Cancer Adoptive Cellular Therapy Network (Can-ACT)

RFA Concept Proposal

from

Developmental Therapeutics Program
(ImmunoOncology Branch, Biological Resources Branch),
Division of Cancer Treatment & Diagnosis

Marc Ernstoff

March 29, 2022

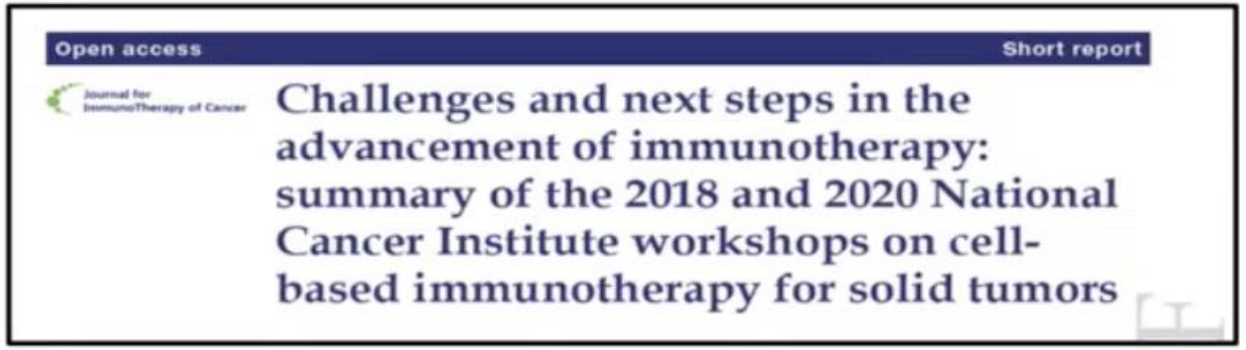
Cancer Adoptive Cellular Therapy Network (Can-ACT)

Think Tank Members

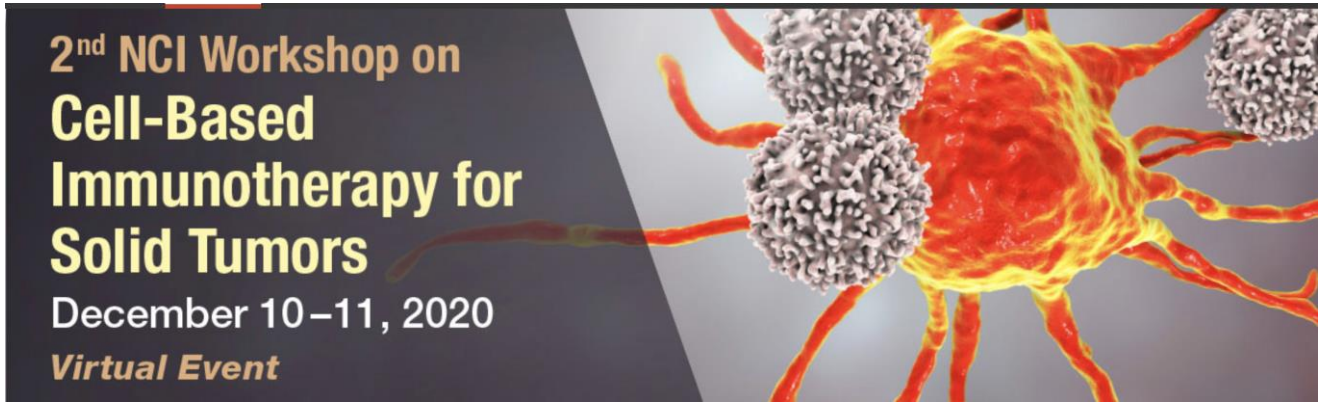
Rose Aurigemma, Kasia Bourcier, Monica Cooper, Janet Eary, Marc Ernstoff, Mike Espey, Piotr Grodzinski, Lyndsay Harris, Ray Harris, Toby Hecht, Leah Hubbard, Laura Hunter, Nina Lukinova, Margaret Mooney, Rachelle Salomon, Lalitha Shankar, Anju Singh, Malcolm Smith, Connie Sommers, Chiayeng Wang, Anthony Welch, Jason Yovandich

Cellular Therapies for Solid Tumors

A priority topic identified by the NCAB Ad Hoc Subcommittee on Experimental Therapeutics



Fogli LK, Aurigemma R, Sommers CL, Singh A, Bourcier K, Ernstoff MS. J Immunother Cancer. 2021 Jul;9(7):e003048. doi: 10.1136/jitc-2021-003048. PMID: 34266886; PMCID: PMC8286786.



Workshop Recommendations for Supporting Advancement of Cell-Based Immunotherapy for Solid Tumors

7 research areas of unmet need identified:

- Preclinical and translational research to advance cell therapy for solid tumors (tumor targets, immune cell fitness and persistence, cell trafficking, the immunosuppressive tumor microenvironment, development of preclinical models, and others) 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 including multigene engineering, alternatives to retroviral-based gene delivery, optimization of closed system manufacturing, new strategies for cell product screening, and others)
- Identification of biomarkers and imaging-based detection of response to therapy

Workshop Recommendations for Supporting Advancement of Cell-Based Immunotherapy for Solid Tumors

Needed services identified:

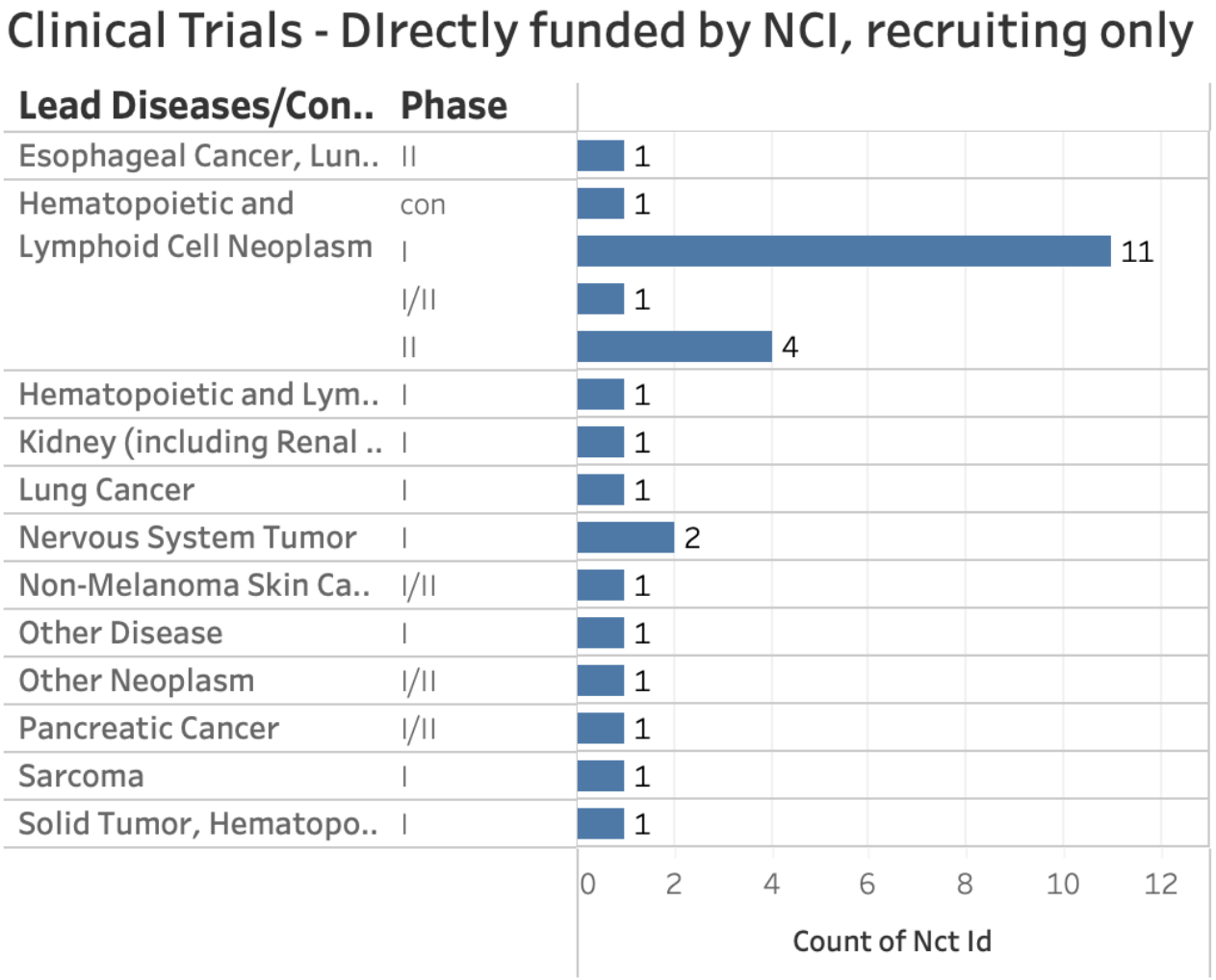
- Standardization of cell product characterization through a Core Laboratory
- QC testing for cell therapy-related reagents (e.g., GMP vectors) needed for manufacturing
- Guidance for investigators on preparing IND submissions

Cell Therapy-Related Manufacturing Resources at FNLCR

CURRENT TECHNOLOGY	CURRENT FACILITY	CURRENT CAPACITY
• Genetically-modified autologous cells (closed-system Prodigy platform-based) • Lentivirus & Gamma Retrovirus vectors	2 GMP suites	4 cell therapy products/month 4 virus vector campaigns/year

FUTURE ADDED TECHNOLOGY	ADDED FACILITY	ADDED CAPACITY
• G-Rex (disposable flask) manufacturing platform • CRISPR-based gene editing: FY2023	3 new GMP suites: Q4 2022	~ 12 cell therapy products/month ~ 8 virus vector campaigns/year

Adoptive Cell Therapy Trials directly funded by NCI and currently enrolling



- Data provided by Coordinating Center for Clinical Trials, Office of the Director, NCI, NIH
- Data cut-off August 28, 2021
- There are 36 NCI-supported Centers with ongoing cell therapy programs
- Some examples of solid tumor ACT advances in 2021:
  - Genetically engineered myeloid Cells in lung mets – preclinical
  - Anti-Her2 CAR macrophages – phase 1
  - Claudin 6 CAR-T in solid tumors – phase 1
  - TGFBR2 gene-edited allogeneic NK cells – preclinical GBM
  - Targeting "public" Neoantigens – preclinical solid tumors
  - Engineered T cells in GBM and Neuroblastoma – phase 1
  - PRAME Directed T cell (TCR) for solid tumors – phase 1
  - CAR-T and ICI in ovarian cancer – phase 1
  - MICA/B CAR-NK for solid tumors – preclinical

Cancer Adoptive Cellular Therapy Network (Can-ACT)

Purpose

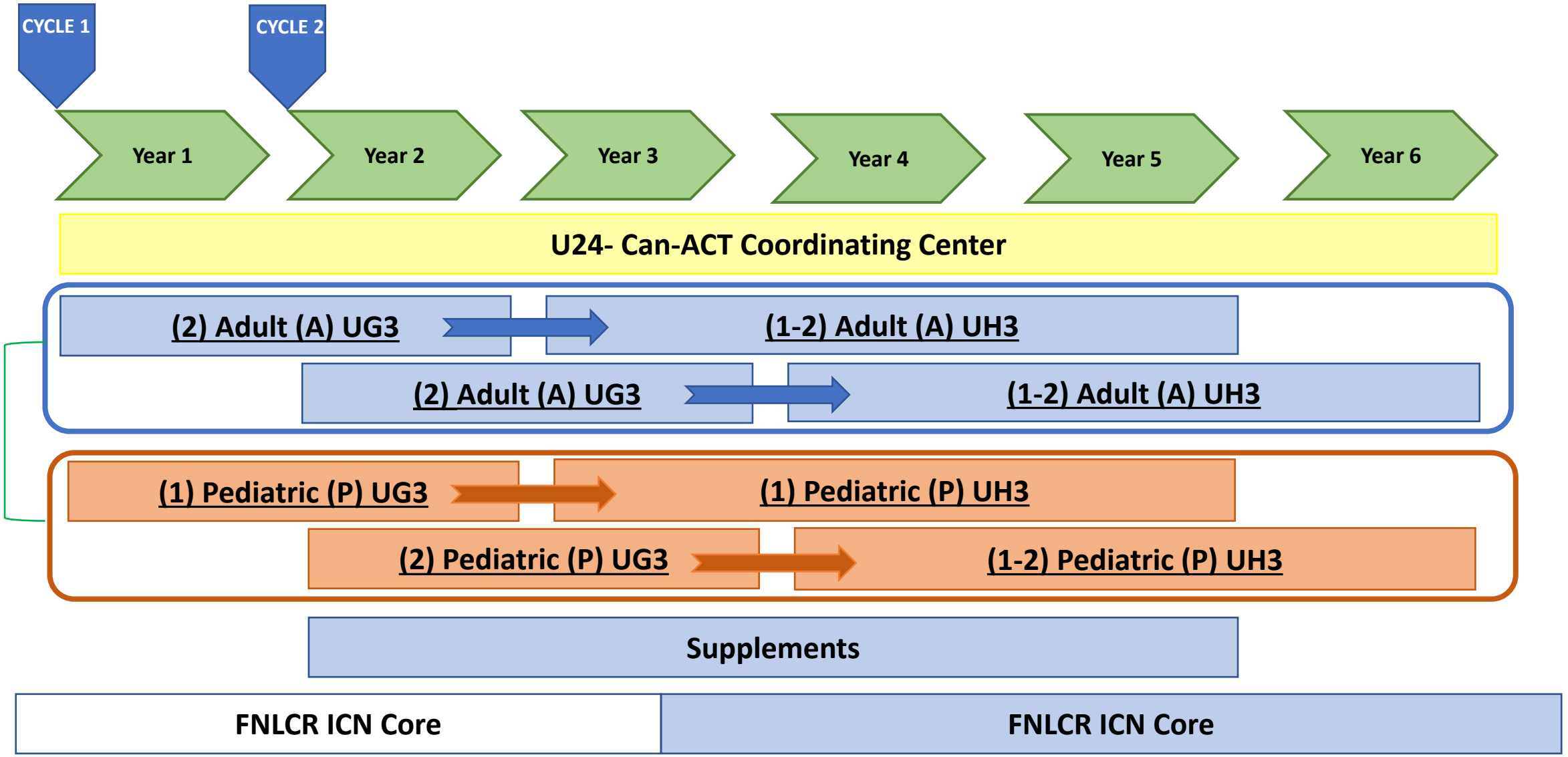
- To foster innovation and promote early-stage clinical testing of novel state-of-the-art cell-based immunotherapies for solid tumors in adults and pediatric patients and leverage NCI resources to support the cell therapy community

Cancer Adoptive Cellular Therapy Network (Can-ACT)

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

Cancer Adoptive Cellular Therapy Network Timeline and Components



Immune Cell Network Core (ICN)
Existing at FNLCR

- 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 – GCP/GMP 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
- Clinical Trials Coordination
  - Communications hub between Core and Network – conferences, annual reviews, etc.
  - Ensure GCP/GMP adherence at Network sites
- Data Coordination
  - Procure, organize, store preclinical and clinical research results and correlative data
  - Provide access to data for Network members

U24 Coordinating Center for Cancer Adoptive Cellular Therapy Network (Can-ACT)

U24 Coordinating Center responsibilities:

- Form Steering Committee for Can-ACT network
- Form EAB
- Coordinate network meetings with Frederick ICN Core to facilitate collaboration
- Coordinate solicitation and evaluation of supplements
- Coordinate with ICN Core to achieve multi-site clinical trial coordination and harmonization of high quality data

Budget: $0.5M/Year 1-6

Cancer Adoptive Cellular Therapy Network
Two Separate UG3/UH3 RFAs: Adult and Pediatric

- UG3/UH3 cooperative agreement provides an opportunity for a milestone-driven biphasic approach to funding developmental research and clinical trials
- UG3 proposals must have at least 2 integrated projects that will advance a new cell therapy concept to clinical testing while also conducting research to advance the understanding and clinical use of cell therapies
- Two separate UG3/UH3 RFAs to support translational research on both adult (4) and pediatric (3) solid tumors with funding pool to support the most meritorious awards
- Delineation of milestones, go/no-go criteria required for submitting the applications
- Transition from UG3 to phase UH3 (total 6) will be determined by success in meeting proposed milestones, program priorities and availability of funds
- UH3 phase component will support a multi-center clinical trial leveraging Frederick ICN Core

Cancer Adoptive Cellular Therapy Network

Potential topics for supplement awards – Empowering collaboration between investigators

1. Pre-clinical cellular product development
2. Manufacturing technology
3. Pre-clinical toxicity/efficacy novel assay development
4. Preclinical Vector/cell transduction/gene editing development

Developmental Therapeutics Program (DTP)

5. Imaging or biomarker development
   a. Can be preclinical models
   b. Can be associated with a clinical trial

Cancer Diagnosis Program (CDP)
Cancer Imaging Program (CIP)

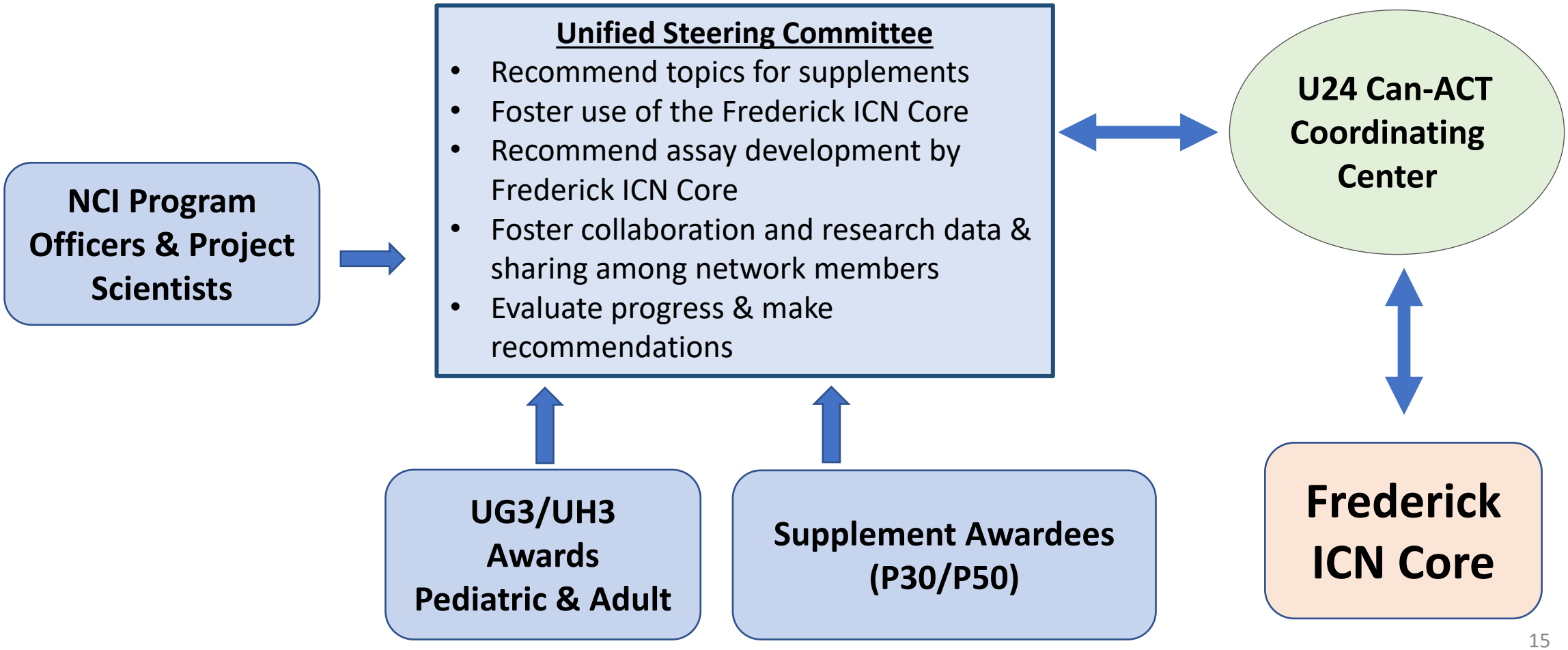
6. Utilize ICN Core for clinical trial

Cancer Therapy Evaluation Program (CTEP)

7. Single site pilot
   i. Site production using ICN Core production facility
   ii. Multi-site pilot using ICN Core production facility
   iii. Clinical trials include costs not covered by P30/P50 grants (e.g., apheresis, shipment)

ICN Core

Cancer Adoptive Cellular Therapy Network Organization



Proposed Can-ACT Budget (Total Costs in $M)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
U24 Coordinating Center	0.5	0.5	0.5	0.5	0.5	0.5
Can-ACT UG3 (Pediatric), Years 1-3 one UG3 Years 1-2 two UG3s Years 2-3	1.5	1.5 3.0	3.0			
Can-ACT UH3 (Pediatric), Years 3-6 one UH3 Years 3-5 one UH3 Years 4-6			2.5	2.5 2.5	2.5 2.5	2.5
Can-ACT UG3 (Adult), Years 1-3 two UG3s Years 1-2 two UG3s Years 2-3	3.0	3.0 3.0	3.0			
Can-ACT UH3 (Adult), Years 3-6 two UH3s Years 3-5 two UH3s Years 4-6			5.0	5.0 5.0	5.0 5.0	5.0
Supplements		1.0	2.0	2.0	2.0	
Sub-Total RFA	5.0	12.0	16.0	17.5	17.5	8.0
ICN Core Support*			4.0	6.0	6.0	6.0
TOTAL	5.0	12.0	20.0	23.5	23.5	14.0

6 year total = $98M (RFA=$76M) (*ICN Core Support to be part of DCTD budget)

UG3 = $1.5M/award for 2 year duration; UH3 = $2.5M/award for 3 year duration; Supplements = $0.5-2M/award

Justification for Use of the RFA Mechanism

- Area of ongoing scientific need and proof of concept clinical trials
- Insufficient representation in the NCI portfolio; only 9 cell therapy clinical trials (currently enrolling) directly supported by NCI for treatment of solid tumors
- Currently no specialized peer review for immune cell therapies for cancer

Justification for Use of the Cooperative Agreement Mechanism

- NCI staff to participate in the Steering Committee to provide programmatic input
- Regular Steering Committee meetings to discuss current challenges in cell therapies, share results, provide overall advice on future research directions and foster collaboration among awardees
- Collaborations will be established post-award using supplemental funds to expand the Network
- NCI staff to provide information to Steering Committee members on use of NCI resources such as NExT and other relevant opportunities

Comments from BSA Reviewers

Reviewers: Nelson Chao, Robert Schreiber, Robert Vonderheide

- Reviewers were enthusiastic and agreed that Can-ACT would meet a significant need in the research community
- Questions about the role of the ICN core and how it could best support investigators
  - For example, reviewers felt the requirement for multi-site studies in order for investigators to receive ICN manufacturing support was too restrictive
- Suggestion that investigators be able to access the CIMAC-CIDC network for correlative studies using samples from Can-ACT clinical trials
- Suggestion that basic science projects are more clearly emphasized as part of the UG3 phase
- Reviewers noted that the budget is restrictive given the high cost of cell therapy studies; request exemption from any further policy cuts to proposed budgets

Summary

- Can-ACT Network will catalyze advancement in Cellular Therapy for Adult and Pediatric Solid Tumors
- The community is poised to transition into solid tumor cell therapy proof of principle trials
- The UG3/UH3 and U24 RFA mechanism are suited to provide a pathway for successful translation to multisite clinical trials