

Targeting Fusion Oncoproteins in Childhood Cancers (TFCC) Network

Presented by Malcolm Smith on behalf of the organizing team:

Malcolm A. Smith, MD, PhD (DCTD); Sharad Verma, PhD (DCTD);

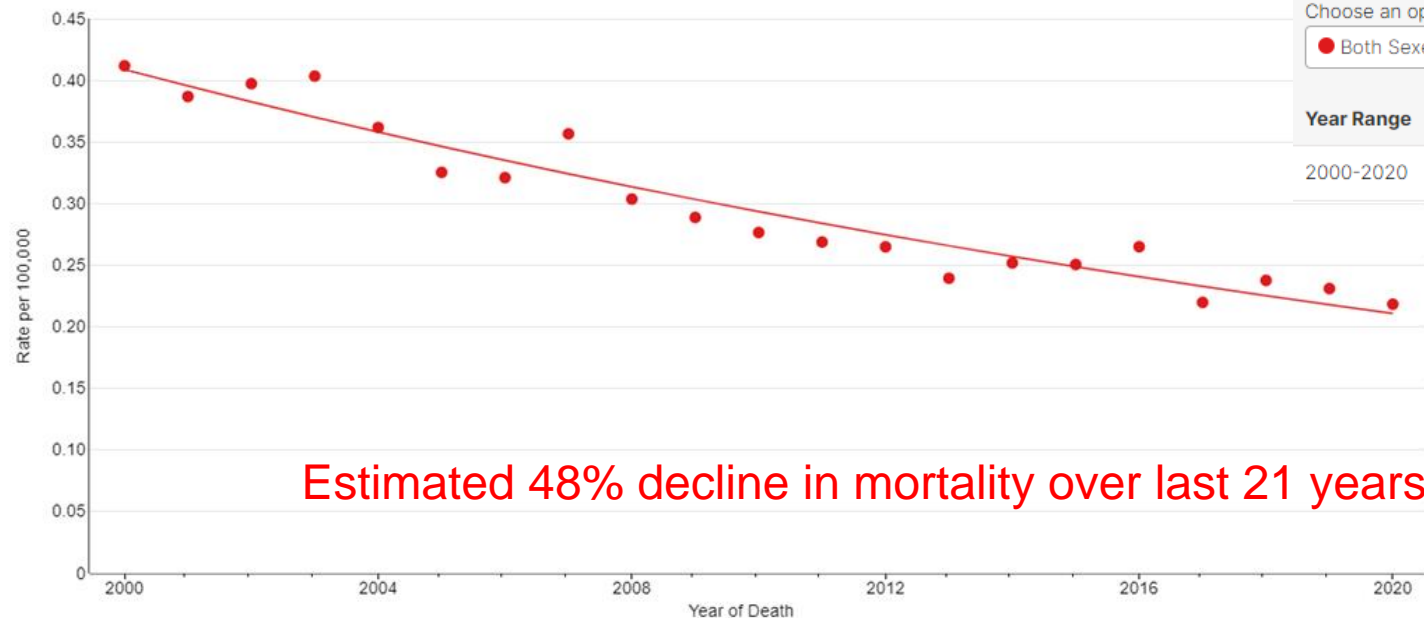
Rose Aurigemma, PhD (DCTD); Keren Witkin, PhD (DCB); Anu Sharman, PhD (DCB)

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 and bone cancers

Acute Lymphoblastic Leukemia Mortality Rates (< 20 years)

Acute Lymphocytic Leukemia (ALL)
Recent Trends in U.S. Age-Adjusted Mortality Rates, 2000-2020
By Sex, All Races, Ages < 20



Annual Percent Change (APC)

Choose an option:

Both Sexes

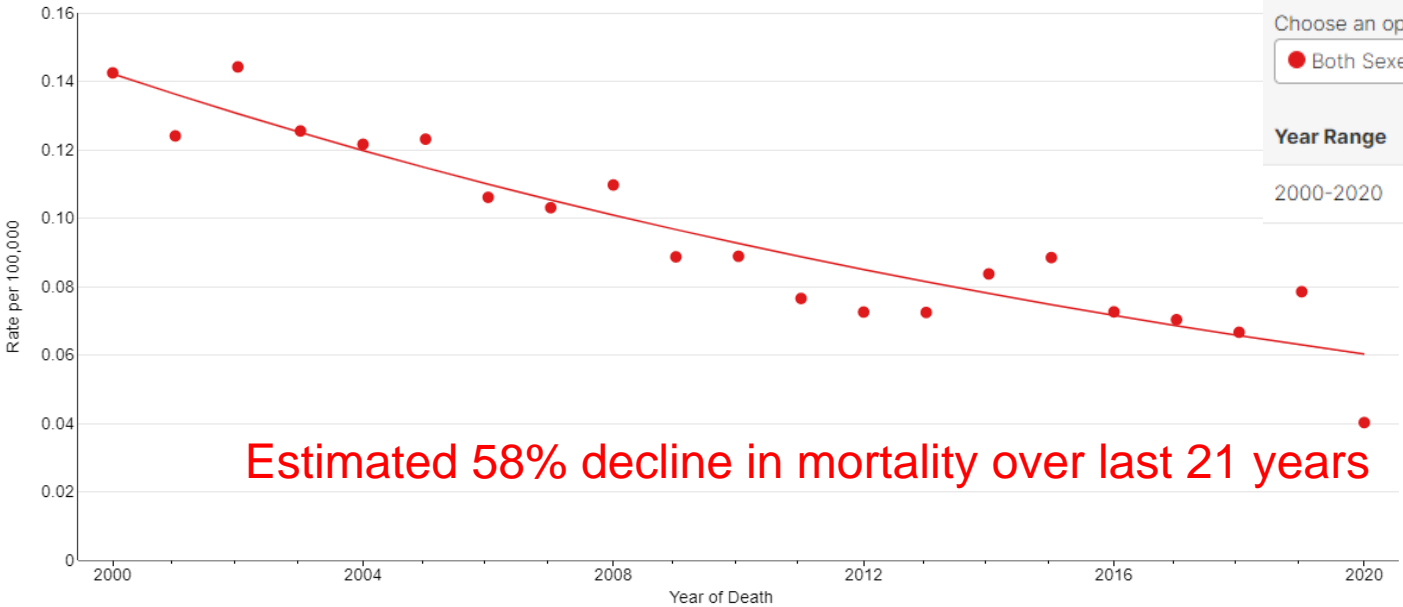
Year Range	APC %	Direction
2000-2020	-3.3	↓

Estimated 48% decline in mortality over last 21 years

Created by <https://seer.cancer.gov/statistics-network/explorer> on Tue Sep 27 2022.

Non-Hodgkin lymphoma mortality rates

Non-Hodgkin Lymphoma
Recent Trends in U.S. Age-Adjusted Mortality Rates, 2000-2020
By Sex, All Races, Ages < 20



Annual Percent Change (APC)

Choose an option:
● Both Sexes

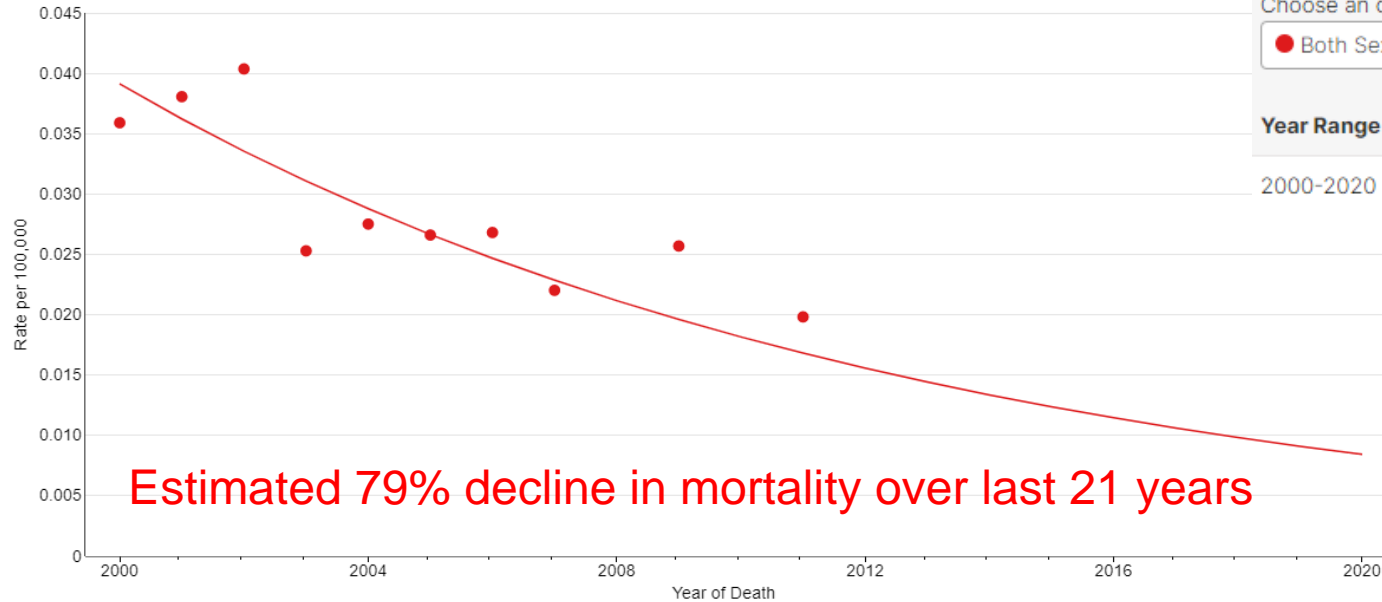
Year Range	APC %	Direction
2000-2020	-4.2	↓

Estimated 58% decline in mortality over last 21 years

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Hodgkin lymphoma mortality rates (< 20 years)

Hodgkin Lymphoma
Recent Trends in U.S. Age-Adjusted Mortality Rates, 2000-2020
By Sex, All Races, Ages < 20



Annual Percent Change (APC)

Choose an option:
● Both Sexes

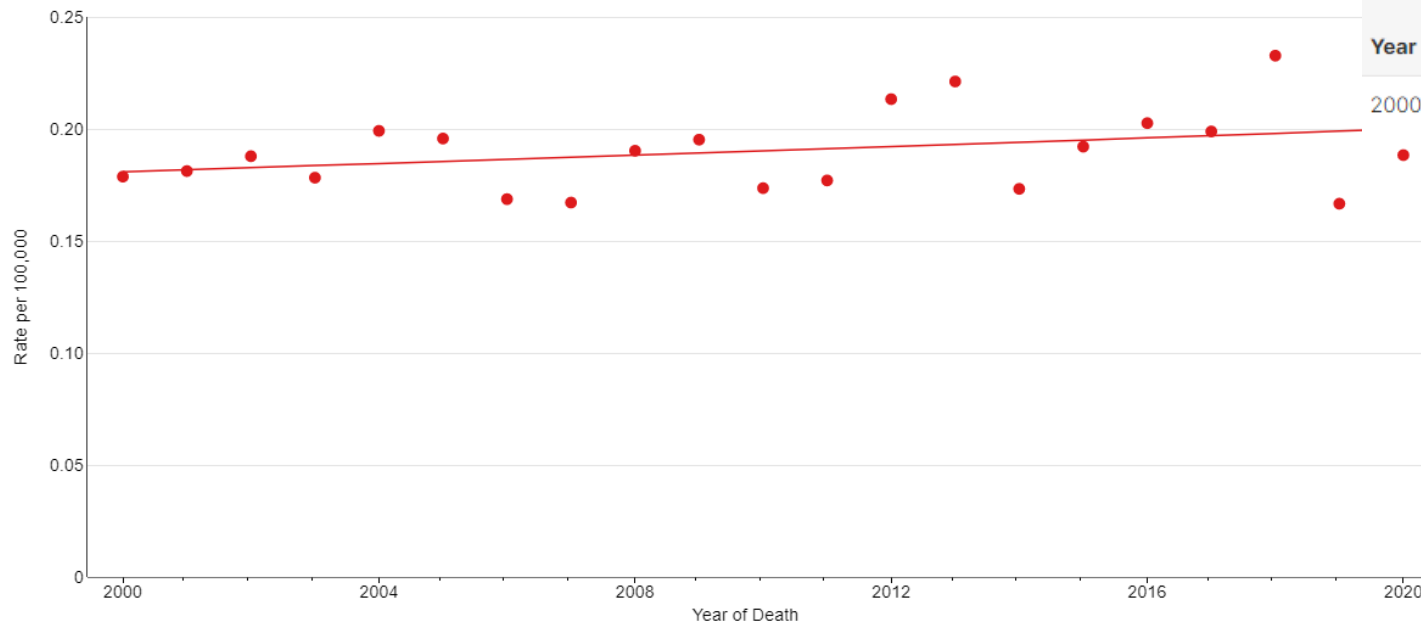
Year Range	APC %	Direction
2000-2020	-7.4	↓

Estimated 79% decline in mortality over last 21 years

Created by <https://seer.cancer.gov/statistics-network/explorer> on Tue Sep 27 2022.

Soft Tissue Cancer Mortality Rates

Soft Tissue including Heart
Recent Trends in U.S. Age-Adjusted Mortality Rates, 2000-2020
By Sex, All Races, Ages < 20



Created by <https://seer.cancer.gov/statistics-network/explorer> on Tue Sep 27 2022.

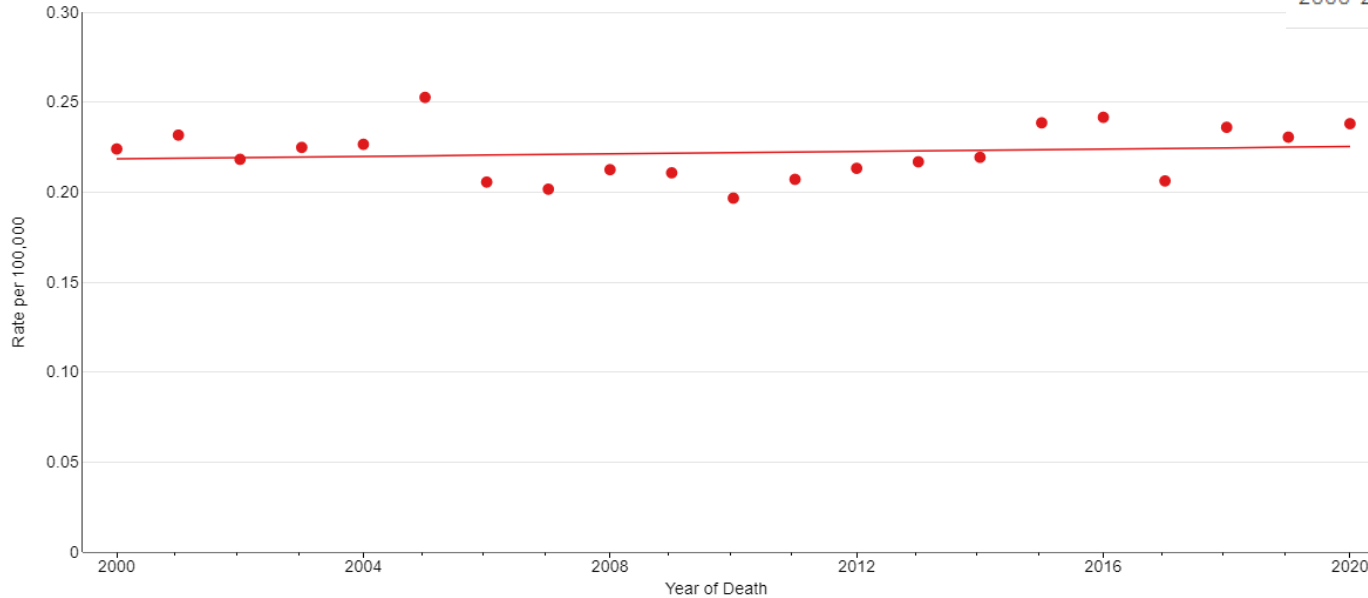
Bone Tumor Mortality Rates

Bones and Joints
Recent Trends in U.S. Age-Adjusted Mortality Rates, 2000-2020
By Sex, All Races, Ages < 20

Annual Percent Change (APC)

Choose an option:
● Both Sexes

Year Range	APC %	Direction
2000-2020	0.153	Not Significant

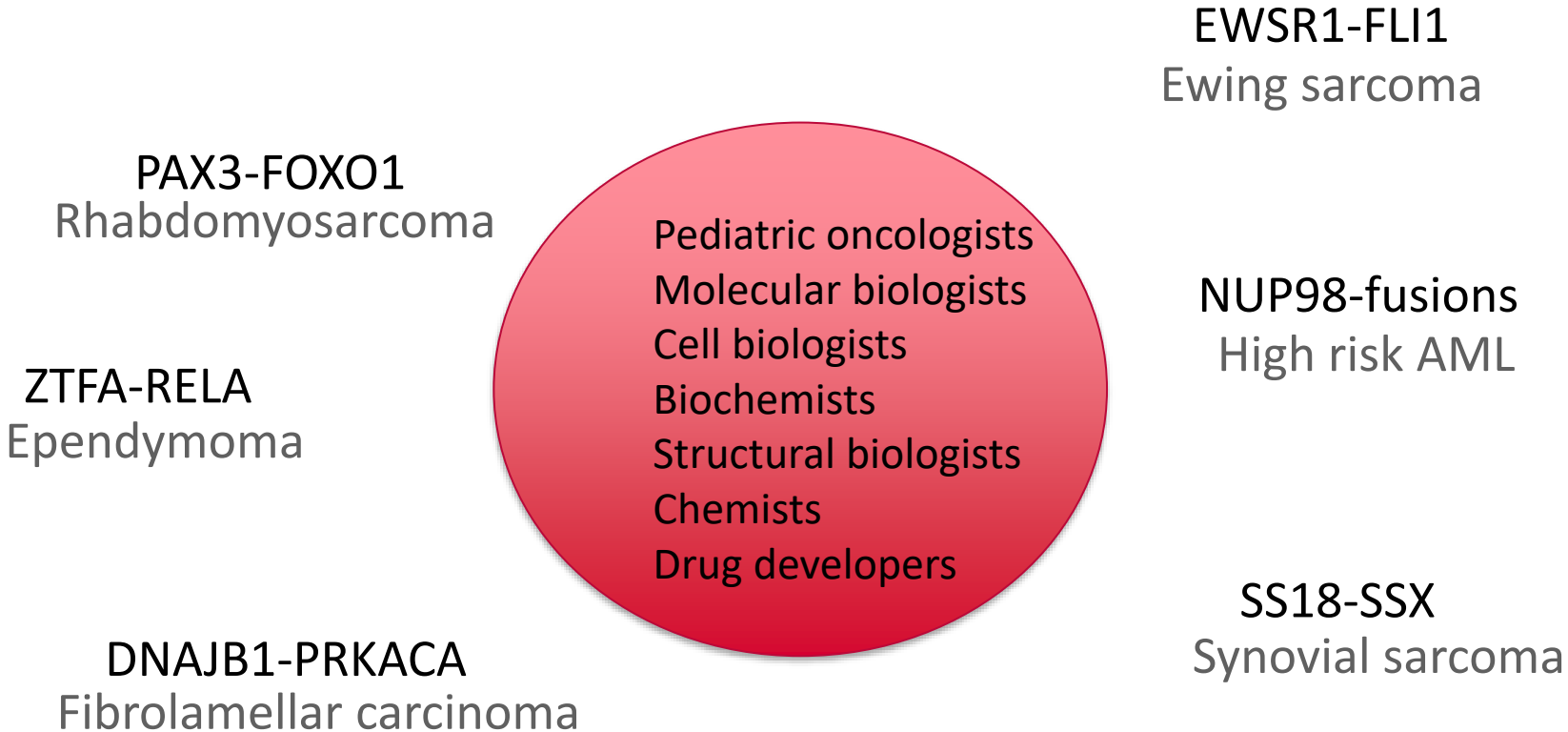


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Difficult cancers require new active targeted agents

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- **Active new agents desperately needed for cancers like Ewing sarcoma and rhabdomyosarcoma in order to cure more children and adults with these cancers**

Fusion Oncoproteins in Childhood Cancers (FusOnC2) Consortium



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**Intrinsically disordered proteins/
phase separation**

EWSR1-FLI1
Ewing sarcoma

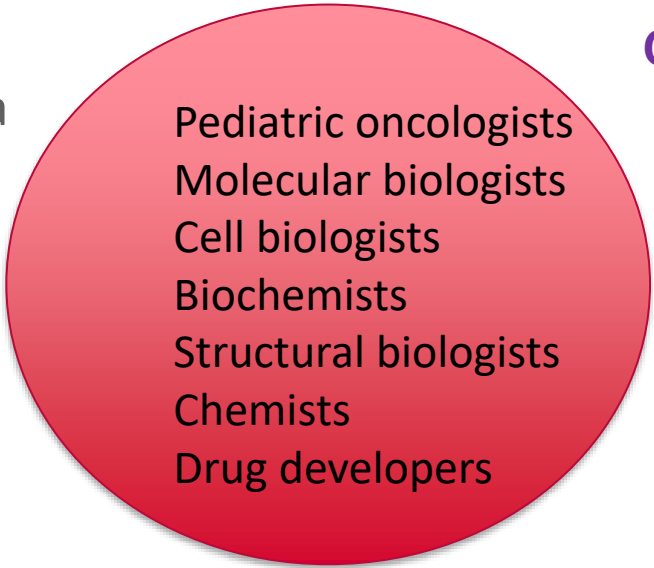
Chromatin remodeling

NUP98-fusions
High risk AML

Critical dependencies

SS18-SSX
Synovial sarcoma

Novel chemoproteomic strategies



PAX3-FOXO1
Rhabdomyosarcoma

Model development

ZTFA-RELA
Ependymoma

PROTACs

DNAJB1-PRKACA
Fibrolamellar carcinoma

Advances through FusOnC2 Consortium

- Identification of TRIM8, a ubiquitin ligase that regulates EWS-FLI1 protein levels, as a critical dependency for Ewing sarcoma (Goldilocks hypothesis)
- Identification of small molecules that stabilize the auto-inhibited conformation of FLI1 and other ETS family transcription factors, shifting the equilibrium away from DNA binding
- Identification of BRD9 as a synovial sarcoma dependency leading to clinical-stage programs for degraders of BRD9 in synovial sarcoma
- Identification of menin as a critical dependency in NUP98-rearranged leukemias
- Development of a high penetrance zebrafish genetic model of Ewing sarcoma that shows strong histologic similarity to human Ewing sarcoma
- Identification of CDK8 as both a novel interacting protein of the PAX3-FOXO1 fusion and as a critical dependency for fusion positive rhabdomyosarcoma
- Identification of a PAX3-FOXO1 small molecule binder with preliminary work to develop this compound into a PROTAC utilizing either cereblon or VHL-based ligands.

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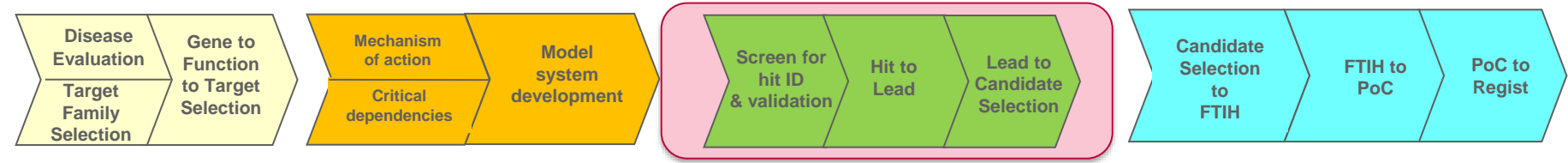
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Feedback from External Scientific Consultants

- Vitally important to continue investment in this research area
- Suggest diversifying the fusion oncoproteins included in future efforts
- Recommend applying state-of-the-art chemoproteomic methods for directly targeting fusion oncoproteins
- Suggest in future efforts 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

Gain insights on technologies to use for targeting Fusion Oncoproteins to develop therapies, and galvanize translational researchers



Novel Chemical Approaches for Targeting Fusion Oncoproteins

Webinar Series: Fridays, 12:00 - 1:00 pm ET (Aug. 19 - Oct. 21, 2022)



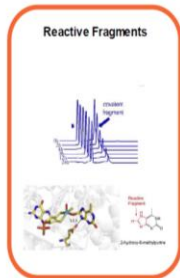
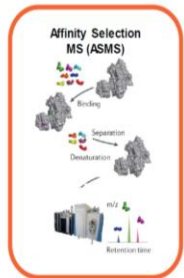
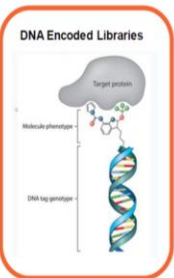
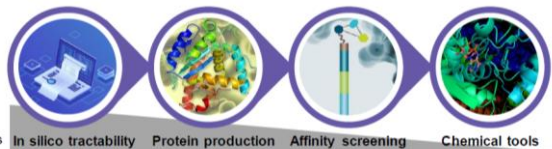
Nearly 1000 registrants

Lectures recorded and archived

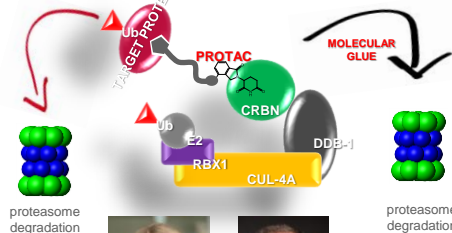
<https://events.cancer.gov/dctd/fusion-targeting-webinar>

Extraordinary Opportunities through Diverse Platforms and Modalities for **Therapeutic** targeting of *Fusion Oncoproteins*

Target ID, screening, hit ID

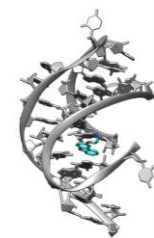


Targeted degraders of proteins and RNA



NATIONAL CANCER INSTITUTE

Jay Schneekloth



UF Scripps

Matthew Disney

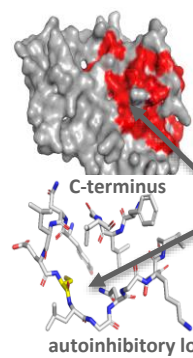


UC San Diego
Fleur Ferguson



Zoran Rankovic
St. Jude Children's Research Hospital

Covalent inhibitors



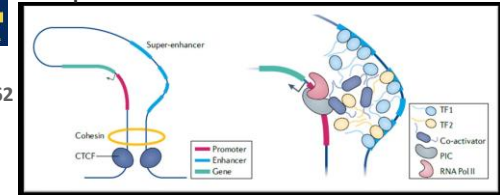
Tomasz Cierpicki
MICHIGAN



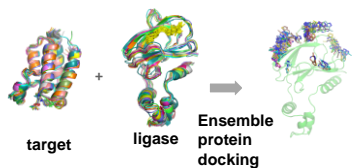
ICR The Institute of Cancer Research

Paul Workman

Ligandless TFs



Computational & AI/ML tools



AMGEN
Huan Rui



gsk
Brandon Turunen



BROAD INSTITUTE
Angela Koehler

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



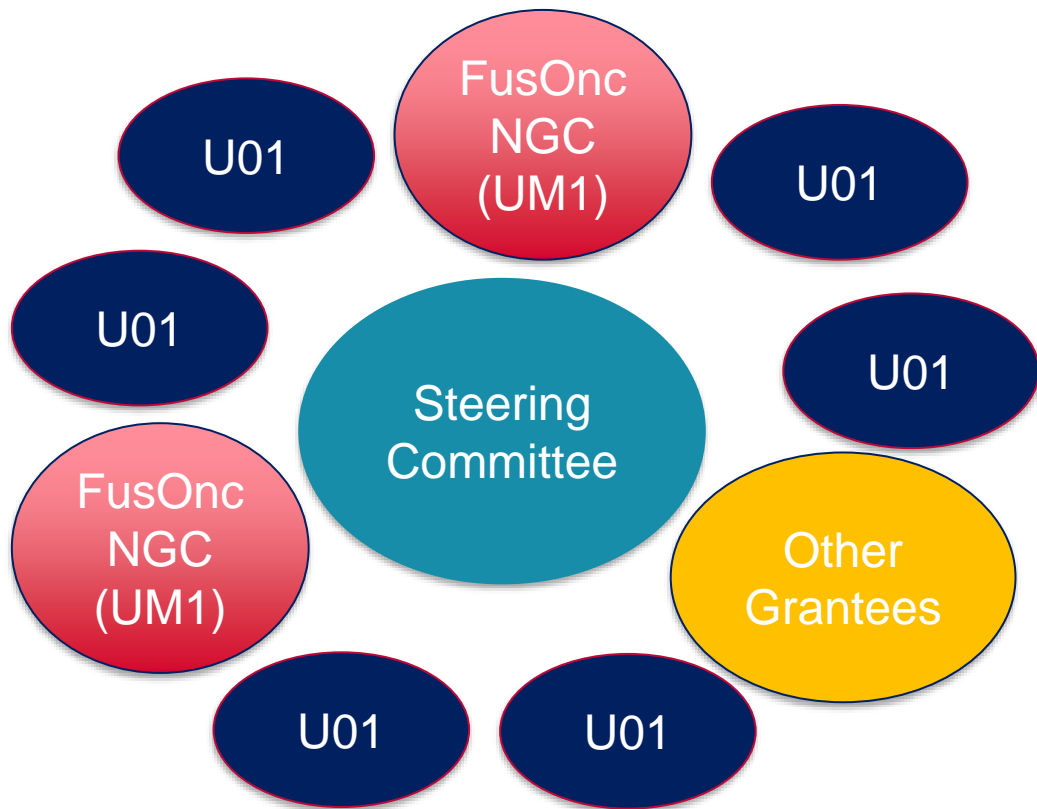
U01



FusOnc
NGC
(UM1)

Proposed 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 (~15%) in Years 2-5 to apply their therapeutic strategies to targets developed by the U01s and others in the scientific community



Targeting Fusion Oncoproteins in Childhood Cancers (TFCC) Network – Additional considerations

- Focus on fusion oncoproteins for tumors with high risk of treatment failure and for which there has been little progress in identifying targeted agents
 - Encourage applications related to solid tumors and brain tumors
 - Exclude fusion oncoprotein targets for which clinical proof of concept has been achieved
- Encourage data sharing as rigorously as possible and collaborate with other NCI programs (e.g., CCDI) to ensure usability, accessibility and shareability of the data

Budget and Logistics

- RFA for U01 awards to better understand molecular mechanisms of fusion-driven oncogenesis and identify novel drug targets
 - Aim to fund 6 U01s at \$325K direct cost (~\$550K total cost) each
- Separate RFA for UM1 awards for Next Generation Chemistry Centers for Fusion Oncoproteins
 - Aim to fund 2 UM1s at \$1.5M direct cost (~\$2.5M total cost) each
 - 15% of UM1 budgets in years 2-5 will be restricted for collaborative projects
- Single receipt date in late 2023 for each RFA; all grants will have 5-year duration
- Review in Special Emphasis Panel

Total Network Cost: \$8.3M annually for 5 years (FY24-FY28)

Markers of Success for this Initiative

- New collaborations established between medicinal chemists, molecular biologists, and pediatric oncologists
- New functional domains, critical dependencies, and vulnerabilities identified
- New technologies and strategies identified for targeting fusion oncoproteins or their critical dependencies through inhibition or degradation approaches
- Chemical probes, tools, or advanced leads for further optimization to new drug candidates



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