Preapplication Webinar for RFA-CA-23-036 and RFA-CA-23-037
Targeting Fusion Oncoproteins in Childhood Cancers (TFCC) Network

Friday, August 11, 2023; 11:00 AM ET

Webinar will begin shortly

Webinar Logistics

- Everyone is muted upon entry.
- Please use the chat box to submit questions. Questions will be answered after the planned presentation.
- This webinar is recorded and will be posted on the DCB/DCTD websites
- Webinar Agenda:
  - ✓ Background and Overview of the TFCC program
  - ✓ Key points for RFAs
  - ✓ Q&A

Preapplication Webinar for

RFA-CA-23-036 and RFA-CA-23-037 Targeting Fusion Oncoproteins in Childhood Cancers (TFCC) Network

Malcolm Smith (NCI, DCTD) and Keren Witkin (NCI, DCB)

with Joseph Agyin (NCI, DCTD), Sundar Venkatachalam (NCI, DCTD), Sharad Verma (NCI, DCTD), and Anu Sharman (NCI, DCB)

NIH NATIONAL CANCER INSTITUTE

August 11, 2023

Difficult cancers require new active targeted agents

- Substantial declines in mortality for pediatric/AYA leukemias and lymphomas between 2000-2020 as active new agents available
  - ~50% decline in ALL mortality
  - ~60% decline in NHL mortality
  - ~80% decline in Hodgkin lymphoma mortality
- No decline in mortality for soft tissue cancers, bone cancers, and other classes of pediatric cancers

Active new agents desperately needed for recalcitrant cancers in order to cure more children and adults with these cancers.

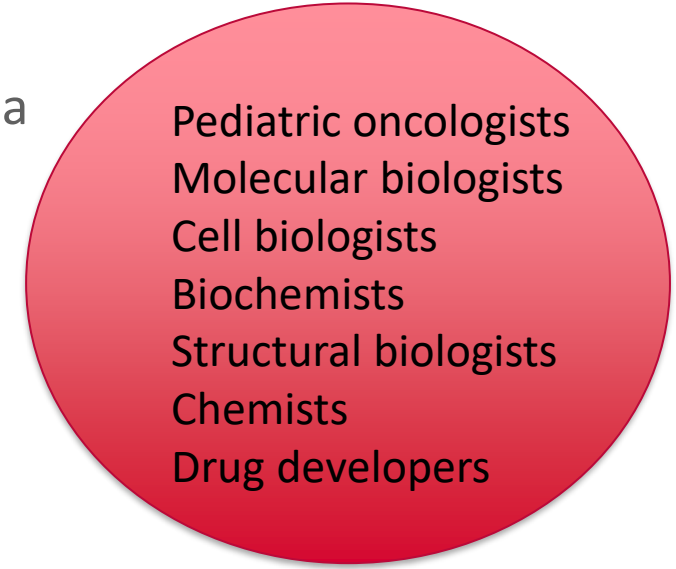
Recommendations of the NCI Cancer Moonshot Blue Ribbon Panel

A. Establish a network for **direct patient involvement**
B. Create a translational science network devoted to **immunotherapy**
C. Develop ways to overcome **resistance to therapy**
D. Build a national cancer **data ecosystem**
E. Intensify research on the major drivers of **childhood cancer**
F. Minimize cancer treatment's debilitating **side effects**
G. Expand use of proven **prevention and early detection** strategies
H. Mine past patient data to predict future **patient outcomes**
I. Develop a 3D **cancer atlas**
J. Develop new cancer **technologies**

Fusion Oncoproteins in Childhood Cancers (FusOnC2) Consortium (FY18-FY24)

EWSR1-FLI1
Ewing sarcoma

PAX3-FOXO1
Rhabdomyosarcoma



NUP98-fusions
High risk AML

ZTFA-RELA
Ependymoma

SS18-SSX
Synovial sarcoma

DNAJB1-PRKACA
Fibrolamellar carcinoma

Fusion Oncoproteins in Childhood Cancers (FusOnC2) Consortium (FY18-FY24) (cont'd)

Intrinsically disordered proteins/ phase separation

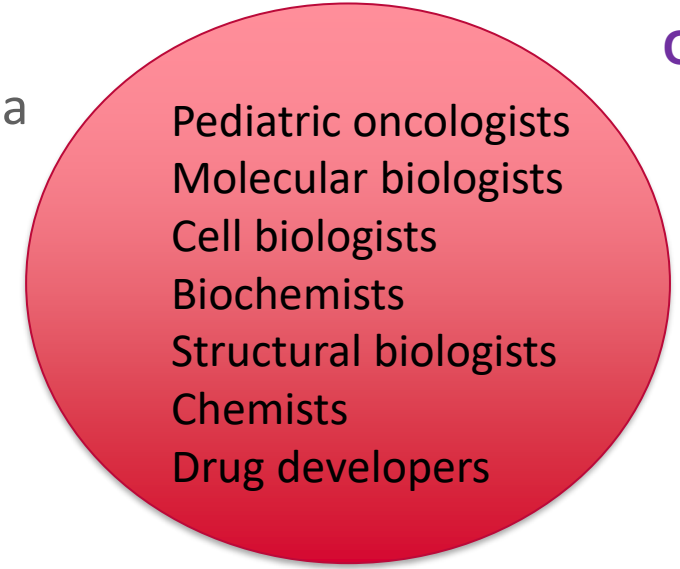
PAX3-FOXO1
Rhabdomyosarcoma

Model development

ZTFA-RELA
Ependymoma

PROTACs

DNAJB1-PRKACA
Fibrolamellar carcinoma



EWSR1-FLI1
Ewing sarcoma

Chromatin remodeling

NUP98-fusions
High risk AML

Critical dependencies

SS18-SSX
Synovial sarcoma

Novel chemoproteomic strategies

NCI Follow-Up and Due Diligence

- FusOnC2 Program evaluation, including feedback from External Scientific Consultants
- Community input through Request for Information
- 2022 Webinar series: Novel Chemical Approaches for Targeting Fusion Oncoproteins

Lectures recorded and archived at https://events.cancer.gov/dctd/fusion-targeting-webinar

NCI Conclusions of Future Research Needs

- **Fusion oncoproteins remain an important clinical need**
- Could be beneficial to diversify the fusion oncoproteins included in future efforts
- Potential benefit to decoupling the chemical biology expertise from the basic science projects to provide expertise in chemoproteomics and innovative drug development methods to all investigators in the consortium
- Applying state-of-the-art chemoproteomic methods for directly targeting fusion oncoproteins and/or their critical dependencies could be a potentially high impact approach

Targeting Fusion Oncoproteins in Childhood Cancers (TFCC) Network

- Projects to better understand basic mechanisms of fusion-driven oncogenesis
  - **Goal:** Identify novel drug targets and critical dependencies
  - **Possible activities:** Dissecting pathways by which these fusions cause cancer, characterizing the composition and structure of fusion oncoprotein complexes, or delineating the roles of ncRNAs and post-translational modifications in fusion oncoprotein function

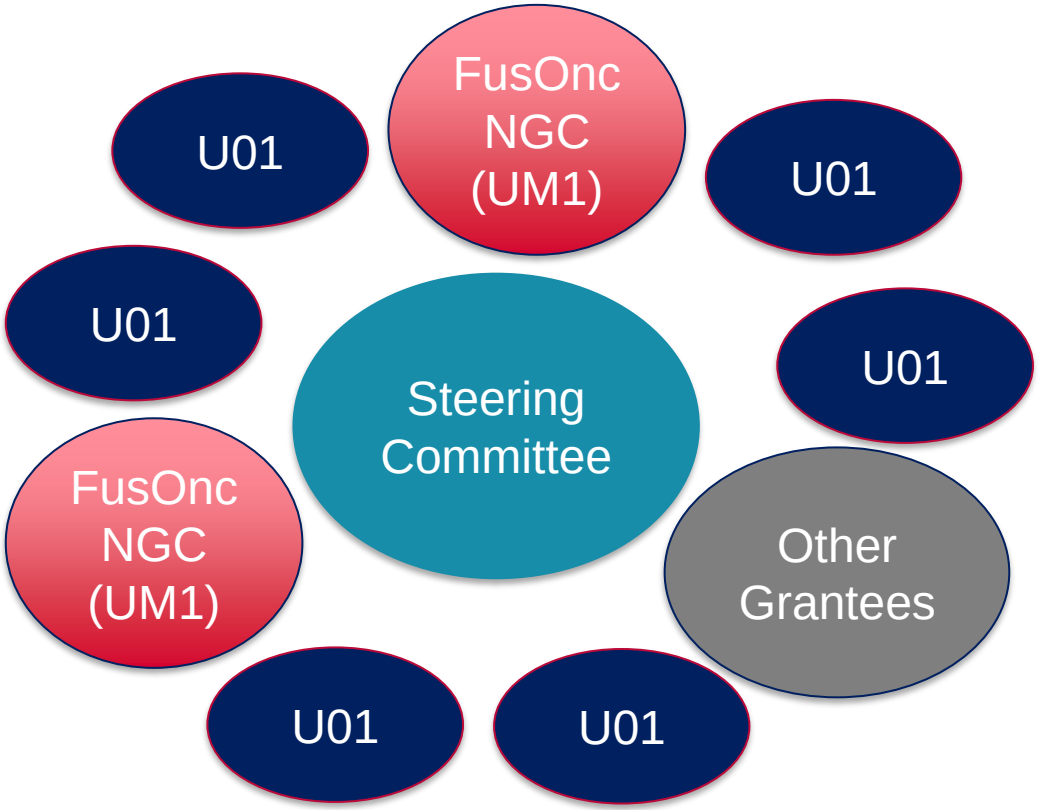
U01

- Next Generation Chemistry Centers for Fusion Oncoproteins
  - **Goal:** Identify and develop small molecules that disrupt activity of fusion oncoprotein drivers for childhood cancers
  - **Possible activities:** Identifying molecules that directly inhibit fusion oncoprotein activity, block critical interactions, or selectively degrade fusions or critical dependencies

FusOnc NGC (UM1)

Structure of the Targeting Fusion Oncoproteins in Childhood Cancers (TFCC) Network

- Steering committee will consist of U01/UM1 PIs and NCI staff
- Additional NCI-funded and intramural investigators will be added as Associate Members
- Patient advocates
- UM1 budget set-aside (~10%) in Years 2-5 to apply their therapeutic strategies to targets developed by the U01s and others in the scientific community



TFCC Network Considerations

- Successful applications must focus on fusion oncoproteins for tumors with high risk of treatment failure and for which there has been little progress in identifying targeted agents
  - Applications related to solid tumors and brain tumors particularly encouraged
  - Fusion oncoprotein targets for which clinical proof of concept has been achieved are excluded from consideration
- Awardees are expected to adhere to NIH and TFCC data sharing policies
- All awardees are expected to participate in bi-monthly Steering Committee Meetings and annual Face-to-Face Meetings
  - The PD/PI is required to serve as a voting member of the TFCC Steering Committee. The Steering Committee, the primary governing body of the network, will discuss community issues, set policies, and plan and evaluate activities to meet program goals

Key Dates for both RFAs

- Open Date (Earliest Submission Date): **October 15, 2023**
- Letter of Intent Due Date: **October 15, 2023**
- Application Due Date **November 15, 2023**

  (by 5:00 PM local time of applicant organization)

  We strongly suggest that applications be submitted a week in advance!
- Scientific Merit Review **March 2024**
- Advisory Council Review **May 2024**
- Earliest Start Date **July 2024**

RFA-CA-23-036: Mechanisms of Fusion-Driven Oncogenesis in Childhood Cancers (U01 Clinical Trial Not Allowed)

RFA Goal: to better understand basic mechanisms of fusion-driven oncogenesis

RFA-CA-23-036 Details

Mechanism of support: U01 Cooperative Agreement mechanism to accommodate substantive programmatic involvement

Application Type: Submissions must be Type 1 (New Applications); may be Single or Multi-PI. A Leadership Plan is required for MPI applications. Each PI/MPI must meet the NCI minimum effort requirements of 1.8 (single PI) or 1.2 (MPI) CM effort throughout the life of the grant

Budget: Application budgets are limited to $325,000/year in direct costs and need to reflect the actual needs of the proposed project. NCI intends to fund up to 6 awards in FY24.

Project Period: Up to 5 years

Note on Eligible Applicants: Foreign (non-U.S.) institutions are not eligible to apply as PD/PI, but foreign components are allowed.

No late applications will be accepted.

Examples of potential areas of investigation for the Research Projects

- Defining the critical dependencies created by specific fusion oncoproteins through functional genomic screening in order to reveal potential drug targets;
- Defining how fusion oncoproteins influence gene expression, altering normal cellular programs to block lineage differentiation and development; and
- Identifying and characterizing protein complexes, non-coding RNAs, and/or post-translational modifications associated with fusion oncoproteins.

Application Details for RFA-CA-23-036

- All instructions in the SF424 (R&R) Application Guide must be followed. Please see RFA for additional instructions.

- **Specific Aims:** Include the specific aims of the project and provide a rationale and description of how it fits into organizing framework of the TFCC program.

- **Research Strategy:** Describe the research strategy using the standard sub-sections of Research Strategy (Significance, Innovation, and Approach) defined in the SF424 Application Guide with additional guidance listed in the RFA. Identify clearly any innovative biological concepts that are proposed to be explored as a potential basis for mechanistic studies of fusion oncoprotein-driven childhood cancers.

- The Research Strategy section has a 12 Page Limit.

Letter of Intent (LOI) for RFA-CA-23-036

Due October 15, 2023

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

Standard elements:

- Descriptive title of the project
- 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 this funding opportunity (RFA-CA-23-036)

Additional recommended information:

- **Provide a brief (3-5 sentence) description of the project**

Email LOI to witkinkeren@mail.nih.gov

RFA-CA-23-037: Next Generation Chemistry Centers for Fusion Oncoproteins (UM1 Clinical Trial Not Allowed)

RFA Goal: To accelerate the development of novel small molecule therapeutic agents to treat fusion oncoprotein-derived childhood cancers

RFA-CA-23-037 Details

Mechanism of support: UM1 Cooperative Agreement mechanism to accommodate substantive programmatic involvement and a complex grant structure

Application Type: Submissions must be Type 1 (New Applications); may be Single or Multi-PI. A Leadership Plan is required for MPI applications and each PI/MPI must meet the NCI minimum effort requirements of 1.8 (single PI) or 1.2 (MPI) CM effort throughout the life of the grant

Budget: Application budgets are limited to $1.5 million/year in direct costs and need to reflect the actual needs of the proposed project. NCI intends to fund up to 2 awards in FY24. 10% of UM1 budgets in years 2-5 must be restricted for collaborative projects.

Project Period: Up to 5 years

Note on Eligible Applicants: Foreign (non-U.S.) institutions are not eligible to apply as PD/PI, but foreign components are allowed.

No late applications will be accepted.

Structure of NGC Centers

- Each proposed NGC Center will be expected to include diverse areas of expertise to facilitate progression from structure-function biochemical data to small molecule drug candidates and setting the stage for preclinical in vivo testing.
- Relevant areas of expertise that could be included are (among others) chemoproteomics, structural biology, molecular biology, computational biology, medicinal chemistry, and experimental therapeutics.
- Multi-institutional collaborations are strongly encouraged to achieve the breadth of expertise required for a comprehensive approach to developing effective therapeutic agents for fusion oncoprotein-derived pediatric cancers.
- An NGC Center can focus on one or more potential target(s), as appropriate for the proposed scope and budget.

NGC Center Organizational Framework

- **Center Leadership Group (CLG):** led by the PD(s)/PI(s) of the Center, responsible for scientific direction, oversight, coordination, and evaluation of NGC Center activities.
- **2-4 Research Projects:** selected and organized by the applicant to optimize the likelihood of the Center's success in identifying small molecules with therapeutic potential against specific fusion oncoproteins.

  Potential areas of focus for the research groups include, but are not limited to, medicinal chemistry, computational and structural biology, biological testing (e.g., in vitro and in vivo studies, and ADME/DMPK), statistics/data management, etc.
- **Administrative Group (AG):** provides administrative support for the Center, organizes meetings, compiles summaries, facilitates communications, prepares reports, and implements fiscal management plan.

Budget Considerations

- The PD/PI must commit a minimum of 1.8 person-months effort per year to the UM1 award. The commitment cannot be reduced in later years of the award. If there are multiple PD(s)/PI(s), each must devote a minimum of 1.2 person-months effort per year.
- To facilitate collaboration within the TFCC Network as well as with external researchers, each NGC Center will:
  - Set aside 10% of its budget in years 2-5 for collaborative projects with either companion U01 grantees or with other research teams; and
  - Be responsible for identifying collaborative projects in years 2-5 and for providing NCI with scientific justification for the merit of these projects.
- Support for participation in Annual Program meetings
- Total budget for the CLG and AG should be limited to 6% ($150,000) of the total cost of the NGC Center budget.

Examples of potential areas of investigation

- Discovery and preclinical testing of novel compounds for fusion oncoprotein-driven pediatric cancers;
- Utilizing novel chemoproteomic approaches to discover small molecules that effectively modulate the activities of individual fusion oncoproteins, block critical fusion protein interactions, interact with coding and/or noncoding RNAs required for fusion protein oncogenesis, or selectively lead to fusion protein degradation;
- Computer-aided drug discovery to allow structure-based drug design and development of small molecule drugs;
- Development and validation of novel, fusion oncoprotein-based functional assays for evaluating therapeutic compounds. Measures with potential translational utility are particularly encouraged;
- Initial Good Laboratory Practice (GLP) toxicology, safety pharmacology, and pharmacokinetics to support an investigational new drug (IND) application.

Application Details for RFA-CA-23-037

- The UM1 is NOT a multi-component mechanism.
- There should be a single **Specific Aims** page for the entire NGC Center application
- There should be a single **Research Strategy** section, with the following subsections with the indicated page limits:
  - Subsection A: **NGC Center: Organization, Leadership and Overall Research Plan**; 12 pages.
  - Subsection B: **Research Groups**; minimum of two Groups, maximum of four Group; 24 pages total.
  - Subsection C: **Administrative Group**: 6 pages.

- **Read all directions carefully!**

Letter of Intent (LOI) for RFA-CA-23-037

Due October 15, 2023

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

Standard elements:

- Descriptive title of the project
- 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 this funding opportunity (RFA-CA-23-037)

Additional recommended information:

- **Provide a brief (3-5 sentence) description of the project**

Email LOI to joseph.agyin@nih.gov

Scientific Review information for both RFAs

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

- 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

- All applications will receive a written critique.

- **Each application will receive a single overall impact score and applications will not be percentiled.**

Scientific Review (continued)

- Appeals of initial peer review will not be accepted.
- Recommended applications will receive a second level of review by the National Cancer Advisory Board.
- The following will be considered in making funding decisions:
  - Scientific and technical merit of the proposed project as determined by scientific peer review.
  - Availability of funds.
  - Relevance of the proposed project to program priorities.

Agency Contacts (See RFA Section VII)

Scientific/Research Contacts:

For RFA-CA-23-036 (U01)

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For RFA-CA-23-037 (UM1)

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Peer Review Contact:

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Financial/Grants Management Contact:

Crystal Wolfrey
National Cancer Institute (NCI)
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Questions Received by Email

- How does the TFCC Network relate to the current FusOnC2 Consortium?
- Do U01 applications in response to RFA-CA-23-036 need to be MPI?
- Should U01 applications focus on one fusion oncoprotein or cancer or should they have a broader scope covering more than one fusion oncoprotein?
- Can you elaborate on target eligibility with respect to “fusion oncoprotein targets for which clinical proof of concept has been achieved”?
- For UM1 applications in response to RFA-CA-23-037, would a peptide-based agent meet the criteria?

Questions??

www.cancer.gov

www.cancer.gov/espanol