DCTD Immunotherapy Initiatives

- FY ‘17 - Renewal of Cancer Immunotherapy Trials Network (CITN) - $1.5M

- FY ‘17 – FOAs: 2 RFAs
  - U24: Cancer Immuno-therapy Monitoring and Analysis Centers - $6.5M
  - U24: Cancer Immunologic Data Commons - $1.5M
Summary of the DCTD Cancer Immunotherapy Workshop
NCI Shady Grove, January 14-15, 2016
Helen Chen, M.D. CTEP, on Behalf of DCTD

A 1.5-day meeting with thought leaders in the field to discuss …
- Opportunities and gaps in cancer immunology/immunotherapy
- What NCI should do to facilitate further development
Speakers and invited guests

Extramural scientists
- Jim Allison, MD Anderson
- Ira Mellman, Genentech
- Karolina Palucka, Jackson Lab
- Liz Jaffee, Hopkins
- Mario Sznol, Yale
- Padnanee Sharma, MD Anderson
- Mac Cheever, Fred Hutchinson

Biomarker/informatics experts:
- Kurt Schalper, Yale
- Elaine Mardis, Wash University
- Lisa Butterfield, Pittsburg
- Anna Wu, UCLA
- Atul Butte, UCSF
- Stan Hamilton, MD Anderson
- Diagnostic: Adaptive, NanoString, Nodality, Immudex

Industry:
- Merck, Incyte, AstraZeneca/MedImmune

NCI Intramural Scientists
- Steve Rosenberg, NCI
- Nick Restifo, NCI
- Jay Berzofsky
- Remy Bosselut
- Stephen Hewitt

DCTD:
- J Doroshow, J Abrams, T Hecht
- CTEP: H Chen, H Streicher, E Sharon, J Zwiebel
- Cancer Diagnostic Program: M Thurin
- Biologics Resource Branch: S Creekmore, A Welch
- Radiotherapy Development Program: M Ahmed
- BRP: R Simon

Division of Cancer Biology:
- C Marks, S McCarthy, K Howcroft, D Singer
What Should NCI Do?

Specific recommendations:

Basic science

- Mouse Models
- Tumor Microenvironment

Clinical Research

- Clinical trials rich in “translation”
- Clinical trials for Adoptive Cell Therapy
- Biomarkers and Database
CITN AWARD to FHCRC

- A network composed of leading immunotherapists and institutions to design and implement early phase multi-site clinical trials.
- Awarded to FHCRC/Mac Cheever, PI: Sept. 2010
  - Funded the Central Operations and Statistical Center
  - 3 million/yr total costs for 5 years
  - Included a central Immunomonitoring Laboratory Core
  - Currently 32 sites
1. **Anti-PD1**: in Merkel cell carcinoma, first systemic therapy  
2. **Anti-PD1**: in mycosis fungoides, advanced, treatment failure  
3. **Anti-PD1**: for advanced malignancy in HIV+ patients  
4. **Anti-CD40**: in pancreas cancer, neoadjuvant  
5. **IL-15** (E. coli–derived, NCI): in NSCLC/H&N/renal/melanoma  
6. **IL-15** (IL-15/IL-15Rα/Fc fusion protein): in melanoma  
7. **IL-7**: in prostate cancer after Provenge vaccine  
8. **IL-7**: in glioblastoma post-temozolomide (**ABTC trial; immune monitoring only**)  
9. **IDO Inhibitor**: in melanoma with MELITAC 12.1 vaccine  
10. **IDO Inhibitor**: in ovarian cancer, neoadjuvant  
11. **Flt3-Ligand + Poly ICLC** + anti-DEC205-NY-ESO-1 vaccine: in melanoma, adjuvant
<table>
<thead>
<tr>
<th>CITN TRIALS ENROLLMENT</th>
<th>NUMBER OF PATIENTS</th>
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<tbody>
<tr>
<td>CITN-12 (Anti-PD1)</td>
<td>Current Enrollment: 3, Total Trial Enrollment: 60</td>
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<tr>
<td>CITN-10 (Anti-PD1)</td>
<td>Current Enrollment: 24, Total Trial Enrollment: 60</td>
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<tr>
<td>CITN-09 (Anti-PD1)</td>
<td>Current Enrollment: 30, Total Trial Enrollment: 60</td>
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<tr>
<td>CITN-07 (Flt3L)</td>
<td>Current Enrollment: 19, Total Trial Enrollment: 60</td>
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<tr>
<td>CITN-06 (IL15Rα)</td>
<td>Current Enrollment: 17, Total Trial Enrollment: 60</td>
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<tr>
<td>CITN-05 (IDO-inh)</td>
<td>Current Enrollment: 8, Total Trial Enrollment: 28</td>
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<tr>
<td>CITN-04 (IDO-inh)</td>
<td>Current Enrollment: 19, Total Trial Enrollment: 28</td>
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<tr>
<td>CITN12-03 (IL7)</td>
<td>Current Enrollment: 21, Total Trial Enrollment: 28</td>
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<tr>
<td>CITN11-02 (IL15)</td>
<td>Current Enrollment: 19, Total Trial Enrollment: 19</td>
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<tr>
<td>CITN11-01 (Anti-CD40)</td>
<td>Current Enrollment: 21, Total Trial Enrollment: 21</td>
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</table>
PD-1 Blockade with Pembrolizumab in Advanced Merkel-Cell Carcinoma


Key collaborations:

Academic (8 universities)

Government (NCI-CTEP-CITN)

Industry (Merck)
Responses to Pembrolizimab therapy in MCC

Fraction responding:
- 44% of virus-neg
- 62% of virus-pos

(difference not significant)

Tumor viral status
- negative
- positive

n = 24
Pembrolizumab (anti-PD1) for Merkel Cell Carcinoma

- Phase II single arm, first line trial, at 7 CITN sites
- Responses (CR/PR) in 15 of 22 evaluable patients (68%); responses are rapid and appear more durable than chemotherapy
- Presentation to European Cancer Congress, Sept. 2015; submitted “late-breaking” abstract for April AACR presentation
- Merck is applying to FDA for “breakthrough” designation for this indication
**Correlative Sciences Status Matrix: Studies in Progress**

<table>
<thead>
<tr>
<th>Table 1. CITN Studies, Correlative Sciences Prioritization and Status Matrix</th>
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<tbody>
<tr>
<td><strong>CITN-05</strong></td>
</tr>
<tr>
<td>iIDO</td>
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<tr>
<td>ALC</td>
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**Immunohistochemical Evaluation of Tumor Biopsies (CS 9.3.1)**

- Whole Blood Immunophenotyping (CS 9.2.1 and 9.2.2)
- T-cell response: IFNγ ELISPOT (CS 9.1.1)
- Whole Blood Immunophenotyping (CS #1)
- Whole Blood T-cell response: IFNγ ELISPOT (CS 9.1.1)
- Whole Blood T-cell response: IFNγ ELISPOT (CS 9.1.2)
- Whole Blood T-cell response: IFNγ ELISPOT (CS #1)
- Whole Blood T-cell response: IFNγ ELISPOT (CS #2)

**Intra Tumor Kyn/Trp Ratios (CS 9.3.2)**

- Whole Blood Immunophenotyping (CS 9.2.1 and 9.2.2)
- T-cell response: IFNγ ELISPOT (CS 9.1.1)
- Whole Blood Immunophenotyping (CS #1)
- Whole Blood T-cell response: IFNγ ELISPOT (CS 9.1.1)
- Whole Blood T-cell response: IFNγ ELISPOT (CS 9.1.2)
- Whole Blood T-cell response: IFNγ ELISPOT (CS #1)
- Whole Blood T-cell response: IFNγ ELISPOT (CS #2)

**Gene Expression Analyses of Tumor Biopsies, Ascites and PBMC (CS 9.3.3)**

- Whole Blood Immunophenotyping (CS 9.2.1 and 9.2.2)
- T-cell response: IFNγ ELISPOT (CS 9.1.1)
- Whole Blood Immunophenotyping (CS #1)
- Whole Blood T-cell response: IFNγ ELISPOT (CS 9.1.1)
- Whole Blood T-cell response: IFNγ ELISPOT (CS 9.1.2)
- Whole Blood T-cell response: IFNγ ELISPOT (CS #1)
- Whole Blood T-cell response: IFNγ ELISPOT (CS #2)

**T-cell response: IFNγ ELISPOT (CS 9.3.4)**

- Whole Blood Immunophenotyping (CS 9.2.1 and 9.2.2)
- T-cell response: IFNγ ELISPOT (CS 9.1.1)
- Whole Blood Immunophenotyping (CS #1)
- Whole Blood T-cell response: IFNγ ELISPOT (CS 9.1.1)
- Whole Blood T-cell response: IFNγ ELISPOT (CS 9.1.2)
- Whole Blood T-cell response: IFNγ ELISPOT (CS #1)
- Whole Blood T-cell response: IFNγ ELISPOT (CS #2)

**IDO inhibitor effects on CD8+ and CD4+ T cell subsets (CS 9.3.5)**

- Whole Blood Immunophenotyping (CS 9.3.6)

- TCR Repertoire (CS 9.3.7)
Other Results in Studies to Date

- **CITN-10: anti-PD1 in Mycosis Fungoides/Sezary Syndrome**
  - 8/24 PRs (33%) and 10/24 stable disease (42%)
  - Extensive immune/genomic correlates underway
  - ASH 2016 abstract planned

- **CITN11-02: NCI rhIL-15 for solid tumors**
  - 18-fold mean increase in NK cells & 2.7-fold mean increase in CD8 T cells at 3 μg/kg, day 15 cycle 1
  - Presentation at May 2016 AAI meeting

- **CITN-07: DC-targeting fusion vaccine plus/minus Flt3L**
  - Immune response change by Flt3L primary objective
  - Substantial increases in dendritic cells, NK cells, monocytes and antigen-specific T cell responses in Flt3L-treated patients
  - ASCO 2016 poster presentation
NCI-supported Immunotherapy Trials

Between 2010 -2015

• 88 Phase I-III immunotherapy trials were activated in the DCTD Clinical Trial Network (NCTN, ETCTN, CITN, and PBTC)
• 8 Phase III trials, 14 Randomized Phase 2 trials
• Clinical settings: common, rare tumors; neoadjuvant, adjuvant and metastatic disease
• Study regimens include single agent and novel combinations

<table>
<thead>
<tr>
<th>Check point inhibitors</th>
<th>Vaccine</th>
<th>T-cell engaging bispecific Ab</th>
<th>Other immune modulators</th>
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<tbody>
<tr>
<td>• Anti- CTLA-4 (Ipilimumab, tremelimumab)</td>
<td>• CDX1401 (against NYSO-1)</td>
<td>• CD19 BiTE (Blinatumomab)</td>
<td>• IDO (INDB0243360) ~ 2 trials</td>
</tr>
<tr>
<td>• Anti-PD-1 (Nivolumab, Pembroliatumab)</td>
<td>• PSA PROSTVAC/TRICOM</td>
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<td>• Lenalidomide, Pomalidomide:</td>
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<tr>
<td>• Anti-PD-L1 (MEDI4736 and MPDL3280A)</td>
<td>• CEA TRICOM/PANVAC</td>
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<td>• FLT3 ligands</td>
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<tr>
<th>Cytokine:</th>
<th>Oncolytic virus:</th>
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<tr>
<td>• IL-15</td>
<td>• T-VEC</td>
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<tr>
<td>• IL-12</td>
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Most randomized trials have mandatory collection of baseline tissues/blood
Many early clinical trials include serial biopsies
Definition of immunotherapy trials excludes MAbs directed at tumor targets or vasculature (e.g., cetuximab or bevacizumab)
Why RENEW the CITN?

- Access to immunologic agents not in DCTD portfolio (e.g. anti-CD40 and IL-7),
- 40% of CITN sites are not in ETCTN providing NCI access to wider pool of qualified immunotherapists,
- Translationally-rich trials
- **Standing apparatus** of immunotherapy sites is an attractive forum for investigators, and CITN is able to rapidly take advantage of new clinical opportunities in immunotherapy.
CITN Renewal

- Limited Competition RFA (UM1)
- Integrate into existing CTEP/ETCTN processes:
  - Theradex to provide data management for all trials and utilize CTEP CIRB
  - CTSU to provide regulatory support system and website
- Subcontract/Member site composition limited to best 20 sites
- Break out immunomonitoring core to serve ALL NCI-sponsored networks/consortia (ie. CITN, ETCTN, ABTC and early NCTN trials) as a SEPARATE Network through a SEPARATE RFA
Next Directions in the CITN
Focus on Combinations (NCI-held or not held)

IL-15:

- **Combinations:**
  - IL-15 plus monoclonal antibody for enhanced ADCC (eg. with cituximab)
  - IL-15 with anti-PD1 (Merck)
- **Admune/Novartis IL-15 fusion protein** with NCI CCR (expansion cohort)

Other anti-PD1 trials:

- Anti-PD1 plus **IL-7** (Merck and Revimmune)
- Anti-PD1 failures – to biopsy, assess actionable reasons for failures

Other combinations:

- **Anti-CD137 (4-1BB)** plus trastuzumab (Pfizer) in breast cancer
- Intratumoral anti-CTLA4 plus local radiation plus anti-PD1 (Merck)
CITN UM1 Budget

- Operations and Statistical Office: $350K
- Scientific Leadership: 50K
- Network Meetings and travel: 30K
- Treatment site support*: 720K
  - Total Direct: 1150K
  - Total Costs: 1500K

*assume 120 patients/yr at $6,000/patient
Review of CITN by an External Panel

• Panel: Immunotherapy experts (5) plus medical oncologists outside of immunotherapy (2); Dr. Kim Lyerly, chair

• Overall recommendation (unanimous): support recompetition
  – Stellar team of investigators at major US immunotherapy sites
  – An infrastructure for coordinated areas of inquiry with a primary focus on immunotherapy, and for high quality and uniformed immunological assessment with the potential to expand the sophistication of analysis
  – Trial selection overall consistent with the aims of the network
  – Accrual appropriate given the focus on immunotherapy, emerging organizational capabilities, and need to address both CTEP and industry requirements
  – Enhances the existing clinical trials infrastructure and developmental therapeutics programs at the NCI
  – Well poised to make contributions in the future

National Cancer Institute
Recommendations

• Infrastructure can be rate limiting as more protocols come on line: to *increase efficiency*, restructure to *utilize the established infrastructure in CTEP*.

• Sites that are also ETCTN sites should *engage appropriate investigators outside of the immunotherapy realm* for testing combinations of targeted drugs with immuno-oncology agents.

• Broaden leadership perspectives for decisions about future CITN trials.