Pediatric Immunotherapy Discovery & Development Network (PI-DDN) Program Overview

Nita Seibel MD on behalf of the PI-DDN Implementation Team
Judy Mietz (co-chair), Susan McCarthy (co-chair), Malcolm Smith(coordinator), David Patton, Tom Gross, Kory Hallett, Sonia Rosenfield, Min Song, Beverly Teicher, Tiffany Wallace,

IMAT Kickoff Meeting
November 30, 2018

NIH NATIONAL CANCER INSTITUTE

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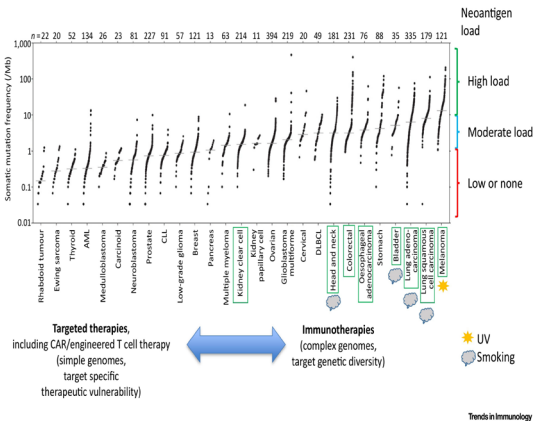
Pediatric Immunotherapy Key Points

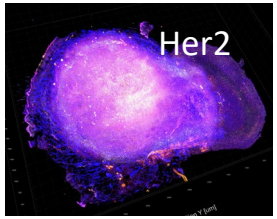
- Pediatric immunotherapy research is distinctive from adult immunotherapy research

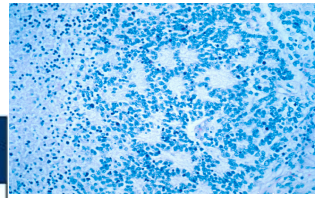
- Pediatric cancers generally have low mutation rates and corresponding low rates of mutated proteins that the immune system can recognize

- Focus of pediatric immunotherapy research on identifying and targeting normal antigens using engineered antibody products and engineered immune cells (e.g., CAR T cells)

Barriers Identified by the BRP Pediatric Cancer WG







- Low mutation burdens, less likely to express neoantigens and be susceptible to immune checkpoint blockade therapies
- Identifying the optimal childhood cancer cell surface antigens for targeting with immunotherapy agents remain a challenge;
- Most immunotherapeutic strategies that are in the pipeline of pharmaceutical companies are based on targeting specific antigens expressed on cancers occurring in adults
- Tumors establish a disabling, immunosuppressive TME

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Cancer Moonshot BRP Recommendation B

Development of a pediatric immunotherapy translational science network that would facilitate the testing of new immunotherapy approaches in childhood cancer and establish a robust research pipeline to help further advance this field of study

Blue Ribbon Panel Pediatric Cancer Working Group Recommendations

- Identification of antigenic epitopes that are uniquely and abundantly expressed in pediatric cancers
- Development of highly specific binders for novel antigenic epitopes
- Development of candidate novel immunotherapy agents
- Identification of cancer cell-intrinsic and -extrinsic mechanisms of immune evasion
- Development of approaches for *in vivo* preclinical testing of novel immunotherapies

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https://www.cancer.gov/research/key-initiatives/moonshot-cancer-initiative/blue-ribbon-panel/blue-ribbon-panel-report-2016.pdf

To Implement Recommendation B

Pediatric Immunotherapy Discovery & Development Network (PI-DDN)

- A collaborative research network with goal of advancing immunotherapy concepts for children and adolescents with cancer toward clinical applications
- Includes U01 research projects and multi-component U54 Programs that support collaborative teams with a focus on:
  - identifying new targets for immunotherapies,
  - developing new pediatric immunotherapy treatment approaches and
  - defining the biological mechanisms by which pediatric tumors evade the immune system
- Network teams will have access to NCI Core Services to support advancement toward clinical testing in children.

FY18 solicitation: RFA-CA-17-050 and RFA CA-17-051

FY19 solicitation: RFA-CA-19-003 and RFA CA-19-004 Open Now!

Receipt Date: December 17, 2018

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Components of the PI-DDN (so far)

- **Discovery and Development of Optimal Immunotherapeutic Strategies for Childhood Cancers (U54)**
  John Maris (Children's Hospital of Philadelphia) and Crystal Mackall (Stanford)

- **Combinations of Synergistic Bispecific Human Antibodies: A Novel Strategy for the Treatment of Neuroblastoma (U01)**
  James Olson and Christopher Mehlin (Fred Hutchinson Cancer Research Center)

- **Multispecific targeting incorporating cytokine receptor pathways in high risk pediatric acute leukemias to improve durability of adoptive cell therapy-induced remissions (U01)**
  Terry Fry (U Colorado) and Sarah Tasian (Children's Hospital of Philadelphia)

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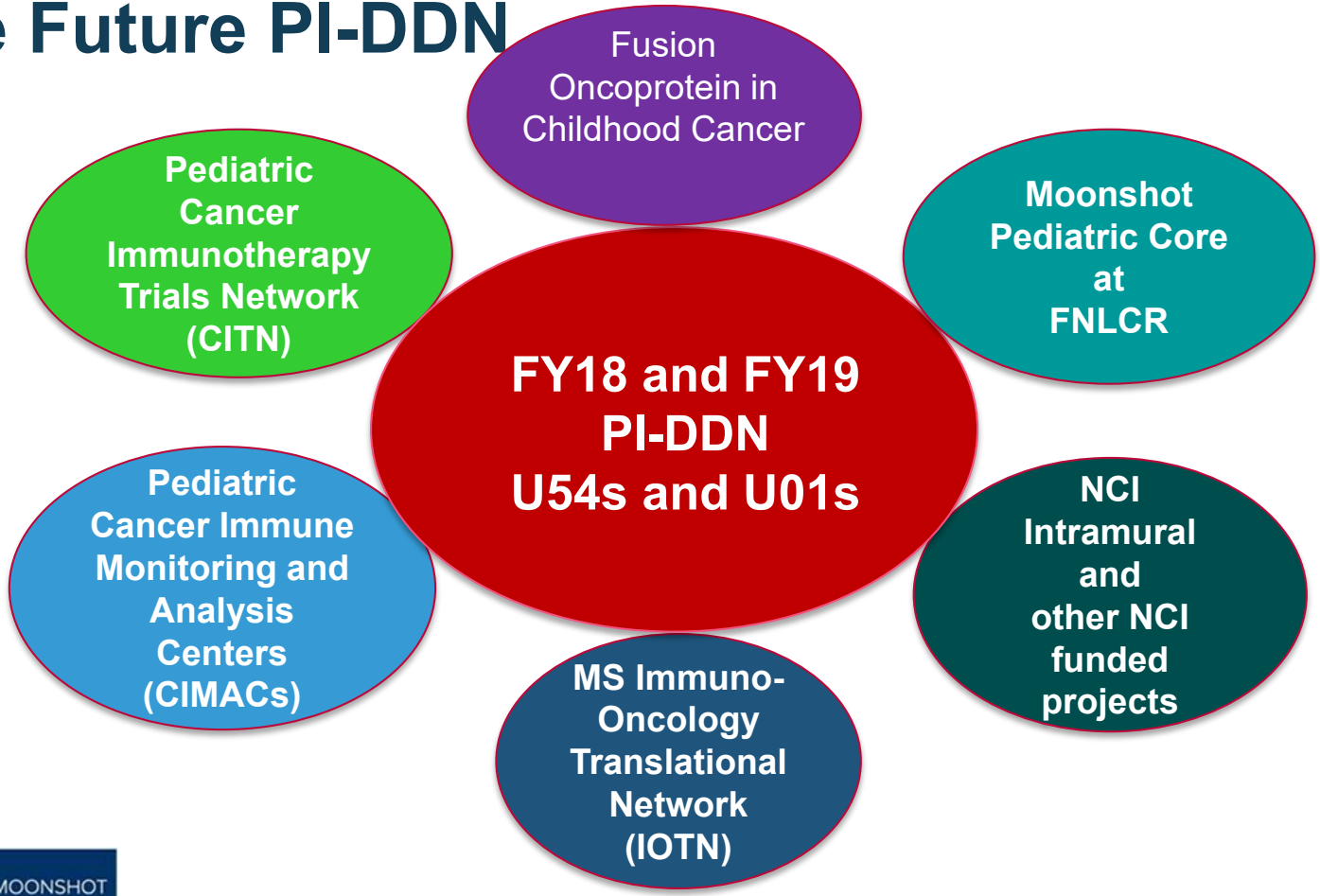
Components of the PI-DDN (so far)

- **Cassette exons in neoplastic pro-B-cells: implications for immunotherapy (U01)**
  Andrei Thomas-Tikhonenko (Children's Hospital of Philadelphia) and Yoseph Barash (University of Pennsylvania)

- **Dual targeting of tumoral microenvironment and tumoral cells by blocking the IL-33/ST2 pathway (U01)**
  Sophie Paczesny (Indiana University-Purdue University at Indianapolis) and Nai-Kong Cheung (Memorial Sloan Kettering Cancer Center)

- **Metabolic reprogramming of tumor microenvironment to maximize immunotherapy for pediatric cancers (U01)**
  Ruoning Wang (Research Institute at Nationwide Children's Hospital)

The Future PI-DDN



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Discovery and Development of Optimal Immunotherapeutic Strategies for Childhood Cancers (U54)

John Maris (Children's Hospital of Philadelphia) and Crystal Mackall (Stanford), Poul Sorensen (British Columbia Cancer Agency), Nabil Ahmed (Texas Children's Hospital), Paul Sondel (University of Wisconsin)

Aim 1

- Discover optimal immunotherapeutic targets and target profiles for HR pediatric cancers
  - Childhood cancer express lineage specific surface proteins abundantly with limited expression on normal tissue, but essential for tumor survival
  - Use of mass spectrometry of tumors from 175 PDX

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Discovery and Development of Optimal Immunotherapeutic Strategies for Childhood Cancers (U54)

Aim 2

- Develop approaches to overcome tumor-intrinsic and tumor-extrinsic mechanisms of immunotherapy resistance
  - Use of state-of-the art technologies (CyToF for AML, multiplexed ion beam imaging (MIBI) for solid tumors) to identify the most promising cell surface antigens
  - Identify new targets and study biology T cell exhaustion in CAR T cells
  - Generate multi-specific next generation CAR T cells therapy

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Discovery and Development of Optimal Immunotherapeutic Strategies for Childhood Cancers (U54)

Aim 3

- Develop readily translatable therapeutic strategies to exploit basic mechanisms of pediatric cancer oncogenesis and prevent immune evasion
  - Explore underlying mechanisms by which tumors avoid T cell detection
  - Use to make “cold tumors” immunogenic
  - Test combination therapy (as *in situ vaccine*) that incorporates radiation, fusion protein linking with IL2 with antiGD2 (focus on NB, sarcomas, medulloblastomas)

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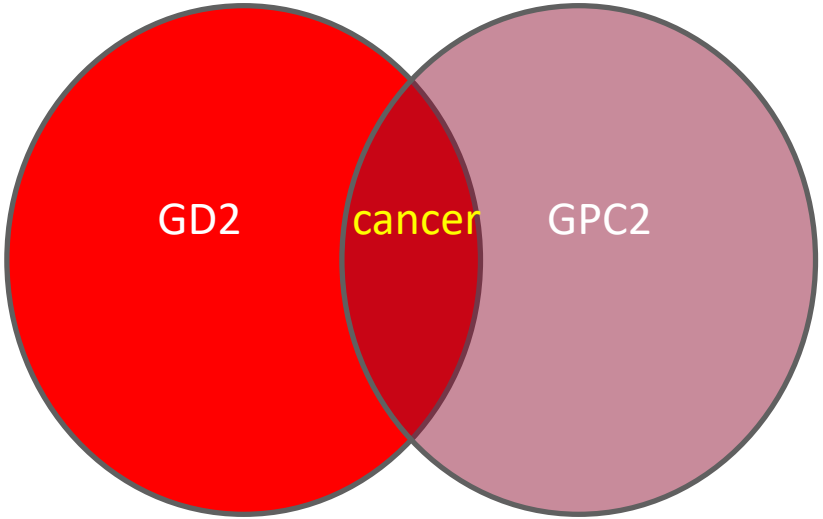
Combinations of Synergistic Bispecific Human Antibodies: A Novel Strategy for the Treatment of Neuroblastoma

James Olson and Christopher Mehlin (Fred Hutchinson Cancer Research Center)

Aims:

- To determine whether paired BiTEs show enhanced cancer cell death and cancer:normal specificity compared to either component of the pair

- To elucidate the optimal BiTE architecture and evaluate prioritized BiTE pairs in state-of-the-art murine models with same patient reconstituted human immune systems.



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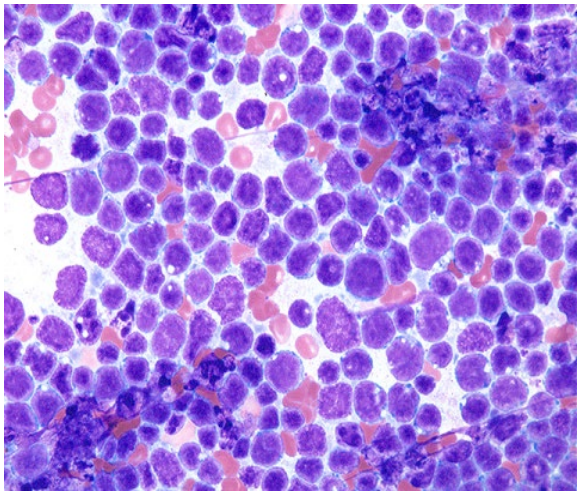
Multispecific targeting incorporating cytokine receptor pathways in high risk pediatric acute leukemias to improve durability of adoptive cell therapy-induced remissions

Terry Fry (U Colorado) and Sarah Tasian (Children's Hospital of Philadelphia)

Aims

- To develop combinatorial CAR constructs targeting CD19 and/or CD22 plus TSLPR and associated signaling pathways to improve remission longevity in Ph-like B-ALL
- To develop combinatorial CAR constructs targeting CD19 and/or CD22 plus CD135 and associated signaling pathways to improve remission induction and longevity in KMT2A-rearranged B-ALL
- To develop combinatorial CAR constructs targeting CD33 plus CD135 and associated signaling pathways to induce sustained remissions in FLT3-mutant AML



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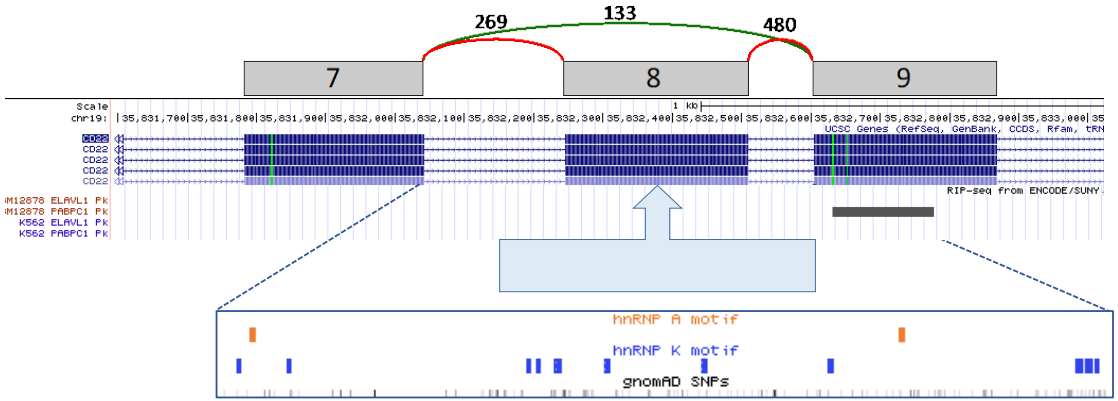
Cassette exons in neoplastic pro-B-cells: implications for immunotherapy (U01)

Andrei Thomas-Tikhonenko (Children's Hospital of Philadelphia) and Yoseph Barash (University of Pennsylvania)



Aims:

- To identify programs and determinants of altered splicing B-ALL cell surface antigens
- To investigate the effects of alternative splicing on B-ALL immunotherapy

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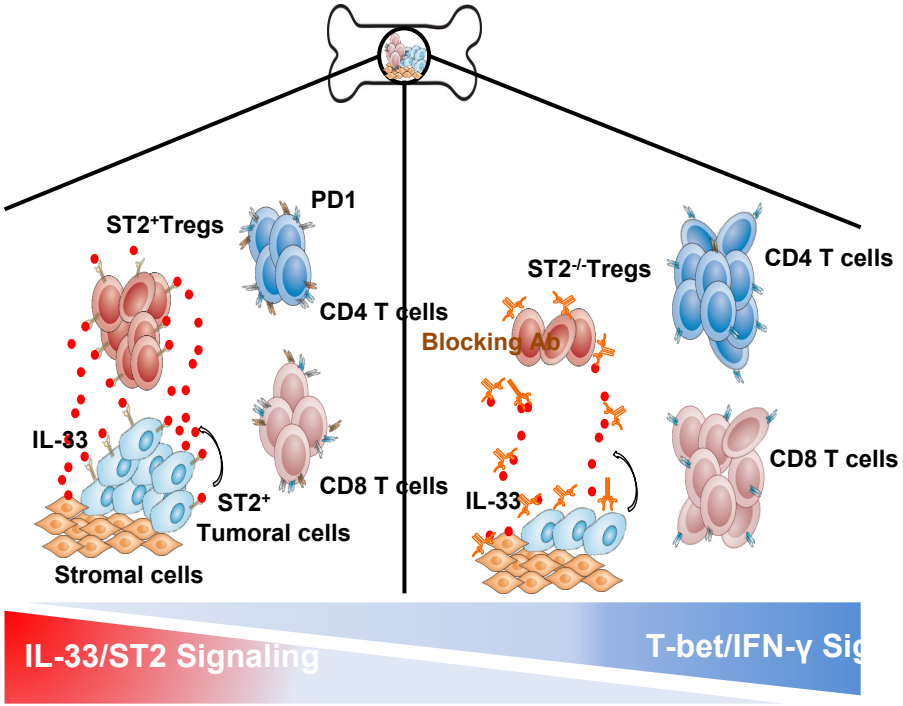
Dual targeting of tumoral microenvironment and tumoral cells by blocking the IL-33/ST2 pathway (U01)

Sophie Paczesny (Indiana University-Purdue University at Indianapolis) and
Nai-Kong Cheung (Memorial Sloan Kettering Cancer Center)

Aims

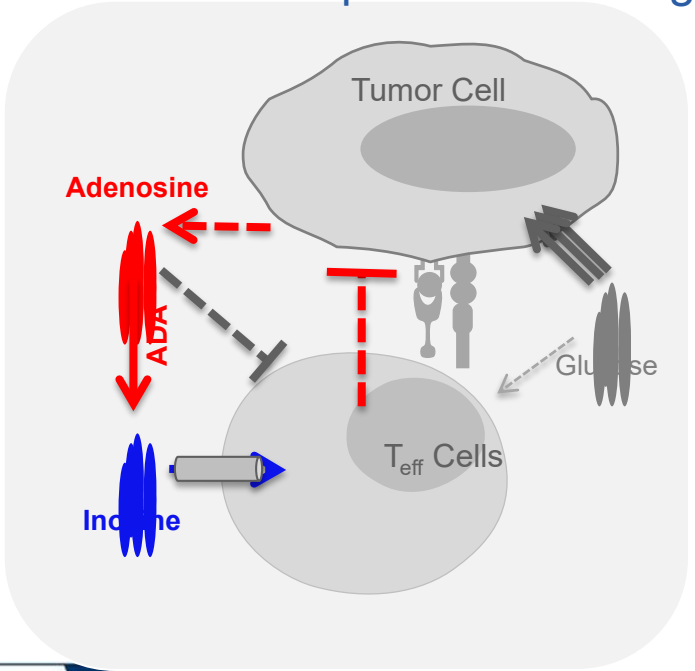
- Explore ST2 and IL-33 expression on tumoral cells and in the tumoral microenvironment from liquid and solid childhood cancers in human and mice
- Examine whether ST2/IL-33 blockade can impact tumor immunity in the malignant BM niche and solid tumor microenvironment as a proof-of-principle of a novel antitumoral immunotherapy
- Optimizing anti-ST2 neutralizing antibodies against murine and human targets for translational purpose



Metabolic reprogramming of tumor microenvironment to maximize immunotherapy for pediatric cancers

Ruoning Wang (Nationwide Children's)

Hypothesis: reprogramming of the adenosine-inosine metabolic axis can maximize anti-tumor immune response in treating pediatric solid tumors



- Decipher the adenosine/inosine metabolic pathways in Teff cells (META)
- Determine the effects of modulating inosine utilization on T cell effector function and anti-tumor immunity
- Develop strategies to reprogram tumor metabolic microenvironment and maximize systemic anti-tumor immunity

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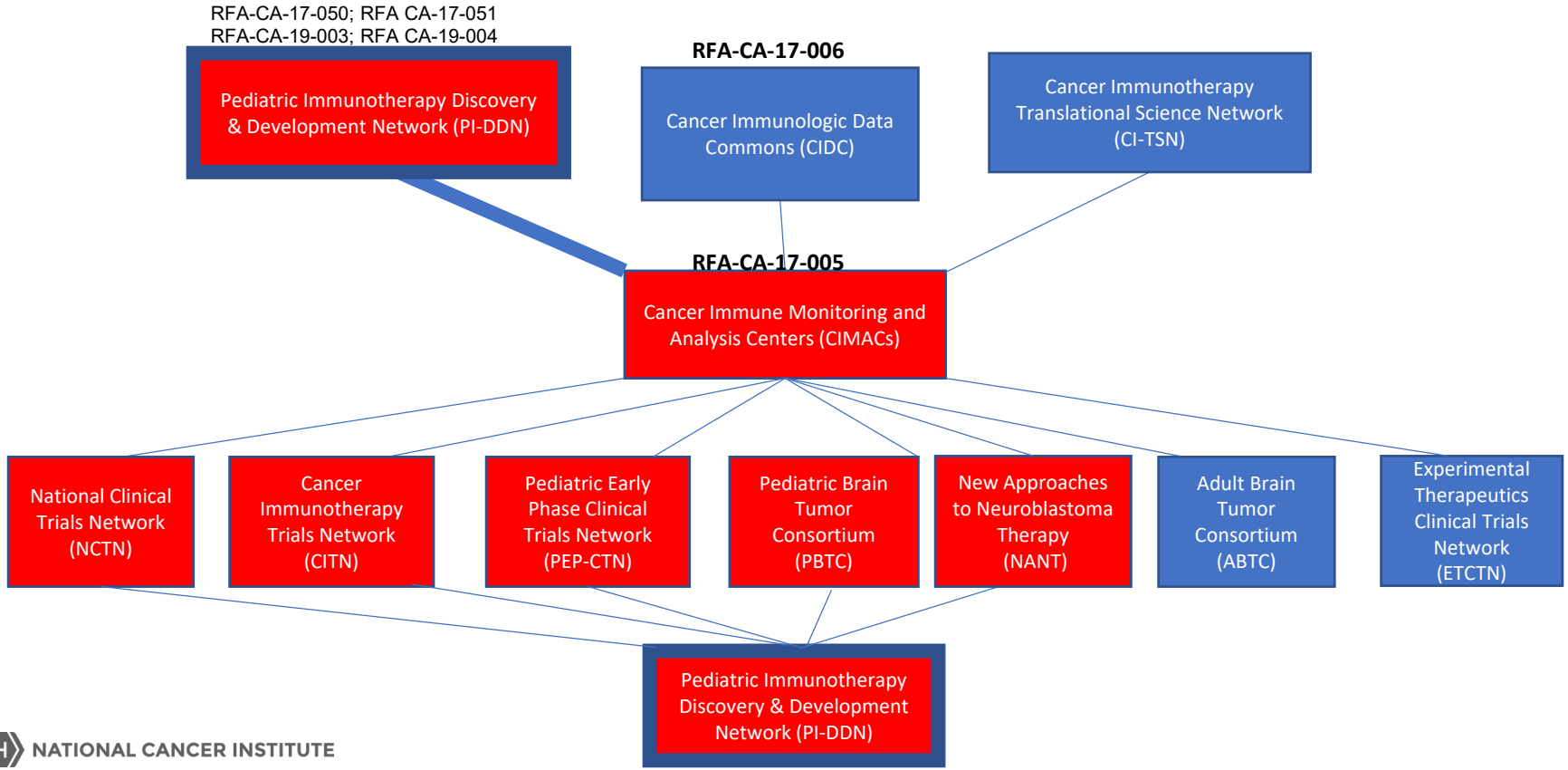
NCI Cancer Immunotherapy Networks (Comprehensive)



Questions??

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