Induced Pluripotent Stem Cells

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• How different from other types of stem cells?
• How would they be useful?
• What are the challenges to make therapy with iPSC a reality?
• First, a little history….
A Short History of Reprogramming and Pluripotency

I. Nuclear transfer and reprogramming of frog cells

*John Gurdon, 1958*

Findings:

- normally, the nucleus from specific cell instructs specific cell function
  each cell has same DNA (genome), different epigenome
- nuclei from intestinal cells could be made to act like sperm cells
- “reprogrammed by “stuff” in the eggs
- intestinal nuclei – “forgot” that they were from intestines
  epigenome erased
A Short History of Reprogramming and Pluripotency

Conclusions:

Frogs are weird

Or basic mechanism underlying all biology?

18 years later……
II. Mammal cloned from an adult somatic stem cell: reprogramming by nuclear transfer

Ian Wilmut 1996

Conclusions:
Frogs aren’t weird.
Some kind of fundamental biological process
Mechanism?
eggs are magic?
III. Direct cell reprogramming with defined factors

*Shinya Yamanaka - 2006*

- 4 genes:
  - Oct
  - Sox
  - Klf
  - Myc

Mouse Embryo Fibroblasts → induced Pluripotent Stem Cells (iPSC)
Nuclear transfer versus “defined factors”
similar result
not magic – real biochemistry/molecular biology
iPSC can be differentiated to many cells and tissues
• 2007 Human iPS cells- Shinya Yamanaka, Jamie Thomson, George Daley labs

• Gurdon, Yamanaka – Lasker Prize 2009
iPSC vs ES cells

• Like embryonic stem cells can (in principle) generate any cells any tissue
• Like ES cells, can make an entire mouse
• As good as ES cells?
  – More later
• Potential advantage over ES cells
  – Alleviates shortage of stem cells
  – Eliminates immunological barriers, transplant rejection and need for immunosuppressive drugs
  • the ultimate in “personalized medicine”
  – Obviates ethical issues regarding embryonic stem cells
Use of Induced Pluripotent Stem Cells (iPSC)

• “Disease in a dish”
  – Many rare, genetic diseases
  – Often affect children
  – Can generate iPSC from small amounts of blood
  – Can generate unlimited quantities – in principle can differentiate to multiple lineages
  – Able to do experiments repeatedly, no effect of medications
NIH Undiagnosed Diseases Program

Mark Gourley
RHEUMATOLOGIST
Evaluated Stiers's medical history for possible autoimmune disorders.

Maria Turner
DERMATOLOGIST
Looked for skin-pigment changes under ultraviolet light.

Thomas Hart
DENTIST AND GENETICIST
Performed an oral evaluation.

Thomas Markello
CLINICAL GENETICIST
Did a DNA analysis of Stiers's blood cells.

Colleen Wahl
NURSE PRACTITIONER
Coordinated the medical-team visits.

William Gahl
LEAD DOCTOR

James Balow
NEPHROLOGIST
Examined the kidney biopsy and helped make a diagnosis for Stiers's scaly leg patches.

Lakshmi Gopal
GASTROENTEROLOGIST
Reviewed Stiers's gastrointestinal history, endoscopies and biopsies.

Adeline Ge
ACUPUNCTURE CONSULTANT
Gave Stiers an acupuncture treatment.

Yoshihiko Yamada
CRANIOFACIAL RESEARCHER
Shared information about basement membranes with the medical team.

Galina Nesterova
CLINICAL GENETICIST
Looked for oddities in Stiers's physical measurements.
Use of iPSC

• Disease in a dish

• Drug screening
  – Unlimited quantities of cells from patients with genetic diseases – identify drugs that correct abnormalities
Use of iPSC

- Disease in a dish
- Drug screening
- Cellular Therapy/Regenerative Medicine
  - Can make:
    - Retinal cells to treat blindness
    - Pancreatic cells for diabetes
    - Blood cells for sickle anemia
    - Etc…
Use of iPSC

- Disease in a dish
- Drug screening
- Cellular Therapy/Regenerative Medicine
  - in principal:
    - Alleviates shortage of stem cells
    - Correction of genetic defects
      - “gene therapy in a dish”
      - Check to see that you’ve got it right before transplanting
    - Eliminates immunological barriers, transplant rejection and need for immunosuppressive drugs
    - the ultimate in “personalized medicine”
    - Obviates ethical issues regarding embryonic stem cells
Towards safe clinical applications
Stem cells: The good, the bad, and the ugly
Question: How are the Fetal Stem Cells treated to ensure their purity and safety?

Answer: The Fetal Stem Cells are treated to ensure their purity and safety. The test is called a PCR-DNA (Polymerase Chain Reaction-DNA) test is used to detect hereditary diseases, clone genes, and perform DNA analysis. These cell are then sent to a world famous laboratory for a complete analysis.

Luca - Down's Syndrome

Luca’s mother - “I was told by my pediatrician my son Luca had Down’s Syndrome and that there was nothing that could be done. After his treatment a miracle occurred, he eventually became completely normal in appearance and his I.Q. actually tested higher than average for his age.”
ESPERATE Elizabeth Taylor — plagued by health problems for years — has turned to bizarre experimental stem cell treatments in the Dominican Republic to beat aging and conquer her excruciating back pain.

The 69-year-old screen queen bravely underwent the controversial procedure in August and friends say the stem cell treatments made her feel better than she has in years!

“Liz has been plagued by a variety of illnesses over the years,” a source told The ENQUIRER, “and she’d almost given up hope of ever being free of pain from her chronic back problems.”

At times her back problems were so severe she was forced to use a wheelchair.

“But after talking to her doctors, she found out about a doctor in the Dominican Republic who was reporting good results,” the source said.

ENQUIRER EXCLUSIVE

Bizarre new

Towards safe clinical applications

- Cell-based therapies
  - Safety issues remain to be defined
    - Potential for becoming cancerous?
  - Require:
    - advances in reprogramming, differentiation and gene correction
- iPS vs ES cells?
  - Functionally similar
  - That pesky epigenome
What regulates cell differentiation?
20th century view

Epigenome - NonDNA factors that influence heritable aspects of phenotype
What regulates cell differentiation vs. plasticity?

21st century view

• “Access” to genes – “epigenetic” memory
• lots of biochemical regulation
• So what?
• some iPSCs don’t “forget” the tissue they came from
• ES cells not equal to iPSCs
• might be good, might be bad – we will see
Induced Pluripotent Stem Cells

Conclusions

• Amazing science
• Extraordinary opportunities
• Lots to be done to make this safe
  – Don’t believe some of the hype
  – Some people engaging in pseudoscience, taking advantage of vulnerable populations
  – Make sure it’s solid science, be skeptical
• No shortcuts—will require lots of hard work, smart people, time, and money
• We’re crazy if we don’t try