Blue Ribbon Panel Immunotherapy and Prevention

Accelerate translation of basic discoveries to clinical applications to improve immunotherapy outcomes for both “hot” and “cold” cancers - and to prevent cancers before they occur.

**Recommendation:** Create a translational science network devoted to immunotherapy

**Implementation Plan:** Outlined a collaborative network focused on:
- Discovering and evaluating novel immune-based approaches to increase the number of patients that benefit from immunotherapy; and
- Developing and validating early intervention vaccines to prevent cancers of all types.
Immuno-Oncology Translational Network (IOTN) - RFAs and Consortium Structure -

**RFA-CA-17-045:** Cancer Immunotherapy Research Projects (U01)

**RFA-CA-17-046:** Cancer Immunoprevention Research Projects (U01)

**RFA-CA-17-047:** Data Management and Resource-Sharing Center (DMRC) (U24)

**RFA-CA-17-048:** Cellular Immunotherapy Data Resource (CIDR) (U24)
Immuno-Oncology Translational Network (IOTN)
- Proposed New FY19 Initiatives -

- Cancer Immunoprevention Research Projects
- Immuno-Engineering to Improve Immunotherapy (i3) Centers
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Goal: Identify actionable targets arising in pre-cancerous lesions; develop and validate early intervention vaccines based on these targets.

Strategy:
Focus on cancers that occur in specific organ sites in high-risk cohorts.
- Lynch Syndrome (colon and endometrial cancer)
- Familial Adenomatous Polyposis (colon cancer)
- BRCA1/2 Carriers (breast and ovarian cancer)
- NF and TSC (neurologic and other cancers)
- Other Genetic Predisposition Syndromes
- Populations exposed to environmental carcinogens
- Other definable high-risk cohorts
The Genetics and Biology of High-Risk Cohorts Can Suggest Targets and Strategies for Immunoprevention

In Lynch Syndrome, recurrent frame-shift mutations create peptide neoantigens as potential vaccine targets.

A simple multivalent neo peptide vaccine can protect against the majority of microsatellite unstable tumors.
In the first round only 11 U01 applications were received; these covered a limited sub-set of high-risk cohorts; numerous investigators felt that they lacked sufficient preliminary data to submit a U01 application.

A UH2/UH3 phased mechanism would encourage investigators interested in entering the immunoprevention field to submit compelling research proposals with little preliminary data.
Cancer Immunoprevention Research Projects (UH2/UH3)

Implementation:

• UH2 phase (~$400K for each of 2 yrs) enable investigators to pursue immune target discovery efforts without the requirement for substantial preliminary data. Projects that achieve specific milestones advance to the UH3 phase.

• UH3 phase (~$400K for each of 3 yrs) will support follow-on studies from successful UH2s (e.g. development and preclinical testing of interventions).
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BRP panel recommendations

- Accelerate translation of basic discoveries to clinical applications to improve immunotherapy outcomes for both “hot” and “cold” cancers.

- Enable precise control of desired immune responses that are more effective, safer, and more broadly available.

- Encourage multi-disciplinary approaches to improve immunotherapy.
**Goal:**

- Support multi-disciplinary teams that incorporate bioengineering and systems biology approaches in the IOTN framework.
  - **Toolkit:** biomaterials, nanotechnologies, gene editing, synthetic chemistry/biology & modeling.

- Quantitatively understand the physical basis of immune system function;
- Build predictive models;
- Regenerate compromised immune systems for therapeutic benefit; and
- Enable precise control of desired immune responses that are more effective, safer, and more broadly available.
Universal CAR T and NK Cells for Cancer Immunotherapy

**Ideal Universal CART**

- Non-classical HLA
- Suicide molecule
- CD16
- Lysis of antibody coating tumor cells
- Antibody dependent cell cytotoxicity

**Tumor cell**
- TNF-α and IFN-γ mediated cytotoxicity
- TRAIL
- FAS-L
- B/trispecific Engagers (BiKES/TriKES)

**NK cell**
- CD16
- Tumor associated antigen


Engineered Immunotherapy Approaches Can Increase the Number of Patients that Benefit from Adoptive Cell Immunotherapy

DNA Nanocarriers to Generate CAR T cells in vivo
Scaffold-Based Cancer Vaccine

Recruitment of immature DCs

Chemotactic gradient

Antigen and adjuvant exposure

Immunomodulatory Scaffold

DC residence within material pores

Mature antigen-primed DCs

Tumor antigens

Adjuvant

MHC-peptide
Co-stimulatory molecules
Pro-inflammatory cytokines
LN homing receptors

Current Opinion in Biotechnology 2016, 40:1-8
Implementation:

*i3 Centers* will contribute to and support the IOTN, using a U54 mechanism, with the following components:

**Projects (3):**

Examples of potential areas of investigation include:
- artificial APCs and/or lymphoid structures;
- biomaterials to control how, where, and when immune cells are stimulated *in vivo*;
- next-gen gene editing and cell therapy engineering;
- “universal” immune effector cells; and
- modeling/predictive analyses of immune response attributes to cancer, cancer vaccines, or other immunomodulatory interventions or responses to therapy.
- The projects in any one *i3* Center will be synergistic.

**Administrative Core:**
- Manage and coordinate the Center’s research activity
- Liaison between each IOTN *i3* Center and IOTN U01s.
FY19 Initiatives will:

- Expand the immunotherapy and immunoprevention U01 groups to create more opportunities for collaboration and acceleration.
- Encourage more investigators to pursue immunoprevention studies using the phased UH2/UH3 mechanism.
- Incorporate immuno-engineering principles to improve upon promising approaches and make immunotherapy more effective, safer, and accessible to more patients.
Text mining the NCI portfolio on:

- “cancer immunoprevention” identified 7 funded projects.

- “immuno-engineering” or “bioengineering and immunotherapy” identified approximately six R01s and one R21. “Nanotechnology and immunotherapy” identified approximately seven U54 and three U01 grants, mostly associated with the NCI Alliance for Nanotechnology in Cancer program and four additional R01 grants.

None of these current grants are focused on the broader goals of immuno-engineering for cancer immunotherapy as outlined above.
**Evaluation Criteria**

**Measures of program success include:**

- More investigators entering the immunoprevention field.
- Identification of pre-malignant immunogenic targets that have been incorporated into vaccine approaches for early intervention or prevention of cancer.
- Incorporation of novel immuno-engineering solutions that make immunotherapy approaches more effective, safer, and accessible to more patients.
- Novel immunotherapy approaches with high potential for translation into the clinic have been established.
# Immuno-Oncology Translational Network

## Budget for new FY19 Initiatives

<table>
<thead>
<tr>
<th>Research Component</th>
<th>Mechanism</th>
<th>Number of Awards</th>
<th>Direct Costs (M/yr)</th>
<th>Fiscal Years</th>
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<tbody>
<tr>
<td>Immunoprevention</td>
<td>UH2/UH3</td>
<td>2-3</td>
<td>1.2</td>
<td>19-23</td>
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<tr>
<td>Immunoengineering</td>
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<tr>
<td>i3 Centers</td>
<td>U54</td>
<td>2-4</td>
<td>4.5</td>
<td>19-23</td>
</tr>
</tbody>
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Direct Costs FY19: **$5.7 M**  
Estimated Total Costs FY19: **$9.69 M**  
Estimated Total Costs FY19-23: **$48.45 M**
Questions