Dates to Remember

- Continuous Assessment
  - 12 Oct (Friday) 245pm~415pm – CA; Using (Part of) Lecture Time Slot; Venue: To-Be-Informed. There are Lectures after CA: 430pm ~ 5pm (or so) explaining CA.

- Self-Study/Revision
  - Chap3-7: About “Neural Stem Cells” No Lecture Class for this Part this part will NOT be included in Exam
  - 28 Sep (Friday, the Last Week before Recess Week) 230~530pm: Self-Revision of first half Sem for CA, No Class.
  - 26 Oct (Friday): Public Holiday, No Class.

Course Administration

- Course materials of relevance to the course will be uploaded on the edveNTUre website

- Students are advised to read EMAIL and check edveNTUre on a regular basis in the event that course Instructors need to communicate urgent info with regard the course

Copyright Declaration:

- All the graphic displays inclusive of images and motion pictures are used for educational, which is non-profit, purposes.
- The instructor of all the lectures in this course does not claim the copyright of all the graphic contents; however, the copyright of the text parts is reserved by the instructor.
- Any absence of references for the graphic displays is completely due to space limitation in lecture slides or other technical reasons. Hereby the instructor declares the respect and acknowledgement for all the cited graphic displays in the entire parts of this course.
Enjoy Your Course!

About This Course

- This is NOT a course about any single fundamental science, but an advanced & Multi-disciplinary one.
- Except for some basic concepts, most of the ideas and methodologies can NOT be simply called “right” or “wrong”, but “good” or “not good enough”.
- This subject is connecting the Lab with real practice, while this course is a guidance avenue from classroom to the Lab.
- This course is organized with MY understanding for your conference. We do NOT compete with others.

Beginning with Sci & Eng
(personal opinion to share. No Argument Please!)

Science
(To answer what’s going on? Why so?)

- Theoretical Sciences: (like physics, not maths)
  - Hypothesis with maths & logic
  - Deduction
  - Preliminary theories
  - Expt observ. Confirmation

- Experimental Sciences: (like chemistry & biology)
  - Experimental observations
  - Summarization with logic
  - Preliminary theories
  - Theoretical Confirmation with Math&Logic

Engineering
(To make sth really useful)

- Mechanics/Principles
- To sum&generate new hypothesis
- To deduce new Expt trials
- Translate into Technology for production
Text/Reference Books

• Stem Cells - From Bench to Bedside: Bongso, A. et al., World Scientific, ISBN: 9812561269

Planning for the Future!

Stem Cell: Overview

• Application:
  Treatment of incurable diseases via transplantation therapy
  Bone marrow/umbilical cord stem cells for leukemic patients
  stem cell-originated islets for diabetes; neurons for neurodegeneration; cardiomyocytes for heart diseases…

• Definition:
  Stem cell markers & transcriptome profiling for “stemness”
  –Self-renewal: indefinite division & self-replication (immortality)
  –Potential of differentiation
  embryonic/fetal & adult (somatic) stem cells

  Embryonic/fetal: versatility and pluripotentiality
  Adult (somatic): less ethical sensitivities, convenient.
Practical Stem Cell Therapy

- **Cancers**—Lymphomas, multiple myeloma, leukemias, breast cancer, neuroblastoma, renal cell carcinoma, ovarian cancer
- **Autoimmune diseases**—multiple sclerosis, systemic lupus, rheumatoid arthritis, scleroderma, scleromyxedema, Crohn’s disease
- **Anemias** (incl. sickle cell anemia)
- **Immunodeficiencies**—including human gene therapy
- **Bone/cartilage deformities**—children with osteogenesis imperfecta
- **Corneal scarring**—generation of new corneas to restore sight
- **Stroke**—neural cell implants in clinical trials
- **Repairing cardiac tissue after heart attack**—bone marrow or muscle stem cells from patient
- **Parkinson’s**—retinal stem cells, patient’s own neural stem cells, injected growth factors
- **Growth of new blood vessels**—e.g., preventing gangrene
- **Gastrointestinal epithelia**—regenerate damaged ulcerous tissue
- **Skin**—grafts grown from hair follicle stem cells, after plucking a few hairs from patient
- **Wound healing**—bone marrow stem cells stimulated skin healing
- **Spinal cord injury**—clinical trials currently in Portugal, Italy, S. Korea

---

**Stem Cells: Potential Classification**

- **Totipotent:**
  - can produce all the cells in the embryo and the embryo’s contribution to the extra-embryonic tissues
    - only for embryo cells: but embryo cells are NOT stem cells — limited cleavage division during early embryo development

- **Pluripotent:**
  - can produce all the cell types in the embryo proper
    - embryonic stem cells (ESCs) & embryonic germ cells (EGCs)

- **Multipotent:**
  - contributes cells to several cell lineages
    - adult (somatic) stem cells

**A Progenitor cell** lies in between a stem cell and a terminally differentiated cell; mostly a committed unipotent precursor cell. **“XX-blast” cell**

---

**Stem Cells: Division Manners**

- **Symmetric cell division** results in two equal daughter cells.
  - This is how ESCs reproduce.
  - During development or under repair circumstances, somatic stem cells may also reproduce by symmetric cell division.

- **Asymmetric cell division** results in two daughter cells with different potential.
  - It is thought that somatic stem cells have asymmetric cell division, producing one daughter cell that remains a stem cell and one daughter cell that is committed to differentiate.
  - ES cells may show asymmetric cell division when producing committed cells.

- **Committed progenitor cells** may show symmetric cell division for a specific number of cell cycles, producing several cells with equal potential. It is then thought that all of their progeny terminally differentiate.
**Primary Development**

- **Processes of development**
  - Cleavage - Cell division without growth.
  - Morphogenesis - Shaping of embryo.
  - Differentiation - Cells take on specific structure and function.
  - Growth - Increase in size of cells.

  - Embryonic development occurs from the second week to the eighth week.
  - Fetal development occurs from the third month through the ninth month.

**Embryonic Pluripotent Stem Cells**

- Embryonic Stem Cells (ESCs)
- Embryonic Germ Cells (EGCs)

**Stem Cells: Sources Classification**

**HUMAN STEM CELLS**

- Embryonic
  - Blastocyst (5-7 days)
  - Embryonic stem cells
  - Embryonic germ cells

- Fetal
  - Gonadal ridge (6 weeks)
  - Placenta
  - Umbilical cord blood
  - Umbilical cord matrix stem cells
  - Spermatagonia
  - Oogonia
  - Hemopoietic
  - Mesenchymal
  - Liver
  - Epidermal (skin, hair)
  - Neuronal
  - Eye
  - Gut
  - Pancreas

- Infant
  - Wharton's Jelly
  - Germline
  - Somatic

- Adult

**Embryonic Pluripotent Stem Cells**

- Embryonic Stem Cells (ESCs)
- Embryonic Germ Cells (EGCs)

**Stages of Development**

1. **Endoderm**
   - Lung, liver, and pancreas/organ specific SCs
   - Esophagus, stomach, intestine/intestinal SCs

2. **Mesoderm**
   - Bone marrow and blood/HSCs and MSCs
   - Muscle and bone/tissue SCs

3. **Ectoderm**
   - Skin/skin SCs
   - Nervous tissue/NSCs

**Gastrulation**

- NCSCs/skin SCs
- HSCs/MSCs/tissue SCs
- Organ SCs/Intestinal SCs

**Day 6 Embryo-Blastocyst**

- (beautiful) human ovum

- Sperms on surface of ovum

**Nanyang Technological University**
Embryonic Stem Cells (ESCs)

- Source of (h)ESCs: Inner cell mass (ICM) of the 5- to 6-day old human blastocyst.
- Potential of differentiation: Pluripotent

Embryonic Germ Cells (EGCs)

- EGCs are pluripotent stem cells with potential of differentiation into all three germ layer derivatives.
- EGCs originate from primordial germ cells of gonadal ridge of 5- to 9-week old fetuses. They transiently exist in the embryo and then become committed as germ cells.

Fetal/Infant Stem Cells

- Fetal Stem Cells:
  - primitive cell types found in the organs of fetuses: fetal blood, placenta, and fetal umbilical cord
  - fetal neural stem cells; neural crest stem cells; fetal hematopoietic stem cells; pancreatic islet progenitors

--- NO STRICT BOUNDARIES with Infant Stem Cells ---
Fetal/Infant Stem Cells

- (Infant) Umbilical Cord Stem Cells:

  Umbilical cord (blood)-originated circulating stem cells, mainly hematopoietic stem cells (HSCs), are distinct and superior from the comparable species sourced from either bone marrow or peripheral blood.
  - Longer time expansion culture; less graft-host reaction
  - Umbilical matrix (Wharton’s jelly): source of mesenchymal stem cells (MSCs)

Adult (Somatic) Stem/Progenitor Cells

- Bone Marrow/Peripheral Blood Derived Hematopoietic Stem Cells (HSCs):
  - Hematopoiesis: production and maintenance of blood stem cells and their proliferation and differentiation into the cells of peripheral blood. Multipotent.
  - HSCs: derived early in mesoderm; deposited in specific hematopoietic sites in embryo – bone marrow, liver, yolk sac.

Adult (Somatic) Stem/Progenitor Cells

- Bone Marrow Derived Stroma Mesenchymal Stem Cells (MSCs):
  - MSCs: derived postnataally in the non-hematopoietic bone marrow stroma, also from periosteum, fat, & skin.
  - Heterogenous population of bone marrow stroma: reticular, adipocytes, osteogenic, smooth muscle, endothelial, macrophage, & MSCs… Turnover in response to injury.
  - Multipotent: differentiating into cartilage, bone, muscle, tendon, ligament and fat – mainly musculoskeletal lineage.
  - minority “pluripotent” or “transgermal plasticity”: mesodermal-endodermal

Adult (Somatic) Stem/Progenitor Cells

- Gut Stem Cells:
  - multipotent stem cells for renewal of gastrointestinal (GI) tract epithelium.
  - Niche (for stem cells): specific in vivo (micro)environment for certain species of stem/progenitor cells to reside, survive, proliferate, and differentiate in proper ways.
  - GI epithelial renewal sustained with gut stem cells in distinct anatomic sties is governed by the corresponding niches.
Adult (Somatic) Stem/Progenitor Cells

- **Bone & Cartilage Stem/Progenitor Cells:**
  - Believed to originate from bone marrow derived MSCs
  - In Bones: mixture of uncommitted bone stem cells and committed osteo-progenitor cells from marrow and/or peripheral blood (hematoma).
  - In Cartilage (articular): No vessels; No nerve system; Poor self-regeneration. Unclear about potential committed chondrocyte progenitors.

- **Neuronal Stem Cells (NSCs):**
  - NSC reservoirs:
    - subventricular zone (SVZ) of the forebrain; and dental gyrus of the hippocampus
  - Fate of NSCs as multipotent stem cells:
    - In Vivo: exclusively neurons;
    - In Vitro: neurons, astrocytes, and oligodendrocytes;
    - Final: environmental control, niche: adult mammalian brain.
  - Unclear about whether SVZ NSCs are multipotent neuronal progenitors or unipotent ependymal cells (becoming glial cells).

- **Epidermal Stem Cells (Skin and Hair):**
  - Epidermal stem cells are residing at the base of the hair follicle.
  - Differentiation of epidermal stem cells -> keratinocytes (epithelial at basal layer of epidermis) -> squame -> hair shaft and/or sebocyte for skin self-renewal (maintenance and regeneration).

- **Retinal Stem Cells**

- **Corneal Stem Cells (Limbal Stem Cells)**
**Adult (Somatic) Stem/Progenitor Cells**

- **Corneal Stem Cells:**
  - Corneal epithelial stem cells reside at limbus of cornea. Also called "limbal stem cells".
  - Competent to proliferate, migrate, and differentiate to replace lost cells in corneal epithelium.
  - Deficiency of limbal stem cells causes re-epithelialization by conjunctiva.

- **Retinal Stem Cells:**
  - Adult retinal stem cells reside at the pigmentary ciliary margin, NOT at the central and peripheral retinal pigmented epithelium.
  - Retinal stem cells can differentiate into retinal-specific cell types: rod photoreceptors, bipolar neurons and Müller glia (progenitor of retinal neurons).

**Adult (Somatic) Stem/Progenitor Cells**

- **Liver Stem/Progenitor Cells (?):**
  - Liver regeneration with liver stem/progenitor cells is capable of recovering over 75% of liver tissue loss/void.
  - Isolation and functional mechanisms of liver stem/progenitor cells are unclear and variable with individuals.

- **Pancreatic Stem Cells (?):**
  - Existence of pancreatic stem cells – progenitors of islet endocrine (insulin-producing beta-cells) is controversy – lack of unequivocal demonstrations.
  - Evidence indicates the participation of potential multi-potent stem cells or unipotent progenitor cells in neogenesis for islet endocrine and/or pancreatic exocrine functionalities.