FDA, Center for Biologics Evaluation & Research

Office of Cellular, Tissue and Gene Therapies Overview

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FDA, Center for Biologics Evaluation and Research

CTGT AC Presentation September 7, 2016

Outline

- Organizational Structure of Office of Cellular, Tissue and Gene Therapies (OCTGT)
- OCTGT Mission and Activities
- OCTGT Regulatory Portfolio
- Researcher Reviewer Model
- Site Visit Report:
  - Gene Transfer and Immunogenicity Branch May 19, 2016

CBER Office of Cellular, Tissue, and Gene Therapies

Celia M. Witten, Ph.D., M.D., Deputy Center Director & Acting Office Director

Stephanie Simek, Ph.D. Deputy Director

Suzanne Epstein, Ph.D. Associate Director for Research

Richard McFarland, Ph.D., M.D., Associate Director for Policy

Theodore Stevens, Associate Director for Information Management

Rachel Anatol, Ph.D., Associate Director for Policy – New Legislation

Kim Benton, Ph.D., Acting Associate Director for Regulatory Management

RPM Staff Chief: Patrick Riggins, Ph.D.

Division of Cellular and Gene Therapies

Raj Puri, Ph.D., M.D., Director

Steven Oh, Ph.D., Acting Deputy Director

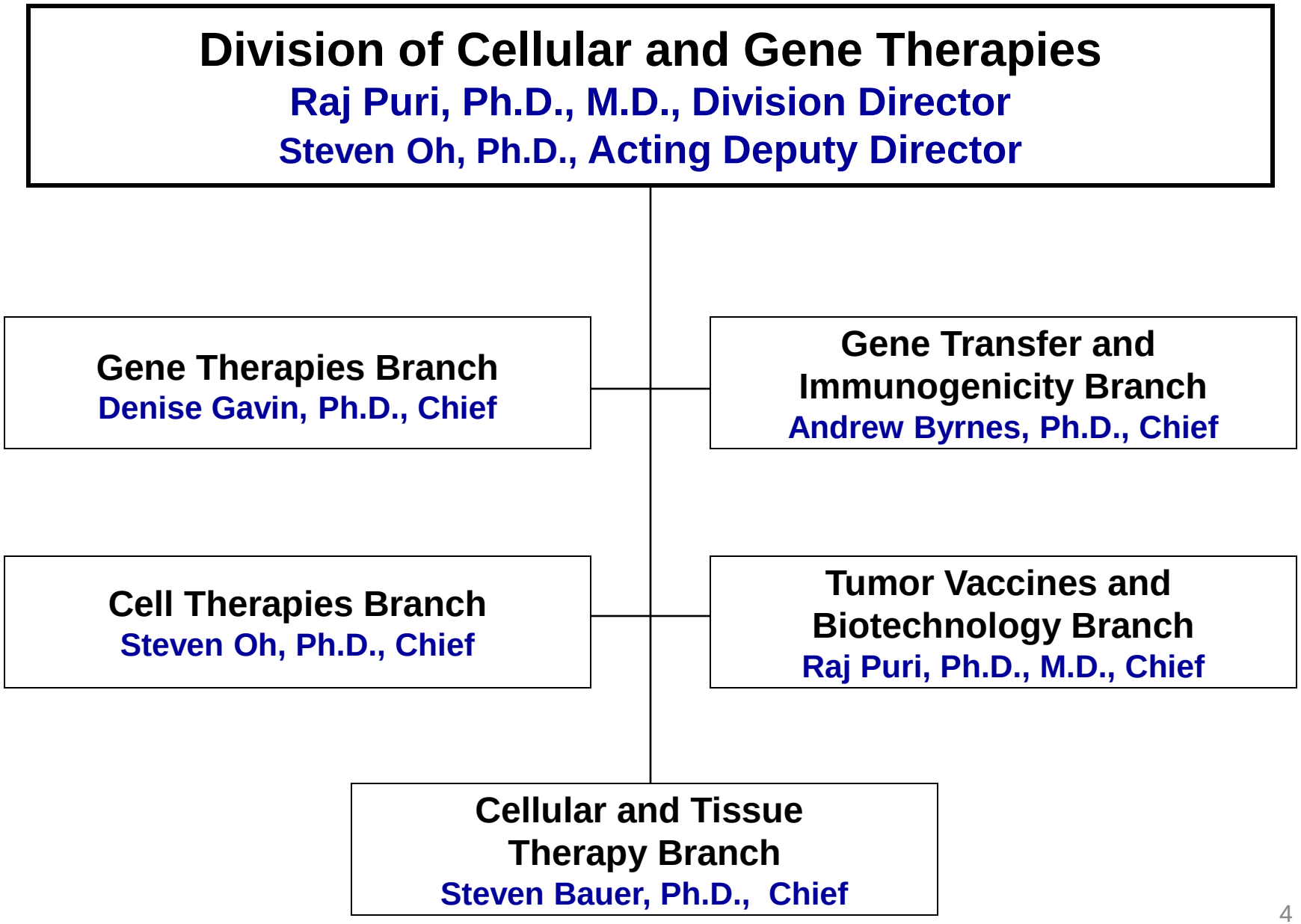
Division of Human Tissues

Larissa Lapteva, M.D., Acting Director

Division of Clinical Evaluation and Pharmacology/Toxicology

Wilson Bryan, M.D., Director

DCGT Structure

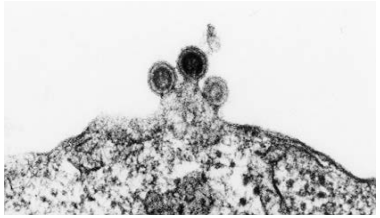


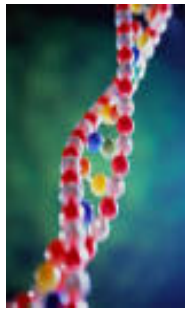
OCTGT Mission

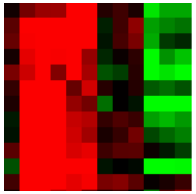
OCTGT's mission is to ensure the safety, potency, and effectiveness of cellular, tissue and gene therapy products for the prevention, diagnosis, and treatment of human diseases.

OCTGT Products

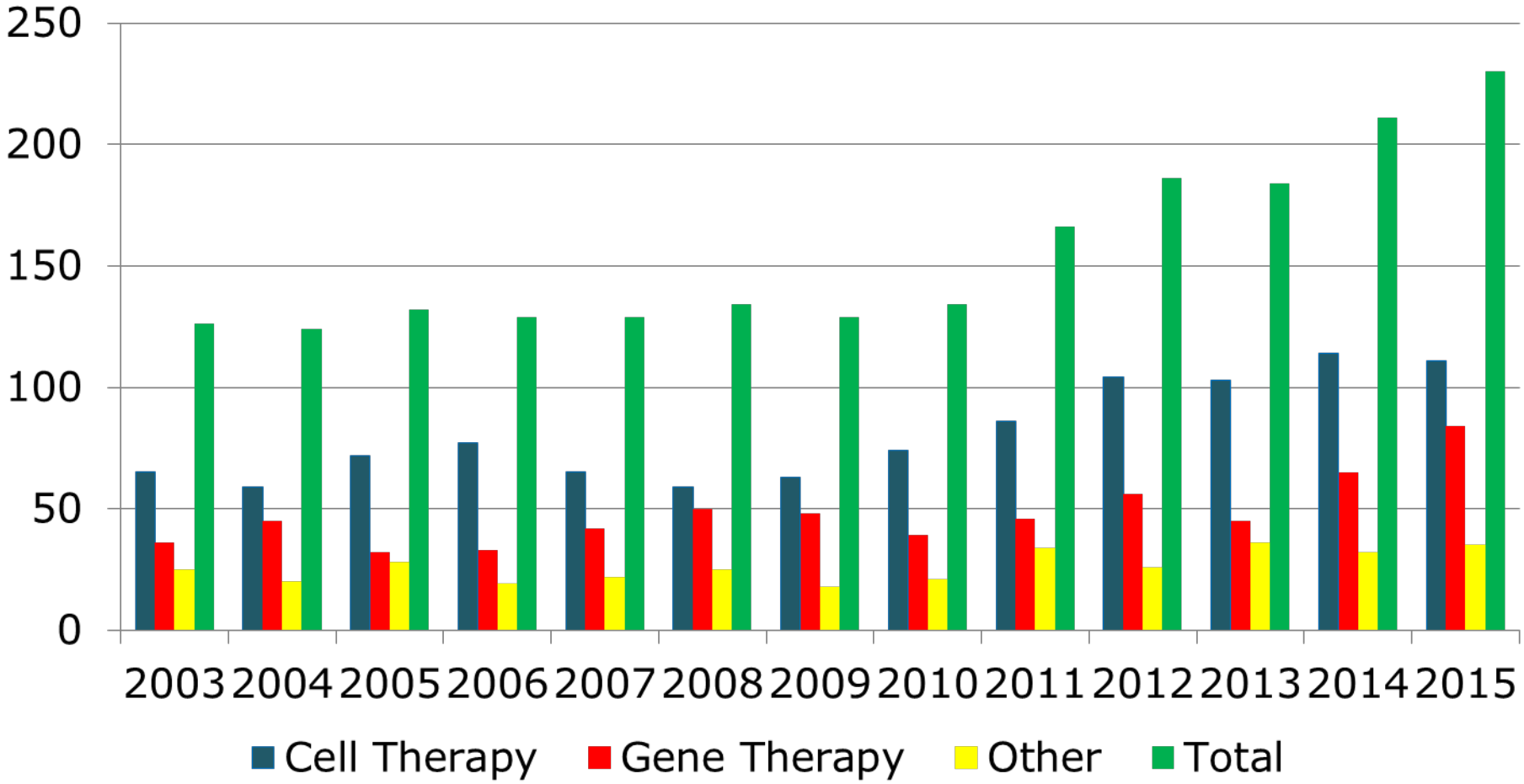
- Cellular therapies
- Tumor vaccines and immunotherapy
- Gene therapies
- Tissue and tissue based products
- Xenotransplantation products
- Combination products
- Devices used for cells/tissues
- Donor screening tests



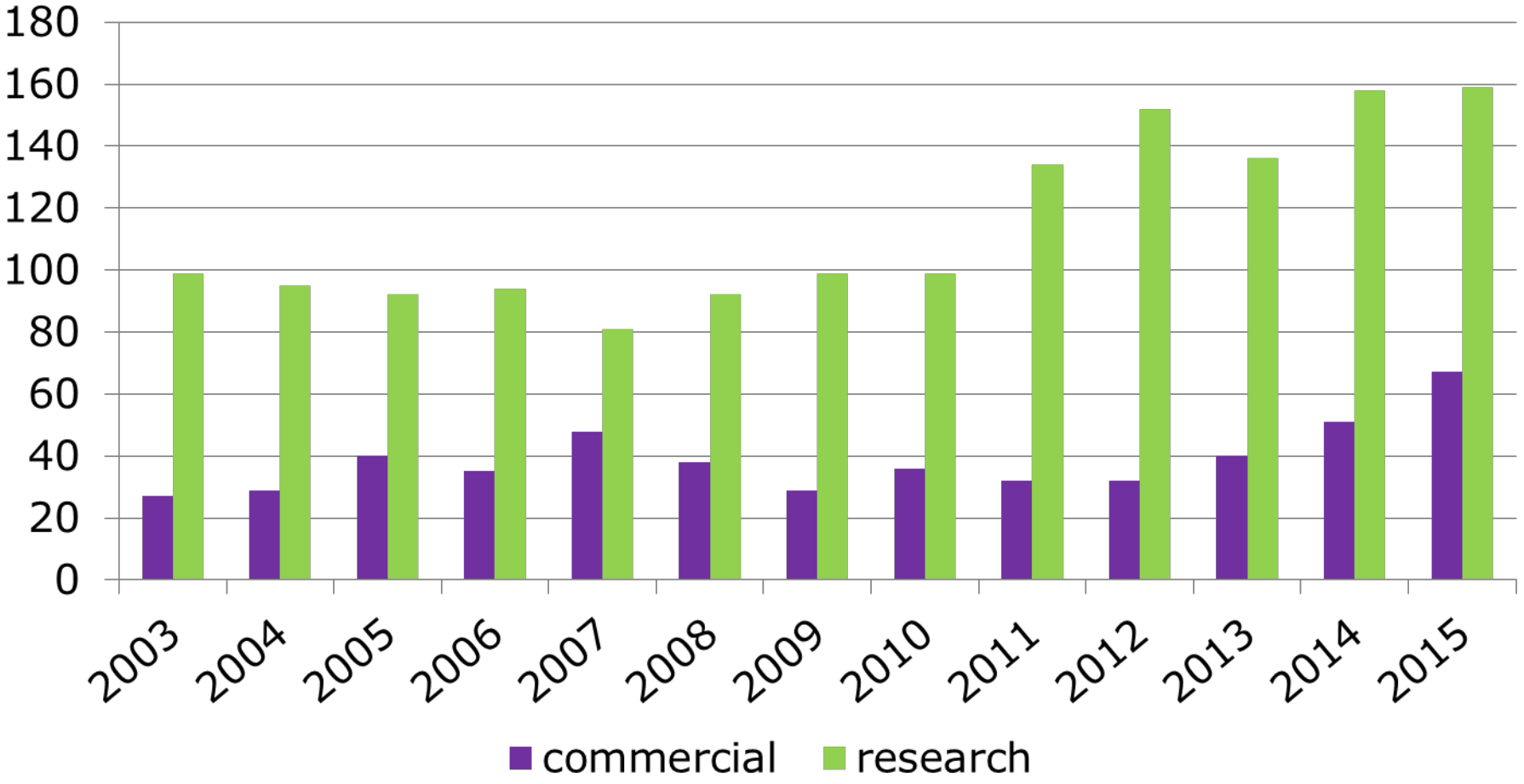




Yearly New IND & IDE Submissions to OCTGT



New IND and IDEs Submitted to OCTGT: Commercial or Research Sponsors



OCTGT Activities

- Reviews, evaluates and takes appropriate action on product applications and amendments or BLA supplements submitted by manufacturers of OCTGT products.
- Pre-INDs, pre-pre-IND, preIDE pre-submission advice
- Participates in inspections of manufacturing facilities for compliance with applicable standards, and other compliance activities including court cases.
- Develops policy and procedures governing the pre-market review and evaluation of cellular, and gene therapy products in keeping with the provisions of the PHS Act and applicable provisions of the FD&C Act.

OCTGT Activities contd..

- Development of FDA Guidances for the regulation of tissues, cellular, tissue engineering and gene therapy products
- Consultation and Education
  - Provide scientific and technical advice to other CBER Offices, FDA Centers, Government Agencies, sponsors
  - Advisory committee meetings
- Community Outreach (professional societies, advocacy)
- Partnership (SDO, NIH, Global regulatory authorities)
- Counterterrorism activities (Continuity of Operations, Lab Red Alert Plan etc.)
- Performs research to support review and progress towards safe and effective medical products

OCTGT Guidances
(2011-2015)

- **Published thirteen guidance documents in 4 years.**
  E.g.,
  - Potency
  - Cancer Vaccines
  - Pharmacology/toxicology
  - Early Phase Clinical Trials
  - Shedding Studies
  - Environmental Assessment
  - Cord Blood, Cartilage, Adipose tissue
  - Minimal Manipulation

OCTGT Research Goals

OCTGT Research Goal 1: **Chemistry, manufacturing, controls: Participation in public health initiatives and research projects to develop and evaluate methods and standards for improved characterization and lot release testing of OCTGT products, including definition of Critical Quality Attributes predictive of safe, effective, and consistent product performance**

OCTGT Research Goal 2: **Preclinical and clinical investigations: Participation in public health research initiatives and research projects to achieve understanding of the underlying biology of in vitro and in vivo preclinical models of pharmacology, toxicology, product rationale relevant to risks of OCTGT products, and of clinical study issues, with the goal of improving the safety and efficacy of OCTGT-regulated products**

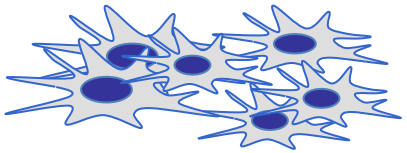
OCTGT Research Goal 3: **Safety issues related to human tissues**

Current OCTGT Research Areas

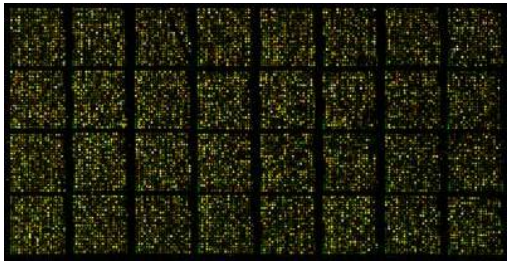
- Virology
  - Retroviruses, lentivirus, adenovirus
- Immunology
  - Immune responses to viral and plasmid vectors, immune modulation by viruses
- Cell and developmental biology
  - Control of differentiation in animal models
  - Cell fate and survival, stem cell biology
- Cancer biology/Immunology
  - Molecular biomarkers, cancer vaccines, immunotherapy, animal models
- Biotechnology
  - Genomics, flow cytometry, proteomics, transgenics, tissue engineering, gene editing
- Microbiology of tissue safety
  - Pyrosequencing and whole genome sequencing

Identification and correlation of MSC attributes with *in vivo* and *in vitro* assays of safety and efficacy: MSC consortium

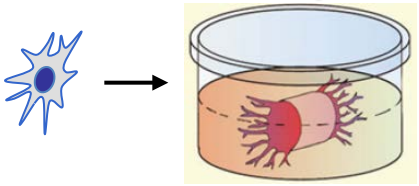
MSC Characterization



Puri Lab: genomics



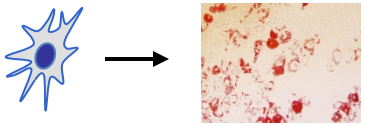
McCright Lab: *in vivo*, *in vitro* models of wound repair



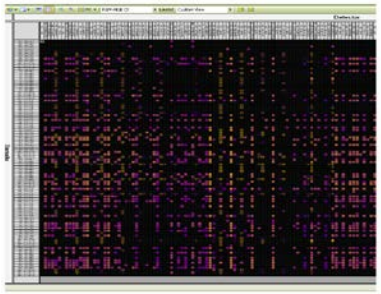
PRODUCT CHARACTERISTICS

CORRELATE CANDIDATE ATTRIBUTES WITH ASSAY OUTCOMES

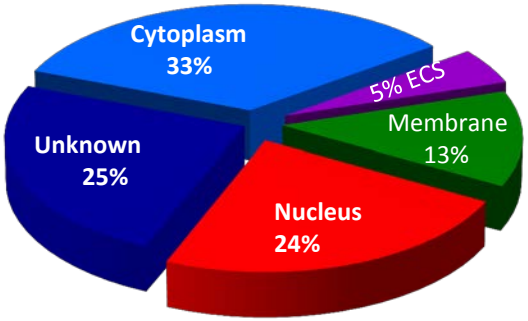
Bauer Lab: *in vitro* quantitative differentiation



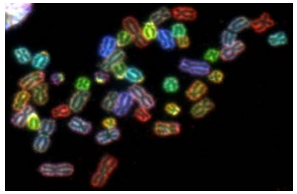
Moos Lab: gene expression, qRT-PCR, single cell PCR, NGS



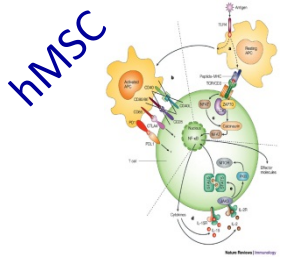
Alterman Lab: proteomics



Hursh lab: epigenetics, karyotypes



Bauer Lab: *in vitro*, *in vivo* immunosuppression



Researcher Reviewer Model

OCTGT products are diverse and rapidly evolving. They use new regulatory paradigms that are developing rather than established

- These novel products raise extraordinarily complex issues
- DCGT seeks to foster a cadre of Researcher Reviewer scientists who:
  - perform regulatory review and participate in the development of policy and guidance documents to promote product development and patient safety
  - perform research in key areas to support the FDA mission and help sponsors solve product development problems to advance products to the market place

Types of Researcher Reviewers

- Principal Investigators (PIs) – tenured or tenure track researcher reviewers
- Staff Scientists – tenured researcher reviewers supporting PIs program: do both review and research
- Technicians: do primarily research, some do limited review work
- Staff Fellows, Commissioner's Fellows and IOTF Fellows: do both review and research work
- Postdoctoral Fellows funded as ORISE: do primarily research

Note: Resources are provided to PIs

Responsibilities of PIs

Product review

INDs, IDEs, PMAs, 510(k)s, HDEs, BLAs, NDAs, master files
- inspections
- regulatory mentoring

Policy development

Working groups, policy and guidance development, advisory committees

Outreach

Pre-submittal advice, scientific and regulatory talks, refereeing and editing for journals, chairing sessions at scientific conferences, scientific collaborations

Research

Lab management, training/mentoring/supervising, publishing papers, grant writing, leveraging/collaboration, expert peer reviewers

Compliance and Enforcement

Inspections, court testimony, expert witness/declarations

DCGT Resources: Budget

- All PIs supplement research activities from inside and/or outside grants e.g.,

- Office of Science and Health Coordination (OSHC)
- Chief Scientist Challenge Grants
- Modernizing Science, Critical Path (CP), and Pan flu
- Department of Defense (DOD)
- Biomedical Advanced Research Development Authority (BARDA)
- Cooperative Research Development Agreement (CRADAs), and royalties from patents

Research Management

Approaches in OCTGT:

- Announcement of explicit regulatory/public health goals
- Analysis of productivity and alignment with those goals
- Support dependent on quality/regulatory alignment
- Input about Regulatory Science related issues, scientific gaps from all staff
- Tracking of outside resources
- PI annual reports address research goals and progress, describe periodic refocusing/adjustment

Research Management

contd..

- Mentoring of PIs and other staff
- Center for Excellence in Regulatory Science Initiative (CERSI) experts input on scientific issues (DCGT's Mesenchymal Stromal Cell (MSC) Consortium projects)
- Site visit and CBER Advisory Committee recommendations
- Promotion and Conversion Evaluation (PCE) Committee review – cyclical review

Annual Review of DCGT Research Programs

Evaluation used to allocate research resources

- Productivity:
  - Scientific publications in peer-reviewed journals - Impact factor of journal, authorship role
  - Regulatory workload and quality
  - Review articles, regulatory articles, patents (or patents filed)
  - Invited presentations
  - Recognition by peers – science citation index, work on editorial boards, grant awards, etc.

Thank You

for providing your insights.

Your input is critical to fulfilling our regulatory mission.

Extras slides

OCTGT Activities cont…

Community Outreach (seminar, panel discussions)

- National and International Cell Therapy Societies
- AACR, ASCO, Lymphoma & Leukemia Society, SITC (Tumor Vaccines and Immunotherapy)
- American Society of Cell and Gene Therapy (ASGCT)
- Tissue Engineering Societies (AAOS)
- Xenotransplantation
- Foundations, Consumers and Patient Advocacy Groups e.g., National Hemophilia Foundation (NHF), Cystic Fibrosis (CF) Foundation, JDRF, California Institute of Regen Medicine (CIRM), etc.

OCTGT Activities contd…

Partnerships

- Participation in standards development organizations (SDO) and others e.g., ASTM, ATCC, USP
- NIH Stem Cell Task Force to address scientific and regulatory issues
- MOUs with NIH NINDS and NHLBI for sharing of information and expertise
- Inter Agency Oncology Task Force (IOTF) between NCI and FDA for joint fellowship training program
- Frequent Interactions with International regulatory bodies e.g., European Medicines Agency (EMA) regarding advanced therapy medicinal products (ATMP), HC, PMDA and others

OCTGT Guidances
(2011-2015)

- Guidance for Industry: Potency Tests for Cellular and Gene Therapy Products, January 2011
- Guidance for Industry: Preparation of IDEs and INDs for Products Intended to Repair or Replace Knee Cartilage, December 2011
- Guidance for Industry: Clinical Considerations for Therapeutic Cancer Vaccines, October 2011
- Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products, November 2013
- Draft Guidance for Industry: Considerations for the Design of Early Phase Clinical Trials of Cellular and Gene Therapy Products, July 2013
- Guidance for Industry and FDA Staff: IND Applications for Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic and Immunologic Reconstitution in Patients with Disorders Affecting the Hematopoietic System, March 2014

OCTGT Guidances

(2011-2015) contd..

- Guidance for Industry: BLA for Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic and Immunologic Reconstitution in Patients with Disorders Affecting the Hematopoietic System, March 2014
- Draft Guidance: Design and Analysis of Shedding Studies for Virus or Bacteria-Based Gene Therapy and Oncolytic Products, July 2014
- Draft Guidance for Industry: Same Surgical Procedure Exception under 21 CFR1271.15(b): Questions and Answers Regarding the Scope of the Exception, October 2014
- Draft Guidance for Industry and FDA Staff: Minimal Manipulation of Human Cells, Tissues, and Cellular and Tissue-Based Products, December 2014
- Draft Guidance for Industry: Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) from Adipose Tissue: Regulatory Considerations, December 2014

OCTGT Guidances
(2011-2015) contd..

- Draft Guidance for Industry: Investigating and Reporting Adverse Reactions Related to Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) Regulated Solely under Section 361 of the Public Health Service Act and 21 CFR 1271, February 2015
- Guidance for Industry: Determining the Need for and Content of Environmental Assessments for Gene Therapies, Vectored Vaccines and Related Recombinant Viral and Microbial Products, March 2015

OCTGT Research Goal 1, Objectives

Goal 1: Chemistry, manufacturing, controls:

Objectives:

- **Define properties of cell therapy products predictive of performance.**
- **Enhance measurement of key attributes of gene therapy products.**
- **Improve characterization of cancer vaccines, immunotherapy products, and therapeutic vaccines.**
- **Develop approaches to characterization of regenerative medicine and xenotransplantation products.**

OCTGT Research Goal 2, Objectives

Goal 2: Preclinical and clinical investigations

Objectives:

- **Characterize preclinical models for cell therapy products and relate function to product properties.**
- **Analyze performance of gene therapy products in preclinical models, including studies of biodistribution and expression of transgenes.**
- **Improve preclinical models for study of cancer vaccines, immunotherapy products, and therapeutic vaccines.**
- **Develop preclinical models for regenerative medicine and xenotransplantation products.**
- **Analyze immune responses to cell and gene therapy products and their impact on product performance.**
- **Analyze clinical trial issues of OCTGT products, including risk assessment, clinical trial design and monitoring, study of rare diseases, and pediatric use.**

OCTGT Research Goal 3, Objectives

Goal 3: Safety issues related to human tissues

Objectives:

- **Microbial safety: evaluate methods and conditions for improved tissue processing.**
- **Microbial safety: develop and evaluate methods for better pathogen inactivation and pathogen detection.**
- **Investigate other safety issues affecting tissue donors and recipients**