“Making the System Work:
Economic & Intellectual Challenges:
Cancer Immunotherapy Trials Network”

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CHALLENGE

THE MAJOR BARRIER for development of effective & curative cancer immunotherapy

• Already invented immunotherapy agents with proven & profound function & high potential to benefit cancer patients are not broadly available for testing!
Biological Challenges: Profound

• Immune tolerance
• Intrinsic mechanisms actively limit T cell activation, expansion, survival & function
  – Checkpoint blockade
  – Regulatory T cells
  – Inhibitory cytokines
  – Limiting T cell growth factor concentrations
• Cancer cell & immune cell induced immune suppression
• Immune incompetence
  – Age
  – Lympholytic chemotherapy
Agents needed to overcome biological restrictions have been invented

- Dendritic cell activators
- Dendritic cell growth factors
- Vaccine adjuvants
- T-cell stimulators
- T-cell growth factors
- Genetically modified T cells
- Immune checkpoint inhibitors
- Agents to neutralize or inhibit suppressive cells, cytokines and enzymes
Challenges to Development of Effective Immunotherapy

• Historical
  – Biological limitations

• Current
  – Agents to overcome biologic limitations have been invented, but are not broadly available
  – Limitations:
    • Funding
    • Organization
    • Vision
    • Will
Prioritization is Mandatory!
NCI Prioritization Workshops Led to CITN

- NCI prioritization workshops
  - Immunotherapy Agents
    - Immunotherapy Agents Workshop (2007)
  - Antigen Targets
    - Cancer Antigen Pilot Prioritization Project (2008)
  - Regimens
    - Immune Response Modifier Pathway Working Group (2009)

- Broad consensus was mandatory
  - Priority lists were well vetted
  - >80 scientists involved in the workshops
# High Priority Agents

<table>
<thead>
<tr>
<th>Category</th>
<th>Agents</th>
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</table>
| T cell growth factors              | **IL-7**  
|                                    | **IL-15**                                                             |
| Dendritic cell activators          | **Anti-CD40**, **CD40L**                                               |
| Dendritic cell growth factors      | **Flt3L**                                                             |
| Vaccine adjuvants                  | **IL-12, CpG, MPL, Poly I:C, Resiquimod, 852A**                       |
| T cell stimulators                 | Anti-CD137, anti-GITR, anti-OX40                                       |
| T cell attracting chemokines       | **CCL21**                                                             |
| Inhibitors of T cell checkpoint blockade | Anti-PD1 & PD-L1, anti-B7-H4, anti-LAG-3, LIGHT                        |
| Inhibitors                         | **IDO inhibitors**, anti-TGF-β, anti-IL10 & anti-IL10R                |
Cancer Immunotherapy Trials Network (CITN)

- Brings together cancer immunologists from 28 foremost universities and cancer centers in North America
  - To design and conduct innovative early phase trials for patients with cancer ([www.CITNinfo.org](http://www.CITNinfo.org)).
  - To provide the essential infrastructure for collaboration
  - To gain access to top-ranked agents not broadly available for testing
    - By focusing on prioritized agents
    - By capitalizing on
      - Prominence of Member Site Principal Investigators (PIs) &
      - Partial trial funding from the NCI
<table>
<thead>
<tr>
<th>Institution</th>
<th>CITN Principal Investigator</th>
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<tbody>
<tr>
<td>Baylor University</td>
<td>Karolina Palucka &amp; Joseph A. Fay</td>
</tr>
<tr>
<td>Case Western Reserve University</td>
<td>Pierre Triozzi</td>
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<tr>
<td>Dana Farber Cancer Center</td>
<td>Steven Hodi</td>
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<tr>
<td>Dartmouth-Hitchcock Norris Cotton Ca Ctr</td>
<td>Marc Ernstoff</td>
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<tr>
<td>Duke University Medical Center</td>
<td>Kim Lyerly &amp; Michael Morse</td>
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<tr>
<td>Emory University</td>
<td>Edmund Waller</td>
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<tr>
<td>MD Anderson Cancer Center</td>
<td>Laurence J Cooper</td>
</tr>
<tr>
<td>H. Lee Moffitt Cancer Center</td>
<td>Scott J. Antonia</td>
</tr>
<tr>
<td>Memorial Sloan-Kettering Ca Ctr</td>
<td>Jedd D. Wolchok</td>
</tr>
<tr>
<td>Mt Sinai Medical Center</td>
<td>Nina Bhardwaj &amp; Karolina Palucka</td>
</tr>
<tr>
<td>NYU Cancer Institute</td>
<td>Silvia Formenti</td>
</tr>
<tr>
<td>Ohio State University</td>
<td>William E. Carson</td>
</tr>
<tr>
<td>Providence Cancer Center</td>
<td>Walter J. Urba &amp; Bernard Fox</td>
</tr>
<tr>
<td>Roswell Park Cancer Center</td>
<td>Kunle Odunsi</td>
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<tr>
<td>Rush University Cancer Center</td>
<td>Howard Kaufman</td>
</tr>
<tr>
<td>Stanford University</td>
<td>Ronald Levy &amp; Holbert Kohrt</td>
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<tr>
<td>University of California, San Diego</td>
<td>Thomas J Kipps</td>
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<tr>
<td>Univ of California, San Francisco</td>
<td>Lawrence Fong</td>
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<tr>
<td>University of Chicago</td>
<td>Thomas Gajewski</td>
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<tr>
<td>University of Miami</td>
<td>Joseph D. Rosenblatt</td>
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<tr>
<td>University of Minnesota</td>
<td>Jeffrey S. Miller</td>
</tr>
<tr>
<td>University of Pennsylvania</td>
<td>Carl June &amp; Robert Vonderheide</td>
</tr>
<tr>
<td>University of Pittsburgh</td>
<td>Robert Louis Ferris &amp; Hassane Zarour</td>
</tr>
<tr>
<td>Univ of Toronto Ontario Ca Inst</td>
<td>Pamela Ohashi</td>
</tr>
<tr>
<td>University of Washington</td>
<td>John A. Thompson</td>
</tr>
<tr>
<td>University of Wisconsin</td>
<td>Paul Sondel &amp; Doug McNeel</td>
</tr>
<tr>
<td>Yale University</td>
<td>Mario Sznol</td>
</tr>
<tr>
<td>National Cancer Institute</td>
<td>Jeff Schlom</td>
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**CITN Institutions & PIs**
CITN: Strategy

• To develop highly informative trials not otherwise possible, by combining
  – Priority agents not generally available.
  – The best peer-reviewed concepts, with submissions open to everyone in the field
  – Optimal trial design by multidisciplinary Concept Working Groups

• To focus on trials likely to achieve the optimal/quickest route to
  – Proof of Concept
  – Demonstration of patient benefit
  – Regulatory approval

• To focus on agents & formulations likely to achieve broad availability through commercialization
<table>
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<tr>
<th>Agent (Rank)</th>
<th>Function</th>
<th>Trial</th>
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<tbody>
<tr>
<td><strong>IL-15 (#1)</strong> (NCI E. Coli derived)</td>
<td>T cell &amp; NK cell growth factor</td>
<td>First in man sub-Q outpatient regimen - solid tumors for combining with vaccines, antibodies and other agents; Protocol approved by CTEP; IRB, FDA; Trial open (March 2013) [PIs: Miller (U Minnesota), Kohrt (Stanford), Sondel (Wisconsin), Thompson (UW), Waldmann (NCI)]</td>
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<tr>
<td><strong>IL15/IL15Ra/Fc fusion (#1) mammalian (Altor)</strong></td>
<td>T cell &amp; NK cell growth factor</td>
<td>Advanced melanoma Phase I at FHCRC/UW + USCF Expansion into NCI &amp; Dartmouth Co-Funded by Melanoma Research Alliance &amp; Altor [PI: Kim Margolin (FHCRC/UW)] Projected to open in August</td>
</tr>
<tr>
<td><strong>Anti-PD-1 (#2)</strong></td>
<td>Check point inhibitor</td>
<td>Negotiating trials in Merkel Cell Cancer [Nghiem (FHCRC/UW)] and Mycosis Fungoides [Holbrook (Stanford)]</td>
</tr>
<tr>
<td><strong>Anti-CD40 (#4) (Pfizer)</strong></td>
<td>DC activator</td>
<td>(1) Neoadjuvant - resectable pancreas cancer: Trial open [PI: Vonderheide (Penn)] (2) Advanced pancreas cancer: In development (Grant at PanCaN) Franchise taken over by VLST in Seattle/ <strong>Trials on HOLD</strong></td>
</tr>
<tr>
<td><strong>IL-7 (#5) (Cytheris) + Provenge (Dendreon)</strong></td>
<td>Homeostatic T cell growth factor</td>
<td>Advanced asymptomatic prostate cancer Protocol and IND approved Developing CRFs [PIs: Fong (UCSF) and Ferrari (NYU)]</td>
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<tr>
<td><strong>IL-7 (#5)</strong> (Cytheris) + 6 infectious disease vaccines</td>
<td>Homeostatic T cell growth factor</td>
<td>Cancer patients &gt; age 60; post-adjuvant chemotherapy with low ALC; Diphtheria, Poliomyelitis, Pneumococcal Conjugate Vaccine, Hepatitis A Vaccine, Recombinant Hepatitis B Vaccine, Influenza vaccine; Co-funding from NCI intramural program; IRB and FDA approved; [PI: Sportes (NCI)]</td>
</tr>
<tr>
<td><strong>IDO Inhibitors (#7)</strong> (Incyte)</td>
<td>IDO Inhibition</td>
<td>Advanced melanoma to evaluate inhibition + / - peptide vaccine on tumor microenvironment; LOI approved; Protocol submitted; awaiting CTEP review; [PI: Slingluff (UVA)]</td>
</tr>
<tr>
<td><strong>IDO Inhibitors (#7)</strong> (Incyte)</td>
<td>IDO Inhibition</td>
<td>Neoadjuvant ovarian cancer to evaluate inhibition on ascites and tumor microenvironment; LOI approved; Protocol submission - December; [PIs: Odunsi (Roswell), Coukos (Penn)]</td>
</tr>
<tr>
<td><strong>Anti-IL10 (#10)</strong></td>
<td>Neutralizes suppression</td>
<td>Negotiating for neoadjuvant trial in ovarian cancer [Odunsi (Roswell Park) and Adams (New Mexico/Penn)]</td>
</tr>
<tr>
<td><strong>Flt3-Ligand (#11)</strong> + (Celldex) Poly ICLC (#15) + (Oncovir)</td>
<td>- Dendritic cell growth factor - TLR3 agonist</td>
<td>Flt3L x 7 days to grow DC + poly ICLC to activate DC + anti-DEC205-NY-ESO-1 vaccine to target activated DC; Co-funding from Celldex and Cancer Vaccine Consortium/CRI; LOI to be submitted by end December; [PIs: Bhardwaj (Mt Sinai/NYU), Odunsi (Roswell Park), Wolchok (MSKCC)] [All are CITN &amp; CVC PIs]</td>
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Why aren’t adjuvants broadly available?

• Priority Adjuvants
  – **IL-12**
  – **CpG**
  – **MPL**
  – **Poly I:C**
  – **Resiquimod**
  – **852A**
Adjuvant Challenge

• Universal Truth
  – Adjuvants are needed to achieve highest levels of immune response
Adjuvant Challenge

• “Catch 22”
  – Adjuvants approved for non-adjuvant purposes are broadly available
  – Adjuvants that function only as adjuvants are not broadly available, regardless of potency
  – Necessary focus on the few drugs that have been approved for other purposes
    • GM-CSF
    • IL-2
    • BCG
    • Imiquimod
Why aren’t adjuvants available?

• NCI
  ~ Billion(s) for vaccines & T cell therapy
    – Little for essential vaccine components
      • Researcher hands tied behind backs
  
• FDA
  – No clear path forward for broad testing of adjuvants that aren’t effective as monotherapy
Why aren’t adjuvants available?

- Industry
  - “Invisible hand of the market”
    - Rational decisions based on regulatory and commercial concerns
    - Don’t see a clear path forward
    - Companies with great adjuvants
      - Develop as components of proprietary vaccines
      - Develop them as monotherapy
      - Leave “on the shelf” if not successful as monotherapy
Solution?

• Major Step
  – Accept gravity of problem
  – First step to solving the problem is to admit there is a problem
    • Too many researchers are comfortable doing studies that are inadequate due to a lack of appropriate agents
    • NCI is comfortable funding vaccine trials without adequate or optimal adjuvants
    • FDA has not provided a regulatory solution
Extraordinary Administrative Effort to Initiate Trials
CITN12-03 (IL7) Protocol Development

**CITN12-03:**

- LOI submitted to CTEP: **4/6/2012**
- CTEP LOI Review: **4/27/12**
- Amended Consensus Review Reply sent to CTEP: **5/18/12**
- CTEP LOI approval: **5/25/12**
- Protocol submitted to CTEP: **8/24/12**
- CTEP Protocol Review teleconference: **10/2/12** (originally scheduled for 9/20/12 rescheduled for conflicts)
- Revised protocol re-submitted to CTEP: **11/30/12**
- Revised Follow-up Review letter received: **12/21/12**
- IND submitted to the FDA – **12/21/12**
- Response to FDA - **1/21/13**
- Response to FDA - **1/24/13**
- FDA requested protocol edits submitted to CTEP – **2/28/13**
- CTEP approval of protocol pending review of study agreement w/industry collaborator – **3/11/13**
- Protocol draft submission to the IRB of record (FHCRC) – pre-review of lead IRB application –
- IRB review pending 3/27/13 – might be issues requiring re-review by CTEP and FDA
CITN12-03 (IL7) Legal Agreements

- **Cytheris** *(providing the IL-7 for this study)*
  - Confidential Disclosure Agreement *(Cytheris – Dendreon – FHCRC)*
  - Drug Supply Agreement *(Cytheris – FHCRC)*
  - Material Transfer / Services Agreement *(Cytheris – FHCRC)* for immunogenicity testing
- **Dendreon** *(providing funding and reagents)*
  - Confidential Disclosure Agreement *(Dendreon – FHCRC)*
  - Confidentiality Disclosure Agreement *(Dendreon – FHCRC – NCI)*
  - Research Support Agreement *(Dendreon – FHCRC)*
  - Material Transfer Agreement *(Dendreon – FHCRC)* for reagents to Central Lab
  - Material Transfer Agreement *(Dendreon – FHCRC)* for PBMC from Dendreon
- **Data management change in support (CTSU/Westat)**
  - SOW *(Scope of Work)* between CTSU and CITN - 5 revisions
  - Westat/Fred Hutchinson – Flow down agreement - 2 revisions
  - Axio Research *(providing data management support)*
    - Fixed Fee Subcontract *(Axio – FHCRC)* - 10 revisions
- **Master Site Agreements** — 13 (average 6 revisions per institution)
- **Work Orders** — 13 (average 3 revisions per institution)
- **Site Payment Agreements** — 13 (average 3 revisions per institution)

*Total number of legal agreements – 50 [>200 revisions]*
ORGANIZATIONAL ISSUES

• "All organizations are perfectly designed to get results they get.
• To get better results, you need to improve the design of the system”

David Hanna (1988), in Designing Organizations for High Performance
Suggestions for Making the System Work Better

- **Continue prioritization**
  - Proactively fund trials vetted by “the field”

- **Focus**
  - Trials on path to FDA approval
    - Until more immunotherapy agents are broadly available, i.e., can be purchased
  - Trials that inform subsequent trials
  - Trials that could make a **substantial** difference

- **Set up better processes for financial leverage: NCI, Companies, Foundation & Insurance**

- **Stimulate FDA to develop a path for approval of components as components (e.g., adjuvants)**

- **Continue to lessen the administrative and legal hurdles.**