

# Fusion Oncoproteins in Childhood Cancers (FusOnC2) Consortium (U54) Pre-Application Webinar

*RFA-CA-17-049*

# The Cancer Moonshot Initiative



2016 State of the Union Address

## Goals:

- Accelerate progress in cancer, including prevention & screening
  - From cutting-edge basic research to wider uptake of standard care
- Encourage greater cooperation and collaboration
  - Break down silos within and between academia, government, and private sector
- Enhance data sharing
  - Genomic Data Commons
  - Annotated patient-level clinical data and -omics

# The Process



Vice President's Office



Federal Task Force



NCI/NIH



National Cancer Advisory Board



Blue Ribbon Panel



BRP Working Groups (ie Pediatric Cancer Working Group)



# Blue Ribbon Panel Recommendations

- 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**



# Cancer Funding in 21<sup>st</sup> Century Cures Act

- The cancer research portion is named the Beau Biden Cancer Moonshot Initiative
- Allows implementation of the BRP recommendations
- Specifies requirements
  - Data sharing
  - Health disparities

*“To support cancer research, such as the development of cancer vaccines, the development of more sensitive diagnostic tests for cancer, immunotherapy and the development of combination therapies, research that has the potential to transform the scientific field that has inherently higher risk, and that seeks to address major challenges associated with cancer.”*

## Recommendation E:

### **E. Intensify research on the major drivers of childhood cancers**

Improve our understanding of fusion oncoproteins in pediatric cancer and use new preclinical models to develop inhibitors that target them.

### **Blue Ribbon Panel Pediatric Cancer Working Group Recommendations:**

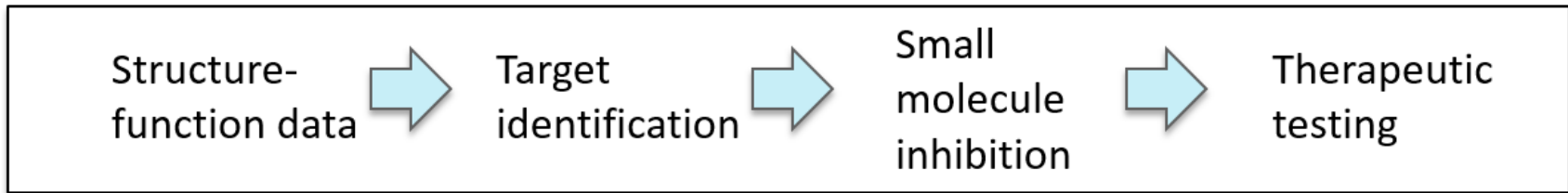
- Enhance our understanding of the molecular and biochemical mechanisms of transformation driven by fusion oncoproteins, to develop faithful models of these pediatric cancers, to identify their key dependencies, and to use this information to develop novel therapeutic approaches that target these mechanisms.
- Use a multi-disciplinary, collaborative approach.
- Focus on fusion oncoproteins found in tumors that have high risk of treatment failure and for which there has been little progress in identifying targeted agents.
- Fusion oncoproteins that control gene expression or chromatin state are of particular interest.

# Recommendation E: The Big Picture

## Bring together these communities (and others)

- proteomics
- structural biology
- genomics/epigenomics
- medicinal chemistry
- experimental therapeutics
- cancer biology

**To learn more about the molecular mechanisms of transformation driven by fusion oncoproteins and apply this knowledge to target identification, small molecule inhibition, and pre-clinical testing.**



# BRP Pediatric Cancer Working Group: Recommended Focus

- Development of model systems to interrogate the role of fusion oncoproteins in specific childhood cancers and facilitate the preclinical assessment of potential therapeutics.
- Defining the critical dependencies created by specific fusion oncoproteins through functional genomic screening.
- Defining how fusion oncoproteins influence gene expression to perturb normal cellular programs and block lineage differentiation and development.
- Identifying protein complexes bound to fusion oncoproteins and defining the three-dimensional structure of the domains within the fusion oncoproteins and the associated protein complex members.
- Identifying small molecules that are able to effectively inhibit activities of individual fusion oncoproteins, block critical interactions, or selectively lead to their degradation.



## Goal of the RFA

- The overall goal is to establish a consortium of collaborating research teams to advance our understanding of the biology and mechanisms of action of fusion oncoproteins in pediatric cancers, and to apply this knowledge towards developing targeted therapeutic approaches.
- The research teams comprising the Fusion Oncoproteins in Childhood Cancers (FusOnC2) Consortium will take a *comprehensive approach to understanding the biology of fusion oncoproteins in childhood cancers and will use this information to inform strategies for therapeutic targeting.*
- This FOA focuses on fusion oncoproteins found in tumors that have high risk of treatment failure and for which there has been little progress in identifying targeted agents.

# Specific Requirements

- Responsive applications must focus on one of the following fusion oncoproteins:
  - EWSR1-FLI1 or related EWSR1 fusion oncoproteins (Ewing sarcoma)
  - PAX-FOXO (alveolar rhabdomyosarcoma)
  - SYT-SSX (synovial sarcoma)
  - C11orf95–RELA (ependymoma)
  - NUP98 fusion proteins that occur in young children with AML.
- Teams should select either a single fusion oncoprotein or a small family of related fusion oncoproteins for *comprehensive study that includes both investigation into biological mechanisms and development of targeted therapeutics.*

## Relevant Areas of Expertise (among others)

- proteomics
- structural biology
- genomics/epigenomics
- medicinal chemistry
- experimental therapeutics
- cancer biology

**Multi-institutional collaborations** are strongly encouraged to achieve the breadth of expertise required for a comprehensive approach to understanding fusion protein mechanisms and therapeutic targeting.

# Examples of potential areas of investigation for the Research Projects

- Development of model systems and approaches to interrogate the function of fusion oncoproteins in specific childhood cancers, including those from racial/ethnic minority and underserved groups, and to provide preclinical assessment of potential therapeutics. Genetic models are of particular interest.
- Defining the critical dependencies created by specific fusion oncoproteins through functional genomic screening (e.g., CRISPR and shRNA) of cell lines derived from these cancers.
- Development of functional assays to measure direct effects of fusion oncoproteins and potentially yield new opportunities for small molecule development.

## Examples of potential areas of investigation for the Research Projects (Continued)

- Defining how fusion oncoproteins influence gene expression to perturb normal cellular programs to block lineage differentiation and development.
- Identifying protein complexes (and/or post-translational modifications) associated with fusion oncoproteins and additionally defining the three-dimensional structure of the domains within the fusion oncoproteins and the associated interacting protein complex members.
- Identifying and developing small molecules able to effectively inhibit activities of individual fusion oncoproteins, block critical interactions, or selectively lead to their degradation.
- Computer-aided drug discovery to allow structure-based drug design.

## Key Dates

- Open Date (Earliest Submission Date): **October 15, 2017**
- Letter of Intent Due Date: **October 16, 2017**
- Application Due Date **November 15, 2017**

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

**We strongly suggest that applications be submitted a week in advance!**

- Scientific Merit Review **March 2018**
- Advisory Council Review **May 2018**
- Earliest Start Date **July 2018**

# Letter of Intent (LOI)

**Due October 16, 2017**

**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-17-049)

## **Additional recommended information:**

- **Provide a brief (3-5 sentence) description of the project**
- **Include relevant expertise and Keywords**

**Email LOI to [witkinkeren@mail.nih.gov](mailto:witkinkeren@mail.nih.gov)**

# Budget

Application budgets are limited to \$2.5 million total costs per year, and need to reflect the actual needs of the proposed project.

**Funds Available and Anticipated # of Awards:** The NCI intends to commit approximately \$7 million dollars total cost in FY 2018, contingent upon receiving scientifically meritorious applications. Up to 3 awards are anticipated from this solicitation.

**Project Period:** Not to exceed 5 years.



# Mechanism of Support

## **U54**, Specialized Center--Cooperative Agreement

*The spectrum of activities comprises a **multidisciplinary attack** on a specific disease entity or biomedical problem area. These differ from program project in that they are usually developed in response to an announcement of the programmatic needs of an Institute or Division and subsequently **receive continuous attention from its staff**. Centers may also serve as regional or **national resources for special research purposes**, with funding component staff helping to identify appropriate priority needs.*

## **Read Cooperative Agreement Terms**

- Oversight by NCI staff
- Participation in FusOnC2 Consortium

## Structure of FusOnC2 Centers:

- **3-4 Research Projects** that address the mechanisms by which fusion oncoproteins drive pediatric cancers and/or apply this knowledge to the development of novel strategies for their therapeutic targeting. They should **closely integrate into the organizing framework and together constitute a comprehensive approach.**
- **Administrative Core** to manage and coordinate all Center research and activities and serve as the liaisons between the Center and the FusOnC2 Consortium.
- **Shared Resource Cores** (optional) may be established to provide expertise and resources that support and integrate multiple Research Projects. Each proposed Core must serve 2 or more Research Projects.

# Participation in FusOnC2 Consortium

- U54 is a cooperative agreement mechanism.
- Grantees are expected to actively participate in a FusOnC2 Consortium
- PDs/PIs will serve on the Consortium Steering Committee (SC), the primary governing body of the Consortium, to discuss community issues, set policies, and plan and evaluate activities to meet Program goals.
- SC will meet regularly by teleconference, and Consortium members will meet in person at an Annual Program Meeting.
- Read cooperative agreement terms carefully.

## Administrative Details

- **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.
- U54 is a multicomponent mechanism.
  - 12 pages for Overall component.
  - 12 pages for Research Projects
  - 6 pages for Admin Core and any optional Cores
- Do not use appendix to circumvent page limits.
- **Read all directions carefully!**

# Overall Component

## PHS 398 Research Plan (FOA Part 2, Section IV):

- Instead of standard sections (significance, innovation, approach), focus on overall vision and plan for the proposed FusOnC2 Center, including:
  - *Center Organization.*
  - *Center Integration.*
  - *Center Expertise.*
  - *Research Projects.*
  - *Shared Resource Cores (optional).*
  - *Health Disparities.* If applicable to the type of research project being proposed, the Research Strategy must address how health disparity populations or data will be integrated into the proposed studies.

# Addressing the Cancer Moonshot Public Access and Data Sharing Policy:

- Utilizing the provision outlined in the 21st Century Cures Act, NCI has established a data sharing policy for projects that are funded as part of the Beau Biden Cancer Moonshot Initiative that requires applicants to submit a Public Access and Data Sharing Plan that **describes their proposed process for making resulting Publications and, to the extent possible, the Underlying Primary Data immediately and broadly available to the public upon publication** or (if applicable) provides a justification to NCI if such sharing is not possible.
- NCI will give competitive preference and funding priority to applications that comply with the strategy described at [NCI Cancer Moonshot<sup>SM</sup> Public Access and Data Sharing Policy website](#).
- The data sharing plan will become a term and condition of award.

## Administrative Core (cont.):

### Budget:

- The Administrative Core Leader is strongly encouraged to propose and budget for a Center Administrator to manage day-to-day operations.
- The budget should include funds to support travel for Center and FusOnC2 Consortium activities, including but not limited to:
  - Supporting the participation of PD(s)/PI(s) in an initial FusOnC2 Consortium Kick-off Meeting.
  - Supporting the participation of the PD(s)/PI(s) and other Center members in an Annual Investigators' Meeting.
    - FusOnC2 Centers are encouraged to include early career scientists in the Consortium activities and should include budget to travel at least one graduate student or postdoctoral fellow to the Annual Investigators' Meeting.

## Administrative Core:

### PHS 398 Research Plan should include (FOA Part 2, Section IV):

- Plans to coordinate and support the Projects within the FusOnC2 Center, foster synergy within the Center, and support planning and evaluation activities.
  - *Management and Communication Plan.*
  - *Annual Meeting and Other Consortium Activities.*
    - Brief description of strategies for connecting and integrating the Center with the broader FusOnC2 Consortium.
  - *Outreach plan.*
    - Promote training and development of researchers in the Center, and disseminate advances and capabilities to broader research community.
  - *Center and Program Evaluation.*



# Research Projects

- Each FusOnC2 Center should have 3-4 Research Projects

## **PHS 398 Research Plan should include (FOA Part 2, Section IV):**

- Overall strategy for the Research Project
- Concise description of how it fits into organizing framework of the FusOnC2 Center.
- Standard sub-sections (Significance, Innovation, and Approach).
- Project Timeline: A timeline (Gantt chart) including yearly milestones is required.

## Shared Resource Cores (optional)

- If included, must support at least 2 Research Projects.
- May be physical or virtual infrastructure providing a resource that supports other Center components in their activities. The services and resources provided to other Center components should be clearly defined.
- Issues to be addressed include, but are not limited to: *value* of the Core services to the Center and Research Projects, *integration* between the Core and Projects, *quality control*, procedures for selecting Projects to use the Core and *allocating resources*, cost effectiveness, and increased *efficiency*.
- Training in complex techniques and methods should be described if they are functions of the proposed Core.
- These shared resources **must not duplicate analogous resources** already established in the applicant institutions (although supplemental funding to such existing resources may be requested).

## Scientific Review

- Reviewers will provide an overall impact score for the entire FusOnC2 Center (Overall Component) and for each individual Research Project.
  - In addition, assigned reviewers will provide individual "criterion scores" for the Overall criteria and for the Research Projects criteria, but not for the other components.
  - The Administrative Core and optional Shared Resource Cores will be evaluated, but each will receive only one overall adjectival (not numerical) rating.
- For the evaluation of the FusOnC2 Center application, the Research Projects will be emphasized as the scientific base of each Center, with additional components enhancing and integrating the overall research program.

## Scientific Review (continued)

- **These grants have additional review criteria (see RFA)**
- 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 FOA Section VII)

## Scientific/Research Contacts:

Keren Witkin, Ph.D.  
Division of Cancer Biology  
National Cancer Institute (NCI)  
Telephone: 240-276-6250  
Email: [witkinkeren@mail.nih.gov](mailto:witkinkeren@mail.nih.gov)

Malcolm Smith, M.D., Ph.D.  
Division of Cancer Treatment and Diagnosis  
National Cancer Institute (NCI)  
Telephone: 240-276-6087  
Email: [Malcolm.Smith@nih.gov](mailto:Malcolm.Smith@nih.gov)

## Peer Review Contact:

Charles Morrow, M.D., Ph.D.  
Center for Scientific Review (CSR)  
Telephone: 301-408-9850  
Email: [morrowcs@mail.nih.gov](mailto:morrowcs@mail.nih.gov)

## Financial/Grants Management Contact:

Crystal Wolfrey  
National Cancer Institute (NCI)  
Telephone: 240-276-6277  
Email: [wolfreyc@mail.nih.gov](mailto:wolfreyc@mail.nih.gov)

Slides will be posted on the NCI DCB website:  
<https://www.cancer.gov/about-nci/organization/dcb>



**NATIONAL  
CANCER  
INSTITUTE**

[www.cancer.gov](http://www.cancer.gov)

[www.cancer.gov/espanol](http://www.cancer.gov/espanol)