Using the CCDI Molecular Targets Platform

CCDI Webinar Series

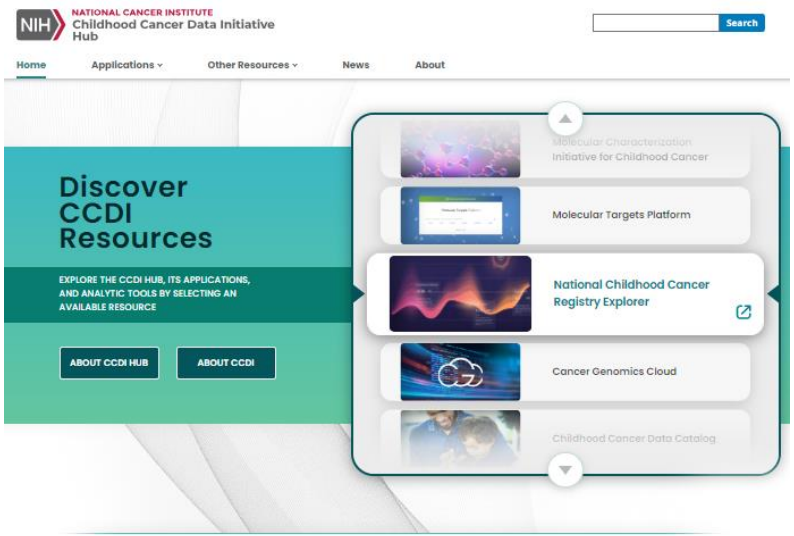
NIH NATIONAL CANCER INSTITUTE

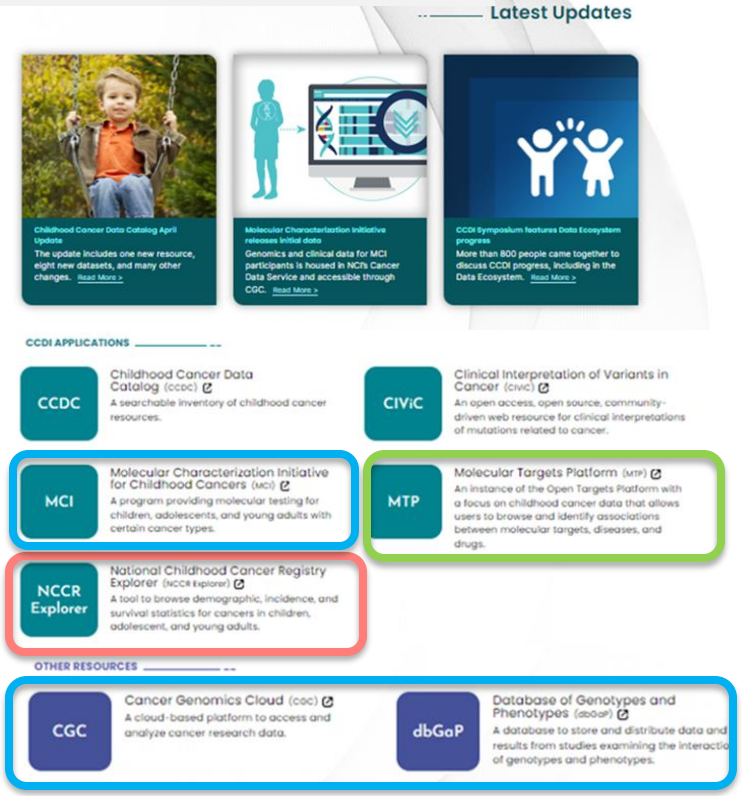
August 21, 2023

1. *CCDI Hub*
2. *Overview of the Molecular Targets Platform (MTP)*
3. *Demonstration of MTP Pediatric Cancer Data Navigation*
4. *MTP Use Cases*

CCDI Hub: ccdi.cancer.gov

Entry point to use and connect with CCDI applications, data, tools, and other resources





Overview of CCDI Molecular Targets Platform

Big Data Approach to Provide Evidence

Thank You to Everyone Who Helped Build the MTP!

National Cancer Institute, Food and Drug Administration, and Frederick National Laboratory

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CCDI Working Group Report

24 specific recommendations

- Landscape of Pediatric/AYA Cancer Research Data & Needs Analysis
- Types of Data for Collection and Aggregation
- Potential Barriers to Progress
- Generating New Data
- Distinction Between Research & Clinical Data
- Engaging Diverse Array of Stakeholders for Input
- Potential Opportunities for Transformative Discoveries

Strategic Plan

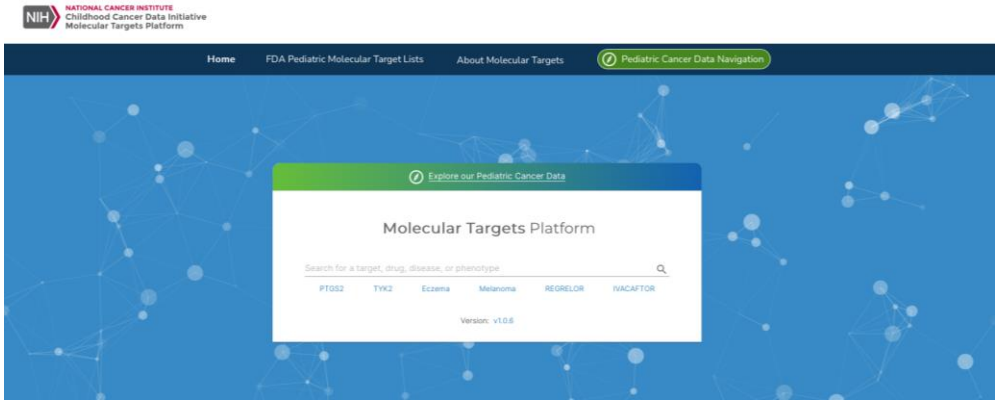
- Established a collaborative working group of multi-disciplinary investigators from the National Cancer Institute (NCI), US Food and Drug Administration (FDA), Foundation for the National Institutes of Health (FNIH), and Children's Hospital of Philadelphia (CHOP).
- Adopted the open source Open Targets Portal (opentargets.org) for pediatric cancer drug development in collaboration with European Molecular Biology Laboratory.
- Developed a node within the CCDI Data Ecosystem to provide the computational infrastructure for academics, industry partners, and advocates to support pediatric cancer drug development.

Open Targets Platform

- A knowledgebase and prioritization tool sourced from numerous public datasets.
- Reduces time spent monitoring and organizing scientific literature.
- A public-private partnership with several large pharmaceutical and biomedical research institutions.
- Includes a broad range of harmonized targets, diseases, and drugs.

CCDI Molecular Targets Platform

- NCI's instance of the Open Targets Platform with a focus on pediatric cancers (launched Aug 2022).
- Allows users to browse and identify associations between molecular targets, diseases, and drugs.
  - 58,867 molecular targets and 64 diseases within the childhood cancer data.
- Includes a computable interpretation of 215 targets from the FDA Relevant Molecular Target List (Sep 2022 release).

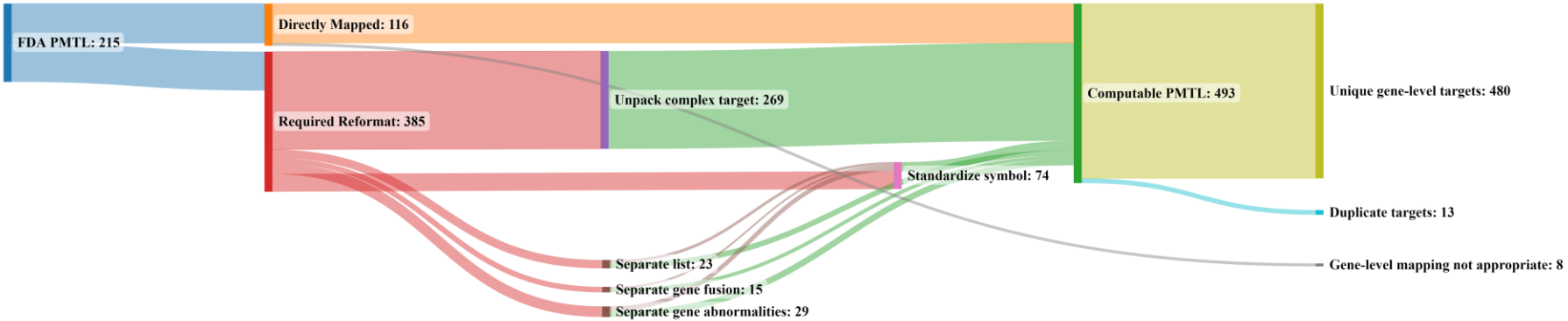


moleculartargets.ccdi.cancer.gov

Computable Pediatric Molecular Target Lists (PMTL)

- The FDA released two lists to address the needs of the RACE Act, which were processed into the PMTL for MTP.
  - **Relevant Molecular Target List**: targets have evidence indicating their relevance in the growth or progression of pediatric cancers. Any new drugs developed for these targets in adult cancers must also be studied for use in pediatric cancers.
  - **Non-Relevant Molecular Target List**: targets have evidence indicating that they are not relevant in the growth or progression of pediatric cancers. Any new drugs developed for these targets in adult cancers will receive an automatic waiver from also studying them in pediatric cancers.

215 targets in FDA Relevant and Non-Relevant Lists → 480 unique, gene-level targets in Computable PMTL (501 including duplicates and non-gene targets)



MTP: Data Flow

Childhood Cancer Datasets

- TARGET
- Kids First
- OpenPBTA
- More to come...

Data Types:
- RNA-Seq
- WGS
- WXS
- Methyl Array
- Panel RNAFusion
- Panel DNA

Adult Cancer & Normal Datasets

- GTEx
- TCGA

Data Harmonization & Analysis

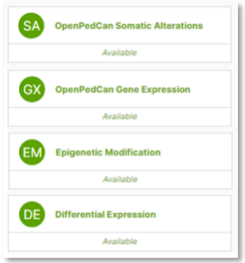
- Harmonized Pediatric Data
- Preclinical Treatment Evidence
- Compatible Ontologies
- Pediatric PMTL
- Analysis and Harmonization Pipelines:
  - Kids First and OpenPedCan
  - (OpenPBTA fork)

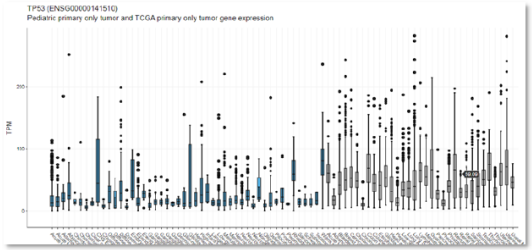
Open Targets Platform

FDA Relevant Molecular Target List

NIH NATIONAL CANCER INSTITUTE
Childhood Cancer Data Initiative
Molecular Targets

- Drug/Disease/Gene evidence
- Plots and interactive visualizations
- Ontological categorizations
- Association scores
- PMTL Relationships
- Target Prioritizations





MTP Pediatric Cancer Data Navigation

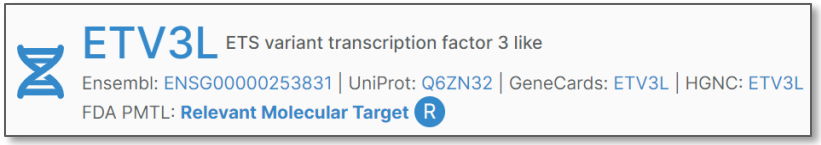
Demonstration

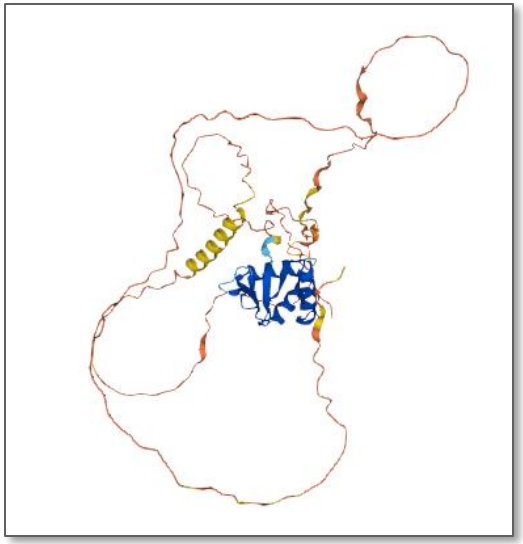
CCDI Molecular Targets Platform Use Cases

Demonstration

Use Case #1: Using MTP to Explore Drug Development

- A lead researcher in a drug company is interested in a particular gene (ETS1) found on the FDA's PMTL list.
- In MTP, the PMTL list has been curated and expanded to include gene family members which are not on the FDA's website (in particular, ETV3L, a member of the ETS transcription factor family).
- If we have an effective treatment for adults with ETV3L mutations, then finding pediatric data for ETV3L mutations could lend support to justify setting up a pediatric cancer clinical trial for this drug.



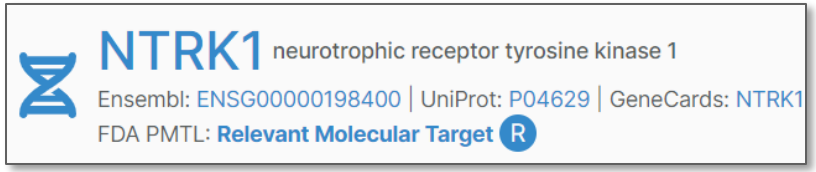


Use Case #2: Using MTP to Explore Mutations

- What is the landscape of FGFR3 mutations in all pediatric cancers?
- Do they exist with a frequency useful for development, and are there specific histologies where they are enriched?
- Investigators may want to know about any somatic alterations (SNVs, CNVs, Fusions), including splice variants, to understand protein-domain specific drugs.
- We can explore the MTP to determine if there are splice variants present in a particular pediatric cancer.

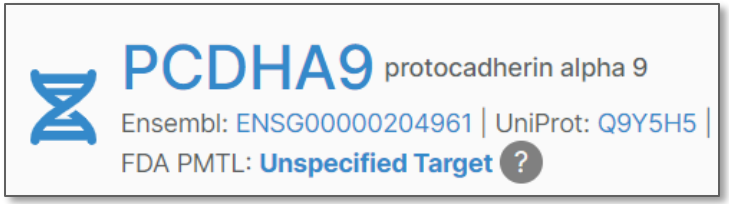
Use Case #3: Using MTP to Explore Clinical Trial Opportunity

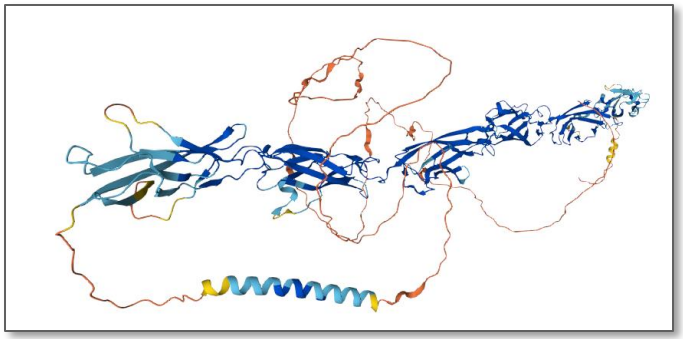
- A drug company has a new pan-TRK inhibitor that crosses the blood-brain barrier and would like to develop this drug for pediatric brain tumors.
- To set up a clinical trial, we need to know what types of brain tumor histologies have TRK fusions and in what frequency.
- We also want to see expression levels of NTRK1-3 across pediatric brain tumor histologies.



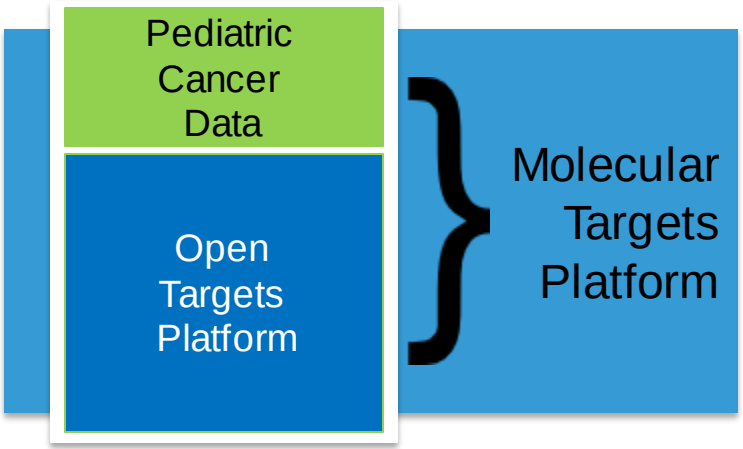
Use Case #4: Using MTP to Help Researchers Plan Additional Experiments

- As a researcher, my experiments have shown incidentally that a gene has little known function in cancer but is associated with HLHS cardiac syndrome and neurodevelopmental impairment.
- PCDHA9 has very high mRNA expression in adult oligodendroglioma cancer cell lines.
- I'm wondering if any pediatric brain cancer patients from various data sets represented in MTP also show this trend of high mRNA expression?





Summary



Allows users to identify associations between molecular targets, diseases, and drugs

Uses FAIR and Computable Pediatric Molecular Target Lists to allow the research community to explore molecular targets relevant to the growth or progression of childhood cancers

The addition of childhood cancer data within MTP has yielded childhood-cancer specific views and utility to the research community

*September 2022 release

Soliciting Feedback!

Gene/Target-Centric Platform:

- Should we develop a gene/target-centric platform that leverages the Computable PMTL, incorporates the necessary genomics data, and enriches the platform with relevant evidence for each gene?

Incorporate New Data Sets:

- Should we include new data sets and if so, what is your feedback on introducing these new data sets without undergoing a complete harmonization process with the existing data sets?

Ideal Home Page:

- Should we keep the main search home page inherited from Open Targets as-is, or should we allow users to land directly on the Pediatric Cancer Data Navigation page as the site entry point?

Find Out More About CCDI

Visit the CCDI Hub and access the CCDI Data Ecosystem.
ccdi.cancer.gov

Subscribe to our monthly newsletter.
cancer.gov/CCDI

Questions? Email us.
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Thank you for attending!

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