Strategies and Prospects for Organ Regeneration in Aging

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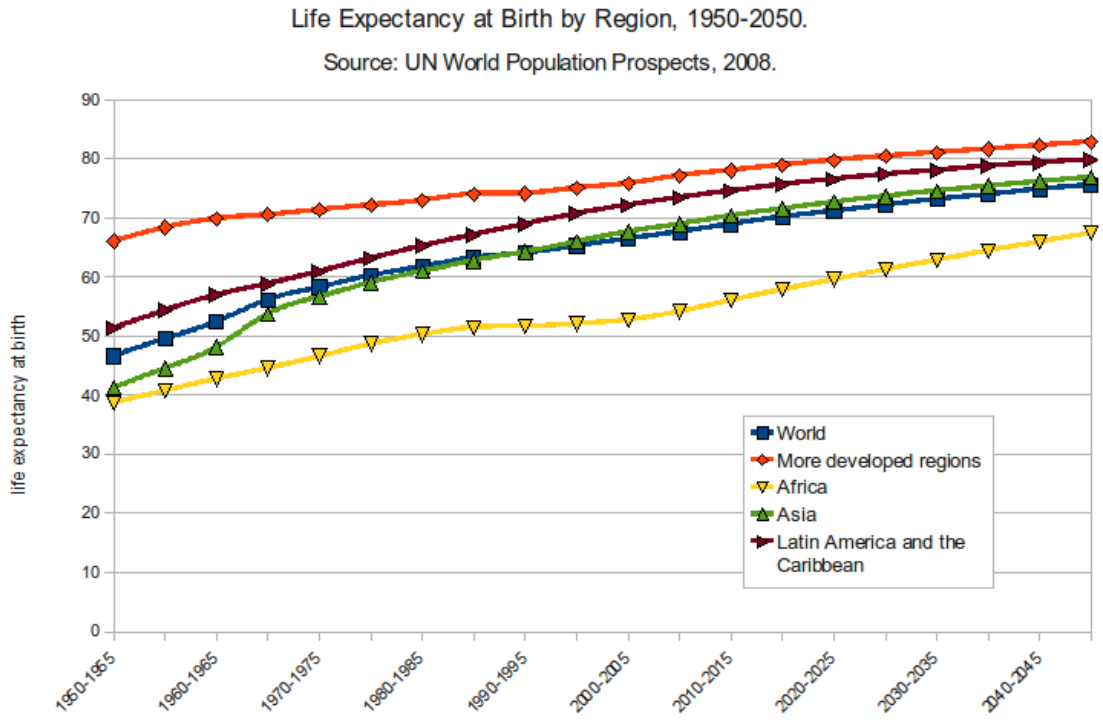
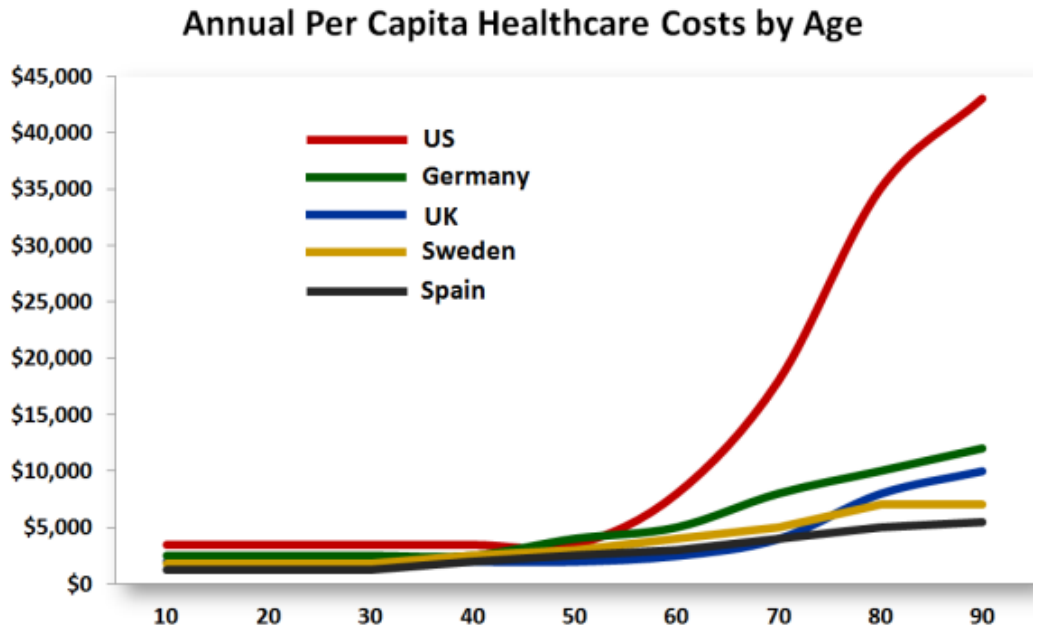
Overview of Talk

- Background on aging and organ function: Statement of the Problem
- Senescence ⟷ Aging-related diseases
- Definitions- emphasis on Stem Cells
- Strategies and limitations for organ regeneration
- Prospects/Future considerations


Life Expectancy at Birth by Region, 1950-2050.
Source: UN World Population Prospects, 2008.
life expectancy at birth
0
10
20
30
40
50
60
70
80
90
1950-1955
1960-1965
1970-1975
1980-1985
1990-1995
2000-2005
2010-2015
2020-2025
2030-2035
2040-2045
World
More developed regions
Africa
Asia
Latin America and the Caribbean


Annual Per Capita Healthcare Costs by Age
$45,000
$40,000
$35,000
$30,000
$25,000
$20,000
$15,000
$10,000
$5,000
$0
10
20
30
40
50
60
70
80
90
US
Germany
UK
Sweden
Spain

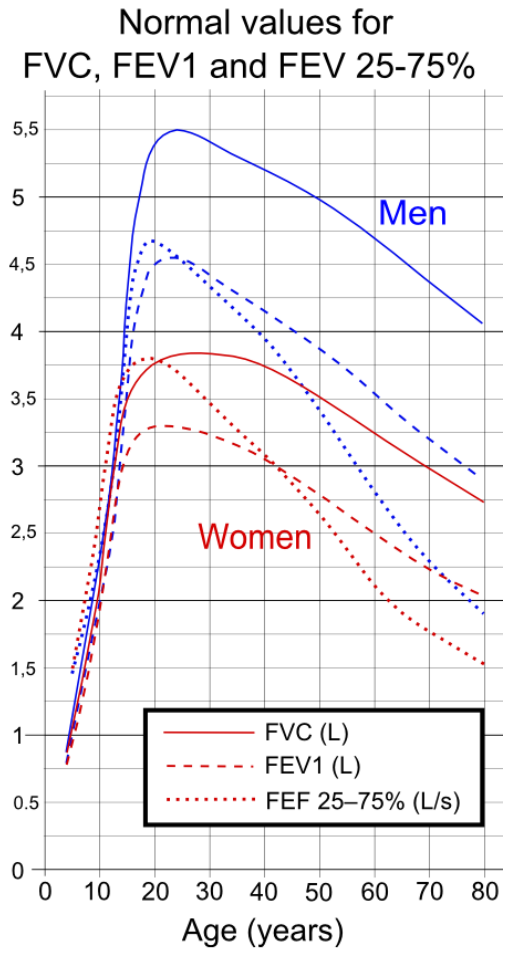
Slate.com

Decline in Organ Function with Aging

- Kidney
- Lung
- Brain
- Heart
- Liver
- Structural tissues (muscle, bone)

- TREATMENTS LARGELY DIRECTED AT SYMPTOMS

Decline in Lung Function



Haggstrom et al Br. Med. J. 1989

Important Points

- Many organs have tremendous reserve (lung)
- Loss of cells that carry-out organ function (*parenchymal*)
- Replacement with non-functional tissue (scar)
- Disease vs. Senescence

Diseases of Aging

- COPD
- Kidney Failure
- Diastolic Heart Failure
- Alzheimer's, Parkinson's
- Osteoporosis
- Diabetes (type II)
- Cancer

Senescence

- Cellular
- Organ
- Organismal
- Theories: evolutionary pressure, oxidants, mutations, immunological, wear and tear, STEM CELLS

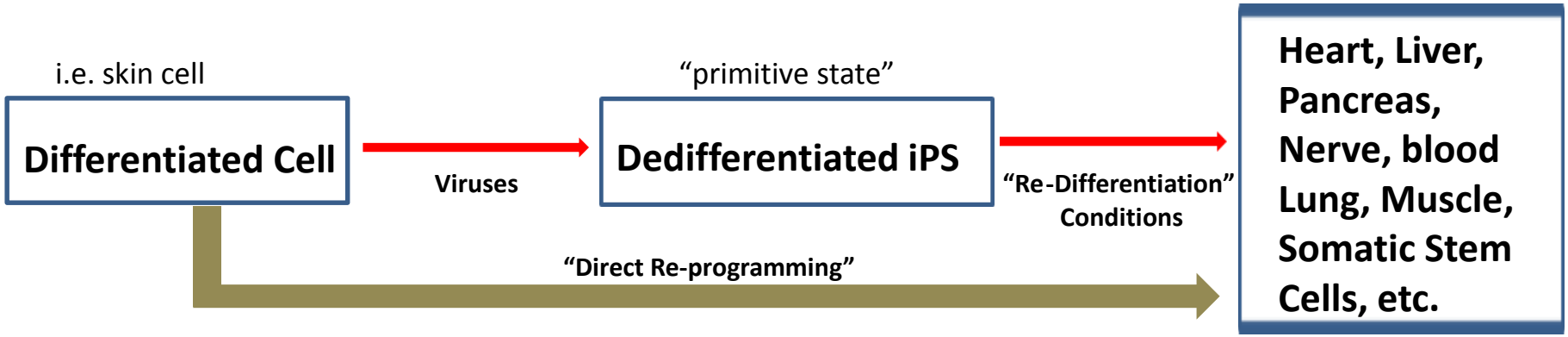
Stem Cell: Definition

- Self renewing cells that have capacity to give rise to defined repertoire of differentiated parenchymal cells (blood, skin, neural)
- Important in development, lower animals,
- Varying degree of potency: uni-potent, bi-potent, pluripotent etc.
- Somatic, germ, embryonic**
- Reside in specialized anatomic sites: niches

Embryonic Stem Cells

- Derived from inner cell mass of embryo
- Pluripotent-can give rise to all tissues of mammalian organism
- Therapeutic potential, immune problems, moral issues
- iPS cells-***i***nduced ***p***luripotent state in a fully differentiated cell (viruses, *in vitro*)

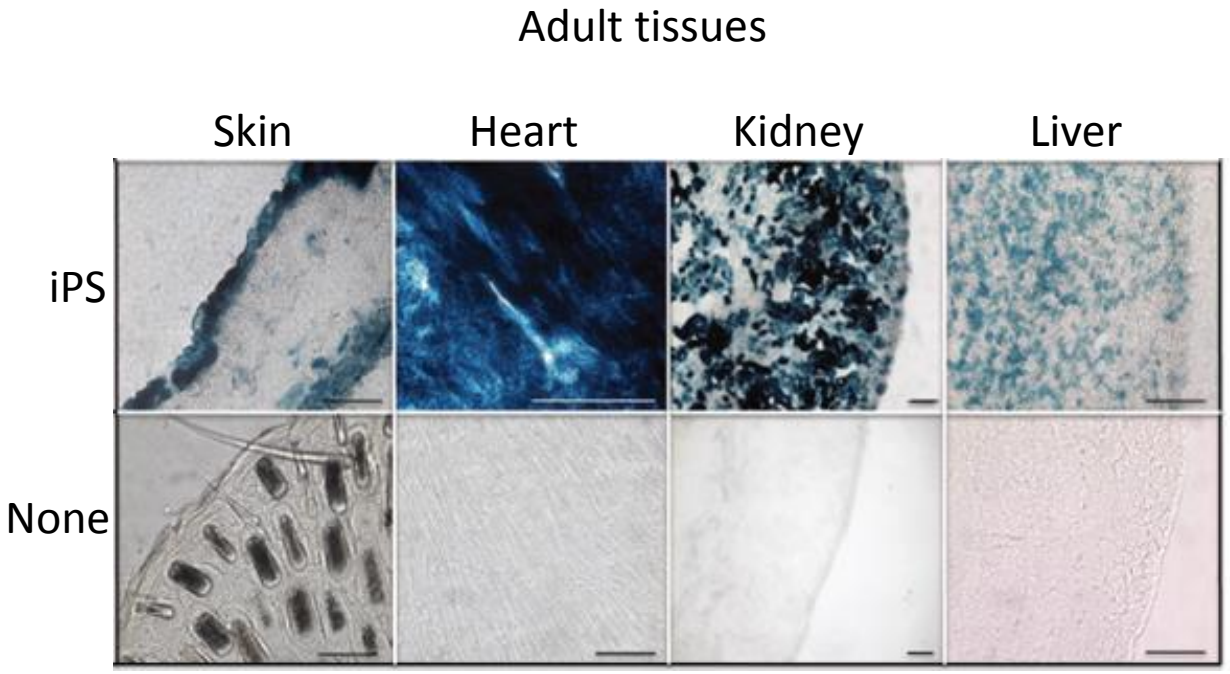
iPS Cells



- Revolutionary, paradigm shifting
- Overcomes moral and immune limitations
- Basic Biology, Disease study, Drug optimization, Fix Genetic defects

(Takahashi and Yamanaka: Cell 2006)

iPS Pluri-potency



(Boland, Nature 2009)

Organ Regeneration in Humans

- Difficult to determine
- Liver, skin, and blood
- Age dependency
- Rodents, invertebrates (worms, zebra fish)

Goal of Organ Regeneration: Restore Function

- Single cells vs. Multi-cellular structure
- How to do it?
- Delivery
- Space

General Strategies for Organ Regeneration

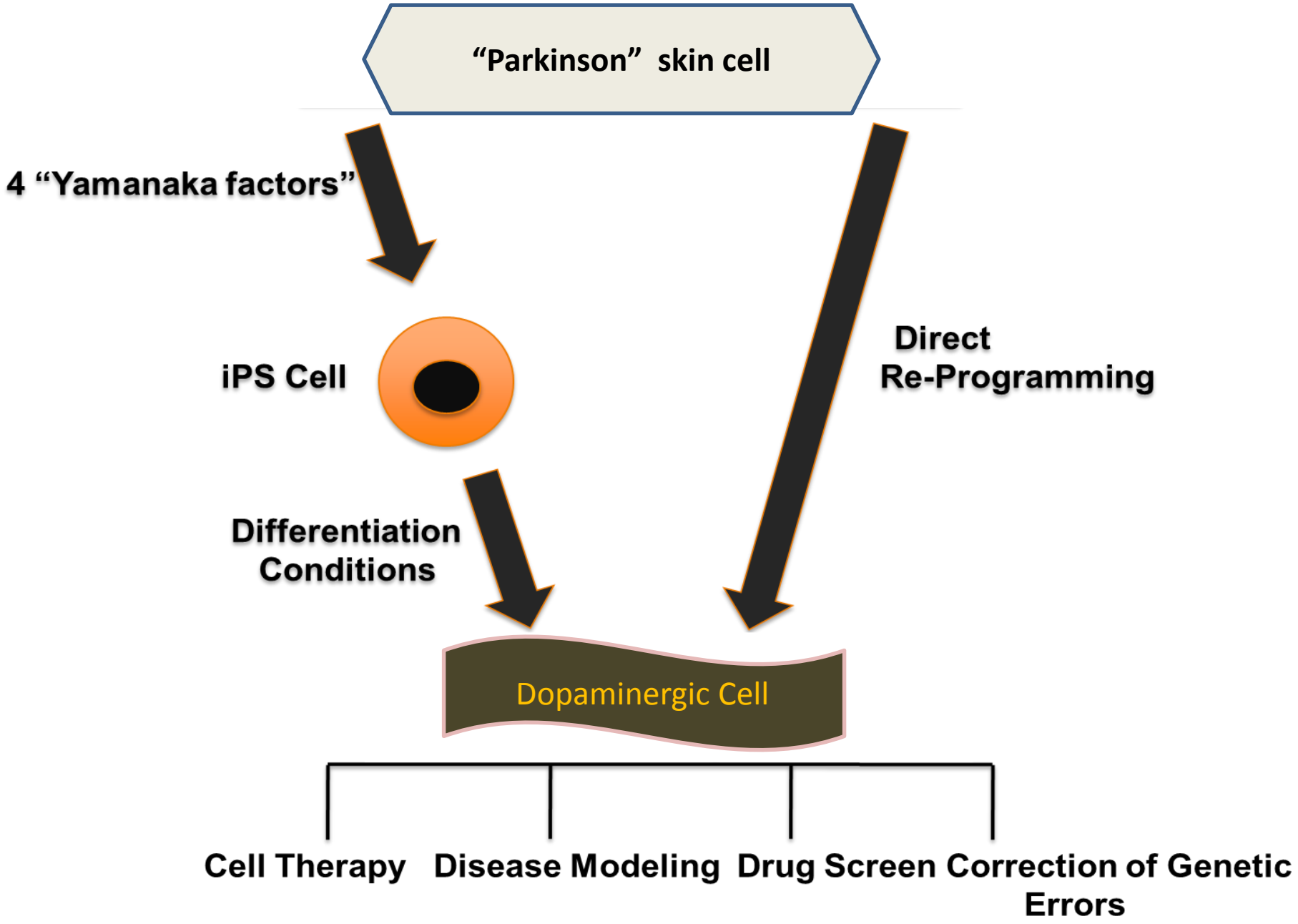
- New organs
- New parenchymal cells
- New stem stems or more stem cells
- Deliver stimulatory or inhibitory signals

Whole Organs

- Transplantation
- Animal source
- De-cellularized organs
- Organoids-stem cells and supporting cells, self-organize *in vitro* (gut, brain, liver)
- Mechanical devices

Parenchymal Cells

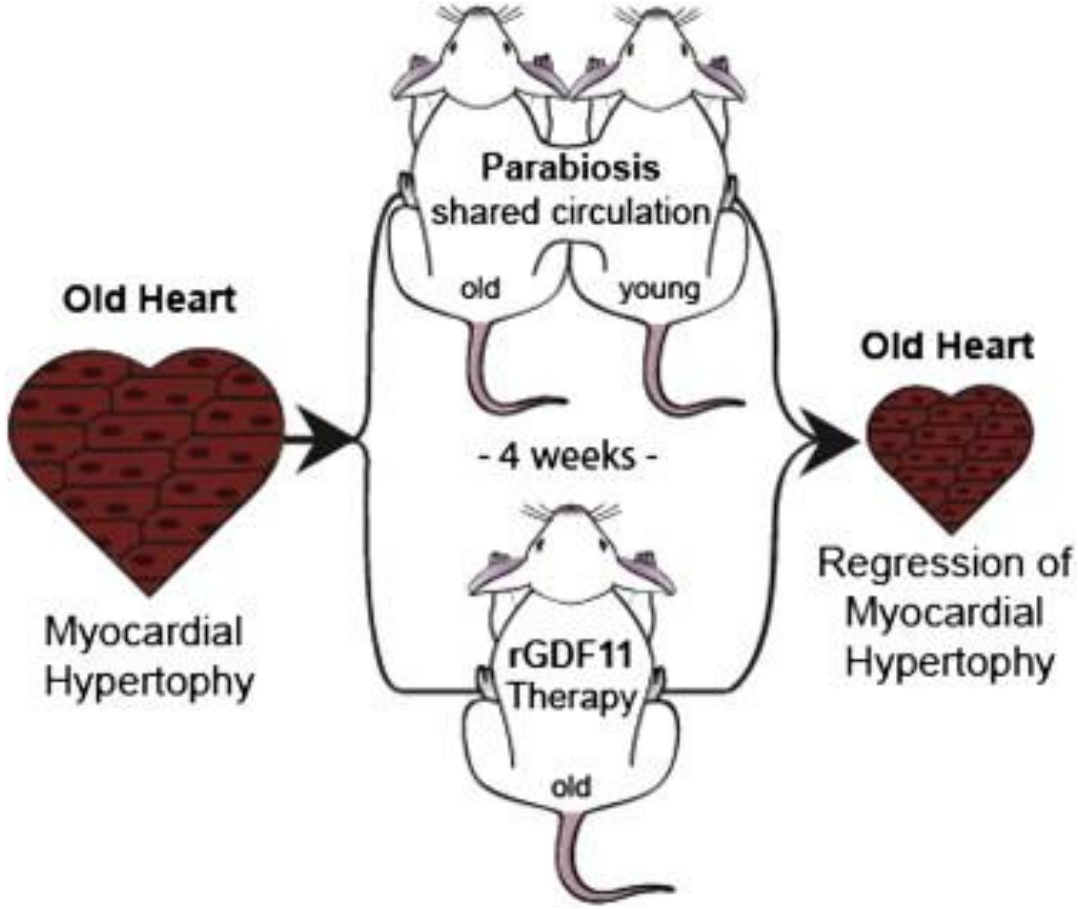
- Deliver fully differentiated cells
- Deliver stem cells
- Deliver iPS cells
- Limitations


"Parkinson" skin cell
4 "Yamanaka factors"
iPS Cell
Direct
Re-Programming
Differentiation
Conditions
Dopaminergic Cell
Cell Therapy
Disease Modeling
Drug Screen
Correction of Genetic
Errors

Deliver Signals

- Circulating Signals (normal)
- Developmental signals
- Signals used in lower animals
- Direct *in vivo* re-programming (heart)
- Inhibit causes of senescence (anti-oxidants, resveratol, rapamycin etc.)

Circulating Factors



(Loffredo et al, Cell 2014)

Prospects/Issues

- Early, applicability to humans
- Basic biology
- Many technical obstacles
- Toxicities
- Costs/Regulations- (Geron^{R} trial)
- Appropriate Priority

-continued-

- Simple
- Low toxicity
- Scalable
- Reality
- Basic research