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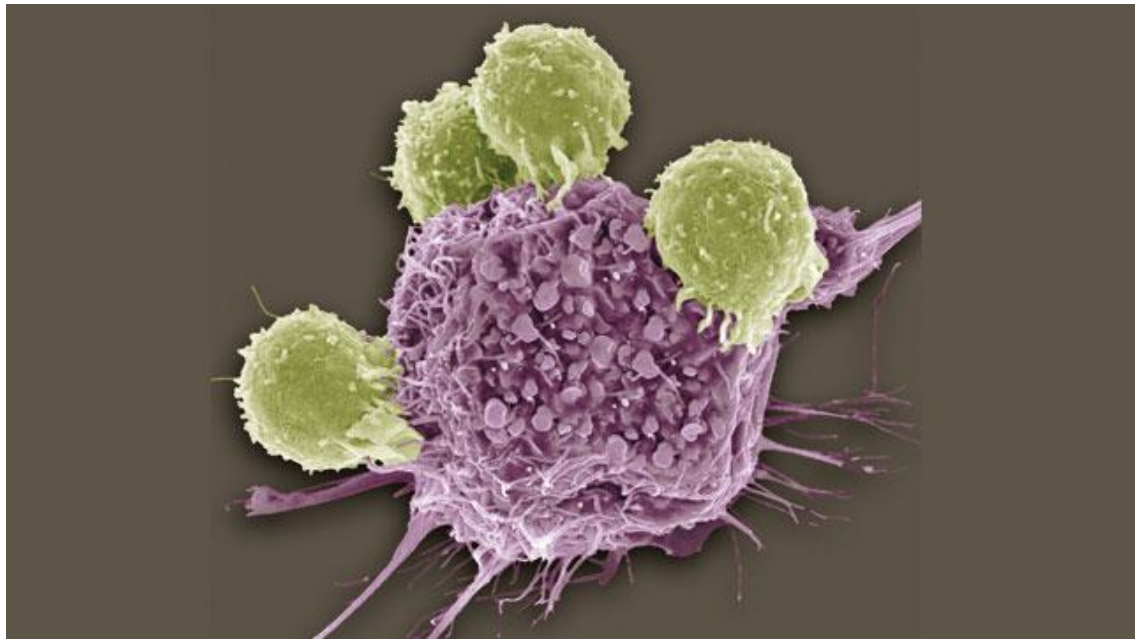
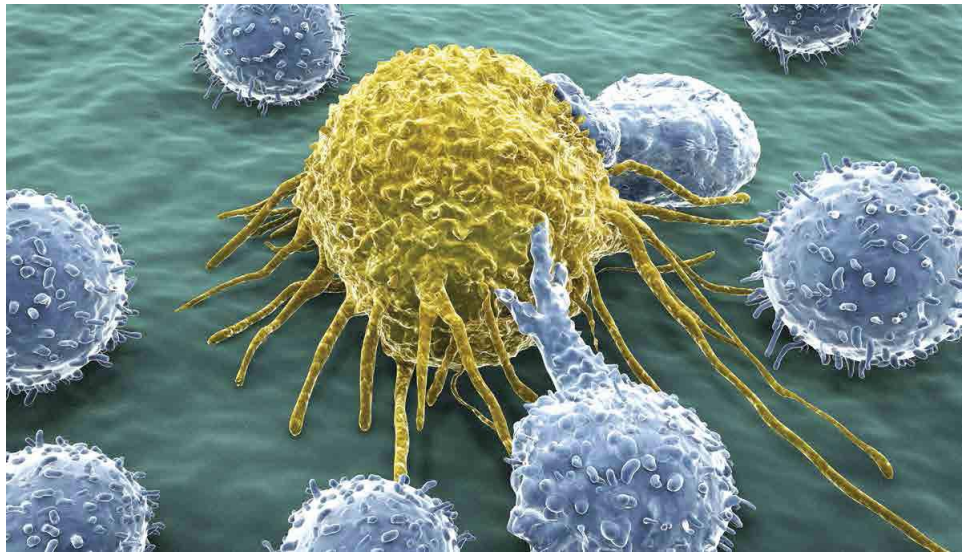
Communicating FNL Services to Scientific Community: Vector Manufacturing Services and Cell Therapy

Rose Aurigemma, PhD
Acting-AD, Developmental Therapeutics Program
DCTD, NCI





June 28, 2020
FNLAC

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Topics

- Review of progress since July 2020
  - Community engagement: Workshop
  - Facility upgrades
  - Capability updates
- Filling the queue
  - Outreach efforts
  - Additional path to support

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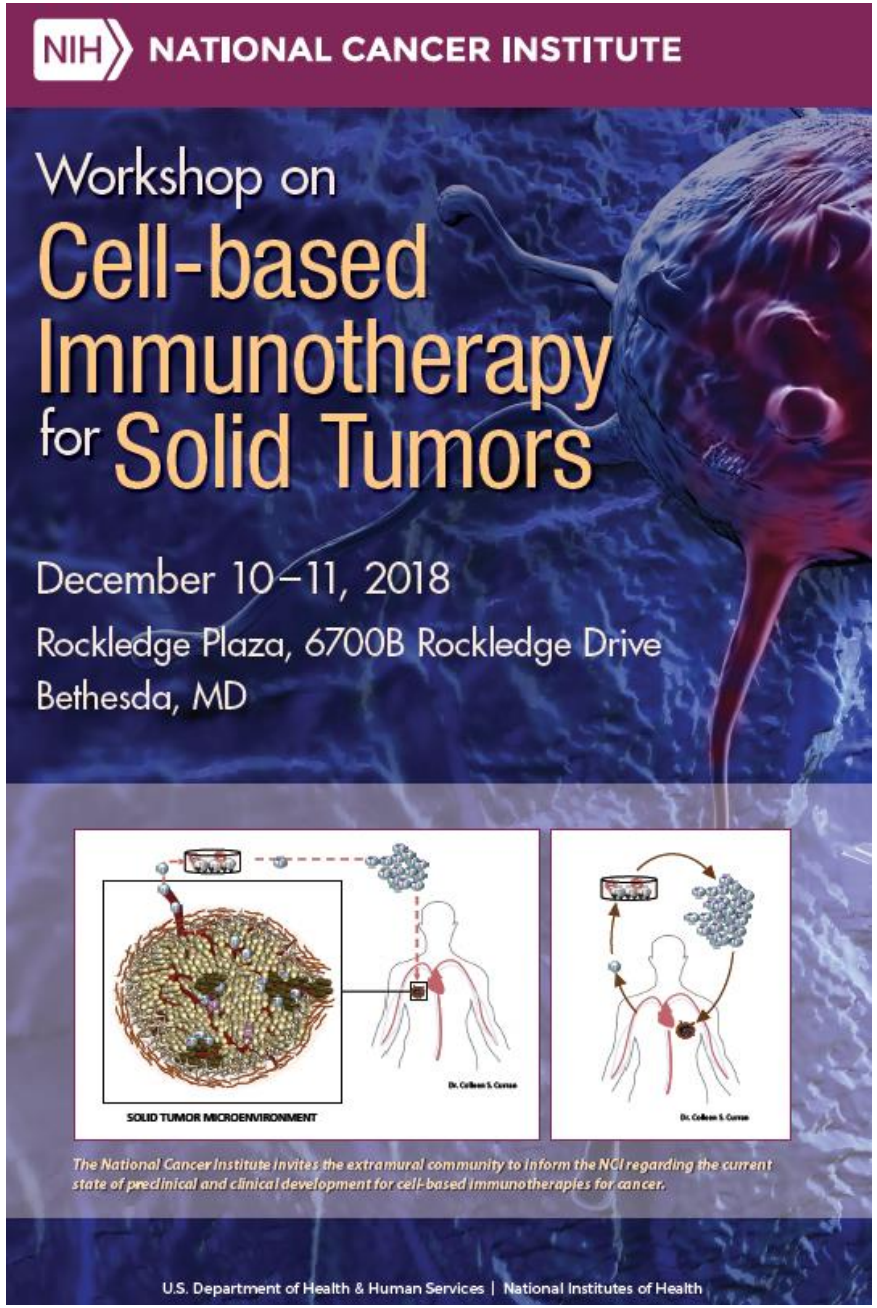


1st NCI Workshop – December 2018

Consensus regarding gaps/opportunities

Research needed:

- Targeting with precision
- Trafficking, tumor penetration
- Non-invasive imaging
- Overcome inhibitory TME
- Explore autologous vs. allogeneic.
- *In vivo* gene editing of immune cells

Clinical development challenges

- Cost, specialized protocols

Technology challenges:

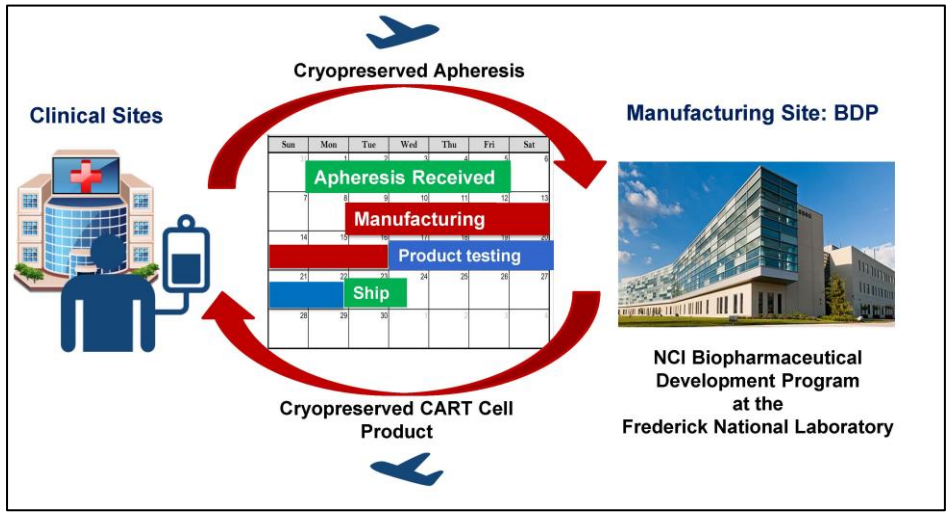
- Gene transfer, cell production

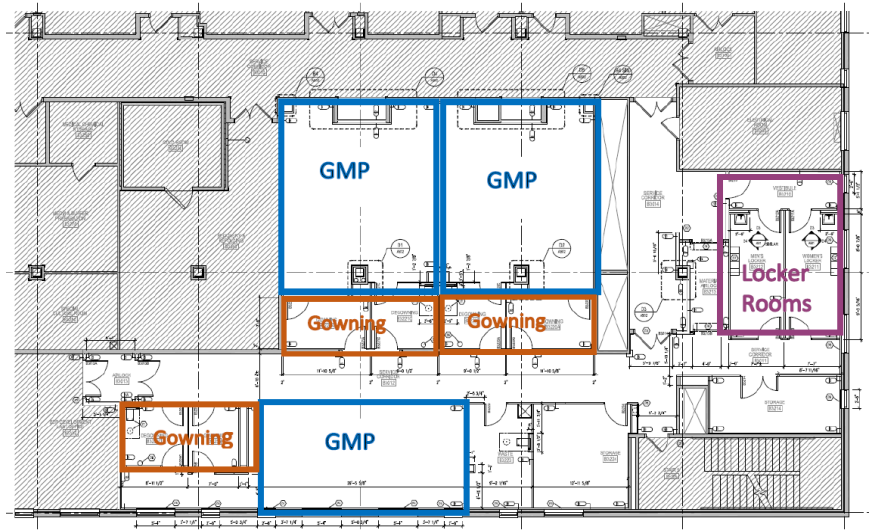
Regulatory challenges

- Unclear guidelines, lack of flexibility

Support for Cell Therapy Development: 2018 to 2021

- New GMP cell therapy/QC suite online Sep 2020
- Virus Production Facility returned to viral vector manufacturing
- IND for anti-GD2 CAR T; now supporting two multi-center autologous cell therapy clinical trials
- Renovation underway for 3 additional GMP suites for flexible cell therapy-related activities





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Support for Cell Therapy Development: 2018 to 2021

- Cell therapy-related SOPs online; over 300 SOPs for GMP biopharmaceutical manufacturing
- Supported 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 process for manufacturing lentivirus and retrovirus products for cell transduction
- CRISPR/cas-based editing development started in September 2020

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

September 2020: Marc Ernstoff, MD
Medical Officer & Chief, ImmunoOncology Branch

Yale U: Medical Oncology and cancer immunology training
U Pittsburgh Cancer Institute: medical oncology and translational immunotherapy program
Dartmouth College's Geisel School of Medicine: Section Chief of Hematology/Oncology & Dep Dir of the Norris Cotton Cancer Center
Cleveland Clinic: Director of the Melanoma Program
Roswell Park Comprehensive Cancer Center: Professor & Chair, Dept of Medicine, SVP for Clinical Investigation, Katherine Anne Gioia Chair of Medicine

- 40 years experience studying immunobiology of human cancer, developing new immune therapies
- 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.

NCAB Ad Hoc Subcommittee on Experimental Therapeutics: Reconvened

- Advise DCTD on opportunities to assist the extramural community to discover and develop new cancer treatments
- Priority topics from September 2020 NCAB:
  - Cellular immunotherapies and other complex biologics for cancer
  - Intelligent drug discovery based on biochemistry, structure, and mechanisms, including artificial intelligence-driven drug discovery

2nd NCI Workshop – December 2020

- Between 650-900 participants logged into meeting each day
- Workshop report drafted; *In press* at JITC

Active Scientific Questions: 2nd Workshop

- Solid tumor challenges
  - Inhibitory tumor microenvironment
  - Targeting, cell trafficking, tumor penetration
  - Better efficacy, avoid on-target/off-tumor toxicity
- Understanding cell product critical quality attributes
  - Predicting/controlling cell activity, persistence, function
  - Durable anti-tumor immunity
- More facile cell engineering process
  - Cell transduction methods, specialized GMP reagents
- 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

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Persistent Logistics Challenges: 2nd Workshop

- Reagent and equipment availability
  - Specialized reagents to select and sort cells
  - Specialized equipment to manufacture and characterize products
- Access to manufacturing GMP vectors, reagents, cells
  - Need faster queue, flexibility for variety of products
  - 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

Established DCTD Cell Therapy "Think Tank"

Developmental Therapeutics Program (DTP)
Cancer Therapy Evaluation Program (CTEP)
Cancer Imaging Program (CIP)
Cancer Diagnosis Program (CDP)

Merge expertise to support cancer cell therapy enterprise and create opportunities to support innovation and progress

Status of clinical trials supported by manufacturing at NCI/FNLCR

Clinical Trial	Sponsor	Status
Phase 1/2 Study of Anti-CD33 Chimeric Antigen Receptor Expressing T-Cells (CD33CART) in Children and Young Adults with Relapsed/Refractory AML	Pediatric Blood & Marrow Transplant Consortium (PBMTC)	• IND: July 2019 • First Subject: Feb 2020 @ CCR • Dosing in 3rd cohort; 8 patients so far, 9th product ready to be dosed at CHOP • No SAEs, seeking to add additional cohort
GD2-CAR PERSIST: Production and Engineering of GD2-Targeted, Receptor Modified T Cells for Sarcoma and Neuroblastoma to Increase Systemic Tumor Exposure	NCI/CTEP Pediatric Cancer Immunotherapy Trials Network (PED-CITN)	• IND submitted September 2020; approved October 2020 • Enrollment imminent at NIH clinical center

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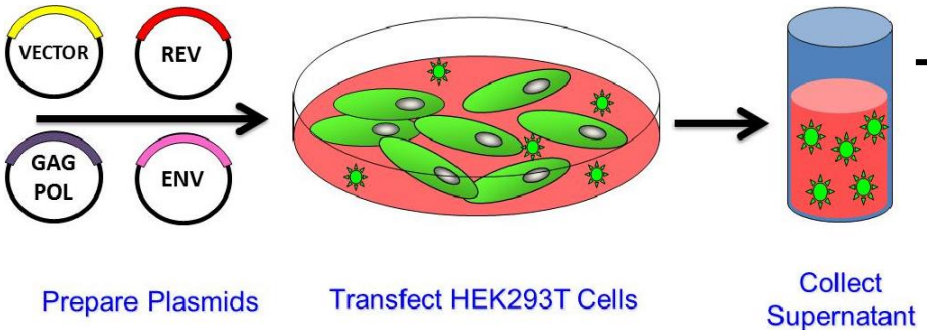
Cell Therapy & Virus Manufacturing Capacity: June 2021

Product Type	Status/Capacity
Autologous cell therapy	• Current: Prodigy-based only • 4 products/ month
Lentivirus vectors	• cGMP process enabled • 4 campaigns per year
Gamma retrovirus vectors	• cGMP process enabled • 4 campaigns per year
Cell therapy or virus vectors	• 3 new suites opening in 2022 • Capacity is product-type dependent (i.e. autologous, allogeneic, manufacturing platform)
CRISPR-based gene editing	• Process development underway

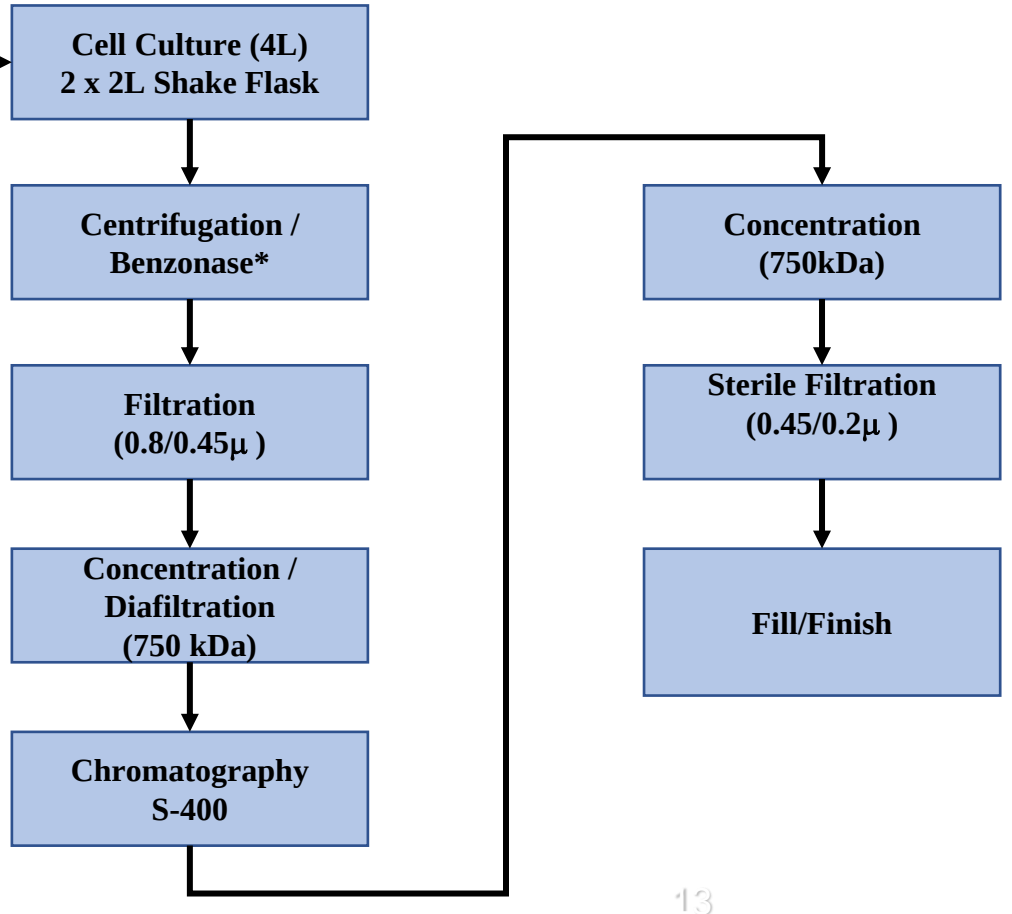
NCI/FNLCR lentivirus production platform

4-plasmid transient transfection, suspension-cell platform



Pilot project: *IL12 lentivirus genetically engineered myeloid cells (GEMys) to limit metastatic progression of solid tumors*

Rosandra Kaplan, MD
Pediatric Oncology
Branch, CCR, NCI, NIH



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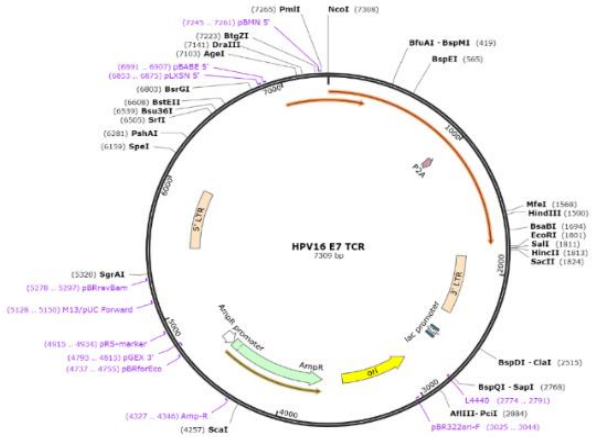
NCI/FNLCR gamma-retrovirus production platform

1-plasmid transient transfection, suspension-cell platform

- Cell line: 293Vec RD114
  - Adapted by BDP to Serum-Free / Suspension
  - MTA Signed between NCI and Biovec Pharma, Canada
- GOI plasmid: Addgene Cat# 122728
- Envelope plasmid: RD114
- Production Method: Transient Transfection

Vector	TCRE7 Physical Titer (Sup-T1) (TU/ml)
NIH/CC (Adherent/Serum) HPV16 E7 TCR	3.4 ± 0.08 X 10^6
FNLCR/BDP (Suspension/Serum-free) HPV16 E7 TCR	2.2 ± 0.3 X 10^6



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June 2021: Virus Development Projects

- **CD123xCD3 RetroV** to engineer CD123xCD3 BiTE-secreting autologous T cells for recurrent/refractory CD123+ myeloid malignancy
  - Collaboration between CCR, NHLBI, NIH Clinical Center, Johns Hopkins School of Medicine. Lead PI: Dr Steven Pavletic, M.D., M.S., ID-CTP, CCR

- **SSTR2 RetroV** for imaging by 68Ga-DOTATATE PET of subjects treated with SSTR2-transduced TIL
  - Lead PI Dr. Scott M. Norberg, D.O., Assistant Research Physician, Genitourinary Malignancies Branch, CCR

- **hYP218 LentiV and CAR T** production to treat mesothelioma
  - Lead PI: Dr Raffit Hassan, M.D., Chief, Thoracic and GI Malignancies Branch, CCR

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NCI/FNLCR CRISPR/Cas9-based gene editing

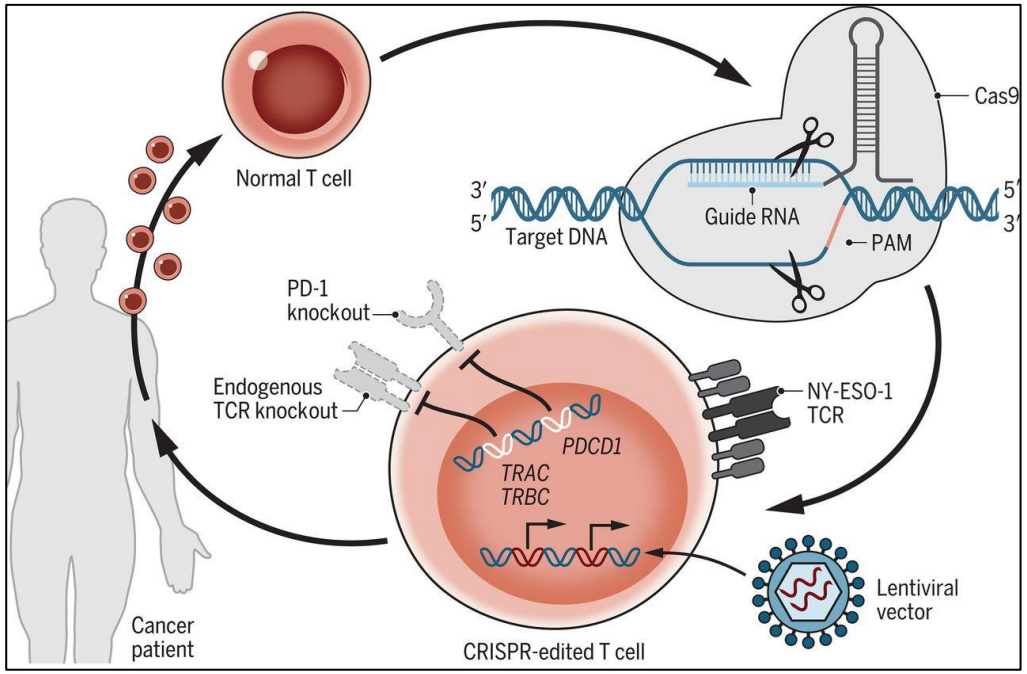
RESEARCH

RESEARCH ARTICLE SUMMARY

CLINICAL TRIALS

CRISPR-engineered T cells in patients with refractory cancer

Edward A. Stadtmauer*†, Joseph A. Fraietta*, Megan M. Davis, Adam D. Cohen, Kristy L. Weber, Eric Lancaster, Patricia A. Mangan, Irina Kulikovskaya, Minnal Gupta, Fang Chen, Lifeng Tian, Vanessa E. Gonzalez, Jun Xu, In-young Jung, J. Joseph Melenhorst, Gabriela Plesa, Joanne Shea, Tina Matlawski, Amanda Cervini, Avery L. Gaymon, Stephanie Desjardins, Anne Lamontagne, January Salas-Mckee, Andrew Fesnak, Donald L. Siegel, Bruce L. Levine, Julie K. Jadlowsky, Regina M. Young, Anne Chew, Wei-Ting Hwang, Elizabeth O. Hexner, Beatriz M. Carreno, Christopher L. Nobles, Frederic D. Bushman, Kevin R. Parker, Yanyan Qi, Ansuman T. Satpathy, Howard Y. Chang, Yangbing Zhao, Simon F. Lacey*, Carl H. June*†



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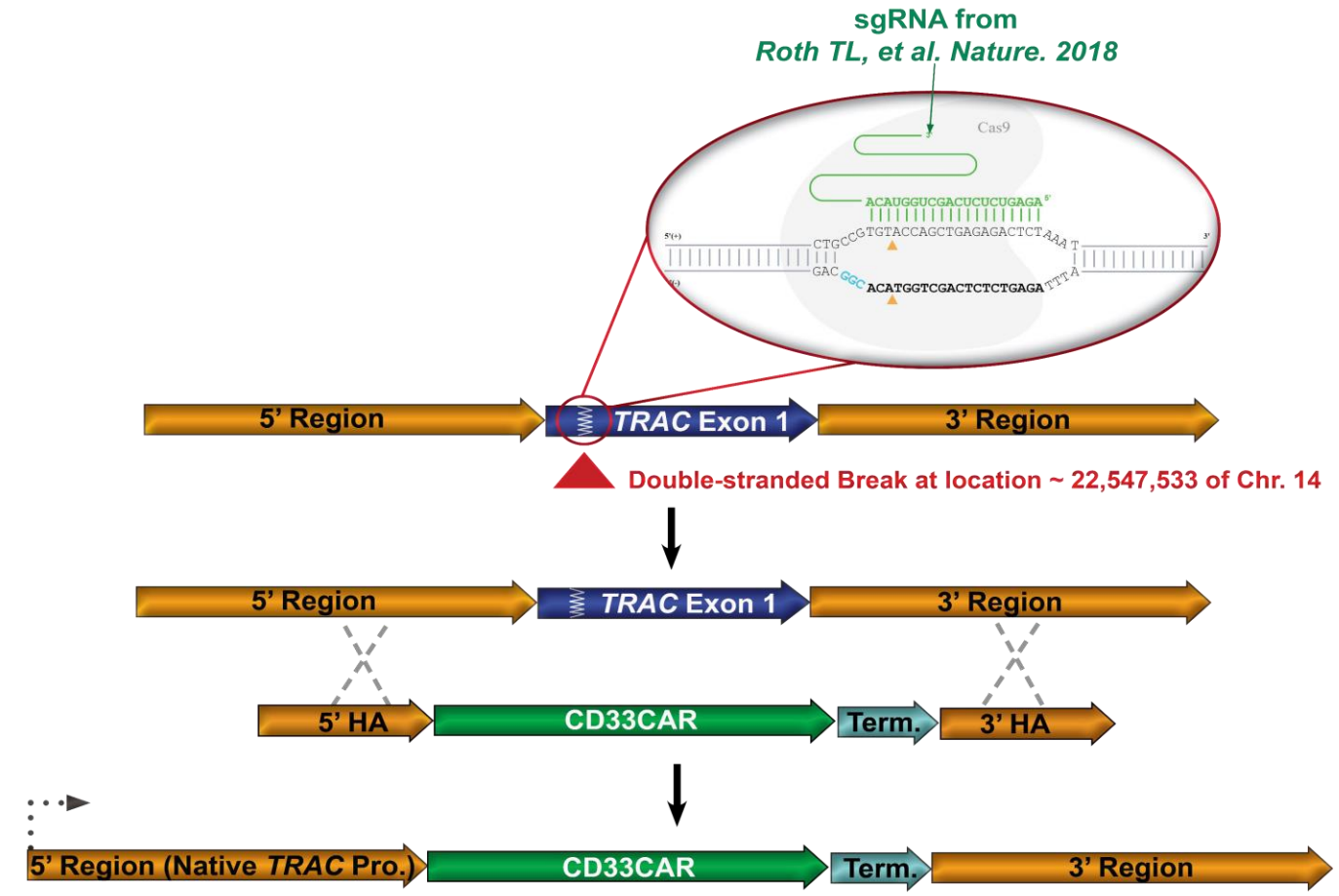
NCI/FNLCR CRISPR/Cas9-based gene editing

1. Genomic *TRAC* Locus edited by RNP complex (sgRNA (Marson) + Cas9)
2. Homology-directed Repair with ssDNA HDR template delivered by **Electroporation**
3. Integration of HDR Template onto *TRAC* Locus and CAR Expression Driven by Native *TRAC* Promoter



NCI/FNLCR CRISPR/Cas9-based gene editing

CRISPR/Cas9-based gene Knock-Out

- TCRA locus selected for knock-out
- sgRNA screened and one selected based on indels and knock out rate (>90%)
- Studying on target indels – identified using Sanger sequence method
- Off target probe insertion by NGS study in progress

Gene Knock-In with HDR ssDNA

- GFP and CD33CAR were tested for knock-in at TRAC locus
- CD33CAR showed > 20% knock-in; Studies are in progress for confirmation
- CD33 CAR off target insertion by NGS in progress

NCI/FNLCR Expand Production Platform Expertise

- Current production platform is CliniMACS Prodigy

- Beginning to work with G-Rex (Gas Permeable Rapid Expansion)

- Greater scalability
- Flask dedicated to one patient

Building the queue: Outreach Efforts

- DCTD News stories – DCTD website has announced workshop proceedings, grant supplements, and updates on the facilities and capabilities
- DCTD Twitter posts
- Emails to NCI grantees with links to information re: available resources
- Dr. Sharpless has mentioned at advisory council meetings
- Informational slide inserted into talks by DCTD staff
- NCI video: https://www.cancer.gov/news-events/cancer-currents-blog/car-t-cell-manufacturing-cancer-clinical-trials-video
- NCI blog: https://www.cancer.gov/news-events/cancer-currents-blog/2020/car-t-cell-nci-manufacturing-clinical-trials

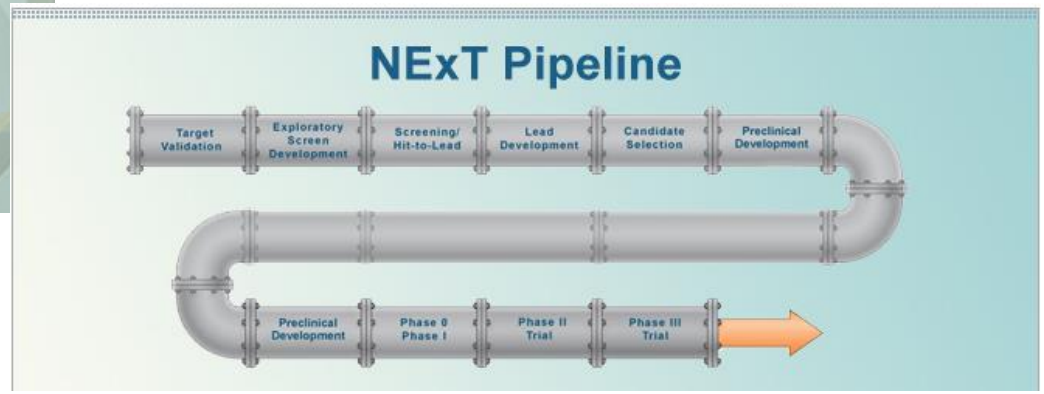
Building the queue: Additional Access Path

May 2021: DCTD Deputy Director Dr. Toby Hecht sent email to over 1000 recipients: “A new resource from the NCI”

- Grantees, Cancer Centers, SPOREs, NCI Cell Therapy Workshop registrants
- Invited to submit Letter of Intent to receive cGMP DNA as a raw material to modify cells directly or for production of viral vectors for cell-based immunotherapy trials
- Five Letters of Intent received
- Three invited proposals under review

Increase in extramural proposals for cell therapy-related resources

- Services for developing small molecules, biologics and cell therapies
- Proposals due Feb 15, June 15, October 15



https://next.cancer.gov

2018 – 2020 Received 3 cell therapy proposals
2021 Received 4 proposals

DTP/DCTD Preclinical Development Consultation Service

https://next.cancer.gov/experimentalTherapeutics/form.htm

- Confidential
- Provides broad product development
- Small molecules, biologics, cell therapies