

Welcome to Module 1

# Drug Discovery



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

February 9, 2023



**Angela Koehler**  
[koehler@mit.edu](mailto:koehler@mit.edu)

Instructor

Koch Institute  
76-361c

Lectures

## Module 1 Office Hours

Thu 2/16	3:30 pm
Fri 2/24	8:30 am
Wed 3/1	3pm

Mon 3/13	9am
Tue 3/14	9am
Fri 3/17	Noon
Fri 3/24	3pm

Join Zoom Meeting

<https://mit.zoom.us/j/93057049755>

Meeting ID: 930 5704 9755



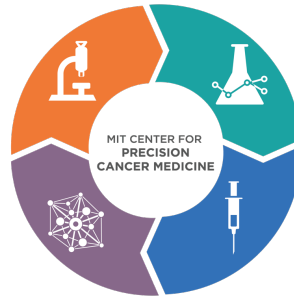
LUDWIG  
CANCER  
RESEARCH



Adenoid Cystic Carcinoma  
Research Foundation



FRONTIER  
RESEARCH  
PROGRAM



THE BRIDGE PROJECT



STARR CANCER  
CONSORTIUM

AACR American Association  
for Cancer Research



Royal G. and Mae H. Westaway  
Family Memorial Fund



Kathy and Curt Marble  
Research Fund



Benjamin and Samuel Krinsky  
Memorial Fund



founded in 2007



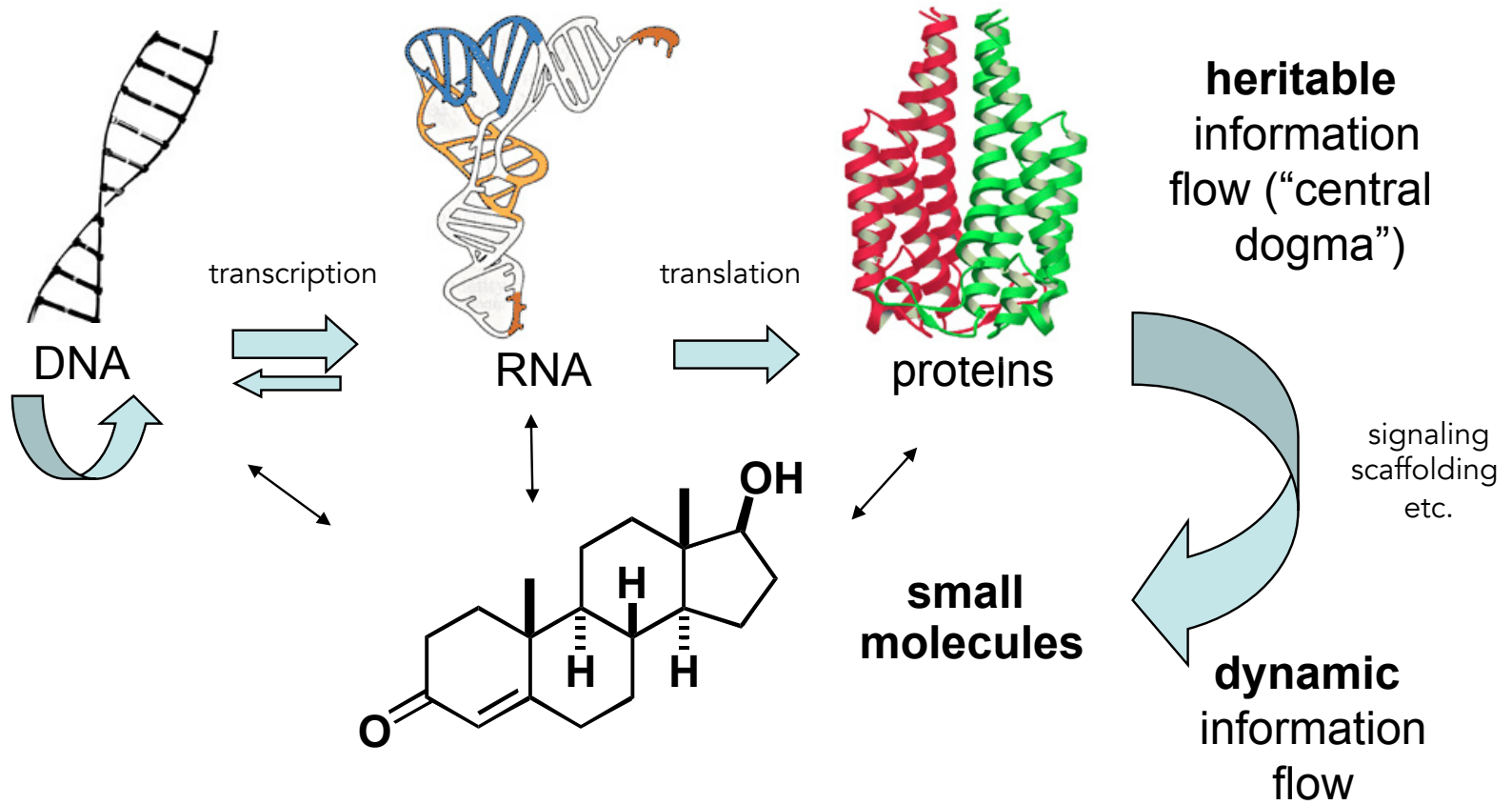
founded in 2017



founded in 2021



# The central dogma

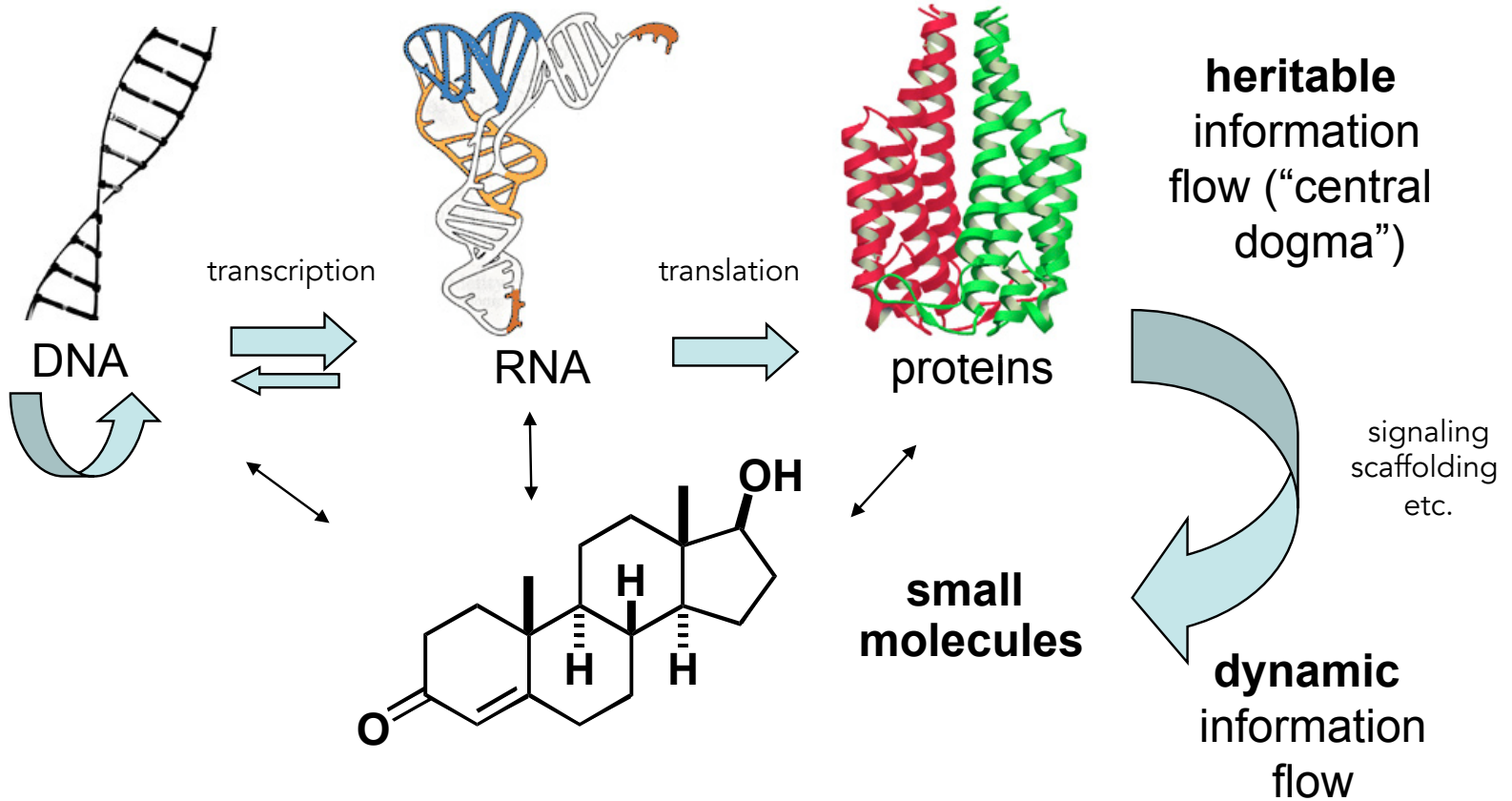


# The central dogma

imaging agents  
carcinogens

antibiotics

drugs



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 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**

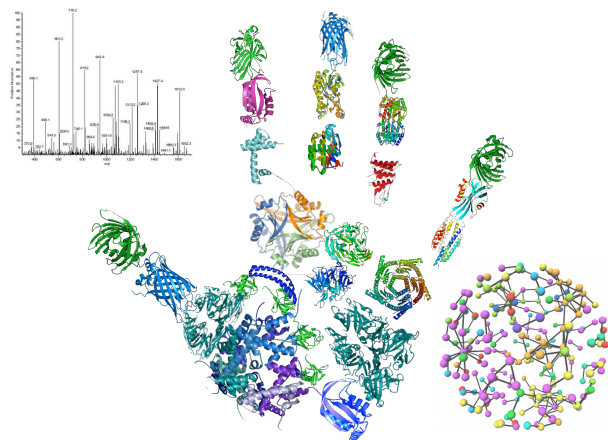
# Defining chemical biology

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**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

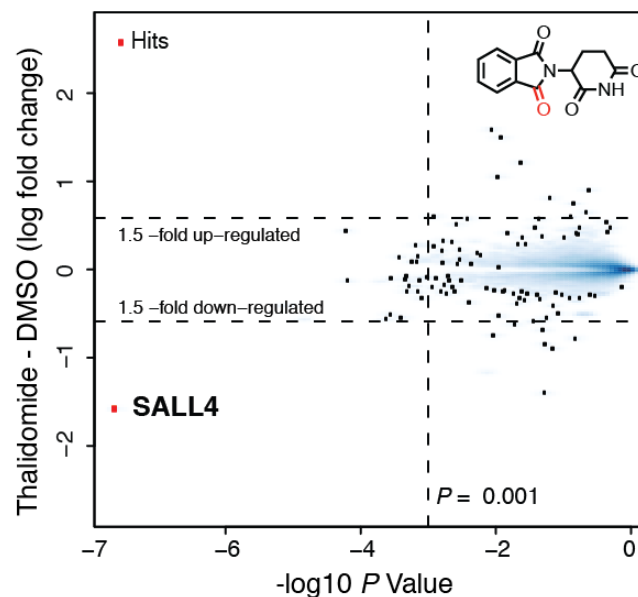


Investigates the set of expressed proteins in a cell at a given time under defined conditions – quantitative, comparative  
*often involves mass spectrometry*

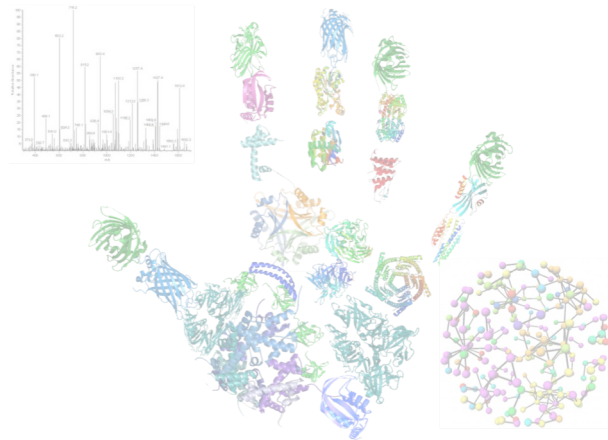
## quantitative proteomics

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

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

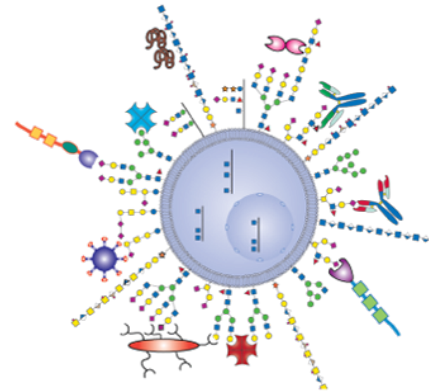


# Systems of interest to chemical biologists



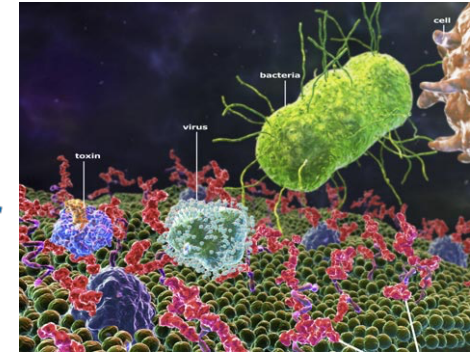
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Bryson, Dedon, Fraenkel, Hynes, Koehler, White Yaffe



## glycobiology

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

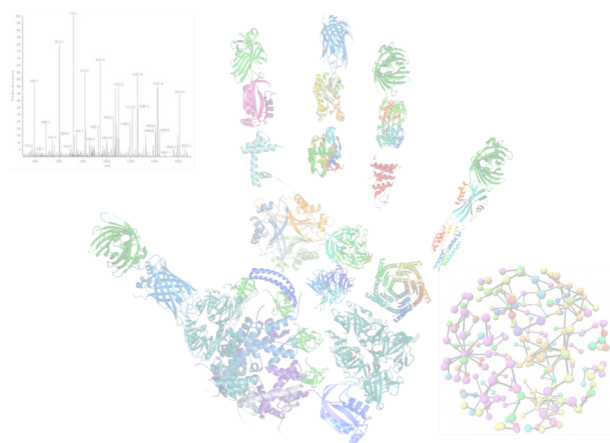


- BE Dept/Course 20
- Bio Dept/Course 7
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Investigates how sugars regulate biology, including cell-virus interactions protein stability, and metabolism, among other functions – quantitative, comparative

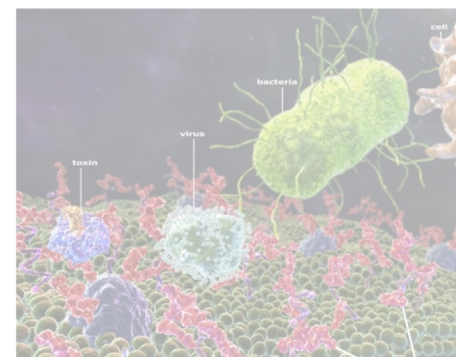
involves many imaging and tracing methods, mass spec

# Systems of interest to chemical biologists



## quantitative proteomics

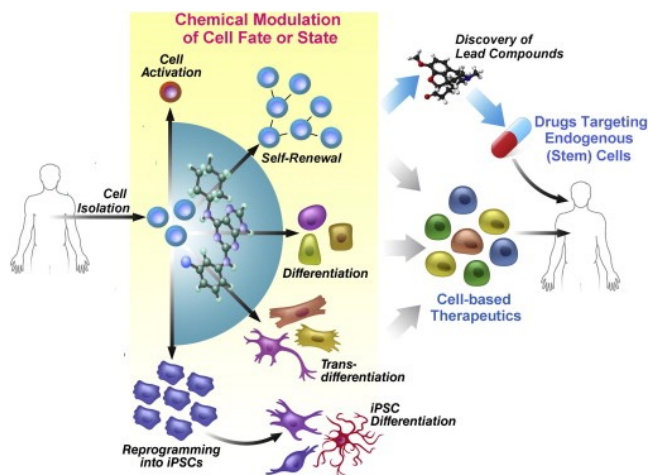
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## glycobiology

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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 biology courses at MIT

suitable for advanced undergraduates

## 20.554 Frontiers in Chemical Biology (F)

*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](#).

## 7.73 Principles of Chemical Biology (S)

*Barbara Imperiali, Jing-Ke Weng*

Spanning the fields of biology, chemistry and engineering, addresses the principles of chemical biology and its application of chemical and physical methods and reagents to the study and manipulation of biological systems. Topics include activity-based protein profiling, [small molecule inhibitors and chemical genetics](#), [fluorescent probes](#) for biological studies, chemical biology approaches for studying dynamic [post-translational modification reactions](#), natural product biosynthesis, and [high-throughput drug screening](#).

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 topics we will address in Mod 1

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**engineering new biomolecules  
and synthetic systems**

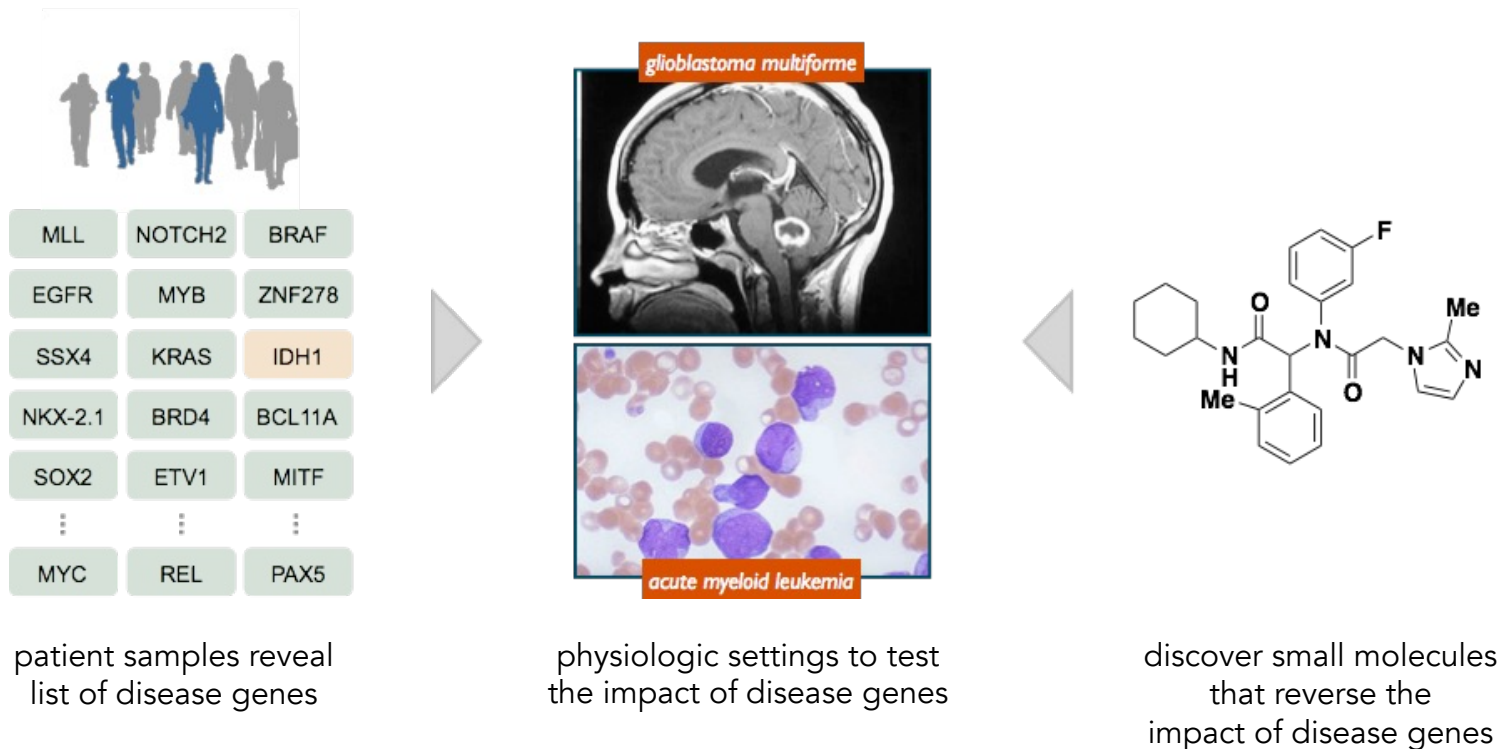
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**modulating natural systems and  
measuring outputs**

# Chemical probes of disease biology

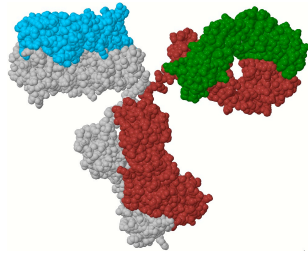


**Approach:** use small molecules to **test emerging concepts in human disease** in physiologically relevant settings

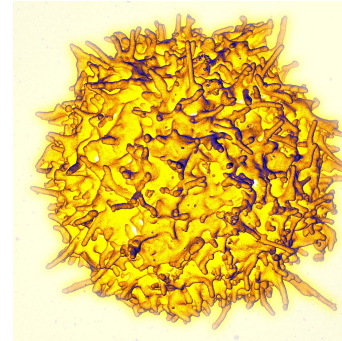
**Output:** validated small-molecule probe to **facilitate human clinical development** or **diagnostic** applications

# How small is a small molecule?

antibodies



T-cells

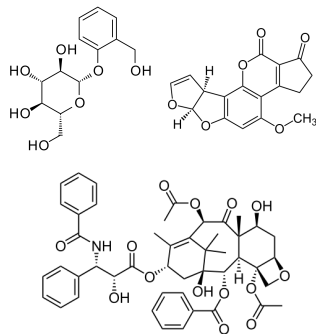


$10^{-9}$  m

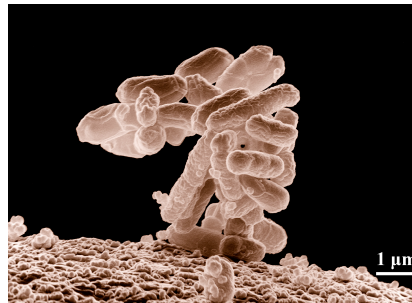
$10^{-6}$  m

$>10^{-4}$  m

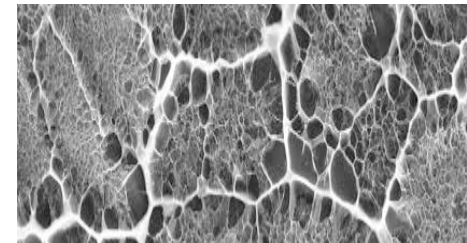
small molecules



microbes



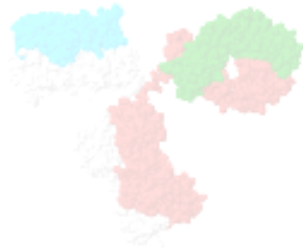
bio-materials



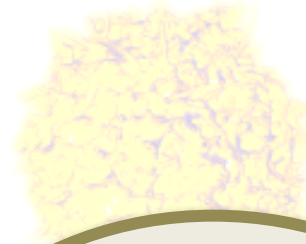


# How small is a small molecule?

antibodies



T-cells



<1000 Da

Typically C, N, O  
(occasionally S, P, B, etc.)

natural or synthetic

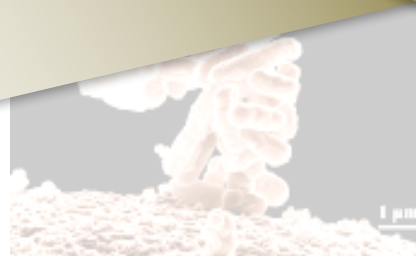
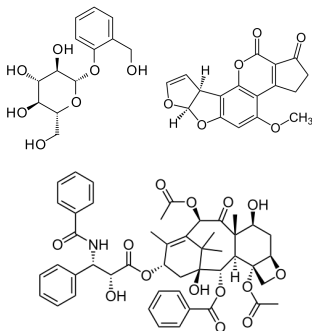
probes/therapeutics

10<sup>-9</sup> m

10<sup>-6</sup> m

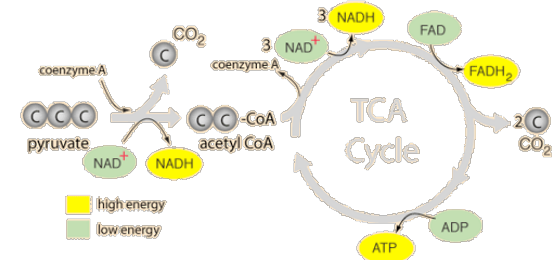
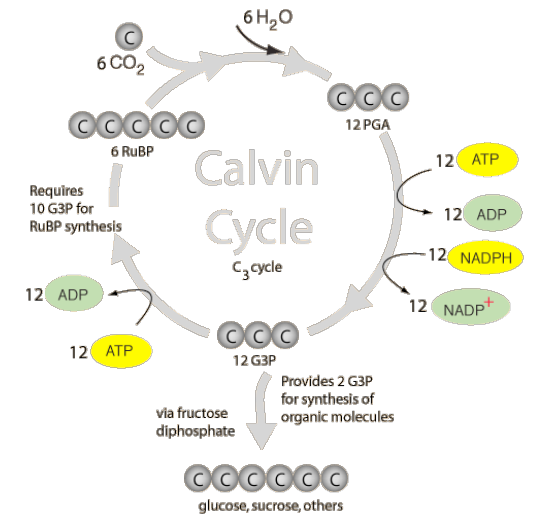
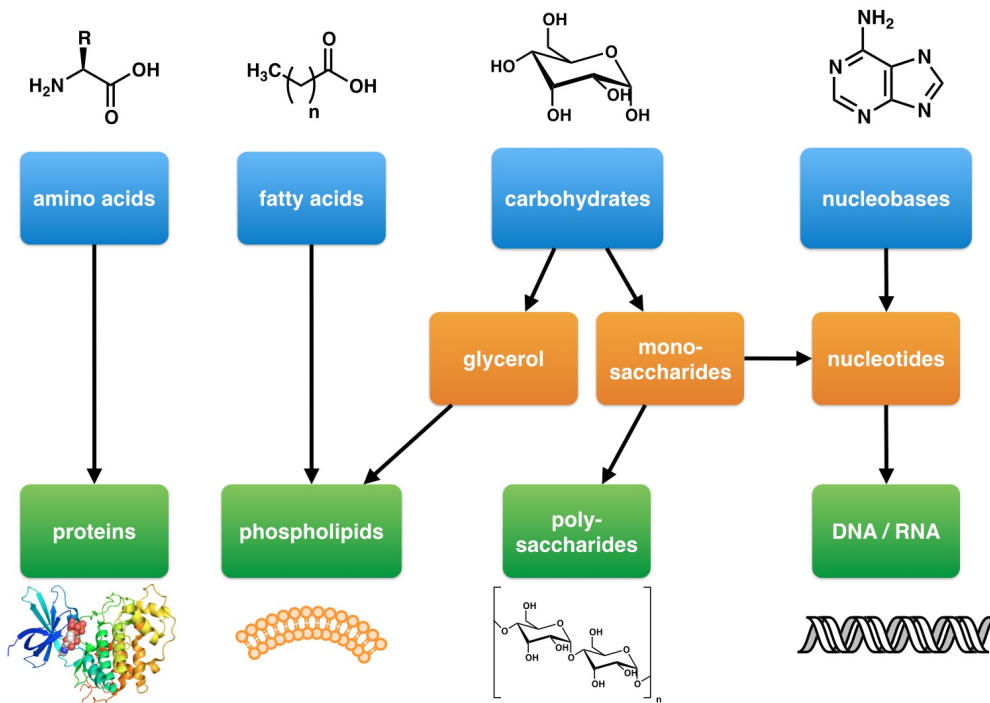
4 m

small molecules



## Small molecules of life

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



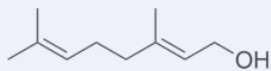
**first messengers** – signaling molecules that control metabolism and cell differentiation (e.g. hormones, biogenic amines)



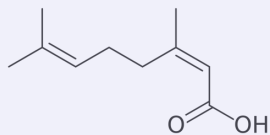
# Small molecules of life

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

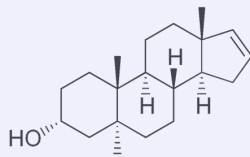
pheromones – social interactions



geraniol



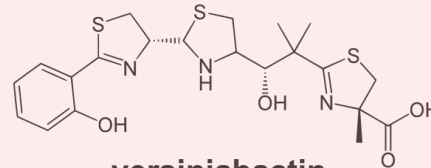
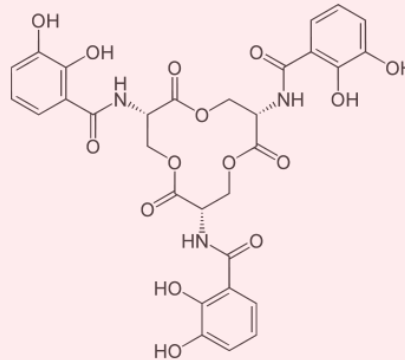
nerolic acid



androstenol

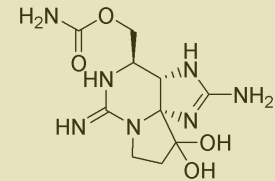
transporters and chelators

enterobactin

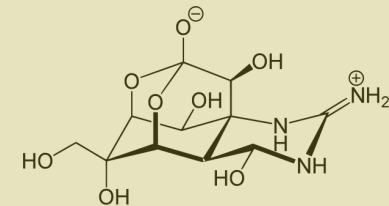


yersiniabactin

toxins – competitive weapons



saxitoxin (TZ)

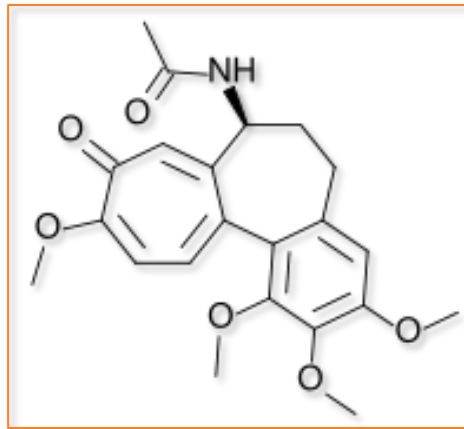


tetrodotoxin (TTX)

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

# Small molecules and their biological partners

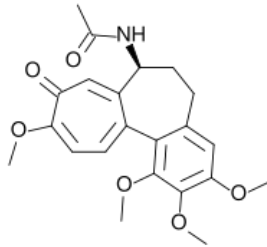
the compound that changed my life



## colchicine

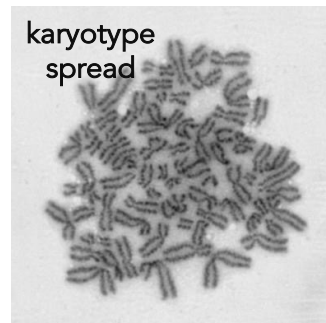
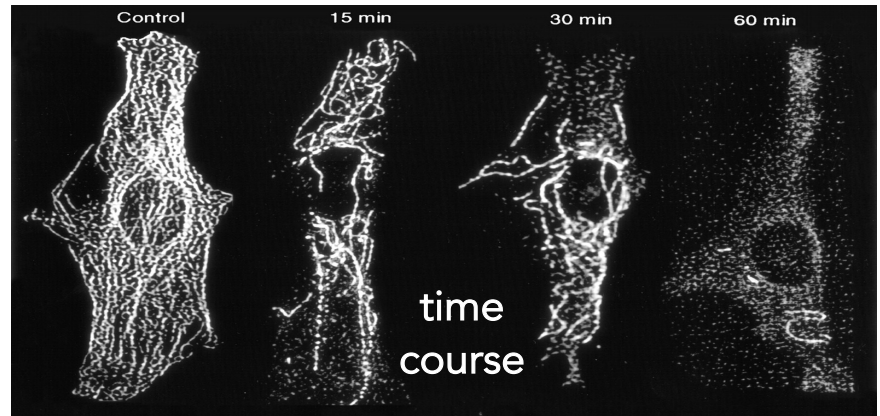
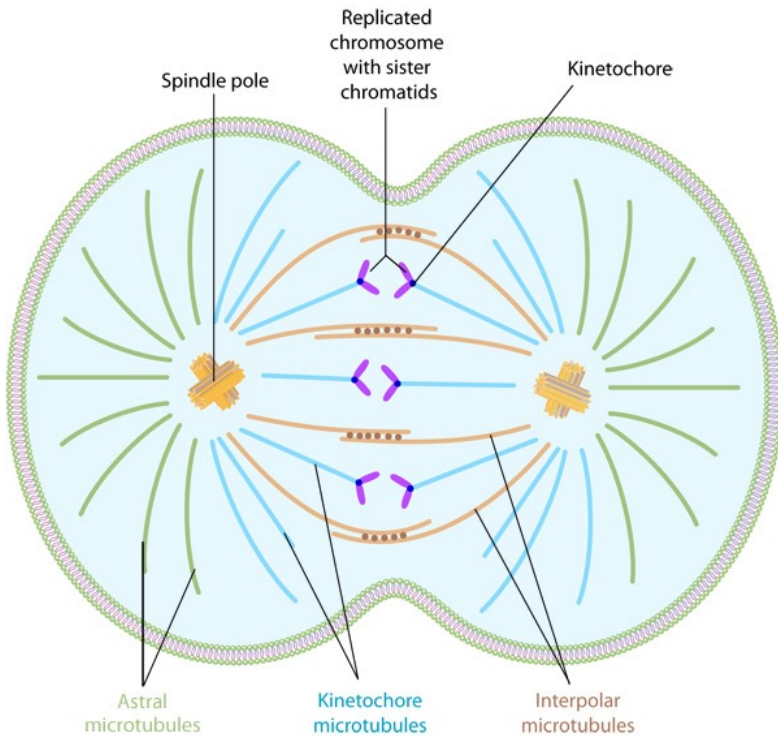
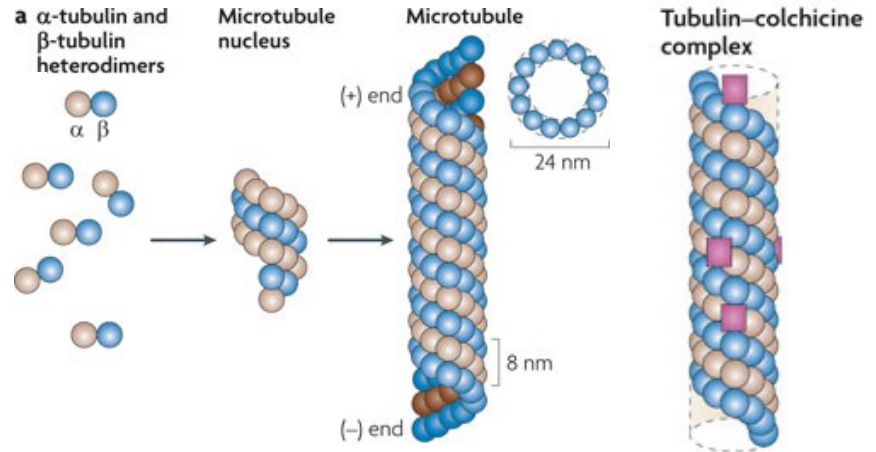
Secondary metabolite from meadow saffron

# 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

mitotic poisons for cancer therapy



*gout*



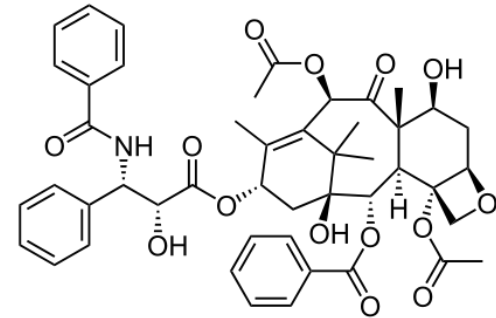
*pericarditis*



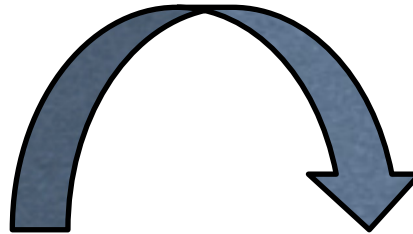
*Behçet's disease*

Egyptians -1500 BC  
Ben Franklin

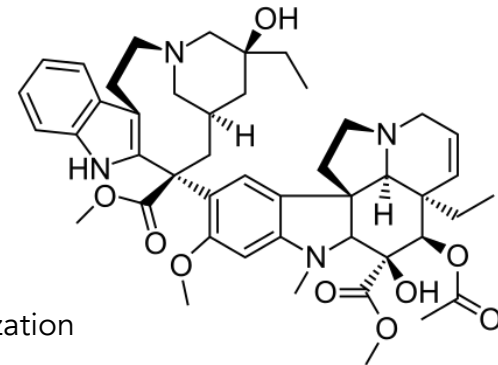
**Taxol**  
stabilizes MTs



*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

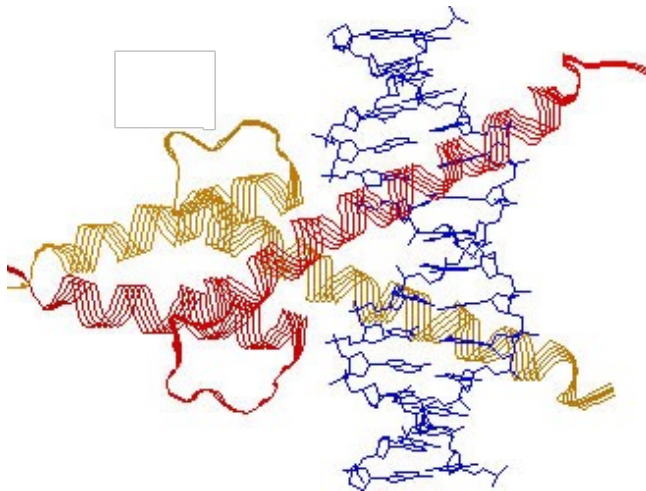
How many specific probes do we need to study the entire 'expressed genome'?

92,000 expressed proteins

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184,000 unique chemical probes?



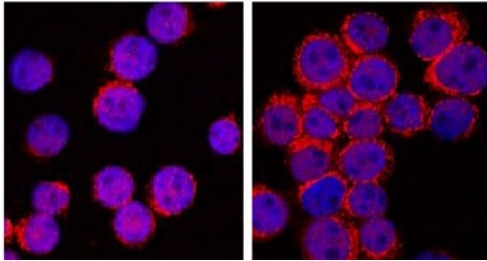
## **MyoD:**

regulates smooth muscle differentiation  
'exercise transcription factor'

*target in my lab for pediatric  
rhabdomyosarcoma*

# How do you find probes??

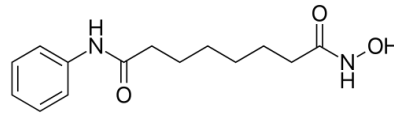
screen for phenotype of interest



- small molecule

+ small molecule

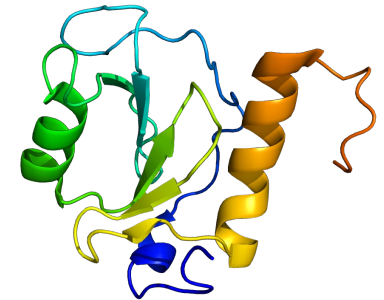
'forward' screens  
phenotypic screens



assay positive



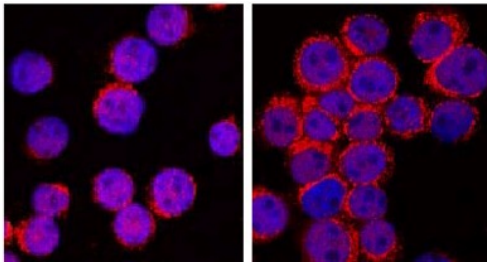
identify protein target





# How do you find probes??

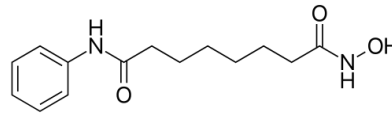
screen for phenotype of interest



- small molecule

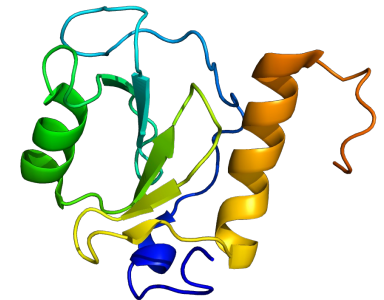
+ small molecule

'forward' screens  
phenotypic screens

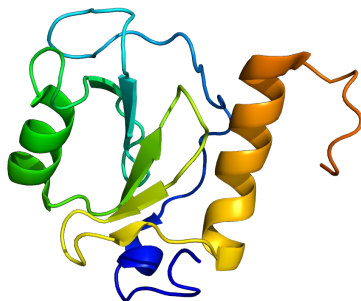


assay positive

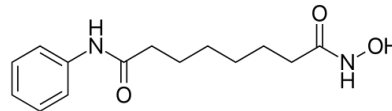
identify protein target



directly bind target of interest

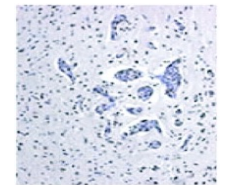
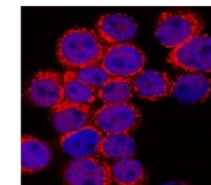
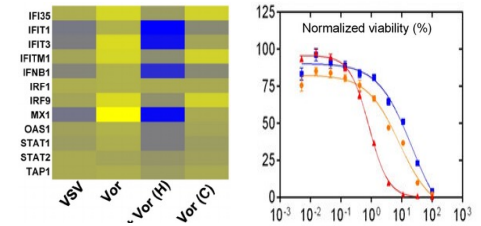


'reverse' screens  
target-directed screens



assay positive

broad survey of  
phenotypic outcomes

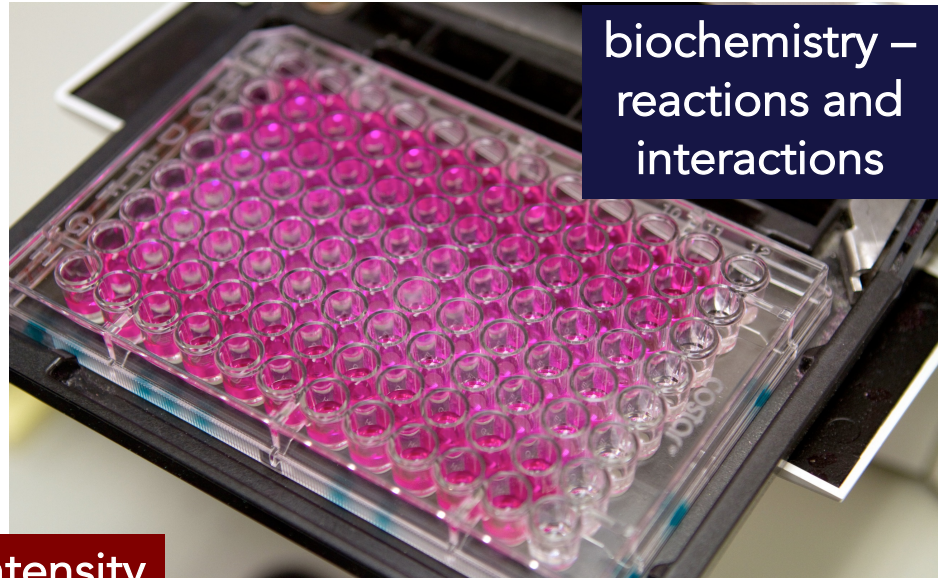


# High-throughput bioassays

viability



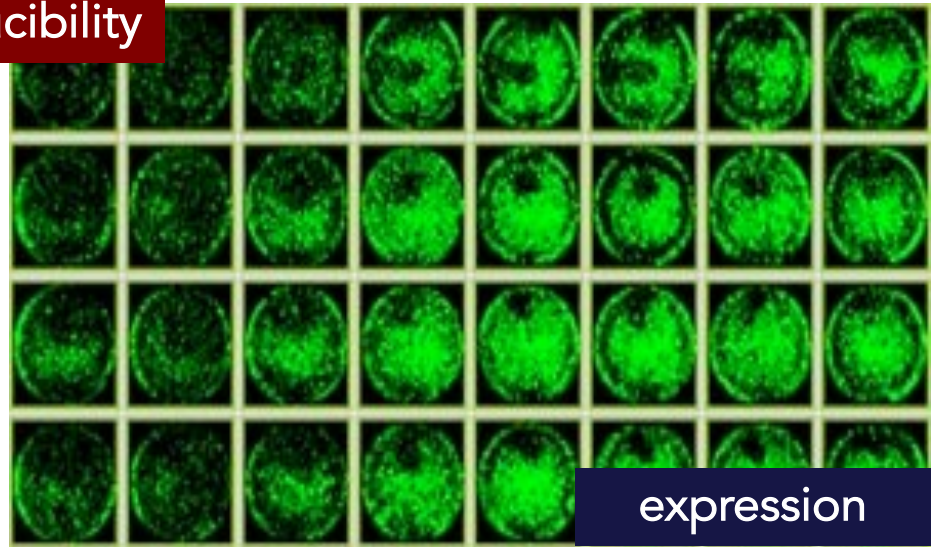
biochemistry –  
reactions and  
interactions



signal intensity  
reproducibility

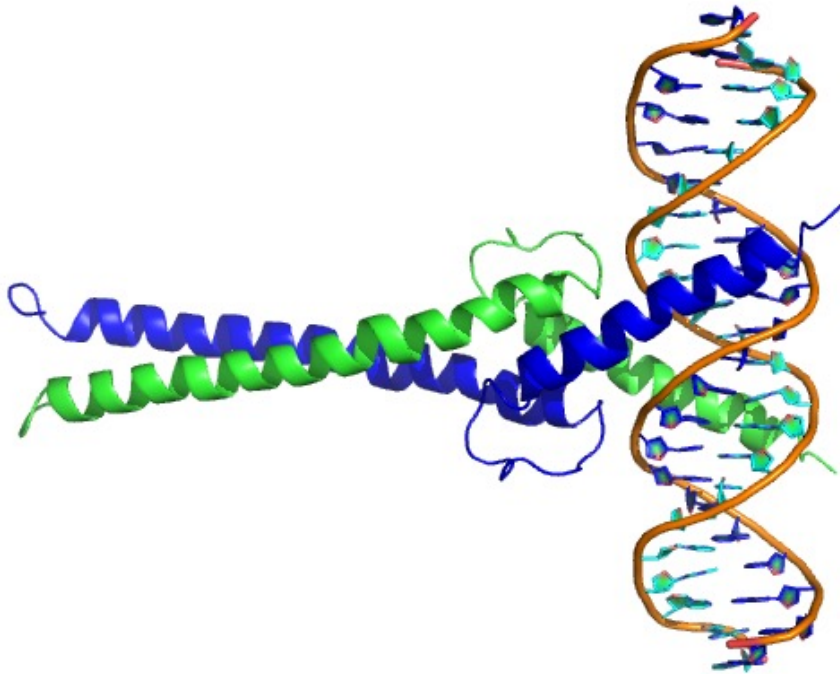


morphology  
localization



expression

# Protein target: **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:

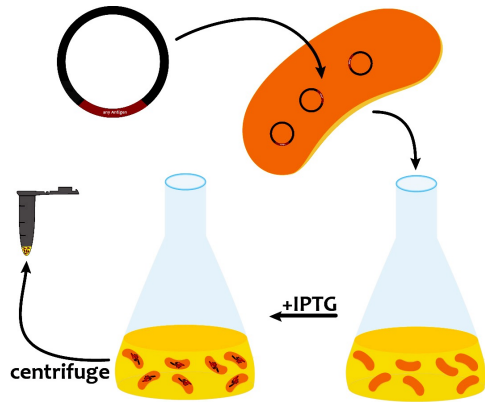
mutated in pheochromocytoma

mutated in small cell lung cancer

potential therapeutic target for MYC-driven tumors (>30% of human tumors)

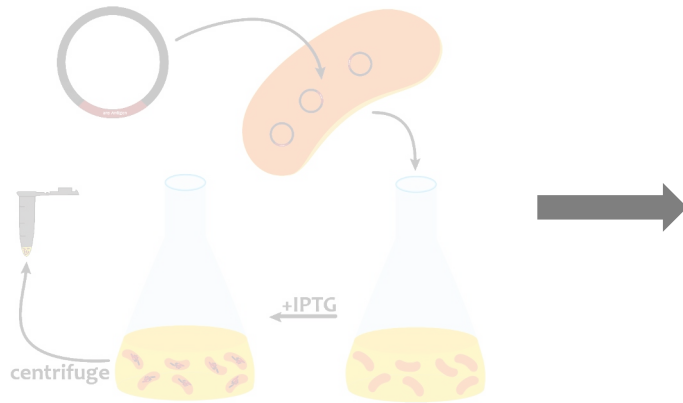
more details to come in Lecture 3!

# Spring 2023 path to probe discovery

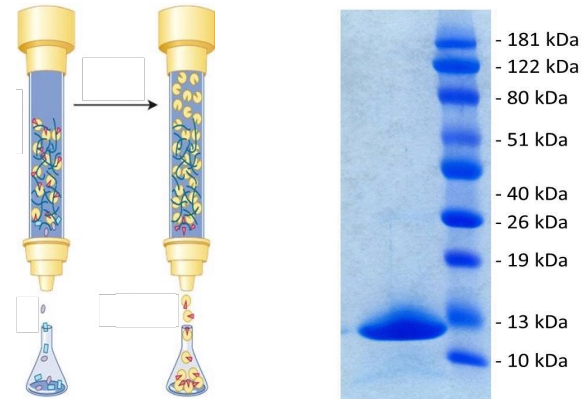


*in silico* cloning; overexpress MAX  
lab day 1

# Spring 2023 path to probe discovery



*in silico* cloning; overexpress MAX  
lab day 1



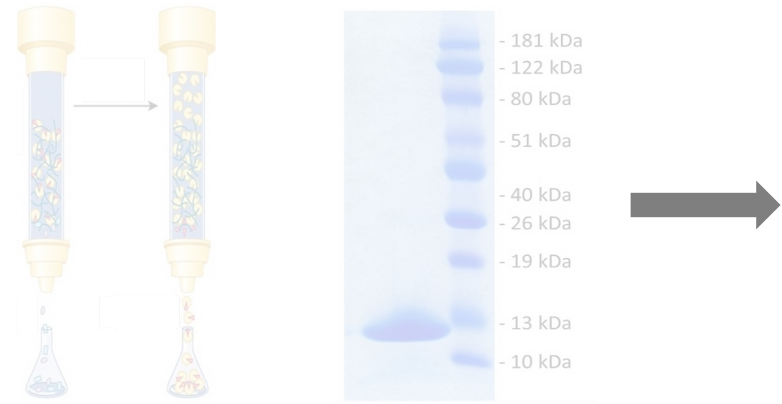
purify and analyze MAX samples  
lab days 2-4



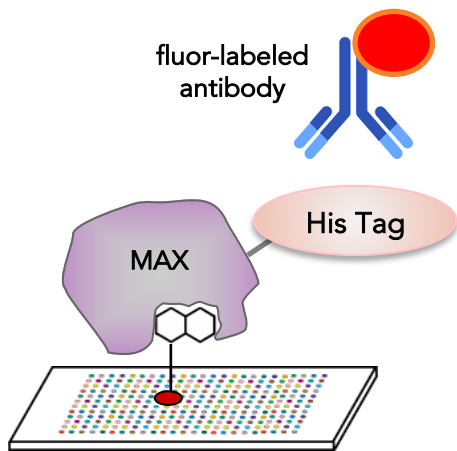
# Spring 2023 path to probe discovery



*in silico* cloning; overexpress MAX  
lab day 1

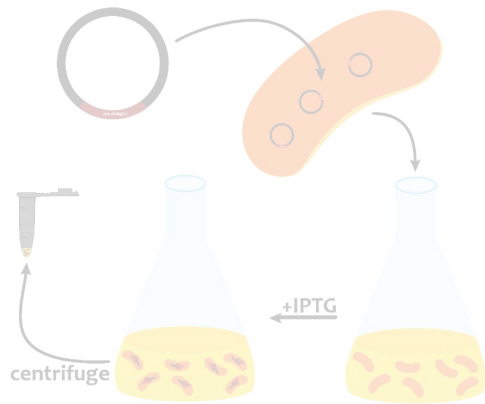


purify and analyze MAX samples  
lab days 2-4

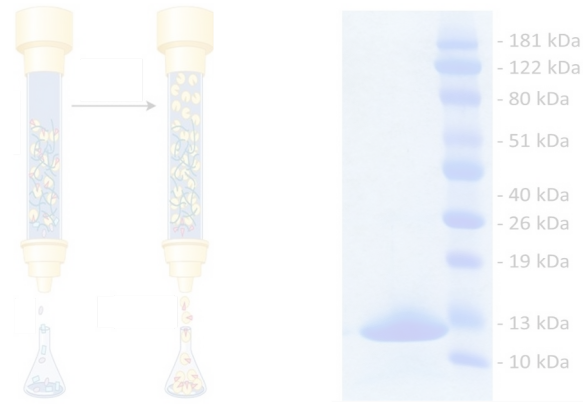


ligand discovery screen  
lab day 5

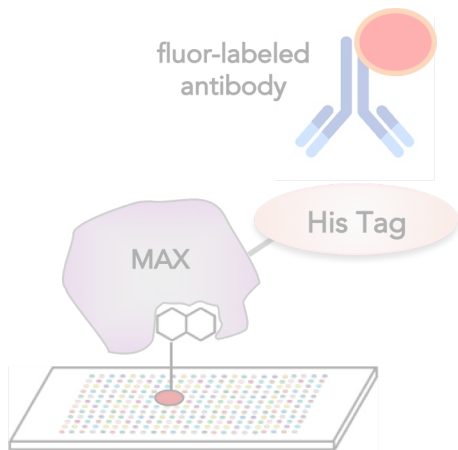
# Spring 2023 path to probe discovery



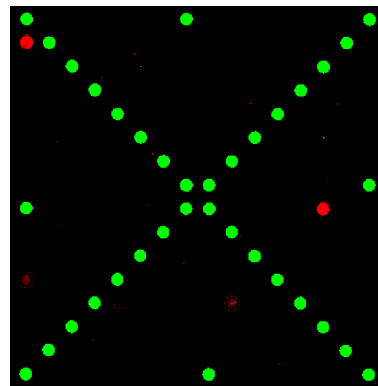
*in silico* cloning; overexpress MAX  
lab day 1



purify and analyze MAX samples  
lab days 2-4

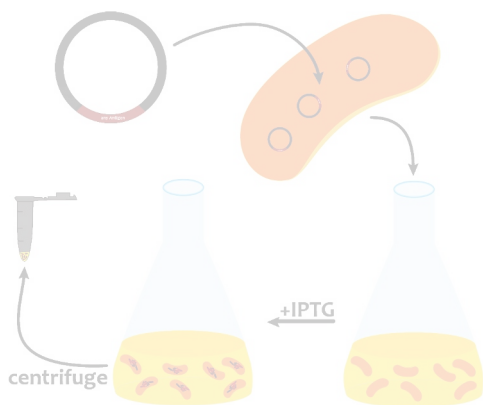


ligand discovery screen  
lab day 5

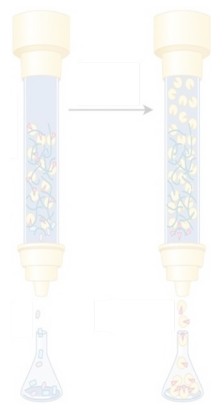


scan images and analyze data  
lab days 5 and 6

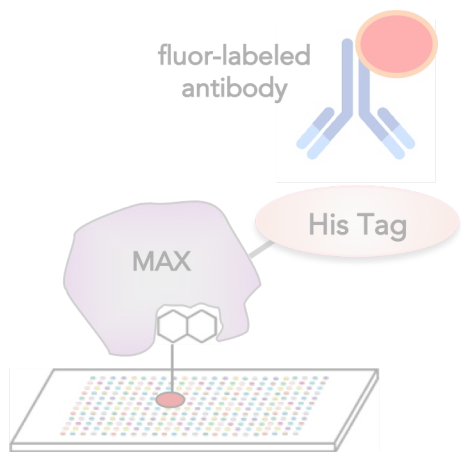
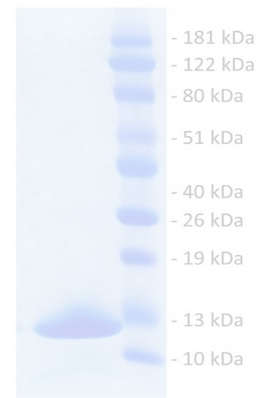
# Spring 2023 path to probe discovery



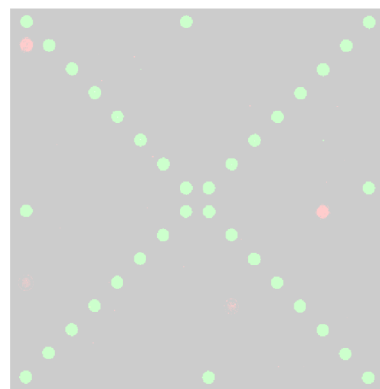
*in silico* cloning; overexpress MAX  
lab day 1



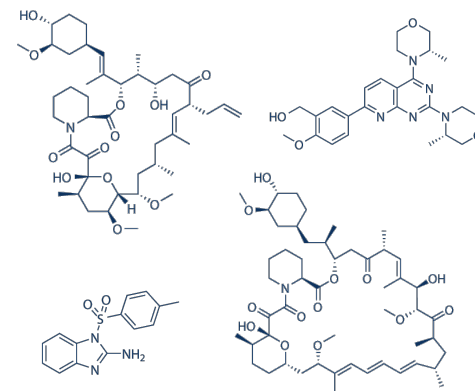
purify and analyze MAX samples  
lab days 2-4



ligand discovery screen  
lab day 5




scan images and analyze data  
lab days 5 and 6



compare hit lists for teams  
lab day 7



A hand on the left holds a rolled-up white document. A hand on the right is reaching out towards the document. The background is a blurred green field.

Spring 2023

Spring 2024

# 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