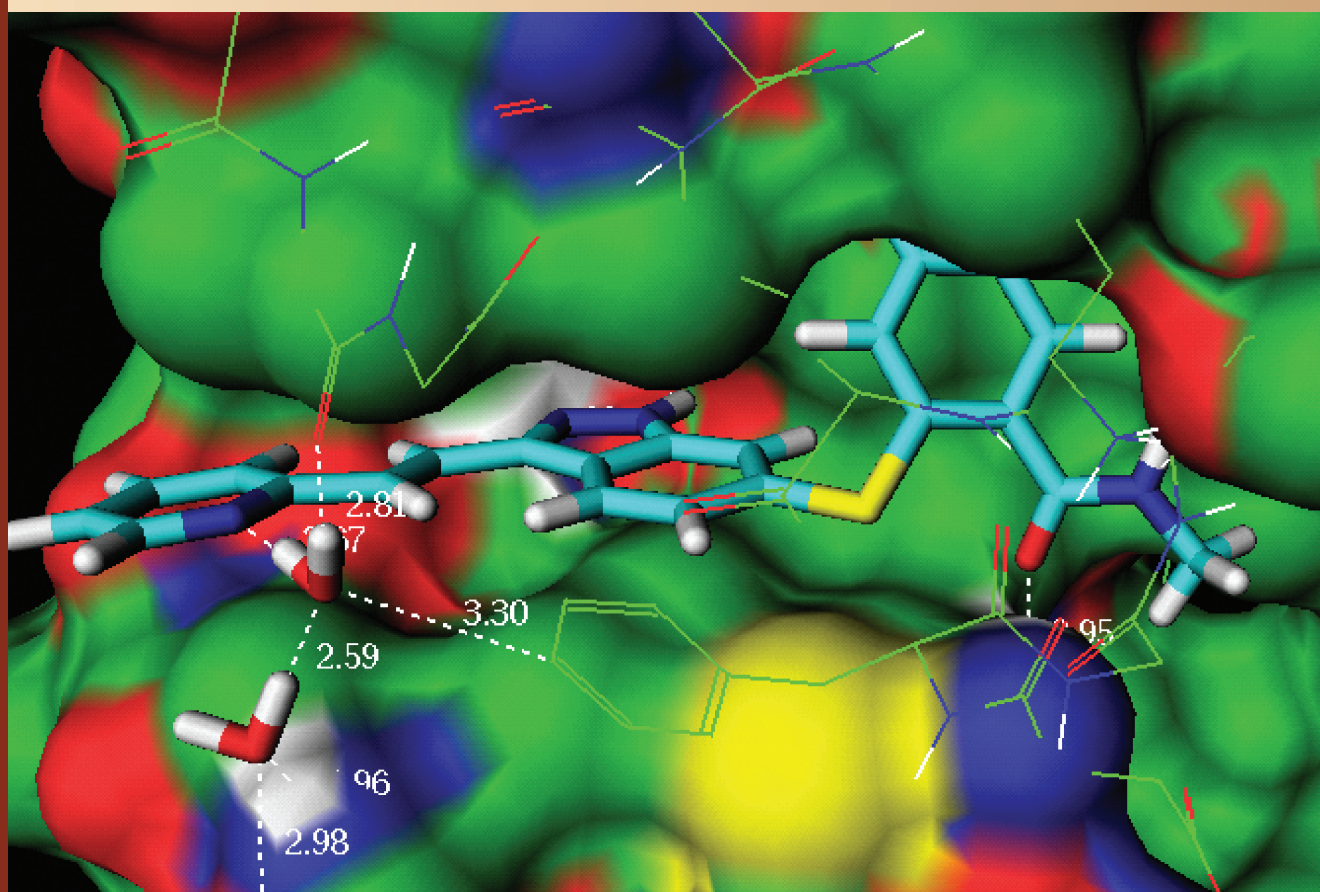
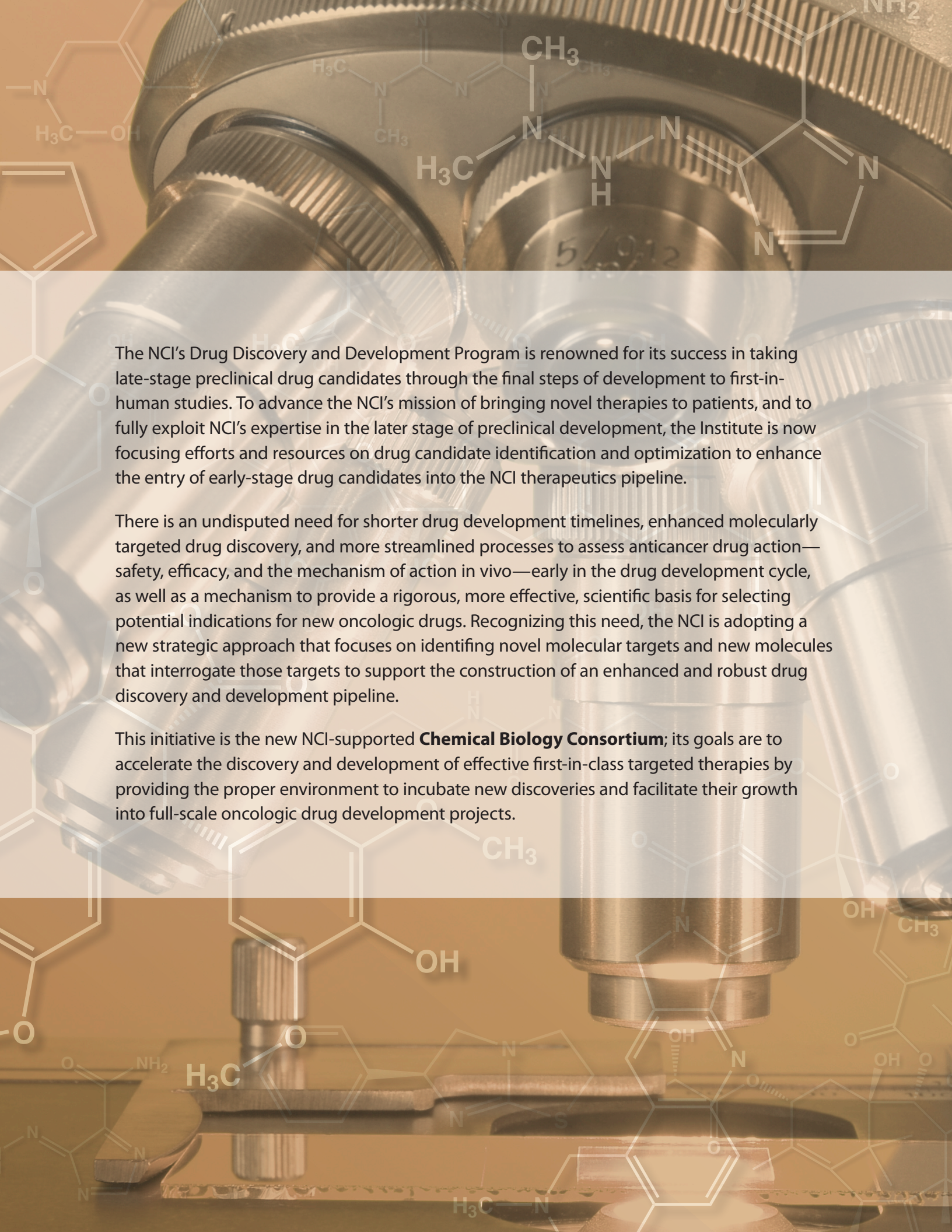


Chemical Biology Consortium

Accelerating the discovery and development of new anticancer agents





The NCI's Drug Discovery and Development Program is renowned for its success in taking late-stage preclinical drug candidates through the final steps of development to first-in-human studies. To advance the NCI's mission of bringing novel therapies to patients, and to fully exploit NCI's expertise in the later stage of preclinical development, the Institute is now focusing efforts and resources on drug candidate identification and optimization to enhance the entry of early-stage drug candidates into the NCI therapeutics pipeline.

There is an undisputed need for shorter drug development timelines, enhanced molecularly targeted drug discovery, and more streamlined processes to assess anticancer drug action—safety, efficacy, and the mechanism of action in vivo—early in the drug development cycle, as well as a mechanism to provide a rigorous, more effective, scientific basis for selecting potential indications for new oncologic drugs. Recognizing this need, the NCI is adopting a new strategic approach that focuses on identifying novel molecular targets and new molecules that interrogate those targets to support the construction of an enhanced and robust drug discovery and development pipeline.

This initiative is the new NCI-supported **Chemical Biology Consortium**; its goals are to accelerate the discovery and development of effective first-in-class targeted therapies by providing the proper environment to incubate new discoveries and facilitate their growth into full-scale oncologic drug development projects.

NCI Chemical Biology Consortium (CBC)

Goals:

- Choose high-risk targets that are of low interest to Pharma
- Re-engineer investigators' assays into high-throughput screens
- Develop screening "hits" into lead agents
- Invite expert medicinal chemists to review data and design optimized analogs
- Select promising candidates based on established development milestones
- Promote candidates with targeted activity to the clinic

The process for accomplishing CBC goals is based on the drug discovery strategy used by Pharma. The CBC differs from the current NCI drug discovery model in that the CBC will select targets, actively screen for agents that affect these targets, and optimize the "drug-like" properties of hits, rather than focus on developing new agents submitted by outside investigators.

The success of the CBC depends as much on the enthusiasm, intellectual talent, and experience of NCI Project Team members as it does on the quality of the targets. These attributes, combined with screening and assay optimization by the NIH Roadmap Screening Centers, the resources of the NCI, validated disease models, imaging technologies, and project management, will accelerate the progress of promising new agents through the drug discovery and development pipeline to Phase 0/I/II clinical evaluation.

The CBC will mobilize a cancer drug discovery group on the scale of a small biotechnology concern, with an R&D pipeline linked to the academic community. The CBC will re-establish the NCI as a world leader in innovative cancer therapeutics discovery.

This document outlines the process of selecting small molecules as potential candidates for preclinical development within the CBC.

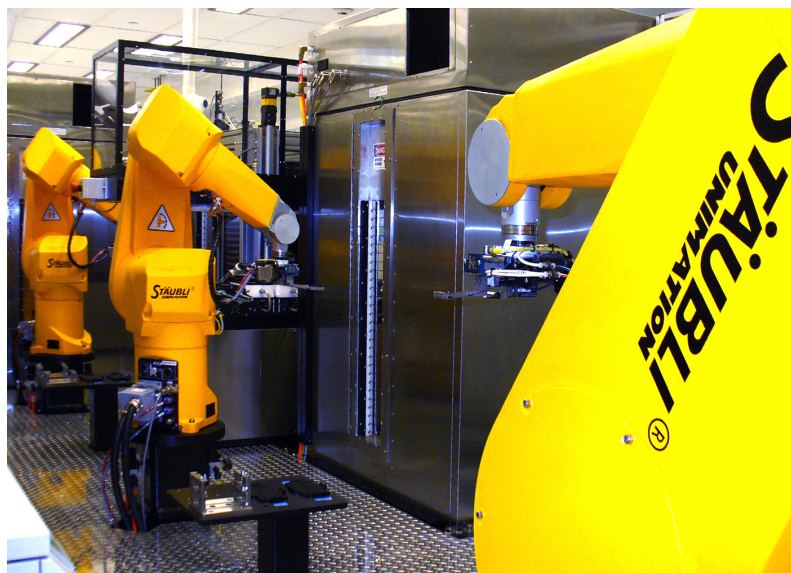
The CBC drug discovery process is divided into four distinct stages, from screening through preclinical evaluation of the lead candidate(s). Inherent to each stage are Stage Gates—milestones that support transition of a molecule to the next stage—as well as project management processes to document and communicate this progress.

The stages are:

1. **Exploratory Screen Development (ESD)**
2. **Screening/Designed Synthesis (SDS)**
3. **Lead Development**
4. **Candidate Seeking**

The NCI Drug Discovery Committee and the Project Team will determine the Stage Gate milestones before preparing the project operational plan. They will evaluate the agent according to these milestones before promoting it to the next stage.

Entry into the CBC pipeline can occur at any discovery stage, from selection of a novel cellular target to lead agent confirmation.



Automated high-throughput screening will be available to the CBC via consortium member screening centers to identify "hits" for further synthetic optimization.

1 Exploratory Screen Development

Objective: Proof-of-concept for a screen against a defined mechanistic target.

The NCI Project Team will initiate an intellectual property plan to confirm freedom-to-operate; prepare a product profile to describe the drug product sought, mechanism of action, and pharmacodynamic (PD) and pharmacokinetic (PK) targets; and prepare a project operational plan to outline project governance and support.

The team will then collaborate with the screening center to develop and validate a high-throughput assay to screen natural product and small molecule repositories for drug candidates.

Exploratory Screen Development Guidelines

1. Initiate intellectual property plan
2. Prepare product profile
3. Develop screening strategy
4. Identify potential biomarkers (efficacy/surrogate)
5. Develop strategy for clinical readiness
6. Prepare medical needs assessment
7. Prepare project operational plan

Measure of Success

Demonstration of project proof-of-concept and development of an assay suitable for screening libraries for agents with targeted activity.

Required for Next Step

Completion of a project operational plan summarizing the successful completion of project milestones listed above for presentation to Senior Management and Drug Discovery Committees.

2 Screening/Designed Synthesis

Objective: Identify and produce at least one high-quality lead agent from initial screening and screening-validation efforts.

The Project Team will review the lead compound criteria for quality, including potency, structure–activity relationship, activity in vitro, and safety. Team project managers will prepare a detailed timeline and budget for lead development.

Data generated from the screening and hit confirmation process will be accessible to all team members and Senior Management.

Screening/Designed Synthesis Guidelines

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 physicochemistry (Rule-of-Five compliant)
7. Evaluate pharmacokinetics
8. Assess amenability to synthesis
9. Evaluate stability
10. Prepare clinical plan outline

Measure of Success

Identification of one or more high-quality lead agents and consensus that they are viable candidates for further development.

Required for Next Step

Endorsement by the Drug Discovery Committee of a lead candidate timeline, budget, and clinical plan outline.

3 Lead Development

Objective: Improve and optimize lead agent characteristics through the application of medicinal chemistry to allow selection of the most promising candidate drug. Lead compound criteria for quality must be met for a lead agent to become a clinical candidate.

Lead Development Guidelines

1. Establish laboratory objectives for clinical efficacy
2. Resolve intellectual property issues
3. Evaluate activity in validated disease models
4. Evaluate physicochemistry and formulation
5. Assess achievability of human PK/PD profile
6. Evaluate differentiation in preclinical models
7. Evaluate preliminary safety issues
8. Validate biomarker(s)
9. Assess feasibility of scale-up and bulk synthesis

Measure of Success

The lead agents have favorable PK/PD/toxicity profiles, and there is reproducible, statistically significant evidence of targeted activity in vitro and in vivo.

Required for Next Step

Completion of a report summarizing the project activities listed above, and endorsement of candidate-seeking activities by the Drug Discovery Committee.

4 Candidate Seeking

Objective: Select the single most promising candidate drug from the list of lead agents. This decision may involve more advanced testing of several agents and will culminate in the preparation of a candidate alert notice (CAN) to guide the clinical development plan. The CAN outlines the resources needed, benefits, costs, and risks of the project, and includes a summary of the scientific rationale for the candidate and how this supports clinical proof-of-concept.

Candidate Seeking Guidelines

1. Evaluate synthesis
2. Evaluate biopharmaceutical properties
3. Assess absorption (rodent and non-rodent)
4. Determine clearance and oral bioavailability
5. Assess potency against clinical efficacy
6. Evaluate biodistribution
7. Evaluate clinical readiness as a pharmacodynamic marker
8. Assess amenability to imaging
9. Evaluate safety issues (most sensitive species)

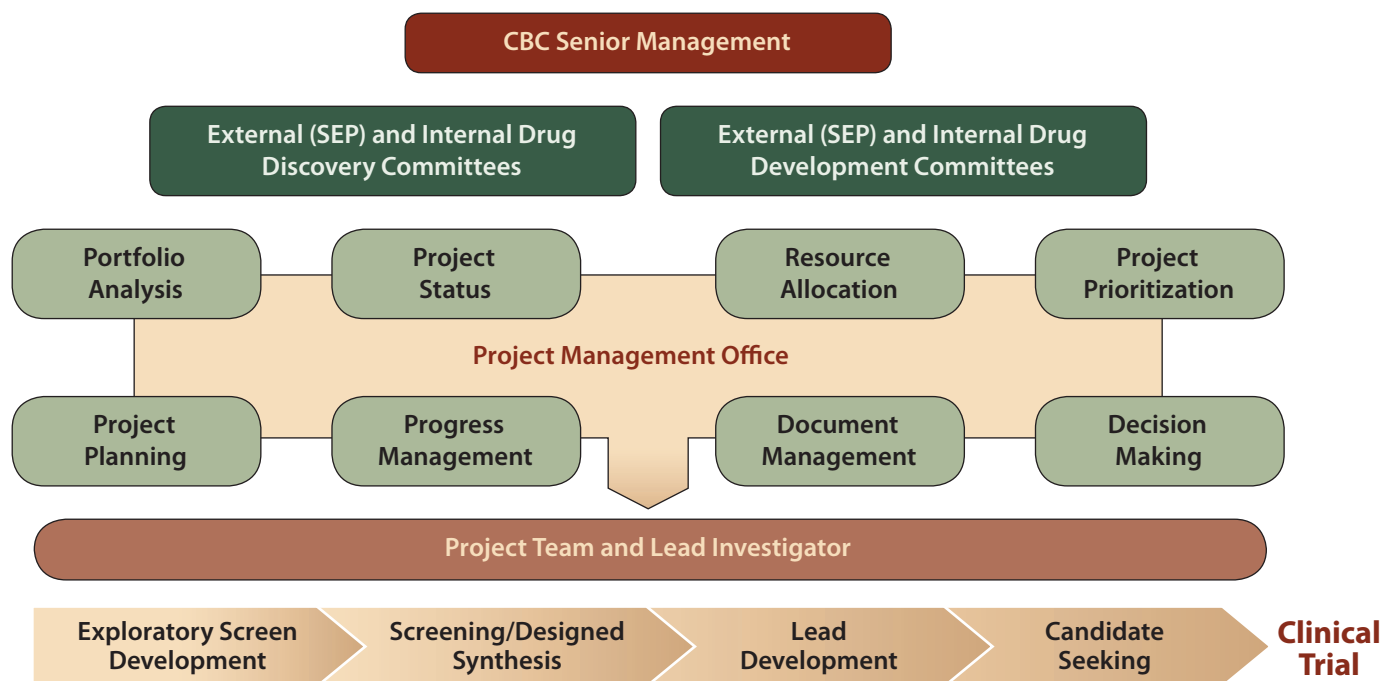
Measure of Success

Preparation of a candidate alert notice.

Required for Next Step

Endorsement of the CAN by both Discovery and Development Committees, approval for IND-enabling studies, and endorsement of a clinical development plan.

CBC Governance



The CBC Senior Management Committee will be responsible for strategic focus, resource allocation, and project oversight and accountability.

The NCI Early Drug Discovery Committee will oversee all discovery projects in the NCI pipeline, guide allocation of resources, and develop strategic plans for projects in the early discovery phase. The committee will perform risk assessments and make Go/No-Go decisions at each Stage Gate. A key responsibility will be to endorse preclinical development plans.

The NCI Drug Development Committee will endorse the critical transition of clinical candidates from discovery phase to development phase and oversee completion of all late-stage preclinical studies. The committee will assess candidate eligibility for Phase 0/I/II clinical evaluation and make appropriate Go/No-Go decisions. The committee will also ensure that resources are focused on the most important and promising clinical opportunities.

External Drug Discovery and Drug Development Special Emphasis Panels (SEPs), comprising chemical biology and drug discovery experts from Pharma and academia, will advise the CBC on targets and molecules, approving project milestones, and prioritizing projects within the CBC portfolio. Project management is a critical component of all aspects of the CBC.

The Project Management Office (PMO) will integrate and coordinate the efforts of all CBC contributors—Senior Management, Discovery and Development Committees, project teams, lead investigators, contractors, medicinal chemists, assay developers, and drug screeners—to ensure activity is focused on achieving Stage Gate milestones. The PMO will provide writing, document management, and training support to the CBC. The PMO will also measure and track CBC portfolio activities for Senior Management and the SEPs.

Project managers in each project team will have the following tasks:

- Work with the lead investigator and other team members to prepare the operational plan for each new project based on Discovery Committee recommendations
- Develop work breakdown structures, timelines, and templates to track project status and deliverables
- Document milestones and progression
- Prepare quarterly reports for the CBC Discovery, Development, and Senior Management Committees

Supporting tools and infrastructure for the CBC will consist of enterprise-wide software systems to manage data, documents, projects, and project portfolios. For example, a database designed to accommodate screening data and to support activities related to structure-based drug discovery (SBDD) will be a shared resource for all screening, assay, and hit-optimization data generated during drug discovery. The data will be available to team members and the CBC Senior Management Committee to support resource management and decision making.

Example of a Drug Development Project Tracking Table

Lead Development Stage	2008					2009			Performance Indicator
	A	S	O	N	D	J	F	M	
Target Concept & Intellectual Property FTO	█								●
Disease Models		█							●
Physiochemistry and Formulation		█							●
Stability		█							●
Metabolism		█	█						●
Pharmacokinetics		█	█						●
Pharmacodynamics				█	█				●
Safety				█	█				●
Clinical Efficacy Objectives					█				●
Scale Up						█	█		●
Clinical Product							█	█	●

Team project managers will provide tools to track and communicate project status, coordinate team activities, and highlight process issues. The tools allow the progress of each project to be followed through the drug discovery and development pipeline, which helps with the planning and coordination of the different tasks at each stage.

For more information, please visit the NCI DCTD Web site: <http://dctd.cancer.gov>

CHEMICAL BIOLOGY CONSORTIUM

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