

Cancer Immunotherapy Trials Network (CITN)

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NCI's Growing Support for Cancer Immunotherapy

In addition to the marked increase in the scientific base for CIT over past decade:

- NCI Intramural Center for Cancer Research (CCR) has broad expertise in Cancer Immunology and Immunotherapy
 - The Center of Excellence in Immunology consists of outstanding programs in cancer immunology, host defense and viral immunology
 - The CCR has sponsored an annual meeting on **Cancer Immunology & Immunotherapy** since 2005, bringing to NIH the best researchers in the field to present state-of-the science research
- NCI Biologics Resources Branch (DTP) has provided a large number of biological products to the extramural community for clinical trials through the RAID program
- NCI CTEP provides links to commercial entities wishing to collaborate with extramural investigators on early phase biologics trials
- The Investigational Drug Steering Committee Immunotherapy Task Force provides input to CTEP on the development of anti-cancer agents that directly affect the immune system
- NCI sponsored an **Immunotherapy Agent Workshop** in July, 2007

2007 NCI Immunotherapy Agent Workshop

- Purpose: to recommend certain agents that hold **particular promise** to become immunotherapeutic drugs to governmental and non-governmental funding agencies, specifically the NCI, and investigators.
- Co-chaired by Drs. “Mac” Cheever (U. Washington) and Steve Creekmore (Director, BRB/DTP); 23 other participants
- Agents ranked based on potential for use, perceived need by multiple investigators, potential for use in more than one clinical setting, not broadly available, and not likely to be approved for commercial use in the near future
- 20 of 124 agents proposed on the final list were ranked, but others were considered to have high interest

Ranked List of Agents with High Potential for Use in Cancer Therapy

AGENT	FUNCTION	AVAILABILITY
1. IL-15	T-cell Growth Factor	NCI/DTP (in production)
2. anti-PD-1 and/or anti-B7-H1 (PD-1L)	T-cell Checkpoint Inhibitor*	Commercial (potential)
3. IL-12	Vaccine Adjuvant	NCI/CTEP (available)
4. anti-CD40 and/or CL40L	APC Stimulator	Commercial (Ab, high potential)
5. IL-7	T-cell Growth Factor	Commercial (potential)
6. CpG	Vaccine Adjuvant	NCI/DTP (probable)
7. 1-methyl-tryptophan	Suppression Enzyme Inhibitor	NCI/CTEP (available)
8. anti-CD137 (anti-4-1BB)	T-cell Stimulator	Commercial (high potential)
9. anti-TGF-beta	Signaling Inhibitor	Commercial (potential)
10. anti-IL10R or anti-IL10	Suppression Inhibitor	Commercial (potential)
11. Flt3L	DC Growth Factor/Adjuvant	Commercial (potential)
12. anti-GITR	T-cell Stimulator	Commercial (long-term)
13. CCL21 Adenovirus	T-cell Attracting Cytokine	NCI/DTP (available)
14. Monophosphoryl lipid A (MPL)	Vaccine Adjuvant	NCI/DTP (probable)
15. Poly I:C and/or Poly ICLC	Vaccine Adjuvant	NCI/DTP (potential)
16. anti-OX40	T-cell Stimulator	Commercial (foreign)
17. anti-B7-H4	T-cell Checkpoint Inhibitor	Commercial (long-term)
18. Resiquimod and/or 852A	Vaccine Adjuvant	Commercial (potential)
19. LIGHT and/or LIGHT vector	T-cell Stimulator	pre-clinical
20. anti-LAG-3	T-cell Checkpoint Inhibitor	pre-clinical
21. IL-21	T-cell Growth Factor	Commercial (potential)

*anti-CTLA-4, a T-cell checkpoint inhibitor, was considered of very high priority but not on original list since it was expected to be approved by the FDA shortly; however, this has not occurred and therefore should be ranked high on this list.

Challenge: Translation of Biologic Agents to the Clinic

- Response criteria based on biomarkers are needed to test agents in appropriate patient populations: why do only certain patients respond?
- Development pathway from tumor antigen to Phase I trials is complex and difficult, and potential agent combinations need prioritization
- Mouse models are not entirely relevant for humans: immune systems differ and single agents used in mice are unlikely to work as monotherapy in patients; need combinations and/or combined with other modalities
- Large amounts of GMP-grade agents for human trials a problem
- INDs required, particularly difficult for combination studies
- Multi-institution approaches needed for larger Phase 2 trials
- **Current NIH funding mechanisms are inadequate to meet this need**

Current Mechanisms to Fund Clinical Trials in Immunotherapy: Problematic

- *R01/R21/P01 grants funded in CTEP have IT aims, **but** these grants are suboptimal for rapid clinical development of the field*
 - Single institution: Combination trials & agent acquisition difficult
 - Fund best grant, not necessarily best possible new trials
 - Timing of funding not in synchrony with trial needs: Funding delays due to grant preparation, review and ultimate funding
 - NCI resources not optimally used (eg. NCI holding INDs, aid obtaining commercial agents, agent distribution, program coordination)
- *Cooperative groups*: focus on later phase trials
- *Pharmaceutical companies*: limited portfolio and focus on single IT agent trials
- *Only a single small cooperative agreement exists (immune reconstitution): NO cooperative agreement for cancer immunotherapy*

A Clinical Immunotherapy Trials Network

- Bring the leading investigators in cancer immunotherapy together to design and implement Phase 1 and 2 IT trials to test novel IT agents (NCI workshop agents) and modalities, primarily in combination studies
- Incorporate high quality, centralized immuno-monitoring services for each trial, along with biomarker assessment and correlative studies using patient samples

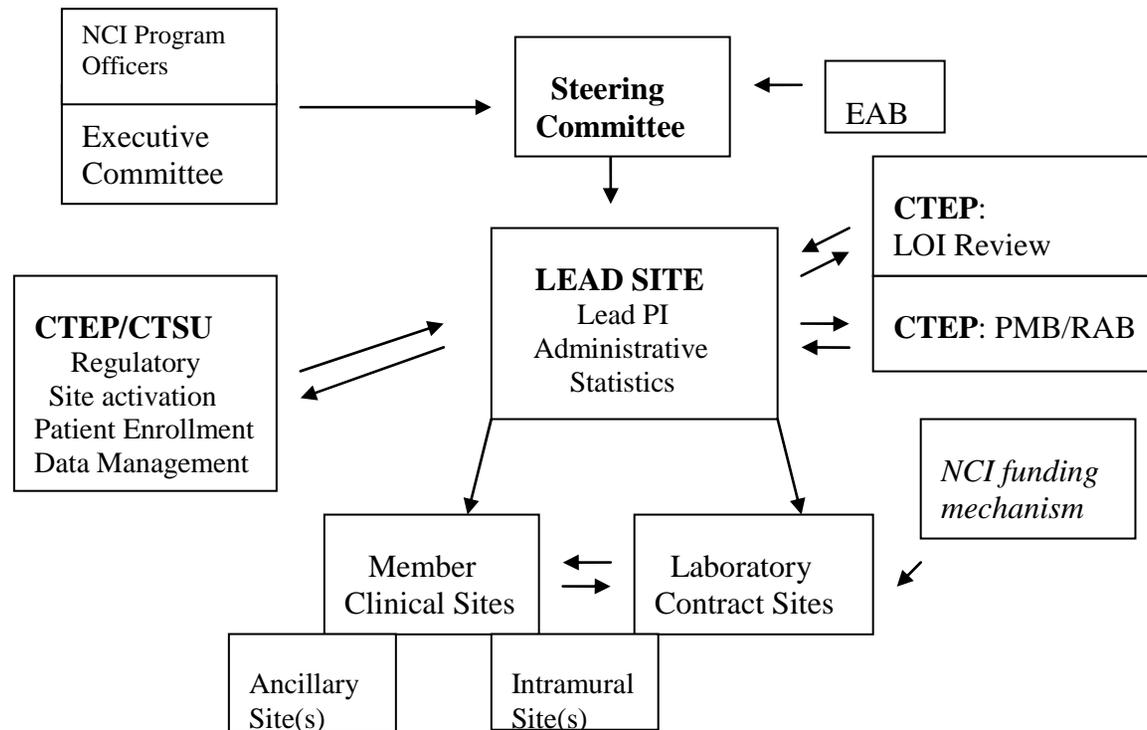
CITN: Fund a Single U01

- Clinical Site “Members” (6-8 sites)
(All site leaders are PIs: NIH multiple PI model)
 - Leading IT programs with record of IT trial expertise
 - Broad range of tumor types and modalities
 - Ancillary clinical sites allowed for novel ideas and for enhanced accrual on a per protocol basis
- Tumor Immunology Laboratories
 - Immuno-monitoring (standardized assays)
 - Biomarker assessments (validated) to predict response
 - Correlative studies to inform future trials
 - Expertise to acquire, store and ship patient samples
 - Subcontracts through the Operations office and/or NCI
- NCI Intramural site(s):
 - May contribute to either clinical or laboratory programs
 - Non-funded from the U01

CITN Key Components

- **Steering Committee:** PIs of Member sites: approve clinical trials together with laboratory sites associated with trial; ancillary site members, correlative studies
- **Operations & Statistical Office:** Lead PI's office; protocol coordinators; office staff; statistical and IT support
- **Executive Committee:** CITN Leader, vice Leader; lead statistician and protocol coordinator; NCI Program staff (CTEP and DCB): set steering committee agenda
- **External Advisory Board:** formal evaluation of scientific program and progress (at least 4 members)
- **Cancer Trials Support Unit (CTSU):** data management (electronic) support, regulatory support, enrollment, website for posting trials
- **Collaboration with DCTD/CTEP**
 - Aid agent access: IT agents developed in DTP/BRB and distributed via PMB/CTEP
 - Organize review and approval of LOIs
 - Can file and hold INDs and assist in audits
- **Collaboration with DCB:** for development of immuno-monitoring assays and correlative studies
- **Partner with industry:** leverage NCI funds to obtain supplemental funding and access novel technologies and obtain agents not in NCI portfolio

CITN Organizational Structure



BUDGET Years 1-2 (Total Costs)

Leadership (Leader & vice-Leader)	\$ 80K
Operations & Statistical support	300K
Clinical Member sites (\$60K per site) (non-accrual responsibilities plus site PI)	480K
Tumor Immunology Laboratories	700K
Meetings	40K
CTSU subcontract (patient capitation, specimen collection & data management)	[1,000K]
TOTAL	\$1,600K

CITN 5-Year BUDGET

CATEGORY	Year 1	Year 2	Year 3	Year 4	Year 5
Leadership	\$80,000	80,000	80,000	80,000	80,000
Operation/Stats Support	300,000	300,000	300,000	300,000	300,000
CTSU Subcontract	[1,000,000]	[2,000,000]	2,000,000	2,000,000	2,000,000
Meetings	40,000	40,000	40,000	40,000	40,000
Clinical Sites	480,000	480,000	480,000	480,000	480,000
Laboratory Sites	700,000	700,000	700,000	700,000	700,000
Total Dollars	1,600,000	1,600,000	3,600,000	3,600,000	3,600,000