Overview Office of Tissues and Advanced Therapies and Division of Cellular and Gene Therapies Research Program

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Cell, Tissue and Gene Therapy Advisory Committee Presentation
Review of Intramural Research Program
Tumor Vaccines and Biotechnology Branch
Cellular and Tissue Therapy Branch
May 8, 2020
Outline

- Organizational Structure of Office of Tissues and Advanced Therapies (OTAT)
- OTAT Mission
- OTAT Regulatory Portfolio and Activities
- Division of Cellular and Gene Therapies (DCGT) Research Program
- Regulatory Scientist and Researcher Reviewer Model
- Resources and Staff Responsibilities
Division of Cellular and Gene Therapies (DCGT)

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OTAT Mission

OTAT’s mission is to ensure the safety, potency, and effectiveness of a wide variety of products including purified and recombinant therapeutic proteins for hematology, cellular therapies, gene therapies, and tissue products, for the prevention, diagnosis, and treatment of human diseases.
OTAT Products

- Stem cell and stem cell-derived products
  - Hematopoietic, mesenchymal, cord blood, embryonic, iPSCs
- Somatic cell therapies
  - Pancreatic islets, retinal pigment epithelial cells, chondrocytes, myoblasts, keratinocytes, hepatocytes
- Therapeutic vaccines and other antigen-specific active immunotherapies
  - Cancer vaccines and immunotherapies, such as dendritic cells, lymphocyte-based therapies, cancer cell-based therapies
  - Therapeutic vaccines including personalized vaccines such as peptides, proteins, mRNA and minigenes
OTAT Products, continued

• Gene therapies
  – Genetically modified cells e.g., CAR-T cells
  – Plasmids, viral vectors, bacterial vectors
  – Oncolytic viruses

• Xenotransplantation products

• Combination products
  – Tissue-engineered & regenerative medicine products
  – Device with a cellular component

• Devices
  – For processing cells/tissues; delivery of cells/genes

• Purified and recombinant proteins for hematology
  – (e.g., coagulation factors, thrombin, botulism antitoxin, diphtheria antitoxin, fibrin sealants)
All OTAT INDs and IDEs
2016 vs. 2019
OTAT Approved Gene Therapy Products: Advanced Therapies at the Leading Edge

FDA News Release: **FDA approval brings first gene therapy to the United States**
CAR T-cell therapy [Kymriah (tisagenlecleucel)] approved to treat certain children and young adults with B-cell acute lymphoblastic leukemia

Yescarta (axicabtagene ciloleucel) is the second gene therapy product approved in the U.S. Indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma (DLBCL)

For Immediate Release
September 28, 2017

www.fda.gov
Luxturna (voretigene neparvovec): Adeno-associated virus vector expressing the gene for human retinal pigment epithelial 65kDa protein (AAV2-hRPE65v2)

**Proposed Indication:** Indicated for the treatment of patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy

**Approved:** December 19, 2017

Source: Spark Therapeutics, Inc.
FDA News Release: May 24, 2019

• **Onasemnogene abeparvovec-xioi (Zolgensma):** for the treatment of patients less than two years of age with spinal muscular atrophy (SMA) with confirmed biallelic mutations in the *survival motor neuron 1 (SMN1)*
  
  - SMA caused by deficiency in the SMA1 protein needed for the survival of motor neurons, most severe forms of SMA commonly present with muscle weakness that is evident at birth or within the first few months of life and children cannot sit unassisted or breathe normally

OTAT Approved Cell Therapy Products

• **Provenge (sipuleucel-T):** Autologous antigen presenting cell (APC) immunotherapy for treatment of asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer

• **HPC (hematopoietic progenitor cells), Cord Blood:** For use in unrelated donor hematopoietic progenitor cell transplantation procedures in conjunction with an appropriate preparative regimen for hematopoietic and immunologic reconstitution in patients with disorders affecting the hematopoietic system that are inherited, acquired, or result from myeloablative treatment.

• **MACI (Autologous Cultured Chondrocytes on a porcine collagen membrane):** Autologous cellularized scaffold product for repair of single or multiple symptomatic, full-thickness cartilage defects of the knee with or without bone involvement in adults.

• **GINTUIT (Allogeneic Cultured Keratinocytes and Fibroblasts in bovine collagen):** For topical (non-submerged) application to a surgically created vascular wound bed in the treatment of mucogingival conditions in adults.

• **LAVIV (Azficel-T):** Autologous fibroblasts for improvement of the appearance of moderate to severe nasolabial fold wrinkles in adults.
OTAT Activities

- Review, evaluate and take appropriate action on product applications and amendments or BLA supplements submitted by manufacturers of OTAT products.
- INTERACT (pre-pre-IND), pre-IND, and pre-IDE submission advice.
- Participate in inspections of manufacturing facilities for compliance with applicable standards, and other compliance activities including court cases.
- Develop 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.
OTAT Activities contd..

- Development of FDA Guidances for the regulation of tissues, cellular, and gene therapy and tissue engineering products –
  
  *14 Guidances in last 4 years*

- Consultation and Education
  - Provide scientific and technical advice to other CBER Offices, FDA Centers, Government Agencies, sponsors
  - Advisory committee meetings

- Community Outreach (professional societies, patient advocacy)

- Partnership (SDO, NIH, NIST, Global regulatory authorities)

- Counterterrorism activities (Continuity of Operations, Lab Red Alert Plan etc.)

- Perform research to support review and progress towards safe and effective medical products
OTAT 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 OTAT products, including identification 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 OTAT products, and of clinical study issues, with the goal of improving the safety and efficacy of OTAT-regulated products.

OCTGT Research Goal 3: Safety issues related to human tissues

Objectives under each goal:
http://inside.fda.gov:9003/ProgramsInitiatives/Biologics/Research/ucm494811.htm
Current DCGT Research Areas

- Virology
  - Retroviruses, lentivirus, adenovirus, AAV
- Immunology
  - Immune responses to viral and plasmid vectors
- Cell and developmental biology
  - Mechanism of cellular differentiation in animal models
  - Cell fate and survival, stem cell biology
- Cancer biology/Immunology
  - Molecular biomarkers, cancer vaccines, immunotherapy, animal models
- Biotechnology
  - Genome editing, Advanced manufacturing, Genomics, flow cytometry, proteomics, transgenics, tissue engineering
- MSC Consortium: MSC attributes as related to safety and efficacy
- Microbiology of tissue safety: Pyrosequencing and WGS
OTAT 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

- 14 Principal Investigators (PIs) – permanent or senior staff fellows researcher reviewers
- Staff Scientists – 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 and other contract mechanisms: 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
    - 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
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.
Summary

Roles of Research in OTAT:

- Provide in-house, hands-on expertise in cutting-edge areas
- Facilitate product development by addressing challenges encountered and helping develop approaches, guidance
- Increase public confidence in and acceptance of novel technologies by addressing concerns
- Respond to Public Health Emergencies (COVID-19 Pandemic)
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Shyh-Ching Lo, M.D., Ph.D.
Tissue safety Program

New PI

Pankaj Mandal, Ph.D.
Advanced Manufacturing of genome edited hematopoietic stem cells
Towards Development of Safe and Effective Cancer Vaccines and Cellular Immunotherapy Products

Public Health Issue and Scientific and Regulatory Challenges

- Cancer, a most difficult public health problem*
- Biology of cancer – appropriate and specific target, tumor microenvironment, immune tolerance
- Appropriate tests and markers for purity, identity and potency of cancer vaccines and immunotherapy products
- Animal models – safety and efficacy
- Biomarkers for immune response, disease monitoring and response

*>1.8M estimated New Cases of Cancer in 2020
~600K estimated Cancer Deaths in 2020
Source: Cancer Facts and Figures, 2019 (American Cancer Society)
Characterization of Tumor Associated Cell Surface Receptors and Antigens

*Discovery of overexpression of Th-2 derived cytokine receptors in human tumors*

- **Interleukin-4 receptors (IL-4R)**
  - RCC, SCCHN, malignant glioma, AIDS-KS, colon cancer, breast cancer, NSCLC, prostate cancer, pancreatic cancer, ovarian cancer, mesothelioma, and hematological malignancies (CLL-B), pancreatic cancer, bladder cancer, anaplastic thyroid and ovarian cancer

- **Interleukin-13 receptors (IL-13R)**
  - RCC, malignant glioma (GBM), medulloblastoma, DIPG, AIDS-KS, SCCNH, ovarian cancer, pheochromocytoma, prostate cancer, pancreatic ductal adenocarcinoma (PDA), glioblastoma multiforme, and adrenocortical cancer
FDA Research Addressing Scientific and Regulatory Challenges

➢ Program Area 1: Cancer Vaccines and Adoptive Cellular Immunotherapy: Identification, characterization, and targeting of novel tumor antigens/receptors for cancer therapy

➢ Discovery of Th2 derived cytokine receptors in cancer: expression, structure and signal transduction

➢ Significance of receptor expression in cancer

➢ Targeting of receptors: IL-4R and IL-13R targeted immunotoxins

➢ Targeting of IL-13Rα2 with modified vaccinia Ankara recombinant virus cancer vaccine – S. Rafat Husain

➢ Targeting IL-13Rα2 with Chimeric Antigen Receptor (CAR) -T cells – Bharat Joshi
Program Area 2: Application of Genomics technology: Characterization of Cancer Vaccines and Cell and Gene therapy products

- Analysis of cytokine receptors as potential biomarkers of disease prognosis and response (TCGA database).

- Characterization of cell banks, cancer vaccines and stem cells by genomics technology.

- Identification, characterization and targeting of glycolytic pathway enzyme, PKM2, in NSCLC

- Characterization of secretome of hMSC by proteomic technology – Ramavati Pal
IL-4Rα is over expressed in human thyroid cancer, but not in normal thyroid.
IL-4-PE causes regression of established ATC tumors and enhances survival of animals

Analysis of tumor growth *in vivo*

A

Nude mice were implanted with 5x10^6 tumor cells s.c. Mice with established tumors were injected i.t. with IL-4-PE on alternate day for 6 injections. *Percent survival is calculated based on the sacrifice time when tumor reached > 2 cm*
IL-13Ra2 overexpression in GBM is associated with resistance to temozolamide chemotherapy.
Adoptive Cellular Immunotherapy for Cancer Using Genetically Engineered CAR-T Cells Expressing scFv-IL-13Rα2

Bharat H. Joshi, Ph.D.
Cancer Vaccine: Modified Vaccinia Ankara Virus Vector Expressing Human IL13-Receptor α2 Antigen

rIL-13Rα2 protein is expressed after recombinant virus infection.

Almost all cells (96.6%) are positive for GFP and IL-13Rα2.

MVA virus can infect tumors cells to express IL-13Rα2 on their cell surface.
Summary

- Human tumors express high levels of IL-4R and IL-13R in cancer compared to normal cells.
- The structure of and signaling through these receptors is different in cancer cells compared to normal cells.
- Overexpression of IL-13R in GBM is associated with poor patient prognosis and resistance to temozolomide therapy.
- Both IL-4R and IL-13R can be targeted with immunotoxins and other therapeutic approaches.
- rMVA-IL-13Ra2 virus was successfully produced.
- rMVA-IL13Rα2 virus showed ability to infect tumor cells and express IL-13Rα2 on their cell surface.
- Third generation CAR-T cells expressing scFv-IL-13Rα2 are generated successfully.
- The CAR-T cells are metabolically active and proliferate in vitro. They are highly potent, killing the target tumor cells and release IFN-γ.
Tissue Microbiology Laboratory
for Safety of Human Tissues
Intended for Transplantation

Shyh-Ching Lo, Ph.D., M.D.
Public Health, Regulatory and Scientific Challenges of Tissue Microbiology Lab:  
To Better Understand the New Scientific Trends and Further Improve the Safety of Human Tissue Grafts and HCT/Ps

- Increasing numbers of human tissues are recovered, processed as grafts by the industry and used by the medical practice each year.

- The OTAT within CBER regulates human cells, tissues, and cellular and tissue-based products (HCT/Ps) in order to prevent the transmission of communicable diseases.

- The tissue microbiology laboratory has been established under the DCGT and the DHT to enhance both the safety and the availability of high quality human tissue grafts and HCT/Ps for therapeutics.

- The scientific capability of the micro program needs a wide spectrum of expertise to cover highly diverse microbial pathogens, including bacteria, fungi, viruses and protozoa parasites.
Research Programs of Tissue Laboratory:

Development of New Technologies and Evaluation of Innovative Methods Applied to Guard the Safety and Quality of Tissue grafts and HCT/Ps for therapeutics

Specific Aims and Research Areas:

- To establish and maintain the required scientific capabilities to directly support regulatory needs for tissue safety
- To adopt new molecular technologies for rapid detection of target infectious pathogens with high sensitivity in human tissues being processed for transplantation
- To develop highly effective genomic sequencing capabilities for identification and characterization of infectious agents that would likely threaten the safety of human tissue grafts and HCT/Ps using NGS and bioinformatics technology
- To explore new scientific approaches for detection and characterization of previously unknown or newly emerging infectious pathogens for the preparedness against biological threats to safety of CBER-regulated bioproducts and general public health

www.fda.gov
Comparative genomics, infectivity and cytopathogenicity of Zika viruses produced by acutely and persistently infected human hematopoietic cell lines

Bingjie Li, Hsiao-Mei Liao, Hebing Liu, Shien Tsai, Jing Zhang, Guo-Chiuan Hung, Pei-Ju Chin, Yamei Gao, Shyh-Ching Lo

1 Tissue Microbiology Laboratory, Division of Cellular and Gene Therapies, Office of Tissues and Advanced Therapies, Center for Biologics Evaluation and Research, Food and Drug Administration, Silver Spring, Maryland, United States of America, 2 Lab of Pediatric and Respiratory Viral Diseases, Division of Viral Products, Office of Vaccines Research and Review, Center for Biologics Evaluation and Research, Food and Drug Administration, Silver Spring, Maryland, United States of America
Identification of the essential molecules and metabolic pathways associated with critical biological functions in the infected human host cells that confer the viral persistence.
Summary of Tissue Micro Lab Research

- Development of rapid, highly sensitive technology for detection of pathogens such as *Candida* in cornea tissues intended for transplantation -- *Real-time qPCR assays of the targeted high-risk microbes that affect the safety of human tissue grafts*

- Development of high-throughput genomic sequencing capability for detection and characterization of established and newly emerging infectious pathogens, such as EBV and ZIKV present in human tissue, cells or tissue-based products -- *Readiness of scientific capability against known and newly emerging microbial threats of public health*

- Development of transcriptomics whole genome expression profiling capability for identification of key molecules, metabolic pathways and biological functions in the human host cells that confer ZIKV persistence-- *Establishment of essential bioinformatics capability to support the needed review of increasingly common IND/pre-IND submissions with genomics/gene expression profiling data*
Advanced Manufacturing of Genome-edited Hematopoietic Stem Cells

Pankaj K. Mandal, Ph.D.
Hematopoietic Stem Cell-based Therapeutics: Challenges and Opportunities

- HSC-based therapeutics is one of the leading advanced therapies.
- Though performed routinely, HSCT is under utilized to treat blood disorders.
- HSCTs remain a high risk procedure.
- Gene Therapies and Genome Editing have expanded the scope of HSCTs.
- Highly efficient and therapeutic meaningful genome editing in HSCs are achievable.
- Optimized methods to maintain/expand HSCs ex vivo have not been established.

Cost-effective reproducible large scale manufacturing of HSC-based therapeutics with defined CQA remains the bottleneck.
Research Program of Advanced Manufacturing Lab

Project Title: Advanced manufacturing of genome-edited HSC-based therapeutics.

- Optimizing large scale manufacturing of HSC-based products
- Developing novel approaches for HSC derivation & expansion
- Evaluating the potency and safety of genome-edited HSC
- Development of reference reagents and regulatory guidelines
Thank you

for reviewing DCGT’s research programs

and providing your insights.

Your input is critical to fulfilling our regulatory mission.