Stem Cell Update
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Virus enters here

72 h

25 μm
VZ is a niche for asymmetric neurogenic divisions

SVZ is a niche for symmetric neurogenic divisions
Location of Tbr2+ cells in the developing cortex

Asymmetric neurogenesis (neuronal diversity)

Symmetric neurogenesis (neuronal multiplication)

Kornack, Rakic, Neuron, 1995
• Do intermediate progenitor cells contribute to the expansion of primate cerebral cortex?

Chenn and Walsh, 2002

Symmetric radial glial divisions expand founder cell population

Symmetric neural stem cell (radial glial) divisions
<table>
<thead>
<tr>
<th>Date</th>
<th>Page</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>2/12/2009</td>
<td>5</td>
<td>Smart et al, 2003</td>
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**Primate**

- Mouse
  - E11 to E17

**Mouse**

- E13.5
  - Sox2
  - Tbr2
  - PH3

**Human**

- GW14
  - Outer SVZ
  - Inner SVZ

**GFP retrovirus and slice culture labels radial clones in the OSVZ**

**Distribution and mode of neural stem and progenitor cell divisions**

- Glutamatergic
- Symmetric neurogenic
- Asymmetric neurogenic / IP-genic
- Symmetric progenitor

**Jan Lui, David Hansen**

**Phenotypes**

- PH3
- Pax6
**Summary**

Radial glia generate neurons directly and through intermediate precursor cells.

Radial glia undergo asymmetric division (generate neuronal diversity).

Intermediate progenitor cells undergo symmetric divisions (expand neuron number).

**Human outer SVZ contains IPCs and ‘displaced’ radial glia.**

After embryonic neurons are produced, radial glia transform into astrocytes.

After embryonic neurons are produced, radial glia transform into astrocytes.
Radial ependymal cells persist in the brains of adult reptiles
Where do stem cells come from?

A stem cell primer

Human developmental continuum

Embryonic stem (ES) cells

Skin biopsy

Factors

Ectoderm

Brain

Skin

Ectoderm

Brain

Mesoderm

Muscle

Blood

Mesoderm

Muscle

Endoderm

Lung

Gut

Liver

Endoderm

Lung

Gut

Germline

Sperm

Egg

Germline

Sperm

Egg

Embryo

3-5 days

Adult organs

Placenta

Cord blood

Bone marrow

The Therapeutic Promise of stem cells

Regenerative therapy (replace dead/injured tissue)

Deliver Genes/Drugs/Trophic factors

Drug Discovery and testing

Understand Human Development

Study Human Disease
**Fetal transplants (‘proof of principle’?)**

- 1987 - open-label trials showed cell survival and function
- 1990s – two NIH funded double-blind sham surgery controlled trials:
Grafted neurons can survive and produce DA

Problems with fetal midbrain grafts that stem cells may overcome:

- Too few neurons (unlimited supply)
- Variable quality and cell preparation (standardized defined cell type)
- Poor migration and integration (better integration?)
- Graft rejection (patient-specific cells)

The Therapeutic Promise of stem cells

For the study of human disease
Embryonic Stem Cells show astrocytes poison motor neurons in ALS


Induced Pluripotent Stem (iPS) Cells for the study of ALS
Clinical Trials

Autologous BM-derived cells stroke, spinal cord injury, etc.
Technology has outpaced our understanding.

<table>
<thead>
<tr>
<th>Status</th>
<th>Cell type</th>
<th>Company</th>
<th>Disease target</th>
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</thead>
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<tr>
<td>On-going</td>
<td>Human fetal NSCs</td>
<td>Stem Cells Inc.</td>
<td>Batten’s disease</td>
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<td>hESC-derived OPCs</td>
<td>Genentech</td>
<td>Spinal Cord Injury</td>
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<td>Approved</td>
<td>ACT Inc., The London</td>
<td>ACT Inc., The London Project to Cure AMD</td>
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<td>Pending</td>
<td>hESC-derived pigment</td>
<td>ReNeuron Group PLC</td>
<td>Macular Degeneration</td>
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<td></td>
<td>epithelia</td>
<td></td>
<td>Stroke</td>
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Also close behind: Osiris Therapeutics Inc., Cytori Therapeutics Inc., Novocell, and others.

Future Prospects

Important Future Directions
Complete the Stem Cell Building
Construction and site development cost of $103M
45,000 sf to house 25 investigators representing cardiovascular, neural, pancreas and liver, hematopoiesis, musculoskeletal, epithelial, and reproduction pipelines.
House core facilities in cell sorting, imaging, cell tracking, histology, high-throughput DNA sequencing, bioinformatics, and clinical trial design, as well as labs to derive new hESCs. An existing GMP facility complements the cores.
Recruit Faculty
Currently comprised of 123 principal investigators, 74 core clinician and scientists
17 experts recruited over four years (including Shinya Yamanaka): skin-derived stem cells, liver regeneration, islet cell production, leukemia-producing stem cells, cell therapy of multiple sclerosis and cerebral palsy, cell reprogramming, brain tumor stem cells, fetal surgery to treat congenital disorders, bioengineering, cartilage and bone regeneration, germ cell production, and spinal cord injury.
Build translational teams linking scientists and clinicians.
iPS-derived cardiomyocytes provide a powerful new platform to study heart rhythm and for safety screening of new drugs

Wichterle et al., Cell, 2002

Park et al., Bio Reprod, 2003

Sanai et al., NEJM, 2005
Human stem cells grown on human placental cell feeders (From the Fisher laboratory at UCSF)

Day 1

Colony size: 156,206 µm²

Day 5

Colony size: 3,674,083 µm²

How embryonic stem cells are derived

IVF Clinic

Stem Cell Definitions

Stem cells are unspecialized cells

- Self-renew
- Inducible fates

Understanding the switch between ES cell self-renewal and differentiation
Global regulators of gene expression

Adapted from Nature 429: 457

Tbr2+ identifies intermediate progenitor cells
Pial-directed radial fibers can be visualized on ‘displaced’ radial glia during mitosis.

4A4 antibody (phosphorylated vimentin)

Sox2

Outer SVZ