



Cancer Moonshot - Immunotherapy

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

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

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:

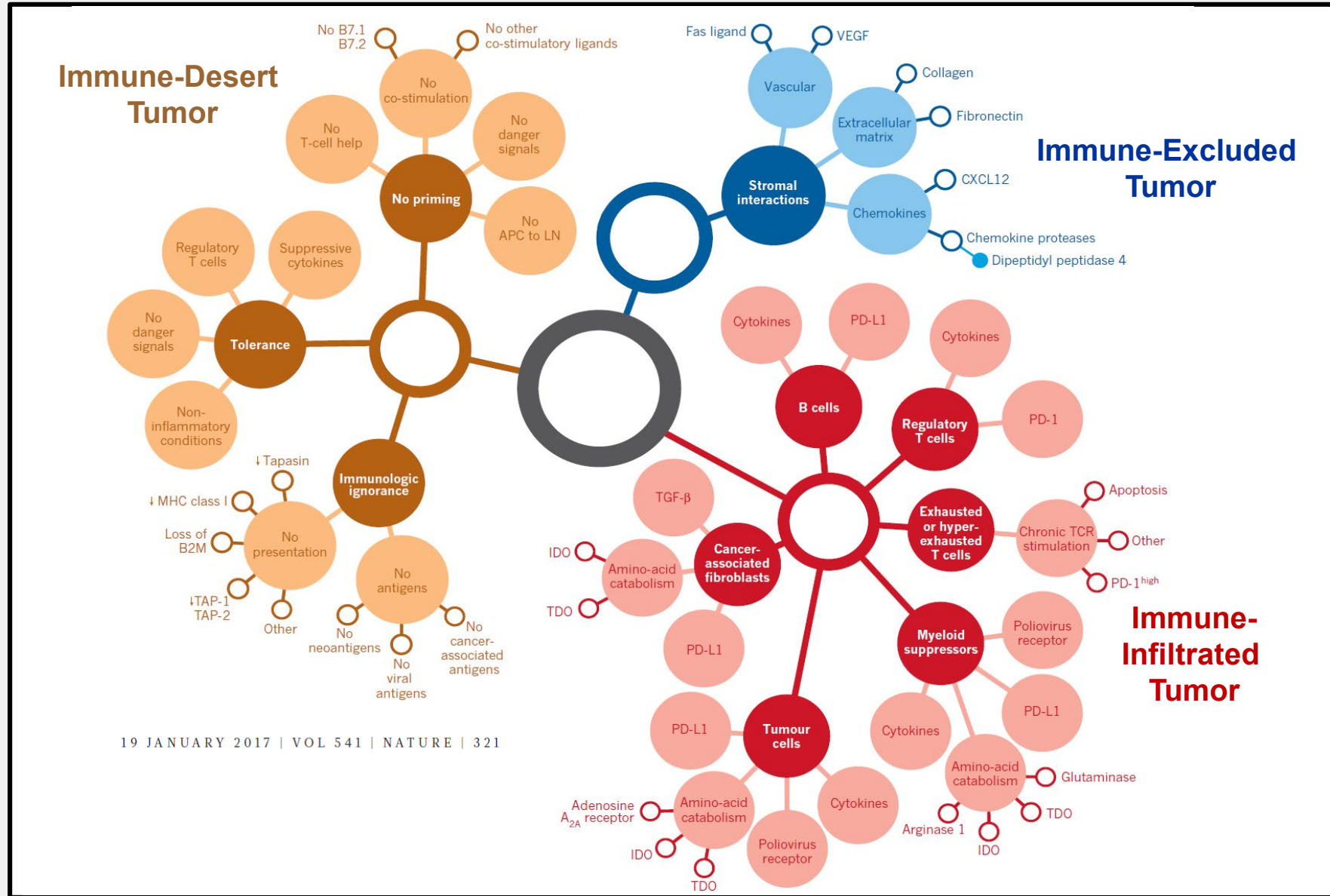
- A one-time FY2020 trans-NIH U01 solicitation, with participation by **NCI, NIAID, NIAMS, NIDCR, and NIDDK**
- To leverage on-going Cancer Moonshot investments in FY2017 trans-NIH collaborative supplements and FY2018-19 U-series awards
- To expand/strengthen existing NCI cancer immunotherapy networks



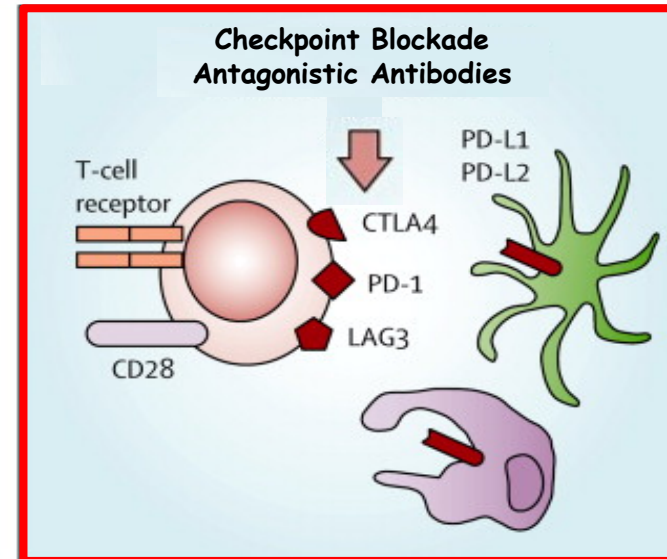
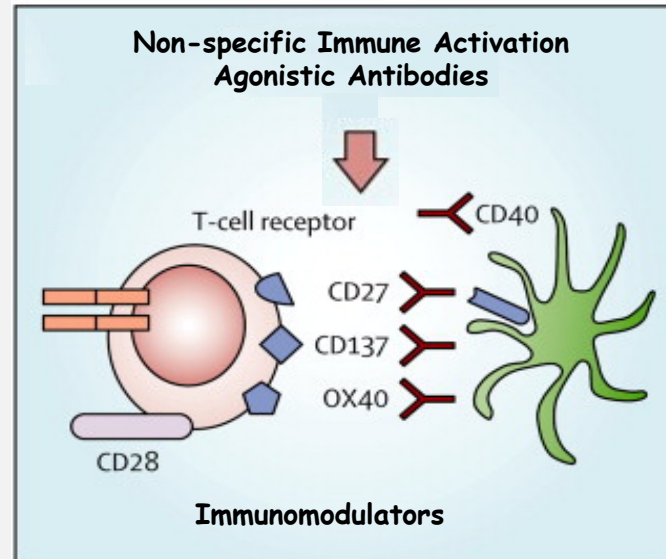
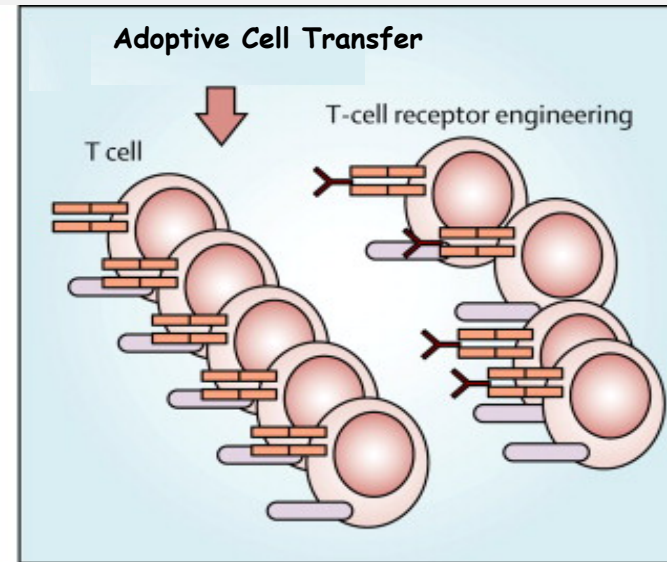
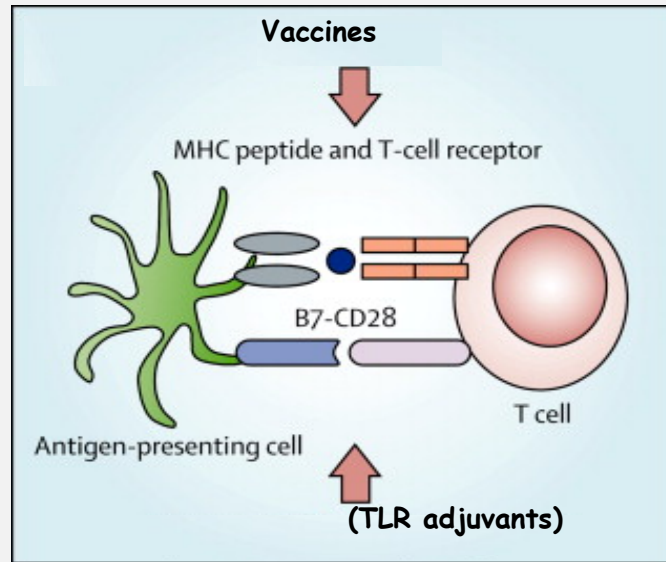
Tumor Microenvironments are Immunosuppressive



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Approaches to Overcome Immunosuppression



Checkpoint Blockade is Associated with A Spectrum of irAEs in Patients

Hypophysitis
Thyroiditis
Adrenal Insufficiency
Enterocolitis
Dermatitis



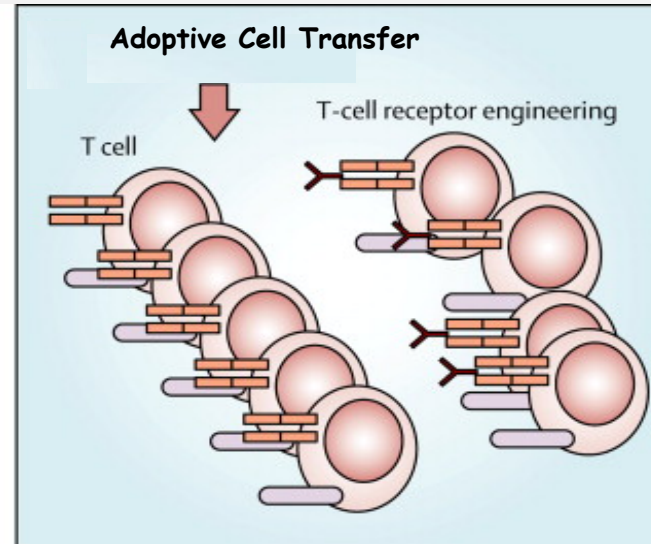
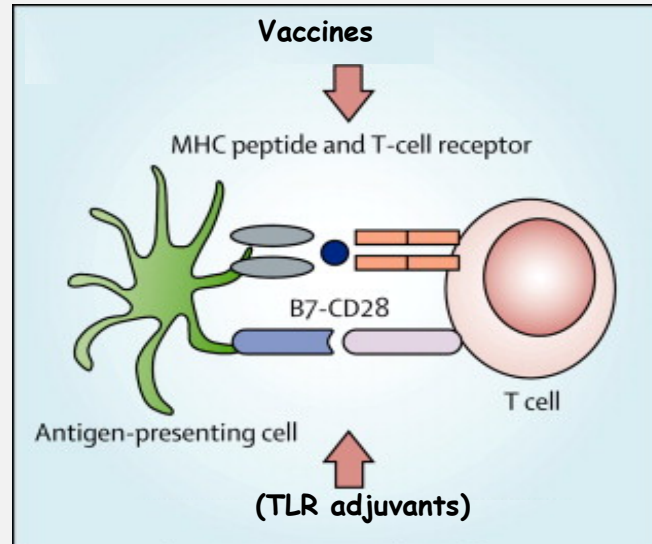
Pneumonitis
Hepatitis
Pancreatitis
Motor and Sensory
Neuropathies
Arthritis

- Less common: hematologic, cardiovascular, ocular, renal

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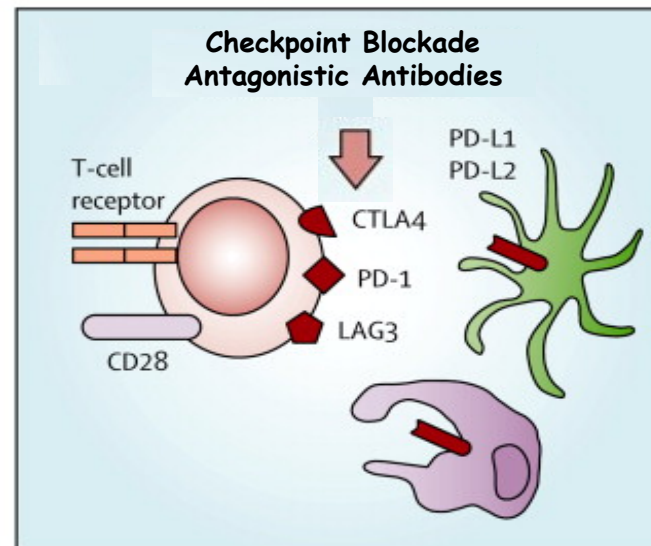
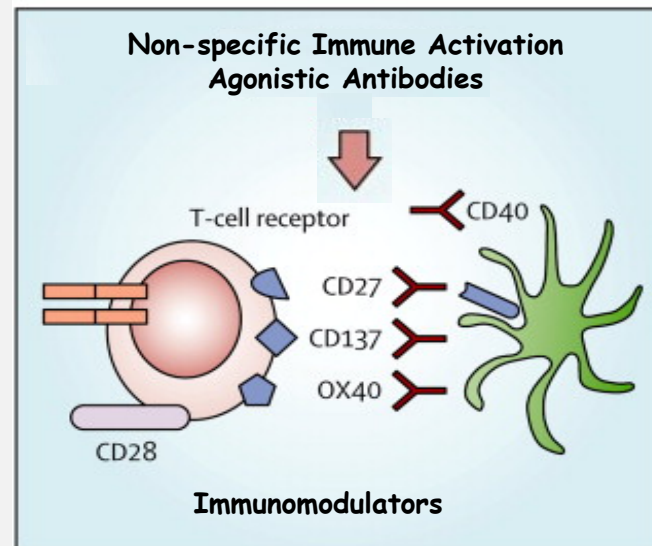
Different Immunotherapies are Likely to be Associated with Different irAEs

Cross-reactivity to antigens on normal tissues; tissue damage



Cytokine storm;
Cross-reactivity to antigens on normal cells; tissue damage, neurotoxicity

Cytokine storm;
invasion into immune-privileged tissues



Cross-reactivity to antigens on normal cells; tissue-specific autoimmunity

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

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