**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. Jeffrey Abrams

CRADA Collaborator Principal Investigator(s)

Term of CRADA

Five (5) years from the Effective Date

**1. Research Goal 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.

**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)

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).

**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 and phase 2 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.

In addition, DCTD may also support assay development via internal mechanisms (DCTD Clinical Support Assays). These assays (described below) will be conducted using internal NCI resources and are intended to further the clinical development of Investigational Agent and provide information regarding targets and assay development to the broader research community.

**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.

In addition to the Steering Committee a Project Team comprised of NCI and Collaborator scientific members will be assembled for the purpose of discussing the DCTD Clinical Support Assays. This Project Team will be a collaborative body to approve projects described in Section 5.C.1., which outlines the DCTD Clinical Support Assays. This Project Team will be a collaborative body charged with the planning and successful execution of experimental objectives. It is intended that study areas approved by the Project Team will be broad enough in scope to allow all necessary experiments to realize the goal of said research without further approval from the Project Team. Submission of new projects/areas of inquiry will be addressed by the Project Teams within seven (7) days of receipt. Disagreements between DCTD and Collaborator will be discussed by the Steering Committee and/or Project Team who may recommend a course of action. In the event that Project Team is unable to reach consensus, it will be the Division Director’s responsibility to resolve any impasse. The Division Director will confer with representatives of the Collaborator before making any decision. Project Teams will meet quarterly, or more often if necessitated by results or submission of a new projects/area of inquiry.

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 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.

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 NCI 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) that are approved by the DCTD’s Protocol Review Committee and Collaborator under this CRADA.

* Supply of Investigational Agent for distribution to NCI 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.
* Provision of Investigational Agent for DCTD Clinical Support Assays as described in Section 5.C.1 of this Appendix A.

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 an NDA or a 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. DCTD may develop and conduct DCTD Clinical Support Assays on Investigational Agent to enhance understanding of the Investigational Agent’s molecular target and mechanism of action (MoA) and to optimize the clinical development program of Investigational Agent.  DCTD’s work may include activities such as the development of assays to detect target modulation; studies of biomarkers; and the conduct of pharmacodynamic (PD) assays in conjunction with DCTD-sponsored clinical studies.  These studies, performed in conjunction with the Pharmacodynamic Assay Development and Implementation Section (PADIS) and the National Clinical Target Validation Laboratories at the NCI, are intended to create research tools that will be accessible to the broader research community through appropriate agreements.  Specifically, these studies will comprise:

a. *In vitro* and *in vivo* MoA studies (including profiling compound for activity in the NCI 60 cell-line panel, COMBO plates, and *in vivo* hollow fiber assays against human tumor cell lines)

b. *In vitro* and *in vivo* PD studies.

c. Efficacy studies in support of the PD studies in (b).

d. Development of Standard Operating Procedure-driven PD assays suitable for early phase clinical trials.

All DCTD Clinical Support Assays shall be conducted under the scope of this Research Plan. Manuscripts and inventions resulting from these studies will be handled in accordance with the terms of the CRADA.

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

3. 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.

4. The DCTD will solicit Protocol Letters of Intent (LOI) 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 received at the DCTD;
* Review the LOIs 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 consensus review to Collaborator. All CTEP approved clinical Protocol LOIs will be sent to Collaborator. Collaborator will provide NCI with the approval or disapproval within two weeks of receiving the CTEP approved clinical Protocol LOIs by signing and returning the drug approval form. Only LOIs that have been approved by both the PRC and Collaborator will lead to the submission of full clinical Protocols.

The Protocols received from investigators in response to the approved LOIs 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 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.

5. Investigational Drug Steering Committee (IDSC)

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 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 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>).

1. 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.

**6. RElated Intellectual Property and Other RELATED Agreements of the Parties**

**NCI Patents and Patents Applications**

None.

**Collaborator Patent Property Covering Investigational Agent**

Investigational Agent is disclosed and claimed in the following representative patents and patent applications. There are other issued patents and patent applications in the US, Europe and other countries not listed under this section.

List here: key patent and patent applications numbers, filing/issuing date, title.

**Related Agreements Between the Parties:**

A Confidential Disclosure Agreement (“CDA”), identified by NCI as CDA #xxx, which was executed on (date) to permit the exchange of information on several collaborator compounds including the investigational agent. Upon execution of this CRADA, the CDA as it pertains to the Research Plan and this CRADA is hereby superseded and succeeded by the terms of this CRADA. Specifically, upon execution of this CRADA, the information exchanged between the Parties under the CDA concerning the Research Plan and this CRADA shall be governed by the terms of this CRADA as if such information had been exchanged after execution of this CRADA, and not by the terms of the CDA.

At the time of execution of this CRADA, there are no Material Transfer Agreements, Clinical Trial Agreements, or other Cooperative Research and Development Agreements or Materials Cooperative Research and Development Agreements related to the Research Plan between the Parties.