e-therapeutics

Network-driven Drug Discovery

INHIBITING AXONAL DEGENERATION IN NEURODEGENERATIVE DISEASE

BACKGROUND

Neurodegenerative diseases which include conditions such as Alzheimer's Disease (AD), Parkinson's Disease (PD), Huntington's Disease (HD) and amyotrophic lateral sclerosis (ALS), are characterized by irreversible, progressive dysfunction of the nervous system.

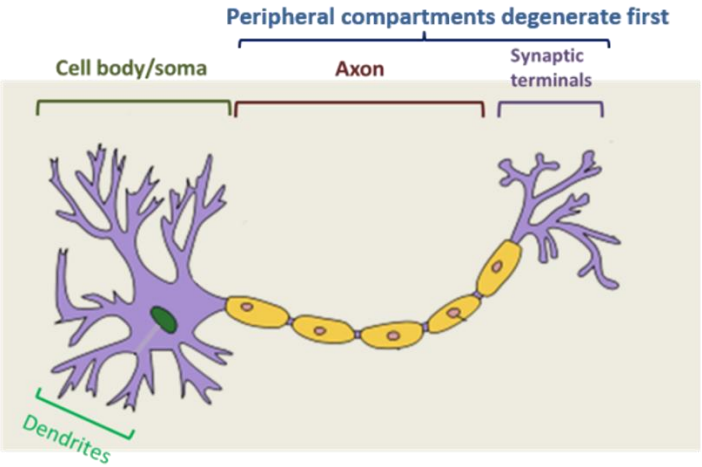
Biologically, neurodegeneration is mediated by a very complex set of processes and is consequently poorly served by existing drugs. With an aging population, incidence of these diseases is on the rise, but there are currently no therapies that can cure neurodegenerative disease and existing medications can only give temporary alleviation of symptoms. Diseases such as PD, AD, ALS and HD have different characteristics in terms of signs, symptoms and progression, but they share mechanisms of pathology, including the mechanisms by which neurons degenerate.

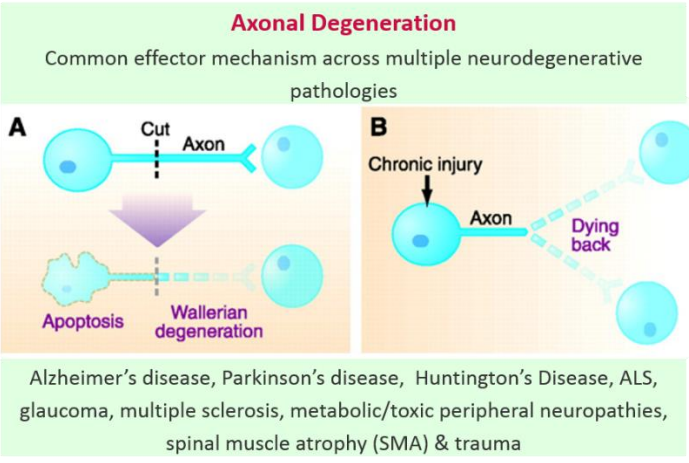
Neurons are structurally complex and divided into sub-compartments – cell body, axon, dendrites and synapses. The peripheral components of neurons, particularly axons, generally degenerate early in the degenerative process before significant death of the cell body is observed. A considerable amount of scientific evidence supports axonal degeneration as the initial pathological mechanism in many neurodegenerative diseases. The axon has its own biochemically distinct self-destruct programs that are activated in neurodegenerative disease and under conditions of stress. Our aim is to stop progression of neurodegenerative diseases by inhibiting axonal degeneration. As axonal degeneration represents a convergent phenotype irrespective of triggering disease, active compounds have the potential to be of utility across many neurodegenerative diseases.

THE OPPORTUNITY

e-therapeutics has successfully applied its **Network-driven Drug Discovery** (NDD) platform to identify small-molecules with neuroprotective activities. The molecules were discovered using human protein interaction networks and showed neuroprotective activity in neurons. It is anticipated that these molecules may be effective across a spectrum of neurodegeneration models.

e-therapeutics' platform can be used to discover novel and differentiated hits for subsequent hit-to-lead and lead optimisation.





THE APPROACH

Network-driven Drug Discovery (NDD)

By combining biological expertise with a powerful computer-based platform, we create and analyse network models of disease. We believe that our approach more realistically reflects the complexity of polygenic diseases such as axonal degeneration, with its multiple and interconnected cellular pathways. In considering the entire pattern of connections between proteins associated with a disease, rather than isolated pathways, we are able to more efficiently select drug-like compounds for screening in relevant phenotypic assays and for subsequent progression to medicinal chemistry and pre-clinical testing.

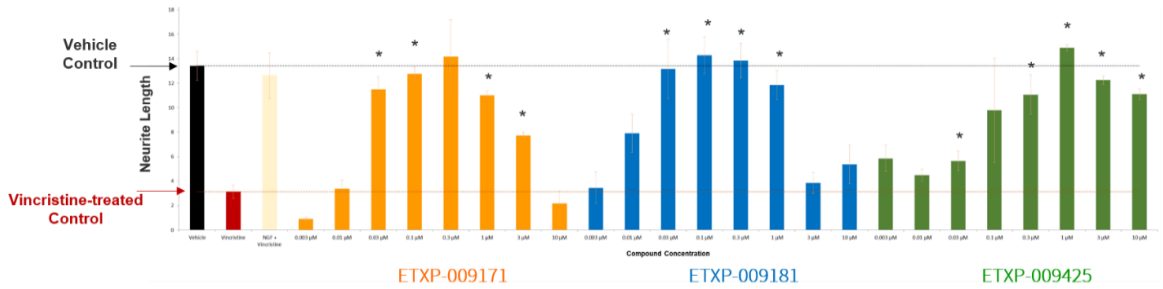
ACTIVITIES

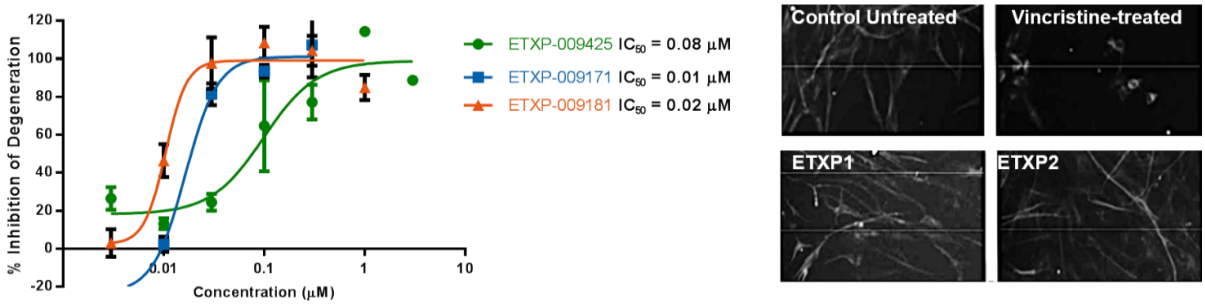
Networks, Compounds and Screening

Intervention strategies were identified aimed at targeting several system level processes, including mitochondrial dysfunction, nicotinamide adenine dinucleotide (NAD) flow, axon-specific protease networks, and axonal outgrowth. Network models of these effector processes were constructed and analyzed using our proprietary NDD analysis tools.

Based on the results of network analyses, 1700 compounds were identified for *in vitro* testing using a cellular model of neurodegeneration. Axon-protective effects of compounds were assessed against vincristine-induced neurodegeneration of rat dorsal root ganglia (DRG). DRG were pre-incubated with compound for 30 min prior to treatment with 10nM vincristine for 24h. Protection was assessed by measuring neurite length using high content image analysis. A preliminary screen using three concentrations of compounds indicated that ~ 20 % of these compounds possessed neuroprotective effects at or below the top concentration of 10μM.

Eighty of the most promising compounds were selected for a second screen to obtain full IC_{50} dose-responses. A subset of 58 compounds were confirmed as actives with IC_{50}s in the nanomolar range. These will be further explored in other models of axonal degeneration, and further work will be performed to establish SAR and to investigate MOA.





Examples of compounds with axon-protective activity and neurite growth image analysis

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