**Appendix A: Research Plan**

Title of CRADA

**Clinical Development of Collaborator’s Proprietary Compound (Agent Name), Agent Class, as an Anti-Cancer Agent**

NIH CRADA Extramural Investigator/Officer(s)

Dr. IDB PI

Dr. Margaret Mooney

CRADA Collaborator Principal Investigator(s)

Term of CRADA

Five (5) years from the Effective Date

**1. Research Goal and scope of CRADA**

The overall goal of this research project is to collaborate with Collaborator on the non-clinical and clinical development of XXXX (Investigational Agent), to demonstrate its safety and efficacy in patients with hematological malignancies and solid tumors. The scope of the CRADA Research Plan is limited to clinical and non-clinical development of Investigational Agent.

**2. Scientific Background**

Will be provided by Collaborator (one or two paragraphs for the general scientific background for the Investigational Agent. e.g. if the agent is an MET inhibitor, a short paragraph to describe the MET pathway and how this pathway is associated with cancer)

**3. background and contributions of collaborator**

An introduction of Collaborator (a couple of sentences, should be provided by collaborator)

Studies (pre-clinical and clinical) that have been done by the Collaborator. (one or two paragraphs, about one page or less in summary/abstract form) (can be provided by Collaborator’s PI or IDB PI)

**4. Description of the CRADA Research Plan**

The Division of Cancer Treatment and Diagnosis (DCTD), NCI and Collaborator are interested in the evaluation of Investigational Agent in a clinical development program that includes various tumor types. DCTD will sponsor Investigational Agent phase 1, phase 2 and phase 3 clinical trials that will help determine the safety, efficacy and the potential spectrum of Investigational Agent anti-tumor activity. DCTD and Collaborator are also interested in evaluating Investigational Agent in combination with other novel investigational agents. (This section will be modified depending on agent’s status and studies to be conducted).

DCTD initially plans to sponsor (x number) clinical trials (xxx). Brief description of SAC approved trials.

As data from the initial studies emerge, DCTD and Collaborator will discuss additional clinical trials to complement and support the development of Investigational Agent. Additional studies will be with the mutual agreement and approval of the parties.

DCTD may also support intramural and extramural Non-Clinical Studies that focus on identifying assays for monitoring the biologic activity of Investigational Agent, as well as studies for combination of Investigational Agent with other anti-cancer agents. These Non-Clinical Studies are aimed to support the clinical trials that will be conducted under the CRADA, and might involve convening a meeting of scientific experts and ultimately sponsoring core laboratories with expertise in the performance of appropriate assays with patient material.

**5. Respective Contributions of the Parties**

**A. Joint Responsibilities**

1. Steering Committee and Communication Plan

A Steering Committee will be employed by the Parties to exchange information and data and to discuss and to plan the proposed and ongoing clinical research. The Steering Committee shall be comprised of at least the NIH CRADA Extramural Investigator/Officer(s) and the CRADA Collaborator PIs from both Parties. In addition, other NCI and Collaborator staff with expertise in toxicology, pharmacology, pharmaceutical development, project management and other disciplines as pertinent to the current development stage of the Investigational Agent at the time of the meeting will be participating members. Both Parties shall report regularly to the Steering Committee on the progress of the clinical research and development efforts covered by this CRADA, will review the current progress, and will make any required decisions. The routes of communication, format of written minutes, etc. will be determined at the Steering Committee meetings and will be driven by the needs of the project.

The Steering Committee will function under the oversight of Co-Chairs, one from NCI and one from the Collaborator. NCI’s Steering Committee Co-Chair will be appointed by the DCTD Division Director and report to the DCTD Division Director or his or her designee. Steering Committee meeting minutes summarizing all key decisions and issues under discussion will be provided to all the Steering Committee members and to the DCTD Division Director within ten (10) days of each meeting. Steering Committee decisions will be made by consensus.

2. The DCTD and Collaborator will explore the clinical utility of Investigational Agent for various cancers. As sensitive tumor types are identified, it will be important to develop combinations of Investigational Agent and other active anti-cancer agents and to compare Investigational Agent and Investigational Agent combinations with standard therapy for these tumor types. Adjuvant studies may be important in diseases where Investigational Agent has activity and where there is a high risk of recurrence following initial primary therapy.

3. Both Parties shall collaborate in the collection and analysis of data generated under the Research Plan.

4. Both Parties will work closely together to ensure that the clinical studies move forward expeditiously.

**B. Collaborator Responsibilities**

1. Collaborator will provide a cross-reference letter of its Investigational New Drug Application (IND) for Investigational Agent to FDA with a copy to DCTD for DCTD to file the NCI-sponsored IND(s) for Investigational Agent with the FDA, or prepare and submit to the FDA an IND, which will cross-reference a DCTD IND, for Collaborator sponsored clinical studies. The cross-reference letters should be provided at the time of LOI or concept approval so as not to delay IND submission.

2. Collaborator, at its own expense, will supply formulated Investigational Agent for all clinical trials and supportive non-clinical studies conducted under this CRADA. This includes:

* Provision of appropriately packaged and labeled Investigational Agent for NCI-sponsored clinical studies.
* Supply of Investigational Agent, or unformulated analytical grade Investigational Agent or metabolites, if available, to DCTD for DCTD to provide to NIH Intramural Investigators and NCI Extramural Investigators for the development of analytical assays or ancillary correlative studies conducted in conjunction with clinical Protocol Letters of Intent (LOIs) or concepts that are approved by the DCTD’s Protocol Review Committee and Collaborator under this CRADA.

* Supply of Investigational Agent for distribution to NIH Intramural Investigators and NCI Extramural Investigators for Non-Clinical Studies designed to enhance the basic understanding and development of Investigational Agent. These will include non-clinical studies designed to support clinical trials in pediatric patients; non-clinical combination studies to provide data in support of a clinical trial; and other pertinent requests.

3. Collaborator will provide resources for data collection and management, beyond that normally carried out by the DCTD as set forth in the CRADA for CTEP-sponsored studies, if Collaborator desires such data collection and management. This would include the collection of the data required to submit a New Drug Application (NDA) or a Biologic License Application (BLA) to the FDA.

4. Collaborator intends and will use reasonable efforts to prepare and submit an NDA or a BLA to the FDA expeditiously when justified by clinical studies, with the object of obtaining pharmaceutical regulatory approval for the commercial marketing of Investigational Agent.

5. Collaborator may sponsor its own clinical trials and carry out its own non-clinical studies using Investigational Agent. Such Collaborator-sponsored trials and studies are outside the scope of this CRADA. For these clinical trials and studies, Collaborator will maintain possession and control of the clinical trial and study results. Collaborator will permit DCTD to review and use the results for DCTD-sponsored clinical trials which are under the CRADA.

**C. DCTD Responsibilities**

1. The DCTD, as sponsor, will prepare and submit to the FDA an Investigational New Drug Application (IND) for Investigational Agent.

2. The DCTD will collaborate solely with Collaborator for Investigational Agent development under this CRADA, and will assist Collaborator in all aspects of the regulatory approval process.

3. Following the Project Team process described in Section 5 of this Appendix A, DCTD will receive LOI or concept from the investigators in the DCTD's clinical trials network for (1) clinical research and (2) non-clinical research.

The Protocol Review Committee (PRC), of the DCTD, will:

* Evaluate the rationale of each LOI or concept received at the DCTD;
* Review the LOIs or concepts for study design, including dose, schedule and comparison groups, if relevant, in order to address any pertinent scientific questions;
* Examine the characteristics of the patient population to be studied;
* Assess the feasibility of the projected accrual, including the ability of each investigator to accrue the appropriate patient population in a timely manner;
* Review competing studies of the investigator in the specified disease(s);
* Provide investigator(s) with consensus review(s) of the PRC's evaluation to be used to revise the Protocol;
* Provide a copy of the approved LOI or concept and consensus review to Collaborator. All CTEP approved clinical Protocol LOIs or concepts will be sent to Collaborator. Collaborator will provide NCI with the approval or disapproval within four weeks of receiving the CTEP approved clinical Protocol LOIs or concepts by signing and returning the Drug Approval Form. Only LOIs or concepts that have been approved by both the PRC and Collaborator will lead to the submission of full clinical Protocols. If Collaborator has not responded within 90 days of receiving the LOI or concept, CTEP will administratively disapprove the LOI or concept. Collaborator must contact CTEP prior to the end of the 90 days if there are extenuating circumstances preventing a timely response.

The Protocols received from investigators in response to the approved LOIs or concepts will be reviewed and evaluated by the PRC. The PRC will:

* Evaluate each Protocol from the agent, disease, statistical and regulatory perspectives in order to ensure that the study design that was approved by the PRC at the LOI or concept stage is carried out;
* Provide each clinical Protocol received by DCTD to Collaborator for review and comment approximately two weeks before it is reviewed by the PRC of CTEP. Comments from Collaborator received by CTEP before the Protocol Review Committee meeting will be discussed by CTEP, will be given due consideration, and incorporated in the Protocol, absent good cause. Comments from either Collaborator or the CTEP staff that are agreed upon in the PRC meeting will be formatted as a consensus review, which will be returned to the investigator for necessary and/or suggested changes before the Protocol can be given final approval and submitted to the FDA. In addition, the PRC will review any correlative laboratory studies, solicited from investigators, to address cellular pharmacological and/or pharmacokinetics questions as necessary.
* Forward a copy of any final Protocol to Collaborator following its submission to FDA.

Protocol revisions and amendments for substantive changes will be forwarded to Collaborator at the same time as CTEP reviews for Collaborator review and comment. Collaborator will have 3 business days to review and provide comments. No response will be deemed as no comment unless Collaborator notifies CTEP of the need for an extension to the timeline.

4. Project Team (PT) and Investigational Drug Steering Committee (IDSC)

The NCI will assemble a Project Team whose charge is (1) to arrive at pre-clinical/translational plan that addresses critical questions that will inform development of the Investigational Agent and (2) to propose innovative disease-based or biomarker-based clinical trials incorporating appropriate safety, pharmacokinetic, pharmacodynamic and efficacy endpoints. The Project Team Announcement (PTA) will be compiled from publicly available sources or unpublished data only if agreed upon by Collaborator. Following Collaborator’s review and comment, the PTA will be broadly disseminated to NCI Investigators. The Project Team members selected for the Project Team will sign confidentiality agreements with NCI and are vetted for potential conflicts of interest before any confidential data is provided for their review. The Project Team members will include NCI staff and extramural clinical researchers, translational scientists, and tumor biologists. The Project Team will conduct its deliberations for 8-12 weeks, and the deliverable will be a drug development plan that will be presented to the to IDSC by the clinical and translational Project Team leaders and will be shared with Collaborator. Following input from the IDSC, execution of the CRADA, and approval by the NCI Senior Advisory Committee, NCI will direct members of the Project Team to submit LOIs or concepts for review by CTEP and Collaborator.

The NCI Clinical Trials Working Group has mandated the formation of the Investigational Drug Steering Committee (IDSC). The IDSC is designed to provide DCTD with broad external scientific and clinical input for the design and prioritization of phase 1 and phase 2 trials with agents for which CTEP sponsors an IND. Membership of the IDSC includes the principal investigators of phase 1 U01 grants and phase 2 N01 contracts, representatives from the NCI Cooperative Groups, NCI staff members, and additional representatives with expertise in biostatistics, correlative science technologies, radiation oncology, etc., as well as patient advocates and community oncologists, as needed. Experts with specific expertise will be included as ad hoc members for consideration of specific agents. Periodically the IDSC will assess, from a strategic perspective, CTEP investigational agent development plans, agent portfolios, and LOIs or concepts submitted by investigators to determine whether the clinical development plan for an agent should be modified. When requested by CTEP, the IDSC will provide input on LOIs or concepts to assist in CTEP decision-making. All participating members will be vetted for conflict of interest and are under confidentiality agreements with DCTD.

The IDSC is described in greater detail on p. 23 of the report of the Cancer Trials Working Group of National Cancer Advisory Board

(<http://integratedtrials.nci.nih.gov/ict/CTWG_report_June2005.pdf>).

5. The DCTD will evaluate each of the active studies as they progress to ensure that the appropriate questions are being addressed and to ensure that the studies are modified as required based on the developing data. The DCTD will utilize its existing procedures and mechanisms to follow the clinical studies to ensure that all studies meet the pertinent FDA regulations.