Cancer Adoptive Cellular Therapy Network (Can-ACT)

RFA-CA-22-028 (adult UG3/UH3)
RFA-CA-22-029 (pediatric UG3/UH3)
RFA-CA-22-030 (U24 Coordinating Center)

Division of Cancer Treatment and Diagnosis
National Cancer Institute

NIH NATIONAL CANCER INSTITUTE

September 7, 2022

Webinar Participants
Division of Cancer Treatment and Diagnosis

- Developmental Therapeutics Program – Associate Director, Dr. Rose Aurigemma
- ImmunoOncology Branch – Dr. Marc Ernstoff, Branch Chief
  - Dr. Anju Singh, Program Director
  - Dr. Zhang-Zhi Hu, Program Director
  - Dr. Connie Sommers, Program Director
- Biological Resources Branch – Dr. Jason Yovandich, Branch Chief
  - Dr. Kasia Bourcier, Program Director
- Information Technology Branch- Dr. Ronald Taylor, Branch Chief

Webinar Participants
Division of Cancer Treatment and Diagnosis

- Cancer Diagnosis Program
  - Diagnostics Evaluation Branch – Dr. Nina Lukinova, Program Director

- Cancer Imaging Program – Associate Director, Dr. Janet Eary
  - Molecular Imaging Branch – Dr. Chiayeng Wang, Branch Chief
  - Dr. Yisong Wang, Program Director
- Cancer Therapy Evaluation Program – Dr. Nita Seibel, Medical Office
  - Clinical Grants and Contracts Branch – Dr. Lori Henderson, Branch Chief

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Marc Ernstoff, MD

ImmunoOncology Branch
Division of Cancer Treatment and Diagnosis
National Cancer Institute

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NCI Workshops on Cellular Therapies for Solid Tumors Unmet Needs

- Research areas of unmet need:
  - Preclinical and translational research to advance cell therapy for solid tumors in both adult and pediatric patients.
  - Small proof of concept studies to rapidly gain knowledge of promising new treatment approaches.
  - Enhancement of cell manufacturing technologies (new cell expansion methods, genetic engineering, optimization of closed system manufacturing, new strategies for cell product screening, etc.)
  - Identification of biomarkers and imaging-based detection of response to therapy.
- Needed services identified:
  - Standardization of cell product characterization through a core laboratory.
  - QC testing for cell therapy-related reagents (e.g., GMP vectors) needed for manufacturing.
  - Guidance for investigators on preparing IND submissions.

NCI Programmatic Objectives

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.

The Organization of the Can-ACT network

- **Three companion FOAs** for the Can-ACT network
  - Can-ACT for Adult Cancers (RFA-CA-22-028)
  - Can-ACT for Pediatric Cancers (RFA-CA-22-029)
  - Can-ACT Coordinating Center (RFA-CA-22-030)
- **The grant mechanisms**: two-phased UG3/UH3 and U24

Single application

  - UG3: preclinical, IND enabling studies, two-year maximum, milestone driven
  - UH3: clinical trial implementation, up to three years; administrative review for the transition
  - U24: coordinating Center, up to five years; no clinical trials allowed
- **Resources provided by NCI** - Immune Cell Network (ICN) Core at FNLCR
  - Quality oversight: provide GCP/GMP/GCLP compliance evaluation
  - Product evaluation: develop and standardize assays for cell therapy products
  - cGMP production for multi-site trials: produce, test, release and distribute cell product

Can-ACT Funding Opportunity
UG3 Phase - Requirements

- The UG3 should address at least **two objectives** that will advance a new cell therapy concept to clinical testing for treating adult or pediatric cancers, for example:
  - Improve cell therapy genetic modifications and/or cell therapy manufacturing
  - Modulate the immunosuppressive TME to enhance cell therapy efficacy
  - Develop biomarkers for cell product activity and host response to guide therapy
  - Optimize existing imaging agents and quantitative tools for monitoring cell trafficking, tumor infiltration, antitumor effects, etc.
  - Develop new imaging agents/approach for longitudinal imaging of cell persistence and long term activity
  - Use combined imaging and biomarker approaches to monitor disease and response
- Clear description of milestone and a go/no go approach
- UG3 phase lasts up to 2 years and must clearly outline milestones and go/no go criteria for potential transition to UH3.

Can-ACT Funding Opportunity
UH3 Phase - Requirements

- The **UH3** phase is included in the 12 page application and must contain a clinical trial which can be completed in the time frame of the application
  - Provide a detailed outline of a sample proposed trial including treatment schema and a statistical plan within the application, as it is recognized that the final trial is predicated on successful completion of the milestones outlined in the UG3 phase.
  - Remember to use the Facilities and Other Resources section of the application to provide a description of the local cell production facilities if needed, pharmacy and blood bank facilities as well as the clinical outpatient and inpatient facilities.
  - Remember to use the Human Subjects to provide a details of patient populations including eligibility criteria, enrollment plan, safety monitoring plan, regulatory plans and reporting

- Single-site or multi-site clinical trials are both eligible

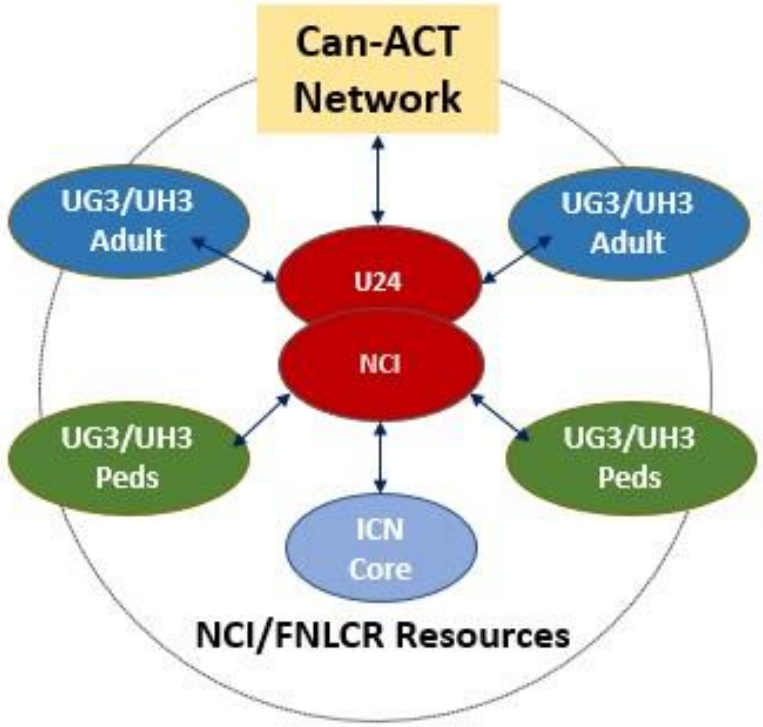
- For multi-site trials ICN Core at FNLCR cGMP support can be requested, while single-site is not eligible for the support

U24 – Requirements

The U24 Coordinating Center (CC) must include:

- Act as the hub for scientific and organizational leadership to the Can-ACT network.
- Facilitate collaborations within the network in conjunction with NCI staff.
- Establish a Steering Committee (SC) comprised of UG3/UH3 awardees, CC members, and representative from the ICN Core and NCI staff for governance of Can-ACT network.
- Operate as a supporting infrastructure for the network for providing both scientific and administrative coordination.

Can-ACT Organizational Structure



Network will be formed after grants are awarded

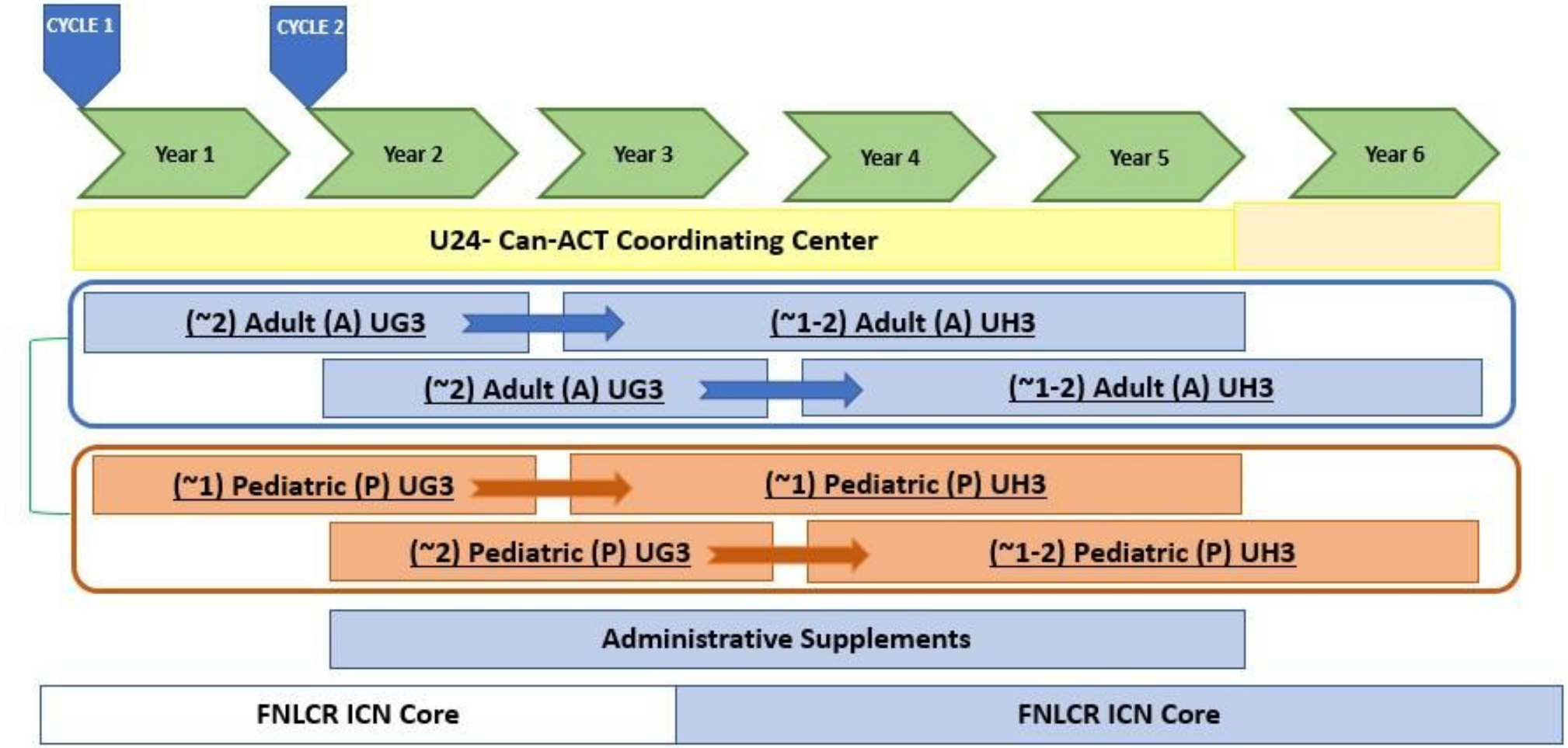
Structure:

- Separate **UG3/UH3** for *adult* and *pediatric* cancers (Total 7)
  - each **UG3/UH3** will conduct
    - Preclinical, IND enabling studies of ACT (UG3)
    - Early Phase clinical trials of ACT for solid tumors (UH3)
- **U24** Coordinating Center (One)
    - Scientific and administrative coordination

Networking and Synergy:

- **Steering Committee** consisting of U24 and UG3/UH3 PD/PIs, NCI extramural and intramural staff, associate members and expert advisors
- **Restricted funds** for intra-network collaborations
- **Working groups** address common goals, challenges, opportunities
- **Sharing** of tools, reagents, data, resources

Can-ACT Timeline and Components



UG3/UH3 – Administrative Supplements

Administrative Supplements will be available in years 2-5 for:

- **Enhancing** intra-network collaborations
- **Expanding** network participation to Spore or CCSG awardees
- **Investigating** newly identified scientific needs

Non-Responsive Applications

- **UG3/UH3 for adult** (RFA-CA-22-028) or **pediatric cancers** (RFA-CA-22-029)
  - Focus on hematological malignancies
  - Basic research and mechanistic studies
  - Animal model development
  - Applications lacking outline of a proposed clinical study protocol
  - Applications lacking milestones and go/no go decisions for UG3/UH3 phases
  - Propose Phase II/III registration trials
- **U24 Coordinating Center** (RFA-CA-22-030)
  - Focus on scientific hypothesis testing or technology development
  - Not address both scientific and administrative aspects of coordination
  - Not include description of collaboration with the ICN Core

Non-Responsive Applications

Read the Can-ACT RFA carefully:

- In initial planning, look for the **"must have" components**
- When writing, look for the **"Describe…" or "Address…" prompts** within each sub-section
- Place emphasis on what the reviewers are looking for in the **Scored Review Criteria** section
  - **"Specific to this FOA: …"**

Data Sharing and Consortium Integration

- Awardees are expected to adhere to Can-ACT data use and sharing policies:
  - Standard NIH Public Access, Data Sharing and Unique Resource Sharing policies
  - Deposition of data, protocols and SOPs with the Can-ACT U24 Coordinating Center
  - New NIH Data Management and Sharing (DMS) policy (effective January 25, 2023)

- Awardees are also expected to participate in Can-ACT Steering Committee (SC), monthly SC Meetings and annual Face-to-Face Meetings
  - The PD/PI is required to serve as a voting member of the Can-ACT U24 Coordinating Center established Steering Committee
  - Participate in regular conference calls with fellow network members
  - Participate and present findings at the annual Can-ACT investigators' meeting

The U24 Coordinating Center

Key Roles: Operate as supporting infrastructure and provide *administrative and scientific coordination* to support the UG3/UH3 awardees and the *Steering Committee.*

- **Scientific coordination**:
  - Organize, lead and administer Steering Committee (SC)
  - Coordinate collaborative research among Can-ACT members
  - Develop governance strategy for data elements requirement, collection and sharing
  - Coordinate receipt and facilitate review of the administrative supplements, etc.
- **Administrative coordination**:
  - Provide infrastructure and develop communication plans to facilitate network activities
  - Serve a communication hub for multi-center trial activities, provide guidance on best practice
  - Coordinate and support annual meetings
  - Facilitate procuring and sharing of reagents and specimens
  - Design and implement a process to establish standards for data types, formats and management

Mechanisms of Support & Funding – UG3/UH3

- **Mechanism of support**: UG3/UH3 Cooperative Agreement, open competition
  - *Used to accommodate substantive programmatic involvement to facilitate integration between UG3/UH3 and U24 grants.*
- **Application Type:** All submissions will be Type 1 (new applications) and Single or Multi-PI. *No resubmissions are allowed; a Leadership Plan is required for MPI applications.*
- **Budget:** Application budgets are limited to $900K/year (UG3) and $1,500K/year (UH3) in direct costs. *Applicants must budget for travel to annual Can-ACT meetings.*
- **Project Period:** Up to 5 years (2-year UG3 and 3-year UH3 after approval).
- **Note on Eligible Applicants:** Foreign (non-U.S.) institutions and components are not eligible to apply.
- **Anticipated Number of Awards:** 7 UG3/UH3 over two submissions

Mechanisms of Support & Funding – U24

- **Mechanism of support**: U24 Cooperative Agreement, open competition
  - *Used to accommodate substantive programmatic involvement to facilitate integration between UG3/UH3 and U24 grants*
- **Application Type:** All submissions will be Type 1 (new applications) and Single (1.8 effort CM) or Multi-PI (1.2 effort CM). *No resubmissions are allowed; a Leadership Plan is required for MPI applications*
- **Budget:** Application budgets are limited to $300,000/year in direct costs and a*pplicants must budget for travel to annual Can-ACT face-to-face meetings.*
- **Project Period:** Up to 5 years.
- **Note on Eligible Applicants:** Foreign (non-U.S.) institutions are not eligible to apply and foreign (non-U.S.) components are not allowed.
- **Anticipated Number of Awards:** 1 x U24.

Letter of Intent (LoI)

Highly encouraged, but not required. Not binding and does not enter into review.

Standard elements:

- Descriptive title of proposed activity
- Name(s), address(es), telephone number(s) of the PD(s)/PI(s)
- Names of other key personnel
- Participating Institution(s)
- Number and title of funding opportunity (RFA-CA-22-028, -029 or -030)

Additional recommended information:

- A brief summary of the Research Project
- Include relevant expertise and keywords

Email LOI to Kasia Bourcier (bourcierkd@nih.gov) by September 28, 2022

PHS 398 Research Plan (UG3/UH3): 12 Page Limit

All instructions in the SF424 (R&R) Application Guide must be followed, please see RFA for additional instructions:

Significance:

- How could the proposed UG3/UH3 Can-ACT cellular immunotherapy research project addresses gaps in cell therapies for solid tumors?

Approach:

- UG3 part must address at least two *hypotheses-driven objectives* that will advance a new cell therapy concept to clinical testing.
- Are the rationale and preliminary data for the proposed ACT clinical trials and correlative studies strong?
- Is the overall strategy appropriate to accomplish the specific aims?
- Are the cellular products available to initiate UH3 clinical trial, and accrual goals realistic?
- Is the overall timeline realistic?
- Are adverse events considered?
- Are pitfalls and alternative approaches presented and well-reasoned?

PHS 398 Research Plan: 12 Page Limit

Investigators and Environment:

- How well does the scientific environment at the participating site(s) stimulate scientific collaborations?
- Is expertise from human cancer researchers sought and incorporated?
- 1.8 (single PI) or 1.2 (MPI) CM effort throughout the life of the grant.
- Are the resource sharing plans conducive to the sharing of data, biological specimens, tools, reagents, therapeutics, genomic data, IP, know-how and proprietary techniques and inventions within and outside the institution, especially with other members of the Can-ACT?

Review Information

- Applications will be evaluated for scientific and technical merit by an appropriate Scientific Review Group convened by the NCI, using the *stated review criteria*.

- As part of the scientific peer review, all applications:
  - May undergo a selection process in which only those applications deemed to have the highest scientific and technical merit will be discussed and assigned an overall impact score – *applications will NOT be percentiled*.
  - Will receive a written critique.

Review Information (continued)

- The following will be considered in making funding decisions:
  - Scientific and technical merit of the proposed project as determined by scientific peer review
  - Relevance of the proposed project to program priorities
- Applications will compete for available funds with all other recommended applications submitted in response to these FOAs.
- Following initial peer review, recommended applications will receive a second level of review by the NCAB/NCI.
- The review panel roster will be available in eRA Commons 30 days prior to review. Applicants may contact the Scientific Review Officer with concerns prior to review.

Key Dates

LOI Due Date (Optional)	Application due Date (*U24 only has one due date)	Review Dates	Earliest Anticipated Start Date
September 28, 2022	*October 28, 2022	February-March 2023	July 2023
May 30, 2023	June 30, 2023	October/November 2023	April 2024

Agency Contacts
Division of Cancer Treatment and Diagnosis at NCI

- **Division of Cancer Treatment and Diagnosis at NCI**
- **Kasia Bourcier, PhD**
  - 202-657-758; bourcierkd@nih.gov
  - RFA-CA-22-028
  - RFA-CA-22-029
  - RFA-CA-22-030
- **Zhang-Zhi Hu, MD**
  - 202-731-8819; zhang-zhi.hu@nih.gov
  - RFA-CA-22-028
- **Anju Singh, BVSc, PhD**
  - 240-276-7603; anju.singh@nih.gov
  - RFA-CA-22-029

- Peer Review Contact:
  - NCI Referral Officer
  - 240-276-6390
  - ncirefof@dea.nci.nih.gov

- Financial/Grants Management:
  - Shane Woodward
  - 240-276-6303
  - woodwars@mail.nih.gov

THANK YOU!

QUESTIONS?

www.cancer.gov www.cancer.gov/espanol

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Structure:

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- Network will be formed after grants are awarded
- The U24 and NCI will be the hub for the Can-ACT Network and coordinate interaction between network members and the NCI/FNLCR Resources

Networking and Synergy:

- **Steering Committee** consisting of U24 and UG3/UH3 PD/PIs, NCI extramural and intramural staff, associate members and expert advisors
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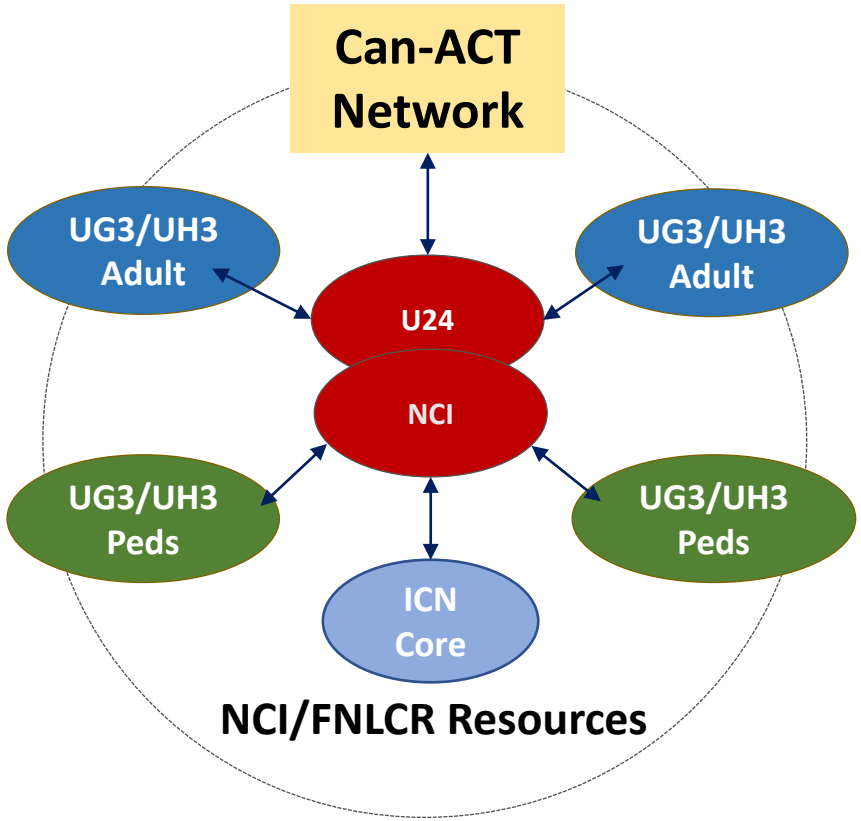
Can-ACT Timeline and Components

- Two dates for UG3/UH3 applications pre-year 1 and pre-year 2
- Separate UG3/UH3 awards for adult and pediatric cancers
- One date for UH3 application pre-year 1
- Each UG3/UH3 will be for 5 years with 2 years dedicated to UG3 phase and 3 years for the UH3 phase
- The U24 will be a 5-year award
- Administrative Supplements will be available in years 2-5 of the Network
- Additional support will be available for the FNLCR in year 3-6 to enhance cell production capacity

Can-ACT Organizational Structure



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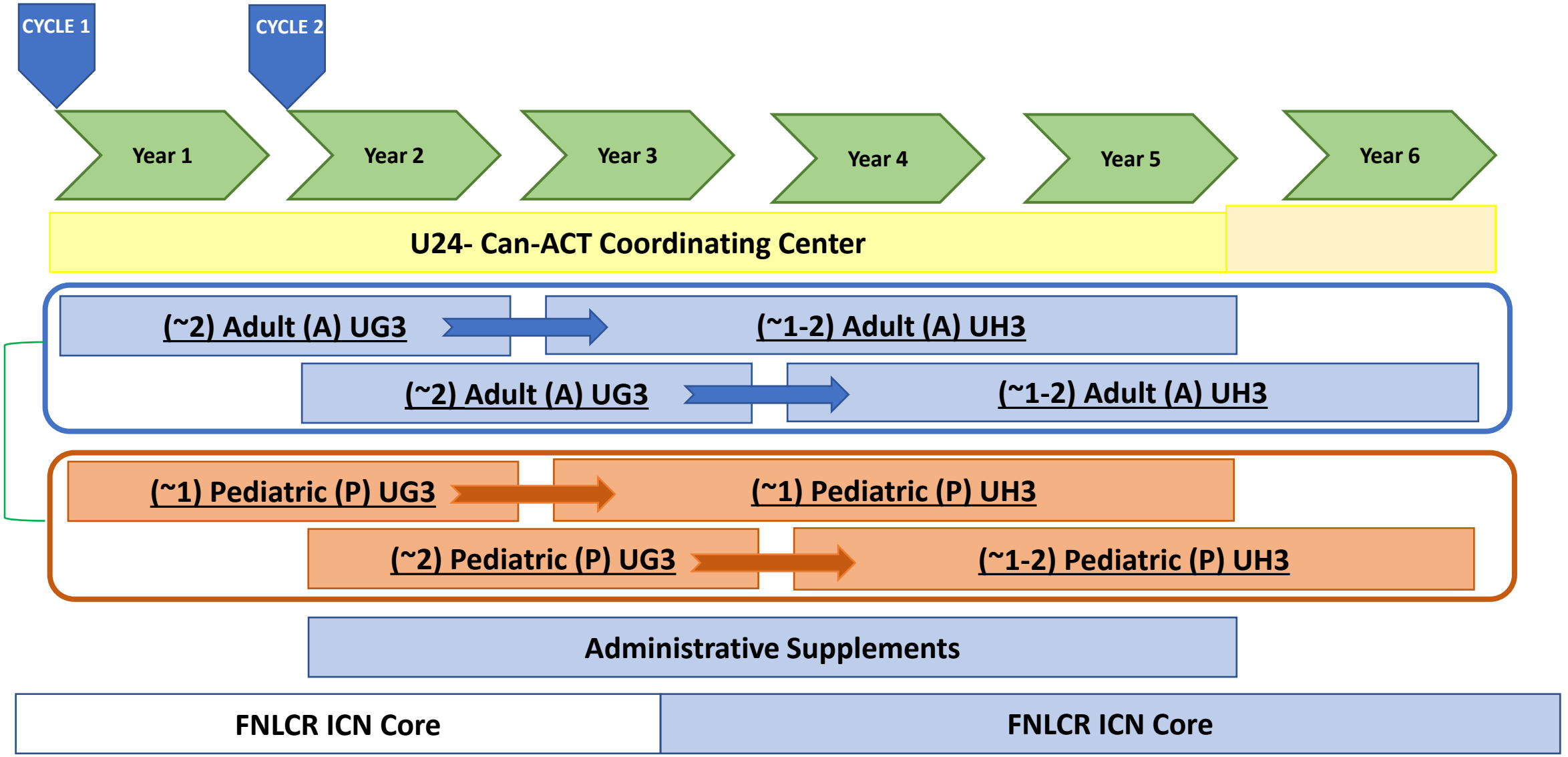

Agency Contacts

Scientific/Research Contacts:

Division of Cancer Treatment and Diagnosis at NCI

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Peer Review Contact:

NCI Referral Officer
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Financial/Grants Management:

Shane Woodward
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woodwars@mail.nih.gov

Can-ACT Pre-application Webinar:

Immune Cell Network (ICN) Core

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September 7, 2022

cGMP Production for Multi-site Trials:

Produce, Test, Release and Distribute Cell Therapy Products

Biopharmaceutical Development Program at the Frederick National Laboratory for Cancer Research

Biomanufacturing Resource Supported by NCI/DCTD

BDP Mission

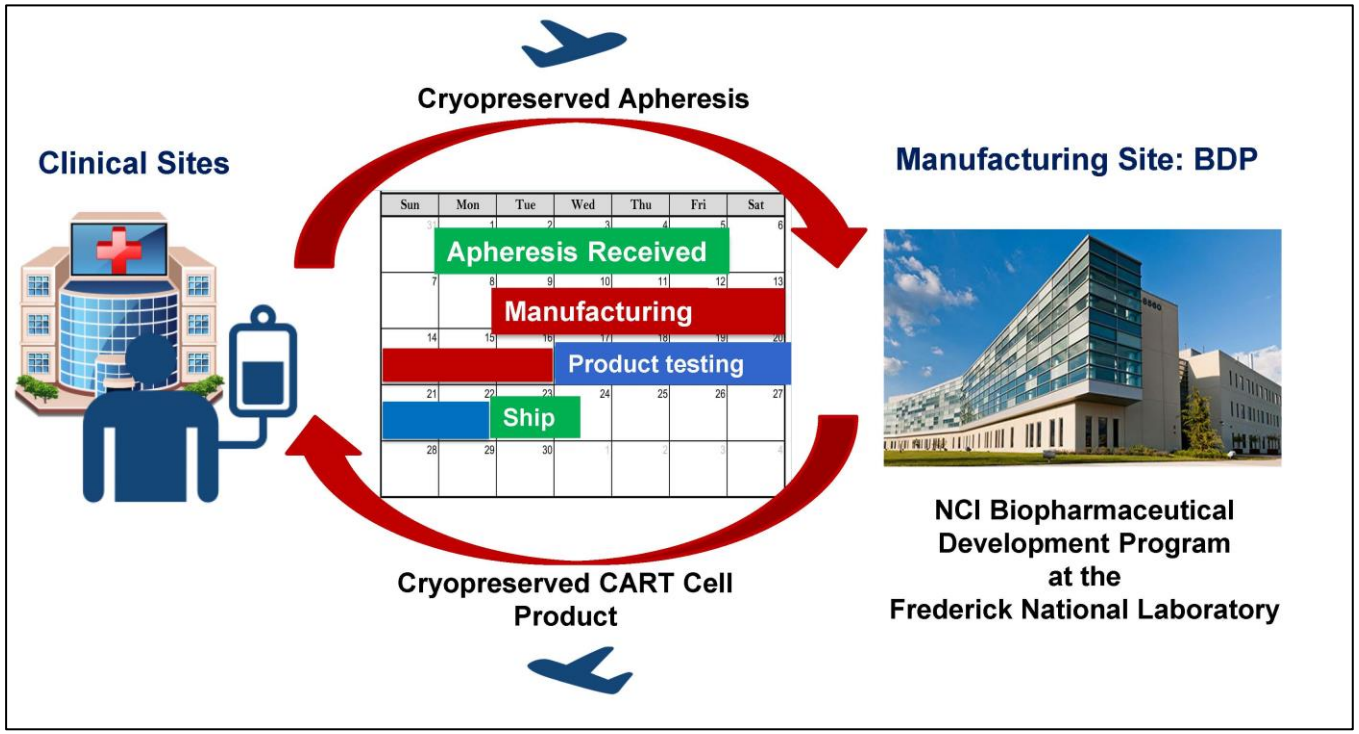
To advance the development of novel therapeutics for treatment of cancer and other diseases by providing manufacturing, process development, process analytics, and quality assurance capabilities and expertise.

Adoptive Cell Therapy and Virus Vector Manufacturing

GMP manufacturing platforms established: Prodigy, Grex

- Other platforms/technologies can be adopted as needed

Shipping logistics – vein-product-vein in ~3 weeks



Prodigy-based cell manufacturing

Lentivirus and gamma-retrovirus GMP manufacturing for cell transduction

- 4-10L scale; transient transfection

Manufacturing Example CART product:

CD33 CART manufactured with 7-day process

Process Flow

Cryopreserved Apheresis Product

Day 0
CliniMACS Prodigy:
Platelet Wash,
$CD4^+/CD8^+$ Enrichment,
Culture Initiation, Activation

Day 1
Transduction with CD33CAR Lentivirus (MOI 20)

Day 3
Transduction Stop:
3 Culture Washes

Day 5
Feed Port
Final Process Volume 250 mL

Day 6
Media exchange (Vol ± 125 mL)

Day 7
Culture Harvest

Cryopreservation
CryoStor CS5

Manufacturing Example CART product:

CD33 CART manufactured with 7-day process

Samples for Testing

Day 0 – Remove Sample
Flow ($CD3^+$, $CD4^+/CD8^+$, $CD33^+$)
Count, Viability

Day 6 – Remove Sample
Flow (Transduction Efficiency – Protein L)
Total Cell Count

Day 7 – Remove Sample
Flow ($CD3^+$, $CD4^+/CD8^+$, $CD33^+$,
Transduction Efficiency – Protein L,
Identity – CD33Fc) Count, Viability

Gram Stain, Mycoplasma qPCR, VCN,
RCL-qPCR, Sterility, Endotoxin LAL

Process Flow

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CryoStor CS5

Manufacturing Example CART product:

CD33 CART manufactured with 7-day process

Process flow and timeline are project-specific

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Day 7
Culture Harvest

Cryopreservation
CryoStor CS5

Onboarding Additional Resources

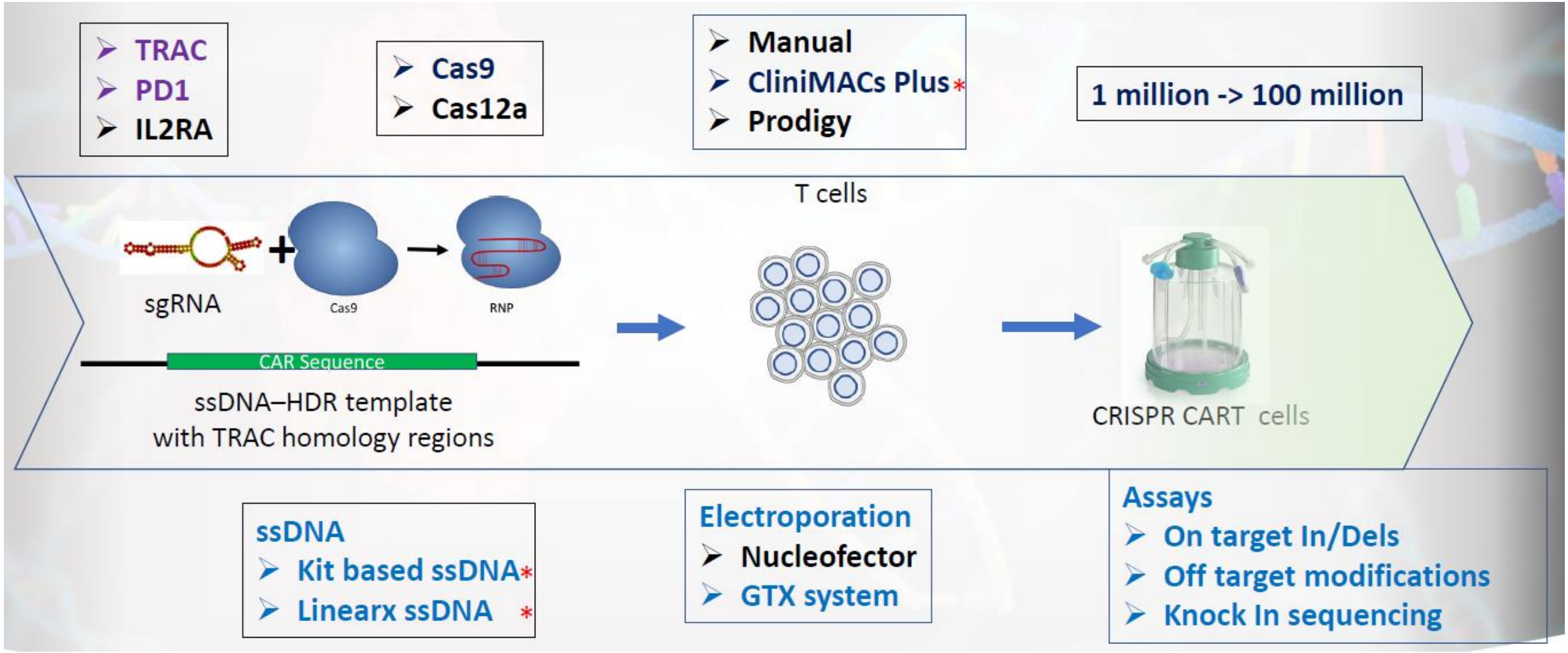
Facilities

Technologies

Cell Therapy Capacity Expansion at BDP

- Increase cell and virus production capacity to 5 manufacturing suites
- 3 new GMP suites commissioned - expected to be ready for GMP work in 2023
- Goal is to expand capacity to ~ 12 cell therapy products/month and ~ 8 virus vector campaigns/year

CRISPR-based CART Engineering Technology Development



CRISPR-CART Closed System Process Steps

Leukopak Thaw → CD4/CD8 Selection → Activation → CRISPR Knock-in → Expansion → Harvest

Product Evaluation:
Develop and Standardize Assays for Cell Therapy Products

Biopharmaceutical Development Program at the Frederick National Laboratory for Cancer Research

Deliverables

- Develop and qualify standardized assays and associated reagents to measure critical quality attributes of starting cell materials and final cell products
  - *Viral vector testing*, e.g., p24 ELISA, RCR/RCL, integrated VCN
  - *Cell product testing*, e.g., cellular fitness, CAR/TCR expression
  - *Raw material testing*, e.g., apheresis cellular fitness
  - *Analytical reagents*, e.g., reference standards, ELISA controls, PCR primers
- Provide SOPs and associated reagents to Can-ACT members through an efficient, documented technology transfer process
- Provide quality assurance and regulatory affairs guidance as it relates to assay development and product testing requirements

Quality Oversight:
Provide GCP/GMP/RA Compliance Evaluation

Biopharmaceutical Development and Clinical Management Research Programs at the Frederick National Laboratory for Cancer Research

Deliverables

- Provide clinical study *guidance* for GCP compliance and human subjects protection
  - *Ensure that IND Sponsor follows 21 CFR 312. and/or ICH/cGCP 5.18 regarding monitoring of a clinical study*
  - *Support clinical protocol development and review with ad hoc subject matter expertise*
- Provide CMC *guidance* to Can-ACT members
  - *Ensure that product manufacturing follows 21 CFR 210/211/600 and current FDA Guidelines*
  - *Conduct cGMP Audits of manufacturing sites and supply vendors*
- Provide *guidance* on IND preparation/filing and assist with FDA communications
- Provide subcontracted vendor support to ensure that Sponsors of multi-site studies provide efficient site activation, logistical oversight, and shipping of cell materials and products to and from the BDP manufacturing facility