Innovative Medicines Initiative

Stem Cells: A Global Perspective

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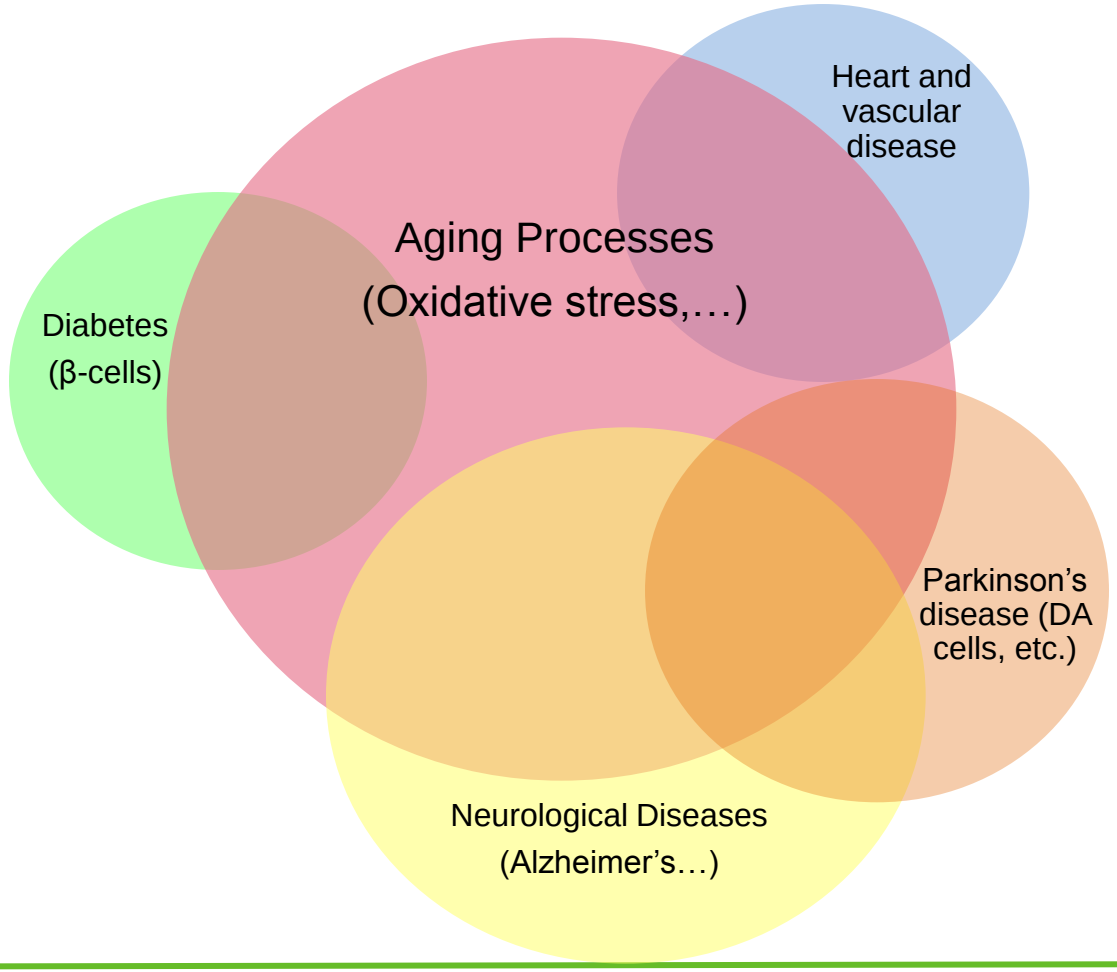
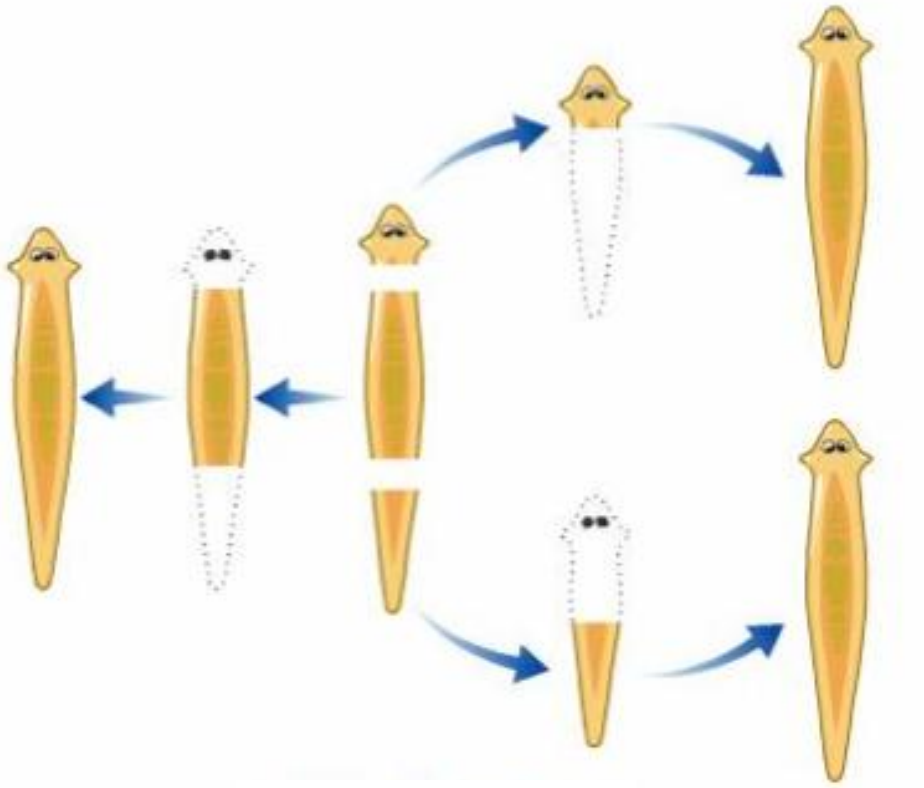
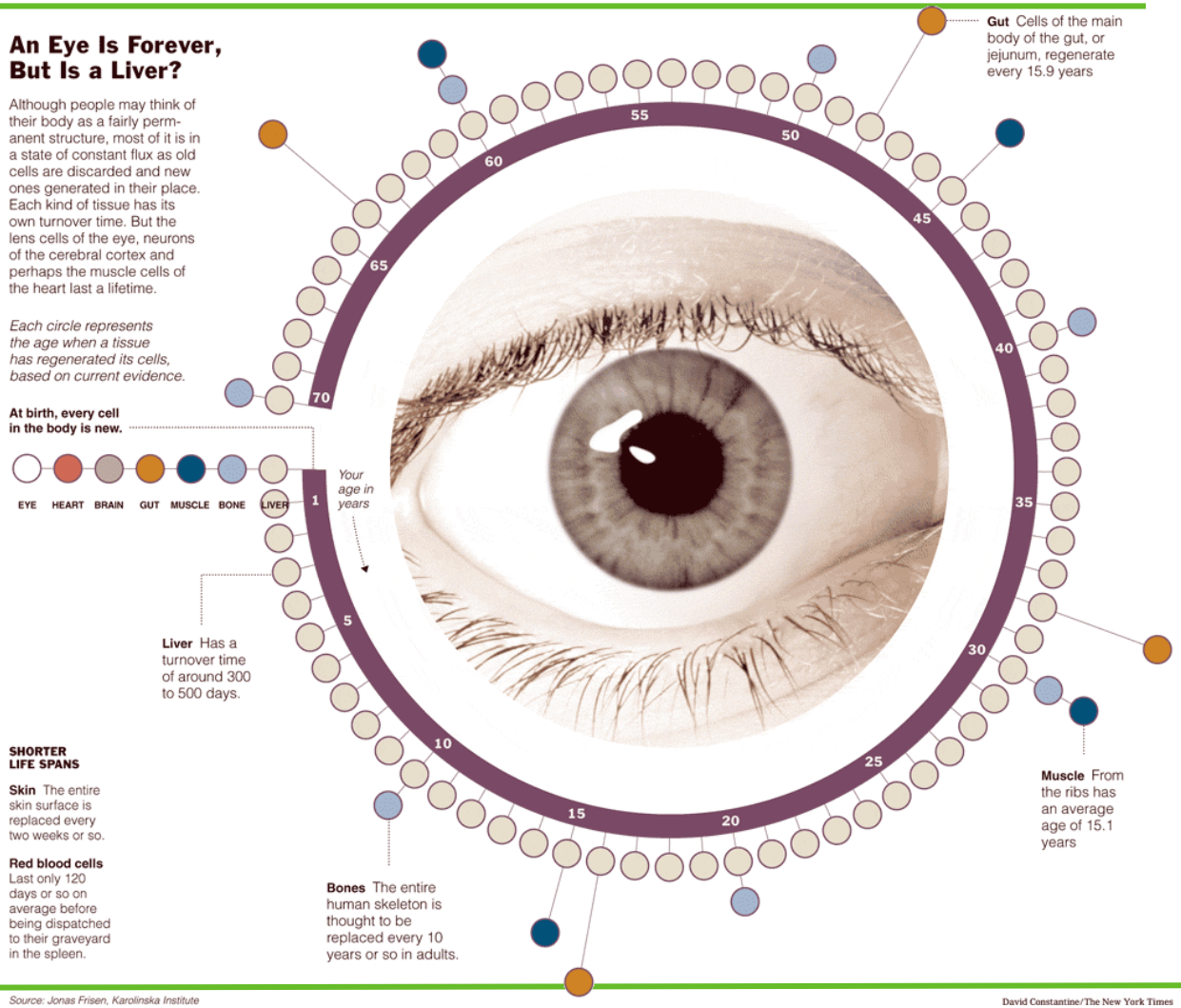
IMI Stakeholder Forum – 21 May 2014 - Brussels

Regenerative Medicine:



Regeneration in Planaria – flatworm




An Eye Is Forever, But Is a Liver?
Although people may think of their body as a fairly permanent structure, most of it is in a state of constant flux as old cells are discarded and new ones generated in their place. Each kind of tissue has its own turnover time. But the lens cells of the eye, neurons of the cerebral cortex and perhaps the muscle cells of the heart last a lifetime.
Each circle represents the age when a tissue has regenerated its cells, based on current evidence.
At birth, every cell in the body is new.
EYE HEART BRAIN GUT MUSCLE BONE LIVER
Your age in years
Gut Cells of the main body of the gut, or jejunum, regenerate every 15.9 years
Liver Has a turnover time of around 300 to 500 days.
SHORTER LIFE SPANS
Skin The entire skin surface is replaced every two weeks or so.
Red blood cells Last only 120 days or so on average before being dispatched to their graveyard in the spleen.
Bones The entire human skeleton is thought to be replaced every 10 years or so in adults.
Muscle From the ribs has an average age of 15.1 years
Source: Jonas Frisen, Karolinska Institute
David Constantine/The New York Times

Regenerative Medicine:

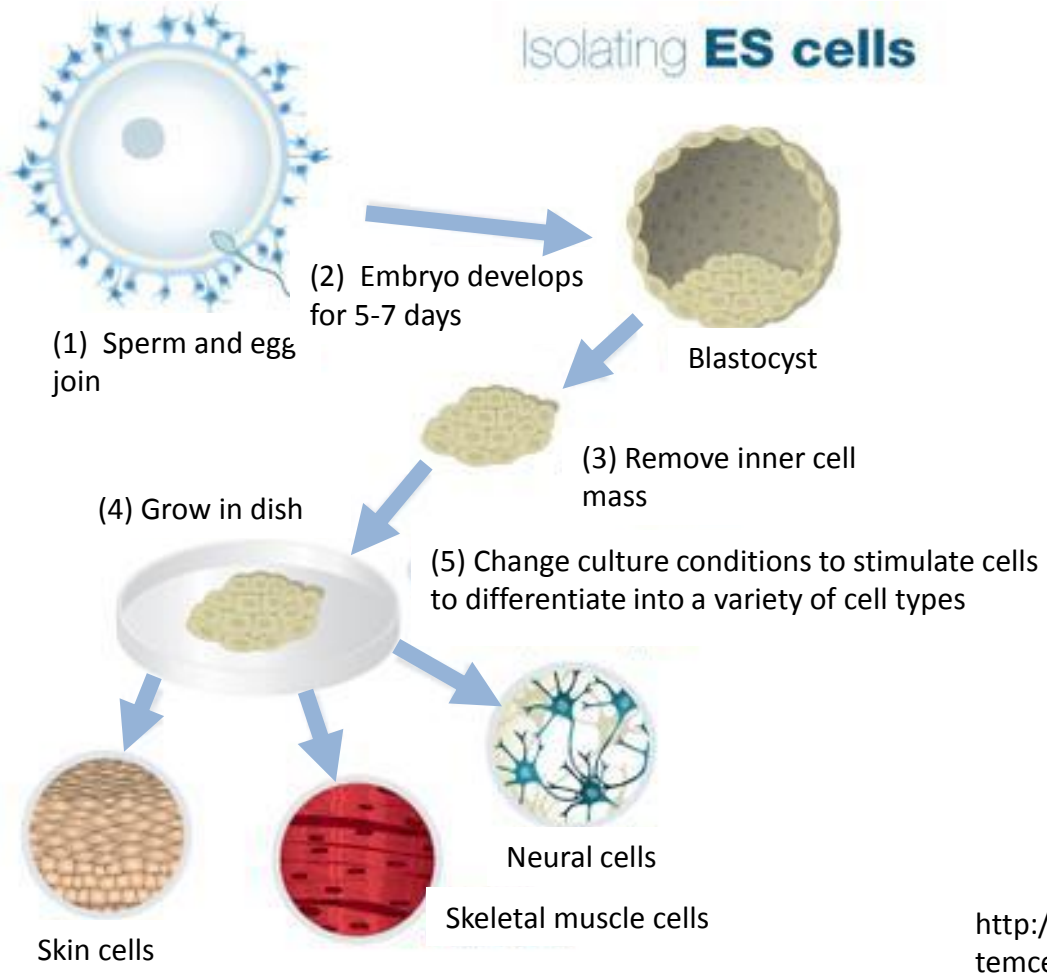
Stem Cell based options

Study of disease and drug screening	Restorative and cell therapy

- Mechanism of disease
- Drug screening
- Cell therapy

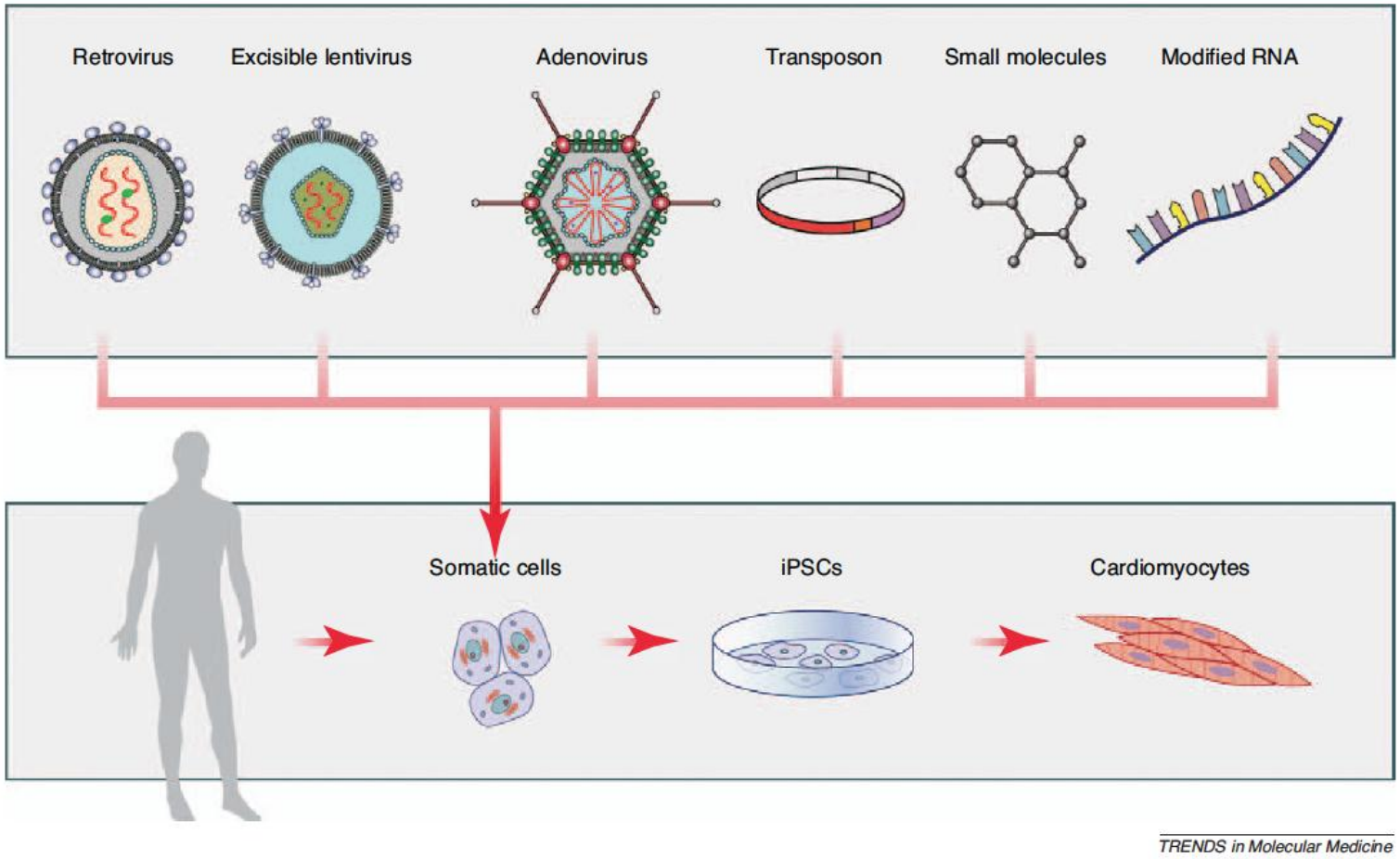
What is a stem cell and an iPS cell?

Embryonic Stem Cells



http://learn.genetics.utah.edu/content/tech/stemcells/quickref/isolatingEScells.jpg

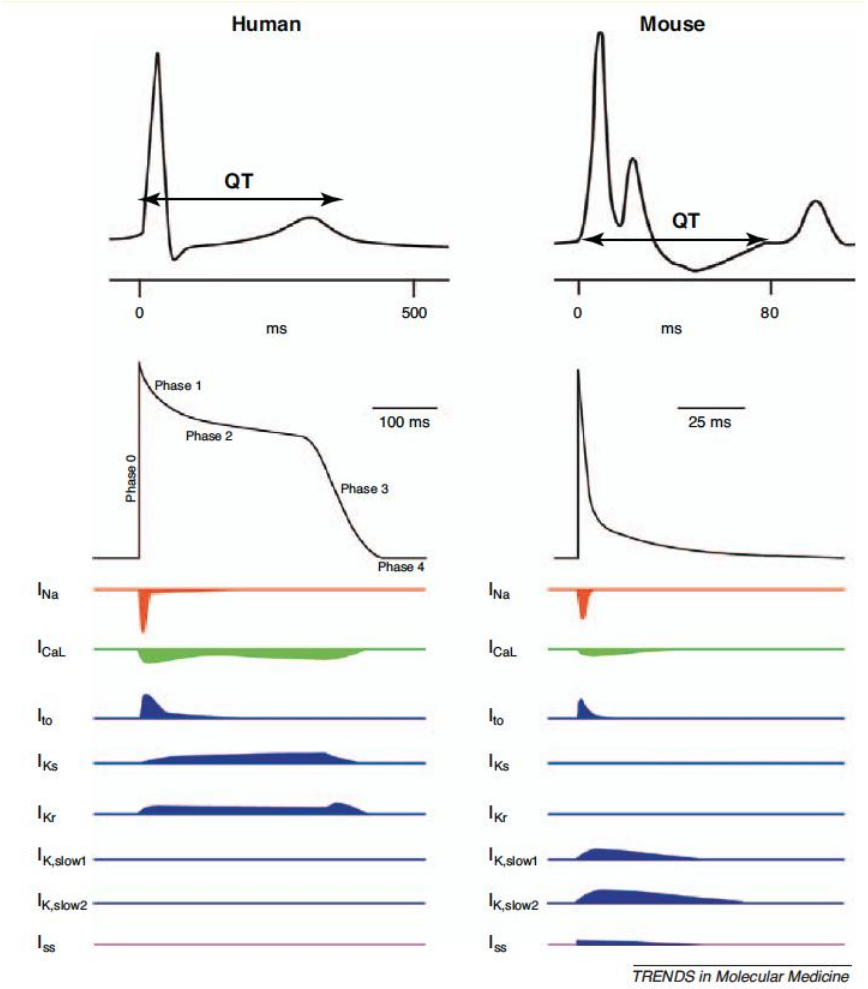
Generation of human induced pluripotent stem cells



Davis et al., Trends in Mol Med (2012)

Why are iPS cells so important?

Electrophysiological differences between adult human and mouse Cardiomyocytes



Davis et al., Trends in Mol Med (2012)

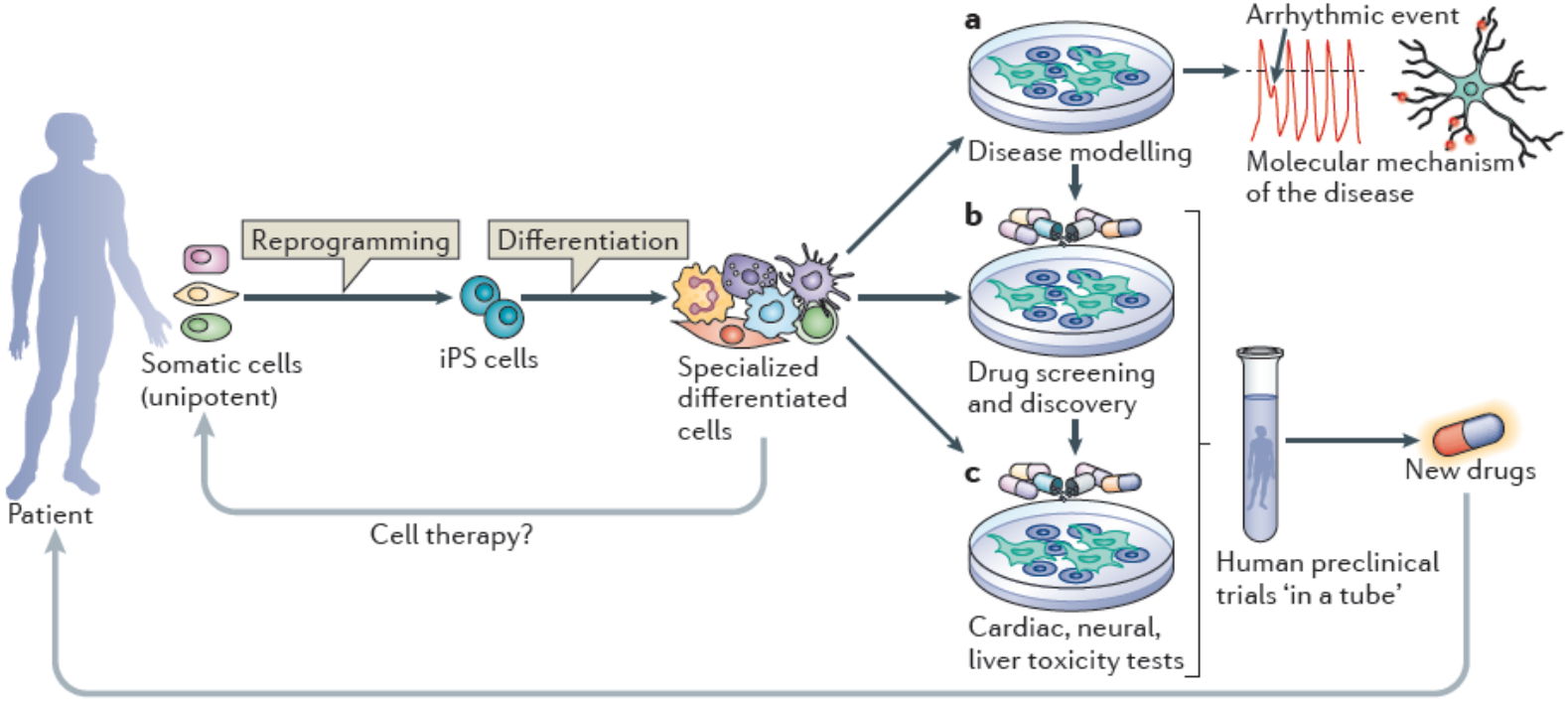
Medicines withdrawn from the market due to cardiotoxicity

Drug	Indication	Market span	Reason for withdrawal
Astemizole (Hismanal)	Antihistamine	1983–1999	Withdrawn from the market due to TdP
Cisapride (Propulsid)	Prokinetic	1988–2000	Withdrawn from the market due to TdP
Droperidol	Antipsychotic/antiemetic	1970–2001	Withdrawn from UK market due to TdP
Grepafloxacin	Antibiotic	1997–1999	Withdrawn from the market due to TdP
Levomethadyl	Opioid agonist	1993–2001	Withdrawn from use in EU due to TdP; use restricted in USA
Prenylamine	Anti-anginal	1960s–1988	Withdrawn from the market due to TdP
Rofecoxib (Vioxx)	Non-sterodial anti-inflammatory drug	1999–2004	Withdrawn because of risk of myocardial infarction
Sertindole	Antipsychotic	1996–1998	Withdrawn from the market due to TdP
Terodiline	Bladder incontinence	1986–1991	Withdrawn from the market due to TdP
Tegaserod (Zelnorm)	5-HT_4 agonist	2002–2007	Withdrawn because of imbalance of cardiovascular ischaemic events (including heart attack and stroke); was available through a restricted access programme until April 2008
Terfenadine (Seldane)	Antihistamine	1982–1997	Withdrawn because of risk of cardiac arrhythmias; superseded by Fexofenadine

TdP: Torsade de pointes.

Braam et al., Trends in Pharmacological Sciences (2009)

Human iPS cell derivation, differentiation and applications

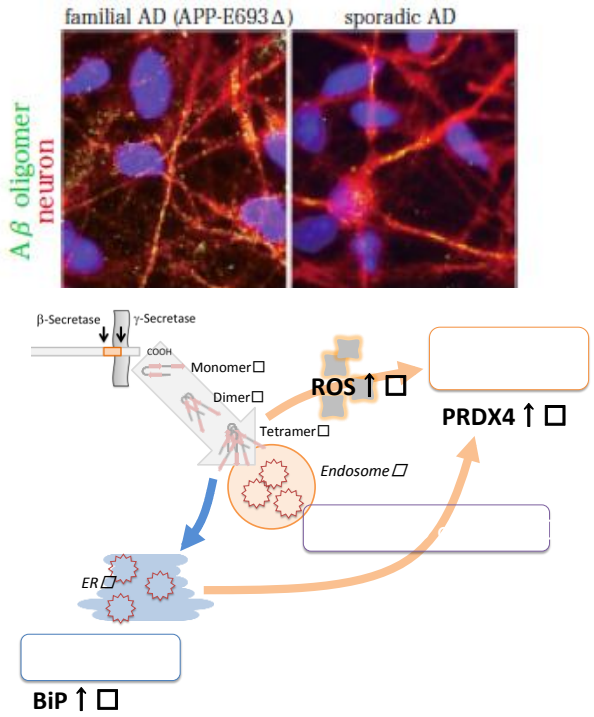


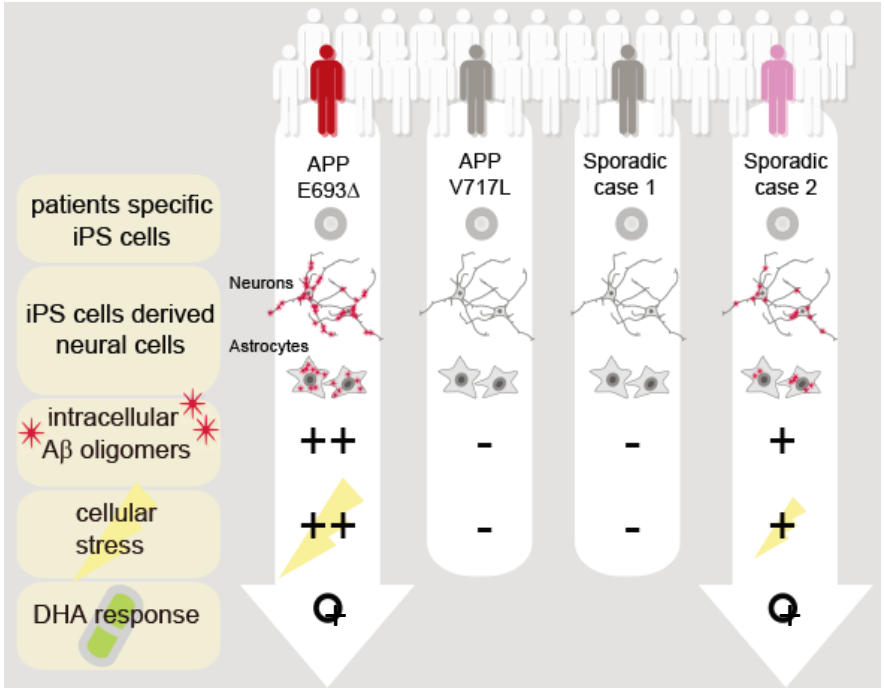
Bellin et al., Nature Reviews: Mol Cell Biol (2012)

The global advancement of medical research & treatment

Latest developments in stem cell research

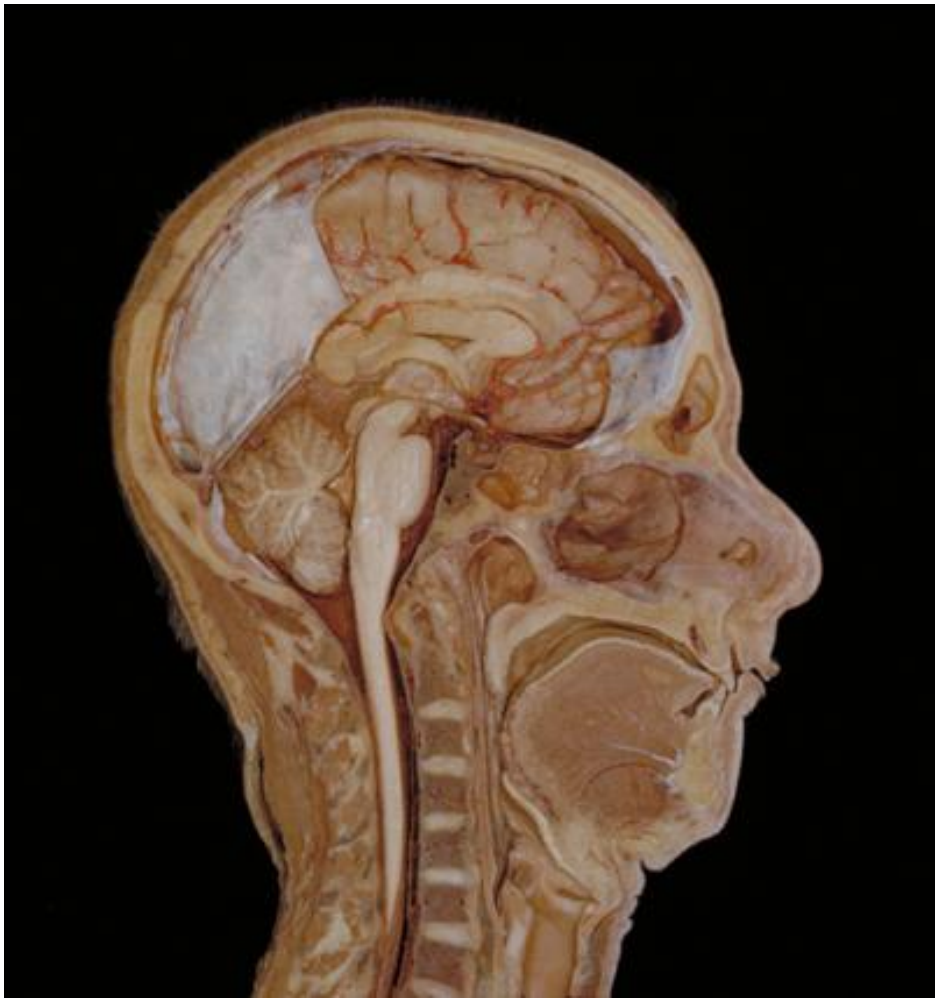
Disease modeling using Alzheimer's disease patient iPSCs



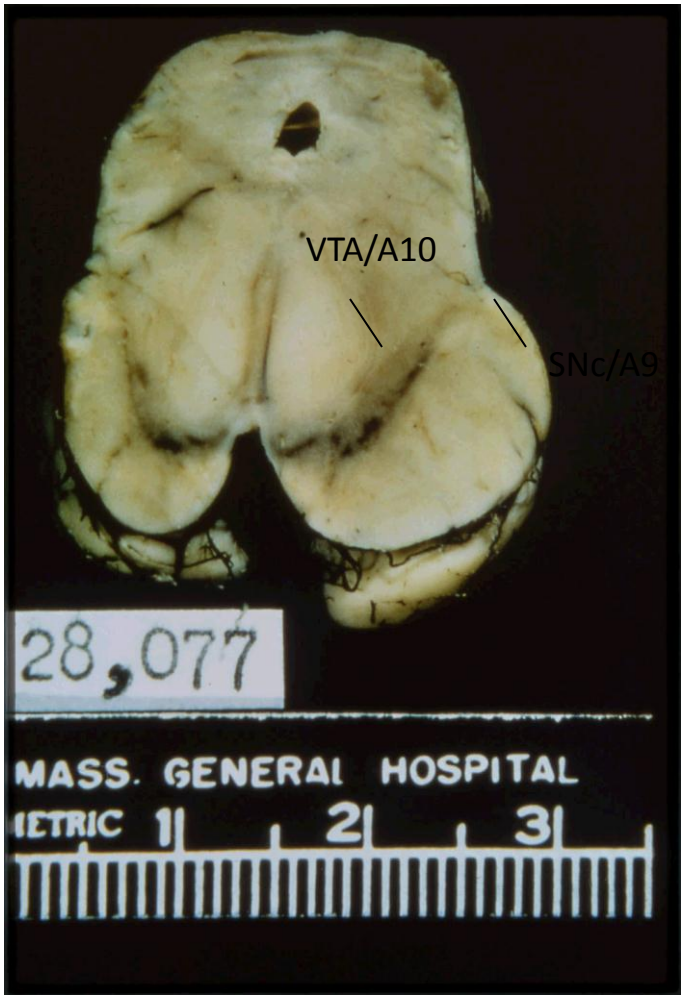


Patient iPSCs would be useful for precision early diagnosis

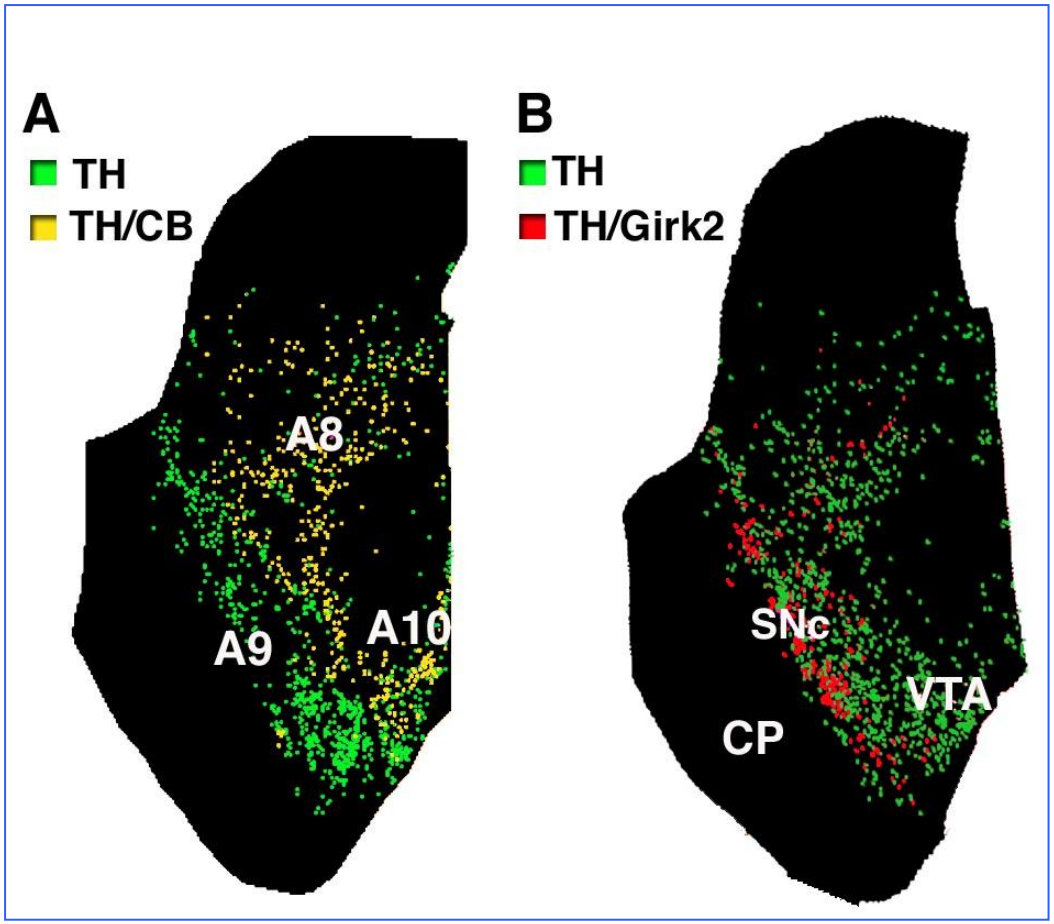
Background: Parkinson's disease



SNc and VTA relevance to Parkinson's disease



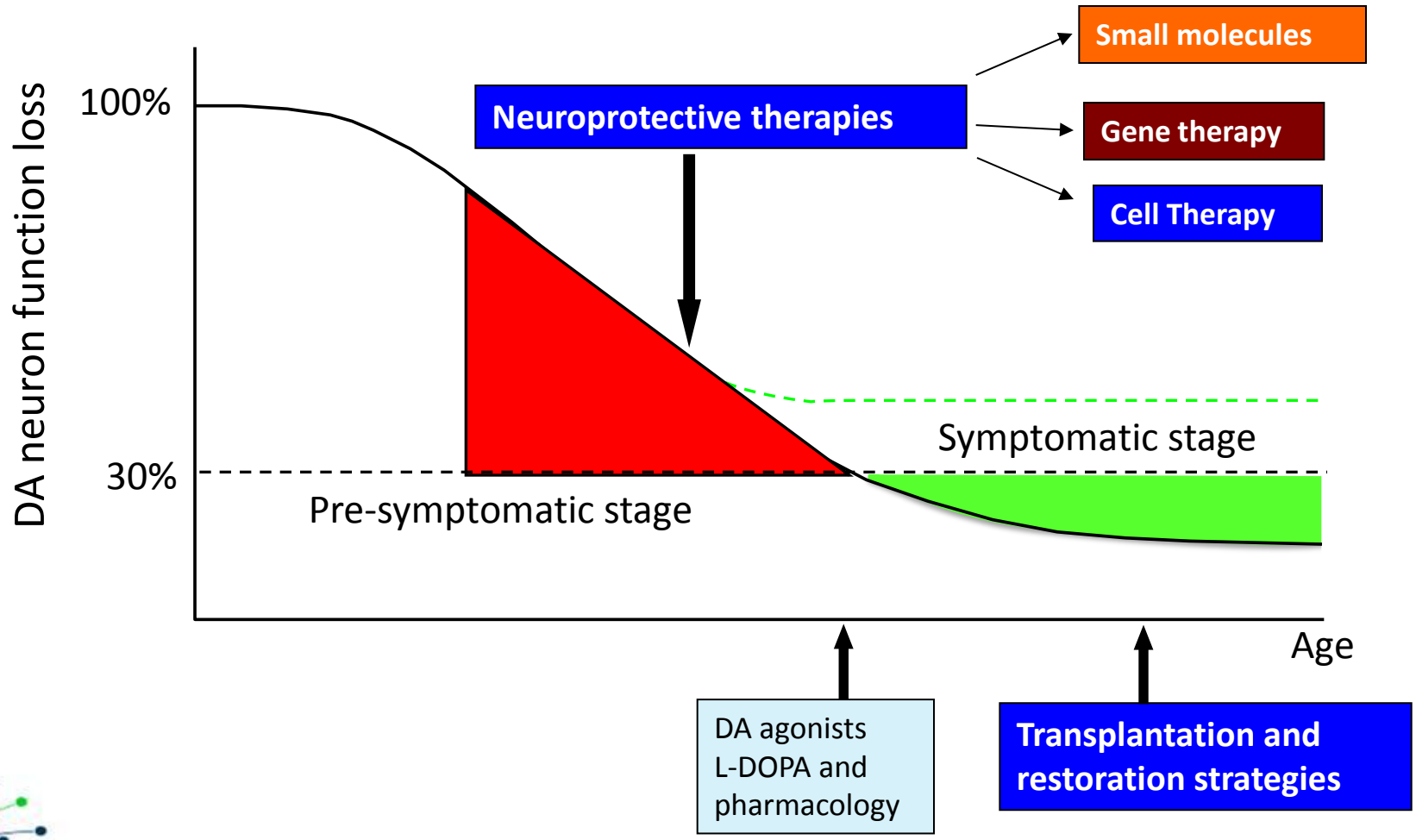
The most vulnerable midbrain DA neuron type (A9) in PD -- allowing basal gangliamovement initiation -- has specific connections, physiology, cell biology and gene expression



1. Cell type specific gene expression of midbrain dopaminergic neurons.. vulnerability and protection. Chung CY et al *Hum. Mol. Genet. 2005*

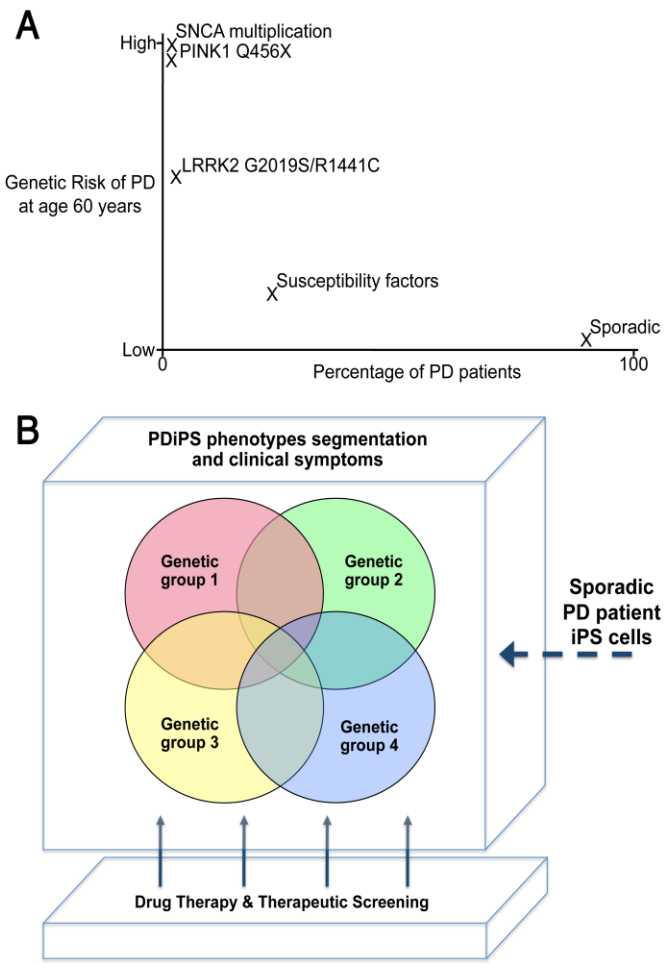
2. Cell type analysis of functional fetal dopamine cell suspension transplants in patients with Parkinson's disease Mendez I et al *Brain 2005*

Initiation, progression and treatments of midbrain dopaminergic (DA) synaptic and cellular loss in Parkinson's disease

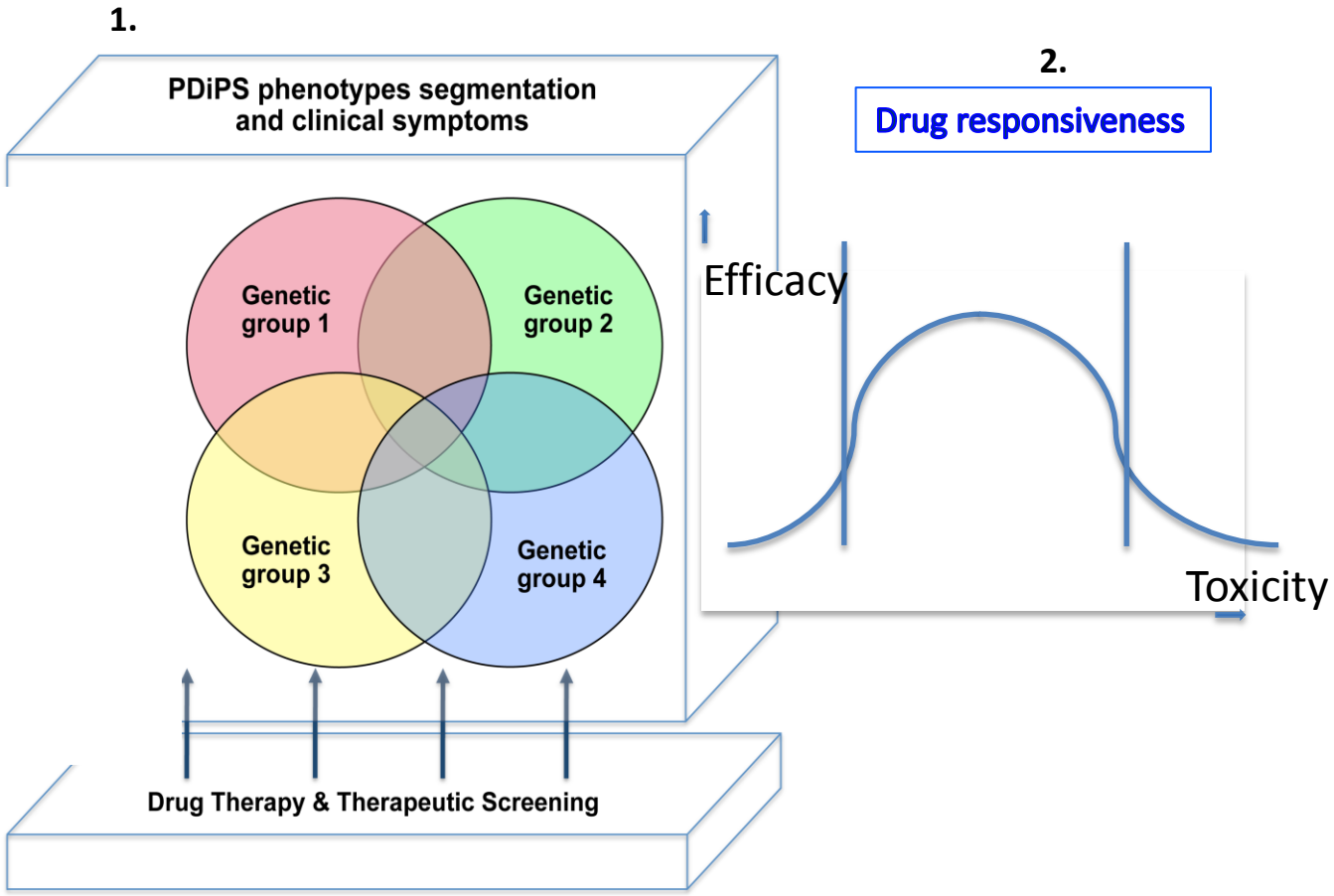


Parkinson's Disease Patients: Causes and diagnostically defined human populations

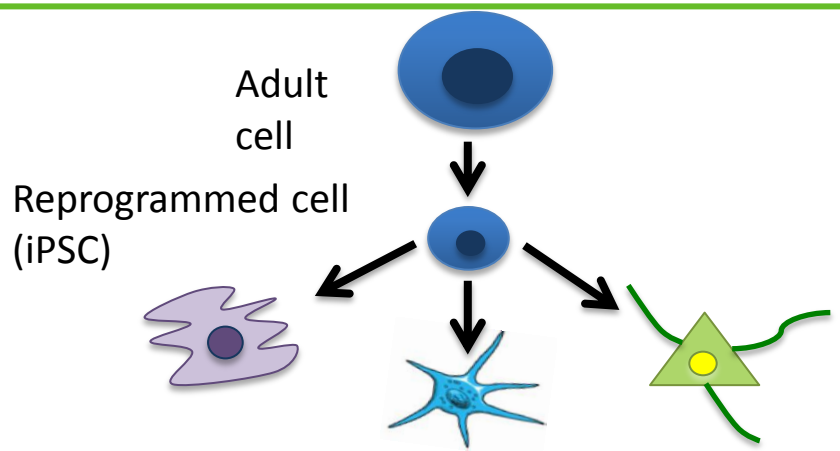
Pure genetic forms are rare but provide contexts For approaches using PD iPS cells



Goal: Matching high risk individuals by iPS cell-derived cell function analyses and drug responsiveness



Strategies for disease modeling in a dish using iPSCs



Disease Simulation Process

1

a) none

b) known genetic inherited

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a) chemically induced

b) genetically induced

c) combined a & b

Time

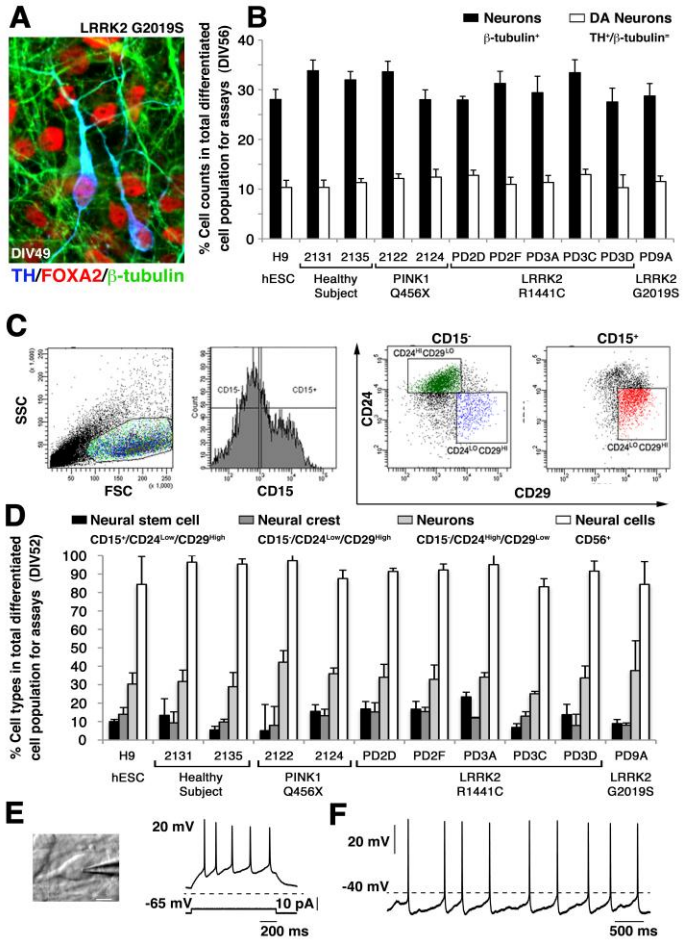
Readout: Disease outcome/pathology of adaptive responses

Cell, organelle and molecular phenotypes

Isacson O

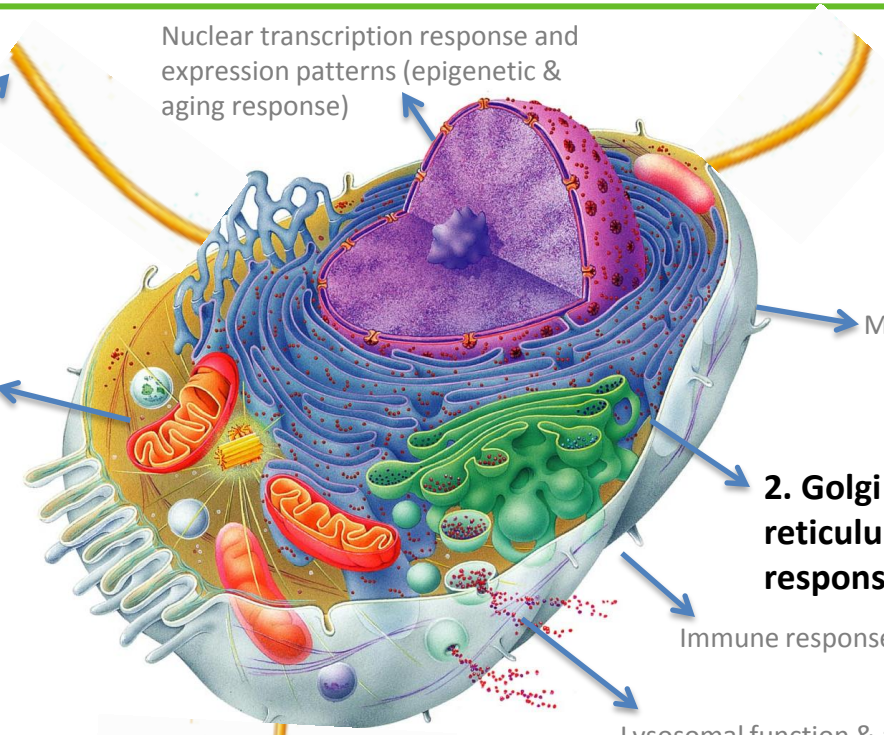
PD patients iPSC derived neural cells: Spontaneous cellular phenotypic changes in dish

Validation and standardization of individuals' PD iPS cells



Cooper et al. *Science Translational Medicine*, 2012

PDiPSC derived neurons can be used to reveal gene or disease specific cell responses



Nuclear transcription response and expression patterns (epigenetic & aging response)

Dendritic input and neurite morphology

Membrane integrity

1. Mitochondrial function and aging

2. Golgi to Endoplasmic reticulum unfolded protein response and function

Immune response

Lysosomal function & autophagy

Electrophysiological parameters

3. Transport, cytoskeletal & neurite extension/retraction responses

Adaptive electrophysiological response

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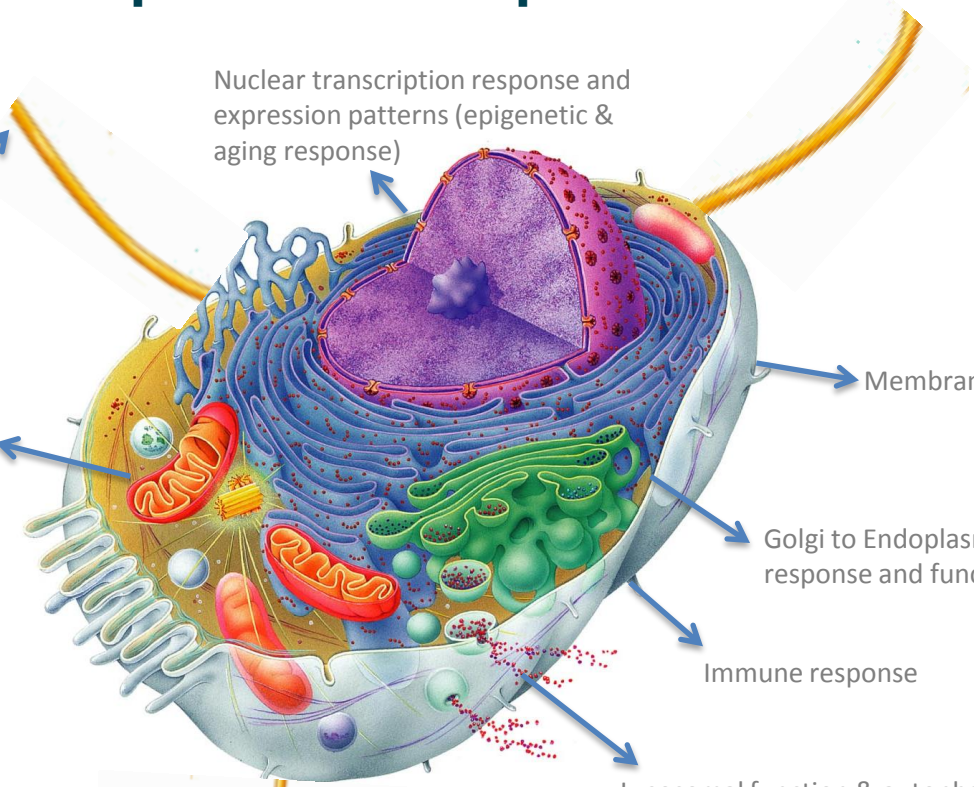
PDiPSC derived neurons can be used to reveal gene or disease specific cell responses



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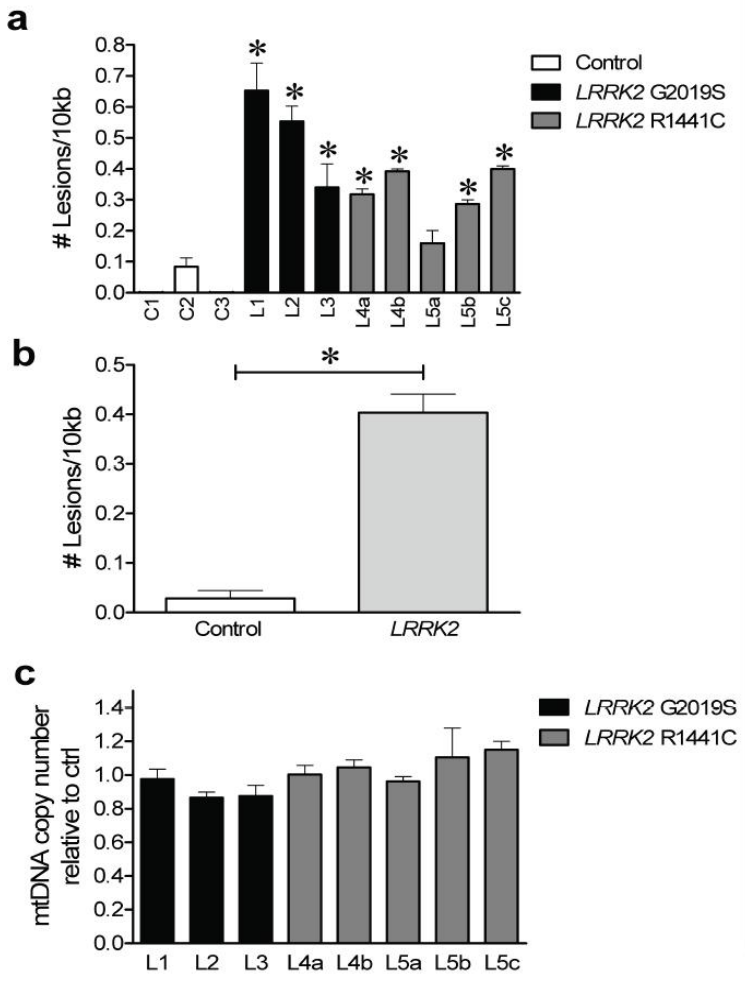
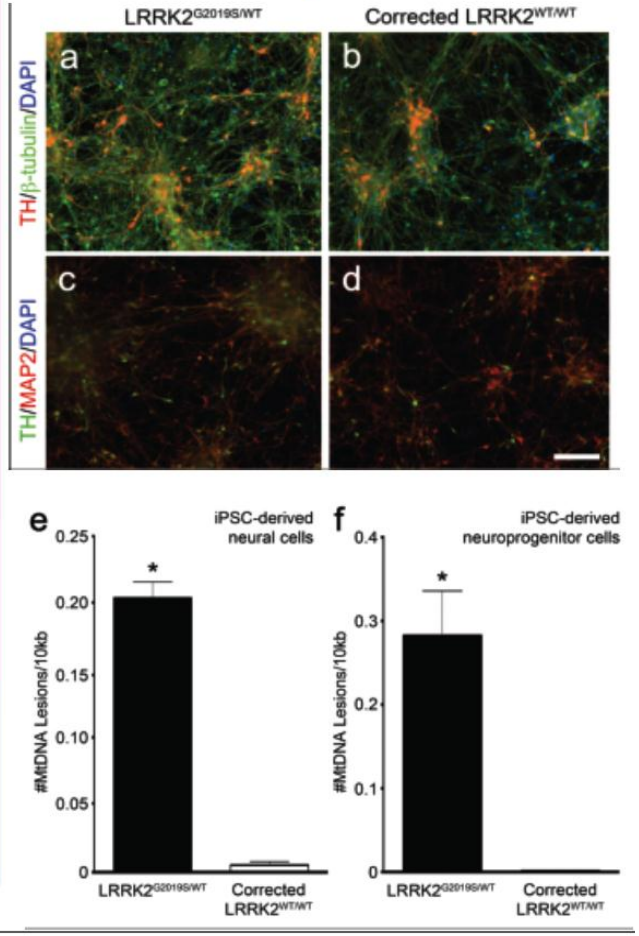
Adaptive electrophysiological response

LRRK2 mutations in human iPS cell-derived neural cells are associated with increased mtDNA damage



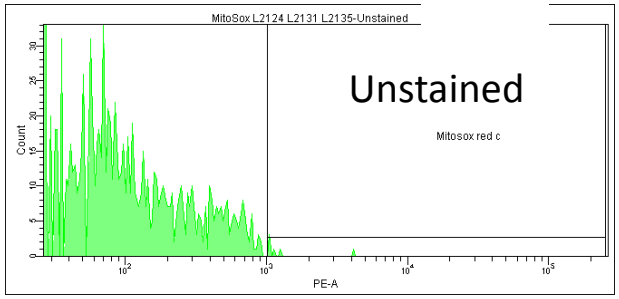
Gene correction of iPS cells from LRRK2 PD patients restores neural mitochondrial gene damage and expression

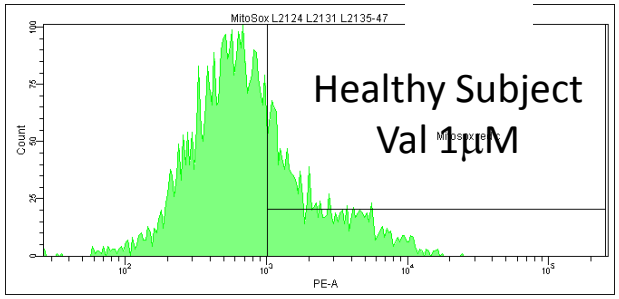


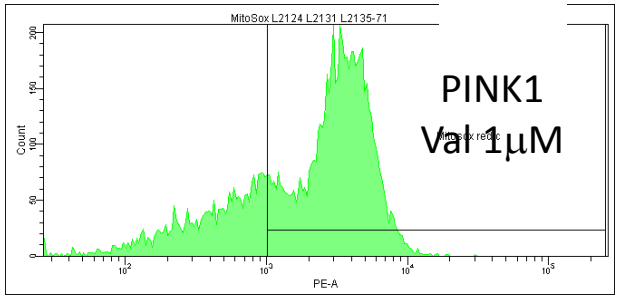
Sanders L et al, 2013

PD patients iPSC derived neural cells: Cellular phenotypic responses after challenge in dish

PINK1 PD iPS cell-derived neuronal cells produce much higher levels of free-radical species after mitochondrial K+ depolarization than sibling controls

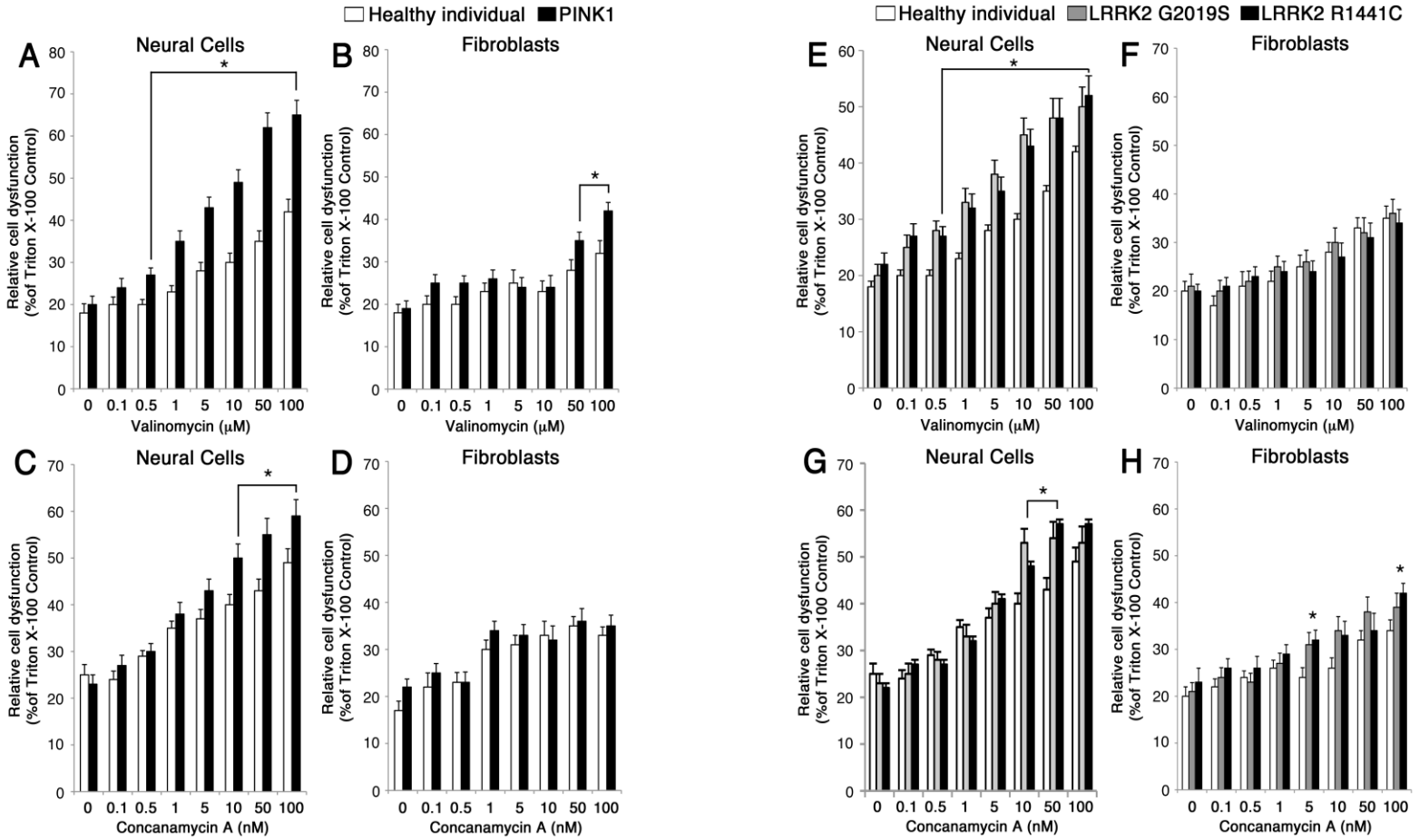






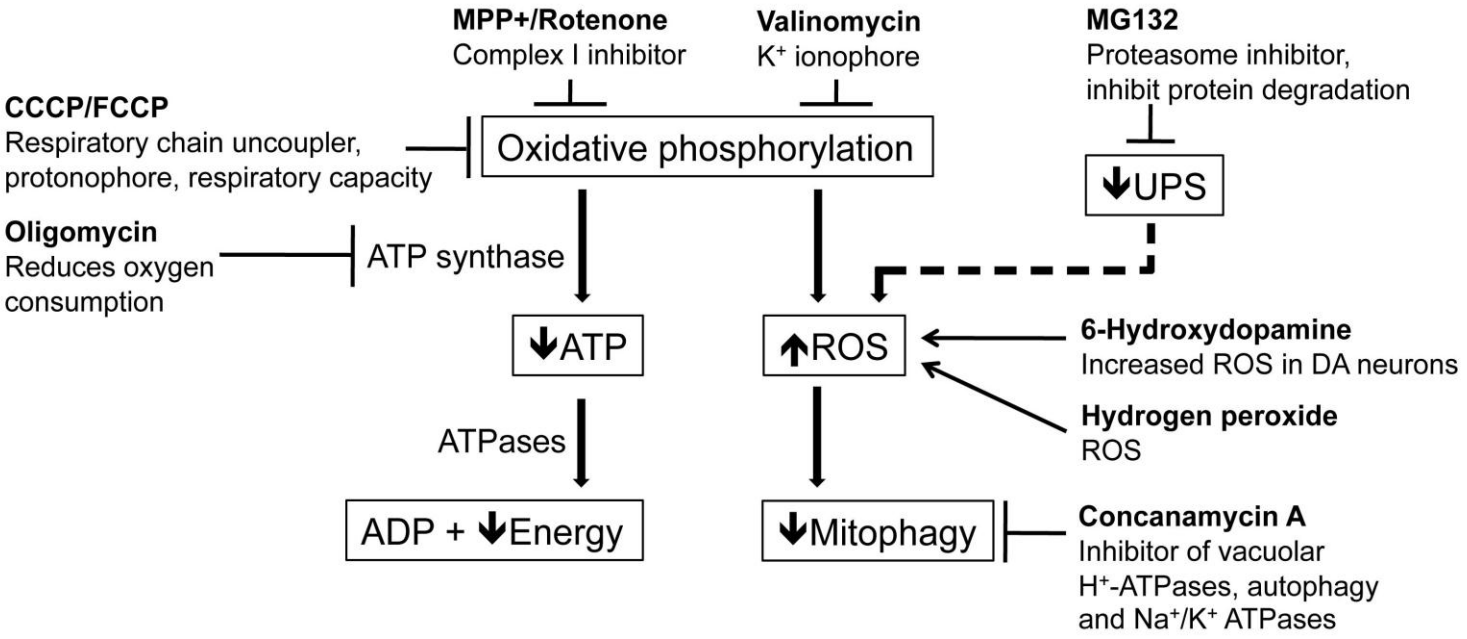
Cooper et al. *Science Translational Medicine*, 2012

Genetically linked PD Neural cells from iPS cells are more sensitive to cellular mitochondrial stress than fibroblasts



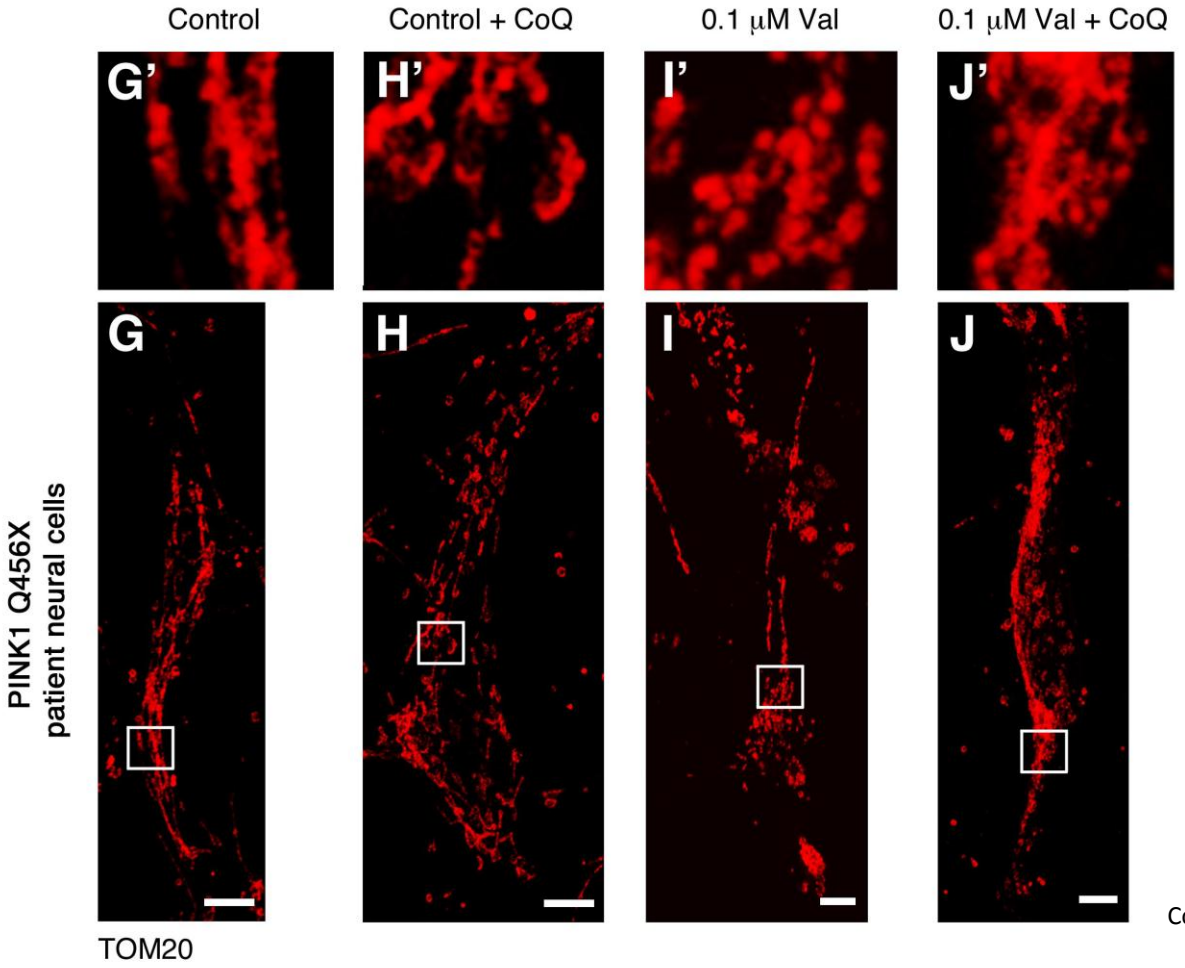
Cooper et al. *Science Translational Medicine*, 2012

Chemical stressors produce both specific and converging responses from *different* genetic forms of PD



PDiPS Genotype	Chemical stressors of differentiated neural cells (phenotypes)
PINK1 Q456X	Valinomycin (with increased mROS), MPP+, Concanamycin A, H_2O_2 & MG312
LRRK2 R1441C	Valinomycin & Concanamycin A
LRRK2 G2019S	Valinomycin & Concanamycin A
SNCA Trip.	MPP+ & MG132

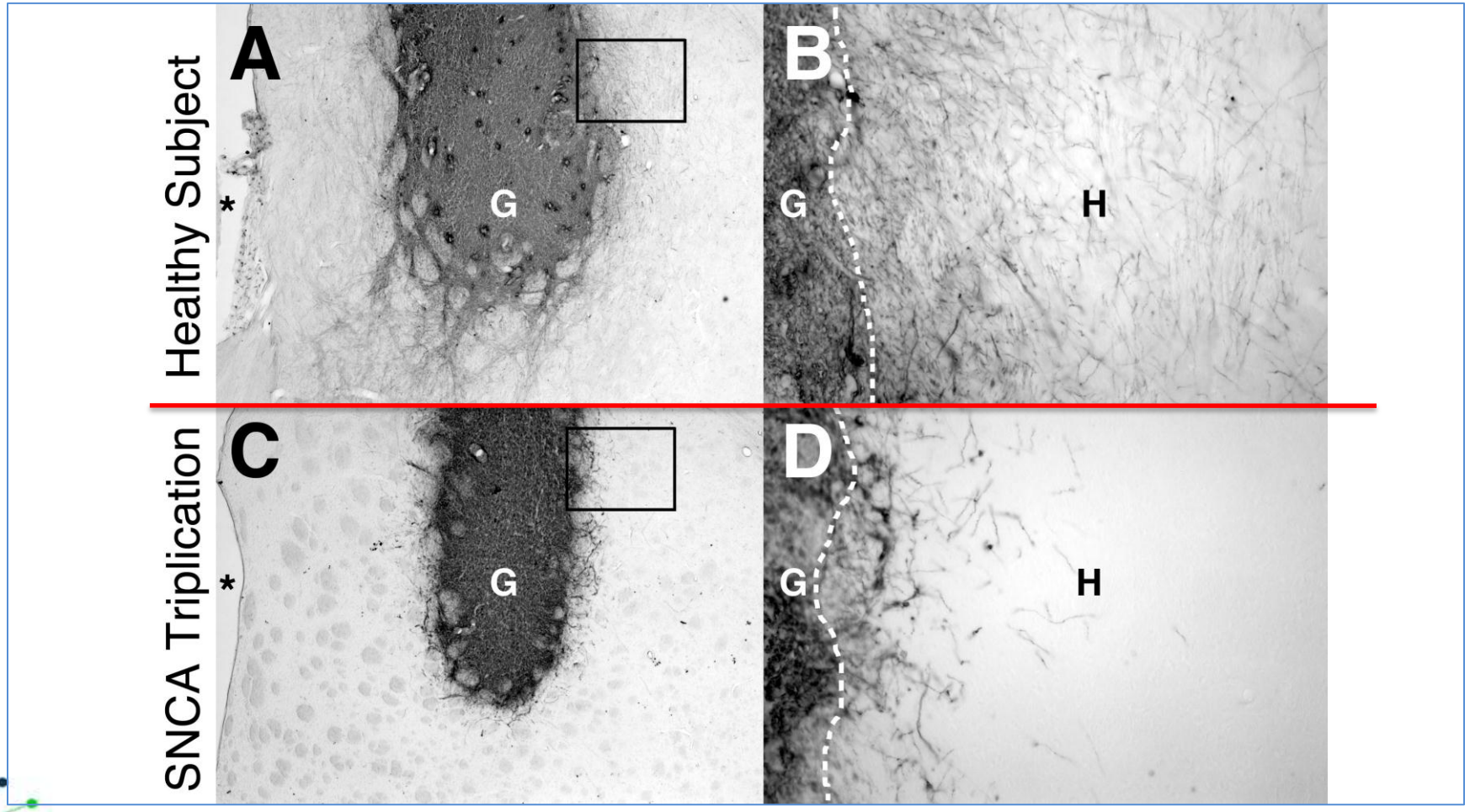
Rescue of PD patient neural cell by antioxidant-like and other drugs



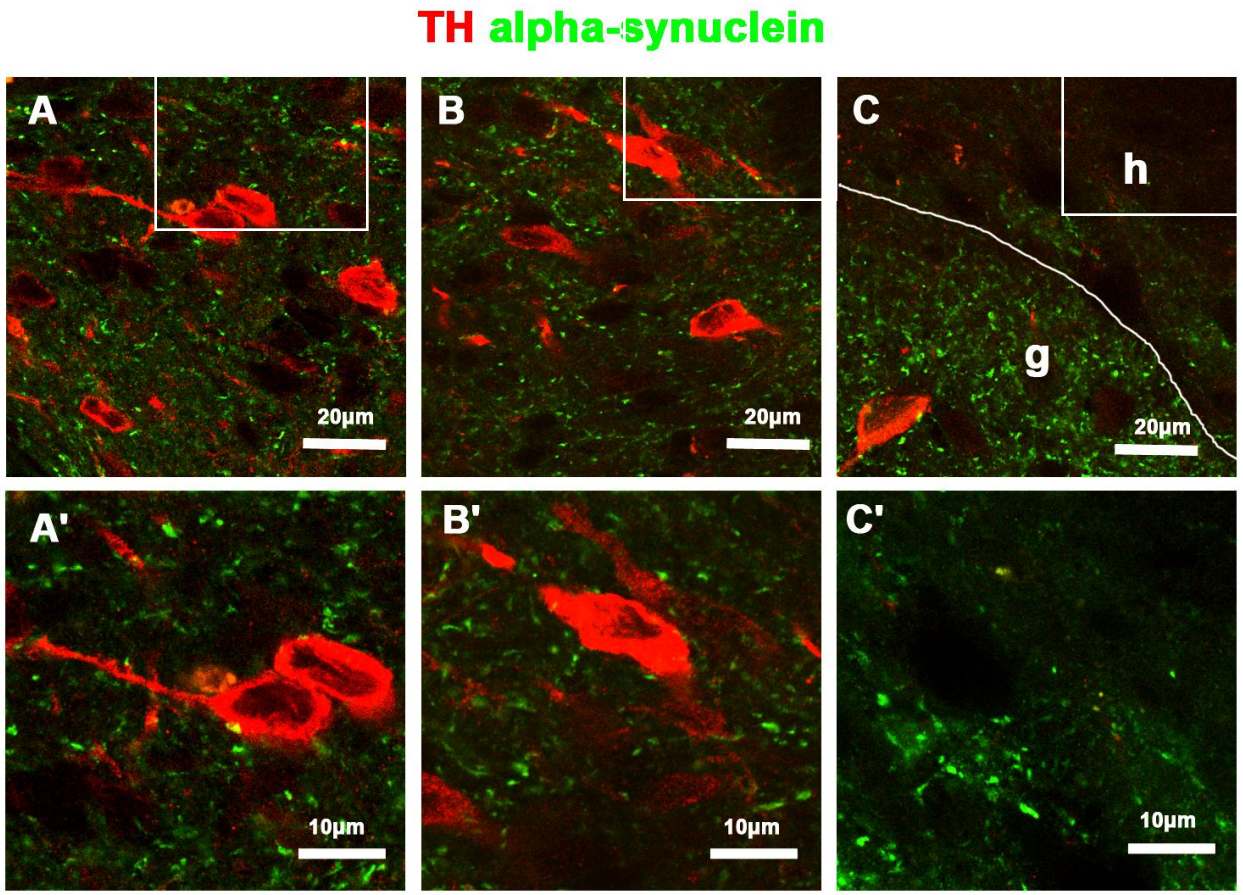
Cooper et al. *Science Translational Medicine*, 2012

PD patients iPSC derived human neurons transplanted as an in vivo brain assay

Transplanted PDiPSC SNCA3x neurons have reduced neurite extension in brain for the 1st month in vivo

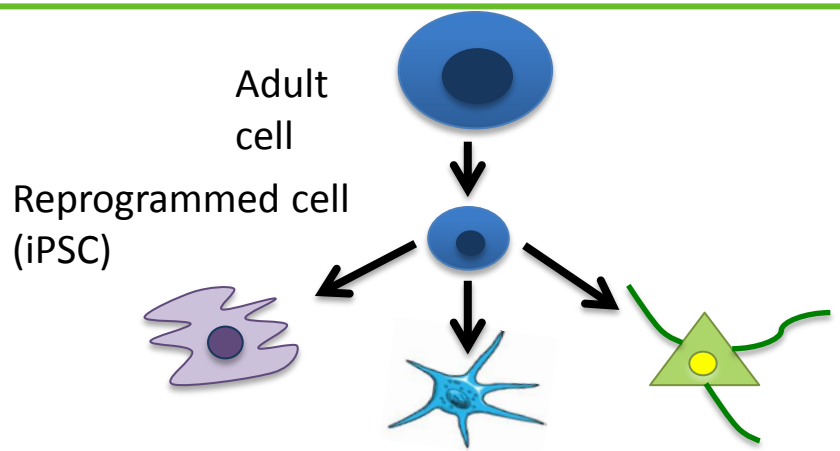


In vitro differentiated then transplanted hPDiPS cells: human specific alpha syn and TH/DA stained after 6 months in vivo



Patients iPSC derived cells in a dish: Summary and Outlook

Strategies for disease modeling in a dish using iPSCs



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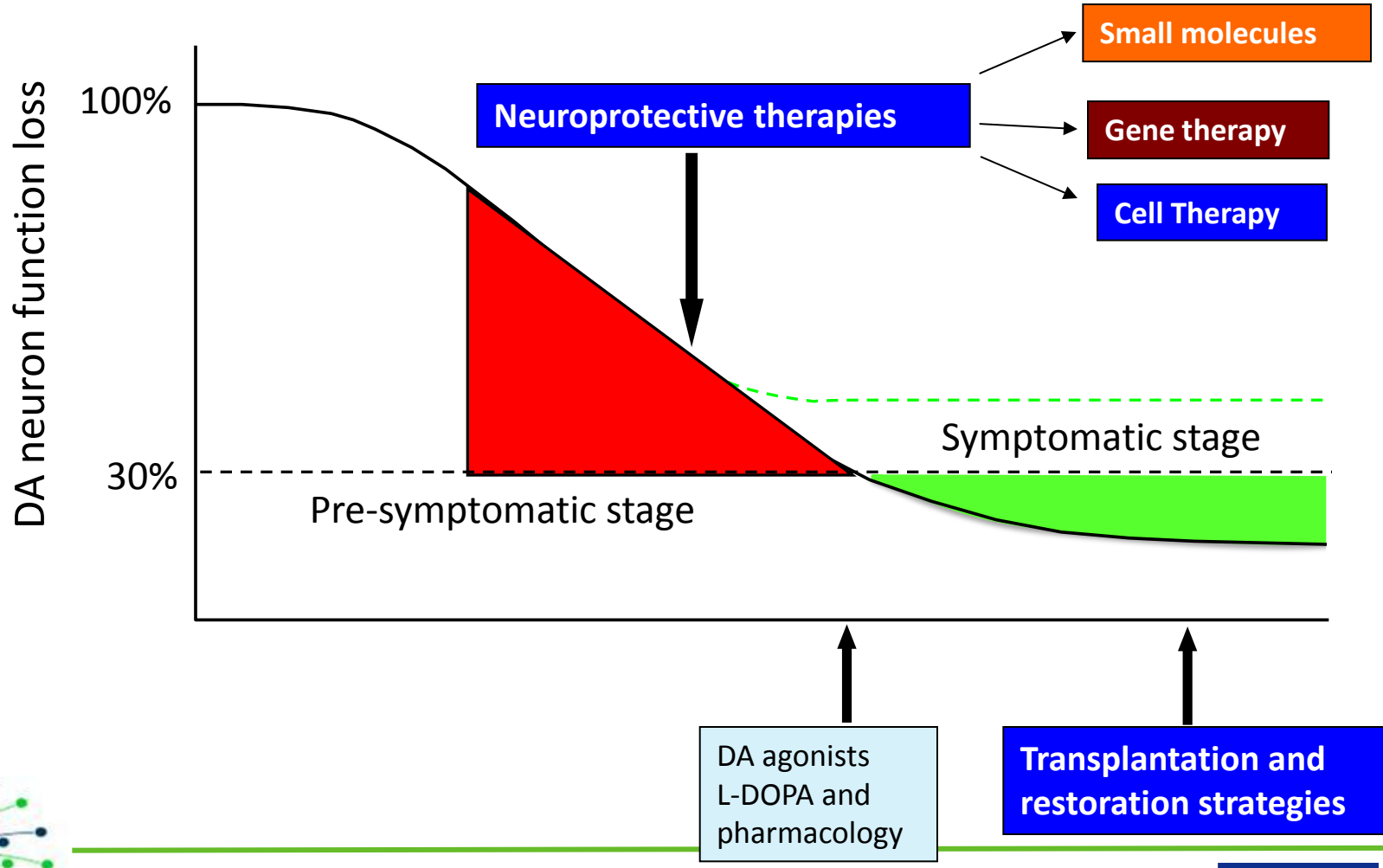
Readout: Disease outcome/pathology of adaptive responses

Cell, organelle and molecular phenotypes

Isacson O

Outlook: iPSC derived neurons can be used to discover cellular pre-symptomatic or pre-disposing neurobiology and neuroprotective treatments



Promises and hurdles in using human iPS cells for disease modeling and drug discovery

- **Controls:** Human induced pluripotent stem (iPS) cells from the same patient can show biological variability
- **Drug discovery and toxicity:** Early risk prediction for new drugs reduces attrition rates and costs
- **Cell-autonomous versus non-cell-autonomous:** Human iPS cells are most suitable for investigating monogenetic diseases with complete penetrance that display cell-autonomous defects on differentiated cells
- **Immaturity of differentiated cells:** Differentiated cells from human pluripotent stem cells are immature
- **Effects of genetic and ethnic backgrounds:** Many diseases manifest with incomplete penetrance so that patients harbouring the same mutation have different phenotypes
- **Novel biological insights:** A key challenge in human iPS cell biology is to generate new (patho)physiological insights.

Bellin et al., Nature Reviews: Mol Cell Biol (2012)

Neuroregeneration Laboratory

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Laurie Sanders

Parkinson's Institute, CA
Birgitt Schuele

NINDS PDiPS Consortium

National Institute of Neurological Disorders and Stroke
National Institutes of Health
Reducing the burden of neurological disease...

THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH

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Thank you