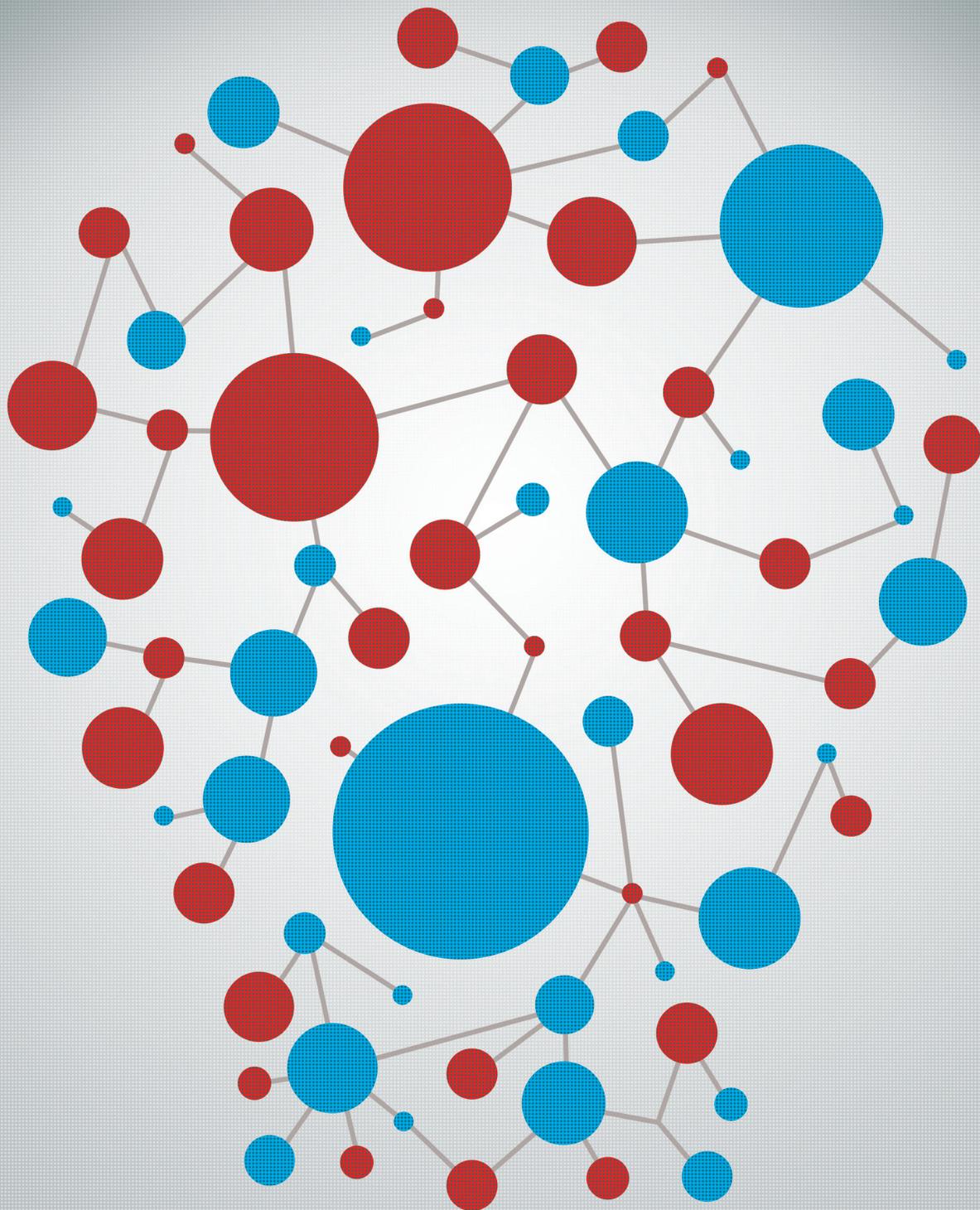
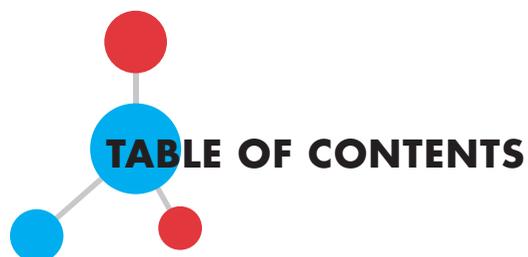


National Cancer Institute



CHEMICAL BIOLOGY CONSORTIUM
THE INAUGURAL MEETING
AUGUST 10, 2009

U.S. DEPARTMENT OF
HEALTH AND HUMAN
SERVICES
National Institutes
of Health



| | |
|--|----|
| INTRODUCTION | 3 |
| 1. PARTICIPANT AGREEMENT AND DATA HANDLING | 5 |
| 2. CONNECTING TO NIH NETWORKS | 6 |
| 3. SCIENTIFIC DATA MANAGEMENT..... | 8 |
| 4. NExT CBC OVERSIGHT AND GOVERNANCE | 15 |
| 5. PROCESS OVERVIEW AND THE PROJECT LIFE CYCLE..... | 18 |
| 6. APPLICATION PROCESS AND REQUIREMENTS | 22 |
| 7. INAUGURAL CBC MEETING PARTICIPANTS..... | 26 |
| 8. NExT/CBC IMPLEMENTATION TEAM | 27 |
| APPENDIX 1: NExT WEB SERVICES ACCESS SUBMISSION FORM | 28 |
| APPENDIX 2: EXAMPLE NCI CHEMICAL BIOLOGY CONSORTIUM PARTICIPANTS AGREEMENT | 29 |
| APPENDIX 3: NCI DRUG DISCOVERY AND DEVELOPMENT RESOURCES..... | 38 |
| APPENDIX 4: CBC PARTICIPANT CAPABILITIES | 45 |
| APPENDIX 5: ACRONYMS LIST | 73 |
| NOTES | 75 |



NCI Director Dr. John Niederhuber, Division of Cancer Treatment and Diagnosis Director Dr. James Doroshow, Center for Cancer Research (CCR) Director Dr. Robert Wiltout, and CCR Clinical Director Dr. Lee Helman, along with the entire CBC Implementation Team, would like to welcome you to Bethesda for this inaugural CBC meeting.

This booklet provides an overview of the CBC infrastructure, processes, and governance; we welcome and encourage your feedback and comments on all aspects of the CBC.

The CBC is a component of the **NCI's Experimental Therapeutics (NExT) Program**, a partnership between the NCI's Division of Cancer Treatment and Diagnosis and Center for Cancer Research. This program is envisioned to streamline the development and testing of promising new anticancer drugs and expedite their delivery to the bedside.

For more than 50 years the NCI's Drug Discovery and Development Program has successfully guided late-stage preclinical drug candidates through the final steps of development to first-in-human studies. It has been estimated that the Developmental Therapeutics Program (DTP) has been involved in the discovery or development of more than 70% of the anticancer drugs currently on the market. As part of its new strategic approach, the NExT Program will place greater emphasis on early drug discovery activities, specifically the application of high-throughput screening (HTS) and medicinal chemistry to identify chemotypes for optimization into "druggable" compounds.

The CBC drug discovery and development process is divided into five distinct stages, from screening through clinical evaluation of the candidate

drug(s). Inherent to each stage are Stage Gates and guidelines—milestones that support transition of a molecule to the next stage, and guidelines that can be applied consistently across projects to provide critical go/no-go decision points. This process is critical to NCI's ability to dynamically manage its pipeline and appropriately allocate finite resources.

Project data generated by CBC Participants will be shared through a communal Web-based bioinformatic database, as these data will be critical for informed scientific decision-making. Policies regarding access to NIH databases, as well as the submission, use, distribution, and management of research data are addressed in Sections 1 through 3.

Participants will retain ownership of their inventions, but it is expected and understood that NCI will have the option to conduct clinical trials with successful agents developed by the CBC. All Participants are required to sign a good-faith Intellectual Property (IP) Agreement; more detailed information on this and the expectations for sharing data and protecting IP are also included in Sections 1 and 3.

The governance, oversight, and decision-making processes, as well as project management procedures to document and communicate project progress are explained in Sections 4 and 5.

Entry into the CBC portfolio can occur at any stage but depends on favorable review of the application's scientific merit by external Special Emphasis Panels and the NExT Discovery or Development Committees. Criteria for approval include a concept that is associated with a compelling hypothesis that warrants clinical evaluation; a concept that will enable clinical evaluation of a new inadequately explored therapeutic approach; or a concept that is not likely to be explored in the absence of NExT

assistance. Strategic fit within the NExT portfolio is also evaluated. NExT is not a grant mechanism, but rather, approved projects will have access to CBC drug discovery and development resources. More details on the application process are provided in Section 6.

NCI resources will be available to help the CBC accomplish its goals beyond the discovery stage. These resources include molecular and small animal imaging, preclinical models, preclinical pharmacology (pharmacokinetics and pharmacodynamics), toxicology, formulation, and clinical support. More information on these resources is included in Appendix 3.

Thank you for your participation in this exciting new initiative.



John E. Niederhuber, M.D.



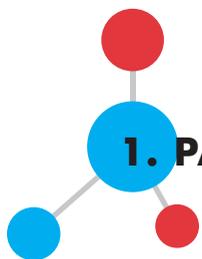
James H. Doroshow, M.D.



Robert H. Wiltout, Ph.D.



Lee J. Helman, M.D.



1. PARTICIPANT AGREEMENT AND DATA HANDLING

It is understood by the Participants that the primary goal of the NExT CBC Program is the efficient development of new drugs for cancer; therefore, projects will be conducted in a manner that promotes cooperation and communication among the CBC Participants through sharing of research resources, drug candidates, and data.

PARTICIPANT AGREEMENT

Whenever a recipient's research work is funded either in whole or in part through NIH research grants, contracts, and cooperative agreements, that activity is subject to the requirements of Public Law 96-517, known as the Bayh-Dole Act of 1980. Bayh-Dole is aimed at turning federally funded research and development into useful patented inventions to benefit American research institutions, industries, and consumers. In general, Bayh-Dole authorizes fund recipients to retain title to inventions resulting from their federally funded research and to license such inventions to commercial entities for development.

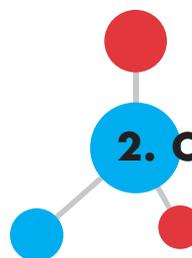
It is expected and understood that NCI will have the option to clinically develop successful compounds created by the CBC. All Participants will be required to sign a good-faith IP Agreement that details the management structure of the CBC; provides a mechanism for cooperation among Participants for pursuing collaborative projects; outlines confidentiality requirements and resource and data sharing; and describes expectations for how IP will be protected and managed under the existing statutory (Bayh-Dole Act) framework. Appendix 2 contains an example of the Participants Agreement.

To ensure that appropriate confidentiality is maintained, Special Emphasis Panel (SEP) members from industry will not have access to information on NCI development projects related to third-party industry agents; academic members will also be screened on a project-by-project basis to ensure conflict-of-interest compliance.

A Technology Transfer Committee has been established to share best practices for transfer agreements and the commercial development of CBC-derived intellectual property.

DATA HANDLING

The CBC uses enterprise-wide software systems to manage data, documents, projects, and project portfolios. Data generated by the CBC is a deliverable and will be accessible by other CBC Participants via a proprietary database.



2. CONNECTING TO NIH NETWORKS

FIRST STEP: OBTAINING AN NIH ACCOUNT

NExT Web-based databases and collaborative communication tools have been integrated with the NIH e-mail account systems for authentication; all users will therefore require a NIH username and password to log on to these systems.

The administrative processing of NIH accounts is handled by the NCI Administrative Office (also known as the Administrative Resource Center, or “ARC”). SAIC-Frederick Project Manager Ms. Gina Hayman (haymanrb@mail.nih.gov) can assist you with initiating the process. To request your e-mail account, you are required to complete the NExT Web Services Access Submission Form provided in Appendix 1. Currently, the administrative processing takes approximately 2 to 3 weeks, so it is advisable to request the account early.

The ARC will enter the information you provided on the submission form into the NCI Enterprise Directory (NED). You will receive an e-mail from the NED system requesting that you proceed to a Web-based application to provide additional personal information. This personal information is required by NIH and is kept confidential. After this information is received, the NED system will send you an e-mail containing your NIH ID number. Once you receive your NIH ID number, call the NIH Help Desk (866-319-4357) to request your NIH username and an initial password.

All NIH account users are required to take online security training, the *Information Security Awareness Course and Securing Remote Computers*. Please log into the training site <http://irtsectraining.nih.gov> using your NIH ID number. Proceed through the training courses, and completion will be noted in your electronic training record. The training will take less than 1 hour to complete.

There are two ways to enter the NExT databases and collaborative communication tools: through a Virtual Private Network (VPN) account and through a remote application program (see descriptions on the next page). Although you may never need to use a VPN account, obtaining one takes time, so it is recommended to request one up front and save the extra step of having to apply for it later. Your SAIC-Frederick Project Manager will assist you with requesting a VPN account.

Note: NIH enforces the use of “rich” passwords—a mix of uppercase, lowercase, numbers, and special characters. Such passwords are not memory friendly, so if you forget your password, you will need to submit a request to the NIH Help Desk (866-319-4357) to have it reset.

NIH has a strict policy that no one from NIH, including technical support staff, should ever ask for your password. If you ever receive such a request, do not comply, and report it immediately.

**Use <http://remoteapps.nci.nih.gov/> for Thin Client/
Web Access**

NIH has implemented a remote application program (“RemoteApps”) that enables you to access many of our applications through a Web, or “thin client”-based approach. This should be your first choice for connecting. If it does not work, then please use VPN. Not all programs are installed on the remote applications server, and the server can be slow at times depending on the workload. To use RemoteApps:

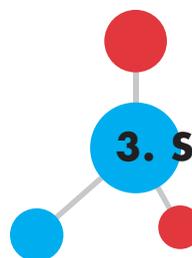
- Open your browser
- Go to http://remoteapps.nci.nih.gov
- Select *Windows* or *Macintosh*
- Enter your NIH username and password in the dialog box
- Press OK

After completing the steps outlined above, you will have something that looks like a Windows or Macintosh desktop running inside a browser window. The desktop is inside the NIH firewall, and you can now access the servers.

Use VPN for Desktop/Thick Client Access

Internet traffic is normally sent over the network as clear text. VPN is a technology that encrypts internet traffic and lets you connect to servers inside the NIH firewall.

NIH provides VPN services via CISCO VPN client software. The CISCO VPN solution will also enable you to access our wireless servers when you visit the NIH campus.



3. SCIENTIFIC DATA MANAGEMENT

OVERVIEW OF THE ARCHITECTURE

The CBC system is based on the CambridgeSoft® Enterprise software suite. It utilizes a relational database management system (Oracle) that has been extended so that it is “chemically aware.” For example, functions such as structure searching and computing chemical properties are available.

Because the system is based on Oracle, many common technologies are available that enable integration of third-party tools. Analytical, data presentation, and data visualization tools are just a few examples of the types of software that can be interfaced to the database. The available technologies are de facto industry standards, and include ODBC, JDBC, SQL, and Web services. These technologies will be used to supply data to software programs such as SharePoint, Spotfire, and Pipeline Pilot.

One of the goals in selecting the architecture was to ensure that software compatibility or capabilities would never become a barrier to scientific participation. For example, we did not want to mandate use of a particular LIMS system or data exchange format. Although the CambridgeSoft database is at the heart of the CBC system architecture, it is front-ended by a powerful system of user-configurable templates for processing and storing data. You can use either the CambridgeSoft tools or your existing systems to process data before the data are loaded into the database.

TOOLS FOR ACCESSING STRUCTURE AND BIOLOGY DATA

The full suite of CambridgeSoft Enterprise and desktop tools is available to consortium members (see <http://www.cambridgesoft.com/solutions/Default.aspx>). Some of these tools are Web-based and can be accessed through RemoteApps or VPN.

Other tools are desktop-based and require that the software be installed on the PC. The tools that require desktop installation will require VPN access. The principal tools are highlighted below.

- **BioSAR** is a form-based Web tool for exploring structure-activity relationships (SAR). It enables the user to retrieve information based on biological and/or chemical search criteria. Users can configure forms that provide data from any combination of screening data. BioSAR is also integrated with the desktop tools, so that search results, including chemical structures, can be exported to a chemically aware spreadsheet. This is a Web-based product and will operate with RemoteApps.
- **eNotebook** follows the paper lab notebook metaphor to allow scientists to replace their paper notebooks with a well-organized electronic interface. Users can easily insert content from Word, Excel, PowerPoint, Acrobat PDF, ChemDraw, and structured data in lists and tables. Scientists can share data, as well as maintain tight security.
- **BioAssay** provides the ability to upload assay data from multiple sources to the central database. Once the data have been captured, users can perform various calculations using the program’s built-in calculation and curve-fitting abilities, or using third-party tools. When a group is satisfied with the validity of its data, the data can be “validated” and published to the larger world, making it available through BioSAR Enterprise. This is a desktop tool and will require VPN if operated outside of the NIH firewall.

- **Chemfinder** is a tool that enables the user to create desktop databases of chemistry and biology data. Chemfinder databases are chemically aware and enable the user to search based on chemical and/or biological properties and calculate a variety of physical chemical properties. Chemfinder is a particularly useful tool as it can import SD files and instantly convert them to a searchable database. Chemfinder is a desktop tool that operates in stand-alone mode or can be interfaced to the central database. Connectivity to the central database will require VPN if operated outside of the NIH firewall.
- **ChemDraw** is a suite of desktop tools that enables editing of structures, including small molecules and proteins, and supports both 2D and 3D. SD files and Smiles strings can be generated and used to search other databases such as PubChem.

DATABASE

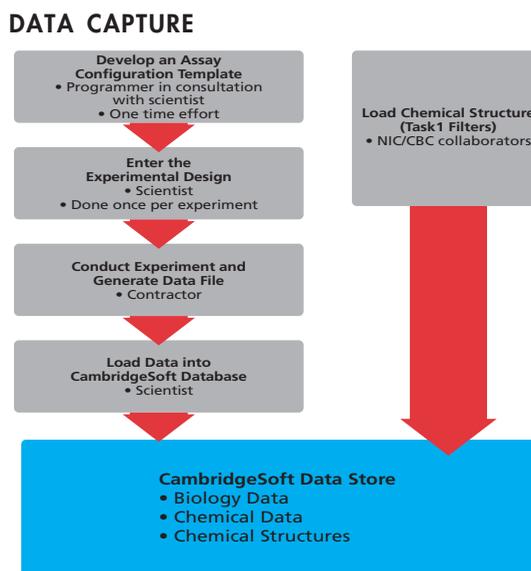
The CambridgeSoft database has been selected for storage and curation of chemical and biology data. The CambridgeSoft database is an Oracle database that has been extended with a “Chemistry Cartridge.” The cartridge extends the native capabilities of the underlying database and its query language so that it understands chemistry-based queries. For example, queries can be constructed that search for compounds with a specified molecular weight range, or that contain a particular atom, collection of atoms, or structural element.

Task 1 will define the filters that govern entry into the database, and will have an impact on the way that CBC users organize data within the database. Although the final design will be fine-tuned based

on the results of task 1, we will be able to move forward on a few overarching design requirements. For example:

- Structure redundancy must be minimized such that each structure will appear only one time in the database.
- Biology data should be indexed to chemical structure and compound batch ID.
- Institutional identifiers such as NSC, CAS, and PubChem IDs should be supported and maintained whenever possible. Each salt of a given structure will be treated as a unique structure.
- Each enantiomer of a given structure will be treated as a unique structure.
- Identical structures of unknown stereochemistry will be treated as a single unique structure.

The data capture process for chemical and biological data is depicted below.



SECURITY MODEL

High Throughput vs. Lead Development and Optimization

Processing requirements change substantially as the screening process proceeds from high-throughput to identification of HTS leads and subsequent lead development and optimization. Consequently, information technology (IT) requirements change. Of particular interest and concern is the need for IP protection beginning with lead development.

Lead Development and Optimization (LDO) begins when the chemists obtain confirmed active structures from one or more primary and confirmatory HTS screens. At this stage of the process, the focus of IT shifts from efficient bulk handling of large volumes of data in a relatively open environment to capturing and maintaining a much richer mix of data in smaller volumes with a much more restrictive and granular set of rules governing data access. The importance of protecting IP may justify some degree of structure redundancy within the database.

HTS Structures and Data

- All consortium members (i.e., anyone who has signed the CDA either individually or corporately) will have access to *all structures* that have been screened in an HTS screen.
- All consortium members have access to *all* HTS biology data from *all* HTS projects, regardless of their specific team membership.
- Anyone who has not signed a CDA cannot access HTS data. For example, NCI employees who do not have a signed CDA on record cannot see HTS structures or HTS results. CDAs will be maintained in a SharePoint library by the PMO.

LDO Structures and Data

- LDO structures will be registered in project-specific structure libraries. This will create some redundancy of structures, but this must be tolerated for the sake of security.
- Only Project Team members will have access to the project structures.
- Upon securing IP, the structures will be “moved” to the larger CBC library that houses HTS structures; this could create redundancy.

eNotebook

Data held in electronic notebooks will be controlled by the owner of the notebook.

GENERAL OPERATING APPROACHES

Several operating scenarios are supported for the CBC data collection. From the perspective of the NCI, the approaches can be categorized as centralized, decentralized, and hybridized. CBC Participants, in collaboration with the CBC IT staff, can select and implement the most appropriate approach based on circumstances related to specific activities.

The centralized approach facilitates data capture and processing at the Participant's site, followed by an upload of the processed screening results data. The Participant will work with NCI staff to agree upon a data exchange format and document it in an interface control document. The Participant will provide all data in the agreed upon format and NCI resources will operate the CambridgeSoft BioAssay software to load it into the database. This approach will be useful when a Screening Center has, and prefers to use, its own data processing systems and does not wish to engage the CambridgeSoft system to process and load its data.

The decentralized approach consists of installing the CambridgeSoft programs (eNotebook and BioAssay) at the Screening Center and assisting the Center with configuring the templates necessary to process screening data. NCI can provide startup support and ongoing technical assistance, but the Screening Center will need to develop in-house expertise with the software to make this approach work. This approach will be useful if new screens are brought online for which in-house processing systems have not been procured or developed.

The hybridized approach involves providing raw (rather than processed) data to the NCI for processing through CambridgeSoft software and subsequent loading into the database. The Screening Center will need to collaborate with NCI IT staff to design and develop templates. A format for the raw data will be established, and the screening center will submit raw data in the agreed upon format. This is anticipated as the most problematic approach, but is supported in case the need arises.

PROJECT MANAGEMENT DATA

Project Web Access (PWA) is part of the Microsoft Windows SharePoint services and is used to track and communicate project status in real-time, coordinate team activities, and highlight critical issues for both Project Team and Senior

Management attention. It is accessible through the Web via RemoteApps or VPN. This interactive tool offers discussion boards for exchanges between Team members on topics relevant to a project and provides a central location to store shared Team documents; sample pages are presented below.

Project Title: TDP1 Targeted Drug Discovery and Development

Human tyrosyl DNA phosphodiesterase 1 (TDP1) is a DNA repair enzyme involved in the repair of lesions created by the trapping of human DNA topoisomerase I (TOP1) following treatment by anticancer agents such as camptothecins and iridomycolines. TDP1 inhibitors are expected to be effective in combination therapy with TOP1 inhibitors for the treatment of cancer. An HTS discovery effort is ongoing for this target to generate a small molecule lead compound.

Stage Gate Objectives:

| Objective | Description |
|---|--|
| Screening/Designed Synthesis (SDS) - Identify and produce at least one high-quality lead agent from initial screening and screening-validation efforts. | 1. Assess mechanism of action for link to disease 2. Determine desirable potency 3. Demonstrate evidence of structure-activity relationship 4. Evaluate functional activity in vitro 5. Determine selectivity for target 6. Evaluate physc |

Project Management Status

| Description | Outcome and decisions | Date | Document |
|---------------------------|--|------------|---------------------------------|
| Series Evaluation | A medicinal chemistry subgroup meeting was held to review data and identify interesting structures for further study. Stanley Halozan chose 3 active compounds and 1 inactive compound, based on results from the gel-based assay. NCGC picked compounds based on results from a second cherry pick followed by gel assay. All compounds were sent for analysis by Andy Stephen using his Biacore chip assay | 4/23/2009 | Meeting notes and presentations |
| Protein Production | Request for new batch of purified full length protein. Estimate for work requested by PMO | 3/17/2009 | |
| Biacore Assay Development | Compounds from each lab will be sent to PCL for analysis Biacore screen. The assay will be run at 25µM dose and using full length protein. An inactive compound is needed as a negative control in the assay. Send name and molecular weights of compounds to Andy Stephen by week of 2/9 | 2/9/2009 | |
| Analog testing | The latest round of analogues synthesized by NCGC Med. Chem. has been handed off to Christophe and Tom for testing in the gel assay. The outcome of this assay will help determine which compounds get sent to Andy Stephen for analysis. | 1/23/2009 | |
| Assessment of top hits | Collect data obtained for all structure to evaluate requirements still needed. Once all data has been collected meet again to reassess top hit candidates | 12/22/2008 | |
| Assay Requirements | Need for an enzymatic assay to evaluate hit leads | 12/11/2008 | |
| Protein Production | Protein requirements and schedule defined | 10/15/2008 | |
| Subgroup meeting | The two main chemotypes , imidazolidine and sulfoxamide chemotypes, were chosen for further studies | 10/3/2008 | |
| Project Requirements | Hit Triage Funnel accepted by team Actions: ➤ Conduct a Medicinal Chemistry subgroup meeting to strategize the scaffold selection process | 9/23/2008 | Meeting Notes and Presentations |

Events Calendar

| Start Time | Title |
|--------------------|----------------------|
| 9/15/2009 2:00 PM | Project Team Meeting |
| 11/17/2009 2:00 PM | Project Team Meeting |

Links

- Web access to CBC CambridgeSoft Database
- Link to triage funnel with assay descriptions
- NCGC data and structures download and SAR analysis site
- Purified TDP1 Protein; TopoGEN, Inc.
- Project Life Cycle Diagram
- CBC Pamphlet
- CBC Stage Gate Descriptions

WARNING NOTICE

This is a U.S. Government computer system which may be accessed and used only for official Government business by authorized personnel. Unauthorized access or use of this computer system may subject violators to criminal, civil, and/or administrative action.

Notes The data contained in this database is confidential and the property of the U.S. Government. It is not to be disclosed to a third party, used in an IND or used in any other publications without the prior written permission of the specific individual within the Division of Cancer Treatment and Diagnosis, NCI that originally generated this data. Use of this data without permission will result in an adverse personnel and/or legal action.

3. Shared Team Documents

| Title | Type | Date Created | Name |
|---|------|--------------------|------------------------|
| 2009-01-08 Testing | | | 2009-01-08 Testing |
| Structures and secondary assay results | | 10/3/2008 12:00 AM | 2008-10-03 TDP1 Admine |
| Structures and secondary assay results | | 10/22/2008 | |
| Structures & secondary assay result | | 10/30/2008 | |
| Structure, secondary assay result & inhibition curves for NCGC S8561S (Powder, Synthesized, and HPLC) | | 11/9/2008 | |
| Structure, secondary assay result & inhibition curves for BTM04-01 | | 11/9/2008 | |
| Structure and secondary assay result | | 11/25/2008 | |
| NCGC00182075-01 comparison WT-F259A | | 11/25/2008 | |

2. Project Team Meetings

| Type | Name | Document Type |
|------|--------------------------------------|---------------|
| | 2008-05-01 - project team | |
| | 2008-07-23 - project team | |
| | 2008-09-23 - project team | |
| | 2008-10-03 - med chem sub group | |
| | 2008-10-15 - protein sub group | |
| | 2008-12-11 - project team | |
| | 2008-12-22 - Med Chem Subgroup | |
| | 2009-03-17 - Project Team | |
| | 2009-04-23 Med Chem subgroup meeting | |
| | 2009-05-19 - Project Team Meeting | |

GVK SAR, PK, TOXICITY, AND BIOMARKER DATABASES

GVK software supports informed scientific decision-making about chemical molecules to formulate data-based hypotheses with regards to SAR, molecular modeling, and the design of focused chemical libraries for screening. GVK Bio contains a large and comprehensive number of manually curated compounds. Data are collected from the scientific literature and from patent and private sources; the databases are updated frequently.

- The SAR databases contain over 3.5 million inhibitors against 11 known druggable targets that have been manually curated from the literature. More than 7.5 million quantitative SAR points (Ki, Km, IC₅₀, etc.), 1.4 million patents, and 200,000 journals have been manually curated.
- The PK databases contain data from more than 70,000 references on drugs evaluated in clinical trials (both launched and discontinued drugs).
- The Mechanism-Based Toxicity Database has more than 15,000 compounds and their associated toxicities, which will allow for better and earlier screening for potential toxicities.
- The Clinical Biomarker Database contains biomarkers that have been reported in clinical trials around the world.

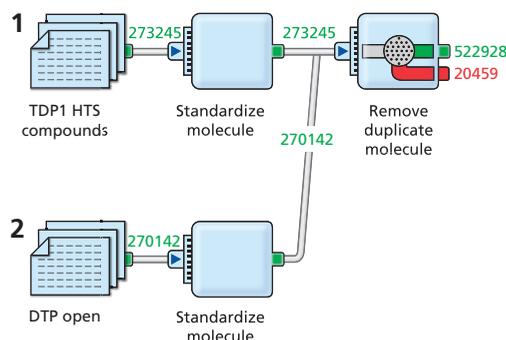
PIPELINE PILOT

The NCI has purchased a Pipeline Pilot site license from Accelrys. Pipeline Pilot enables scientists to graphically construct pipelines of logic without the need for a programmer. It is also a platform where new functionality/components can be developed as a using a rich programming language. These new components further enrich an already diverse library of pre-packaged logic modules.

These pipelines (protocols) can be integrated with thick-client software tools like Discovery Studio. Many modules are available to perform functions such as calculating physical chemical properties, making absorption, distribution, metabolism, excretion, and toxicity (ADME/Tox) predictions, and filtering duplicates, etc. The license is available and administered through the Advanced Biomedical Computing Center (ABCC) in Frederick, MD (<http://www.abcc.ncifcrf.gov/>; also see Appendix 3). The license makes the Pipeline Pilot application available to all NCI employees and contract staff who are working on NCI drug discovery processes.

The following screen shot is an example of a Pipeline Pilot protocol that was used to:

- Standardize the representation of molecules from the CBC TDP-1 screen,
- Standardize the representation of molecules from the DTP open compound set,
- Filter out duplicate structures,
- Merge biology data from records that represented duplicate structures, and
- Output the results to an SD file:



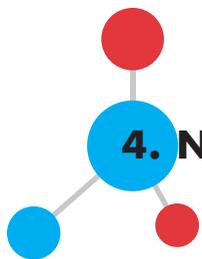
This processing identified 20,459 duplicate structures in a collection of 543,387. Subsequently, 522,928 unique structures were placed into the output file. This work was accomplished in less than 5 minutes.

You will use your NIH username and password to use Pipeline Pilot. Pipeline Pilot is based on a client server architecture. The user interface runs on your desktop PC, and the processing is done on a server in the ABCC. The user interface software must be downloaded and installed on your computer. It is available from the ABCC Web site.

DISCOVERY STUDIO

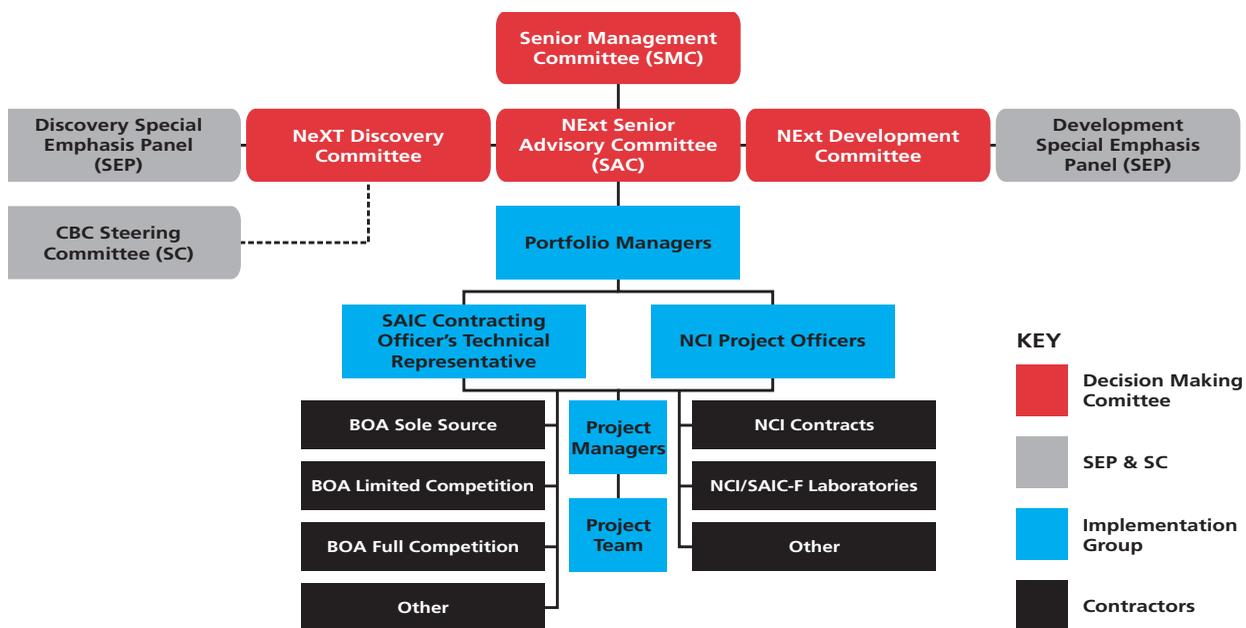
The NCI has purchased a Discovery Studio site license from Accelrys; Discovery Studio is available through the same mechanism as Pipeline Pilot. Discovery Studio provides software solutions from discovery to lead optimization. It includes a diverse collection of software applications compatible with Linux- or Windows-based environments. Discovery Studio is built upon Pipeline Pilot, enabling any software that you need to be integrated into the research environment, whether it is software from Accelrys, in-house developers, or other vendors. Application areas include:

- ADME/Tox descriptors
- Biopolymer building and analysis
- Pharmacophore modeling and analysis
- Predictive toxicology
- Protein modeling and sequence analysis
- Quantitative SAR (QSAR)
- Simulations
- Structure-based design
- Visualization



4. NEXt CBC OVERSIGHT AND GOVERNANCE

Governance of individual projects as well as the entire drug discovery and development portfolio is performed by specific committees with defined roles and responsibilities (see schematic below).



THE NCI SENIOR MANAGEMENT COMMITTEE (SMC)

Overall oversight and accountability of the NCI pipeline will be provided by the Senior Management Committee (SMC). The SMC consists of members of NCI's senior leadership, including the NCI Director and Directors of DCTD and CCR, Associate Directors of relevant programs including DTP, and ad hoc government participants, depending on their expertise, as determined by the NCI Director.

The SMC will perform evaluative functions and provide guidance, final conflict resolution, and resources for the fiscal stability of the NCI pipeline. It will also have final authority in establishing policies for the operations of the NCI pipeline.

THE NEXt SENIOR ADVISORY COMMITTEE (SAC)

The Senior Advisory Committee (SAC) will oversee governance and allocation of resources for all projects in the NCI pipeline. It will approve operational plans and execute projects for both the Discovery and Development Committees. The SAC will be responsible for implementing the scientific recommendations of the NEXt Drug Discovery and Development Committees. The SAC will meet bi-weekly and will review the NCI portfolio to ensure that projects are on time and on budget. The SAC will have the authority to re-allocate resources based on prioritization of projects in the portfolio by the NEXt Drug Discovery and Development Committees (subject to final approval by the Division Director who manages any particular resource).

NExT Committees: Operational Management of the portfolio will be undertaken by two committees, the NExT Drug Discovery Committee (“Discovery Committee”) and the NExT Drug Development Committee (“Development Committee”), which report to the SAC on a regular basis. Committee voting membership will be approved by the SAC and consist entirely of NCI staff. Other NCI contract employees may serve on the committee in a liaison capacity.

The NExT Discovery Committee will oversee governance of all Discovery projects in the NCI pipeline. It will approve (decide and weigh scientific merit), monitor execution, and determine viability of projects in early discovery phase.

The Discovery Committee will also be the steward of the NCI Drug Discovery Candidate Guidelines. These Guidelines will provide a consistent framework against which all small molecule clinical candidates will be measured. The Guidelines represent a living document modeled after biotech/pharma benchmarks. The Guidelines are an evolving set of quality attributes that will be updated and revised annually by the Discovery Committee. The Guidelines will serve as a tool for prioritization of projects in the NCI pipeline and will safeguard the portfolio from having too many high-risk or duplicative projects.

On a quarterly basis, or as judged necessary by the Discovery Committee, the Project Teams will provide information about the overall project status, activity, and fiscal expenditures. This information will be collated by the Strategic Portfolio Management Group for presentation to the SAC. A key responsibility of the Discovery Committee will be to identify scientific gaps in the research plans and to ensure that the projects are on time and on budget.

The Discovery Committee will be responsible for approving transitions through the Stage Gates.

The Discovery Committee will ensure that all the scientific objectives have been met to trigger nomination of a clinical candidate. Once a clinical candidate has been nominated by the Project Team and approved by the Discovery Committee, it will be presented for review and endorsement by the Development Committee. At the point at which a clinical candidate is proposed for development, the Portfolio Management Group will perform a risk assessment of the candidate to ensure informed decision-making by both Committees.

The NExT Development Committee oversees and endorses the critical transition of clinical candidates from the discovery phase to the development phase.

The Development Committee will assess eligibility of candidates for NCI Phase 0, I, and II clinical trials and make appropriate decisions at each phase. This will include overseeing the clinical evaluation of novel anticancer agents brought into the pipeline through the Cancer Therapy Evaluation Program (CTEP), which is renowned for its efforts to forge collaborations with industry and the academic research community to develop new drugs for patients with cancer. The Development Committee will also be responsible for recommending promising agents to NCI for allocation of clinical development resources. For example, clinical trials can be conducted by the DCTD/CCR Developmental Therapeutics Section clinic at the NIH Clinical Center.

The Development Committee will address issues related to target patient population, dosing schedule, potential safety issues, correlative studies, and basis of differentiation with FDA-approved treatments. These efforts will ensure that resources

are directed towards the most promising drugs that support the NCI vision to target unmet needs in therapeutic oncology, including pediatric and niche indications, and natural products.

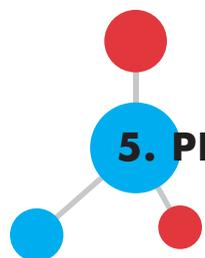
External Special Emphasis Panels: External Special Emphasis Panels (SEP) will adhere to the Federal Advisory Committee Act. SEP membership is fluid in that individuals recruited to serve will not have specific terms of service, nor should any individual be used on a regular basis.

External Special Emphasis Panels will bring diverse perspectives to the conduct of a quarterly evaluation of the NCI portfolio. Their responsibilities include 1: providing expert views on what targets and understudied rare cancers to focus on, and which novel agents or combinations the NCI should be advancing, 2: providing input on the scientific merit of projects, and 3: providing input on the feasibility of scientifically or technically challenging projects. These External Special Emphasis Panels and the SMC will be responsible for offering insight into the scientific direction of the NCI pipeline and ranking the relative priority of each project. These external committees will consist of key thought leaders in therapeutic discovery and development chosen by the SAC (in conformity with NIH guidelines) and will be subject to appropriate confidentiality and conflict-of-interest (COI) requirements to ensure confidential information is kept secure; SEP members from industry will not have access to information on NCI development projects related to third-party industry agents. Academic members will also be screened on a project-by-project basis to ensure COI compliance.

CBC Steering Committee: The CBC will be most effective if the collective insight, experience, and expertise of its Centers and Participants can be shared with senior NCI officials. The CBC Steering Committee will meet on a quarterly basis to provide intellectual contributions on operational strategy and suggestions for improving CBC operations, as many of the PIs have been instituting similar programs in academia. Creating this body of expertise within the CBC will provide far-ranging benefit for all Participants, enhancing the therapeutic significance of new scientific findings and the recognition of unexpected opportunities. The CBC Steering Committee will consist of Participants, most notably, PIs from the Specialized and Comprehensive Screening and Chemistry Centers.

Project Teams include a project leader, portfolio manager (senior NCI staff member), project manager, and scientific staff to support transition through appropriate stage gate. The Team is responsible for developing the project charter, plan, milestones, and budget, and has responsibility for overseeing day-to-day project workflow. Each Team will come up with a critical path to meet project goals, review data, and determine project readiness for Stage Gate progression.

The Project Management Office (PMO) is responsible for the execution and coordination of individual projects; project managers will partner with the project leader and portfolio manager to develop the project charter, integrate and coordinate the efforts of all CBC Participants, document milestones and project status, and prepare quarterly reports for the Discovery, Development, and Senior Advisory Committees.



5. PROCESS OVERVIEW AND THE PROJECT LIFE CYCLE

The project manager, project leader, and portfolio manager will develop the project plan and manage execution accordingly. This will be done in a *standardized* project management life cycle involving 4 phases, which are *concept*, *planning*, *execution*, and *closing*. Each phase is designed to capture specific project information in a standardized document to enable key decision bodies in the Governance scheme to make informed decisions to guide a project through agreed milestones and deliverables.

1. Concept Phase

The purpose of the concept phase is to decide whether the NCI wants to undertake a submitted project proposal. A concept or proposal is presented to the relevant governance bodies (SEPs and Discovery and/or Development Committee) for review. The governing bodies approve or disapprove the proposal based on scientific merit and strategic fit. If approved, the project leader partners with the Portfolio Planning Group and conducts a feasibility assessment that evaluates technical, scheduling, and operational requirements, defines the medical and scientific need for the new drug, and outlines its proposed MOA. The rationale for screening will be summarized, with an emphasis on identifying assays and biomarkers that can increase confidence that the MOA targeted is linked to the proposed clinical indication. A detailed review of the competitive landscape will be conducted to assess freedom-to-operate and IP status; cooperative or licensing agreements will be established later during development as appropriate. Technology resources needed for the project from screening through clinical evaluation will also be identified, including selection of appropriate

transgenic models and application of chemical genomics tools. This information is captured in a standardized document called the Project Charter. The Charter will be reviewed by the appropriate committee, and recommendations incorporated for final review. If the Charter is approved, a portfolio manager will be identified and the proposal, now an official NCI project, will be moved to the next project life cycle phase.

2. Planning Phase

The purpose of the planning phase is to finalize a research plan and assign resources. The project manager assists the project leader, portfolio manager, and Project Team members in developing project objectives and outlining the critical path and budget needs to support the project through the current Stage Gate. The information is documented in a Project Scope/Plan and is reviewed by the relevant Portfolio Planning Group prior to approval by SAC. If approved for resources, the project moves to the next phase and any relevant agreement negotiations with outside parties will commence.

3. Execution Phase

The purpose of this phase is to monitor whether the project is *delivering* on time. The project leader, with assistance from the project manager, will monitor execution of the project via regular monthly team meetings. It is the responsibility of the project leader and portfolio manager to make day-to-day scientific decisions necessary to meet project objectives. The Project Team will develop a quarterly Project Status Report to be presented to the relevant Portfolio Planning Group, thereby enabling the governing bodies to assess progress and ensure that the

project is moving in an “upward trajectory.” In addition, the Project Team will report regularly to the SAC. The governing bodies are expected to make scientific recommendations to the Project Team, especially when an impasse is encountered. The project leader can also request additional budget if needed, in which case the Portfolio Planning Group can present the recommendations to the relevant committees.

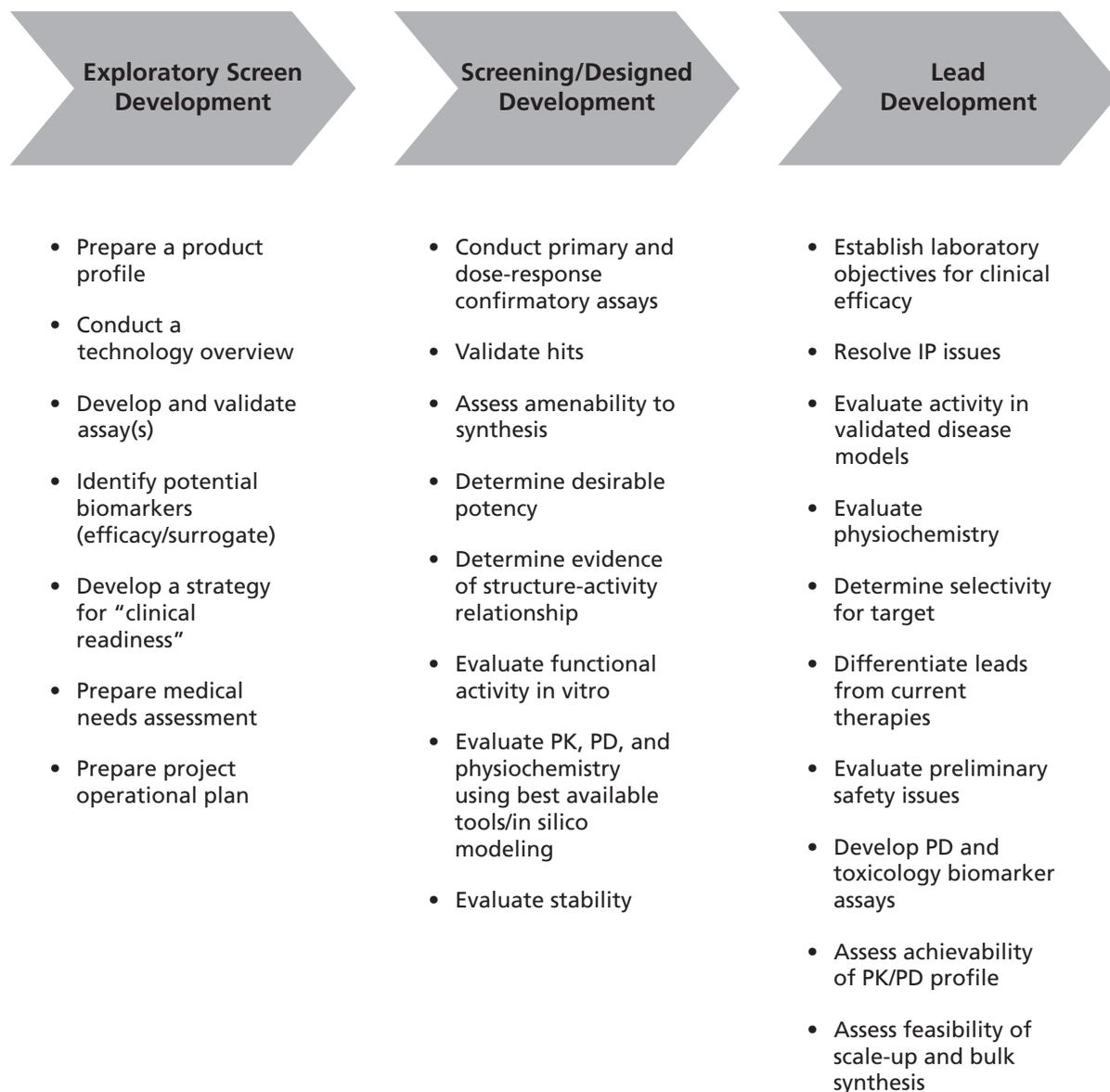
The Stage Gates (see figure on next spread) represent milestones for the progression of a project through the Execution Phase. The Stage Gates and accompanying Discovery Guidelines are a blueprint for discovery projects to guide and inform discussions about the project as it progresses. They provide a common language and common goals that will make collaboration across sites, divisions, and programs easier and decision making more transparent to the entire Institute.

4. **Closing Phase**

The purpose of this phase is formal closure of the project. The project leader, with assistance from the project manager, will develop a complete Project Report outlining key lessons learned and recommendations for not revisiting mistakes. The SAC has the final decision on closing or in some instances “parking” projects until more scientific data can be collected (e.g., better understanding of MOA).

In all of these phases, it is the responsibility of the project manager to communicate the project management process requirement to the project leader, and to assist the project leader with capturing the necessary information and organizing this information per standardized templates. The project manager will be responsible for facilitating team communication, Project Team meetings, and sharing of data and documents via Project Web Access.

NExT CBC Stage Gates



Candidate Seeking

- Evaluate synthesis and proposed clinical formulation
- Evaluate biopharmaceutical properties
- Assess potency against clinical efficacy
- Evaluate biodistribution
- Evaluate clinical readiness of PK/PD assays(s) and specimen handling SOPs
- Assess amenability to imaging
- Evaluate safety issues (most sensitive species) in range-finding toxicology studies
- Prepare clinical plan

Clinical Candidate

- Manufacture GMP-grade bulk drug
- Conduct IND-directed toxicology studies
- Define GLP- and GMP-grade toxicology/toxicokinetics
- Determine preclinical MTD and DLTs
- Validate PK/PD assay(s) and specimen handling SOPs
- Develop and validate product characterization and release assays
- Characterize clinical product
- Prepare CMC package and toxicology summary report
- Prepare and review clinical protocol
- Prepare and file IND

6. APPLICATION PROCESS AND REQUIREMENTS

Proposals are accepted online four times per year through the secure eNExT Web site: <https://dctd.cancer.gov/nextapp>.

NEXT PROPOSAL DEADLINES

February 15

May 15

August 15

November 15

Submissions will open beginning 30 days prior to each of the above application deadlines. An investigator may not submit the same application more than twice (i.e., for no more than 2 application cycles) and may not submit more than 2 applications per cycle.

Detailed instructions for submitting an application are provided here and on the eNExT Web site.

Questions about the application process or electronic submission system may be addressed to NCINExTinfo@mail.nih.gov.

REGISTERING FOR AN ACCOUNT

The application system is password protected and uses an encrypted link (https) to protect the content of your files. The first time you use the application submission program, you will need to apply for an account. This account is separate from your NIH account. However, if you have already registered for DTP services (e.g., compound submission or RAID), your existing DTP username and password can be used for submission.

- Complete the short online form, which includes choosing a username and password. Username and password selection rules, as well as Help and FAQs are available on the site.
- An administrative support person will validate your request and send you an e-mail when your account is approved. This should take less than 48 hours.
- Once your account has been confirmed, you can start the submission process.

INSTRUCTIONS FOR THE ONLINE SUBMISSION OF A NExT APPLICATION:

1. After obtaining your user name and password, log into the NExT Electronic Application and go to "Create New Application." Enter the required information, including a project title and abstract, your affiliation, if this is a new application or a re-submission, and whether your proposal is in the discovery or development stage (see below), then click "Continue."

Projects classified as **discovery** would include, but are not limited to, the following:

- Identification of targets (genes, pathways, molecules, biologics, etc)
- Biological function of targets (pathway dissection, miRNA/siRNA/shRNA studies, model building (in vitro and in vivo))
- Exploratory screen development and HTS optimization
- Novel lead new chemical entities (NCEs) for medicinal chemistry optimization

Projects classified as **development** would include, but are not limited to, the following activities to support IND filing for biologics and NCEs:

- In vivo efficacy studies
- Bulk synthesis (GMP or non-GMP)
- Scale-up production (lab scale to clinical trials lot scale)
- Analytical methods development for bulk material
- Formulation studies
- Production of clinical dosage forms
- Stability testing of clinical dosage forms
- Development of pharmacology assays
- Pharmacokinetic studies
- Pharmacodynamic studies
- Range-finding toxicology studies
- Planning of clinical trials
- IND filing advice

2. Each element of the application (NExT Concept Proposal, Intellectual Property Status, Current Support, PI Biosketch, Clinical Letter of Commitment, Appendices) should be created off line and saved as separate Adobe PDF files. True PDF files are preferred over PDF files that are created from scanned documents (images). The individual PDF files should then be uploaded using the appropriate buttons in the electronic form.

3. As each document is uploaded, the corresponding button will disappear and a complete list of the successfully uploaded document types will appear at the bottom of the screen. Documents can be viewed at any time or replaced up to the application deadline, at which point the submission will be considered complete.

NExT APPLICATION REQUIREMENTS

To ensure the expeditious review of NExT proposals, a highly focused application is desired. In contrast with lengthy NIH grant applications, the NExT Concept Application outlining the scientific nature and rationale of the proposed project is only 3 pages long. This document should be accompanied by a PI biosketch, clinical letter of commitment, and details about the project's IP status and current support, as outlined below and on the eNExT Web site.

1. Concept Application

This 3-page application should be structured according to the following format:

- **Background:** A summary of the field sufficient to allow an appropriate understanding of the scientific and medical context from which the opportunity emerges.
- **Hypothesis:** A clear statement of the hypothesis(es) to be tested with entry of the relevant molecule or target into the clinic. This should be in accord with the NCI's emphasis on molecular targeted drug development. NExT applications must provide a hypothesis-driven therapeutic agent or target with the eventual opportunity for hypothesis-based testing in the clinic. Proposals must meet the NExT

criteria and will undergo internal review on such matters by the various governing bodies.

- **Justification:** An explanation of why the proposed project represents a particularly innovative or promising approach to the prevention, detection, diagnosis, or treatment of cancer. Also include the anticipated cancer types and their prevalence, if possible, a description of the medical need (i.e., unmet need, poor current therapies, etc.), and the competitive advantage (i.e., improved efficacy or safety).
- **Uniqueness:** A discussion by the applicant of related or similar molecular agents already on the market or in preclinical development. This should include an assessment of how the proposed agent or target differs from current investigative or marketed therapies.

2. IP Information

A Participant will have to include a listing of any patents issued or pending with respect to either the agent of interest or to any non-commercially available technology/material required for the development of their agent. In the event that an application requires the use of non-commercially available technology/equipment which is patented by a third party, the applicant must provide documentation that the patent holder does not object to the applicant's use in conjunction with the proposed project. Each NExT application must include the information described below signed by an authorized staff member overseeing intellectual property and/or technology transfer for their affiliated institution. This verifies that they have reviewed the NExT request and that the technology is

or is not eligible for consideration by the NExT program. If the technology is found not to be eligible for use in as outlined in the NExT application, and it is central to the investigator's proposal, submission to the NExT program is not encouraged.

The following information is requested:

- Details of all the following rights which your institution owns and which are used in the project (the "institution's IP"):
 - Patents and patent applications
 - Registered trademarks, applications for registered trademarks and other marks
 - Registered designs, applications for registered designs and significant other designs
 - Significant know-how
 - Significant copyright works and other IP rights
- Details of all employees, consultants and other parties involved in the development of the institution's IP related to the NExT project submission. Please specify whether there are contributors outside the institution, and if so, define their role in development.
- A complete list and brief description of all agreements with third parties related to the NExT project submission:
 - Granting rights to those third parties under the institution's IP
 - Granting rights to those third parties under the institution's IP

- A complete list and brief description of all confidentiality agreements with third parties related to the NExT project proposal
- Details of any:
 - Claims made by third parties against the institution related to the project proposal that the institution has infringed a third party's IP rights
 - Circumstances where a third party has or may have infringed the institution's IP or other intellectual property used in the institutions' business related to the project proposal

3. **Current Support**

Participants should reveal their current funding sources. For those in academia, this would include currently funded grants from both government and non-government sources, and any research resources provided directly from their institution. Individuals working directly for the government should provide an annual budget for their laboratory and any additional outside funding sources.

4. **Principle Investigator Biosketch**

The Principle Investigator Biosketch should follow the NIH standard format. In the list of PI publications please highlight any that are directly related to proposed project by preceding them with a double asterisk (**).

ADDITIONAL DOCUMENTATION AS APPROPRIATE

Additional information to be submitted as appropriate includes a letter of commitment for any proposals containing a clinical component and any preliminary or supporting data as appendices.

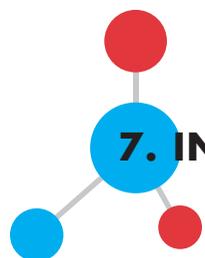
5. **Clinical Letter of Commitment**

All investigators requesting production of clinical lot and/or IND-directed toxicology must provide a letter of commitment from their institute.

This letter is intended to insure the reviewers and NCI that the products and data produced by NExT have a clinical outlet, and as such the letter should indicate that the institution is committed to the filing of an IND and conduct of a clinical trial once the NExT activities are completed. The letter of commitment should be signed by the head of the cancer center or the director of clinical research at the institution(s) at which the clinical trial will occur, or other party with obvious authority to commit the institution to conducting a clinical trial. Further, if neither the signatory of the letter or the applicant is a practicing medical oncologist, the letter of commitment should additionally contain the signature and contact information of the clinician who will be the PI of the clinical trial; it may be advisable for the applicant to include a supplemental letter from the clinician indicating that they are willing to undertake the trial.

6. **Appendices**

Up to 5 additional supporting documents can be uploaded as appendices. These can include relevant publications, pre-prints, or unpublished supporting data.



7. INAUGURAL CBC MEETING PARTICIPANTS

COMPREHENSIVE CHEMICAL BIOLOGY SCREENING CENTERS

Burnham Institute for Medical Research

Nick Cosford, PhD
Kristiina Vuori, MD, PhD

NIH Chemical Genomics Center

Christopher Austin, MD
Jim Inglese, PhD

Southern Research Institute

W. Blaine Knight, PhD
David Harris

SRI International

Lidia Sambucetti, PhD
Patricia Larenas

University of North Carolina at Chapel Hill

Stephen V. Frye, PhD
William P. Janzen

CHEMICAL DIVERSITY CENTERS

Georgetown University

Milton L. Brown, MD, PhD

University of Minnesota

Gunda L. Georg, PhD
Derek Hook, PhD

University of Pittsburgh

Donna Hury, PhD
Gabriela Mustata, PhD

Vanderbilt Institute of Chemical Biology

Gary Sulikowski, PhD
Alex Waterson, PhD

SPECIALIZED APPLICATION CENTERS

Emory University

Haian Fu, PhD
Fadlo Khuri, MD
Dennis Liotta, PhD
Cheryl Meyerkord, PhD

University of California, San Francisco

James A. Wells, PhD
Michelle Arkin, PhD

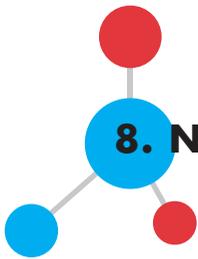
University of Pittsburgh Drug Discovery Institute

John Lazo, PhD
Paul Johnston, PhD

CONSULTANTS

Cambridge MedChem Consulting

Chris Swain, PhD



8. NExT/CBC IMPLEMENTATION TEAM

Heba Barazi, PhD

Project Manager, PMO
baraziho@mail.nih.gov

Jason Cristofaro, PhD, JD

Intellectual Property Advisor, DCTD
cristofaroj@mail.nih.gov

Gina Hayman

Project Manager, PMO
haymanrb@mail.nih.gov

Sanjay Malhotra, PhD

*Contracting Officer's Technical
Representative: Chemistry*
malhotrasa@mail.nih.gov

Barbara Mroczkowski, PhD

Liaison to the Director, DCTD
mroczkowskib@mail.nih.gov

Ralph Parchment, PhD

Director, LHTP, and Acting Director, PMO
parchmentr@mail.nih.gov

David Segal

*Computer Specialist, DCTD Information
Technology Officer*
segaldav@mail.nih.gov

Shizuko Sei, MD

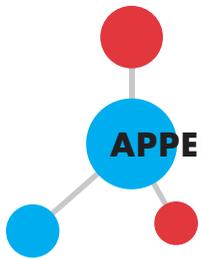
*Contracting Officer's Technical
Representative: Biology*
seis@mail.nih.gov

Tom Stackhouse, PhD

Associate Chief, Technology Transfer Branch
stackhot@mail.nih.gov

Joe Tomaszewski, PhD

Deputy Director, DCTD
tomaszej@mail.nih.gov



APPENDIX 1: NExT WEB SERVICES ACCESS SUBMISSION FORM

This form must be completed before registration to NExT pipeline Web resources can be processed; please allow 4-6 weeks for registration.

To be completed by the requestor:

Name:

Title:

Institution:

Contact Information (Address, E-mail, Phone Number):

Associated Project(s) and Role:

Associated Agreement(s) (e.g., CDAs, Participant's Agreements, CRADAs, CTAs):
(Type name of Agreement here)

By signing this agreement I affirm that I have read and agreed to the terms described in the agreement(s) above. I agree to abide by those terms. I also agree that I will not share my login or password to the DCTD Project Web Access site with any other person and will protect my login and password with due care.

| | | | |
|------------|--|-------|--|
| Signature: | | Date: | |
|------------|--|-------|--|

Please send completed forms (either electronic in PDF format or hard copies) to:

Dr. Jason Cristofaro
31 Center Drive, Room 3A44
Bethesda, MD 20892-2580
cristofaroj@mail.nih.gov

To be completed by the PMO:

- | | |
|---|--|
| <input type="checkbox"/> Access to PWA Project Workspace: | <input type="checkbox"/> Create Cambridge Soft eNotebook |
| <input type="checkbox"/> Access to PWA Project Portfolio | <input type="checkbox"/> Access to Cambridge Soft BioSar |
| <input type="checkbox"/> Access to PWA PD Portfolio | <input type="checkbox"/> Access to CBC Program Workspace |

Permission Level:

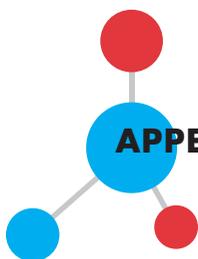
- Project Team Member (can view only) Project Team Contributor (can view, add, update, and delete)
 Committee Member:

Date of Expiration (1 year from initiation):

Approvals Signatures:

| | | | |
|----------------------|--|---------------|--|
| PMO Account Sponsor: | | NCI Approval: | |
|----------------------|--|---------------|--|

Please send completed forms to:
Regina Hayman, Project Manager, SAIC Frederick Inc, DCTD PMO support, 6116 Executive Blvd Suite 109, Rockville, MD 20852



APPENDIX 2: EXAMPLE NCI CHEMICAL BIOLOGY CONSORTIUM PARTICIPANTS AGREEMENT

Mission: The mission of the National Cancer Institute's ("NCI") Chemical Biology Consortium ("CBC") is to increase the flow of early stage drug candidates into NCI's drug development pipeline. By establishing an integrated network of chemical biologists and molecular oncologists from government, industry and academia, these CBC associate organizations and the NCI (collectively "Participants") can further address the unmet needs in therapeutic oncology focusing on areas such as "undruggable" targets and under-represented malignancies. Through the CBC and the interactions among the various Participants, the NCI's drug discovery and development pipeline can be enabled from target identification through proof-of-concept (POC) clinical trials. It is expected and understood that NCI will have the option to clinically develop successful compounds (NMEs) created by the CBC.

DESCRIPTION AND GOALS OF CBC:

The CBC is a consortium designed to integrate chemical biology and molecular oncology research with governmental development resources. CBC Participants will:

- a. Participate as an integrated network of chemical biologists and molecular oncologists to support lead development of promising new molecular entities
- b. Focus on unmet needs in therapeutics not adequately addressed by the private sector.
- c. Enable a clear, robust NCI pipeline all the way from target discovery through NCI POC clinical trials for academic, small biotech, and pharma investigators.

PARTICIPANT ENTRANCE CRITERIA:

CBC Participants will initially consist of participating government entities (NCI and associated NIH programs including the NIH Roadmap) and CBC contract awardees. Other organizations may be added to the Consortium at the discretion of the Senior Management Committee described below. Such organizations agree to be signatories to this Agreement.

Participant Interactions: Drug discovery and development requires teams of experts in different fields to advance the candidate from the early stages of discovery through preclinical development to the clinic. Participants will comprise a network of knowledge and expertise crossing scientific disciplines. It is anticipated that through this interaction, Participants can identify potential collaborations, navigate scientific roadblocks and obtain essential research resources from other Participants. These interactions are expected to accelerate the discovery and development of novel therapeutics. To accomplish this effectively, Participants will manage all of the resources generated under this Agreement, including intellectual property (IP), in a manner which promotes the sharing of research resources, therapeutic and diagnostic candidates, and data among the CBC Participants. It is understood by the Participants that the primary goal is the development of cancer therapeutics and diagnostics through cooperation and communication among the CBC Participants.

MANAGEMENT OF THE CBC¹:

A. Senior Management Committee:

Overall management of the CBC will be conducted by the Senior Management Committee (SMC) of the NCI. The SMC will consist of members of NCI's senior leadership, including the NCI Director, Directors of the Division of Cancer Treatment and Diagnosis and the Center for Cancer Research, Associate Directors of relevant programs including the Developmental Therapeutics Program and *ad hoc* Participants depending on their expertise as determined by the NCI Director.

The SMC will be responsible for the following:

- resource allocation
- strategic focus
- oversight and accountability
- coordination of intramural and external Drug Discovery and Drug Development committees

The overall responsibility of the SMC will be to oversee CBC implementation plans concentrating on the CBC as a whole and on high priority areas. Management of individual projects will be undertaken by two committees, the Drug Discovery Committee ("Discovery Committee") and the Drug Development Committee ("Development Committee"), which report to the SMC on a quarterly basis.

Day-to-day operation of the CBC will be the responsibility of Project Teams (PT) created by the Discovery and Development Committees. The PTs will focus on a single area of therapeutic research interest. Each PT will be headed by a Project Leader (PL) assigned by the Discovery and Development Committees and determined to have the necessary experience and expertise to manage the PT. PLs will

report progress to the SMC on a quarterly basis to facilitate decisions or implement mid-course corrections (focus-driven with outcomes).

B. Drug Discovery Committee

The Discovery Committee will report to the SMC and oversee governance of all Discovery projects in the NCI pipeline. It will guide allocation of resources and develop strategic plans for individual projects in early discovery phase. Early discovery phase will encompass the following disciplines: *in silico* evaluations of pharmaceuticals, pharmacology and toxicology; target discovery and validation; assay development and high throughput screening (HTS) assay development and screening; hit-to-lead chemistry, lead optimization (structural activity relationships incorporating structure-based drug design (SBDD) where appropriate); pharmaceuticals; target pharmacology (selectivity, *in vitro* and *in vivo* pharmacokinetics (PK), *in vivo* PK and *in vitro* and *in vivo* pharmacodynamics (PD), biomarker discovery, assay development and validation) and early toxicology (*in vitro* human tissue assays, molecular toxicology and limited range-finding *in vivo* studies). Accordingly, the Discovery Committee is expected to provide input to the PTs in the following technical areas: synthesis, biopharmaceuticals, absorption, clearance, potency, distribution, metabolism, pharmaceuticals, pharmacology (animal models and biomarkers), and safety. The Discovery Committee will perform risk-assessment at each stage-gate in the pipeline to ensure informed decision-making. Ideally, membership in this committee should include Participant representatives with expertise in each of the afore-mentioned discovery disciplines.

The Discovery Committee will also be the steward of the CBC Drug Discovery Guidelines.

¹ This is an example CBC Participants Agreement; current governance is defined in greater detail in Section 4.

These Guidelines will provide a consistent framework against which all clinical candidates will be measured. The Guidelines represent a living document modeled after biotech/pharma benchmarks. The Guidelines are an evolving set of quality attributes that will be updated and revised annually by the Discovery Committee. The Guidelines will serve as a tool for prioritization of projects in the NCI pipeline and will safe-guard the portfolio from having too many high-risk or duplicative projects.

On a quarterly basis PTs will provide information about the overall project status, activity and fiscal expenditures to the Discovery and Development Committees, and if necessary, the SMC. A key responsibility of the Discovery Committee will be to identify scientific gaps in the research plans and to ensure that the projects are moving toward completion. The Discovery Committee will be responsible for making decisions at each stage-gate.

The Discovery Committee will ensure that all the scientific objectives have been met to trigger nomination of a clinical candidate. Once a clinical candidate has been nominated by the PT and approved by the Discovery Committee it will be presented for review and endorsement by the Development Committee. At the point at which a clinical candidate is proposed for development, the PT will perform a risk assessment of the candidate to ensure informed decision-making by both Committees.

C. Drug Development Committee

The Development Committee will report to the SMC and endorse the critical transition of clinical candidates from Discovery phase to Development phase and oversee completion of all late-stage preclinical studies (e.g. Investigational New Drug (IND)-enabling toxicology studies, Good

Manufacturing Practice (GMP) manufacturing, validation of clinical biomarkers including imaging modalities; establishment of SOP-driven PK and PD assays) to support IND filing and first-in-human clinical trials. The Development Committee will assess eligibility of candidates for NCI Phase 0, I, II and make appropriate decisions at each phase. In addition, the development committee will be responsible for shepherding promising agents into NCI clinical development resources. The Development Committee will address issues related to: target patient population, dosing, clinical benefits, and basis of differentiation with FDA approved treatments to ensure that resources are focused on the most important and promising opportunities that match with the NCI vision of developing drugs to fill unmet needs, pediatric and niche indications and targeting natural products. Ideally, membership in this Committee should include Participant representatives with expertise in each of the afore-mentioned development disciplines.

D. Overall Project Management

The Discovery and Development Committees will assign "Projects" that will focus on a target, agent, compound or class of compounds determined by the SMC to be of high priority. The Discovery and Development Committees will each assign a PL to a specific Project. The PT will be made up of Participants with interest and expertise related to the specific Project. The PL will provide day-to-day direction, including organizing meetings and directing project work-flow. Oversight of the individual Projects will be the responsibility of the Discovery and Development Committees, which will monitor progress and identify problems with implementation, both by regular monthly meetings and by electronic communication.

Discovery PTs will also make recommendations to the Discovery Committee regarding the development status of therapeutic technology, and whether that technology is ready to be transferred to the Development Committee.

Monitoring will occur via quarterly reports submitted by the PTs to the Discovery, Development and Senior Management Committees. These reports will be prepared by Discovery and Development PTs and will encompass updates on the entire CBC endeavor. These reports will be made available for the quarterly meetings of the SMC.

E. External Review

The Discovery Committee and the Development Committee each will have an External Advisory Committee. These External Advisory Committees and their NCI counterparts will be responsible for overseeing the scientific direction of the CBC consortium. Membership of these external committees will consist of key thought leaders in therapeutic discovery and development chosen by the SMC (in conformity with NIH guidelines) and will be subject to appropriate confidentiality and conflict of interest requirements to ensure any confidential information is kept proprietary. Both External Advisory Committees will be tasked with portfolio prioritization that will be tied into a fiscal appropriation for each project. Biannual Meetings will be held for the External Discovery and Development Advisory Committees.

ACCESS TO THE CENTRAL CBC DATABASE:

Central CBC Database access will be limited to Participants approved by the SMC with molecular oncology and drug discovery/development expertise that are signatories to this Agreement. Participants that have left the CBC will no longer have access to the Central CBC Database.

PLs will be responsible for ensuring that PT data is entered into the database in a timely fashion. In general, members will be able to enter their data remotely, and will be expected to do so in a timely fashion once appropriate allowances are made for filing of necessary patent applications (described below).

Participants will have access to all data contained in the database, subject to the confidentiality terms in this Agreement.

TECHNOLOGY TRANSFER COMMITTEE

Each Participant is expected to assign one Technology Transfer Representative (TTR) to the CBC. A Technology Transfer Committee (TTC) will be established for the CBC and will be made up of the CBC TTRs. The purpose of the TTC is to maintain lines of communication related to the IP developed from the CBC and to share best practices for commercial development of their respective technologies and establish common guidelines for the management of CBC-related partnership and other technology transfer agreements.

THIS AGREEMENT sets forth the framework for cooperation among the Participants for pursuing collaborative projects. It is understood by the Participants that separate agreements among the individual Participants, which compliment the spirit of this Agreement, may be required to implement the NIH Research Tools Policies, maintain this cooperative framework and reach commercial endpoints.

Therefore, in support of these goals and objectives of the CBC, Participants agree to the following:

Article 1 Participation

1.1 Participants agree to participate in the CBC in good faith under the terms of this Agreement.

1.2 Participants acknowledge that to become a Participant under this Agreement the membership criteria described above must be met as determined by NCI at its sole discretion.

1.3 Nothing in this Agreement will be construed to limit the freedom of a Participant from engaging in research with other parties consistent with its obligations under this Agreement.

1.4 It is anticipated and encouraged that Participants will enter into separate agreements with one another to accomplish specific projects or tasks. The terms of these separate agreements will be consistent with and compliment the spirit of this Agreement and follow the NIH Guidance for Government-funded research including the NIH Research Tool Policy at http://ott.od.nih.gov/policy/research_tool.html.

1.5 Each Participant represents to the best of its knowledge that it has no conflicts of interest or relationships that would preclude it from entering into this Agreement or participating in the CBC.

1.6 The relationship of the Participants is that of independent contractors and not agents of each other or joint venturers or partners; thus, no Participant may act for or bind another Participant. Each Participant shall maintain sole and exclusive control over its personnel and operations.

Article 2 Confidentiality

2.1 Participants agree to keep information provided by another Participant(s) that is marked 'Confidential' ("Confidential Information")

confidential for a period of five (5) years from the date the Confidential Information was provided and to employ all reasonable efforts to maintain the Confidential Information of the disclosing Participant secret and confidential, such efforts to be no less than the degree of care employed by each Participant to preserve and safeguard its own confidential information. Oral disclosures of confidential information will be reduced to writing within fifteen (15) days, marked 'Confidential' and provided to the receiving Participant by the disclosing Participant. The obligations of a Participant shall not extend to any part of the Confidential Information of the disclosing Participant that:

- (a) can be demonstrated to have been in the public domain or publicly known at the time of disclosure; or
- (b) can be demonstrated to have been in the possession of or that can be demonstrated to have been readily available to the receiving Participant from another source not subject to a confidentiality obligation prior to the disclosure; or
- (c) becomes part of the public domain or publicly known by publication or otherwise, not due to any unauthorized act by the receiving Participant; or
- (d) can be demonstrated as independently developed or acquired by the receiving Participant without reference to or reliance upon such Confidential Information;
- (e) is disclosed by a receiving Participant(s) with the written approval of the disclosing Participant, or
- (f) is or was disclosed by the disclosing Participant to a third party without restriction; or

(g) is required to be disclosed by law by a court order or regulatory body of competent jurisdiction, or by the Freedom of Information Act (FOIA).

2.2 All Participants acknowledge and agree that any information that may be obtained from any Central CBC Database to which a Participant may have access is included in the Confidential Information.

2.3 To the extent permitted by law, it is the intention of NCI to protect Confidential Information provided by Participants to the Central CBC Database under the exemptions provide in the Freedom of Information Act; however, the applicability of exemptions is determined solely by the NCI FOIA Office. The party providing the Confidential Information will be given a 60 day notice of any said FOIA request for its Confidential Information to permit the necessary action to protect its Confidential Information.

Article 3 Intellectual Property

3.1 Each Participant will retain ownership of inventions made by its employees. Ownership of joint inventions made by two or more Participants will be determined by applicable patent law. It is expected that Participants with joint ownership of an invention will establish an appropriate agreement among them which establishes the rights and responsibilities of each Participant and reflects cooperation to efficiently develop such an invention to an appropriate commercial endpoint. Furthermore it is expected that groups of Participants which own individual inventions which collectively may produce a beneficial commercial product(s) will similarly cooperate to reach an appropriate commercial endpoint. Participants will report inventions made as part of the CBC to the Technology Transfer Committee on a semi-annual basis.

3.2 Consistent with the spirit of sharing resources and data within the CBC community, it is expected that each Participant will manage intellectual property in a manner which allows sharing of technology within the CBC for research purposes and also protects those inventions which may benefit from IP protection to facilitate downstream development (i.e., therapeutics, diagnostics).

3.3 Each Participant will license inventions according to its own institutional policies or applicable laws and regulations. Preference for nonexclusive licensing or limited exclusive licensing to facilitate broad commercial application and wide use of research resources by the research community is expected. When appropriate to encourage investment in and development of a technology, exclusive licensing might be considered. Participants that exclusively license a technology should retain the right to use the invention for research purposes for itself and the broader research community.

3.4 Each Participant will assign one Technology Transfer Representative (TTR) to the CBC. The TTRs will collectively establish a CBC Technology Transfer Committee (TTC) to maintain lines of communication related to the IP developed from the CBC and to share best practices for commercial development of their respective technologies and establish common guidelines for the management of CBC-related partnership and other technology transfer agreements.

3.5 The TTC will prepare CBC Technology Transfer Guidelines ("TT Guidelines") and have the TT Guidelines ratified by Participants within twelve (12) months of execution this Agreement. The TT Guidelines will be considered ratified by approval of a two-thirds majority of the Participants and approval of the SMC.

Participants will operate according to the ratified TT Guidelines. By signing this Agreement, Participants joining the CBC following the ratification of the TT Guidelines agree to operate according to the TT Guidelines.

3.6 The TTC and TTRs will assemble for a face-to-face Technology Transfer meeting at least annually. The TTC and TTRs will participate in quarterly technology Transfer teleconferences.

Article 4 Sharing of Research Resources and Data

4.1 Consistent with the intellectual property management described in Article 3, the Participants agree to share research materials among the other Participants for CBC research under an agreement that is consistent with this Agreement and no more restrictive than the NIH Material Transfer Agreement, the NIH Simple Letter Agreement or the Uniform Biological Material Transfer Agreement found at

http://ott.od.nih.gov/forms_model_agreements/forms_model_agreements.aspx#MTACTA.

Such agreements would not include reach-through to future inventions or restrictions on the sharing of modified derivatives which may be produced using the research materials.

4.2 Participants will share data from CBC research in confidence pursuant to Article 2 to facilitate the efficient development of cancer therapeutics and diagnostics through cooperation and communication among the CBC community.

Article 5 Publications and Press Releases

5.1 Participants are encouraged to make publicly available the results of their research and development activities. Before a Participant(s) submits a paper or abstract for publication or otherwise intends to publicly disclose information, such Participant(s) will allow another Participant which has provided Confidential Information thirty (30) days to review the proposed publication or disclosure to assure that Confidential Information is not inappropriately disclosed. A Participant may request in writing that the proposed publication or other disclosure be delayed for up to thirty (30) additional days as necessary to file a patent application.

5.2 Participants agree to provide proposed press releases that reference the CBC or that rely on work from another Participant for review and comment by the NCI or other Participants as appropriate at least ten (10) days prior to its release.

5.3 Participants will provide the TTC with a list of its publications related to the CBC on a semi-annual basis.

Article 6 Liability

6.1 No indemnification for any loss, claim, damage or liability is intended or provided by any Participant under this Agreement. To the extent permitted by law, each Participant shall be liable for any loss, claim damage, or liability that said Participant incurs as a result of its activities under this Agreement. The NCI or any other agency of the federal or a state government assumes liability only to the extent provided by law.

6.2 THE PARTICIPANTS MAKE NO EXPRESS OR IMPLIED WARRANTY AS TO ANY MATTER WHATSOEVER RELATED TO THIS AGREEMENT INCLUDING THE MERCHANTABILITY, OR FITNESS FOR A PARTICULAR PURPOSE OF THE RESEARCH OR ANY INVENTION OR MATERIAL, OR THAT A TECHNOLOGY UTILIZED BY A PARTICIPANT UNDER THIS AGREEMENT DOES NOT INFRINGE ANY THIRD-PARTY PATENT OR OTHER INTELLECTUAL PROPERTY RIGHTS.

Article 7 Termination or Withdrawal

7.1 A Participant may withdraw from the CBC and this Agreement with thirty (30) days written notice.

7.2 The NCI may terminate this Agreement unilaterally with thirty (30) days written notice.

7.3 The provisions of Articles 2-7 will survive withdrawal by a Participant or the termination of this Agreement.

Article 8 General Terms

8.1 By entering into this Agreement, no Participant directly or indirectly endorses any product or service of another Participant whether directly or indirectly related to this Agreement. A Participant will not in any way state or imply that this Agreement is an endorsement of any product or service by another Participant or any of its organizational units or employees.

8.2 This Agreement may be amended by the NCI to reflect programmatic changes in the CBC or the addition or departure of Participants. The NCI may implement a substantive change to this Agreement to be applied prospectively thirty (30) days following an announcement by NCI. All amendments and changes to this Agreement must be approved by

a simple majority of the SMC and approved by the NCI Director.

8.3 Participants acknowledge that there is no additional funding from any source associated with this Agreement. This Agreement does not prohibit Participants from otherwise submitting prospective targets, lead compounds and drug candidates to NCI for evaluation or possible access to additional resources; however, access to any future NCI resources or programs including the NCI pipeline or clinical resources will be only after approval by appropriate committees or NCI units not necessarily associated with the CBC. Participants acknowledge that the NCI, should it so decide has the express right to enter lead compounds into NCI's clinical development program.

8.4 Any dispute arising under this Agreement will be submitted jointly to the signatories or their designee of this Agreement. If the signatories, or their designees, are unable to jointly resolve the dispute within thirty (30) days after notification thereof, the Assistant Secretary for Health (or his/her designee or successor) will propose a resolution. Nothing in this Paragraph will prevent any Party from pursuing any additional administrative remedies that may be available and, after exhaustion of such administrative remedies, pursuing all available judicial remedies. Pending the resolution of any dispute or claim pursuant to this Article, the Parties agree that performance of all obligations will be pursued diligently.

8.5 Participants will operate in accordance with all appropriate federal, state and local laws and regulations including those related to safety, human subjects research and animal welfare.

(Signatures Begin on the Following Page)

By signing below the Participant agrees to the terms contained herein.

NCI: _____
(Authorized Signature)

Name:
Title:

CBC Contact: Name
Title
Phone
Email

TBD: _____
(Authorized Signature)

Name:
Title:

CBC Contact: Name
Title
Phone
Email

TBD: _____
(Authorized Signature)

Name:
Title:

CBC Contact: Name
Title
Phone
Email

TBD: _____
(Authorized Signature)

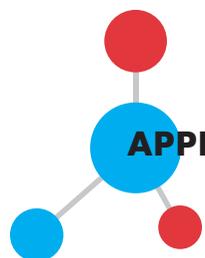
Name:
Title:

CBC Contact: Name
Title
Phone
Email

TBD: _____
(Authorized Signature)

Name:
Title:

CBC Contact: Name
Title
Phone
Email



APPENDIX 3: NCI DRUG DISCOVERY AND DEVELOPMENT RESOURCES

The NCI's success at taking drug candidates through preclinical evaluation towards filing an IND is due to the expertise and experience of its staff in late-stage drug development activities, including the conduct of toxicology studies and production of clinical-grade material—activities and resources that are the most expensive and least available in the academic sector. The NCI will make these resources, including molecular and small animal imaging, preclinical models, preclinical pharmacology (PK and PD), toxicology, formulation, and clinical support, available to help the CBC accomplish its goals. Some of these resources are described below.

The NCI's Natural Products Resource

The NCI maintains the world's largest and most diverse repository of natural product extracts. These extracts, derived from terrestrial, marine, and microbial organisms, are a unique source of chemical diversity for the discovery of compounds that may interact with specific molecular targets associated with human cancers. The Natural Products Branch currently stores approximately 160,000 crude extracts that are available either in a vial or plated format. <http://dtp.nci.nih.gov/branches/npb/index.html>

Drug Synthesis And Chemistry Branch (DS&CB)

DS&CB is responsible for the following activities in support of the discovery and development of novel anti-cancer agents: worldwide scientific liaison activities with universities and industries to stimulate the input of a wide variety of synthetic compounds, natural products, and combinatorial libraries for in vitro cancer screening; management of the storage, inventory, documentation, and distribution of samples for research purposes; and synthesis of cold and radiolabeled compounds for in vivo studies.

DRUG DEVELOPMENT RESOURCES IN DTP

DTP has supported the development of hundreds of new agents since its inception in 1955. The drug development resources and capabilities of the different DTP branches are described below.

Biological Resources Branch (BRB)

The BRB Program Staff oversee a pilot multi-product current Good Manufacturing Practices (cGMP) facility known as the Biopharmaceutical Development Program (BDP) at the NCI-Frederick. The BDP produces a variety of cGMP-grade biopharmaceuticals for clinical trials or advanced preclinical animal testing. <http://wwwbdbp.ncifcrf.gov>

Biological Testing Branch (BTB)

BTB provides preclinical screening and evaluation of new agents in the development pipeline. A considerable number of quality-controlled xenograft, orthotopic, and hollow-fiber mouse models are used to confirm efficacy, drug effect on molecular target, and the "clinical readiness" of PD assays to quantify this effect. http://dtp.nci.nih.gov/branches/btb/btb_index.html

Pharmaceutical Resources Branch (PRB)

PRB staff has extensive expertise in synthetic chemistry and drug formulation to provide researchers with high-quality, well-characterized chemical substances and drug products. Purification methods are established with the goal of delivering a material suitable for IND-directed toxicology and possibly clinical trials. Studies to elucidate an agent's molecular structure, including determination of stereochemistry, are performed using a variety of instrumental techniques. Compounds also undergo basic physico-chemical characterization. Specific methods for quantitation are developed for the assessment of potency and impurity profiles; these

analytical methods also provide the basis of related assays used in GLP monitoring of drug production and stability. http://dtp.nci.nih.gov/branches/prb/prb_operations.html

Toxicology And Pharmacology Branch (TPB)

The primary responsibility of TPB is to obtain the toxicology and pharmacology data necessary for the

NCI to file an IND to conduct early-phase clinical trials of new chemotherapeutic agents. <http://dtp.nci.nih.gov/branches/tpb/index.html>

The resources and expertise of TPB are outlined below, including how this work is integrated into the overall drug development process.

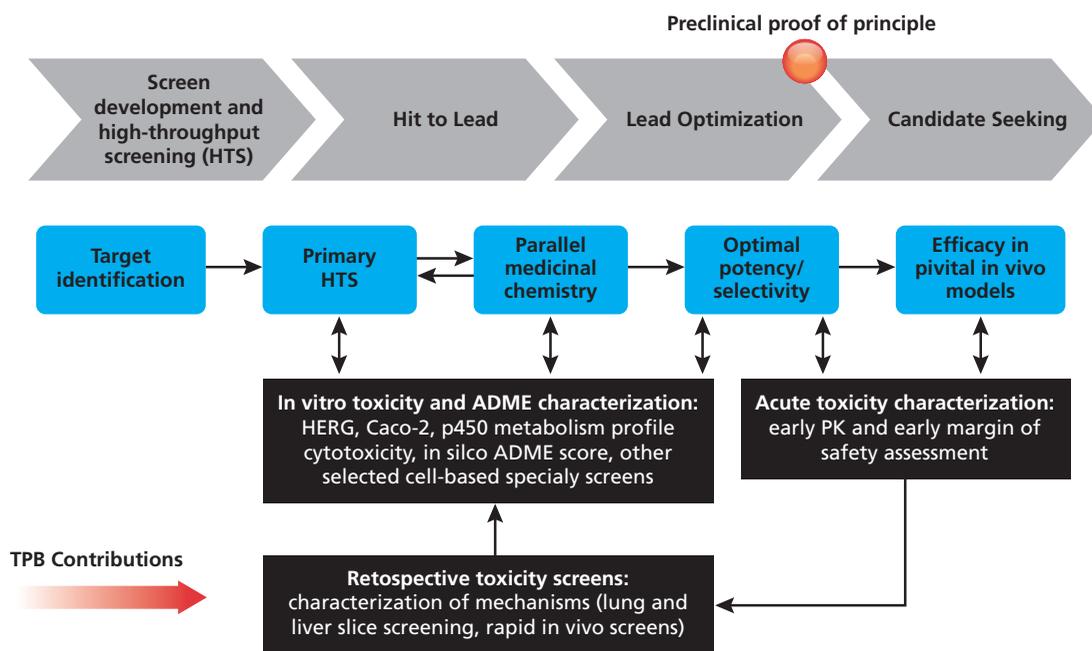
PK/ADME Capabilities in TPB

| In vitro assays and in silico assessments | In vivo screening and methods development |
|---|---|
| Plasma protein binding | Comparative exposure assessments |
| Plasma stability | Mouse versus rat exposure |
| Simulations plus ADME prediction | Canine exposure |
| Metabolic stability | Bioavailability |
| hERG inhibition* | PD endpoint evaluation/tissue collection |
| Assessment for PD endpoints: organ and cell based | In vivo assessment of compound stability |

* Early toxicology evaluation

Lead and candidate PK/ADME evaluation

- Full PK profiling in relevant species
- Full PK/PD assessment in one or more species (in partnership with PD assay development plan)
- Protein binding and bioavailability assessments
- Metabolic profiling (issue driven)
- Assessment of compound clearance



Adapted from Kramer JA, et al. Nat Rev Drug Discov. 2007;6:636-49.

THE DCTD PHARMACODYNAMICS PROGRAM

This program is supported preclinically by the Laboratory of Human Toxicology & Pharmacology (LHTP) and clinically by the National Clinical Target Validation Laboratory (NCTVL). LHTP uses humanized treatment and assessment conditions in mouse models to validate the analytical performance of PD assays prior to their use in clinical trials. Validated PD assays and Standard Operating Procedures (SOPs) for specimen handling, processing, and storage are then transferred to NCTVL for measurement of drug effects in clinical specimens.

In the context of the CBC, rapid preclinical PD evaluation in murine models of human cancer will be used to confirm that an optimized lead acts on its intended molecular target. The Pharmacodynamics Assay Development & Implementation Section (PADIS) will be responsible for adapting a discovery assays from CBC Centers into “fit-for-purpose” PD assays, with the minimal adaptation required for them to provide yes/no results concerning

modulation of the intended molecular target. Once a project is accepted into early development, PADIS will pursue further development and validation of a SOP-driven assay, so that it will be ready for use during later stage development and clinical trials.

DCTD’s Laboratory Of Synthetic Chemistry (LSC)

The Laboratory of Synthetic Chemistry (LSC) provides chemistry support to the drug discovery and development efforts of DTP/DCTD. In the context of the CBC, the LSC will interact with various DCTD centers, programs within NCI, and outside contract laboratories to identify hits and potential leads that would be developed to drug candidates.

NCI DEVELOPMENTAL THERAPEUTICS SECTION FOR PHASE 0, I, AND II CLINICAL TRIALS

The NCI established the Developmental Therapeutics Section (DTS) within the CCR so that DCTD could use Phase 0 clinical trial designs as permitted by the FDA’s Exploratory IND Guidance to evaluate agents early in the clinical development process.

DTS also designs and conducts Phase I and II trials of novel agents; many of the trials are multicenter collaborations with other specialist cancer centers and oncology groups and consortia. The potential for rapid patient accrual combined with the world-class resources of the CCR allow the optimum evaluation of promising new anticancer agents. <http://bethesdatrials.cancer.gov/clinical-programs/therapeutics/default.aspx>

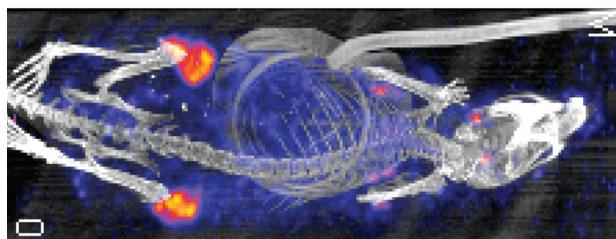
NCI'S CANCER IMAGING PROGRAM (CIP)

DCTD's Cancer Imaging Program (CIP) is catalyzing the development of molecular imaging that visualizes the physiological, cellular, or molecular processes in living tissues in real time. In vivo molecular imaging elucidates how targets integrate into the complex systems of tumor biology and allows noninvasive treatment monitoring. CIP plays a critical role in the activities of the NCI, contributing to the integration of imaging with emerging technologies such as nanotechnology, proteomics, and HTS. <http://dctd.cancer.gov/ProgramPages/cip/default.htm>

To meet the need for greater access to imaging facilities for clinical trials conducted in the NIH Clinical Center, the NCI Imaging Clinic was established by the collaborative efforts of DCTD, CCR, and the NIH Clinical Center; it is anticipated that CBC projects with imaging as an endpoint will qualify for use of this facility.

NCI-FREDERICK, THE FEDERALLY FUNDED RESEARCH AND DEVELOPMENT CENTER AT THE NCI

For CBC agents that require specific genetically engineered mouse models, it is anticipated that the CCR's Mouse Cancer Genetics Program (MCGP), through the newly established Center for Advanced Preclinical Research, will conduct efficacy studies in those models or supply animals for BTB to do so. The MCGP uses molecular mouse genetics as a primary tool to better understand the fundamental processes underlying mammalian development and disease.



SPECT/CT image of a mouse with bilateral thigh SKOV tumors administered In-labeled Trastuzumab (courtesy of SAIP).

The NCI-Frederick Small Animal Imaging Program (SAIP) provides NCI investigators with a state-of-the-art in vivo imaging facility (3.0 Tesla MRI unit, a Xenogen IVIS SPECTRUM for bioluminescence and fluorescence imaging, a CRi Maestro for fluorescence imaging, a VisualSonics Vevo 770 40Mhz Ultrasound unit for real-time sonography, a Siemens Inveon MicroPET scanner, Siemens Inveon microSPECT/CT imaging platform docked to the microPET device, and a Fuji FLA-5100 for autoradiography/fluorescence/chemiluminescence). It is anticipated that CBC agents that require imaging in animal studies will qualify for the use of these facilities. <http://web.ncifcrf.gov/rtp/lasp/intra/saip>

ADVANCED TECHNOLOGY PROGRAM

The Advanced Technology Program (ATP) laboratories at the NCI-Frederick, operated by SAIC-Frederick, Inc., were established to provide NCI and other NIH laboratories and initiatives with access to leading-edge technologies and specialized expertise through a tightly integrated, highly effective approach to the study of complex biological problems. <http://web.ncifcrf.gov/atp/>



At the forefront of their respective fields, the ATP laboratories continuously meet challenges with new technologies and make significant contributions to collaborative research projects with NIH scientists and extramural collaborators. A wide range of cutting-edge technologies can be easily accessed to assist in basic scientific discovery projects and to accelerate the translation of basic research discoveries into new treatments for patients with cancer and AIDS.

Powerful Tools

Each ATP laboratory devotes a substantial portion of its efforts to technology development, resulting in advanced methods and approaches designed for maximum impact on discovery and translational research. The ATP can be accessed through a variety of funding, contractual, and partnership mechanisms.

Research Collaborations

The resources available to you include the opportunity to partner with the biomedical research scientists on our staff. They are engaged daily in everything from routine laboratory processes to complex experimental design and interpretation of results. Projects frequently flow across the range of expertise within the ATP. Our scientists have already enabled many investigators to extend their inquiries to depths and in directions perhaps otherwise inaccessible.

For more information about how the ATP can assist you in your research, please contact:

Bruce Crise, PhD

Director, Business Development

Scientific and Technical Operations

criseb@ncifcrf.gov

Laboratories And Expertise

The Laboratory of Proteomics and Analytical Technologies (LPAT) has a wide range of technologies and expertise for characterizing both single proteins and multiple proteins present within complex mixtures, as well as for cell profiling using custom separation techniques and mass spectroscopy technologies. The LPAT also has small-molecule NMR capabilities. Contact: Tim Veenstra, veenstrat@mail.nih.gov

The Protein Chemistry Laboratory (PCL) has expertise in macromolecular interactions and experience with surface plasmon resonance spectroscopy. Also available are fluorescence spectroscopy, high-sensitivity protein identification (using both Edman sequencing and mass spectrometry), HPLC purification, and quality control of proteins and oligonucleotides. Contact: Robert Fisher, fisher@ncifcrf.gov

The Protein Expression Laboratory (PEL)

develops and adopts innovative gene cloning, cell culture, protein expression, and protein purification technologies to deliver cells, clones, and recombinant proteins for a broad range of applications. Additionally, the PEL provides lenti- and adenoviral vectors, custom, pathogen detection assays, and Lumenix and ELISA assays. Contact: Jim Hartley, hartley@ncifcrf.gov

The Laboratory of Molecular Technology (LMT)

is an integrated molecular biology laboratory focusing on high-throughput gene discovery and analysis, including advanced sequencing, genetics and genomics technologies, gene expression (microarrays and qPCR), and molecular CLIA diagnostics. Contact: Daniel Soppet, soppetdr@mail.nih.gov

The Optical Microscopy and Analysis

Laboratory (OMAL) provides state-of-the-art confocal microscopy for imaging living cells. The OMAL also offers FRAP, FRET and two photon microscopy techniques, as well as a full suite of quantitative image analysis capabilities. Contact: Stephen Lockett, slockett@ncifcrf.gov

The Electron Microscopy Laboratory (EML)

provides ultrastructural analysis of cells, bacteria, nanoparticles, and viruses using state-of-the-art electron microscopes. The EML has microscopes capable of TEM, SEM, STEM, X-ray energy dispersed element analysis, cryo-TEM, and 3D tomography. Contact: Kunio Nagashima, nagashim@mail.ncifcrf.gov

The Nanotechnology Characterization

Laboratory (NCL) provides preclinical efficacy and toxicity testing of nanotech cancer therapeutics and diagnostics to accelerate the development and commercialization of nanoscale particles and devices for clinical applications. The NCL has a wide range of physicochemical, in vitro, and in vivo assays for characterizing nanoparticles. Contact: Scott McNeil, ncl@mail.nih.gov

The Advanced Biomedical Computing Center

(ABCC) provides high-performance computing support to biological researchers in all areas of bioinformatics, including proteomics and genomics. The ABCC also assists in molecular modeling, imaging, data-intensive classification and knowledge discovery, structural biology, and nanotechnology modeling and simulation. Contact: Jack Collins, collinja@mail.nih.gov

THE CANCER GENOME ATLAS

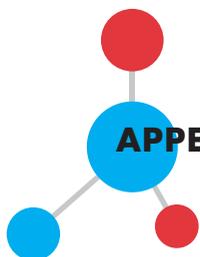
The Cancer Genome Atlas (TCGA) is a comprehensive effort by NCI and the National Human Genome Research Institute (NHGRI) to accelerate understanding of the molecular basis of cancer through the application of genome analysis technologies, such as large-scale genome sequencing. This project is assessing the feasibility of a full-scale effort to systematically explore genomic changes involved in human cancer, focusing on three types: brain (glioblastoma multiforme), lung (squamous carcinoma), and ovarian (serous cystadenocarcinoma). This information could lead to an expanded catalog of new therapeutic targets (for potential investigation by the CBC) and new ways to categorize tumors in terms of those most likely to respond to specific treatments. <http://cancergenome.nih.gov>

NANOTECHNOLOGY PROGRAMS

The NCI's Nanotechnology Program is in the initial stage of product development and could provide important new platforms for the development and delivery of novel molecules discovered by the CBC. <http://nano.cancer.gov/index.asp>

CENTER OF EXCELLENCE FOR HUMAN CANCER GENETICS

Perhaps the most exciting trend in the development of new targets for oncologic therapeutics is the focus upon mutations in the human cancer genome. It is anticipated that the NCI's Division of Cancer Epidemiology (DCEG) and CCR will collaborate in the area of human cancer genetics for the selection, refinement, and prioritization of molecular targets for the CBC.



APPENDIX 4: CBC PARTICIPANT CAPABILITIES

Burnham Center for Chemical Genomics

Emory Chemical Biology Discovery Center

**Fragment Discovery Center at the
University of California-San Francisco**

Georgetown University Medical Center

The NIH Chemical Genomics Center (NCGC)

**North Carolina Comprehensive
Chemical Biology Center**

Southern Research Institute

SRI International

**The University of Minnesota
Chemical Diversity Center**

**The University of Pittsburgh
Chemical Diversity Center**

**University of Pittsburgh Specialized
Application Center (PSAC)
Facilities and Equipment**

Vanderbilt Chemical Diversity Center

BURNHAM CENTER FOR CHEMICAL GENOMICS

A COMPREHENSIVE CHEMICAL BIOLOGY SCREENING CENTER

Burnham Institute for Medical Research is one of seven NCI-designated basic research Cancer Centers. In addition, Burnham Center for Chemical Genomics participated in the pilot phase of the MLSCN during the past 3 years, and is one of four Comprehensive Centers in the production phase of the Molecular Libraries Probe Production Centers Network. Burnham's infrastructure for chemical biology and drug discovery resides in 10 core facilities that are staffed by skilled professionals with extensive pharmaceutical industry experience that encompasses the breadth of HTS assay development, chemical library screening, cheminformatics, medicinal chemistry, hit-to-lead optimization, and project management.

The 10 core facilities include: (1) *Protein Expression*, which utilizes bacteria or insect systems for large-scale protein production and chromatographic purification of multi-milligram quantities of proteins for use in screening assays or for structure determination; (2) *Assay Development*, which provides expertise and instrumentation to create and optimize high-throughput (HT) assays in a variety of formats (96-, 384-, 1536- well) and using the full diversity of assay technologies, including biochemical, cell-based, and high-content screening (HCS) assays based on multi-spectral cell imaging; (3) *Chemical Library Screening & Compound Library Management*, which provides access to an in-house ~300,000 compound library, unique natural product libraries, coupled with several fully integrated, robotic liquid handling systems for HTS and ultra-HTS in 96, 384, or 1536 well formats, representing a throughput of nearly 500,000 compounds per day at Burnham's San Diego site and with μ HTS capabilities of more than 2.2 million compounds per day at the Institute's Orlando, Florida site, which accommodates all types of biochemical, traditional cell-based assays, and

multi-spectral HCS assays using high-throughput microscopy (HTM)-based cell image analysis; (4) *In Silico Screening/Computational 3D Modeling*, which utilizes a dedicated Linux cluster, and applies docking algorithms for screening a virtual library of > 1 million compounds for hits against protein targets when a 3D structure is available; (5) *NMR*, which includes dedicated 700 MHz, two 600 MHz, and 500 MHz instruments equipped with automatic sample changers for studying interactions of chemical compounds with protein targets, along with a ~4,000 chemical fragment library for fragment-based screens, in addition to 300 MHz, 400 MHz, and 500 MHz instruments dedicated for compound structure determination; (6) *x-Ray Crystallography*, which provides robotic protein crystallization capabilities and x-ray diffractometers for determination of protein/chemical compound complexes at atomic resolution; (7) *Medicinal Chemistry*, which performs synthesis and purification of small molecules using a broad range of medicinal, combinatorial, and automated microfluidics-based chemistry approaches, encompassing 18 dedicated chemical fume hoods as well as automated compound purification systems; (8) *Data Management & Cheminformatics*, which includes relational databases, supporting software, and technical support for cheminformatics applications, with on-line access to an inventory of > 8 million commercially available compounds for structure-based searches for identifying readily available analogs of hits; (9) *Exploratory Pharmacology*, providing *in silico* ADME/Tox prediction, analytical PK and *in vitro* ADME/Tox analysis and profiling, and Rapid Assessment of Compound Exposure (RACE) and comprehensive *in vivo* rodent PK; and (10) *Functional Genomics*, with HTS of siRNA libraries that currently cover ~9K human and ~8K murine targets at 4-fold degeneracy (~32-36K siRNAs each), plus several focused libraries addressing classes of

targets, such as ubiquitin-ligases, kinases, GPCRs, proteases, and microRNAs on a genome-wide basis, and with an institutional commitment to expand to human full-genome coverage in 2009, as well as an effort underway to co-develop a large cDNA library for gain-of-function screens in partnership with a leading reagent supply company, in addition to a viral vectors core that packages shRNA and cDNA vectors as infectious lentivirus for target validation.

Burnham's scientific expertise in cancer biology is validated by our 28 consecutive years as an NCI-designated basic research cancer center. Burnham is among the world leaders in areas of fundamental interest to anticancer drug discovery, including

studies focusing on mechanisms of cell survival and cell death, cell motility, invasion and angiogenesis, and cell stress and intracellular signaling. Most notably, dedication at Burnham to apoptosis and cell death research translates into a wealth of domain-specific expertise and an abundance of unique reagents that has been applied for devising HTS bioassays for chemical library screening. With a track record of strong performance in serving a diverse user community and a team of experts with talents that span cancer biology and the entirety of target identification and drug discovery, Burnham is poised to contribute to the CBC to bridge the gap between basic scientific investigation and clinical benefits.

EMORY CHEMICAL BIOLOGY DISCOVERY CENTER

Emory University

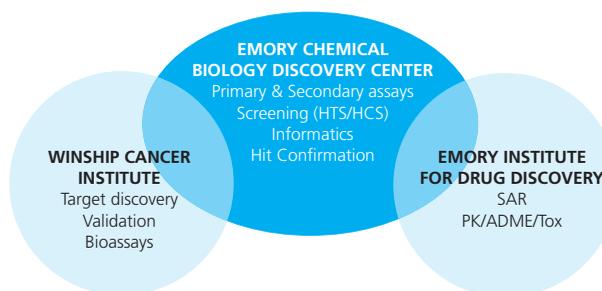
MISSION

- (i) To discover novel chemical leads targeted to disease-related proteins for research tools and therapeutics.
- (ii) To train the next generation of drug discovery scientists.

The Emory Chemical Biology Discovery Center (ECBDC) was created in 2003 to enhance Emory's capabilities in small molecule drug discovery and development. It subsequently became a node of the NIH MLSCN. Through operations with both the NIH MLSCN and Emory projects, the center has built a powerful infrastructure for high-throughput small molecule screening and subsequent hit optimization via medicinal chemistry. The ECBDC offers the state-of-the-art HTS and HCS capabilities with multiple integrated robotic systems and has access to a collection of small molecule compound libraries. These capabilities are complemented by our expertise in assay development, HTS, HCS, screeninformatics and cheminformatics, and in medicinal chemistry. The ECBDC's assay and screening expertise spans from conventional biochemical and cell-based assays and screens to state-of-the-art multiplexed assays, phenotypic imaging screening, and label-free pathway signature-based screens, with a particular strength in developing both traditional and multiplexed assays and screens for protein-protein interactions. For such a purpose, we have developed an information-rich HTS platform termed iHTS for monitoring protein complex interactions. With established infrastructure, the ECBDC provides expertise and support to drive mechanism-driven screens and hit identifications for innovative cancer agent discovery.

ORGANIZATION

ECBDC is organized around the following three functions: Assay Development and Implementation, High-Throughput Screening, and Informatics. The ECBDC is anchored by investigators within the Emory Winship Cancer Institute (WCI) and functionally integrated with drug discovery and development capabilities of the Emory Institute for Drug Discovery (EIDD). Through these partnerships, the ECBDC has access to additional resources including target identification and validation and animal models (WCI) as well as medicinal chemistry and ADME/PK analysis (EIDD), which enhance the ECBDC's ability to fulfill CBC directives.



ASSAY CAPABILITIES

The primary objectives of the Assay Program are to develop bioassays for valuable targets that can be efficiently adapted for HTS/ μ HTS or HCS operations and to develop various secondary assays for hit confirmation and optimization. ECBDC has various plate readers to accommodate different types of assay formats and readouts.

- *Multi-mode microplate readers (96/384/1536-well plate format)*
 - Absorbance
 - Fluorescence intensity
 - Fluorescence polarization (FP)
 - Time-resolved fluorescence
 - Time resolved resonance energy transfer (TR-FRET)

- AlphaScreen
Luminescence
- *Automated image readers (384/1536-well plate format)*
Automated fluorescence microscopy
- *Corning Epic Optical Biosensor System for label free detection (384-well format)*
Molecular interactions in solution
Cell-based dynamic mass redistribution
signature assays
- *FlexStation II fluorescence readers (96/384-well plate format)*
Real-time measurement of intracellular calcium and membrane potential transients
- *Guava automated flow cytometer (96-well microplate format)*
Cell cycle, apoptosis, cell proliferation, and cytotoxicity

Example assay expertise in 384/1536-well format:

- Macromolecular interactions (FP, TR-FRET, AlphaScreen):
Protein-protein interactions
Protein-RNA interactions
Multiplexing protein-protein interactions
- Cellular signaling pathway assays
Dynamic mass redistribution assay for pathway analysis (label-free optical biosensor)
Cell based cAMP/GPCR pathway assay (TR-FRET)
- Reporter assays (luminescence)
Luciferase protein functional reporters (e.g. protein folding)
Luciferase as transcriptional reporters (cell-based HTS)
- HCS assays (automated imagers)
Protein nuclear translocation assays
Whole organism imaging (e.g., transgenic zebrafish imaging)

- Angiogenesis assay (automated imager)
Angiogenesis tube formation assay
Zebrafish angiogenesis assay
- Cell viability and apoptosis (absorbance, FI, imager)
- Soft agar assay for anchorage-independent cell growth (FI, 384-well)
- Biochemical assays, including enzyme kinetics assay for enzyme modulators (FI, TR-FRET)
- Viral infection assays (cell-based FI, automated imager)

Additional established assays for secondary screens include various protein-protein interaction assays, such as protein pull-down assays, cyto blots, Western blots, ELISA, two-hybrid assays, and PCA/ Split luciferase assay. Oncology-related assays include cytotoxicity, cell proliferation, apoptosis (e.g., Annexin V staining, caspase activation, mitochondrial depolarization), cell cycle analysis, tumorigenesis, cell migration, and cell invasion assays.

SCREENING CAPABILITIES

Screening systems

We have established multiple independent, parallel robotic systems for HTS/ μ HTS/iHTS and HCS operations that are capable of handling 96-, 384-, and 1536-well plate formats. These systems accommodate a variety of assay formats and are particularly well-suited for conventional and multiplex protein-protein interactions and phenotypic screens.

- *HTS/HCS system I:* The first system features a central vertical robotic system with three outpost readers: (i) EnVision multimode reader (HTS in 96/384/1536 well format), (ii) FlexStation II agonist-injectable, 384-well fluorescence reader, and (iii) ImageXpress (HCS in 96/384-

well format). This system is integrated with a cell hotel, plate stacker, and various liquid handlers equipped with pin tools for low-volume (nL) transfer. All of these components are in an enclosed environment, facilitating live-cell HCS screens under aseptic conditions.

- *HTS/HCS system II*: The second system features the Twister II robot integrated with (i) an EnVision multimode reader (HTS in 96/384/1536-well format) and (ii) ImageXpress (HCS in 96/384/1536 well format) supported by the Sciclone liquid handling workstation.
- *System III*: Corning's Epic system for label-free molecular interaction screens provides a third platform for hit identification and confirmation by direct detection of protein-compound binding and cell-based screens under physiological conditions.

Screening expertise

The integrated robotic screening systems permit different screening platforms:

- *HTS*, biochemical and cell based high throughput screening in 384-well plate format
- μ *HTS*, biochemical and cell based ultrahigh throughput screening in 1536-well plate format
- *HCS*, cell and organism based high content screening in 384/1536-well plate format
- *iHTS*, information-rich HTS in 384/1536-well plate format
- *Biosensor-based label-free cell pathway screen in 384-well plate format*

To enhance the productivity of the HTS operation and the quality of hit discovery especially for multiprotein interactions, we have developed a number of multiplexed HTS strategies that we collectively term *iHTS* (information-rich HTS) to distinguish this format from HCS or conventional HTS. The *iHTS* format integrates multiple parameters in one well for protein-protein interaction modulator screens with the recognition that protein interactions often occur in a multiprotein complex and often with a selective member of the target protein family.

Quality Control

Agilent 6100 Series Quadrupole LC/MS is used for hit compound screening and molecular weight confirmation. The HTS team also executes quality control procedures (LC-MS, NMR, elemental analysis) on each confirmed hit that passes secondary screens to ensure the transfer of high quality hit compounds to the next phase of the project. To prevent unnecessary efforts around an impure compound, the structure and purity of hit compounds are confirmed using LC/MS, NMR, and elemental analysis when appropriate.

INFORMATICS CAPACITIES

The CambridgeSoft Enterprise software serves as the backbone of the informatics environment at the center. It provides an integrated method of analyzing HTS/HCS assay results. Tools such as Inventory Loader, Inventory Manager, BioAssay HTS, and BioSAR are used for consolidating assay results into a central database for analysis and mining. The CambridgeSoft system consists of a CambridgeSoft Web Server that contains the Inventory Manager and BioSAR tools, an Oracle database, and a proxy server that provides the network connectivity of tools such as Inventory Loader and BioAssay HTS.

Example usages include:

- BioAssay Enterprise – data reduction, data management
- BioSAR Enterprise – data presentation, result query
- Registration Enterprise – compound library management
- Inventory Enterprise – compound library management, plate management
- ChemFinder – Sd file preprocessing, report preparation
- ChemDraw – manuscript preparation, chemical query definition

Custom in-house software for project management:

- ECBDC LabView – Web-based document management, project management

ECBDC supplements HTS/HCS capabilities and expertise with predictive calculations including 2D clustering, protein-ligand molecular modeling, receptor and ligand-based virtual screening, and ADME/Tox calculations. Information derived from these calculations is used to aid medicinal chemistry efforts to choose a lead from the myriad HTS hits and guide synthetic optimization of the selected lead compounds. The molecular modeling software tools used include LeadScope, Pipeline Pilot, Glide, and QikPro.

ECBDC anchoring institutes for cancer drug discovery

Animal models and novel cancer target discovery

We have access to cancer animal models for compound testing, which include both animal imaging and conventional xenograft tumor models through our integrated interactions with programs at the WCI. Animal tumor models include lung cancer, breast cancer, prostate cancer, and head and neck cancer models. The WCI is a matrix organization that promotes and supports interactions among a diverse group of individuals from various Emory units and departments. The WCI is organized into four interdisciplinary research programs: Cancer Genetics and Epigenetics, Molecular Pathways and Biomarkers, Discovery and Developmental Therapeutics, and Cancer Control and Population Sciences. Seven shared resources support research across the continuum from basic to translational to clinical to population sciences. WCI provides depth of cancer biology for target discovery, mechanism-driven assay development for HTS and HCS, and various tumorigenesis assays for drug discovery, e.g., imaging with animal tumor models.

Preclinical drug discovery capabilities through the Emory Institute for Drug Discovery (EIDD)

The EIDD was founded to provide an organization to carry out hit-to-lead medicinal chemistry research and preclinical development. The EIDD is staffed with recognized leaders in the drug discovery arena and has extensive capabilities to perform hit-to-lead medicinal chemistry, PK profiling, *in vivo* pharmacology, and early *in vitro* and *in vivo* toxicology studies. It has the medium throughput capability for ADME/Tox and has developed sensitive and selective bioanalytical assay methodologies using a state-of-the-art LC/MS/MS system (Applied Biosystems/MDS SCIEX 3000 and 4000 Q TRAP

LC/MS/MS Systems) for the determination of analog plasma levels and the identification and characterization of metabolites. The EIDD will work closely with ECBDC in support of the NCI CBC to provide medicinal chemistry perspective for hit selection and medicinal chemistry capabilities for hit optimization to promote the identification of lead compounds for cancer drug discovery.

Contact:

Cheryl Meyerkord, PhD
Administrative Project Manager
emory-ncicbc@pharm.emory.edu

Haian Fu, PhD
Director
hfu@emory.edu

THE FRAGMENT DISCOVERY CENTER (FDC)

The FDC is a research consortium at the University of California-San Francisco (UCSF). The mission of the FDC is to bring innovative small-molecule discovery approaches to challenging targets, such as protein-protein interactions and allosteric regulation, with a strong focus on cancer. The administrative hub of the FDC is located in the Small Molecule Discovery Center (SMDC), a core facility at UCSF. Professor Jim Wells directs both the FDC and the larger core facility; Dr. Michelle Arkin is the associate director of the FDC and runs the HTS and biology groups in the SMDC.

BIOLOGY EXPERTISE

The centerpieces of the fragment-screening effort are a high-throughput surface plasmon resonance instrument, the Fujifilm AP3000, and a 3500 compound fragment library. Using HT-SPR, we are able to screen ~2000 fragments/day/target, thus completing a primary fragment screen and dose-response follow-up screen in one week. The FDC benefits from the infrastructure of the SMDC, which includes high-performance servers and database management, a 200,000-compound library, liquid handlers, and HCS. Structural biologists in the FDC consortium include NMR spectroscopists Tom James and Mark Kelly, and crystallographers Robert Fletterick and Robert Stroud.

CHEMISTRY AND INFORMATICS EXPERTISE

Computational and synthetic chemistry play central roles in fragment discovery and optimization. Matthew Jacobson, Brian Shoichet, and John Irwin use computational methods to select new fragments for each screening target, and also model binding poses for fragments that have been identified by SPR. Synthetic chemists Adam Renslo and Jack Taunton optimize fragments based on a combination of structural/modeling data and traditional medicinal chemistry. The deliverables from the fragment-discovery process are compounds with the properties of well-validated hits, directed towards challenging drug targets.

The chemical diversity center at Georgetown University Medical Center has expertise in computational modeling, synthetic and medicinal chemistry, cancer biology, and preclinical modeling.

Computational support includes:

- structure-guided modeling
- homology modeling
- ligand-based modeling, including pharmacophore-based approaches
- virtual screening resources including a >150-million compound virtual library

Our PhD chemistry expertise includes both medicinal and organic chemistry. Our medicinal chemists support:

- analog synthesis for hit-to-lead studies
- structure-activity analysis
- optimization
- development of spectroscopic ligands

Our synthetic organic chemistry supports:

- asymmetric synthesis of lead compounds
- small peptide and peptidomimetic synthesis
- library hit and standard re-synthesis
- natural product chemistry
- non-GMP scale-up (gram to kilogram)

Taking advantage of our location within the Lombardi Comprehensive Cancer Center, we have amassed a strong team of cancer biologists with expertise for specialized assays including:

- siRNA validation of targets in human cancer cells
- dose-dependent evaluation of compounds with low to medium throughput in human cancer cell lines (IC_{50} , etc.)
- compound evaluation on human cancer cell lines for effects on cell cycle, migration, apoptosis, and cell signaling (Western analysis)
- cellular chemosensitization and radiosensitization models

- cellular fluorescent imaging
- angiogenesis models (e.g., scratch assay, tube formation, aortic ring, and endothelial cell proliferation and selectivity)

Finally, our preclinical capabilities include:

- an array of mouse xenograft models
- mouse toxicity models (acute and chronic)
- state-of-the-art live animal imaging of fluorescent compounds to assist in tracking pharmacodynamic properties and drug localization
- animal histology
- human tissue distribution studies (for fluorescent compounds)

THE NIH CHEMICAL GENOMICS CENTER (NCGC)

The NCGC is an ultrahigh-throughput screening center of the Molecular Libraries Screening Center Network (MLSCN) that generates chemical probes to understand molecular and cellular functions and serve as starting points for drug development, particularly for rare and orphan diseases. Collaborating with an enormous diversity of biomedical researchers worldwide, the NCGC brings a biopharmaceutical approach to academic chemical biology, using state-of-the-art assay technologies, fully automated robotic screening, a unique screening paradigm and informatics platform, and high-throughput parallel synthetic and analytical chemistry to discover and develop probe compounds that define novel biology. The NCGC has a particular focus on developing chemical probes for currently “non-druggable” targets and pathways, and developing new paradigms for HTS, informatics, and chemistry to make probe development more efficient. NCGC’s titration-based quantitative HTS (qHTS) paradigm enables the comprehensive profiling of the biological activities and physiochemical properties of large chemical compound libraries. The long-term goal of the NCGC is to discover general principles by which small molecules and their targets interact, delineate gene/protein functions and their relationships based on small molecule interactions, and catalyze the development of new drugs for human disease by making both its data and its chemical probes available to the research community without restriction. <http://www.ncgc.nih.gov/>

The MLSCN is a consortium of HTS centers that perform biological assays submitted by the research community against the Molecular Libraries Small Molecule Repository, and perform optimization chemistry on the actives to produce chemical probes. All of the results from the MLSCN’s activities are placed into a public database called PubChem, and information about chemical probes is being made available to all researchers, in both public and private sectors, for their use in studying biology and disease.

Informatics at the NCGC include: hardware and software solutions for assay design, qHTS analysis, computational chemistry, modeling and compound management; novel algorithm and tool development; integral part of project teams, close collaboration with biologists and chemists; “build, buy, and integrate” approach to analysis systems.

NCGC’s HTS is fully automated on several state-of-the-art automation platforms, the Kalypsys and High Resolution Biology systems and includes a variety of reagent dispensing/handling devices and detectors, including: Kalypsys multichannel cell and reagent dispenser/aspirators, Dual-Kalypsys 1536-pin compound delivery systems, Aurora BioRAPTR FRD, Aurora PicoRAPTR, PE Evolution, CyBio Cybi-well and Cybi-disk TTP LabTech Acumen eX3 Explorers, GE/Amersham InCell 1000, PerkinElmer ViewLux, Tecan Safire Plate Reader, and PerkinElmer EnVision.

Chemistry at NCGC is build upon enthusiastic collaboration between all departments fostered by the project team paradigm. Academic freedom coupled with industry resources and experience means:

- Frequent interaction with scientific community, including leaders in academia and industry, access to the vast resources of the NIH, and open opportunities for publication and creativity
- Dedicated and dynamic informatics resources for efficient data analysis and visualization
- Dedicated analytical resources to ensure the highest quality of compound data
- Latest tools available for efficient parallel synthesis and strong support from engineering to automate and streamline processes

NIH Chemical Genomics Center Capabilities

| Assay Formats | Screening Capabilities | Biological Expertise |
|--|---|---|
| Absorbance | 1536-well plates; HTS (primary) and secondary screens | Enzyme assays (kinase, phosphatase, protease, etc.) |
| AlphaScreen | 1536-well plates; HTS (primary) and secondary screens | Protein-protein interaction, replacement of ELISA assay, protein-peptide interaction |
| Fluorescence Intensity | 1536-well plates; HTS (primary) and secondary screens | Enzyme assays (kinase, phosphatase, protease, beta-lactamase reporter, etc.); Receptor binding assay |
| Fluorescence Polarization | 1536-well plates; HTS (primary) and secondary screens | Protein-peptide interaction, protein-DNA/RNA interaction, kinase assay (IMAP) |
| Time Resolved Fluorescence | 1536-well plates; HTS (Primary) and secondary screens | Redox enzyme systems |
| HTRF/LANCE (FRET) | 1536-well plates; HTS (primary) and secondary screens | cAMP assay, Kinase assay |
| Luminescence | 1536-well plates; HTS (primary) and secondary screens | Enzyme assays, luciferase reporter-gene assay, cytotoxicity/ cell growth assay (ATP content) |
| Laser scanning cytometry (Acumen Explorer) | 1536-well plates; HTS (primary) and secondary screens | GFP assay, nuclear translocation assay |
| Microscopy-based imaging (INCell 1000) | 1536-well plates; secondary screen | GFP-based assays, antibody/dye staining assays |
| FDSS-7000 Kinetic Reader | 1536-well plates; HTS (primary) and secondary screens | Intracellular calcium kinetic assay (GPCRs and calcium channels), ion flux assay (ion channels), aequorin assay (GPCRs) |
| Real-time cell analyzer (Acea's impedance-based platform) | 16-well strip/96-well plate; secondary kinetic assay | Cell growth rate, cytotoxicity kinetic measurement BLS-2 level assays for infectious diseases |

NORTH CAROLINA COMPREHENSIVE CHEMICAL BIOLOGY CENTER

Stephen Frye, PI

The North Carolina Comprehensive Chemical Biology Screening Center joins together existing facilities, staff, equipment and expertise of three local partners: The University of North Carolina (UNC), North Carolina Central University (NCCU), and the Hamner Institute for Health Sciences (the Hamner). The participating research centers within these organizations possess considerable cancer research and medicinal chemistry drug discovery expertise. Specifically, the UNC Lineberger Comprehensive Cancer Center (LCCC) has a strong track record of target discovery, characterization, validation and basic oncology biology; the UNC Center for Integrative Chemical Biology and Drug Discovery (CICBDD) has expertise in assay development, computational chemistry, cheminformatics and high-throughput medicinal chemistry; and the NCCU Biomanufacturing Research Institute and Technology Enterprise (BRITE) has created a state-of-the-art HTS and medicinal chemistry group. The CICBDD and BRITE have both recruited highly experienced drug discovery scientists from the pharmaceutical industry. Additionally, the Center for Nanotechnology in Drug Delivery (CNDD) within the UNC Eshelman School of Pharmacy has capabilities for preclinical and clinical formulation development with expertise in targeted delivery and formulation of drug candidates with challenging physical-chemical properties. The Hamner is an independent, nonprofit organization that specializes in toxicology and translational research. Taken together, these organizations create a highly integrated oncology drug discovery team to contribute significantly to the NCI's vision for delivering new cancer therapeutics.

UNC LCCC – 277 total faculty – 45 faculty in molecular therapeutics program; Protein Expression Core, Structural Biology core facility, Mouse Phase 1 for drug testing in genetically engineered mouse

models of human cancer (GEMM) and RNAi facilities; 80,000 sq.ft. research and administrative building.

UNC CICBDD – 5 research and 2 tenured faculty positions supported by 12 staff scientists; extensive industry expertise and capabilities in assay development, medicinal chemistry and drug design; 100,000 compound drug-like small molecule library; 5000 member kinase inhibitor focused screening set; >5000 sq.ft. of laboratory space with cell culture and chemistry hoods (10) and equipment for assay development, screening and medicinal chemistry.

UNC CNDD – 5 faculty members focused on nanotechnology and advanced drug delivery systems to decrease attrition of drug candidates caused by poor absorption, distribution, metabolism, excretion, and toxicity; delivery approaches include, for example, micellar solubilization and nano-entrapment methodologies; >5000 sq.ft. of laboratory space with cell culture and chemistry hoods (10) to facilitate application of nanotechnology to drug formulation.

NCCU BRITE – 12 faculty members supported by 9 staff; extensive industry expertise; fully operational HTS facility with medicinal chemistry team; 52,000 sq.ft. facility opened in spring 2008; equipment and labs for both HTS and medicinal chemistry; 55,000-member drug-like small molecule library.

Hamner – 20 senior scientific staff; facilities and equipment to support preclinical *in vivo* and molecular toxicology, PK and dynamics; extensive animal model capabilities for preclinical studies; 138,000 sq.ft. of administrative and laboratory space.

Southern Research is a not-for-profit research organization that has been in operation since the 1940s. John A. Secrist III, PhD, is the president and CEO. The institute consists of three divisions: Engineering (Vice President Michael Johns), Drug Development (Vice President Andrew Penman, PhD), and Drug Discovery (Vice President Wilson Blaine Knight, PhD).

The institute is focused on the development of therapies for infectious diseases, CNS diseases (including CNS tumors), and oncology. The cancer research programs in the two life sciences divisions at Southern Research have resulted in the discovery and patenting of five FDA-approved anticancer drugs (lomustine, carmustine, dacarbazine, fludarabine, and clofarabine) and one cytoprotective agent (Ethyol) that reduces toxicities associated with cancer chemotherapy and radiotherapy. The Institute discovered these therapies and developed them through NCI-supported research and by collaborating with various pharmaceutical companies. There are additional compounds in development that originated from Southern Research. Clofarabine is a good example of a long-term lead optimization program at Southern Research that ultimately led to a drug. Clofarabine (Clolar®) is marketed by Genzyme for pediatric leukemia, and is currently being examined in clinical trials for various other indications, with adult AML being the most advanced of those indications. 4'-Thio-Ara-C, mitopterine, isophosphoramidate mustard, and PDX (pralatrexate, discovered/developed jointly among Southern Research, Memorial Sloan Kettering Cancer Center and SRI International), represent other well-known examples of Southern Research's success in cancer research. In addition, scientists at Southern Research have also evaluated approximately 50% of all FDA-approved cancer drugs currently available for patients in various studies.

The Southern Research Comprehensive Biological Center has the capabilities to identify and develop oncology drug targets (molecular, phenotypic, and pathway), develop assays, identify and optimize hits to generate candidate molecules, generate ligand-bound molecular targets, and produce the preclinical data (PK and toxicology) to progress compounds to IND applications. Southern Research has extensive experience in chemical lead optimization programs leading to chemical probes for biological systems, development candidates, and drugs on the market. The Southern Research Comprehensive Biological Center has all of the capabilities to deliver on tasks from target identification, assay development, hit identification including high throughput and "focused" screening, lead optimization, target structural studies, PK/ADME, and animal models for both safety and toxicology. We can support scale-up for animal studies and conduct early formulation work. We have a close relationship with companies for more extensive formulation work. The capabilities include both experimental work as well as predictive computational studies. We use a team approach over all of these disciplines, and our success—as measured in drugs brought to the clinic and to the marketplace—is testimony to the success of this approach. Our teams have been both internal, where we have integrated chemistry and biology successfully to find clinical candidates, and external with both commercial and academic entities.

Target Discovery, Validation, and Progression:

Southern Research has a number of internal oncology drug discovery projects. These projects have led to the development of specific cellular and *in vivo* assays such as in radiosensitization, angiogenesis, and cellular signaling. We also collaborate with the Comprehensive Cancer Center at the University of Alabama and other organizations to develop oncology targets.

The research focus of these laboratories provides many points for interactions with the NCI programs and could provide targets and/or development compounds to the Consortium. Furthermore, the oncology expertise resident in Southern Research will contribute to other CBC programs.

Hit Identification, Characterization, and

Optimization: Southern Research uses an integrated hit identification strategy. This includes not only HTS but also medium throughput screening of smaller focused or targeted sets of compounds based upon knowledge of the target, *in silico* (virtual) screening, and structure- and mechanism-based drug design.

Compound Collection: The Southern Research HTS Center currently stores and manages over 600K compounds (one 300K library, three non-overlapping 100K libraries, and several smaller libraries ranging in size from several hundred compounds to 28K). We have focused sets (for example, a protein kinase targeted set) as well as pharmacophore-based sets (such as a 3K nucleoside analog set and a natural product set). These smaller, focused libraries total approximately 32K compounds. The three 100K libraries each have smaller (3K-10K) diversity subsets. The 100K sets were selected for scaffold diversity and cluster size (using the software packages SYBYL, Pipeline Pilot, and LeadScope), as well as filtering for chemical and relevant physical properties, including reactivity, hydrophilicity, and other known biological activities that suggest that the compounds would be good drug candidates. The various sets of compounds are stored and managed in 384-well plates. In addition, Southern Research also has a solid compound repository of more than 35K compounds.

High Throughput Screening Center: Since 2000, Southern Research has invested millions of dollars in a state-of-the-art HTS Center. The Center has capabilities to screen in a wide variety of cell-based and protein-based formats including high content cellular assays (using the Evotec Opera, Luminex and Meso Scale Discovery systems). It possesses the logistics to maintain and rapidly screen 1,000,000 compounds or more per campaign and to confirm hits with counter screens and *in silico* techniques. The compound management capabilities allow Southern Research to easily import hundreds of thousands of compounds from other organizations and place them into screening assays. Our system allows us to track and limit access to proprietary compounds and thus maintain IP rights for suppliers. Furthermore, collaboration with the other biochemistry and cell biology groups allows the confirmation of compound mechanism of action and progression of compounds through secondary assays. The Center is a suite of laboratories designed for efficient screening of large compound libraries while maintaining the capacity for a wide variety of assay types. The staff within the HTS Center has in-depth experience and a demonstrated proficiency in transferring bench top assays to the robotics platform and executing cell-based and biochemical screens.

Our primary data management system is IDBS' ActivityBase7, which writes to our Oracle 10g database; we also use the LIMS system. For most of our compound related exports, ActivityBase is coupled with Accelrys' Pipeline Pilot. Pipeline Pilot allows users to create a useful workflow and also allows for additional user generated components. Compound data stored in our system can be queried and exported in a variety of formats. SD files are the most common format used to transfer structural data; however we are capable and accustomed to

working with our collaborators to identify other suitable formats (delimited text, Excel files, etc.) where applicable.

Medicinal, Structural and Computational

Chemistry: The Organic Chemistry Department currently has a large staff of senior chemists, bench-level synthetic chemists, chemistry support personnel, structural chemists, and computational chemists. Our approaches to hit characterization and optimization vary depending upon the nature of the screen, the quality of the data, and background knowledge of the particular hit including the cluster size (number of related compounds that are active). Typically, minimal characterization of confirmed hits would include mass spectrometric, NMR spectroscopy, and HPLC analysis, and comparison with a freshly purchased or prepared sample. Resynthesis is the definitive confirmation of hit structure. Once a decision is made to consider chemical optimization, we employ a team approach, blending bioinformatics, computational chemistry, structural biology, and iterative synthesis to systematically identify the structural features of the molecule that contribute to activity. Synthetic target compounds and libraries for follow-up screening are selected by cluster analysis (Distill in SYBYL, ChemTree, Pipeline Pilot, LeadScope), and common structural elements among the actives are identified and their relevance to activity evaluated using various criteria known to increase the likelihood of relevant biological activities. Privileged scaffold cluster members as well as active singletons are aligned to maximize the overlap of such atom groups to develop pharmacophore model(s) through the application of software tools such as Discotech, Galahad (SYBYL), and Search/Compare (InsightII). Analog searches include substructure and similarity-based methods as well as pharmacophore-based 3D searches of available compound databases. To

facilitate database searches we have generated in-house 3D databases totaling approximately 3.4 million commercially available compounds, complementing Zinc and other public databases. Where experimentally derived protein structures of screening targets are available for screening targets, X-ray/NMR structures of the target and its ligand-binding pocket are evaluated, along with other targets amenable to homology modeling. In such cases, we perform docking and scoring predictions using Glide, Autodock, Gold, and LigandFit, and multiple scoring functions are employed to evaluate predicted ligand binding. The computational group also conducts virtual screening, virtual toxicology, and QSAR.

Thus, proposed synthetic targets will have been analyzed for a variety of relevant physical properties, such as drug-likeness (as one measure of biological relevance), reactivity, hydrophilicity, other known biological activities, and, in the case of second generation libraries, overall chemical diversity of the new compounds within the structural context of the identified hit and previously screened agents. Later in the optimization process, prodrug strategies will be employed if appropriate, and we will always remain mindful of pharmacokinetic, metabolic, and other issues that may redirect the synthetic program. A laboratory dedicated to large-scale (up to hundreds of grams) synthesis of intermediates and final targets is also available.

PK/ADME: To more efficiently select chemical series for further optimization, Southern Research has implemented a rapid PK program (“PK-kwik”) to select compounds with the most desirable PK properties early in the design cycle. The center has extensive experience in all of the preclinical studies required to file an IND. These include ADME/DMPK, toxicology, bioanalysis, and animal and cellular

efficacy models for oncology. In addition, the center uses *in silico* models to predict the “developability” of compounds. The center currently utilizes several software packages such as the ADMET Collection in Pipeline Pilot, Discovery Studio, QikProp in Schrödinger, and VolSurf as implemented within SYBYL. The ADMET Collection provides capabilities to predict many properties, including aqueous solubility, human intestinal absorption, blood-brain barrier penetration, plasma protein binding, cytochrome P450 2D6 inhibition, and hepatotoxicity. The QikProp module of Schrödinger provides additional predictive capabilities, including aqueous solubility, Caco-2 Cell permeability, human oral absorption, blood-brain barrier permeability, skin permeability, serum albumin binding, and hERG inhibition. The ADMET models included in VolSurf cover aqueous and water-DMSO solubility, Caco-2 permeation, blood-brain barrier permeability, biopharmaceutical classification, protein binding, volume of distribution, hERG inhibition, and CYP3A4 metabolic stability. Other modeling packages provide additional functionality. We recognize the limitations of software models and, where possible, employ multiple algorithms to compare predictions.

The small animal imaging facility at Southern Research will contribute to the Cancer Imaging Program to both facilitate progression of compounds through animal studies as well as provide the potential for the translation of these technologies to human clinical trials and FDA approval. The center also provides bioanalysis data for samples from clinical studies.

Southern Research’s Information Technology System Support Group:

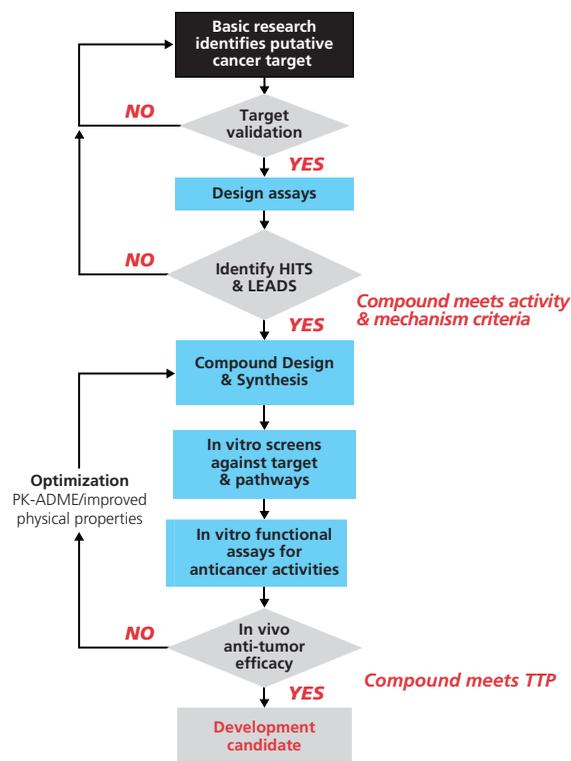
Our Information Systems department is a centralized group that provides a wealth of experience to support the computational, data storage, and transfer needs of Southern Research Institute. The group has technical expertise in network support, database administration, ERP, security, 21 CFR Part 11 compliance, validation, and document management/control.

SRI International is an independent nonprofit research and development organization with decades of experience in successfully identifying, developing, and advancing novel compounds from “Idea to IND.”

SRI's Center for Cancer Research (CCR) is dedicated to the fight against cancer through the discovery and development of innovative therapies to alleviate patient suffering and save lives. Composed of biologists and medicinal chemists with expertise in fundamental and applied cancer research, SRI's CCR is focused on the study of the tumor microenvironment, tumor metabolism, and aberrant signaling pathways that cause cancer. Through collaborative partnerships, the Center has been successful in generating an extensive drug pipeline translating discoveries into beneficial treatments. The Center has one drug on the market (bexarotene, Targretin®) and another in the FDA approval process (pralatrexate, PDX®). In addition, SRI's CCR has advanced several drug candidates into clinical trials and is investigating multiple innovative discovery programs in earlier stages of R&D.

SRI's Comprehensive Chemical Biology Screening Center (CSC), together with its Chemical Diversity Center and Specialized Assay Center offers integrated processes that will advance ideas from basic research into preclinical development. These include: identification and validation of novel targets, development and implementation of biochemical and cell-based screening assays, identification of hits, selection of leads guided by targeted and functional assays, exploration of SAR with medicinal chemistry, and lead optimization through iterative cycles of testing for drug-like properties and potency.

To accelerate the drug discovery process, SRI works with BioComputing Group, Inc., using computational screening, hit-to-lead, and lead optimization tools with particular emphasis on structure-guided drug discovery. The best candidates will be tested in mouse models of human cancer (xenograft models). PK/ADME tests will also be conducted and chemical/physical properties will be measured. Specialized assays, such as multilayer cell cultures and tumor spheroids will be used to evaluate effects of tumor-like microenvironments on the efficacy of experimental therapies, including radiotherapy, chemotherapy, and rational combinations. Novel compounds will be designed, synthesized, and screened in an iterative process until compounds are identified that meet the Target Product Profile, and from these, candidates for preclinical development will be selected.

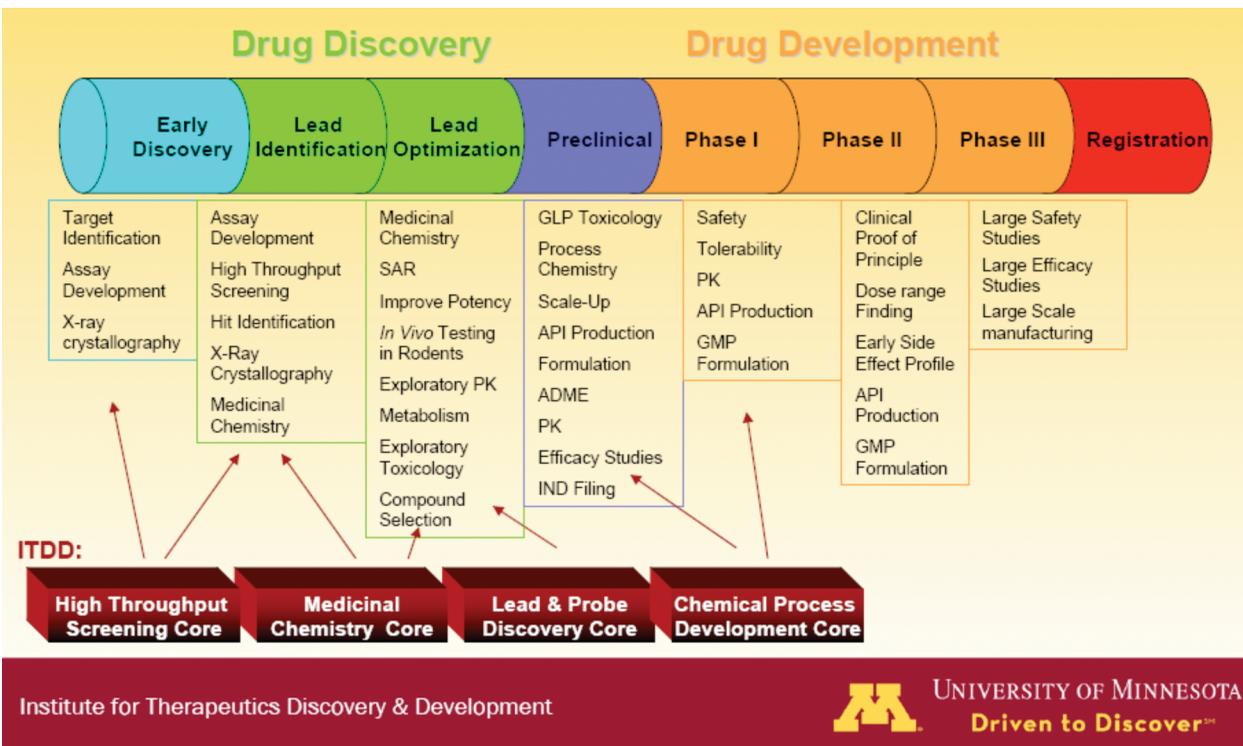


UNIVERSITY OF MINNESOTA CHEMICAL DIVERSITY CENTER

Director: Dr. Gunda I. Georg

The University of Minnesota Chemical Diversity Center is based primarily on the capabilities of the Institute for Therapeutics Discovery and Development (ITDD) and the Department of Medicinal Chemistry in collaboration with the NCI-designated Masonic Comprehensive Cancer Center, the College of Pharmacy, the Center for Translational Medicine, and the Minnesota Supercomputing Institute. The University of Minnesota Chemical Diversity Center's research focus is the discovery and development of anticancer agents, using state-of-the-art chemical, biological, computational, pharmacological and imaging approaches. Its mission is to become an effective partner in the NCI's effort toward innovative cancer therapeutics discovery.

Drug Discovery Expertise in Synthetic Medicinal Chemistry, Computer-Aided Drug Design (CADD), and Structural Biology: The expertise of the University of Minnesota Center includes strong synthetic medicinal chemistry capabilities coupled with expertise in computer-aided drug design, molecular modeling and visualization, and experimental structural biology to fully exploit structural information in the selection and optimization of chemical series for lead development. The capabilities of the CADD/molecular modeling group include docking, pharmacophore mapping, library refinement, and QSAR formulation to guide efficient compound optimization. The structural biology group can characterize compound-target molecular interactions based on X-ray crystallographic data. The synthetic capabilities include state-of-the-art parallel synthesis and high-throughput purification systems that allow rapid synthesis and purification of chemical libraries.



The Chemical Process Development facility allows the synthesis of lead molecules, drug candidates and advanced intermediates (mg to kg), chemical process development and optimization, scale up, and analytical method development. Small molecules, cell- and protein-therapeutics can be prepared under cGMP conditions for preclinical investigations and Phase I clinical trials in the University of Minnesota Molecular and Cellular Therapeutics facility.

Screening and Assay Development Expertise:

The High-throughput Screening Laboratory provides rapid automated screening of large number of chemical compounds against various biological targets. The facility carries out assay development and screening using biochemical and cell based assays, including HCS and the development of secondary assays. The facility's unique capabilities include a) the Caliper LabChip LC3000 microfluidic assay system that can profile the activity of compounds over the human kinome to assess selectivity. The LC3000 can also be used as an HTS platform for the identification of kinase and protease inhibitors; b) the FLIPR Tetra for assay and screening GPCRs; c) the Meso-Scale Discovery Electrochemiluminescence assay system that can be used for multiplexed ELISA assays and ligand-ligand interaction targets; and d) the BD-Atto Pathway 855 confocal high-content imaging system used for secondary assays for compound mechanistic profiling. The chemical library available for screening at the ITDD consists of a 200,000-compound commercial library. Additional small focused libraries of peptidomimetics, natural products, and current drugs are also available for screening.

Drug Development Capabilities: The Cancer Center, the College of Pharmacy, the Center for Translational Medicine and The Clinical and Translation Science Institute (CTSI) provide support for drug development, regulatory requirements, clinical trials, and data analysis. Available are animal models of cancer, preclinical testing support for small molecule-, cell-, protein-, tissue-based, and combination therapies. These include drug formulation, in vivo preclinical efficacy studies, safety pharmacology, preliminary toxicology, PK and metabolism studies, and help with the design and execution of clinical trials. In vivo high field magnetic resonance imaging of animals is available through the Center for Magnetic Resonance Research. GMP toxicology is under development in the Experimental Surgical Services (ESS) laboratories.

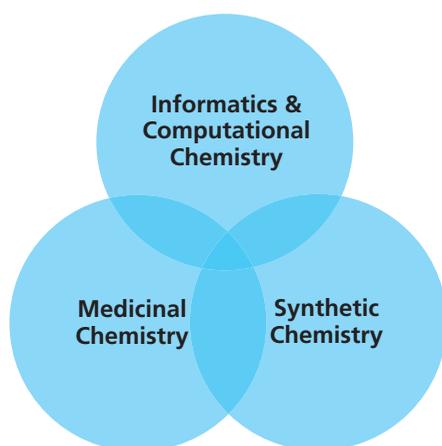
THE UNIVERSITY OF PITTSBURGH CHEMICAL DIVERSITY CENTER

Chemistry-Driven Drug Discoveries

The University of Pittsburgh Chemical Diversity Center (UP-CDC) takes advantage of the capabilities and expertise that reside in the Informatics & Computational Chemistry, Medicinal Chemistry and Synthetic Chemistry Cores of the University of Pittsburgh Drug Discovery Institute (UPDDI) and the University of Pittsburgh Center for Chemical Methodologies and Library Development (UPCMLD). Specifically, we have capabilities, experience and expertise in ChemInformatics, synthetic methodology, computational chemistry, laboratory automation, library synthesis, library QC, medicinal chemistry, natural products chemistry, organic synthesis on milligram to multi-gram scale, pharmaceutical properties (ADME/Tox) analysis and optimization, structure-based drug design, and drug discovery and development. We have in place protocols for hit/scaffold assessment, triage, and optimization; library purification by mass-guided LC/MS and QC analysis, including heavy metal content by ICP-OES, lead optimization for potency, selectivity and pharmaceutical properties; and identification and development of clinical candidates. We have a strong tradition of collaborative research with internal as well as external scientists that have resulted in significant scientific contributions in the areas of chemical biology and drug discovery and to the advancement of nearly 40 small molecules into clinical trials, as well as to the discovery and development of two marketed cancer drugs.

Three cores comprise the UP-CDC. The **Medicinal Chemistry Core** is led by the PI, Professor Donna Huryn, and contributes to hit validation and triage; hit-to-lead activities; the design and synthesis for SAR and Structure-Property Relationships (SPR) development (e.g., lead optimization); design and synthesis of analogs to address ADME/Tox deficiencies; and the preparation of labeled versions of lead compounds. The **Synthetic Chemistry Core** has responsibility for synthesis route selection and methodology development; library synthesis; natural product chemistry; analytical chemistry support; compound storage, handling and shipping; and scale-up synthesis. Professor Peter Wipf leads the Synthetic Chemistry Core. The **Informatics & Computational Chemistry Core**, led by Dr. Gabriela Mustata, has state-of-the-art capabilities in cheminformatics, virtual screening, pharmacophore modeling, quantitative SAR (QSAR); quantitative SPR (QSPR); *in silico* ADME and Toxicology model development and prediction; *in silico* library enumeration and diversity analysis, library design, docking, and scoring; and structure-based drug design. Even though we have assigned specific activities to each core, all three cores work collaboratively.

- Chem-informatics
- Virtual screening
- Pharmacophore modeling
- QSAR/ QPSR
- *In silico* ADME/Tox modeling and prediction
- *In silico* library enumeration and diversity analysis
- Library design and docking
- Structure-based drug design



- Hit validation and triage
- Hit-to-lead activities
- Design and synthesis for SAR and SPR development
- Metabolite identification
- Microsomal stability
- Pro-drugs and targeting
- Design to address ADME/Tox deficiencies
- Labeled probes/analogs
- Mechanism of action studies

- Synthesis methodology and route development
- Library synthesis
- Natural products chemistry
- Analytical chemistry
- Compound libraries
- Compound storage, handling, and shipping
- Library QC analysis
- Scale-up synthesis
- Small molecule screening libraries

CORES OF THE UP-CDC: Key Affiliations

University of Pittsburgh Center for Chemical Methodology and Library Development (UPCMLD)

The membership of the UPDDI Chemistry Core overlaps and synergizes with that of the UPCMLD. The UPCMLD was established in 2002 as one of the original two centers funded by NIH, and was reselected in the fall of 2008 as one of the five new centers funded through the second grant period (2008-2013). It is a leader in the development of novel chemical methodologies and their application to library synthesis, as well as in synthesis automation and library purification; since 2002, UPCMLD scientists have published >150 papers on these topics. To date, the UPCMLD Diversity-Oriented Synthesis (DOS) Core has completed the production of 23 novel libraries, comprising >3,000 individual compounds. While the primary focus of the UPCMLD is on the development of new synthetic methodologies, we have always pursued an active and highly successful biology outreach program that has led to the identification of novel biological probes from UPCMLD libraries. For example, the UPCMLD developed the first selective probe of the heat shock protein, HSP70. Subsequent optimization libraries based on the structure of this probe have generated additional novel agents that are currently being evaluated in models of malaria, cancer, and *T. brucei* infection. In addition, a probe of MKP-1 was identified from a CMLD library compound.

University of Pittsburgh Drug Discovery Institute (UPDDI)

UPDDI is committed to identifying small molecules that can be used as chemical probes for biological activities and as leads for new therapies for human diseases. The UPDDI uses the latest advances in

scientific understanding of cell signaling processes and disease states, laboratory automation and compound storage/retrieval, data management, combinatorial chemistry and diversity-oriented synthesis as a foundation for its drug discovery efforts. The Institute is a model of collaboration, comprising faculty members from three schools at the University of Pittsburgh, housed in a recently built research facility. It is in the unique position to balance academic research flexibility with industrial compound screening and development efficiency.

University of Pittsburgh Cancer Institute Molecular Therapeutics and Drug Discovery/Development Program

The UPDDI is closely linked with the University of Pittsburgh Cancer Institute (UPCI), which is an NCI-designated Comprehensive Cancer Center. The UPCI has more than 625 research faculty members specializing in disciplines ranging from cancer prevention and early detection to novel therapeutic discovery, survivorship, and end of life care. The Molecular Therapeutics and Drug Discovery/Development Program (MT/DD) based in the UPCI promotes interactions of basic, preclinical, and clinical researchers to develop innovative approaches to drug treatment. The program comprises a multidisciplinary group of scientists committed to making basic laboratory observations about therapeutic targets and potential strategies, exploring their feasibility in preclinical models, and translating the most promising approaches and molecules into the clinical setting. The MT/DD Program has focused on establishing a strong basic science foundation for the development of small molecule anti-cancer agents and novel therapeutic approaches to malignancy.

UP-CDC Expertise in Target Class, Compound Class/Scaffolds, Chemistries & Technologies

| | |
|--|--|
| Target Classes | ABC Transporters, Anti-metabolites, Cell Cycle Inhibitors, Cell Adhesion Molecules, GPCR's, Heat Shock Proteins, Hormone Receptors, Ion Channels, Kinases, Microtubule Stabilizing Agents, & Destabilizing Agents, Mitochondrial Targeting, Nucleic Acid Binding Proteins, Oncogenes, Phosphatases, Polymerases, Proteases, Protein-protein Interactions Reverse Transcriptase, ROS-Scavenging, Steroid Receptors, Transporters, Whole Organism Assays, Zebrafish Assays |
| Compound Classes/ Scaffolds | Amino Acids, Amino Acid Isosteres, Azepines, Azoles, Carbohydrates, Ceramides, Imidazoles, Indoles, Marine Natural Products, Peptides, Natural Products, Nucleic Acids, Nucleosides, Oxazoles, Peptide Isosteres, Peptidomimetics, Piperidines, Pyrrolidines, Steroids, Terpenes, Thiazoles, Thiolactones, Thiophenes |
| Chemistries | Cascade Radical Reactions, Heterocyclic Chemistry, Multi-component Reactions, Natural Product Total Synthesis & Semi-synthesis, Organometallic Reactions, Peptide Synthesis, Pericyclic Reactions, Transition Metal Catalyzed Reactions |
| Technologies | Automation, Flow Reactor Chemistry, Fluorous-phase Synthesis, ICP-ORS for Trace and Heavy Metal Analysis, Library Synthesis, Mass-directed Preparative HPLC, Microwave Chemistry, Solid-phase Organic Synthesis, Solid-phase Peptide Synthesis, Photoaffinity Labeling, Radiolabelling, Analytical and Preparative Supercritical Fluid Chromatography, Trace Metal Analysis |
| Computational Chemistry Capabilities | Ligand-based Design (GALAHAD, Tuptlets, Topomer CoMFA, QSAR, VolSurf and Almond/Tripos, QuaSAR, Pharmacophore Discovery/MOE); Structure-based Design (SurflexDock and CScore/Tripos, LigX/MOE); Cheminformatics (Topomer Search, UNITY Base, Unity 3D, CONCORD, StereoPlex/Tripos); Virtual Library Design and Analysis (CombiLibMaker/Legion, Selector, Diverse Solutions/ Tripos, MOE); Protein-protein Interactions (ClusPro, SmoothDock, FastContact); Homology Modeling (Modeller and Consensus); Diversity Analysis (Principle Component Analysis, Chem GPS); Property Prediction (QikProp, ADMET Predictor) |
| Other Capabilities | Microsomal Stability, Metabolite Identification, Mechanism of Action Studies, Pro-drugs and Drug Targeting |

UNIVERSITY OF PITTSBURGH SPECIALIZED APPLICATION CENTER (PSAC) FACILITIES AND EQUIPMENT

HTS & HCS Facility: The UPDDI HTS/HCS facility occupies 2,400 ft² of laboratory space on the 9th floor of the recently constructed Biomedical Science Tower-3 (BST-3). Included in this research space are: the main HTS facility room (1,200 ft²); a dedicated HCS laboratory (412 ft²); a dedicated assay development laboratory (414 ft²); 2 fully functional tissue culture rooms (100 ft² each); one room (201 ft²) for HTS reagent preparation, to house the liquid nitrogen cell store, and HTS consumables storage; and 2 offices (120 sq. ft. each).

Compound Storage and Retrieval: To provide secure storage at -20°C and to maintain the integrity of our compound libraries the UPDDI uses a Matrical MatriMinistore™ with 3 VLM modules to provide automated compound storage and retrieval. The system has a capacity for 12,900 384-well plates, ~ 4.95 M compounds.

Zebrafish Facility: The PSAC has access to 11,000 zebrafish tanks in a fully automated facility for use in compound screening and secondary assay development.

Automated Liquid Handlers for Compound Handling and Assay Implementation: (2) Biomek 2000 automated liquid handling systems, (1) Velocity 11 V-prep liquid handling system with 96-well and 384-well transfer heads, (1) Velocity 11 Bravo liquid handling system with 384-well transfer head, (1) Perkin Elmer Multiprobe 8-Tip with a 16 plate deck configuration liquid handling system outfitted with (1) dual 50-plate magazine plate stacker (1) Perkin Elmer Evolution EP3 liquid handling system equipped with both 96-well and 384-well transfer heads and

(2) dual 50-plate magazine plate stackers, (1) Perkin Elmer Janus Multiprobe 8-Tip with a 24 plate deck configuration liquid handling system outfitted with (1) dual 50-plate magazine plate stacker, (1) Perkin Elmer Janus MDT liquid handling system equipped with both 96-well and 384-well transfer heads integrated with an Abgene automated plate sealer and outfitted with (2) dual 50-plate magazine plate stackers, (1) Titertek Zoom dispenser outfitted with (1) dual 50-plate magazine plate stacker, (1) Titertek MAP-C2 plate washer and reagent dispenser outfitted with (1) dual 50-plate magazine plate stacker, (1) Molecular Devices AquaMax DW4 96- and 384-well plate washer and reagent dispenser integrated with the Synchromax ET plate handler, (1) Perkin Elmer FlexDrop IV reagent dispenser with 50-plate stacker capacity, (1) Perkin Elmer Unifilter-96 Harvester, (2) Biotek Elx405 Plate Washers with (2) dual 25-plate magazine plate stackers, (1) Biotek Microflo Bulk Reagent Dispenser with (1) dual 50-plate magazine plate stacker.

The V-prep, Bravo, EP3 and Janus MDT robotic liquid handling platforms are each equipped with 96-well and 384-well transfer heads that are used for replicating compound master plates, preparing compound daughter plates, transferring diluted compounds to assay plates, adding reagents to assays plates, adding controls to assay plates, and serially diluting compounds for IC₅₀/AC₅₀ determinations. The Multiprobes and Biomek 2000 automated liquid handling systems are used to cherry pick active compounds from compound libraries, reformat compound libraries, and to serially dilute compounds for IC₅₀/AC₅₀ determinations. The Zoom, MAP-C2, AquaMax DW4, and Microflo bulk reagent dispensers are utilized for adding buffer to compound plates and reagents or buffers to assay plates. The Zoom, MAP-C2 and Microflo dispensers are also utilized for automated cell seeding into

96- and 384-well plates. The MAP-C2, AquaMax DW4 and Elx405 (Biotek) plate washing platforms are utilized for automating HCS and ELISA assay formats; cell fixation, cell permeabilization, blocking buffer addition, and plate washing.

HTS Detection Instruments: The UPDDI has (3) Molecular Devices SpectraMax M5 plate readers integrated with dual 40-plate magazine StackMax plate stackers, (1) Molecular Devices Flexstation III kinetic microtiter plate reader, (1) Perkin Elmer EnVision multilabel plate reader with AlphaScreen capability with dual 50-plate magazine plate stackers, (1) Perkin Elmer 96-well 2-detector Topcount scintillation and luminescence counter. The M5, Flexstation III and Envision detection platforms are all multimode detection instruments; absorbance, luminescence, fluorescence intensity, fluorescence polarization, time resolved fluorescence, and time resolved fluorescence resonance energy transfer.

HCS Detection Instruments: The UPDDI has four HCS automated imaging platforms; the ArrayScan 3.5 and ArrayScan VTI (AS-VTI) are field based imaging platforms, and the two ImageXpress Ultra (IXU) platforms are confocal imagers. The ArrayScan® VTI houses a Zeiss 200M inverted fluorescence microscope outfitted with selectable 5x/0.25 NA, 10x/0.3NA, 20x/0.4 NA and 40x/0.5 NA Zeiss objectives. Illumination is provided by a full spectrum (300-2000 nm) Hg-halide arc lamp source (EXFO, Quebec, Canada) and fluorescence is detected with a high sensitivity cooled Orca CCD Camera (Photometrics Quantix). The ArrayScan VTI uses an image-based auto-focus system, and using a fast excitation filter wheel combined with a multi-band emission filter it can image up to six fluorescence channels excited and acquired sequentially. The IXU platforms are fully-integrated point-scanning confocal imaging systems with four

solid-state lasers providing up to 4 simultaneous excitation wavelengths (405, 488, 532 or 561, 635 nm) each with a dedicated photomultiplier tube for detection. Images in each fluorescent channel may be acquired sequentially, or with the correct combination of fluorescent probes and filters may be acquired in parallel. The IXU utilizes a dedicated high-speed laser auto-focus system, has a 4-position automated objective changer with air objectives (10x, 20x, 40x & 60x), and the detection pinhole diameter of the confocal optics is configurable in the software.

Robotic Plate Handlers: (1) Zymarker Twister I plate handler, (1) Molecular Devices Synchromax ET plate handler, (1) Caliper Twister II plate handler, all operated with iLink control software. (1) CRS Catalyst Express plate-loading robot operated by Polaris control software.

Servers, Network and Data Backup Systems:

The UPDDI network has 9 servers: (2) Dell PE 1850's Domain controller servers; (1) Dell PE 2850 Windows file server with 8 GB memory and two Dual Core 2.8GHz/2MBx2 CPUs; (1) Dell PE 2850 Oracle Database and IDBS ActivityBase® LIMS server with 8 GB memory and two Dual Core 2.8GHz/2MBx2 CPUs; (1) Dell PE2950 server with 4GB memory and two Dual-Core 2.0 GHz/1333 MHz FSB/4MB Cache CPUs attached to a 6TB SATA disk storage to house the a ArrayScan IV Cellomics Store™ database; (1) Dell PE2950 server with 16 GB memory and two Quad Core 66GHz/1333MHz FSB/4MBx2 Cache CPUs with 16TB SAN storage to house the ArrayScan VTI Cellomics Store database; (1) high-performance Dell 2950 application server with four analysis engines and two high-speed quad-core CPUs to house the Definiens image intelligence suite; (2) Dell PE2850 server with 4 GB memory and two Dual Core 2.8GHz/2MBx2 CPUs to house

one PubChem raw data FTP/WEB server to provide the public access to the raw data and images from MLSCN screening campaigns completed by PMLSC. A scalable EMC CX300 Storage Area Network (SAN) solution has been deployed and upgraded to be the central data warehouse with 50 TB of formatted storage configured with 7 TB of high performance fiber channel disk storage, and 43TB of SATA disk storage. The SAN is connected to a PowerVault™ PV-124T tape drive with a 16 slot tape library for data backup and recovery.

The UPDDI network provides a secure environment for capturing, analyzing, storing, and sharing the large volume of data and information acquired during an HTS/HCS campaign. The data and information backup to tape provides a secure source and location for data recovery should it be necessary.

LIMS and HTS/HCS Analysis Software: The UPDDI has (3) IDBS ActivityBase LIMS Biology seats, (3) IDBS XE Seats (3) IDBS XLfit seats, (2) IDBS ActivityBase Chemistry seats, (1) IDBS Protocol Transfer Assistant, (7) IDBS SARview seats, (10) Spotfire® data visualization licences, (3) Leadscope Enterprise 2.4. 15-6 Chemical Structure analysis software seats. Cellomics platinum package of Bio-Application image analysis algorithms (V2 & V3) for their ArrayScan® imaging platforms; Cell Cycle, Cell Health Profiling, Cell Motility, Cell Spreading, Compartmental Analysis AS, Cyto-Cell Membrane, Cyto-Nuc Translocation, Extended Neurite OG, GPCR Signaling, Micronucleus, Molecular Translocation, Morphology Explorer, MP Cytotoxicity, Neuronal Profiling, Neurite Outgrowth, Spot Detector, Target Activation, and Tube Formation. (3) vHCS Discovery Toolbox and (3) vHCS View licenses. Molecular Devices ImageXpress application and informatics software package with (10) MetaXpress and AcuityXpress

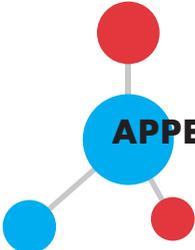
licenses and the parallel computation Cephalopod package. The ImageXpress Ultra imaging platform also has a portfolio of image analysis modules; Cell cycle, Angiogenesis Tube formation, Granularity, Mitotic Index, Multi-wavelength Cell Scoring, Multi-wavelength Translocation, Neurite Outgrowth, Nuclear Translocation, Transfluor, Translocation, and Translocation enhanced. Definiens image intelligence suite for custom image analysis includes; (1) developer, (1) architect, and (1) Cellenger license with (4) data analysis engines.

The UPDDI has deployed the industry standard ActivityBase 7.0 LIMS from IDBS to register compound libraries, manage the compound inventory, and process and upload the HTS compound and bioassay data from detection instrument platforms into the UPDDI Oracle database. The UPDDI has added three XE modules to the existing clients to support and accelerate HTS/HCS data analysis, permit 1536-well and other template building, and data processing. The Vitesse software and inventory module, which controls the Matrical Ministore automated compound storage and retrieval system has been integrated with ActivityBase. XLfit is used to fit curves for concentration dependence (IC50/EC50) assays. SARview 6 is used to query the database and generate HTS data reports containing the required chemical and biological information. The Spotfire DecisionSite 9.1 package provides the project team with data visualization tools for quality control and data analysis. The Leadscope Enterprise 2.4.6-1 software provides structure-based classification and clustering of the active compounds identified in primary screens and/or follow up assays based on recursive partitioning. Co-investigator Dr. Tong Ying Shun has developed two custom software packages, APAC Reporter and Cytominer, to generate specific UPDDI data reports.

VANDERBILT CHEMICAL DIVERSITY CENTER (VCDC)

Alex Waterson and Gary Sulikowski, co-PIs

The Vanderbilt Chemical Diversity Center (VCDC) provides a full range of chemistry capabilities needed for drug discovery and development. This includes custom synthesis of known and unknown compounds, synthesis of compound libraries, lead optimization, large-scale synthesis, and compound purification. Medicinal chemistry support includes in vitro screening for and optimization of ADME/DMPK properties, and preliminary compound formulation studies. The VCDC also provides expertise in natural product extract isolation, purification, and characterization in addition to semi and total synthesis of complex natural products and their analogs. In silico support comprises similarity searches for compound identification and prediction of ADME and toxicologic properties, generation of quantitative SAR models to predict biological activity from chemical structure, and structure-guided compound design based on crystal structure of target proteins when available. The VCDC possesses a 180,000- compound library, approximately 96% of which was obtained from ChemDiv and ChemBridge, using a Lipinski filter to select a structurally representative sample of those larger compound collections. The remaining 4% of compounds include unique structures synthesized at Vanderbilt, and a growing collection of natural products isolated and/or synthesized by Vanderbilt researchers or obtained through collaborations with the University of Alabama-Huntsville, MIT, and the University of Mississippi. The compound library is currently growing at a rate of about 3,000 compounds a year from all of the above sources.



APPENDIX 5: ACRONYMS LIST

| | |
|-------|---|
| ABCC | Advanced Biomedical Computing Center |
| ARC | Administrative Resource Center |
| ATP | Advanced Technology Program (NCI-Frederick) |
| BDP | Biopharmaceutical Development Program (DTP, NCI) |
| BOA | Basic Ordering Agreement |
| BRB | Biological Resources Branch (DTP, NCI) |
| BTB | Biological Testing Branch (DTP, NCI) |
| CBC | Chemical Biology Consortium |
| cGMP | Current Good Manufacturing Practices |
| CIP | Cancer Imaging Program (DCTD, NCI) |
| CCR | NCI Center for Cancer Research |
| CTEP | Cancer Therapy Evaluation Program (DCTD, NCI) |
| DCEG | NCI Division of Cancer Epidemiology and Genetics |
| DCTD | NCI Division of Cancer Treatment and Diagnosis |
| DS&CB | Drug Synthesis and Chemistry Branch (DTP, NCI) |
| DLT | Dose-limiting toxicity |
| DTP | Developmental Therapeutics Program (DCTD, NCI) |
| DTS | Developmental Therapeutics Section (CCR, NCI) |
| eNExT | Application submission Web site for the NExT program |
| FCRDC | Frederick Cancer Research and Development Center |
| GLP | Good laboratory practice |
| GMP | Good Manufacturing Practices |
| HCS | High-content screening |
| HTS | High-throughput screening |
| IND | Investigational new drug |
| IP | Intellectual property |
| IT | Information technology |
| LASP | Laboratory Animal Sciences Program (NCI-Frederick) |
| LHTP | Laboratory of Human Toxicology and Pharmacology (NCI-Frederick) |
| MCGP | Mouse Cancer Genetics Program (NCI-Frederick) |
| MLSCN | NIH Molecular Libraries Screening Centers Network |
| MOA | Mechanism of action |
| MTD | Maximum tolerated dose |
| NCE | New chemical entity |
| NCGC | NIH Chemical Genomics Center |
| NCI | National Cancer Institute |
| NCTVL | National Clinical Target Validation Laboratory (DCTD, NCI) |

| | |
|--------|--|
| NED | NCI Enterprise Directory |
| NEXT | NCI Experimental Therapeutics Program |
| NHGRI | National Human Genome Research Institute |
| NPB | Natural Products Branch (DTP, NCI) |
| PADIS | Pharmacodynamic Assay Development and Implementation Section (NCI-Frederick) |
| PD | Pharmacodynamics |
| PK | Pharmacokinetics |
| PMO | DCTD Project Management Office |
| PRB | Pharmaceutical Resources Branch (DTP, NCI) |
| SAC | Senior Advisory Committee |
| SAIC-F | Science Applications International Corporation-Frederick (NCI Contractor) |
| SAIP | Small Animal Imaging Program (NCI-Frederick) |
| SAR | Structure-activity relationship |
| SEP | Special Emphasis Panel |
| SMC | Senior Management Committee |
| SOP | Standard operating procedure |
| SPR | Structure-property relationship |
| TCGA | The Cancer Genome Atlas |
| TPB | Toxicology and Pharmacology Branch (DCTD, NCI) |
| VPN | Virtual private network |



NATIONAL[®]
CANCER
INSTITUTE
