UNIT FIVE: INDUCED PLURIPOTENT STEM CELLS

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CA Science Standards
Biology/Life Sciences
1. d. *Students know* the central dogma of molecular biology outlines the flow of information from transcription of ribonucleic acid (RNA) in the nucleus to translation of proteins on ribosomes in the cytoplasm.
4. c. *Students know* how mutations in the DNA sequence of a gene may or may not affect the expression of the gene or the sequence of amino acids in an encoded protein.
4. d. *Students know* specialization of cells in multicellular organisms is usually due to different patterns of gene expression rather than to differences of the genes themselves.
5. c. *Students know* how genetic engineering (biotechnology) is used to produce novel biomedical and agricultural products.
5. d.* *Students know* how basic DNA technology (restriction digestion by endonucleases, gel electrophoresis, ligation, and transformation) is used to construct recombinant DNA molecules.
5. e.* *Students know* how exogenous DNA can be inserted into bacterial cells to alter their genetic makeup and support expression of new protein products.

Goals/Objectives
- Distinguish among multipotent, pluripotent, and totipotent stem cells (review Unit 1).
- Explain the advantages and disadvantages of iPS cells as compared to embryonic stem cells.
- Describe the various methods for creating iPS cells, including transfection methods using plasmids, retroviruses, small molecules, and adenoviruses. Discuss the advantages and disadvantages of each.
- Describe issues that must be resolved before iPS cells can safely be used in human cell-based therapy.

NOTE: Prior to teaching this unit students should have a basic understanding of embryonic stem cells. Teaching some materials from Unit 1 or delivering the CIRM PowerPoint introductory presentation should be sufficient. Unit 5 is intended for advanced or AP biology students.

Outline of Unit Five

I. Invitation

A. Watch Nova Science Now documentary on induced Pluripotent Stem Cells. 13:39. http://www.pbs.org/wgbh/nova/sciencenow/0305/03.html

B. Students record responses on the Unit 5 NOVA scienceNow Question Sheet.
   a. Download student version here
   b. Download teach version here

C. Go over answers from the Question Sheet during a group discussion (NOVA scienceNow questions from B.)

D. Review basic stem cell biology by watching the Learn. Genetics animation The Nature of Stem Cells and if time, explore the other resources available from the University of Utah.

II. Exploration

A. Lecture - Introduction to iPS technology. Create a lecture that fits the level of your students using information from the Teacher Background Information document for Unit Five. Assign this article, A Brief History of iPSCell Research, as background reading or incorporate into your lecture.

1. Review how embryonic stem cells are made
2. Discuss pluripotency
3. Summarize iPS technology.
4. What does reprogramming mean? How does it relate to Somatic Cell Nuclear Transfer, the procedure used to clone Dolly the sheep?

B. Discuss the research paper summary describing the discovery of iPS cells: Yamanaka 2006 Induction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors. Before moving on to the jigsaw study below, students should understand the following:

1. What is a "transcription factor?"
2. What are the four transcription factors that are used in iPS cell creation?
3. How did Yamanaka's team turn somatic cells into embryonic stem cell-like cells?
4. What transfection method did the researchers use?
5. How did the researchers detect cells that had turned into iPS cells?
6. How did the researchers test whether the iPS cells were pluripotent?
7. How efficient was this technique?

C. The Promises and Risks of iPS cells: A jigsaw reading of iPS cell paper summaries and an optional simulation activity (under Application section III.B.) For the reading activity instruction, download Unit 5 jigsaw instructions. To download readings—either actual research articles or abbreviated summaries—click the links below. It is recommended that advanced students try to read both the original article (where available) as well as the summary. *Note: If you choose to do the simulation activity, the group of students who read article 6 will act as an Ethical Review Board and have additional responsibilities.*

1. **Yamanaka, 2008: Generation of Pluripotent Stem Cells from Adult Mouse Liver and Stomach Cells.** This paper demonstrates that other cell types can be used for reprogramming. Stomach and liver cells are more difficult to acquire, but this study indicates they are less likely to develop into cancer than skin.
   Download paper [free registration required]
   Download summary

2. **Eggan, 2008: iPS Generated From Patients with ALS can be Differentiated into Motor Neurons**. iPS and ALS - creating diseased cells in culture from iPS cells.
   Download paper [free registration required]
   Download summary

3. **Jaenisch, 2007: Treatment of Sickle Cell Anemia Mouse Model with iPS Cells Generated from Autologous Skin**. Sickle cell disease and a mouse model of an iPS cell-based therapy.
   Download paper [free registration required]
   Download summary

4. **Plath, 2008: The Many Ways to Make an iPS cell**. An alternative to the use of retroviruses.
   Download summary

5. **Yamanaka, 2008: Generation of Induced Pluripotent Stem Cells without Myc from Mouse and Human Fibroblasts**. Creation of iPS cells without using c-Myc have a lower transformation efficiency but are less likely to develop cancer.
   Download summary

6. **Chiang, 2010: Scientists Make Stem Cells that are Accepted by the Ethical Community**.
   Download article

D. Review

1. Deliver or assign as homework the Unit Five PowerPoint presentation: Human Induced Pluripotent Stem Cells. Alternatively, this PowerPoint can be used to accompany any part of the lesson the teacher chooses.

2. Read and discuss Unit 5 "iPS Questions and Answers."

III. Application

A. Form in-class groups to discuss the following and report back students' positions:

List advantages and disadvantages of human embryonic stem cells compared to iPS cells in the following categories

- Ethics
- Efficiency in creation of cell lines
- *In vitro* disease models
- Safety in cell transplant therapy

B. Simulation activity using Jigsaw readings

Several students in the class comprise an Ethical Review Board (ERB). These students do not participate in jigsaw for iPS treatment options, but instead, google what an ERB is and how they normally make decisions as well as read **Chiang, 2010: Scientists Make Stem Cells that are Accepted by the Ethical Community**. ERB members give a short presentation on ERB background and purpose. Student groups present and discuss various treatment options (including different reprogramming techniques versus using embryonic stem cells or adult stem cells) to the ERB, which then comes to a consensus on the safest and best treatment options.

IV. Assessment

A. Students read the following scenario and write their responses on an essay exam. Teacher's guide with the answer to the following question: Unit Five Thalassemia

Q: You are a doctor who wants to treat a patient for thalassemia. Thalassemia is a genetic disease caused by a mutation in hemoglobin that disrupts the molecule's ability to carry and deliver oxygen in the body. You want to try to treat your patient with iPS cells. Describe how you would obtain or produce the iPS cells. Include the original cell type and transfection method and why you have chosen these methods. Also describe how the iPS cells would be treated before transplantation.