Creating Nanomedicine Research Teams (a personal/university perspective)

Institutional barriers (and solutions). (1) Cultural (rapidly changing). (2) Space. (3) Professional staff – career development, hiring, P.I. rights. (4) Stable funding.

Sine qua non. Committed leadership – not a side activity.

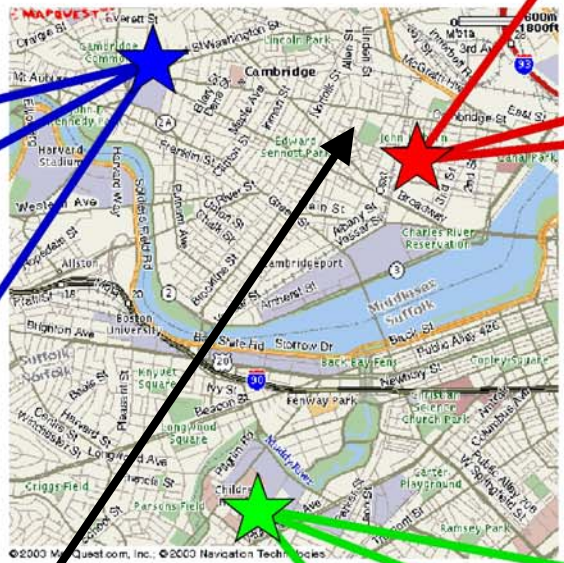
Team assembling. Idea-driven, research opportunity-driven, rather than funding-driven.

NIH-based coordination with new and existing centers. (1) Network of Centers/Committee of Center directors: coordinate efforts, identify bottlenecks and new directions. (2) Facilitate the development of databases and analysis tools by coordinating efforts to define controlled vocabularies/allowed fields/allowed values, define the matrix of “Objects” and “Activities performed on objects”.

ICCB's mission (sponsored by the NCI and NIGMS): To create and share data and reagents derived from small molecule investigations of disease biology.

ICCB-Kendall Square

ChemBank



ICCB-Harvard Square

future site of Harvard/MIT's Broad Institute

ICCB-Longwood

- **small molecules**
- **small molecule screening**
- **ChemBank (a small molecule and assay data analysis environment)**

Harvard/MIT Broad Institute's Mission: Medical advances via chemical biology and genomics

- **Scientific mission**

  Create **comprehensive tools** for genomic medicine
  Make tools **broadly available**
  Pioneer **applications** toward disease understanding and treatment

- **Organizational mission**

  Enable **collaborative projects** not readily performed in individual labs
  Empower scientists through access to tools and approaches

Organization

Programs

- Cell Components, States and Circuits
- Chemical Biology
- Medical and Population Genetics
- Cancer Biology

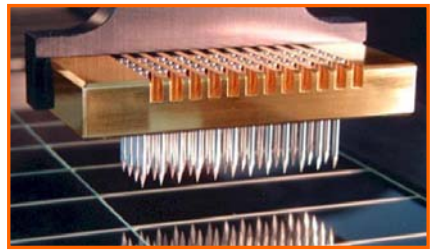
Initiatives

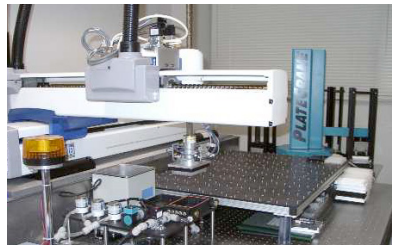
- Metabolic Disease
- Psychiatric Disease
- Infectious Disease
- Inflammatory Disease

Platforms

- Sequencing
- Genotyping
- Chemical synthesis, screening, informatics
- Profiling (RNA, protein, metabolites)

Platforms





Professional organizations able to carry out major projects in partnership with programs

Repositories of expertise in capabilities, informatics, automation, management

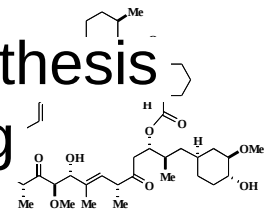
Not core facilities

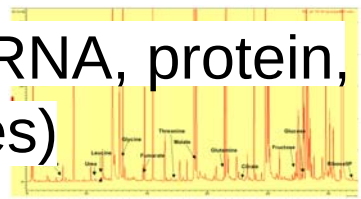
Led by platform directors and senior staff

Platforms

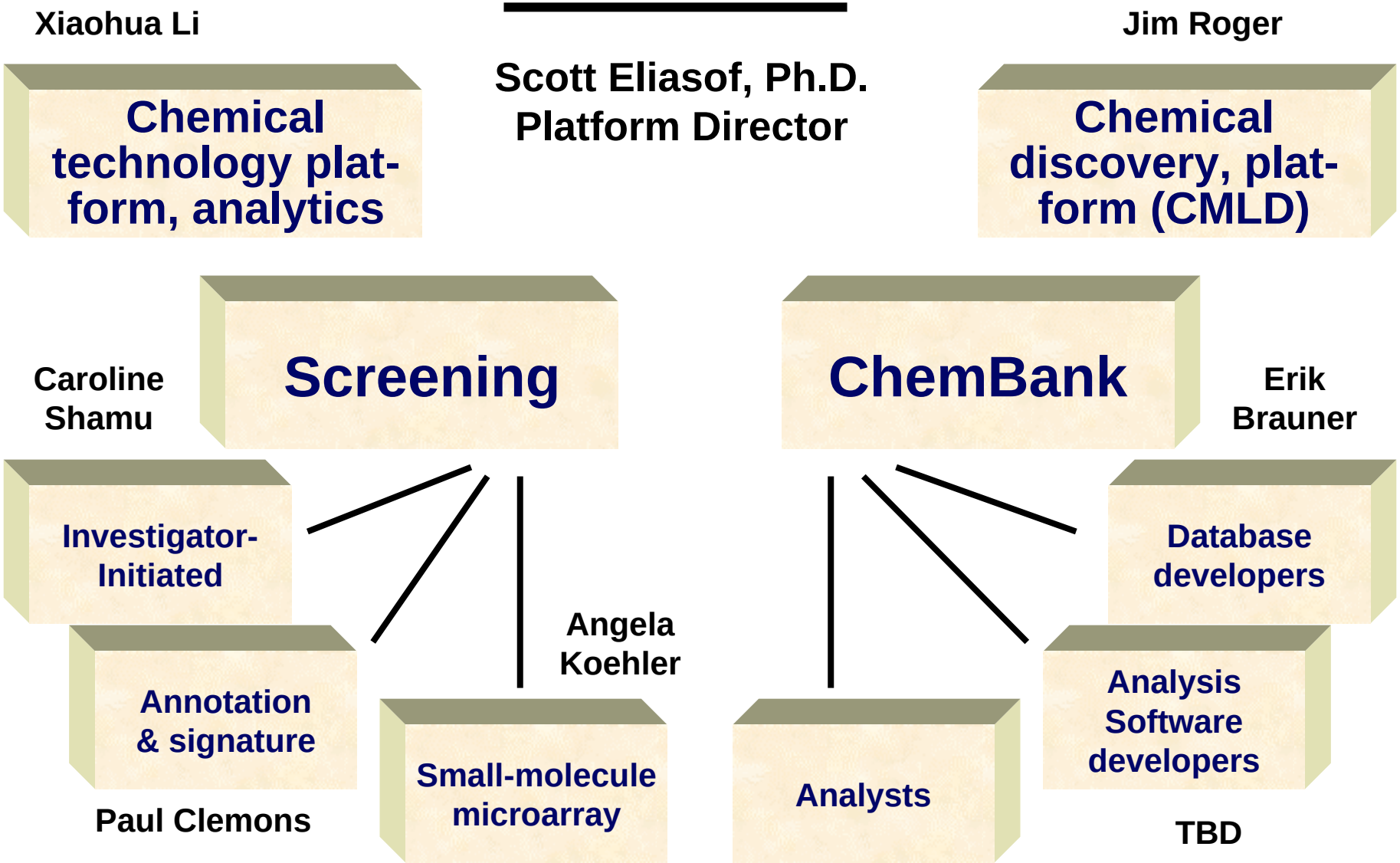
Sequencing 

Genotyping 

Chemical synthesis and screening 

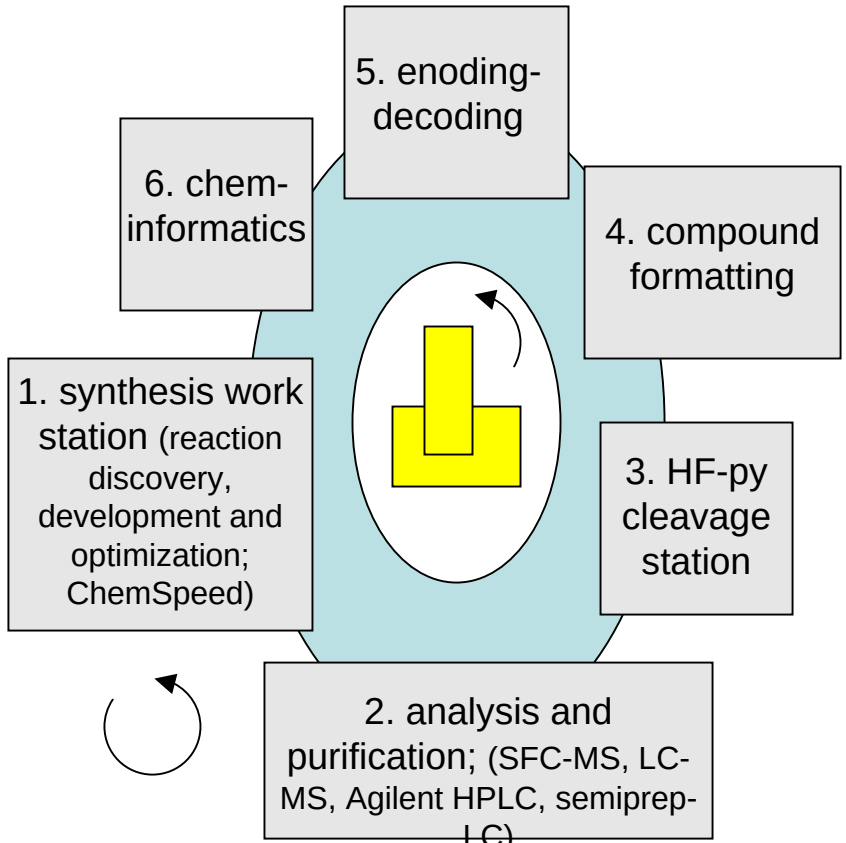
Profiling (RNA, protein, metabolites) 

Broad Institute/ICCB Chemical Biology Scientific Platform



Broad Institute/ICCB Chemical Synthesis Discovery and Technology Platform

other remote chemistry technology platforms

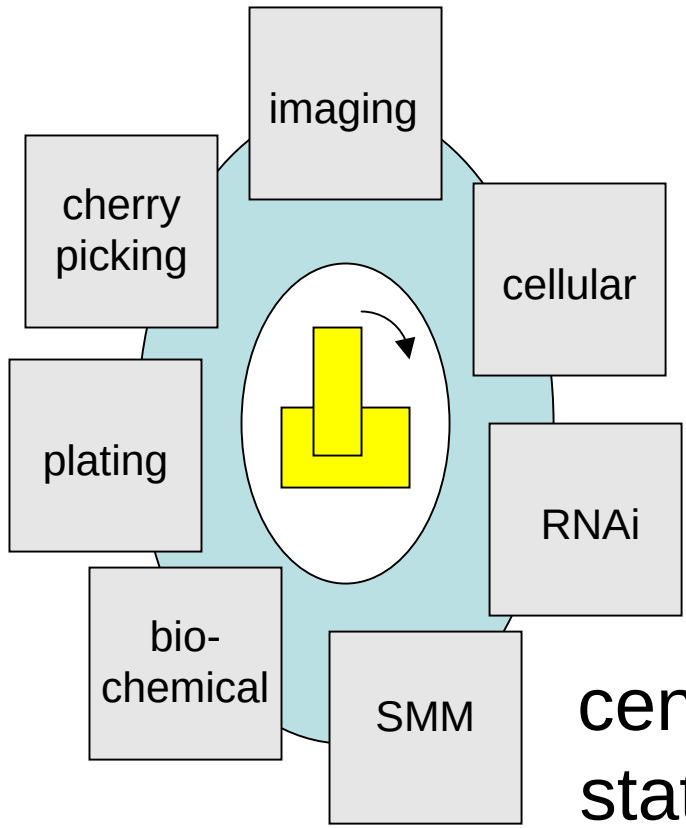


central platform

CCB technology platforms

analytical chemistry (NMR, MS, LC-MS, GC-MS

Broad Institute/ICCB Chemical Biology Screening Platform



central station

local piloting station

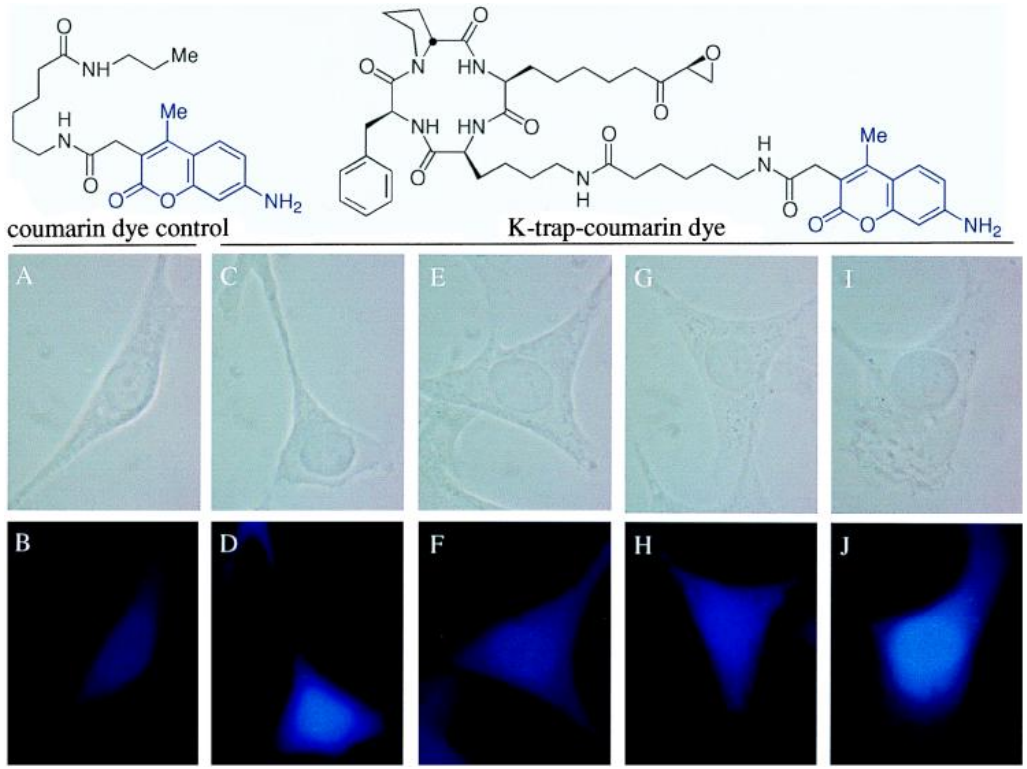
distant piloting station(s)

compound refrigeration and storage

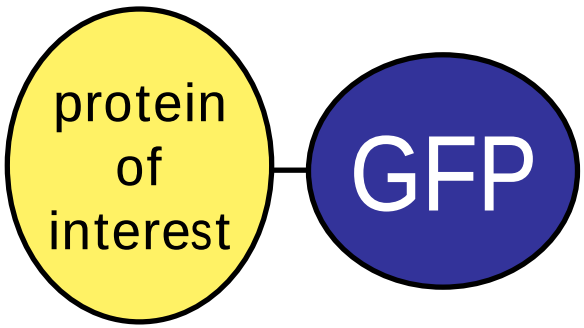
Broad Institute/ICCB Chemical Biology Informatics Platform

Broad Institute/ICCB Chemical Biology Scientific Program (example)

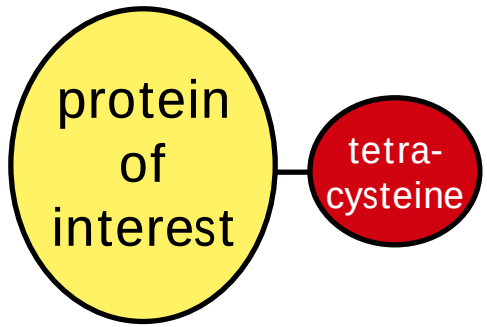
Imaging. The BICBP aims to foster the development of methods for imaging single-molecules, cells, and organisms. Imaging agents will be used for both *screening* and *probing* cells.



Genetically-encoded imaging elements that provide image contrast suitable for different imaging techniques



fluorescence microscopy



ReASH

(ReASH = cell permeable small molecule)

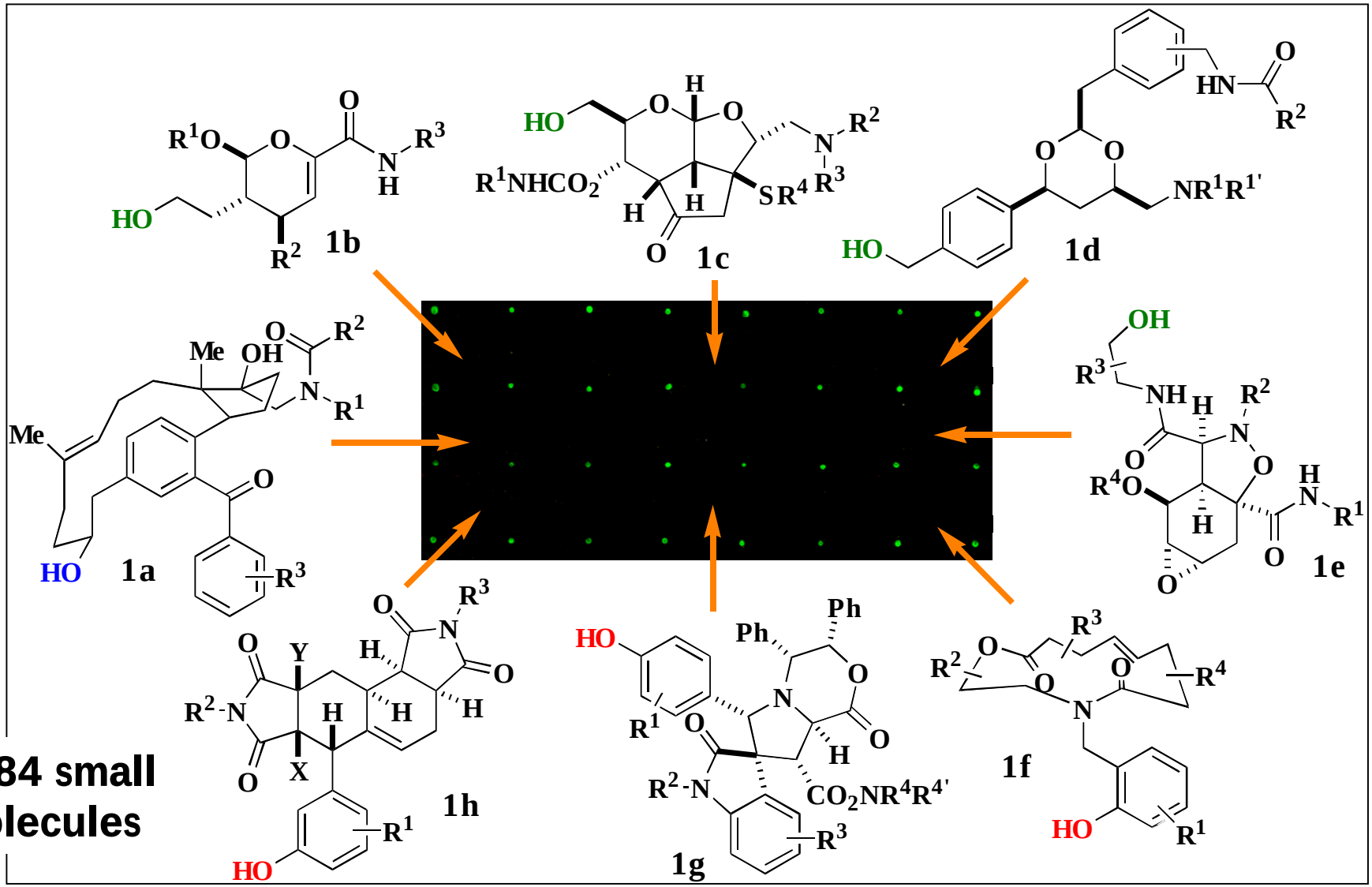
ReASH

fluorescence microscopy

electron microscopy

It is reasonable to anticipate the discovery of short RNA and protein tags that cause otherwise non-fluorescent small molecules to emit light in cells

Screening for molecular recognition agents using DiversityArray

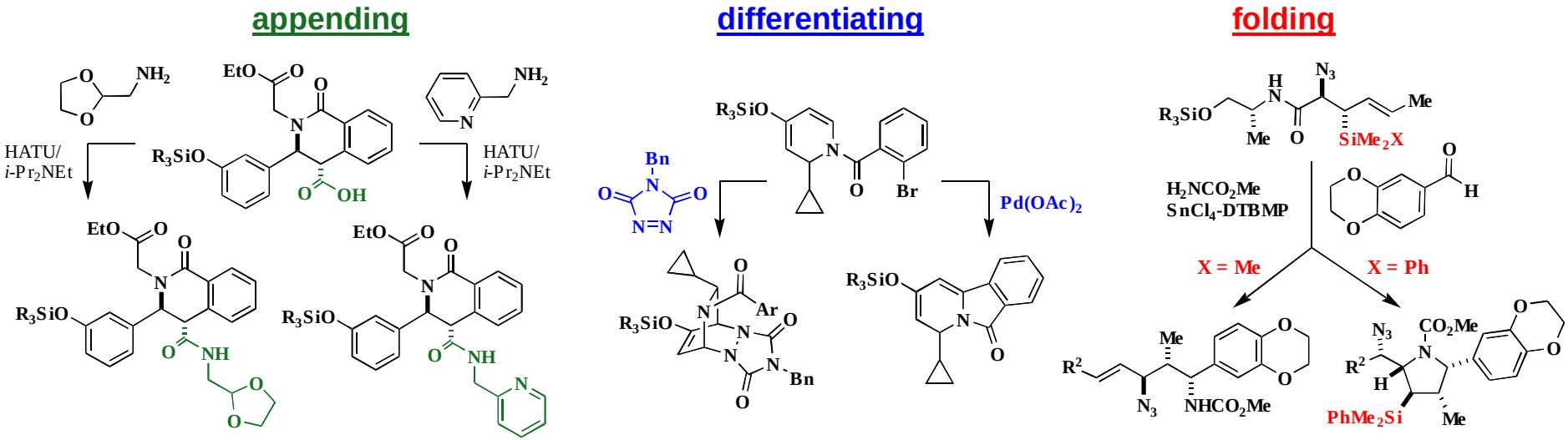


Broad Institute/ICCB Chemical Biology Scientific Program (example)

Synthetic Biology: Self-assembly vs. self-organization. Biological systems are exploratory – they have no master organizer. They instead rely on a self-organization principle, using an individual contingency mechanism. This is seen in many biological systems, including the nervous system and the immune system. It will be even more challenging, but arguably more rewarding, for nanotechnologists to search for self-organizing systems in the way that they have searched for self assembling for many years now.

The key chemical insight above is that self-organizing systems use catalysis to destabilize a self-assembled polymer. Thus, it should be possible to emulate such a system. If successful, such synthetic, dynamic nano-objects might be useful for understanding the principles that underlie life AND for creating molecular prostheses.

Broad Institute Chemical Biology Scientific Program



1. Small-molecules from diversity-oriented synthesis (DOS), eDNA, chemists nationwide, and government and commercial sources. The BICBP enables chemistry efforts to prepare small molecules suitable for screening (and possibly suitable for genotyping).

Broad Institute Chemical Biology Scientific Program

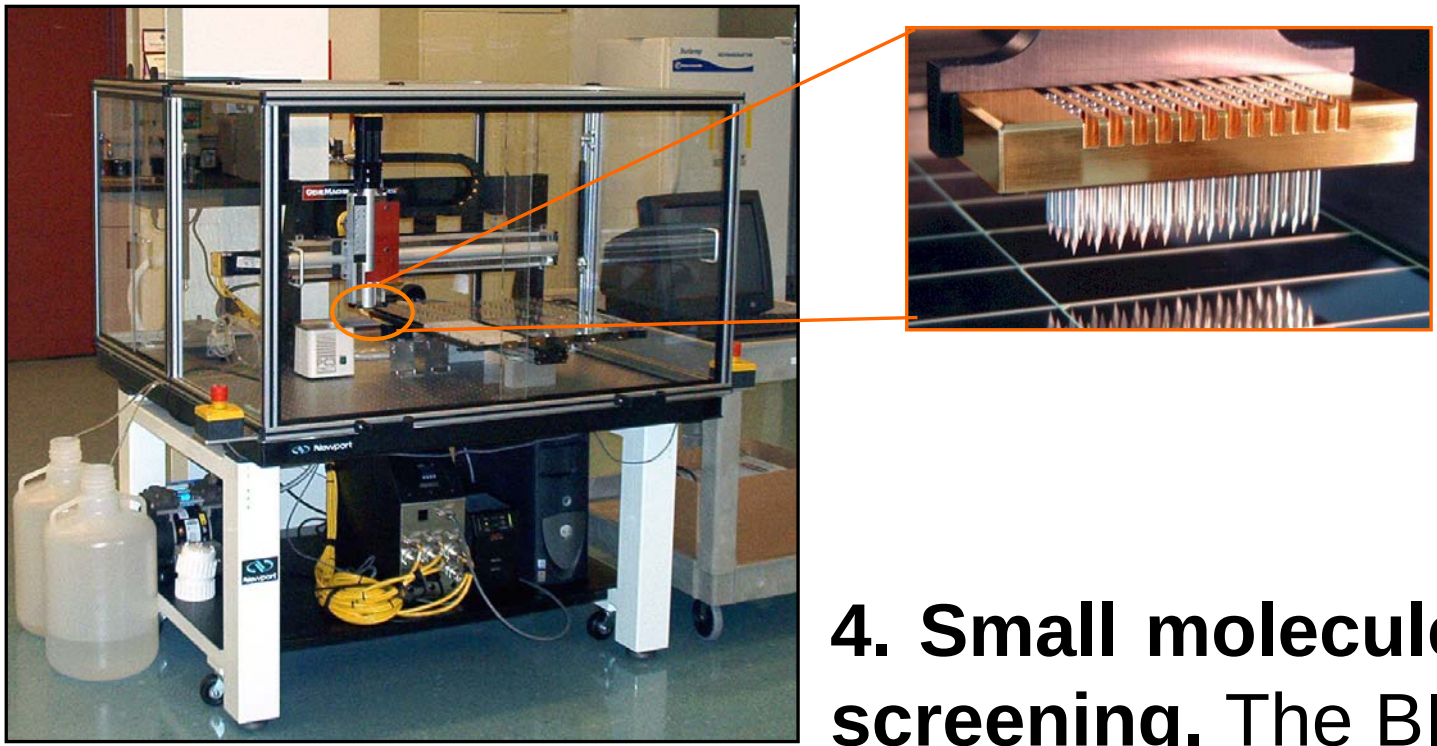
2. Investigator-initiated screening. The BICBP enables the scientific community to interrogate basic and disease biology through the use of small molecule screens, especially cell-based screens.

Broad Institute Chemical Biology Scientific Program



3. Signature discovery screening. The BICBP enables the scientific community to acquire biological measurements of small molecule perturbations yielding signatures of cellular states.

Broad Institute Chemical Biology Scientific Program

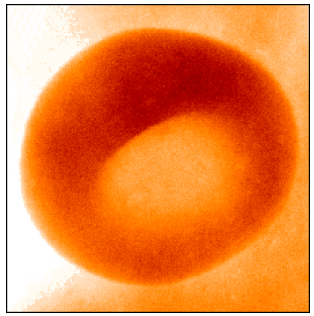
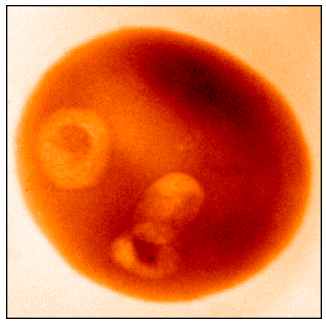
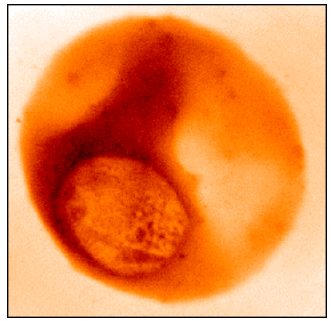


4. Small molecule microarray screening. The BICBP enables the scientific community to perform screens to detect interactions between small molecules and proteins for use as probes and imaging agents.

Broad Institute Chemical Biology Scientific Program

5. ChemBank. The public database ChemBank aims to facilitate the navigation and population of chemical descriptor space and assay measurement space, the identification of macromolecules to which small molecule modulators bind, and the mining of matrix datasets aimed at identifying signatures of cell states.

Broad Institute Chemical Biology Scientific Program

6. Small molecule screening and disease biology. The BICBP aims to foster the development of small molecule screening efforts aimed at advancing disease biology, especially in the areas of cancer, infectious disease (malaria and tuberculosis), psychiatric disease (bipolar and schizophrenia), metabolic disease (type II diabetes), and cardiovascular disease.

Broad Institute members and staff

Core members (4; can grow to 12)

Associate members (58)

- Steering committee
- At-large

Scientific staff

All welcome to affiliate, participate in all programs and initiatives

MIT, FAS, HMS, HSPH, WIBR, MGH, BWH, DFCI, BID, CH

Culture

- **Community**
  - Sustained commitment by all members to building intellectual communities, open sharing of ideas, and active collaboration
- **Leveraging resources**
  - Judicial application of resources to catalyze new projects, maximize impact & attract further funding
- **Valuing Professional Staff**
  - Attract and retain experience professional scientists and managers to build successful Platform organizations.
- **Empowering young scientists**
  - Provide students and trainees with access to tools and resources to become leaders of tomorrow

Programs and initiatives

Programs

- Cell Components, States and Circuits
- Chemical Biology
- Medical and Population Genetics
- Cancer Biology

Initiatives

- Metabolic Disease
- Psychiatric Disease
- Infectious Disease
- Inflammatory Disease

Program meetings:

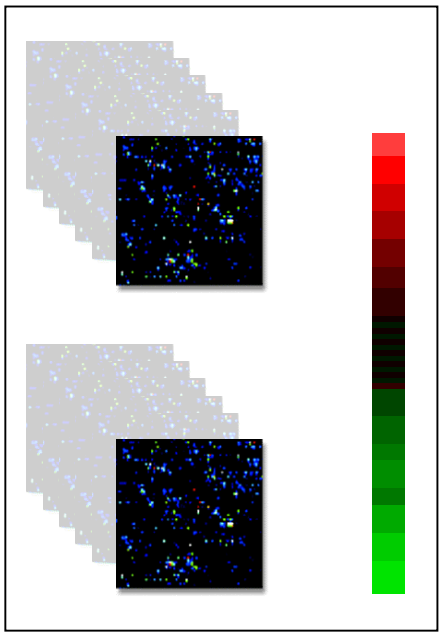
- Weekly, 90 min
- All invited
  (includes labs)
- Topics to be posted

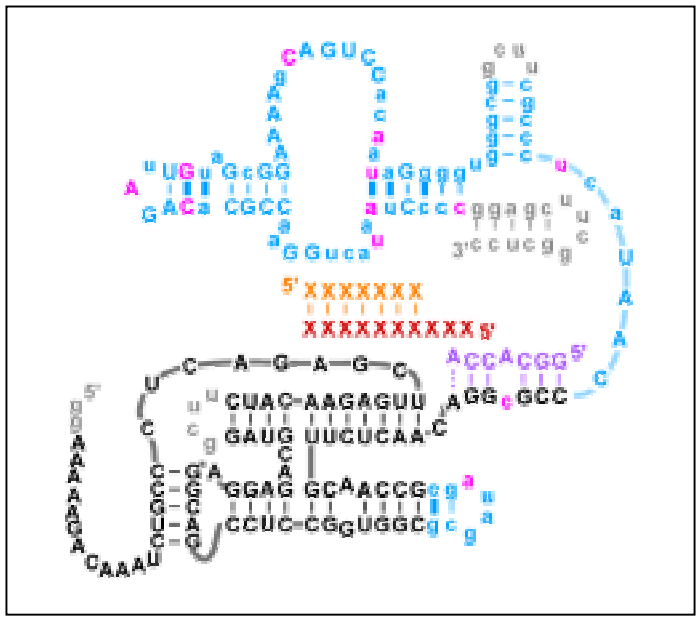
Purpose:

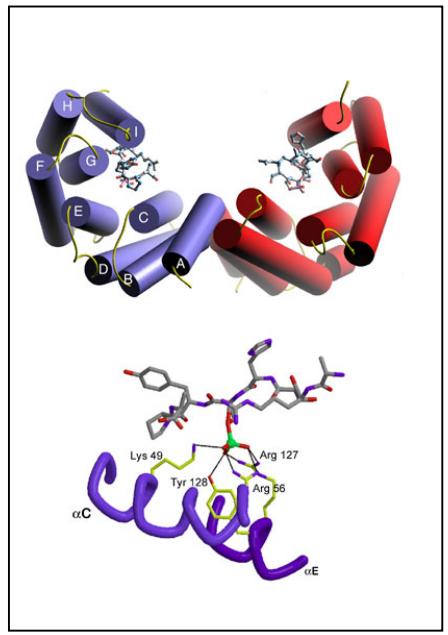
- Joint group meetings
  - Scientific talks
  - Extensive discussion
- Steering Committee
  - Propose projects
  - Oversee projects

Cell components, states and circuits (CCSC)

1. Comparative genomics: Identify all functional elements in genome
2. Connectivity map: Recognize all cellular states
3. Regulatory networks: Infer circuitry
4. Chromatin: Structure and regulation
5. Protein kinases: Infer networks
6. RNAi consortium: Comprehensive tools for modulation







Program in Medical and Population Genetics

QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

Goal: understand the contribution of genome sequence variation to phenotype, with a particular focus on common diseases and clinically important traits.

Key themes:

- Genome-wide characterization of sequence variation in humans and models
  population genetics
  genome-wide variation databases

- Creation of tools required to associate genetic variation and disease

- In depth genetic dissection of target diseases:
  Metabolic disease, Cancer, Psychiatric disease, Inflammatory disease

- Ethical, legal and social implications of genetic research

Broad Institute Cancer Program

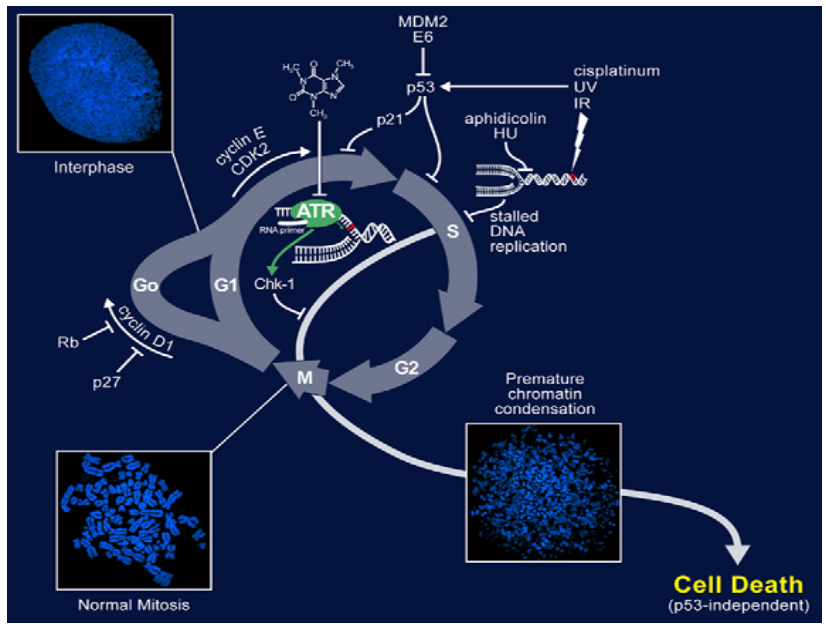
I. Molecular description of cancer Kinome, Tumor RNA (mRNA, microRNA) profiling, Protein biomarker discovery, Metabolic profiling, Animal models, Pharmacogenomics, Computational methods

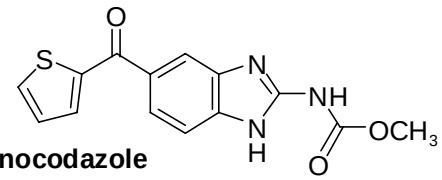
II. Systematic functional validation studies

Essential genes in cancer (siRNA), Small molecule screening

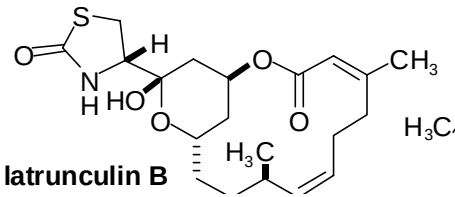
III. Toward clinical implementation

Signature detection methods, Computational, Methods, Ethical/ educational issues, Clinical trials

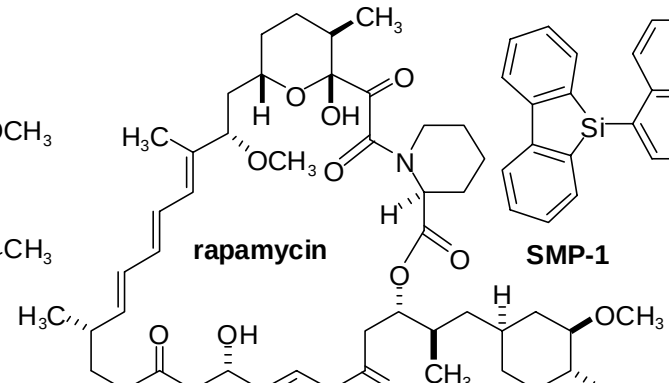




nocodazole

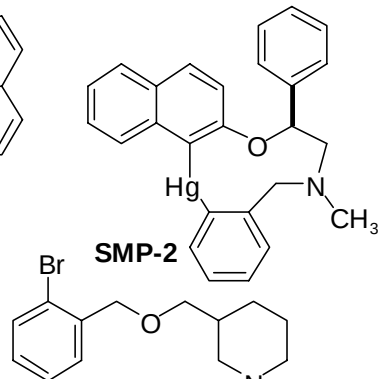


latrunculin B

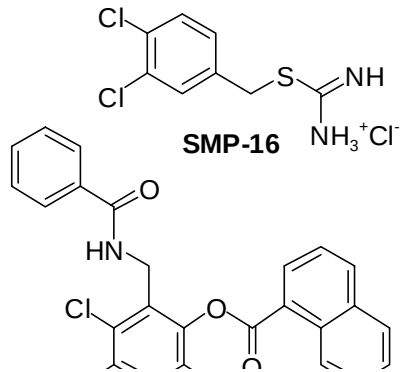


rapamycin

SMP-1

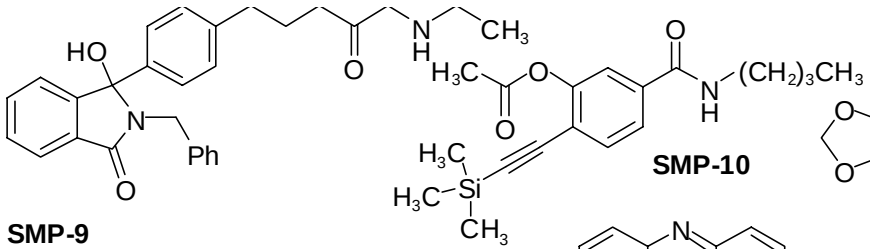


SMP-2



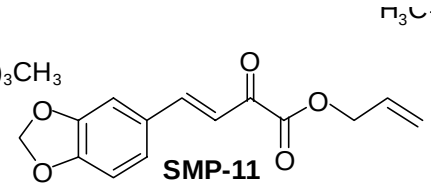
SMP-16

Broad Institute Chemical Biology Program



SMP-9

SMP-10



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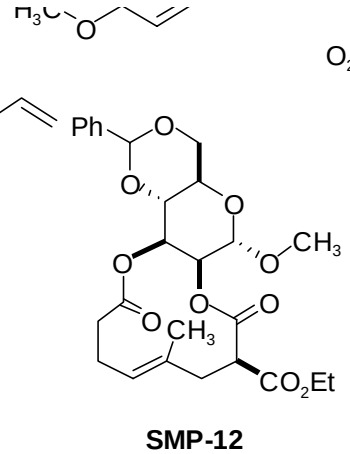

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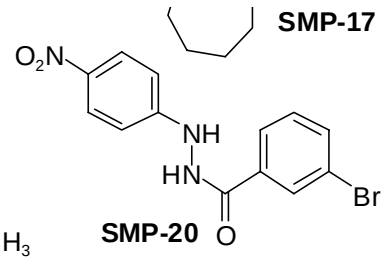
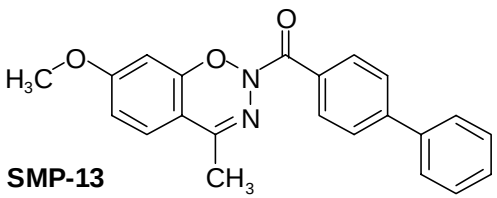


SMP-17

SMP-20



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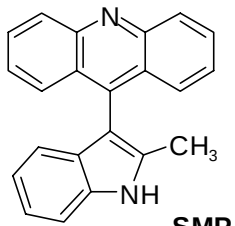

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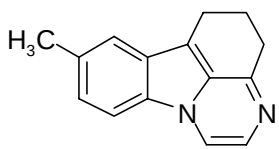
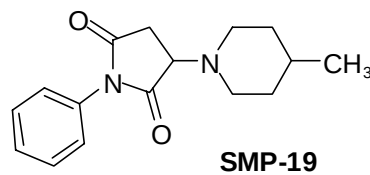


SMP-15

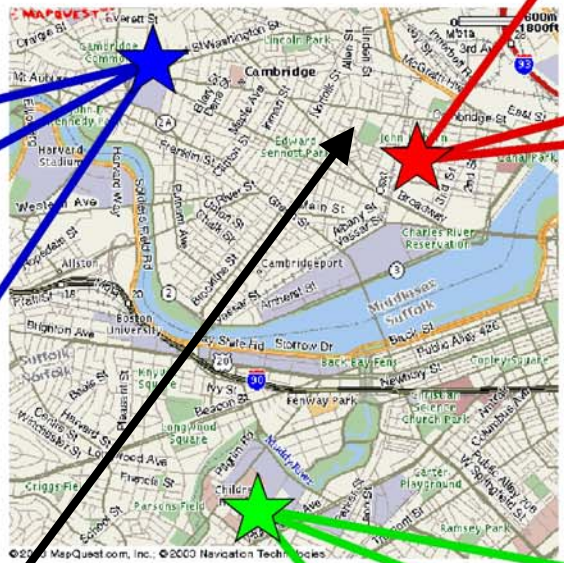


SMP-19

ICCB-based scientific platform, an extended scientific program, and consolidation

ChemBank

ICCB-Harvard Square



ICCB-Kendall Square

ICCB-Longwood

a new building that will be constructed for the broad institute at 7 cambridge center. completion will take about two years. we will be renting interim space so that we can both consolidate and house expanded programs and projects for associate members; interim space may be functioning in about six months.

Harvard/MIT Broad Institute

- **Joint partnership**

  Governed by Harvard (FAS/HMS) and MIT

- **Chemical biology: New adjacencies, consolidation**

  Integrating Harvard's ICCB with the Whitehead's CGR

- **Founding gift**

  $10M/yr x 10 yrs — seed collaborative projects
  Additional fundraising around projects