resTORbio™

Targeting the biology of aging to treat aging-related diseases

Corporate Presentation

December 2019

Forward-looking statements

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These statements are also subject to a number of material risks and uncertainties that are discussed in the section entitled "Risk Factors" in resTORbio’s annual report on Form 10-K for the fiscal year ended December 31, 2018, as well as discussions of potential risks, uncertainties, and other important factors in resTORbio's subsequent filings with the Securities and Exchange Commission. Any forward-looking statement speaks only as of the date on which it was made. Neither we, nor our affiliates, advisors or representatives, undertake any obligation to publicly update or revise any forward-looking statement, whether as a result of new information, future events or otherwise, except as required by law.

Certain information contained in this presentation relates to or is based on studies, publications, surveys and other data obtained from third-party sources and the Company’s own internal estimates and research. While we believe these third-party sources to be reliable as of the date of this presentation, we have not independently verified, and we make no representation as to the adequacy, fairness, accuracy or completeness of any information obtained from third-party sources. In addition, all of the market data included in this presentation involves a number of assumptions and limitations, and there can be no guarantee as to the accuracy or reliability of such assumptions. Finally, while we believe our own internal research is reliable, such research has not been verified by any independent source.

resTORbio highlights

Extensive preclinical data demonstrate that TORC1 inhibition may ameliorate multiple aging related diseases, including neurodegenerative diseases

TORC1 inhibition may be a promising approach for the treatment of Parkinson's disease (PD)

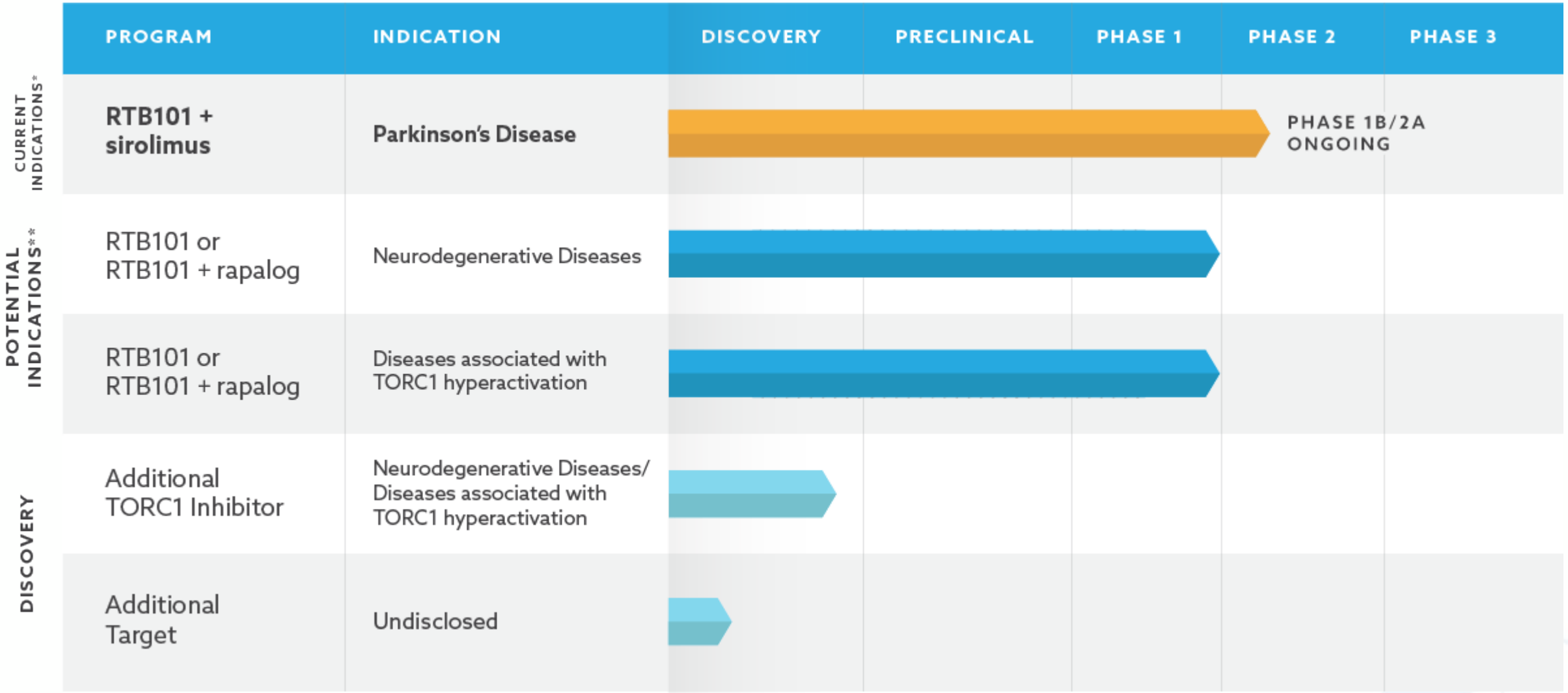
- Induces lysosomal biogenesis and autophagy, clears alpha-synuclein aggregates and improves mitochondrial function in preclinical models
- Ameliorates levodopa-induced dyskinesia in preclinical models
- Lead candidate, RTB101, is an oral, selective and potent TORC1 inhibitor that has been observed in preclinical models to cross the blood brain barrier

Ongoing Phase 1b/2a clinical trial of RTB101 +/- sirolimus for PD

- Safety, tolerability and cerebrospinal fluid (CSF) exposure data are expected by mid-2020 in PD patients
- RTB101 may offer the first opportunity to slow disease progression by inducing autophagy in the brain of PD patients as well as potentially ameliorate levodopa-induced dyskinesia

Cash, cash equivalents and marketable securities of $117.3 million as of September 30, 2019

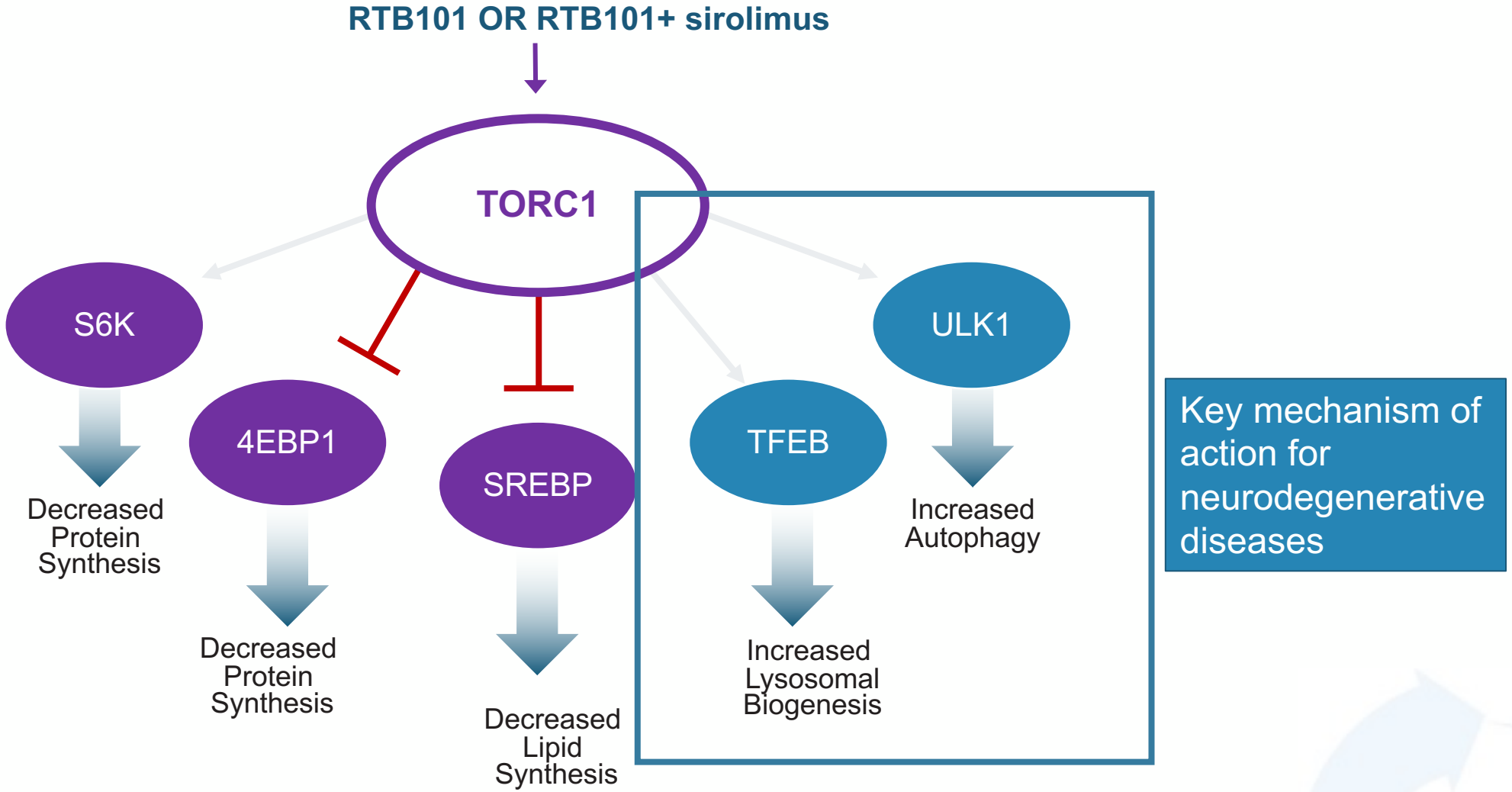
Pipeline



* For Parkinson's disease, we may be required to file an investigational new drug application, or IND, prior to initiating Phase 2 clinical trials

** For neurodegenerative diseases and diseases associated with TORC1 hyperactivation, subject to review by the U.S. Food and Drug Administration, we believe we may have the ability to initiate Phase 2 clinical trials without the need to conduct additional Phase 1 trials.

TORC1 substrates include TFEB & ULK1, regulators of autophagy and lysosomal biogenesis

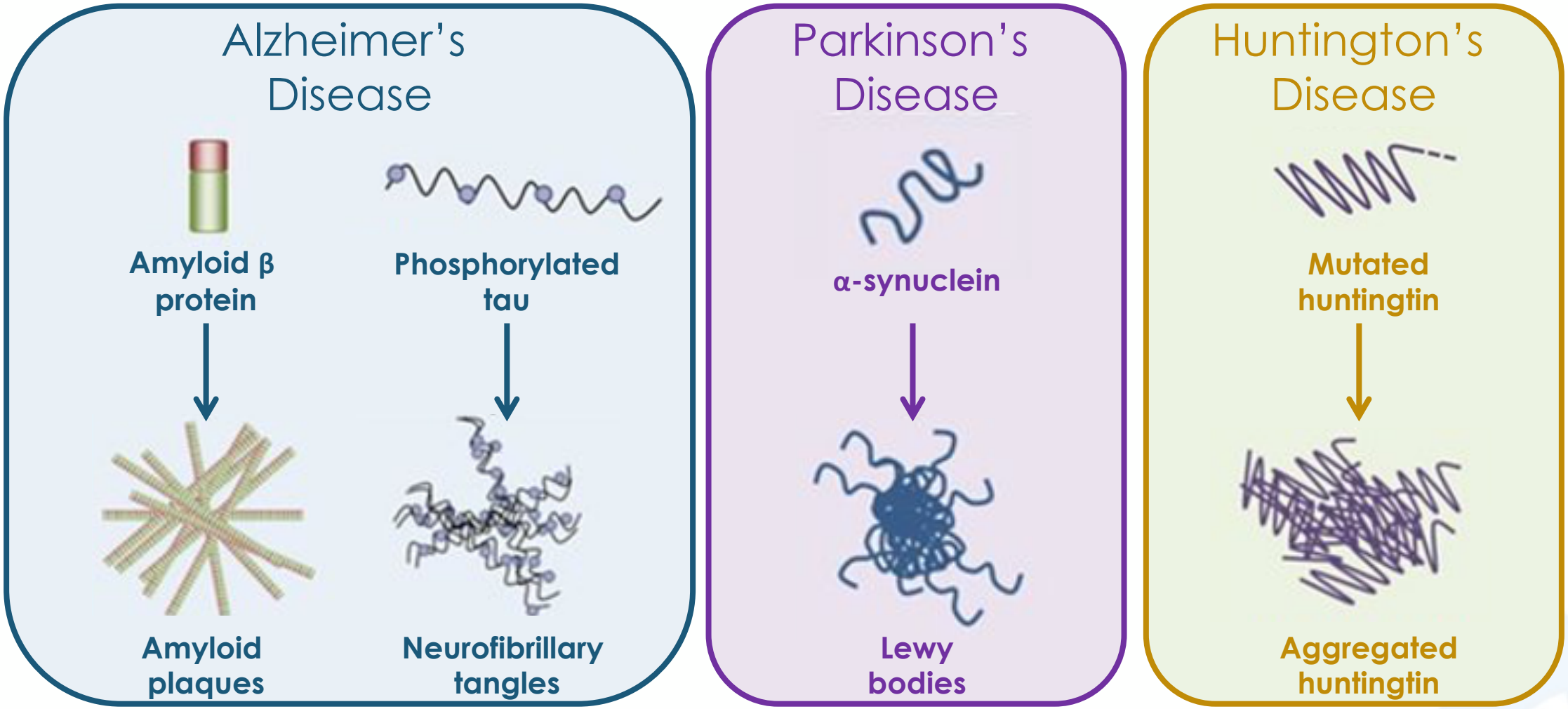


Nyfeler et al. *Molecular and Cellular Biology*, 2011; Nyfeler et al. *PLoS ONE,* 2012; Eid et al. *PNAS*, 2017; Roczniak-Ferguson et al. *Sci Signal*, 2012

Neurodegenerative Diseases

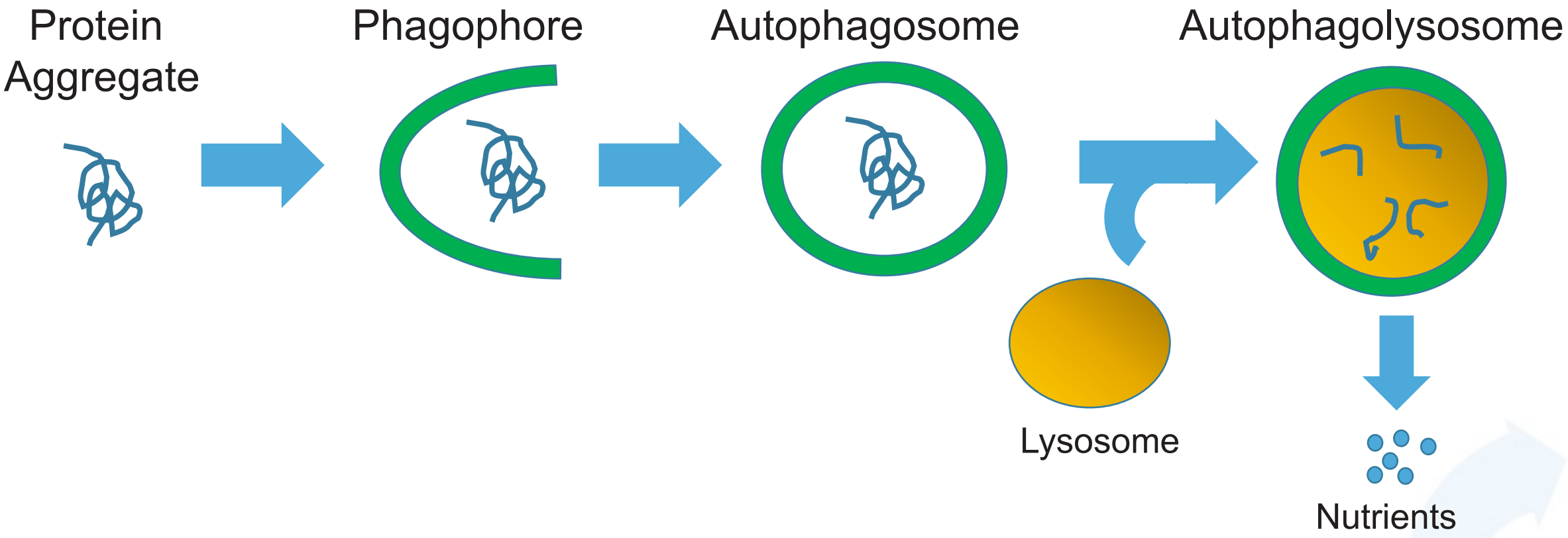
Parkinson’s Disease

Protein aggregation is a common pathogenic mechanism in aging-related neurodegenerative diseases



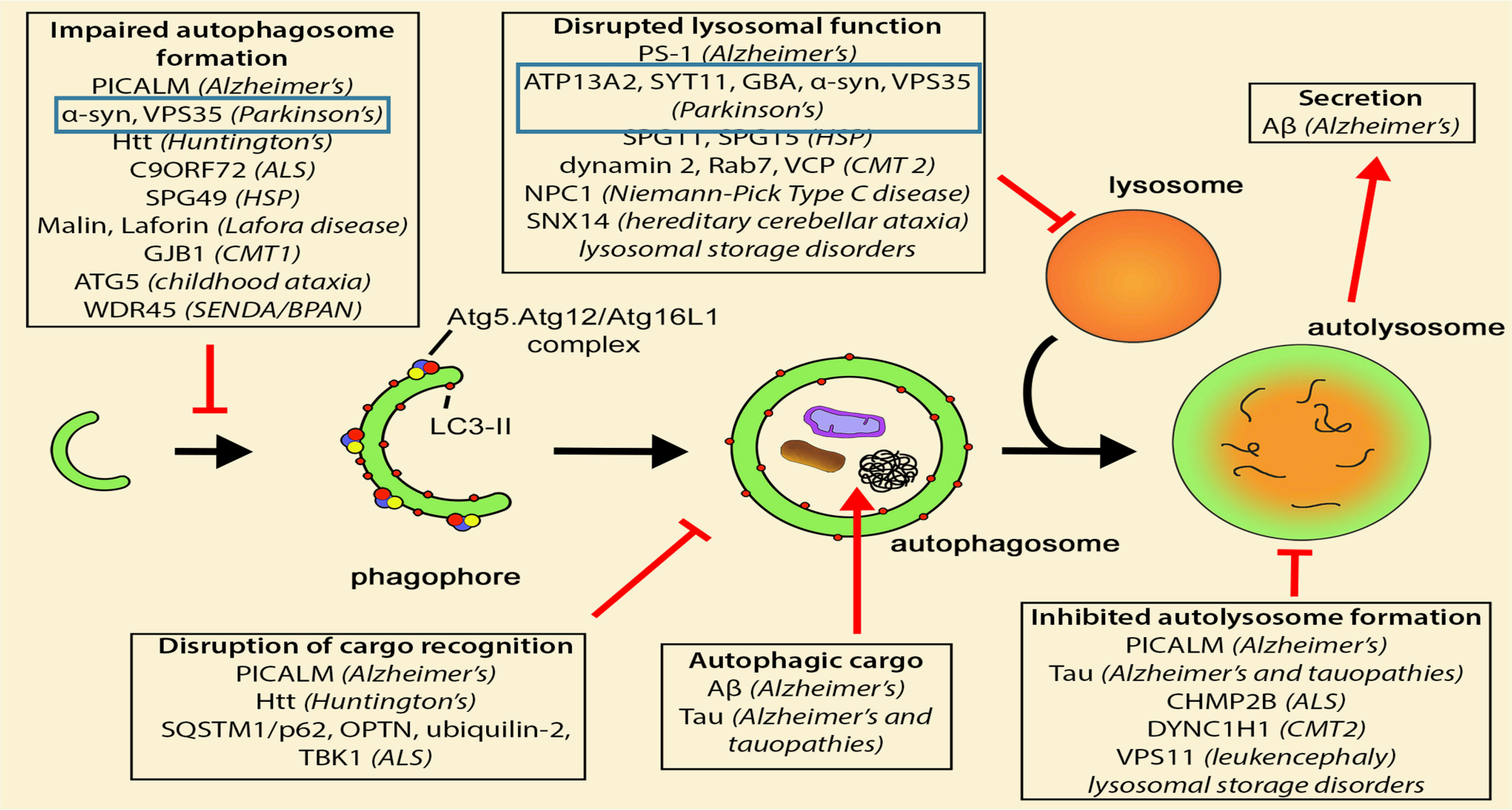
Defective autophagy may contribute to the accumulation of aggregated proteins in neurodegenerative diseases

Autophagy is a mechanism by which aggregated misfolded proteins and dysfunctional organelles are broken down and recycled into nutrients in cells



Menzies et al. *Neuron*, 2017

Mutations in autophagy-related proteins are found in multiple neurodegenerative diseases



Menzies et al. *Neuron*, 2017

TORC1 inhibition stimulates autophagy in preclinical models and therefore may have benefit in Parkinson's disease

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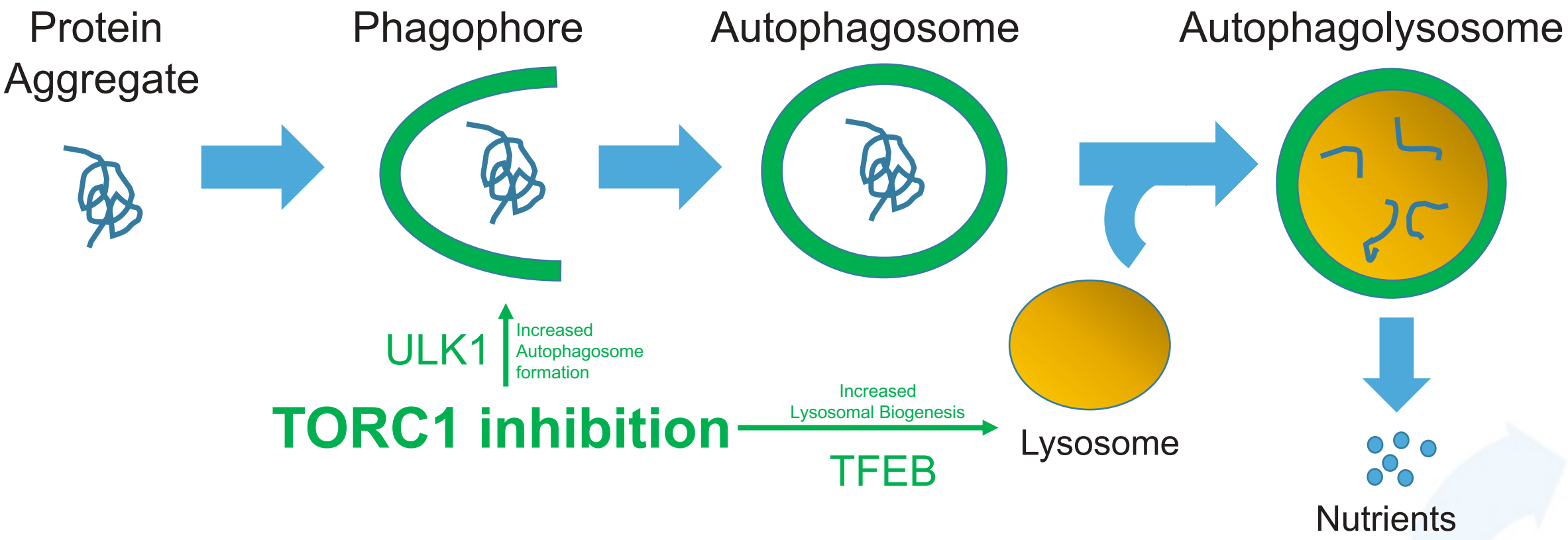
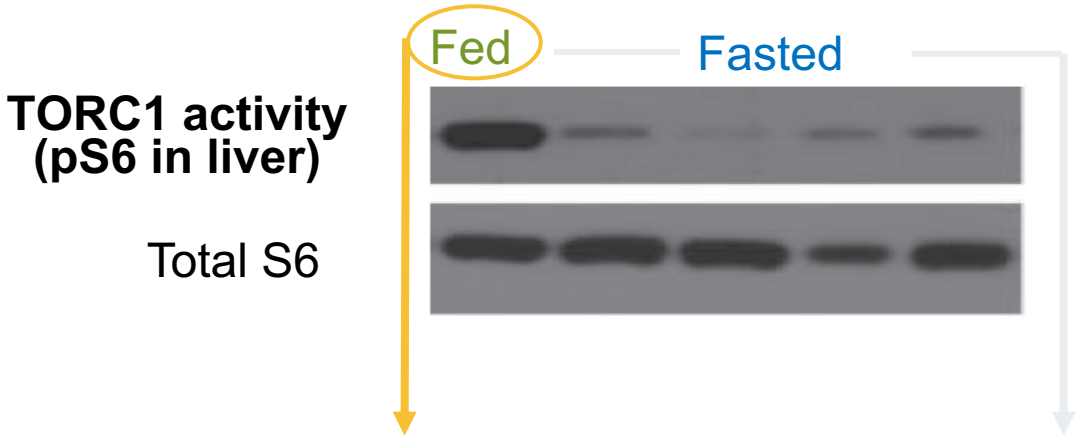


Menzies et al. *Neuron*, 2017; Roczniak-Ferguson et al. *Sci Signal*, 2012; Nyfeler et al. *Molecular and Cellular Biology*, 2011

TORC1 may become dysregulated during aging and contribute to a decline in autophagy

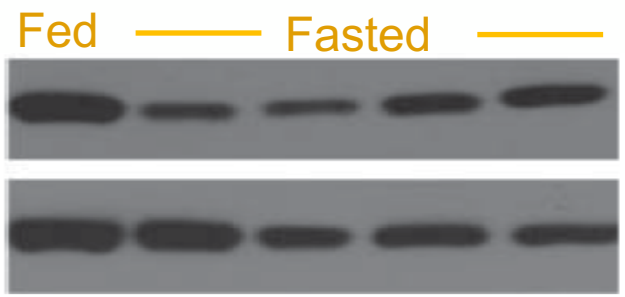
Young Mice



Feeding activates TORC1 leading to increased protein and lipid synthesis

In young mice, fasting inhibits TORC1 leading to upregulation of autophagy

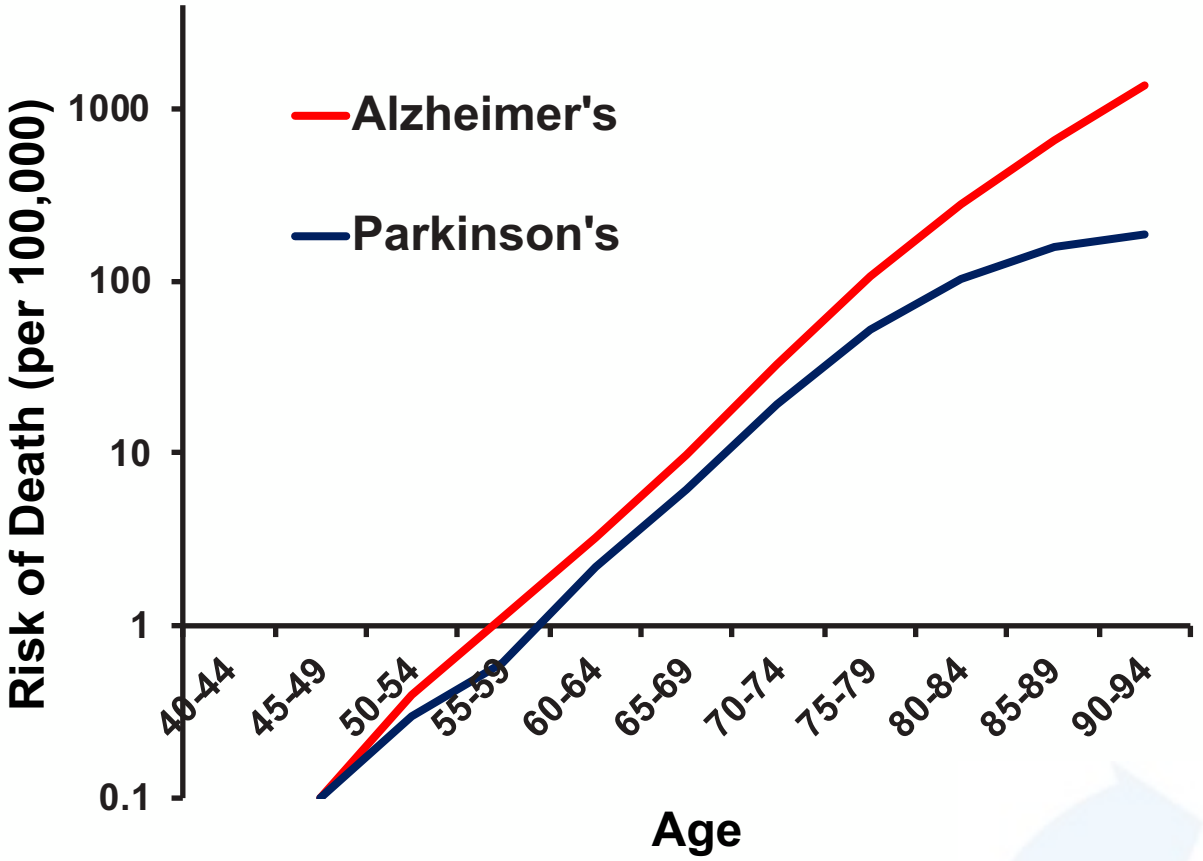
Old Mice



In old mice, TORC1 activity remained aberrantly elevated during fasting, **preventing upregulation** of autophagy

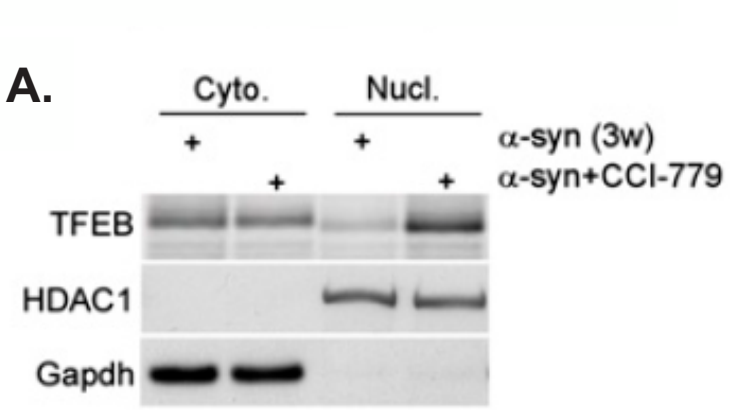
Sengupta et al. *Nature*, 2010

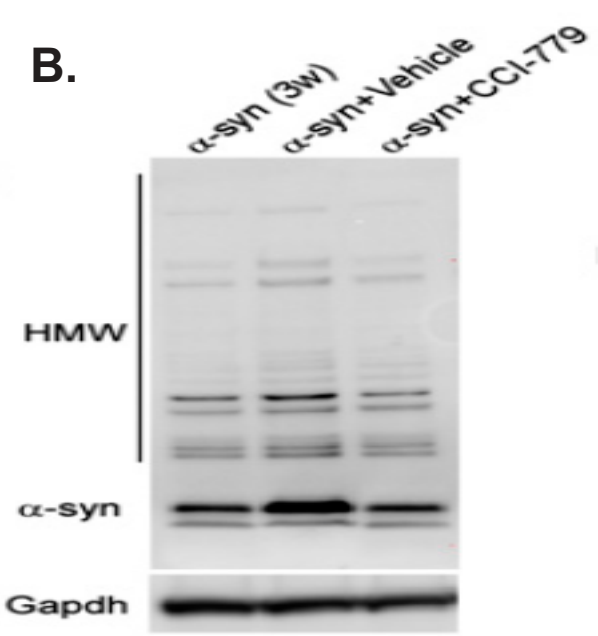
Age is the greatest risk factor for neurodegenerative disease

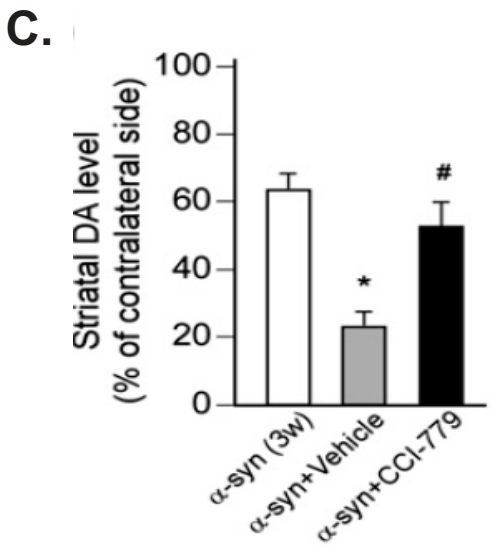


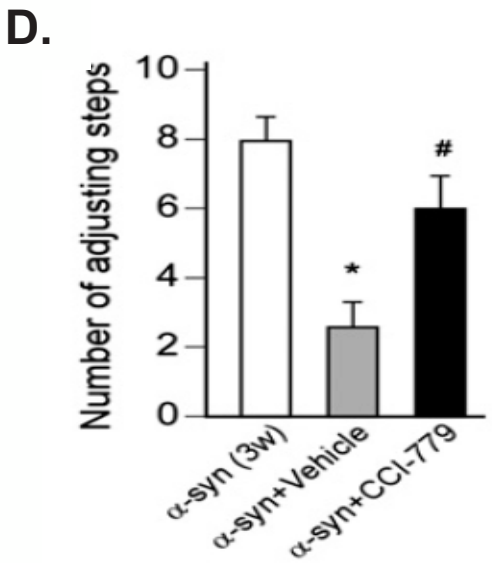
Intermittent TORC1 inhibition is disease-modifying in a PD rat model

Increased TFEB activation → **Clearance of toxic a-syn aggregates** → **Improved Neuronal Survival** → **Improved Motor Performance**









*p < 0.05 compared with the 3-wk α-syn group
#p < 0.05 compared with α-syn+vehicle group

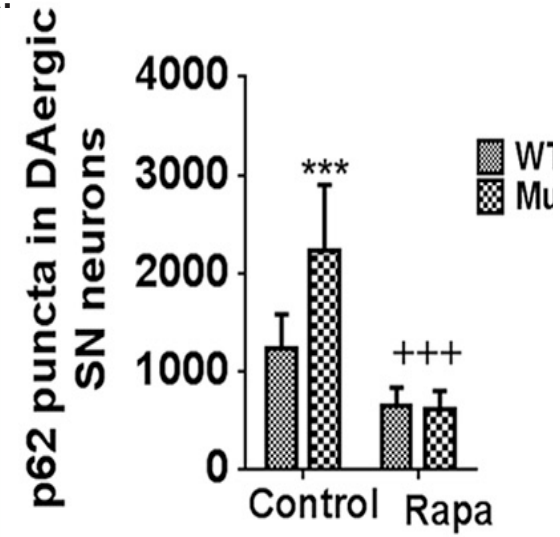
In an adeno-associated virus rat PD model that overexpresses a-syn in the substantia nigra, the TORC1 inhibitor CCI-779 started 3 weeks after adenoviral delivery (3w) and given every other day for 5 weeks was shown **(A)** to correct impaired TFEB function (as reflected by increased TFEB nuclear translocation), **(B)** decreased striatal a-syn levels (both monomeric and high molecular weight (HMW) aggregates), **(C)** increased dopaminergic neuron survival and **(D)** improved motor function.

Decressac et al. *PNAS*, 2013

TORC1 inhibition is disease modifying in a mouse model of PD

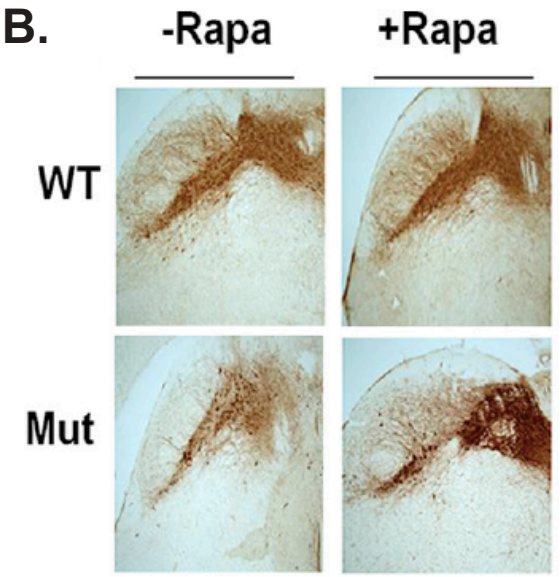
Increased Autophagy → **Improved Neuronal Survival** → **Improved Motor Performance**

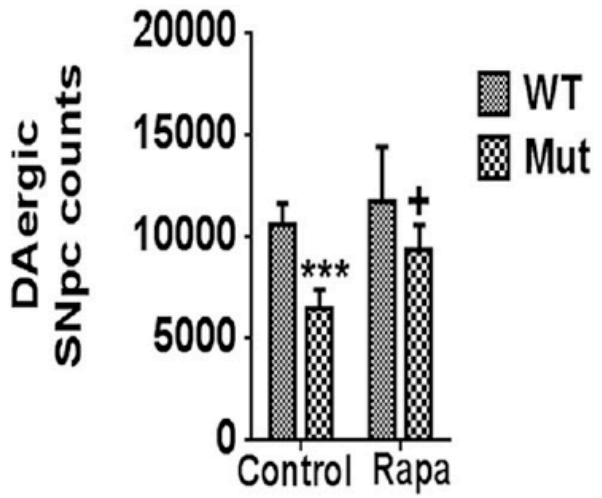
A.



*** p< 0.001 vs WT, +++p< 0.001 vs Mut

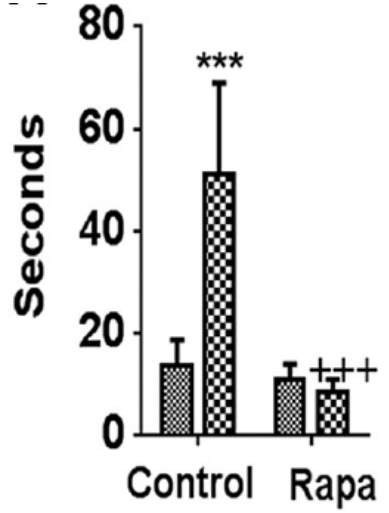
B.





***p<0.001 vs WT,+p<0.05 vs Mut

C.

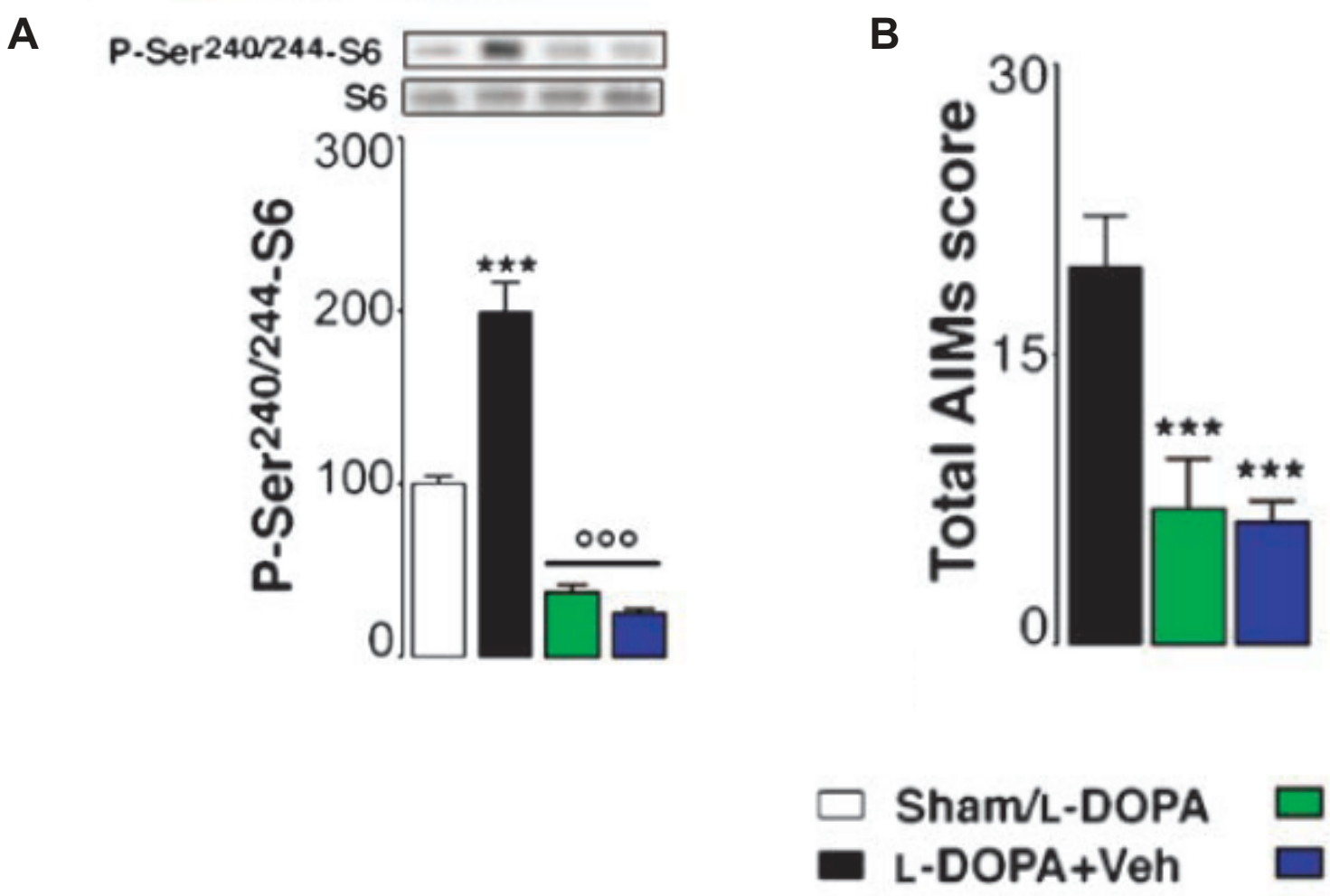


*** p< 0.001 vs WT, +++p< 0.001 vs Mut

In the mutant parkin Q311X mouse model of PD, the TORC1 inhibitor rapamycin **(A)** increased autophagy in dopaminergic neurons (as evidenced by decreased p62 levels), **(B)** increased the number of dopaminergic neurons (as assessed by tyrosine hydroxylase staining) in the substantia nigra, and **(C)** improved motor coordination as assessed by time to turn downward during a pole test.

Siddiqui et al. *J. Neurosci*. 2015

TORC1 inhibition also ameliorates levodopa-induced dyskinesia in preclinical PD models



A: Administration of levodopa in a mouse model of PD (unilateral 6-OHDA lesion) activated TORC1 selectively in medium spiny neurons and led to the development of dyskinesia.

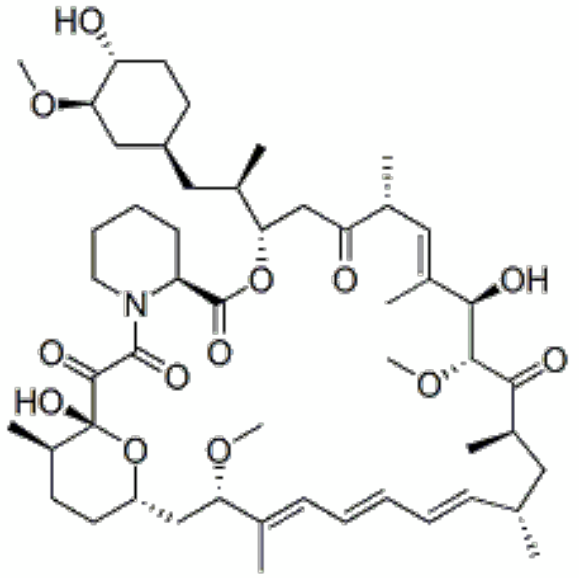
B: Rapamycin inhibited TORC1 activation and ameliorates dyskinesia, as assessed by an abnormal involuntary movement score (AIMs), determined by an observer blind to treatment assignment. Rap2 = rapamycin 2 mg/kg and Rap5= rapamycin 5 mg/kg. ooo,*** P<0.001 versus untreated control.

Santini et al. *Sci Signaling*, 2009

TORC1 inhibitors under evaluation in a Phase 1b/2a trial in Parkinson's disease

sirolimus (rapamycin):

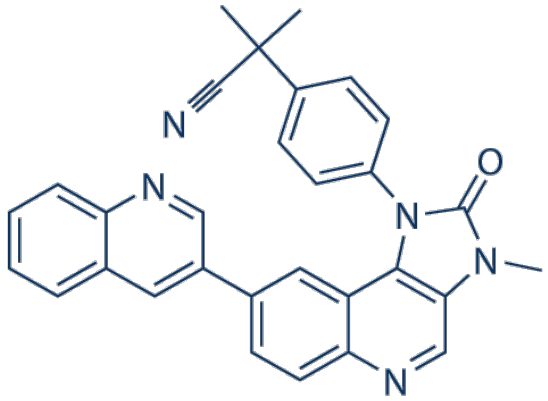
- Allosteric inhibitor of TORC1
- Partial TORC1 inhibitor that does not consistently induce autophagy or activate TFEB in all cell types
- Approved for use in humans



sirolimus
(rapamycin)

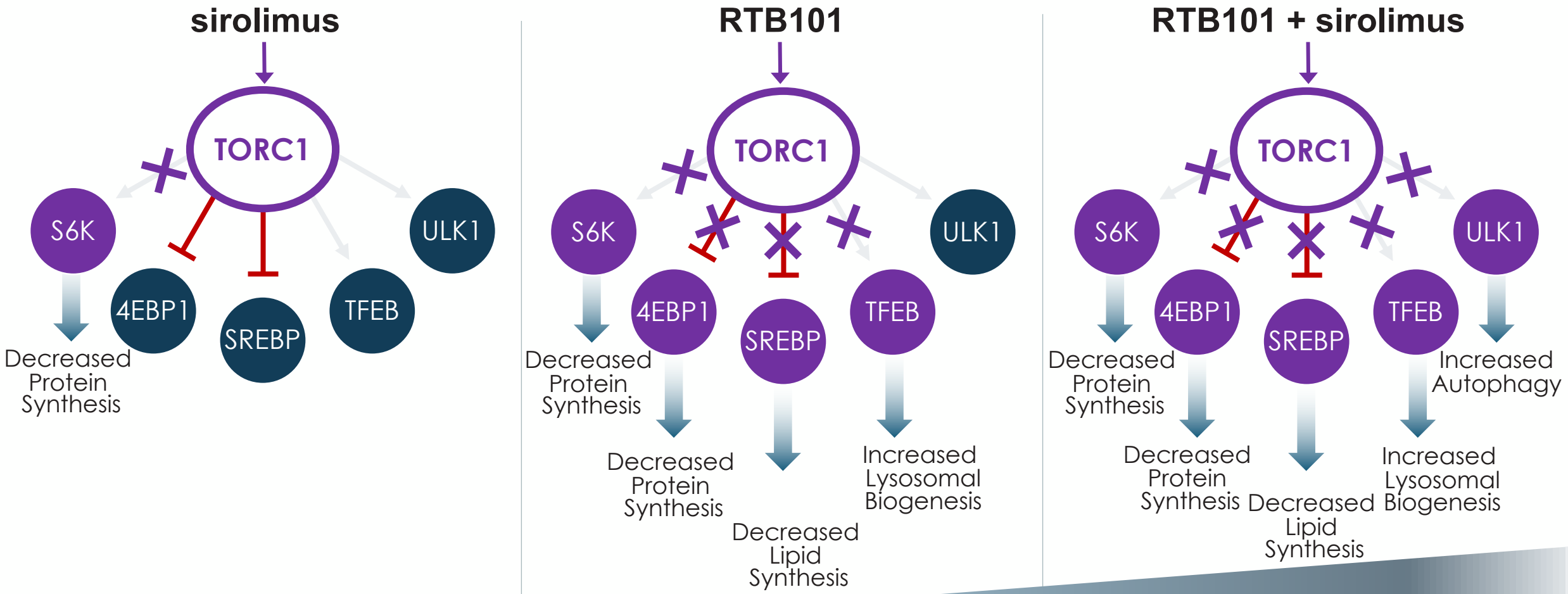
RTB101:

- ATP competitive catalytic site inhibitor of mTOR protein kinase
- Inhibits phosphorylation of more targets downstream of TORC1 than sirolimus-like drugs and consistently induces autophagy in all cell types tested
- Crosses the blood brain barrier in animal models
- Tested in >1,000 humans
- Human maximum tolerated dose: 1,200 mg/day



RTB101

Potential spectrum of TORC1 inhibition with RTB101 and sirolimus



Inhibits the phosphorylation of more targets downstream of TORC1

Nyfeler et al. *Molecular and Cellular Biology*, 2011; Nyfeler et al. *PLoS ONE,* 2012; Eid et al. *PNAS*, 2017; Roczniak-Ferguson et al. *Sci Signal*, 2012

RTB101 and sirolimus synergize to induce autophagy in neuronal cells

	Total	Free (5%)	>80% Maximal Induction of Autophagy									
RTB101 (nM)	87.50	4.38	130.58	114.37	156.80	170.61	173.28	181.56	196.15	174.61	158.67	216.07
	43.75	2.19	91.48	71.47	123.06	118.25	166.88	154.73	189.63	194.12	190.70	214.89
	21.88	1.09	31.89	25.16	81.50	100.98	125.12	137.82	212.58	197.37	166.87	218.33
	10.94	0.55	0.02	4.25	29.25	41.45	88.97	138.95	155.32	184.65	146.93	179.15
	5.47	0.27	-12.14	-14.12	-1.11	8.36	44.22	81.09	103.23	143.72	120.56	123.57
	2.73	0.14	-12.10	-6.71	-0.19	-1.19	25.53	43.99	75.14	96.76	73.48	100.10
	1.37	0.07	-7.40	-17.37	0.03	0.09	13.03	29.69	41.98	54.65	60.23	68.35
	0.68	0.03	-23.25	-25.36	3.41	-2.42	5.87	16.31	26.84	52.55	33.51	31.80
	0.34	0.02	-16.81	-28.70	-7.67	-5.83	5.18	14.95	9.42	33.10	21.35	43.68
	0	0	-11.63	-20.72	-6.80	-6.46	-1.54	9.74	2.82	13.34	10.25	-4.02
	Free (2.5%)		0	0.000053	0.000214	0.000854	0.003418	0.013672	0.054688	0.218750	0.875000	3.5
		Total	0	0.002136	0.008545	0.034180	0.136719	0.546875	2.187500	8.75	35.00	140.00
			sirolimus (nM)									

resTORbio Phase 1b/2a Parkinson's disease trial

Design	**Randomized, Placebo-Controlled Phase 1b/2a Study (4-week dosing)** • Mild-moderate PD patients (mH&Y I-III) • On standard of care PD drugs • Once weekly dosing
Study Size	N=45 (2:1 randomization)
Key Endpoints	**Primary endpoint:** • Safety and tolerability **Secondary endpoint:** • Exposure in blood, plasma and CSF **Exploratory endpoints:** • Biomarkers in plasma and CSF • Clinical assessments, wearables

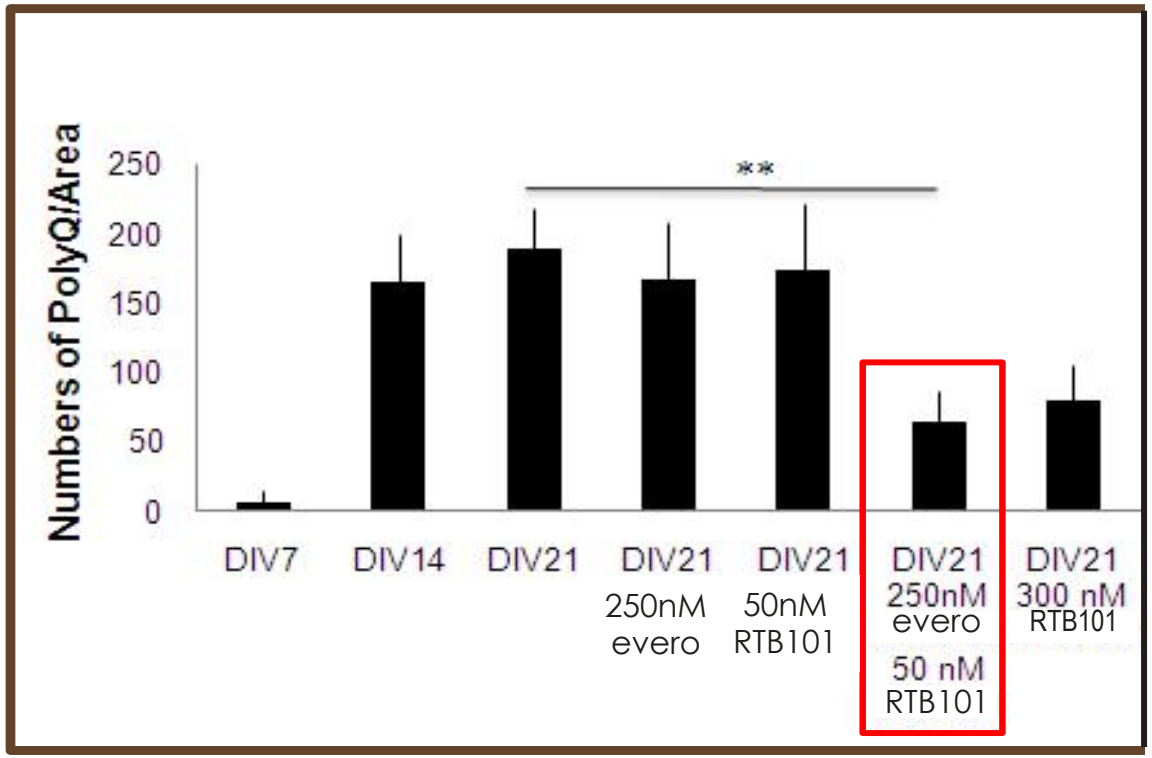
Cohort	RTB 101 dose (mg)	sirolimus dose (mg)
1	300	0
2	0	2
3	300	2
4	300	4
5	300	6

or matching placebo

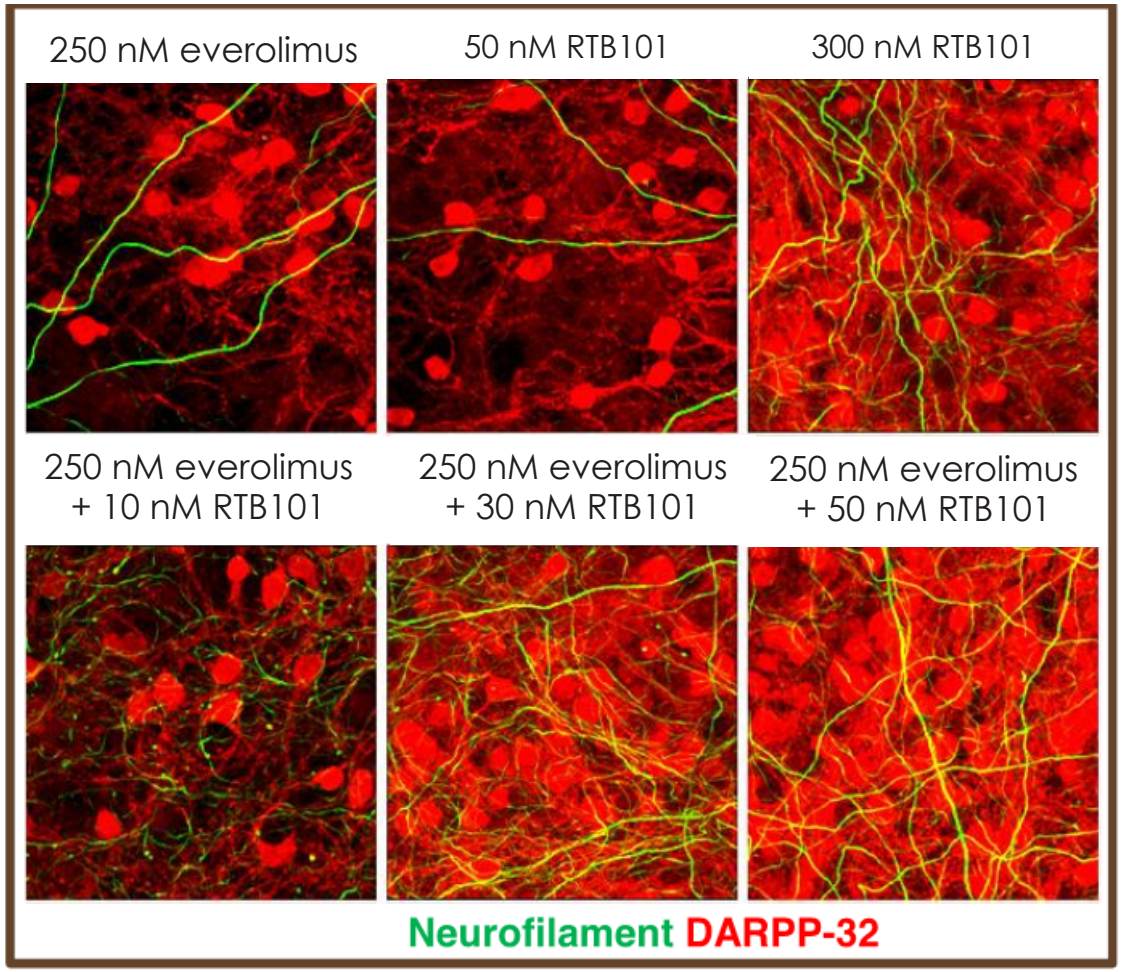
- **Study initiated in 1Q19**
- **Data expected by mid-2020**

The combination of RTB101 and a rapalog may have potential benefit in other neurodegenerative diseases including Huntington's disease

Aggregated mHtt protein levels in cultured cortico-striatal slices from R6/2 Huntington's disease mouse.



Drug concentrations in the figures are total concentrations



Neurofilament is a marker of axons

DARPP-32 is a marker of cell soma

Source: Novartis Data on file

Parkinson's Disease

Prevalence

- Second most common neurodegenerative disease
- Affects 1% of population over 55 years of age

Pathology

- Characterized by loss of >50% of the neurons that produce the neurotransmitter dopamine in a specific area of the brain (substantia nigra)

Clinical manifestations

- Four cardinal motor symptoms:
  - Resting tremor
  - Bradykinesia (slowed movement)
  - Muscle rigidity
  - Postoral instability

Current therapies treat symptoms of PD but do not alter disease progression

- Levodopa is used to treat PD; however, its effect tends to wear off over time and can lead to levodopa-induced dyskinesia

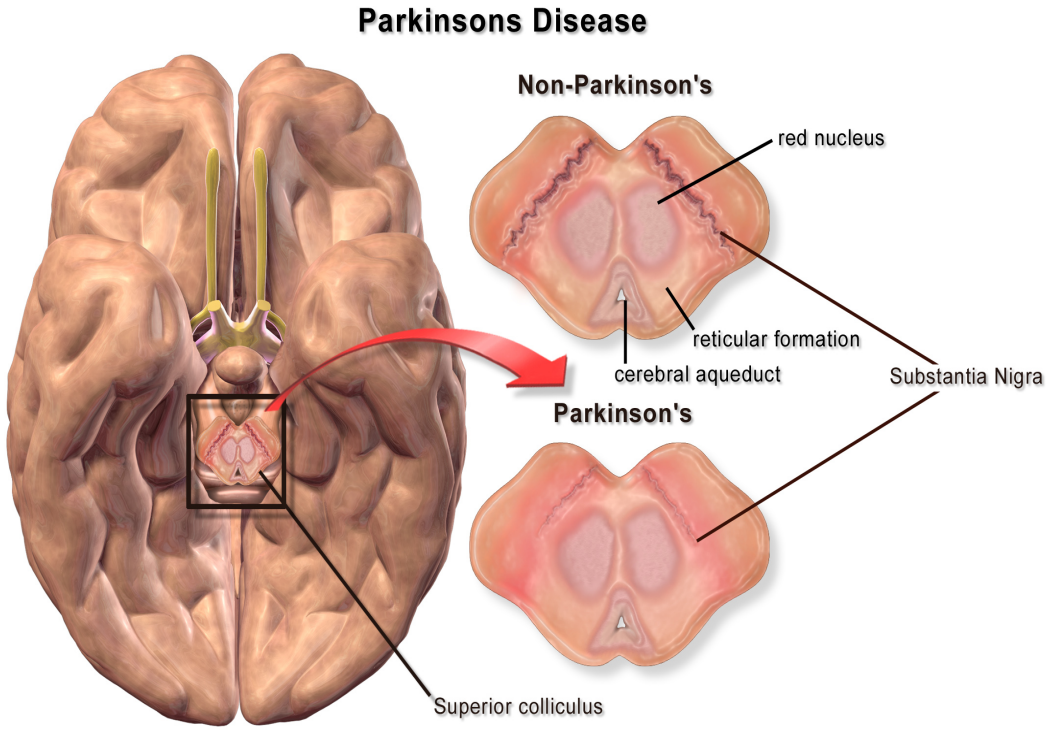


Image from Wikiwand

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