GMP Facilities in US Academic Centers: Their Trials and Tribulations

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Manager, Quality Assurance
The Need for Academic GMP Facilities

- Maturity of R &D in cell based therapies → movement from bench to bedside
- Obligation to make possible these new therapies with a safe and hopefully, effective product
- Availability of techniques and cell processing equipment
- Developments in regulation that stress conformity of IND products to appropriate standards
- Reluctance of Pharma to enter at earlier phases of investigation
US Academic Centers with GMP Facilities

- Approximately 40-45 GMP facilities in the US
- Associated with research based medical centers
- Established under the Production Assistance for Cellular Therapies by the NHLBI
- Association of Academic Biologics Manufacturers

(AABM, Scientific symposium @ ASGCT meeting in Seattle, May 2011)
Clinical Products

- Monoclonal Antibodies
- Recombinant Proteins
- Vaccines
- Hematopoietic Cell Isolations
- Islet Cells
- Antigen specific Cells
- Artificial APCs
- Tumor Vaccines
- Working Cell Banks
- Master Cell banks
- Pleuripotent Stem Cells
- Isolated and Expanded T cells
- Gene modified T cells
- Gene modified HPSCs
- Mesenchymal Stromal Cells
- GMP grade FACS sorted cells
- GMP grade Plasmid DNA
- Vectors-Lentivirus, Adenovirus, Retrovirus, AAV, HSV, VSV, Yeast and bacterial systems, Pichia pastoris and E coli
- Radiolabeling of MAbs for PET
- Peptide loaded DCs
- Targeted Nanodroplet Imaging
- Activated Pharmaceutical Ingredients
Code of Federal Regulations

- 21CFR, Part 210-cGMP in Manufacturing, Processing, Packing or Holding of Drugs
- 21CFR, Part 211-cGMP for Finished Pharmaceuticals
- 21CFR, Part 600-cGMP for Biological Products
- 21CFR, Part 606- cGMP for Blood and Blood Components
- 21CFR, Part 1271-Current Good Tissue Practice for Manufacturers of Human Cellular and Tissue-based Products
- 21CFR, Part 11- Electronic Records an Signatures
- 21CFR, Part 610-General Biological Standards
- 21 CFR, Part 640-Standards for Human Blood and Blood Products
Process Oriented Quality Management System

Monitor and Maintain

- Qualified Reagents
- Qualified Supplies
- Qualified Equipment
- Reliable IT Systems
- Effective Procedures
- SOPs & Forms
- Qualified Personnel
- Qualified Donors
- Adequate Facilities

Validate Process

Controlled Process

Safe & Effective Therapy that meet requirements

Improve

that meet specifications
The Facility

- Compliant with regulations but must maintain flexibility
- Most centers employ class 10,000 cleanrooms with class 100 BSCs
  - Requires special air handling systems
  - Preference for “Unidirectional” Flow for personnel, supplies, product and waste
  - Expensive to build, maintain and monitor
Cleanroom 1 - Plasmid DNA Production
Cleanroom 2 - Pre clinical investigations
Cleanroom 3 - Viral Vector Production
Cleanroom Suite 4 - 2 Cleanrooms for Patient Material
Room 5 - Pre-Gowning Room
Room 6 - Release room for Inventory
Room 7 - Quarantine room for Inventory

*All cleanrooms are Class 10,000 rated
Proposed Cell Therapy and Cell Engineering Facility
<table>
<thead>
<tr>
<th>Proposal</th>
<th>Assessment</th>
<th>Development</th>
<th>Validation</th>
<th>Clinical Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>-Product Information</td>
<td>-Opportunity &amp; Strategy</td>
<td>-Process Timelines Events</td>
<td>-Timeline of Validation Review</td>
<td>-Product Conformance</td>
</tr>
<tr>
<td>-Space-Clinical Requirements</td>
<td>-Materials</td>
<td>-Equipment Plans</td>
<td>-Risk Based Assessments</td>
<td>-Clinical Outcomes</td>
</tr>
<tr>
<td>-Clinical Information Equipment</td>
<td>-Equipment Budgets</td>
<td>-Product Quality</td>
<td>-Materials Qualification</td>
<td>-Quality Monitors</td>
</tr>
<tr>
<td>-Contractual Productivity</td>
<td>-Quality Agreement</td>
<td>-Budget Review</td>
<td>-Budget Review</td>
<td>-Customer Satisfaction</td>
</tr>
<tr>
<td>-Intellectual Enhancement Agreement</td>
<td>-Enhancement of Academic Strategies</td>
<td></td>
<td></td>
<td>-Documentation</td>
</tr>
</tbody>
</table>
Protocol Development and Review Process

- **Protocol Development**
  - **DMS Team(s) Review and Approval**
    - Review for: Quality, science, department priority [Protocol management/planning]
  - Service-Level Review and Approval

- **Protocol Review**
  - **DEPARTMENT PROTOCOL REVIEW**
    - Sub-Committee Review(s)
  - **RESEARCH COUNCIL REVIEW**

- **Protocol Approval**
  - **IRB REVIEW**
  - NIH-Office of Biotechnology (Recombinant DNA Advisory Committee)
  - Food and Drug Administration (CBER)

- **Consultation and Planning**
  - Data Management, Statistics

- **Advisory Committees:**
  - Committee on Radiation
  - Institutional Biosafety
  - Investigational Device Committee
  - Psycho/Social Task
  - Radioantibody Review Committee

- **Human Subjects Protection Review**

- **Must be reviewed and signed-off by all participating Departments**
GTF ORGANIZATION CHART

Office of Clinical Research
Collette Houston
Lee McDonald

Director
I. Rivière, Ph.D

Cell Engineering,
Vector Production &
Molecular Monitoring
Supervisor
X. Wang, Ph.D

QA/QC Unit
Quality Assurance Manager
S. Bartido, Ph.D
Quality Assurance Specialist
Quality Control Assistant
Quality Assurance Assistant

Plasmid DNA production
Retroviral & Lentiviral Vector Production
Transduction Patient Cells

7 Senior Technicians
Quality Control/ Quality Assurance Group
Role in the Gene Transfer Facility

• Responsible for as well as approving/rejecting all materials used in manufacture, packaging and labeling of the product, products in process or finished products.

• Ensures the accuracy of all production and testing records.

• Approves all procedures and specifications impacting the identity, strength (potency), quality or purity of the finished product.
Quality Control/Quality Assurance Group
Role in the Gene Transfer Facility

• Performs internal audits to confirm that all manufacturing and testing functions are operating in compliance with established procedures and established standards.

• Ensures that all personnel in the GMP facility are fully trained in the concepts and the means of compliance-training is documented and level of expertise is tested.
Clinical Trials

• A Phase I Trial for the Treatment of Purine Analog-Refractory Chronic Lymphocytic Leukemia using Autologous T cells Genetically Targeted to the B cell Specific Antigen CD19 [IND #13266; IRB # 06-138]- PI: R. Brentjens

• A Phase I Trial of Precursor B Cell Acute Lymphoblastic Leukemia (B-ALL) Treated with Autologous T Cells Genetically Targeted to the B Cell Specific Antigen CD19 [IND #13266; IRB #09-114]- PI: R. Brentjens

• Adoptive Transfer Of Autologous T Cells Targeted To Prostate Specific Membrane Antigen (PSMA) For The Treatment Of Castrate Metastatic Prostate Cancer (CMPC) [IND #14028; IRB #09-036 ]-PI: S. Slovin
Clinical Trials

• A Pilot Trial to Assess the Feasibility and Safety of G-CSF Mobilization of CD34+ Hematopoietic Progenitor Cells in Patients with Beta-thalassemia Major (IRB # 08-030) PI: F. Boulad, MD)

• A Phase I Clinical Trial for the Treatment of ß-Thalassemia Major with Autologous CD34+ Hematopoietic Progenitor Cells Transduced with Thalagen™, a Lentiviral Vector Encoding the Normal Human ß-Globin Gene (IRB # 10-164) PI: F. Boulad

• A Phase I Clinical Trial for the Treatment of ß-Thalassemia Major with Autologous CD34+ Hematopoietic Progenitor Cells Transduced with TNS9.3.55m, a Lentiviral Vector Encoding the Normal Human ß-Globin Gene [NHLBI] (IRB# 11-046) PI: F. Boulad
**CAR+ T cell Manufacturing Flow**

- **Day 0**
  - Thaw/Wash
  - Cytomate

- **Day ≥0**
  - Incubation
  - Dynabeads CD3/28
  - CLL patient T cells

- **Selection**
  - ClinExVivo MPC
  - CD3+ enriched activated T cells
  - 1928z+ transduced T cells

- **Day ≥10**
  - Debeading
  - ClinExVivo MPC
  - 1928z+ expanded T cells

- **Day ≥5**
  - Transfer
  - WAVE Bioreactor

- **Biosafety/ QC release tests**

- **Infusion**

- **Wash/Formulation**
  - Cytomate

- **Effector/Memory phenotype**
  - In vitro CTL assay
  - In vivo antitumor activity in SCID Beige mice

- **Hollyman et al, Journal of Immunotherapy, 2009**
References

• Cell Therapy cGMP Facilities and Manufacturing, A Gee, 2009, Springer

• Cellular Therapy: Principles, Methods, and Regulations
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Those stem cells were meant for someone who LOST an organ!

Thank you