

Moonshot Implementation: Collaborative Research Network for Fusion Oncoproteins in Childhood Cancers

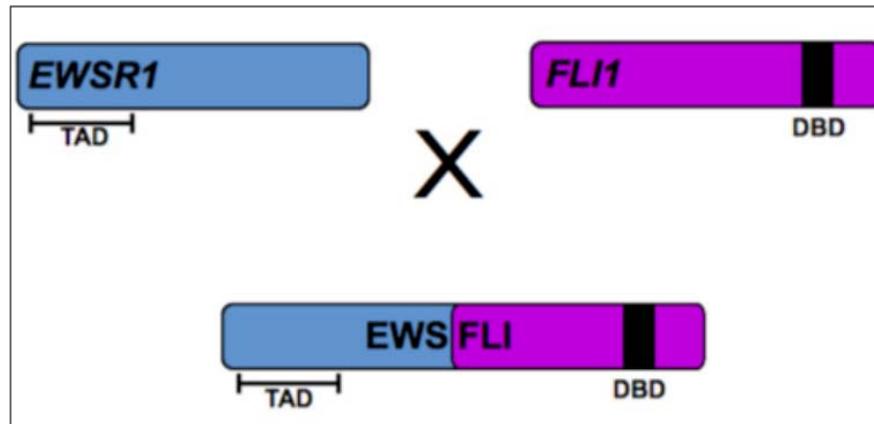
Cancer Moonshot Blue Ribbon Panel Implementation Team E

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Fusion Oncoproteins in Childhood Cancers

- Ewing sarcoma (*EWSR1-FLI1*)
- Alveolar Rhabdomyosarcoma (*PAX-FOXO1*)
- Synovial sarcoma (*SYT-SSX*)
- AML and ALL leukemias (*NUP98*- and *MLL*-rearrangements)
- Ependymomas (*C11orf95-RELA*)



Common thread for many of these cancers;
Aberrant transcriptional regulation → transformation of unique cell of origin

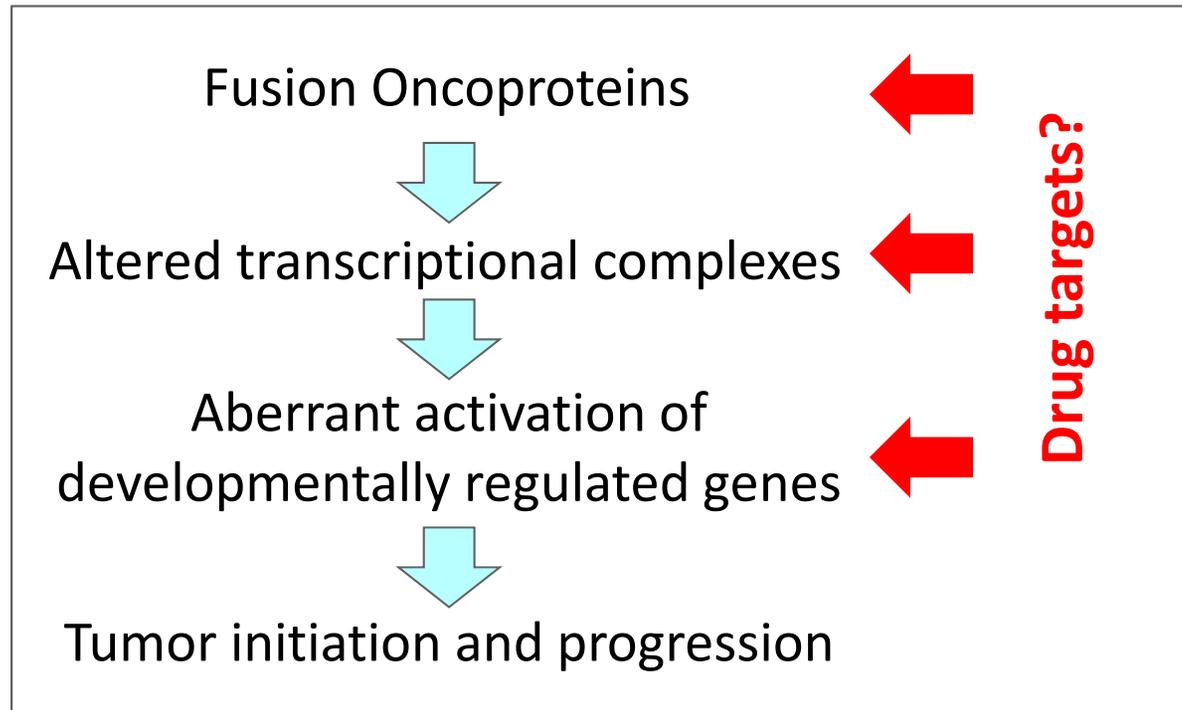
Fusion Oncoproteins as Therapeutic Targets

- ✓ Absolute specificity for tumor cells
- ✓ Found in cancers with few other genomic lesions

Challenges to Therapeutic Targeting:

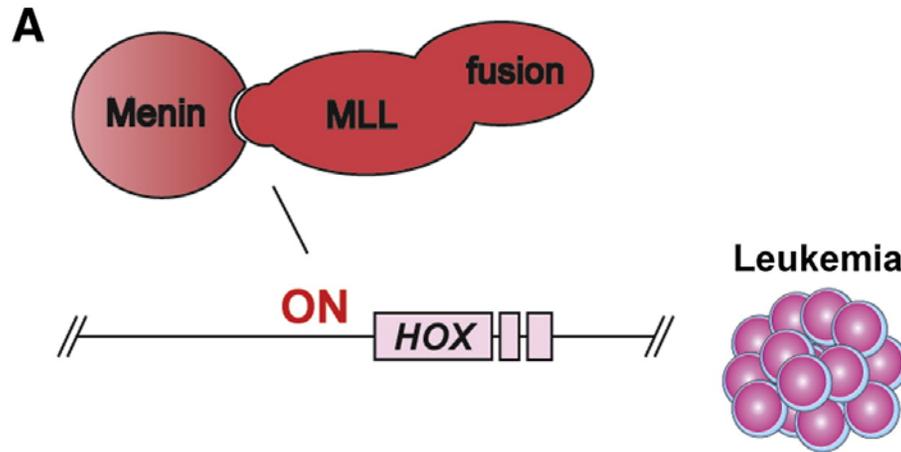
- Difficulty in targeting transcription factors with small molecules
- Uncertainty about the cells of origin
- Mechanistic understanding of fusion proteins, protein complexes and their key dependencies remains rudimentary
- Paucity of model systems

A Promising Approach to Therapeutic Targeting

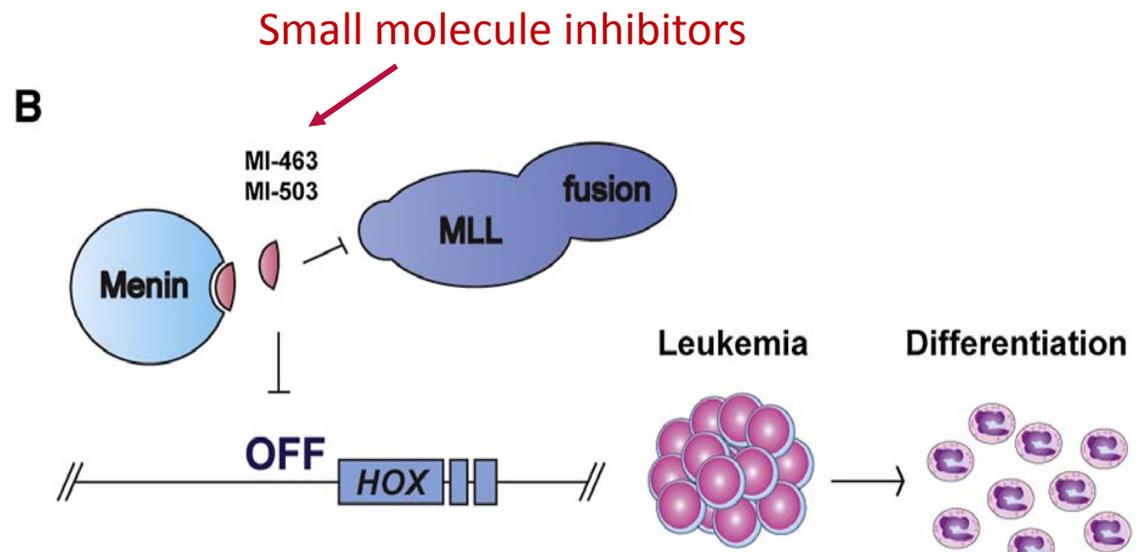


MLL Leukemias Provide Proof of Principle:

- Identification of druggable target



- Development of small molecule inhibitors to this target



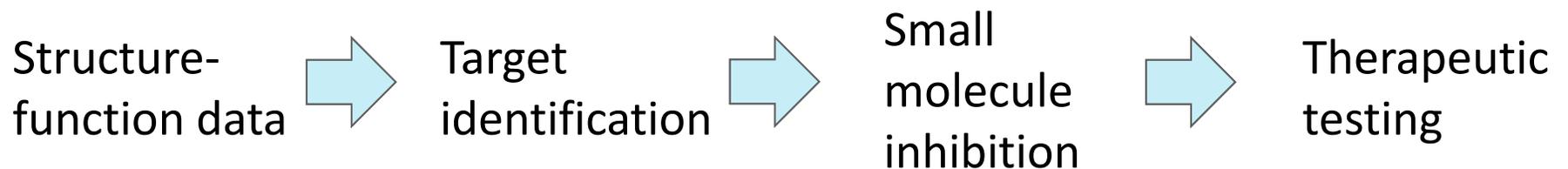
Blue Ribbon Panel Pediatric Cancer Working Group Recognized Fusion Oncoproteins as Key Area for Research Acceleration

- Area where targeted investment could have big impact.
- Well-credentialed oncogenic drivers of high risk cancers, including some with no promising targeted treatment options.
 - Ewing sarcoma
 - Alveolar rhabdomyosarcoma
 - Synovial sarcoma
 - NUP98-fusion leukemias
 - RELA-fusion ependymoma
- Provide a unique opportunity to reveal how fusion oncoproteins drive tumorigenesis in adult cancers as well.



Blue Ribbon Panel Pediatric Cancer Working Group Recommendation

- **Multi-disciplinary, collaborative, comprehensive** approach to studying fusion oncoproteins in childhood cancers
 - Genomics/epigenomics
 - Proteomics
 - Structural Biology
 - Chemistry
 - Experimental Therapeutics
 - Cancer Biology



Areas of Research Focus Identified by Blue Ribbon Panel Pediatric Cancer Working Group

- Development of model systems for preclinical studies
- Defining the critical dependencies created by specific fusion oncoproteins
- Defining how fusion oncoproteins influence gene expression and developmental programs
- Identifying protein complexes bound to fusion oncoproteins and defining the three-dimensional structure of oncoprotein domains and associated 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.

Currently Active Funding Announcements

- **PA-16-217/PA-16-218** Research Answers to NCI's Pediatric Provocative Questions (R01/R21)
(June 23, 2017; November 24, 2017 Receipt)
- **PA-16-251/PA-16-252** Gene Fusions in Pediatric Sarcomas (R01/R21)
(Standard Receipt Dates through May, 2019)
- **PA-17-138** Administrative Supplements to Promote Research Collaborations on Fusion Oncoproteins as Drivers of Childhood Cancer
(November 8, 2017; March 28, 2018 Receipt)

Fusion Oncoproteins in Childhood Cancers (FusOnC2) Consortium

- U54 multi-component program to support multi-disciplinary collaborative teams taking a **comprehensive approach** to understanding the biology of fusion oncoproteins and developing therapeutics.
- Each team to focus on a single fusion oncoprotein and overall program limited to a few **high risk fusion-driven cancers** without existing effective targeted agents.
- **Milestones** will be used to evaluate progress throughout the duration of funding.
- Annual Meeting/Engagement with other relevant NCI efforts.

Budget and Logistics

- RFA for U54s.
- Set-aside of \$7 million per year for 5 years.
- Single receipt dates in FY18 and FY19.
- Review in Special Emphasis Panel.
- Aim to fund 3 centers; \$2-2.5M/year Total Costs each.
- A separate set-aside to provide supplements for collaborations across the network for each of years 2-5.
- Access to shared NCI Pediatric Core services.

Markers of Success for this Initiative

- Development of **faithful models** of fusion-driven childhood cancers;
- Identification of the **critical dependencies** created by fusion oncoproteins;
- Understanding of the **binding partners** of fusion oncoproteins and the **pathways** by which they influence gene expression and developmental programs; and
- Identification of **small molecules** with potential for therapeutic value.



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