

Welcome to Module 1

Discovering Protein-Ligand Interactions



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

February 5th, 2020



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SMM Team

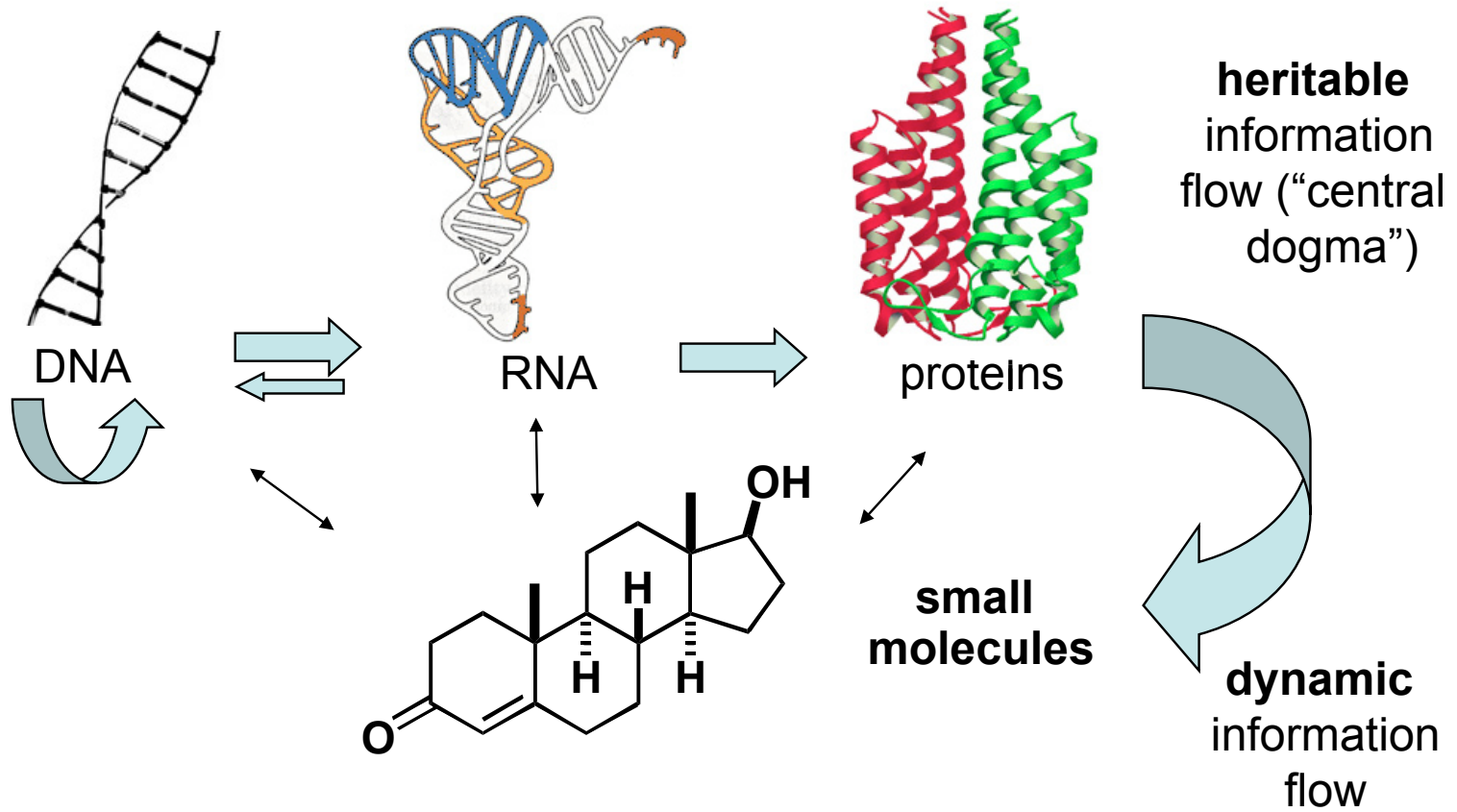


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SMM Team

The central dogma

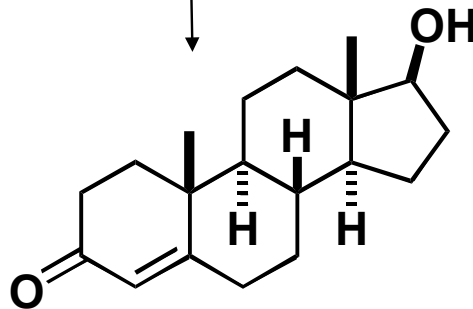
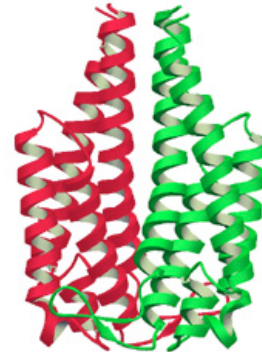
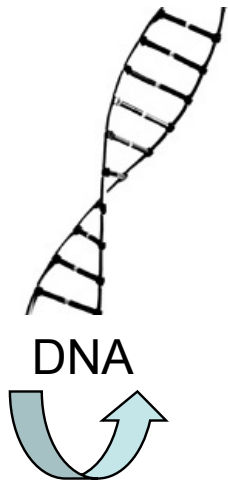


The central dogma

imaging agents
carcinogens

antibiotics

drugs



heritable
information
flow ("central
dogma")

dynamic
information
flow

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**

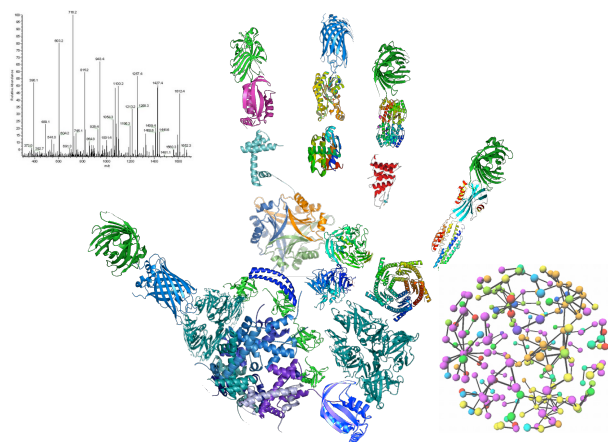
Defining chemical biology

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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 biology, including basic, disease, and synthetic applications.

Systems of interest to chemical biologists

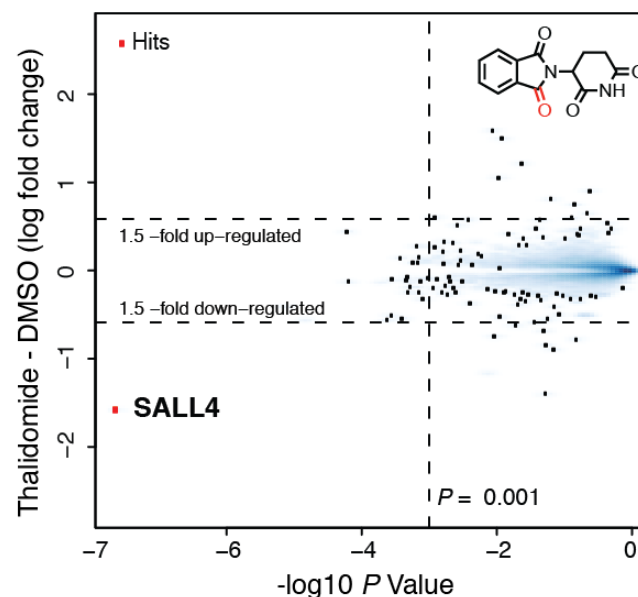


Investigates the set of expressed proteins in a cell at a given time under defined conditions – quantitative, comparative

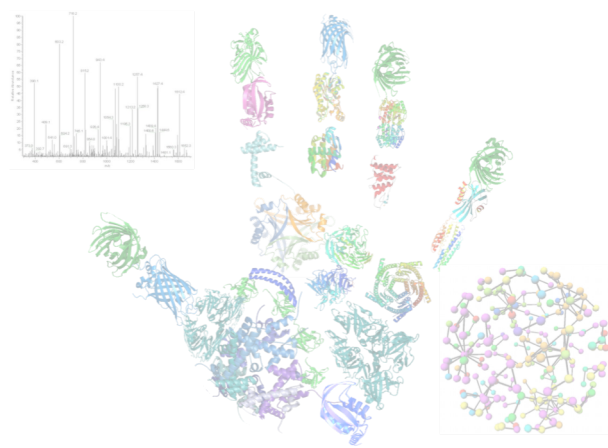
quantitative proteomics

Dedon, Fraenkel, Hynes, Koehler, White, Yaffe

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

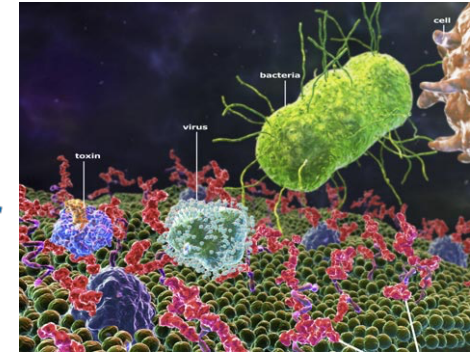
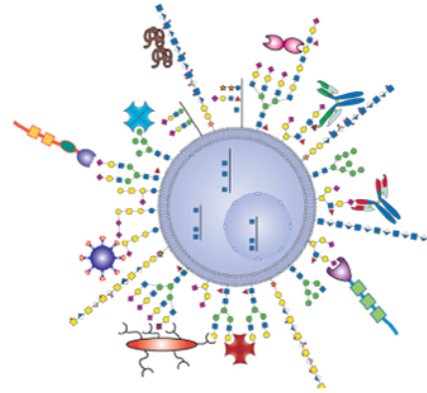


Systems of interest to chemical biologists



quantitative proteomics

Dedon, Fraenkel, Hynes, Koehler, White Yaffe



glycobiology

Imperiali, Kiessling, Ribbeck, Sasisekharan, Vander Heiden

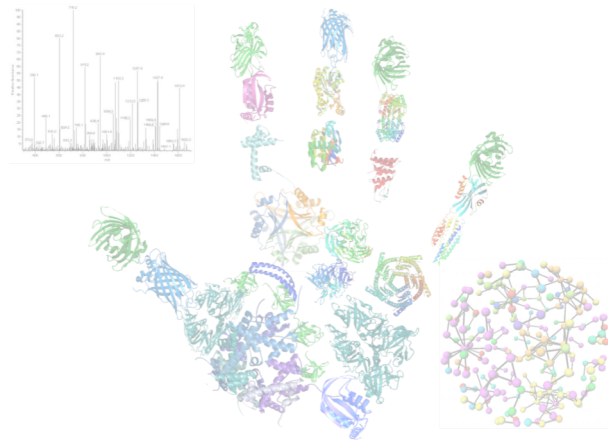
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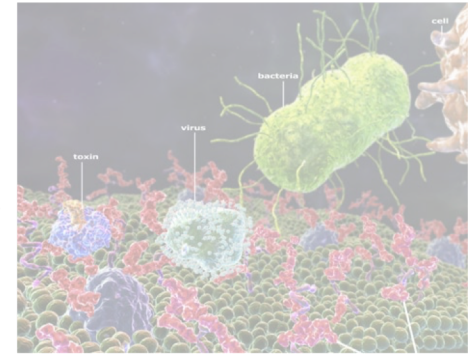
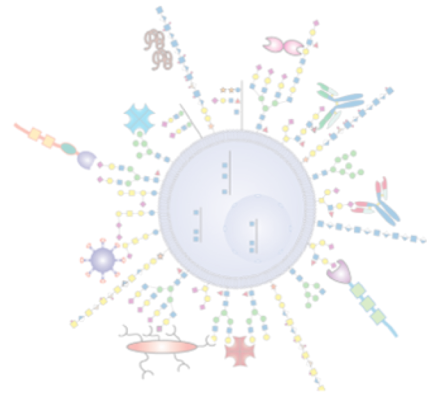
Investigates how sugars regulate biology, including cell-virus interactions and protein stability, among functions – quantitative, comparative

Systems of interest to chemical biologists



quantitative proteomics

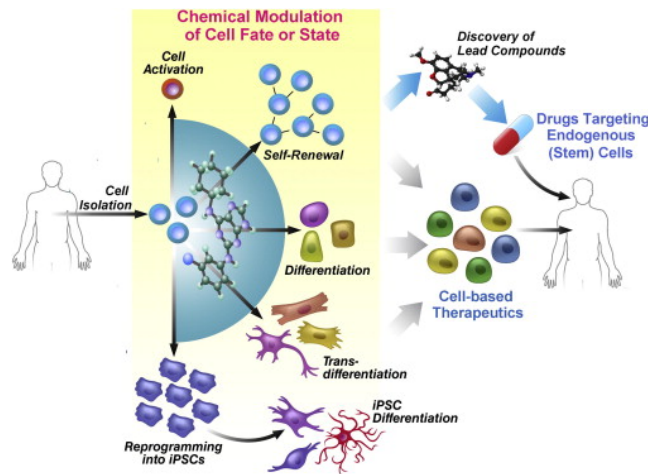
Dedon, Fraenkel, Hynes, Koehler, White Yaffe



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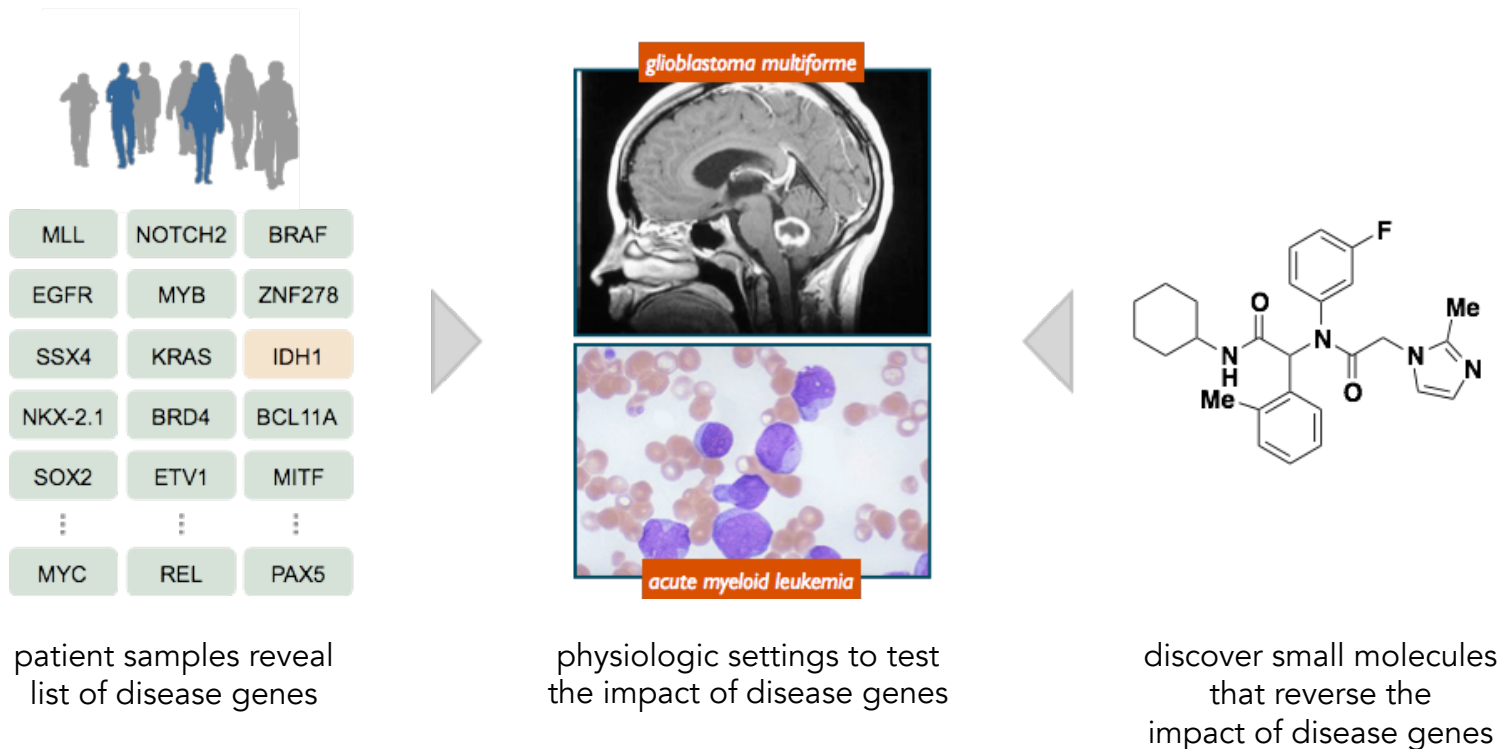


Often involves using chemicals to perturb signaling systems that govern cell state

stem cell biology and programming cell fate

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

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

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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**engineering new biomolecules
and synthetic systems**

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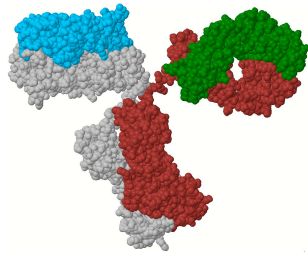
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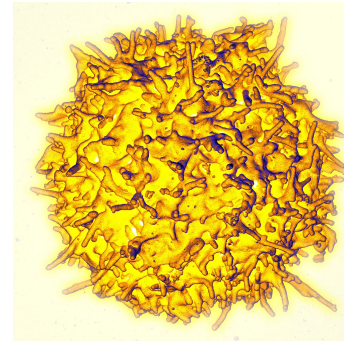
**modulating natural systems and
measuring outputs**

What is a small molecule?

antibodies



T-cells

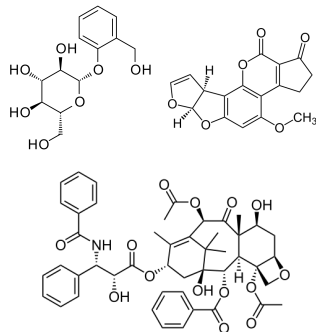


10^{-9} m

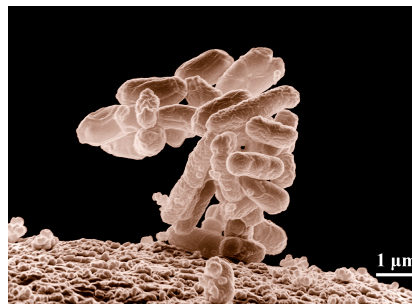
10^{-6} m

$>10^{-4}$ m

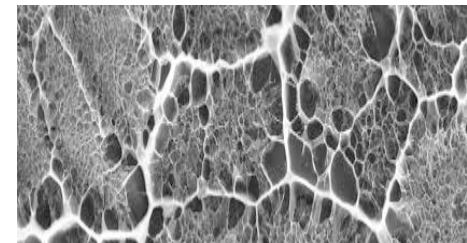
small molecules



microbes



bio-materials

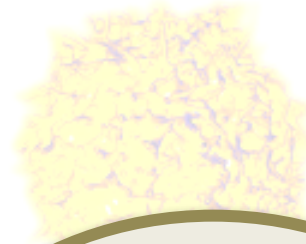


What is a small molecule?

antibodies



T-cells



<1000 Da

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

natural or synthetic

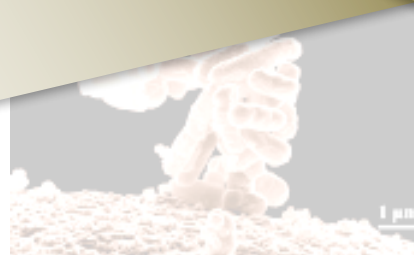
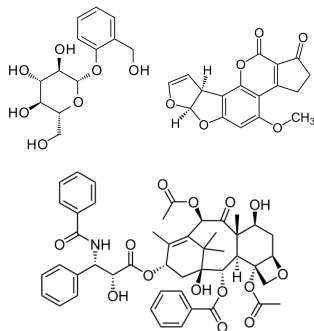
probes/therapeutics

10⁻⁹ m

10⁻⁶ m

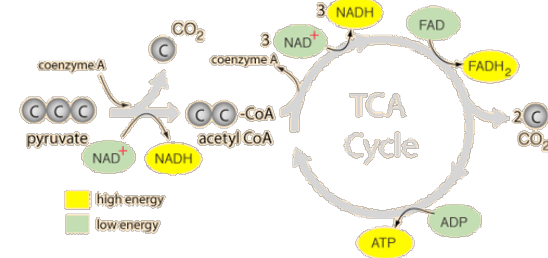
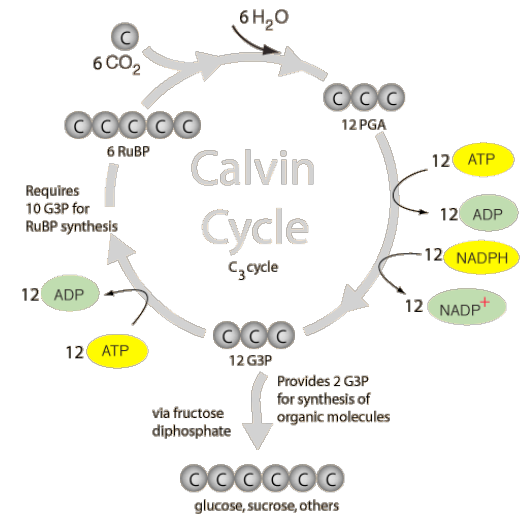
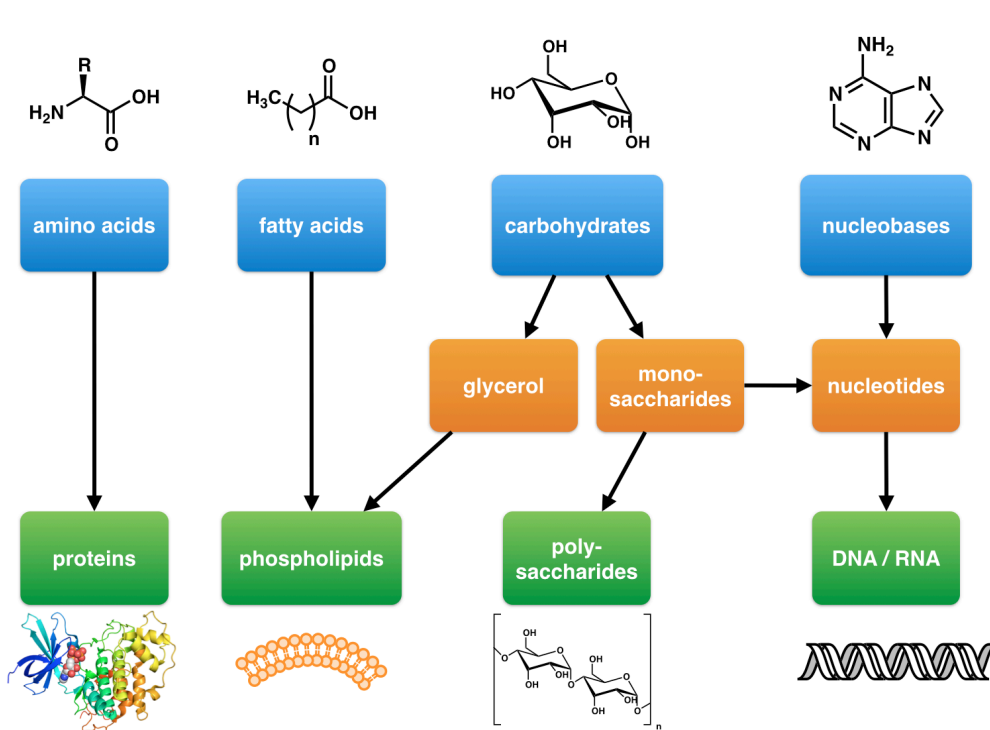
4 m

small molecules



Small molecules of life

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

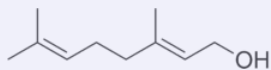


first messengers – signaling molecules that control metabolism and cell differentiation (e.g. hormones, biogenic amines)

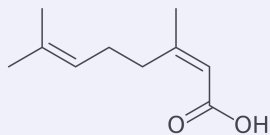
Small molecules of life

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

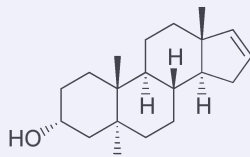
pheromones – social interactions



geraniol



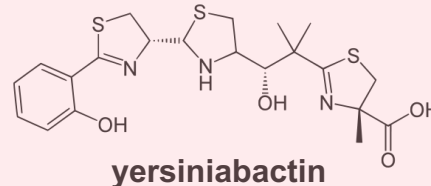
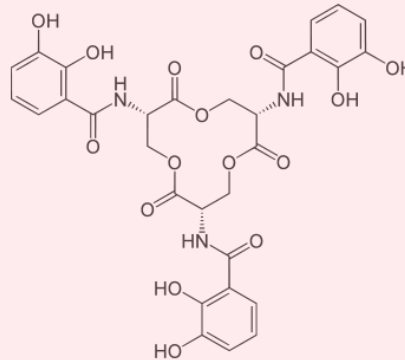
nerolic acid



androstenol

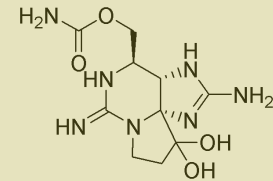
transporters and chelators

enterobactin

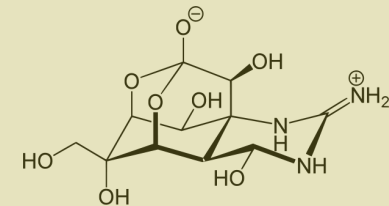


yersiniabactin

toxins – competitive weapons



saxitoxin (TZ)

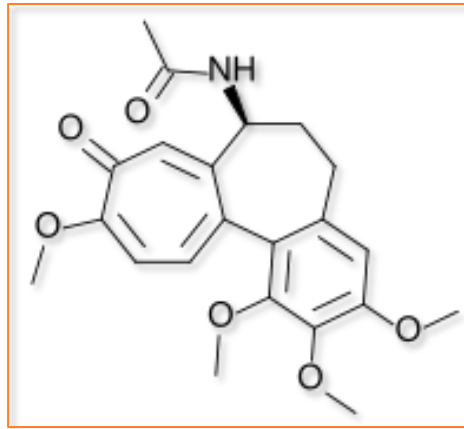


tetrodotoxin (TTX)

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

Small molecules and their partners

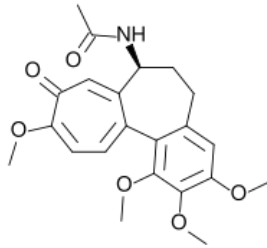
the compound that changed my life



colchicine

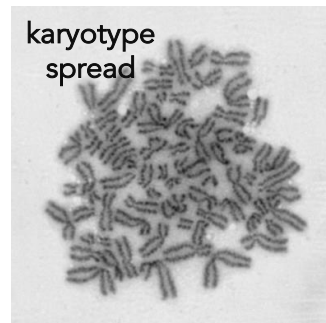
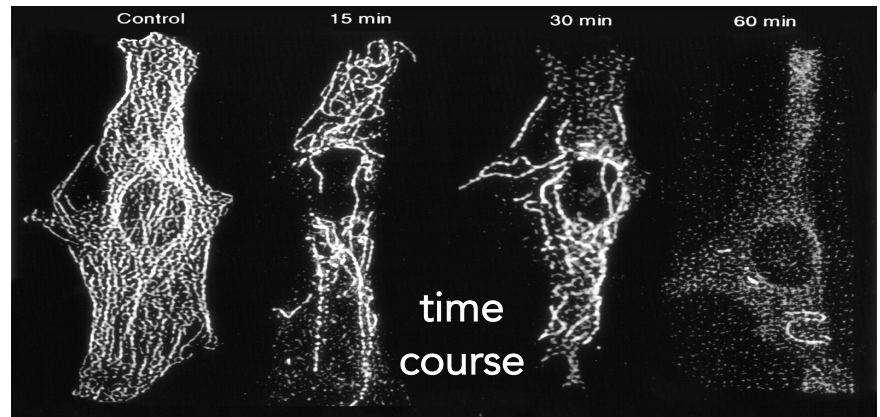
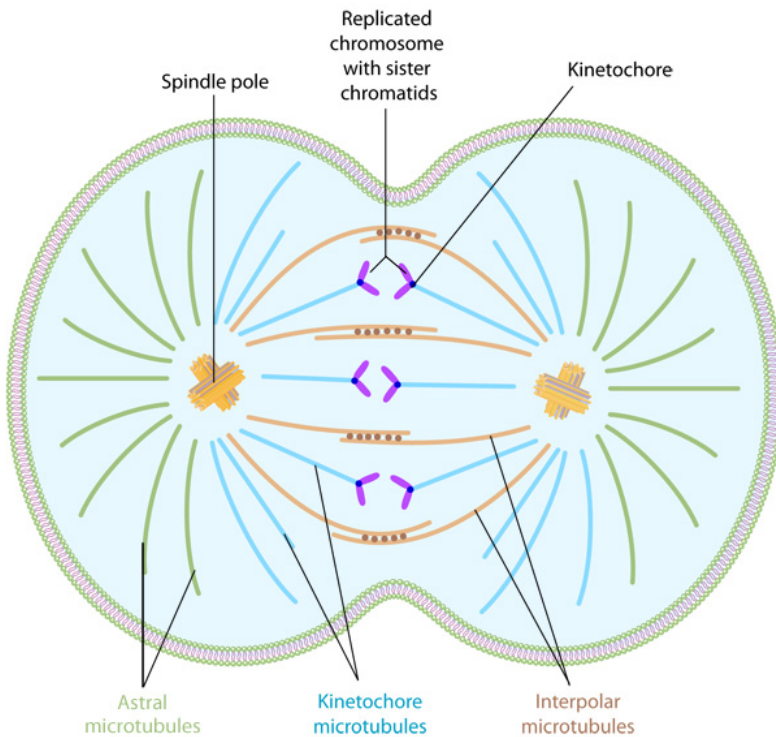
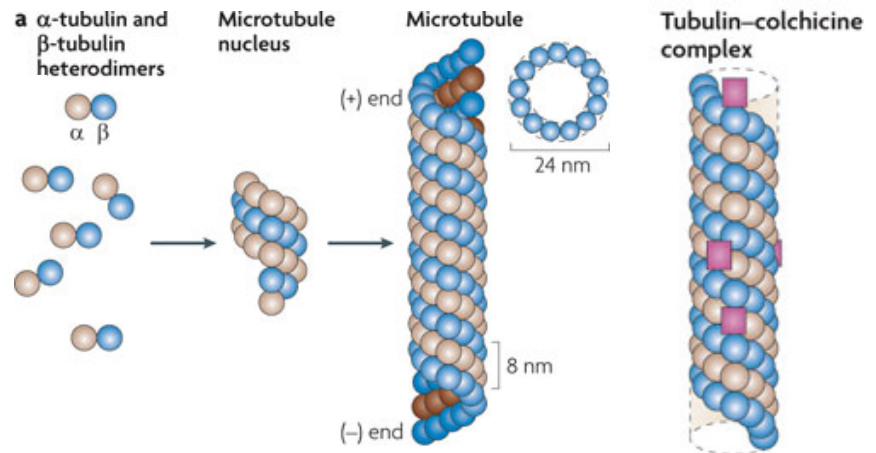
Secondary metabolite from meadow saffron

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



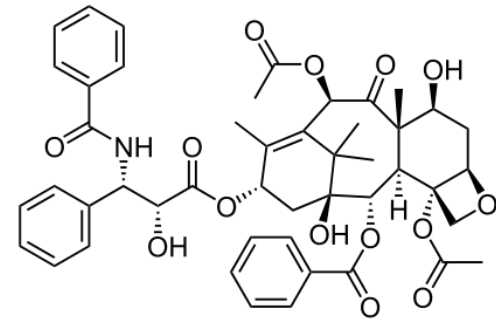
pericarditis



Behçet's disease

Egyptians -1500 BC
Ben Franklin

Taxol
stabilizes MTs



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

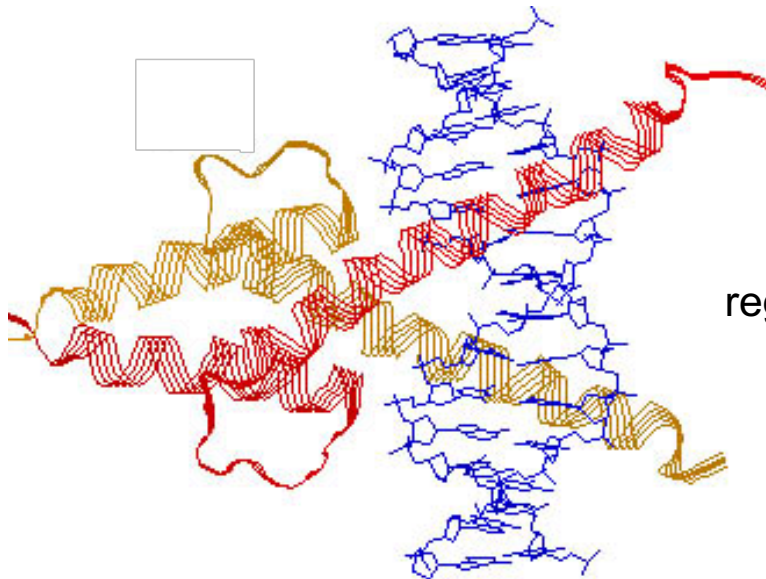
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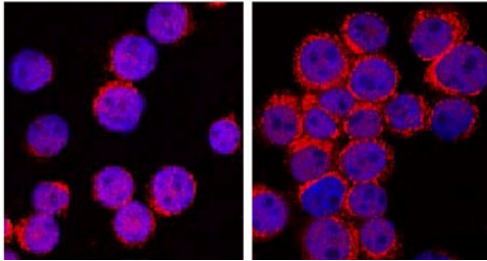
MyoD:

regulates smooth muscle differentiation
'exercise transcription factor'

Approaches to probe discovery

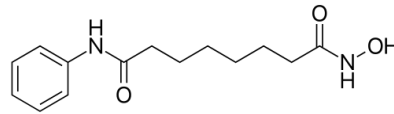
'forward' chemical genetics

screen for phenotype of interest



- small molecule

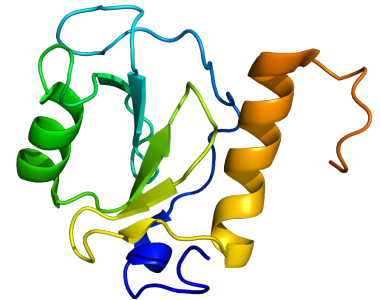
+ small molecule



assay positive



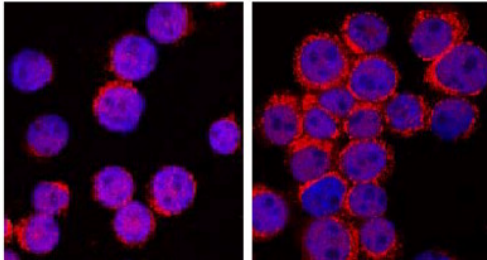
identify protein target



Approaches to probe discovery

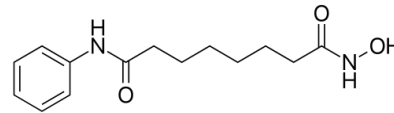
'forward' chemical genetics

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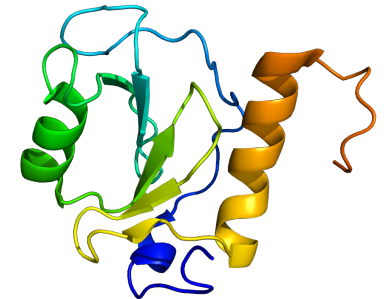
+ small molecule



assay positive

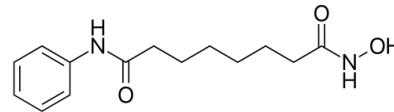
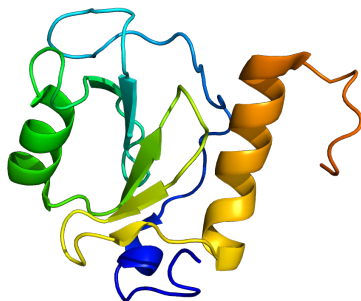


identify protein target



'reverse' chemical genetics

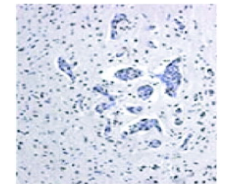
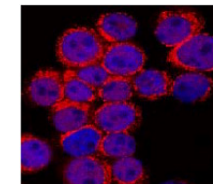
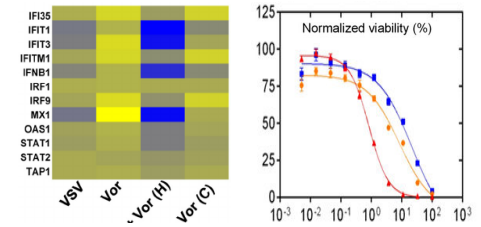
directly bind target of interest



assay positive



broad survey of phenotypic outcomes

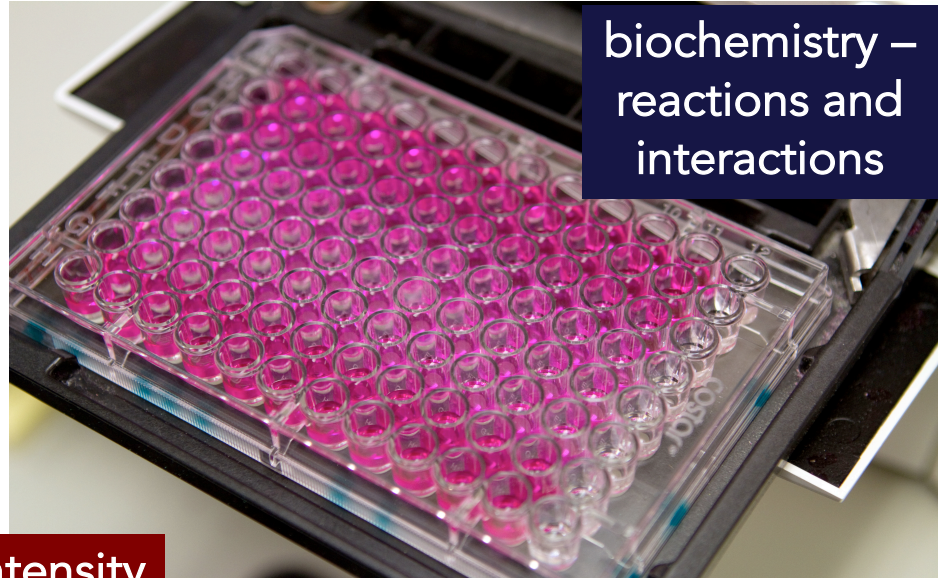


High-throughput bioassays

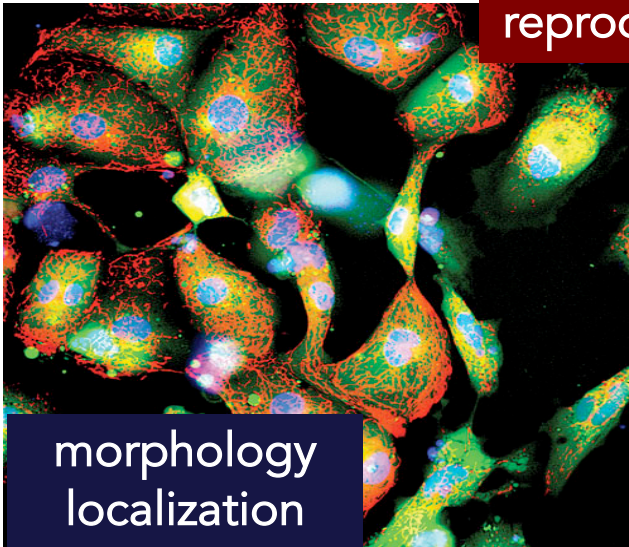
viability



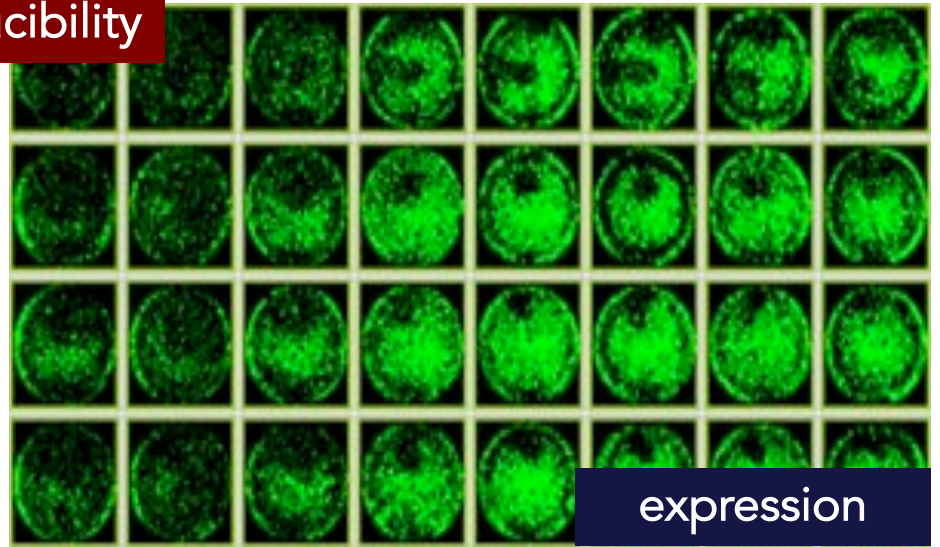
biochemistry –
reactions and
interactions



signal intensity
reproducibility

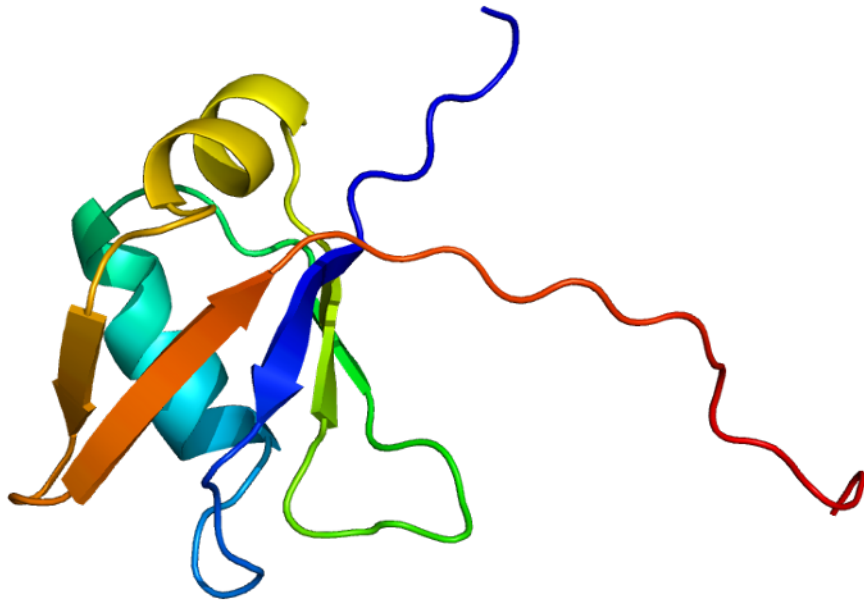


morphology
localization



expression

Protein target: TDP-43



Molecular functions:

RNA binding protein
DNA binding protein
binds several other proteins

Cellular roles:

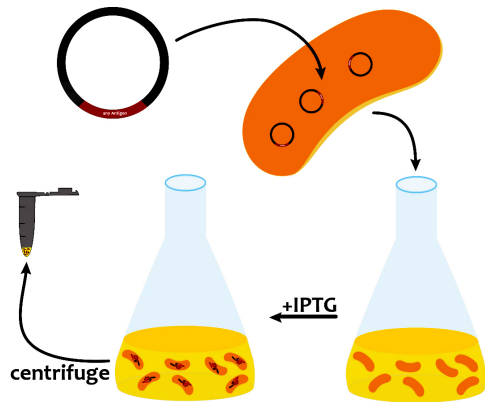
plays a role in [transcriptional repression](#)
plays a role in [DNA repair](#)

Clinical Significance:

implicated in [amyotrophic lateral sclerosis](#)
implicated in [Alzheimer's and dementia](#)
elevated in athletes with [repeated brain injury](#)
roles in [hypercholesterolemia, cystic fibrosis, and HIV](#)

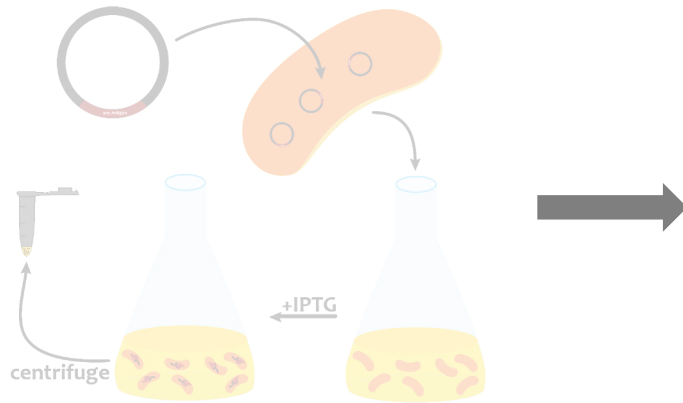
more details to come in Lecture 2!

Spring 2020 Mod 1 path to probe discovery

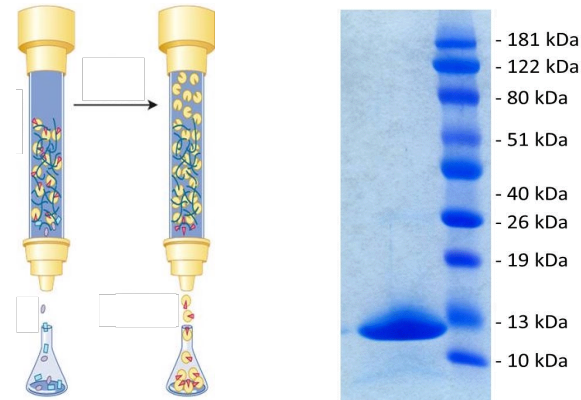


in silico cloning; overexpress TDP-43
lab day 1

Spring 2020 Mod 1 path to probe discovery



in silico cloning; overexpress TDP-43
lab day 1

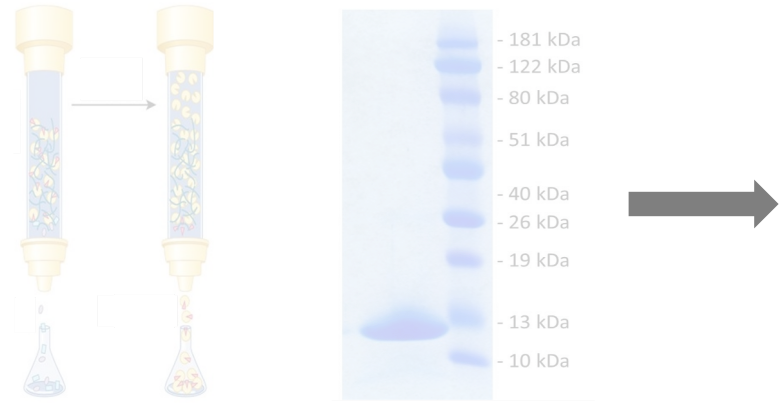


purify and analyze TDP-43 concentration
lab days 2 and 3

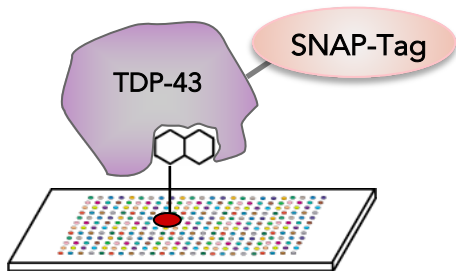
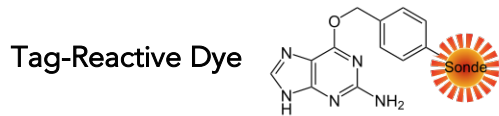
Spring 2020 Mod 1 path to probe discovery



in silico cloning; overexpress TDP-43
lab day 1

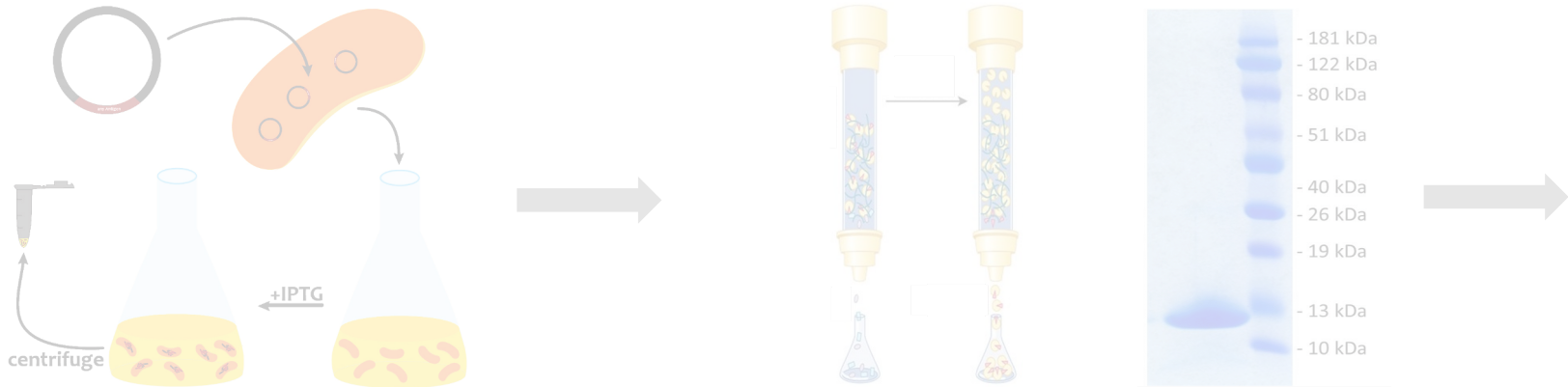


purify and analyze TDP-43 concentration
lab days 2 and 3



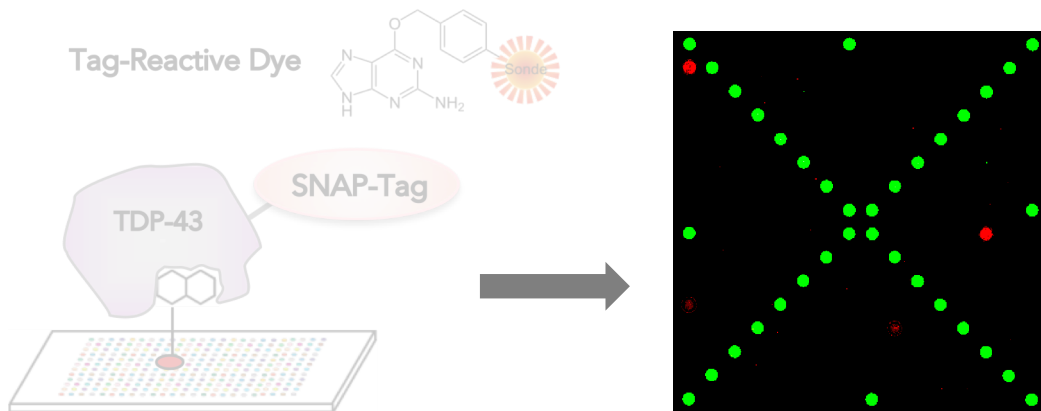
ligand discovery screen
lab day 4

Spring 2020 Mod 1 path to probe discovery



in silico cloning; overexpress TDP-43
lab day 1

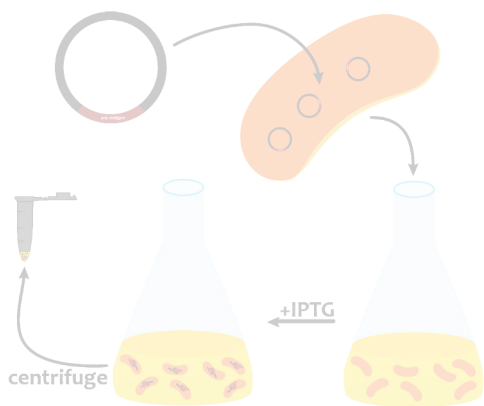
purify and analyze TDP-43 concentration
lab days 2 and 3



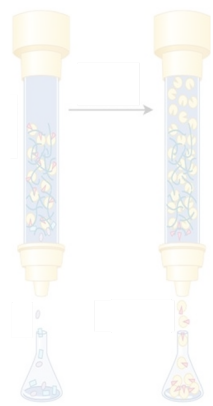
ligand discovery screen
lab day 4

scan images and analyze data
lab days 5 and 6

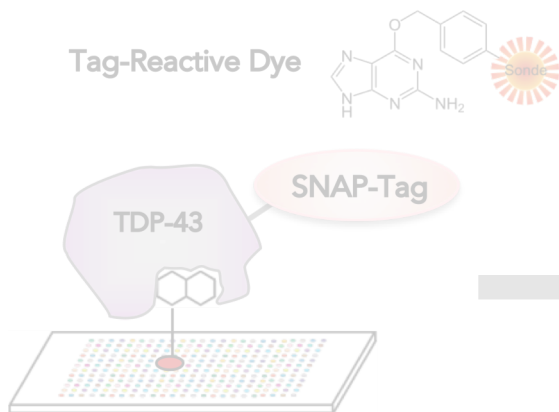
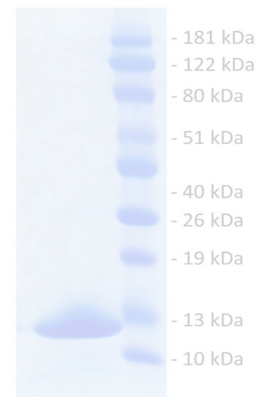
Spring 2020 Mod 1 path to probe discovery



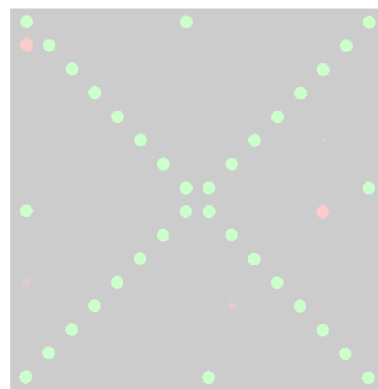
in silico cloning; overexpress TDP-43
lab day 1



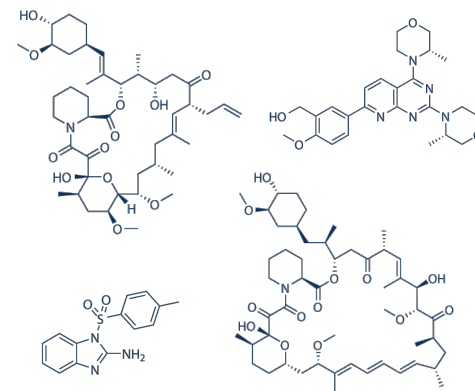
purify and analyze TDP-43 concentration
lab days 2 and 3




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 diploma, while another hand on the right reaches out to receive it. The background is a blurred green field.

Spring 2020
















Spring 2021

Our path to finding ligands - lectures

2/5/20	Lecture 1	Intro to chemical biology: small molecules, probes, and screens
2/11/20	Lecture 2	Our protein target: TDP-43
2/13/20	Lecture 3	Small molecule microarrays
2/18/20	No Lecture	
2/20/20	Lecture 4	Quantitative evaluation of protein-ligand interactions
2/25/20	Lecture 5	A ligand discovery vignette: sonic hedgehog
2/27/20	Lecture 6	Engineering transcriptional responses with a small molecule
3/3/20	Lecture 7	Wrap up discussion: suggestions for how to report your findings

Belmont, MA 10 Day Weather

9:06 am EST [Print](#)

DAY		DESCRIPTION	HIGH / LOW	PRECIP	WIND	HUMIDITY
TODAY FEB 6		Rain	38°/37°	80%	ENE 10 mph	86%
FRI FEB 7		Rain/Wind	50°/22°	80%	SE 20 mph	77%
SAT FEB 8		Sunny	32°/12°	0%	W 17 mph	36%
SUN FEB 9		Mostly Sunny	36°/29°	20%	S 6 mph	36%
MON FEB 10		Showers	48°/33°	60%	SW 14 mph	75%
TUE FEB 11		Rain/Snow Showers	43°/30°	40%	WSW 6 mph	80%
WED FEB 12		Mostly Sunny	42°/31°	20%	W 10 mph	53%
THU FEB 13		Rain/Snow Showers	43°/31°	40%	WSW 8 mph	61%
FRI FEB 14		Rain/Snow Showers	42°/26°	40%	WNW 8 mph	55%
SAT FEB 15		Mostly Sunny	36°/22°	10%	WNW 11 mph	46%
SUN FEB 16		Partly Cloudy	37°/23°	20%	W 7 mph	42%
MON FEB 17		Snow Showers	38°/26°	40%	WNW 8 mph	55%
TUE FEB 18		Snow Showers	40°/27°	40%	WNW 8 mph	59%
WED FEB 19		Rain/Snow Showers	42°/26°	40%	W 10 mph	57%
THU FEB 20		Partly Cloudy	42°/24°	20%	WNW 9 mph	55%

A final note about snow...

