



# Stem Cells, Regenerative Medicine and cGMP (GTP)



# Stem cell based therapies activities



## ■ Encompass

### – Collection

- source

### – Purification

- Isolation from other cell types if needed

### – Manipulation

- Minimal vs Moderate vs Maximal

### – Characterization

- Including existing infection (esp. viral) and genetic variants

### – Delivery of cells

- Form and route are major issues



# Stem cell based therapies



- Current use (2014 – world wide)
  - 13% human embryonic stem cells (hESC or iPSC)
  - 2% fetal stem cells
  - 10% umbilical cord stem cells
  - 75% adult stem cells
    - Most often patient-specific therapy
  
- Adult Stem Cells
  - Multipotent
  - Tissue / organ lineage specific

# Stem cell based products (SCBP)



- “Products intended to be administered to a patient and that contain or are derived from stem cells.”
- Regulatory Challenges
  - Safety
    - Bacterial
    - Fungal
    - Endotoxin
    - Mycoplasma
    - Viral
    - Genetic (often use karyotyping)
    - Process of enrichment

# Stem cell based products (SCBP)



## ■ Regulatory Challenges

### – Effectiveness

- Pass *in vitro* functional assay that acts as a surrogate for effectiveness
- Issue – developing validated tests, standards and controls

### – Quality

- Scarcity of classical toxicology studies during pre-clinical development
  - Inherent limitations of human cells in animals (immunocompromised)
  - Often no direct animal models for the human condition
- In many cases, develop the required safety, effectiveness and quality simultaneously with the clinical trial – not ideal

# FDA and Public Health Service Act Regulations



- IND 21 CFR 312
- Biologics 21 CFR 600 (CBER)
- cGMP 21 CFR 211
- cGTP 21 CFR 1271
  - Cells, Tissues, and Cellular and Tissue-Based Products (HCT/P)
  - All cGMP regulations also apply
- Cell Therapy in PHSA
  - “351” and “361” products
    - E.g., traditional blood and bone marrow progenitor cells and other tissues
    - Codified under the GTP regulations

# FDA and Public Health Service Act Regulations



- Based on three general rules

- Prevention of the use of contaminated tissues or cells (e.g., AIDS or hepatitis)
- Prevention of inadequate handling or processing that may damage or contaminate those tissues or cells
- Clinical safety of all tissues or cells that may be processed, used for functions other than normal functions, combined with components other than tissues, or used for metabolic purposes



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# Clinical translation remains a barrier to the widespread use of cell-based therapies

Cell-based therapeutics include active pharmaceuticals produced by transformed/transfected cells as well as stem cells and regenerated tissues or organs.

APIs have been produced under GMP regulations for decades, a model that we all know well.

# Examples of early approved (pre-2011) therapies include



- ApliGraf
  - Wound treatment using cultured foreskin (allogeneic)
  - Esp. diabetic ulcers and venous ulcers
  - Moderate manipulation
- Carticel
  - Autologous (aka, homologous) cultured chondrocytes
  - Treatment of Femoral condyle and knee cartilage
  - Minimal manipulation
- Epicel
  - Cultured Epidermal Autograft
  - Minimal manipulation

All drugs and biologics – cell therapies included – administered to humans are required to be manufactured according to cGMP guidelines.



cGMP minimally covers

- Facilities design
- QC/QA systems
- Documentation and records
- Validated production and process controls
- Metrology
- Personnel qualifications
- Environmental monitoring

Issues related to cell therapies vs APIs

- The therapeutic is a living entity vs. a small molecule
- Unique donor and cell source considerations
- Methodology of production is unique
- Therapeutic product (stem cell, tissue, organs) can not be sterilized post-production



# Considerations of chemistry, manufacturing and controls



- APIs

- The processes and reagents used in drug manufacturing and all testing that is conducted on the drug product. I.e., how it is made and what is used to make the product.

- Cell therapies

- Cell or tissue source (donor)
  - Autologous, allogeneic, xenogeneic
- Entire history of reagents, components and equipment used in production
- Safety tests – sterility, endotoxin, mycoplasma, etc.
- Quality tests – viability, identity, purity, stability, compatibility
- Risk of disease that may be present in the donor

## Regulations based on Good Tissue Practices (USA) and Human Tissue Act (EU)



Level of regulation is based on cell source and increasing degree of processing

- Autologous – minimal manipulation
  - Within same surgery; washing, cryopreservation
  - Not combined with a drug or device
  - Individually, do not require FDA approval
  - Procedure does require approval by appropriate agency(ies)

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- Regulations based on Good Tissue Practices (USA) and Human Tissue Act (EU)

Level of regulation is based on cell source and increasing degree of processing

- Allogeneic (Homologous) – moderate manipulation
  - Cell culture and scale up
  - FDA considers this a “somatic cell therapy”
  - Multiple patients treated from single cell source
  - May result in a cell bank (consistency)
    - One donor => many recipients
  - Requires IND exemption or FDA license
- Xenogeneic – maximal manipulation



# Clinical Master Cell Banking



- Under cGMP (cGTP) regulations
  - Large scale up of single cell type
  - Consistency in treatment and outcome for multiple patients
  - Matched to a Master Research Bank cell line
    - Research directly relates to clinical product to improve translation
    - Not GMP regulated but closely monitored
  - Feeder independent growth
    - More difficult for human stem cells but feeder layers (commonly mouse embryonic fibroblast) add multiple layers of additional components
  - Fully tested for viruses and adventitious agents (FDA Reg)

# Regenerative Medicine



## Autologous stem cell transfer

“from the patient, for the patient”

- Acute myocardial infarction
- Amyotrophic lateral sclerosis
- Anal fistulas
- Breast cancer
- Critical limb ischemia
- Diabetes
- Hypoplastic left heart syndrome
- Intracranial saccular aneurysms
- Liver repair and tolerance induction
- Lymphoma and ovarian cancer
- Renal stenosis
- Stage IV glioblastoma