Treatment with IPL344, an Akt activator, improves neuro-muscular function in SOD1G93A ALS model mice

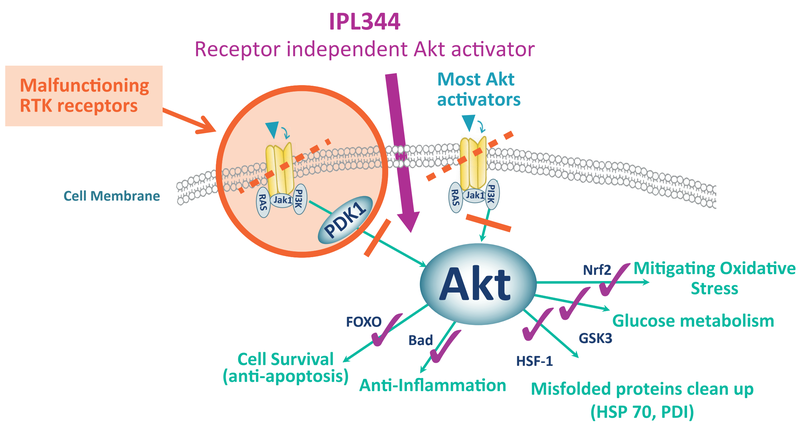
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Background

- The progression of amyotrophic lateral sclerosis (ALS) is characterized by damage to cell-membrane receptors and impaired external signaling.[1] Hence, effective treatments are likely to be independent of membrane receptors.
- The PI3K (Phosphoinositide 3-Kinases)-Akt pathway is an intracellular signal transduction pathway that promotes cell survival and growth. Dysfunction of the Akt signaling pathway is common to many age-related neurodegenerative diseases, including ALS where it is downregulated in motor neurons and skeletal muscles (**Figure**).[1-3]
- Akt activation prevents neurodegeneration and apoptosis, regulates glycogen metabolism and reduces inflammation, oxidative stress, and protein misfolding and aggregation. It reduces endoplasmic reticulum (ER) stress and the unfolded protein response (UPR), which are major drivers of ALS and neurodegenerative diseases in general.[4]
- The SOD1G93A mouse model of ALS is genetic, but the model features ER stress, UPR, and other disease characteristics.[5-8] Thus, the mouse model is suitable for assessing ALS treatments that affect ER stress and related disease drivers.
- IPL344 is a hepta-peptide shown to activate Akt and inhibit apoptosis *in vitro*. IPL344 crosses cell membranes and bypasses the damaged cell-membrane receptors associated with ALS disease progression.[9]
- Here, we report that IPL344 administered therapeutically IV and IP to SOD1G93A transgenic mice at disease onset results in enhanced survival, arrested weight loss, and neurologic preservation (as measured by limb function).

Akt Activation targets the key pathologies that drive ALS

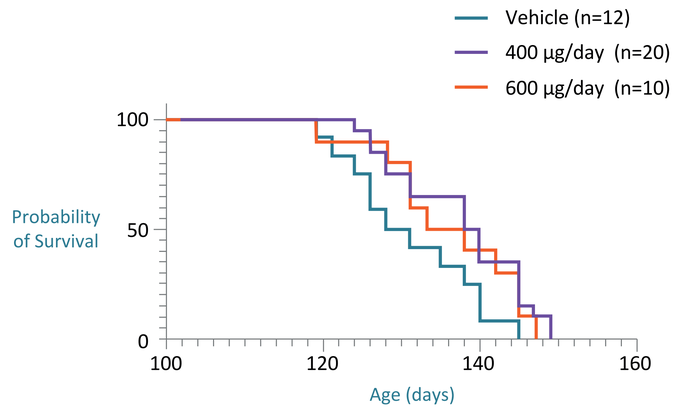


Methods

- The minimal therapeutic dose (≥200 µg/day) and optimal administration route (IV and IP) of IPL344 were first established in a preliminary study using the SOD1 G93A mouse model (Jackson Laboratory).
- In the concluding two experiments (Studies A and B), SOD1 G93A transgenic mice were treated with IPL344 given IV and IP or the control vehicle
  - Study A was a dose selection study in which age-matched female SOD1 G93A transgenic mice were treated with vehicle (N=12), IPL344 400 µg/day (N=20), or IPL344 600 µg/day (N=10).
  - In Study B, age- and sex- matched SOD1 G93A transgenic mice were treated with vehicle (N=21) or IPL344 400 µg/day (N=21).
- In line with current recommendations,[10, 11] treatment was initiated after disease onset as detected by weight loss. Treated and control mice were matched according to date of disease onset.
- Mice were observed and weighed 3 times a week. Disease progression was assessed by the neurologic scoring system (scale of 0-4) and death was determined according to humane criteria.[11]

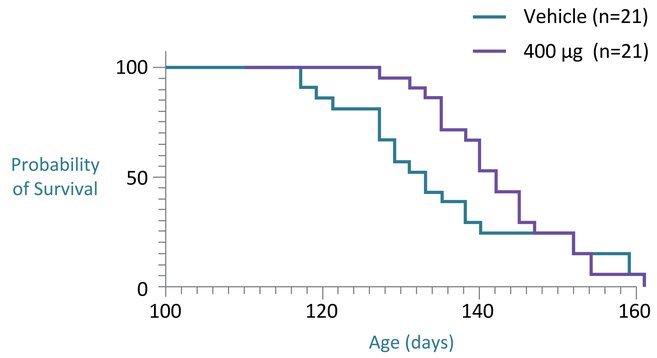
Results

Dose Selection Study A: Median survival was significantly extended in SOD1 mice treated with IPL344 from symptom onset compared with vehicle control (p=0.03)



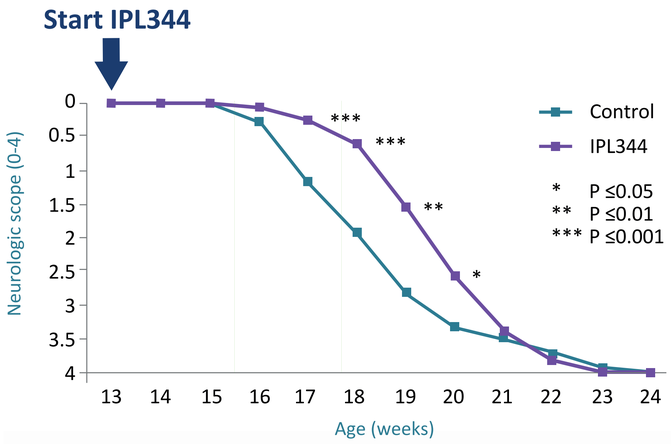
Kaplan-Meier curve of survival data in SOD1 mice treated with IPL344 daily injections (IP and IV) from symptoms onset (average mouse age of 88 days). IPL344 doses of 400 µg/day and 600 µg/day had a similar effect, with 400 µg/day extending median survival by 9.5 days compared to vehicle-treated animals (p=0.03)

Study B: Median survival was significantly extended by 9 days in SOD1 mice treated with IPL344 400 µg/day from symptom onset compared with vehicle control (p=0.02)



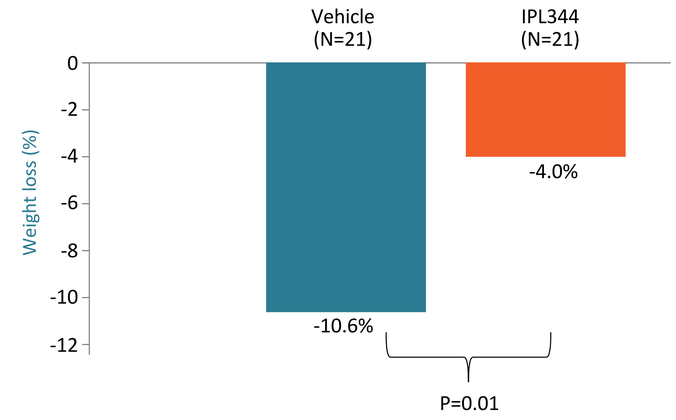
Kaplan-Meier curve of survival data in SOD1 mice treated with IPL344 daily injections from symptoms onset (average mouse age of 91 days). IPL344 400 µg/day (200 µg IP + 200 µg IV) extended median survival by 9 days compared to the vehicle-treated animals (p=0.02)

Study B. Treatment with IPL344 delayed neurologic deterioration (as assessed by the neurologic scoring system) compared to control treatment



IPL344 400 µg/day (200 µg IP + 200 µg IV) delayed disease deterioration as assessed by the neurologic scoring system (0-4 scale) in SOD1 mice treated with IPL344 daily injections from symptoms onset (average mouse age of 91 days). Between Days 107-119, mice treated with IPL344 400 µg/day showed a 12% loss of neurologic function compared with a 40% decline in vehicle-treated animals (p=0.001).

Study B. Treatment with IPL344 delayed disease deterioration (as assessed by weight loss) compared to control treatment



IPL344 400 µg/day (200 µg IP + 200 µg IV) delayed disease deterioration as assessed by weight loss in SOD1 mice treated with IPL344 daily injections from symptoms onset (average mouse age of 91 days). Between Days 114-125, mice treated with IPL344 400 µg/day showed a weight loss of 4.0% compared 10.6% in vehicle-treated animals (p=0.01).

Conclusions

- IPL344 treatment at disease onset significantly enhanced survival, arrested weight loss, and preserved neurologic function in the SOD1G93A mouse model of ALS.
- A Phase 1/2a clinical trial of IPL344 (administrated IV) in ALS patients is currently underway.
- The initial impression is that IPL344 treatment is generally safe, and shows signs of 49–67% slower disease progression in several outcome parameters.

References

1. Wu et al. Proc Natl Acad Sci U S A 2006;103(32):12132-12137. 2. Dewil et al. Neuropathol Appl Neurobiol 2007;33(5):499-509. 3. Léger et al. Faseb j 2006;20(3):583-585. 4. Ghemrawi et al. Int J Mol Sci 2020;21(17). 5. Kanekura et al. Mol Neurobiol 2009;39(2):81-89. 6. Nagata et al. Neurol Res 2007;29(8):767-771. 7. Nagano et al. Life Sci 2002;72(4-5):541-548. 8. Warita et al. Apoptosis 2001;6(5):345-352. 9. Herkel et al. Immunology 2017;151(4):474-480. 10. Ludolph et al. Amyotroph Lateral Scler 2010;11(1-2):38-45. 11. Scott et al. Amyotroph Lateral Scler 2008;9(1):4-15.

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