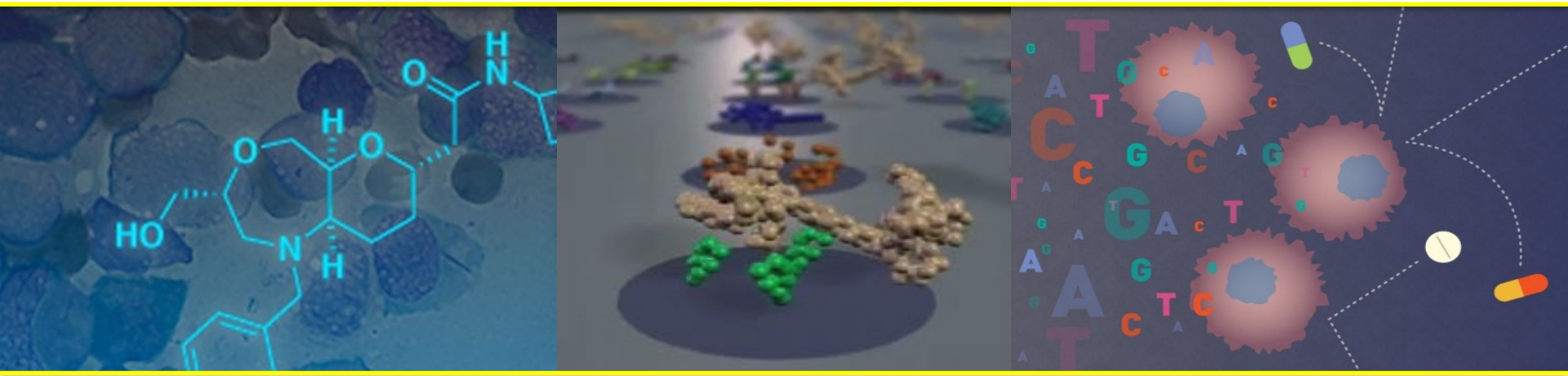
Welcome to Module 1

Drug Discovery



L1 Intro to chemical biology: small molecules, probes, and screens

February 8, 2024

Angela Koehler
koehler@mit.edu

Instructor

Koch Institute
76-361c

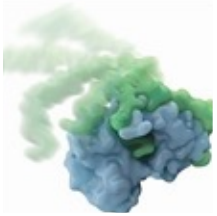
Lectures

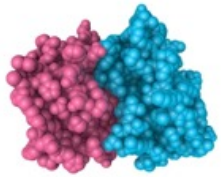
Module 1 Office Hours

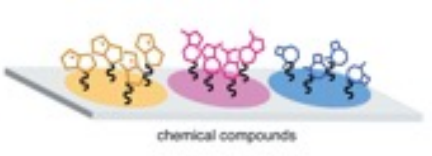
Fri 2/16	noon
Mon 2/26	9am
Tue 3/5	1pm
Mon 3/11	3pm
Fri 3/15	noon
Fri 3/22	noon

Join Zoom Meeting
https://mit.zoom.us/j/93057049755

Meeting ID: 930 5704 9755



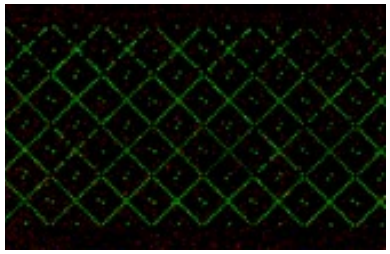




KOEHLER LAB
@ MIT

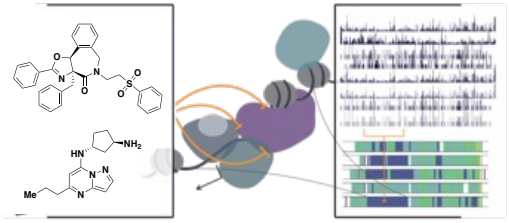
expanding the repertoire
of tractable targets

transcription factors, RBPs, cytokines



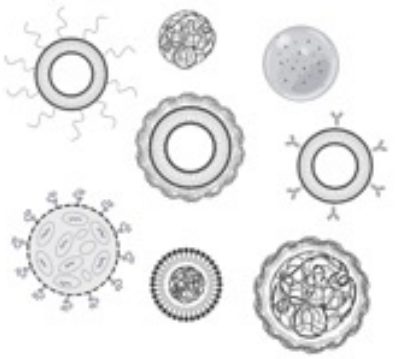
exploring novel
probe/drug mechanisms

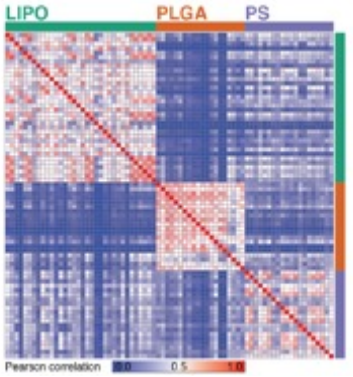
degradation, modulating interactomes, etc.

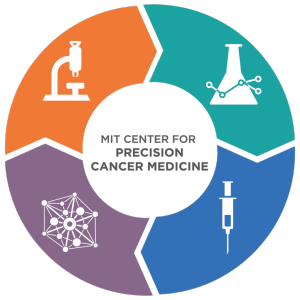


expanding materials toolkit for targeted
drug/cell delivery:

targeting ligands for delivery
understand MoA for materials
priming cells for nP uptake
avoiding fibrotic response
biomarkers for patient selection







Royal G. and Mae H. Westaway
Family Memorial Fund

Kathy and Curt Marble
Research Fund

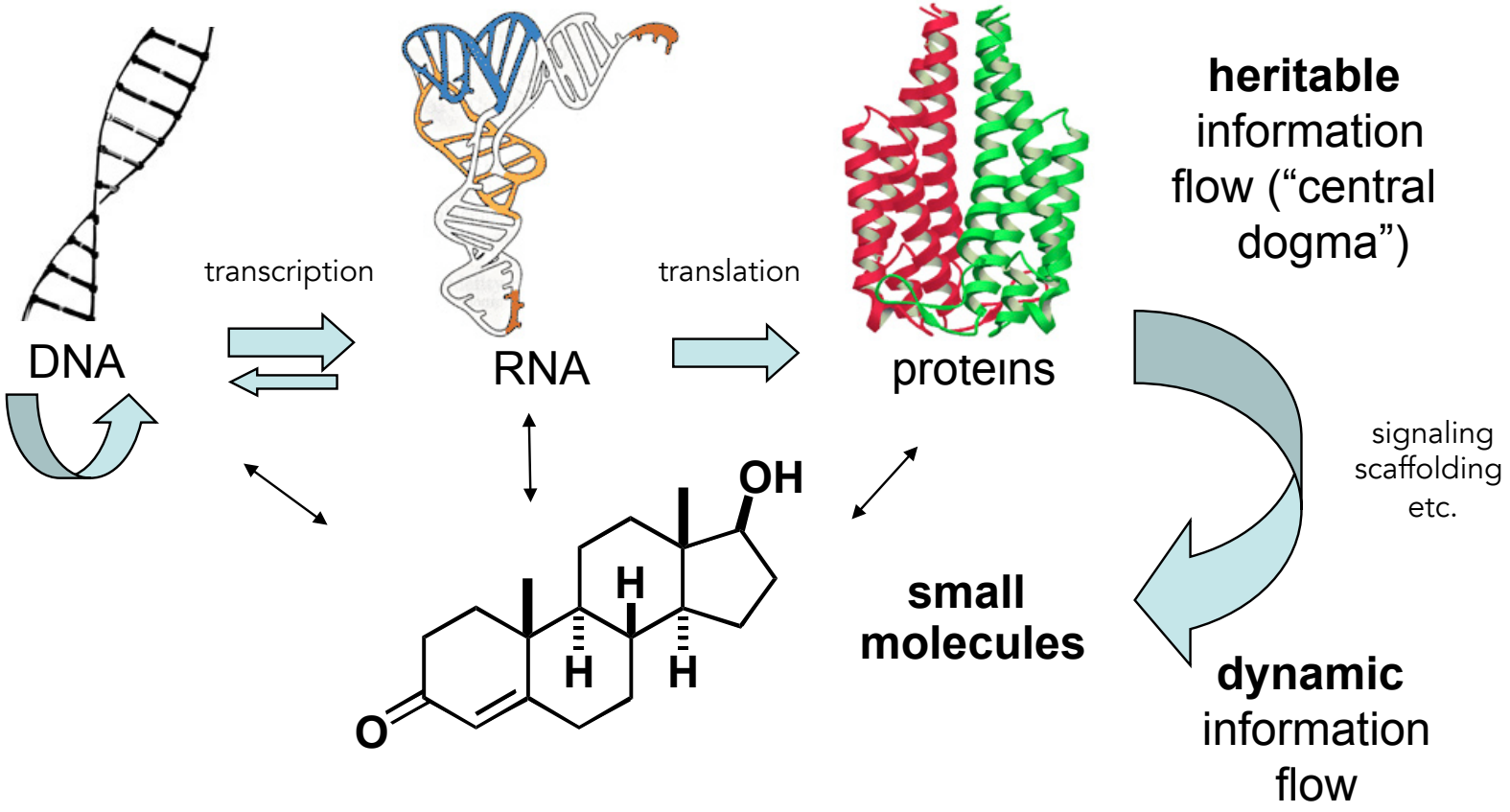
Benjamin and Samuel Krinsky
Memorial Fund

founded in 2007

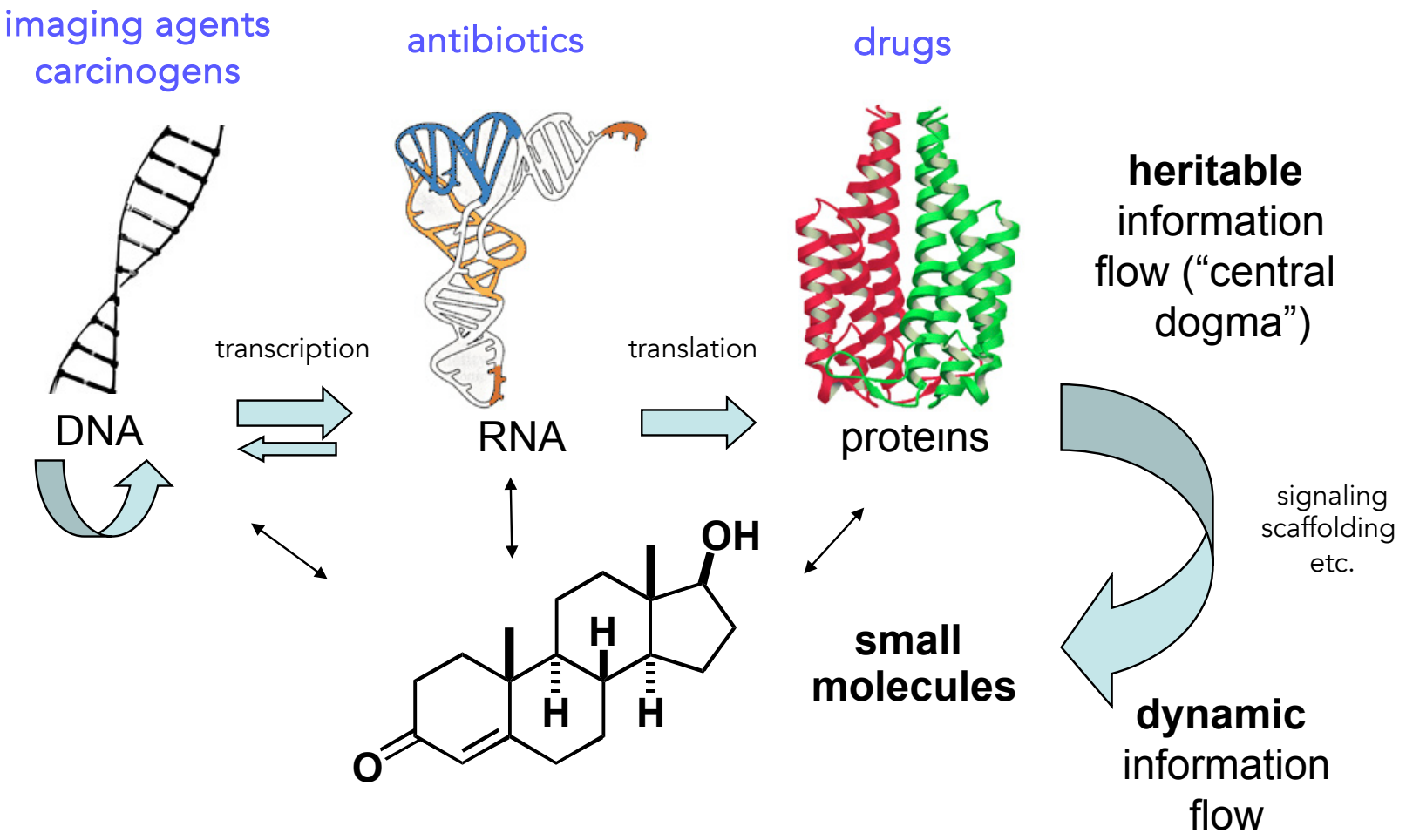
founded in 2017

founded in 2021

The central dogma



The central dogma



cell signaling, cognition, metabolism, life's origins
chemical probes and drugs

Defining chemical biology

Chemical biology is a discipline that spans multiple fields and involves the application of chemical or molecular techniques, tools, and analyses to the study and manipulation of biological systems

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Chemical biologists attempt to use chemical approaches to modulate systems to either investigate underlying biology, typically using quantitative measures, and to engineer new functions

Defining chemical biology

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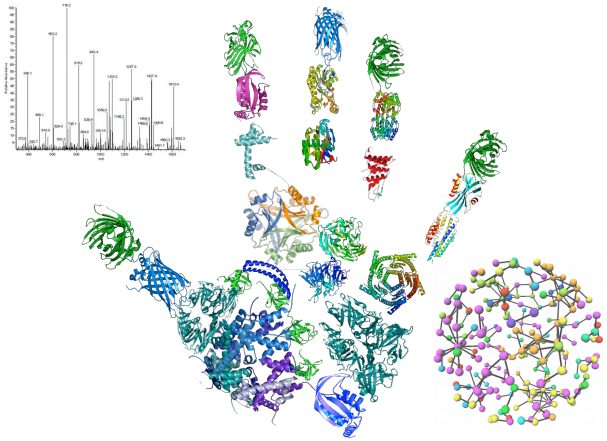
Chemical biologists attempt to use chemical approaches to modulate systems to either investigate underlying biology, typically using quantitative measures, and to engineer new functions

Research done by chemical biologists is often more closely related to cell or systems biology than biochemistry. Biochemists study the chemistry carried out by biomolecules and how metabolites function in pathways while chemical biologists apply novel chemical tools to study biology, including basic, disease, and synthetic applications.

Systems of interest to chemical biologists



quantitative proteomics

Bryson, Dedon, Fraenkel, Hynes, Kiessling, Koehler, White, Yaffe

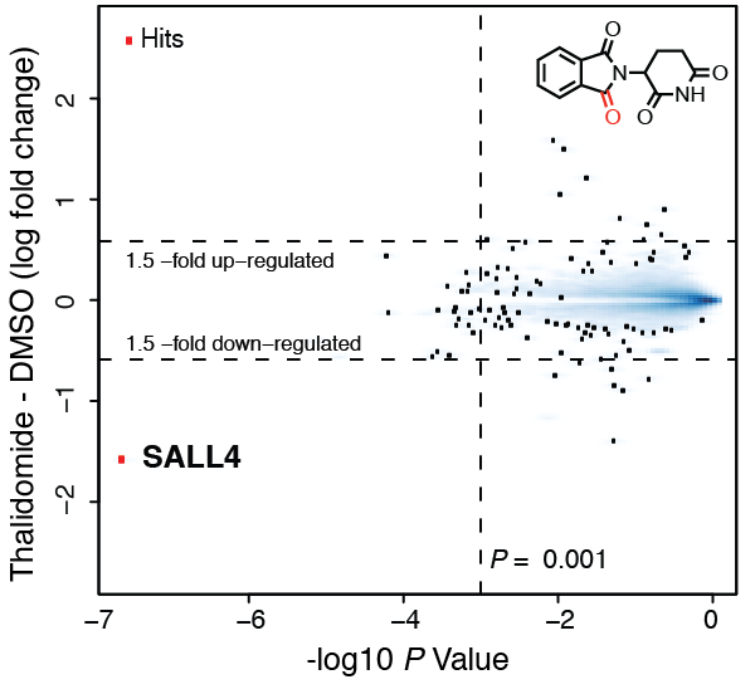
BE Dept/Course 20

Bio Dept/Course 7

Chem Dept/Course 5

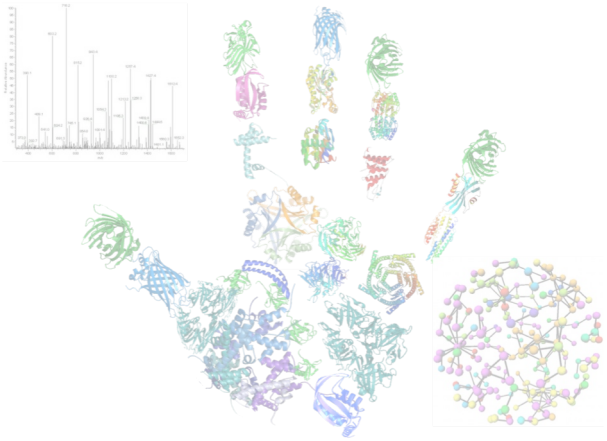
Investigates the set of expressed proteins in a cell at a given time under defined conditions – quantitative, comparative

often involves mass spectrometry



Dr. Eric Fischer, Harvard

Systems of interest to chemical biologists



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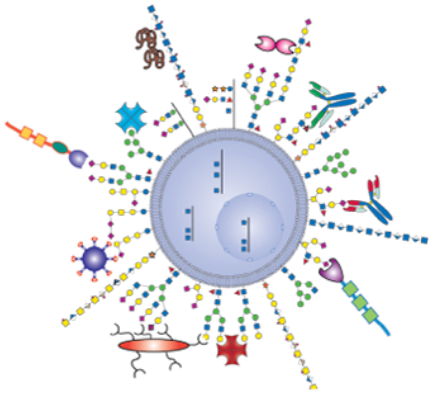
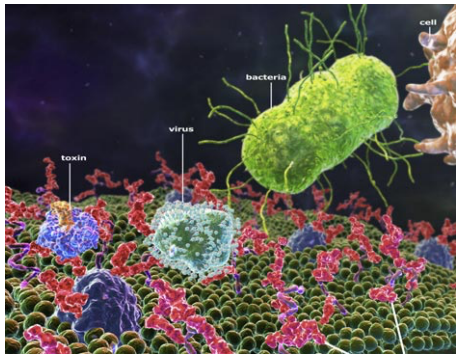




glycobiology

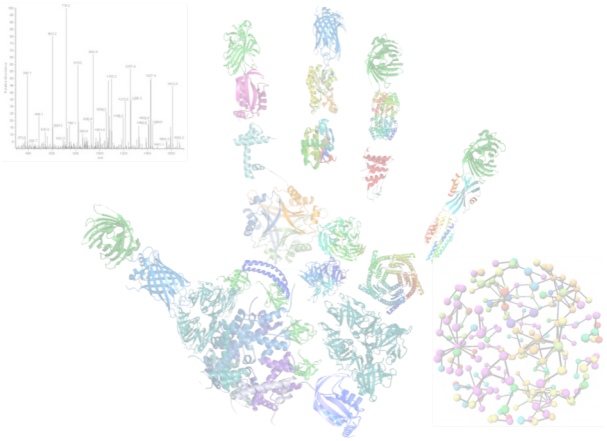
Imperiali, Irvine, Kiessling, Ribbeck, Sasisekharan, Stark, Vander Heiden

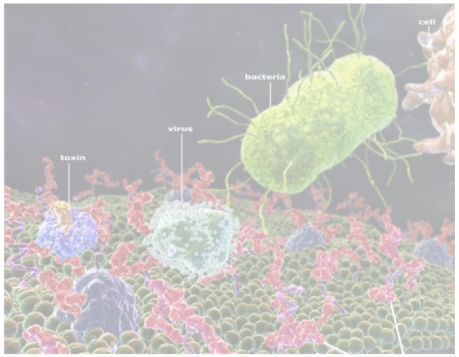
- BE Dept/Course 20
- Bio Dept/Course 7
- Chem Dept/Course 5

Investigates how sugars regulate biology, including cell-virus interactions protein stability, and metabolism, among other functions – quantitative, comparative

involves many imaging and tracing methods, mass spec

Systems of interest to chemical biologists





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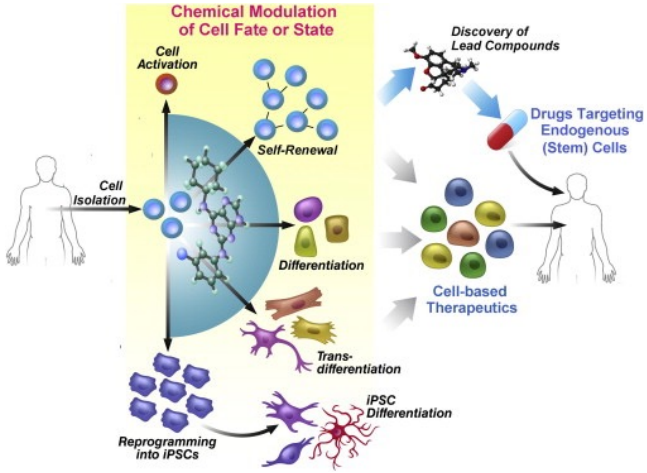


Often involves using chemicals to perturb signaling systems that govern cell state

stem cell biology and programming cell fate

Boyer, Bryson, Collins, Griffith, Guarente, Jaenisch, Kiessling, Koehler, Langer, Lauffenburger, Lu, Lodish, Weinberg, Weiss, Yilmaz, Young

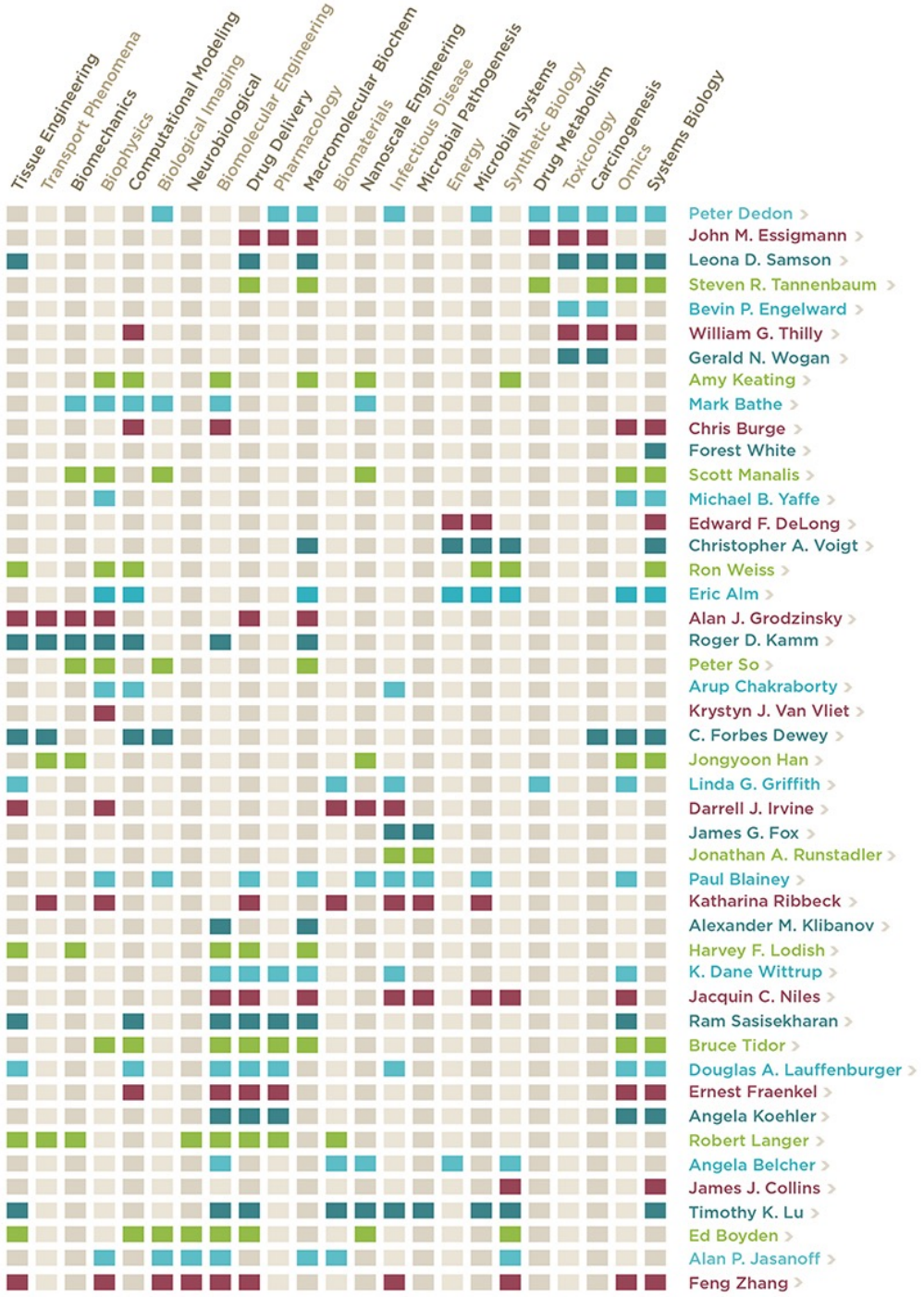
Chemical tools & methods
are a vital aspect of
MIT BE Research Programs

Measure
Model
Manipulate
Make

Imaging, Biomaterials, Bio-factories

MIT BE
BIOLOGICAL ENGINEERING

Creating biological technologies
from discovery to design.



Chemical biology courses at MIT

suitable for advanced undergraduates

20.554 Frontiers in Chemical Biology (G Fall)

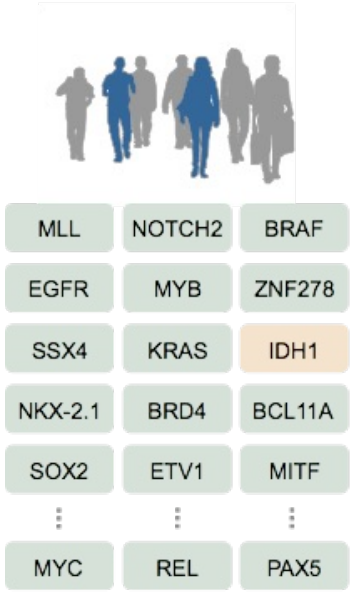
Laura Kiessling, Matthew Shoulders

Introduction to current research at the interface of chemistry, biology, and bioengineering.

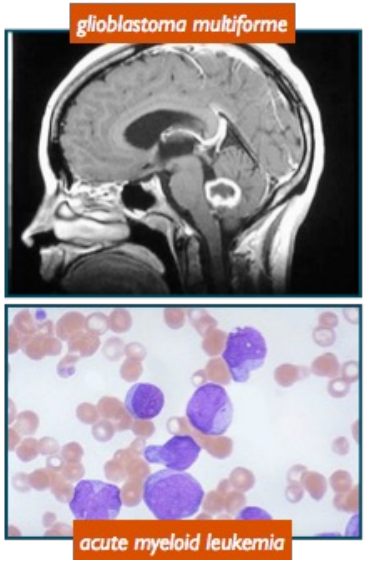
Topics include imaging of biological processes, metabolic pathway engineering, protein engineering, mechanisms of DNA damage, RNA structure and function, macromolecular machines, protein misfolding and disease, metabolomics, and methods for analyzing signaling network dynamics.

Lectures are interspersed with class discussions and student presentations based on current literature.

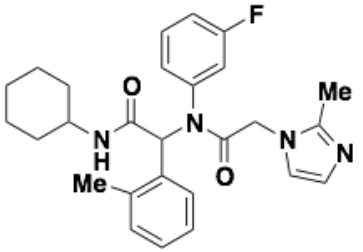
Chemical probes of disease biology



patient samples reveal
list of disease genes



physiologic settings to test
the impact of disease genes



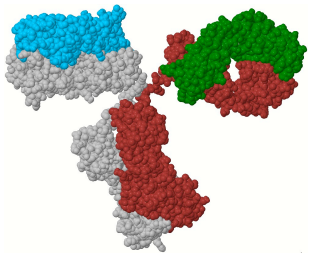
discover small molecules
that reverse the
impact of disease genes

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

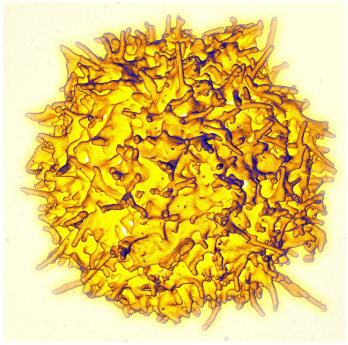
Output: validated small-molecule probe to facilitate human clinical development or diagnostic applications

How small is a small molecule?

antibodies

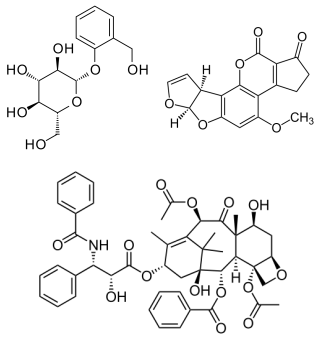


T-cells

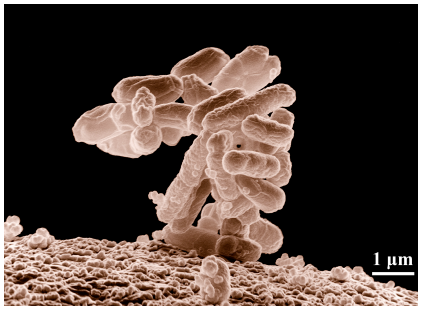


10^{-9} m — 10^{-6} m — $>10^{-4}$ m

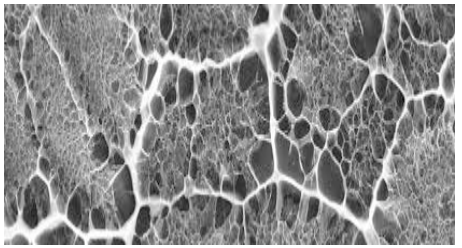
small molecules



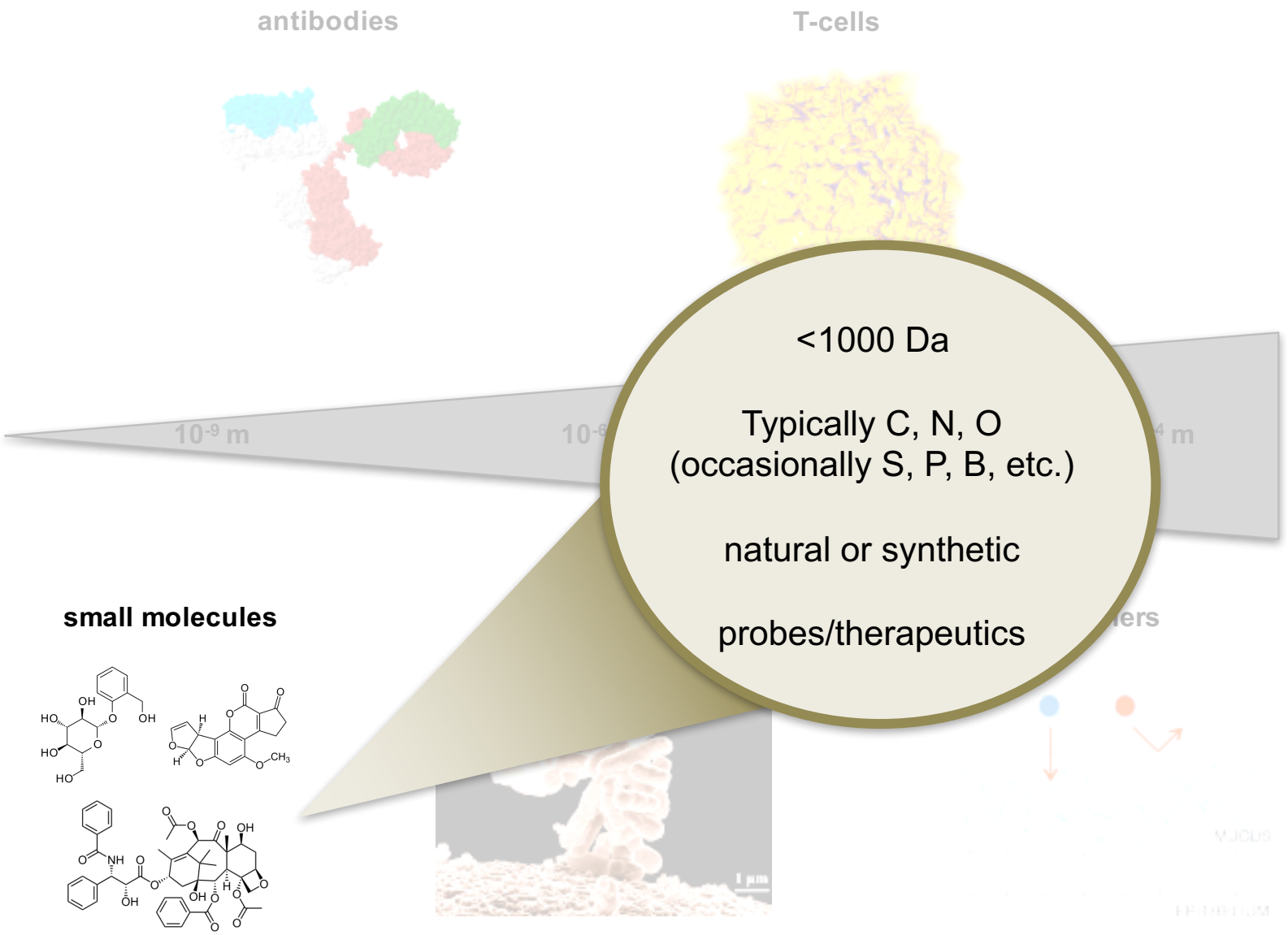
microbes



bio-materials



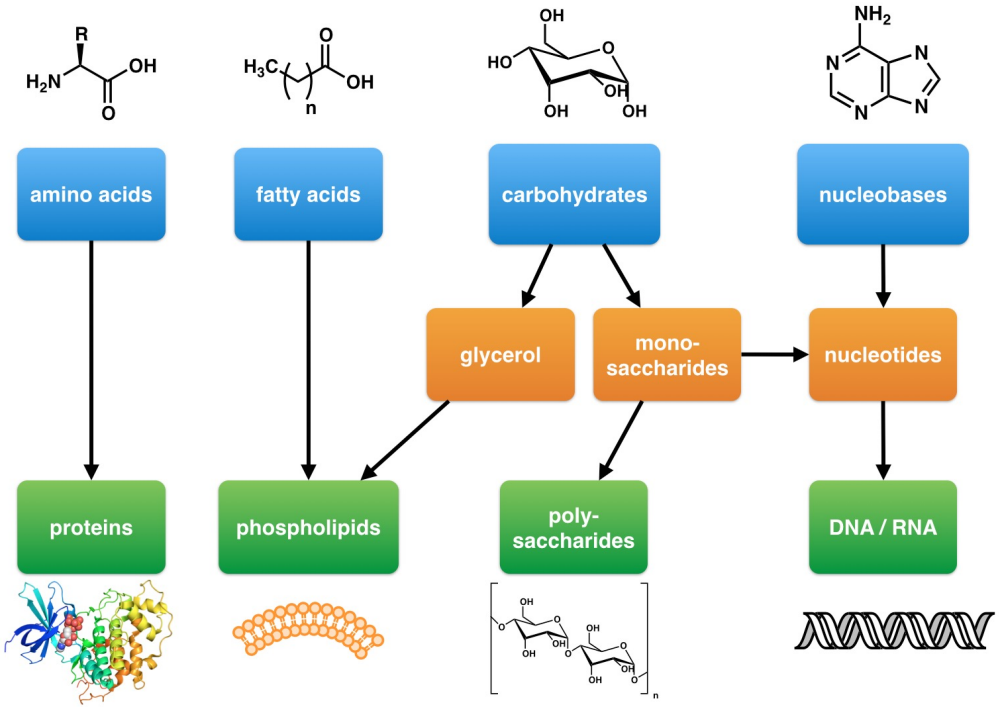
How small is a small molecule?

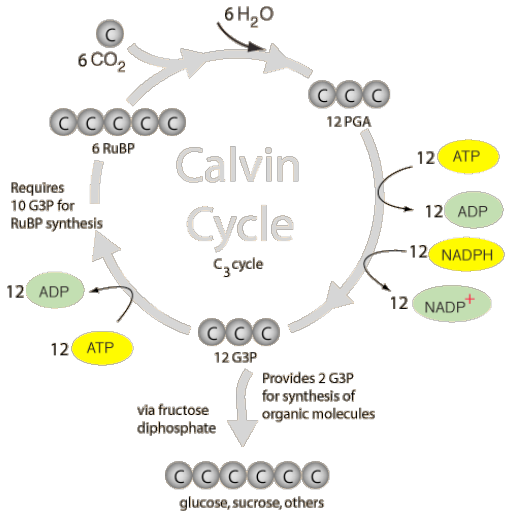


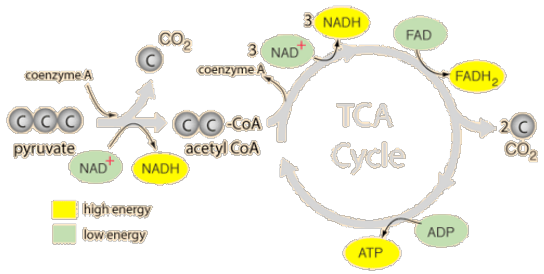
Small molecules of life

7.05

primary metabolites - intrinsic function is **essential to survival of organism**







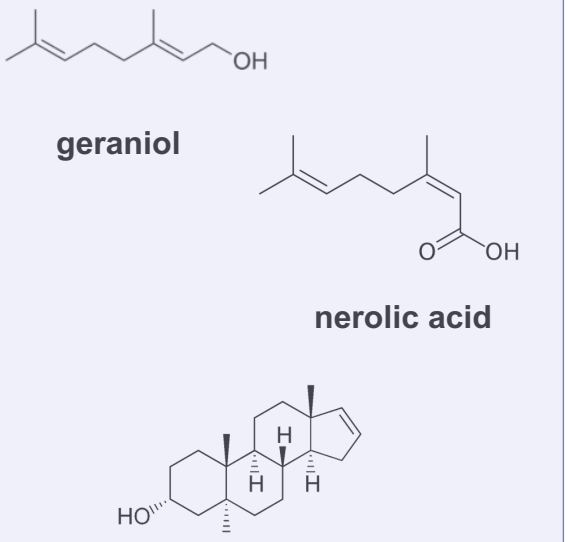
first messengers – signaling molecules that control metabolism and cell differentiation (e.g. hormones, biogenic amines)

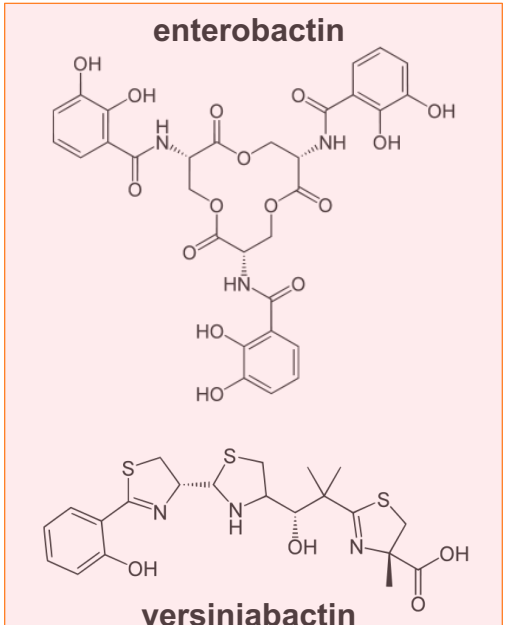
Small molecules of life

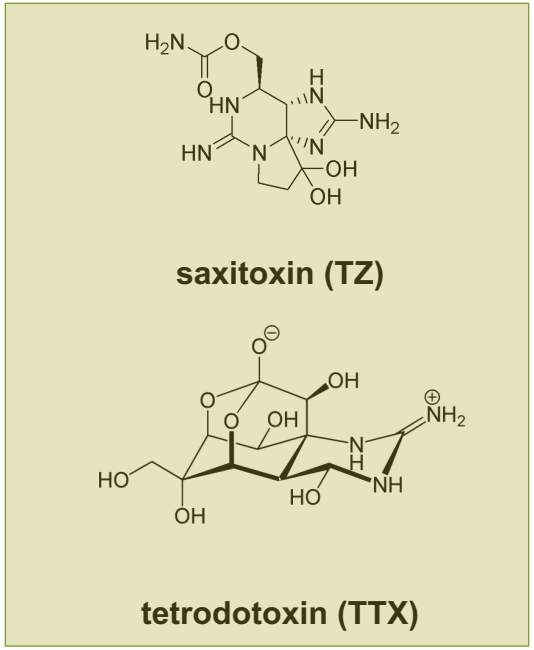
secondary metabolites – non-essential to organism, extrinsic function that affects other organisms; broad range of functions, narrow species distribution

increase competiveness of an organism

pheromones – social interactions	transporters and chelators	toxins – competitive weapons



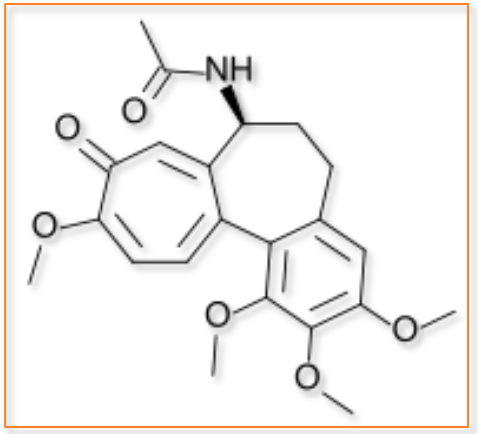




significant interest in exploring bioactivity of these ‘natural products’ for biological probe and therapeutic applications

Small molecules and their biological partners

the compound that changed my life

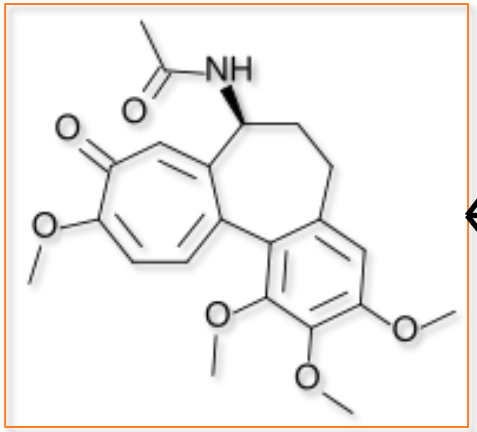


colchicine

Secondary metabolite from meadow saffron

Small molecules and their biological partners

the compound that changed my life



Chemistry class
biosynthesis in plants
lab synthesis

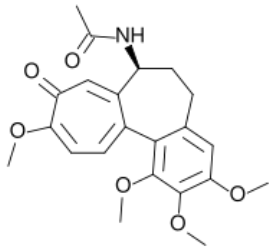
Cell Biol class
tool in lab

Physiology class
use as a therapy

colchicine

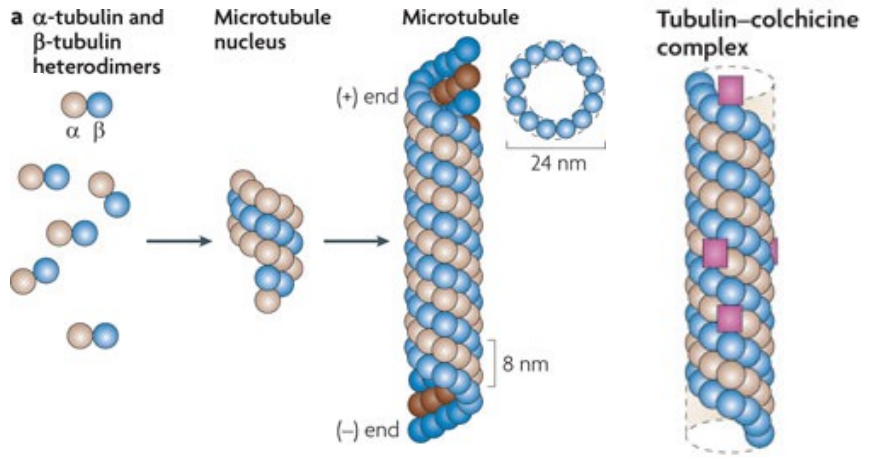
Secondary metabolite from meadow saffron

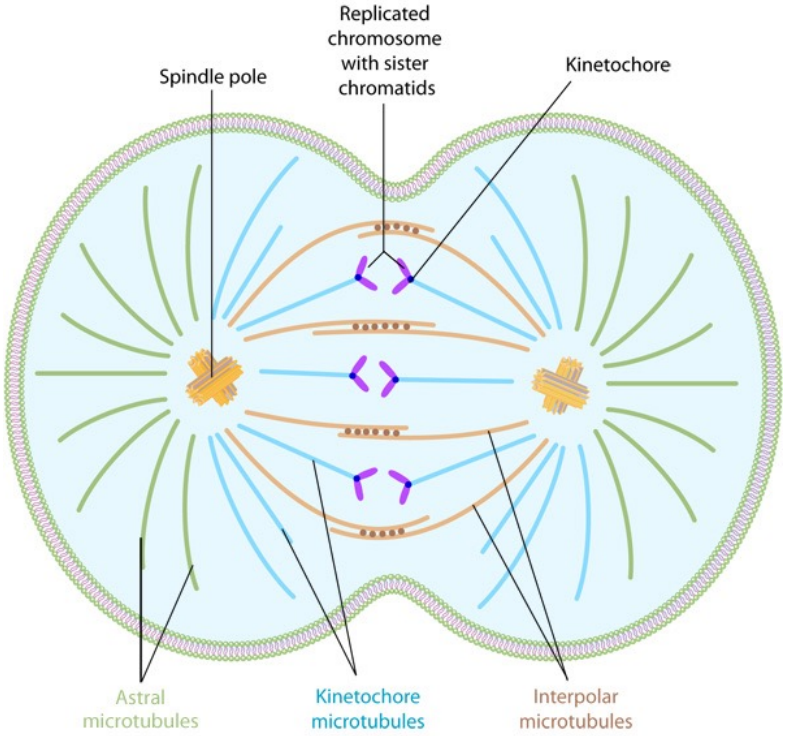
Colchicine is a *mitotic spindle poison*

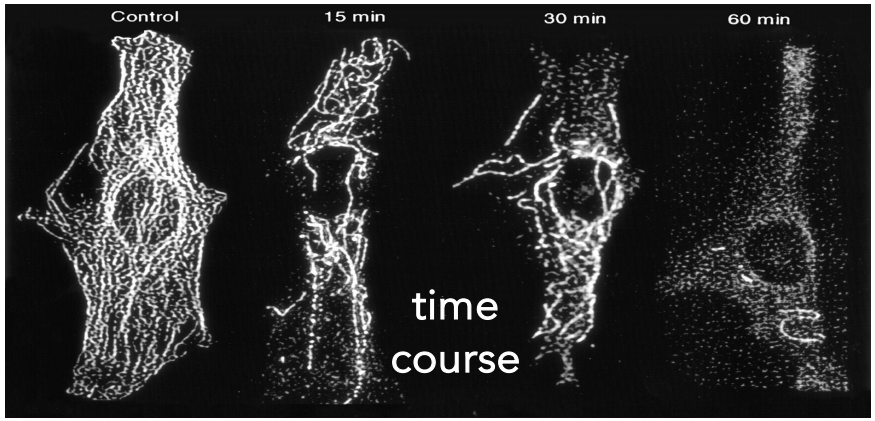


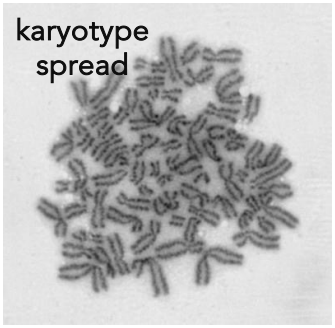
colchicine

binds to tubulin protein
blocks microtubule polymerization









colchicine prevents chromosome segregation and enables study chromosome count and physical characteristics

Colchicine informs therapeutic strategies

inflammatory diseases – neutrophil motility

gout

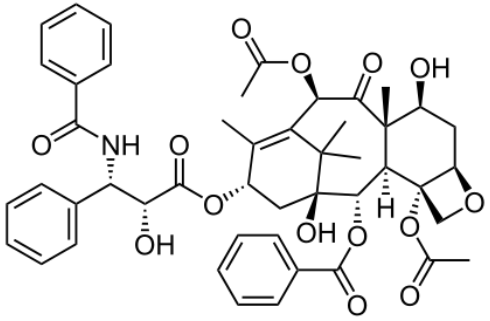
pericarditis

Behçet's disease

Egyptians -1500 BC
Ben Franklin

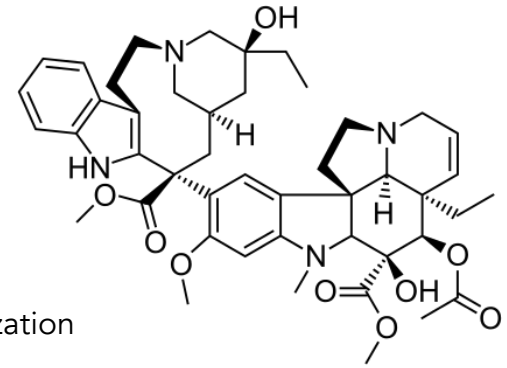
mitotic poisons for cancer therapy

Taxol
stabilizes MTs



lung, ovarian, breast, sarcomas

Vinblastine
blocks MT polymerization



leukemia, lymphoma, breast, testicular

‘Chemical genomic’ toolkit

How many specific probes do we need to study the entire ‘expressed genome?’

‘Chemical genomic’ toolkit

How many specific probes do we need to study the entire ‘expressed genome?’

92,000 expressed proteins
1 inhibitor of function
1 activator of function

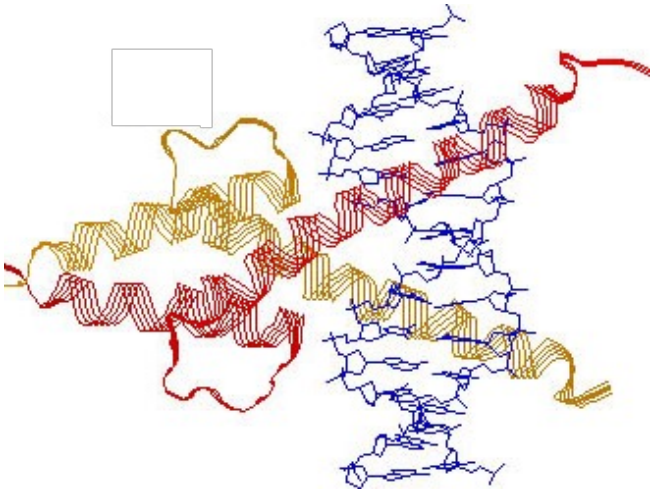
184,000 unique chemical probes!

‘Chemical genomic’ toolkit

How many specific probes do we need to study the entire ‘expressed genome?’

92,000 expressed proteins
1 inhibitor of function
1 activator of function

184,000 unique chemical probes?



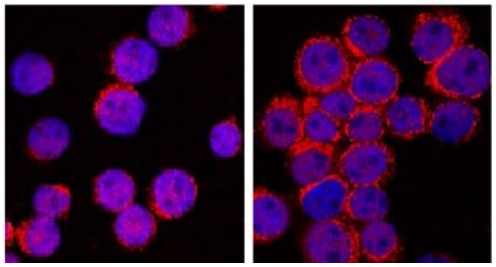
MyoD:
regulates smooth muscle differentiation
‘exercise transcription factor’

target in my lab for pediatric rhabdomyosarcoma

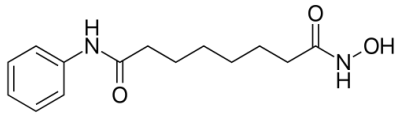
How do you find probes??

'forward' screens
phenotypic screens

screen for phenotype of interest

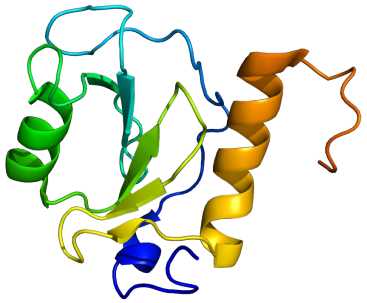


- small molecule + small molecule



assay positive

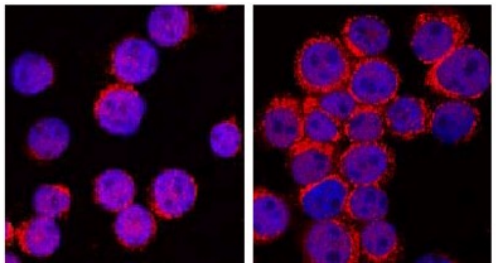
identify protein target



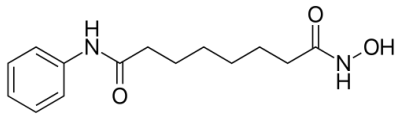
How do you find probes??

'forward' screens
phenotypic screens

screen for phenotype of interest

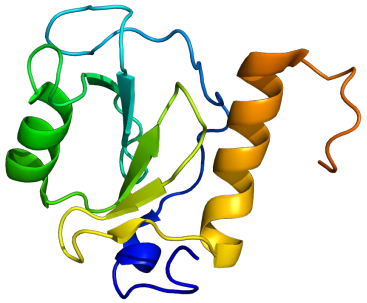


- small molecule + small molecule



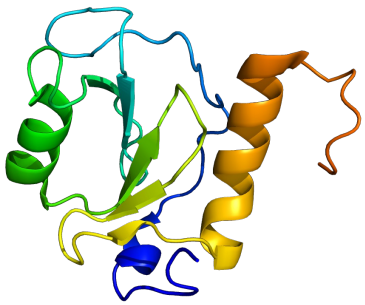
assay positive

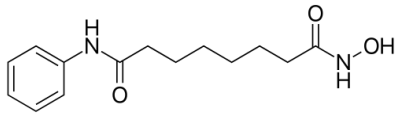
identify protein target



'reverse' screens
target-directed screens

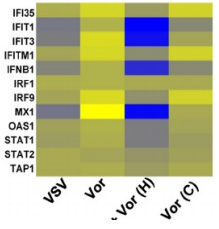
directly bind target of interest

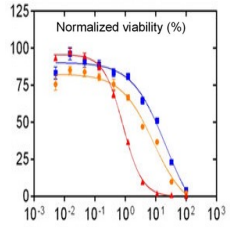


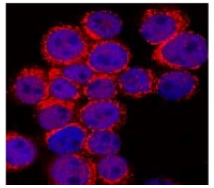


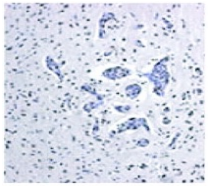
assay positive

broad survey of
phenotypic outcomes

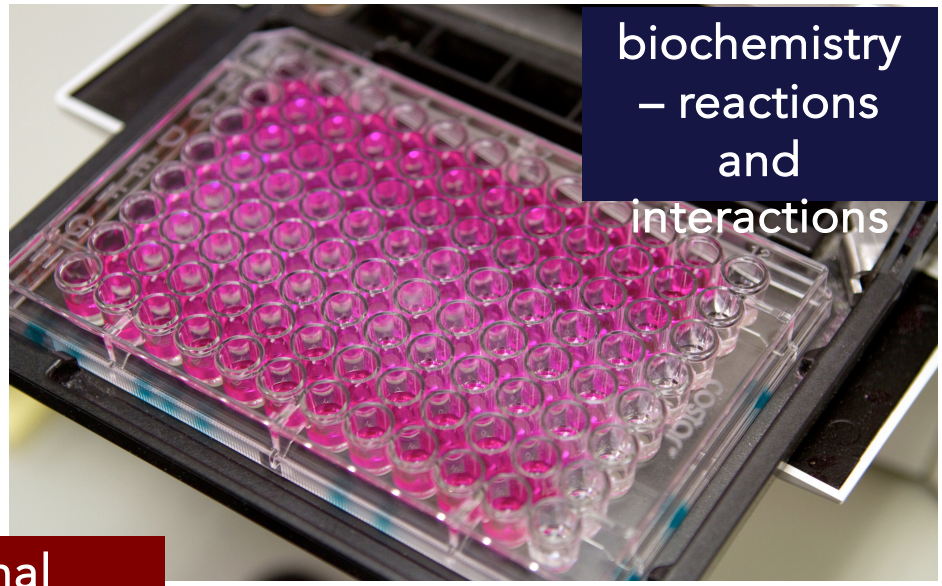




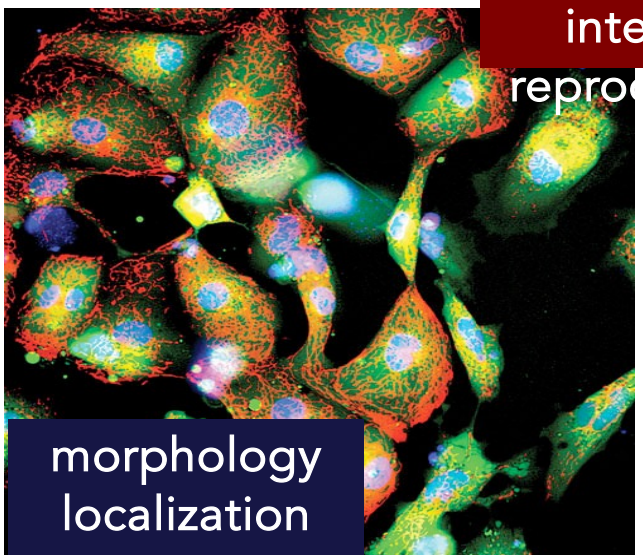


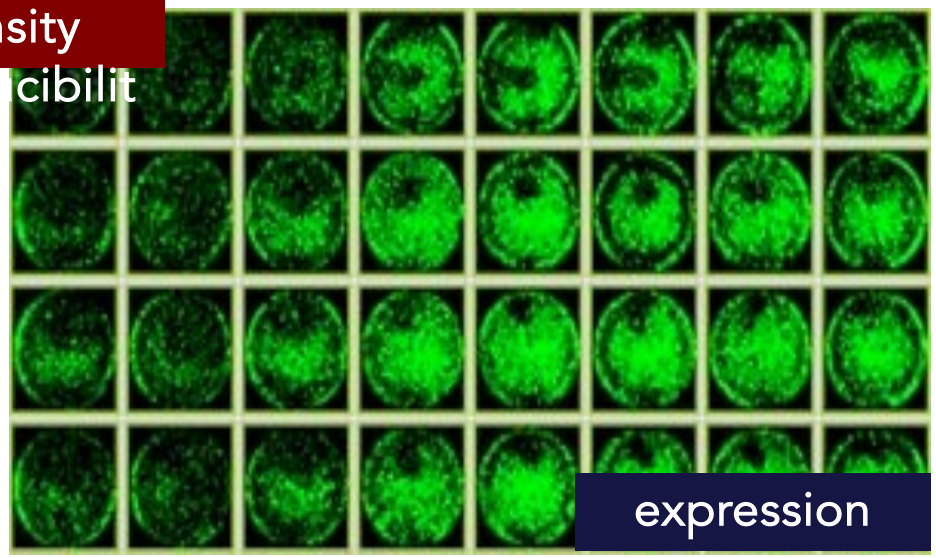


High-throughput bioassays

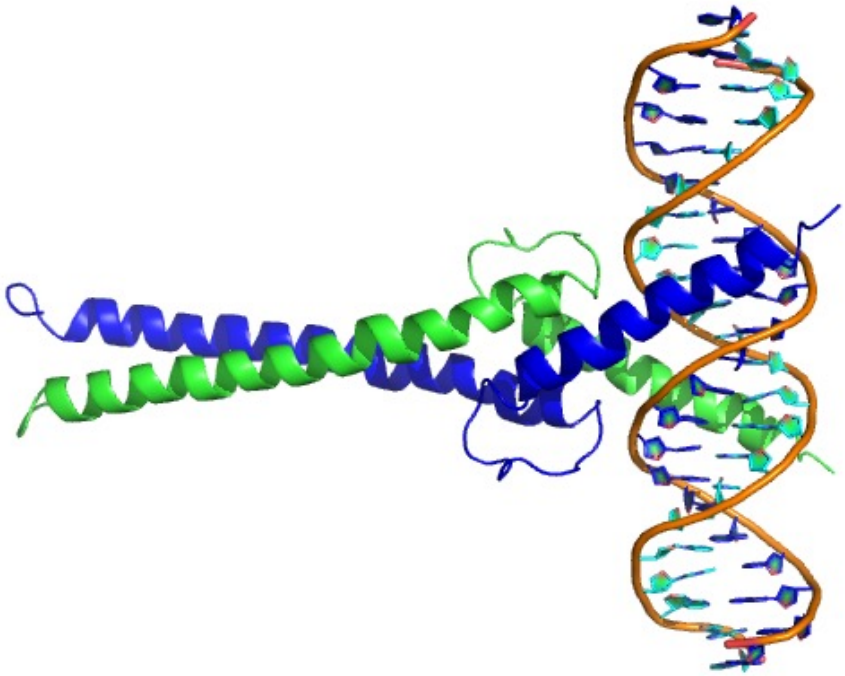


signal intensity reproducibility





Protein target of interest: MAX



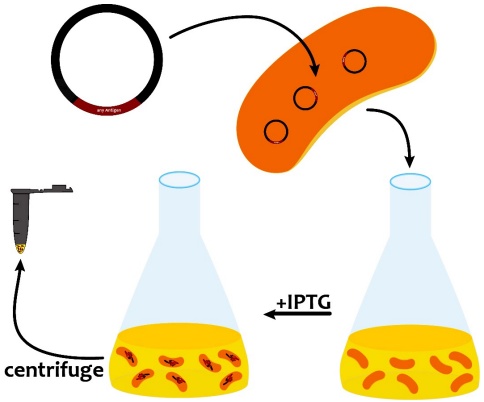
Molecular functions:
DNA binding protein
binds several other proteins (e.g., MYC)

Cellular roles:
plays a role in transcriptional repression
plays a role in transcriptional activation

Clinical Significance:
mutated in pheochromocytoma
mutated in small cell lung cancer
potential therapeutic target for MYC-driven tumors (>30% of human tumors)

more details to come in Lecture 3!

Spring 2023 path to probe discovery



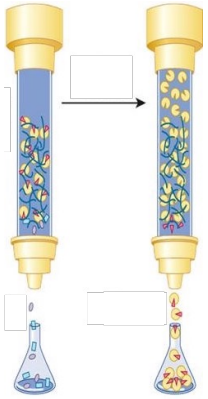
in silico cloning; overexpress MAX

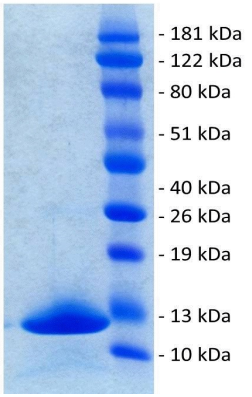
lab day 1

Spring 2023 path to probe discovery

in silico cloning; overexpress MAX

lab day 1





purify and analyze MAX samples

lab days 2-4

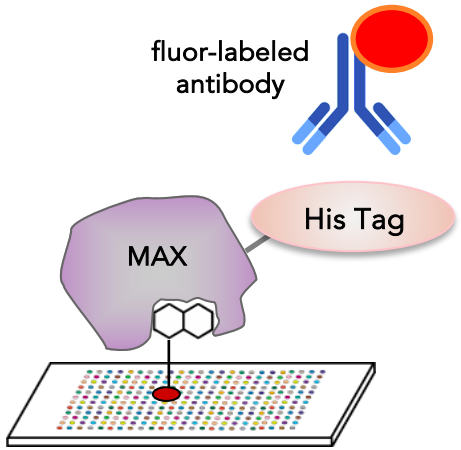
Spring 2023 path to probe discovery

in silico cloning; overexpress MAX

lab day 1

purify and analyze MAX samples

lab days 2-4



ligand discovery screen

lab day 5

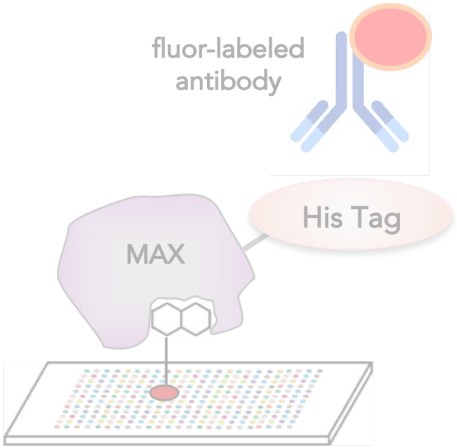
Spring 2023 path to probe discovery

in silico cloning; overexpress MAX

lab day 1

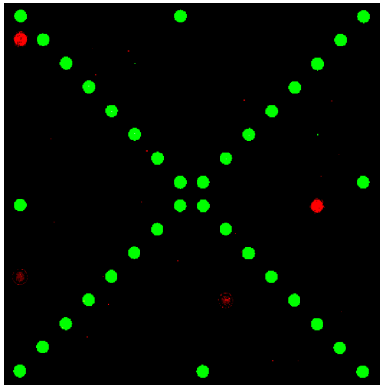
purify and analyze MAX samples

lab days 2-4



ligand discovery screen

lab day 5



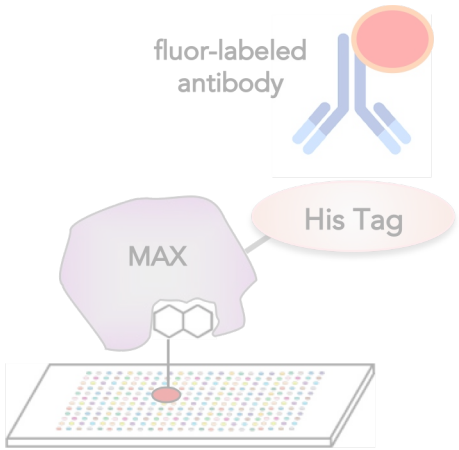
scan images and analyze data

lab days 5 and 6

Spring 2023 path to probe discovery

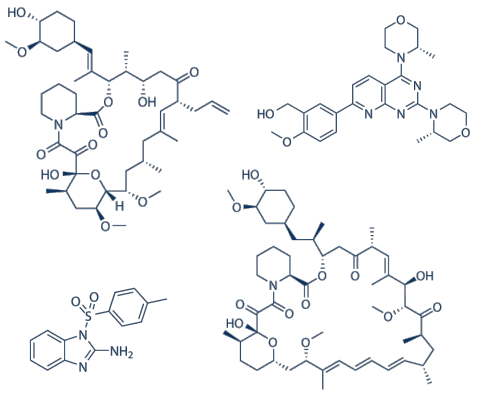
in silico cloning; overexpress MAX
lab day 1

purify and analyze MAX samples
lab days 2-4



ligand discovery screen
lab day 5

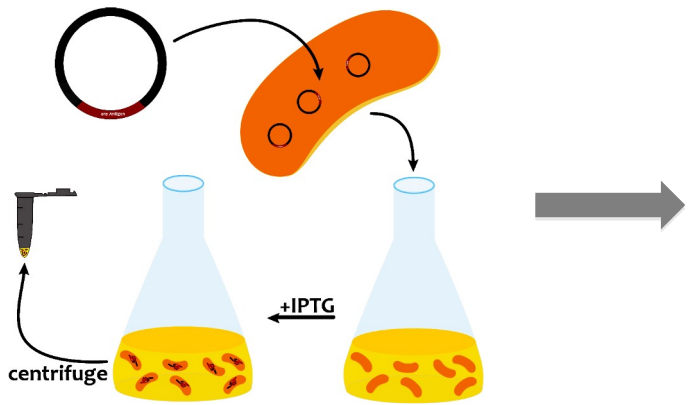
scan images and analyze data
lab days 5 and 6



compare hit lists for teams
lab day 7


Spring 2023
Spring 2024

Spring 2024 path to validating probes



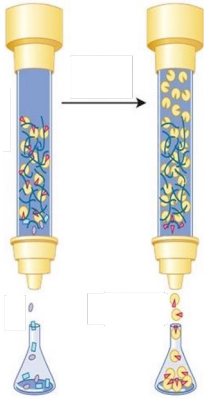
in silico cloning; overexpress MAX

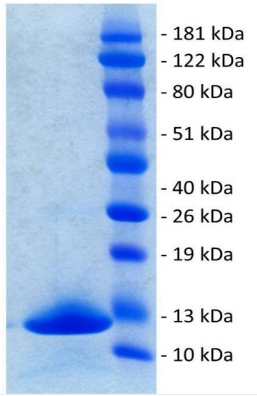
lab day 1

Spring 2024 path to validating probes

in silico cloning; overexpress MAX

lab day 1





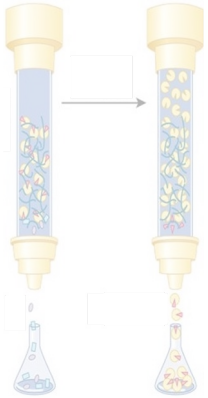
purify and analyze MAX samples

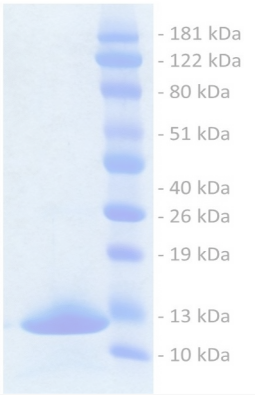
lab days 2-3

Spring 2024 path to validating probes

in silico cloning; overexpress MAX

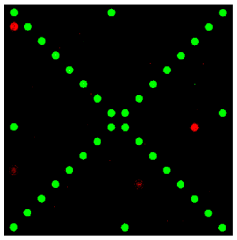
lab day 1

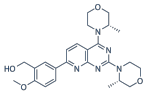


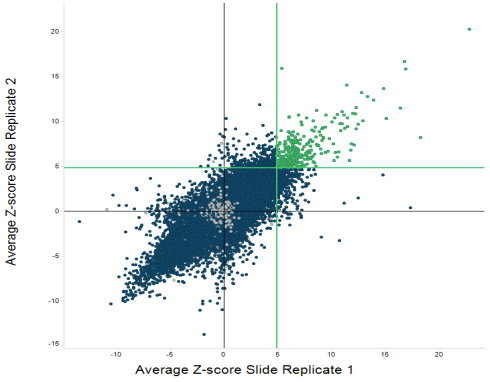


purify and analyze MAX samples

lab days 2-3







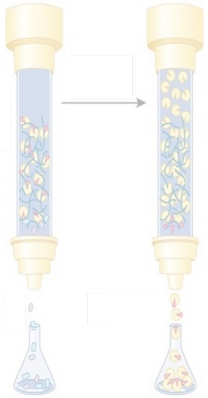
examine legacy SMM screens for MAX

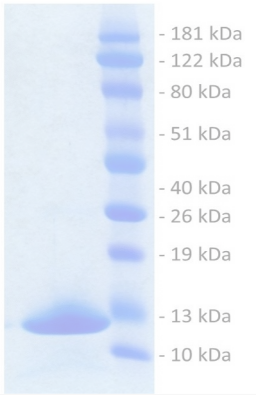
lab day 4

Spring 2024 path to validating probes

in silico cloning; overexpress MAX

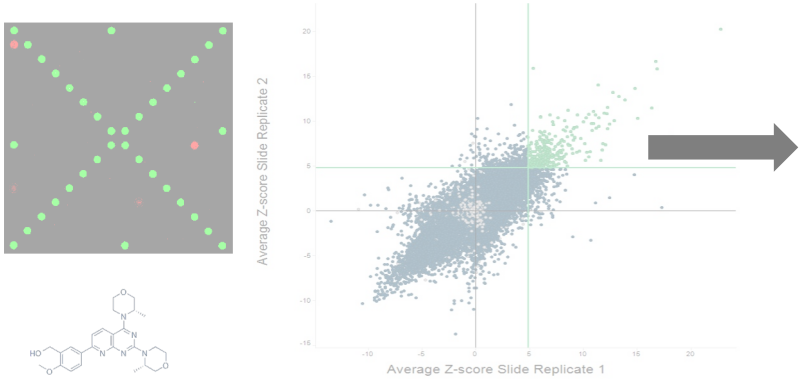
lab day 1





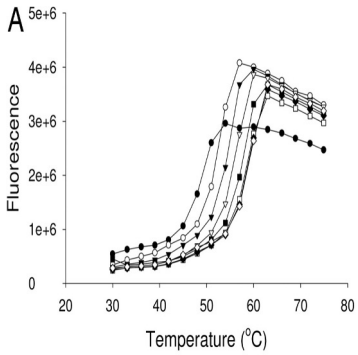
purify and analyze MAX samples

lab days 2-3



examine legacy SMM data sets for MAX

lab day 4

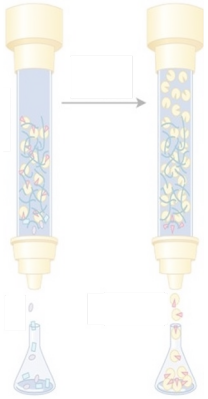


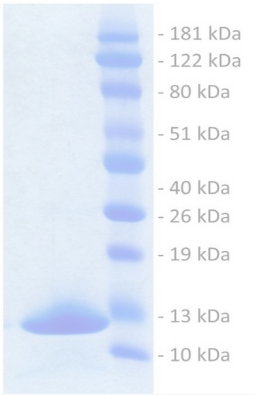
DSF binding assays for MAX SMM hits

lab days 5-6

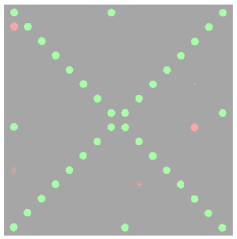
Spring 2024 path to validating probes

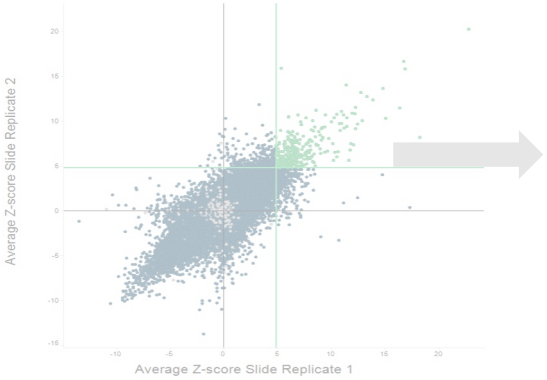
in silico cloning; overexpress MAX
lab day 1



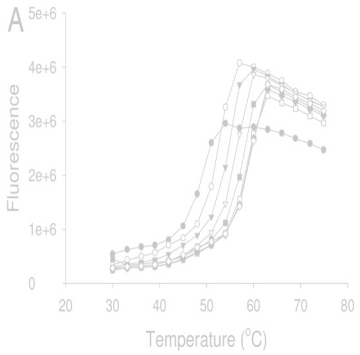


purify and analyze MAX samples
lab days 2-3

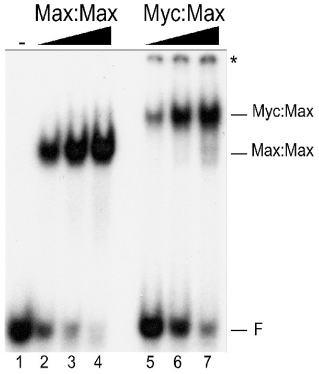




examine legacy SMM data sets for MAX
lab day 4



DSF binding assays for MAX SMM hits
lab days 5-6



EMSA assays for SMM hits
lab day 7

Upcoming Lectures

2/8/24	Lecture 1	Intro to chemical biology: small molecules, probes, and screens
2/13/24	Lecture 2	Small Molecule Microarray (SMM) technique
2/15/24	Lecture 3	Our protein target – MAX
2/20/24	No Lecture	
2/22/24	Lecture 4	Quantitative evaluation of protein-ligand interactions
2/27/24	Lecture 5	An SMM ligand discovery vignette for sonic hedgehog
2/29/24	Lecture 6	KB-0742: A Phase 2 clinical candidate discovered by SMMs
3/5/23	Lecture 7	Wrap up discussion for Mod 1 experiments and report