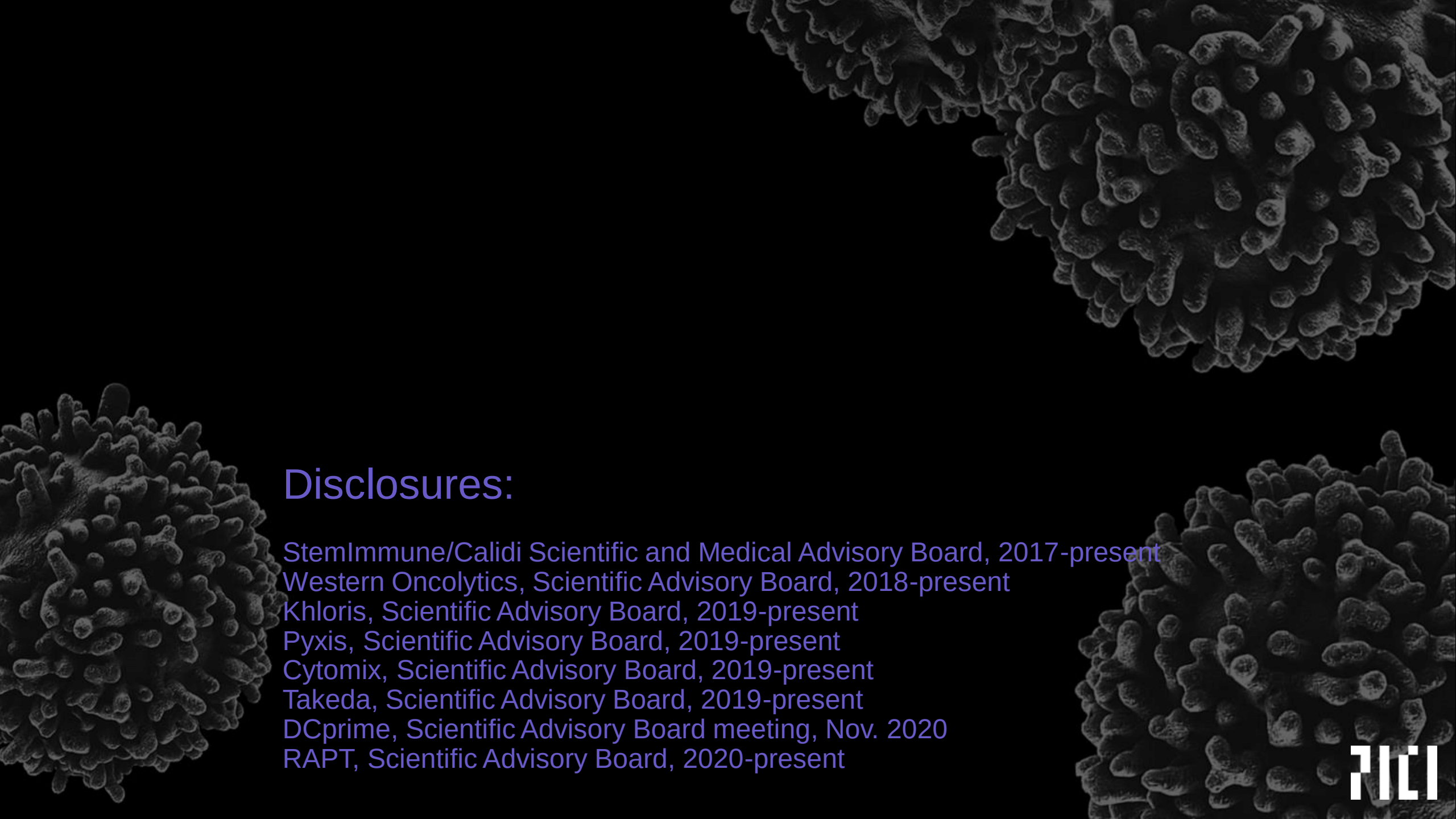
cGMP for Cell Therapy

"It's not science, it's manufacturing"

Regulatory compliance for the bench-to-bedside scientist

Lisa H. Butterfield, PhD.
Vice President, PICI Research and Development
Adjunct Professor, Microbiology and Immunology, UCSF
Past President, SITC

PARKER INSTITUTE FOR CANCER IMMUNOTHERAPY

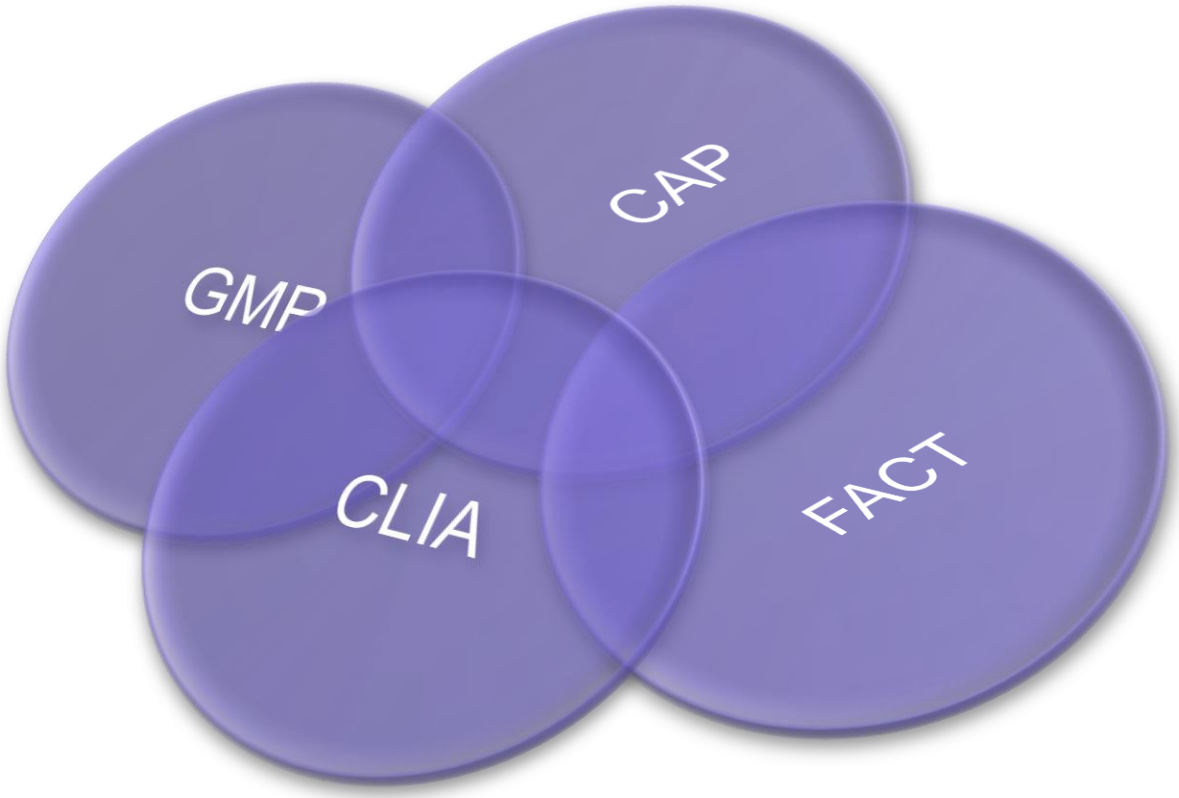


Disclosures:

StemImmune/Calidi Scientific and Medical Advisory Board, 2017-present
Western Oncolytics, Scientific Advisory Board, 2018-present
Khloris, Scientific Advisory Board, 2019-present
Pyxis, Scientific Advisory Board, 2019-present
Cytomix, Scientific Advisory Board, 2019-present
Takeda, Scientific Advisory Board, 2019-present
DCprime, Scientific Advisory Board meeting, Nov. 2020
RAPT, Scientific Advisory Board, 2020-present

Outline

- Background and history
- Many acronyms, a few central messages
- Academic medical center setting examples from this PhD



One Example: The Immunologic Monitoring and Cellular Products Laboratory

- The Cellular Products Laboratory (CPL) is dedicated to preparation of products for tumor vaccines and for cellular and gene therapy of cancer.
  - cellular product preparation; identity, sterility and safety evaluations
  - assists in the preparation of INDs
  - operates according to FDA criteria for current Good Manufacturing Practice (cGMP)
- The Immunologic Monitoring Laboratory (IML) is responsible for serial monitoring of immunologic functions in patients with cancer.
  - state-of-the-art immunologic assays
  - rigorous quality control program
  - development of new assays
  - advice on test selection and result interpretation
- The Tissue Procurement Facility (TPF) provides tissue and blood banking support under current Good Tissue Practice (cGTP) criteria.

CLIA certified; inspected by CAP and the state of PA; registered with FDA (3004571535)
FDA Master file: BB-MF-12244; FACT accredited

IMCPL certifications

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Services

MANUFACTURING RELATED

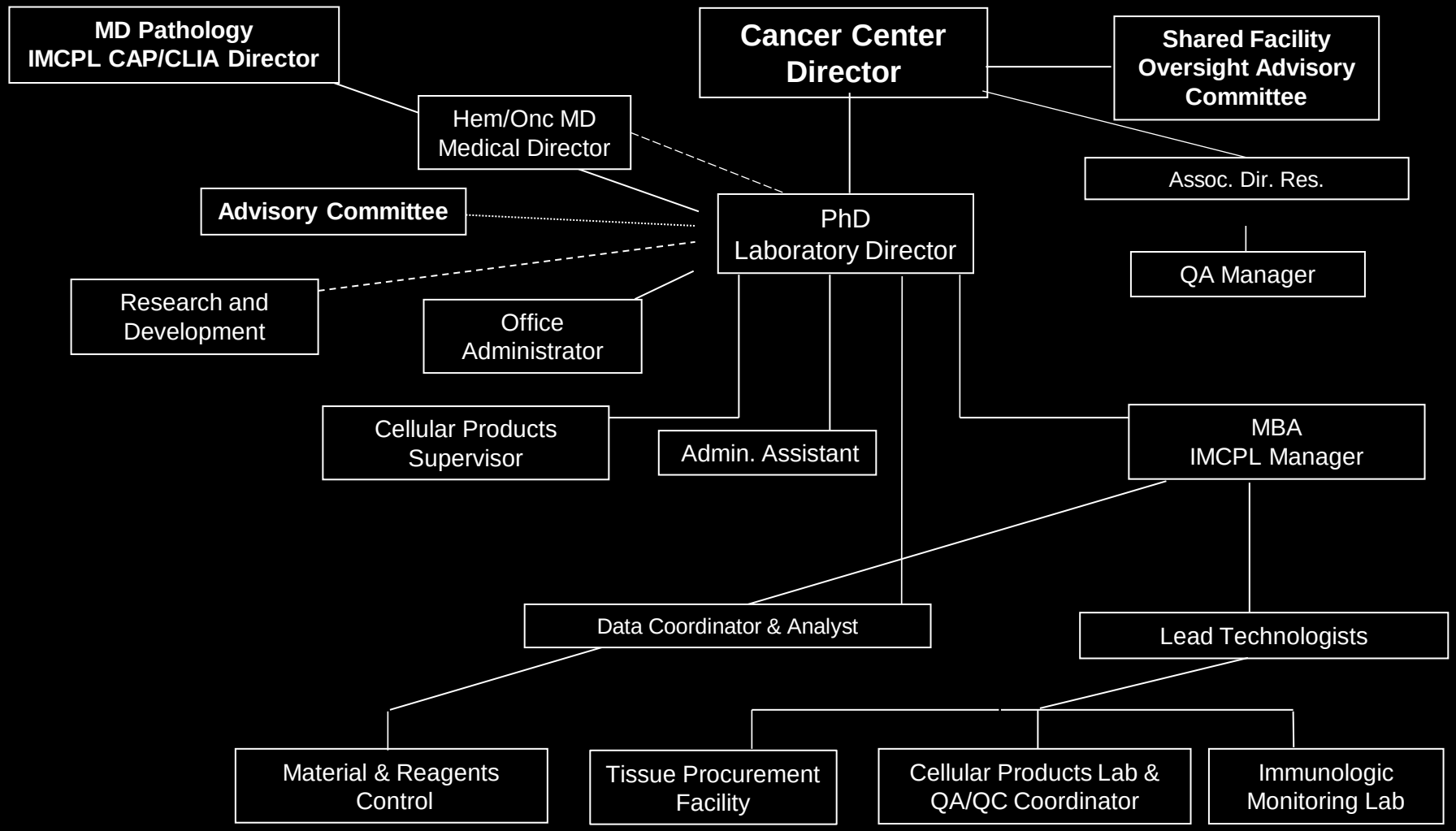
- Specimen intake, processing, banking
- Cell bank preparation
- Culture of peptide-specific T cells
- Culture of tumor infiltrating lymphocytes (TIL)
- DC preparation (peripheral blood, stem cells)
- Gene transfer: any human cells
- Expansion of stem cells
- Vaccine production for intra-tumor,-nodal, -lymphatic or intra-venous administration
- Peptide lyophilization, testing
- Adenovirus and vaccinia production (not fully GMP, with Vector Core)

ASSAY RELATED (profiling and testing cells)

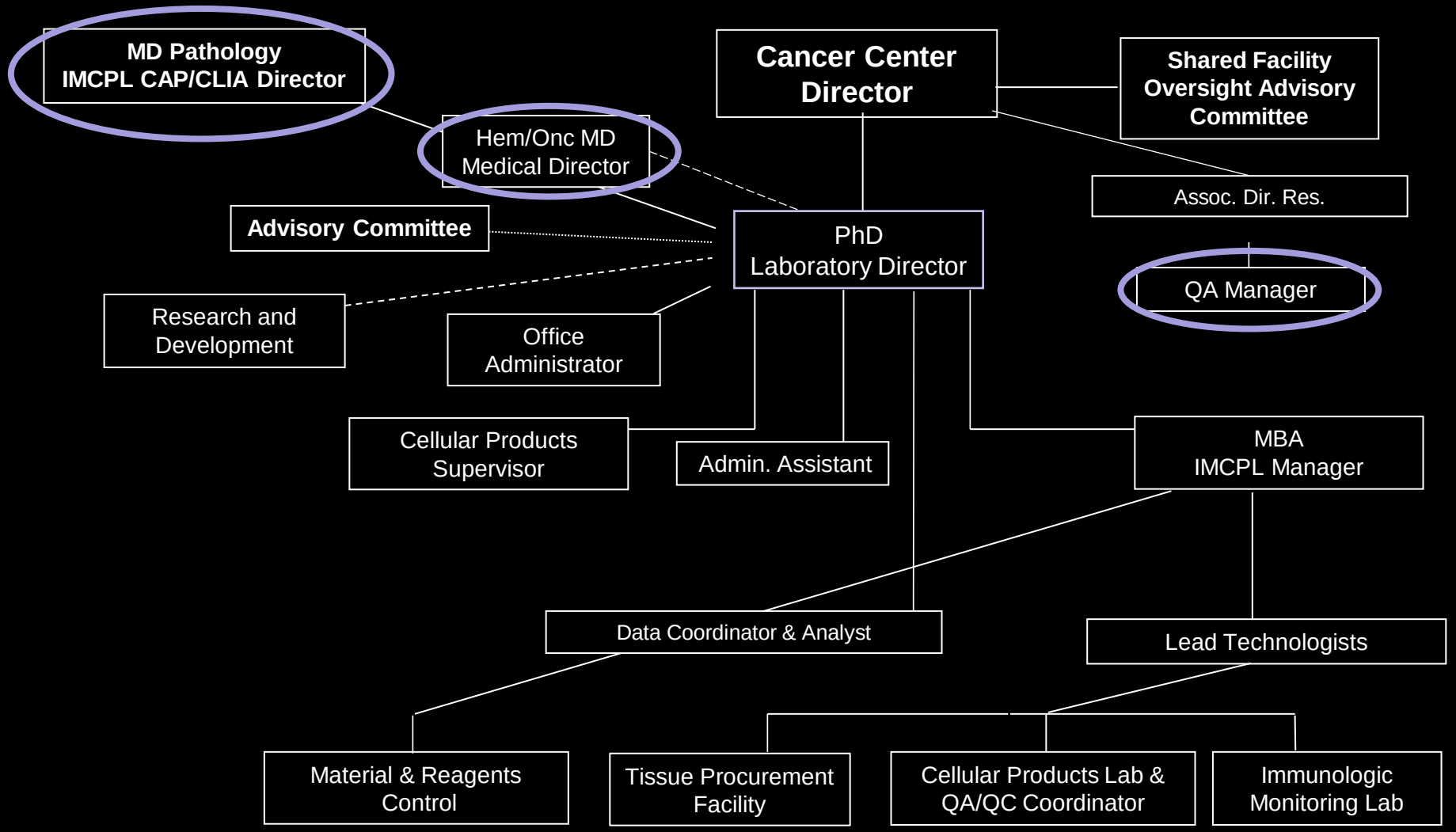
- Assay standardization, normal control ranges
- Mixed lymphocyte-tumor cultures
- Cytotoxicity (^{51}Cr-release, FLOCA, CD107a, Granzyme B ELISPOT)
- Proliferation (^{3}H-thymidine and CFSE)
- Multiparameter flow cytometry (effectors, regulatory (Treg, MDSC) cells)
- Single-cell assays (ELISPOT (2-color, fluorescence), CFC, and multimer)
- Signaling molecules
- Frequency of apoptotic T cells
- Anti-tumor antibodies
- Cytokine/chemokine analysis (Luminex, ELISA)
- Data entry and analysis

Focus on first-in-human, academic bench-to-bedside trials

Administrative Organizational Chart

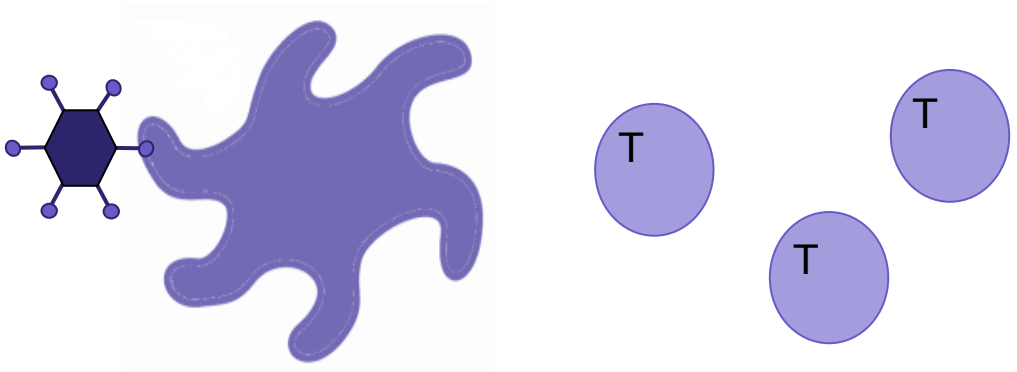


Administrative Organizational Chart

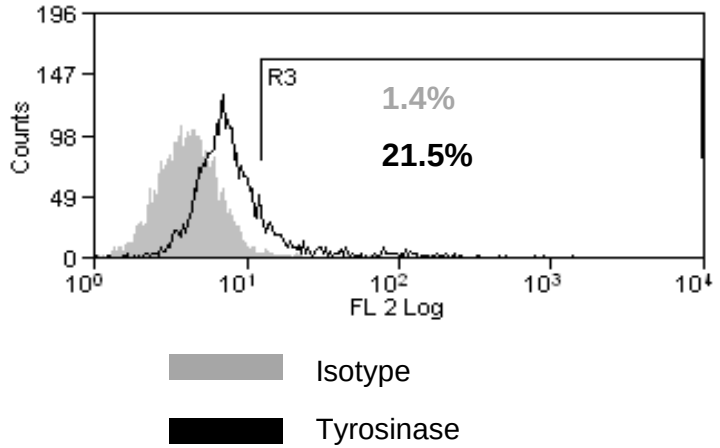


Replication-deficient Adenovirus AdVTMM2 Production for Autologous dendritic cell (DC) vaccines

A novel adenovirus encoding melanoma antigens was prepared by the University Vector Facility and IMCPL. Testing results for virally-transduced DC vaccine scale up studies and vaccines are shown. The clinical trial was RAC-exempt, had IND #15044, was IBC and IRB approved, and 35 patients were vaccinated.



DC transduction with antigen



DC identity phenotype

	HLA-DR+	MFI	CD86+	MFI	CD80+	MFI	CD83+	MFI	CCR7+	MFI	CD40+	MFI	CD11c+	MFI
#1	98%	25.6	95%	24	93%	5.45	88%	2.57	28%	1.34	95%	176	96%	23.5
#2	100%	21.4	98%	31.7	95%	4.87	81%	2.49	45%	1.89	98%	184	98%	28

Manufacturing labs in an academic medical center/cancer center: one model

CELLULAR PRODUCTS LABORATORY (CPL) IN IMCPL

- Provides cell manufacturing for a variety of clinical trials with internal and external investigators, specializing in **more-than-minimal-manipulation** of cells (both autologous and allogeneic).

HEMATOPOIETIC STEM CELL LABORATORY (HSCLAB)

- Provides cell processing for the stem cell transplant program and other departments, specializing in cell separation and minimally-manipulated autologous and allogeneic cells.

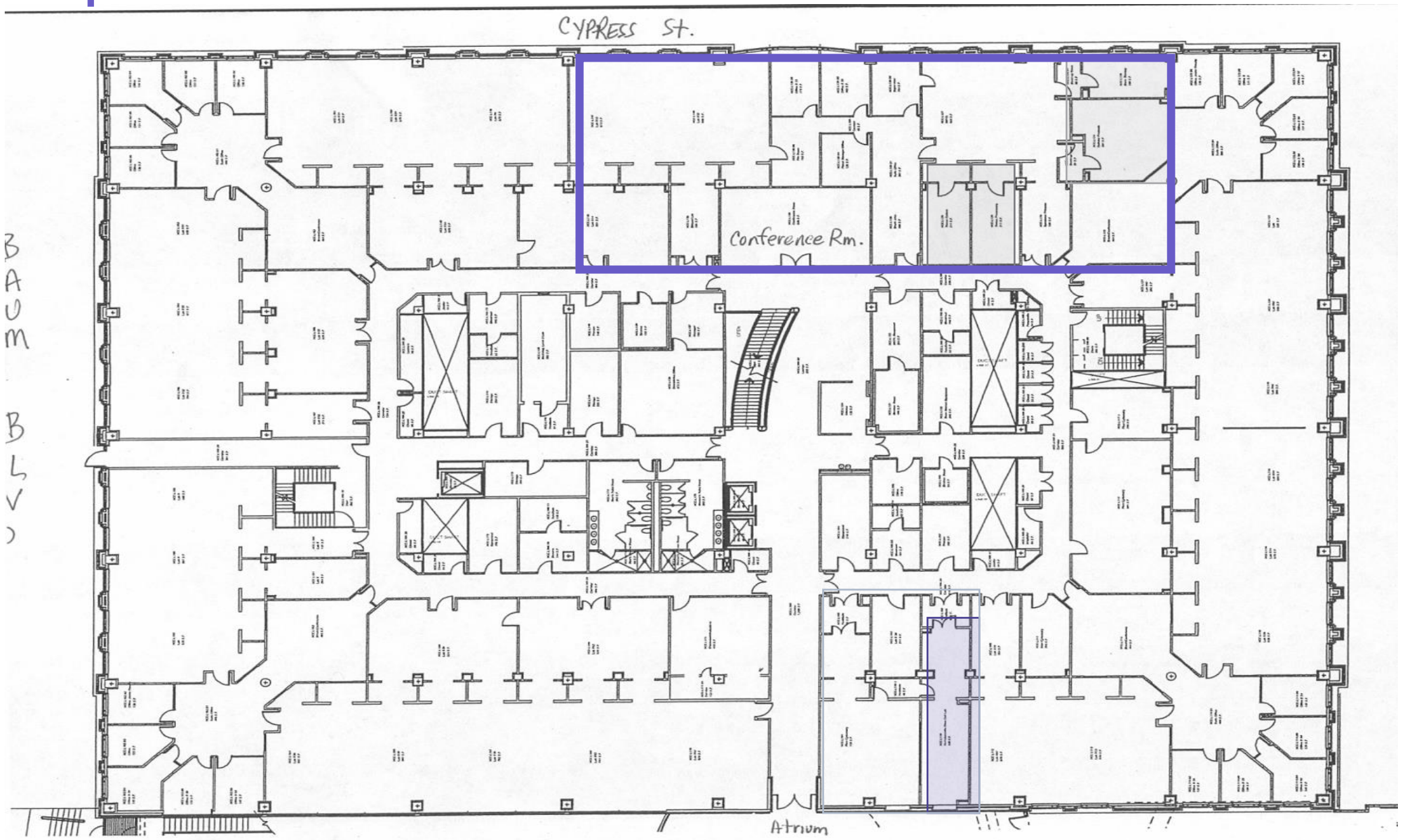
Physical Environment

- Designed after discussions with the FDA
- Stainless steel casework
- Coved epoxy terrazzo floors with a seamless join with the wall
- Solid ceilings
- Water-resistant epoxy paint
- Preliminary and terminal HEPA filtration
- Positive and negative air pressure areas
- Temperature and humidity controlled
- Secured area with restricted access

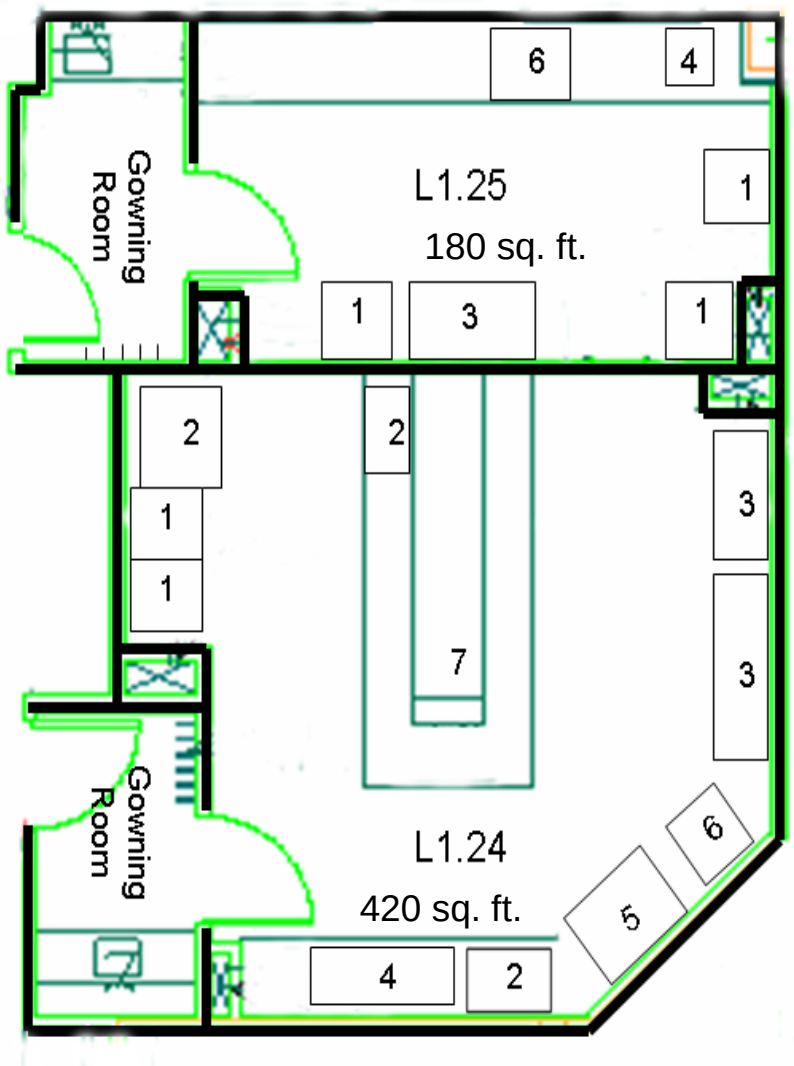
Facility Design

- Planning, design and documentation are keys to building a cGMP facility
- Separate, defined areas for each operation of the laboratories:
  - Accessioning of products
  - Product labeling
  - Processing
  - Storage of products, short-term and long-term
  - Waste disposal
  - Supply and reagent storage
  - Testing
- Interlocked anterooms between outer labs and cleanrooms
- Surfaces are non-shedding and non-porous
- Card-key access to authorized-user areas

Blueprint



Floor Plan



The floor plans and equipment in two of the three cleanrooms

LEGEND:

*	Indicates the pass-through
1	CO_2 Incubators
2	CliniMACS magentic bead purification
3	Biosafety cabinets
4	Centrifuges
5	ELUTRA system
6	Refrigerators
7	Microscopes

Cellular Products

- CPL consists one large testing laboratory with several smaller attached labs and three cleanrooms
- Main laboratory
- contains
  - Flow Cytometer
  - Centrifuges
  - Incubators
  - Microscopes
  - Refrigerators &
  - Freezers
  - Controlled-rate Freezers

- Cleanrooms contain
  - Biological safety cabinets
  - Centrifuges
  - Incubators
  - Microscopes
  - Elutra
  - CliniMACS

Autologous Products from Cancer Patients

- Cell Quality – often from heavily treated patients
  - May not grow or function as expected
- Uniform collection procedures
  - Training and competency, donor screening
- Transportation
  - Carrier/Packaging/Monitoring
- Processing
  - Regulated by FDA
- Cryopreservation
  - Effects?
  -

Regulatory compliance and quality measures can eliminate as many variables as possible, and provide a plan for unexpected issues

Other Labs seeking certifications:

SITE A

- One hood shared with blood bank
- 1.5 FTE for 70 transplants/year
- LN_2 tanks in office area, no O_2 monitors
- No secure facility in which to process products
- Bloodbank refrigerators in processing area, constant traffic in front of processing area
- No cleanrooms

SITE B

- Office area/eating area from accessioning and testing area by tape on the floor
- Carpet
- Old equipment, standard lab cabinets, cramped space

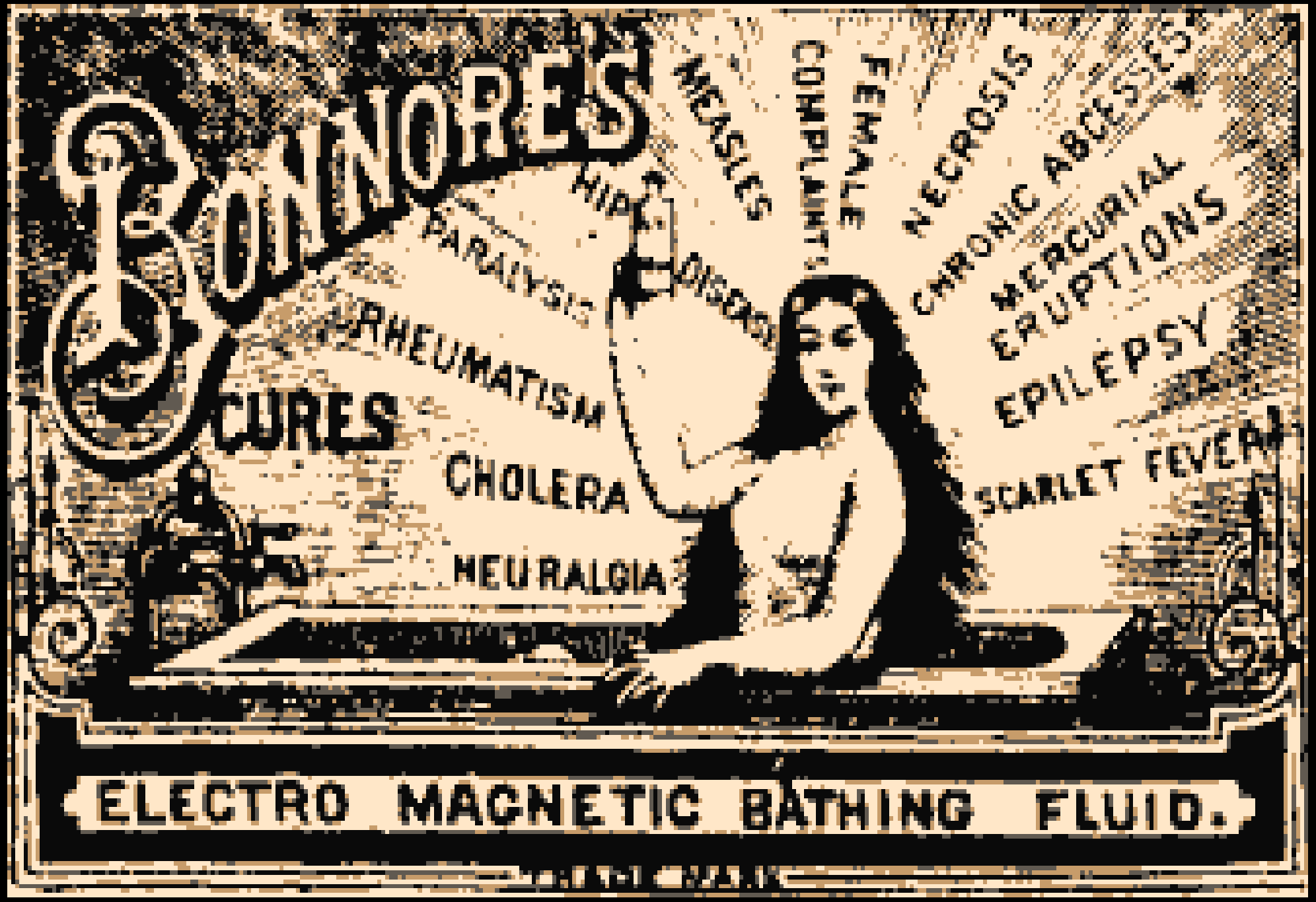
GxP

Where the X stands for any of several FDA regulations and the c stands for “current”:

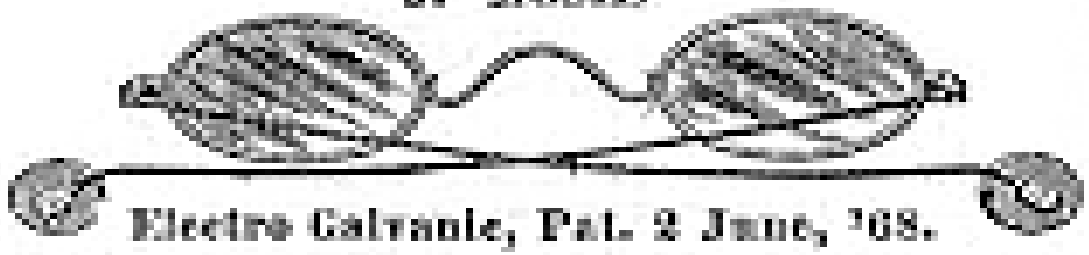
- GCP – Good Clinical Practise
  21 CFR 50, 54, 56
- GLP – Good Laboratory Practise
  21 CFR 58
- GTP – Good Tissue Practise
  21 CFR 1271
- cGMP – Good Manufacturing Practise
  21 CFR 210, 211

History of the FDA (1880s)

- 1880s Snake oil salesmen
- “Patent” medicines being sold
  - *wikipedia.org ›A patent medicine is a commercial product advertised as a purported over-the-counter medicine, without regard to its effectiveness. It is typically characterized as pseudoscience.*
- Adulterated food
- “Medical” devices
- Grassroots “pure food” movement


RENNORES
CURES
RHEUMATISM
CHOLERA
NEURALGIA
PARALYSIS
MEASLES
FEMALE COMPLAINTS
NECROSIS
CHRONIC ABSCESS
MERCURIAL ERUPTIONS
EPILEPSY
SCARLET FEVER
ELECTRO MAGNETIC BATHING FLUID.

J. MOSES'



Electro Galvanic, Pat. 2 June, '68.

Startling and Beautiful Invention!

A continuous stream of Electricity conveyed to the Optic Nerve!!

The organ of SIGHT restored to its original strength!!!

Eye employment, however continuous, rendered free from discomfort!!!!

BY J. MOSES'S

Patent Electro Galvanic Spectacles.

WHOLESALE DEPOTS,

10 CORTLANDT ST.,

NEW YORK,

AND

398 MAIN STREET,

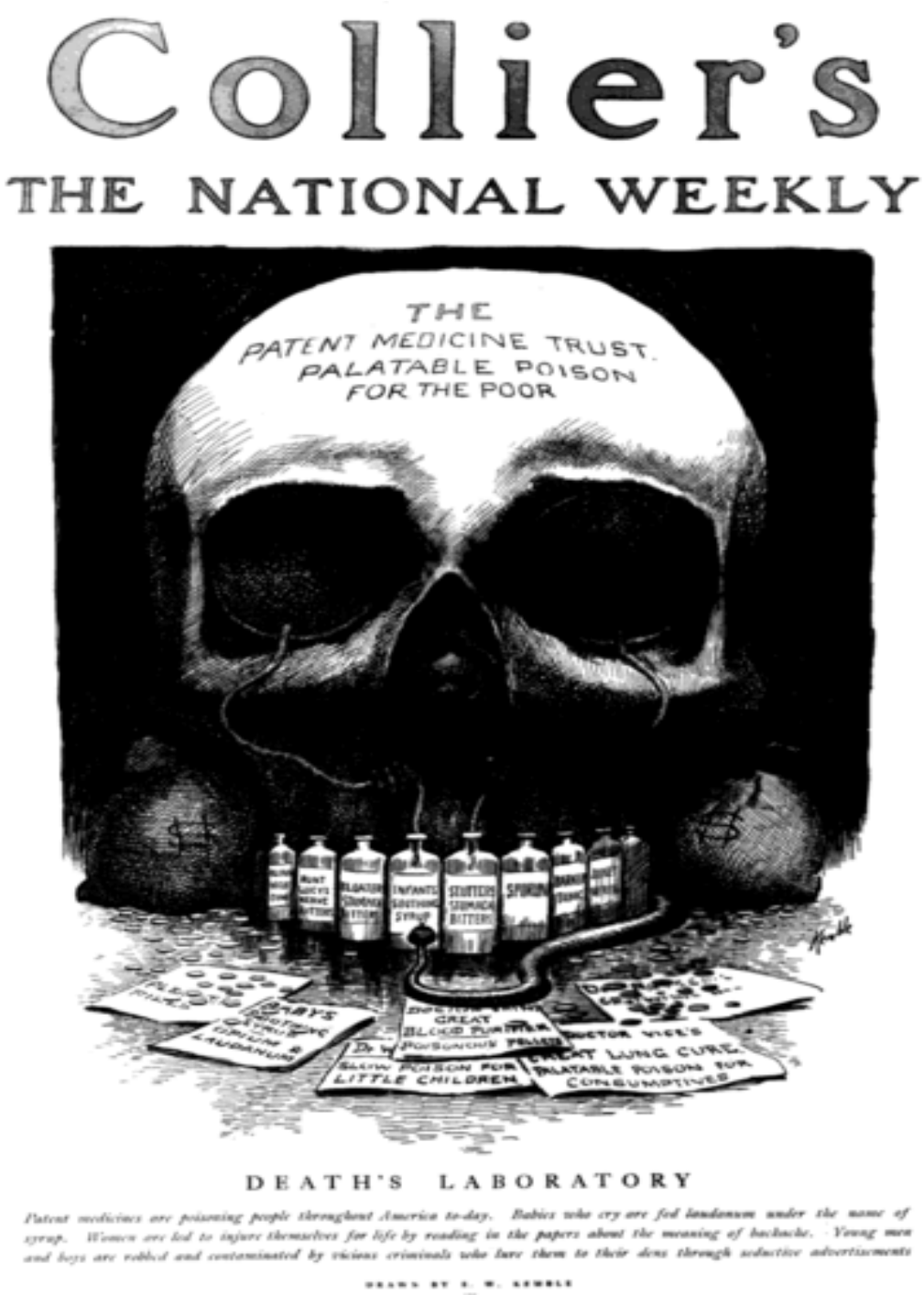
HARTFORD, CONN.

Jim the Horse

- 1901
- Used Jim’s serum to produce diphtheria vaccine
- Jim contracted tetanus
- Children contracted tetanus from the vaccine
- Led to the passage of the Biologics Control Act of 1902

FDA (1906)

- Pure Food and Drug Act regulated
  - Food preparation
  - Medical devices
  - Ingredients in medicines
- Federal regulations, no longer state jurisdiction



FDA (1927)

Became a law enforcement agency but receives funding and direction from Congress.

Permitted to

- Ban product
- Control distribution
- Control marketing

CBER, formed in 1902 by the Biologics Control Act to control vaccine manufacture, predates the FDA and was incorporated into the Agency in 1972.

History of the FDA (1930s)

- Elixir Sulfanamide - Antibiotic 1937
- Unpalatable as a pill
- Massengill decided to make soluble formulation
- Added pink color and cherry flavor
- Soon after its release, people started dying
- Testing performed by EMK Geiling, and assisted by Frances Oldham Kelsey, it turned out the solvent was diethylene glycol (*i.e.,* antifreeze)
- 107 deaths attributed, Massengill not held accountable due to FDA not requiring safety data. Fined for “misbranding” product.

History of the FDA (1938)

- Federal Food Drug and Cosmetic Act
- Required pharmaceutical companies to provide
    - Evidence of SAFETY of products
    - Warnings of potential hazards
- Covers:
    - Drugs
    - Cosmetics
    - Food additives including colorings

History of the FDA (1932-1972)

TUSKEEGEE SYPHILIS TRIAL

- 399 infected/200 uninfected poor, illiterate, African-American sharecroppers
- Purpose: study natural history of disease
- Participants:
  - Not informed of diagnosis
  - Told they had ‘bad blood’ and could receive
    - Free treatment
    - Free ride to clinic
    - One hot meal/day
    - $50 for their funeral

History of the FDA (1932-1972)

Participants (continued)

- Not given antibiotics when it became available (SOC) in 1940s
- Prevented from participating in syphilis treatment programs
- Received lumbar punctures under the guise of a special free treatment
- Hundreds of men died of syphilis, many wives infected and many children born with congenital syphilis

- Investigator goal: how the disease spreads and kills, but trial ended due to whistle-blower
- 1974 National Research Act
  - Commission to study and write regulations governing studies involving human participants

GCP

GOOD CLINICAL PRACTISE

- Not directly applicable to the laboratory
- PI, Physicians and Nurses are responsible for meeting GCP

- 21 CFR 50 Informed Consent
- 21 CFR 54 Financial Disclosure by Clinical Investigators
- 21 CFR 56 IRB
  - How clinical trials should be conducted, roles and responsibilities of staff

GLP

GOOD LABORATORY PRACTISE

- NON-CLINICAL laboratory testing
  - 21 CFR 58
- Ensures consistency and reliability
  - Results
  - Resources
  - Knowledge transfer
  - Well-defined audit trail

Often related to animal toxicology studies for new therapeutics

GTP

GOOD TISSUE PRACTISE

- Clinical laboratory testing
- Processing of tissue and cellular products intended to treat a disease or condition
- 21 CFR 1271

- Prevention of spread of communicable disease due to cellular and tissue based products
  - SAFETY of product being manufactured
  - Reporting mechanisms
  - Donor Eligibility

cGMP

CURRENT GOOD MANUFACTURING PRACTISE

- Only the US uses the little “c” to emphasize that this is the current thinking of the Agency and is a dynamic interpretation
- Intended primarily for pharmaceutical manufacturing processes
- 21 CFR 210, 211
- Worldwide: regulations from the World Health Organization are in use in over 100 countries
- Document every aspect of the processing, activities and operations

CBER Products

- Tissue & Tissue Products
  - Bone, Skin, Corneas, Ligaments, Tendons, Stem Cells, Sperm, Heart Valves
- Vaccines
  - Vaccines for Use in Children and Adults, Tuberculin Testing
- Xenotransplantation
  - Transplantation of Non-Human Cells, Tissues or Organs Into a Human

CBER is who regulates Cellular Therapy Labs

Accountability and Deviation Management

- Report errors that you discover
- Deviation management is not something to fear – it's an opportunity to make improvements, and shows that issues that are identified are addressed
- If you don't document it, it didn't happen

Worksheet Name: Deviation Management Record
Worksheet #: QA-006
Version: 10
Effective Date: 03/20/13

UNIVERSITY OF PITTSBURGH CANCER INSTITUTE
IMMUNOLOGIC MONITORING AND CELLULAR PRODUCTS LABORATORY

DEVIATION MANAGEMENT RECORD

DM # 14-006

Report Date: 2/7/14	**Staff: M. DeRiggi**	**Section: TPF ☐ CPL ■ IML ☐**
Event Dates: 11/25/13-1/30/14	**Protocol: 10-052/13-106**	**Specimen ID: See below**

Description: ■ Internal ☐ External

UVB lamps were used past their calibration due date of 10/29/13 to irradiate tumor cells for 13-106 and 10-052.

Date: **2/7/14** Tech: **MD**

Director Notified: ☐ Yes ■ No Date/Time: ---------- Tech: **MD**

QA Manager Notified: ☐ Yes ■ No Date/Time: ---------- Tech: **MD**

QA Analysis: ☑ Regular DM Process ☐ CAPA Process/Possible Reportable event QA 2/26/14

Category: ☐ Facilities ☐ Environmental control ■ Equipment ☐ Supplies & reagents ☐ Recovery
☐ Processing ☐ SOPs ☐ Labeling ☐ Storage ☐ Receipt, shipment & distribution ☐ Records & database
☐ Personnel ☐ Sterility/testing ☐ Donor eligibility, screening/testing ☐ Complaints ☐ Other _____

Investigation:
On 1/30/14 while preparing tumor lysate for patient DC on 10-052, technologist KK discovered the UVB lamp she was going to use had a sticker reading "calibration due: 10/29/13." All 5 UV lamps are sent at the same time for calibration to Spectronics Corporation where the lamps' intensities are measured and bulbs replaced if necessary. The past-calibration lamps were used for the following products:

- 11/19/13- TPF-13-472 Patient PW 10-052 tumor lysate UVB irradiation, lysate used for DTHs
  - Sterility result- No growth 14 days
- 11/25/13- CPL-13-24 Patient RS 13-106 tumor UVB irradiation, irradiated cells were used for co-culture
  - ApTu sterility result- No growth 14 days
  - 84% PI, 33% Annexin
- 01/23/14- TPF-14-9 Patient GH 10-052 tumor lysate UVB irradiation, lysate used for DTHs
  - Sterility result- No growth 14 days
- 01/30/14- TPF-14-32 Patient DC 10-052 tumor lysate UVB irradiation, lysate used for DTHs
  - Sterility result- No growth 14 days

Certificate of Conformance from Spectronics Corporation received and approved by Materials Management on 2/13/14.

Materials Manager confirmed that the devices contained the same bulbs before and after testing.

The procedures above use gamma irradiation to stop proliferation and UVB for sterilization (bacterial). All products tested NO GROWTH 14 days.

Date: 2/13/14 Tech: MD

Worksheet Name: Deviation Management Record
Worksheet #: QA-006
Version: 10
Effective Date: 03/20/13

Corrective Action, Short Term: ☐ Not applicable
All 5 UV lamps were immediately sent for calibration on 1/30/14.

Date: 2/7/14 Tech: MD

Corrective Action, Long Term: ☐ Not applicable
A preventive maintenance spreadsheet was made to include due dates for all equipment.
I:\CPL schedules

Date: 2/7/14 Tech: MD

Review by Supervisor/Lead Tech:
Problem resolved? ☑ Yes ☐ No Comment —

Follow up required? ☐ Yes ☑ No Comment —

Date: 2/26/14 Tech: VS

Additional/follow up comments and Final Review:

Supervisor/Designee Review/Date:	**Staff Review of finalized DM/Date:**
Veronica Sutherland 2/24/14	MDeRiggi 2/27/14

*Attach additional pages if necessary, including documentation.
QA documented in database: MD 2/7/14 Tech/date
Original filed in: patient folders
DM finalized/PDF made: MD 2/27/14 Initial/date

DEVIATION REPORT:

1. What happened
2. What it might have impacted
3. Information gathered, additional testing performed
4. Steps taken to fix problem
5. Confirmation that problem was fixed
6. Review and sign off

The Foundation for the Accreditation of Cellular Therapy

(FACT) is a non-profit corporation co-founded in 1996 by the International Society for Cellular Therapy (ISCT) and the American Society of Blood and Marrow Transplantation (ASBMT) to provide a peer network of experts committed to improving stem cell transplantation and cellular therapy practices by formulating and disseminating evidence-based guidelines.

These guidelines have until recently been formulated in 3 documents: 1) FACT Common Standards for Cellular Therapies, 2) FACT-JACIE Hematopoietic Cell Therapy Standards, and 3) NetCord-FACT Cord Blood Banking Standards.

FACT also offers a voluntary accreditation program for hematopoietic progenitor cell (HPC) therapy programs and UCB banks, with over 90% of eligible US HPC facilities and programs holding accreditation.

Achieving FACT accreditation after a comprehensive inspection performed every 3 years demonstrates to patients, physicians, commercial manufacturers, regulatory agencies, and insurance payers that a given program/laboratory is committed to quality measures and oversight in cell therapy practices and downstream patient care.

The why, what, and how of the new FACT standards for immune effector cells, M. Maus and S. Nikiforow, Journal for ImmunoTherapy of Cancer 2017

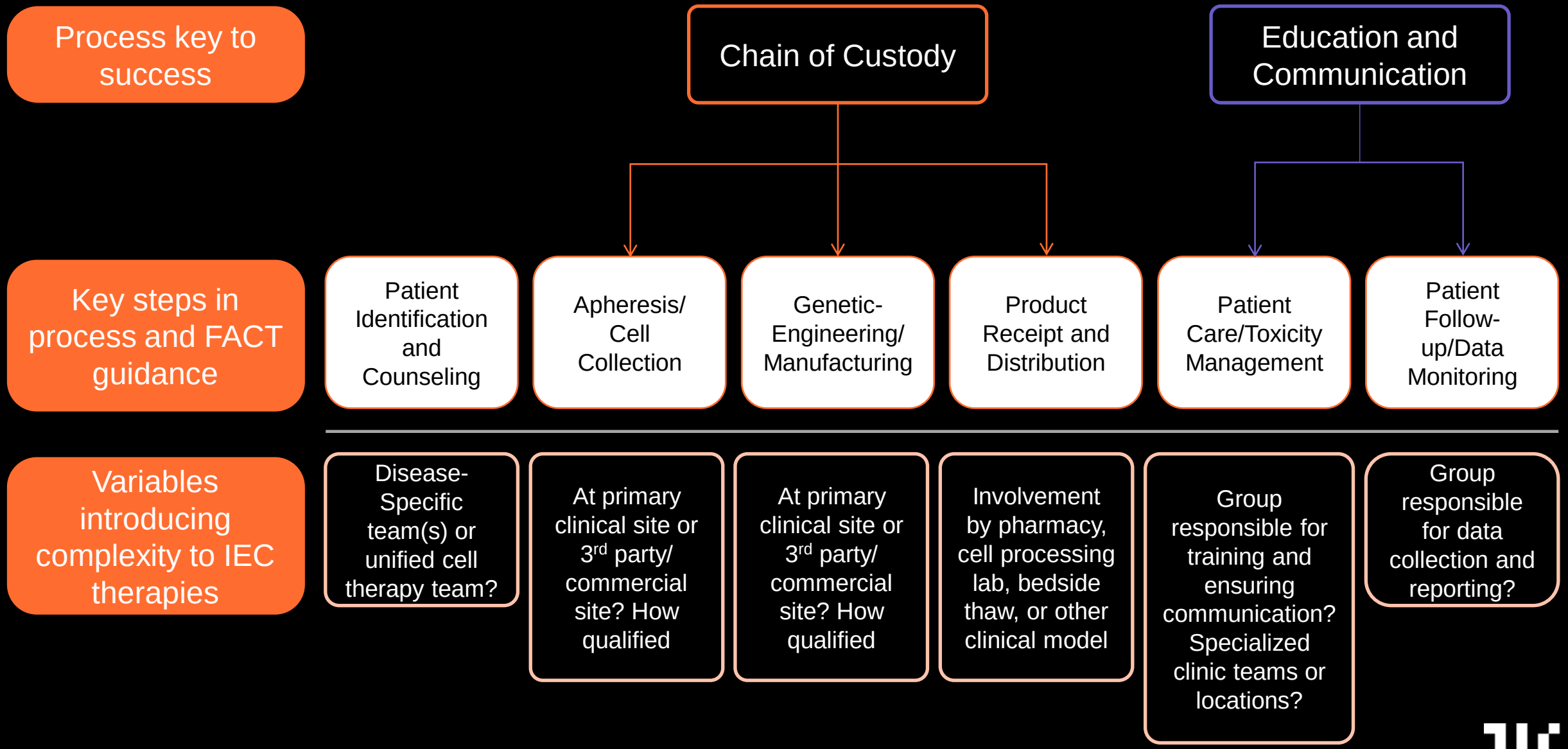
Current Cellular Products

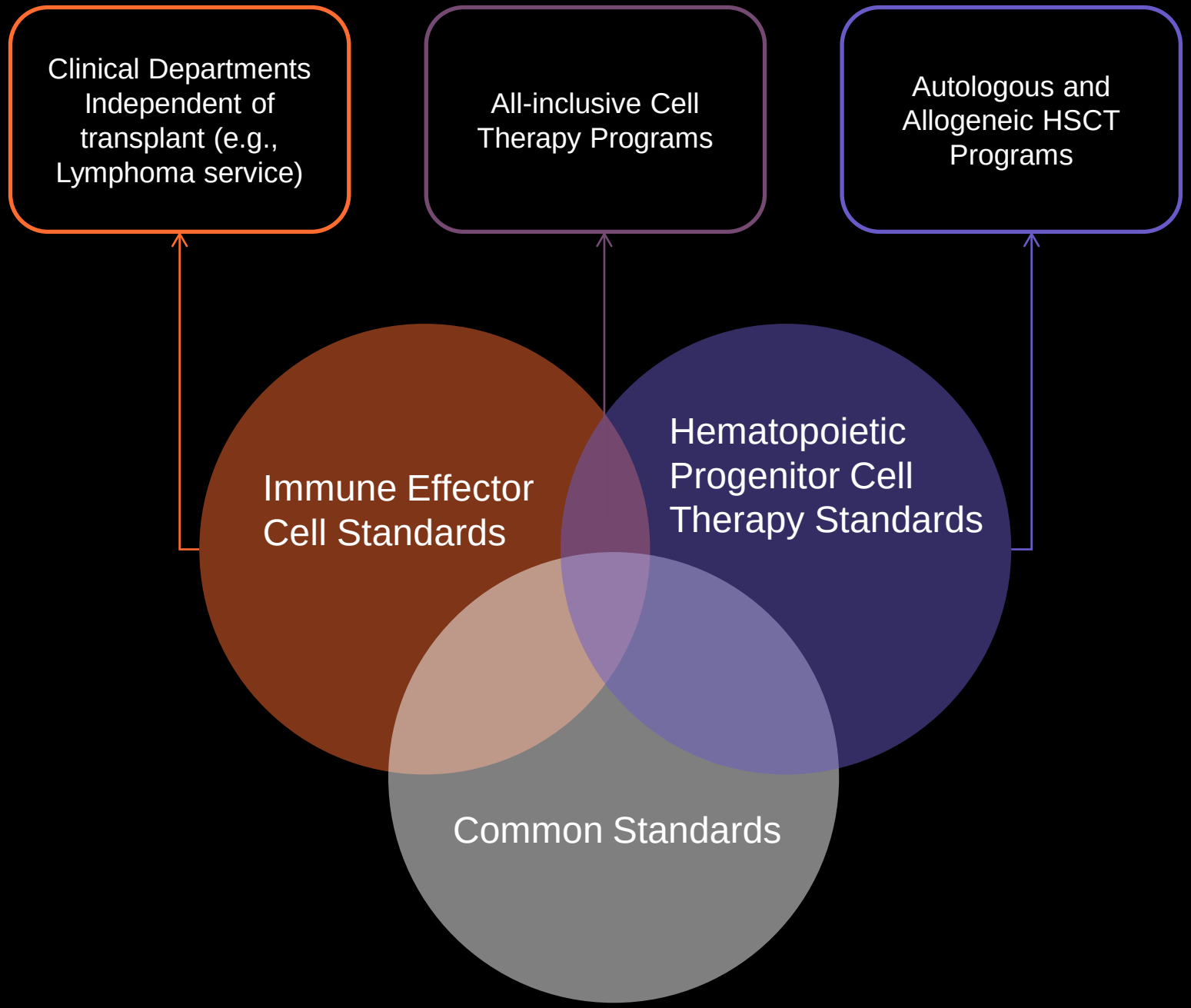
The administration of CAR-T cells can consume significant effort from: transfusion medicine, the cell-processing laboratory, pharmacy, outpatient and inpatient clinical teams, and consultants.

A robust clinical infrastructure is required to handle the complex scheduling logistics, maintain the chain-of-custody and chain-of-identity of the cellular product, and facilitate communication to manage potentially severe toxicities.

Cells are not stored in vials, nor are they mixed and re-labeled in the pharmacy. These products must be temperature-controlled at all times during preparation, shipping, and administration, and can only be manipulated under aseptic conditions.

The importance of the chain-of-custody and absolute certainty regarding identity of the cellular product, along with its label and attendant paperwork, cannot be overstated, as administration of the wrong product can have lethal consequences.


Process key to success
Chain of Custody
Education and Communication
Key steps in process and FACT guidance
Patient Identification and Counseling
Apheresis/ Cell Collection
Genetic-Engineering/ Manufacturing
Product Receipt and Distribution
Patient Care/Toxicity Management
Patient Follow-up/Data Monitoring
Variables introducing complexity to IEC therapies
Disease-Specific team(s) or unified cell therapy team?
At primary clinical site or 3rd party/ commercial site? How qualified
At primary clinical site or 3rd party/ commercial site? How qualified
Involvement by pharmacy, cell processing lab, bedside thaw, or other clinical model
Group responsible for training and ensuring communication? Specialized clinic teams or locations?
Group responsible for data collection and reporting?



Relationship between different FACT standards. Individual programs will reference standards and seek accreditation as best suits their needs.

While all cellular therapy manufacturing and distribution should comply with the guidelines in the Common Standards, clinical teams may operate and apply for accreditation within an HSCT program, an IEC program or one that involves both types of cell therapies.

Maus, JITC 2017

Scope of FACT Immune Effector Cell Standards

- Cells used to modulate an immune response for therapeutic intent
- May elicit a response or mitigate a response
- Cell types include DC, NK, T, and B (does not include MSCs)
- Common products
- Chimeric antigen receptor T cells (CAR-T cells)
- Therapeutic vaccines using dendritic cells

PROCESSES –NOT SCIENCE

- Donor selection and management, collection, preparation for administration, administration of cells, management of adverse events, and evaluation of clinical outcomes
- Quality Management (QM) program that establishes, maintains, monitors, and implements improvements
- Education

FDA Cell Therapy Lab Registration

See Instructions for OMB Statement. FORM APPROVED:OMB No.0910-0543. Expiration Date: 6/30/2020

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

ESTABLISHMENT REGISTRATION AND LISTING FOR HUMAN CELLS, TISSUES, AND CELLULAR AND TISSUE-BASED PRODUCTS (HCT/Ps)
(See reverse side for instructions)

1. REGISTRATION NUMBER
(FDA Establishment Identifier)
FEI: 3004571535

2. REASON FOR SUBMISSION
a. ☐ INITIAL REGISTRATION / LISTING
b. ☒ ANNUAL REGISTRATION / LISTING
c. ☐ CHANGE IN INFORMATION
d. ☐ INACTIVE

VALIDATION--FOR FDA USE ONLY 1
VALIDATED BY FDA:19-NOV-2016
DISTRICT: Philadelphia
PRINTED BY FDA:15-NOV-2017

PART I - ESTABLISHMENT INFORMATION

3. OTHER FDA REGISTRATIONS
a. BLOOD FDA 2830 NO. _____
b. DEVICES FDA 2891 NO. _____
c. DRUG FDA 2656 NO. _____

4. PHYSICAL LOCATION (Include legal name, number and street, city, state, country, and post office code)
University of Pittsburgh Cancer Institute Hillman Cancer Center
5117 Centre Avenue
Suite 1.27
Pittsburgh, Pennsylvania 15213-1863

a. PHONE 412-623-1418 EXT
b. ☐ SATELLITE RECOVERY ESTABLISHMENT (MANUFACTURING ESTABLISHMENT FEI NO._____
c. ☐ TESTING FOR MICRO-ORGANISMS ONLY

5. ENTER CORRECTIONS TO ITEM 4

6. MAILING ADDRESS OF REPORTING OFFICIAL (Include institution name if applicable, number and street, city, state, country, and post office code)
University of Pittsburgh Cancer Institute Hillman Cancer Center
Attn: Lisa H. Butterfield, Ph.D.
5117 Centre Avenue
Suite L1.27
Pittsburgh, Pennsylvania 15213-1863

a. PHONE 412-623-1418 EXT

7. ENTER CORRECTIONS TO ITEM 6 b. PHONE

8. U.S. AGENT

a. E-MAIL

9. REPORTING OFFICIAL'S SIGNATURE

a. TYPED NAME Lisa H. Butterfield, Ph.D.
b. E-MAIL butterfieldl@upmc.edu
c. TITLE Director, IMCPL d. DATE 18-NOV-2016

PART II - PRODUCT INFORMATION

10. ESTABLISHMENT FUNCTIONS AND TYPES OF HCT / Ps

Types of HCT / Ps	Establishment Functions: Recover	Screen	Test	Package	Process	Store	Label	Distribute	11. HCT/Ps DESCRIBED IN 21 CFR 1271.10	12. HCT/Ps REGULATED AS MEDICAL DEVICES	13. HCT/Ps REGULATED AS DRUGS OR BIOLOGICAL DRUGS	14. PROPRIETARY NAME(S)
a. Bone												
b. Cartilage												
c. Cornea												
d. Dura Mater												
e. Embryo ☐ SIP ☐ Directed ☐ Anonymous												
f. Fascia												
g. Heart Valve												
h. Ligament												
i. Oocyte ☐ SIP ☐ Directed ☐ Anonymous												
j. Pericardium												
k. Peripheral Blood Stem ☐ Autologous ☐ Family Related ☐ Allogeneic												
l. Sclera												
m. Semen ☐ SIP ☐ Directed ☐ Anonymous												
n. Skin												
o. Somatic Cell Therapy Products ☒ Autologous ☒ Family Related ☒ Allogeneic			X	X	X	X	X	X	X		X	
p. Tendon												
q. Umbilical Cord Blood ☐ Autologous ☐ Family Related ☐ Allogeneic												
r. Vascular Graft												
s. Parathyroid					X	X	X	X	X			
t.												
u.												
v.												

FORM FDA - 3356 (7/17)

Lab Director definitions: overlapping and non-overlapping regulations

CAP definition of Lab Director: The individual who is responsible for the overall operation and administration of the laboratory, including provision of timely, reliable and clinically relevant test results and compliance with applicable regulations and accreditation requirements. This individual is listed on the laboratory's CAP and CLIA certificate

CAP TLC11425 Defines the Directors delegation of functions, including what can and cannot be delegated. If delegated, the Lab Directory still remains the responsible party for ensuring the task is done properly and carried out by the designee. All Lab Director

Oversight and Responsibilities are clearly defined in the Team Leader Assessment Checklist (TLC).

1. Functions that may be delegated include review of QC data, proficiency testing performance, and test methodology performance studies. The laboratory director remains responsible [A] that all persons performing delegated functions are qualified to do so; and [B] that the delegated functions are properly carried out.

2. Functions that may not be delegated include provision of appropriately trained supervisory and technical staff and the identification of their responsibilities. The laboratory director must document personal, on- site assessment of physical and environmental conditions and the adequacy of staffing.

3. The responsibilities and duties of supervisors, consultants, and testing personnel involved in pre-analytic, analytic, and post-analytic phases of testing must be defined in writing, with records of authorization to perform testing, and the level of supervision required, as applicable.

FACT: D3.1.1 There shall be a Processing Facility Director with a medical degree, doctoral degree, or equivalent degree...

FACT 3.1.2 Defines: The Processing Facility Director shall be responsible for all procedures, administrative operations, and the Quality Management Program. This also discusses what can be delegated and is in agreeance with CAP. The Lab Director is the overall responsible party for ensuring any designated task is carried out by the designee as defined.

cGMPs provide for systems that assure proper design, monitoring, and control of manufacturing processes and facilities.

Adherence to the cGMP regulations assures the identity, strength, quality, and purity of drug products by requiring that manufacturers of medications adequately control manufacturing operations.

This includes establishing strong quality management systems, obtaining appropriate quality raw materials, establishing robust operating procedures, detecting and investigating product quality deviations, and maintaining reliable testing laboratories.

This formal system of controls, if adequately put into practice, helps to prevent instances of contamination, mix-ups, deviations, failures, and errors. This assures that drug products meet their quality standards.

The cGMP requirements were established to be **flexible** in order to allow each manufacturer to decide individually how to best implement the necessary controls by using scientifically sound design, processing methods, and testing procedures.

The flexibility in these regulations allows companies to use modern technologies and innovative approaches to achieve higher quality through continual improvement. Accordingly, the "C" in CGMP stands for "current," requiring companies to use technologies and systems that are up-to-date in order to comply with the regulations.

Systems and equipment that may have been "top-of-the-line" to prevent contamination, mix-ups, and errors 10 or 20 years ago may be less than adequate by today's standards.

It is important to note that CGMPs are minimum requirements. Many manufacturers are already implementing comprehensive, modern quality systems and risk management approaches that exceed these minimum standards.

21 CFR Part 210.
Current Good Manufacturing Practice in Manufacturing Processing, packing, or Holding of Drugs.

CFR - Code of Federal Regulations Title 21

The information on this page is current as of Oct 01, 2021.

For the most up-to-date version of CFR Title 21, go to the Electronic Code of Federal Regulations (eCFR).

New Search Help | Mo

TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER A - GENERAL

PART 11 ELECTRONIC RECORDS; ELECTRONIC SIGNATURES

Code of Federal Regulations

A point in time eCFR system

Recent Changes

Title: Title 21

Modified Date: 01/13/2022

Search | Reset

Displaying changes to Title 21 introduced between 12/17/2020 and 1/13/2022. previous

Hierarchy display: Displaying full hierarchy | Display limited hierarchy

1/13/2022

- Title 21 - Food and Drugs *(7 sections changed)*
  - Chapter I - Food and Drug Administration, Department of Health and Human Services
    - Subchapter B - Food for Human Consumption
      - Part 169 - Food Dressings and Flavorings
        - Subpart B - Requirements for Specific Standardized Food Dressings and Flavorings
          - § 169.115 French dressing.
    - Subchapter H - Medical Devices
      - Part 814 - Premarket Approval of Medical Devices
        - Subpart C - FDA Action on a PMA
          - § 814.40 Time frames for reviewing a PMA.

Site Feedback

Example of a Manufacturing SOP

Pg. 1 of 8

One of the major steps in preparing the vaccine product

UNIVERSITY OF PITTSBURGH CANCER INSTITUTE
IMMUNOLOGIC MONITORING AND CELLULAR PRODUCTS LABORATORY

PROCEDURE FOR ADENOVIRAL TRANSDUCTION OF DC FOR UPCI 09-021 PROTOCOL

1. Purpose and Scope

1.1. The purpose of this procedure is to describe the methodology for transfecting DNA into Dendritic Cells (DC) using the adenoviral vector AdVTMM2 (Tyrosinase, MART-1, and MAGE-A6; melanoma associated antigens, MAA).

1.2. Dendritic cells (DC) have been a major focus of basic and clinical research for several years. Their putative therapeutic value is related to the fact that DC are potent antigen presenting cells. As such, they are often used for immunotherapy. Transfection is a frequently used method to achieve in vitro antigen expression in DC. With adenoviral vectors, gene transfer into human DC can be achieved with up to >90% efficiency.

1.3. Transduced DCs maintain antigen expression for at least 7 days. Before or after transduction, they can be matured or used directly as antigen presenting cells in order to achieve anti-tumor CD4+ and CD8+ T cell responses.

2. Responsibility

2.1. Technologist: Responsible for the following this procedure and for documenting results.

2.2. Lab Manager: Responsible for review of results for accuracy, completeness and acceptability.

2.3. QA Manager: Responsible for reviewing and approving this procedure.

2.4. Laboratory Director: responsible for final review and approval of this procedure when originated, revised and on a biannual basis.

3. Safety and Precautions

3.1. **ALL HUMAN SAMPLES ARE POTENTIALL BIOHAZARDOUS!** All equipment, supplies and reagents in contact with human blood, body fluids, and/or tissues should be handled and disposed of as biohazardous. **HANDLE ALL MATERIALS AS IF CAPABLE OF TRANSMITTING INFECTIOUS AGENTS!** When performing this procedure, follow the UPCI IMCPL Biohazard Precautions as outlined in the IMCPL.

3.2. AdV particle measurements (by OD) include both infectious (plaque-forming units, PFU) and non-infectious, defective virions. Particle: PFU ratios can be up to 100:1. Therefore, a viral titer (concentration measurement) of "particles per ml" is of interest (and FDA-required, as toxicity can be from total particles used), but use is based on infectious pfu measurement, which is performed by plaque assay on permissive 293 cells, or by hexon titer kit (immunohistochemistry assay for AdV hexon protein-producing cells, which means cells which are successfully infected and making hexon protein). It is customary to derive the MOI for a batch of GMP virus, then maintain that number of *particles*, even if infectious titer changes over time, at annual re-certifications of virus. The decision to modify the amount of virus after an annual recertification will depend on the protocol and IND.

Example of Facilities Master File for the FDA

Table of Contents……

Good and less good issues with GMP

GOOD NEWS:

- Flexibility allows for the possibility that you can make the product you want to make the way you want it to be.
- Phase I trials have extra flexibility in GMP regulations.

#1 is safety

LESS GOOD NEWS:

- The lack of strict rules allows for reviewers to disallow what you propose.
- It is challenging to know exactly what to propose to guarantee it can be approved.

A Solution: PICI-FOCR “Future of cell therapy”

Meeting in Washington DC on May 17, 2019

Efficiencies Gained Through Early Stage Manufacturing

CMC Activity	Typical Time[1] Investment	Areas of Proposed Flexibility	Potential Time[2] Savings	Potential Cost Savings[3]
Use of R&D Reagents	3-6 months	Increasing options for use of R&D reagents and reducing cost and time to either enable or negotiate GMP manufacture of reagents	1-3 months	$ to $$$
Plasmid Manufacturing	4 months (+ 3 to 6 months in queue)	Reduced plasmid characterization & infrastructure requirements	5-7 months	$$
Viral Manufacturing	6 months (+ 9 to 12 months in queue)	Waive RCL testing in lieu of surrogate testing; reduced cGMP requirements for ancillary reagents	4 months	$
Cell Product Engineering Runs (3 runs)	3 months	Use representative pilot virus for parallel cell product engineering runs	2 months*	N/A

Strategies to Facilitate Development of Cellular Therapies

	Description/Process
Early Phase	
Parent-Child IND	Parent IND would contain common sections providing all relevant information for the candidates or manufacturing alterations. Each child IND would cross-reference common sections while providing only the candidate or process specific information
Exploratory IND paradigm	Enrollment in trials with exploratory cellular therapy INDs would be limited to patients with advanced cancers and limited or no treatment alternatives. Early planned safety reporting would support an open regulatory dialog. This pathway would facilitate the efficient generation of clinical data and inform whether more formal trials should be pursued.
Late Phase	
Adaptive Manufacturing Process	An adaptive manufacturing process with the goal of generating a highly similar drug product from the patient-specific starting material is needed. A regulatory strategy that adjusts a process as product and process knowledge increases and based on patient or patient-specific raw material information to maximize product quality for all patients will permit the avoidance of extensive costly and lengthy clinical studies.
Post-marketing Product Optimization and Modifications	…modifications to manufacturing processes could be managed via a pre-negotiated plan with health authorities (e.g., Post-Approval Lifecycle Management or Comparability Protocol). Filing requirements for the change may include a combination of an analytical comparability assessment, and/or a small clinical study, analogous to a bioequivalence study for a new process.

cGMP for Cell Therapy
“It’s not science, it’s manufacturing”