STATEMENT OF WORK

Technical Information Research Resources for Cancer Preventive Agent Development

Background

The National Cancer Institute, Division of Cancer Prevention (DCP) requires the continuation of technical information support resources for cancer preventive agent identification, development, and qualification for clinical trials. The projects required to satisfy the RFP workscope shall provide the diverse and specialized technical support services and products needed for the preclinical and clinical development of the most promising cancer chemopreventive agents.

Technical support products include agent background, rationale, chemistry, and testing documents for use in decision making and in planning clinical development strategies by the DCP Agent Development Committee; by the Chemopreventive Agent Development Research Group and other DCP Research Groups; by the Rapid Access to Preventive Intervention Development (RAPID) Program; by regulatory support, clinical trial monitoring, and repository acquisition, formulation, and distribution personnel under contract to the DCP; and, as appropriate, by investigators conducting the preclinical studies and clinical trials; by DCP program staff for analysis and planning; by NCI program review committees established following recommendations of the NCI Board of Scientific Advisors; and by other NCI staff, officials of other government agencies, and other scientists (e.g., at universities, research institutes, medical centers, pharmaceutical and other private sector collaborator sites, etc.). Sophisticated, comprehensive and multi-disciplinary technical resources are required because currently the DCP senior scientists scrutinize and prioritize hundreds of candidate agents yearly for initial preclinical evaluation, continually evaluate dozens of agents in clinical development tracks at milestone decision points for further development with the objective of qualifying agents for INDs and early clinical trials, and oversee a portfolio of advanced clinical trials of potential cancer preventive agents. Additionally, advances in "-omic" technologies, molecular modeling, and bio-informatics related to agent identification, optimization, development, and qualification for clinical testing are increasing information management requirements in order to make informed decisions and strategic planning.

The DCP has established and implemented a clearly defined integrated plan for evaluating chemopreventive agents. The plan includes: (1) identifying potential cancer preventive agents from epidemiological observations, experimental carcinogenesis and pharmaceutical literature, applications to the RAPID program, interactions with private industry and academic investigators, and/or theoretical considerations, (2) qualifying agents for potential further development through *in vitro* and *in vivo* screening assays, (3) conducting efficacy, pharmacology, intermediate endpoint, and toxicity studies of candidate agents in animal models, and (4) preparing supplies of cGMP investigational agents and conducting phase 1 pharmacokinetic and safety trials, phase 2 efficacy and intermediate endpoint trials, and phase 3 efficacy endpoint trials of the most promising agents. Detailed criteria are delineated for classifying the quantity and quality of information that currently exists on any chemopreventive agent and thus defining what additional information and investigations are required to qualify the experimental use of an agent in intervention trials of human cancer.

Thus, the primary purpose of this project shall be to provide research, technical support, and analysis to assist in evaluating ongoing and proposed activities.

The workscope of this RFP is divided into different task areas. These task areas are fully integrated and cohesive. Offerors are required to respond to all task areas of this RFP as one package. Comprehensive details of the information management system are expected to be provided by the offeror based on their knowledge of the disciplines required in the Statement of Work, as well as experience working in the multi-disciplinary fields of chemoprevention. However, the information management system must be compatible with and migrate to the existing DCP Enterprise System Knowledge base (DESK) requirements, as specified below. These details as well as the whole proposal shall be evaluated under the evaluation criteria in the RFP.

STATEMENT OF WORK

Task Area #1: CANCER PREVENTIVE AGENT IDENTIFICATION AND DOCUMENTATION

This task identifies, documents and prioritizes potential new chemopreventive agents for preclinical testing through literature searches; class studies; program, private sector, and academic agent nominations; the RAPID program, and theoretical structure/activity relationships.

1. Update on a quarterly basis, the published scientific literature; ongoing research projects sponsored by the Division of Cancer Prevention, Chemopreventive Agent Development Research Group (CADRG); and other relevant sources to identify candidates for initial and continued evaluation. These data are currently maintained in the database components of the Master List Agent (Desktop) Databases in Microsoft Access. The individual components of the Master List Agent Databases are:

    Chemical Structures Database
    Biological and Chemical Categories Database
    Animal Efficacy Database
    Short Term Test Results Database
    Human Studies Database
    Combination Agents Database
    Related Activities Database

    The bibliographic database is also included under the term Master List Agent Desktop Databases.

    The contractor shall incorporate the data and functionality of the existing system into an agent development information system within DESK (see Task #3). This shall involve interaction with the NCI Center for BioInformatics in order to use existing appropriate database models.

2. Conduct up to 3 chemical class studies, *e.g.*, non-steroidal anti-inflammatories, hormone receptor agonists / antagonists, per year to identify candidate agents for testing. The steps include:

(a) selecting high priority classes for evaluation
(b) identifying agents belonging to each class
(c) eliminating agents in each class with toxicities or other properties that preclude their use clinically as chemopreventive agents
(d) developing and carrying out a selection rationale for the remaining candidates in each class

3. Conduct structure-activity studies to identify new candidates for testing. These studies shall include:

(a) searching commercial and other databases for compounds which are similar in structure to high priority chemopreventive agents. Searches may be made on the basis of factors such as similar functional groups or similar shape and conformation.

(b) analyzing the structure activity relationships of a series of analogues to identify the most promising candidates. Both qualitative and quantitative structure - activity relationships should be analyzed, as feasible and appropriate. It is estimated that 5 structure-activity studies should be performed in the first year and 5 in each of the following years.

4. Score up to 50 candidate agents per year based on documented criteria which shall include:

(a) availability
(b) efficacy
(c) toxicology/regulatory status
(d) relevance of class to chemoprevention
(e) other considerations, such as cost, patent status, etc.

5. Rank the agents twice per year and assign high, moderate, and low priority for screening

6. Recommend testing in the *in vitro* and *in vivo* screening, preclinical efficacy and intermediate endpoint testing, preclinical toxicology, or phase 1 clinical trials, twice per year.

7. Document the selection process, including sources reviewed, the methods for selecting candidates, the scoring criteria, a list of the candidates reviewed ranked by their scores, and a list of the agents selected with a summary of the rationale for their selection.

8 Prepare worksheets on the newly selected candidate agents and on any other agents in the CADRG testing program for which such documentation does not exist (up to 50 worksheets per year are anticipated). These worksheets shall contain the following information in brief narrative summary and tabular form:

(a) chemical identification (i.e., name, synonyms, CAS Registry Number, structure, UNII code when available)

(b) chemical and biological categories (e.g., structure classes, pharmacological activities, commercial use classes)

(c) commercial availability (e.g., source, cost, synthesis information)

(d) evidence of chemopreventive activity

(e) toxicity

(f) relationship to other agents in the testing program

(g) rationale for selection and testing status (i.e., a listing of the tests sponsored by the DCP in which the agent is being evaluated)

9. Update worksheets as necessary

10. Provide documentation and status reports to the DCP Staff during the Chemopreventive Agent Development Committee meetings approximately every 2 months and on an *ad hoc* basis as needed, documenting the process of prioritization and selection. Minutes of the meetings shall be prepared and provided within 30 days of meeting.

11. The contractor shall incorporate the documentation generated under items 2 through 10 above into the DESK electronic system. However, for all the items 1 through 10 above, the Project Officer will specify on a case-by-case basis to the contractor which chemical entity data is proprietary and subject to ethical and legal agreements of protection negotiated with private sector, academic, and other investigators. Access to such data in DESK will have restricted access.

Task Area #2: CANCER PREVENTIVE AGENT DATA AND REPORT ANALYSIS, STATUS AND DOCUMENTATION

This task documents and tracks the agent development activities of the cancer preventive agents under evaluation. The contractor shall provide technical information management for these agent development activities of the DCP. The contractor shall plan with the DCP and implement an electronic process for managing and transmitting data supporting preclinical and clinical agent development activities, including the following:

1. Transition from the Master List Agent (Desktop) Databases to an agent development information system in DESK (see system specifications under Task #3). The existing databases track the progress of agents in the preclinical and clinical programs. They cover the *in vitro* and *in vivo* screens, the preclinical efficacy and intermediate endpoint testing, the preclinical toxicity testing, and clinical trials performed under separate testing contracts. The contractor shall input test results and testing progress information from the testing contractor's

progress and final technical reports. Administrative information shall include investigators, organizations, and reporting deadlines.

Additionally, the entry of new clinical data from research sites has transitioned to an Oracle clinical remote data capture system and chemical, formulation, and related information about agents in development has transitioned to an Oracle preventive agent management system. The contractor shall electronically input data from these systems in order to prepare sections of Investigational New Drug applications and annual reports, as detailed in #9 below.

2. Generate a complete printed copy of the preclinical agent development testing data annually and deliver to the CADRG in accordance with the Reporting Requirements.

3. Twice yearly updates of the preclinical agent development testing data on CDs in IBM compatible format in Adobe Acrobat 5.0 (or later) PDF file format shall be delivered in accordance with the Reporting Requirements.

4. Generate a summary, listing chemicals with +/- preclinical test results, twice yearly with recommendations for future testing.

5. Perform a scientific review of preclinical data and conclusions reported by testing contractors. Progress reports and draft final reports, approximately 24 per year, will be supplied by the CADRG and shall be inspected for scientific accuracy and completeness.

6. Analyze, at 12 months after the beginning of the contract and on an annual basis thereafter, the testing results in the preventive agent development information system to aid in planning further testing, evaluating mechanisms of action, and identifying promising new classes of chemopreventive agents.

7. Review and document new assays, models, and intermediate endpoints being considered for the DCP CADRG testing programs approximately 5 per year.

8. Develop enterprise project management time lines for all agents in development including anticipated testing requirements, test results, milestone go/no go decision points, etc. to aid in planning and tracking for preclinical and clinical testing. Approximately 150 time lines shall be maintained.

9. Prepare summaries, reviews, presentation graphics, and other documentation on DCP's agent development activities. Summaries and reviews shall include electronically compiling information from the literature and the DCP agent development program to provide content for the following sections of Investigational New Drug (IND) applications and annual reports to existing INDs: (a) Scientific Background and Rationale, (b) Chemistry, Manufacturing, & Control (CMC), (c) Preclinical Efficacy and Biomarker Testing, (d) Preclinical Safety and Toxicity Testing. The supportive CMC data will be provided to the contractor through the Project Officer of a separate Repository and Agent Distribution contract under which the necessary data is acquired,

e.g., formulation, packaging, release and stability testing results, etc. Data shall be up to date and available to a separate Regulatory Support contractor, whose information management system will also be integrated into DESK, through the Project Officer. The Regulatory Support contractor will prepare the final documents. Over the performance period of this contract, DCP will implement a system to support electronic submissions to the FDA. It is anticipated that 3-5 new INDs per year and 30 continuing INDs (annual reports) will be supported.

10. Summaries, reviews, and presentation graphics shall also be prepared for meetings with the FDA and other preclinical & clinical investigators and, in close collaboration with DCP senior staff, for peer-reviewed publication. Approximately 4 sets of presentation graphics in Powerpoint and 6 reviews for publication shall be prepared per year.

11. Prepare 5 to 7 Agent Development Plans each year, addressing rationale for evaluation, supportive preclinical efficacy and biomarker data, preclinical safety and toxicity data, clinical experience, availability, and other topics as appropriate. Annual updates shall be made of all new plans and plans written under previous contracts. Prepare appropriate content, see #9 above, for 2 Investigational Drug Brochures each year. Update existing Investigational Drug Brochures; the contractor shall provide content to update 3 Investigational Drug Brochures each year. Data shall be up to date and available to a separate Regulatory Support contractor, whose information management system will also be integrated into DESK, through the Project Officer; the Regulatory Support contractor will prepare the final documents.

12. Attend, make presentations, and prepare meeting summaries/reports/minutes for approximately 6 Chemopreventive Agent Development Project Team meetings per year held in Rockville, MD. These are internal decision making meetings involving 8-20 participants. Supporting documentation is derived from the agent development information system.

13. Provide agent information and reports to support the DCP clinical trials consortia conducting phase 1 and 2 studies (see http://www.cancer.gov/prevention/ctr/consortia). In particular, see "Step 1: Developing a Cancer Prevention Trial" for information about letters of intent and agent announcements. Specifically, prepare up to 5 agent announcements 2 times per year, based on existing worksheets, agent development plans, investigational drug brochures, and decisions reached by the Chemopreventive Agent Development Project Team (see #12 above). Provide background data on agents (such as investigational drug brochures) for use in protocol development to consortia investigators with approved letters of intent. Provide background information about agents proposed in unsolicited letters of intent (20 per year).

14. Perform scientific reviews of chemoprevention concepts, letters of intent, protocols, protocol revisions, and amendments. Provide staff member to present review comments at concept and protocol review meetings at DCP. Reviews shall be returned to the DCP Protocol Information Office within 1 week of assignment. Up to ten reviews per month shall be conducted.

15. Provide technical support for up to 2 workshops per year on strategy development for chemoprevention which shall include assistance in program planning, list of invitees, and receipt and editing of manuscripts. The workshops will last 1 day and approximately 12 investigators and 12 DCP attendees will participate. The workshops will be held in Rockville, MD and this task explicitly excludes all logistical support and reimbursement of travel expenses for participants.

16. Provide technical support for one RAPID program peer review meeting per year to be held in Rockville, MD. The meeting will last 1 day and approximately 8 reviewers and 4 CADRG attendees will participate. Technical support shall include assistance in planning, abstracting applications, coordinating, and preparation of draft meeting minutes and explicitly excluding all logistical support and reimbursement of travel expenses for reviewers.

Task Area #3: INFORMATION MANAGEMENT SYSTEM

Under this task the contractor shall maintain and enhance standard procedures for information management to support cancer preventive agent development activities.

1. If awarded to a new contractor, the new contractor shall transfer the Master List Agent Databases to its own computers and ensure full functionality and provide appropriate support, updates, upgrades, and enhancements. Contractor shall maintain appropriate documentation and ensure full portability of these databases. The current Master List Agent Databases use Microsoft Access for data entry and reporting, and export in Oracle format into DESK. The databases are in the process currently of being restructured in an Oracle format for future migration to DESK.

2. The contractor shall design and implement a new agent development information management system to support the tasks in the statement of work. The contractor shall incorporate components of the existing data model and databases when possible. DESK includes an agent module as one of its core components. The contractor shall build upon the existing module.

3. The contractor shall maintain and enhance standard procedures for information management for chemopreventive agents and test results. The requirement under this contract is that any new source code developed be an open source and based on de jure or de facto standards (including J2EE, ANSII compliant SQL and Eclipse). Deviation from this requirement should be clearly identified in the contractor's response to this RFP.

4. The contractor shall integrate the agent development information system with the DESK and ensure that the system provides data to support DESK users.

    (a) The contractor shall ensure that the agent development information system is fully interfaced with the DESK and have a remote access capability for DCP and its designees. Data must be shared between the agent development information system and DESK in an automated, labor-free process. The

process shall not involve duplicate storage of the same data in both systems. Data sharing with DESK shall not require a manual reconciliation process.

(b) The contractor shall ensure, to the extent possible, that the databases use the presentation layer and user interface that is standard across all new DESK applications. Deviation from this requirement should be clearly identified in the contractor's response to this RFP.

(c) The contractor shall ensure that the agent development information system provides designated DCP personnel the capability to perform ad-hoc queries of information.

(d) The contractor shall maintain and update/upgrade/enhance standard procedures for information management for chemopreventive agents and test results. The contractor shall ensure that the agent development information system conforms and integrates with appropriate industry standards and NCI technology infrastructure.

(e) All messages between the agent development system and external systems should conform to HL7 messaging standards, preferably HL7 3.x (XML) version of standard. Deviation from this requirement should be clearly identified in the contractor's response to this RFP.

(f) The contractor shall ensure that data used by the agent development information system complies with the National Cancer Institute's Cancer Data Standards Repository (caDSR) metadata standards, and that all data are represented as Common Data Elements approved by DCP. The agent development system data shall be integrated with the caDSR so that Common Data Element meta data may be accessed directly wherever appropriate.

(g) The contractor shall ensure that the agent development information system is fully integrated with the NCI Enterprise Vocabulary Services (EVS) and will use EVS as the source of terminology wherever possible. Specifically, the contractor shall use the CaBIO API to access EVS services, and shall implement an e-mail-based mechanism for the agent development information system users to requests changes to EVS content.

(h) The agent development information system shall provide an indicator that identifies whether or not an agent is proprietary. All non-proprietary agents should be identified using EVS concept codes in addition to any other codes or identification that may be required. All proprietary agents must indicate an agent's UNII code, if available. (UNII is a soon-to-be-released FDA coding system for new compounds.)

(i) The agent development information system shall keep a complete audit trail of all changes to any data stored. Regular reporting of audit trail changes must be provided.

(j) Where possible, the contractor shall leverage applications developed by NCICB.

5. The contractor shall implement a document management system (for Agent Development Plans and other documents required under this statement of work) that will:

   (a) Handle document version control and review tracking.

   (b) Provide safe and secure electronic and physical storage conditions

   (c) Allow all active and archived materials to be readily retrievable and available to DCP staff within 24 hours from the time of a request.

   (d) Store electronic copies of reports prepared in mandated electronic formats and provide electronic delivery of these data upon request.

   (e) Archive records in accordance with regulatory and other requirements.

6. The contractor shall ensure that the agent development information system and literature database are capable of supporting a large base of concurrent users (up to 100) via a web-based user interface at study sites. The system performance must be adequate so that use is not hindered by long wait times (3-5 seconds for most queries).

7. The contractor shall have appropriate experience in database management, object oriented development, J2EE, Web Services, XML, and other technical skills to provide support and maintenance of the agent development information system. Contractor shall have appropriate Oracle licences and any licences required for literature searching.

8. Contractor shall utilize TestTrack Pro or a comparable tool to track bugs, issues and change requests. Remote web access to the tool and its contents should be provided to NCI-designated representatives.

9. The contractor shall ensure that the agent development information system complies with 21 Code of Federal Regulations Part 11, the FDA regulations regarding electronic records and signatures, as well as other applicable regulations and laws. 21 CFR 11 and current guidance are found at http://www.fda.gov/ora/compliance_ref/part11/.

10. Changes to the agent development system will require approval by the DCP Change and Configuration Group (CCG). The contractor will provide a representative to participate on the CCG. The contractor will participate in other DCP IT status meetings and activities as requested by DCP.

11. User documentation and training shall be provided for the Agent Development System.

Task Area #4: GENERAL TASKS

1. The contractor shall participate as subject matter experts in DCP and NCI informatics design and development activities, as directed by the Project Officer. This may include attending knowledge acquisition sessions to define requirements and data model reviews, and participating in user testing efforts for DESK enhancements and other systems.

2. The contractor shall prepare and submit draft schedules of procedures (SOPs) for all functions described in the Statement of Work, Submit to DCP for review and approval within 120 days of contract award. SOPs shall be updated as needed and submitted to DCP

3. The contractor shall establish a written plan for quality assurance and quality control of all data and procedures described in this statement of work (SOW). This plan shall include:

   (a) Defining parameters for the security of paper and electronic records;

   (b) Verification of accuracy of data entry in information management systems. Including the reconciliation of data discrepancies from different sources (such between legacy systems and current systems).

   (c) Ensuring the accuracy of all information provided to DCP, particularly data used for regulatory submissions.

   (d) Ensuring documents and their copies are complete and free of grammatical and typographical errors.

4. The contractor shall assist in the transition of this contract to a successor contract. The transition period shall consist of the final 60 calendar days of the contract. The following shall apply only to a transition wherein the contractor is not the recipient of the successor award.

   (a) The contractor shall provide the successor contractor with detailed briefing regarding the policies and procedures for managing all aspects of the project. As part of these detailed briefings, the contractor shall provide the successor contractor with the Procedures Manual for regulatory support. The Manual provided shall be complete, with all procedures detailed and current as of the date of the initial briefing.

   (b) The contractor shall provide instruction to the successor contractor in the policies and procedures utilized in the performance of the contract. This instruction shall be accomplished by permitting personnel of the successor contractor to work with the current contract personnel in an apprentice capacity.

   (c) The contractor shall submit a plan for the transfer of all materials and data stored 90 days before completion of the contract.