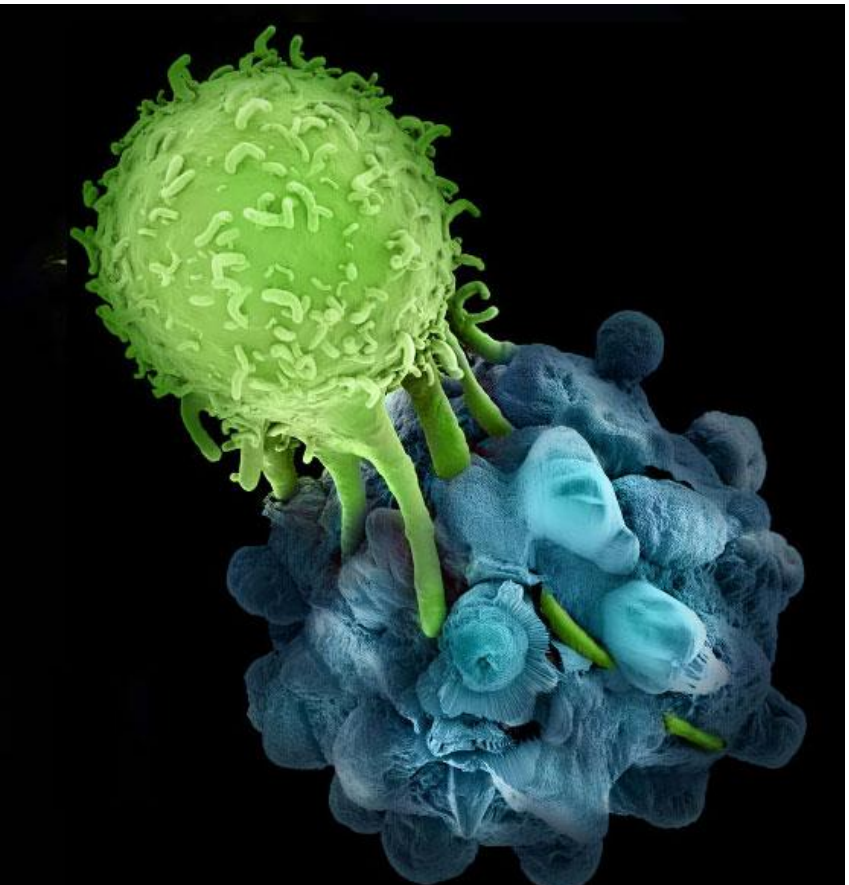
SITC: Cancer Immunotherapy Clinical Trials: Concepts & Challenges

"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

Category	Agents
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).
  - 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

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CITN Institutions & PIs

Institution	CITN Principal Investigator
Baylor University	Karolina Palucka & Joseph A. Fay
Case Western Reserve University	Pierre Triozzi
Dana Farber Cancer Center	Steven Hodi
Dartmouth-Hitchcock Norris Cotton Ca Ctr	Marc Ernstoff
Duke University Medical Center	Kim Lyerly & Michael Morse
Emory University	Edmund Waller
MD Anderson Cancer Center	Laurence J Cooper
H. Lee Moffitt Cancer Center	Scott J. Antonia
Memorial Sloan-Kettering Ca Ctr	Jedd D. Wolchok
Mt Sinai Medical Center	Nina Bhardwaj & Karolina Palucka
NYU Cancer Institute	Silvia Formenti
Ohio State University	William E. Carson
Providence Cancer Center	Walter J. Urba & Bernard Fox
Roswell Park Cancer Center	Kunle Odunsi
Rush University Cancer Center	Howard Kaufman
Stanford University	Ronald Levy & Holbert Kohrt
University of California, San Diego	Thomas J Kipps
Univ of California, San Francisco	Lawrence Fong
University of Chicago	Thomas Gajewski
University of Miami	Joseph D. Rosenblatt
University of Minnesota	Jeffrey S. Miller
University of Pennsylvania	Carl June & Robert Vonderheide
University of Pittsburgh	Robert Louis Ferris & Hassane Zarour
Univ of Toronto Ontario Ca Inst	Pamela Ohashi
University of Washington	John A. Thompson
University of Wisconsin	Paul Sondel & Doug McNeel
Yale University	Mario Sznol
National Cancer Institute	Jeff Schlom

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

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Agent (Rank)	Function	Trial
IL-15 (#1) (NCI E. Coli derived	T cell & NK cell growth factor	First in man sub-Q outpatient regimen - solid tumors for combining with vaccines, antibodies and other agents; Protocol approve by CTEP; IRB, FDA Trial open (March 2013) [PIs: Miller (U Minnesota), Kohrt (Stanford), Sondel (Wisconsin), Thompson (UW], Waldmann (NCI)]
IL15/IL15Ra/ Fc fusion (#1) mammalian (Altor)	T cell & NK cell growth factor	Advanced melanoma Phase I at FHCRC/UW + USCF Expansion into NCI & Dartmouth Co-Funded by Melanoma Research Alliance & Altor [PI: Kim Margolin (FHCRC/UW] Projected to open in August
Anti-PD-1 (#2)	Check point inhibitor	Negotiating trials in Merkel Cell Cancer [Nghiem (FHCRC/UW)] and Mycosis Fungoides [Holbrook (Stanford)]
Anti-CD40 (#4) (Pfizer)	DC activator	**(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/ **Trials on HOLD**
IL-7 (#5) (Cytheris) + Provenge (Dendreon)	Homeostatic T cell growth factor	Advanced asymptomatic prostate cancer Protocol and IND approved Developing CRFs [PIs: Fong (UCSF) and Ferrari (NYU)]

Agent (Rank)	Function	Trial
IL-7 (#5) (Cytheris) + 6 infectious disease vaccines	Homeostatic T cell growth factor	Cancer patients >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)]
IDO Inhibitors (#7) (Incyte)	IDO Inhibition	Advanced melanoma to evaluate inhibition + / - peptide vaccine on tumor microenvironment LOI approved; Protocol submitted; awaiting CTEP review [PI: Slingluff (UVA)]
IDO Inhibitors (#7) (Incyte)	IDO Inhibition	Neoadjuvant ovarian cancer to evaluate inhibition on ascites and tumor microenvironment; LOI approved; Protocol submission - December [PIs: Odunsi (Roswell), Coukos (Penn)]
Anti-IL10 (#10)	Neutralizes suppression	Negotiating for neoadjuvant trial in ovarian cancer [Odunsi (Roswell Park) and Adams (New Mexico/Penn)]
Flt3-Ligand (#11) + (Celldex) Poly ICLC (#15) + (Oncovir)	- Dendritic cell growth factor - TLR3 agonist	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 & CVC PIs]

Why aren't adjuvants broadly available?

- Priority Adjuvants
  - **IL-12**
  - **CpG**
  - **MPL**
  - **Poly I:C**
  - **Resiquimod**
  - **852A**

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Adjuvant Challenge

- Universal Truth
  - Adjuvants are needed to achieve highest levels of immune response

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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

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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

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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

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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

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Extraordinary Administrative Effort to Initiate Trials

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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]

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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*)

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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 hurtles.

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