**DAMNPATHS Project.**
**Elucidation of common transcriptional targets in vulnerable dopamine, motor neuron and frontotemporal dementia disease pathways**

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*Abstract*
Neurodegenerative diseases preferentially affect specific neuronal populations with distinct corresponding clinical features, even if pathogenic and causative proteins are often ubiquitously expressed in the human body. Thus, protective pathways might compensate for or alleviate shared pathogenic pathways in relatively resilient neurons. The efforts of our consortium were directed to uncover specific and shared neurodegenerative pathways in ALS, SMA, SBMA, FTD, and PD as well as potentially neuroprotective pathways.

To this end, we established techniques that allowed us to precisely profile the transcriptome of individual neurons in mouse and human tissue (LCM-Seq, Hedlund and Sandberg labs) and of axons from cultured stem cell-derived neurons (Axon-Seq, Hedlund Lab). In resilient neurons, we indeed identified detrimental pathways associated with disease burden but also counteracting responses, including neuroprotective IGF-2 and SYT13 signaling (Hedlund and Corti labs). To functionally target disease pathways, we established state-of-the-art in-vitro models for several diseases from human induced pluripotent stem cells (iPSC) and excited disease-like states in the derived neurons (Hedlund, Corti, and Sanchez-Pernaute labs). We thus recreated ALS/SMA-sensitive spinal motor neurons as well as bona fide ALS/SMA-resilient oculomotor neurons and confirmed their differential vulnerability and neuroprotective pathways in vitro. In dopaminergic neurons derived from iPSC from patients with genetic forms of Parkinson disease, the convergence of molecular disease pathways for several PARK genes (PINK1, LRRK2 and SNCA) was established (Sanchez-Pernaute lab).

The picture emerging from our amassed data indicates that specific and shared pathological pathways underlie the different diseases whereas protective pathways can explain differential vulnerabilities across cell types. Our current efforts are directed at confirming the identified pathways across ALS and FTD (Graff lab) and modulating these pathways in vitro (Hedlund and Corti labs) and in animal models using AAV-mediated gene delivery and ablation (Corti lab). Our findings will guide the development of effective treatments by targeting pathways relevant across diseases.