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Pre-Clinical Efficacy Round Up – Dec 2024

A summary of recent assays used to present positive Pre-Clinical Data in the Industry

- HGF/MET Signalling Driven Neuroprotection
- Topoisomerase Inhibition in NSCLC
- Mutant Huntingtin (mHTT) Level Drop
- sTREM2 Target Engagement in Alzheimer's
- LRRK2 inhibition in Parkinson's
- ITK Inhibition in Systemic Sclerosis
- THR-β agonist in NASH
- TUSC2 Modulated Reduction in T reg

Including Relevant Methods in Zebrafish Models

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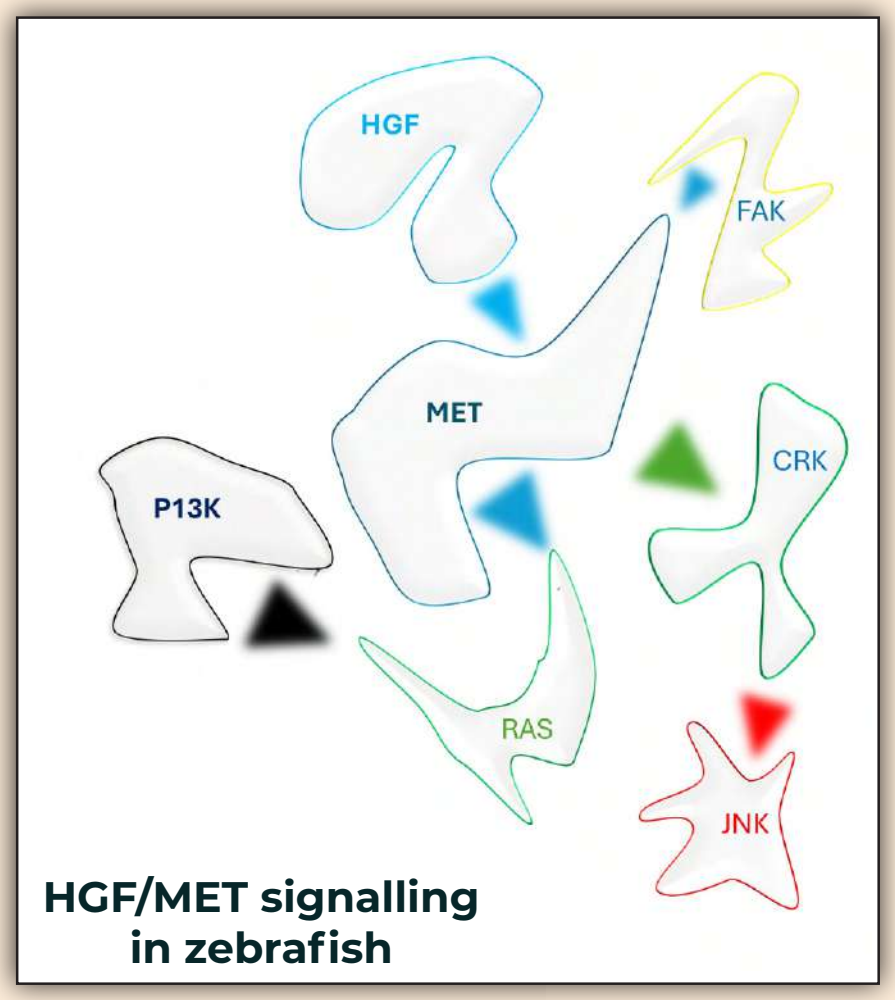
HGF/MET Signalling Driven Neuroprotection



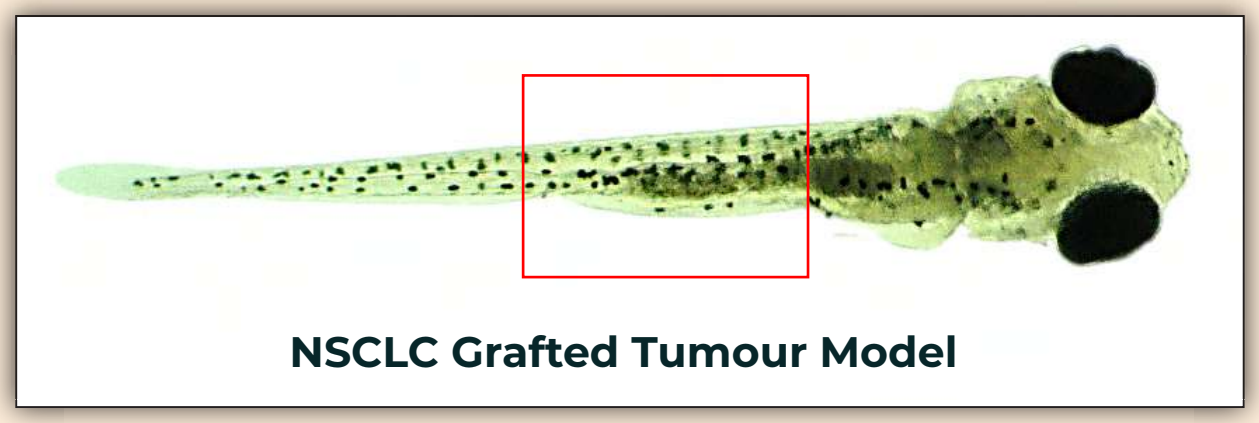
HGF/MET signalling in zebrafish

HGF signalling through MET pathway can counteract oxidative stress driven neurodegeneration and overall neuroinflammation, with enhancements in neuroprotection and cognitive effects.

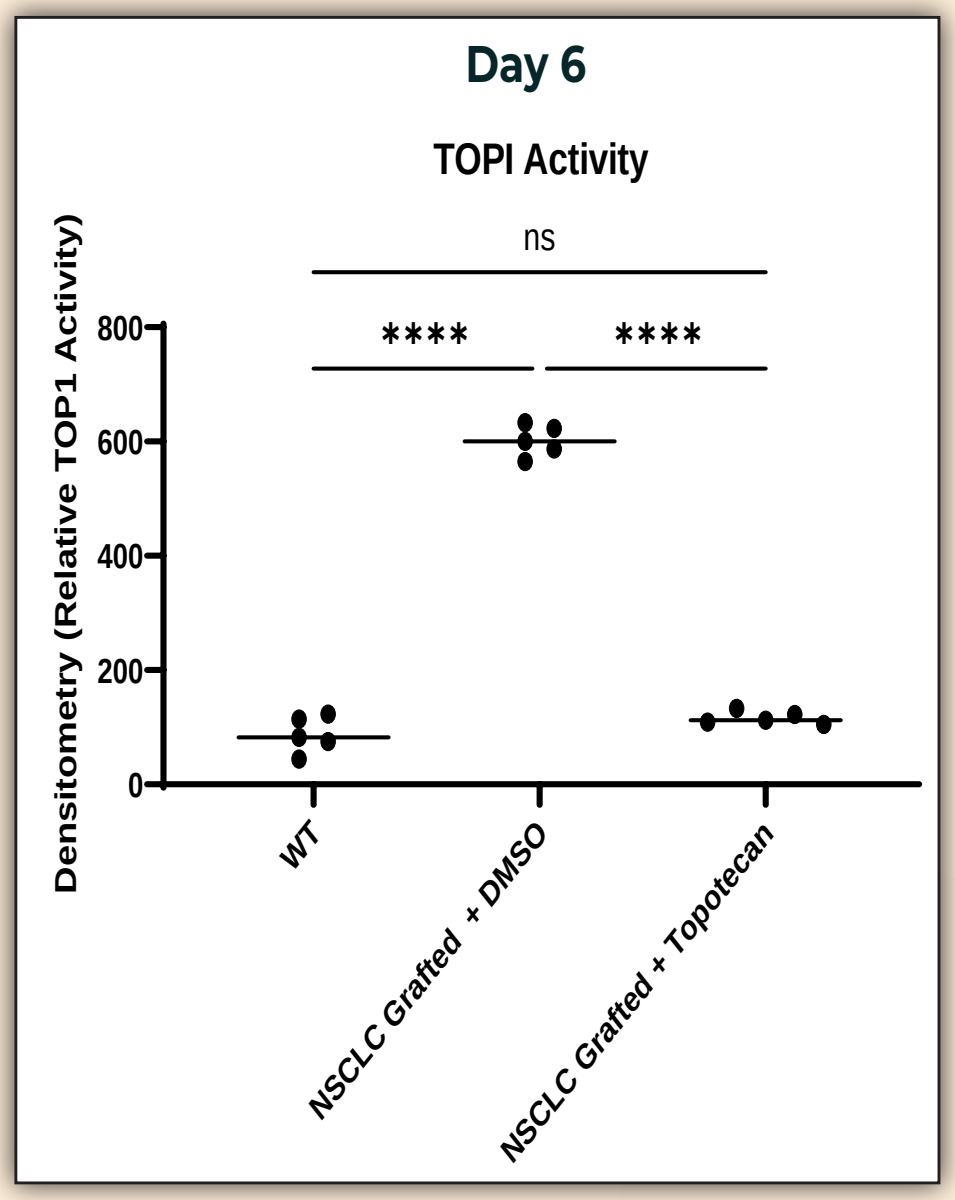
HGF/MET signalling is central to cell growth regulation and repair with a central role in tumour development when unregulated. Positive modulation of HGF have neurotrophic effect in both LPS and Scopolamine induced rodent models.

Topoisomerase Activity Inhibition

TOP1 inhibition rescued tumour bearing larvae with improvements in pathological score, and carcinoembryonic antigen biomarker with an overall reduction in mortality rates.



NSCLC Grafted Tumour Model

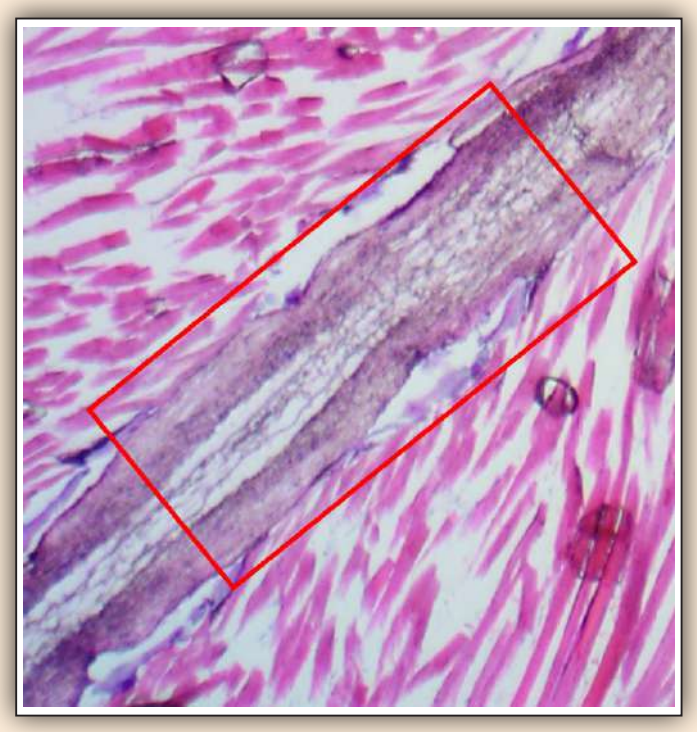


Topoisomerase I inhibitors are evolving in tumour applications. The primary challenge with non specificity has been addressed with conjugates as targeted delivery. However, with several tumours developing resistance to Topo inhibitory activity, combinatorial approaches are proving helpful in overcoming drug resistance.

Zebrafish helps to decipher combinatorial ratios during different phase of the disease to slow down progress of tumor metastasis and retain positive pathological scores.

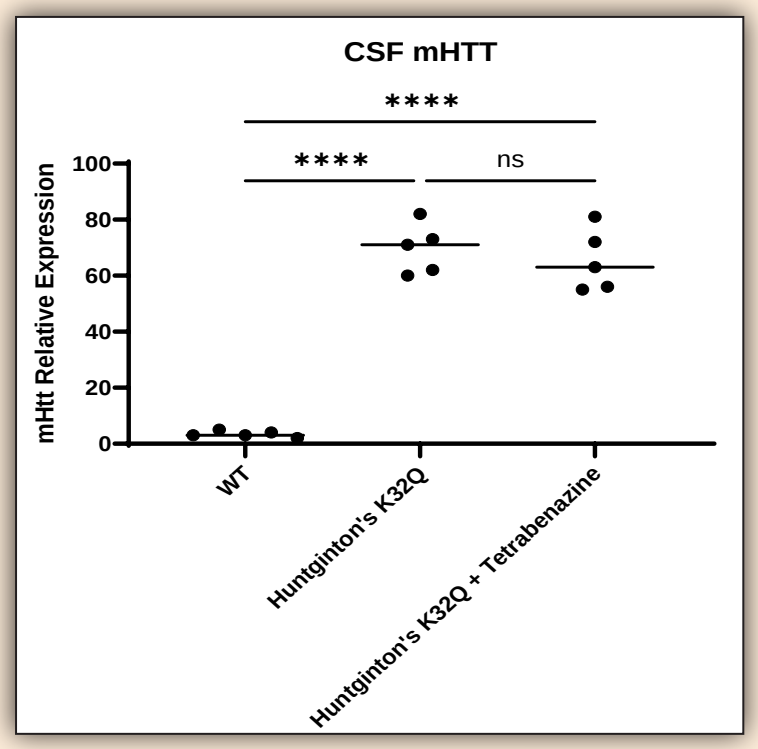
Mutant Huntingtin (mHTT) Level Drop

mHTT levels drop during rescue of pathology in huntington's model. mHTT levels continue to increase during manifest to progress period of the Huntington's disease with direct corelation of motor capability loss.



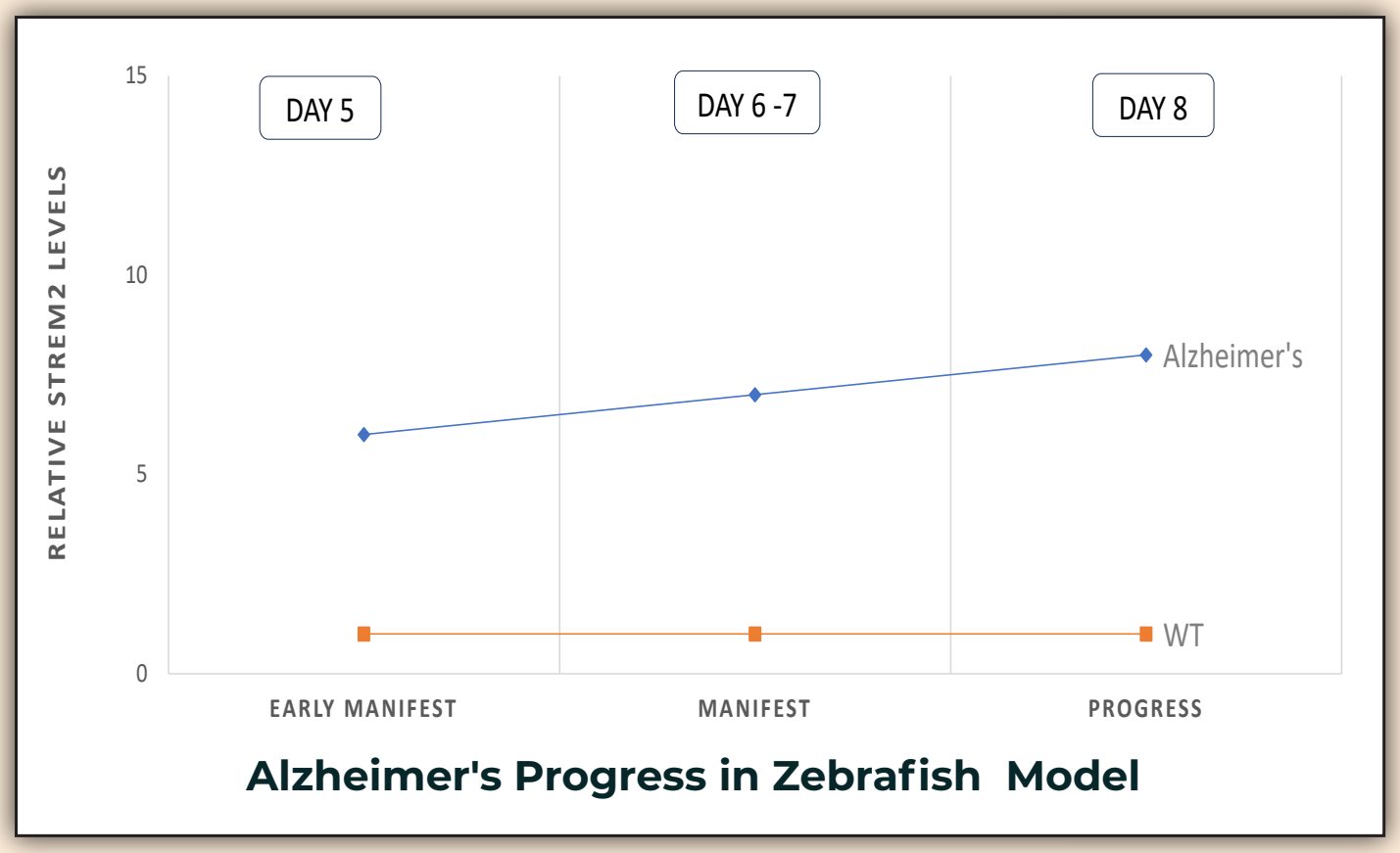
Htt K32Q Model

mHTT pathology is observed along with jerky movements, loss of memory and grip strength in zebrafish model. Loss of learning ability corelates with aggressive behaviour and caudate atrophy observed in huntington's zebrafish model. Repeat dose treatment with small molecules and ASOs have demonstrated significant rescue of mHTT pathology.



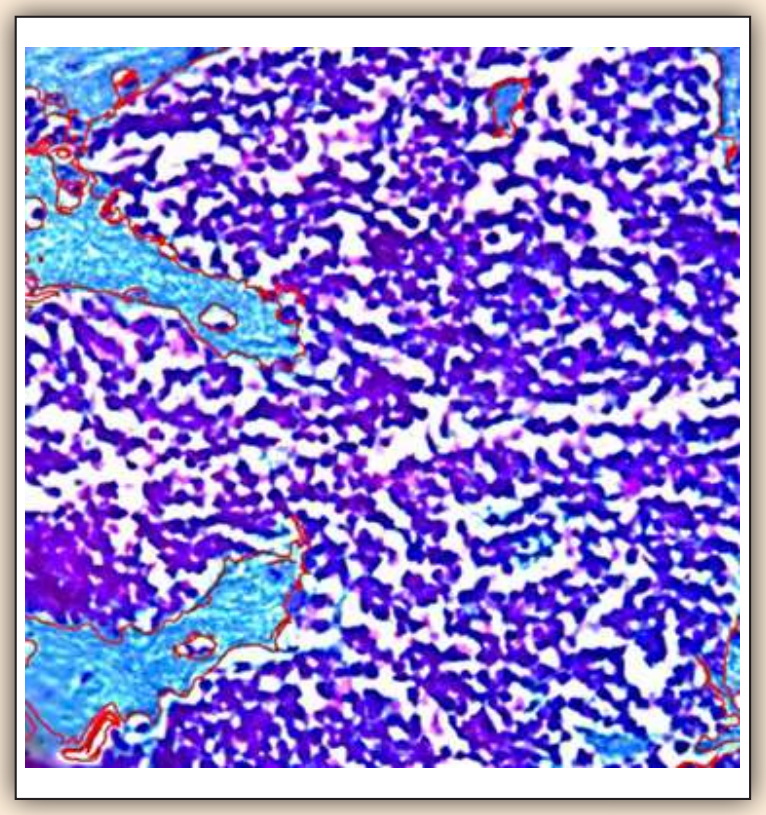
sTREM2 Target Engagement in Alzheimer's

Engagement of TREM2 receptors in the CNS helps microglia maintain homeostatic inflammatory response preventing progressive pathological neurodegeneration.



Variants of TREM2 bearing individuals show high risk to Aβ and Tau pathology. In this context Pre-Clinical studies have demonstrated that soluble TREM2 (sTREM2) treated Alzheimer's mouse could evade clinical progress to neurodegenerative pathology. Engagement of TREM2 is therefore a possible therapeutic option with sTREM2 as a biomarker in several neuroinflammatory disease including Multiple Sclerosis, Parkinson's and Prion disease.

LRRK2 inhibition in Parkinson's – BUT Before Lysosomal Dysfunction



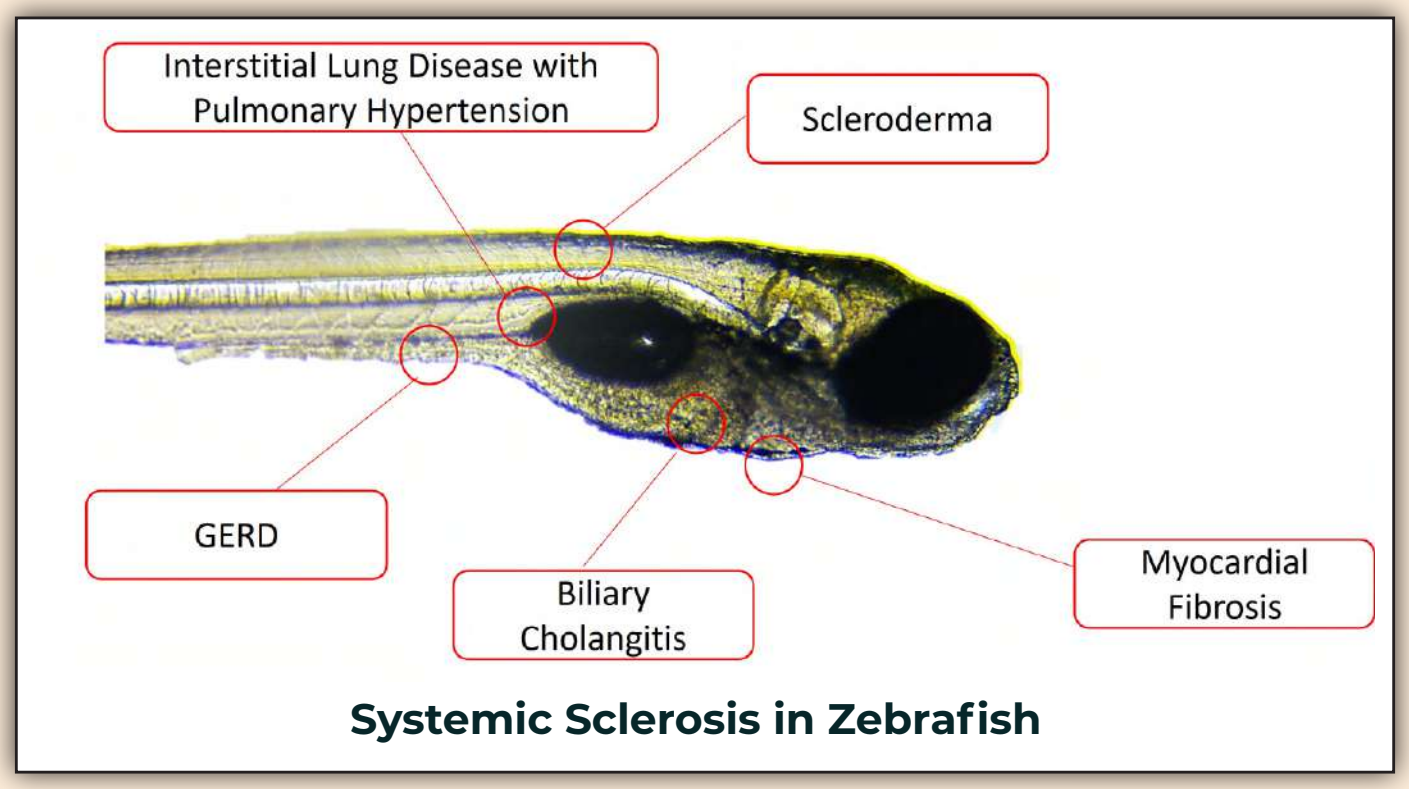
Inhibition of LRRK2 activity has demonstrated restoration of lysosomal function in animal models and clinical studies. Since post lysosomal dysfunction, LRRK2 inhibitors may not be effective at all, a staging based LRRK2 based treatment might be effective.

Section of Parkinson's zebrafish brain showing pre lysosomal dysfunction stage – ideal for LRRK2 inhibitors

Cellular partners that can drive LRRK2 outcome of kinase activity would be noteworthy to understand since several LRRK2 inhibitors have failed to stop pathogenicity of Parkinson's suggesting a possibility of leaky LRRK2 activity. Also targeting LRRK2 in specific tissues such as organs are widely discussed to avoid the possibility of undesired shut down of kinase activity.

ITK Inhibition in Systemic Sclerosis

Autoimmune diseases with hallmarks of inflammation and subsequent pathology of fibrosis with vascular damage leads to end stage pulmonary hypertension.

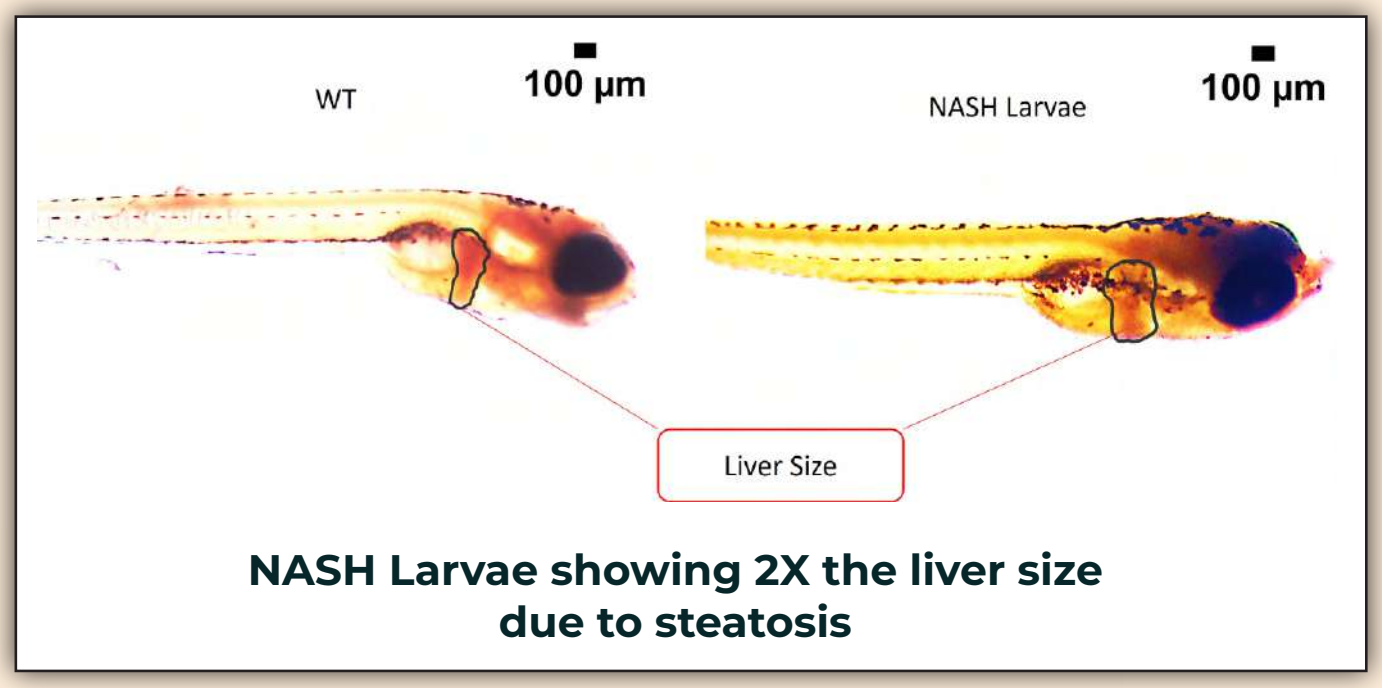


Systemic Sclerosis in Zebrafish

Interleukin-2 inducible T-cell kinase (ITK) inhibitors, regulates TH2 mediated inflammation and modulates TH17 cells leading to applications in T cell mediated inflammatory diseases. This includes autoimmune diseases and tumour. In mice studies ITK inhibitors have shown positive results in lung histology grading and pulmonary hypertension with applications in systemic sclerosis.

THR-β agonist in NASH – Improvements in Hepatic Steatosis and Circulating Cholesterol

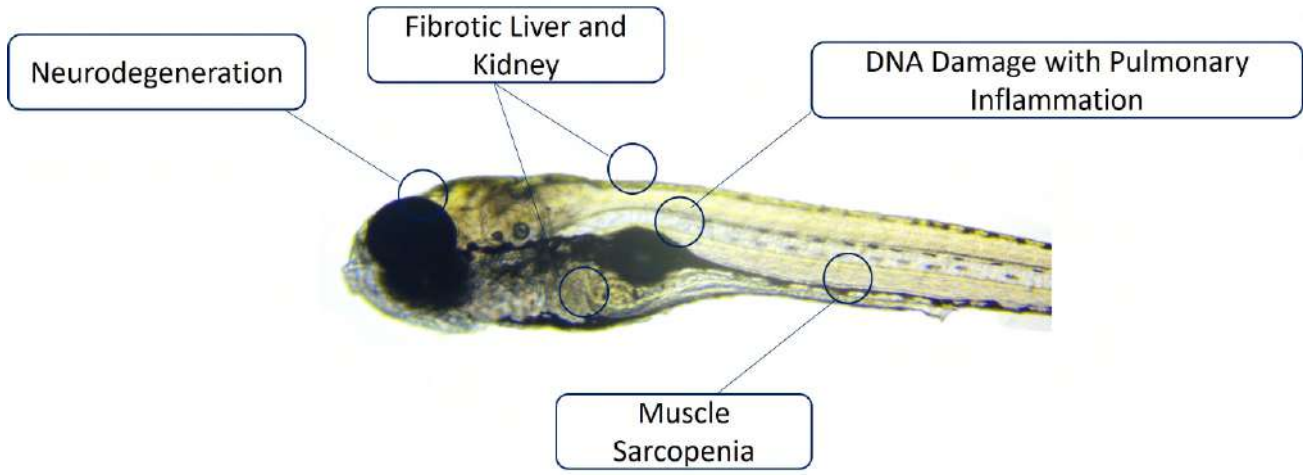
THR-β agonist treated mice showed improvements in liver function, hepatic steatosis and metabolic function in terms of serum cholesterol and glucose. Gene expression biomarkers of fibrosis and NAFLD pathology grading further confirmed to this.



NASH Larvae showing 2X the liver size due to steatosis

Similar results were observed in patients during clinical trials confirmed through MRI assessments of fat in the liver. The duration of treatment is expected to have improved outcomes with increase in duration of treatment with specific improvements in fibrosis and circulating cholesterol levels.

TUSC2 Modulated Reduction in T reg – Applications in Aging and Tumour



Mitochondria DNA damage - zebrafish outcomes

TUSC2 plays multiple roles including regulating immune response, tumour suppression, calcium movement and can prevent premature aging in sporadic Alzheimer's.

TUSC2 also has the ability to inhibit EGFR, PDGFR and promote apoptosis making it a promising target for tumour applications. Mice overexpressing TUSC2 showed amelioration of lung cancer and senescence through increased mitochondrial survival.

References

1. https://investors.athira.com/news-releases/news-release-details/athira-pharma-announces-publication-preclinical-data
2. Filipello F, Goldsbury C, You SF, Locca A, Karch CM, Piccio L. Soluble TREM2: Innocent bystander or active player in neurological diseases? Neurobiol Dis. 2022 Apr;165:105630. doi: 10.1016/j.nbd.2022.105630. Epub 2022 Jan 15. PMID: 35041990; PMCID: PMC10108835.
3. https://www.globenewswire.com/news-release/2024/11/14/2981360/0/en/Corvus-Pharmaceuticals-Announces-New-Preclinical-Data-Highlighting-Potential-of-Soquelitinib-to-Treat-Systemic-Sclerosis.html
4. Tesauro, C., Simonsen, A.K., Andersen, M.B. et al. Topoisomerase I activity and sensitivity to camptothecin in breast cancer-derived cells: a comparative study. BMC Cancer 19, 1158 (2019). https://doi.org/10.1186/s12885-019-6371-0
5. https://www.biospace.com/neuroinflammation-the-natural-next-alzheimer-s-target
6. Sahu N, August A. ITK inhibitors in inflammation and immune-mediated disorders. Curr Top Med Chem. 2009;9(8):690-703. doi: 10.2174/156802609789044443. PMID: 19689375; PMCID: PMC2770952.
7. https://haliatx.com/halia-therapeutics-to-unveil-new-clinical-program-targeting-the-lrrk2-protein-for-alzheimers-disease-at-discovery-europe-2024/
8. Uzhachenko, R., Shimamoto, A., Chirwa, S.S. et al. Mitochondrial Fus1/Tusc2 and cellular Ca2+ homeostasis: tumor suppressor, anti-inflammatory and anti-aging implications.
9. Cai N, Wu Y, Huang Y. Induction of Accelerated Aging in a Mouse Model. Cells. 2022; 11(9):1418. https://doi.org/10.3390/cells11091418
10. https://investors.vigilneuro.com/news-releases/news-release-details/vigil-neuroscience-announces-interim-data-its-ongoing-phase-1
11. https://www.biospace.com/wave-clears-phase-ib-iia-study-in-huntington-s-disease-eyes-accelerated-approval
    https://ir.zymeworks.com/news-releases/news-release-details/zymeworks-presents-new-preclinical-data-antibody-drug-conjugate
12. Chen Y, Liang R, Shi X, Shen R, Liu L, Liu Y, Xue Y, Guo X, Dang J, Zeng D, Huang F, Sun J, Zhang J, Wang J, Olsen N, August A, Huang W, Pan Y, Zheng SG. Targeting kinase ITK treats autoimmune arthritis via orchestrating T cell differentiation and function. Biomed Pharmacother. 2023 Dec 31;169:115886. doi: 10.1016/j.biopha.2023.115886. Epub 2023 Nov 22. PMID: 37992572.

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