

STATEMENT OF WORK

TITLE: Chemical Biology Consortium Small Molecule Repository

Background:

The Chemical Biology Consortium (CBC) has been developed by the OD, DCTD in conjunction with CCR and the OD, NCI to facilitate the discovery and development of new agents to treat cancer., The goal of the CBC is to develop a network coordinating academic and private drug discovery efforts with DCTD's own pre-clinical resources thereby establishing a complete drug discovery and development platform for oncology therapeutics. This network of multidisciplinary scientific expertise along with varied technical and infrastructure resources within the network will work together to support execution of drug discovery and development projects from discovery to first in human in a team centric approach. One critical infrastructure resource that this platform will require is chemical repository services to function as the network central resource to procure, receive, manage and distribute chemical compounds expected to be generated throughout project execution. In our current assessment of the progress of this program it is anticipated that in addition to the management of compound libraries acquired from commercial and other external sources, we will also need management of 2,500-5,000 CBC member generated dry samples in the first year and 5,000-7,000 dry samples in the second year The number is expected to grow with addition of nearly 7,500-15,000 compounds per year for the subsequent years.

The Small Molecule Repository will procure, handle, store and distribute a chemically diverse small molecule collection of up to 250,000 compounds along with handling associated informatics data over the life of the contract. The goal will be to progressively populate biologically relevant chemical space with compounds having >500 chemical scaffolds. This collection will be established from commercial compound suppliers and ongoing programs within NCI, and will include FDA-approved drugs, compounds with known biological actions, a structurally diverse collection of compounds of unknown biological activities, compounds derived from natural product templates, molecules submitted from the public and private sectors, and new compounds generated by diversity-oriented and target-oriented synthesis. The collection will be used for screening of known and novel targets at various CBC partner centers, with distribution of compounds of known action to investigators in academia and industry. In addition, sub-collections of compounds with specificity for gene families of biological importance, as well as 'diversity sets' of several thousand compounds having widely diverse chemical scaffolds, will be distributed in microtiter plates to academic investigators for screening in individual laboratories.

Objectives:

The objectives of the contract are:

1. Identify and acquire, in coordination with the NCI advisory groups, candidate compounds from government, academic, industry, and commercial sources and assemble a collection of compounds meeting specified criteria;
2. Array all compounds in sets suitable for high-throughput screening (HTS) and long-term storage; Distribute compound arrays to the CBC members and screening centers.
3. Communicate with CBC members and screening centers in regards to distribution of requested samples.
4. Store, maintain and track the compound collection inventory and periodically monitor the stability of compounds in the library;
5. Monitor the compound inventory to ensure that threshold quantities of all compounds are available to support screening needs and to locate and re-acquire depleted compounds to replenish the inventory; and
6. Provide the necessary informatics support to file, maintain and update chemical information on each sample and track compound inventory and distribution.
7. Serve as the chemical structure registrar for all molecules of interest to the CBC. This will include evaluating each structure submitted to the CBC for correct and full structure integrity and assigning a

unique identifier to each unique structure. This unique identifier will then be used as an index for all subsequent test results.

SERVICES TO BE PERFORMED:

A. Organizational Structure

All work under this contract shall be monitored by the Project Officer (PO) whose position is defined in Section G of this contract; the Project Officer (PO) shall be the Contractor's primary point of contact for technical matters under this contract;

B. Specific Technical Requirements

Independently, and not as an agent of the federal government, the Contractor shall furnish all necessary labor (qualified and experienced personnel), services, equipment, materials, supplies, and facilities, except as otherwise specified herein, as needed to perform the work set forth below.

Task 1. Compound Identification and Development of a Diverse Collection of Small Molecules

1. Identification - The Contractor shall, in coordination with the PO, identify candidate compounds from government, academic; industry and commercial sources and assemble a collection of compounds meeting criteria to be specified by the PO (i.e., stability, solubility, availability of sufficient quantities, ease of re-supply or re-synthesis, diversity). Contractor shall search for candidate compounds from a variety of sources including scientific literature, patent literature, pharmaceutical databases, and any other government, industry, commercial, or academic sources available to the Contractor. Contractor shall actively participate in the identification of candidate compounds by providing lists of compounds with all supporting information to the PO, to assess which compounds shall be chosen for inclusion in the collection.
2. Acquisition — the contractor shall undertake all activities necessary to acquire sufficient quantities (typically 5-30 mg) of compounds selected for inclusion in the Small Molecule Repository collection. The collection will expand on a continuing basis and evolve over time based on the biological activity/utility of the compounds as assessed by screening. It is anticipated that the collection will grow to a target of 250,000 Compounds derived from direct purchase from commercial compound suppliers, academic and industry contributions, and compounds developed under the CBC initiatives. The contractor shall acquire the majority of the compounds in the collection through direct purchase. From time to time larger samples (50 mg-10 gm) of specific compounds may need to be acquired.

Task 2. Arrayed Sets and Distribution

1. Compound Arrays — the contractor shall have the capability for automated arraying of compounds suspended in DMSO into both 96 and 384 well plates to produce arrays in a format suitable for long-term storage and for distribution to high-throughput screening centers. The contractor shall also have the capability to array compounds in other formats suitable for high-throughput screening (HTS) (i.e., daughter-plates developed from plate replication or reformatting into higher density 1536 or 3456 well plates), and in smaller, selected subsets (i.e., cherry-picking to create NCI-selected specialized plates). It is anticipated that up to 250,000 compounds will be plated over the life of the contract. In the 384 well format this would involve the production of 650 mother plates. Depending on demand, up to 100 replicates of each mother plate may be produced over the life of the contract. The total numbers of plates will be higher when focused sets in the 96 or 384 formats are included.

2. Distribution ⁷- The Contractor shall distribute compound arrays to the CBC member institute, as needed. It is anticipated that this will involve regular shipments with the capability to ship on a daily basis... The contractor shall have the capability of 'next business day' shipment or mix of 'same day' and 'next business day' • for domestic shipments. The Contractor should also have the capability to ship internationally including regions in India and China. It is anticipated that 10-15 institutes will comprise the CBC. Compound shipments shall be made in such a way as to ensure the integrity of the arrays and shall comply with all applicable federal, state, and local regulations and international shipping and custom regulation. It is anticipated that 1000 individual shipments will be made annually with 5000 shipments over the life of the contract. These shipments may include dry samples and compound arrays.

Task 3. Storage and Quality Control

1. Storage — Compounds shall be stored under conditions that ensure optimal stability and purity. The contractor should have the capability to store samples and plates long-term at -78, -20, and 0°C in addition to ambient temperature and should have sufficient storage space to accommodate the anticipated acquisition of compounds. It is anticipated that 20% of the dry compound collection will require storage at sub-0°C temperatures and the entire plated collection will be stored at sub-ambient temperatures. The contractor shall provide dry storage of compounds in vials (typically less than 30 mg of each compound). From these dry stores, compounds shall be weighed and solubilized and stored in solution in DMSO although other solvents may be used when necessary. The preferred storage method is in microtubes with an associated storage and retrieval system allowing for rapid and efficient cherry-picking of compounds for the creation of 'plates. Alternative systems allowing comparable speed and efficiency of compound selection shall also be acceptable. The contractor shall have the ability to routinely store solubilized compounds under inert gas at temperatures that optimize compound stability. The contractor shall also have the ability to store compounds in arrayed sets (i.e., master plates), organized thematically (i.e., by chemical class, target, etc). The contractor shall provide all the necessary expertise, equipment, and facilities to store, maintain, and track the Small Molecule Repository inventory. The contractor shall provide a compound tracking and retrieval system suitable for a large compound library and shall propose a method for long-term storage of compounds, both dry and in solution, which will ensure optimal stability for a maximum number of compounds. Storage and handling should, comply with all applicable local, state and Federal regulations.
2. Quality Control — The contractor shall have the ability to perform rapid analyses of chemical purity (e.g., LC/MS, HPLC, and/or NMR) and shall propose a cost-effective plan to monitor the stability of compounds in the repository detailing a recommended method and frequency of analysis. The plan will be reviewed and require approval of the PO. The contractor shall also propose a plan for assessing/analyzing the purity of compounds acquired for inclusion in the collection. The analysis method(s), associated infrastructure and staff should be capable of sufficiently rapid turnaround to accommodate the anticipated acquisition of compounds. It will be the Contactor's responsibility to interpret the analyses.
3. QC requirement- The QC requirement (purity and composition) shall include but is not limited to ability to carry out high throughput analysis by 1H-NMR, GC-MS or LC-MS and interpret results as passing or failing to meet QC criteria by showing specified purity (as specified by the PO). The primary method of analysis will be LC-MS and/or GC-MS. When these methods are not suitable the Contractor should have the capability to routinely perform purity analysis by 1H-NMR. Structure not confirmed by lack of observed molecular ion by MS or NMR spectra inconsistent with structure is deemed as failing.
4. Disposal — Disposal of samples, solvents and other chemicals shall comply with all local, state and Federal regulations.
5. The Contractor shall have in place at the time of the proposal submission all local, state and Federal licenses and permits necessary for the execution of the proposed work.

Task 4. Re-Supply and Re-Synthesis

1. Inventory Monitoring- The contractor shall monitor the compound inventory to ensure that sufficient threshold quantities, as specified by the PQ, of all compounds (typically 5-30 mg) are available to support screening needs.
2. Re-purchase - As compounds become depleted the Contractor shall undertake all activities necessary to purchase or acquire sufficient quantities of the compound to replenish the inventory. It is anticipated that no more than 2.5% of the dry sample collection will be need to be replenished annually. It is estimated that this would be 5,000 compounds over the life of the contract with 1,000 compounds in the first year and 2,00Q in fifth year although these figures may vary depending on the number of projects

Task 5. Informatics and Data Management

1. Compound structure database — the contractor shall maintain an electronic library containing each chemical structure and associated physiochemical data, and assign a unique identifier to each unique structure. This unique identifier will provide the mechanism that will be used to map all subsequently collected data (in vitro, in vivo, in silico, etc) back to the structure. The contractor will eliminate redundant and ambiguous chemical structures in the compound structure database. Specifically:
 - a. Salts: each salt of a given structure will be treated as a unique structure
 - b. Hydrates: each hydrate of a given structure will be treated as a unique structure
 - c. Geometrical; each geometrical (e.g. double bond) isomer will be treated as a unique structure
 - d. Diastereomers: each diastereomer of a given structure will be treated as a unique structure
 - e. Optical isomers; each enantiomer of a given structure will be treated as a unique structure
 - f. Isomeric ambiguity: Identical structures of unknown stereochemistry will be treated as a single unique structure.
 - g. Mixtures: different compositions will be treated as a unique mixture

The contractor will also maintain a list of alternative IDs associated with each structure (e.g. PubCherft and SID, DTP NSC number, CAS number, IUPAC name, commercial name, and MLS number). In many cases, these mappings will be 1 to many.

The contractor will maintain the registration database directly in the CambridgeSoft or other suitable database as specified by the PO. However, if this presents insurmountable logistics or technical issues, then the contractor will devise an interchange mechanism based on SD files.

In addition to curating the structure database, the contractor will record related chemistry data including molecular weight, molecular formula, SMILES strings, IUPAC name, common names, physical properties, physical appearance, solubility, optimal storage conditions, QC data and material data safety information,

2. Inventory database - Compound Inventory database — the compound inventory database records information about actual samples that are, or have been, stored in the repository. The source, including supplier and lot id, will be recorded for each physical sample that is processed through the repository. When compounds are shipped to screening centers for testing, the sample information will be relayed in such a manner that subsequent test results can be indexed to the inventory sample identifier.
3. At the individual compound level, the contractor will also maintain information that might be available such as sample specific physical properties, date of purchase or synthesis, data of analysis, purity, amount in stock, physical appearance, and physical constants.
4. Distribution databases — the contractor will maintain a comprehensive database with all details of the shipping history. These details will include such items as the structure and sample identifier, shipping date,

destination, and purpose for each shipment. The contractor may use the government supplied CambridgeSoft database, or their own in-house system. However, if an in house system is used, interactive and programmatic interfaces must be available to the NCI and the data should be readily transferrable to other common databases. Access to the in-house system must be made available to CBC members via a web-based system.

5. Interfacing — a significant aspect of the CBC program will be the development of a large chemical informatics database. It is anticipated that all CBC activities will interface with other planned chemical informatics systems. Therefore, the platforms used for all databases must be compatible with databases such as PubChem.
6. All databases developed with contract funds shall be the property of the Federal Government.
7. All IT systems and procedures must conform to the NIH IT Security policies and procedures, if applicable.

Task 6. Project Management

The contractor shall designate a project manager(s) in addition to a PI within the chemical management resource. The PI will act as a single point of contact for the CBC, the medicinal chemistry centers (compound suppliers), and the HTS screening centers (plate recipients), and, the project manager will interface with the NCI project managers to assist in the management of the day to day operations of the projects.

Task 7.

Confidentiality

1. The Contractor shall protect the confidentiality of any proprietary compound synthesized or received under the contract. The Contractor shall not release information regarding a proprietary compound without the express written consent of the NCI.
- 3.- The Contractor may be asked to sign agreements such as CBC Participant agreements, Confidentiality and Nondisclosure Agreements or Material Transfer Agreements, etc. (see <http://ott.od.nih.gov> for examples) and the Contractor agrees to do so; compound recipients may also be asked to sign such agreements, and the Contractor agrees to ensure this is accomplished.

Task 8. Special Licenses

It is expected that the Contractor will acquire special licenses for specific classes of compounds if and when required (e.g. DEA controlled substances and HHS/CDC select agents and toxins).

DEA Controlled Substances (see, http://en.wikipedia.org/wiki/Controlled_Substances_Act)

MIS/CDC Select Agents and Toxins (see, <http://www.selectagents.gov/>)

C. Schedule of Work

1. Period 1 — the first period of the contract will consist primarily of acquisition of compounds and arraying of these initial members of the collection. Distribution of compound arrays to the first of the CBC member-institutes/investigators will therefore begin. The contractor shall also set-up the program informatics management system.

2. Periods 2 and 3 — the contractor shall continue to acquire and array compounds selected for inclusion in the collection, and to distribute compound arrays to the CBC member institutes/investigators, as and when needed.

Re-purchase and re-synthesis activities are expected to begin. Informatics and compound tracking activities will progressively increase.

3. Periods 4 and 5 — Acquisition will continue on a smaller scale, with increased re-supply and re-synthesis activities, as well as increased compound arraying and distribution as the number of Screening Centers increases.

D. Option to Extend the Term of the Contract

The NCI shall have the unilateral option to extend the performance period of this contract for up to three (3) additional 12-month periods (a 2-year base period and 3 one-year option periods). During each 12-month period, the Contractor shall perform essentially the same work as required for Contract Periods 4-5 as requested by the PO, with a progressive reduction in the amount of new compound purchases as the compound collection reaches its anticipated size. The majority of direct compound purchase will be for the purpose of re-supply of the inventory. It is anticipated that there will be a leveling off of re-supply, arraying, distribution of plates, informatics and tracking over the course of the option periods.

E. Transition to the subsequent Contractor

1. At least twelve (12) months prior to the completion date of this contract, the Contractor shall submit a written plan/system to the PO for the potential transfer of all compounds and Government property to an offsite storage facility (potentially a successor contractor or the NCI). A general inventory of compounds and other Government property shall be included.
2. Upon request by the PO, at least three (3) months prior to the completion of the contract, a full and complete inventory of compounds in the repository and all Government-owned property including scientific equipment, software programs and databases, data files, etc., shall be provided. At this time, the Contractor shall also describe their specific plans for packaging and shipping all such compounds, data and Government property to a successor contractor or the NCI, and a cost estimate for this transition.
3. The contractor shall fully cooperate with any successor contractor and NCI to ensure the smooth, efficient and timely transfer of all such data and Government property, including providing access to any essential uniquely trained staff to complete the transfer of informatics and any other critical components of the operation.