Assignment 11: Stem Cells

Cell and Tissue Engineering

Problems

1. Please identify which stem cell type or types (embryonic, somatic, or iPS) fit each of the following descriptions. Some have 1 answer, some have more than 1 answer.
   a. Derivation requires informed consent
      embryonic

   b. Has forced expression of several transcription factors
      iPs

   c. Includes mesenchymal stem cells
      somatic

   d. Totipotent
      sembryonic

   e. Low efficiency in creation
      iPS

   f. Limited quantities in the body
      somatic

   g. Used in the Advanced Cell Technology clinical trial
      embryonic

   h. Self renews and differentiates
      embryonic, somatic, iPS

2. Understanding the three models of stem cell proliferation please discuss which model a tissue engineer would hope is correct and why?
   Clonal succession model: in this model, stem cells are in a dormant state waiting to be activated and once triggered any of these stem cells could differentiate and proliferate into a large population of mature cells. These stem cells are available for the lifetime of the organism and have a limited lifespan. The mature clone eventually burns out and a new stem-cell clone take over for cell production.
   Deterministic model: this model assumes that the stem cells can self-renew and differentiate into a mature cell and a stem-cell daughter. The probability of

self-renewal may not be exactly 50% depending on tissue environment and may be subject to telomere length.

Stochastic model: the behavior of the outcome of differentiation is random in nature; i.e., a stem cell can generate 0, 1 or 2 stem cells as daughter cells; and can be regulated like the deterministic model by factors external to the dividing cell.

A tissue engineer, would like to rely on the deterministic model, which, is based. on the notion that stem cells exhibit a deterministic behavior given their response to differentiation stimuli.

3. As we saw this week in lecture, there are a limited number of clinical trials using embryonic stem cells. One company, Geron, which pioneered clinical use of hESCs stopped their trial. Begin by reading the article from ScienceMag about Geron. Please explain why Geron halted their clinical trial utilizing hESC-derived oligodendrocytes to treat spinal cord injuries? And second, explain why they stopped pursuits of stem cell research entirely? Does this surprise you?

After a year, Geron decided to stop a trial to treat 8 patients with spinal cord injury, injected with hESC-derived oligodendrocytes stem cells. At that time, it has already spent $170 million from which $25 million was a loan from the California Institute for Regenerative Medicine, a government funded institution (Lukovic et al.). It is reasonable to assume that the cost would have at least doubled as such study to be approved by the FDA, requires a continuous monitoring of the patients for injury improvements, adverse events, or comorbidities issues for many years. Also, from 2011 until today (slide 10-11D), there has been much more NIH funding in non-embryonic and iPSC research compared to human embryonic research. In addition, Geron funded Dr Thomson research in 1998. In 2011, 3 years after, Geron did not yet have any FDA approved stem cell therapy. Geron executive committee, probably then, realized that the investment needed to continue the trial but also their stem cell research; was too steep, and could jeopardize; maybe; other more promising research. With this context; it seems expected that Geron; as a public company under the pressure of investors, took the only decision they could have financially made and decided to stop pursuing stem cell research altogether.

4. The following review article discusses how chromatic regulation and structure is involved in stem cell creation (iPSCs), pluripotency and differentiation. At the beginning of this semester, we started a discussion on epigenetics - how chromatin compaction can regulate protein expression. In reading this article, you will continue that discussion. After reading, please provide a critical review of no more than 400 words.

   This review should include the following points:

   - how histone acetylation and methylation regulate gene expression
   - the differences in chromatin structure between stem and differentiated cells

- the model of nuclear compartmentalization
Article: Serrano, L., Vazquez, B.D., and Tischfield, J. Chromatin Structure, pluripotency and differentiation. Experimental Biology and Medicine. 238: 259-270. 2013.

https://www-science-org.proxy1.library.jhu.edu/content/article/geron-bails-out-stem-cells

Lukovic, Dunja, et al. "Perspectives and Future Directions of Human Pluripotent Stem Cell-Based Therapies: Lessons from Geron's Clinical Trial for Spinal Cord Injury." *Stem Cells and Development*, vol. 23, no. 1, Jan. 2014, pp. 1–4. *DOI.org (Crossref)*, https://doi.org/10.1089/scd.2013.0266.

Rubric

Question	Component	Total Point Value
1	A	1.5
	B	1.5
	C	1.5
	D	1.5
	E	1.5
	F	1.5
	G	1.5
	H	1.5
2		5
3		5
4		8
Total		**30**