

True Confessions: Ancillary Materials in a Cell Processing Lab

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Mission

Provide cellular and gene therapy products and services for Clinical Center patients

Major Activities

- **Serves as a core manufacturing facility to support phase I/II clinical trials (IND)**
- **Manufacture, cryopreserve, store and distribute standard products (non-IND)**



1325 clinical products through August FY11
27 IND/IDEs

Products Manufactured: Support Hematopoietic Stem Cell Transplantation (Non IND)

Hematopoietic Stem Cells for Transplantation

- **Peripheral blood stem cells (PBSCs) – CD34+ cell selected, CD3/CD19 depleted and minimally processed**
- **Marrow – CD34+ cell selected and minimally processed**
- **Cord blood**

Other

- **Donor lymphocyte infusions (DLI)**

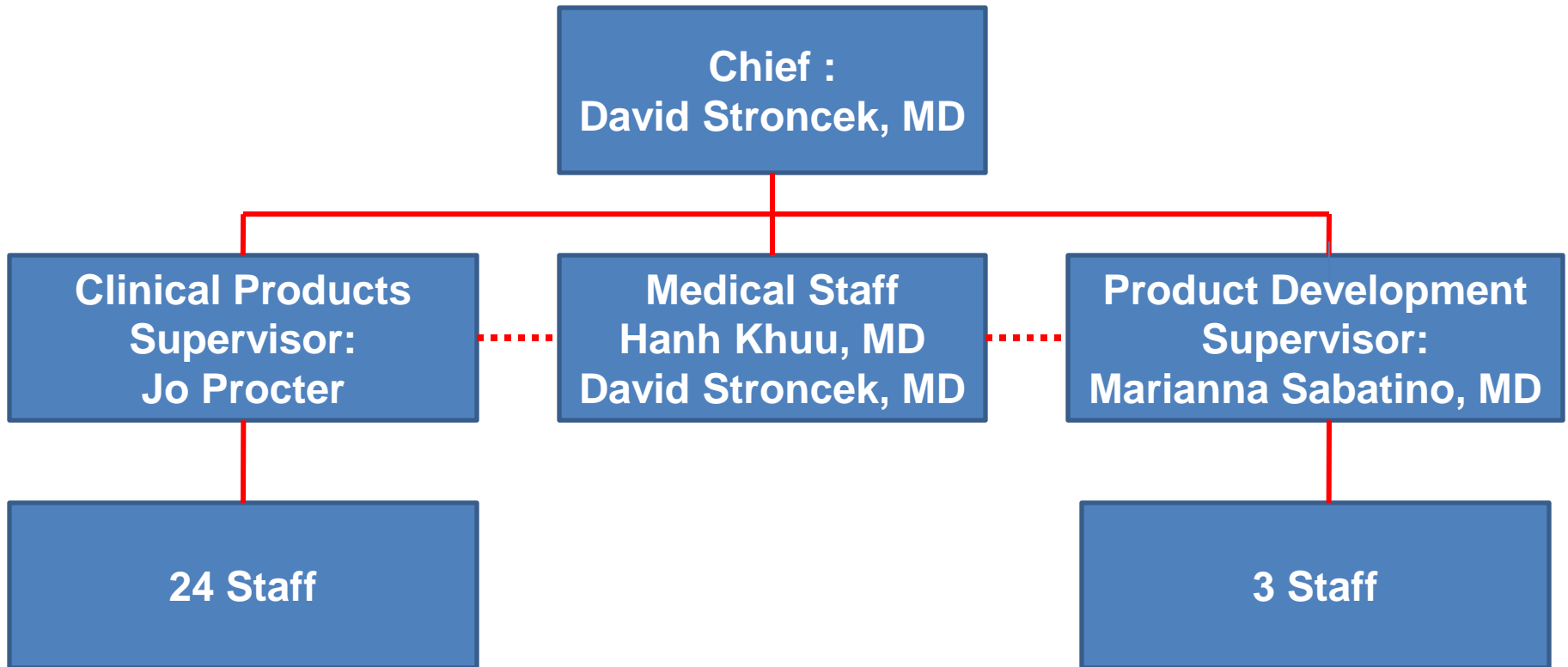
Types of Donors

- **Allogeneic, unrelated and autologous**

Products Manufactured - IND

- **Dendritic cells – 3 different products**
- **Natural Killer (NK) cells (IL-2 and LCL expansion)**
- **NK cells (IL-15 and APCs expansion)**
- **Th2 Rapamycin cells**
- **Gene therapy for Severe combined immune deficiency (SCIDs)**
- **Gene therapy for Chronic Granulomatous Disease (CGD)**
- **Th1/TC1 Rapamycin cells**
- **Third party Bone Marrow Stromal Cells (BMSCs)**

Cell Processing Section: Organization



Facilities

- **GMP Space – 3500 ft²**
- **Product Development Space – 500 ft²**
- **Office/storage space 1500 ft²**



Ancillary Materials Used at the NIH

Cytokines and Growth Factors

IL-2*
IL-4
IL-15
IFN- γ *
IFN- α *
GM-CSF*

Media and Solutions

Several types
PlasmaLyte A*

Media Supplements

AB Plasma
AB Serum
FBS
HSA*

Feeder Cells

LCL
K562 Derived APCs
Auto PBMCs
Allo PBMCs

Antibody Selections Depletion (Miltenyi)

CD34
CD4
CD3
CD19
CD56

Genetic Cell Engineering

Vectors
Retronectin

Cytoprotectant

DMSO

Pentastarch

Other

LPS
Anti-CD3/CD28 beads
Anti-CD3*
Rapamycin*
Intravenous IgG
Gentamycin

Some Reagents are Provided by a Single Manufacture and are Expensive

- **Antibody isolation/selection kits**
- **CD3/CD28 magnetic Beads**
- **Retronectin**
- **Cytokines**

Some Materials are Manufactured at Other Academic Health Centers

- **Vectors**
- **K562 based APCs**
- **LCLs**
- **Pentastarch**

- **Sometimes difficult to get more material**
 - **Quality might be better if produced commercially**

GMP But Not Made for Administration to Humans

- **Media**
- **IL-4**
- **Retronectin**
- **DMSO**
- **Commercial Cryoprotectants**

**Cryoprotectants are worrisome since thawed cells
are generally not washed prior to infusion**

Removal of Material is Problematic or Not Possible

- **CD3/CD28 Beads: removed with a magnet**
- **Antibody-paramagnetic beads: retained by cells**
- **FBS**

Reagent Shortages

- **CD3 antibodies**
- **Intravenous immunoglobulin**
- **AB plasma**
- **Vectors: may not be able to do scale up studies with vector used for clinical studies**

AB Serum

- **Limited pathogen testing**
- **Pooled serum from many donors:
increased risk of contamination with
untested or unknown pathogens**
- **Lot-to-lot variability**

FBS and Bone Marrow Stromal Cells (BMSCs)

FBS was used to manufacture BMSCs for:

- **clinical trials that successfully treated acute GVHD**
- **repair bone defects in animal models**

Potency tests for BMSCs are lacking

**Replacement of FBS could result in a
change in potency**

Feeder cells

Cell Lines

- K562-based APCs
- LCLs

Difficult to show that feeder cells are not viable at the end of production

Third party donor cells

- Peripheral blood mononuclear cells

Third Party Donors

- Screened and tested as cellular therapy donors
- Meet all criteria
- Mechanisms for following up on post-donation and information and recalling products should be in place

Clinical Investigators/Protocol PIs

Believe that safety and efficacy are important
Terrific understanding of scientific and medical issues
Good understanding of regulatory issues
More concerned about phase I and II than phase III

Time matters

- Competition with other groups
- Need to show progress for continued support
- Technology changes

Collaborative

- Want to use the same or similar protocols and materials as other investigators

Pressure to modify, validate and implement protocols quickly

Not Enough Ancillary Materials

- **Anti-CD62L selection sets**
- **Peptide pools for producing virus specific CTLs**

High cost of materials



Thank You!

