DCTD's Biopharmaceutical Development and Production at FNLCR

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NIH NATIONAL CANCER INSTITUTE

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Topics

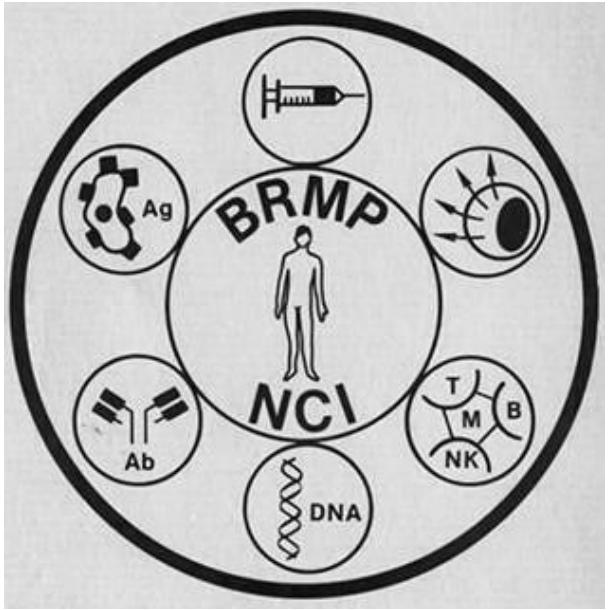
- Brief History and Overview of Biopharmaceutical Development in DCTD
- Capabilities and Recent Accomplishments of the Biopharmaceutical Development Program (BDP)
- Support for Cell Therapy and the Cancer Adoptive Cell Therapy (Can-ACT) Initiative
- Access to the BDP and Collaboration Opportunities

Why Does DCTD Support Biopharmaceutical Development and Production?

- *Provide resources directly to the extramural community, i.e. NExT Program*
- *Fill gaps and foster development of new biotechnologies, i.e., Can-ACT*
- *Disseminate knowledge and share unique resources with other NIH partners*

A Brief History and Overview

Biological Response Modifiers Program, DCT/NCI



- Interferon studies in the 1970s
- NCI grants, contracts, and clinical trial support
- Monoclonal antibody production and acquisition
- Tumor vaccines
- Oncolytic viruses and bacteria
- Cell and gene therapies

Evolution of Biologics

- Biologic isolates and extracts
- Recombinant proteins
- Antibodies
- ADCs and imaging agents
- Viruses/VLPs and bacteria
- Autologous TIL and CAR T cells
- *Engineered Cells and Synthetic Biology*

Typical Milestones for Translation of a Biologic

- Is it what you think it is? Due diligence with R&D/preclinical material and analysis of starting materials for GMP suitability (SISQP, cell line history, etc.)
- Can you make enough? Process development for scale-up feasibility, purification, assay development and SOPs, formulation stability, etc.
- Generate reference material: reference lot, cell banks, virus banks

Pre-IND Meeting

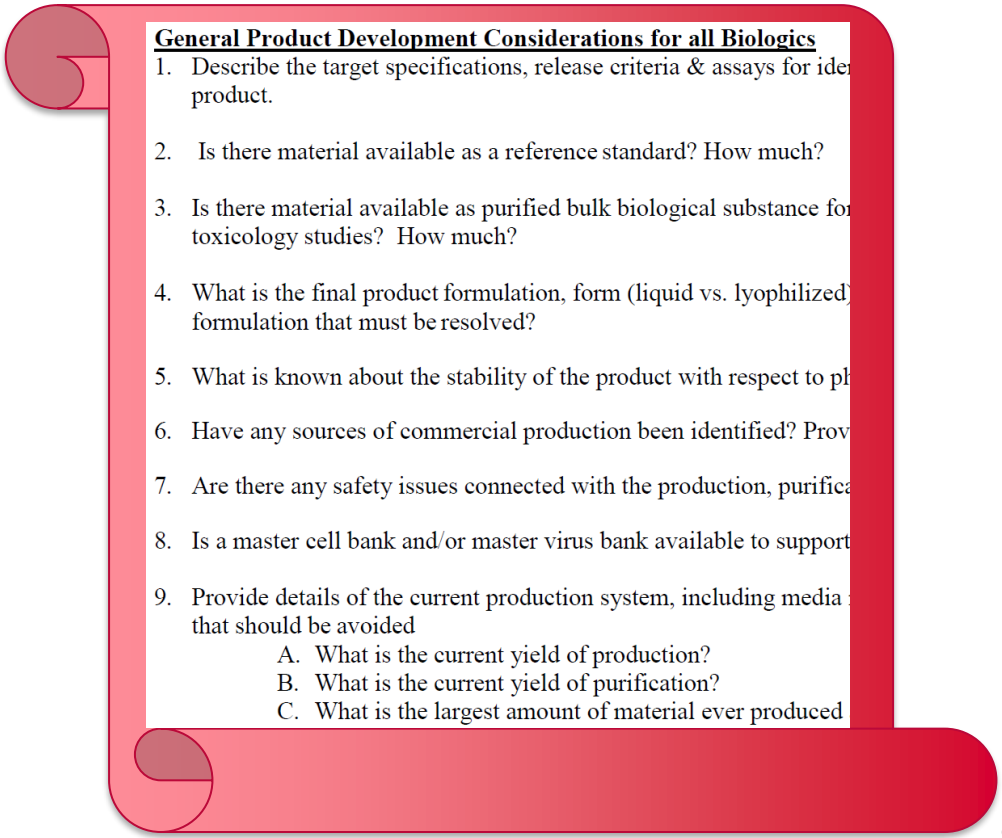
- Set testing specifications: Analytical qualification for QC product release; forced degradation studies to inform the stability program
- Can you make the clinical lot? Pilot manufacturing, "GMP dress rehearsal": often use product for IND-directed toxicology and infusion stability studies
- Pre-clinical safety studies: Range finding, toxicology, biodistribution
- cGMP manufacturing: QC/QA release - CoA, CMC, IND submission

- Real-time stability: Subset of release assays that will detect degradation and contamination

Generic Questionnaire for Biologics

https://next.cancer.gov/content/docs/Biologics_Product_Development_Questionnaire.pdf

- Gauge the developmental readiness of a biologic
- Address SISQP
- Specific questions for recombinant proteins, viral vectors, oligonucleotides, peptides, and cell products



General Product Development Considerations for all Biologics

1. Describe the target specifications, release criteria & assays for ide product.
2. Is there material available as a reference standard? How much?
3. Is there material available as purified bulk biological substance fo toxicology studies? How much?
4. What is the final product formulation, form (liquid vs. lyophilized) formulation that must be resolved?
5. What is known about the stability of the product with respect to ph
6. Have any sources of commercial production been identified? Prov
7. Are there any safety issues connected with the production, purifica
8. Is a master cell bank and/or master virus bank available to support
9. Provide details of the current production system, including media that should be avoided
   A. What is the current yield of production?
   B. What is the current yield of purification?
   C. What is the largest amount of material ever produced

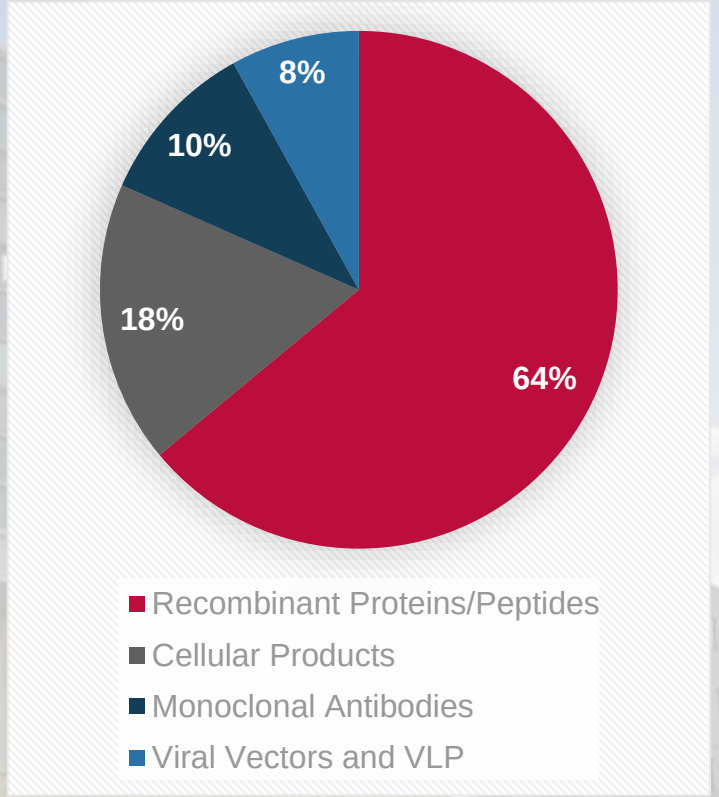
Capabilities and Recent Accomplishments of the BDP

Biopharmaceutical Development Program at the Frederick National Laboratory for Cancer Research

NCI/DCTD established the BDP in 1993 to:

- Provide specialized and unique technical expertise and services not readily available in the commercial market
- Conduct feasibility studies on project candidates
- Development of manufacturing process and assays
- Perform GMP manufacturing, filling, testing, and product release
- Produce and submit FDA and international regulatory filings
- Transfer technology to commercial entities
- Provide cGMP training to staff and partners

>260 investigational agents since 1998



BDP is a Multi-Product Pilot Facility for Biopharmaceuticals and Cellular Products

- Overall facility size is ~66,000 ft^2
- Main GMP manufacturing area is ~22,000 ft^2
  - Separate trains for eukaryotic and prokaryotic production and purification
  - Suites for fill/finish, vial labeling, and inspection up to 10,000 vials per run
- Self-contained virus manufacturing suite is ~2,500 ft^2
- Four cell therapy suites total ~2,300 ft^2
- Multiple labs for analytics, process development, and product and raw material warehousing

State-of-the-Art Equipment Facilitates Biopharmaceutical Development and Production

BDP Quality Systems - cGMPs

- **BDP follows 21 CFR 211 - Current Good Manufacturing Practices for Finished Pharmaceuticals**
  - Organization and Personnel
  - Facilities / Equipment / Laboratory Controls
  - Manufacturing:
    - Raw Materials / Holding and Distribution
    - Production and Process Controls
    - Vialing and Labeling Controls
  - Records and Reports
- **BDP Quality Manual: A phased-approach to meeting cGMP Requirements**

BDP Quality Systems
– Organization and Personnel

- **Personnel**
  - Highly trained staff with GMP training provided on a regular basis
    - Training curriculum for each employee based on department, job functions, and responsibilities
  - QA, QC, and RA groups provide oversight and internal/external auditing
  - Independent QA reporting structure
- **Documentation**
  - SOPs for manufacturing, QC testing, Facility/Equipment Operations, and Environmental Monitoring
  - Master and Batch Production Records
  - QC Test Reports
  - Master Specifications and Certificates of Analysis
  - Validated Electronic Document Management System – Master Control

BDP Quality Systems – Facilities and Equipment

- **Facilities and Equipment**
  - Facility design was reviewed by FDA in a Type C meeting in April 2011
  - Utilities and sterilization equipment are validated and undergo recertification annually
  - Quantitative instrumentation undergo scheduled calibration
  - Product-contact equipment is validated using a risk-based approach based on product safety and quality impact
  - Automated filling equipment is revalidated within six months of a product fill

BDP Quality Systems – Manufacturing

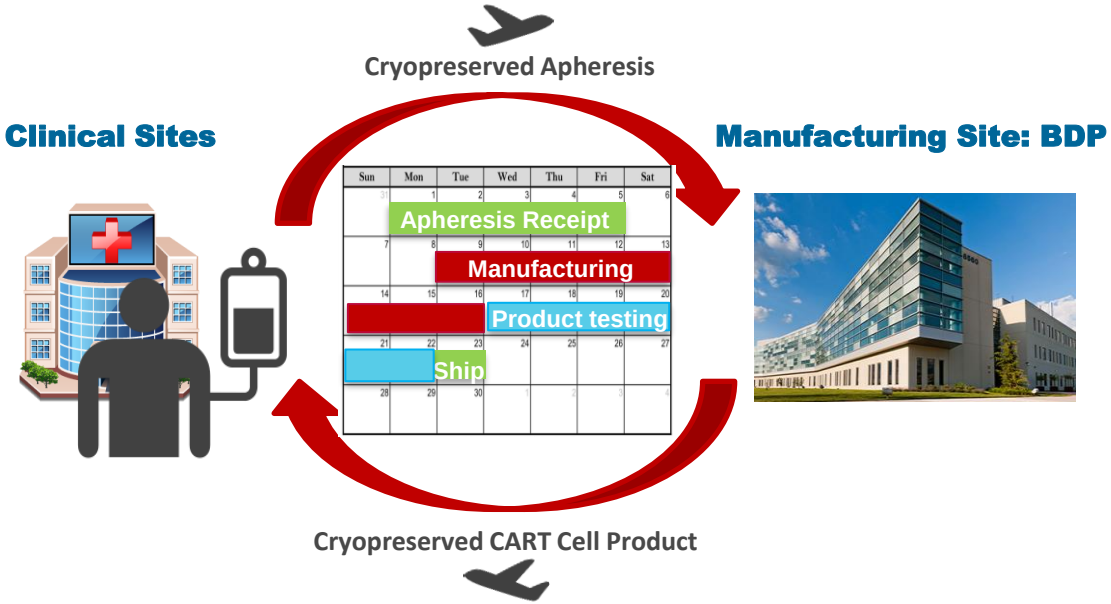
Manufacturing

- Raw materials are assigned part numbers with master specifications and criticality levels depending on its product contact; receiving numbers are assigned to differentiate specific shipments
- Facility area and operational area clearances are performed by QA
- Master Production Records/Batch Production Records document the manufacturing process
- Fill/Finish and critical cGMP manufacturing steps include QA observation
- QC testing includes environmental and water monitoring, raw materials, in-process, and product release and stability
- QA reviews completed batch records and releases products for clinical use
- RA generates the CMC document for regulatory filing

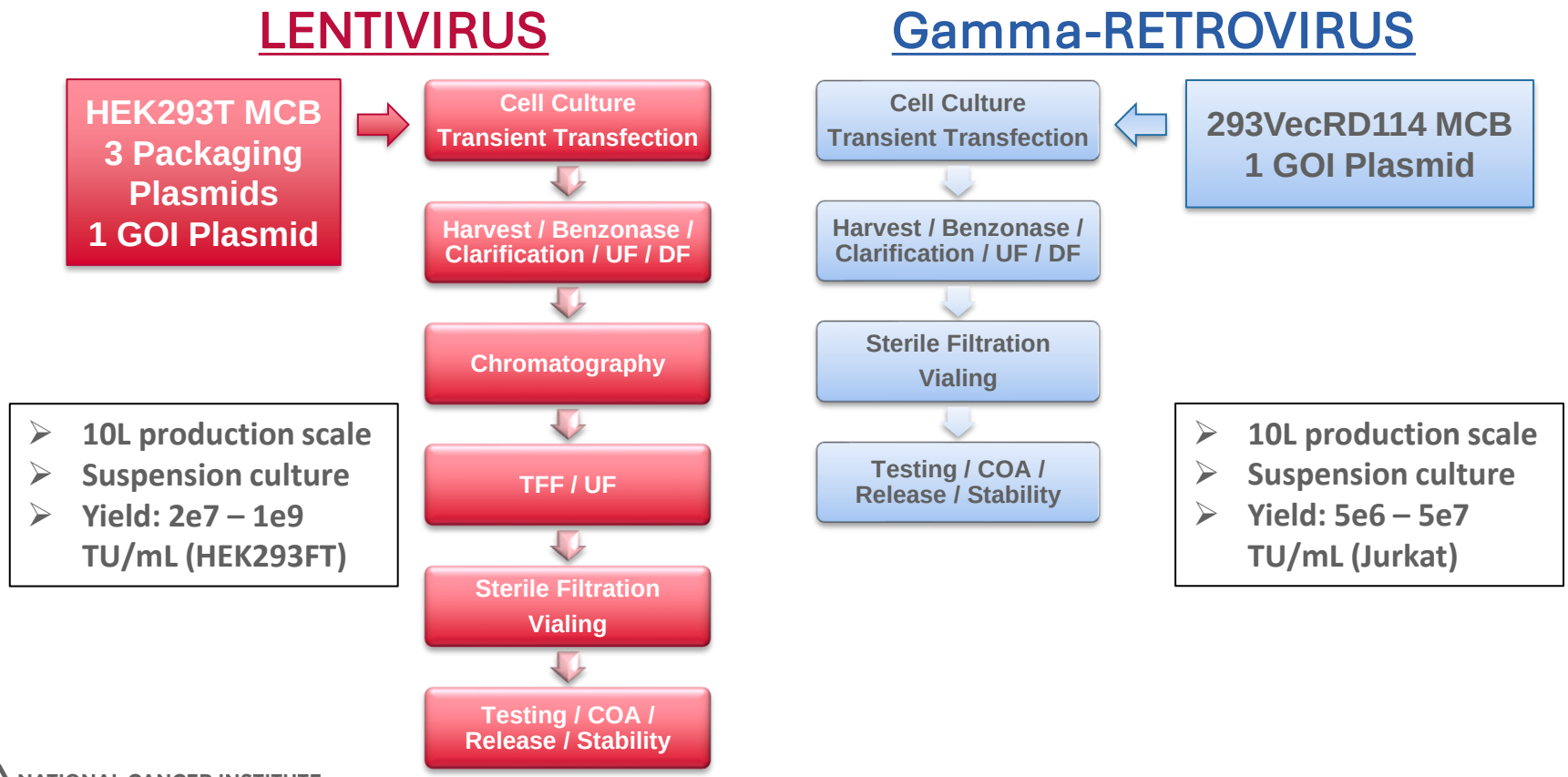
Autologous CART Cell Manufacturing for Multi-site Trials

Capabilities & Benefits

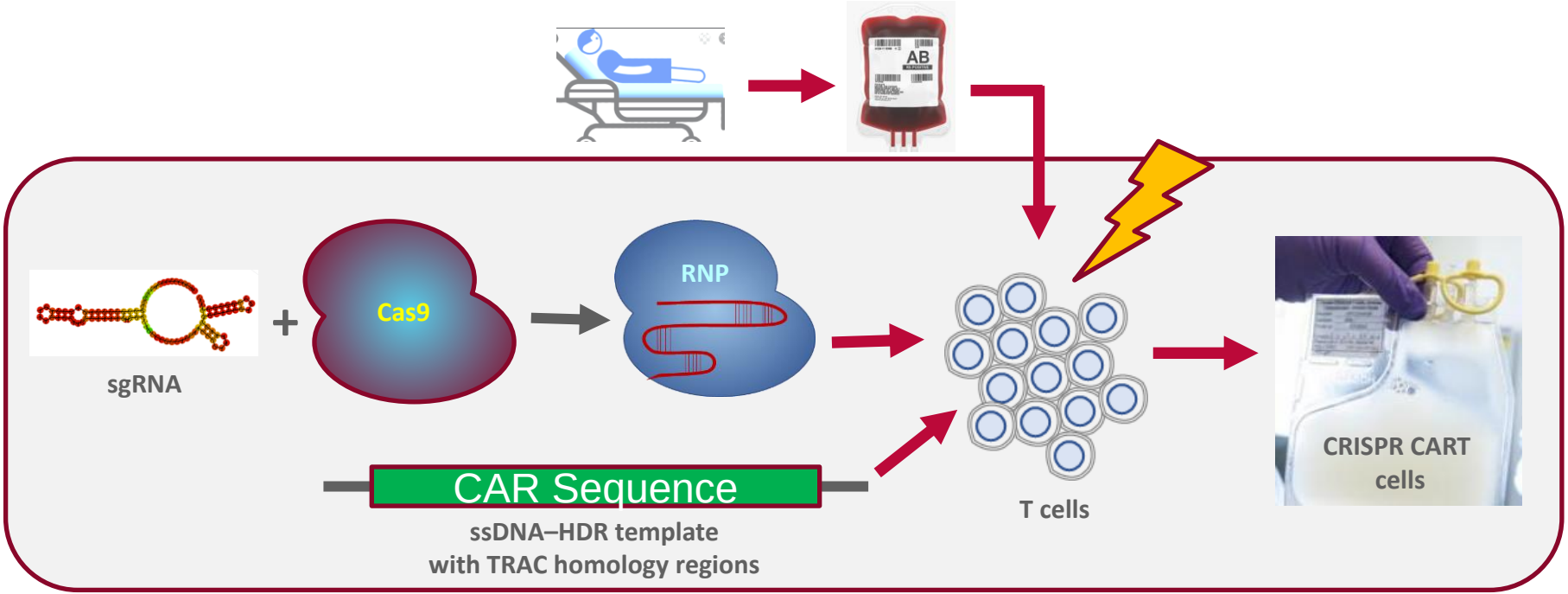
- 5 GMP suites (2 are flexible for virus manufacturing)
- Closed manufacturing systems
- Aseptic process validations
- Process qualification
- Rapid product release
- Shipping qualification
- Standardized product testing
- Product chain logistics to support multi-center trials
- Quality manufacturing adds rigor and reproducibility to clinical research
- Phase I/II trials benefit from multi-site accrual



Viral Vector Production Platforms for Cell Therapy Manufacturing



CRISPR-based Cell Engineering



- Efficient endogenous TRAC and TCRB knockout: >98%
- Knock-in efficiency up to 40%

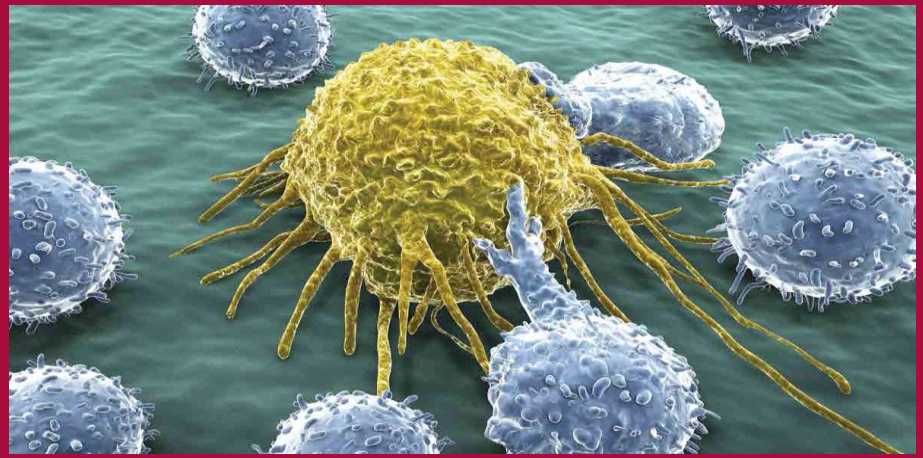
Successful Commercialization and Product Licensure

LUMOXITI™
moxetumomab pasudotox-tdfk
for injection

- *Lumoxiti – hairy cell leukemia*
- *Unituxin – pediatric neuroblastoma*
- *Lerapolturev (PVSRIPO) – recurrent glioblastoma, melanoma, non-muscle-invasive bladder cancer*
- *Anselamimab (ch11-1F4) – primary amyloidosis*

istari ONCOLOGY

ALEXION®
AstraZeneca Rare Disease



Support for Cell Therapy and Can-ACT

Centralized CD33 CART Cell Manufacturing for Multi-site Clinical Trial

Description

Title: CD33CART Clinical Trial in Children and Young Adults With Relapsed/Refractory Acute Myeloid Leukemia *(NCT03971799)*

IND Sponsor: The National Marrow Donor Program (NMDP)
Study PI: Nirali Shah, MD (NCI)

Manufacturing Sponsor: NCI/DCTD

Clinical Sites & Leads

*"Please keep trying to save lives. Keep doing what you are doing so that other families don't have to suffer the horror of a losing battle with Leukemia. Thank you for taking care of *** at the NIH. Keep his memory alive." - patient's family*

Accrual Status

Cohort	Status	Observations
1 (3e5 CD33CART/kg)	3 patients treated – *accrual complete*	no CART expansion or anti-tumor effects
2 (1e6 CD33CART/kg)	3 patients treated – *accrual complete*	no CART expansion or anti-tumor effects
3 (3e6 CD33CART/kg)	7 patients treated – *accrual complete*	no CART expansion or anti-tumor effects
MTD → 4 (1e7 CD33CART/kg)	13 patients treated – *accrual complete*	CART expansion 10 patients – evaluable 2 patients – complete response (no MRD for 90 days); 1 w/ successful HCT

Recent Updates

- Autologous arm has been halted for futility
- Abstract was presented at 2023 ASH Annual Meeting
- IND amendment to support manufacture of allogeneic CD33CART cells from healthy donors matched to the AML patient recipients.

Centralized GD2 CART Cell Manufacturing for Multi-site Clinical Trial

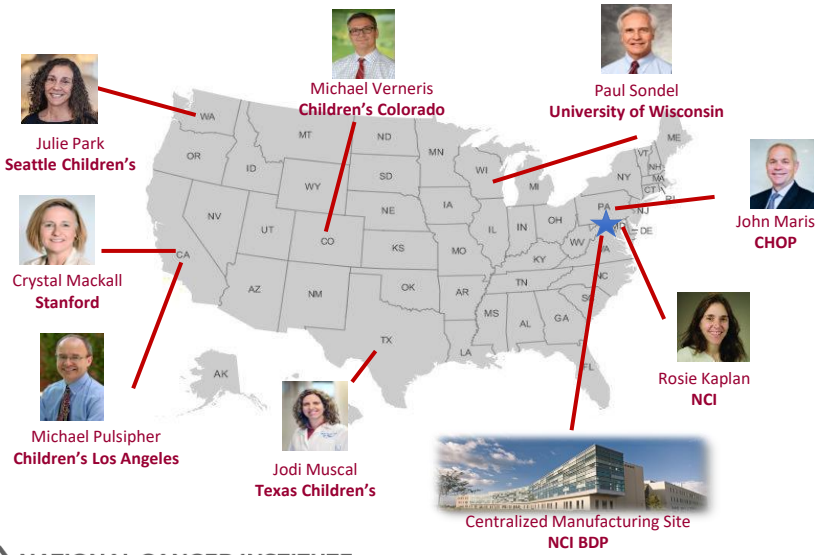
Description

Title: GD2-CAR PERSIST: Production and Engineering of GD2-Targeted, Receptor Modified T Cells (GD2CART) for Osteosarcoma or Neuroblastoma to Increase Systemic Tumor Exposure (NCT04539366)

IND Sponsor: NCI/DCTD
Study PI: Rosie Kaplan, MD (NCI)

Manufacturing Sponsor: NCI/DCTD
Trials Network: Pediatric Early Phase Clinical Trials Network (PEP-CTN)

Clinical Sites & Leads



Accrual Status

Cohort	Status	Observations
1 (1e6 GD2CART/kg)	6 patients treated- *accrual complete*	DLT toxicity observed in 2 patients: MTD exceeded
2 (3e6 GD2CART/kg)	*MTD exceeded at DL1*	
-1 (3e5 GD2CART/kg)	*1 patient treated*	

Recent Updates

- NIH Clinical Center, Stanford, CHOP and CHLA Sites are active
- Enrollment paused for transition to PEP-CTN

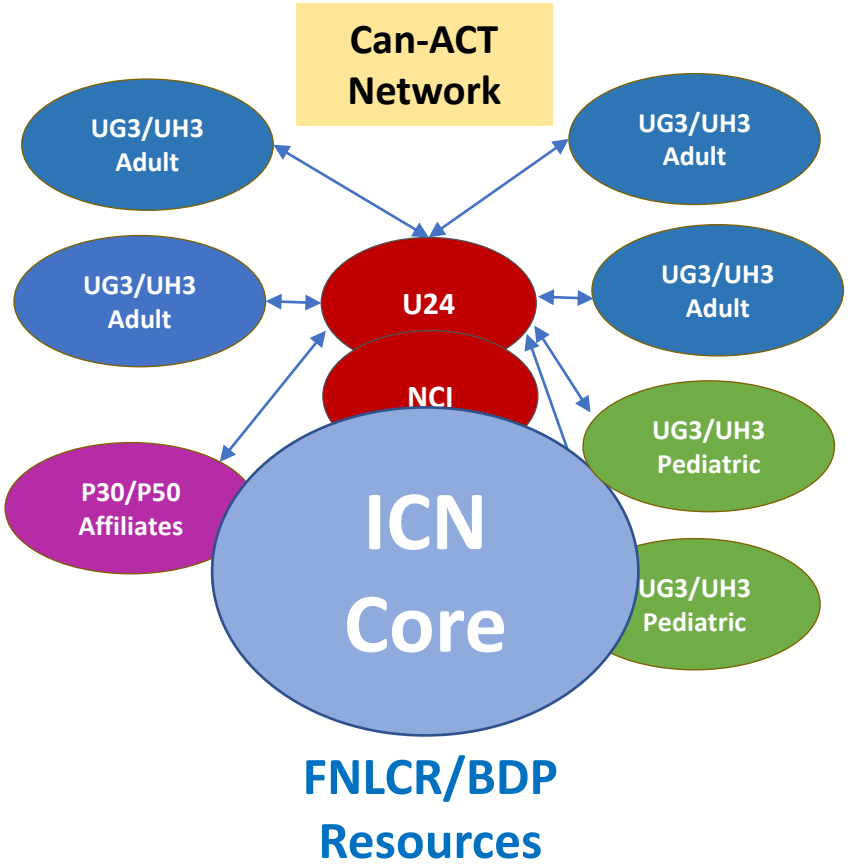
Can-ACT: Cancer Adoptive Cell Therapy Network

The purpose:

- To foster innovation and promote early-stage clinical testing of novel state-of-the-art cell-based immunotherapies for solid tumors **in adults and pediatric patients** and leverage NCI resources to support the cell therapy community

The goals:

- Develop and enhance immune cellular products modified genetically or through other manipulations for the treatment of adult and pediatric patients with solid tumors
- Support early phase clinical trials
- Explore imaging and biomarker development
- Expand our understanding of the mechanism of action as well as natural and acquired resistance
- Evaluate strategies to modulate the immunosuppressive tumor microenvironment



Can-ACT UG3/UH3 Network

ICN Core / BDP Support for Three of the Four Current Grantees

ICN Core Support

Marcela Maus: Massachusetts General Hospital

- CAR T cell strategy
- Dual targeting: CAR – mesothelin; trafficking FAP-CD3

Beatriz Carreno: University of Pennsylvania

- TCR T cell strategy targeting mKRAS G12V (HLA-A*11:01)
- Knockout TCR and exhaustion
- Myeloid checkpoint inhibitor (scFv)

Prasad Adusumilli: Memorial Sloan Kettering Cancer Center

- CAR specific for mesothelin
- CD28 ad KITv costimulatory domains
- PD1DNR checkpoint blockade
- Non ablative, tumor-targeted RT

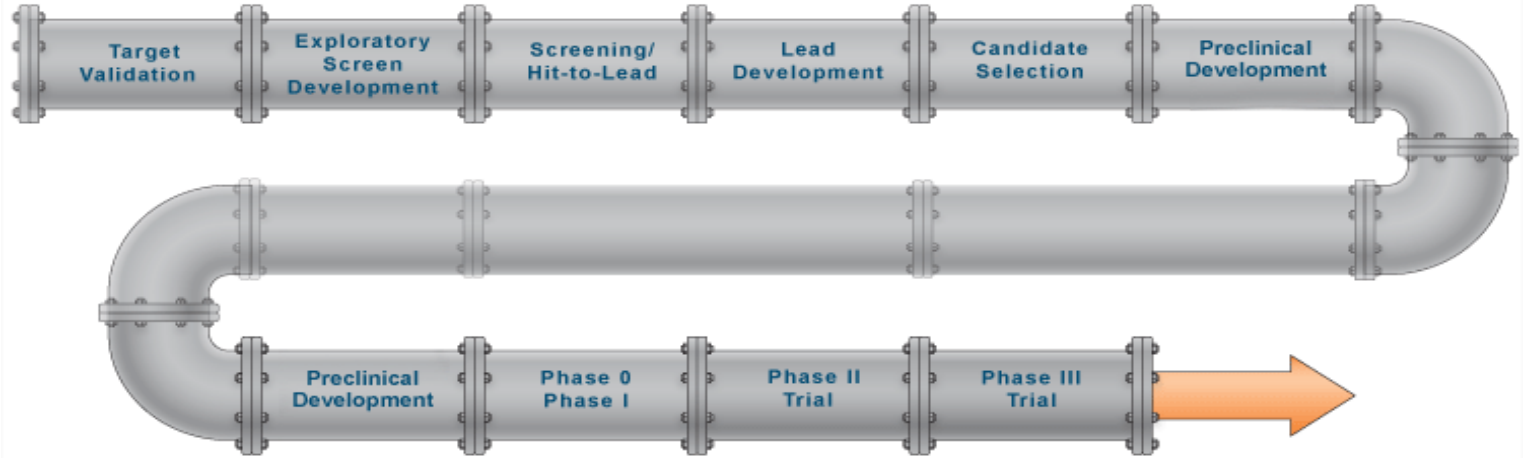
BDP Task Areas:

- Quality Systems and Regulatory Affairs Guidance
  - Develop and standardize assays for product critical quality attributes
  - Provide reagents and SOPs to Network members
  - Provide regulatory guidance – GxP audits, assistance with IND submission, etc.
- Multi-site Trial cGMP Production
  - Provide viral vectors and cell products with logistics for multi-site trials
  - Assess and develop novel production technologies

Access to the BDP

NCI Experimental Therapeutics Program - NExT

https://next.cancer.gov

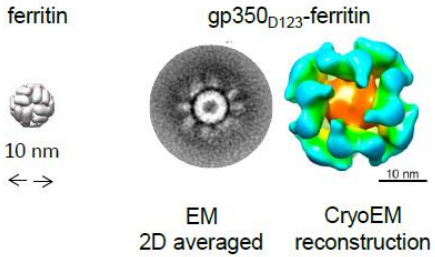


- Not a grant; no funding is provided to applicant
- Requires a clear path to the clinic and/or patient benefit
- Provides access to NCI drug development resources
- Applicant is a key member of the Project Team: involved in project planning, implementation, and has full access to data
- Free consultation service is available

Collaborations with BDP

NIAID/NCI Collaboration to Manufacture Ferritin Nanoparticle EBV Vaccines

Jeffrey Cohen, M.D.



Product	Type	Qty.	Release Date
EBV gp350 Lot L1804003	FVP	795 vials	6/8/2020
Diluent for EBV Vaccine Lot L1910004	FVP	5,125 vials	4/17/2020
EBV gHgLgp42 Lot L2001009	FVP	5,544 vials	12/9/2021

Clinical Trial Status

- Phase 1 Study of the Safety and Immunogenicity of an Epstein-Barr virus (EBV) gp350-Ferritin Nanoparticle Vaccine in Healthy Adults With or Without EBV Infection — Active IND
- Phase 1 Study of the Safety and Immunogenicity of a Combination of Epstein-Barr virus (EBV) gp350-FNP and gHgLgp42-FNP Vaccines in Healthy Adults With or Without EBV Infection — Pending IND

Ongoing Collaborations

- Collaboration with the Korean National Cancer Center under a MOU in place with NCI:
  - Initial meeting with BDP cell therapy staff and a tour of the GMP, QC, and R&D labs
  - Potential collaborations include DCTD hosting a visiting scientist and providing guidance on establishing a BDP-like program in Korea
  - SOP exchanges have been initiated

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Ongoing Collaborations

- BDP was invited to contribute to Health and Environmental Sciences Institute (HESI)'s Cell Therapy-TRAcking, Circulation, & Safety (CT-TRACS) Committee Efforts to address iPSC safety and regulatory hurdles:
  - BDP is generating iPSC safety data in alignment with their efforts on CRISPR-based technology development
  - Study Title - "*Multi-site Study with Droplet Digital PCR (ddPCR) for the Detection of Undifferentiated Pluripotent Stem Cells*"

Ongoing Collaborations

- Discussions with NIST Flow Cytometry Standard Consortium and contribution of expertise to two working groups of the consortium:
  - Assay Standardization Working Group to enable more comparable and quantitative assays commonly used for cell and gene therapy
  - Gene Delivery Systems Working Group to develop measurement solutions and standards for gene delivery systems, both viral and non-viral

NIST
National Institute of Standards and Technology
U.S. Department of Commerce

BDP SOPs and Regulatory Guidance

https://frederick.cancer.gov/research/biopharmaceutical-development-program

- Over 300 SOPs for manufacturing, testing, and quality systems

Patient Impact

In July 2023, BRB and BDP hosted a visit by the Sandi and Lindberg families, who are active advocates for pediatric cancer research, and Nirali Shah (POB/CCR).

- Visitors included Carlos Sandi *(St. Baldrick's Empowering Pediatric Immunotherapies for Childhood Cancer Team (EPICC) advocate)*, Tina Sandi, and their son Phineas who was successfully treated by Nirali in an earlier CD19 CART trial for ALL.
- Gavin Lindberg *(The EVAN Foundation and St. Baldrick's EPICC advocate)*, whose son Evan lost his battle to neuroblastoma also participated.
- BDP provided a tour and demonstrations of the development, manufacturing, and analytical labs and equipment used for CART production.
- In an all-hands meeting following the tour, the visitors discussed the impact that these therapies have had on patients' lives.

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Jeff Cohen

THANK YOU!

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