Application for Member Sites in the NCI Cancer Immunotherapy Trials Network (CITN)

**The NCI is accepting applications for Member Site status in the CITN (RFA CA-10-007) as described in NOT-CA-10-034 as subcontract sites to the RFA awardee. The Fred Hutchinson Cancer Research Center (M. Cheever, PI) is the recipient of the RFA award and, as the Central Operations and Statistical Center for the CITN, will provide overall organizational infrastructure and leadership for this network. Member Sites will serve as clinical sites to implement the early phase clinical trials chosen by the network as well as contribute to the scientific leadership of the network.**

**This website provides the specific information that should be submitted to the NCI for those institutions who wish to apply as well as the selection and review process.**

**BACKGROUND for the CITN (adapted from RFA-CA-10-007 “Research Objectives”)**

The need to intensify efforts towards clinical developments of immunotherapeutic modalities reflects also considerable progress in our understanding of biology of anti-tumor immune responses. These advances include an elevated appreciation of immune parameters characteristic of highly effective antitumor T cells as well as the identification of multiple immune suppressor mechanisms in the tumor microenvironment. Consequently, investigators understand now better the reasons for the failures mentioned above and may suggest new avenues for manipulating the immune response for a more favorable therapeutic outcome. A wide variety of studies are now in various stages of pre-clinical and clinical development that either enhance the immune response to tumor, provide ways to block inhibitory signals, or enhance the longevity of adoptively transferred T cells. Taking advantage of the rapidly advancing field, the NCI organized an “Immunotherapy Agent Workshop” in July of 2007 <http://web.ncifcrf.gov/research/brb/newsEvents.aspx> to gather leading investigators in tumor immunology/cancer immunotherapy. The group discussed the scientific value and clinical potential of a large number of immunotherapeutic agents that showed promise but were unavailable for clinical trials at that time. This workshop provided a ranked list of 20 such agents, including cytokines, antibodies, and adjuvants , for development as promising anti-cancer therapeutics.,. Since that list was developed, the NCI has promoted the production of some of these agents listed at or near the top of that list. In summary, it is now an opportune time to bring a new mechanism for the clinical translation of not only these agents but others as well that investigators in immunotherapy feel should be developed in appropriate combinations for optimized early phase trials.

**OVERALL GOALS (Specific Aims) for the CITN (adapted from RFA-CA-10-007 “Research Objectives”)**

**Aim #1:** The overall goal of the CITN is to create a single network composed of the leading investigators and institutions in the field of cancer immunotherapy to design and implement early phase multi-institute clinical trials in this field. The network should consist of members capable of proposing trials that utilize a variety of immunotherapeutic modalities, e.g., cell-based approaches, vaccines, antibodies, and/or cytokines.

**The expectation is that the CITN will design, develop and conduct trials not otherwise possible.** The trials will combine: (1) the best peer reviewed concepts with submissions open to everyone in the field regardless of whether they are from a CITN member site, (2) optimal design provided by the CITN Steering Committee composed of Member Site PIs and (3) the best agents available provided by the investigators, NCI and/or industry.

**Additional expectations are that:**

* + Trials will focus on developing regimens that prospectively and predictably greatly increase the number, function, trafficking and longevity of T cells specific for known and defined antigens.
	+ Trials will focus on developing “off the shelf” regimens that can be used by multiple investigators in multiple circumstances and thus can serve as the backbone for further immunotherapy agent development.

The network is expected to initiate at least 15 Phase I or Phase II trials over the course of the funding period. The most favorable approaches developed by the Network could hopefully be brought to the NCI Cooperative Groups for development of Phase III trials.

**Aim #2:** A second goal is to integrate several tumor immunology laboratories into the CITN to enable the network to utilize specimens obtained from patients on the clinical trials for: 1) immunomonitoring; 2) developing and credentialing biomarkers that assess pharmacodynamic effects or can serve as predictors of response; and 3) correlative studies to facilitate an understanding of the biological mechanisms underlying the results of the clinical trials. to inform future clinical trial designs. .

**Desirable Capabilities and Anticipated Activities of CITN Member Site Institutions**

Member Sites are expected to have:

* Experience in leading or participating in Phase I or II immunotherapy trials;
* Ability to carefully monitor patients treated in the course of Phase I and II trials, with requisite medical, nursing, and pharmacy personnel and dedicated research staff;
* Capability of reporting clinical trial data in a timely manner to CITN data management structure;
* Capability for specimen collection and shipping including image guided tumor biopsies and/or fine needle aspiration;
* Ability to contribute to scientific leadership of the CITN;
* Ability to help leverage CITN funds to attract funding from other sources to supplement the goals of the CITN (e.g., foundation support, pharmaceutical company support and grants for correlative studies);
* Ability (optional) to provide tumor immunology laboratory expertise to support the trials, i.e., immunomonitoring, biomarker development and validation, and/or correlative studies to inform future trial development.

The relevant specific activities of the Member Sites include:

* Participation in the research design and development of clinical protocols by serving as protocol Chairs or members of protocol teams;
* Participation in Scientific and Administrative committees needed to support CITN research objectives;
* Participation in the regular meetings of the CITN Steering Committee, which is charged with evaluating and approving all potential treatment concepts and correlative study proposals presented at these meetings;
* Recruit eligible patient to CITN studies and enter a sufficient number of patients to meet accrual targets;
* Following the CITN standard operating procedures (SOPs) for the conduct of clinical research;
* Implementing the core data collection method and strategy of the CITN: It is the responsibility of each Member Site to ensure that the procedures for data submission for each CITN clinical trial protocol are understood by investigators at the site and that protocol-specific data are submitted accurately and in a timely manner to the COSC;
* Complying with mechanisms for quality assurance and quality control of therapeutic and diagnostic modalities employed in CITN trials. Institutional responsibilities for quality control include, but are not limited to, submission of appropriate data to allow determination of clinical trial compliance in dose administration and dose modification of immunotherapy agents used in the clinical trials;
* Participating in the on-site monitoring/auditing program established by the CITN;
* Complying with the Department of Health and Human Services (HHS) Office of Human Research Protections (OHRP) and Food and Drug Administration (FDA) regulations concerning protection of human subjects, with member institutions being required to implement the procedures established by the CITN in order to meet such requirements;
* Adverse events reporting: Implement the procedures established by the CITN for assuring timely reporting of all serious and/or unexpected adverse events;
* Implementing the procedures established by the CITN for assuring that CITN investigators performing clinical trials involving DCTD Investigational Agents are NCI-registered investigators (Form 1572);
* Acquiring and submit protocol-specified tumor specimens, biological fluids, and relevant clinical data to the appropriate laboratories where these specimens will tested and/or stored for future studies;
* Serving as a resource for conduct of protocol-specified laboratory assays and studies (specifically related to conduct of immunomonitoring assays and biomarker studies) -- the CITN steering committee will establish a process for the selection of the laboratories to perform these studies, which may be supported by an Immunomonitoring/Biomarkers/Correlative Sciences Fund of the CITN or by independent funding;
* Participating in CITN procedures for the timely publication of major findings; and
* Complying with the conflict-of-interest policies of the CITN to ensure that there is no reasonable probability that the design, conduct, and/or reporting of research conducted by the CITN will be biased by any conflicting financial interest of an investigator.

Funds to Member Sites will be dispersed based on accrual to the clinical trials at a base rate of up to $7,000 per patient accrual ($5,000 for research costs plus up to $2,000 per patient for specimen collection costs). Higher capitation may be available for more complex trials.

**Interested institutions are asked to provide the following**:

**Cover Letter** -- Citing Notice **NOT-CA-10-034** and providing the following information:

* Project Director (PD) name;
* Name and title of the institutional official;
* Phone, e-mail, and address information for both the PD and institutional official; and
* Purpose of the application.

The cover letter must be signed by the authorized organizational representative/institutional official.

**A brief proposal with the following components:**

**Face page** (PHS 398 Form Page 1 is recommended)

* The title of the project (Box 1) should include “Cancer Immunotherapy Trials Network (CITN)” plus subcontract site.
* The remaining items on the face page should be filled out in accordance with the PHS 398 application instructions.
* Dates of support are January 1, 2011, through September 31, 2015.

**Project Summary, Performance Sites and Key Personnel** (PHS 398 Forms Page 2 and 3 are recommended)

* Provide a Summary of the proposed work as a Member Site under the COSC award.
* List all Performance Sites and Key Personnel.

**Personnel (including Biographical Sketches for all Key Personnel)**

* State the Senior (Key) personnel available for participation at your site, listing time available, and the roles of each person. Include a PHS 398 form biosketches for each of these personnel.
* State all OTHER personnel that will be involved in the research, both for clinical trials implantation, administrative, and laboratory staff for any immunomonitoring or ancillary studies.

**Resources and Environment**

* Describe the specific resources at your institution that are available for CITN participation, including all relevant clinical and laboratory sites (PHS 398 form).
* Describe any other aspects of your institution environment, which bear on your ability to perform your proposed studies in support of the goals of the CITN.

**Expertise and Proposed Research Activities (limit 13 pages, not including references), which should include:**

* 1. **Introduction** **and Specific Aims** (1 page) describing specifically how the proposed activities relate to the overall goals of the CITN award (1 page)
	2. **Immunotherapy Expertise and Experience** (6 pages):

 Include relevant information on:

1. Participation in **ALL** immunotherapy clinical trials in the last 10 years, either as the protocol Chair or co-chair or as a participating member of a multi-site trial. Distinguish between single site trials and multi-site trials that you led, co-led or were a participant. Provide dates of activation, and whether pilot, Phase I or Phase II. Also, please list protocol title and category (adoptive immunotherapy, antibody, vaccine, combination, etc.). If numerous trials are involved this information may be best supplied as a table with summary explanatory text. For each trial, be sure to list the accrual to the trial from your site.
2. Evidence for scientific development of the field of immunotherapy, as shown by advances in one or more directions; this can be shown in a reference list attached to this section and a summarization of findings of the studies in this list. State overall significance and innovation of the findings.
3. All experience, expertise and infrastructure at your institute in support of the management of the trials listed in 1) above. This should include methods for data collection and storage, quality control for data collection and compliance to protocols, adverse events reporting, data analysis, and protocol-specific submission of specimens.
4. Evidence for development of standardized immunomonitoring, immune-based biomarkers, and/or correlative studies associated with immunotherapy clinical trials; this can be shown in the reference list attached to this section with a summarization of the findings of these studies. State overall significance and innovation of the findings as well as a summary of specific experience, expertise and infrastructure at your institute in support of these laboratory studies.
5. Evidence for successful negotiation with pharmaceutical companies or foundations for immunotherapy agents and/or research support to leverage the costs of clinical trials

 **C.Research Strategy** (6 pages):

 Given the Overall Goals and Specific Aims of the CITN (above):

1. Describe your vision of the overall research directions needed to achieve these goals.

 2) Describe your expected contribution to the directions indicated above that you envision bringing into the CITN based on your experience to date as well as any planed new directions for the future as a logical extension of this expertise.

3) Present draft trial synopses for at least one but no more than three specific concepts that are practical and would help achieve the goals of the CITN. Focus on agents that are available or might be available from the NCI, industry or other investigators through appropriate negotiations. The synopses might be presented as single trials or as a series of iterative early phase clinical trials towards a prospectively identified goal. Consider and describe the target(s), immune modulating agent(s),formulations and combination regimens, as well as the assays for immune responses, assays for relevant patient subsets, and correlative studies (effects on targets versus outcomes). [http://clincancerres.aacrjournals.org/content/14/18/5664.full.pdf+html](http://clincancerres.aacrjournals.org/content/14/18/5664.full.pdf%2Bhtml)) <http://web.ncifcrf.gov/research/brb/newsEvents.aspx>; Cheever et al Clinical Cancer Research 15: 5323, 2009). Describe the principles expected to be elucidated and the extent to which the principles might be applied to other immunotherapy regimens and circumstances. These could be trials that you might propose and lead yourself or trials that the CITN might ask others to propose and lead.

Indicate if the proposed agent(s) is listed as an agent identified as a high priority agent at the NCI 2007 Immunotherapy Workshop agent (see <http://web.ncifcrf.gov/research/brb/newsEvents.aspx> ). If the agent(s) are not on the list, explain why they should be prioritized by the CITN.

4) Describe standard immunomonitoring, biomarker, and/or correlative science studies that you would advise the CITN to include in most trials as well as novel correlative studies that should be considered for selected trials.

**Human Subjects/ Vertebrate Animal documentation**

Guidance on Human Subjects Research and Vertebrate Animals is provided under Part II of the PHS 398 instructions (<http://grants1.nih.gov/grants/funding/phs398/phs398.html>).

**Budget:**

Funds to Member Sites will be disbursed based on accrual to the clinical trials Therefore, no budget is required in this application.

**Review and Selection Process**

Member Site Requests for Participation in the CITN will be reviewed for their scientific merit by a review panel consisting of NCI Program staff, NCI intramural scientists and scientists from the extramural community. Selection factors will include the following:

* Expertise and experience in Immunotherapy: Does the applicant bring sufficient experience and expertise in devising and implementing early phase clinical trials in immunotherapies, both in terms of scientific expertise but also experience in managing such trials? Does the applicant have a track record of excellent accrual to immunotherapy trials? Will the applicant also be able to provide expertise in immunomonitoring or biomarker assay and/or correlative studies expertise (optional expertise, secondary to clinical expertise)?
* Personnel and resources: Does the applicant provide appropriate personnel and resources for the conduct of clinical protocols in immunotherapy, and if applicable to the site, ancillary laboratory studies?
* Proposed vision for immunotherapy research and specific research plan: Does the applicant propose significant research directions, appropriately prioritized, for the future course of immunotherapy trials, and are the specific research concept(s) and protocol(s) included in the application timely, innovative, and feasible?
* Overall Impact: will the proposed applicant provide significant impact to the overall success of the CITN?

Sites will be chosen by NCI staff based on summary critiques and in consultation with the Principal Investigator of the CITN.

**Submission of Requests**

The NIH Center for Scientific Review (CSR) and the Division of Extramural Activities (DEA) ARE NOT involved in receipt and processing of these requests. Supplement requests are not to be electronically submitted via Grants.gov (and the ERA commons) or electronically on paper to the Division of Receipt and Referral, CSR.

This notice is a one-time announcement and formal requests musts be received on or before 11/15/2010. Requests must be signed by the Authorized Organizational Representative (OAR).

A letter of intent to submit should be received by 10/08/2010.

Applicants are strongly encouraged to submit requests and LOIs electronically as an email attachment in PDF format; however, the signature of the OAR must be clearly visible. The email address for submission is: **merrittw@mail.nih.gov**

Applicants may also submit a hard copy to:

William D. Merritt, Ph.D.

Clinical Grants and Contracts Branch

Cancer Therapy and Evaluation Program

Division of Cancer Treatment and Diagnosis

National Cancer Institute

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**General inquiries** **concerning program and review matters should be directed to:**

William D. Merritt, Ph.D. as above

**Inquiries regarding administrative and fiscal matters should be directed to:**

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