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Welcome Dr. Marc Ernstoff, MD
Medical Officer & Chief, ImmunoOncology Branch

Marc brings to DTP 40 years of experience studying immunobiology of human cancer and development of new immune therapies.

- Most recently Professor and Chair, Department of Medicine, SVP for Clinical Investigation, The Katherine Anne Gioia Chair of Medicine at Roswell Park Comprehensive Cancer Center

Previously:

- Dartmouth College's Geisel School of Medicine: Section Chief of Hematology/Oncology and Deputy Director of the Norris Cotton Cancer Center.
- Cleveland Clinic: Director of the Melanoma Program
- U Pittsburgh Cancer Institute: medical oncology and translational immunotherapy program
- Yale U: Medical Oncology and cancer immunology training

Marc has over 250 original research manuscripts in the areas of renal cell cancer, melanoma and immune therapy strategies including cytokine therapies, dendritic cell vaccines, immune checkpoint inhibition, targeted therapies and ex vivo expanded effector cells for adoptive transfer.

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Topics

1) Recap: Developmental Therapeutics Program (DTP) and NCI Experimental Therapeutics (NExT) program
2) Priority topics from September 2020 meeting:
   - Cellular immunotherapies and other complex biologics for cancer
   - Intelligent drug discovery based on biochemistry, structure, and mechanisms, including artificial intelligence-driven drug discovery
3) Stakeholder Workshop Summary
   - State of the Field
   - Challenges and Opportunities

Developmental Therapeutics Program

- Supports and Assists the Extramural Community to Advance New Therapeutic Concepts toward Clinical Use
- 10 Branches provide resources spanning discovery to IND-enabling activities along the regulatory critical path: small molecule, natural products, biologics/biopharmaceuticals
- Oversee largest grants portfolio in NCI focused on discovery and development of new cancer therapies

Bench-to-Bedside
Product Development

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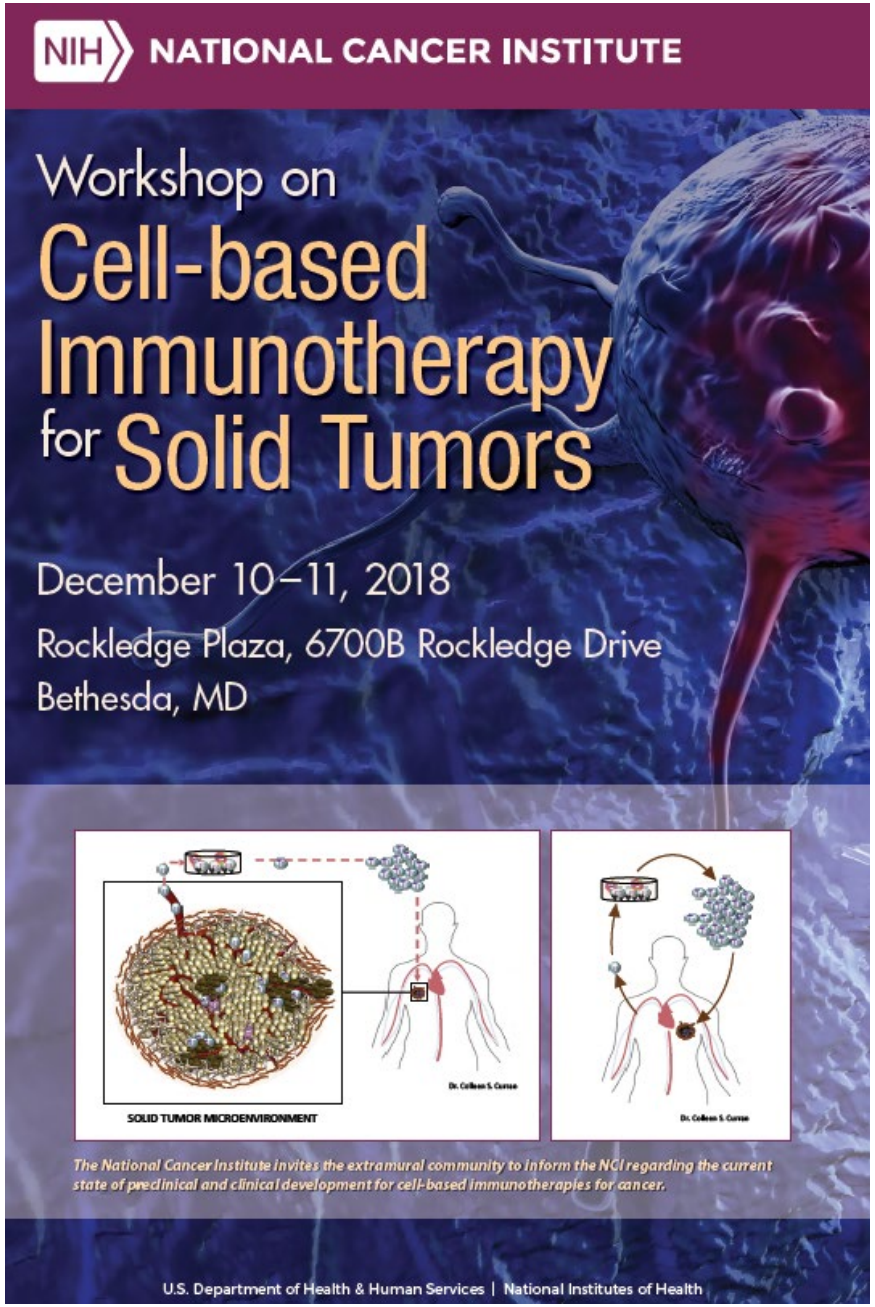

1st NCI Workshop – December 2018

Consensus regarding gaps/opportunities

Research needed:

- Targeting, affinity, cross-reactivity
- Improve trafficking and tumor penetration, non-invasive imaging
- Overcome inhibitory TME
- Explore autologous vs. allogeneic products; CAR-T vs. TIL vs. NK vs. DC vaccine, etc.
- *In vivo* gene editing of immune cells

Clinical development challenges

- Cost, specialized protocols

Technology challenges:

- gene transfer, cell production

Regulatory challenges

- Unclear guidance, lack of flexibility

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Recommendations from 2018 Workshop Stakeholders

- **Manufacturing cell therapies, including vectors and reagents**
- **Develop and share standard operating procedures** for manufacturing and analytics
- **Targeted funding** for research: ideal target characteristics; critical quality attributes of cell products; noninvasive imaging to assess cell trafficking; validate useful animal models
- Funding for clinical trials and data sharing among trial sites
- Training programs for technical staff; scarcity of skilled staff in this field requires help to recruit, train, and retain technical workforce
- Work with the Food and Drug Administration (FDA) to harmonize product characteristic specifications

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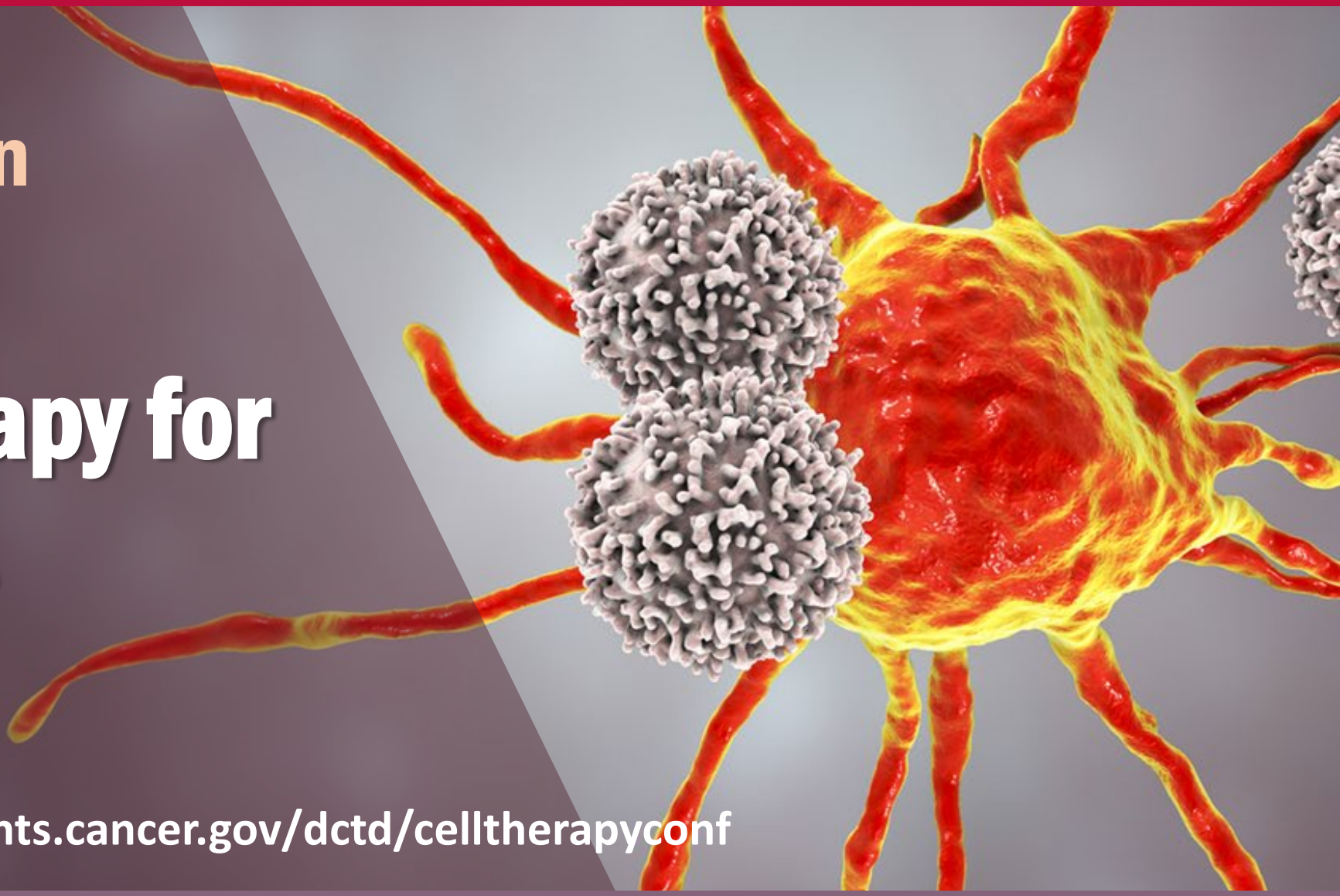


2nd Workshop on Cell-Based Immunotherapy for Solid Tumors

December 10-11, 2020

https://events.cancer.gov/dctd/celltherapyconf

Active Scientific Questions: 2nd Workshop

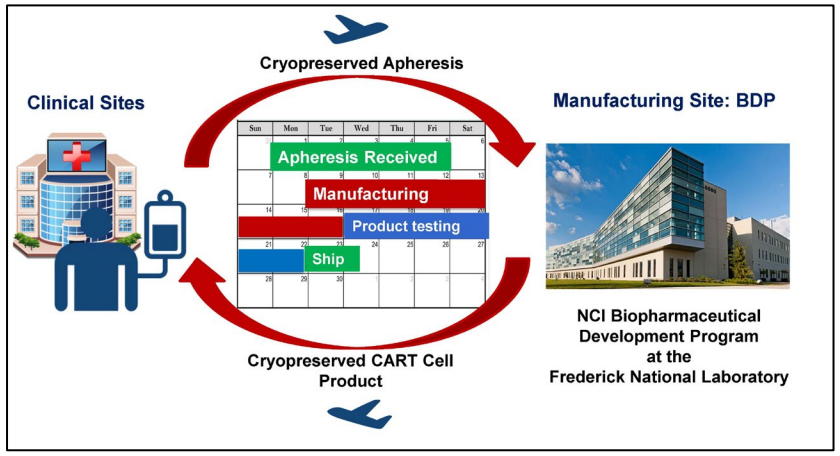
- Solid tumor challenges
  - Defining and overcoming the inhibitory tumor microenvironment
  - Improving and measuring cell trafficking, tumor penetration
  - Improving tumor targeting; better efficacy, avoid on-target/off-tumor toxicity
- Understanding cell product critical quality attributes
  - Predicting and controlling adoptive cell activity, persistence and function, durable anti-tumor immunity
- More facile cell engineering process
  - Cumbersome cell transduction, requirement for GMP reagents throughout
- Poorly representative animal models
  - Access to specialized mouse colonies, development of new models
- Imaging to understand cell trafficking, persistence and efficacy
  - PET and SPECT/CT probes; MRI tracer agents; Metabolic tracers; Reporter genes

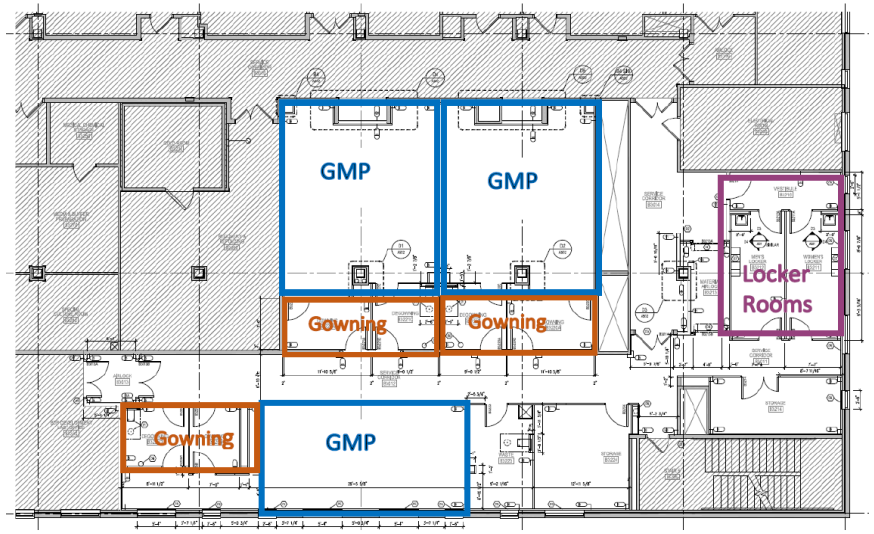
Persistent Logistics Challenges: 2nd Workshop

- Reagent and equipment availability
  - Need antibody reagents for GMP sorting of specific cell populations
  - Need specialized equipment to manufacture and characterize products (closed manufacturing systems, high-throughput cell sorters, electroporators)
  - Need cytokines, manufacturing and assay reagents, gene delivery reagents
- Access to manufacturing of GMP vectors, reagents, cells
  - Need faster queue, flexibility for variety of products
- Cumbersome and inflexible manufacturing platforms
  - Need low cost, high throughput, point-of-care manufacturing
- Ability to perform small, proof-of-concept trials
  - Ability to translate into small, proof-of-concept clinical studies is a critical need

Current Status of Development Support for Cell Therapy Summary of Progress: 2018 to 2021

- Renovated space for a GMP cell therapy suite; returned Virus Production Facility from cell therapy to viral vector manufacturing
- Established expertise and capability to support two multi-center autologous cell therapy clinical trials
- Began renovations to create 3 additional flexible GMP suites for cell therapy-related activities





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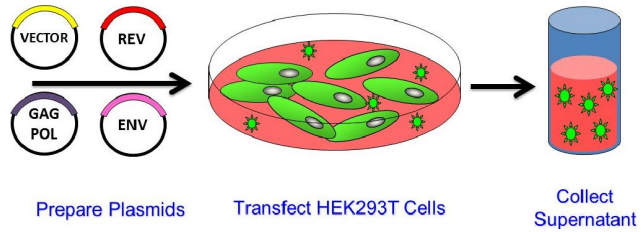
Current Status of Development Support for Cell Therapy Summary of Progress: 2018 to 2021

- Added cell therapy-related SOPs to public site; over 300 SOPs on all aspects of GMP biopharmaceutical manufacturing
- Awarded six P30 and P50 grant supplements for development of technologies to overcome barriers to broad-based adoption of cell therapy for hematologic or solid human cancers
- Developed capability to manufacture lentivirus and retrovirus products for cell transduction; CRISPR/cas-based editing is under development

Over 300 Standard Operating Procedures Online

- Operations, Facilities/Equipment, Validation
- Safety and GMP Audits
- Development Analytics and Process Development
- GMP manufacturing:
  - Cell Culture, Fermentation
  - Purification (protein, plasmid, virus), Fill/Finish
- Materials management and inventory control
- Quality Assurance, Quality Control



Remaining Opportunities

Innovation support

- Funding for transformative research on technology development (may need to be iterative – not favored in study sections)
- Funding support for development of more predictive animal models

Access to resources

- Speed access to NExT support (timeline for review and project initiation)
- Develop alternate path for access to NCI resources

Reagent and equipment support

- Provide critical reagents for manufacturing, cell sorting, analytical assays
- Provide supplements for equipment purchase to cancer centers/ SPORE programs
- Provide gene delivery reagents and technologies

Clinical trial support

- Mechanism for translating knowledge into small clinical studies; iterative, parent/child
- Support for combinatorial trials – adoptive cell transfer plus agents to disrupt TME, etc.
- Provide regulatory support; master protocol, IND submission consultation

Recommendations: High Feasibility

- Support standardization of assays, Critical Quality Attributes of cell products, clinical trial templates for IND submission
- Improve NExT recruitment of high-quality proposals for projects related to cell-based immunotherapy of solid tumors; provide bridge to small clinical studies
- Provide testing service for vector and cell products (product release tests)
- Evaluate and advertise reagents that could be made available (e.g. cytokines, antibodies for cell selection and characterization)

Recommendations: Challenging Feasibility

- Support small, proof of concept clinical studies to gain early read-out regarding anti-tumor efficacy, pre-conditioning regimens, biomarkers as correlates of treatment efficacy, image-based detection of response and immune cell trafficking, combinatorial studies, etc.

- Support preclinical and translational research on topics such as solid tumor targets, immune cell fitness and persistence, cell trafficking, the immunosuppressive tumor microenvironment (NOSI, RFAs, contracts)

- Support development of novel approaches to cell manufacturing (new cell expansion methods, genetic engineering including multi-gene engineering, alternatives to retroviral-based gene delivery, optimization of closed system manufacturing including metabolic fitness, evaluating new approaches for cell product screening)

- Establish core laboratory for characterization of manufactured products

Potential RFAs

- Preclinical and translational projects to discover:
  - Solid tumor targets that avoid on-target/off-tumor toxicity
  - Adoptive immune cell product fitness, persistence, exhaustion and trafficking
  - Blocking the immunosuppressive TME in combination with Adoptive Cell Transfer

Creating Community Infrastructure

- Provide standardized, quality-controlled testing for GMP products
- Clinical trial protocol templates for IND submissions
- Establish a community resource to measure safety of vectors