Chapter 16
Reproductive Technology, Gene Therapy, and Stem Cells
(modified)
Assisted Reproductive Technologies (ART)

• Artificial insemination (AI)
• In vitro fertilization (IVF)
• Gamete intrafallopian transfer (GIFT)
• Intracytoplasmic sperm injection (ICSI)
IVF
ICSI

The process of an individual sperm being injected into an egg through Intracytoplasmic Sperm Injection (ICSI).

http://www.ivi.es/eng/tratamientos/img/fiv_g.jpg
GIFT

After the retrieval of the eggs from the ovary, both sperm and eggs are injected through the catheter directly into the fallopian tube. Fertilization may then take place normally in the fallopian tube.

http://www.fertilityjourney.com/Authfiles/Images/588_91156.gif
Ethical Issues:
Risks to Parents and Children

• 3X increase in ectopic pregnancies
• Multiple births: 35% twins or triplets
• Increased risk of low birth weight
• Increased risk of transmitting genetic defects (eg. Y deletions)
• Possibility of increased risk of birth defects
Ethical Issues:
Selected Donor Siblings

- Prenatal diagnosis (PGD) to select compatible stem cell donor
- Diagnosis for diseases
- Concern that reproductive technologies “could get out of control”
PGD

Polar Body Biopsy  Blastomere Biopsy
Gene Therapy strategies for cancer

Replace deleted p53 with intact p53

Enhance immune response to tumor cells

Make tumor cells more prone to damage by radiation

Make tumor cells more prone to suicide (gancyclovir/TK)

Prevent angiogenesis/metastasis
Methods for gene therapy

Deliver virus to cells inside patient’s body (Canavan’s)

*In vivo*

Virus vectors - modified adenovirus, retrovirus, herpes virus

*Ex vivo (SCID)*
Setbacks in Gene Therapy

• Over 4,000 people have undergone gene transfer
• In 1999 Jesse Gelsinger died
  – Massive immune response to the vector
• In 2000 two French children died of leukemia after being treated for SCID
  – The recombinant virus inserted itself into a gene for cell division
Potential problems with gene therapy

Virus can infect healthy cells

Insertion into ‘wrong’ location in chromosomes

Insertion into germ cells

Adverse immune reactions

Improve viral vectors and delivery method
Ethical Issues

Currently

- Strict guidelines
- All patients are volunteers
- Informed consent
- Gene transfer is started after the case has been reviewed several times
Types of Gene Therapy

• **Somatic gene therapy**
  – Targets somatic cells in only a single target tissue

• **Germ-line therapy**
  – Currently prohibited; would alter all cells in the embryo

• **Enhancement gene therapy**
  – Consensus is that we should not use
  – Would add genes to enhance the individual
Stem cells

What is the potential for stem cells?
Embryonic stem cells
Ethical issues in stem cell research
Adult stem cells
Stem Cells

- Multipotent
- Capable of Self Renewal
Stem Cells from the Inner Cell Mass

In Vitro Fertilization → Totipotent Cells → Blastocyst → Fetus
The Promise of Stem Cell Research

Drug Development and Toxicity Tests

Cultured Pluripotent Stem Cells

Experiments to Study Development and Gene Control

Tissues/Cells for Therapy

- Bone Marrow
- Nerve Cells
- Heart Muscle Cells
- Pancreatic Islet Cells

http://www4.od.nih.gov/stemcell
Sources of embryonic stem cells

Inner cell mass cells

Fetal cells

Umbilical cord cells
Additional issues

- Possible immune responses against differentiated stem cells
- Need to generate enough stem cells for transplants

Possible solutions

Use fetal tissue (Parkinson’s Disease)

Therapeutic cloning
Fetal Transplants in Parkinson’s Disease

- Fetal cells survive in the brain after transplant

- Fiber outgrowth was observed from transplanted neurons

- Patients (<60 yrs) receiving fetal cells show significant clinical improvement

- After 3 years 15% of recipients showed increased involuntary movement due to high dopamine levels

Freed, et al., NEJM 2001
Therapeutic cloning

Use stem cells as gene therapy vectors

http://whyfiles.org/148clone_clash/images/thera_diagram.jpg
Ethical Issues

- Does a fetus have intrinsic value and rights?

- Does the use of aborted fetal tissue for therapeutic research encourage women to have abortions?

- Is it possible to separate stem cell research from the abortion debate?

- Is it wrong to use discarded human embryos (from IVF) in stem cell research?

- How do we weigh potential medical benefits to those already born with the rights of embryos?

- Is it possible to separate stem cell research from the human cloning debate?
Adult Stem Cells

- Cells with stem cell properties have been found in the adult
- Identified in brain, bone marrow, peripheral blood, muscle, liver
- Adult stem cells divide without differentiating for years
- Can then differentiate into a mature tissue type
- Adult stem cells may be at least multipotent
Potential sources of adult stem cells

- Hematopoietic stem cells
- Neural stem cells
- Bone marrow stromal cells
- Sperm???
Adult Stem Cells—Limitations

- Adult stem cells may have limited cell-type potential

- They may not exist for some organs (insulin-producing cells?)

- Numbers of cells and isolation may be limiting

- Adult stem cells may have limited proliferative potential
Sperm-derived stem cells

-sperm are generated throughout life from spermatogonial stem cells (SSCs)

-2006 report in Nature showed culture of adult mouse SSCs

-cells were obtained from a mouse testis

-the cells acquired embryonic stem cell properties- multipotent adult germ line stem cells (maGSC)
Sperm-derived stem cells

- maGSCs can develop into cells from all three germ layers \textit{in vitro}

- and \textit{in vivo}

- following injection of cells into blastocysts
Funding for human stem cell research

- No federal funds before 2001

- August 9, 2001 funds available for stem lines made earlier- no new lines (currently 21 available- IVF)

- Four states now fund human stem cell research- New Jersey, Maryland, Connecticut, California, (MA?)

- California Proposition 71 (2004) set aside $3 billion- lawsuits have held up distribution