



The NIH Chemical Genomics Center

Bringing Biopharmaceutical Technologies to Academic Chemical Biology and Drug Discovery

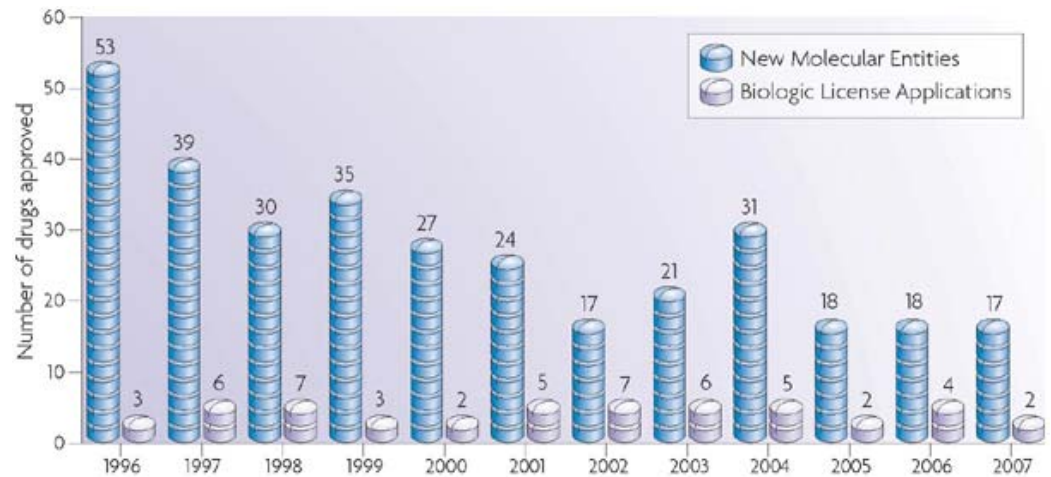


Christopher P. Austin, M.D.
Director, NIH Chemical Genomics Center
National Institutes of Health

Visit of UK House of Lords
4 June 2008



The best of times, the worst of times

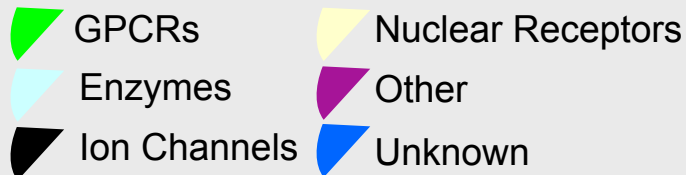
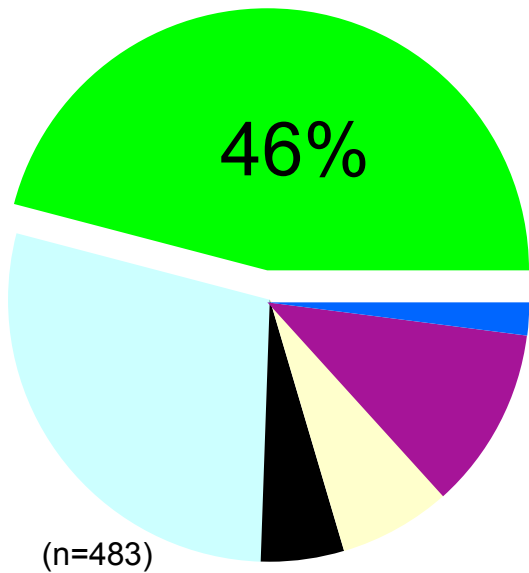


Nature Reviews | Drug Discovery

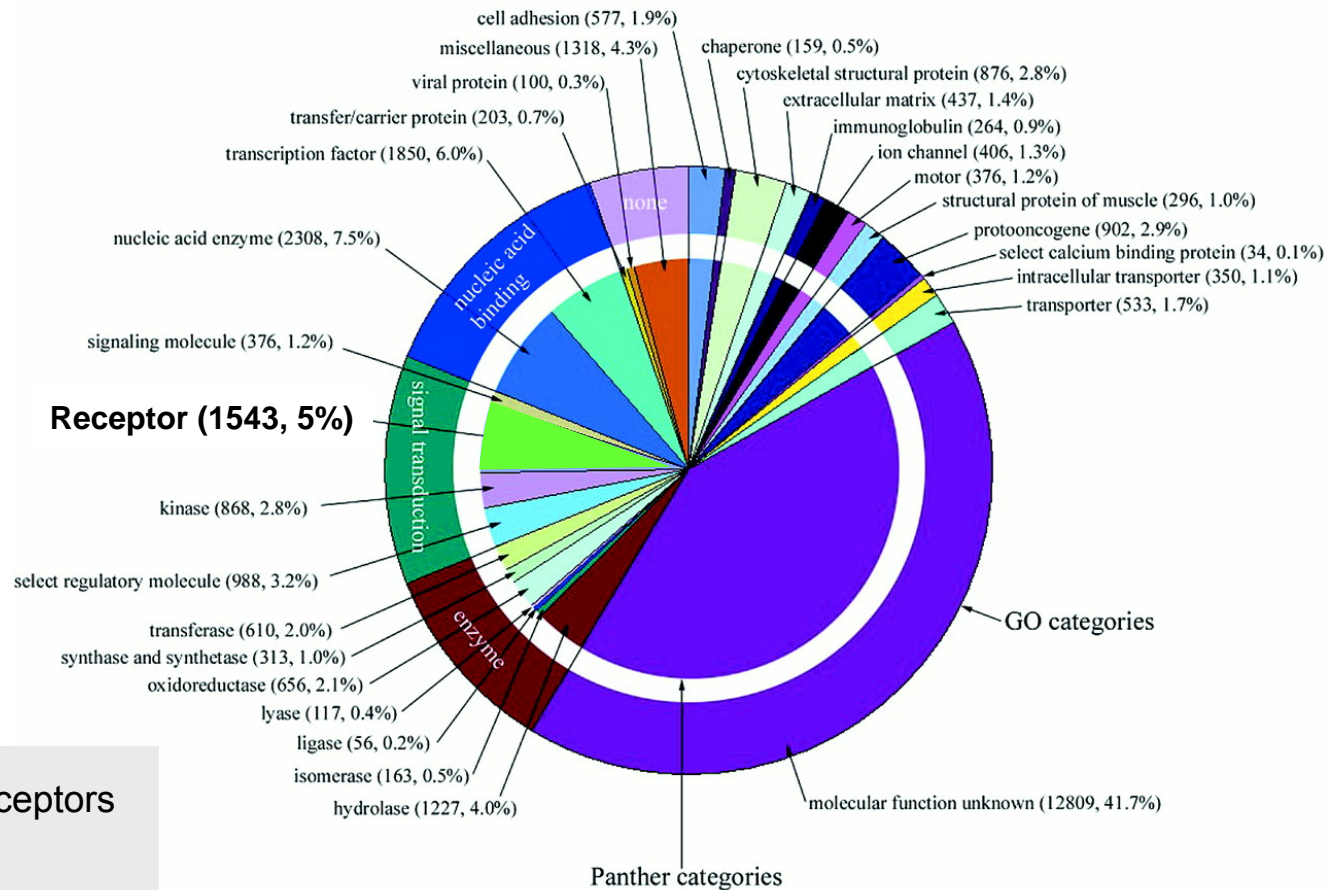
How to translate the genome into biological insights and therapeutics?

The “Non-Druggable” Genome Problem

Drug Target Classes



Human Genome





Home Page



Molecular Libraries and Imaging

- Overview
- [Implementation Group Members](#)
- [Funding Opportunities](#)
- [Funded Research](#)
- [Related Activities](#)

Molecular Libraries and Imaging

OVERVIEW

Small molecules, often with molecular weights of 500 or below, have proven to be extremely important to researchers to explore function at the molecular, cellular, and in vivo level. Such molecules have also been proven to be valuable for treating diseases, and most medicines marketed today are from this class.

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Genome Technology

Jan/Feb 2005

Inside Integrated Biology

SMALL MOLECULES GO PUBLIC



“...To empower the research community to use small molecule compounds in their research, whether as tools to perturb genes and pathways, or as starting points to the development of new therapeutics for human disease.”

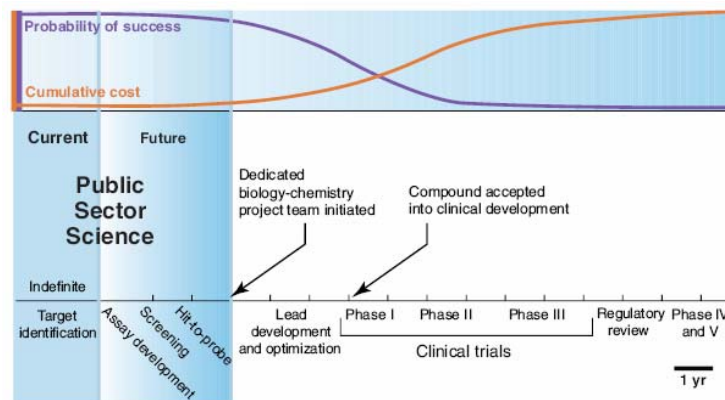
POLICY FORUM

MOLECULAR BIOLOGY

NIH Molecular Libraries Initiative

Christopher P. Austin,^{1*} Linda S. Brady,² Thomas R. Insel,² and Francis S. Collins¹

12 NOVEMBER 2004 VOL 306 SCIENCE www.sciencemag.org



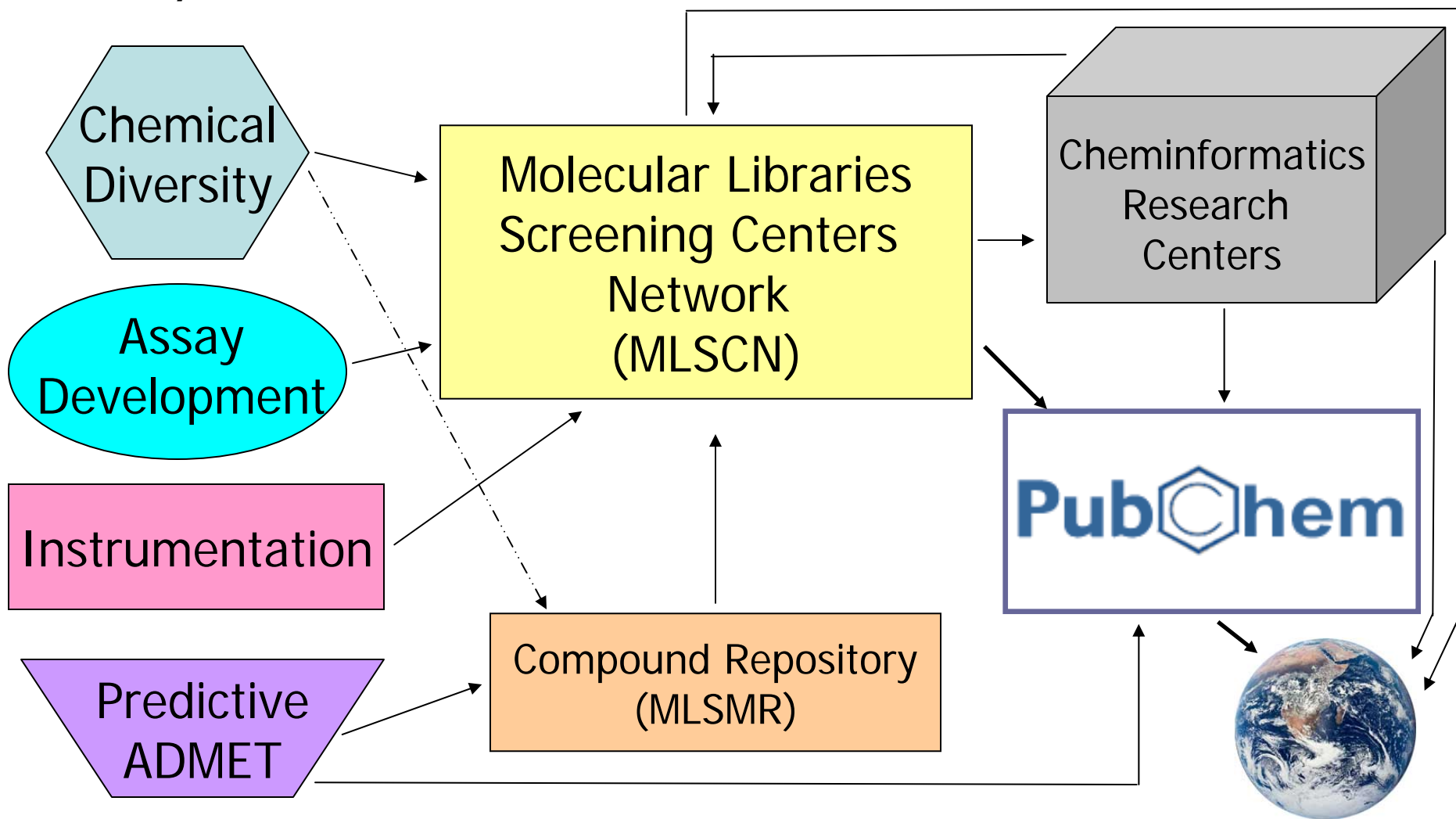
Interface of the MLI and drug development.

The Molecular Libraries Roadmap: An Integrated Initiative

*Technology
Development*

Data Production

Data Analysis/Dissemination





Unique features of the MLSCN

- All Centers screen same compound collection
 - Allows comparison of compounds' activities in many assays
- Capability to screen very wide variety of assay types
- Medicinal chemistry to transform hits into probes
 - Chemical probes of gene, pathway, and cell functions
- Data are released without restriction
 - *PubChem*: Screening data
 - *Probe reports*: activity, SAR, purity, compound source data
 - Enabling for all researchers to use probes and compute on the data
 - Sharing is catalytic to the transformation of data into information

<http://mli.nih.gov>

Molecular Libraries Initiative » HOME - Microsoft Internet Explorer

File Edit View Favorites Tools Help

Back Forward Stop Refresh Home Search Favorites RSS Mail Print

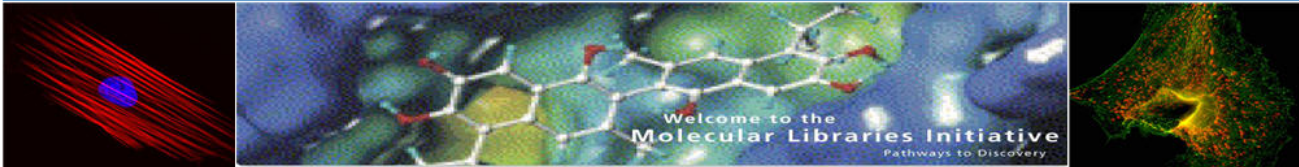
Address <http://mli.nih.gov/mli/> Go Links

Google Go Bookmarks 5 blocked Check AutoLink AutoFill Send to Settings

MolecularLibraries
Pathways to Discovery

MOLECULAR LIBRARIES INITIATIVE

Pathway to Discovery



Welcome to the
Molecular Libraries Initiative
Pathways to Discovery

HOME MLSCN MLSMR PubChem Tech Development Funding Opportunities Funded Research Selected Assays Publications
NEWS & EVENTS RESOURCES

User Login Required

- MLI
- CARS
- CARS Training
- Assay Wiki
- Assay Annotation

HOME

New Highlights & Resources!

MLSCN SYMPOSIUM AT THE APRIL 6, 2008 SBS MEETING IN ST. LOUIS, MO

Click here for more information on the MLSCN Symposium: [NIH Roadmap Molecular Libraries Screening Centers Network: A Resource for the Research Community](#)

PROBE DEVELOPMENT OPPORTUNITIES

Solicitation of Assays for HTS in the Molecular Libraries Probe Production Centers Network (MLPCN) (X01) PAR-08-034

Solicitation of Assays for HTS in the Molecular Libraries Probe Production Centers Network (MLPCN) (R03) PAR-08-035

ASSAY DEVELOPMENT OPPORTUNITIES

Assay Development for High Throughput Molecular Screening (R21) PAR-08-024

Development of Assays for High-Throughput Drug Screening (R01) PA-07-320

COMPOUND SOLICITATION FOR HIGH-THROUGHPUT SCREENING IN THE MLSCN

Solicitation of Compounds for High Throughput Screening (HTS) in the MLSCN

PROBE PRODUCTION CENTERS

NIH Homepage

NIH


NIH Roadmap

Search

type, hit enter

Calendar

Categories:

< Feb  Apr >

March 2008

S	M	T	W	T	F	S
						1
2	3	4	5	6	7	8
9	10	11	12	13	14	15
16	17	18	19	20	21	22
23	24	25	26	27	28	29
30	31					

Internet

MLSMR Compound Collection (260,000 Compounds)

DC = Diversity Compounds

NC = Non-commercial

TL-KIN = Kinase Targeted Library

TL-GPCR = GPCR Targeted Library

TL-IC = Ion Channel Targeted Library

TL-PRO = Protease Targeted Library

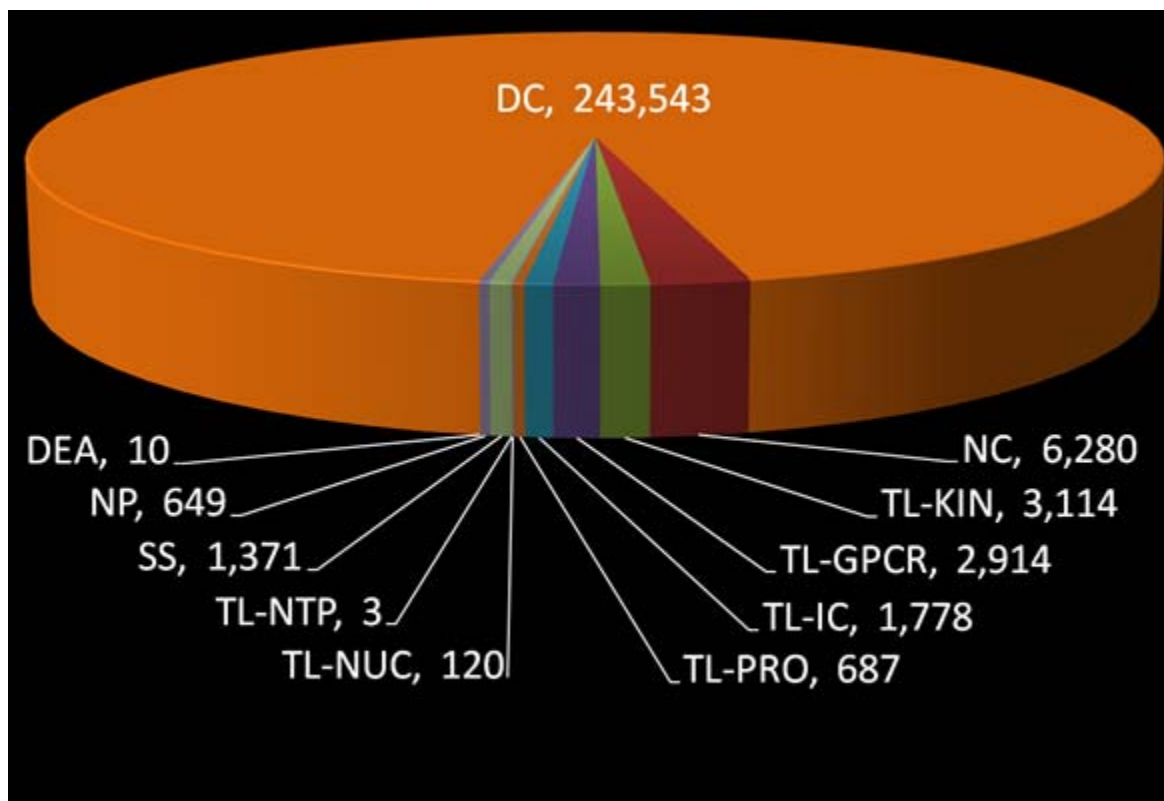
TL-NUC = Nuclear Receptor Targeted

TL-NTP = National Toxicology Program

SS = Known Bioactives

NP = Natural Products

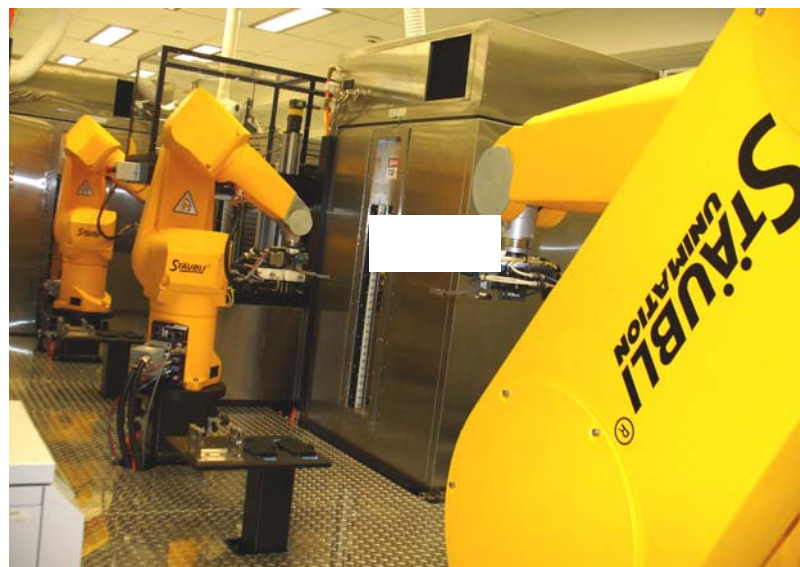
DEA = DEA Controlled Substances



NIH Chemical Genomics Center



- Founded 2004
- 54 scientists – biologists, chemists, informaticians, engineers
- Collaborates with >100 investigators worldwide
 - 60% NIH extramural
 - 25% NIH intramural
 - 15% Foundations, Research Consortia
- Focus on novel targets, rare and orphan diseases
 - Equal number of projects for basic research chemical probes and starting points for disease drug development

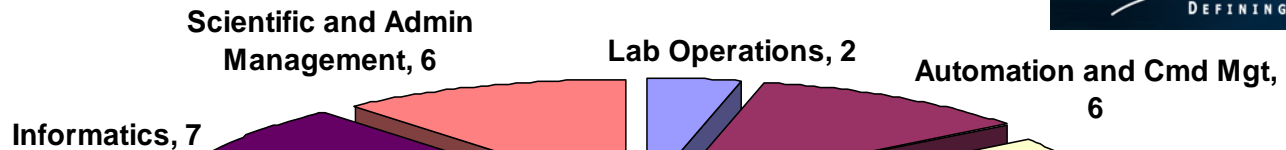




NIH Chemical Genomics Center: Founding Principles

- Bring the best of the **technologies, equipment, experience, and people** from pharma and biotech, and apply them to the 95% of the genome and 95% of human diseases not worked on by biopharma
- **Scale** must be equal to or greater than a pharma
- **Automate** everything
 - Cheaper, faster, more accurate
 - Allows recruitment and retention of finest scientists
- **Collaborate** extremely widely
- Produce **chemical probes of demonstrated biological utility**
 - Requires major Medicinal Chemistry presence

NCGC Staff May 2008

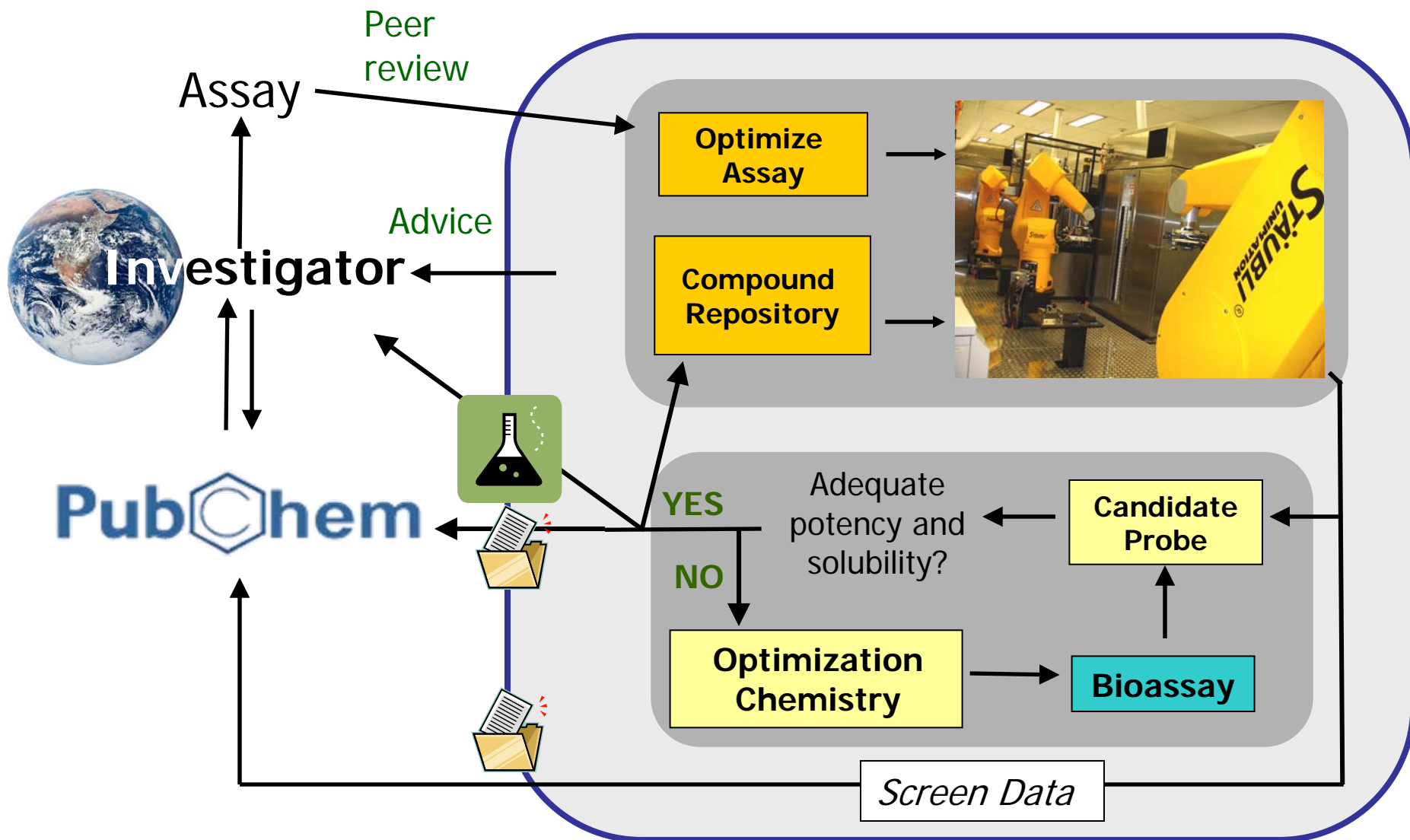


Chemistry, 15

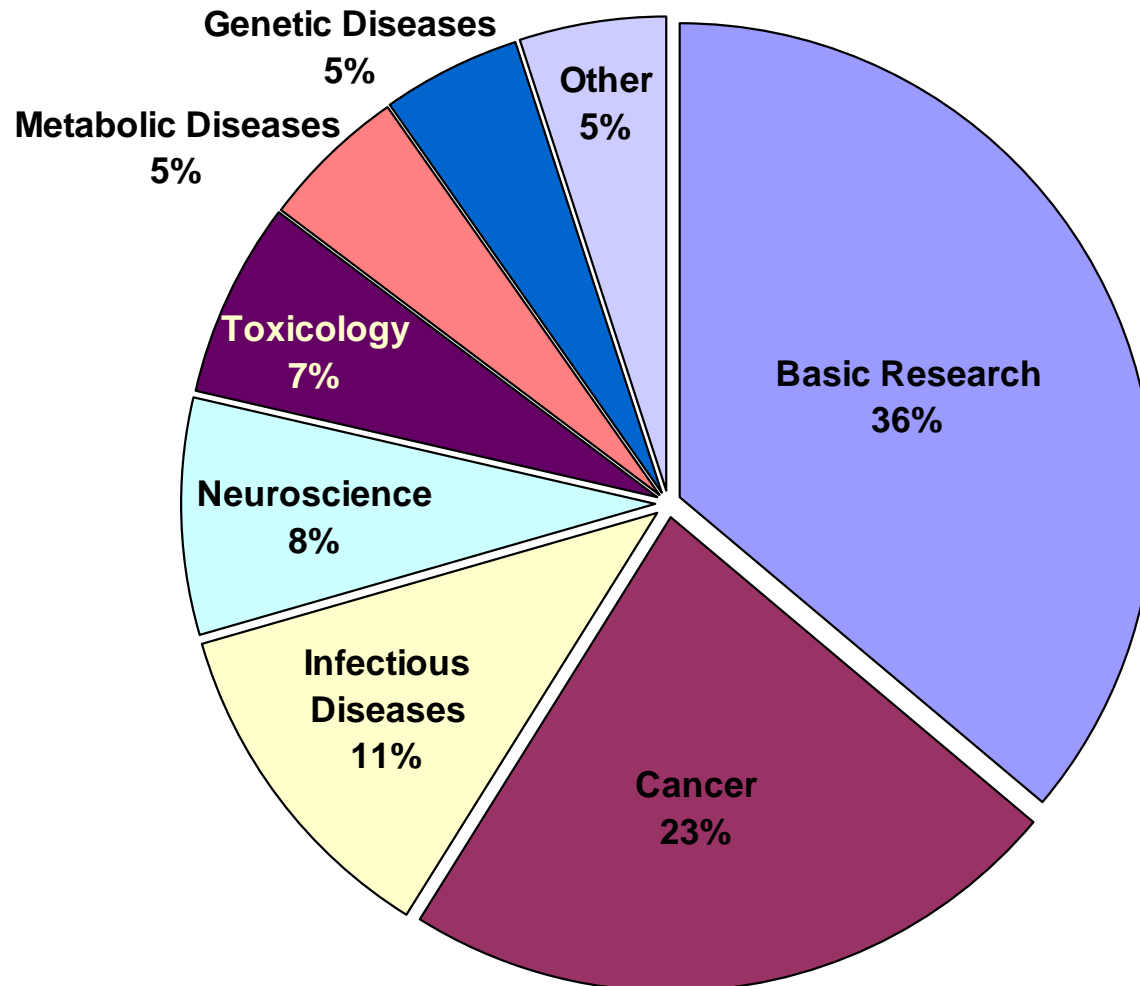
Assay Development and Biology, 18



NCGC Operation



Disease areas of NCGC projects 2005-2007



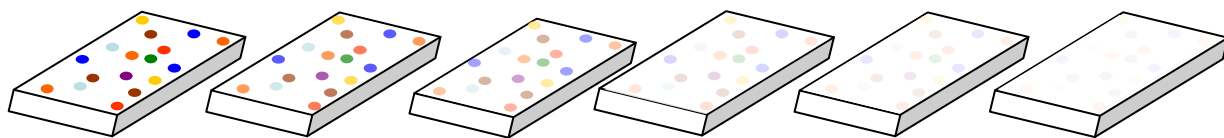
Establishing a paradigm for chemical genomics

For each assay, **efficiently** and **comprehensively**
describe the biological activity of a chemical library

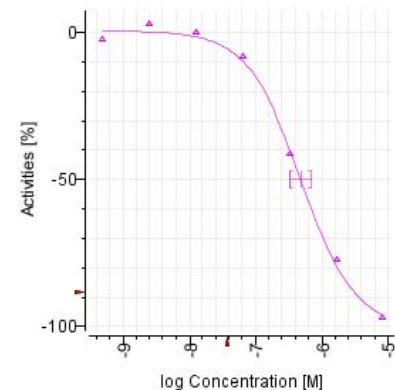
1. Direct us toward chemical series:
 - suitable probes
 - probe potential
 - ❖ SAR for probe optimization
2. Populating a "Chemical Genomics" database
 - reliable activity of all library members for all assays that are screened at NCGC
 - → useful for profiling actives against all subsequent assays

Quantitative high-throughput screening (qHTS)

- Conventional HTS: done at one concentration (typically 10 μM)
- qHTS: All compounds tested in titration
 - 15 concentrations
 - Concentration range 0.5 nM to 92 μM
 - Concentration-response curve generated for each compound
- Assay volumes $\sim 5 \mu\text{L}$
- 1536-well plate format
- Informatics pipeline for data processing, curve fitting & classification
- Higher quality data



Compound concentration



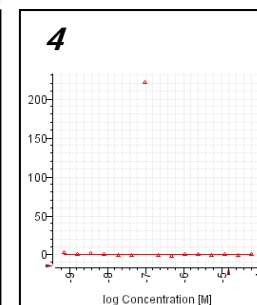
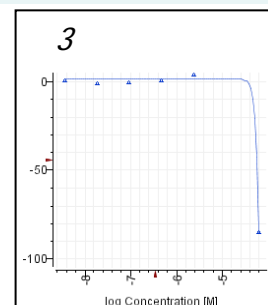
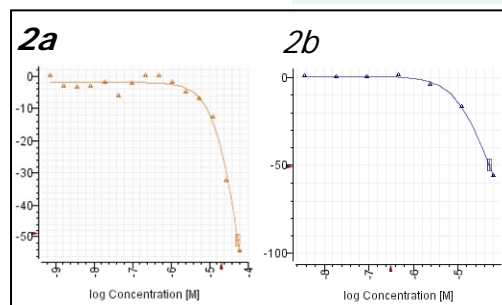
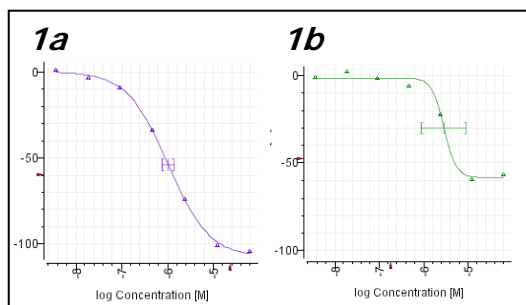
qHTS curve classification criteria

Curve Class	Description	Efficacy	r^2	Asymptotes	Inflection
1*	Complete curve (a)	> 80% (a)	≥ 0.9	2	yes
	Partial curve (b)	$\leq 80%$ (b)			
2†	Incomplete curve	> 80% (a)	> 0.9 (a)	1	yes
		< 80% (b)	< 0.9 (b)		
3	Single pt activity	> Min‡	NA	1	no
4	Inactive	NA	NA	0	no

NOTES: * AC_{50} derived from data; † AC_{50} extrapolated from data; ‡Min is > 3 SD from the mean activity of the sample field at the highest tested concentration

Examples

Lower confidence data

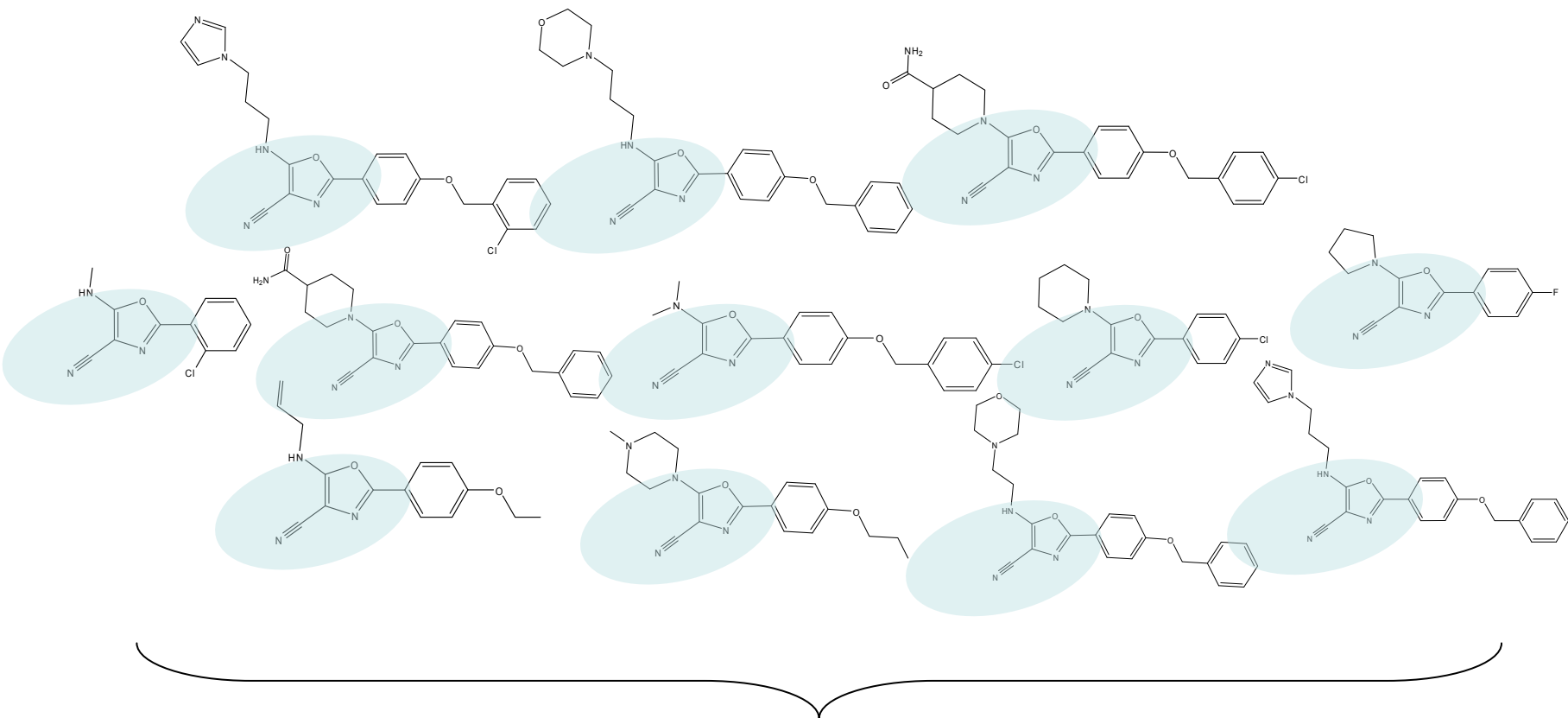


Derivation of nascent SAR from qHTS

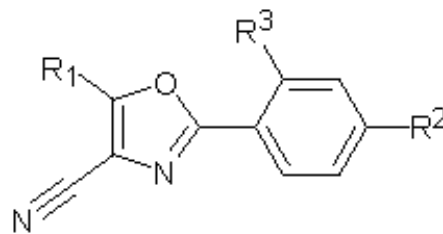
- Class 1 and 2a – Hierarchical clustering
 - Leadscope fingerprints
 - Tanimoto cutoff = 0.7
 - 55 clusters
- Maximal common substructure (MCS) extracted for each cluster
 - MCS used to search entire screening collection
 - 40 series composed of 4-25 active analogs
 - Results associated with biological data

Classes 1a, b and 2 ► 12 cpds

Cluster 5, 2-phenyloxazole-4-carbonitrile



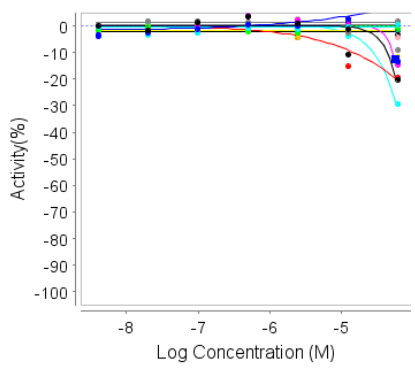
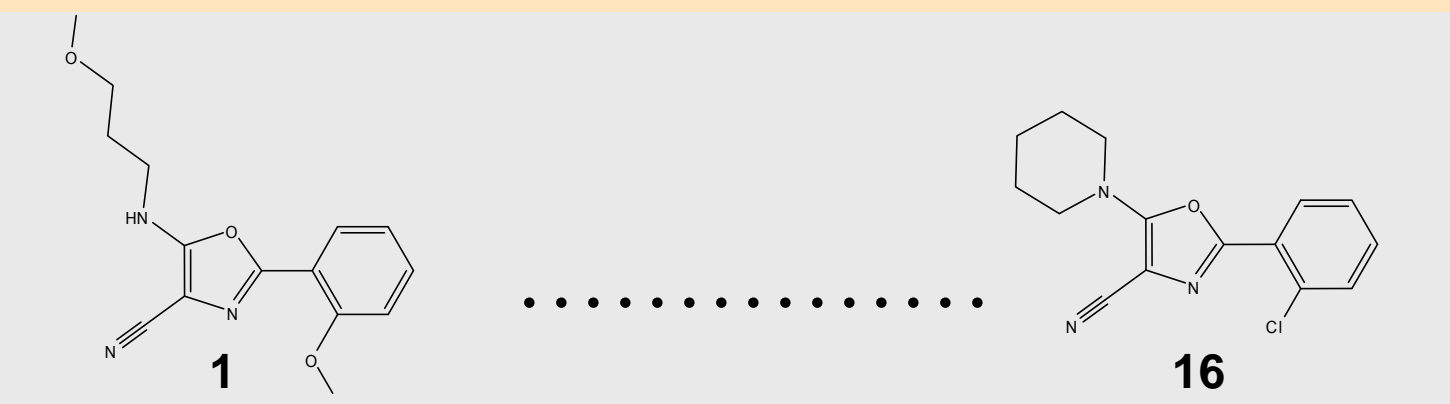
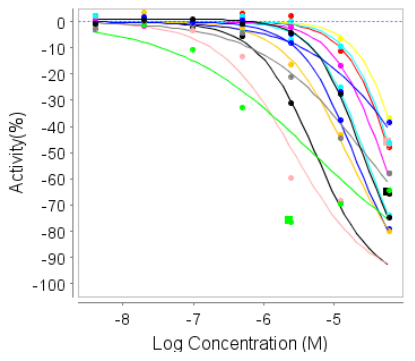
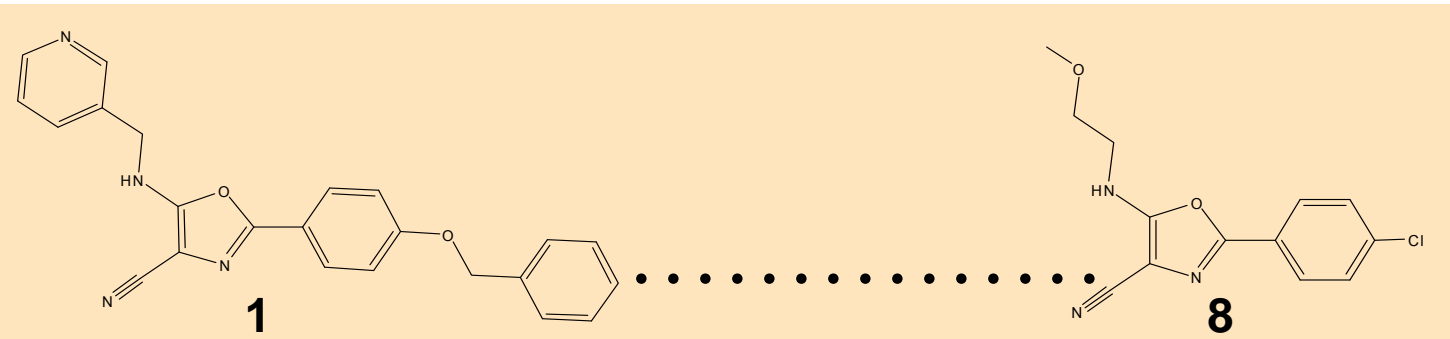
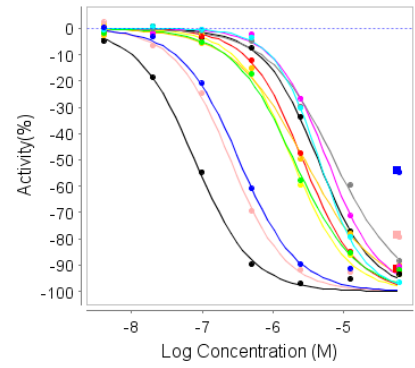
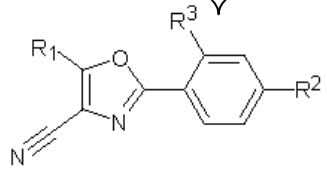
MCS



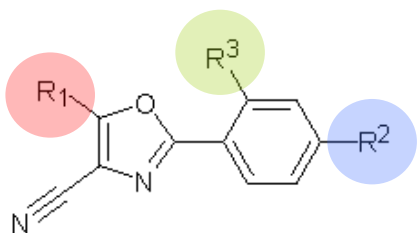
Classes 1a, b and 2 ► 12 cpds, Cluster 5



MCS



Structure-Activity Relationship (SAR) Report



2-phenyloxazole-4-carbonitrile series

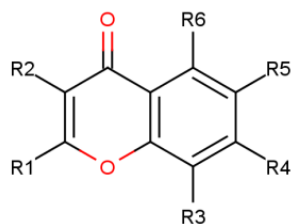
- The SAR report is a 'map' to enabling chemical optimization of a lead series

#	R1	R2	R3	NCGC ID	Curve Class	Rank	AC50 (uM)	Act Max Conc	hill Coeff
1			H	NCGC00067413-01	1.1	1/20	0.08	-92	1.1
2			H	NCGC00067270-01	1.1	5/20	1.9	-93	1.1
10			H	NCGC00067494-01	2.1	12/20	4.5	-96	1.4
21		F	H	NCGC00023889-01	3	20/20	42	-32	1.6
30		H	F	NCGC00039456-01	4		inactive	1	
39		H	Cl	NCGC00052762-01	4		inactive	1	

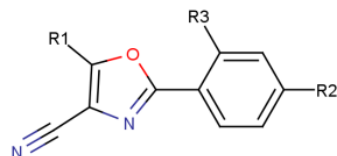
Electronic counterscreens across >100 assays

Active Chemical Series For Kinase Assay

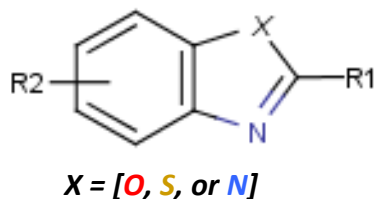
Series 1



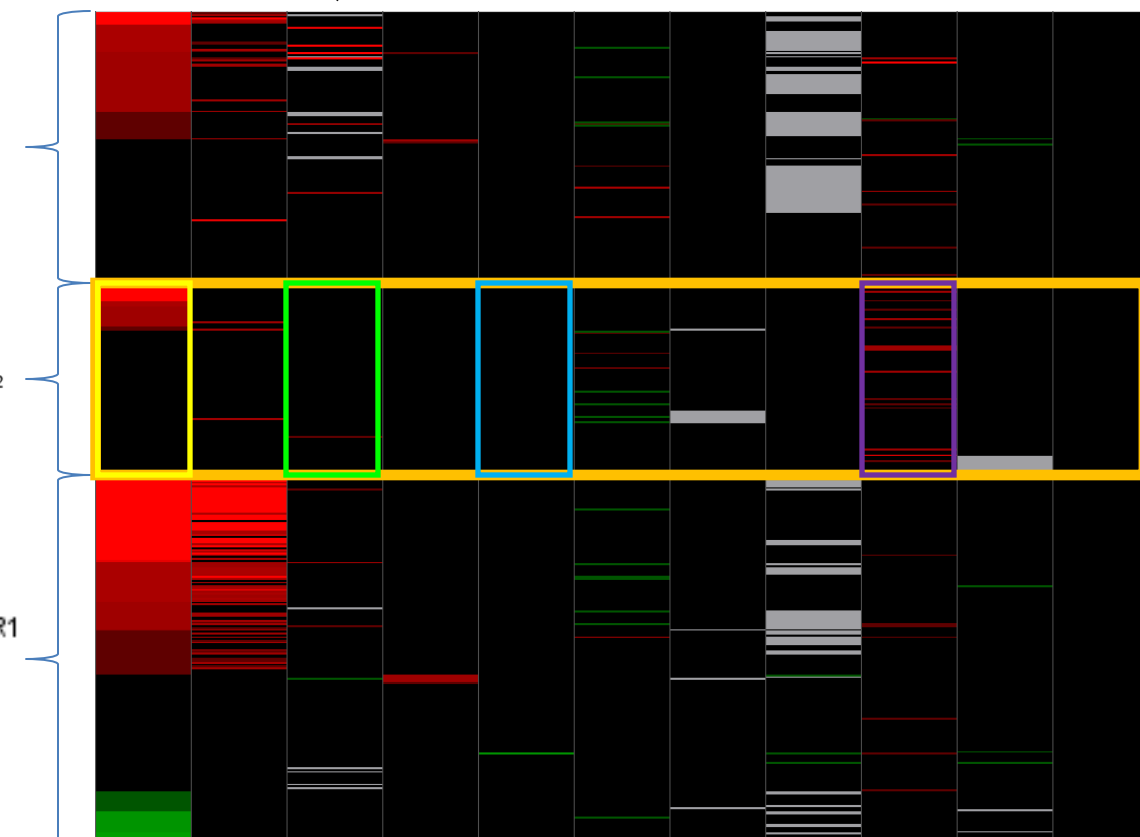
Series 2



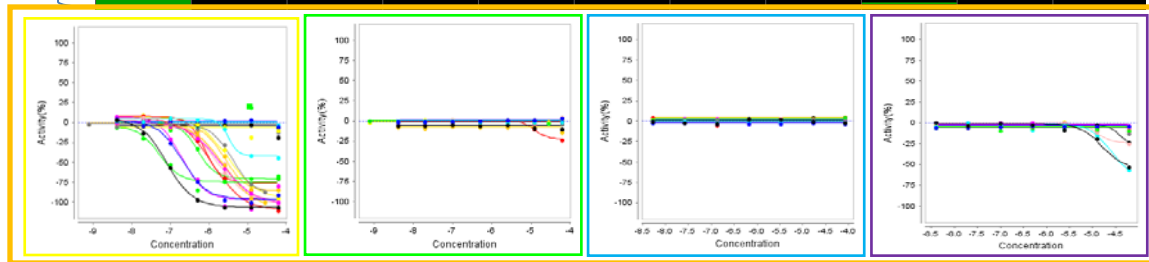
Series 3



Pk Luc Pol III sOGT YjeE Prx2 Prot β -Thal Hsp90 LDR AmpC >100



~300,000



NCGC Chemical Genomics Browser

qHTS Navigator

File Options

Heatmap View Cluster View

Assay Selection Show options...

Source: Assay Name

Selection	Assay Name	Data Type
<input checked="" type="checkbox"/>	cre	ratio_new
<input checked="" type="checkbox"/>	cre-lance	ratio
<input checked="" type="checkbox"/>	cre-luci	set1
<input checked="" type="checkbox"/>	cre-pde	set1
<input checked="" type="checkbox"/>	cre-pde-camp	ratio
<input checked="" type="checkbox"/>	cre-pka	ratio
<input checked="" type="checkbox"/>	cre-viability	pingjun
<input checked="" type="checkbox"/>	cruzain-d	delta60s
<input checked="" type="checkbox"/>	cruzain-nd	delta60s
<input checked="" type="checkbox"/>	dnapolyIII	set1
<input checked="" type="checkbox"/>	erk-phos	set2
<input checked="" type="checkbox"/>	glucocerebrosidase...	gd
<input checked="" type="checkbox"/>	grtranslocation	set1
<input checked="" type="checkbox"/>	hadh5G0	digit4
<input checked="" type="checkbox"/>	hresignaling	ratio
<input checked="" type="checkbox"/>	hsdb130	gd
<input checked="" type="checkbox"/>	hsp90	set1

Remember Settings Collapse Samples

Sample Selection

Source: Sample ID

Sample ID Substructure

Data Selection

Source: Curve Class Density 1

Organize Visualize Cancel

Heatmap Legend

N/A -1.1 -1.2 -1.3 -1.4 -2.1 -2.2 -2.3 -2.4 -3 4 5 3 2.4 2.3 2.2 2.1 1.4 1.3 1.2 1.1

Heatmap Tabular

NCGC

cre

cre-lance

cre-luci

cre-pde

cre-pde-camp

cre-pka

cre-viability

cruzain-d

cruzain-nd

dnapolyIII

erk-phos

glucocerebrosidase...

grtranslocation

hadh5G0

hresignaling

hsdb130

hsp90

cre

cre-lance

cre-luci

cre-pde

cre-pde-camp

cre-pka

cre-viability

cruzain-d

cruzain-nd

dnapolyIII

erk-phos

glucocerebrosidase-red

huntington-atb

hsvrivatekinase

tau

usd2

ao1 sialina

nos-agonist

addref

arx

brca737-green

artranslocation

hresignaling

amocnd

vieered

thalassemic-betaalobin-soli

soot

proteasome

dk-leishmania

o53-null-39deq

o53-39deq

o53-32deq

luciferase

ldr

imorintina

huntington-atb

hsp90

12hLO

amocd

caspaase1

cho-dfb-counterscreen

cre-pka

cruzain-d

dnapolyIII

NCGC00063798-01

cre

Activity

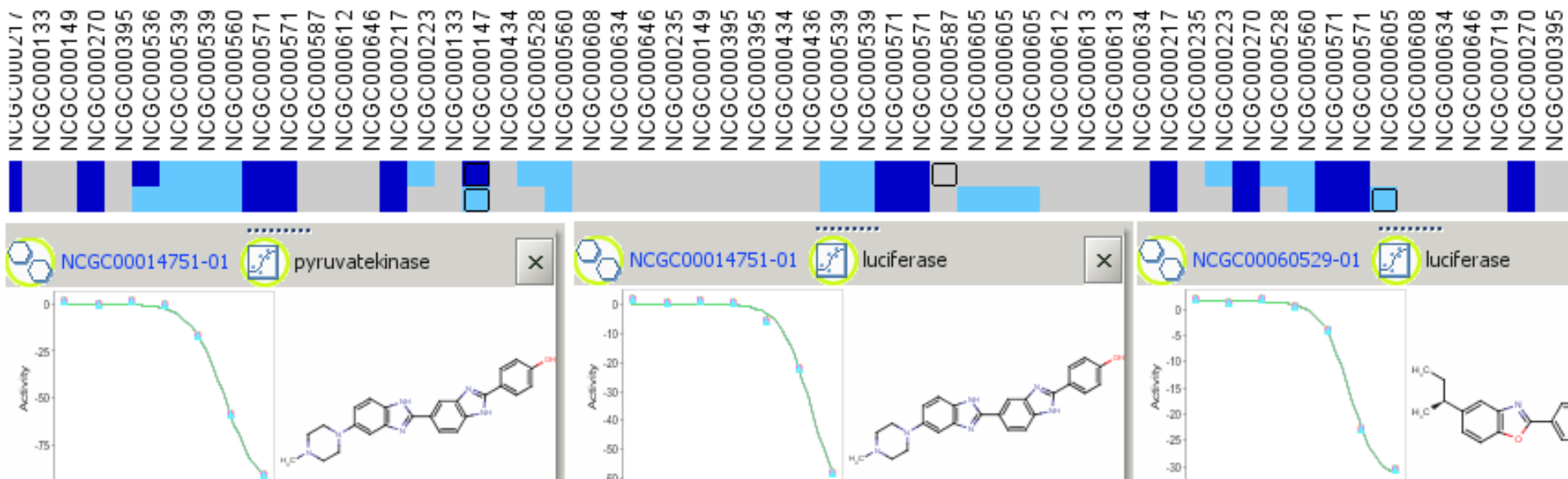
Concentration (Log)

Chemical Structure

Property	Value
AC50	1.258925411
CURVE_CLASS	1.1
HILL_COEF	1.372261
INF_ACTIVITY	129.289702
MAX_RESPONSE	133.0750647
PROTOCOL_NAME	cre-p2
PUBCHEM_SID	861119
R2	0.993826610
SAMPLE_ID	NCGC00063798-01
SMILES_CAN	COc1ccc(OC)c1
SMILES_ISO	COc1ccc(OC)c1

NCGC Stats

- 174 Assays deposited in PubChem (since Feb05)
- Wells tested: 42.5 million
 - Number of data points: 302 million
- Concentration-response (CR) profiles: 4.4 million
 - Data fields deposited into PubChem: >40M
- 32 probe projects / 34 probes/33 publications
- Screening throughput 2.5 million wells/wk



Case Study: Development of Inhibitors of *Schistosoma mansoni* Peroxiredoxins

**NCGC Collaboration with
David Williams
Department of Biological Sciences
Illinois State University, Normal, IL**



ILLINOIS STATE
UNIVERSITY

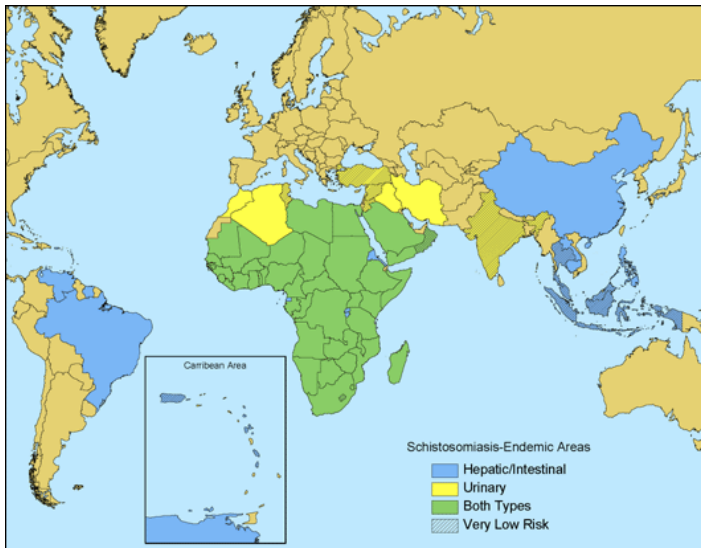


NIH CHEMICAL GENOMICS CENTER

Schistosomiasis



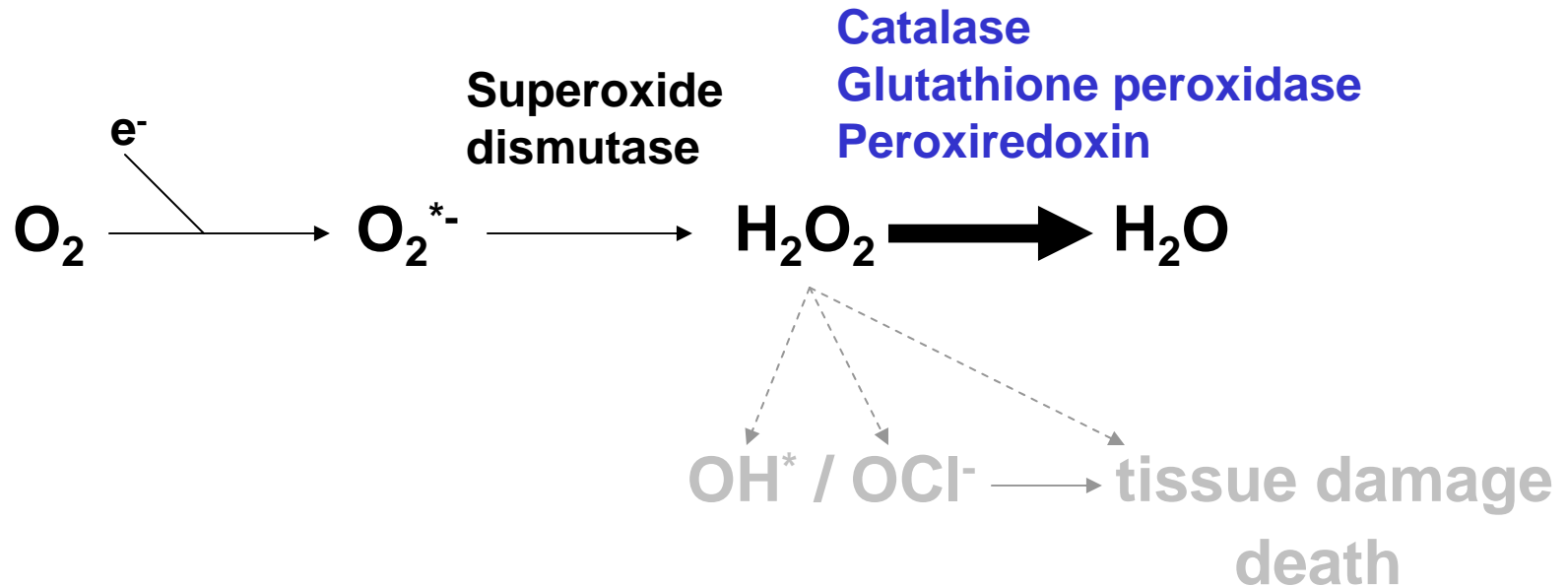
- **250,000,000** infections
- **20,000,000** with significant pathology
- **280,000** deaths/year
- **Major cause of morbidity**
- **Endemic in 75 countries**
- **> 80% infections in sub-Saharan Africa**



CDC®

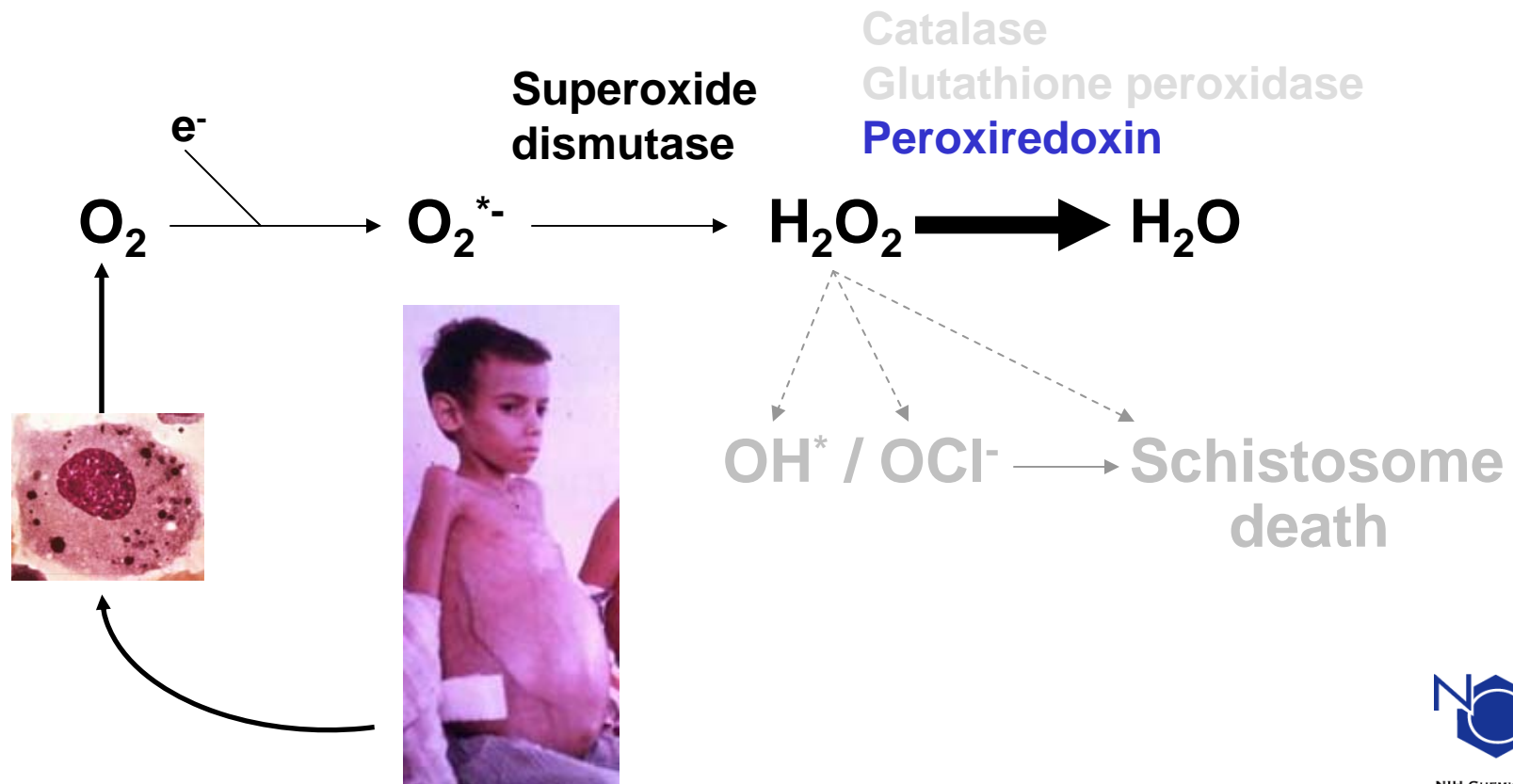
Targeted Redox Pathway

Humans have three enzymes that degrade hydrogen peroxide made from superoxide radicals



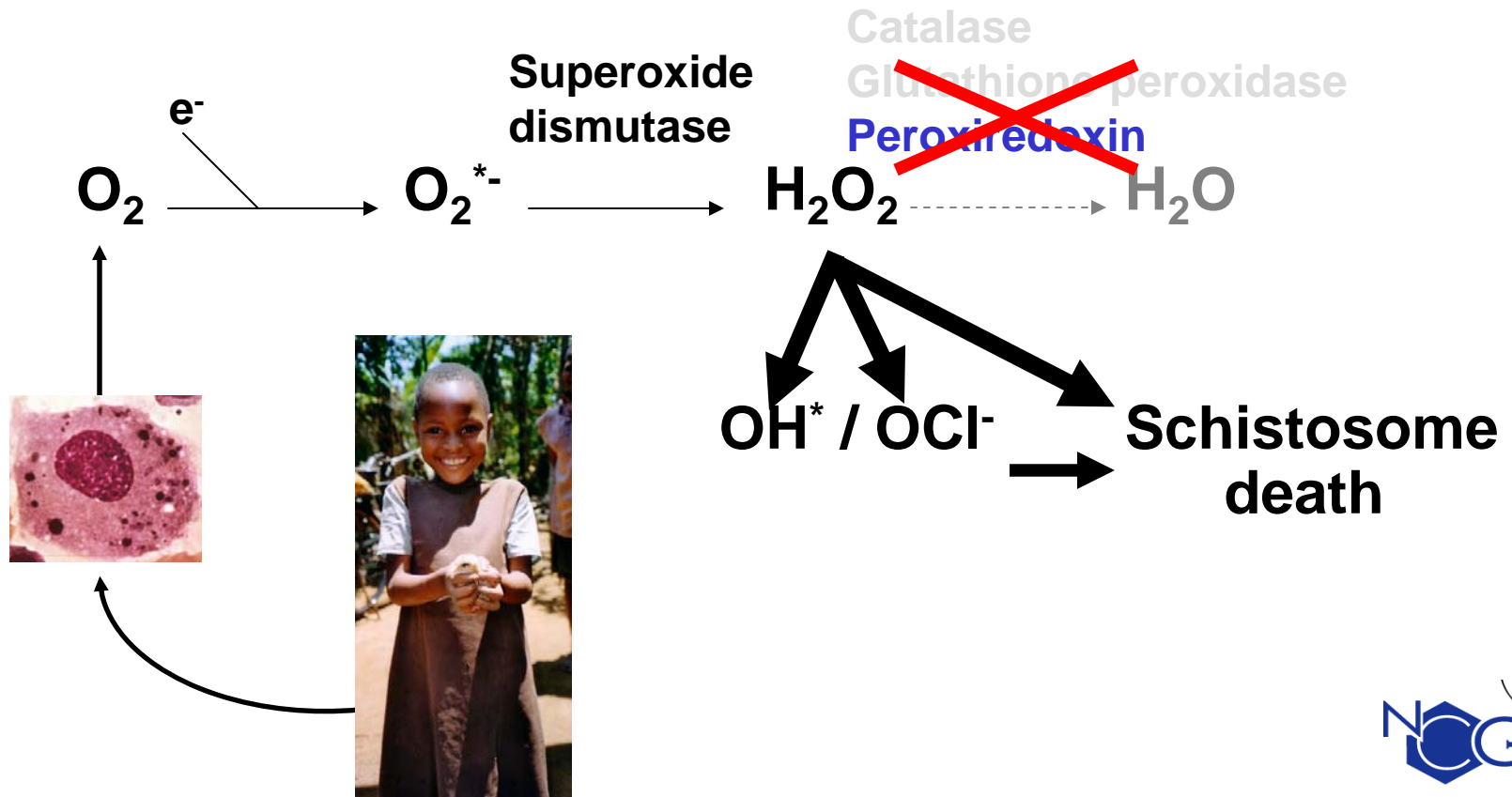
Targeted Redox Pathway

- *S. mansoni* has no catalase or glutathione peroxidase.
- Survives in humans due to parasite-specific peroxiredoxin that degrades reactive oxygen species produced by human innate immune response.



Targeted Redox Pathway

Inhibition of *S. mansoni* peroxiredoxin would prevent worm degradation of hydrogen peroxide and kill schistosomes



Discovery of Pathway: 2002



Molecular & Biochemical Parasitology 121 (2002) 129–139

MOLECULAR
& BIOCHEMICAL
PARASITOLOGY

www.parasitology-online.com

The disulfide redox system of *Schistosoma mansoni* and the importance of a multifunctional enzyme, thioredoxin glutathione reductase[☆]

Heather M. Alger, David L. Williams *

Department of Biological Sciences, Illinois State University, Normal, IL 61790-4120, USA

Received 26 December 2001; accepted in revised form 8 February 2002

Identification of Target: 2006

Thioredoxin Glutathione Reductase from *Schistosoma mansoni*: An Essential Parasite Enzyme and a Key Drug Target

Angela N. Kuntz¹, Elisabeth Davioud-Charvet^{2,3}, Ahmed A. Sayed¹, Lindsay L. Califf¹, Jean Dessolin^{2,4}, Elias S. J. Arnér⁵, David L. Williams^{1*}

1 Department of Biological Sciences, Illinois State University, Normal, Illinois, United States of America, **2** Biochemie-Zentrum der Universität Heidelberg, Heidelberg, Germany, **3** Centre National de la Recherche Scientifique (CNRS), Paris, France, **4** Institut Européen de Chimie et Biologie, CNRS UMR 5144, Bordeaux University, Pessac Cedex, France, **5** Medical Nobel Institute for Biochemistry, Department of Medical Biochemistry and Biophysics, Karolinska Institutet, Stockholm, Sweden

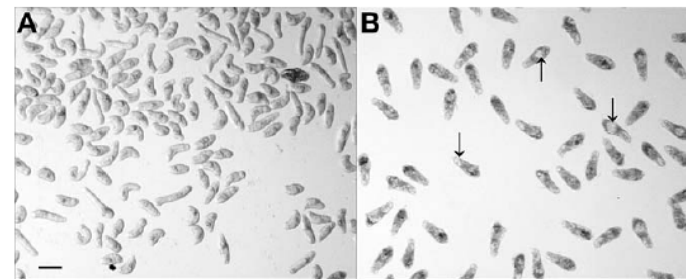
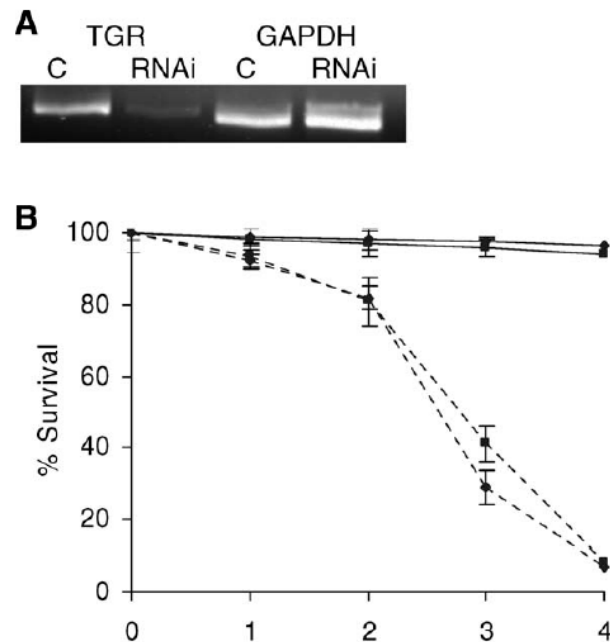
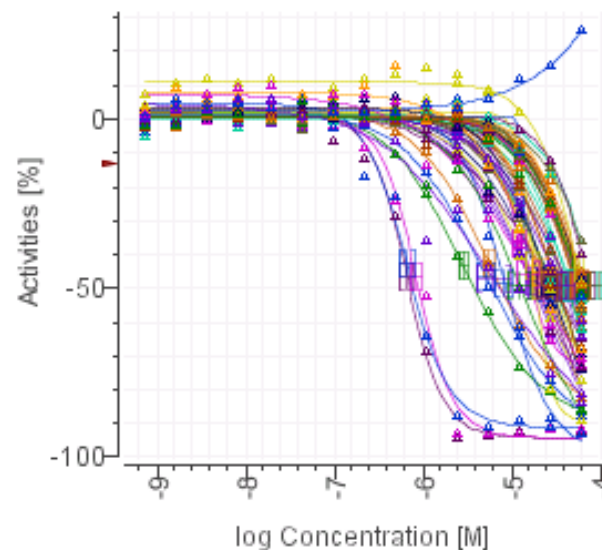


Figure 8. Photomicrographs (100 \times) of Irrelevant dsRNA-Treated Schistosomula (left image) and TGR dsRNA-Treated Schistosomula (right image) after Three Days of Treatment

All organisms in the left image are alive; parasites have different shapes, elongated, contracted, and curved during movement. In the right image, all of the parasites are dead and have roughly the same shape (no movement) and internal vacuoles (arrows). The bar represents 250 μ m. doi:10.1371/journal.pmed.0040206.g008

Quantitative HTS:2007

- **70,000 compounds at 7 concentrations (qHTS)**
 - Dose-response curve for all compounds (PNAS 103, 11473-8 (2006))
 - ~10,000,000 data points (16 Time-Point Reads)
 - 31 hours of robot time
- **Results: 100 compounds with $IC_{50} < 40 \mu M$**
 - 71 compounds
 - 6 different structural classes



Quantitative High-Throughput Screen Identifies Inhibitors of the *Schistosoma mansoni* Redox Cascade

Anton Simeonov¹, Ajit Jadhav¹, Ahmed A. Sayed², Yuhong Wang¹, Michael E. Nelson¹, Craig J. Thomas¹, James Inglese¹, David L. Williams^{2*}, Christopher P. Austin^{1*}

¹ NIH Chemical Genomics Center, National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland, United States of America, ² Department of Biological Sciences, Illinois State University, Normal, Illinois, United States of America

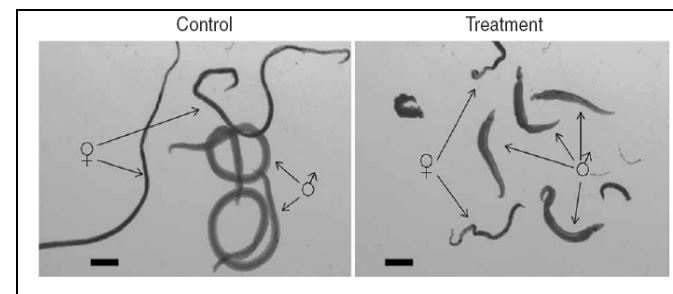
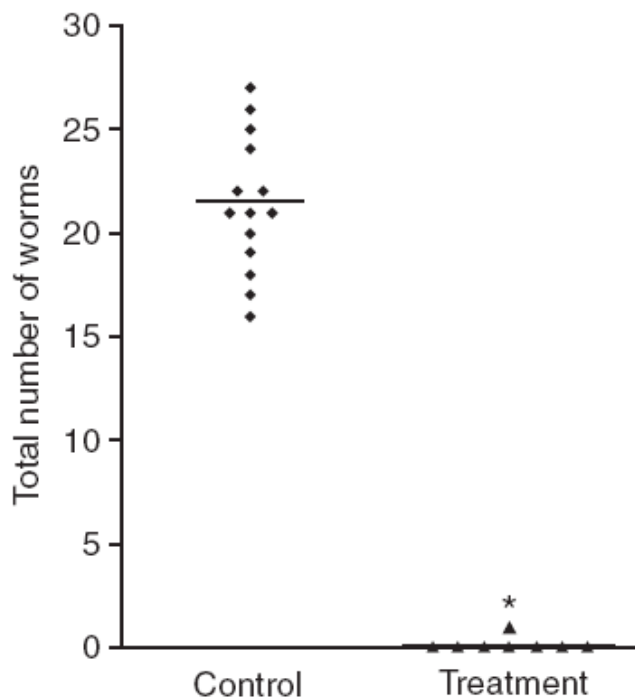
Abstract

Schistosomiasis is a tropical disease associated with high morbidity and mortality, currently affecting over 200 million people worldwide. Praziquantel is the only drug used to treat the disease, and with its increased use the probability of developing drug resistance has grown significantly. The *Schistosoma* parasites can survive for up to decades in the human host due in part to a unique set of antioxidant enzymes that continuously degrade the reactive oxygen species produced by the host's innate immune response. Two principal components of this defense system have been recently identified in *S. mansoni* as thioredoxin/glutathione reductase (TGR) and peroxiredoxin (Prx) and as such these enzymes present attractive new targets for anti-schistosomiasis drug development. Inhibition of TGR/Prx activity was screened in a dual-enzyme format with reducing equivalents being transferred from NADPH to glutathione via a TGR-catalyzed reaction and then to hydrogen peroxide via a Prx-catalyzed step. A fully automated quantitative high-throughput (qHTS) experiment was performed against a collection of 71,028 compounds tested as 7- to 15-point concentration series at 5 μ L reaction volume in 1536-well plate format. In order to generate a robust data set and to minimize the effect of compound autofluorescence, apparent reaction rates derived from a kinetic read were utilized instead of end-point measurements. Actives identified from the screen, along with previously untested analogues, were subjected to confirmatory experiments using the screening assay and subsequently against the individual targets in secondary assays. Several novel active series were identified which inhibited TGR at a range of potencies, with IC_{50} s ranging from micromolar to the assay response limit (\sim 25 nM). This is, to our knowledge, the first report of a large-scale HTS to identify lead compounds for a helminthic disease, and provides a paradigm that can be used to jump-start development of novel therapeutics for other neglected tropical diseases.

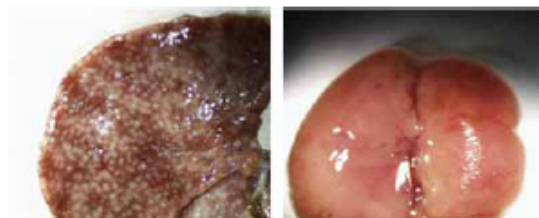
Identification of oxadiazoles as new drug leads for the control of schistosomiasis

Ahmed A Sayed¹, Anton Simeonov², Craig J Thomas², James Inglese², Christopher P Austin² & David L Williams¹

¹Department of Biological Sciences, Illinois State University, Normal, Illinois 61790, USA. ²NIH Chemical Genomics Center, National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland 20892-3370, USA. Correspondence should be addressed to D.L.W. (dlwilli@ilstu.edu) or C.P.A. (austinc@mail.nih.gov).



Treated worms



Livers of treated mice



NCBI

PubChem

PubChem BioAssay

[PubMed](#) | [Entrez](#) | [Structure](#) | [PubChem](#) | [Help](#)[PubChem](#) > [BioAssay Services](#) > [BioAssay Summary](#)

BioAssay Summary:

AID: 448Name: [Schistosoma Mansoni Peroxiredoxins \(Prx2\)](#).Data Source: [NCGC \(prx2\)](#)Activity Outcome Method: [Confirmatory](#), [Concentration-Response Relationship Observed](#)**BioAssay Results:** [Data Table\(Active Substances\)](#) [Data Table\(All Substances\)](#)**BioActive Compounds:** 40[BioActivity Summary](#) [Structure-Activity Analysis](#) [Structure Clustering](#)**Related BioAssays:** [Target Similarity \(1\)](#) [Activity Overlap \(159\)](#)**Links:****Compounds:** All: [63787](#) Active: [40](#) Inactive: [63393](#) Inconclusive: [364](#)**Substances:** All: [64651](#) Active: [44](#) Inactive: [64241](#) Inconclusive: [366](#)**Protein Target:** [1 Link](#)**Taxonomy:** [1 Link](#)**Related BioAssay, Depositor:** [2 Links](#)**Description:**

NIH Molecular Libraries Screening Centers Network [MLSCN]

NIH Chemical Genomics Center [NCGC]

David Williams [Illinois State University]

NCGC Assay Overview:

Schistosoma mansoni, a causative agent of schistosomiasis, resides in the bloodstream of their host up to 30 years without being eliminated by the host immune attack. One proposed survival mechanism is the production of an antioxidant "firewall" that neutralizes the oxidative assault of the host's immune attack. Schistosoma mansoni peroxiredoxins (Prx) are important parasite antioxidant proteins that play a crucial role in redox balance mechanisms. Data strongly suggest the possible use of Prx as novel drug targets. First, the proteins are essential for the parasite survival. Second, the proteins exhibit sufficient biochemical





BioActivity Analysis: 1 BioAssay and 63787 Compounds

Summary Data Table Structure-Activity

AID: 448

Total BioAssay Result Count: 63787

Data Table, Concise Data Table, Complete Plot Select



Page: 1 of 3190 Display: 20 Go To Page 1

Sort: (Click the result table header to sort.)

#	Structure	SID	CID	Score	Outcome	Links	Activity Direction	Activity Qualifier	Qualified AC50	Log of AC50	Hill Coefficient	Curve R2	Data Type	Compound QC	Data Analysis QC	NCGC Comment	Curve Fit Model	Hill S0	Hill Sinf	Hill ds	Log AC50 Std Error	Excl. Pair
1		3715577	2311082	74	Active		decreasing	=	3.74e-008	-7.428	2.86	0.97	qHTS Primary	QC'd by DPI	Verified	Full Curve	3pHill (AC50, n, Sinf)	0	-77	77	0.119	{
2		11110959	1730	64	Active		decreasing	=	4.41e-007	-6.355	3.31	0.99	qHTS Primary		Verified	Full Curve	3pHill (AC50, n, Sinf)	0	-81	81	0.022	{
3		4253459	16683706	63	Active		decreasing	=	4.96e-007	-6.304	2.33	1	qHTS Primary		Verified	Full Curve	3pHill (AC50, n, Sinf)	0	-82	82	0.03	{
4		857882	659226	63	Active		decreasing	=	5.3e-007	-6.276	10.72	0.98	qHTS Primary	QC'd by DPI	Verified	Full Curve	3pHill (AC50, n, Sinf)	0	-78	78		{

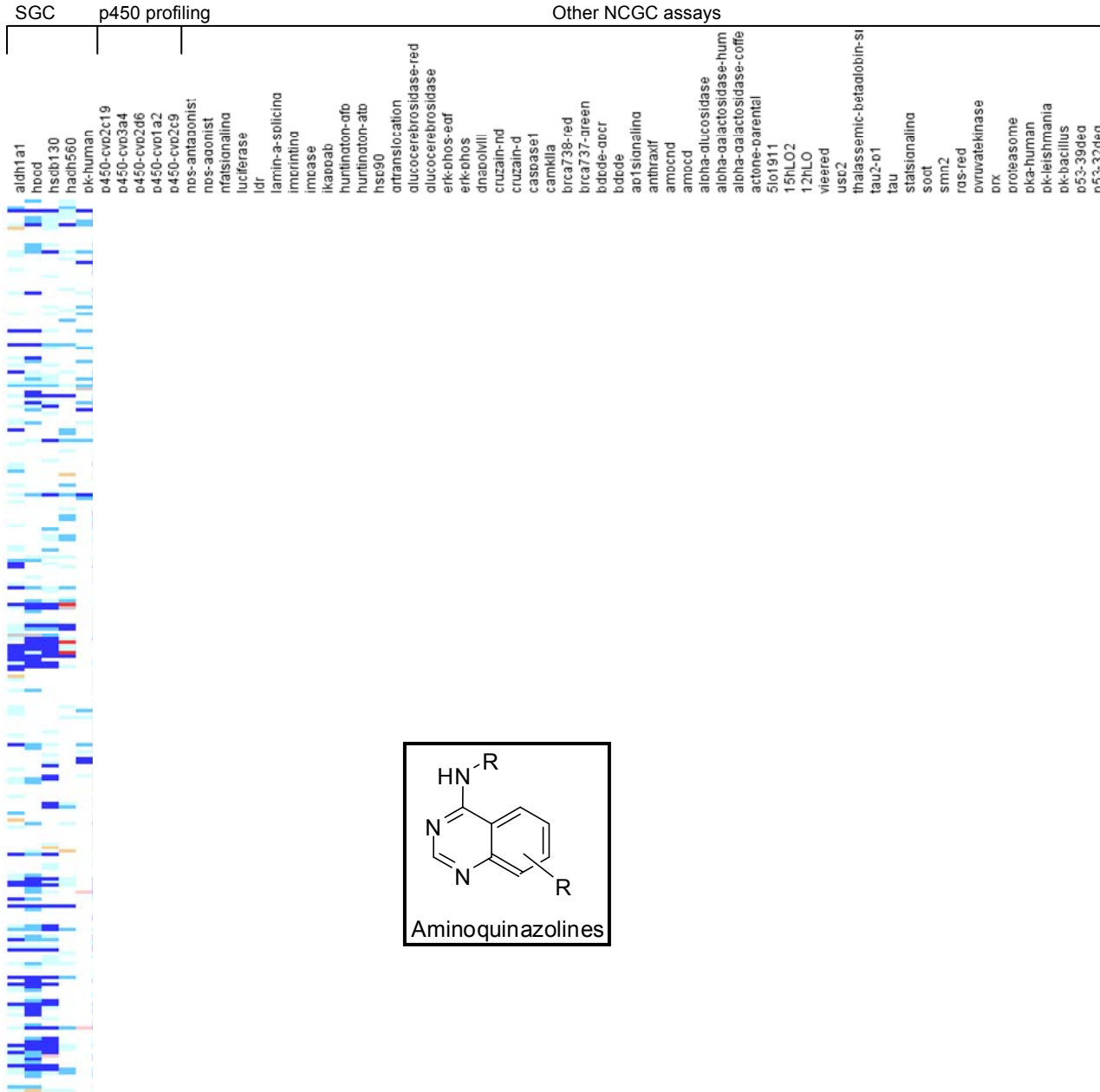
Full Concentration-Response

Number of Points	Activity at 0.732nM [%]	Activity at 1.636nM [%]	Activity at 3.658nM [%]	Activity at 8.18nM [%]	Activity at 18.291nM [%]	Activity at 0.041uM [%]	Activity at 0.091uM [%]	Activity at 0.204uM [%]	Activity at 0.457uM [%]	Activity at 1.022uM [%]	Activity at 2.286uM [%]	Activity at 5.111uM [%]	Activity at 11.429uM [%]	Activity at 25.556uM [%]	Activity at 0.057mM [%]	Compound Type
7			2		-9		-72		-81		-66		-81		-81	qHTS MLSMR
15	-4	-1	0	-3	3	-4	0	-5	-43	-75	-86	-85	-78	-75	-84	qHTS ECL - SigmaAldrich
7			1		0		1		-37		-78		-79		-86	qHTS ECL - NCI
7			-8		-1		-1		-13		-78		-84		-72	qHTS MLSMR

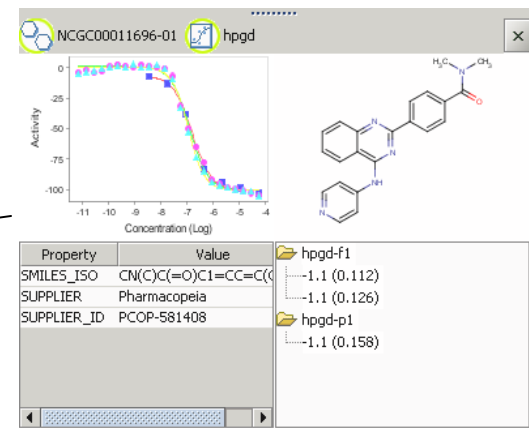
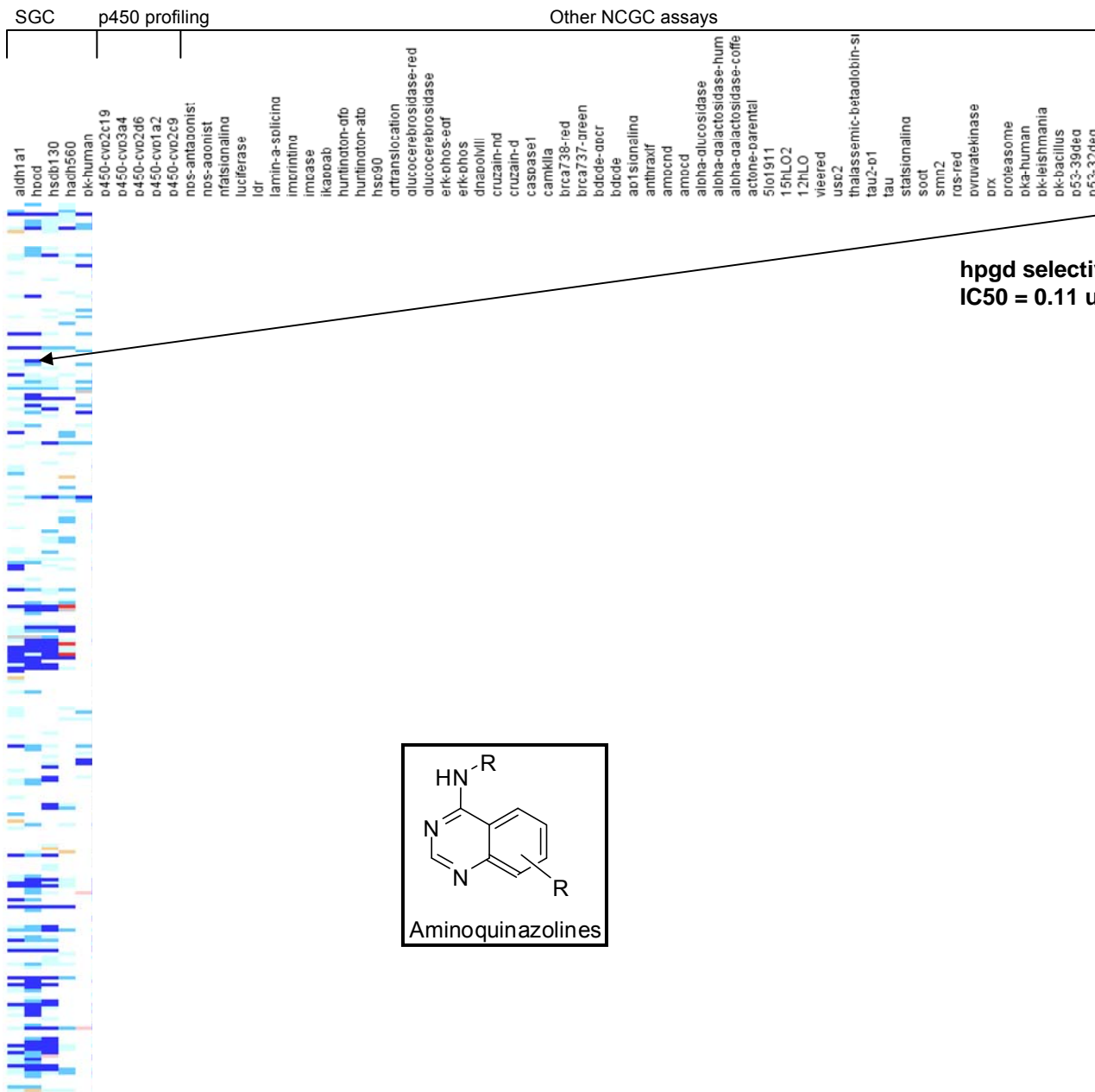
SGC Collaboration: Chemical Probes of Gene Families

- Discussions started 4Q 2004 (Edwards)
- Dehydrogenases (SGC-Oxford) chosen as first targets, enzymes received 1Q 2006
 - 4 enzymes screened against the full collection
- Collaboration expanded 2Q 2007 to new targets from all SGC sites
- Epigenetics collaboration begun 4Q 2007
 - Joint application to WT submitted last week
- NCGC PIs
 - Anton Simeonov
 - Doug Auld (Human PK)

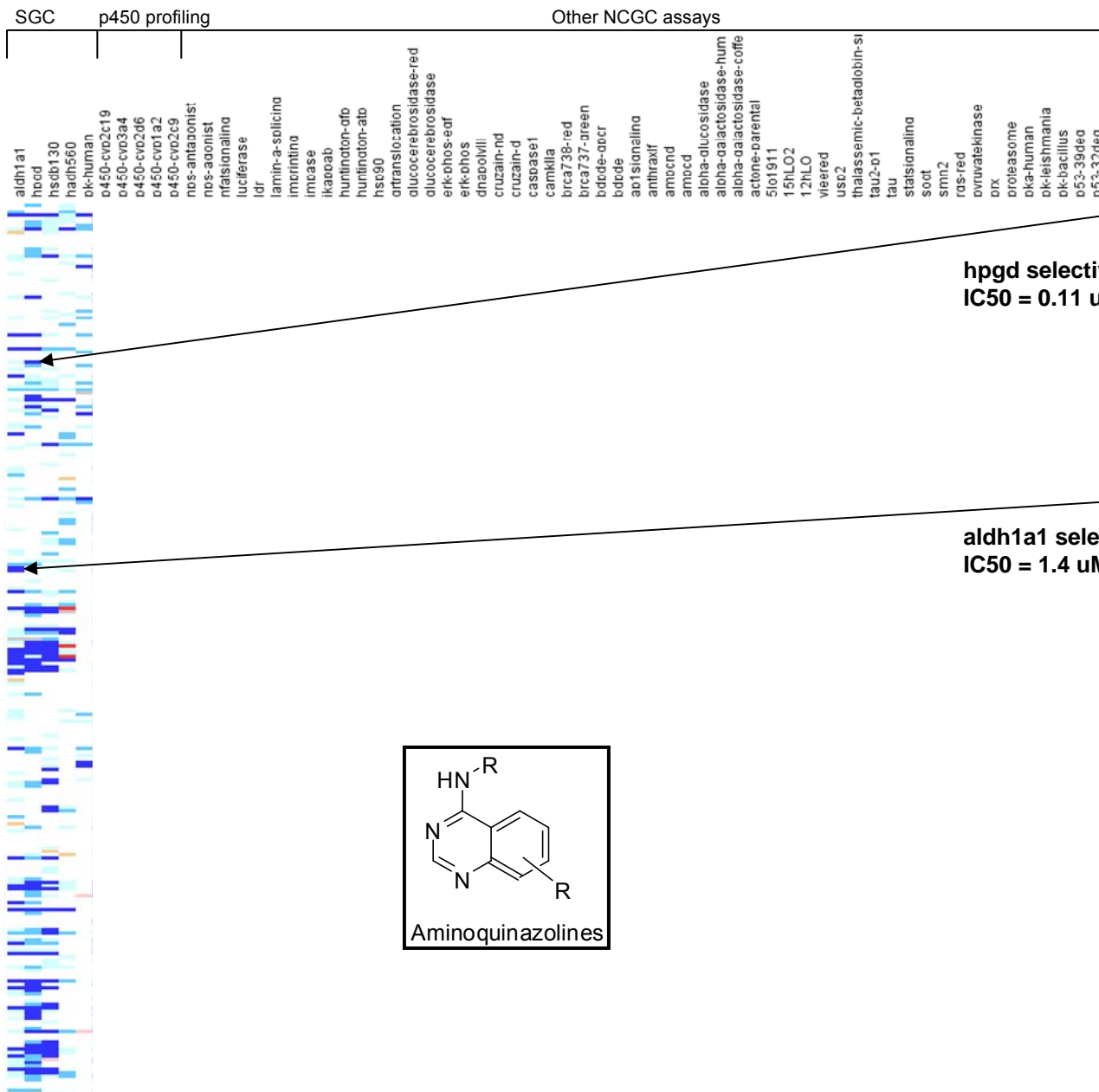
High Content Scaffold 'Family' Profiling of SGC Target Families



High Content Scaffold 'Family' Profiling of SGC Target Families

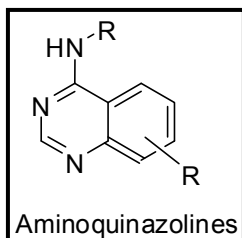


High Content Scaffold 'Family' Profiling of SGC Target Families



hpgd selective
IC50 = 0.11 uM

aldh1a1 selective
IC50 = 1.4 uM



hpgd

Activity vs Concentration (Log)

Property	Value
SMILES_ISO	CN(C(=O)C1=CC=C(C=C1)C2=CC=CC=C2)
SUPPLIER	Pharmacopeia
SUPPLIER_ID	PCOP-581408

hpgd-f1
-1.1 (0.112)
-1.1 (0.126)
hpgd-p1
-1.1 (0.158)

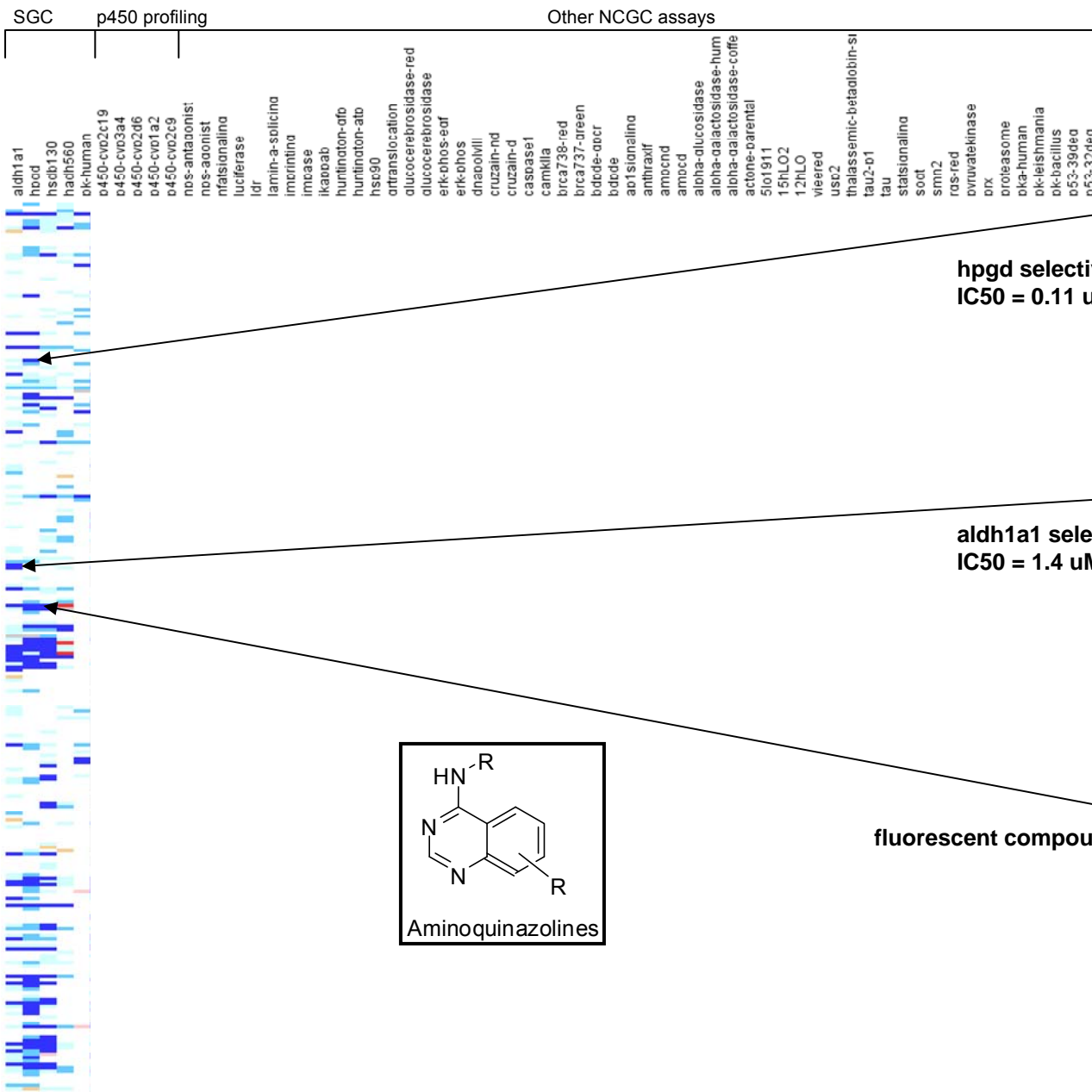
aldh1a1

Activity vs Concentration (Log)

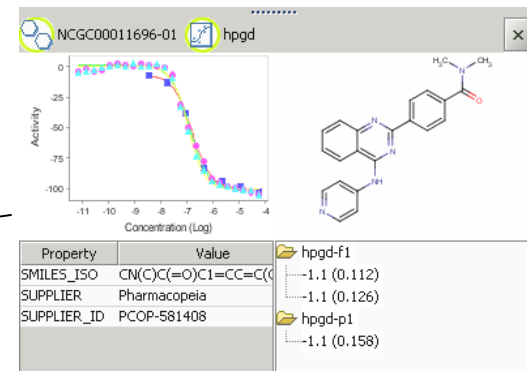
Property	Value
SMILES_ISO	C1CCCN(CC1)C2=CC=CC=C2
SUPPLIER	DPISMR
SUPPLIER_ID	STOCK25-5...

aldh1a1-p1
-2.1 (1.413)

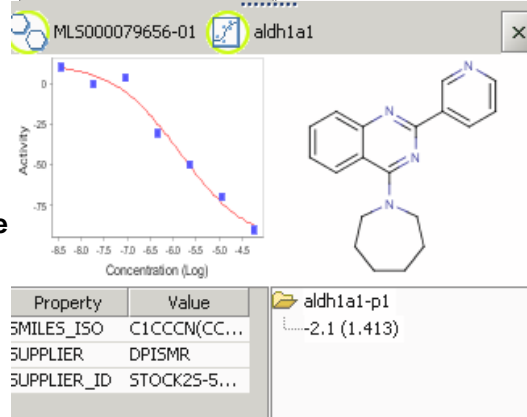
High Content Scaffold 'Family' Profiling of SGC Target Families



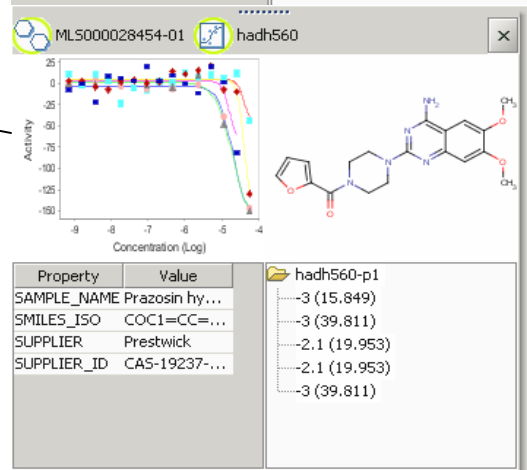
hpgd selective
IC50 = 0.11 μ M



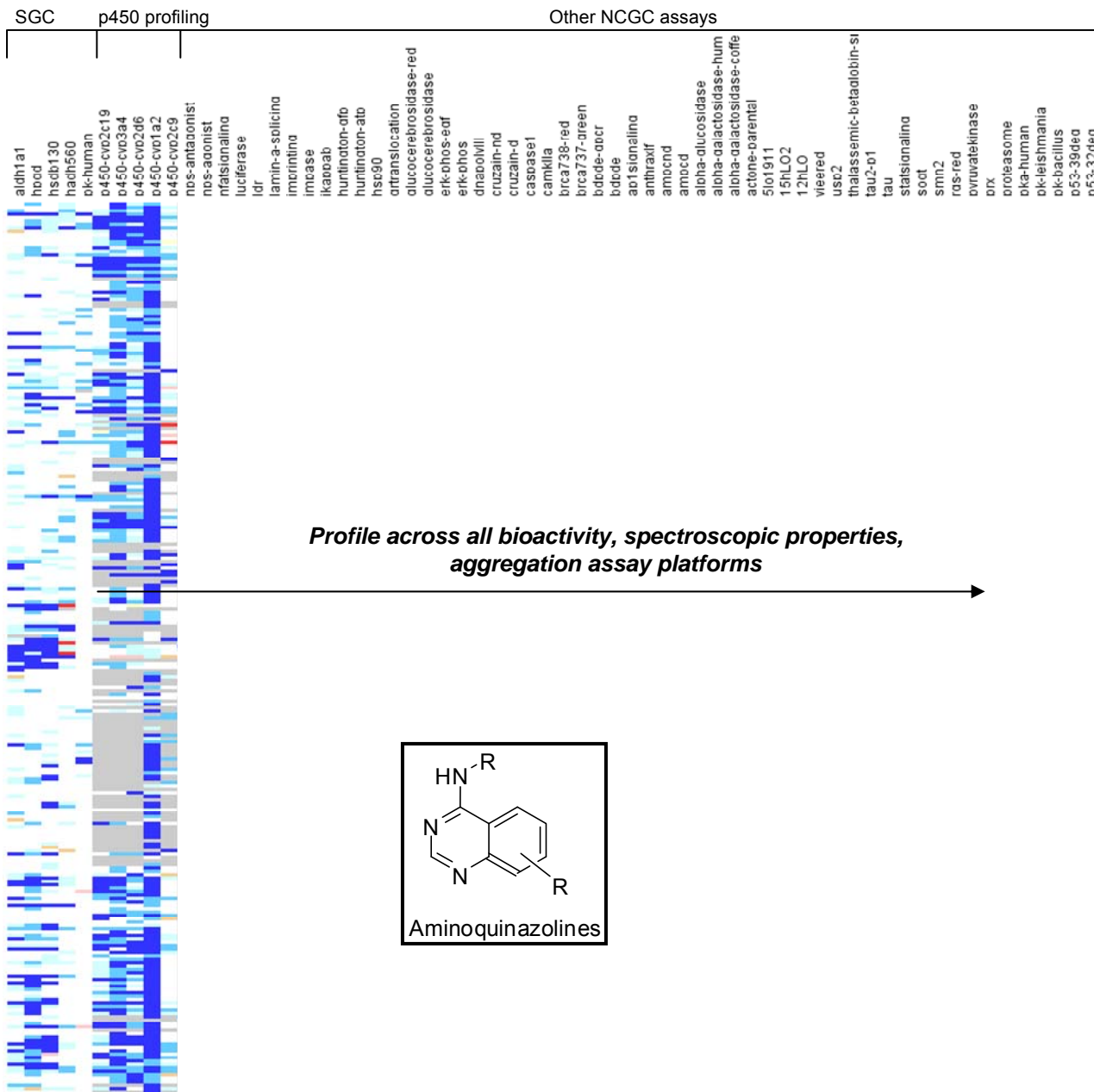
aldh1a1 selective
IC50 = 1.4 μ M



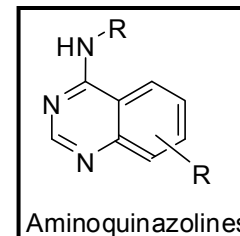
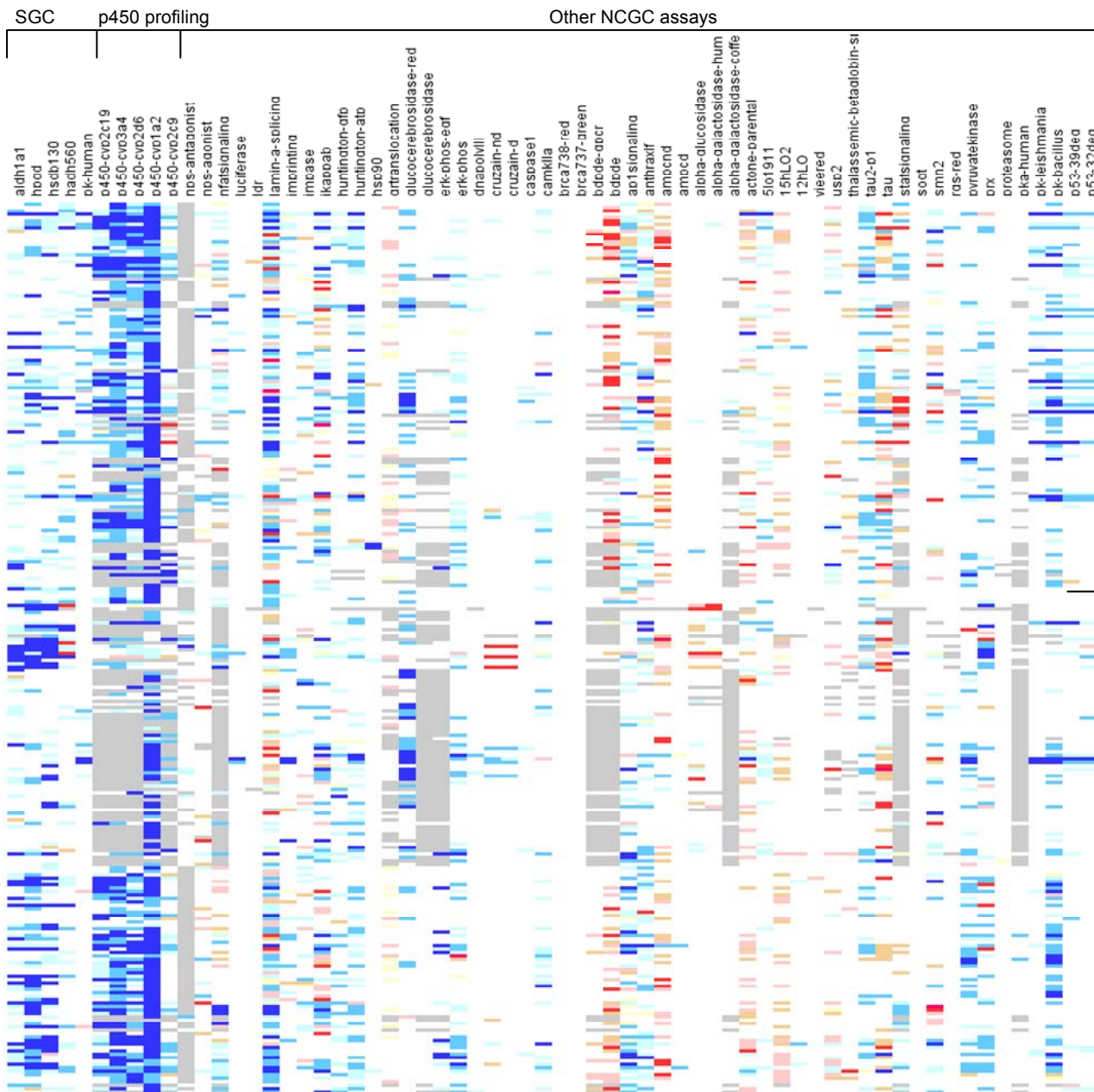
fluorescent compound



High Content Scaffold 'Family' Profiling of SGC Target Families



High Content Scaffold 'Family' Profiling of SGC Target Families



- Profiles mined for each scaffold tested, known drugs, etc

-Annotated assays organized by:
biological relationships,
assay platform, or
activity profiles



REVIEW

nature
chemical biology

High-throughput screening assays for the identification of chemical probes

James Inglese, Ronald L Johnson, Anton Simeonov, Menghang Xia, Wei Zheng, Christopher P Austin & Douglas S Auld

High-throughput screening (HTS) assays enable the testing of large numbers of chemical substances for activity in diverse areas of biology. The biological responses measured in HTS assays span isolated biochemical systems containing purified receptors or enzymes to signal transduction pathways and complex networks functioning in cellular environments. This Review addresses factors that need to be considered when implementing assays for HTS and is aimed particularly at investigators new to this field. We discuss assay design strategies, the major detection technologies and examples of HTS assays for common target classes, cellular pathways and simple cellular phenotypes. We conclude with special considerations for configuring sensitive, robust, informative and economically feasible HTS assays.

COMMENTARY

Reporting data from high-throughput screening of small-molecule libraries

James Inglese, Caroline E Shamu & R Kiplin Guy

Publications reporting results of small-molecule screens are becoming more common as academic researchers increasingly make use of high-throughput screening (HTS) facilities. However, no standards have been formally established for reporting small-molecule screening data, and often key information important for the evaluation and interpretation of results is omitted in published HTS protocols. Here, we propose concise guidelines for reporting small-molecule HTS data.

NCGC CurveFit

Large scale dose response curve fitting and curve classification software

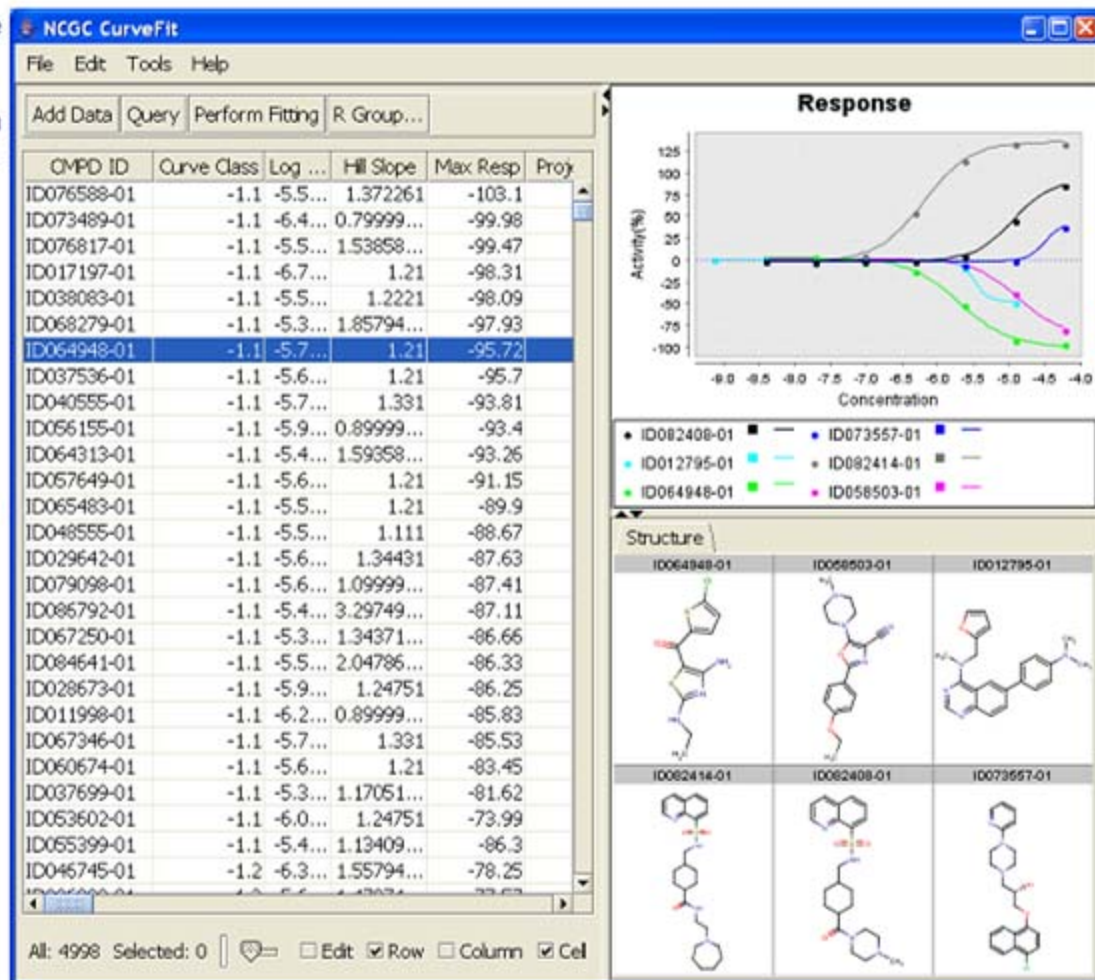
Download: [Application](#). (requires Java WebStart)

Download: [Sample Data File](#).

Download: [Source Code](#).

Software Features

- Automated curve fitting and classification software
- Algorithm recognizes bell shaped curves, implements standard Hill equation, extensible for other models; distinguishes activation vs inhibition
- Stand alone tool designed explicitly for public use and for source code reference
- Analyzes 10k curves with good performance, capacity to handle >100k curves with memory usage on user machine being the limit
- Provides activity ranking of complete and incomplete curves
- Fast chemical similarity and substructure searching (including smarts support) enabled using path-based fingerprints
- Ability to export results, curve images
- Web deployed software, keeps users current with latest features





>> Assay Guidance

Assay Guidance
Manual - Version 4.1

Introduction

Transfer of Validated
Assays

Assay Operations for SAR
Support

Enzymatic Assays

Receptor Binding Assays

GTPγS Binding Assays

Tissue Culture Assays

Cell-Based Elisa (C-Elisa)
and Westerns Blots for
Quantitative Antigen
Detection

FLIPR™ Assays to
Measure GPCR and Ion
Channel Targets

Immunoassay Methods

Data Standardization for
Results Management

Glossary of Quantitative
Biology Terms

Comment Form

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- Signal Window and Z-Factor Formulas
- Signal to Background and Signal to Noise
- Plate Uniformity Assessment
- Inter-Plate and Inter-Day Tests
- Summary of Acceptance Criteria
- Higher Plate Density Formats

C. CONFIRMATION AND REPRODUCIBILITY OF POTENCY AND EFFICACY VALUES

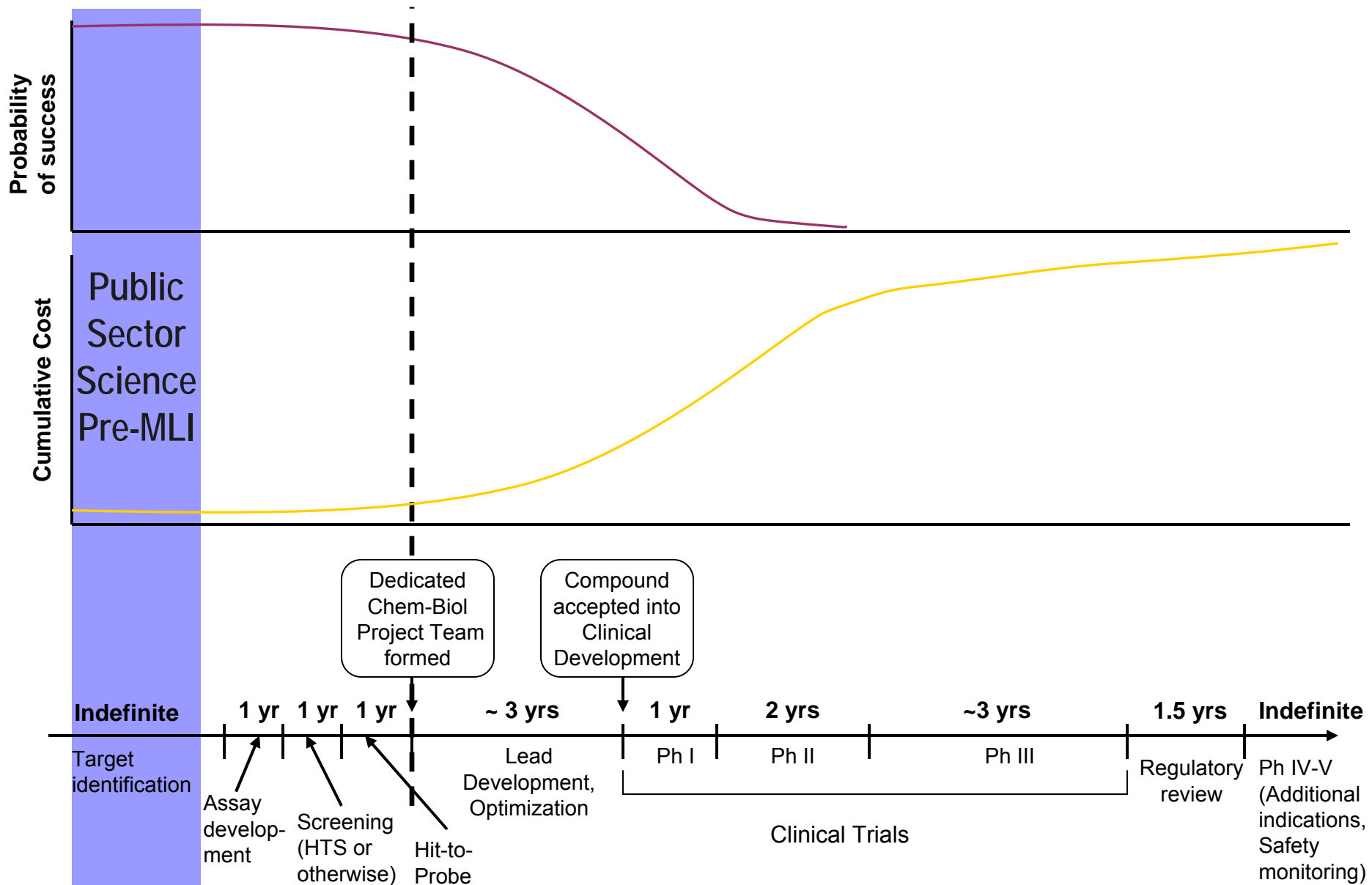
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- Rationale
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- Analysis (Potency)
- Diagnostic Tests (Potency)
- Analysis (Efficacy)
- Diagnostic Tests (Efficacy)
- Summary of Acceptance Criteria
- Notes

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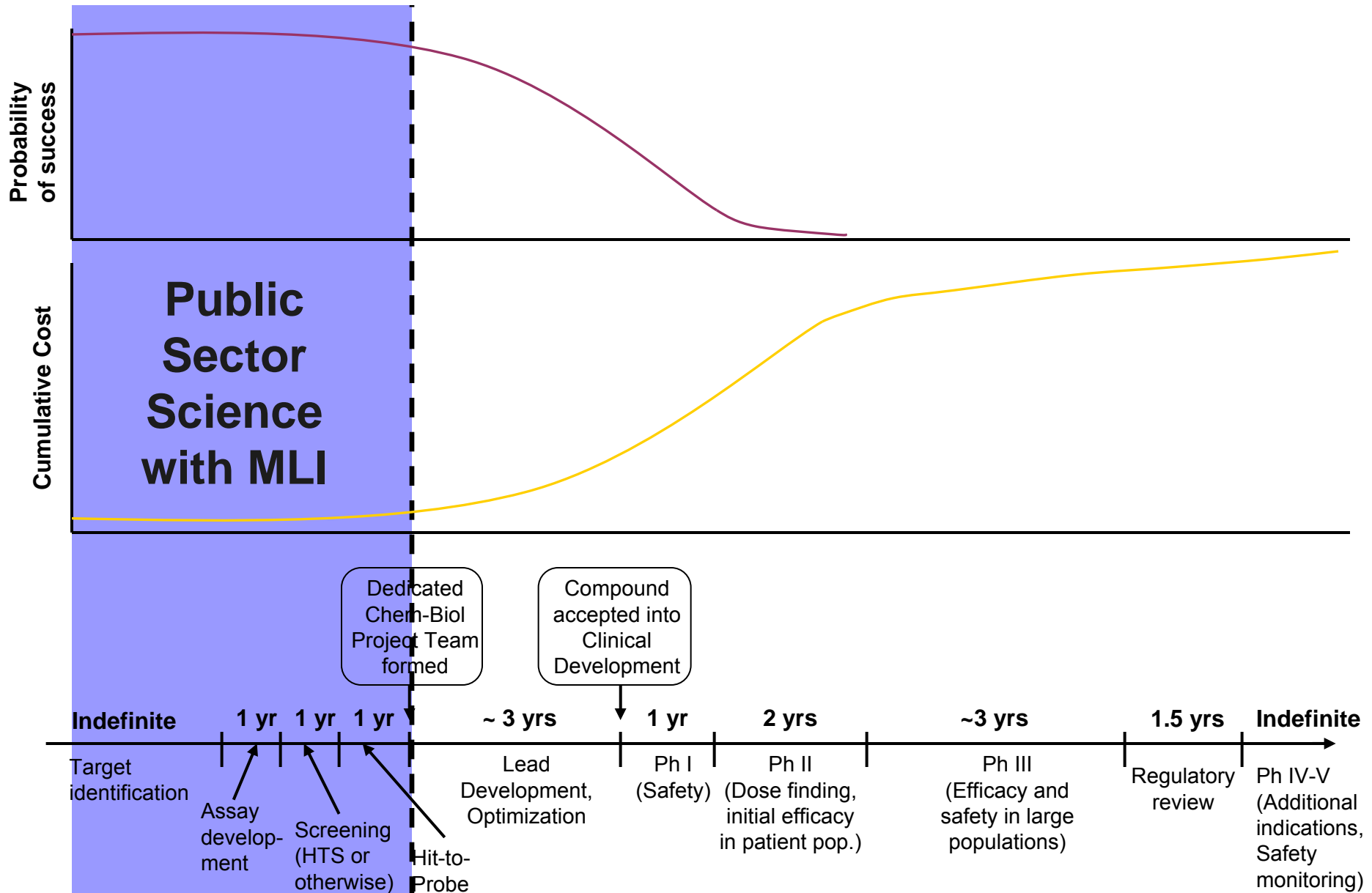
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- Reagent Stability and Storage Requirements

Probes are just the start of drug development



Probes are just the start of drug development



Biology

- Doug Auld
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