IkT-148009 As A Potential Disease-Modifying Therapy in Parkinson's Disease

Poster 789

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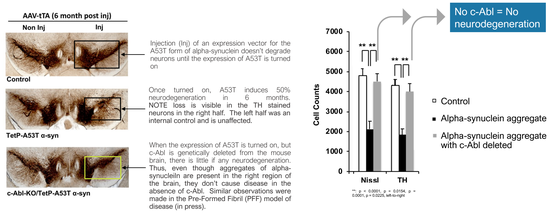
ABSTRACT

Modeling Parkinson's disease in mice suggests c-Abl activation is required for PD initiation and progression, and therefore inhibition of c-Abl could be a strategy for disease-modification of Parkinson's (1). PD pathology is characterized by the accumulation of misfolded alpha-synuclein. Animal models of PD demonstrate that internalization of misfolded alpha-synuclein activates c-Abl which phosphorylates alpha-synuclein and promotes alpha-synuclein pathology within the affected neurons. Additionally, c-Abl inactivates parkin, disrupting mitochondrial quality control and biogenesis, promoting neurodegeneration. Models of inherited or sporadic PD dependent on alpha-synuclein were used to evaluate therapeutic potential of the c-Abl inhibitor IkT-148009. These studies were followed by clinical assessment of the safety, tolerability and pharmacokinetics in older healthy human subjects and the assessment of the safety, tolerability, pharmacokinetics and therapeutic benefit of IkT-148009 in Parkinson's patients. IkT-148009 once daily protected neurons, restored function, reduced pathological alpha-synuclein and suppressed markers of neuroinflammation in models. Daily oral administration in older and elderly healthy volunteers (N=88) between 12.5 mg and 325 mg for up to seven days was well-tolerated and exhibited linear dose proportionality, high systemic exposure, penetration into the CNS and only 3 adverse events which were not clinically significant. The safety and tolerability profile of IkT-148009 in healthy subjects was consistent with chronic toxicology studies in rat and monkey. PD patients with mild to moderate disease (Hoehn & Yahr < 3.0) displayed a similar profile of safety and tolerability. Measures of motor and non-motor features of disease displayed trends, but conclusions as to clinical benefit cannot be drawn from 7-day dosing. Orally administered IkT-148009 is a mechanistically-defined interventional therapy and a possible disease-modifying treatment. These outcomes support further clinical evaluation of IkT-148009 for potential efficacy as a treatment or disease-modifying therapy (ongoing under NCT05424276).

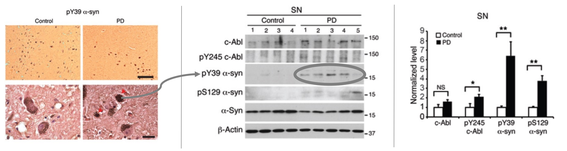
[1]Werner MH and Olanow CW (2022) Mov. Disorders 37(1):6-15.

The Abelson Tyrosine Kinase c-Abl is Essential for Disease Initiation and Progression



Full details in Brain 142:2380ff (2019)

c-Abl Phosphorylates Alpha-synuclein Aggregates at Tyr[39] (pY39) as seen in Post-Mortem Patient Brain



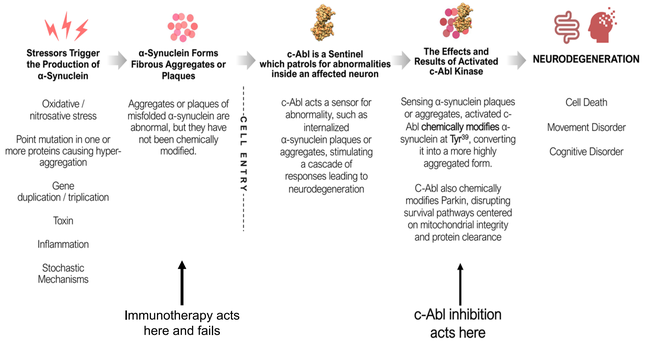
Full details in J Clin Invest. **126**, 2970-88 (2016)

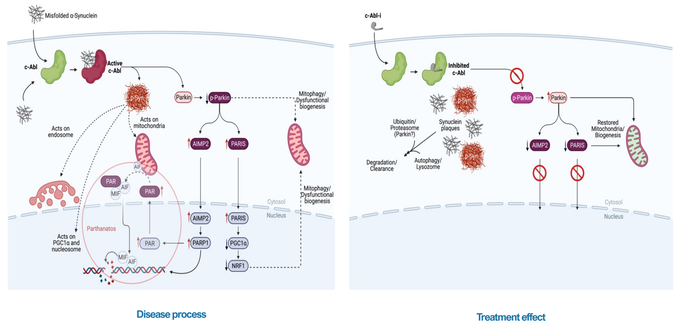
Conclusion:

c-Abl is essential for disease initiation and progression.

Proc Natl Acad Sci U S A 107:16691ff (2010)
J Clin Invest. 126:2970ff (2016)
Science 353:aah3374 (2016)
Brain 142:2380ff (2019)
Mov. Disorders 37:6-15 (2022)

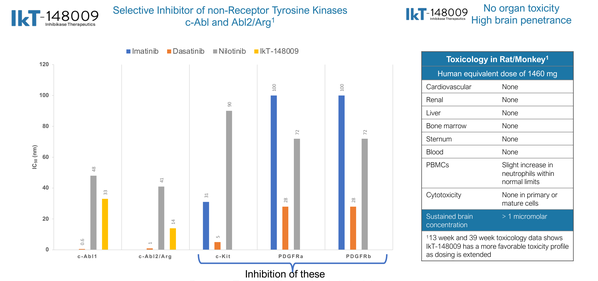
THE PROCESS OF NEURODEGENERATION





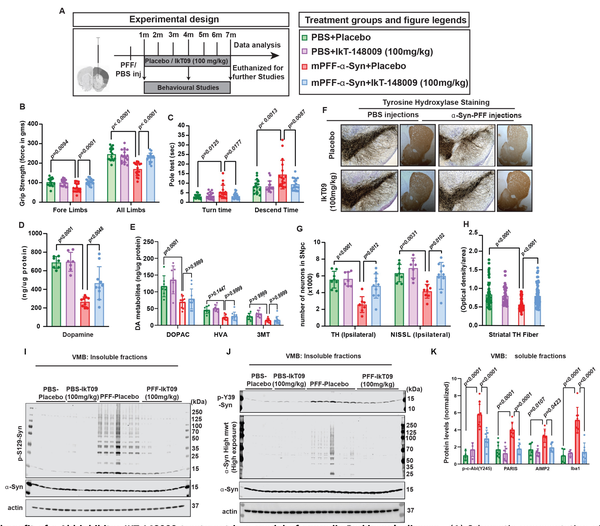
C-Abl phosphorylation of internalized alpha-synuclein aggregates and of parkin has profound effects on neuronal physiology and homeostasis. We have come to believe that while alpha-synuclein aggregate formation is necessary for Parkinson's disease initiation and progression, it is not sufficient to cause disease on its own. Rather, internalization of aggregates by the affected neurons results in c-Abl activation and all the downstream processes of neuronal dysfunction/degeneration arise from internal processes, at least in early phases of disease. By contrast, c-Abl inhibition not only shuts down processes driving dysfunction/degeneration, c-Abl inhibition also restores clearance processes capable of reducing or clearing pathological alpha-synuclein from the affected neurons.

IkT-148009 IS A SELECTIVE NON-RECEPTOR C-ABL INHIBITOR THAT THERAPEUTICALLY SUPPRESSES NEURODEGENERATION IN A MODEL OF SPORADIC PD



Toxicology in Rat/Monkey[1]	
Human equivalent dose of 1460 mg	
Cardiovascular	None
Renal	None
Liver	None
Bone marrow	None
Sternum	None
Blood	None
PBMCs	Slight increase in neutrophils within normal limits
Cytotoxicity	None in primary or mature cells
Sustained brain concentration	> 1 micromolar

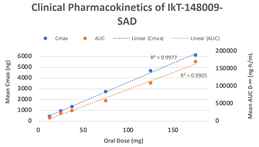
[1]13 week and 39 week toxicology data shows IkT-148009 has a more favorable toxicity profile as dosing is extended



Therapeutic benefit of c-Abl inhibitor IkT-148009 treatment in a model of sporadic Parkinson's disease. (**A**) Schematic representation of the experiment. Stereotaxic PFF injection occurred 4 weeks prior to initiation of oral daily therapy with IkT-148009 at 100 mg/kg/day. Behavioral assessments were performed 12 weeks and 24 weeks after initiation of dosing (**B**) measuring forelimb and all limb grip strength, (**C**) turning and decent time (sec) in the pole test. (**D-E**) Neurochemical measurement of dopamine and metabolism levels by employing HPLC-ECD. (**F-H**) Representative TH and NISSL immunostaining of midbrain sections from the SNpc of PBS-injected or PFF-injected mice. Quantitation of neural counts and striatal fiber density suggests preservation of > 80% of normal neural anatomy in the SNpc. Behavioral test (n=15-18mice/groups), HPLC (n=7-10 mice/groups), and histology (n=7-10 mice/groups). Error bar represents the mean ± SEM. One-or Two-way ANOVA was used to test significant and followed with post-hoc Bonferroni's multiple comparisons test. Respective p values were denoted in the figures and comparison between control versus different treatment groups. (**I-J**)) Higher order aggregates of pathological a-synuclein accompanies functional recovery as measured by both phosphorylated Tyr[39] and Ser[129] a-synuclein antibodies. (**K**) Reduction of pathological aggregates occurs concomitantly with suppression of c-Abl activation assessed by downregulation of phosphorylated Tyr[245] c-Abl. Downregulation of activated c-Abl and reduction of pathological aggregates occurs with suppression of PARIS and AIMP2 levels and reduction in IBA1 microglial activation. Error bar represents the mean ± SEM. One-or Two-way ANOVA was used to test significance, followed with post-hoc Bonferroni's multiple comparisons test.

IkT-148009 CLINICAL DEVELOPMENT PHASE1/1B (NCT04350177)

Category	Demographic	Healthy Subjects Value (% of Total N=88)	Parkinson Patient Value (% of Total, N=13)
Gender	Female	34 (38.6)	6 (42.8)
	Male	54 (61.4)	7 (57.2)
Age	Average (SD)	57.9 (5.72)	62.5
	Median	58.0	62
	Range	45, 69	57, 70
Ethnicity	Hispanic or Latino	13 (14.8)	3 (23.1)
	Not Hispanic or Latino	75 (85.2)	10 (76.9)
Race	Black or African American	54 (61.4)	2 (15.4)
	White	33 (37.5)	11 (84.6)
	Other	1 (1.1)	0 (0)
Adverse events		7 (7.9), all clinically insignificant	5 (38.5), only 2 possibly drug related and clinically insignificant



Complete Adverse Event Listing for Phase 1/1b trial with IkT-148009					
Category	Active or Placebo	SAD or MAD[1] (Dose mg)	# Occurrences Healthy Subjects (N=88)	# Occurrences PD Patient (N=14)	Grade[2]
Cardiovascular (Palpitations)[3]	Active	SAD (75)	1		1
Common cold	Placebo	MAD (25)	1		0
Lower Leg Edema[4]	Active	MAD (25)	1		1
Dermatitis	Active	MAD (50)		1	1
Pneumonia	Active	MAD (50)		1	1
Intermittent vaginal bleed[4]	Placebo	SAD (175)	1		1
Sporal Headache[3]	Active	MAD (50)		1	0
Orthostatic Hypotension	Placebo	MAD (100)		1	1
Diarrhea	Active	SAD (325)	2		1
Constipation (1 day after Day 7 dose)	Active	MAD (100)		1	1

[1]SAD = single dose, MAD = Single daily dose for 7 days; [2]Using Common Terminology Criteria for Adverse Events (CTCAE) version 5.0; [3]From CSF collection; [4]Present on admission pre-dose, continued during dosing; [4]appeared 28 days after last dose; [4]Appeared 2 weeks post-dose, no clinical basis found even after following by 3-day Holter monitoring.

Phase 1b Parkinson's Assessments

		IkT-148009 (N=6)		Placebo (N=2)	
Parameter	Dose (mg)	Pre-dose	Day 7 Dose	Pre-dose	Day 7 Dose
UPDRS I	50	7.8 ± 2.0	9.2 ± 5.0	8.5 ± 6.4	4 ± 4.2
UPDRS II		11.2 ± 5.0	10.2 ± 5.8	15 ± 8.5	4 ± 4.2
UPDRS III		28.2 ± 9.6	34.3 ± 10.2	46.5 ± 20.5	44.5 ± 20.5
NMSS		36.5 ± 23.5	28.3 ± 19.5	46.5 ± 51.6	26 ± 26.9
PDQ-39		18.5 ± 11.1	17.5 ± 8.2	26 ± 36.1	26.6 ± 37.6
PGI-S		2.2 ± 0.8	2.2 ± 0.8	2.5 ± 0.7	2

		IkT-148009 (N=5)		Placebo (N=1)	
Parameter	Dose (mg)	Pre-dose	Day 7 Dose	Pre-dose	Day 7 Dose
UPDRS I	100	5.4 ± 3.5	4.8 ± 3.6	10	9
UPDRS II		8.4 ± 3.9	8.2 ± 4.9	3	4
UPDRS III		41.0 ± 18.3	48.4 ± 20	27	24
NMSS		18.4 ± 16.1	15.2 ± 9.5	41	30
PDQ-39		12.4 ± 5.1	14.9 ± 14.1	1.3	0
PGI-S		2.0 ± 0.7	2.4 ± 0.5	1	1

Patients were enrolled ages 45 to 70 with mild to moderate disease defined as Hoehn & Yahr < 3.0. No PD-related medications were withdrawn, but PD assessments were made in the practically-defined off-state. Thus, on each assessment day, PD medications were withheld at midnight and PD assessments made the following morning prior to dosing on Day 1. PD-related medications were resumed after assessments were completed on Pre-dose (baseline) Day 1, continued on days 2 through 6 and then were withdrawn again at midnight prior to PD assessments performed on the seventh dosing day.

Conclusions

Using alpha-synuclein-dependent, slowly progressive disease models of inherited or sporadic PD, we have shown that c–Abl is essential to PD initiation and progression, that c-Abl activation occurs in the human disease. Our studies suggest that that the role of synuclein aggregates is to activate c-Abl, which in turn activates the the downstream processes of neurodegeneration that have been characterized in a series of publications referenced herein. Building on that information, **IkT-148009** was taken into the clinic. IkT-148009 is a selective, brain penetrant c-Abl inhibitor that is highly effective at halting disease progression and rescuing function in animal models of disease. In clinical studies of elderly healthy volunteers (N=88) or in mild-to-moderate PD patients (N=13), IkT-148009 induced no clinically significant side effects, no organ specific side effects and was linearly dose proportional over a wide range of oral doses given once daily. PD assessments in the practically-defined off state in a small number of PD patients demonstrated that IkT-148009 does not worsen disease, but we cannot conclude anything about potential benefit from a short-duration dosing study in a small number of patients. IkT-148009 has begun a Phase 2, 3-month dosing study under NCT05424276.