Department of Transfusion Medicine

CENTER FOR CELLULAR ENGINEERING

National Institutes of Health
Turning Discovery Into Health

Harvey G. Klein, M.D.
Chief, Department of Transfusion Medicine
NIH Clinical Center
February 2, 2018

CENTER FOR CELLULAR ENGINEERING

Presentation Outline

PRESENTATION OUTLINE

- History and Current Status
- Center Concept
- Center Structure & Management
- Financial Position
- Implications
- Questions/Open Discussion

History of Cellular Therapies at the Clinical Center

- 1984 - Special Services Laboratory
  - Bone marrow, monocytes, trafficking
- 1990 – Dowling Clinic/ Cell Processing Section
  - Bone marrow/Stem cell transplantation/Culture
  - Cellular Gene Therapy –September 14, 1990
- 1997 - Baxter CRADA (Isolex ™ System)
  - Hematopoietic graft engineering (NHLBI, NCI)
- 2002 – Cellular Processing
  - Islet Cells – NIDDK (Harlan, Carter, Kirk et al.)
  - Cord blood
  - Dendritic Cells
- 2008 - Bone Marrow Stromal ("Mesenchymal") Cell Transplant Center
  - NIDCR, NCI, NIAID, NIAMS, NINDS, NIBIB, (NHLBI)

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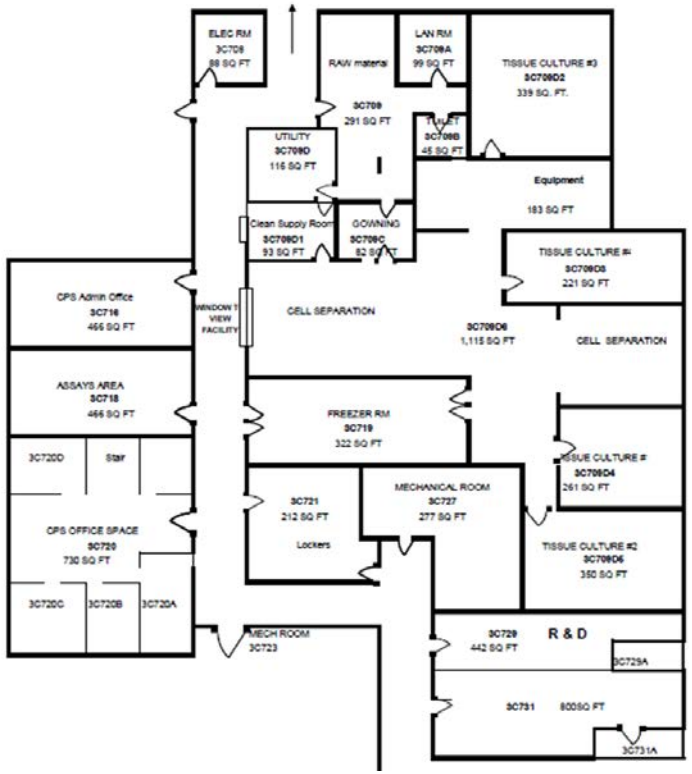
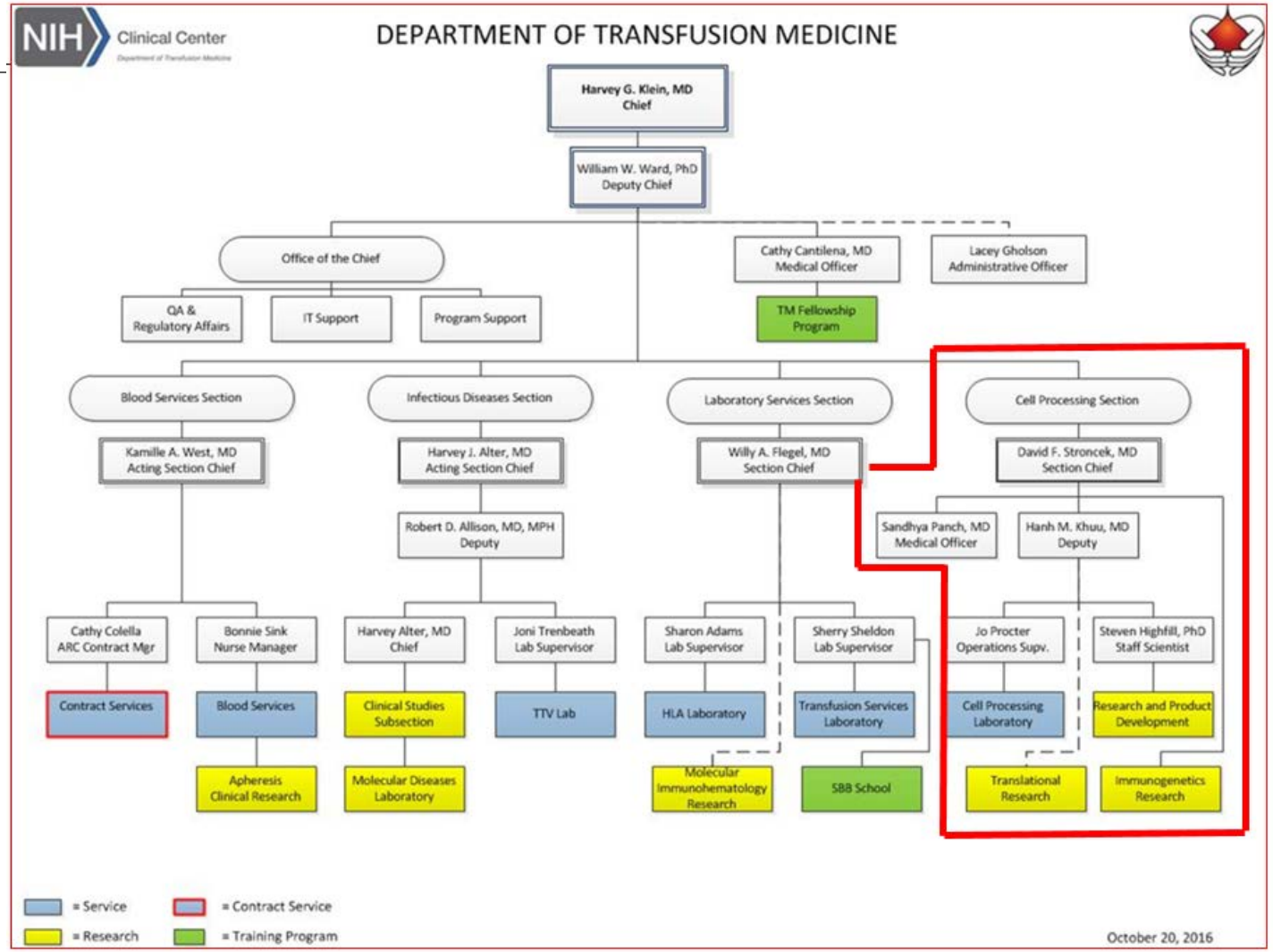
Current Situation



3T – The Best 20th Century Facility Money Could Buy



Cell Processing Activities

cGMP Manufacturing

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

cGMP Joint Manufacturing Support

- Ship, receive, store, and issue products manufactured jointly (Kite, Lonza, Bluebird, etc.)
- Manufacture non-clinical products for process validation and/or distribution to investigators

Development

- Develop new products and procedures

Investigator Support

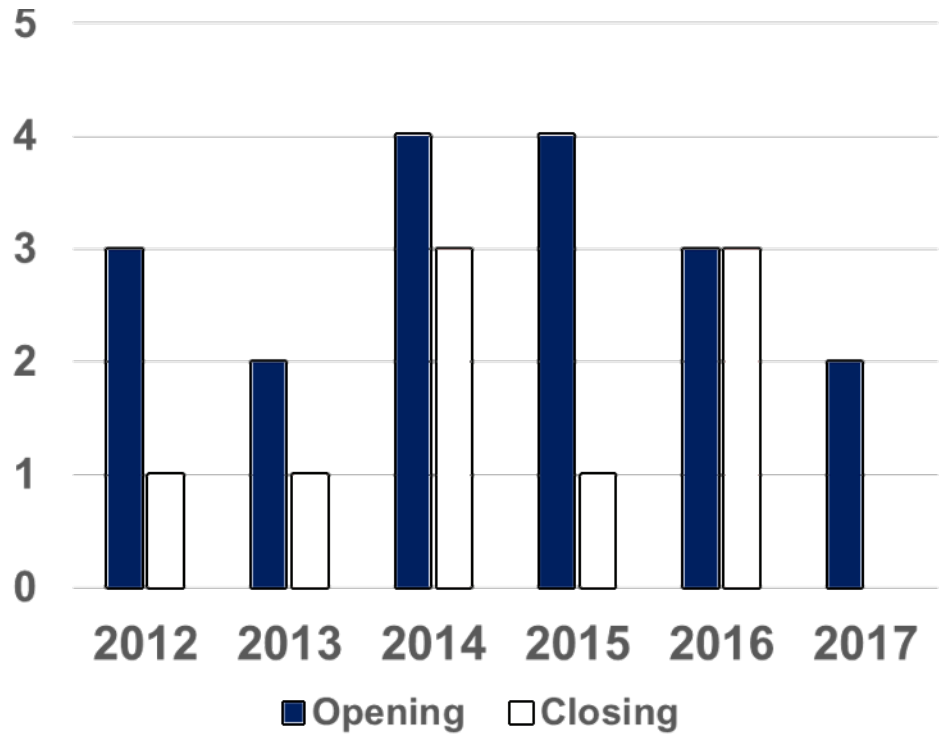
- Regulatory-IND development and support
- Clinical consultative and therapy management services

Testing

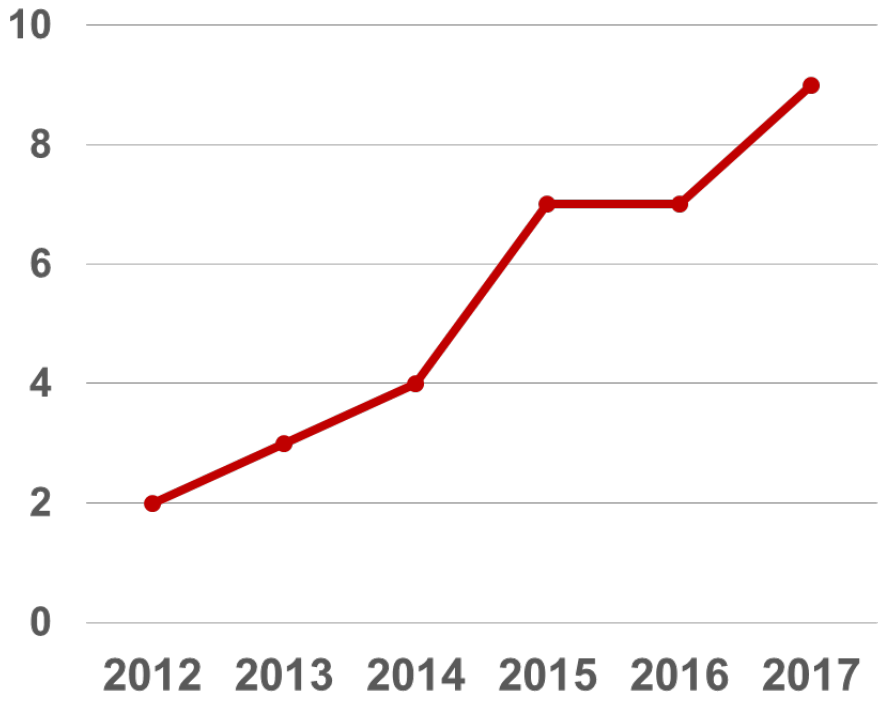
- Characterization and release assays (PBSC and other Cellular Products)

Change in the Number of IND Cell Processing Protocols: 2012-2017

Number of Protocols Opening and Closing Each Year



Accumulative Change in Protocol Number



Activity in Cell Processing

- 32 Active Protocols
  - 2 Complex Hematopoietic Stem Cell Transplants
  - 15 Complex Cell and Gene Therapy
  - 5 Collaborative Manufacturing
  - 10 Minimally manipulated HSCs
- 8 New protocols in product development (2 per quarter)
- 14 Projected future protocols identified by ICs (November 2017)
  - 4 ready by 2019
  - 10 ready by 2020

Products Manufactured – Non–IND (361)

- Peripheral Blood Stem Cells (PBSC) for Transplantation
  - Auto, Haplo-, Matched/MUD
- Bone Marrow
  - Minimally Processed, CD34+ selected
- Haplo- Umbilical Cord
- Lymphocyte Infusions

Products Manufactured – IND (351)

Gene Therapy for Inherited Disorders

- X-linked CGD, X-linked and ADA – deficient SCID - Gene Correction of autologous CD34+ cells (retroviral, lentiviral vectors)

Post Transplant Immunotherapy

- CMV, EBV, AdV and BKV specific T cells to prevent infection post transplantation
- TH2 Rapamycin following allo transplants for lymphoma
- TH1 Rapamycin cells follow autologous transplantation for multiple myeloma
- NK cells following allo transplantation for sarcoma

Bone Marrow Stromal ("Mesenchymal Stem") Cells

- Allo BMSCs for acute GVHD
- Allo BMSC for inflammatory bowel disease
- Auto BMSCs for left ventricular failure

Products Manufactured – IND (351), continued

- **Immunotherapy for cancer and hematologic malignancies**
- **NK cells as primary therapy**
- **TARP-specific pulsed Dendritic Cells - Prostate cancer**
- **Her2/neu-specific pulsed Dendritic Cells – Breast cancer**
- **Anti-CD19 CAR T cells (ALL) Anti-CD22 CAR T cells (ALL)**
- **Anti-GD2 CAR T cells (Sarcoma)**
- **Anti-B Cell Maturation Antigen (BCMA) CAR T cells (Multiple Myeloma)**
- **IFN-activated Monocytes (Ovarian cancer)**
- **Haplo- Expanded Cord Blood Transplants**

iPSC and Regenerative Medicine

- **Retina**

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Current Situation

Under Development

Bispecific anti-CD19/CD22 CAR T cells for the treatment of B cell leukemia
(Shah and Fry)

Bispecific anti-CD19/CD20 CAR T cells using stem memory T cells
(Gattinoni and Kochenderfer)

Induced pluripotent stem cell-derived retinal pigment epithelial cells for age related macular degeneration
(Miller and Bharti)

Anti-CD33 CAR T cells for acute myeloid leukemia
(Shah and Fry)

Anti-CD19 heavy chain CAR T cells for B cell malignancies
(Kochenderfer)

Anti-CCR4-CAR T cells for T cell leukemia
(Conlon)

Anti-TSLPR-CAR T cells for B cell malignancies
(Shah and Fry)

TKK-LC-1 specific TCR engineered T cells for the treatment of HPV-associated cervical cancer
(Hinrichs)

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Current Situation

Under Development

Isolation and expansion of stem memory T cell for CD19 CAR T cell the
(Gattinoni and Kochenderfer)

Humanized anti-CD19 CAR T cells using a le
(Kochenderfer)

Polyoma virus specific T cells to trea ocal Leukoencelphopathy
(Muranski)

Induced pluripote ed retinal pigment epithelial cells to treat age related macul
(Miller and Bharti)

Genetically engineered T cells specific to human papilloma virus
(Hinrichs)

Patients Enrolled

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Current Situation

CURRENT STATUS

- **DTM Cell Processing Section (CPS) does not meet growing demands for cellular therapy by IRP investigators and the changing science in precision medicine**
- **Expansion into a Center for Cellular Engineering (CCE) will address major resource limitations:**
  - **Facilities**
  - **Staffing**
  - **Space**
  - **Organizational Structure**

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Current Situation

BALANCING RESOURCES TO MEET STRATEGIC NEEDS

Operational capacity expected to grow from 4 to 18 cell processing rooms by 2021

Facilities are only one aspect of growing CPS operations

Staffing, space, and organizational structure are vital for effective collaboration and customized products for IRP investigators

The CCE's total estimated operating cost after opening all new facilities in FY 2020 is $35.7 million – a $22.7 million increase from FY 2017

CENTER CONCEPT

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Turning Discovery Into Health

CENTER OVERVIEW

The CCE provides core facilities to connect NIH investigators to the cellular engineering process

Five CCE services

- New Product Development & Management
- Cell Therapy Manufacturing
- Product Assurance & Characterization Testing
- Research & Practice Development
- Technical & Operational Support

Create the processes, tools, and training to respond to changing clinical or scientific needs, while controlling cost and quality

An investigator-focused model for rapid, customized changes in the cellular engineering process to move from concept to clinic in a safe, reliable, efficient method while adhering to cGMP regulations

The NIH Center for Cellular Engineering:
The Concept

- **Trans Intramural Program**
  - Centrally Funded
  - Clinical Center Embedded
- **Operations Overseen Through DTM, CC**
- **QA Oversight – DTM QA with linkage to ORSC**
- **Policy Oversight Steering Committee of Participating Institutes**
- **Utilization – Scientific Prioritization Process (Associate Director for Clinical Research)**
- **User's Advisory Committee**

CENTER FOR CELLULAR ENGINEERING

Center Concept - Overview

Vertically Integrated

The CCE Singularity

- Multiple Small Batch Customized Products
- Personalized Interaction with Network of PIs
- Proximity to Patients
- Flexibility for Quick, Customized Modifications
- "Vertical Integration" – Collection, Development, Testing, Storage, Issue, Outcome
- Regulatory Experience – "Special Relationship"
- Access to Specialized Biologicals
- Leverages CC Resources - QA, IT, CCM, Clinical Labs (Micro, HLA, Heme, Immunology, Chemistry)

CENTER STRUCTURE & MANAGEMENT

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Turning Discovery Into Health

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Center Structure & Management – Shared Governance Model

Aligned Expectations

Shared governance creates alignment among stakeholders

Lines of Communication

Open communication to confront the difficult issues and to build strategies to address them.

Outcomes Orientation

An outcomes orientation to identify the appropriate metrics to measure success.

Mission Focused

Shared governance to facilitate the development of effective checks and balances needed to ensure a mission-focus.

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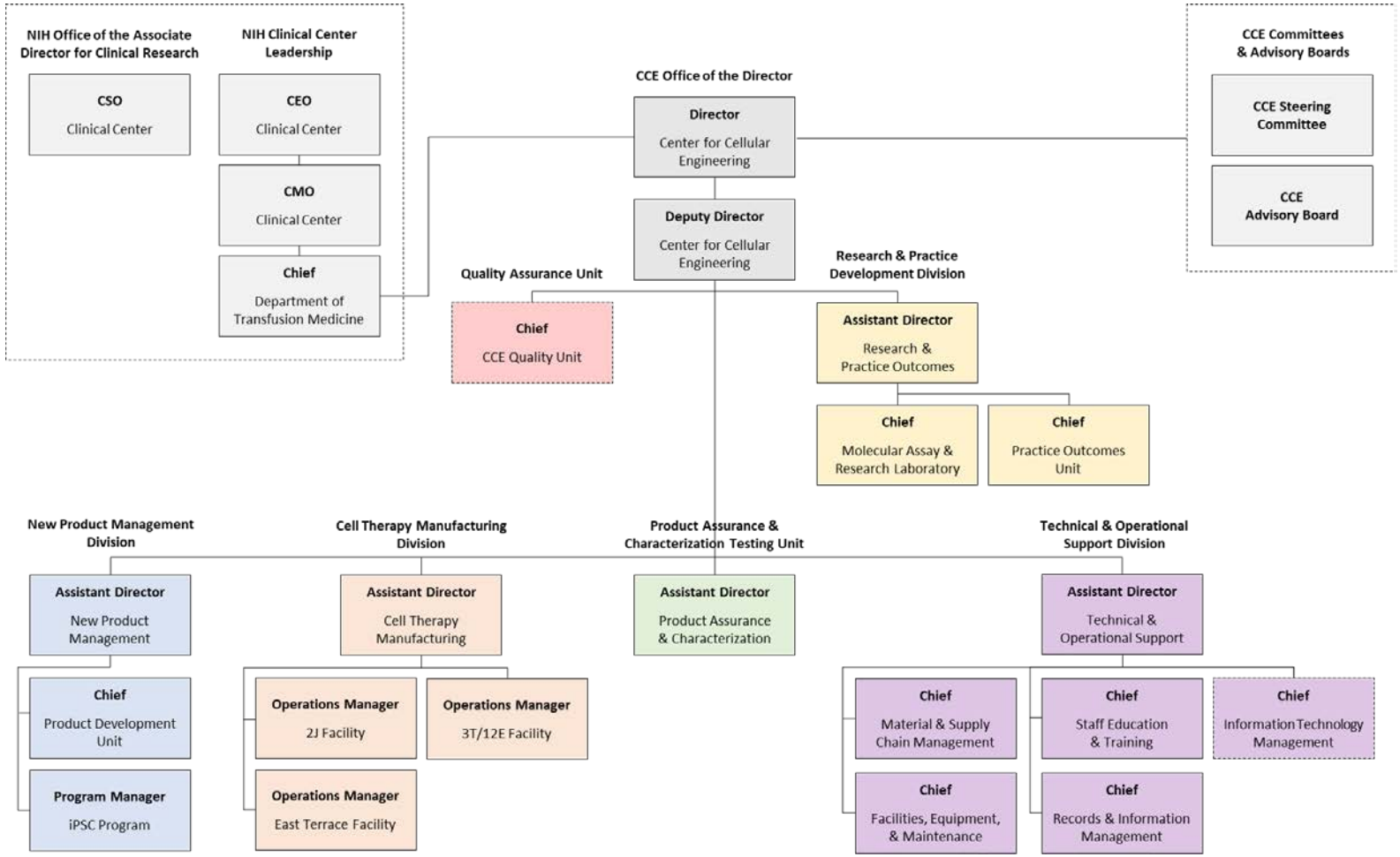
Center Structure & Management – Proposed Organizational Structure



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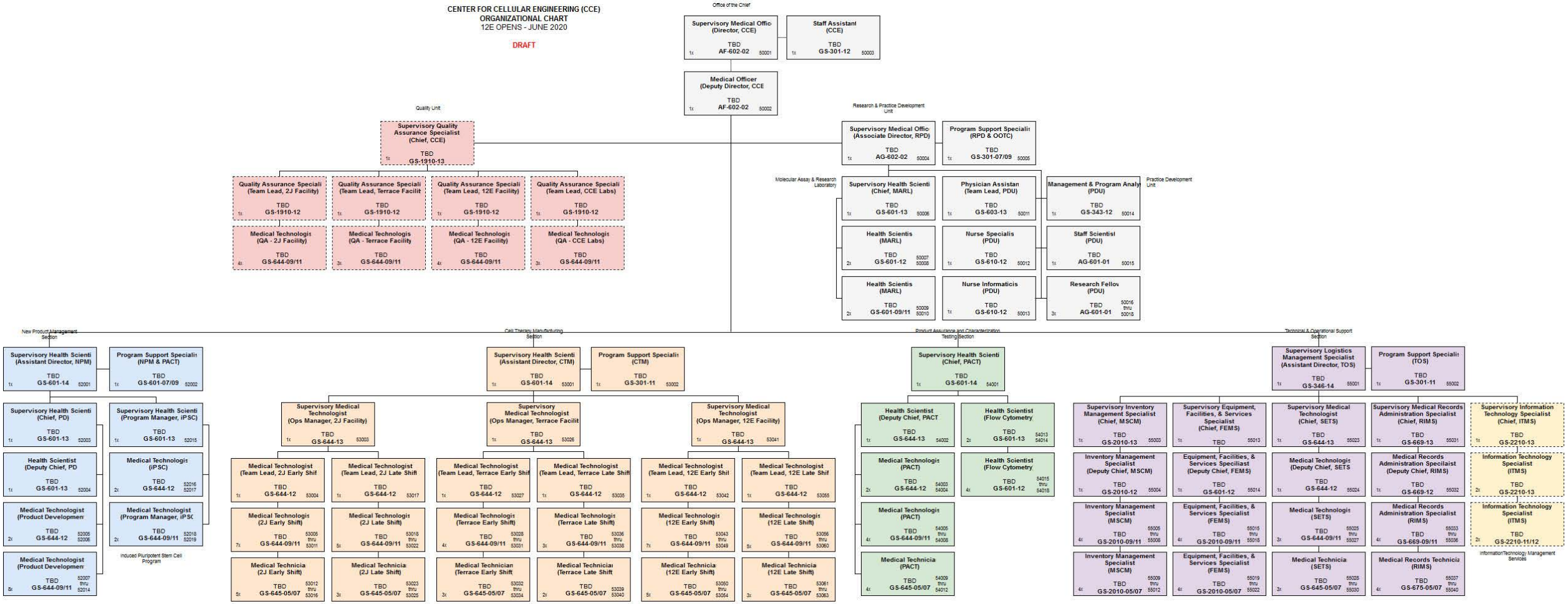

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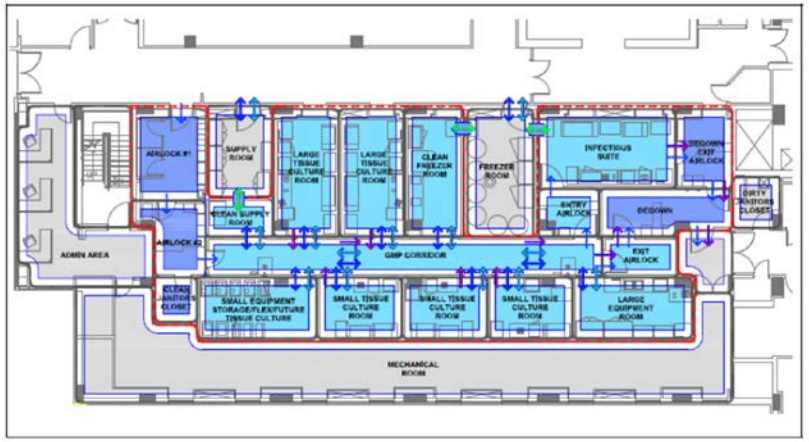
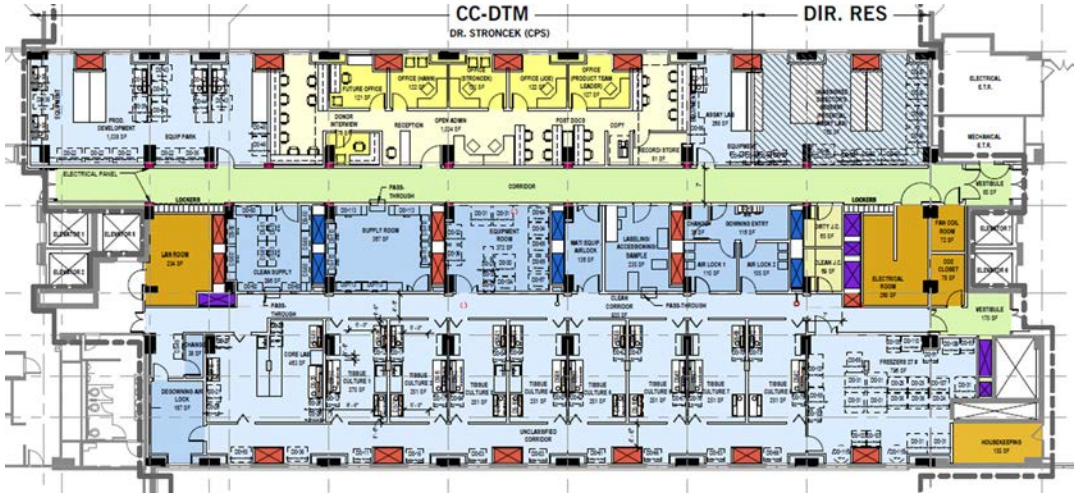
Center Structure & Management

Building 10 - 2J



Building 10 – 12 E



Building 10C – 3T

Building 10 Modular East Terrace

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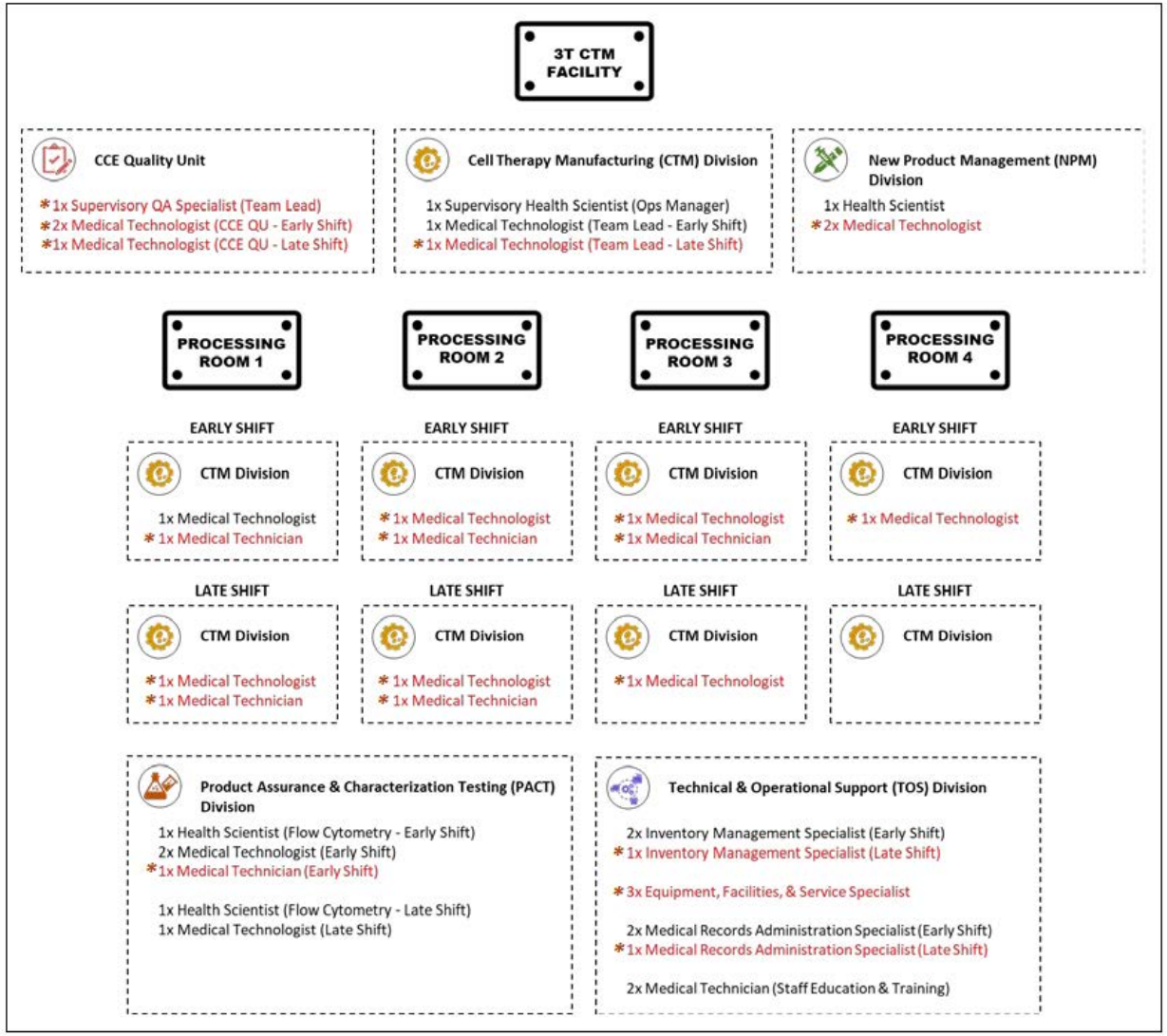
Center Structure & Management – Proposed Staffing (3T Facility)

PROPOSED FACILITY STAFFING

- Three "Facilities"
  - 18 Rooms plus Core Space
- Two Shifts and Weekend Coverage PRN
  - Cell Manufacturing
  - Product Assurance, Characterization, Testing
  - QC Functions
  - Technical and Operational Support
- New Product Management



Note: * and Red indicates positions still needed to be filled in FY2018

FUNDING

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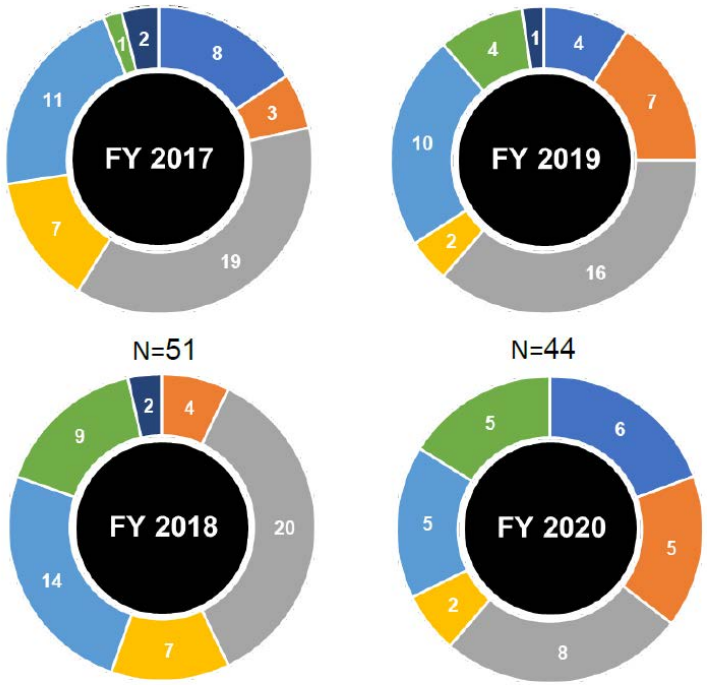
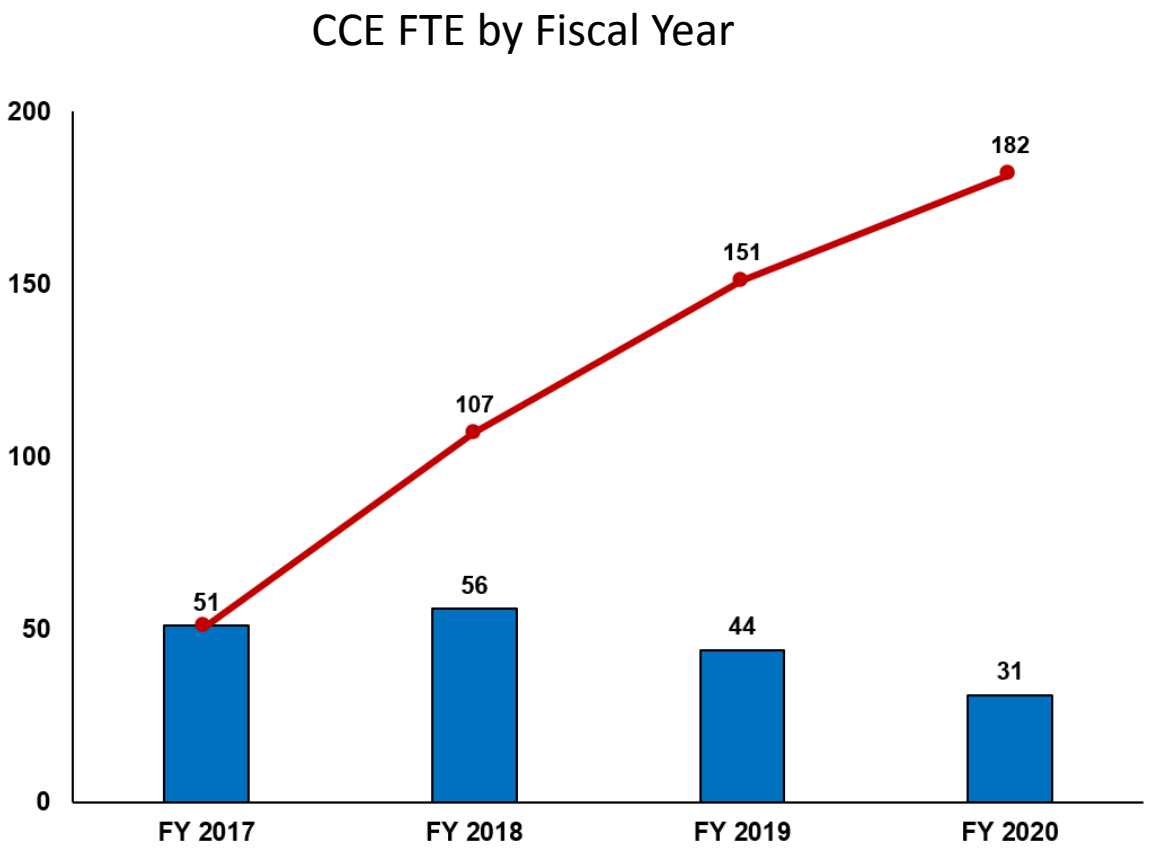
Funding



Division	FY 2017	FY 2018	FY 2019	FY 2020
Technical & Operational Support	11	14	10	5
New Product Management	3	4	7	5
Cell Therapy Manufacturing	19	20	16	8
Product Assurance & Characterization Testing	7	7	2	2
Research & Practice Outcomes	8	0	4	6
DTM -- Quality Program	1	9	4	5
DTM – IT Support	2	2	1	0



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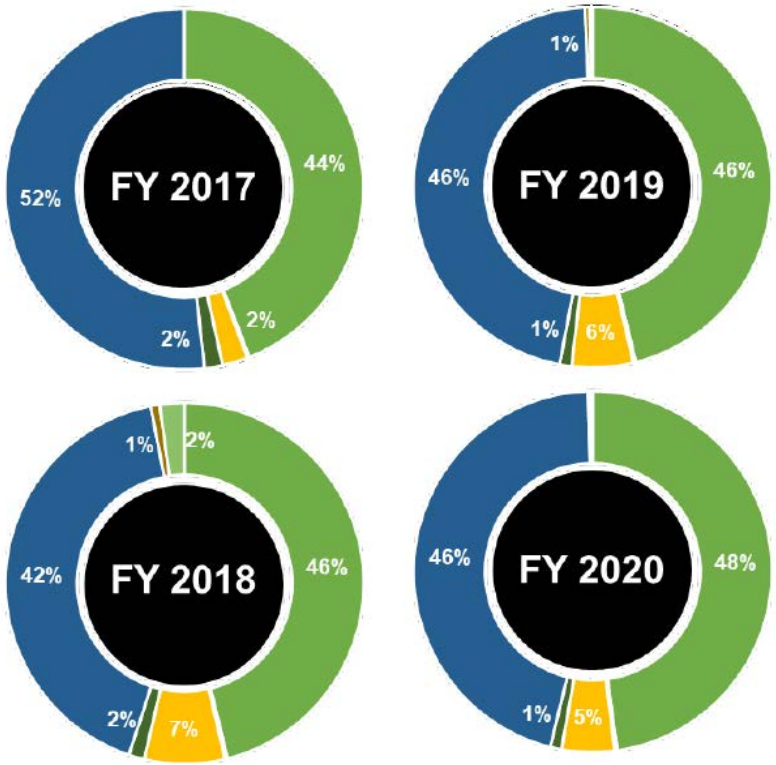
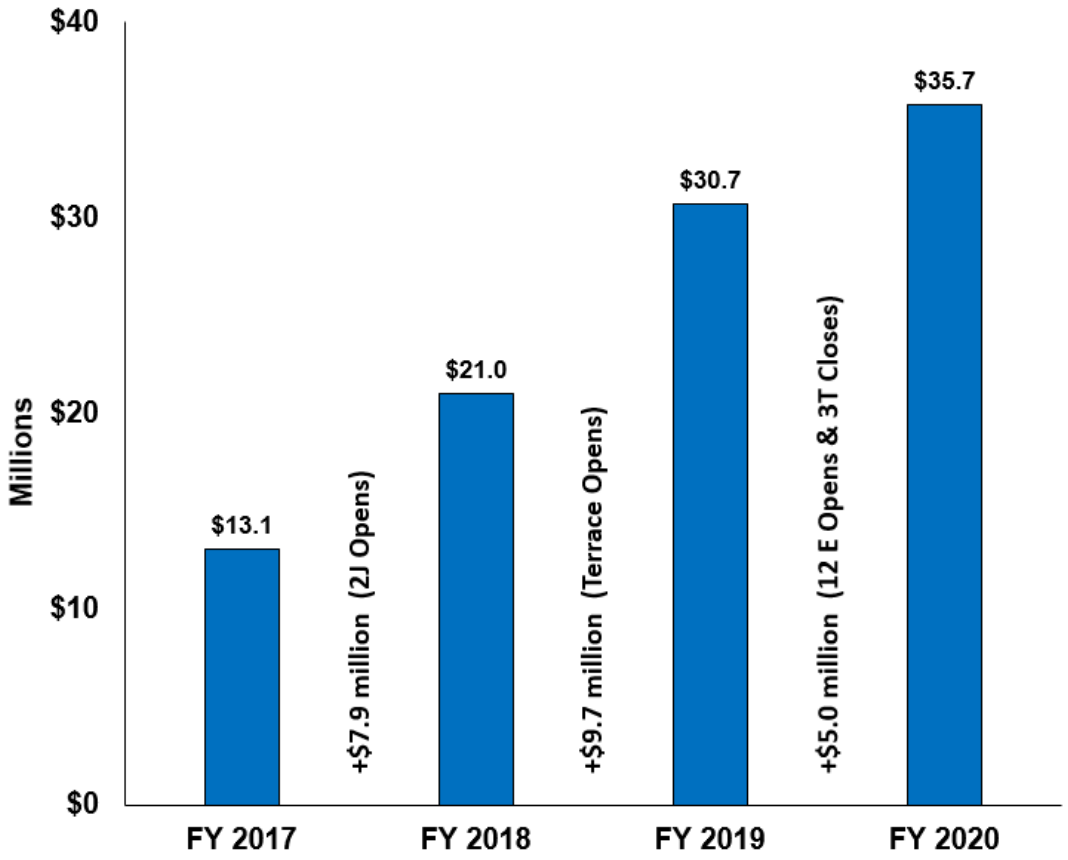
Funding – Operational Costs by Fiscal Year



Costs	FY 2017	FY 2018	FY 2019	FY 2020
Personnel	44%	46%	46%	48%
Training	0%	0%	0%	0%
Equipment	2%	7%	6%	5%
Maintenance	2%	2%	1%	1%
Supply & Material	52%	42%	46%	46%
Furniture, Fixtures, & Equipment (FFE)	0%	1%	1%	0%
IT & Business Systems	0%	2%	0%	0%

Total CCE Operating Costs by Fiscal Year



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Funding – Operational Costs by Fiscal Year

Expenditure Category	FY 2017	FY2018	Δ	%
Personnel *	$5,763,016	$9,691,724	$3,928,709	68.2%
Training *	$24,908	$52,259	$27,350	109.8%
Equipment **	$300,000	$1,516,012	$1,216,012	405.3%
Maintenance *	$213,750	$299,250	$85,500	40.0%
Supply & Material *	$6,774,605	$8,806,986	$2,032,381	30.0%
Furniture, Fixtures, & Equipment (FFE) **	$0	$168,000	$168,000	NA
IT & Business Systems */ **	$0	$468,755	$468,755	NA
CCE Operating Costs, Total	**$13,076,279**	**$21,002,986**	**$7,926,708**	**60.6%**

*Recurring operational expense
**One-time capital expense

IMPLICATIONS

CENTER FOR CELLULAR ENGINEERING

Implications

FACILITY CONSTRUCTION - MILESTONES

The CCE has a compressed start-up schedule, due to the aggressive facilities construction plan

Planned increase in physical operating capacity require associated increases in staffing, training, materials, supplies, and space to support and operate the new facilities.

The major milestones for the growth are dictated by the construction schedule:

Time	Event	Facilities Availability for Processing	Total Tissue Culture Rooms Available for Processing
August 2017	Current Status	3T	4
January 2018	2J opens	3T and 2J	11
October 2018	Terrace opens & 3T closes for renovations	2J and Terrace	11
March 2019	3t opens	3T, 2J and Terrace	15
June 2020	12E opens &3T closes	2J, 12E and Terrace	18

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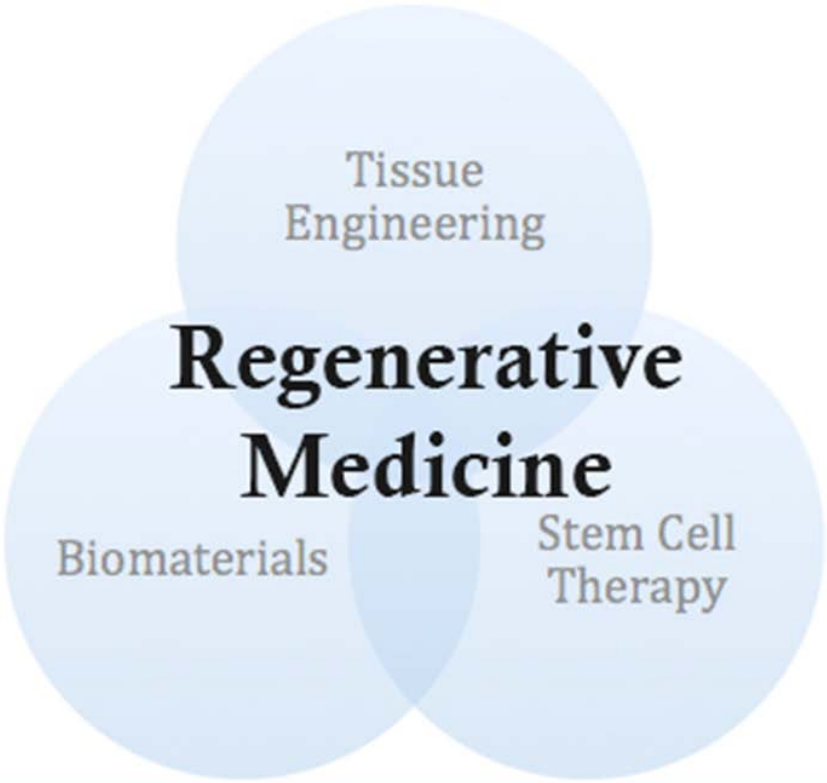
Implications



IMPLICATIONS

- Costs & Impact of Outsourcing Cellular Products
- Recruitment & Retention of NIH IRP Investigators
- NIH Clinical Center Hospital Patient Census
- Leading the Direction of Precision Medicine

The CCE will offer the **easiest** and **most dependable** solution to create, manufacture, test, and bring to scale customized cellular therapies for NIH clinicians and scientists.

ISSUES TO CONSIDER

- For cGMP, space is double “working space” – There is a role for automation, bioreactors, and closed systems
- It takes years to build and validate suitable cGMP space. Think of a new “wing” to the hospital
- It is likely that Regulations will become stricter for Phase I/II cellular biologicals – We are Preparing
- Staff take time to recruit and train – See automation, bioreactors, and robotics
- Think it’s expensive? Try contracting out! Expensive, Inflexible, and Inefficient

A Strategic Development Plan

Strategic Goals

- **Develop End-to-End Closed System Process with IT Tracking for Cellular Therapies**
- **Develop Vector-free Technology for Insertion of Constructs such as CRISPR for Customized Cellular Therapies**
- **Incorporation of Vector-free Technology into Closed System Process**