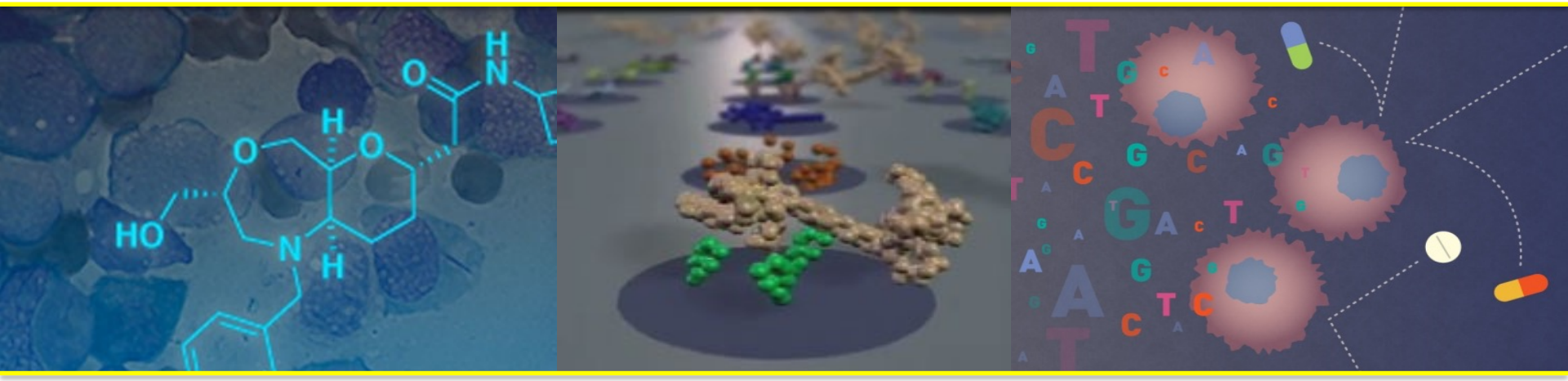
Welcome to Module 1

Drug Discovery



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

February 3, 2022

Angela Koehler
koehler@mit.edu

Instructor

76-361c

Lectures

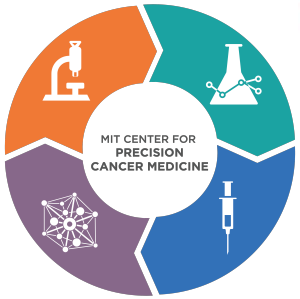
Module 1 Office Hours

Fri 2/11	9am
Wed 2/16	Noon
Fri 2/25	Noon
Thur 3/3	Noon
Mon 3/7	3pm
Wed 3/9	8:30am
Fri 3/11	3pm

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

Meeting ID: 930 5704 9755

LUDWIG CANCER RESEARCH



STARR CANCER CONSORTIUM

Royal G. and Mae H. Westaway Family Memorial Fund

Kathy and Curt Marble Research Fund

Benjamin and Samuel Krinsky Memorial Fund

ligondiscovery

founded in 2007

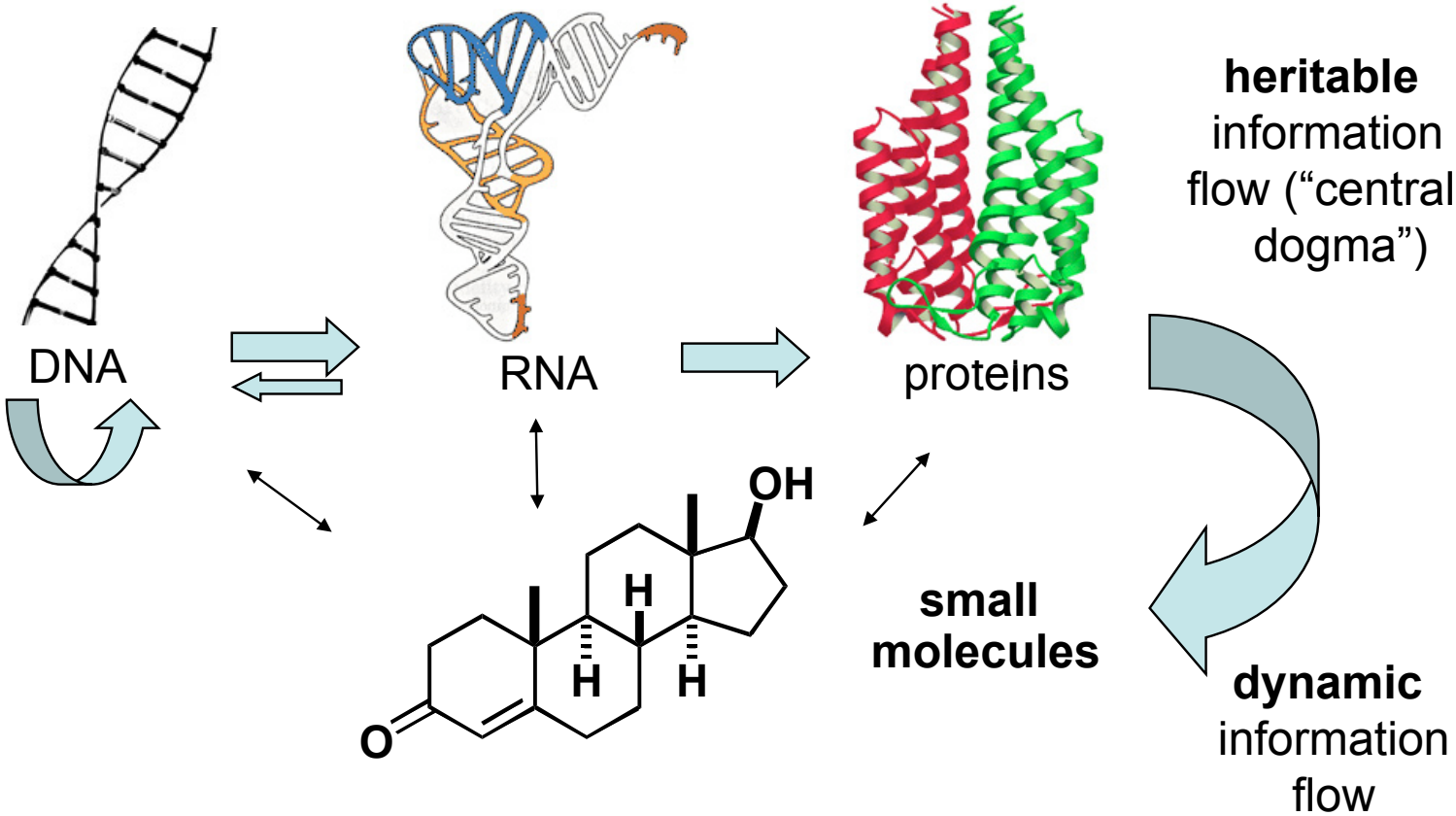
KRONOS·BIO

founded in 2017

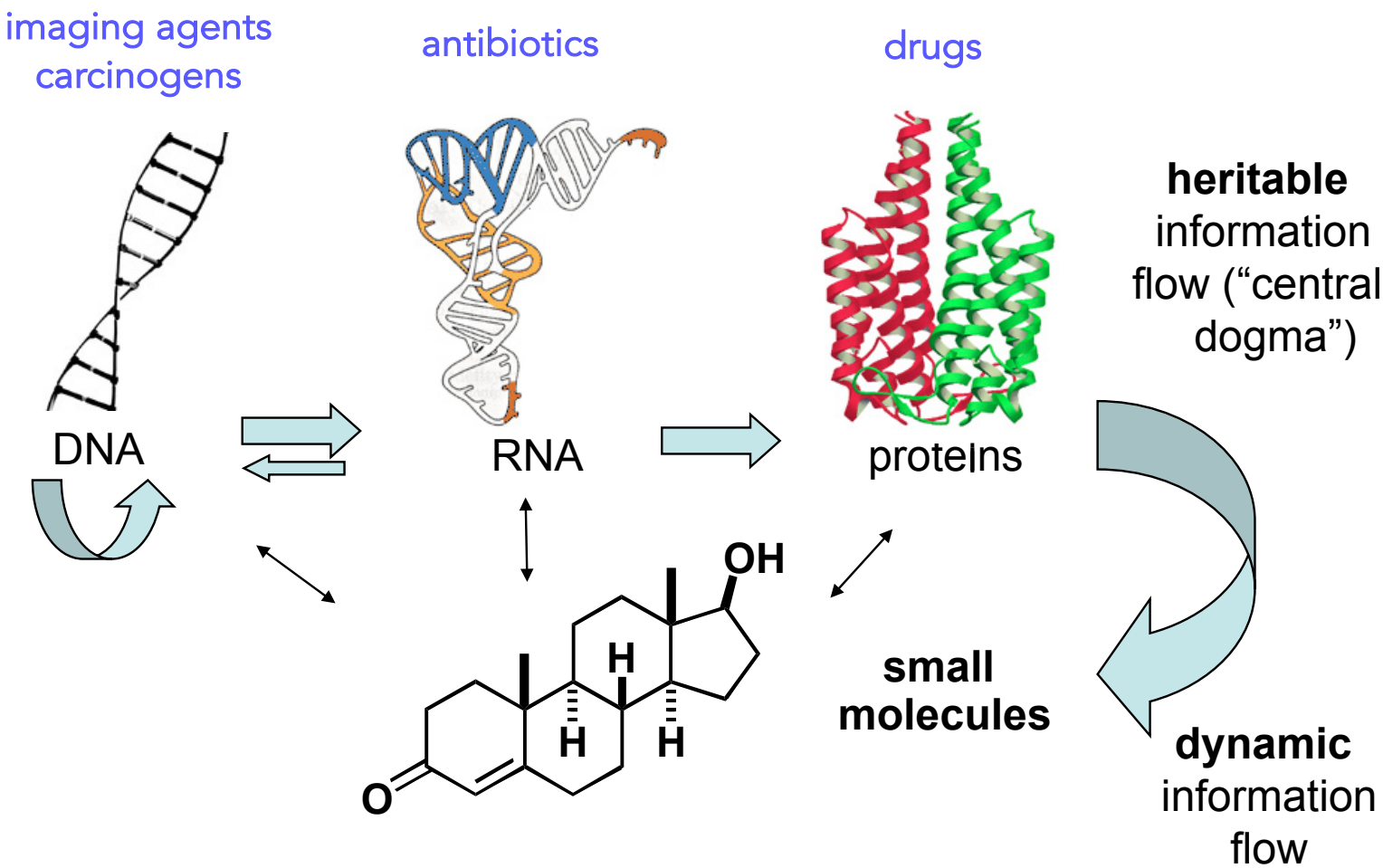
76 BIO

founded in 2021

The central dogma



The central dogma



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

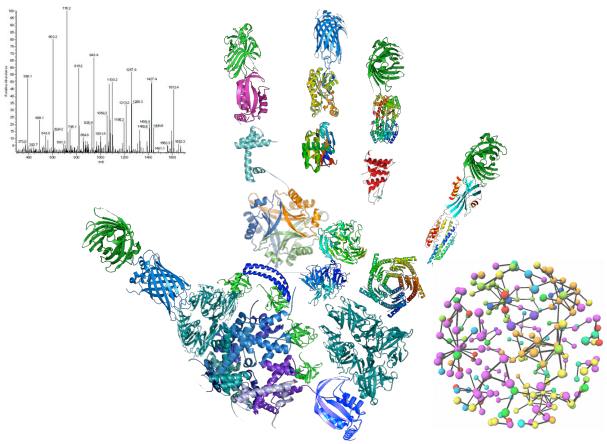
Defining chemical biology

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

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



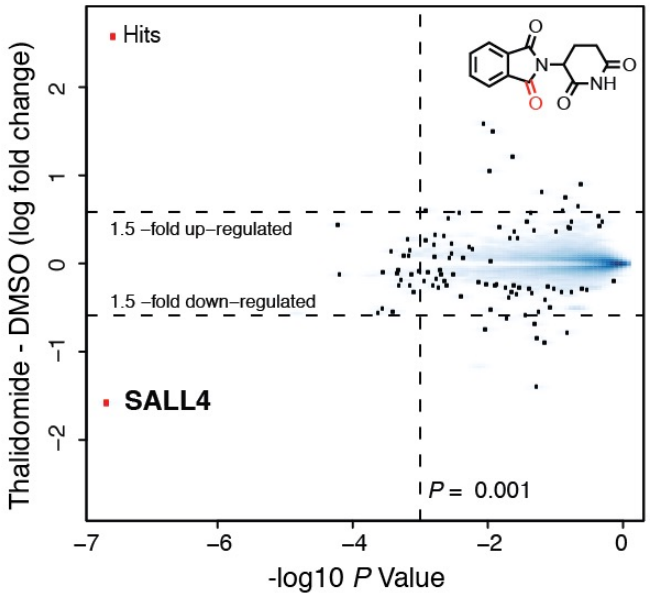
Investigates the set of expressed proteins in a cell at a given time under defined conditions – quantitative, comparative

often involves mass spectrometry

quantitative proteomics

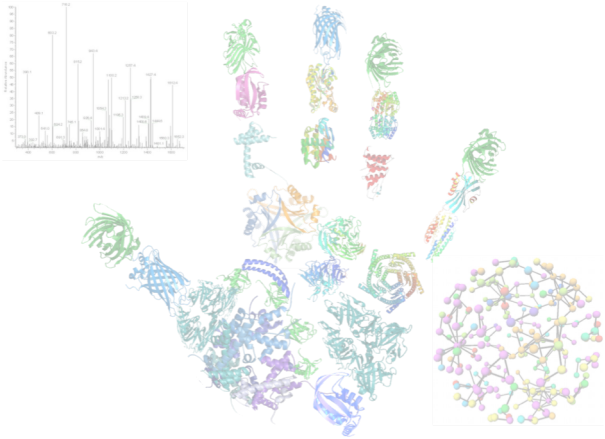
Bryson, Dedon, Fraenkel, Hynes, Koehler, White, Yaffe

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



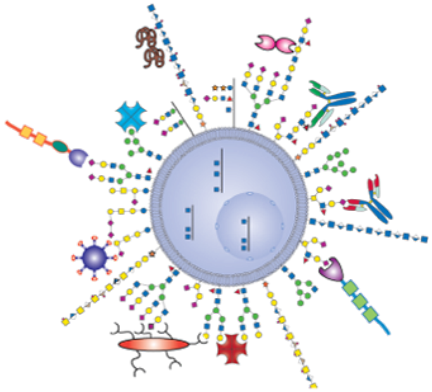
Dr. Eric Fischer, Harvard

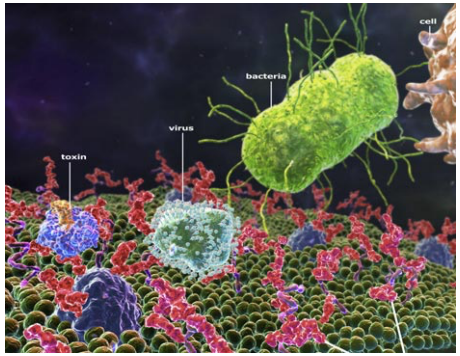
Systems of interest to chemical biologists



quantitative proteomics

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





glycobiology

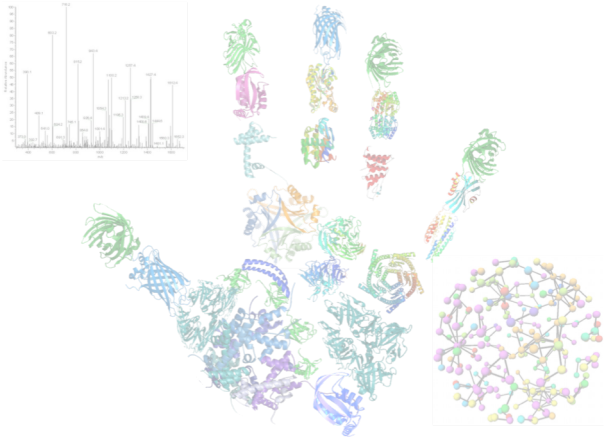
Imperiali, Irvine, Kiessling, Ribbeck, Sasisekharan, Vander Heiden

- 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

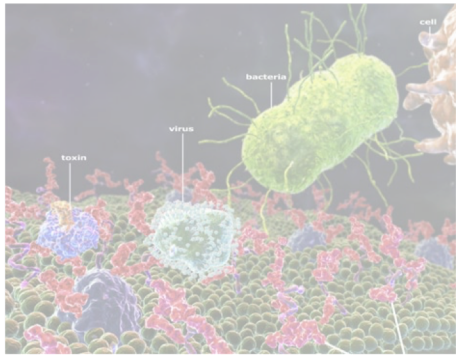
involves many imaging and tracing methods, mass spec

Systems of interest to chemical biologists



quantitative proteomics

Dedon, Fraenkel, Hynes, Koehler, White Yaffe



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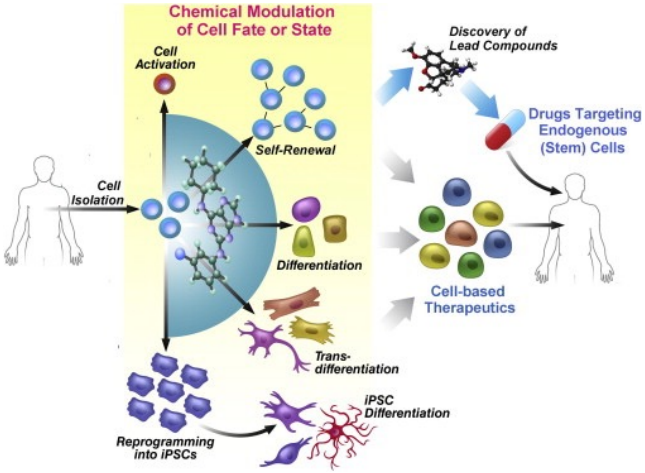


Often involves using chemicals to perturb signaling systems that govern cell state

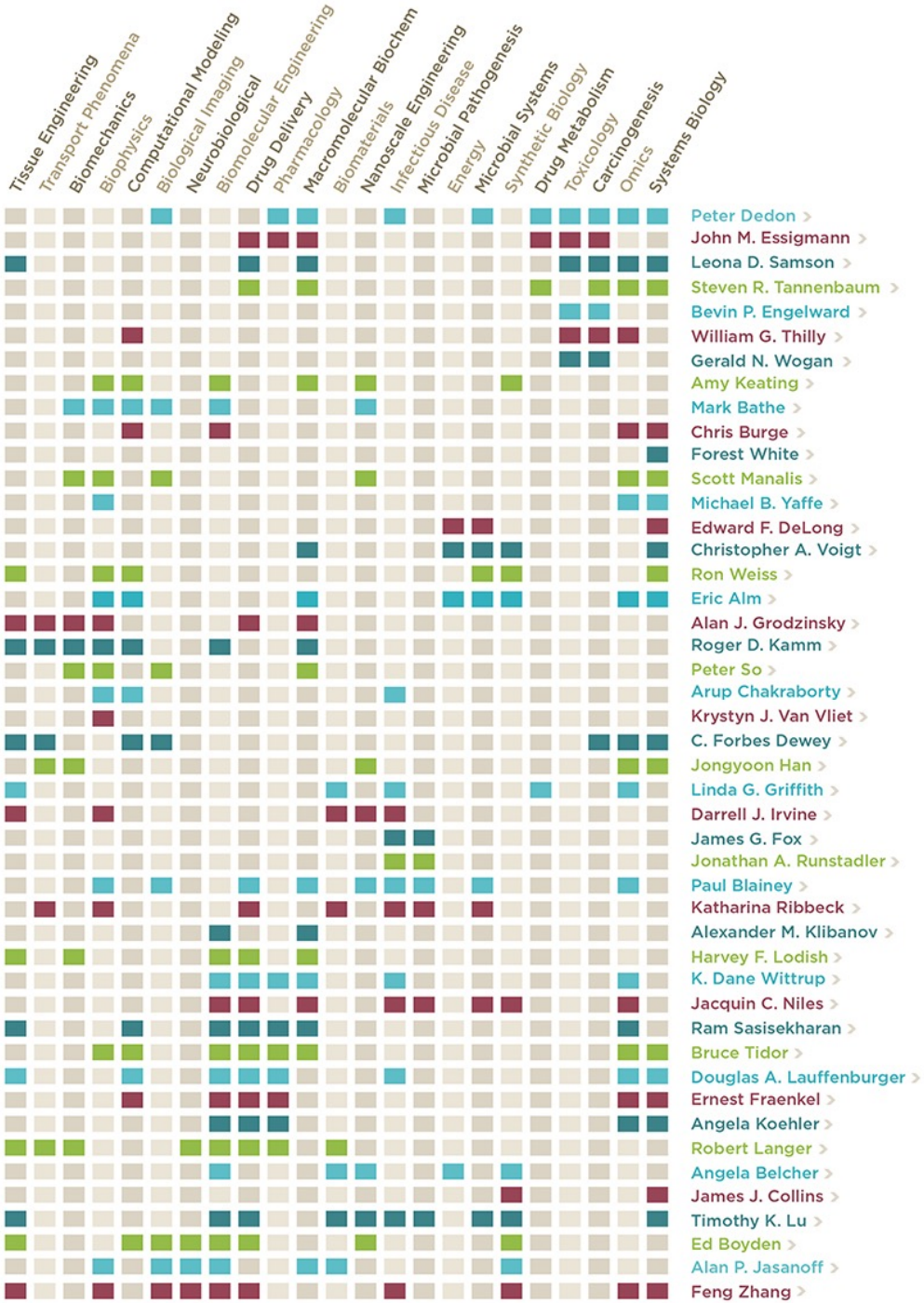
stem cell biology and programming cell fate

Boyer, 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 (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.

engineering new biomolecules and synthetic systems

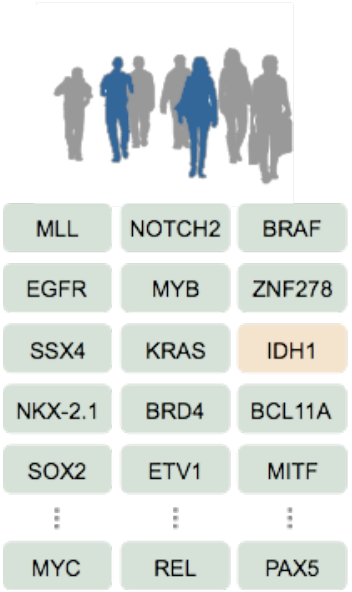
7.73 Principles of Chemical Biology (S)

Barbara Imperiali, Jing-Ke Weng

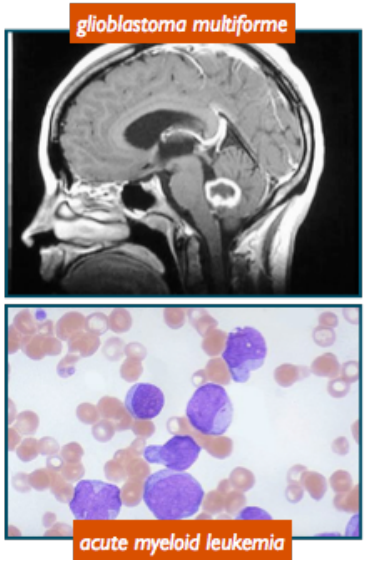
Spanning the fields of biology, chemistry and engineering, addresses the principles of chemical biology and its application of chemical and physical methods and reagents to the study and manipulation of biological systems. Topics include activity-based protein profiling, small molecule inhibitors and 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.

modulating natural systems and measuring outputs

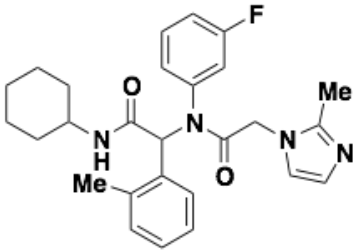
Chemical probes of disease biology



patient samples reveal
list of disease genes



physiologic settings to test
the impact of disease genes



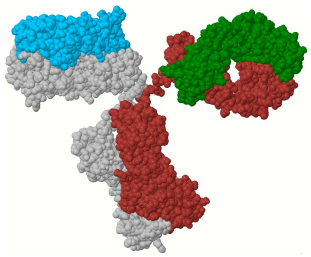
discover small molecules
that reverse the
impact of disease genes

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

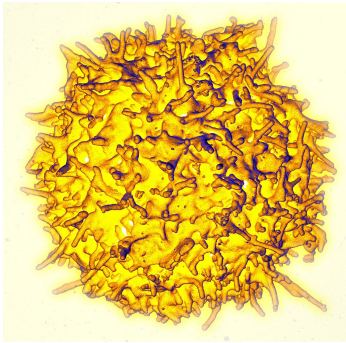
Output: validated small-molecule probe to facilitate human clinical development or diagnostic applications

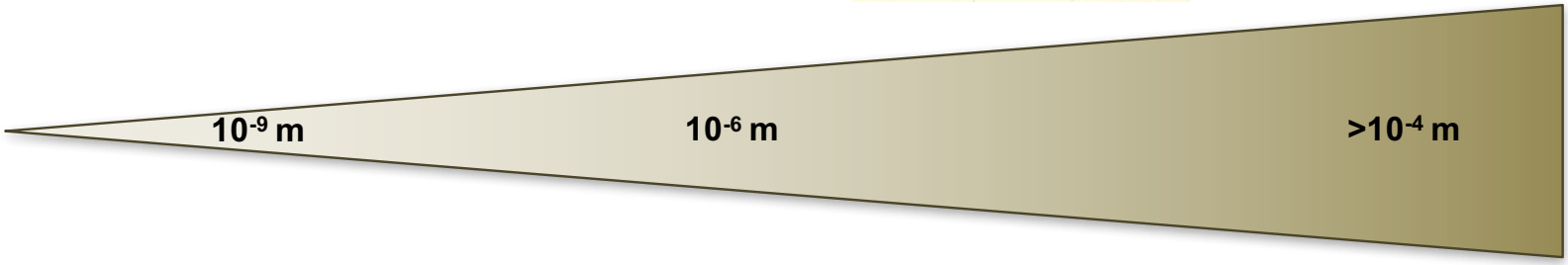
How small is a small molecule?

antibodies

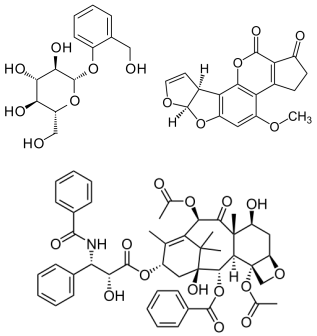


T-cells

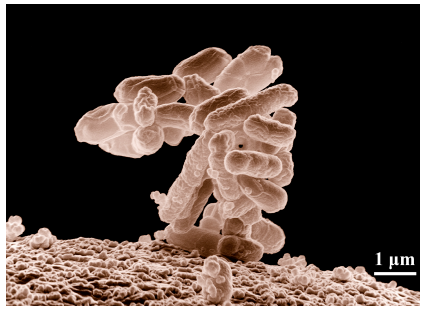




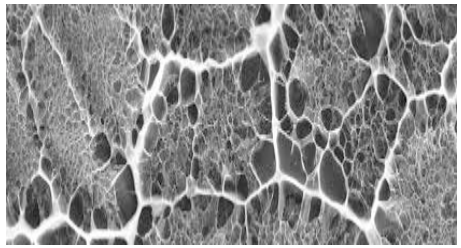
small molecules



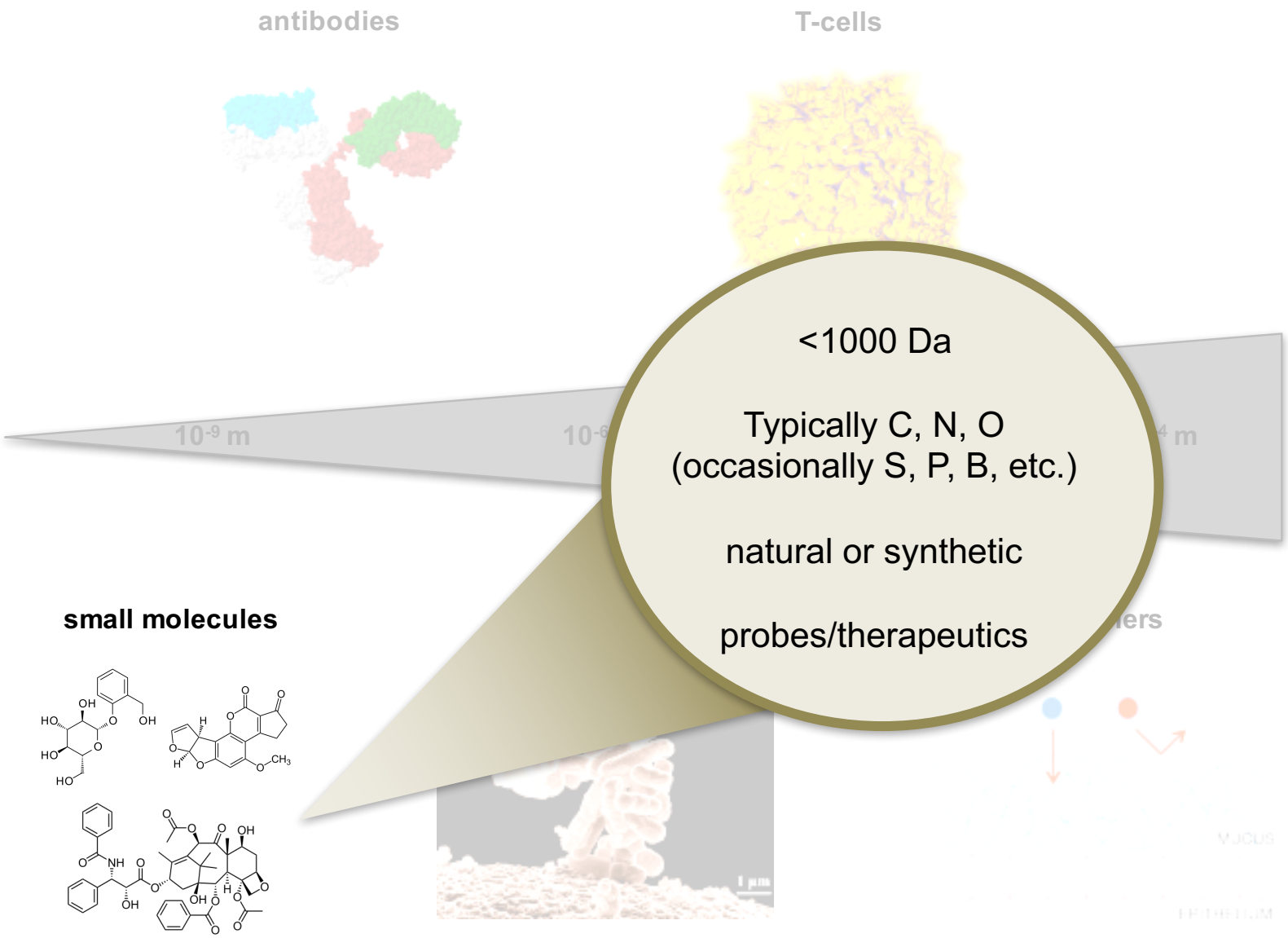
microbes



bio-materials



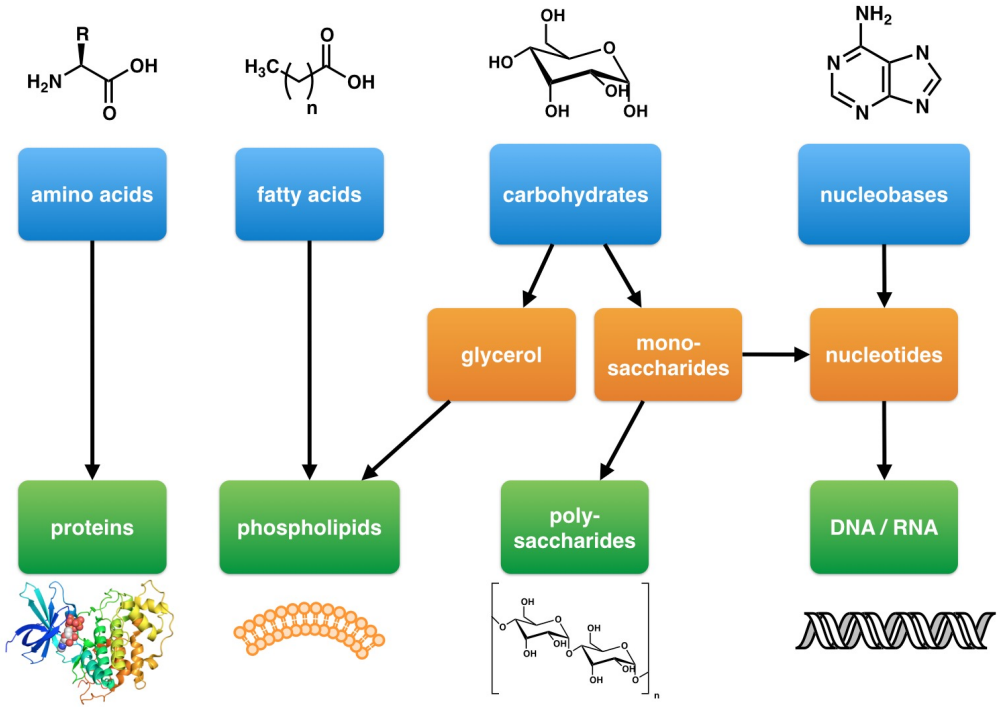
How small is a small molecule?

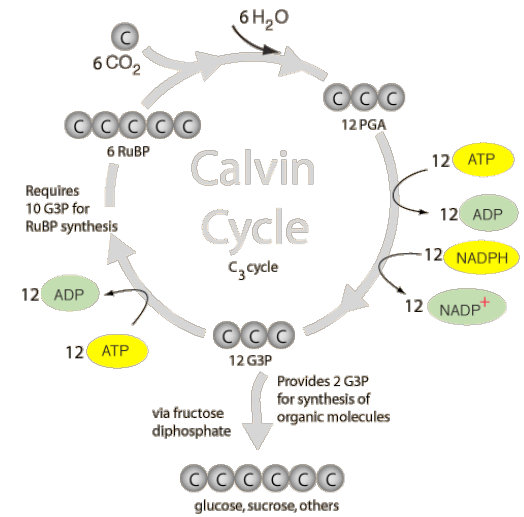


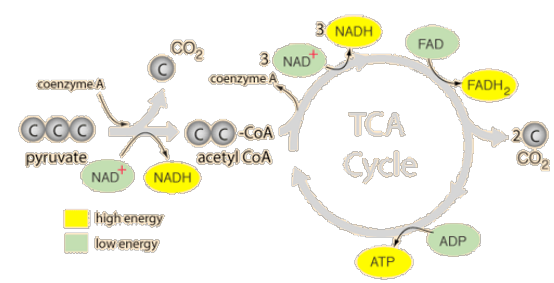
Small molecules of life

7.05

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







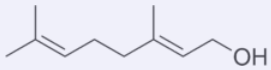
first messengers – signaling molecules that control metabolism and cell differentiation (e.g. hormones, biogenic amines)

Small molecules of life

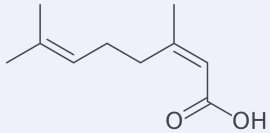
secondary metabolites – non-essential to organism, extrinsic function that affects other organisms; broad range of functions, narrow species distribution

increase competiveness of an organism

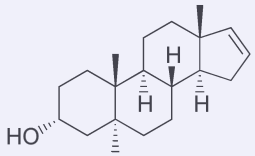
pheromones – social interactions



geraniol



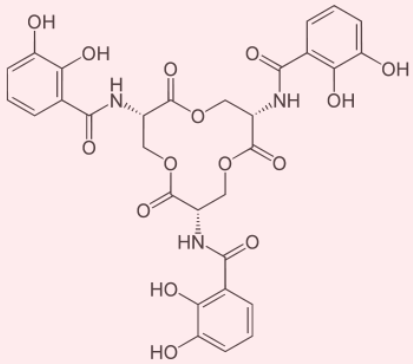
nerolic acid

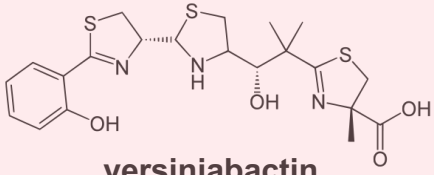


androstenol

transporters and chelators

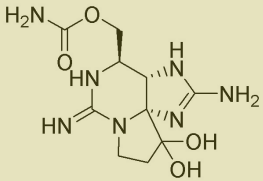
enterobactin



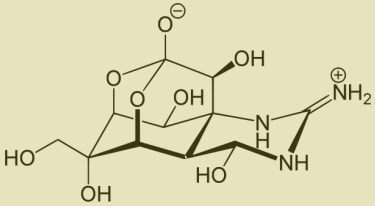


yersiniabactin

toxins – competitive weapons



saxitoxin (TZ)

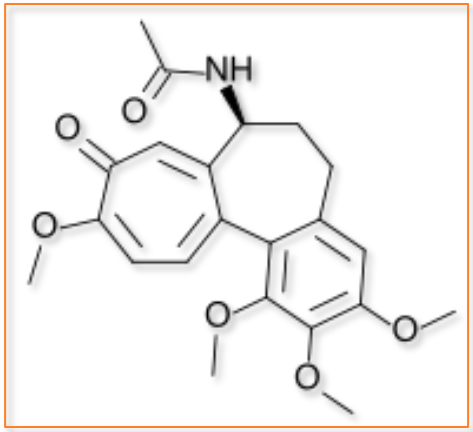


tetrodotoxin (TTX)

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

Small molecules and their biological partners

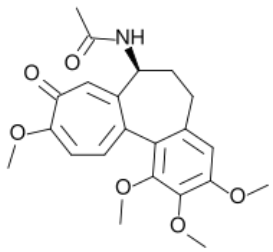
the compound that changed my life



colchicine

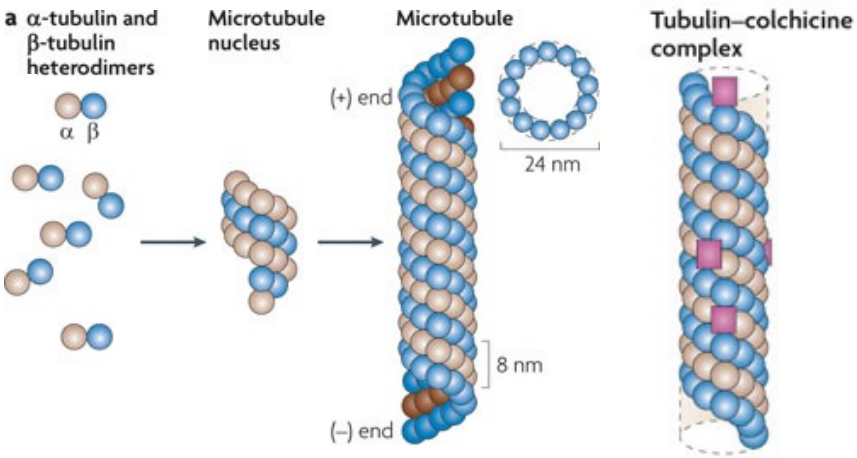
Secondary metabolite from meadow saffron

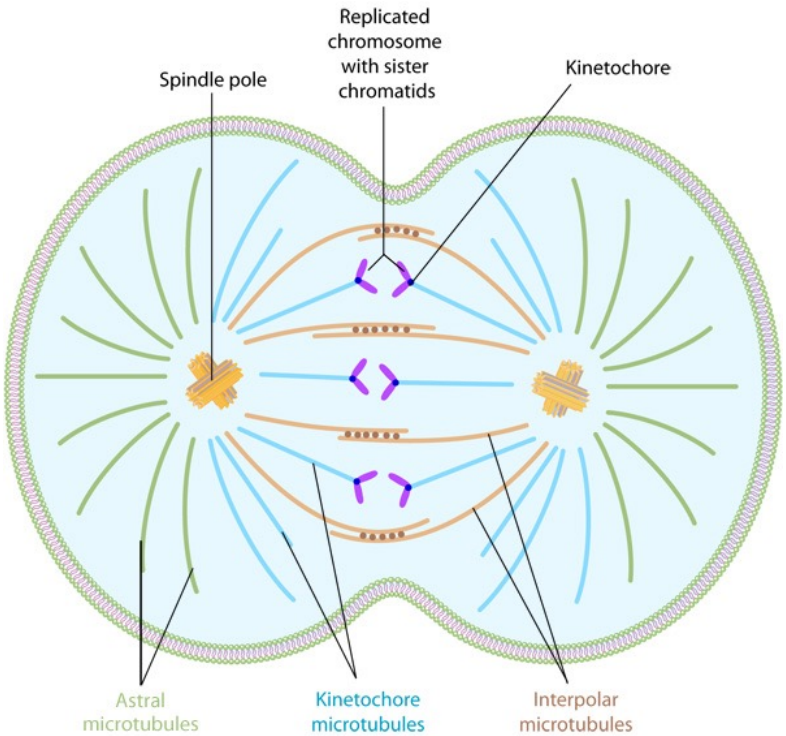
Colchicine is a *mitotic spindle poison*

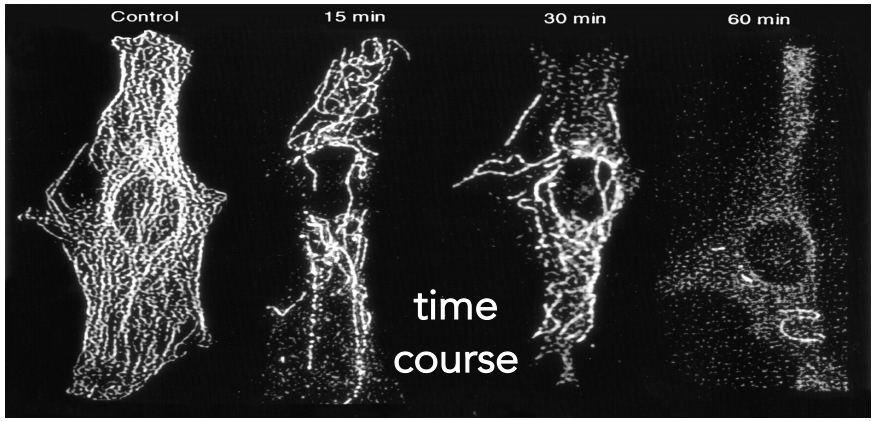


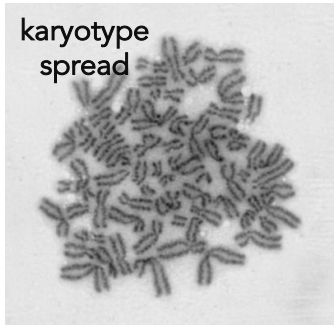
colchicine

binds to tubulin protein
blocks microtubule polymerization









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

freezes chromosomes in metaphase

Colchicine informs therapeutic strategies

inflammatory diseases – neutrophil motility

gout

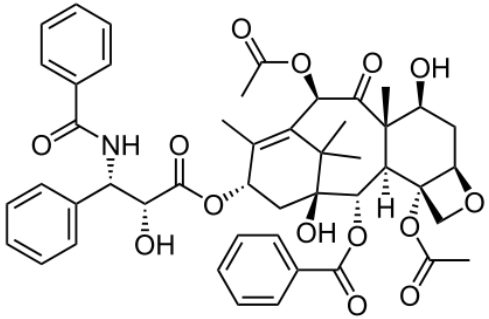
pericarditis

Behçet's disease

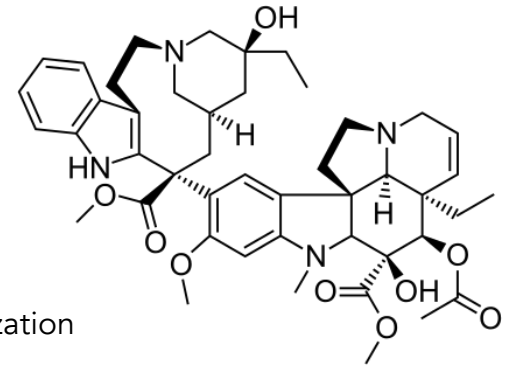
Egyptians -1500 BC
Ben Franklin

mitotic poisons for cancer therapy

Taxol
stabilizes MTs



lung, ovarian, breast, sarcomas



Vinblastine
blocks MT polymerization

leukemia, lymphoma, breast, testicular

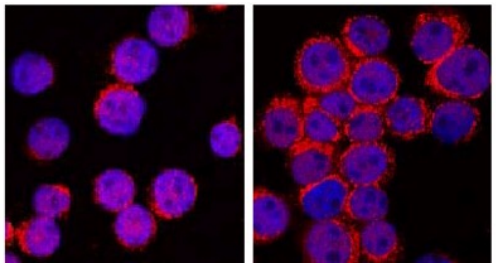
‘Chemical genomic’ toolkit

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

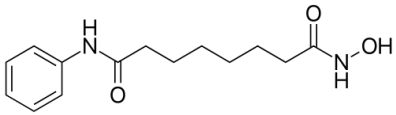
How do you find probes??

'forward' chemical genetics

screen for phenotype of interest

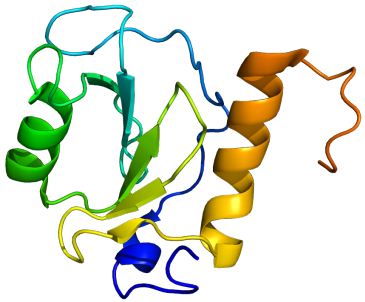


- small molecule + small molecule



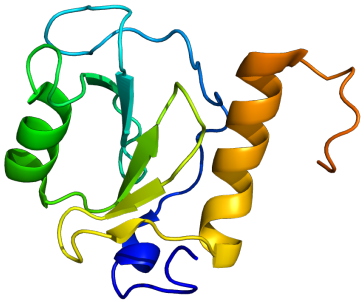
assay positive

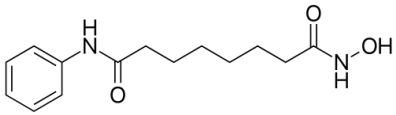
identify protein target



'reverse' chemical genetics

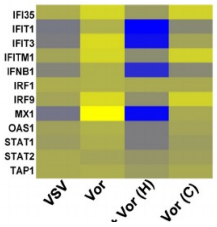
directly bind target of interest

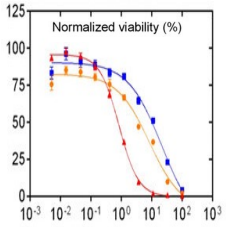


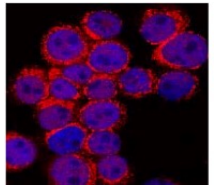


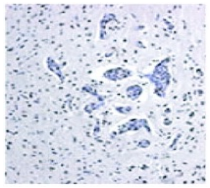
assay positive

broad survey of phenotypic outcomes

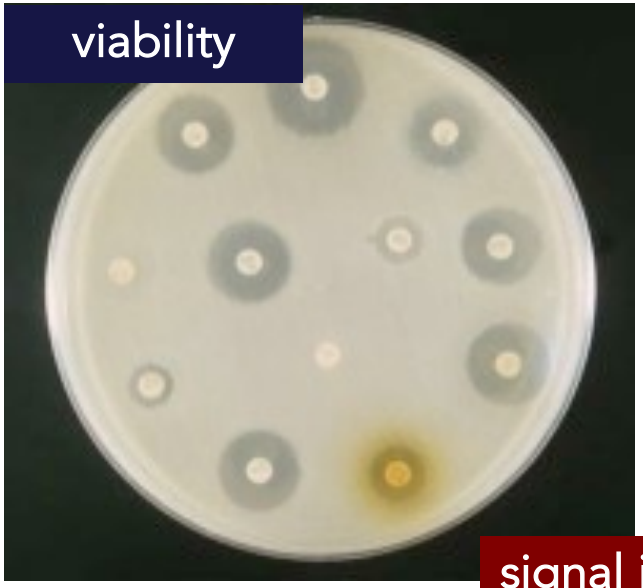


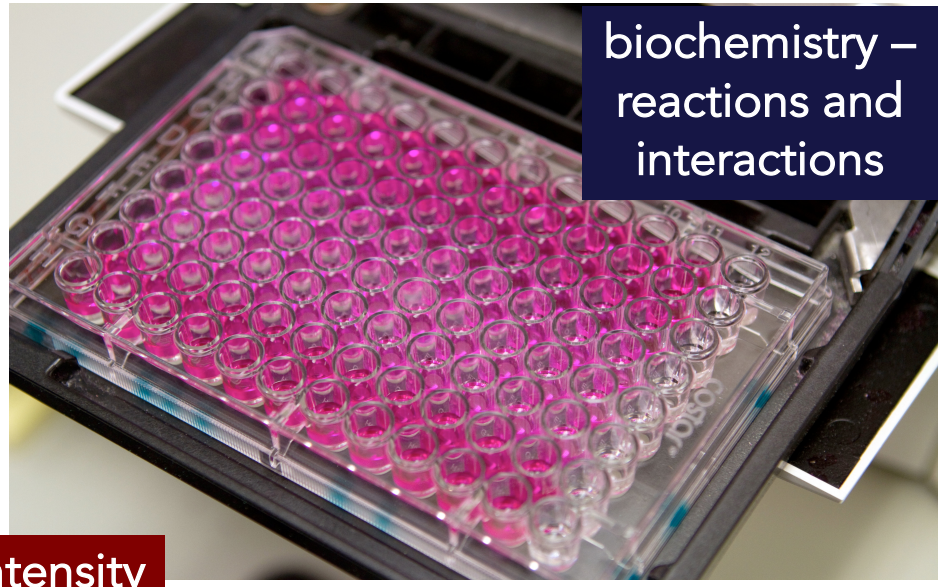




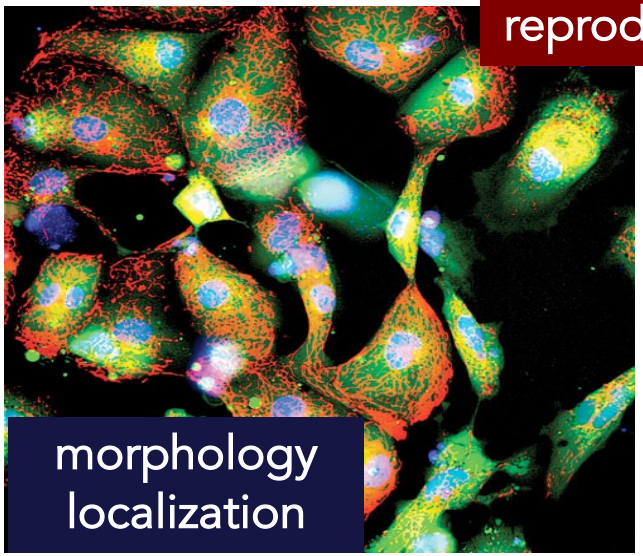


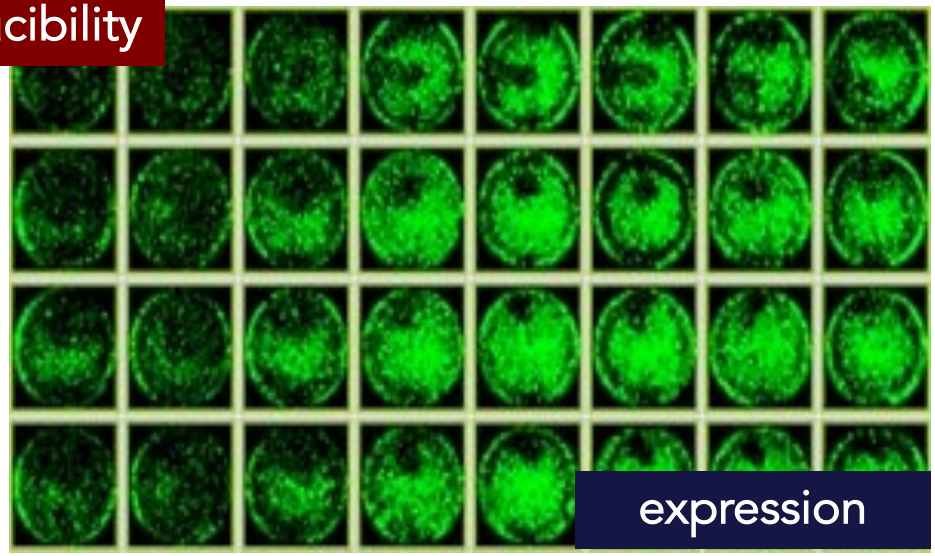
High-throughput bioassays





signal intensity
reproducibility





Protein target: TDP-43

<u>Molecular functions:</u>
RNA binding protein
DNA binding protein
binds several other proteins

<u>Cellular roles:</u>
plays a role in transcriptional repression
plays a role in DNA repair

<u>Clinical Significance:</u>
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!

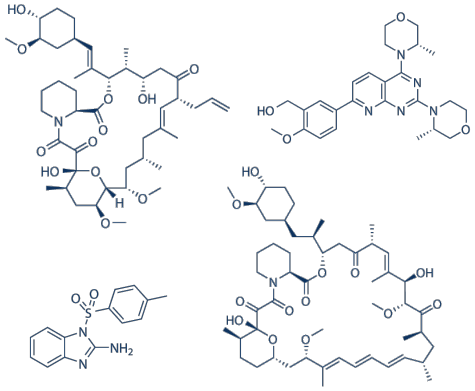
Spring 2020 path to probe discovery

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

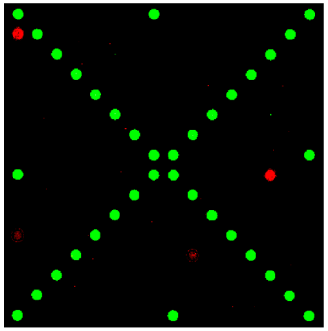
scan images and analyze data
lab days 5 and 6

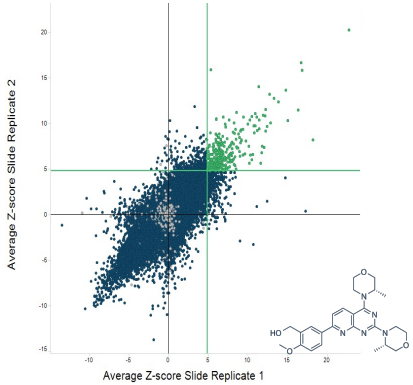


compare hit lists for teams
lab day 7


Spring 2020
Spring 2022

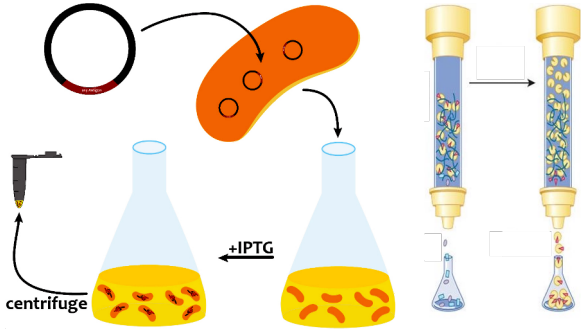
Spring 2022 path to validating probes





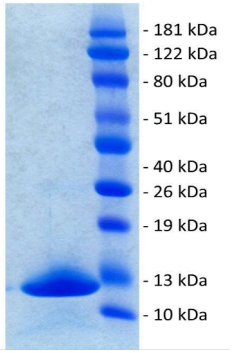
examine legacy SMM screens for TDP-43

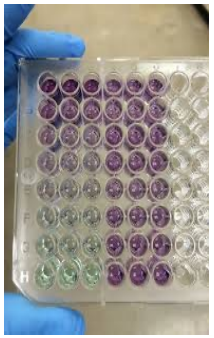
Days 1-2



express and purify TDP-43 protein

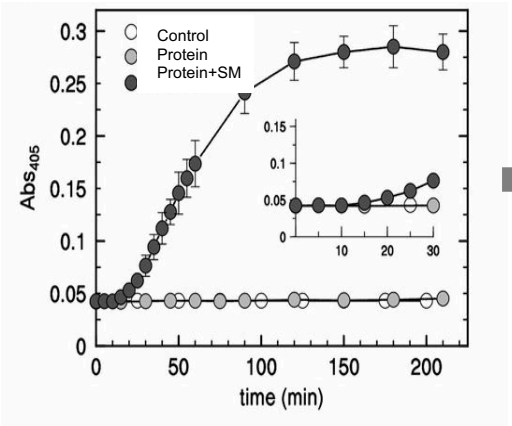
Day 3





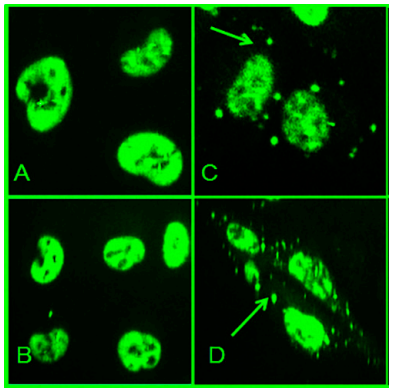
assess purity and concentration

Day 4



aggregation assays

Day 5



cellular localization staining

Days 6-7

Upcoming Lectures

2/3/22	Lecture 1	Intro to chemical biology: small molecules, probes, and screens
2/8/22	Lecture 2	Our protein target: TDP-43
2/10/22	Lecture 3	Small molecule microarrays
2/15/22	Lecture 4	Quantitative evaluation of protein-ligand interactions
2/17/22	Lecture 5	A ligand discovery vignette: sonic hedgehog
2/22/22	No Class	
2/24/22	Lecture 6	Engineering transcriptional responses with a small molecule
3/1/22	Lecture 7	Wrap up discussion for Mod 1 experiments and report