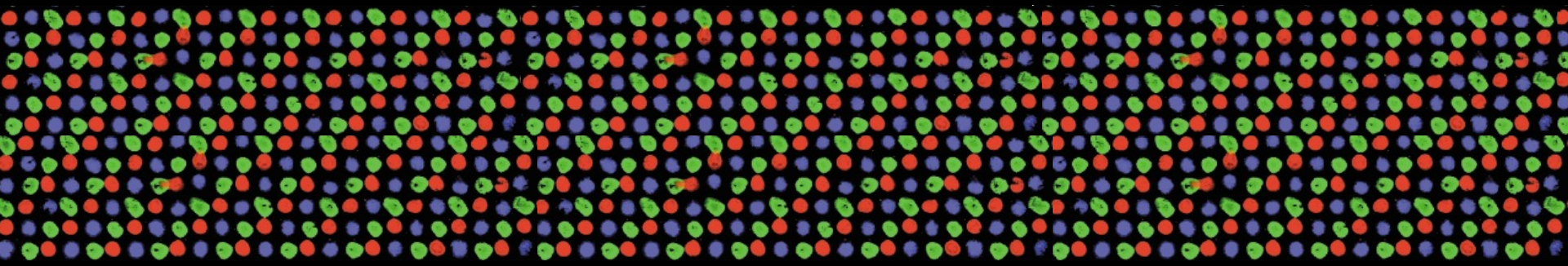
L2 – Small Molecule Microarrays



a low-tech ligand discovery platform

February 14, 2023

The view from 2000

Diabetes (type 2)

< 100 Mendelian disease genes

(e.g. CFTR in cystic fibrosis, HEXA in Tay-Sachs)

12 common disease genetic variants

(e.g. CTLA4^{Thr17Ala} in Type 1 Diabetes, PRNP^{Met129Val} in Creutzfeld-Jacob)

PPARγ

2000

>20 years on from the Human Genome Project

Asthma
Atrial fibrillation
Breast cancer
Crohn's disease
Diabetes (type 1)
Diabetes (type 2)
Hypercholesterolemia
Lupus
Macular regeneration
Myocardial infarction
Obesity
Prostate Cancer
Others…

Thousands of loci affecting hundreds of common diseases

2000	2001	2002	2003	2004	2005	2006	Q1,2 2007	2023
PPARγ	IBD5 NOD2	CTLA4	KCNJ11	PTPN22	CD25 IRF5 PCSK9 CFH	IFIH1 PCSK9 CBF/C2 LOC387715 8q24 IL23R TCF7L2	LSP1 HHEX CDKAL1 ORMDL3 4q25 TCF2 TCF2 GCKR FTO CDKN2B/A FGFR2 TNRC9 MAP3K1 CD226 16p13 PTPN2	CDKN2B/A 8q24 ATG16L1 5p13 10q21 IRGM NKX2-3 IL12B 3p21 1q24 PTPN2 IGF2BP2 8q24 C12orf30 ERBB3 KIAA0350

2023 – Gene-Disease Catalog (GDC)

https://www.ebi.ac.uk/gwas/diagram

Drugging the Genome

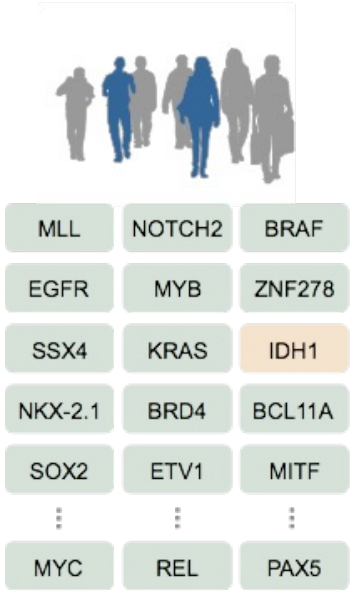
Asthma
Atrial fibrillation
Breast cancer
Crohn's disease
Diabetes (type 1)
Diabetes (type 2)
Hypercholesterolem
Lupus
Macular degeneratio
Myocardial infarctio
Obesity
Prostate cancer
Others…

# of proteins targeted
by the full armamentarium of
drugs on the market <735

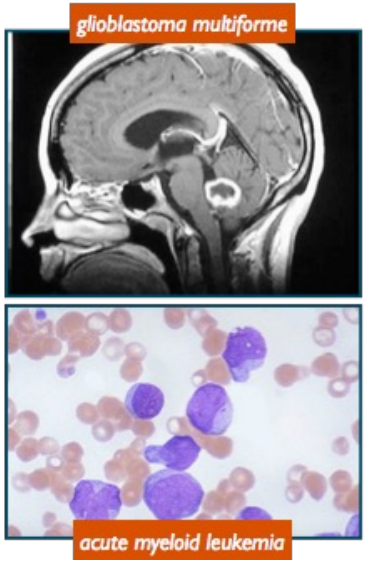
John P. Overington, EMBL-European
Bioinformatics Institute

2000	2001	2002	2003	2004	2005	2006	Q1,2 2007	2023
PPARγ	IBD5 NOD2	CTLA4	KCNJ11	PTPN22	CD25 IRF5 PCSK9 CFH	IFIH1 PCSK9 CBF/C2 LOC387715 8q24 IL23R TCF7L2	10q21 IRGM NKX2-3 IL12B 3p21 1q24 PTPN2 IGF2BP2 8q24 LSP1 HHEX	CDKN2B/A C12orf30 ERBB3 KIAA0350 CD226 16p13 PTPN2 SH2B3 FGFR2 TNRC9 MAP3K1	**Thousands of loci affecting >200 common diseases**

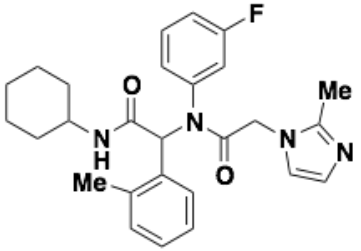
From L1 - Chemical probes of disease biology



patient samples reveal
list of disease genes



physiologic settings to test
the impact of disease genes



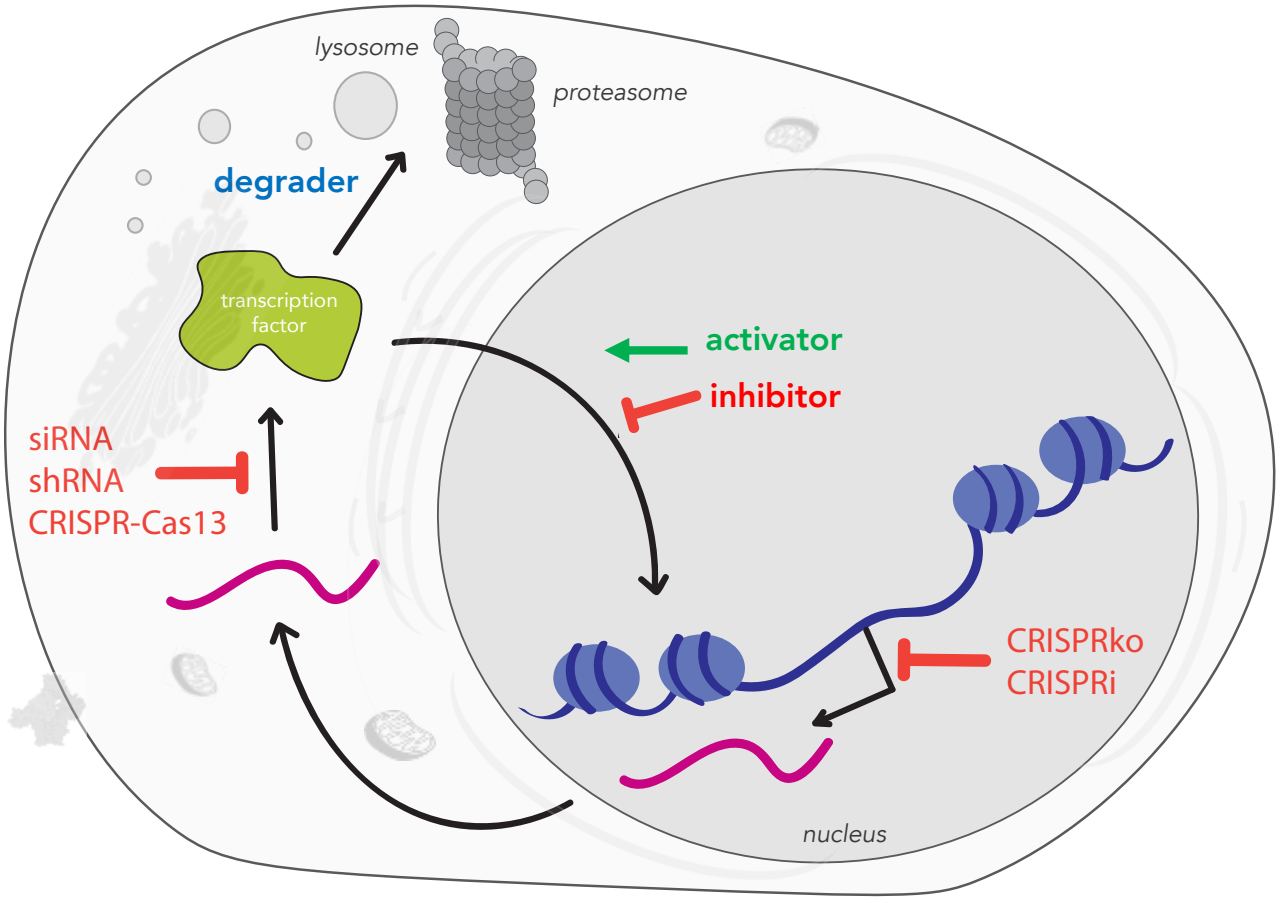
discover or develop small
molecules that reverse the
impact of disease genes

Approach: use small molecules to test emerging concepts in human disease in physiologically relevant settings

Output: validated small-molecule probe to facilitate human clinical development or diagnostic applications

An engineer's perspective on perturbation of proteins

intervention can take place at various parts of the system



genetic perturbants

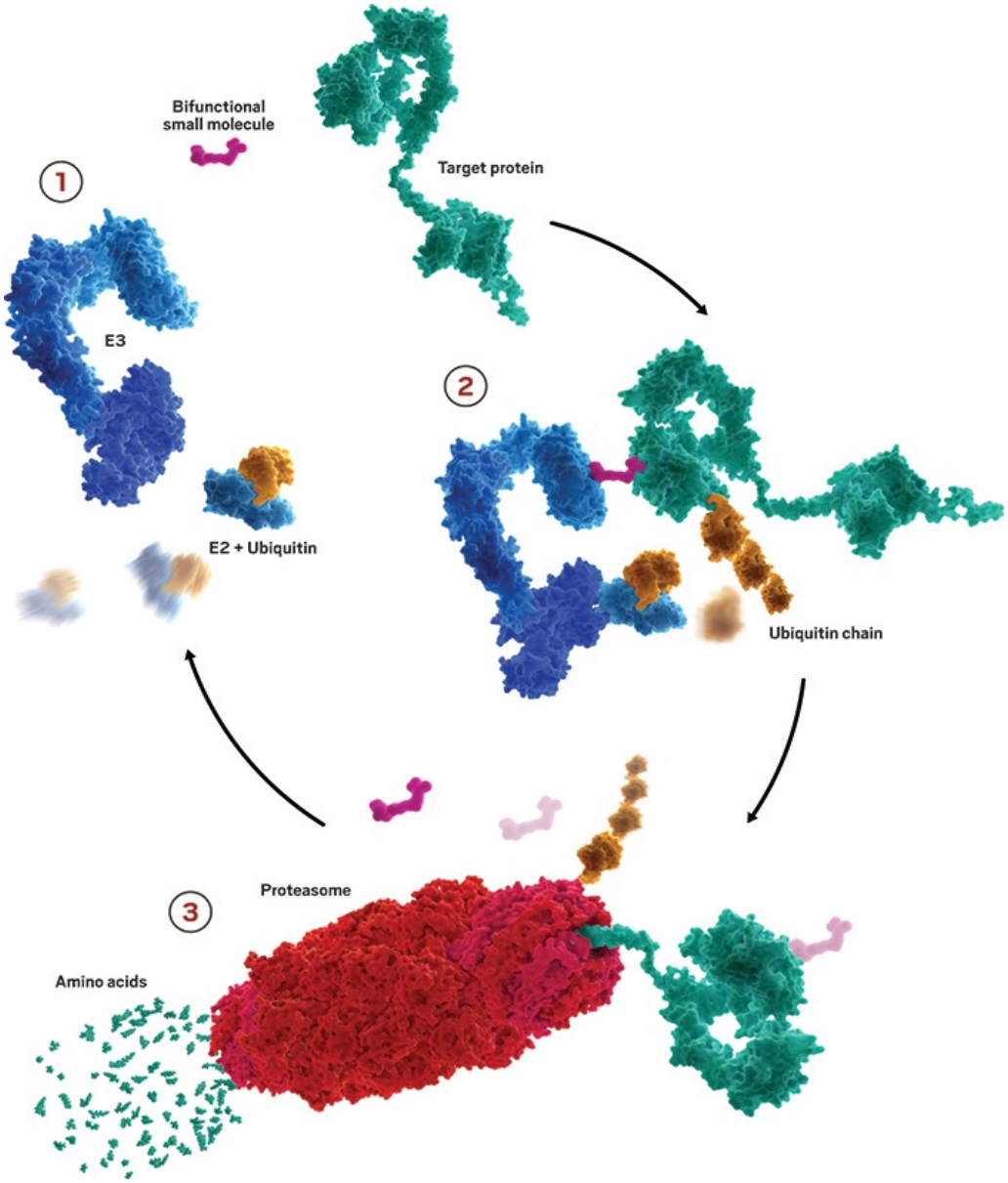
- ✓ shRNA
- ✓ CRISPR

chemical perturbants

- inhibitor
- activator
- degrader

Your TDP-43 screens may uncover molecules that can achieve any of these mechanisms

Targeted Protein Degradation

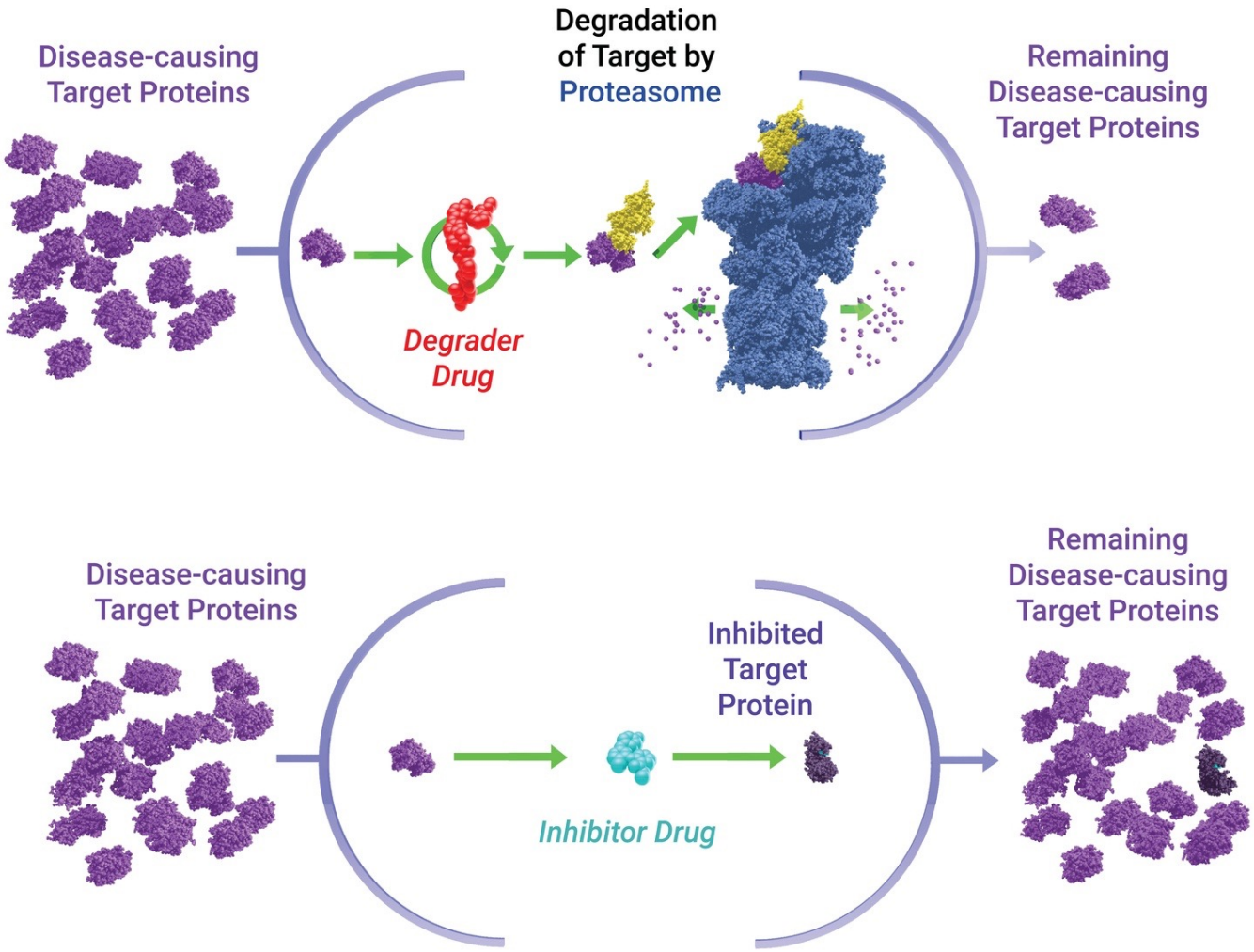


Nathanael Gray
Stanford University

Jay Bradner
Novartis

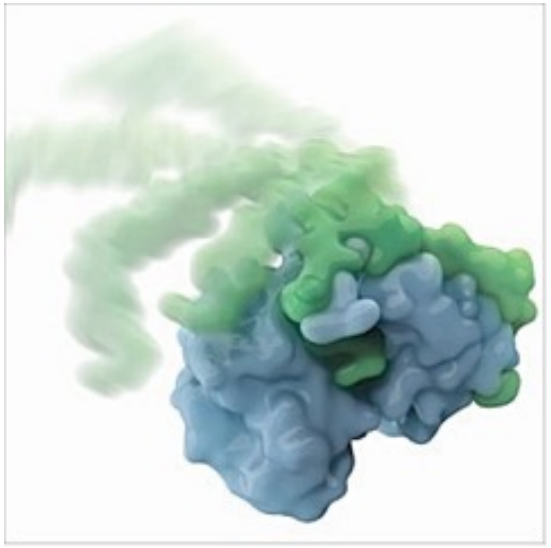
Craig Crews
Yale University

Targeted Protein Degradation



C4_logo_color

‘Undruggable’ targets are aplenty



disordered proteins

e.g. amyloids, transcription factors, enzymes

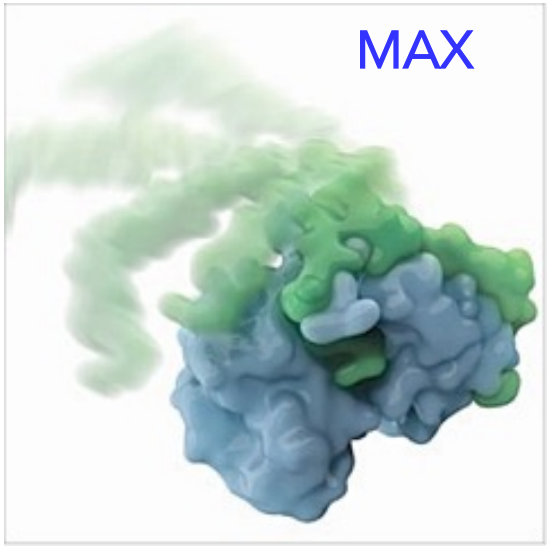
DNA binding proteins
protein-protein interactors

e.g. transcription factors, extracellular growth factors, scaffold proteins

integral membrane proteins

e.g. cell adhesion proteins, enzymes, receptors

‘Undruggable’ targets are aplenty



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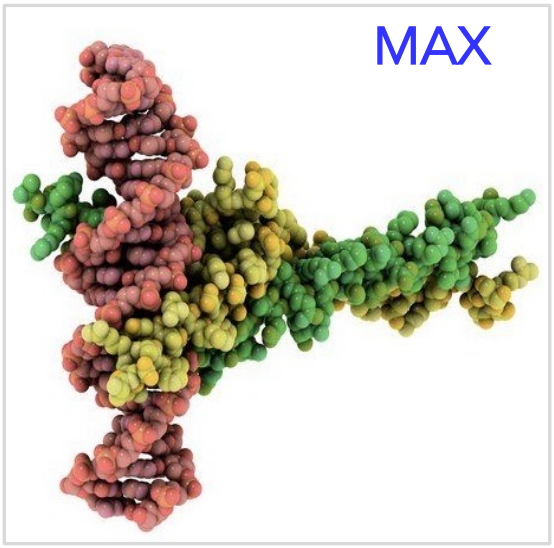


DNA binding proteins
protein-protein interactors

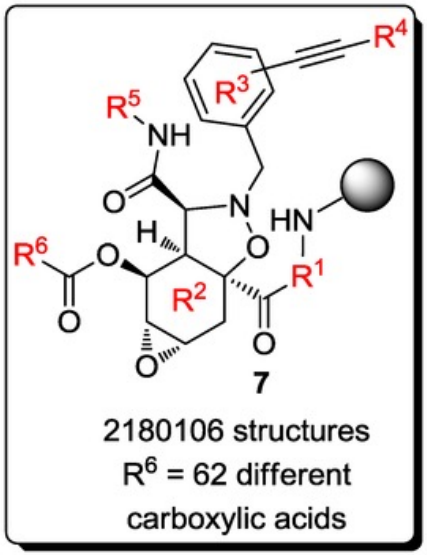
e.g. transcription factors, extracellular growth factors, scaffold proteins

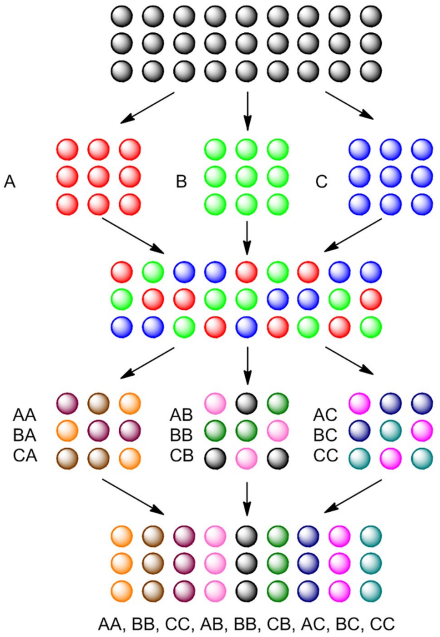
integral membrane proteins

e.g. cell adhesion proteins, enzymes, receptors

1998 – ‘on-bead’ binding assays

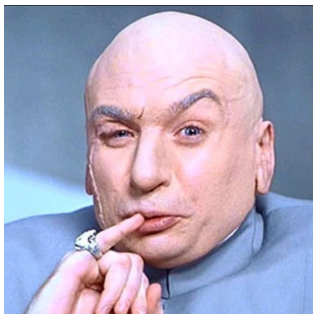
Chemical Library =
2.18M compounds on
90 µm Tentagel beads





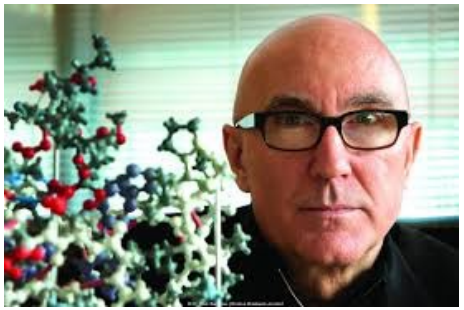
Split-Pool
Combinatorial
Synthesis

Dr. Evil



Millions?

Dr. Schreiber, Harvard



Billions!

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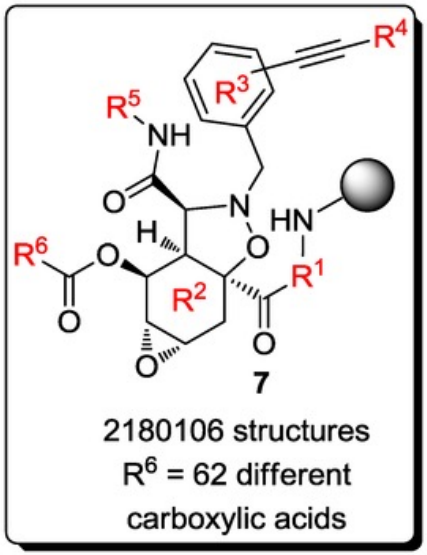

‘Gradbot’
Angela
@ Harvard

1998 – 'on-bead' binding assays

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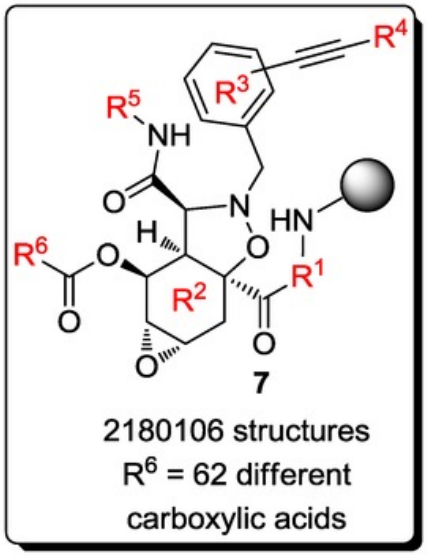

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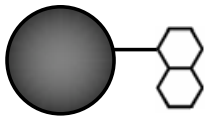
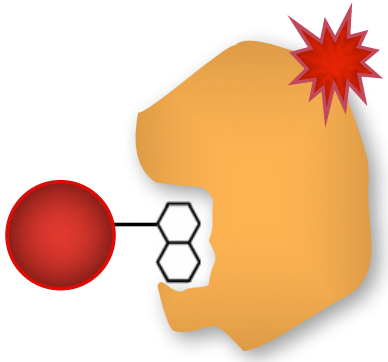
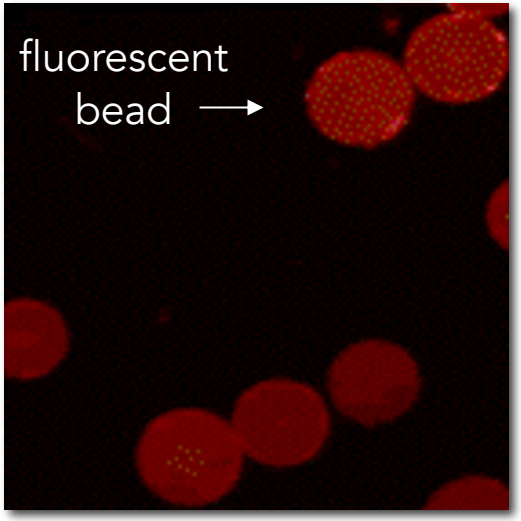


no
binding

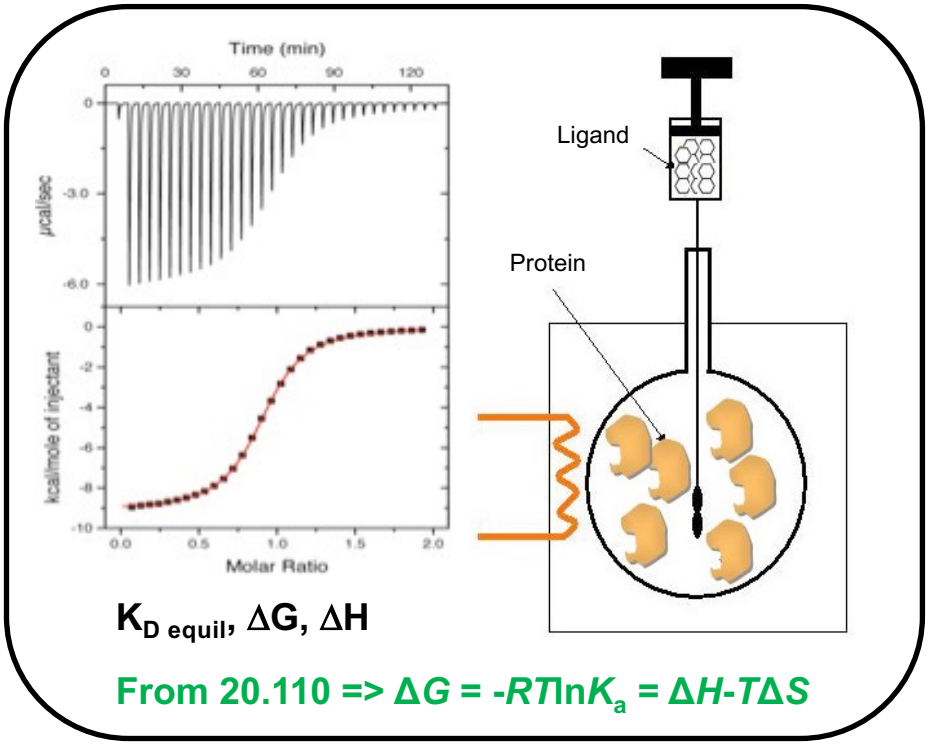


assay
positive



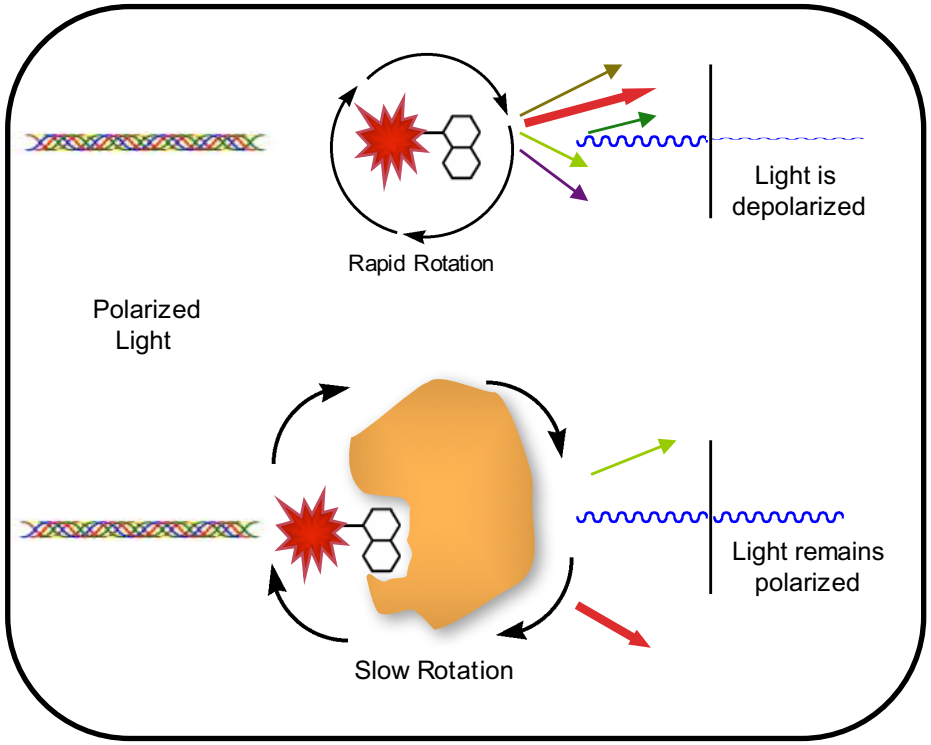
rhodamine dye
540/625 nm

1998 - other binding assay formats



isothermal titration calorimetry

measure changes in temperature upon binding, plotted as power needed to maintain a constant T



fluorescence polarization

measure changes in rate of rotation upon binding

Late 1990s - ‘Spatially addressable systems’

Quantitative Monitoring of Gene Expression Patterns with a Complementary DNA Microarray

Mark Schena,* Dari Shalon,*† Ronald W. Davis,
Patrick O. Brown‡

A high-capacity system was developed to monitor the expression of many genes in parallel. Microarrays prepared by high-speed robotic printing of complementary DNAs on glass were used for quantitative expression measurements of the corresponding genes. Because of the small format and high density of the arrays, hybridization volumes of 2 microliters could be used that enabled detection of rare transcripts in probe mixtures derived from 2 micrograms of total cellular messenger RNA. Differential expression measurements of 45 *Arabidopsis* genes were made by means of simultaneous, two-color fluorescence hybridization.

SCIENCE • VOL. 270 • 20 OCTOBER 1995

Exploring the new world of the genome with DNA microarrays

Patrick O. Brown[1,3] & David Botstein[2]

Departments of [1]Biochemistry and [2]Genetics, and the [3]Howard Hughes Medical Institute, Stanford University School of Medicine, Stanford, California 94305, USA. e-mail: pbrown@cmgm.stanford.edu

Thousands of genes are being discovered for the first time by sequencing the genomes of model organisms, an exhilarating reminder that much of the natural world remains to be explored at the molecular level. DNA microarrays provide a natural vehicle for this exploration. The model organisms are the first for which comprehensive genome-wide surveys of gene expression patterns or function are possible. The results can be viewed as maps that reflect the order and logic of the genetic program, rather than the physical order of genes on chromosomes. Exploration of the genome using DNA microarrays and other genome-scale technologies should narrow the gap in our knowledge of gene function and molecular biology between the currently-favoured model organisms and other species.

Dr. Patrick O. Brown

follow changes in gene expression during yeast sporulation

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fluorescence hybridization.

SCIEN

Exploring the new
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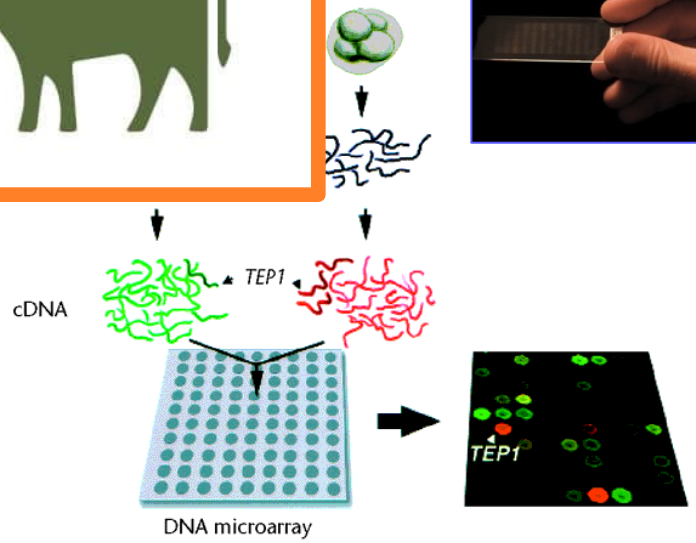
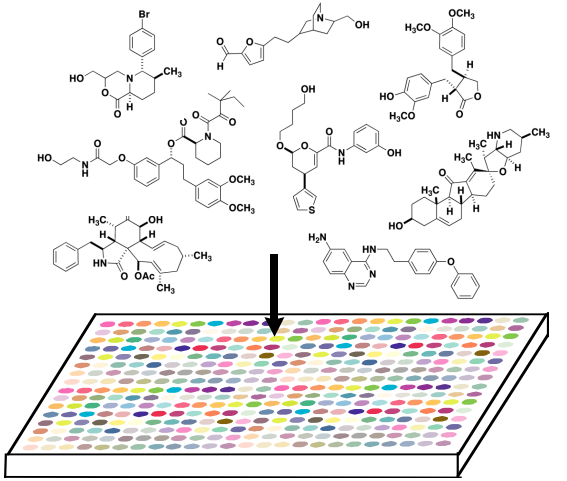
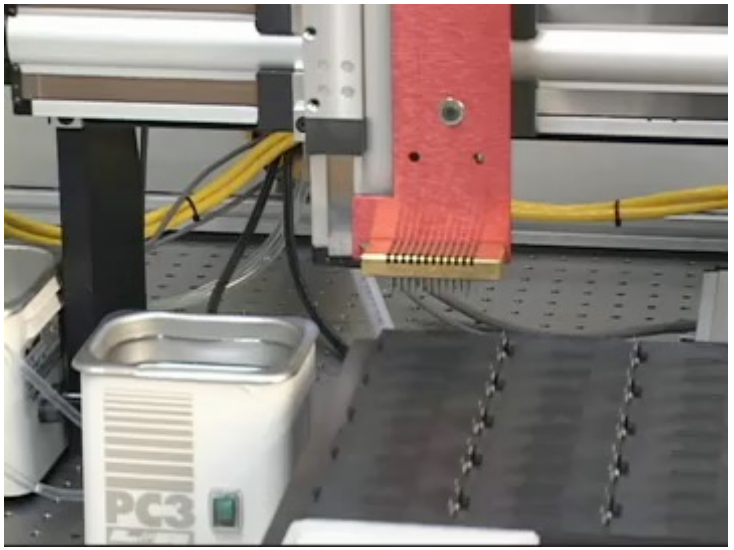


follow changes in gene expression during yeast sporulation

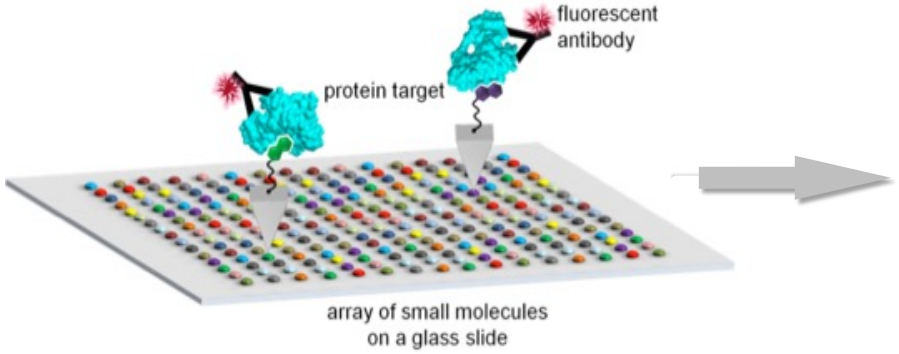
Small Molecule Microarrays (SMMs)

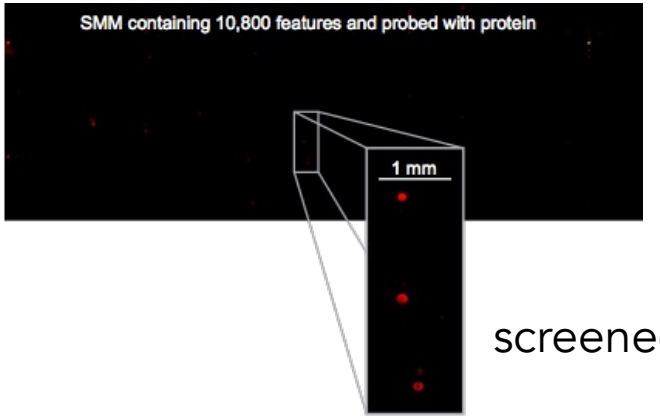


compound stock solutions



SMM manufacture and screening

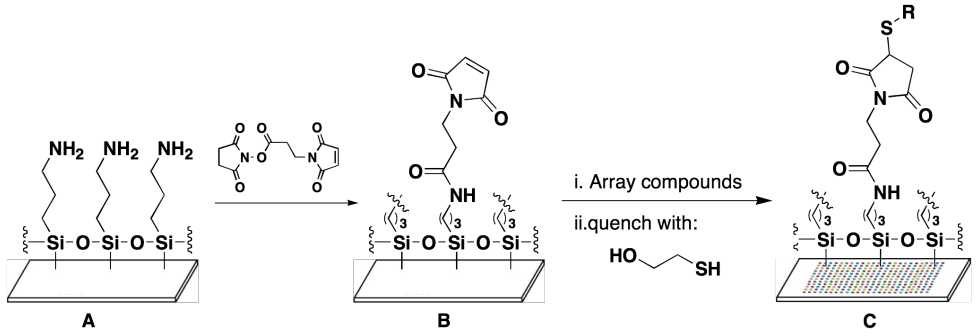


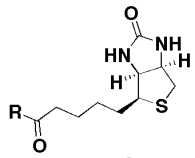


screened SMM

Proof-of-concept experiments for SMMs

detecting known protein-ligand interactions

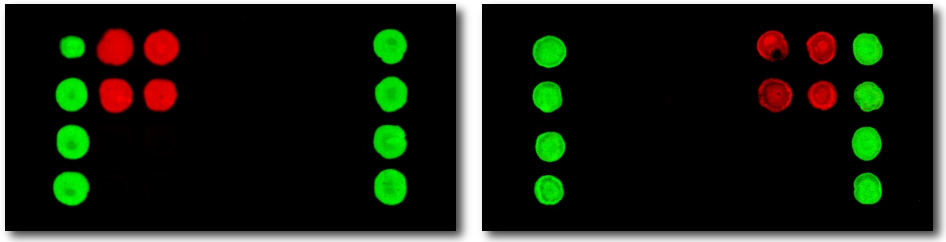


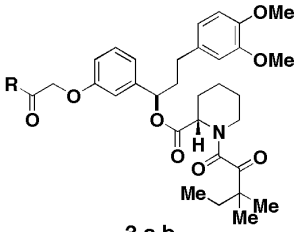


1 a,b

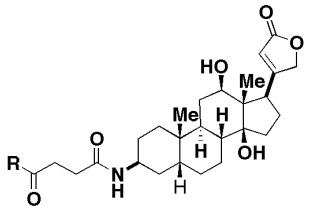
Streptavidin

FKBP12

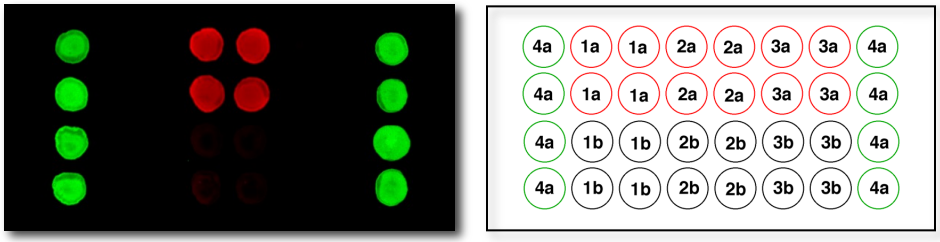




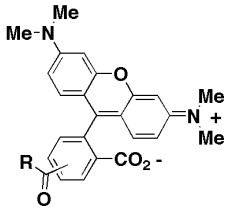
3 a,b



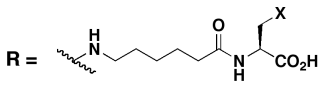
2 a,b



Anti-Digoxin mAb



4 a

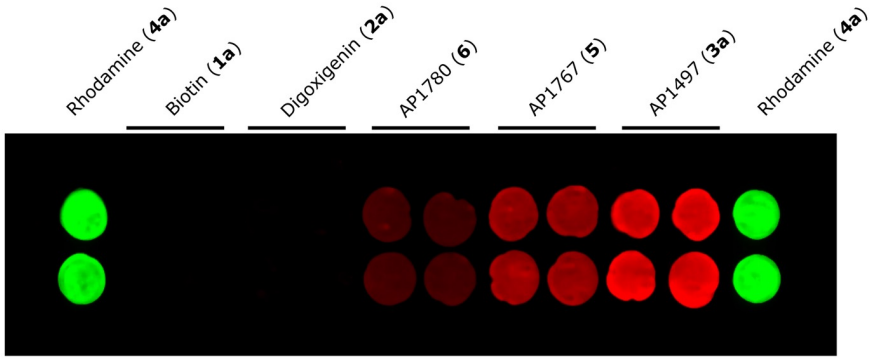


a: X = SH **b**: X = H

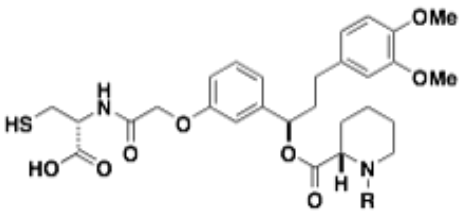
J. Am. Chem. Soc. **121**, 7967-7968, 1999

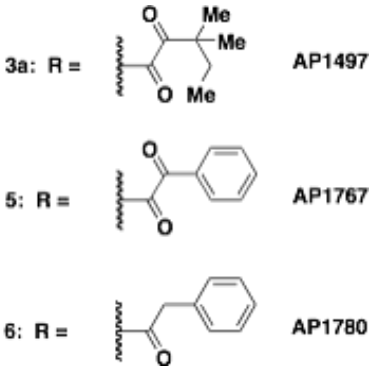
Proof-of-concept experiments for SMMs

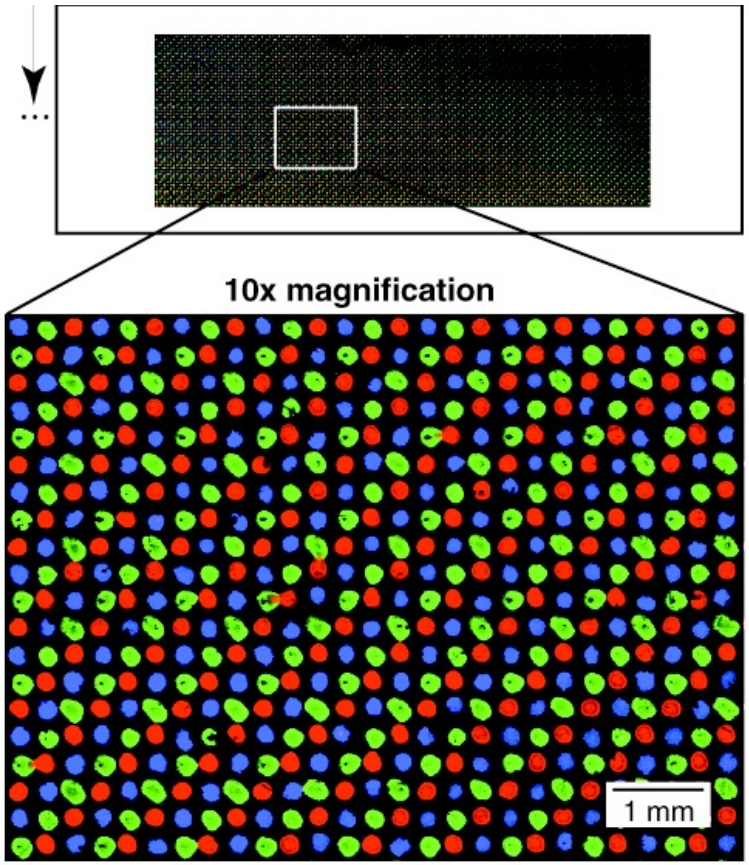
evaluating affinities and multiplexed formats



K_D (nM): 2,600 140 8.8

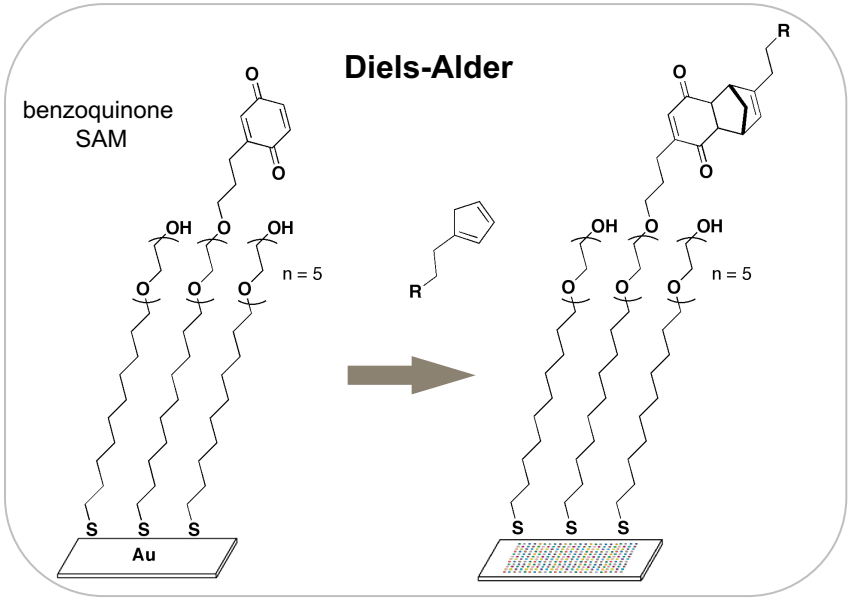




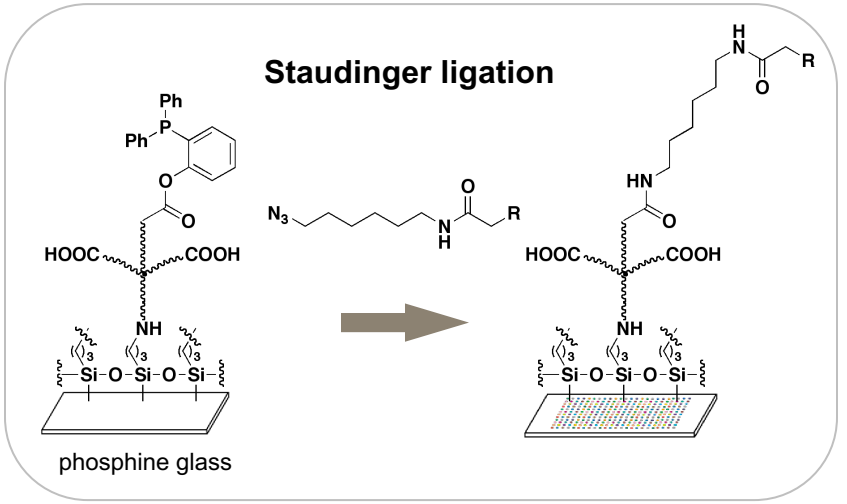


J. Am. Chem. Soc. **121**, 7967-7968, 1999

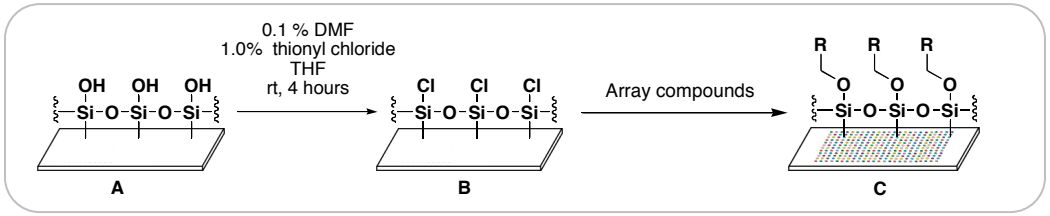
Capture chemistries for making SMMs



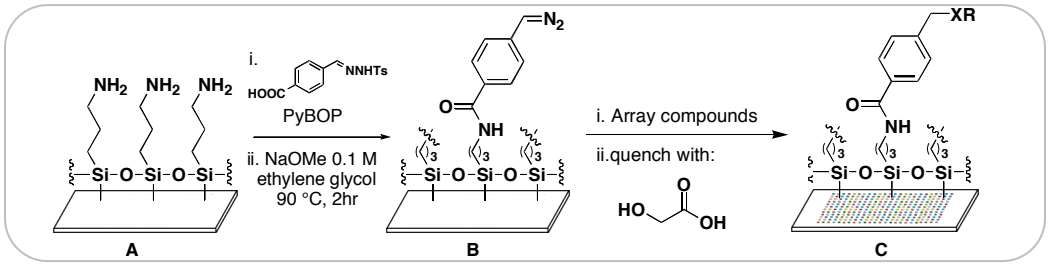
Houseman, B.T., Mrksich, M. *Chem. Biol.* 9, 443-454, 2002



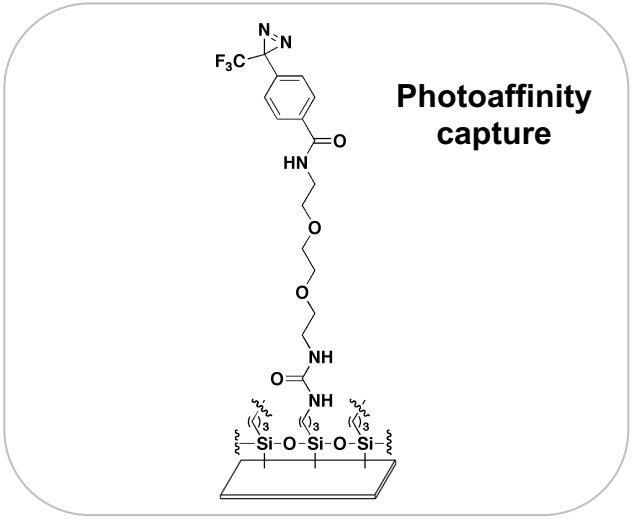
Köhn et al., *Angew. Chem. Int. Ed.* 42, 5830-5834, 2003



Hergenrother et al., *J. Am. Chem. Soc.* 122, 7849-7850, 1999

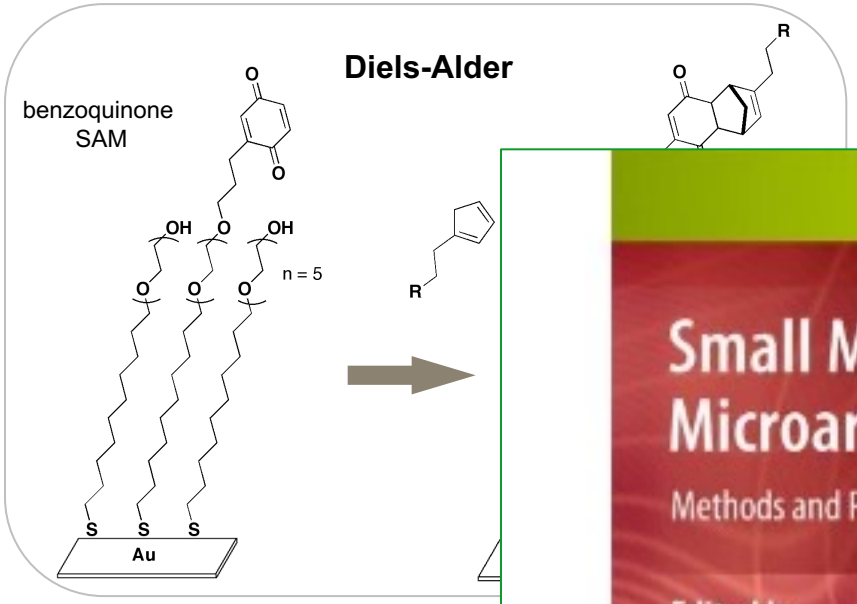


Barnes-Seeman et al., *Angew. Chem. Int. Ed.* 42, 2376-2379, 2003

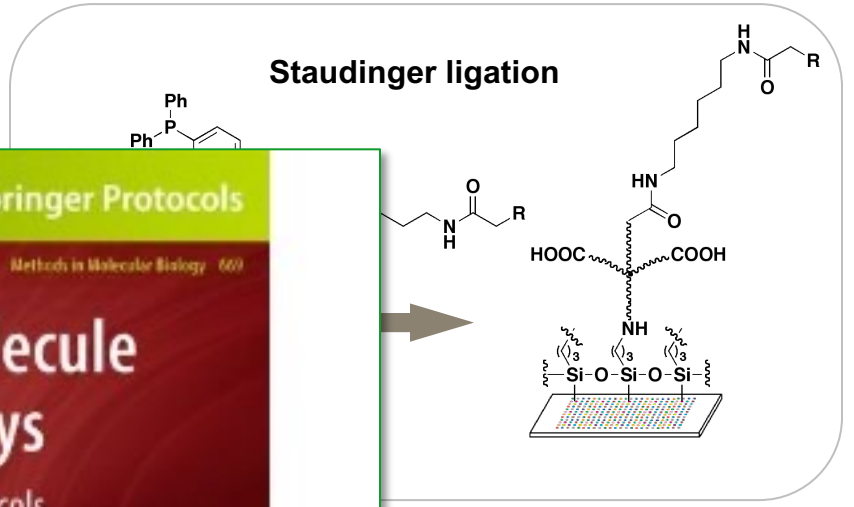


Kanoh et al., *Angew. Chem. Int. Ed.* 42, 5584-5597, 2003

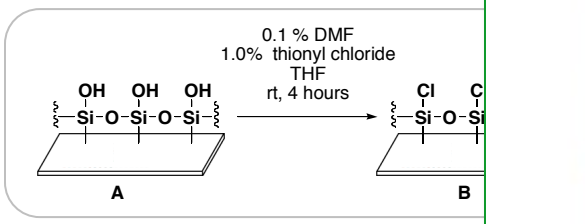
Capture chemistries for making SMMs



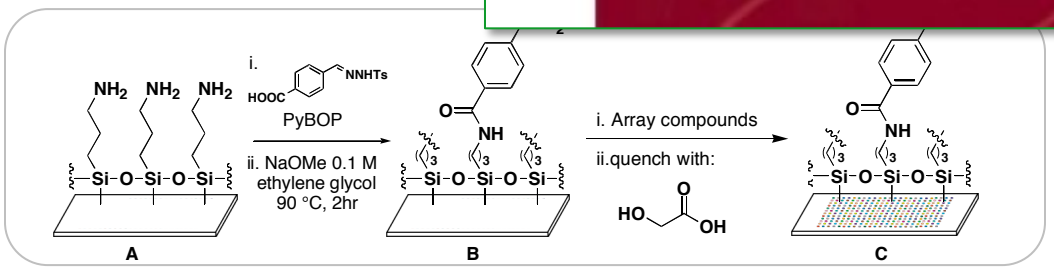
Houseman, B.T., Mrksich, M. *Che*



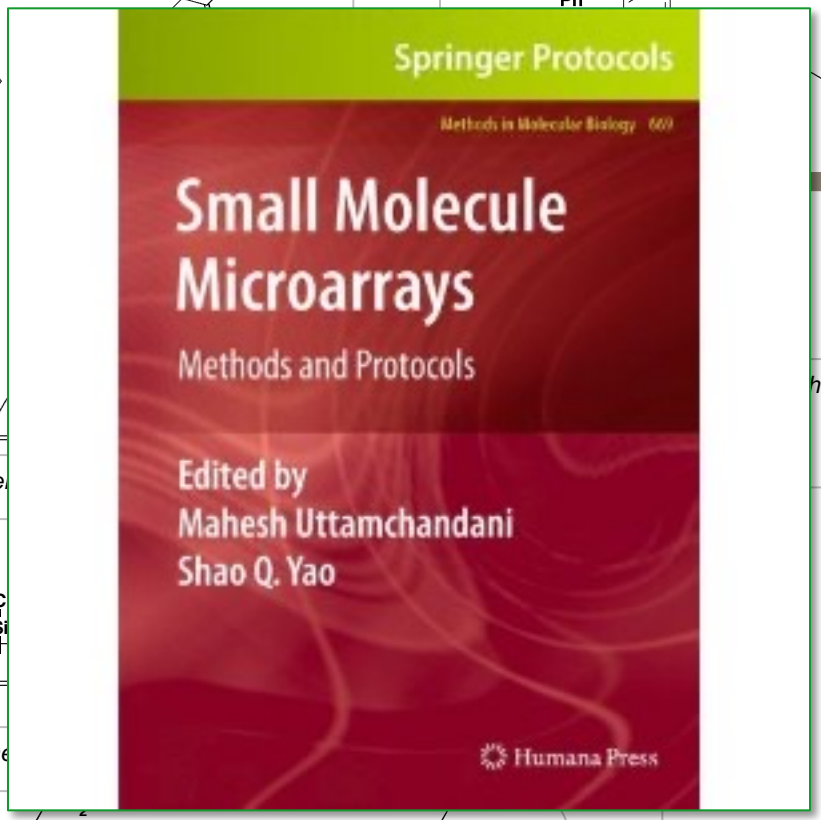
hem. Int. Ed. 42, 5830-5834, 2003

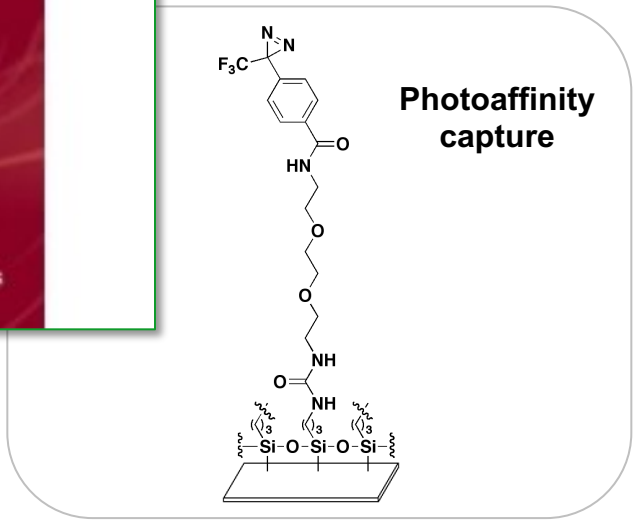


Hergenrother et al., *J. Am. Che*



Barnes-Seeman et al., *Angew. Chem. Int. Ed.* 42, 2376-2379, 2003

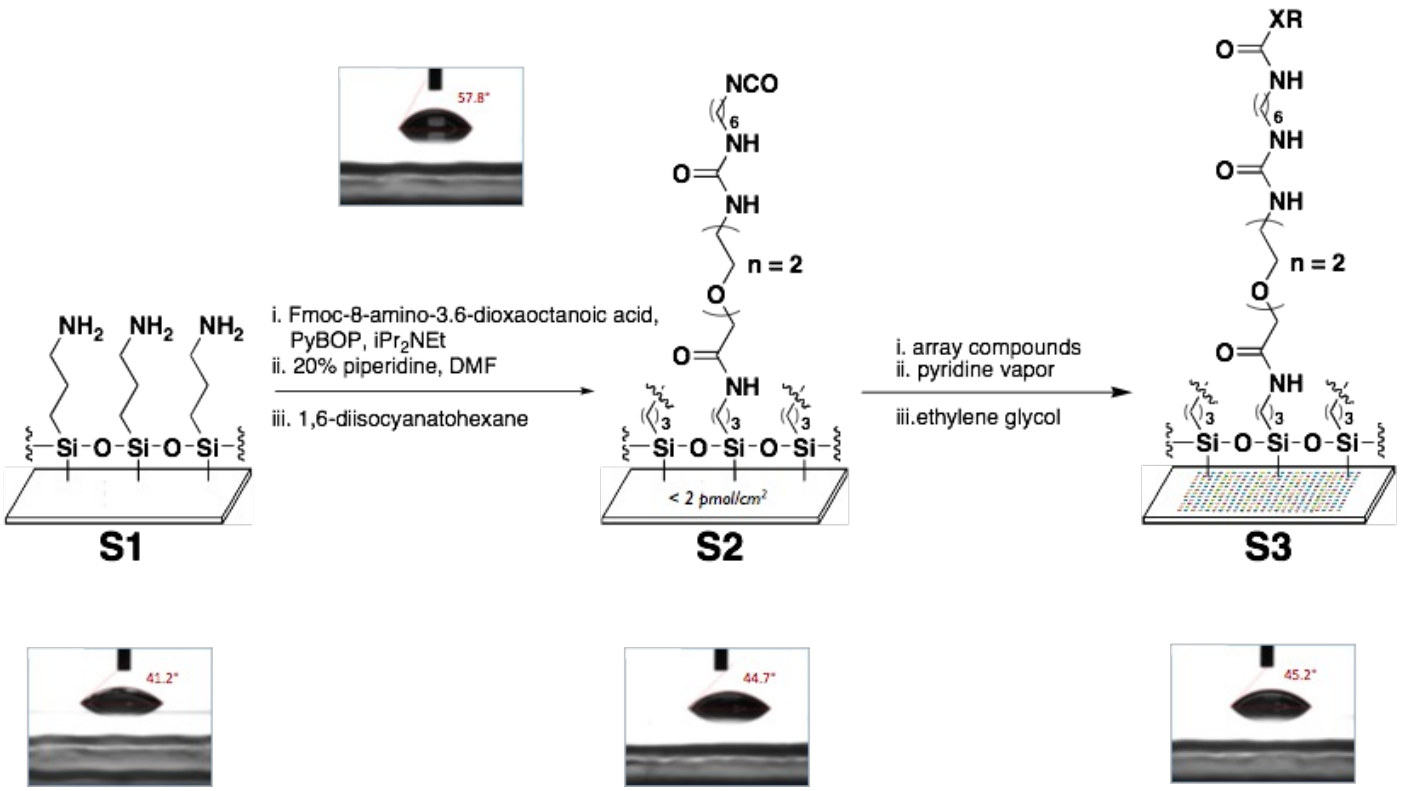




Kanoh et al., *Angew. Chem. Int. Ed.* 42, 5584-5597, 2003

Primary capture chemistry for making SMMs

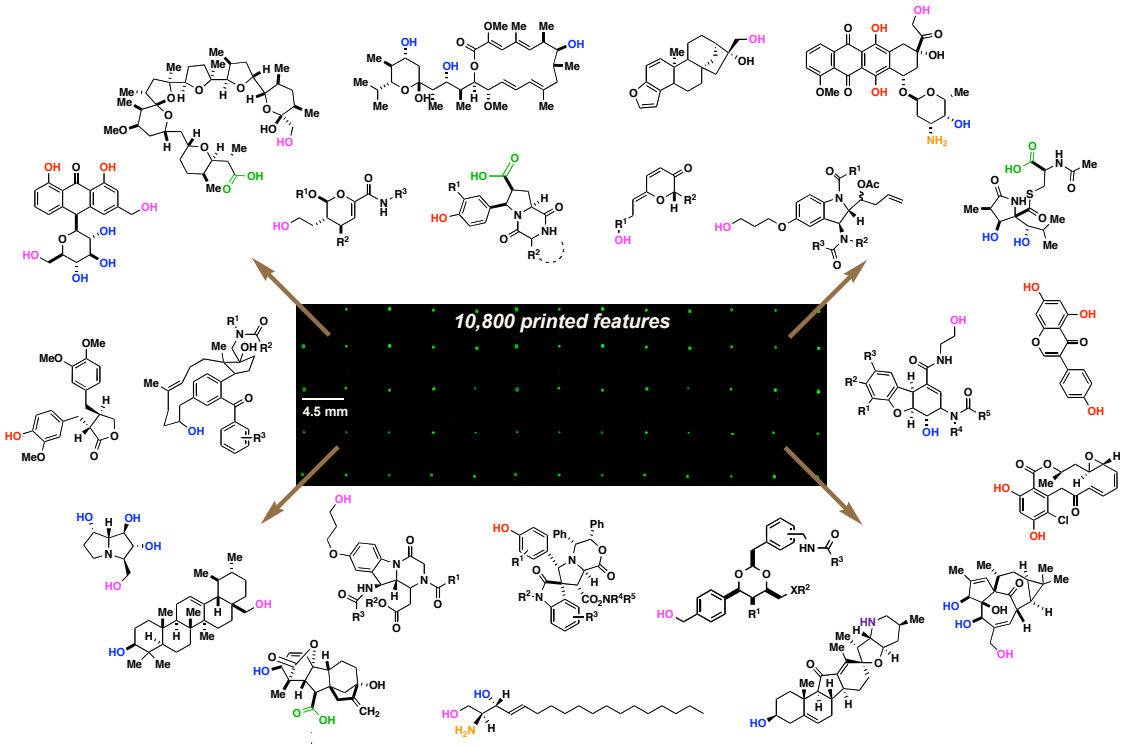
isocyanate coating reacts with nucleophilic functional groups



Bradner, J. E., McPherson, O. M., Mazitschek, R. M., Barnes-Seeman, D., Shen, J. P., Dhaliwal, J., Stevenson, K., Duffner, J. L., Park, S. B., Nghiem, P. T., Schreiber, S. L., Koehler, A. N., Chem Biol, 13, 493-504 (2006)

Bradner, J. E., McPherson, O. M., Koehler, A. N., Nature Protocols, 1, 2344-2352 (2006)

SMMs contain compounds from a variety of sources



KOCH INSTITUTE for Integrative Cancer Research at MIT

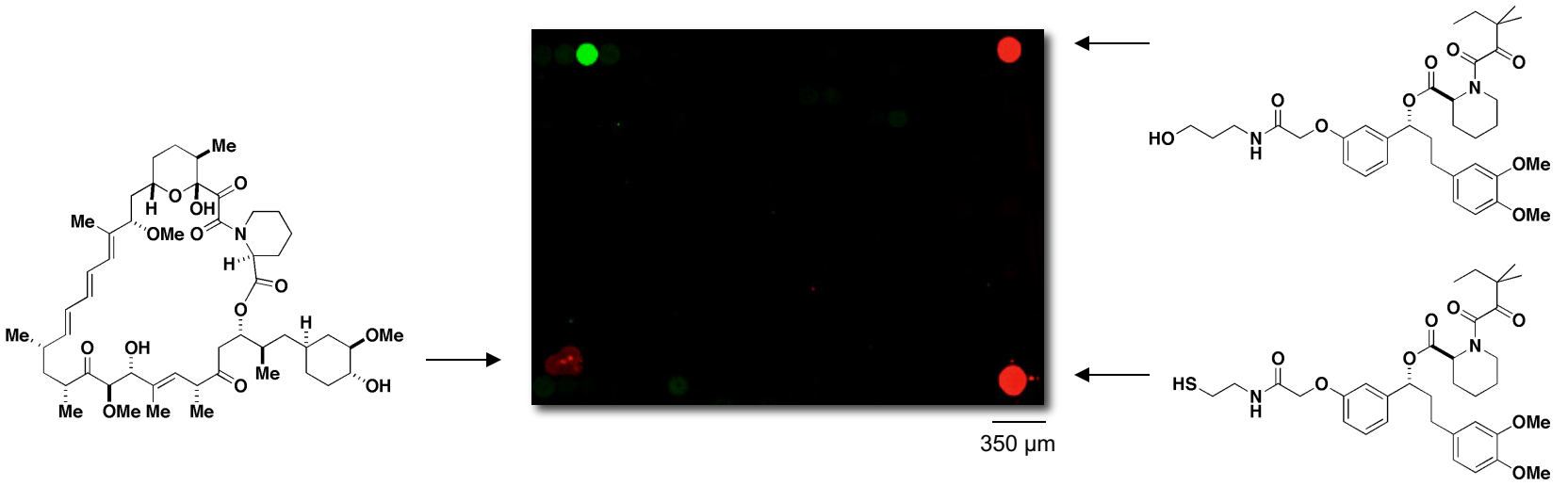
MIT CENTER FOR PRECISION CANCER MEDICINE

>100,000	commercials
~4,000	macrocycles
~4,000	bioactives, drugs
~4,000	Boston University
<1,000	MIT synthetics
100,000	Broad

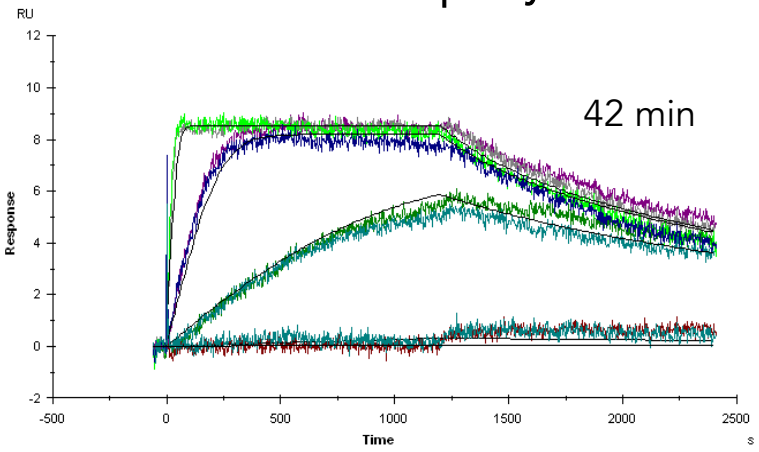
In silico analysis of 400,000 'National Library' for screens:

>75% isocyanate-reactive

Interactions with varying kinetics can be visualized

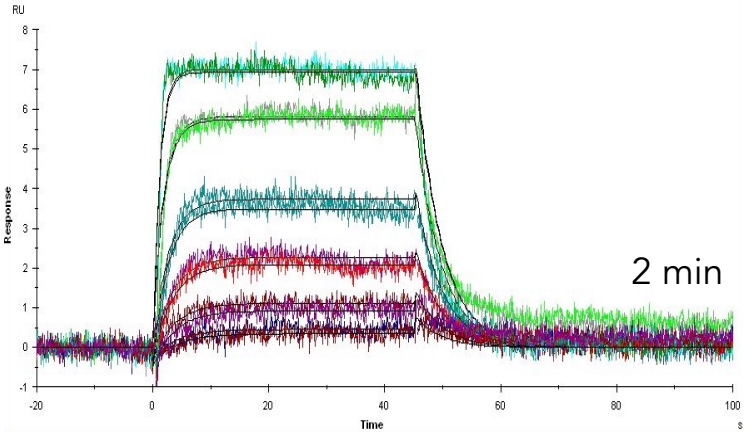


FKBP12 + rapamycin



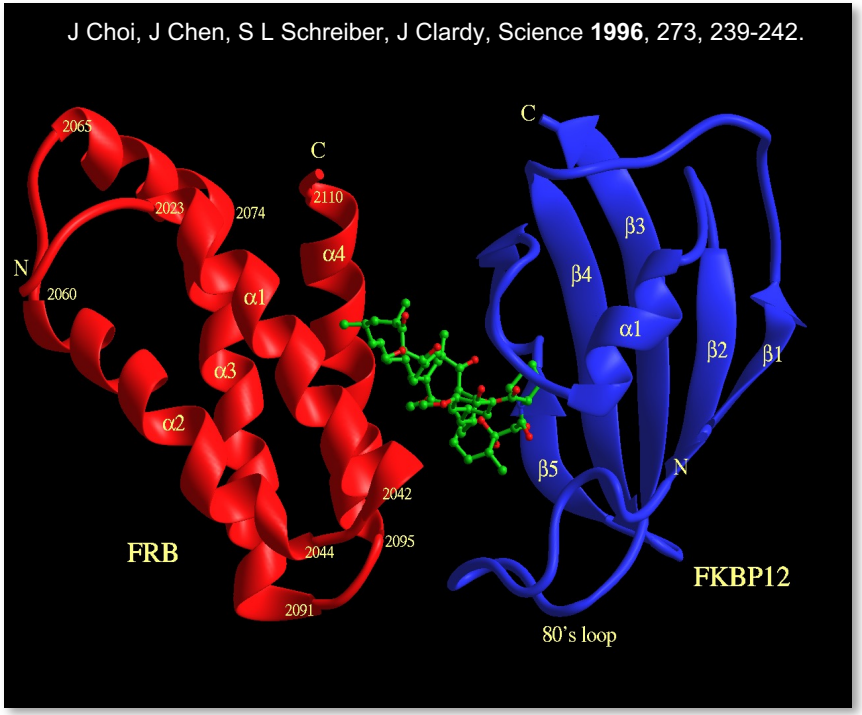
K_D = 0.5 nM
K_d = 0.000965 sec^{-1}

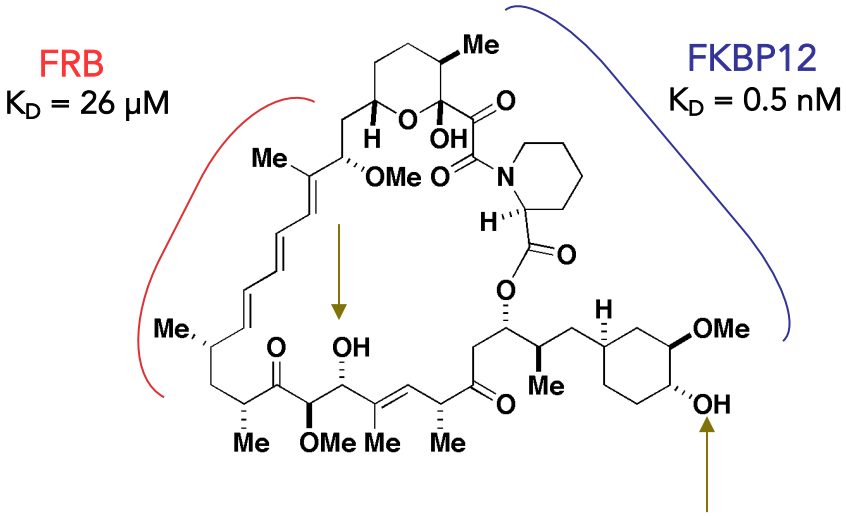
FKBP12 + AP1497

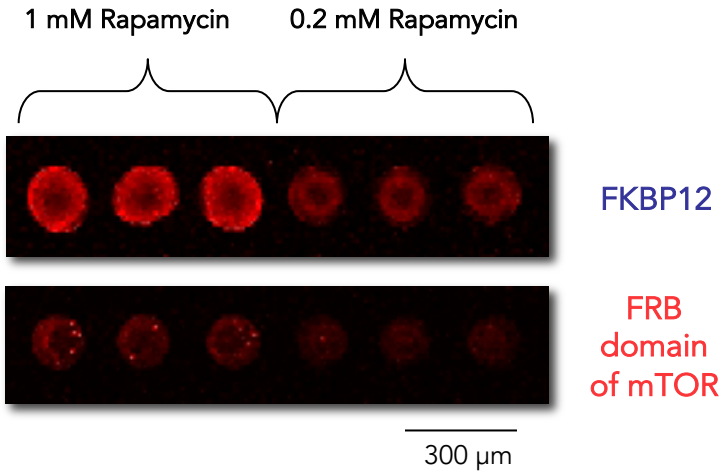


K_D = 18 nM
K_d = 0.226 sec^{-1}

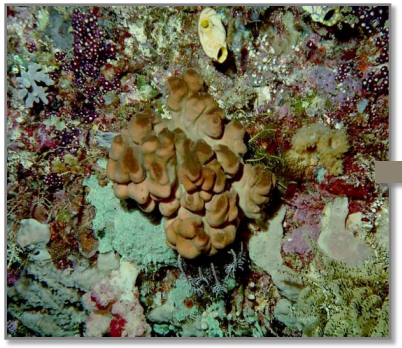
Detecting multiple interactions with Rapamycin





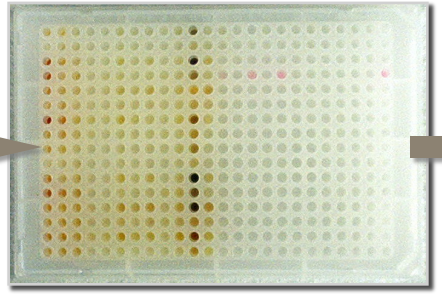


SMMs containing natural product extracts

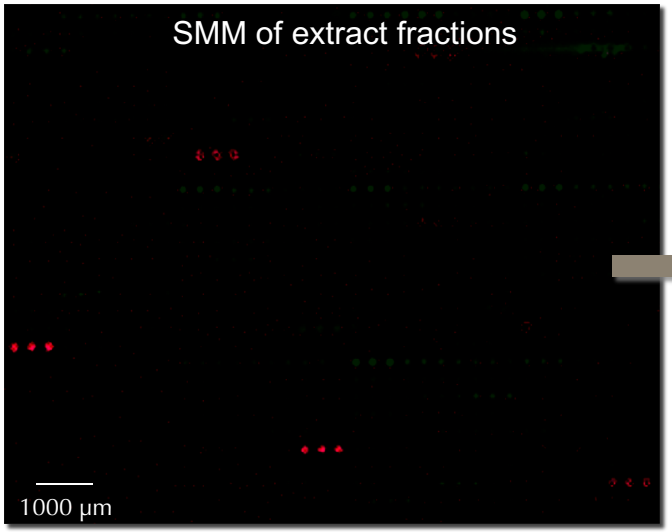


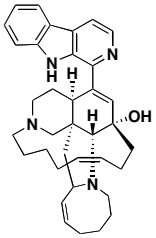
Didemnum roberti

crude extracts



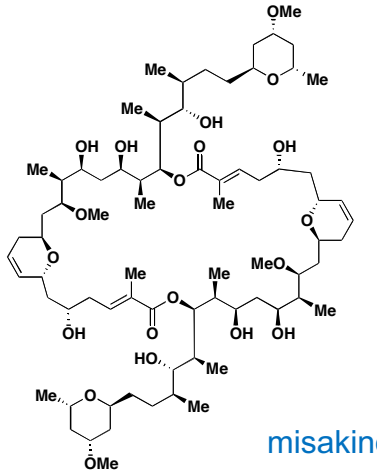
fractions of varying purity





manzamine A

eIF4a binder
stimulates IRES- and
cap-dependent translation



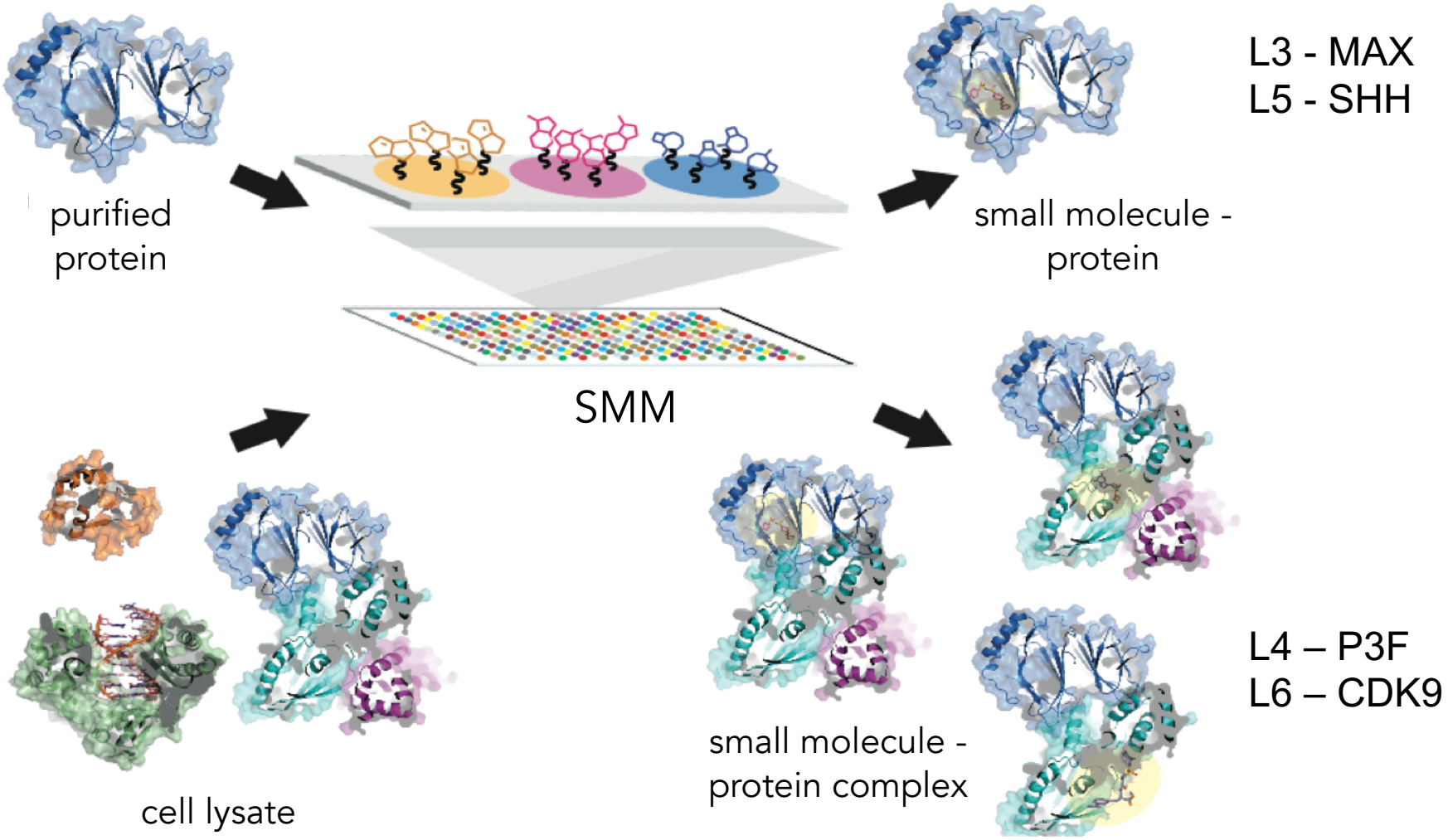
misakinolide A

tubulin binder

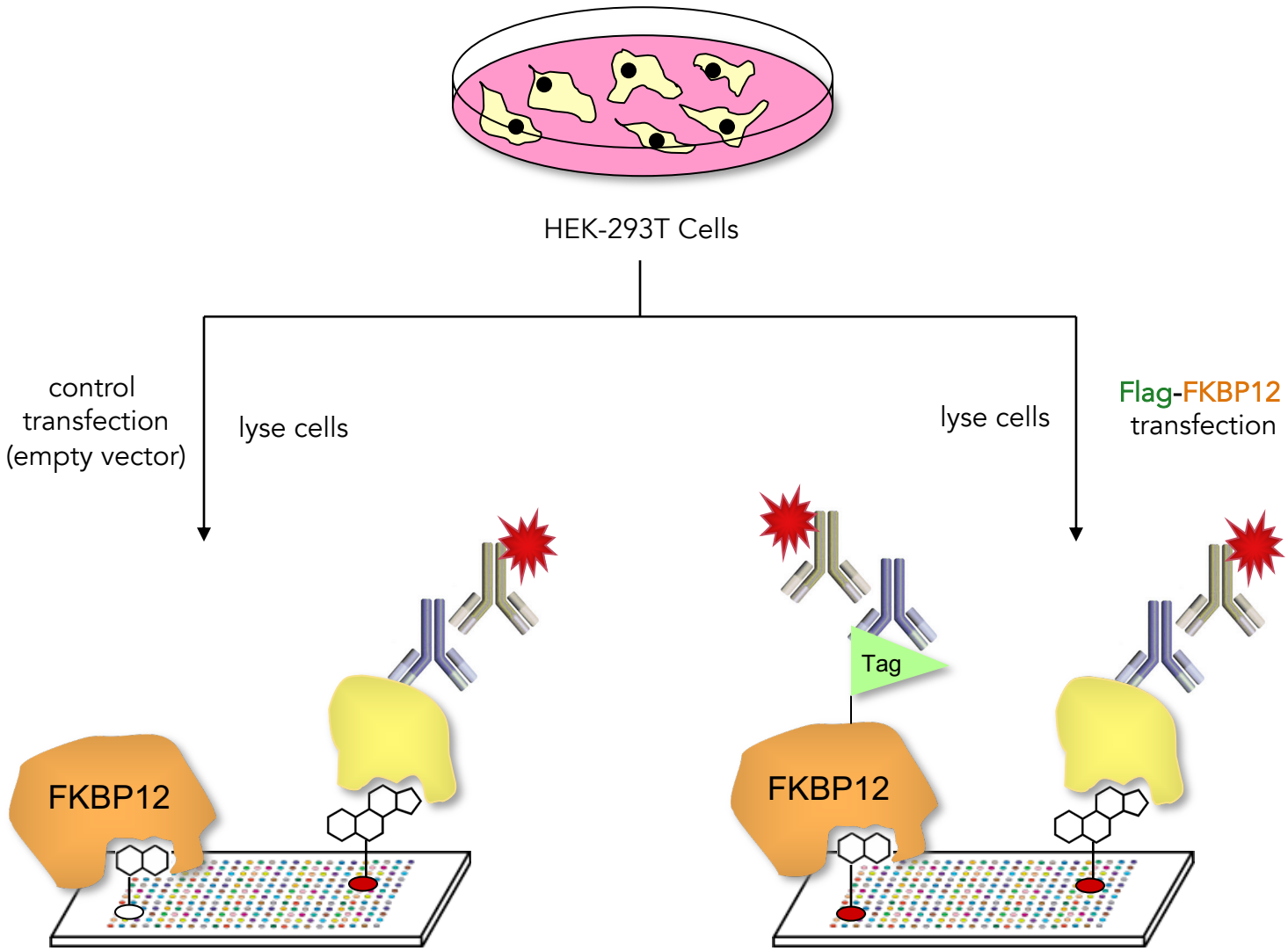
Schmitz, K., Haggarty, S.J., McPherson, O. M., Clardy, J., Koehler, A. N., *J. Am. Chem. Soc.*, *129*, 11346-11347, 2007

SMMs enable a new type of screen

target-directed assays in a native environment

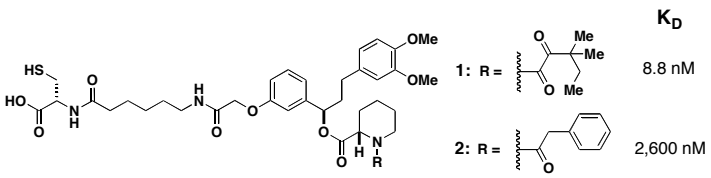


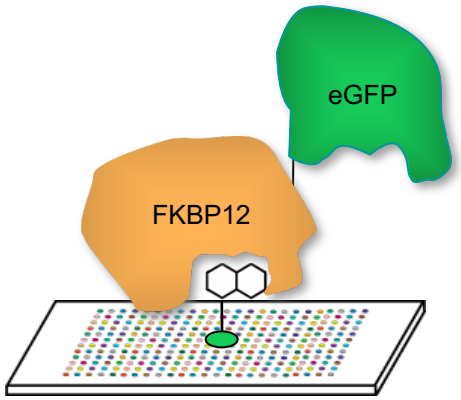
Binding screens involving cell lysates



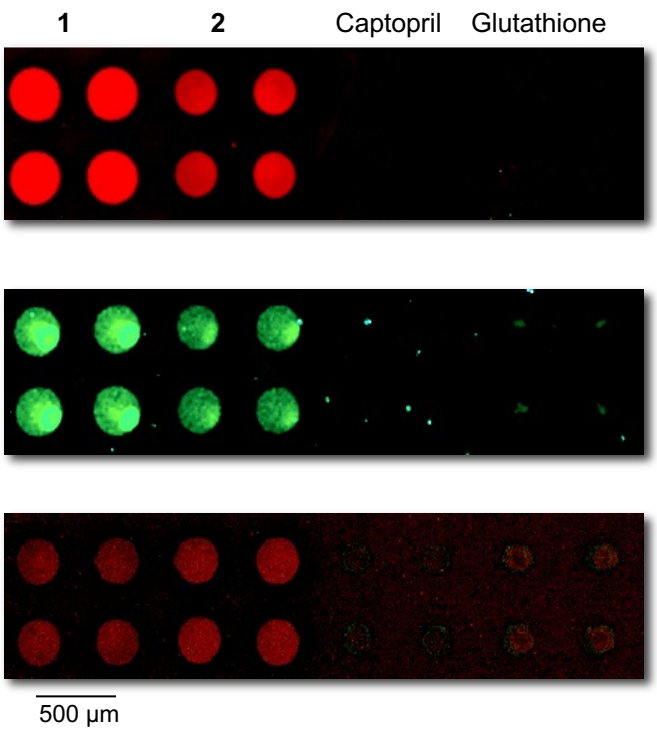
Bradner, J. E., McPherson, O. M., Koehler, A. N., Nature Protocols, 1, 2344-2352 (2006)

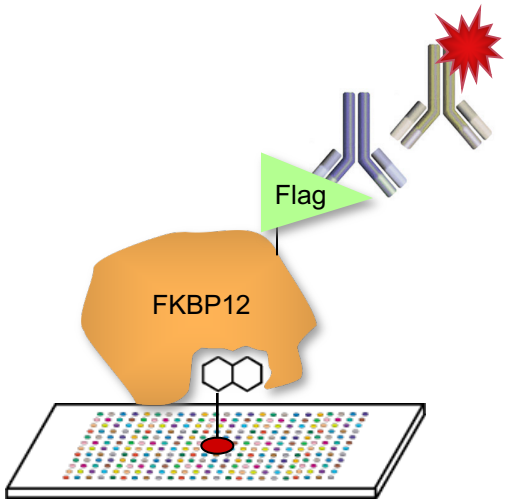
Comparing detection methods using lysates



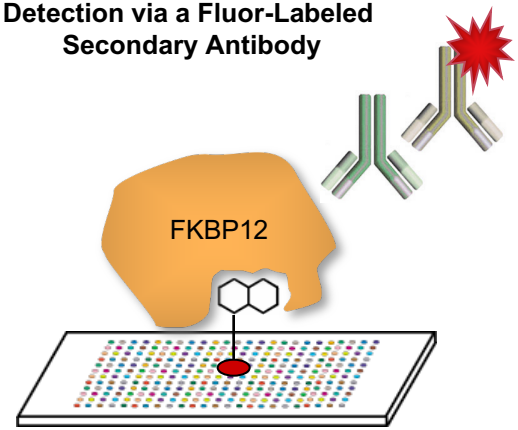


Detection via Green Fluorescent Protein





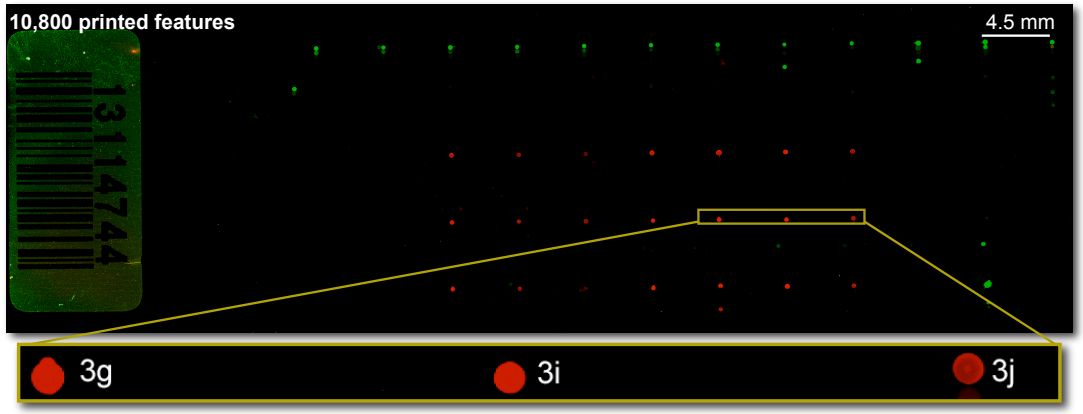
Detection via a Fluor-Labeled Secondary Antibody

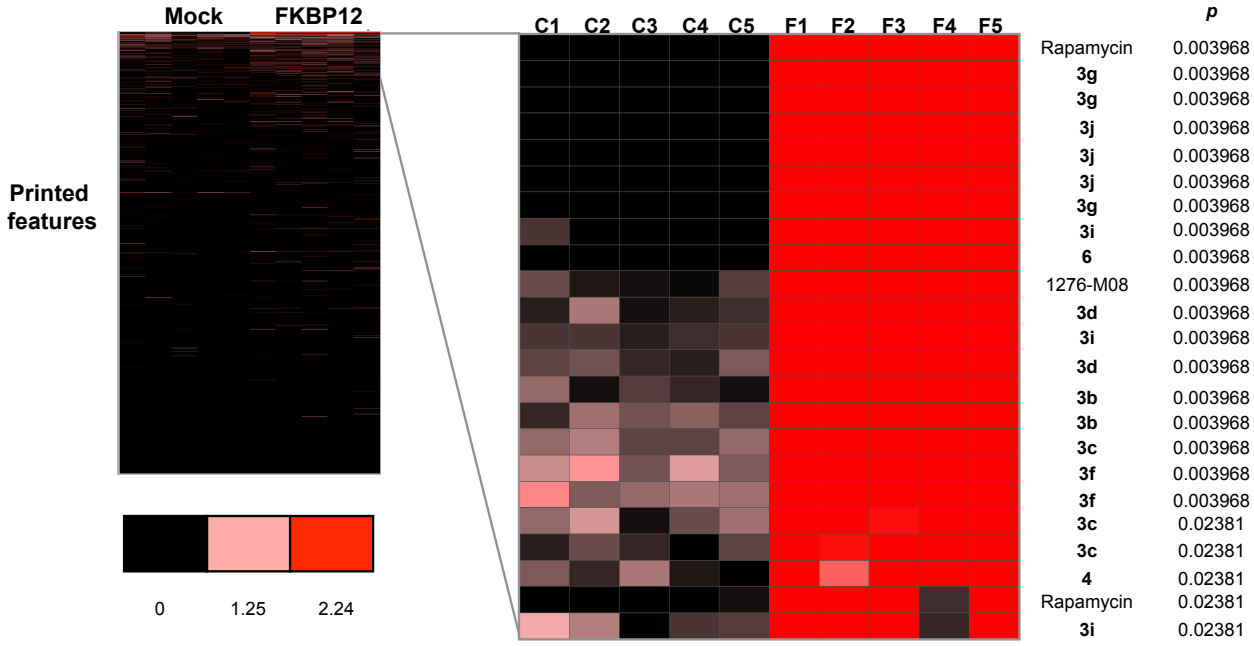


Detection via anti-FKBP12 Antibody and Labeled Secondary

Bradner, J.E., McPherson, O.M., Mazitschek, R., Barnes-Seeman, D., Shen, J.P., Dhaliwal, J., Stevenson, K., Duffner, J.L., Park, S.B., Nghiem, P., Schreiber, S.L., Koehler, A.N. *Chem. Biol.* 13, 493-504, 2006

Binding screen using in cell lysates





	p
Rapamycin	0.003968
3g	0.003968
3g	0.003968
3j	0.003968
3j	0.003968
3j	0.003968
3g	0.003968
3i	0.003968
6	0.003968
1276-M08	0.003968
3d	0.003968
3i	0.003968
3d	0.003968
3b	0.003968
3b	0.003968
3c	0.003968
3f	0.003968
3f	0.003968
3c	0.02381
3c	0.02381
4	0.02381
Rapamycin	0.02381
3i	0.02381

Bradner, J.E., McPherson, O.M., Mazitschek, R., Barnes-Seeman, D., Shen, J.P., Dhaliwal, J., Stevenson, K., Duffner, J.L., Park, S.B., Nghiem, P., Schreiber, S.L., Koehler, A.N. *Chem. Biol.* 13, 493-504, 2006

SMM Discovery Process:
From target selection to validated hits in 9-12 months

2-3 months

Assay dev

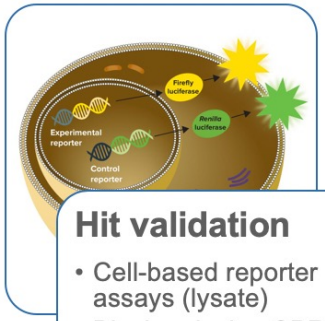
- SMM slide printing
- Cell line engineering
- Optimize protein purification / lysate conditions

1 month

SMM screen

- Slide treatment
- Image analysis
- Algorithmic filters
- Hit calling

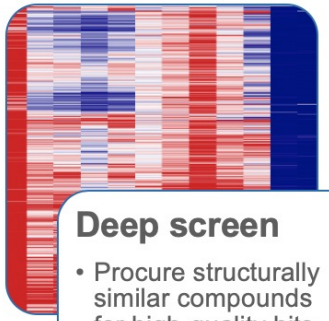
3-4 months



Hit validation

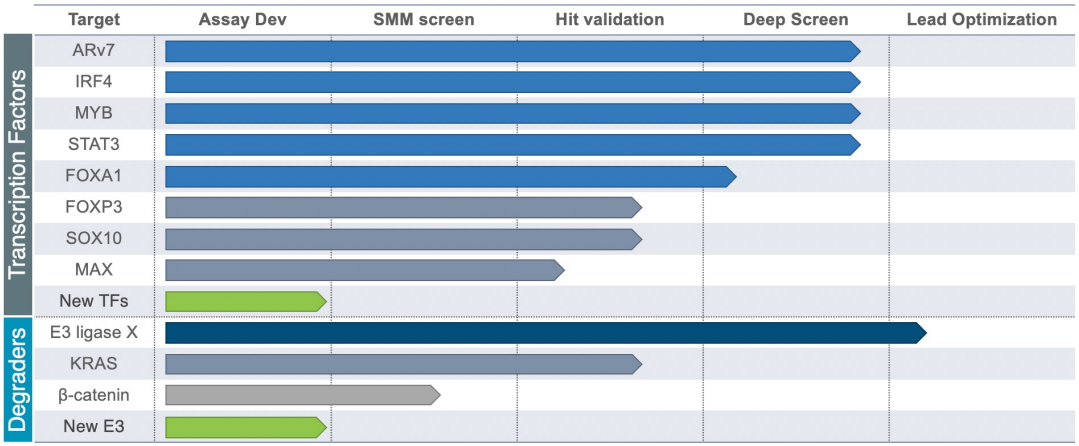
- Cell-based reporter assays (lysate)
- Biochemical or SPR assays (purified)
- Counter screen
- Med chem evaluation

3-4 months

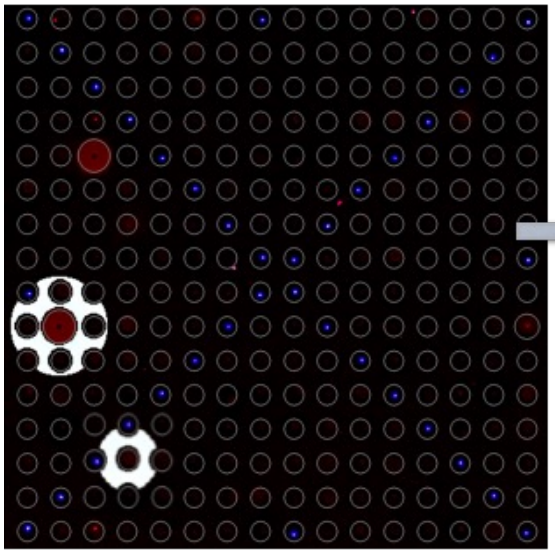


Deep screen

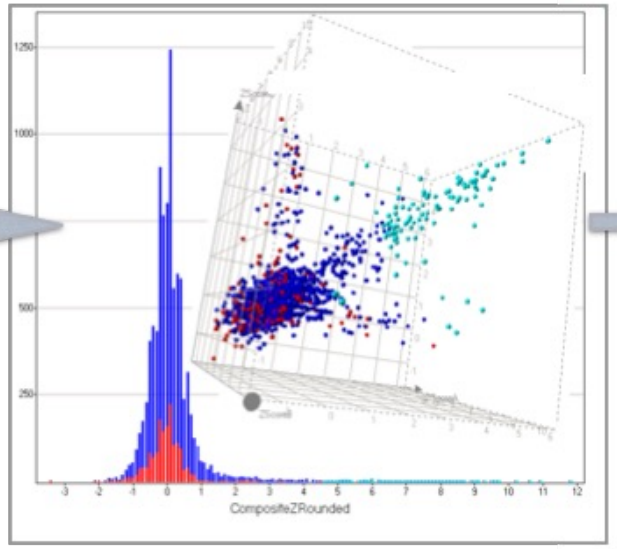
- Procure structurally similar compounds for high-quality hits
- Repeat validation assays
- Cell-based profiling of potency/selectivity



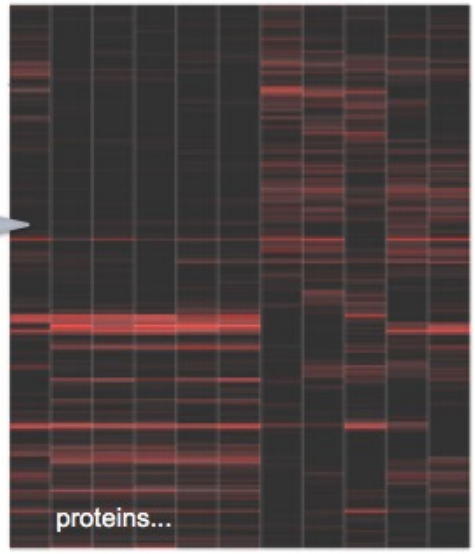
Analysis pipeline – the simple version



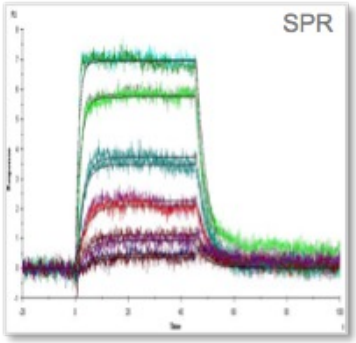
fluorescent features reveal putative interactions

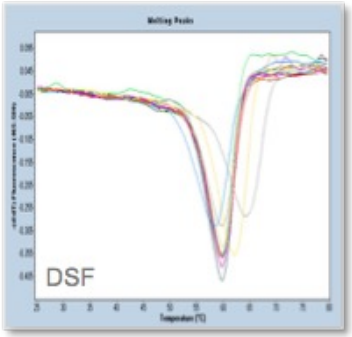


compute composite Z-scores (hit calls)



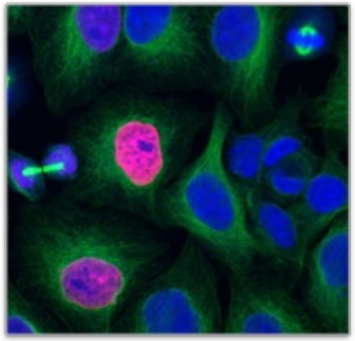
specificity analysis

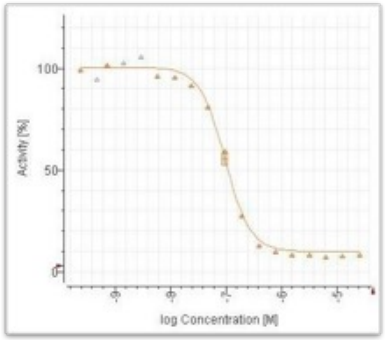




secondary binding assays

+





functional assays

A community effort

Printed molecules

Prabhat Arya, Steacie Institute for Molecular Sciences
Aaron Beeler, Boston University
Kay Brummond, University of Pittsburgh
Tom Chang, Utah State University
Young-Tae Chang, Singapore
Jon Clardy, Harvard Medical School
Mike Foley, Broad Institute
Dennis Hall, University of Alberta
Eric Jacobsen, Harvard University
Ohyun Kwon, UCLA
Tim Lewis, Broad Institute
Lisa Marcaurelle, Broad Institute
Ralph Mazitschek, MGH
Andy Myers, Harvard University
Jim Panek, Boston University
Andy Phillips, Yale
John Porco, Boston University
Scott Schaus, Boston University
Karl Scheidt, Northwestern University
Stuart Schreiber, Broad Institute
Matt Shair, Harvard University
Jared Shaw, UC Davis
Derek Tan, Memorial Sloan-Kettering Cancer Center
Junichi Tanaka, University of the Ryukyus
Stefan Werner, University of Pittsburgh
Peter Wipf, University of Pittsburgh
Keith Woerpel, NYU

Biology collaborators

Cris Bragg, MGH
Manoj Duraisingh, Harvard School of Public Health
Benjamin Ebert, Brigham and Women's Hospital
Levi Garraway, Dana-Farber Cancer Institute
Barbara Gilchrest, Boston University Medical School
Laurie Glimcher, Weill Cornell Medical College
Todd Golub, Broad Institute, Dana-Farber Cancer Institute
Isabella Graef, Stanford University
Stephen Haggarty, MGH
Michael Hecht, Princeton University
Peter Howley, Harvard Medical School
Elliott Kieff, Brigham and Women's Hospital
Sam Lee, MGH
Jon Madison, Stanley Center for Psychiatric Research
Anna Mandinova, MGH
Martin Matzuk, Baylor College of Medicine
Karl Münger, Brigham and Women's Hospital
Paul Nghiem, Fred Hutchinson Cancer Center
Stuart Orkin, Dana-Farber Cancer Institute, Children's Hospital
Stephane Richard, McGill University
Stuart Schreiber, Broad Institute
Stan Shaw, MGH
David Spiegel, Yale
David Spring, University of Cambridge
Robert Tjian, UC Berkeley
Jeff Toretsky, Lombardi Comprehensive Cancer Center, Georgetown
Greg Verdine, Harvard University
Warren Zapol, MGH

...

A community effort

Printed molecules

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Ohyun Kwon, UCLA
Tim Lewis, Broad Institute
Lisa Marcaurelle, Broad Institute
Ralph Mazitschek, MGH
Andy Myers, Harvard University
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Scott Schaus, Boston University
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Stefan Werner, University of Pittsburgh
Peter Wipf, University of Pittsburgh
Keith Woerpel, NYU

SMM positives that score in functional assays

Biology collaborators

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Barbara Gilchrest, Boston University Medical School
Laurie Glimcher, Weill Cornell Medical College
Todd Golub, Broad Institute, Dana-Farber Cancer Institute
Isabella Graef, Stanford University
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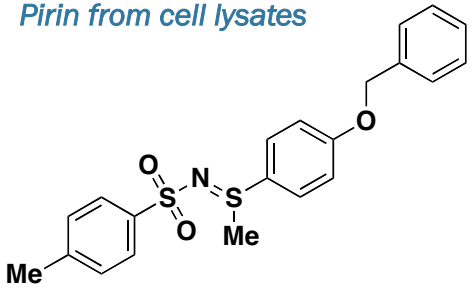
Paul Nghiem, Fred Hutchinson Cancer Center
Stuart Orkin, Dana-Farber Cancer Institute, Children's Hospital
Stephane Richard, McGill University
Stuart Schreiber, Broad Institute
Stan Shaw, MGH
David Spiegel, Yale
David Spring, University of Cambridge
Robert Tjian, UC Berkeley
Jeff Toretsky, Lombardi Comprehensive Cancer Center, Georgetown
Greg Verdine, Harvard University
Warren Zapol, MGH
...

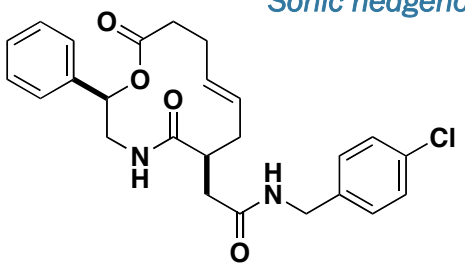
>50 published chemical probes from SMMs

Pirin from cell lysates



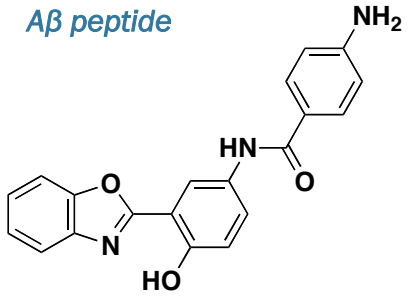
K_D = 0.6 μM (ITC)
inhibits pirin-Bcl3 interaction in cells
inhibits melanoma cell migration
Miyazaki *et al*, ACS Chem Biol 2010

Sonic hedgehog

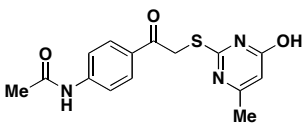


K_D = 3.1 μM (SPR)
analog of SMM hit that inhibits Shh signaling in cells and synthetic skin model
Stanton *et al*, Nature Chem Biol 2010

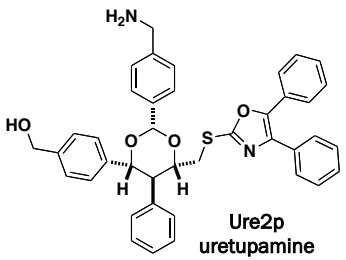
Aβ peptide



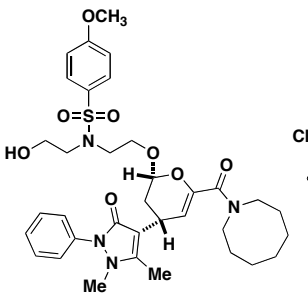
K_D Aβ40$_{mon}$ ~ 9-17 μM (various methods)
inhibits Aβ42-induced cytotoxicity in PC12 cells, accelerates fibril formation
Chen *et al*, J. Am. Chem. Soc. 2010



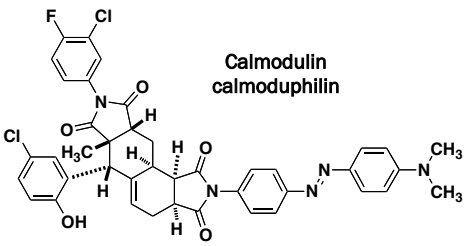
HDAC inhibitor
BRD-2577



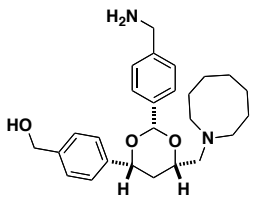
Ure2p
uretupamine



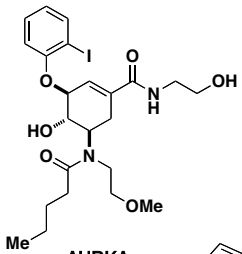
FKBP12
FKL-01



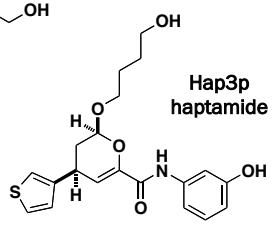
Calmodulin
calmoduphilin



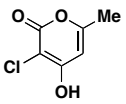
Calmodulin
calmodioxane



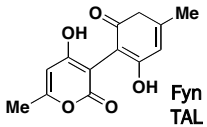
AURKA
1106.I16



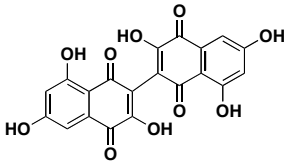
Hap3p
haptamide



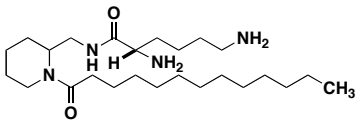
Fyn
TAL-Cl



Fyn
TAL

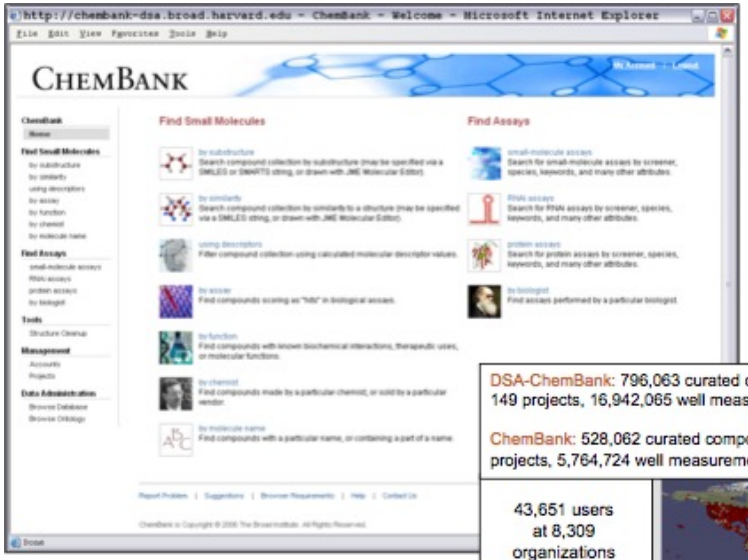


Fyn
Bi-TAL



Calmodulin
NPC-15437

Public access for SMM data sets

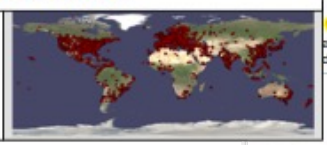


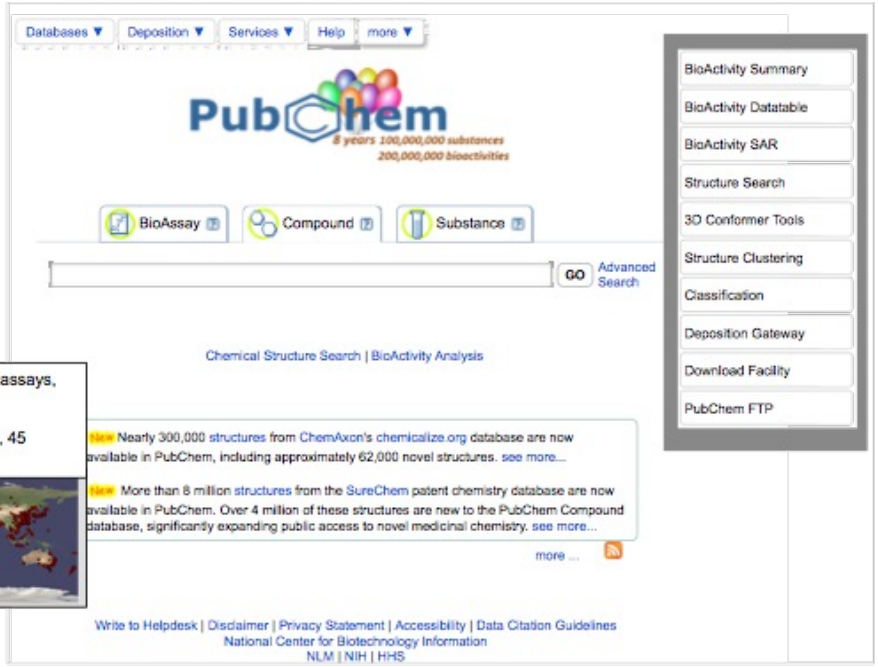
http://chembank.broad.mit.edu

DSA-ChemBank: 796,063 curated compounds, 1,963 assays, 149 projects, 16,942,065 well measurements

ChemBank: 528,062 curated compounds, 529 assays, 45 projects, 5,764,724 well measurements

43,651 users at 8,309 organizations in 154 countries





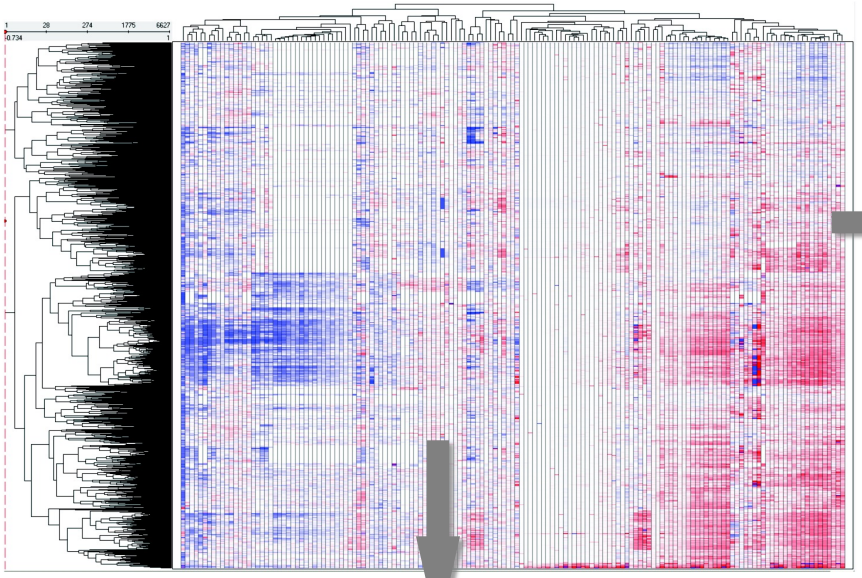
http://pubchem.ncbi.nlm.nih.gov

http://bard.nih.gov/drupal

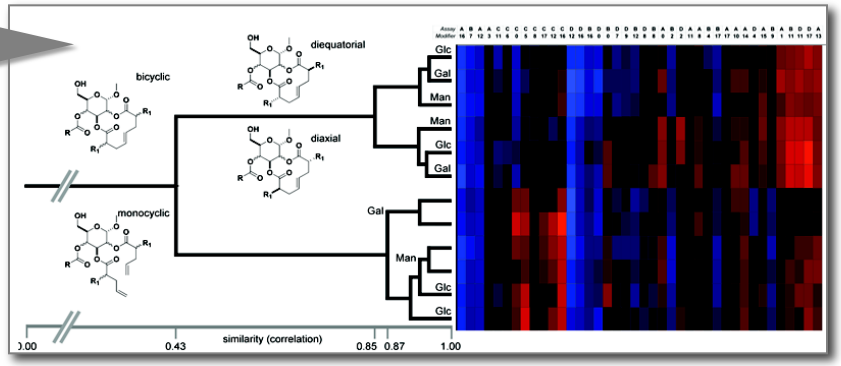
ChemBank: an analytical tool for the community

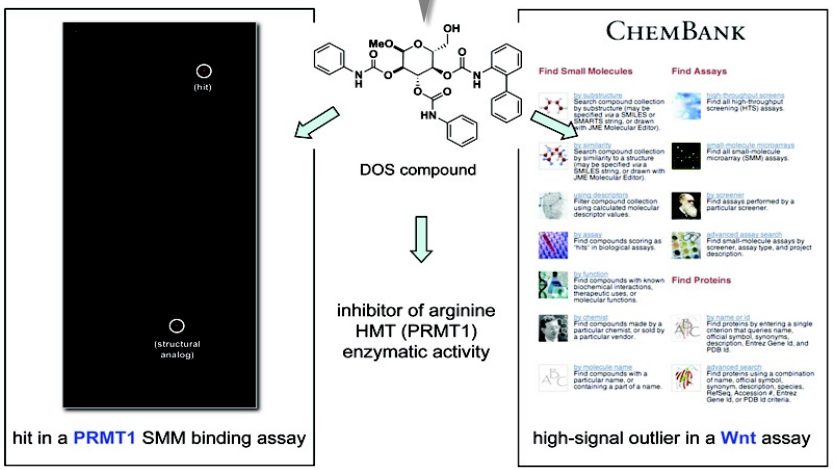
assays (cell-based, biochemical, binding)

small molecules



relationship of structure to screen performance



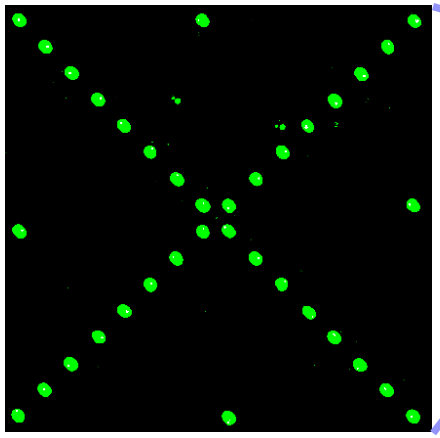


relationships between assays (protein and phenotype)

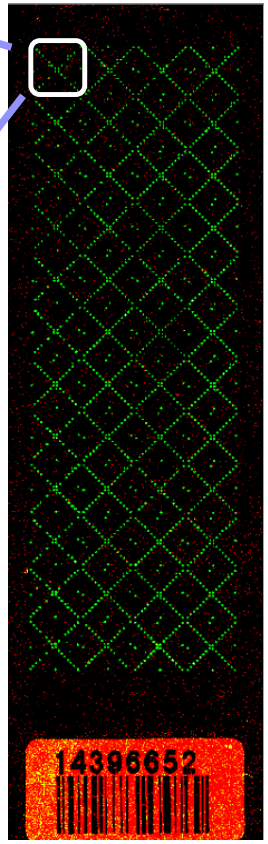
Initiative for Chemical Genetics

National Cancer Institute

20.109 MAX screens

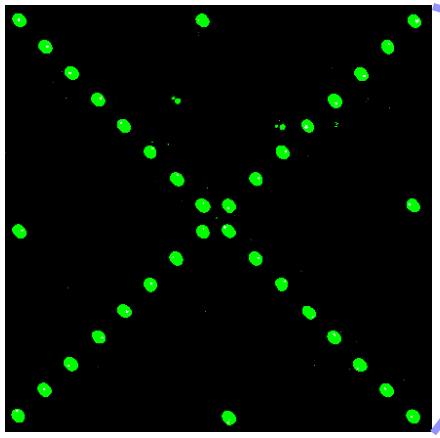


subarray with
sentinel pattern for
alignment

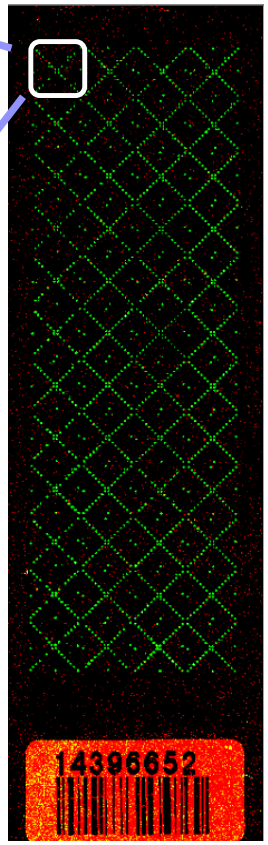


full array with 48
subarrays (4 x 12)

20.109 MAX screens



subarray with
sentinel pattern for
alignment

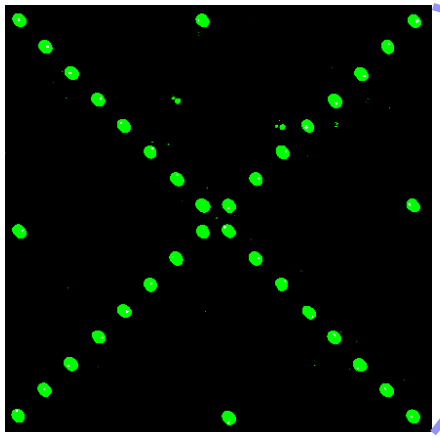


full array with 48
subarrays (4 x 12)

each team screens
~10,000 unique
compounds

16x16x48 = 12,288
2 replicate slides
4 replicates for each compound

20.109 MAX screens



subarray with
sentinel pattern for
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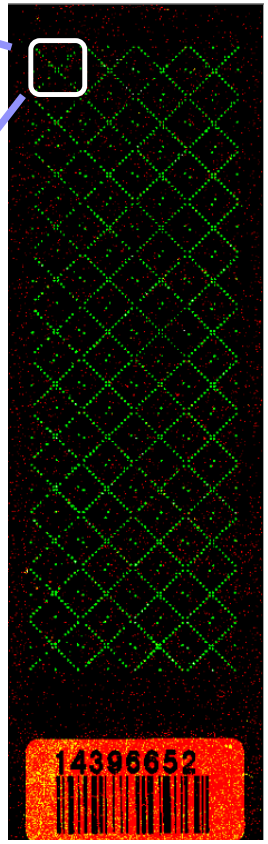
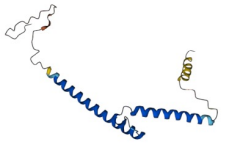
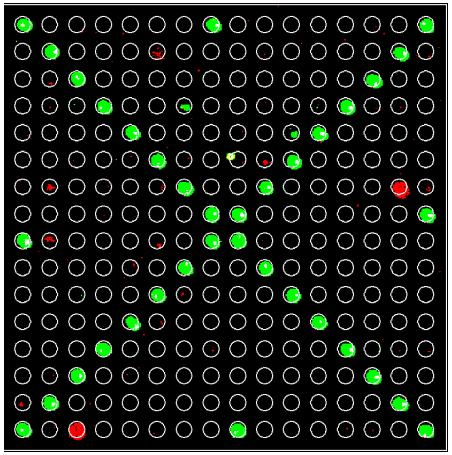


full array with 48
subarrays (4 x 12)

student-
purified
MAX



scan



subarray with 'gal file'
(genepix alignment) file
superimposed

small molecule 'hits'

Upcoming Lectures

2/9/23	Lecture 1	Intro to chemical biology: small molecules, probes, and screens
2/14/23	Lecture 2	Small Molecule Microarray (SMM) technique
2/16/23	Lecture 3	Our protein target – MAX
2/21/23	No Lecture	
2/23/23	Lecture 4	Quantitative evaluation of protein-ligand interactions
2/28/23	Lecture 5	An SMM ligand discovery vignette for sonic hedgehog
3/2/23	Lecture 6	KB-0742: A Phase 2 clinical candidate discovered by SMMs
3/7/23	Lecture 7	Wrap up discussion for Mod 1 experiments and report