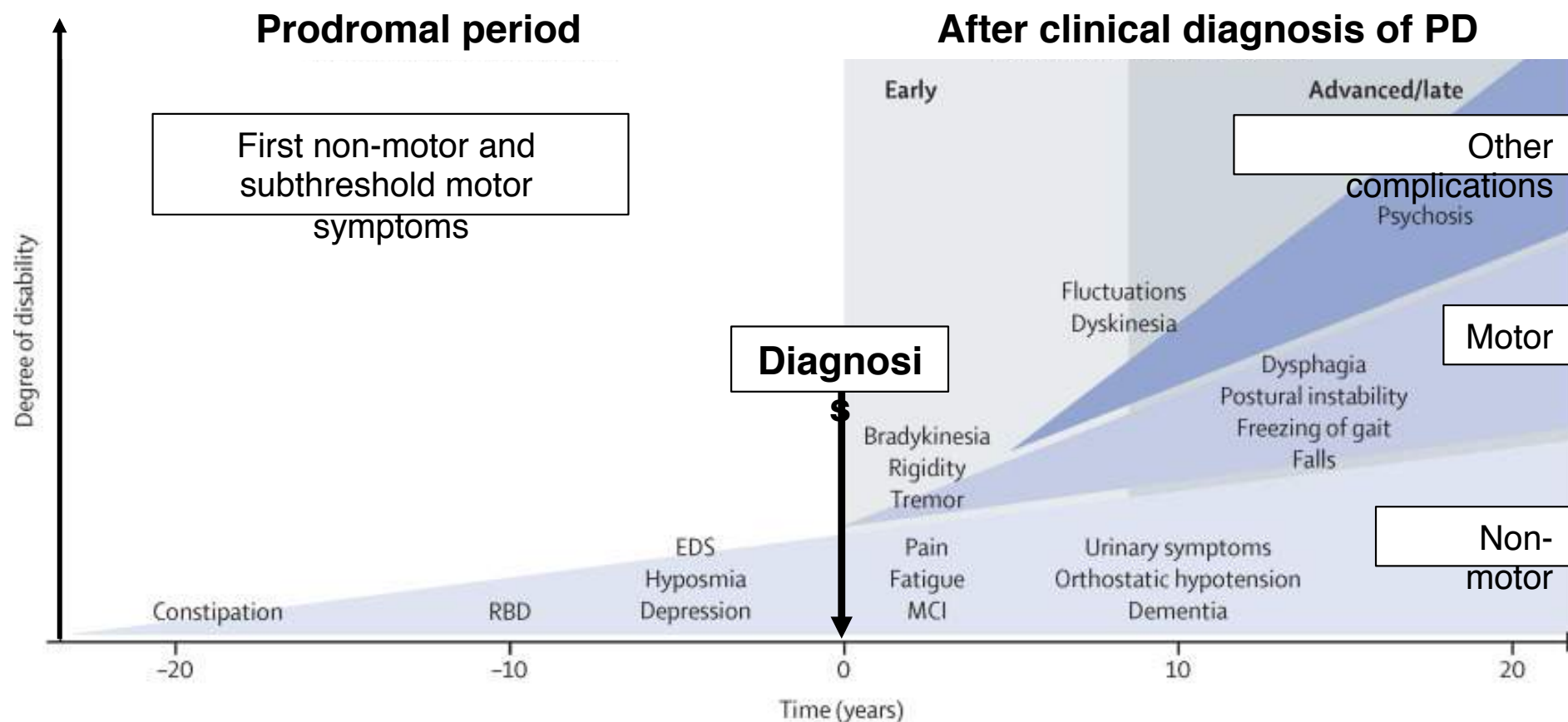
Image via Prothena



Image via Nature

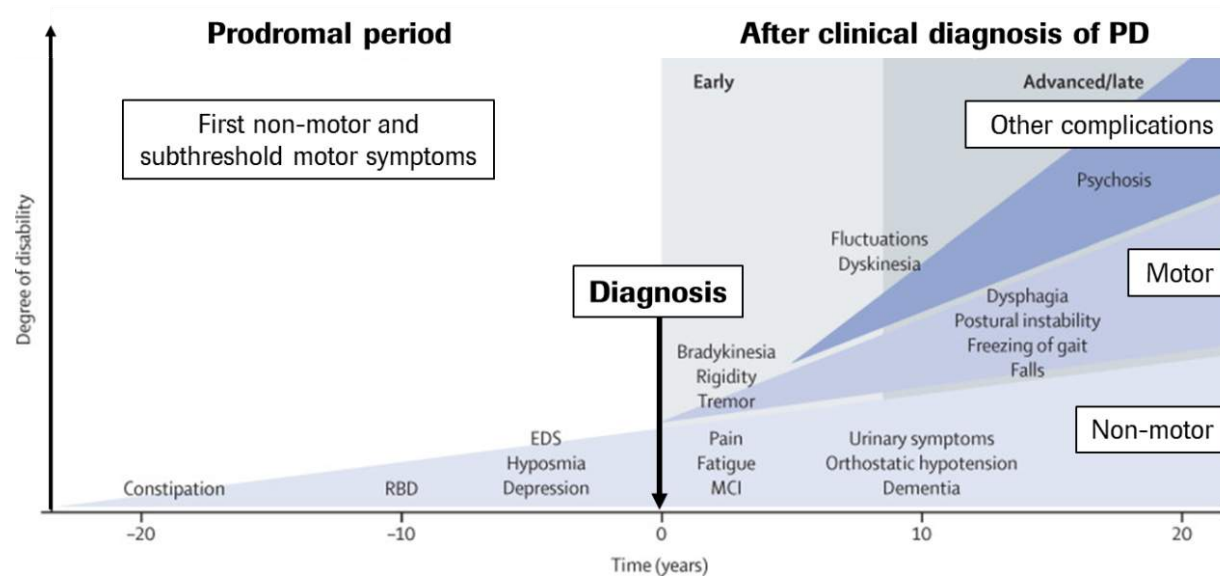
http://blogs.nature.com/news/2009/05/post_26.html

Parkinson's disease is a progressive neurodegenerative disorder



Patients suffer from wide spectrum of worsening motor and non-motor symptoms

High unmet medical need for disease modifying therapies in Parkinson's disease

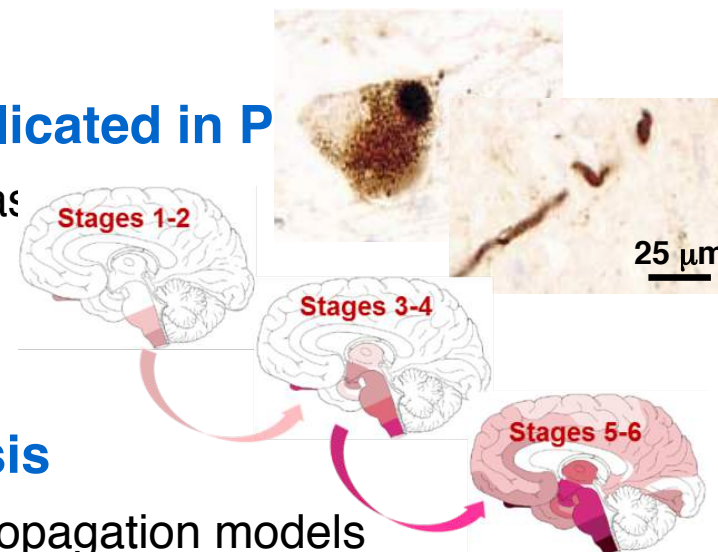


- Available therapies do not target the underlying cause of PD
- Symptomatic therapies lose effectiveness, often leading to debilitating side effects as the disease progresses

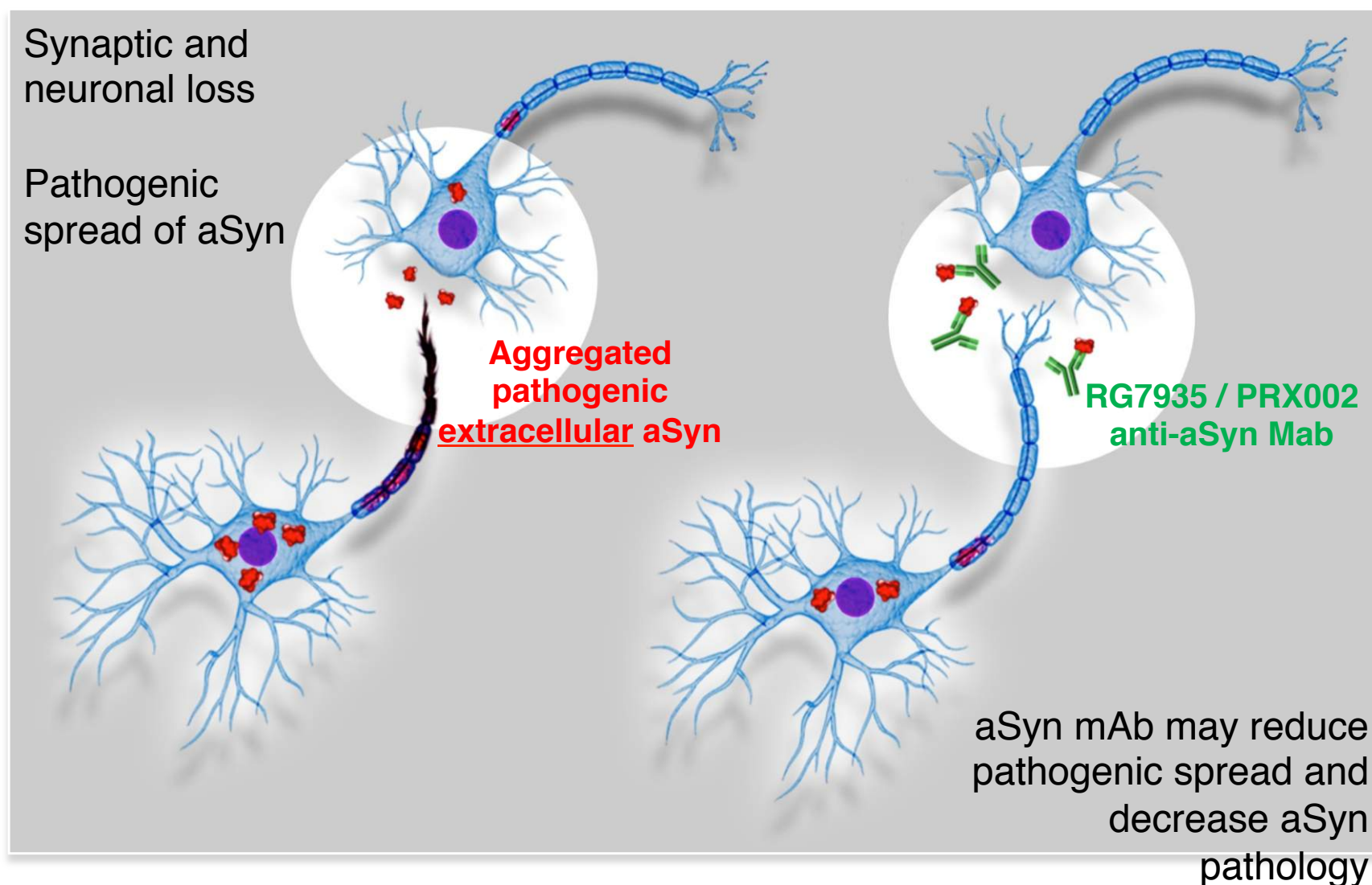
There is a profound need for disease-modifying therapies in PD

Strong scientific evidence supports anti- α -synuclein therapies for Parkinson's disease

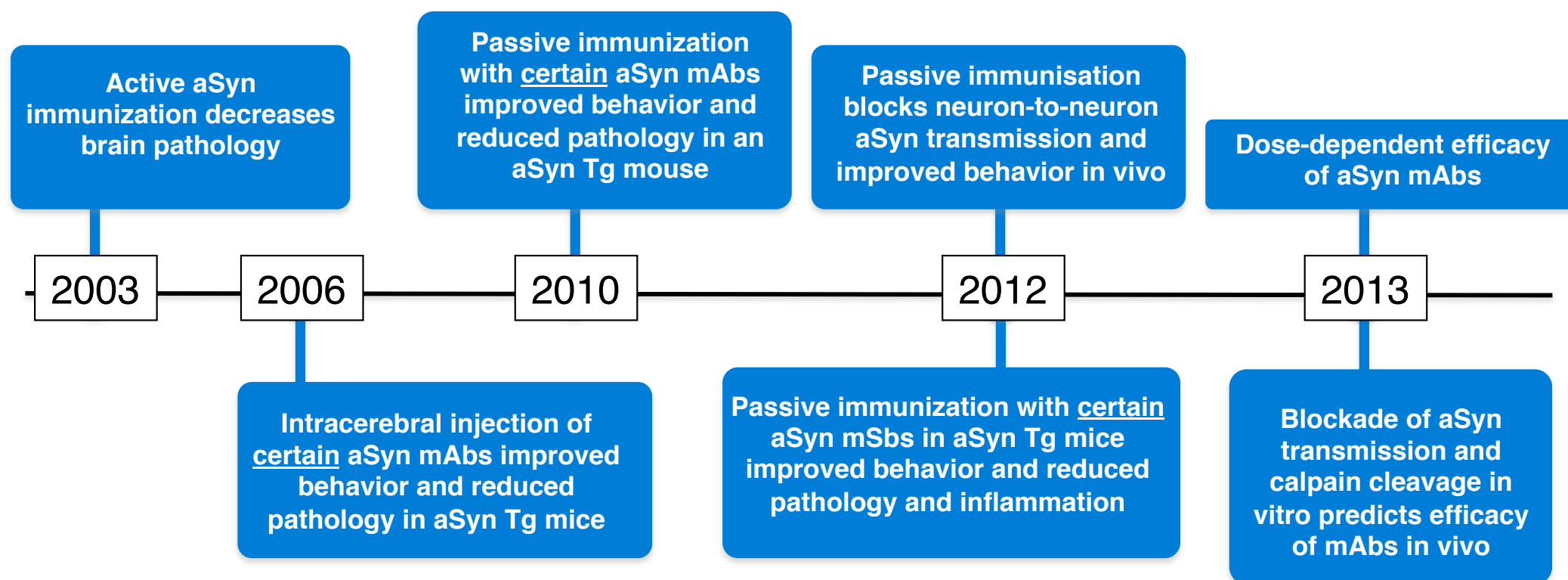
- **Alpha-synuclein (aSyn) pathology is strongly implicated in PD**
 - Lewy pathology follows topological progression of disease
 - Genetically validated target
- **aSyn as an extracellular target during pathogenesis**
 - Caudal-rostral staging, host-to-graft transfer, various propagation models
 - Possible common mechanism among misfolded proteins in CNS (eg, amyloid-beta, tau, TDP43, SOD1)
- **Passive anti-aSyn immunization is a potential disease-modifying therapy for PD**
 - aSyn is not deposited extracellularly in brain vessels and parenchyma in PD
 - Strong preclinical efficacy in various in vivo alpha-synucleinopathy models



Hypothesized mechanism of action for a passive immunotherapy in PD



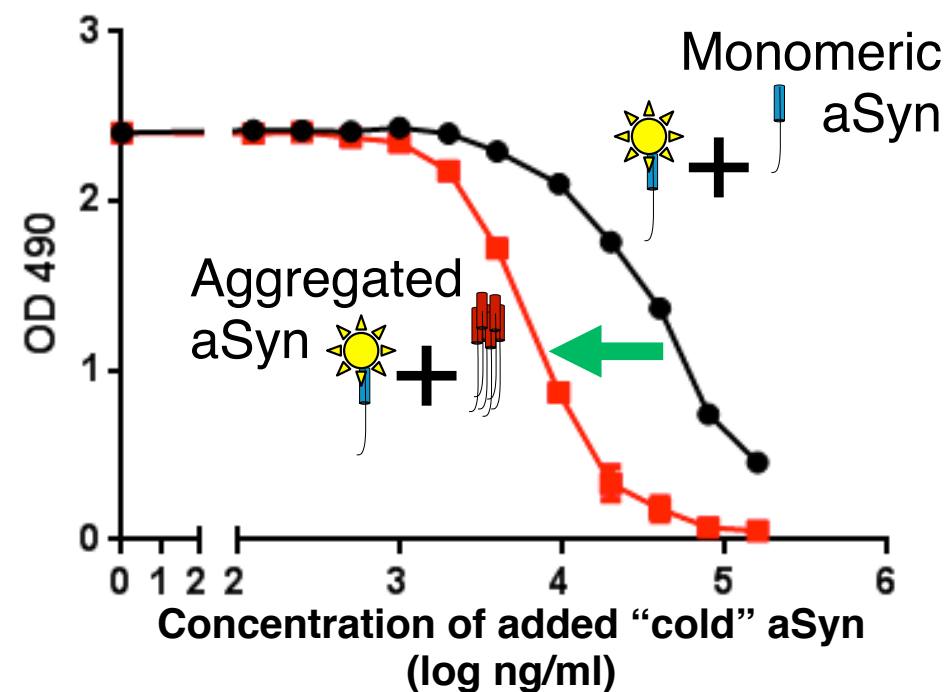
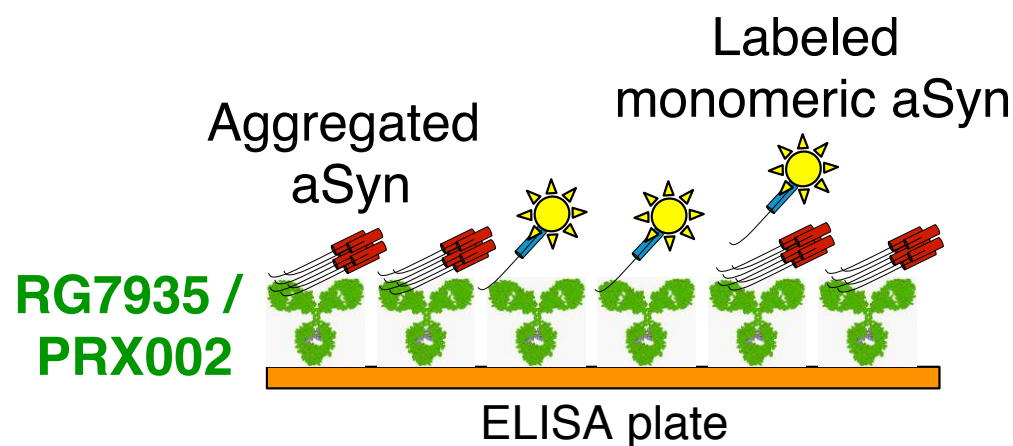
Studies that led to the selection of RG7935/PRX002 as clinical candidate



Study completion dates are approximate.

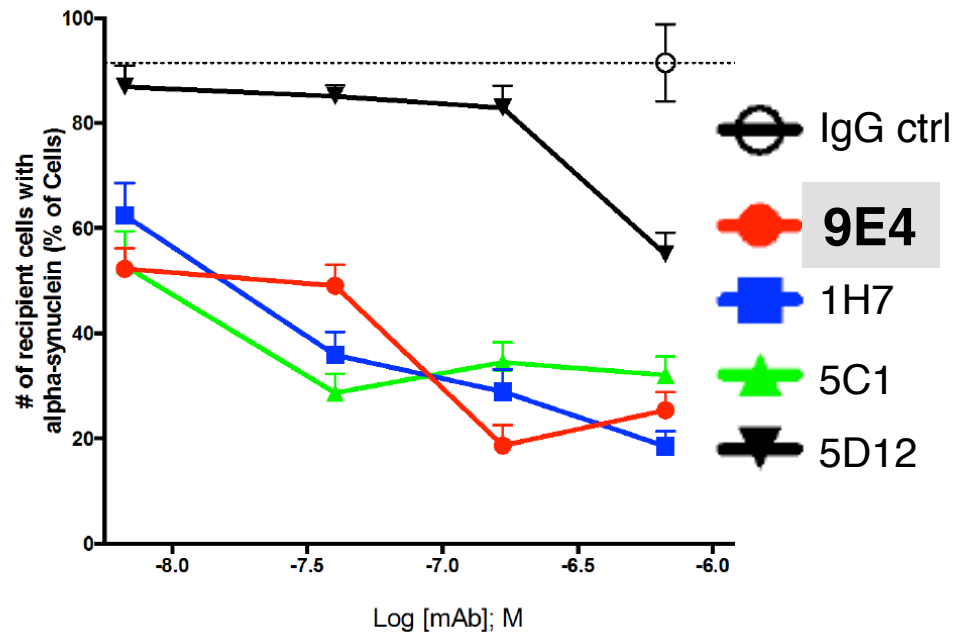
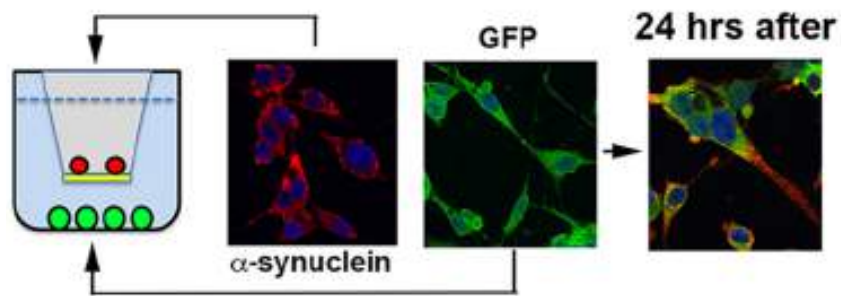
PRX002/RG7935 demonstrates preferential binding to aggregated over monomeric aSyn *in vitro*

ELISA-based competition assay

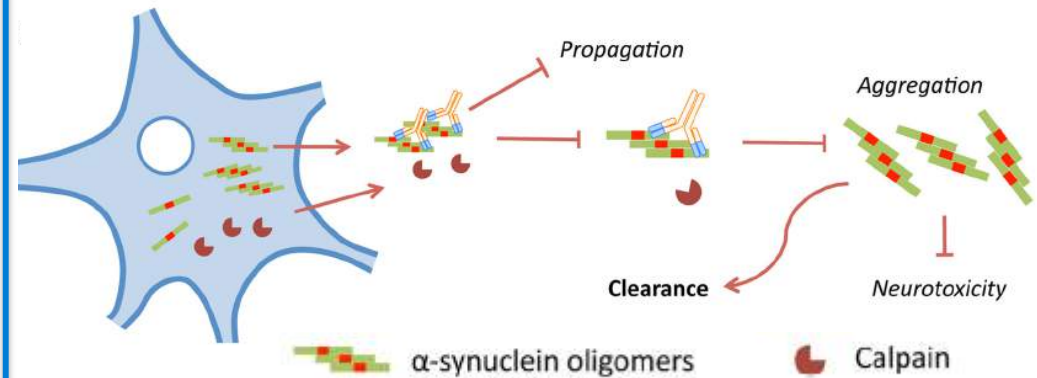


9E4 (murine form of PRX002) blocks cell-to-cell transmission and cleavage of aSyn in vitro

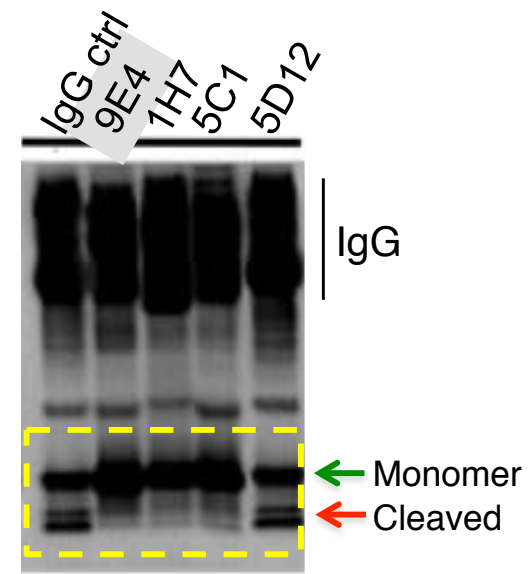
Cell-to-Cell Transmission



aSyn cleavage by Calpain-1



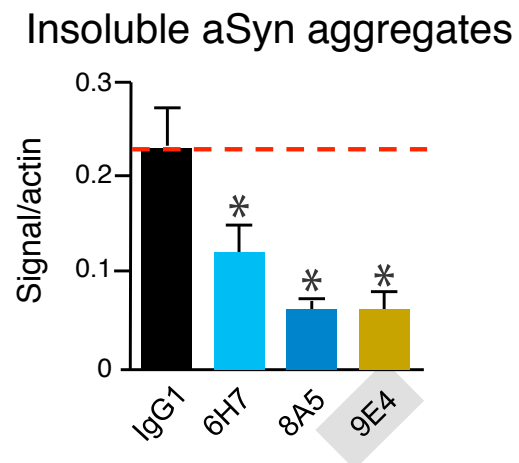
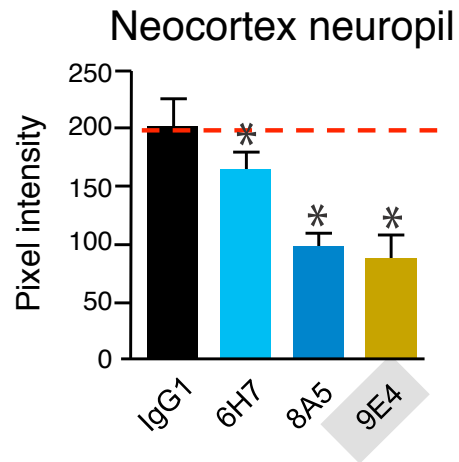
aSyn + Calpain-1 + aSyn Mabs



Passive immunization with 9E4 promotes clearance of aSyn in animal models

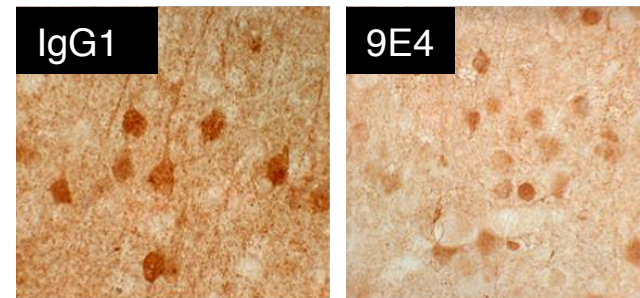


Line D aSyn tg mice

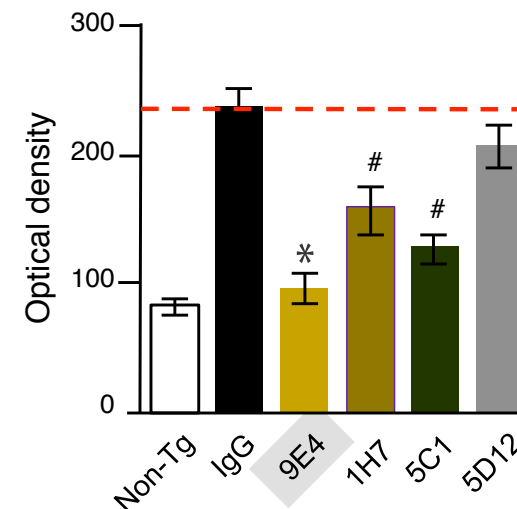


Masliah E et al. *PLoS ONE*. 2011.

Line61 aSyn tg mice



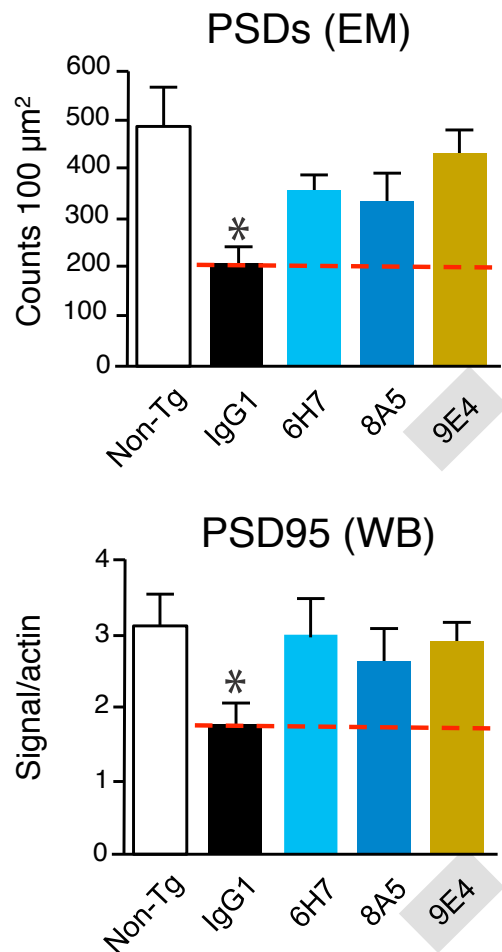
aSyn (neuropil)



Games D et al. *J Neurosci*. 2014.

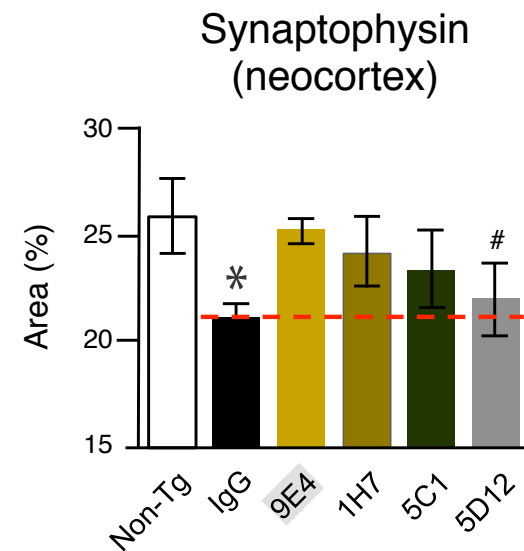
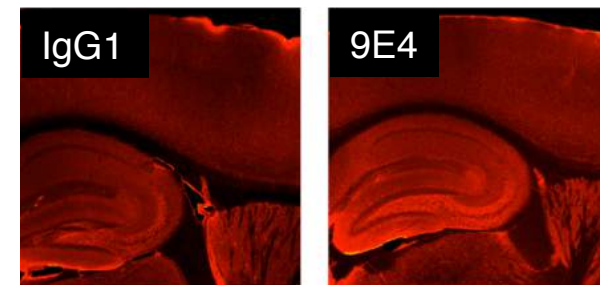
Passive immunization with 9E4 protects against neuronal and synaptic loss in animal models

Line D aSyn tg mice



Masliah E et al. *PLoS ONE*. 2011.

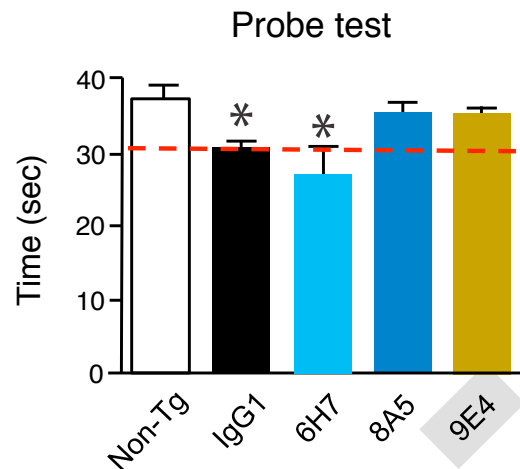
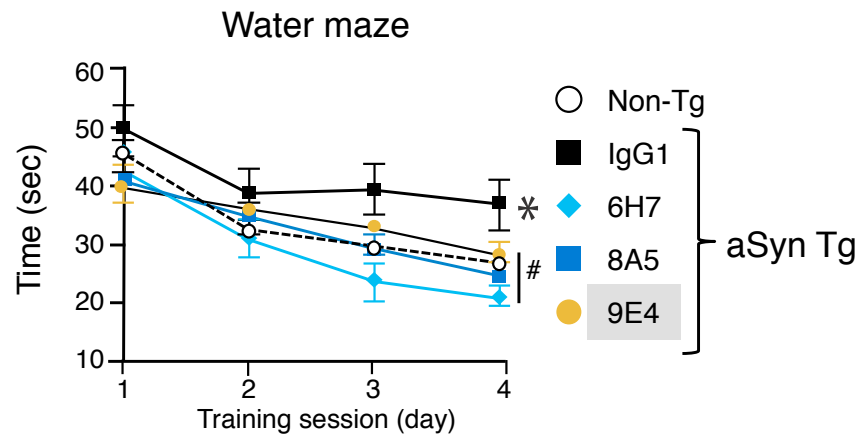
Line61 aSyn tg mice



Games D et al. *J Neurosci*. 2014.

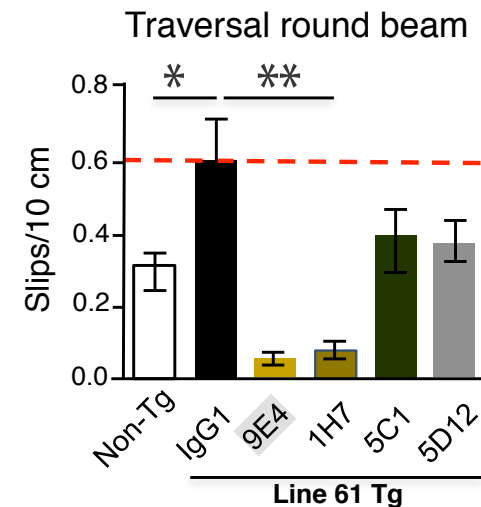
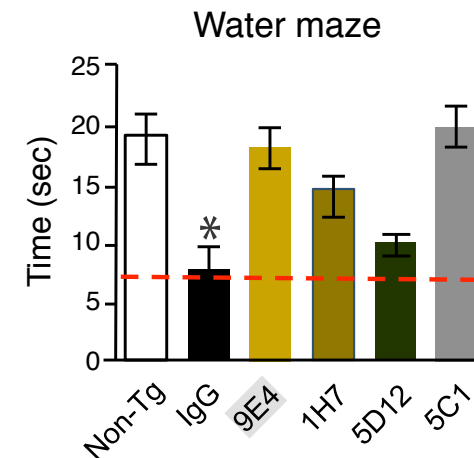
Passive immunization with 9E4 reduces behavioral deficits in animal models

Line D aSyn tg mice



Masliah E et al. *PLoS ONE*. 2011.

Line61 aSyn tg mice

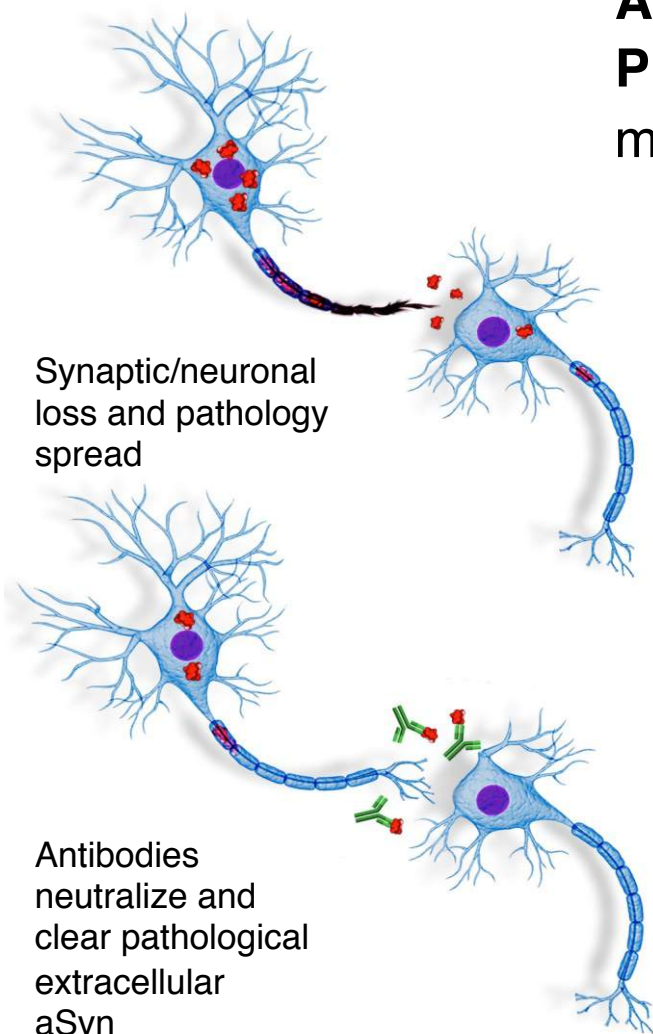


Games D et al. *J Neurosci*. 2014.

Summary of findings with 9E4

Anti-aSyn immunotherapy with 9E4, the murine form of PRX002, demonstrated in various animal and in vitro models of synucleinopathy to promote:

- Reduction of aSyn pathology
- Blockade of cell-to-cell transmission of aSyn
- Blockade of aSyn cleavage by calpain
- Reduction of gliosis
- Preservation of synaptic integrity
- Amelioration of motor, cognitive, and sensorimotor behavioral deficits



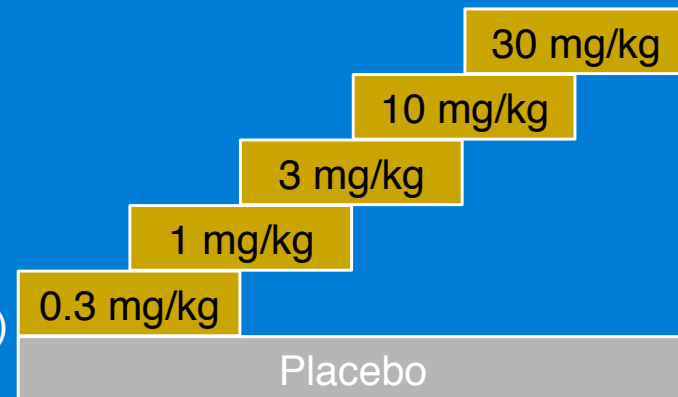
Targeting specific epitopes of aSyn with antibodies is **suitable for testing the aSyn hypothesis in Parkinson's disease**

Phase 1 SAD trial design with RG 7935 / PRX002



Single-ascending dose

- N = 40 total subjects (30 RG7935/PRX002, 10 PBO)
- 5 dose-level cohorts
- Randomized: n= 8/cohorts (6:2, RG7935/PRX002:PBO)



Primary objectives

- Evaluate safety and tolerability of RG7935 / PRX002
- Evaluate serum pharmacokinetics of RG7935 / PRX002

Secondary objectives

- Evaluate immunogenicity of RG7935 / PRX002

Exploratory objectives

- Evaluate pharmacodynamic effects of RG7935 / PRX002

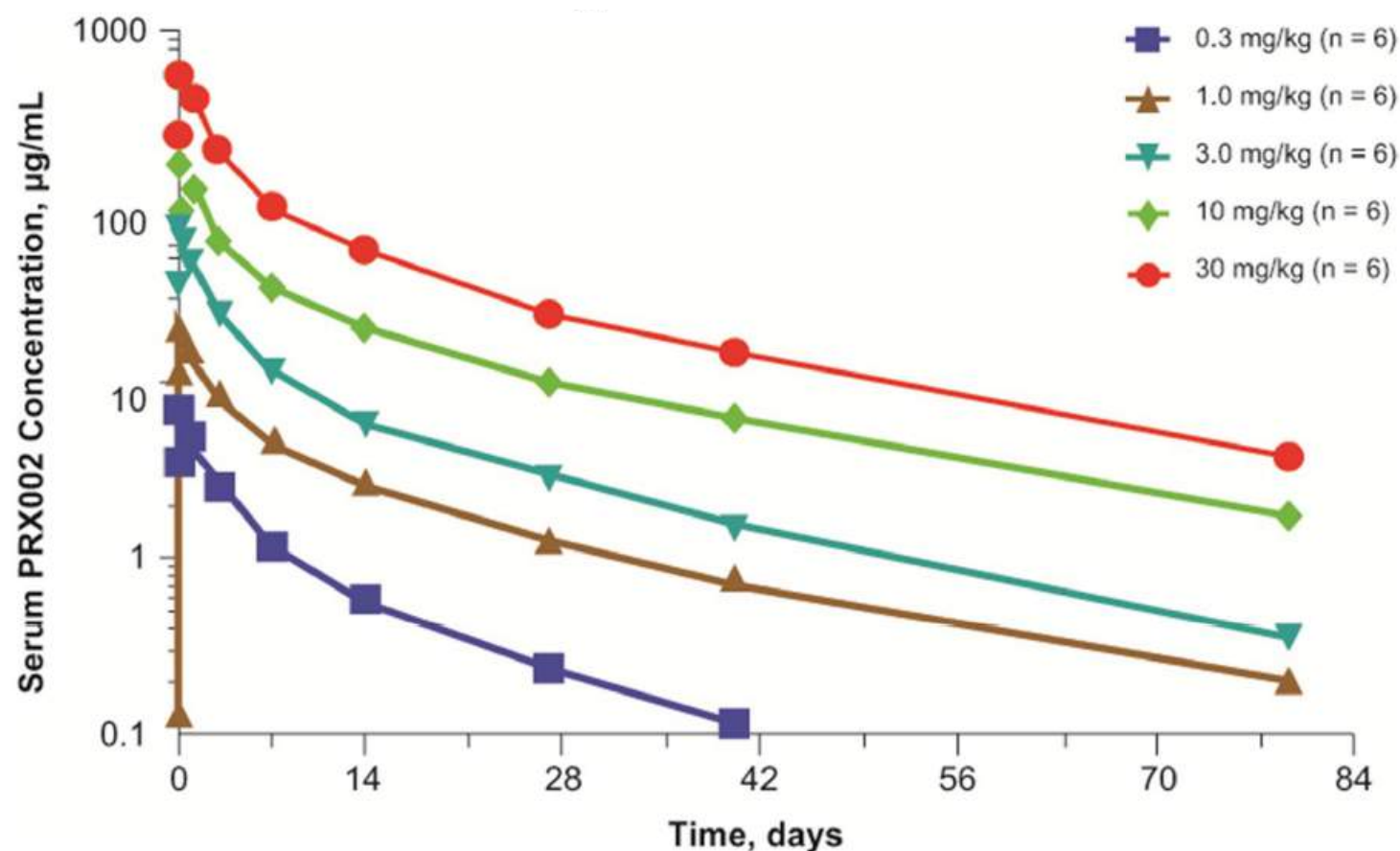
PBO, placebo

In this first study RG7935 / PRX002 was safe and well tolerated

- No serious AEs, hypersensitivity reactions, or dose-limiting toxicities were reported
- All subjects completed the study, except 1 subject in the 0.3 mg/kg dose group who was lost to follow-up after day 15 evaluations
- 18 subjects reported treatment-emergent AEs
 - 6 moderate AEs were unrelated to study drug (2 occurred in placebo recipients)
 - Only 1 severe AE, neutropenia, was reported and was assessed by the investigator to be of viral cause and unrelated to study drug
- No anti-drug antibodies were detected

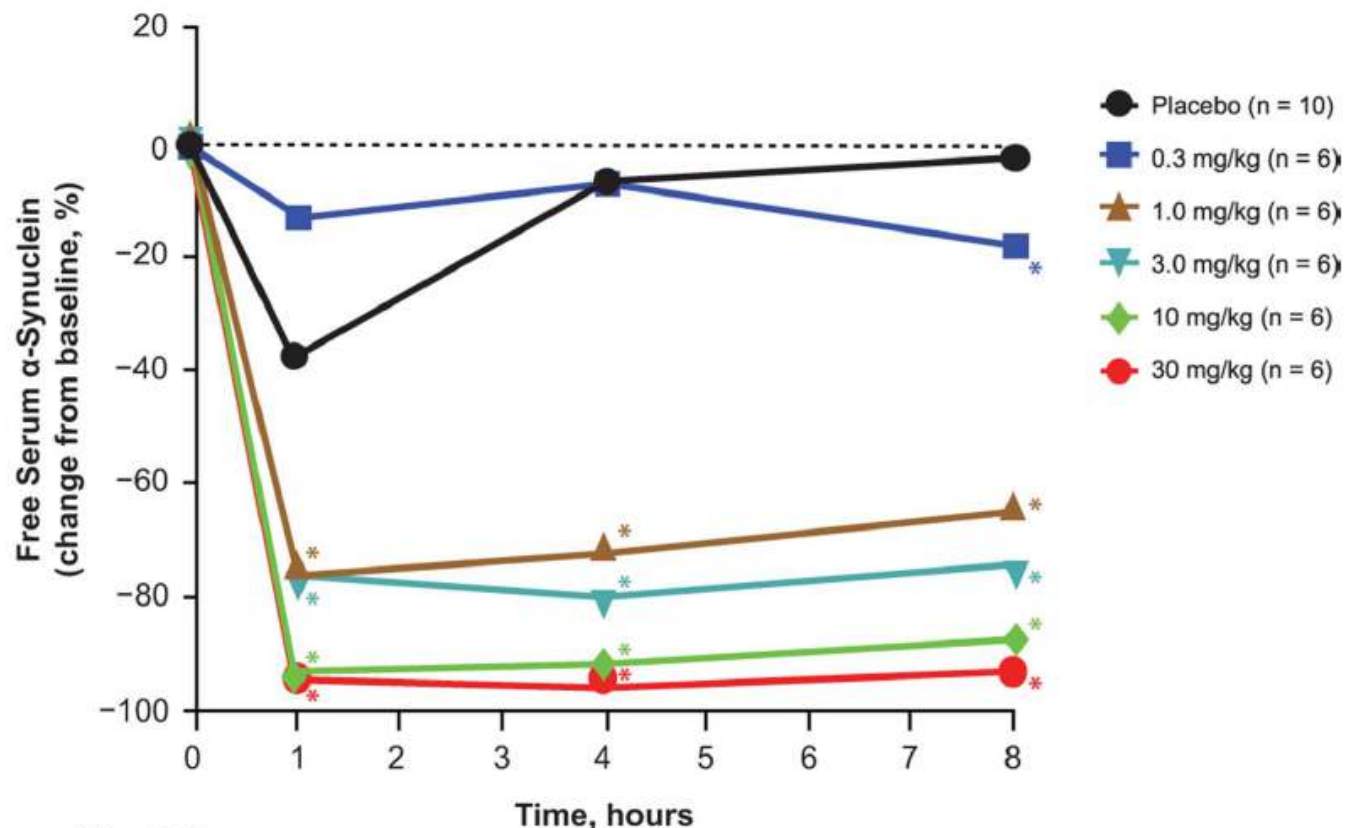
Pharmacokinetics of RG7935 / PRX002

- Serum RG7935 / PRX002 exposure was approximately dose proportional
- Average terminal half-life ($t_{1/2}$) across all doses was ~18 days



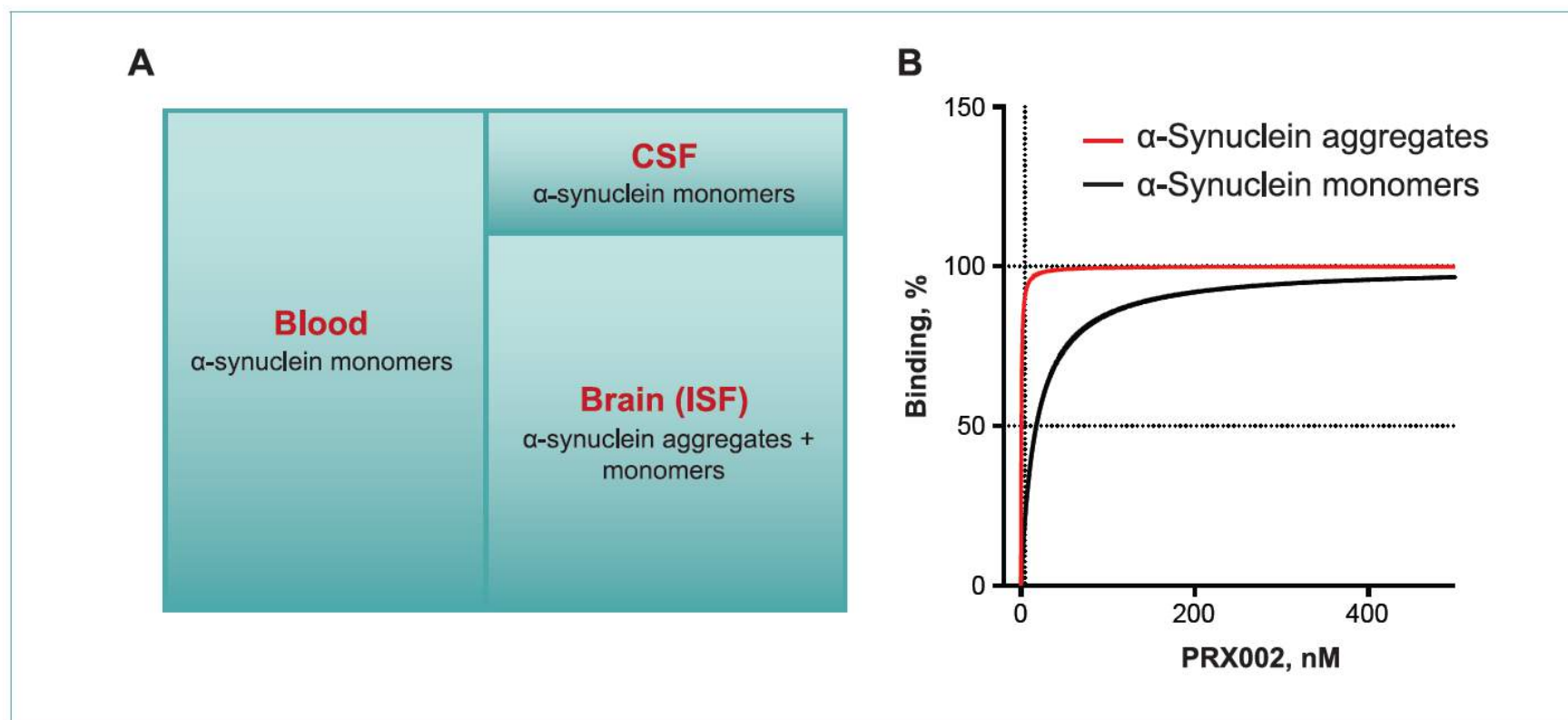
Pharmacodynamics of RG7935 / PRX002

- Administration of RG7935 / PRX002 led to **mean reductions of free serum aSyn levels of up to 96%**
- Dose- and time-dependent, statistically significant reduction in free serum aSyn was apparent within 1 hour, which was the first post-infusion time point sampled (*P < 0.0001)



Pharmacokinetic /pharmacodynamic conceptual framework

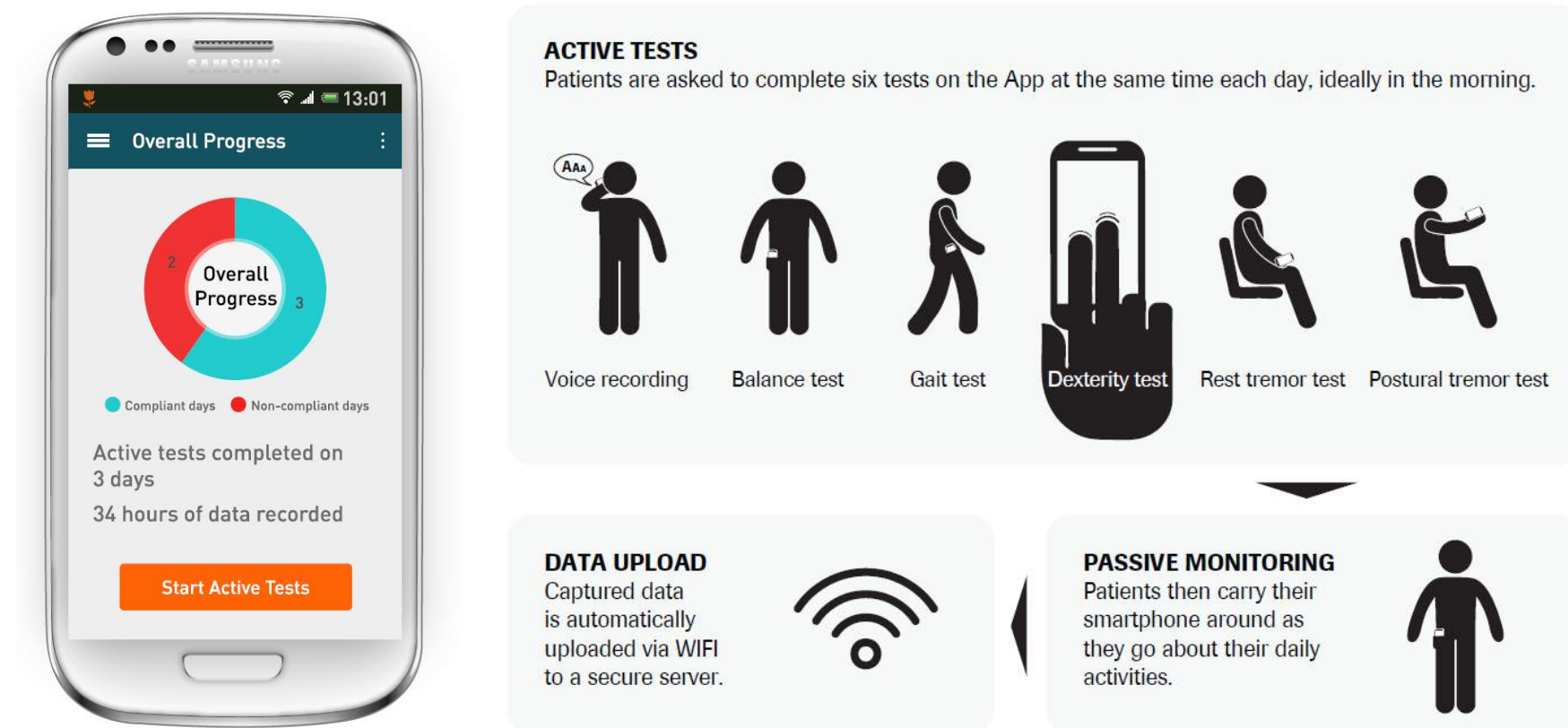
- **PK/PD concept takes into consideration**
 - Relative concentrations of RG7935 / PRX002 in peripheral and central compartments
 - Relative concentrations of aSyn in the periphery, cerebrospinal fluid, and brain
 - Proposed effect of PRX002 on aggregated aSyn (the pathogenic form) at the relevant site of action in the brain



Conclusions for this first in-human study with RG7935 / PRX002

- Single doses demonstrated favorable safety, tolerability, and pharmacokinetic profiles at all dose levels tested, up to and including 30 mg/kg
- RG7925 / PRX002 significantly reduced free serum aSyn
- First time that **serum aSyn can be safely modulated in humans** in a dose-dependent manner **following single intravenous infusions of the anti-aSyn antibody, RG7935 / PRX002**
- These results support the design of the ongoing multiple ascending-dose, phase 1 study evaluating PRX002 in patients with PD

Remote digital biomarker monitoring of PD patients in MAD phase of clinical trial with RG7935 / PRX002



- Pioneering a smartphone-based monitoring system for patients with PD
- To complement the traditional conventional physician-led assessments
- App-based tests continuously measure the patient's symptoms and thus thoroughly capture day-to-day fluctuations

Acknowledgements (partial list)



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Silke Nuber

***Doing now what patients need
next***