The Science of Stem Cells

Interagency Autism Coordinating Committee

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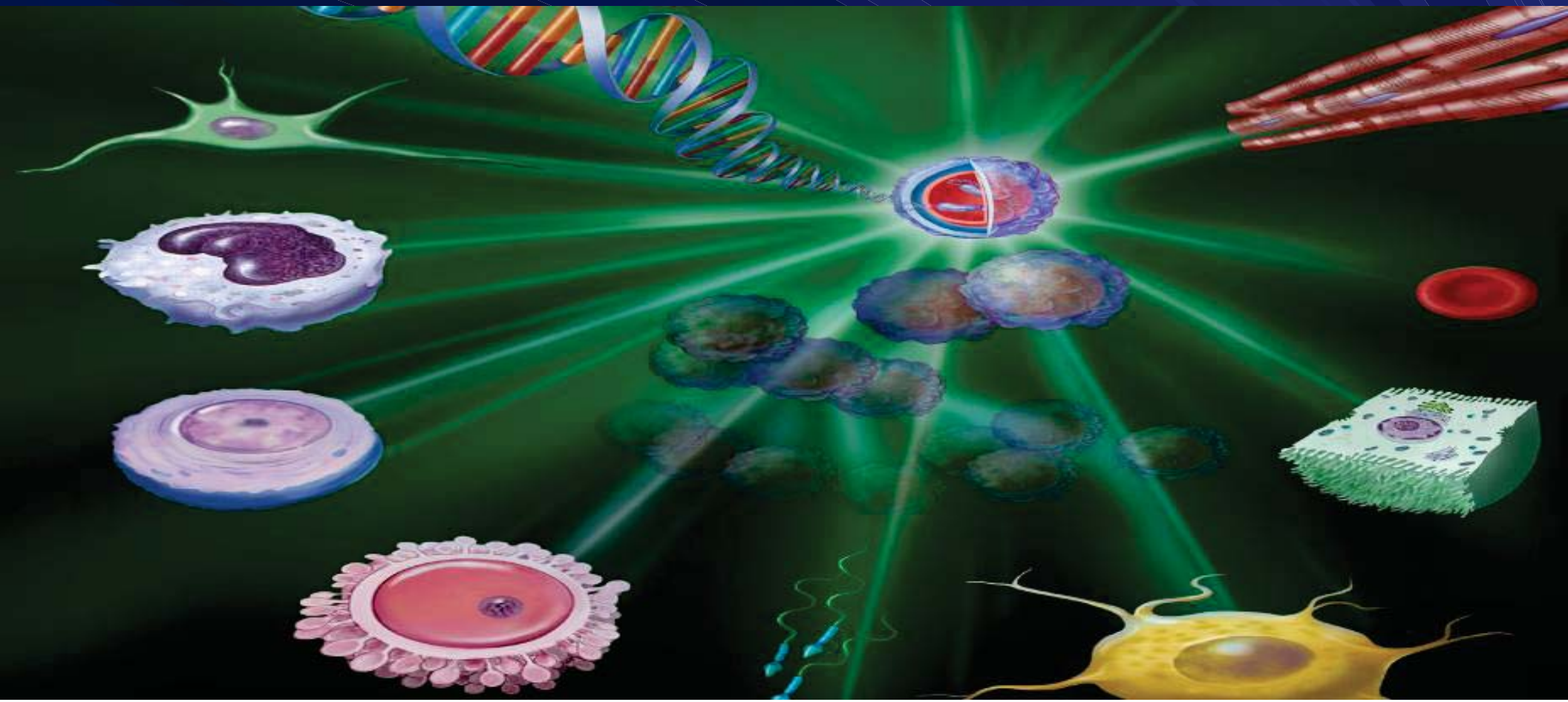
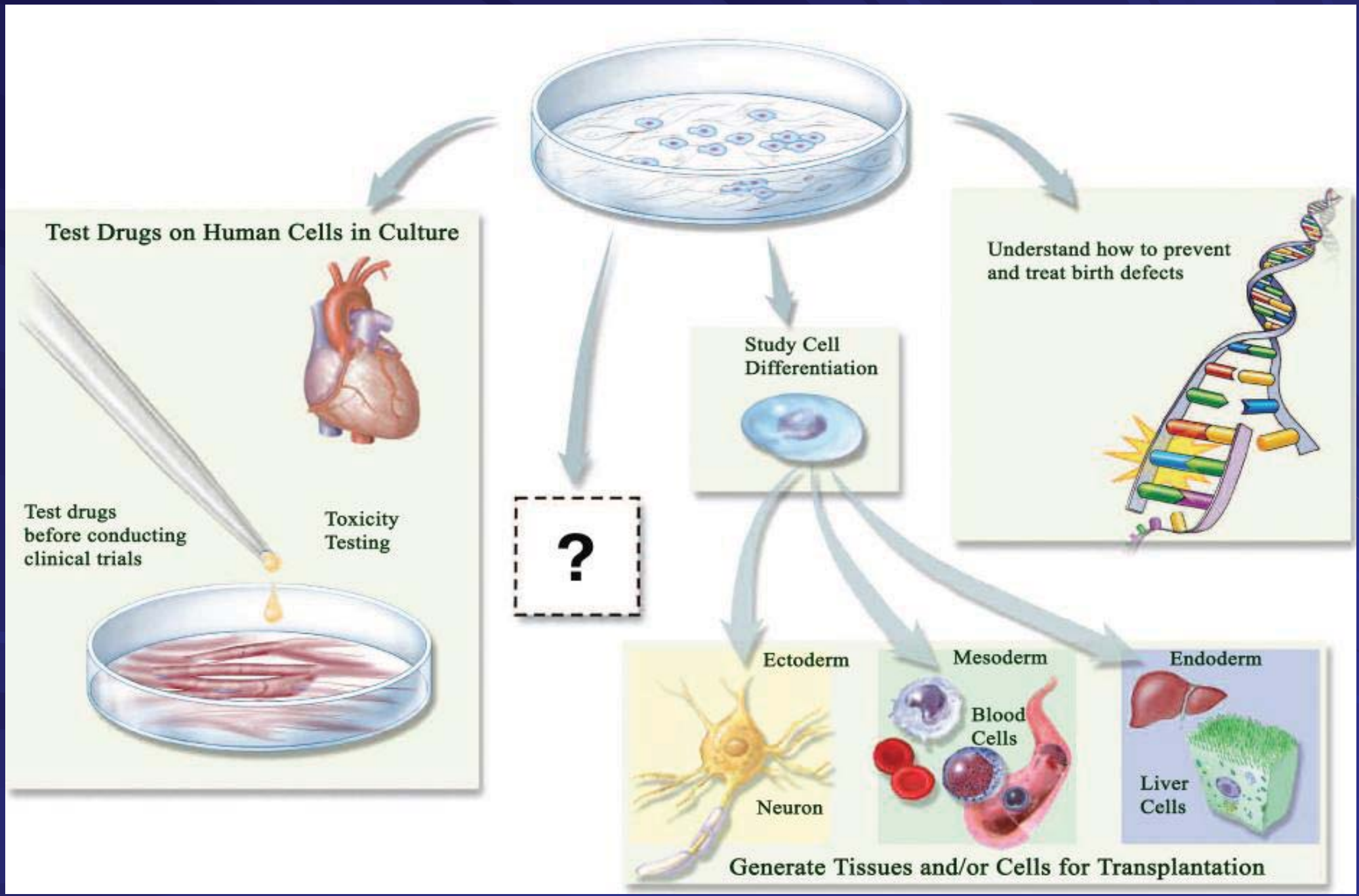


What is a Stem Cell?

- Stem cells can develop into many different cell types in the body during early life and growth.
- Serve as internal repair system throughout life, dividing to replace worn out or damaged cells.
- When a stem cell divides, each new cell has the potential either to remain a stem cell or become another type of cell with a more specialized function, such as a muscle cell, a red blood cell, or a brain cell.

The Promise of Stem Cell Research



Mouse Embryonic Stem Cells

- Techniques for culturing mouse embryonic stem cells (mESCs) from the inner cell mass of blastocyst first reported in 1981.
  - Evans, M.J. and Kaufman, M.H.; and Martin, G.R.
- Studies of embryonal carcinoma (EC) cells from mice and humans helped establish parameters for growing and assessing ES cells.
  - Andrews, P.W., *et al*. (1996).

Embryonic stem cells (ESCs)

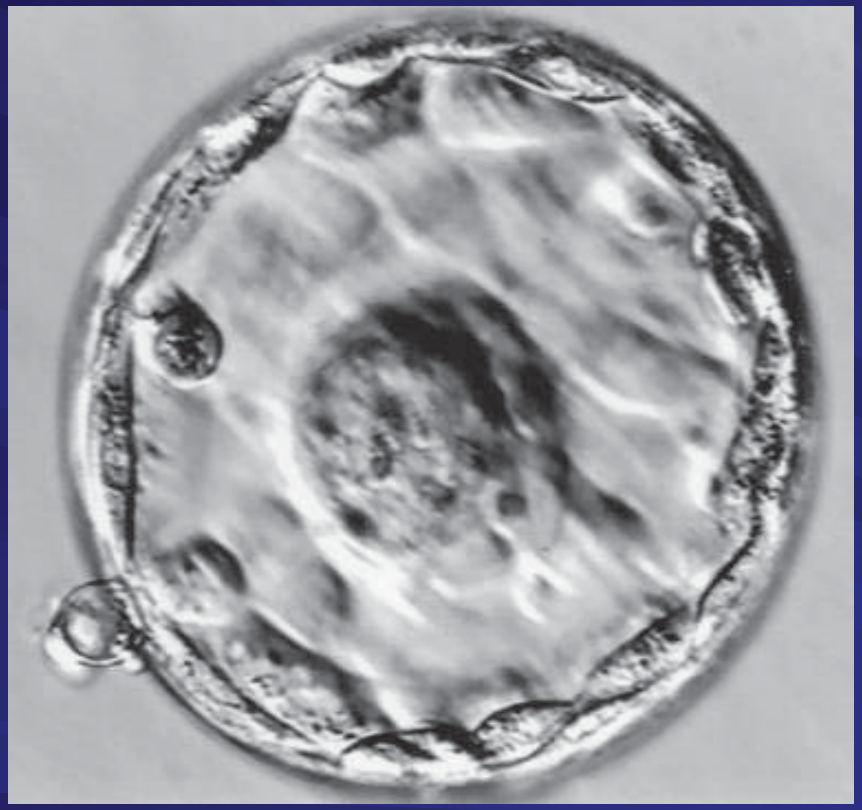
- ESCs are capable of dividing without differentiating for a prolonged period in culture – This is called **self-renewal**.
- ESCs are capable of differentiating into any cell type in the body (under the proper conditions)—This is called **pluripotency**.
- Human ESC culturing techniques based on 17 years' experience with mouse ESCs.
  - Thomson *et al.*, 1998

How Are Embryonic Stem Cells Generated?

In Vitro Fertilization

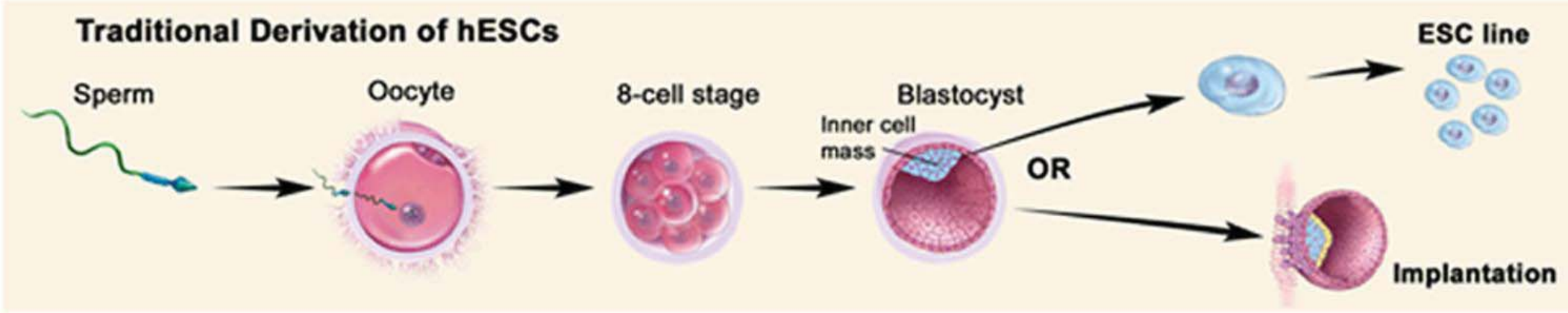
Courtesy of J.M. Jones, University of Wisconsin- Madison

A Five-Day Old Blastocyst



Courtesy of J.M. Jones, University of Wisconsin- Madison

Derivation of hESCs from a 5 Day Old Human Blastocyst



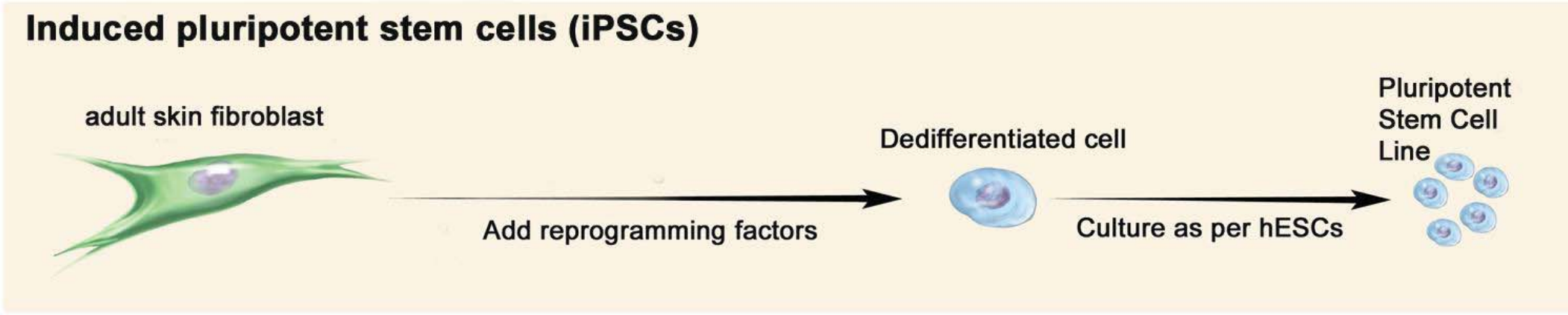
Non-Embryonic Stem Cells

- Include Fetal, Umbilical Cord Blood, and Adult Stem Cells.
- Found in many organs such as bone marrow, gut, skin, nervous system, and liver.
- Relatively rare (1/1000 to 1/10,000).
- Limited capacity for self renewal in the laboratory.
- Limited capacity for differentiation—usually limited to cell types in organ of origin.

New Type of Adult Stem Cells: Induced Pluripotent Stem Cells (iPSCs)

- November 2007: 2 teams reprogrammed adult human skin cells to behave like human embryonic stem cells (hESCs).
- Both teams forced adult skin cells to express genes important for maintaining the so-called "stemness" properties of stem cells.
- These genes were identified from their experiences studying hESCs.
- They called the reprogrammed adult cells “induced Pluripotent Stem Cells” (iPSCs). Human iPSCs demonstrate important characteristics of pluripotency.
  - *Cell* laboratory of S. Yamanaka; *Science* laboratory of J. Thomson.

How Are iPSCs Generated?



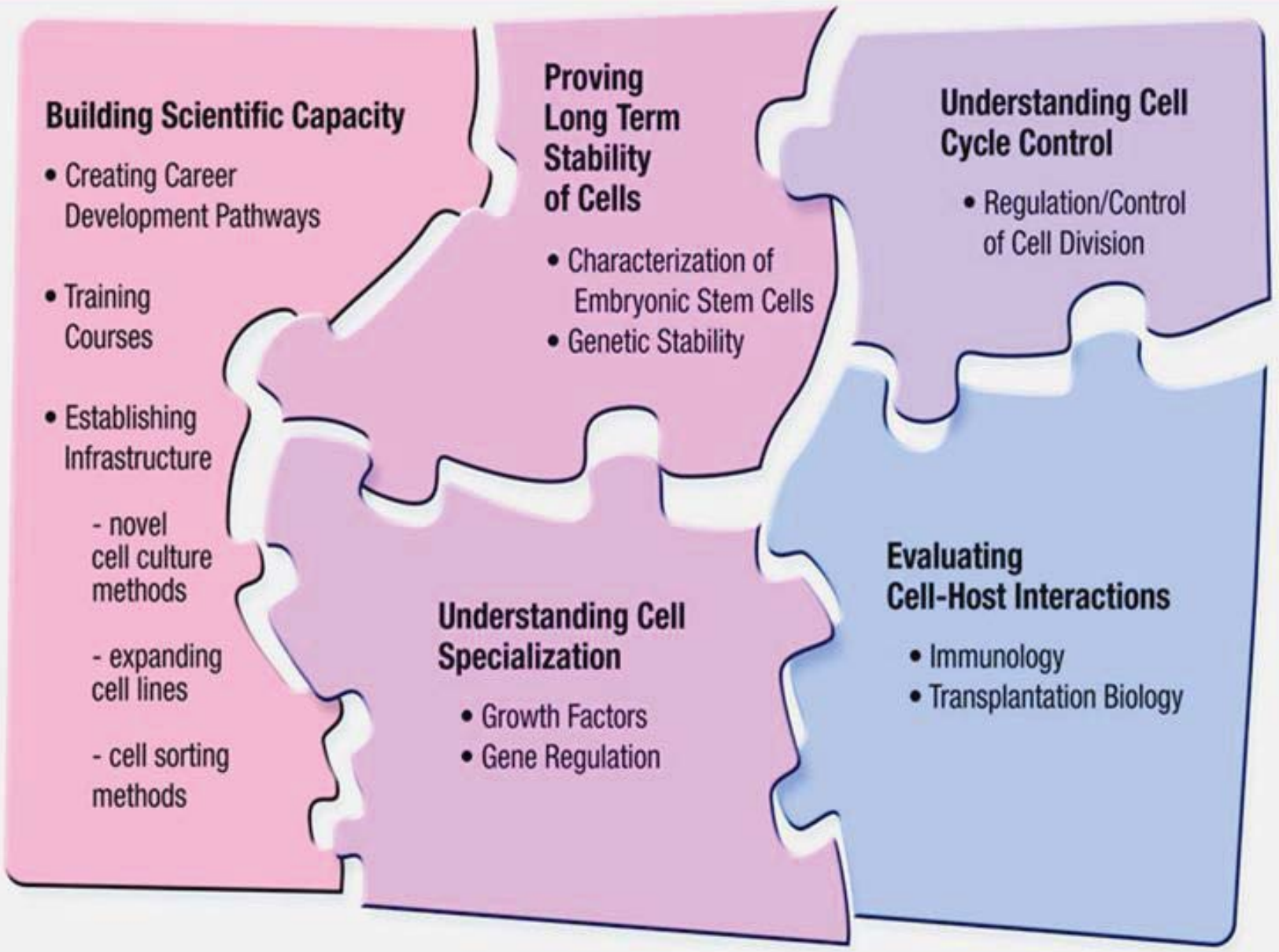
Why are iPSCs so Exciting?

- Scientists can now generate patient-specific and disease-specific human stem cell lines for laboratory study, and test potential drugs on human cells in culture.
- However, viruses used could generate tumors. In 2009, virus-free reprogramming reported , and reprogramming factors themselves can also be removed.
- Safety remains a concern, but iPSCs are still very valuable research tools.

How Can Stem Cells Help with Human Diseases?

The Scientific Challenges of Human Stem Cells

Basic Research Phase →



If We Know What Tissue is Damaged, Stem Cells Could Replace It

- Bone marrow stem cells: Regularly used to treat human blood cancers and other blood disorders (20+ years).
- hESCs: Geron received FDA clearance to begin the first human clinical trial of hESC-derived oligodendrocyte cells that have restored movement to spinal-cord injured rats.
- iPSCs: Have improved symptoms in rodent models of human diseases, such as sickle cell anemia and Parkinson's Disease - laboratory of Rudolf Jaenisch.

Challenge for Stem Cell Research and Autism Spectrum Disorders: What's Our Target?

- Autism spectrum disorders affect a wide range of organs and systems.
- Which one or ones could be replaced/repaired in order to reverse the condition?
- It's hard to "fix it" if you're not sure what's broken.
- Autism spectrum disorders are developmental in nature, and there may be limited critical period(s) when repair is helpful.

Challenge for iPSC Research: Will iPSCs Recapitulate Diseases?

- If you derive iPSCs from an individual with a specific disease, will the iPSC-derived cells show symptoms of that disease?
- Scientists aren't sure: could vary from disease to disease. – Is its cause genetic, environmental, or both?
- May also be affected by time of disease onset: Childhood? Adulthood? Late Adulthood?

iPSC-Derived Motor Neurons Show Symptoms of Muscle Wasting Disease

- To study spinal muscular atrophy (SMA), scientists made an iPSC line from an affected child and from the child's mother, who does not have SMA.
- Motor neurons derived from the SMA-affected (SMA-iPSC-derived) child began to die after a month in culture, while motor neurons derived from the child's mother's iPSCs survived.
- SMA-iPSC-derived motor neurons behaved like those in an affected individual; this means that the cells exhibit at least one important characteristic of SMA.
- These SMA-iPSC-derived motor neurons provide an important new *in vitro* model of SMA, and scientists can use them to test new drugs for SMA and to study how and when SMA develops.

Nature 457: 277-280 , laboratory of C. Svendsen. 2009 Jan. 15.

NIH-supported Research on Autism Spectrum Disorders and iPSCs

- 2008 NIH Director's Pioneer Award "Using induced pluripotent stem cells to identify cellular phenotypes of autism" – R.E. Dolmetsch
- "Patient iPS cells with Copy Number Variations to Model Neuropsychiatric Disorders" – J.R. Ellis
- "Exploring the Neuronal Phenotype of Autism Spectrum Disorders Using Induced Pluripotent Stem Cells" – J.F. Hallmayer
- "High Content Screens of Neuronal Development for Autism Research" – S.L. Halpain
- "Autism iPSCs for Studying Function and Dysfunction in Human Neural Development" – J.F. Loring
- "Biological correlates of altered brain growth in autism" – M.B. Gerstein, E.L. Grigorenko, F.M. Vaccarino, S.M. Weissman
- "An Open Resource for Autism iPSCs and Their Derivatives" – P.H. Schwartz

NIH Funding of Stem Cell Research

- FY2009 investment in human non-embryonic stem cell research
  - Includes iPSCs.
  - Approximately $397 million
- FY2009 investment in human embryonic stem cell research – Approximately $143 million
- NIH will continue to support all types of stem cell research in the future, as permissible.

NIH Stem Cell Internet Sites

- Stem Cell Information
  http://stemcells.nih.gov

- Email: stemcell@mail.nih.gov