

Welcome to Module 1

Studying Protein-Ligand Interactions



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

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Instructor
76-361c

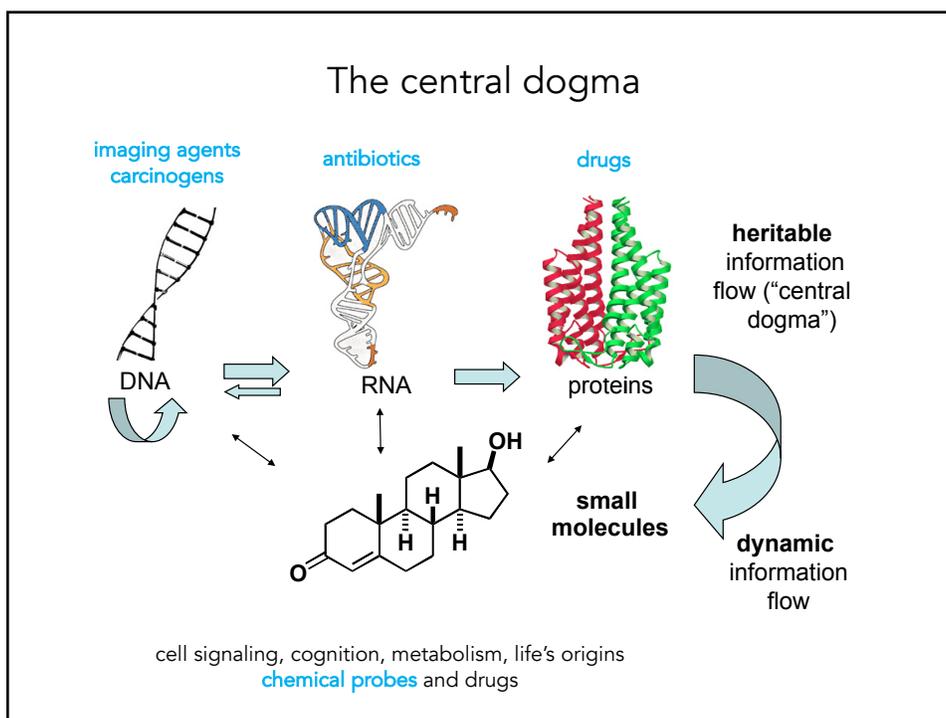
Lectures



Catherine Henry
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BE Graduate Student
Koehler Lab

Class TA
Labs



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 biology, including basic, disease, and synthetic applications.

Systems of interest to chemical biologists



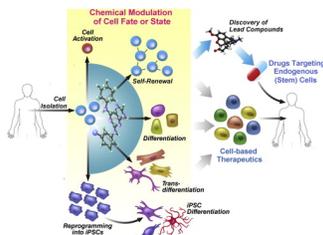
quantitative proteomics

Dedon, Fraenkel, Koehler, White



glycochemistry

Imperiali, Kiessling, Ribbeck, Sasisekharan, Vander Heiden



stem cell biology and programming cell fate

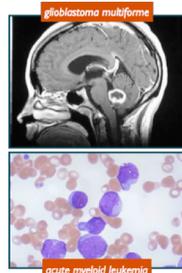
Boyer, Guarente, Gupta, Jaenisch, Kiessling, Koehler, Weinberg, Yilmaz, Young

Chemical probes of disease biology

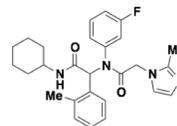


MLL	NOTCH2	BRAF
EGFR	MYB	ZNF278
SSX4	KRAS	IDH1
NKX-2.1	BRD4	BCL11A
SOX2	ETV1	MITF
⋮	⋮	⋮
MYC	REL	PAX5

patient samples reveal list of disease genes



physiologic settings to test the impact of disease genes



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

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

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

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

Measure
Model
Manipulate
Make

MIT BE BIOLOGICAL ENGINEERING
Creating biological technologies from discovery to design.

Peter Dedon >
 John M. Essigmann >
 Leona D. Samson >
 Steven R. Tannenbaum >
 Bevin P. Engelward >
 William G. Thilly >
 Gerald N. Wogan >
 Amy Keating >
 Mark Bathe >
 Chris Burge >
 Forest White >
 Scott Manalis >
 Michael B. Yaffe >
 Edward F. DeLong >
 Christopher A. Volgt >
 Ron Weiss >
 Eric Alm >
 Alan J. Grodzinsky >
 Roger D. Kamm >
 Peter So >
 Arup Chakraborty >
 Krystyn J. Van Vliet >
 C. Forbes Dewey >
 Jongsoo Han >
 Linda G. Griffith >
 Darrell J. Irvine >
 James G. Fox >
 Jonathan A. Runstadler >
 Paul Blainey >
 Katharina Ribbeck >
 Alexander M. Kilbanov >
 Harvey F. Lodish >
 K. Dana Wittup >
 Jacquie C. Niles >
 Ram Sasisekharan >
 Bruce Tidor >
 Douglas A. Lauffenburger >
 Ernest Fraenkel >
 Angela Koehler >
 Robert Langer >
 Angela Belcher >
 James J. Collins >
 Timothy K. Lu >
 Ed Boyden >
 Alan P. Jasanoff >
 Feng Zhang >

Chemical biology courses at MIT

suitable for advanced undergraduates

20.554 Frontiers in Chemical Biology (F)
Laura Kiessling

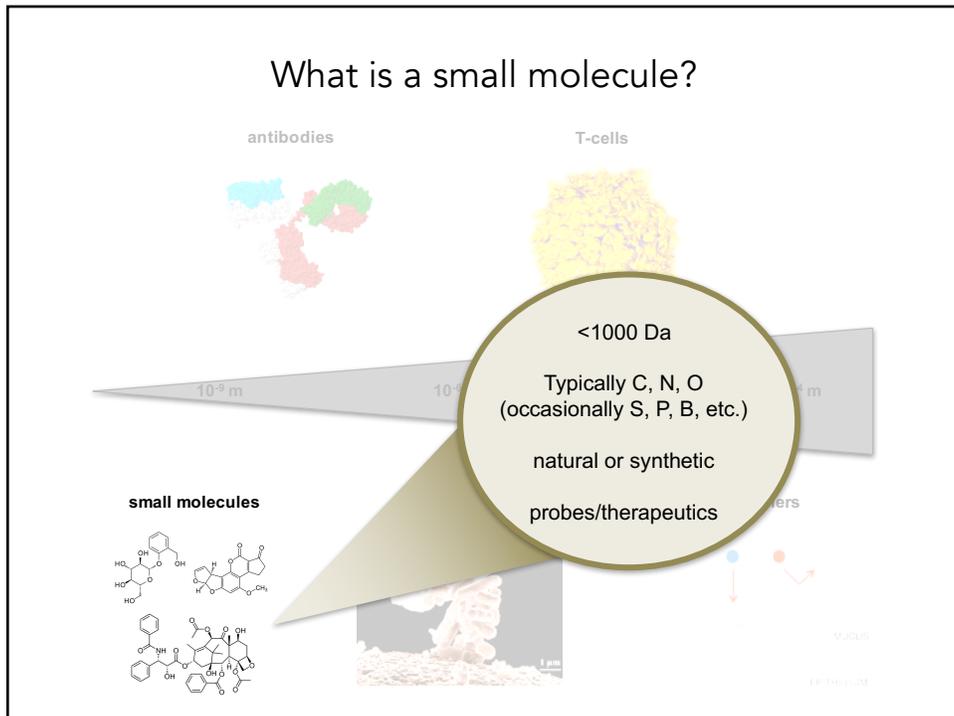
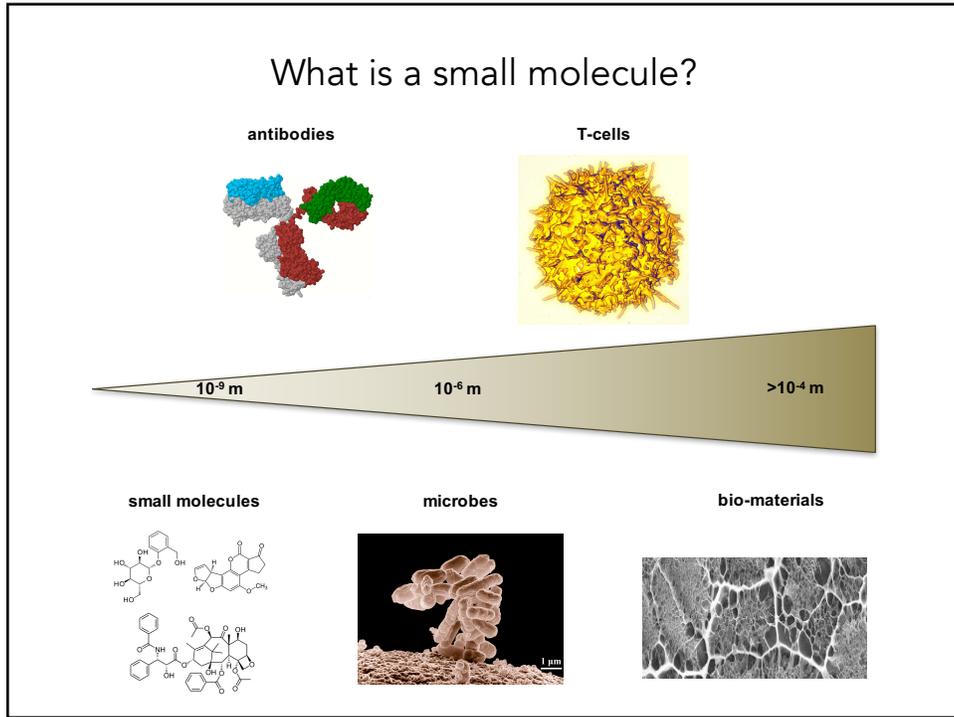
Introduction to current research at the interface of chemistry, biology, and bioengineering. Topics include [imaging of biological processes](#), [metabolic pathway engineering](#), [protein engineering](#), [mechanisms of DNA damage](#), RNA structure and function, macromolecular machines, protein misfolding 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

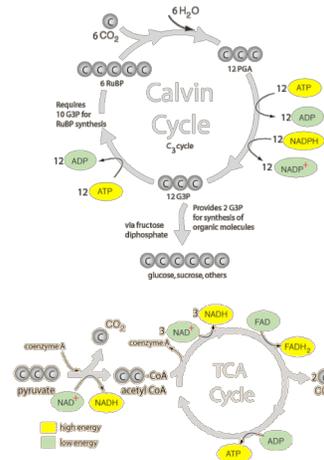
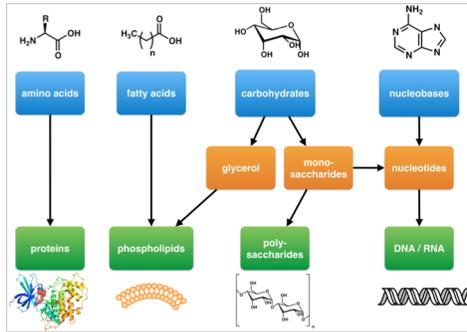
Spanning the fields of biology, chemistry and engineering, addresses the principles of chemical biology and its application of chemical and physical methods and reagents to the study and manipulation of biological systems. Topics include [activity-based protein profiling](#), [small molecule inhibitors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



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, etc.)

7.05

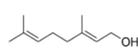
Small molecules of life

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

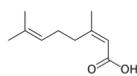
pheromones – social interactions

transporters and chelators

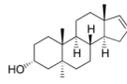
toxins – competitive weapons



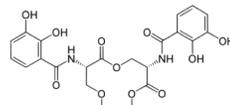
geraniol



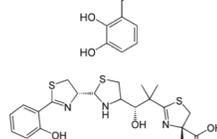
nerolic acid



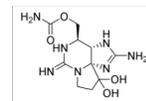
androstrenol



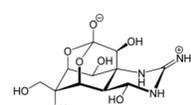
enterobactin



yersiniabactin



saxitoxin (TZ)

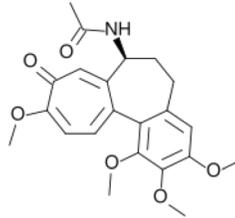


tetrodotxin (TTX)

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

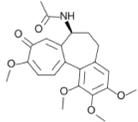
Small molecules and their partners

the compound that changed my life



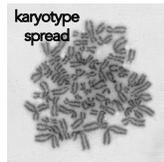
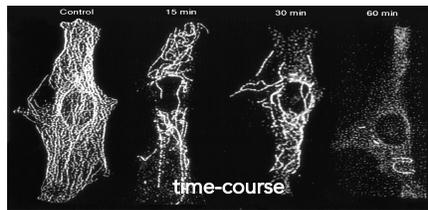
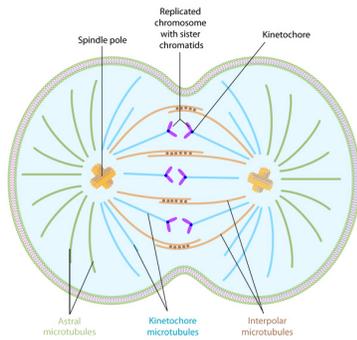
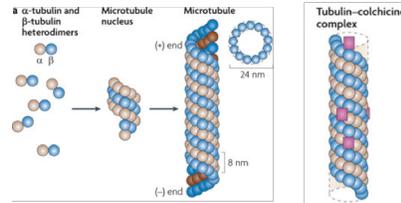
colchicine
meadow saffron

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



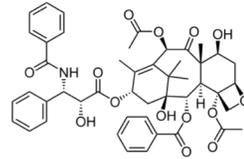
pericarditis



Behçet's disease

Egyptians -1500 BC
Ben Franklin

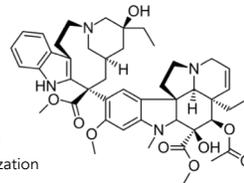
Taxol
stabilizes MTs



lung, ovarian, breast, sarcomas



Vinblastine
blocks MT polymerization



leukemia, lymphoma, breast, testicular

Chemical genomic toolkit

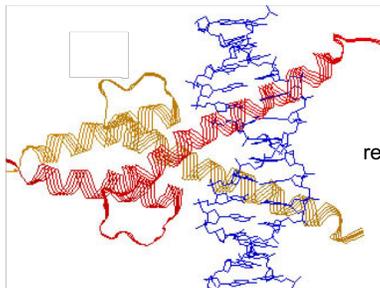
How many specific probes do we need to study the entire 'expressed genome?'

92,000 expressed proteins

1 **inhibitor** of function

1 **activator** of function

184,000 unique chemical probes?



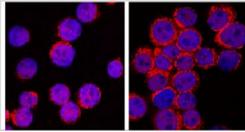
MyoD:

regulates smooth muscle differentiation
'exercise transcription factor'

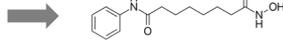
Approaches to probe discovery

'forward' chemical genetics

screen for phenotype of interest



- small molecule + small molecule



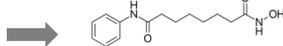
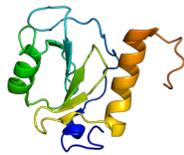
assay positive

identify protein target



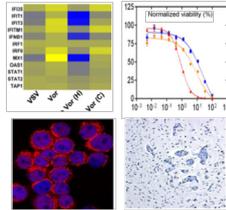
'reverse' chemical genetics
our approach for this class

directly bind target of interest

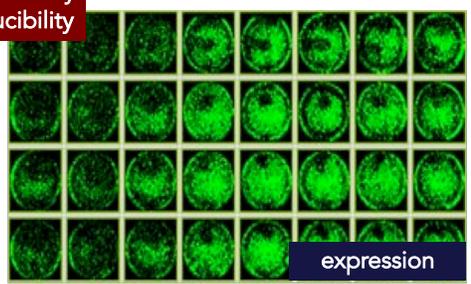
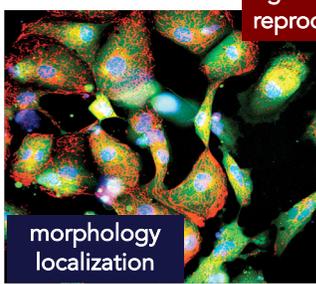


assay positive

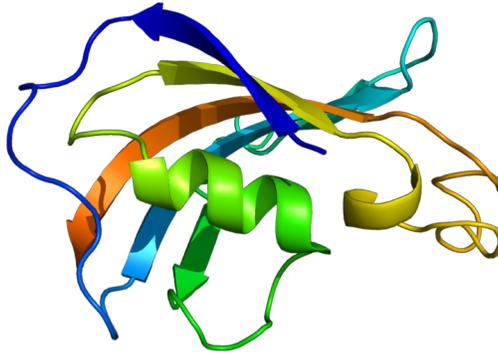
broad survey of phenotypic outcomes



High-throughput assays



Spring 2017 20.109 protein target: FKBP12



Cellular roles:

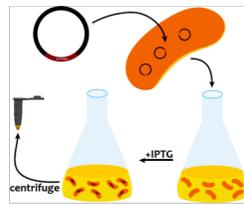
plays a role in immune regulation
regulates protein folding
regulates protein trafficking in the cell

Molecular functions:

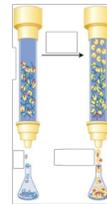
peptidyl-prolyl cis-trans isomerase
binds several other signaling proteins
target of several immunosuppressants

more details to come in our next lecture!

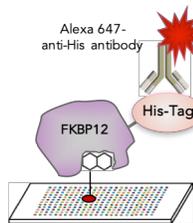
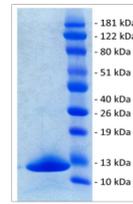
Spring 2017 Mod 1 path to probe discovery



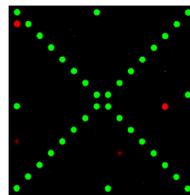
in silico cloning; overexpress FKBP12
lab days 1 & 2



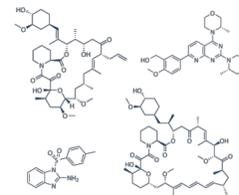
purify and analyze FKBP12 concentration
lab days 3 and 4



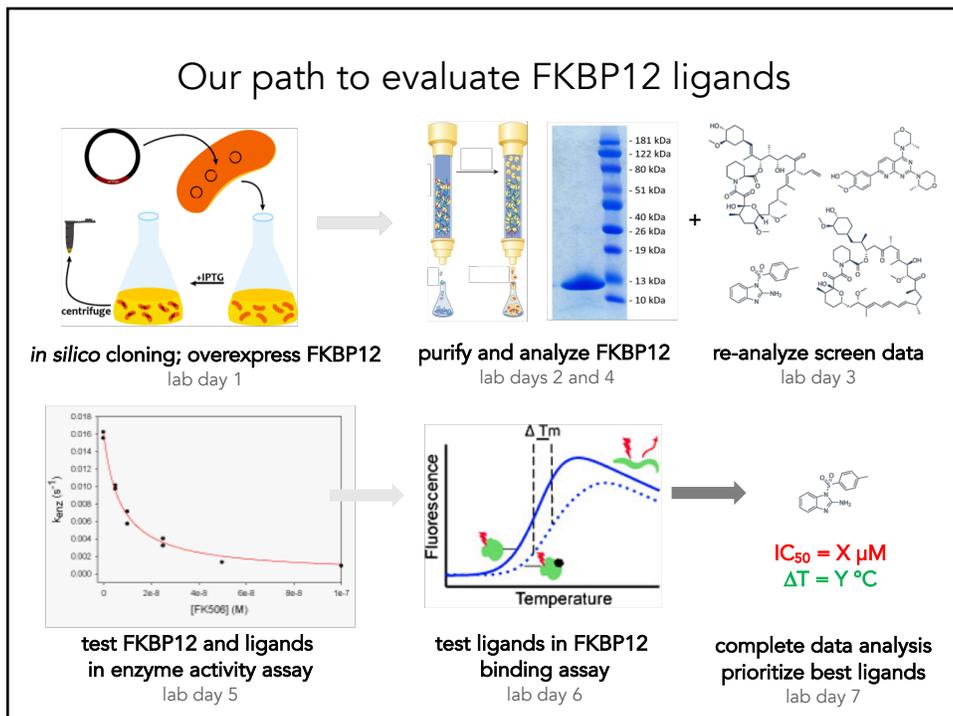
SMM screen
lab day 5



scan images and analyze data
lab days 6 and 7



compare hit lists for teams
lab day 8



Our path to evaluate ligands - lectures

2/9/19	Lecture 1	Intro to chemical biology: small molecules, probes, and screens
2/12/19	Lecture 2	Small Molecule Microarrays
2/14/19	Lecture 3	<i>For the love of proteins: FKBP12 and immunophilins</i>
2/19/19	No Lecture	
2/21/19	Lecture 4	Quantitative evaluation of protein-ligand interactions
2/26/19	Lecture 5	A ligand discovery vignette: sonic hedgehog
2/28/19	Lecture 6	Engineering transcriptional responses with a small molecule
3/5/19	Lecture 7	Wrap up discussion: suggestions for how to report your findings