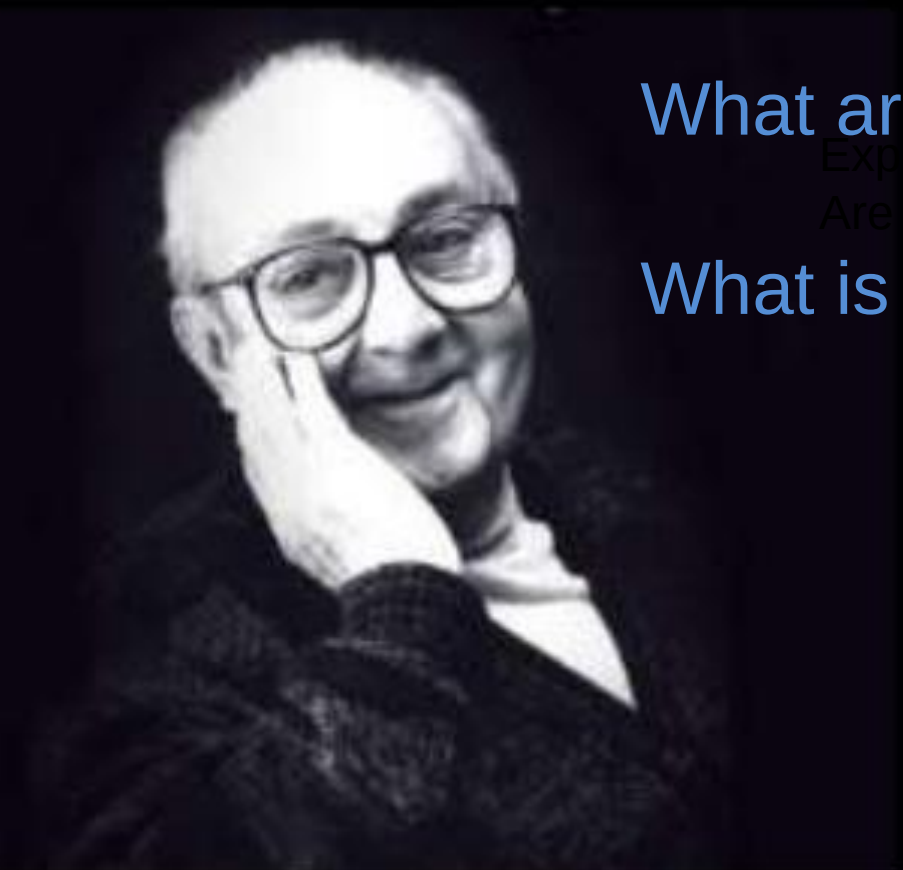
All models are wrong

but some are useful



What are appropriate expectations?

What is the right measure of utility?

George E.P. Box

Non-human Models of Neurodegenerative Disease

Causes for Concern

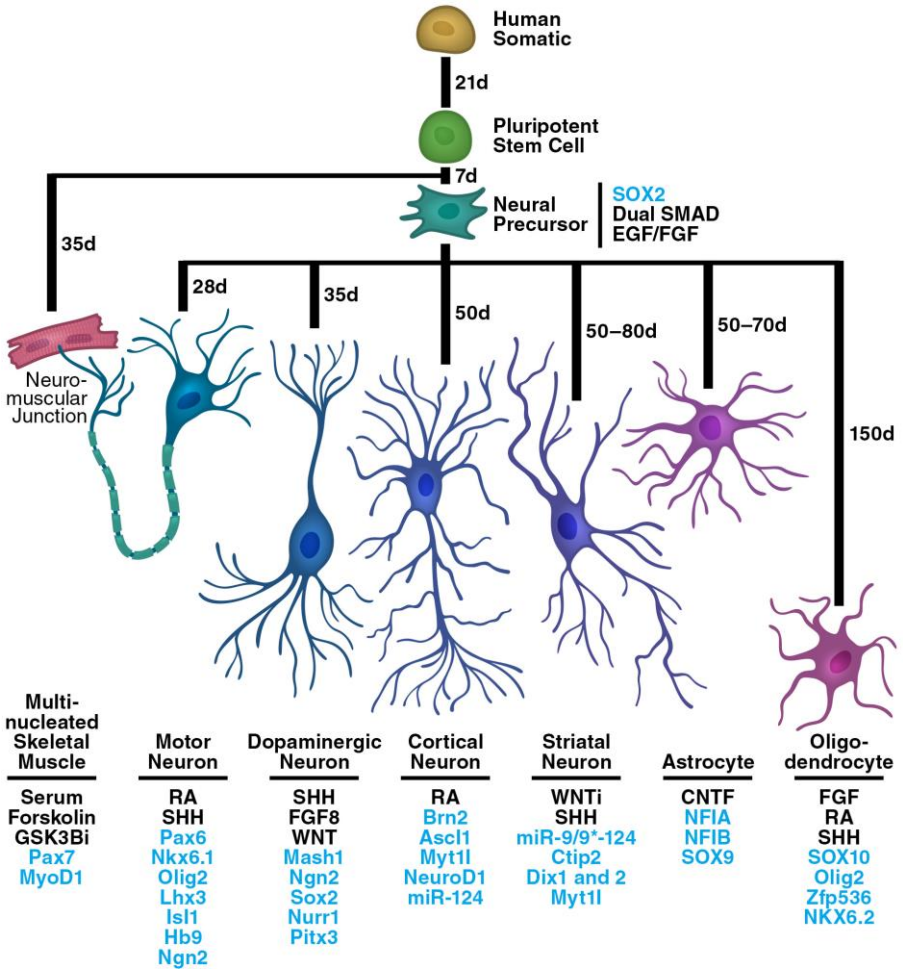
- Failure to reduce risk of drug development
- Species-specific differences in disease relevant genes, anatomy, physiology, aging, pharmacokinetics, etc… (Liao and Zhang (2008) *PNAS*)
- Will there ever be a “better” model?

Unrealistic Expectations?

- Don’t normally develop AD, PD, etc…
- Focus on recapitulation of human pathology may be misplaced, even counter productive
- Concept of complex adapted systems and “phenologs” (McGary et al. (2010) PNAS; Woods et al. (2013) *BMC Bioinformatics*)

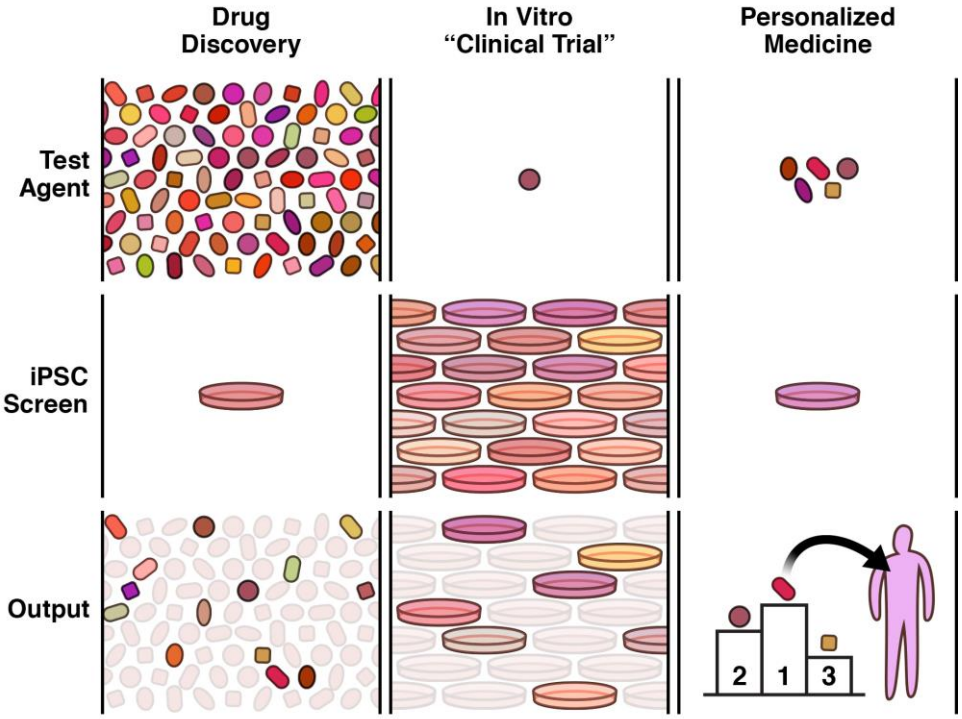
What is the power of a model to predict a clinical observation?

Can iPSC-based Disease Models Make Translation More Reliable and Help Deliver on the Promise of Precision Medicine?



Haston and Finkbeiner, Ann. Rev. Pharm. Tox, (2016)

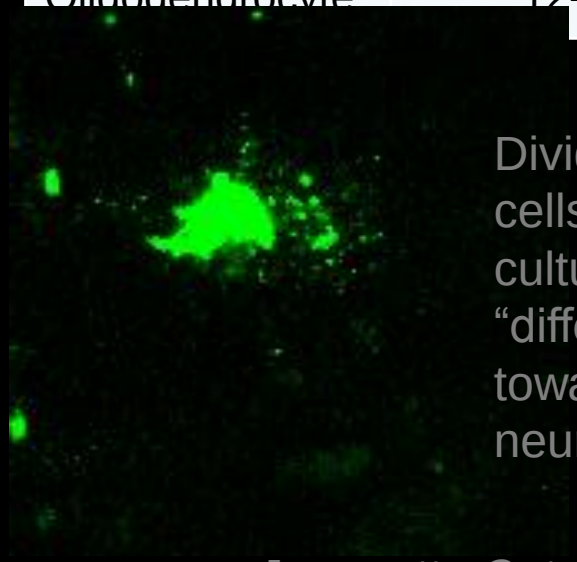
- Human brain cells from patients with clinically defined disease
- iPSCs can be differentiated toward a variety of brain cell types
- Potential applications in drug discovery, patient stratification, etc…



Challenges: Heterogeneity by Accident or Design

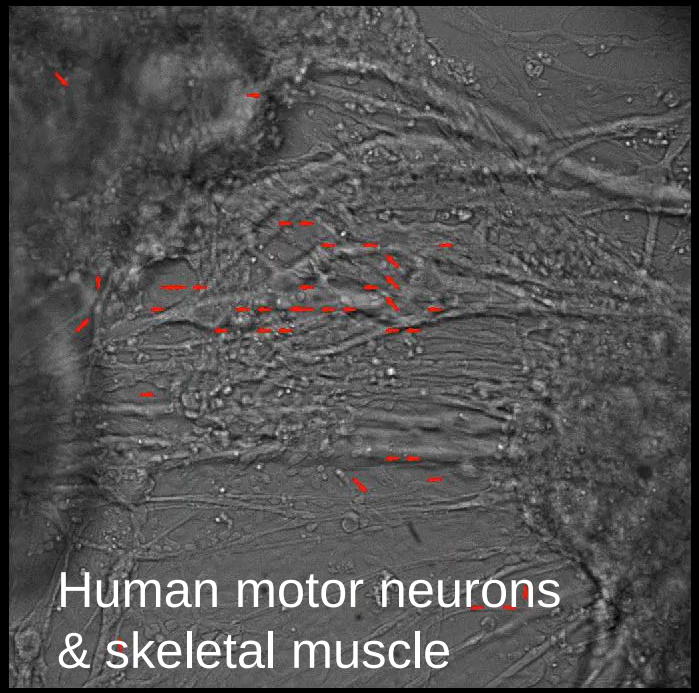
Cell type	Differentiation (weeks)	Efficiency (%)
Forebrain neuron	2	90-95
Dopaminergic neuron	4	40-50
Motor neuron	2-4	40-50
Striatal neuron	4	5-12
Astrocyte	5	60
Oligodendrocyte	12-13	10-20

- Differentiation protocols imperfect, long and complex
- Maturity, aging?
- HT Single cell analysis methods may be critical



Dividing Hb-9+ cells in an iPSC culture “differentiated” toward motor neurons (day 18)

Jeannette Osterloh and Kelly Haston

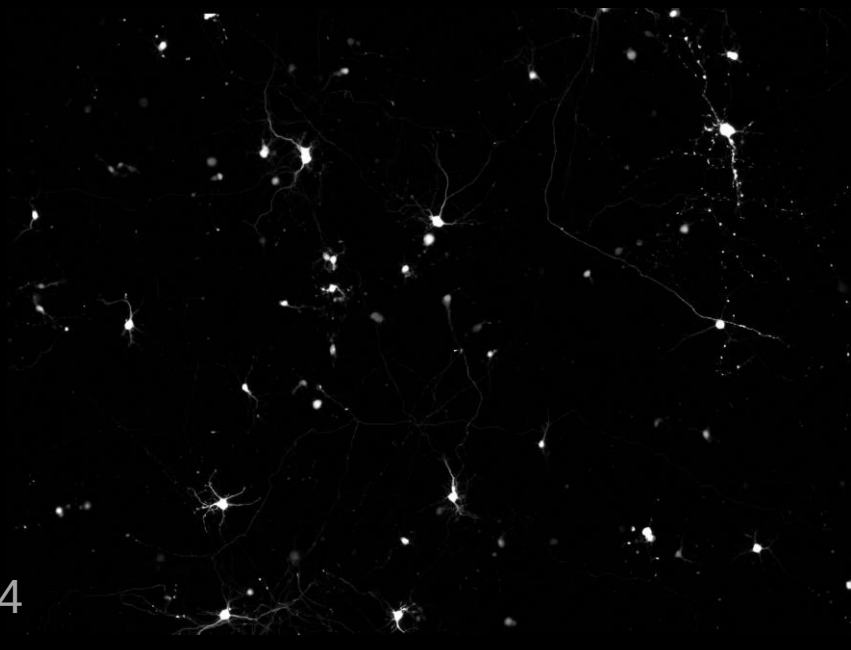


Automated Single Cell Analysis

- 100-1000 fold more sensitive detecting phenotypes & drug effects

7 day movie

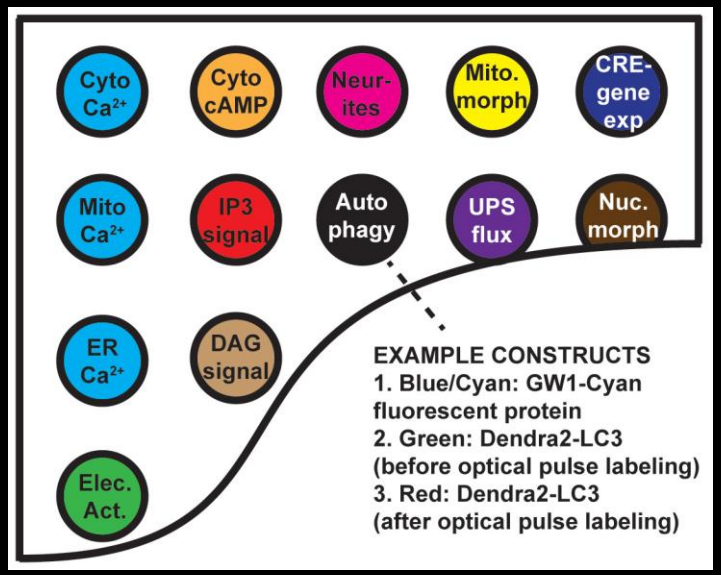
#thebrainbot



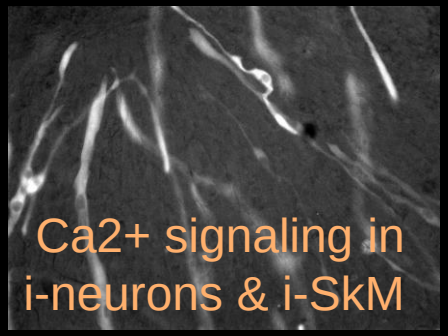
Nature, 2004; PNAS, 2005; Nat. Chem Biol. 2014

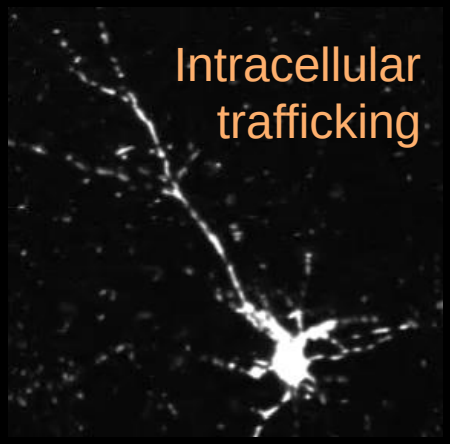
High Throughput High Content Deep Phenotyping of iPSC Models

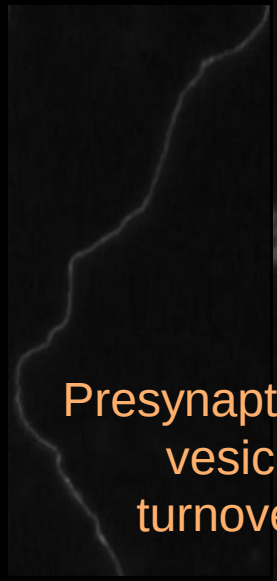
"Physical Exam" of the Cell

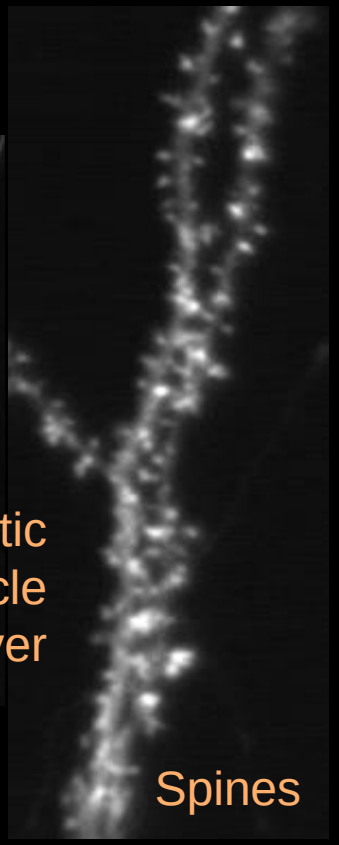


~ Array of 270 biosensors Multiplexed









Neuron, 2015

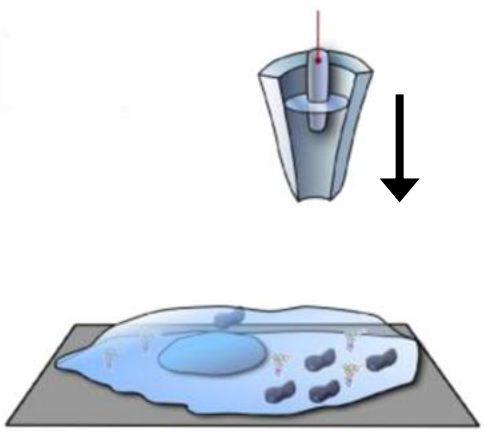
The NIH Common Fund

National Institute of Neurological Disorders and Stroke

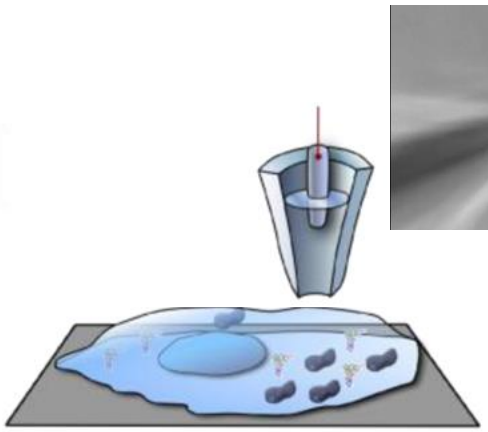
- "All optical" electrophysiology to stimulate and record
- Synapse structure / function
- Ca^{2+} signaling
- Neurite extension and retraction

- Mitochondrial structure, trafficking
- Bioenergetics, metabolism
- Proteostasis flux, autophagy
- DNA damage and repair
- Protein aggregation, metabolism

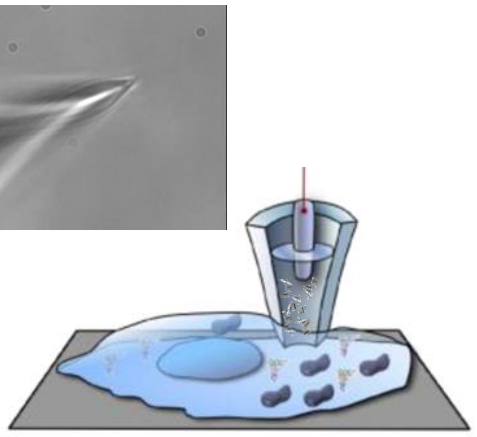
Fully Automated Dynamic Single Cell Transcriptomics



1. Image-guided approach

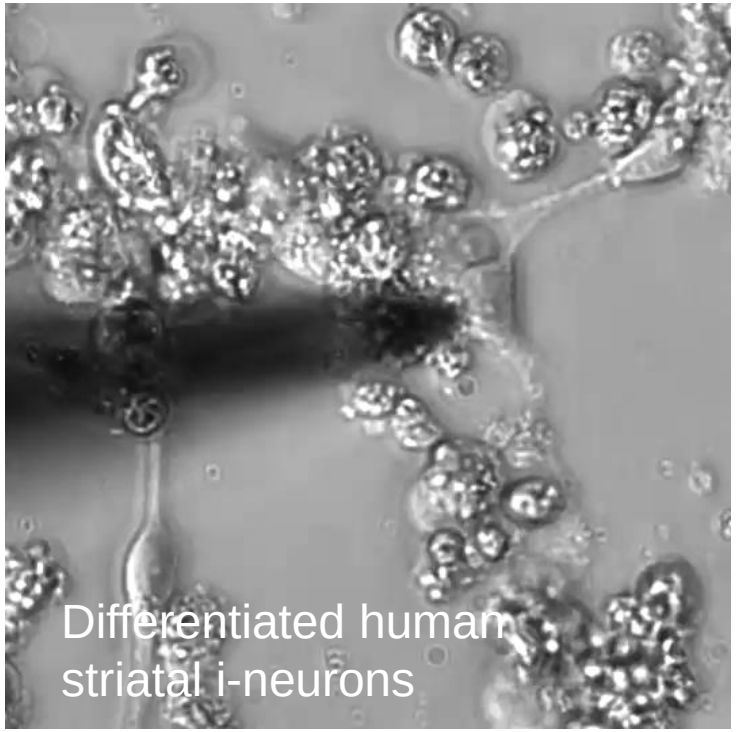


2. Electrical detection of cell



3. Electrical guided penetration & aspiration

4. Electrical guided ejection



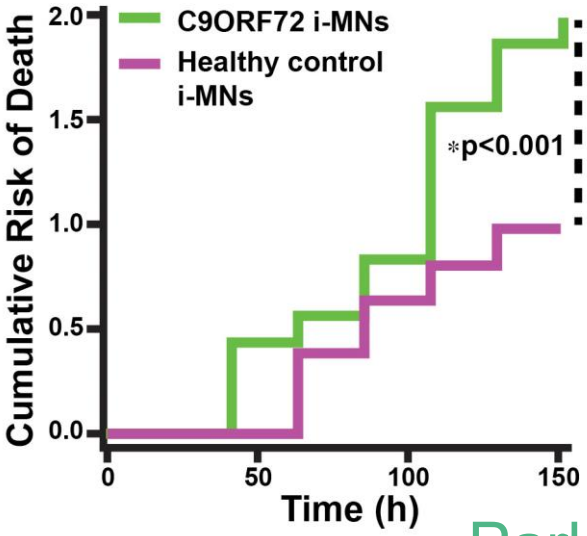
Differentiated human striatal i-neurons

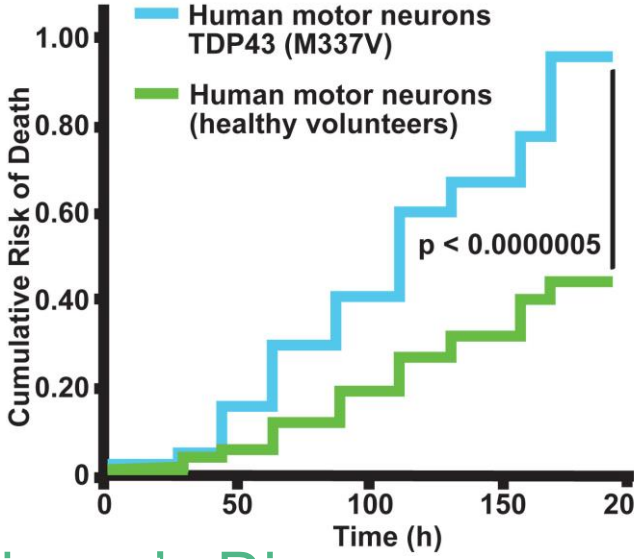
- Relate to patient transcriptomics
- Understand molecular basis for phenotypic differences according to
  - Cell type
  - Adaptive response
  - Perturbagen
- Target ID from genetic screens

Seger et al. (2012) Nanoscale; Actis et al. (2014) ACS Nano

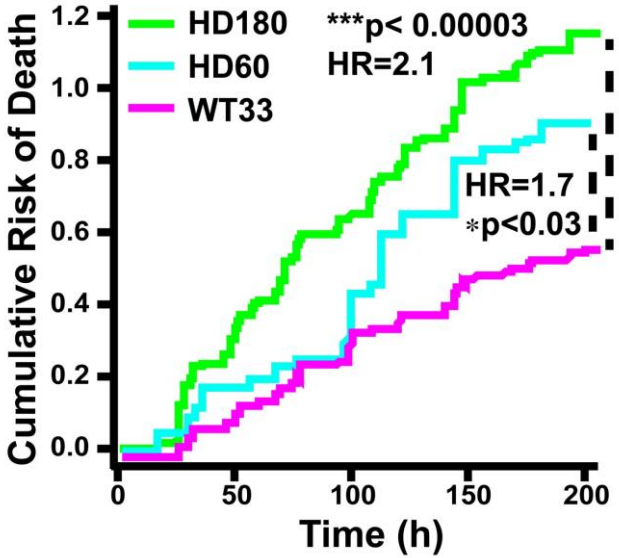
Human Disease Model Phenotypes – No Stressors

ALS / Frontotemporal dementia

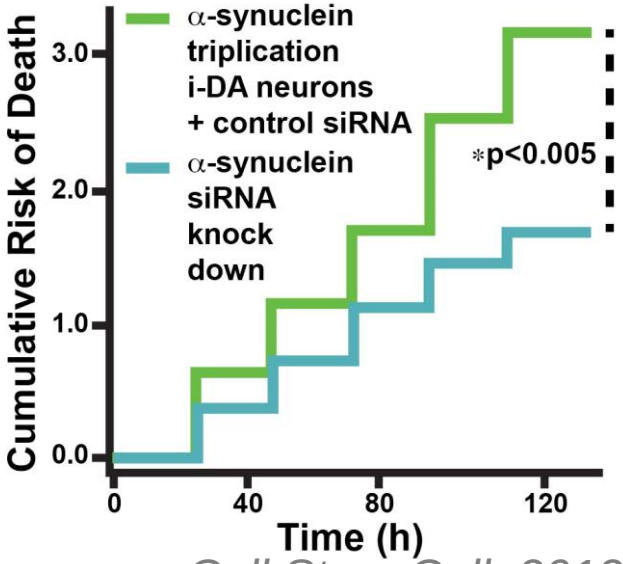


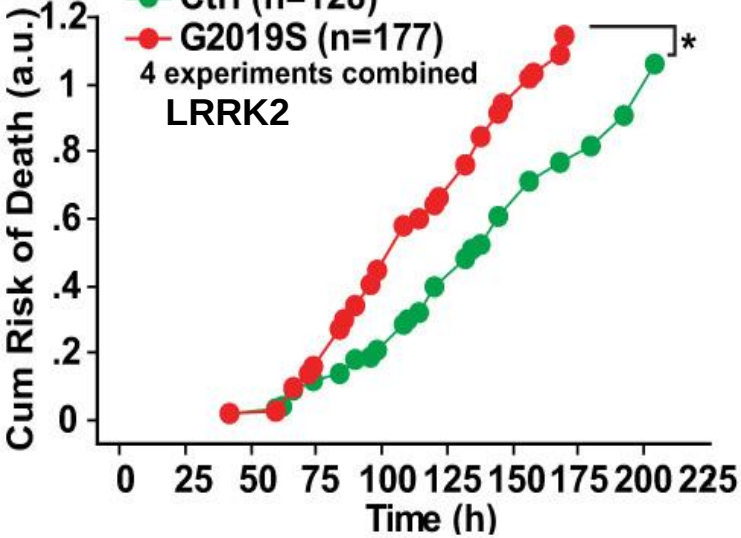


Huntington's Disease



Parkinson's Disease

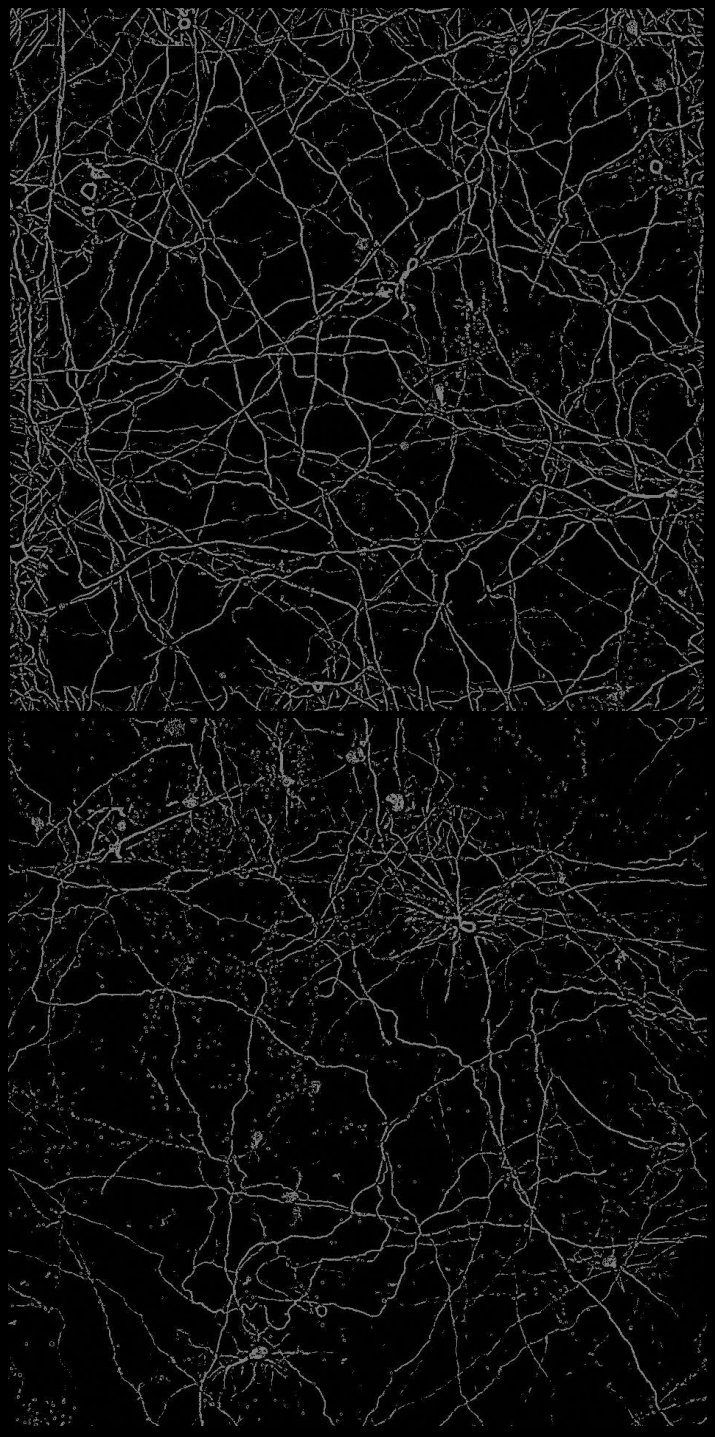




Disease-relevant phenotypes:

- Survival
- Neurite length
- Calcium signaling
- Glial phenotypes
- Electrophysiology changes
- Gene profiling changes

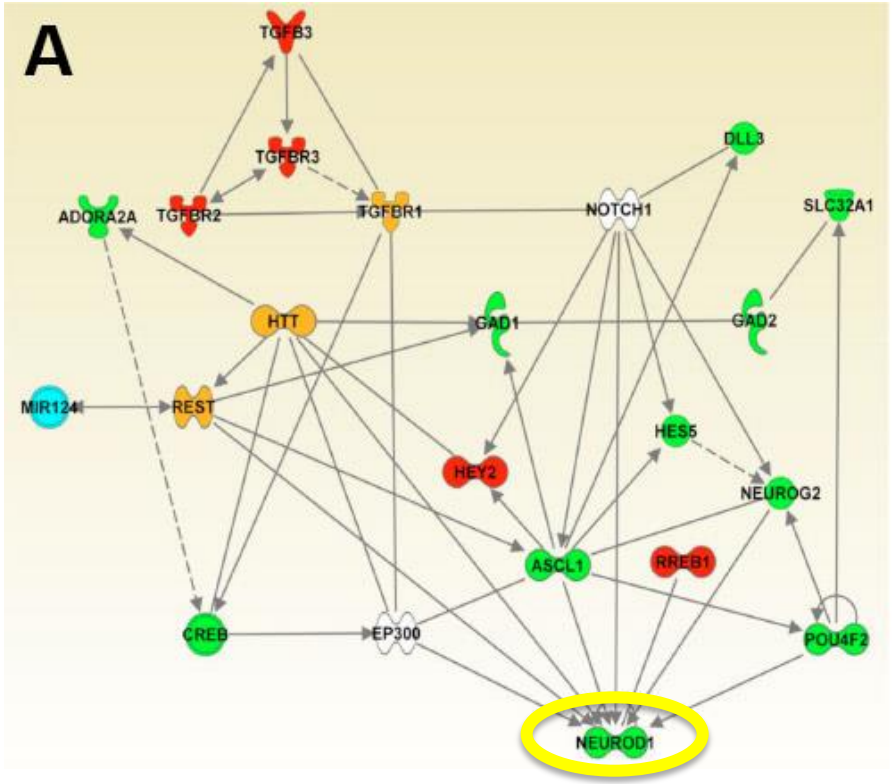
Cell Stem Cell, 2012; PNAS, 2012; PNAS 2013, J. Neurosci. 2014

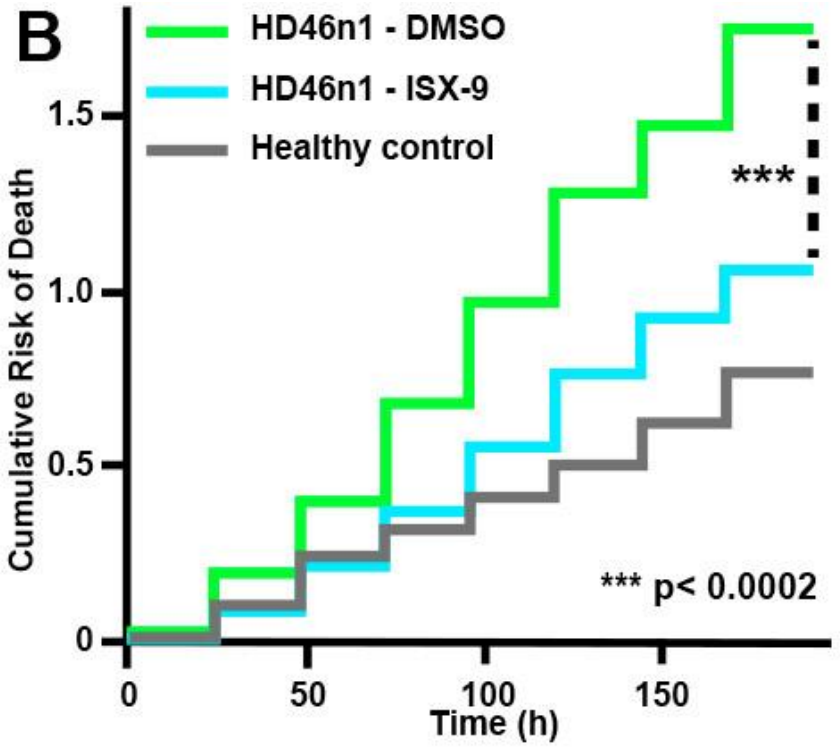


Applications of Deep Learning to See Things Better:

Automated Neurite Analysis &
“Diagnose a Well”

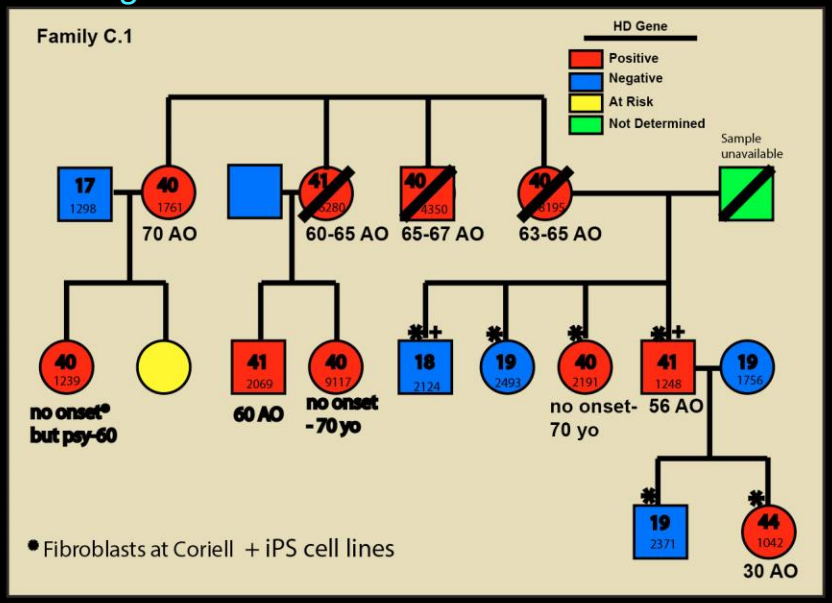
Roles of iPSCs in HD – Mechanisms of Pathogenesis





- Whole transcriptome analysis suggests a major deficit in several developmental pathways
- NeuroD and its downstream targets significantly downregulated in HD i-neurons
- Survival and physiology deficits mitigated by a NeuroD activator, ISX-9

Leslie Thompson, Julia Kaye, Mariah Dunlop; HD iPSC Consortium, Nat. Neurosci., in revision



Whole Genome Analysis of HD Families:

A Rare Genetic Variant of a Proteastasis Gene is Associated with Delayed Symptom Onset

Julia Kaye, unpublished

Alicia Holloway, Stacia Wyman

Answer ALS: Largest most comprehensive clinical and biological assessment of ALS

alsFINDINGaCURE

- **Part 1**. A comprehensive and longitudinal deep clinical data set from at least 1,000 ALS patients
  - ~2 year followup (Guid assignment); 5 visits
    - Extensive deep clinical data: EMG, clinical, MRI, pulmonary
    - Biofluids and tissue: Blood, CSF (~10%), Autopsy (~10%), DNA, PBMC
    - Personal monitoring device: 24/7 clinical data
- **Part 2**. Generate iPS cells from every patient (after visit 1)
  - iPS Motor neurons and astroglia

- **Part 3.** Perform comprehensive biological analytics these human brain cells:
  - Whole genome, Transcriptome, proteome, epigenome, metabolom, lipome), robotic serial neuronal analytics.
- **Part 4.** Data Analytics:
  - clinical/'omics based sub
  - Pathways
  - Biomarkers

- *Future clinical trials based on data sets/biologicc; New biomarkers*
- *New ALS Druggable Pathways*

Private sector environment for proceeding in absence of animal models to predict efficacy

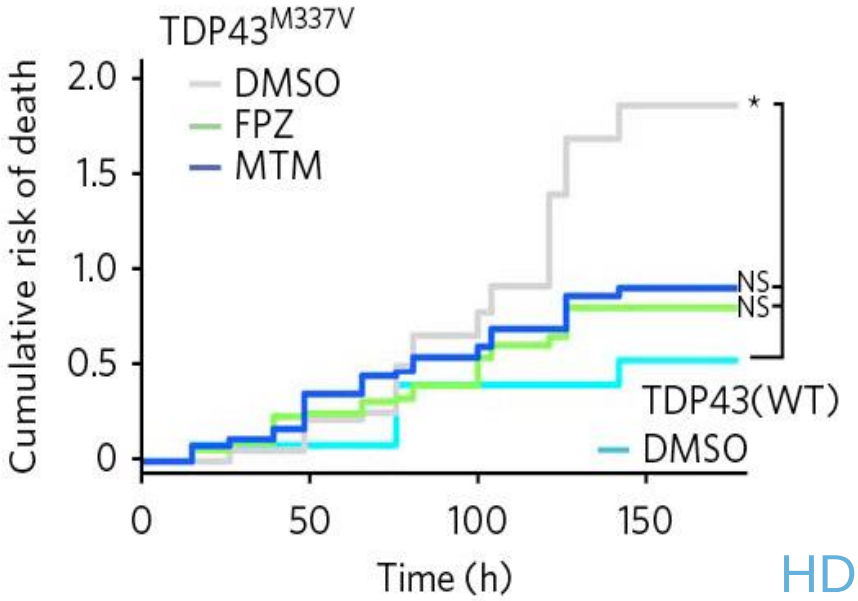
DENALI

~ 50% tell us they are willing to proceed without in vivo efficacy if they have:

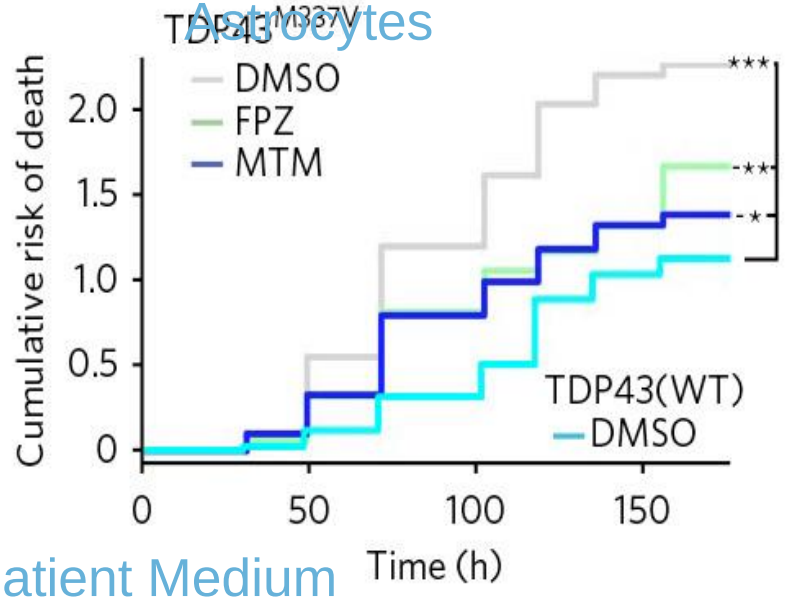
1. Efficacy in iPSCs
2. *In vivo* tox
3. Target engagement biomarker in humans

Autophagic Induction Protects Patient Human Neurons from Degeneration

ALS Patient Motor Neurons

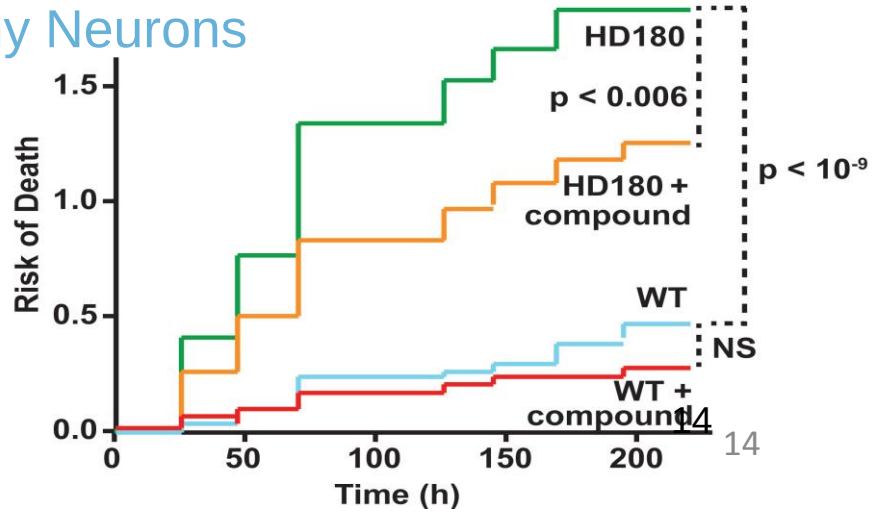


ALS Patient Astrocytes



- Accelerate the neuronal clearance of disease proteins in i-neurons
- Mitigate cytopathology
- Lead optimization
- Nanomolar potency, BBB penetrant

HD Patient Medium Spiny Neurons



Yush Goyal, Ashkan Javaherian, Julia Kaye

Tsvetkov et al. Proc. Natl. Acad., 2010; Tsvetkov et al. Nat. Chem. Biol., 2013; Barmada et al. Nat. Chem. Biol., 2014