Advancing Cancer Immunotherapy by Mitigating Immune-Related Adverse Events (irAEs)

Adult and Pediatric Immunotherapy Implementation Teams

Presentation by Susan McCarthy, on behalf of the CMITs
Cancer Moonshot Blue Ribbon Panel Recommendation B: Create a network to accelerate translation of basic discoveries to clinical applications to improve immunotherapy outcomes.

The overarching goal of this concept is to support research that improves cancer immunotherapies by eliminating or reducing the incidence and/or severity of inflammatory and/or autoimmune adverse-event responses, while retaining anti-tumor efficacy.

This RFA Concept Proposes:

• A one-time FY2020 trans-NIH U01 solicitation, with participation by NCI, NIAID, NIAMS, NIDCR, and NIDDK
• To leverage on-going Cancer Moonshot investments in FY2017 trans-NIH collaborative supplements and FY2018-19 U-series awards
• To expand/strengthen existing NCI cancer immunotherapy networks
Tumor Microenvironments are Immunosuppressive

Immune-Desert Tumor

- No T-cell help
- No co-stimulatory ligands
- No danger signals
- No APC to LN

Immune-Infiltrated Tumor

- Cancer-associated fibroblasts
- Dendritic cells
- Regulatory T cells
- Tumor cells

Immune-Excluded Tumor

- Vascular
- Extracellular matrix
- Chemokines
- Chemokine proteases
- Dipeptidyl peptidase 4

Tolerance

- Immuneologic ignorance
- Non-inflammatory conditions
- Loss of MHC
- Inflammatory presentation

IDO

- Amino-acid catabolism
- Poliovirus receptor
- Arginase 1
- IDO

TDO

- Amino-acid catabolism
- Glutaminase
- TDO

VEGF

- Vascular
- Extracellular matrix
- Chemokines

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Approaches to Overcome Immunosuppression

- Vaccines
  - MHC peptide and T-cell receptor
  - Antigen-presenting cell
  - B7-CD28
  - T cell
  - (TLR adjuvants)

- Adoptive Cell Transfer
  - T cell
  - T-cell receptor engineering

- Non-specific Immune Activation
  - Agonistic Antibodies
  - T-cell receptor
  - CD40
  - CD27
  - CD137
  - OX40
  - CD28

- Checkpoint Blockade
  - Antagonistic Antibodies
  - PD-L1
  - PD-L2
  - CTLA4
  - PD-1
  - LAG3
  - CD28
Checkpoint Blockade is Associated with A Spectrum of irAEs in Patients

- Hypophysitis
- Thyroiditis
- Adrenal Insufficiency
- Enterocolitis
- Dermatitis

- Pneumonitis
- Hepatitis
- Pancreatitis
- Motor and Sensory Neuropathies
- Arthritis

Less common: hematologic, cardiovascular, ocular, renal
Different Immunotherapies are Likely to be Associated with Different irAEs

- Vaccines: Cross-reactivity to antigens on normal tissues; tissue damage
- Adoptive Cell Transfer: Cytokine storm; Cross-reactivity to antigens on normal cells; tissue damage, neurotoxicity
- Non-specific Immune Activation: Cytokine storm; invasion into immune-privileged tissues
- Checkpoint Blockade: Cross-reactivity to antigens on normal cells; tissue-specific autoimmunity

**Immunomodulators**

- CD27
- CD137
- OX40
- CD28
  - T-cell receptor
  - CD40

**Agonistic Antibodies**

- T-cell receptor
  - CD27
  - CD137
  - OX40

**Antagonistic Antibodies**

- T-cell receptor
  - CD28
  - CTLA4
  - PD-1
  - PD-L1
  - PD-L2
  - LAG3
Overview of the U01 RFA Concept

Goal:
• Improve cancer immunotherapies by eliminating or reducing the incidence and/or severity of inflammatory and/or autoimmune adverse-event responses, while retaining anti-tumor efficacy

Strategies:
• **Immune mechanisms:** Support researchers/teams with expertise in cancer immunotherapy as well as in mechanisms of immune tolerance, autoimmunity, and/or irAEs

• **Patient characteristics:** Support researchers/teams with expertise in identifying and understanding patient parameters indicative of increased risk of irAEs

• **Research tools:** Support researchers/teams with expertise in developing experimental models, technologies, and computational analyses that can advance research on mitigating irAEs
### Examples of Potential U01 Research Areas

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<th>Category</th>
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| **Compartmentalize the immune response to the tumor site:** | - Identify tumor epitopes that do not cross-react with normal cells/tissues/organs; design multi-epitope targeting strategies  
- Localize effector cell activation to the tumor site; provide checkpoint blockade only at the tumor site; relieve immune suppression only at the tumor site; direct effector cell trafficking only to the tumor site and not to normal tissues |
| **Protect bystander tissues:** | - Strengthen immune tolerance at normal tissue sites  
- Prevent or repair tissue damage in affected organs |
| **Personalize immunotherapy based on patient characteristics:** | - Select treatments to accommodate patient genetics, biology  
- Anticipate irAEs, based on patients’ traits, to protect tissues |
Cancer Moonshot Immunotherapy Networks, Collaborative Partners for irAE PIs

Adult Immunotherapy Network
- FY2018 Awards
  - Immunotherapy projects: 10 U01s (NCI, NIDCR, NIAAA)
- FY2019 Awards (planned; awaiting applications)
  - Immunotherapy projects: 10 U01s
  - Immunoengineering projects: 2-3 U54s

Pediatric Immunotherapy Network
- FY2018 Awards
  - Immunotherapy projects: 5 U01s, 1 U54 (NCI)
- FY2019 Awards (planned; awaiting applications)
  - Immunotherapy projects: 5 U01s, 1U54
Implementation Plan

Mechanism:
- U01; Five-year awards, FY20-24 (one-time solicitation)
- Maximum $375K Direct Costs per year per award
- $600K Total Costs (approx.) per year per award
- $3M per year for five years requested for this RFA
- Can support 5-8 U01 awards with $3M per year (NCI pays all costs for CA awards, but only 2/3 of costs for other IC awards)
- U01 PIs will join existing adult and pediatric Cancer Moonshot immunotherapy networks
  - Expected participating ICs: NCI, NIAID, NIAMS, NIDCR, NIDDK
  - Review coordinated by the NCI Division of Extramural Activities
Questions?
Portfolio Analysis

- A recent search of NIH RePORT for active awards, using “cancer”, “immunotherapy”, and “adverse events” as the search terms, identified 36 awards:
  - 6 NCI intramural awards
  - 30 extramural awards: about half R01s and R21s, plus some R, U, P, K, and F awards; about two-thirds NCI, plus some NIAID, NIAMS, NIDDK, and NIA awards

- 7 two-year collaborative supplements, from PA-17-248, were also awarded in late FY17, with Cancer Moonshot plus IC funds, and will be completed in late FY19:
  - 5 NCI/NIAID and 2 NCI/NIAMS collaborations
  - 32 paired-applications were submitted for that FOA, indicating a likely solid applicant pool for this U01 RFA FOA