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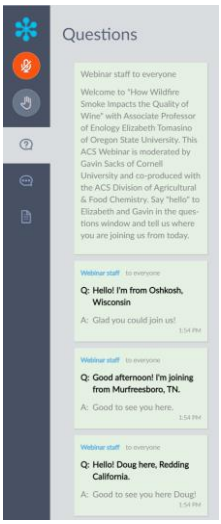

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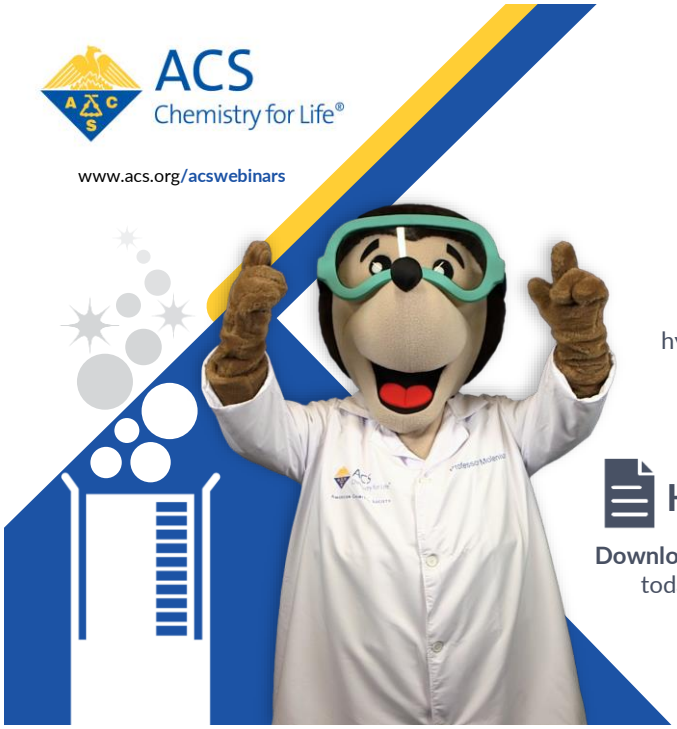

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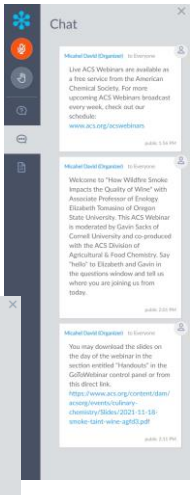

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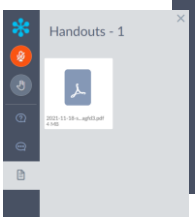

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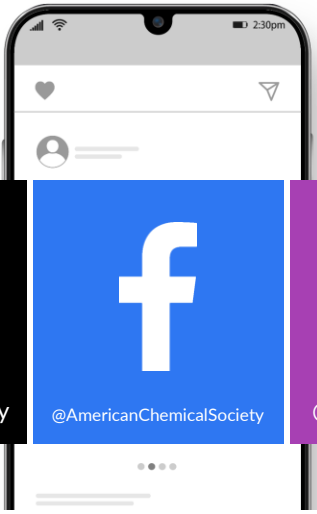

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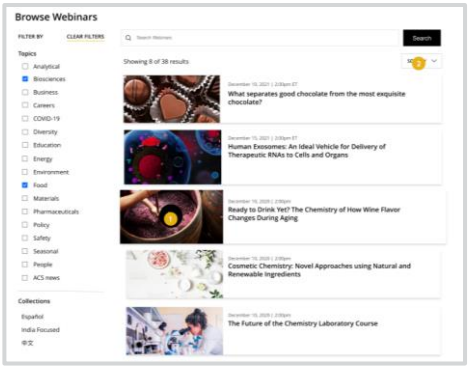

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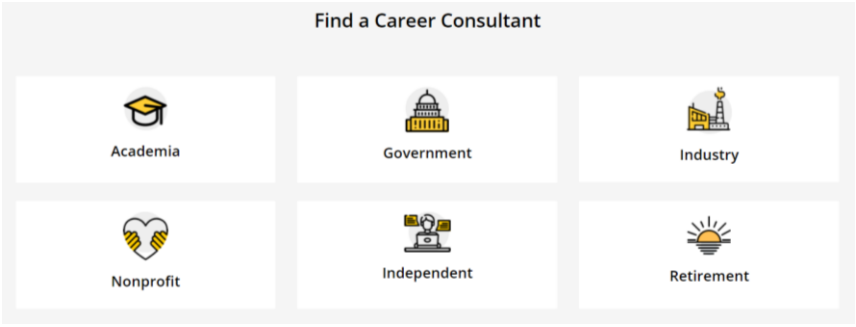

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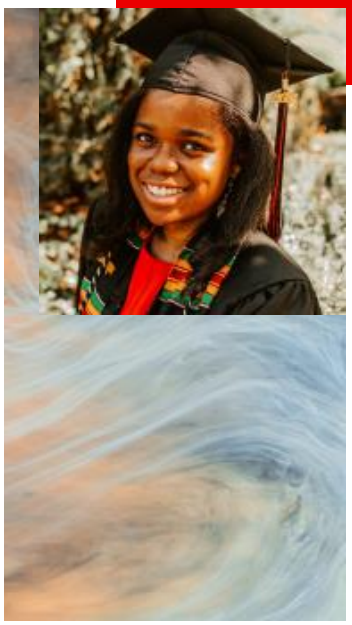

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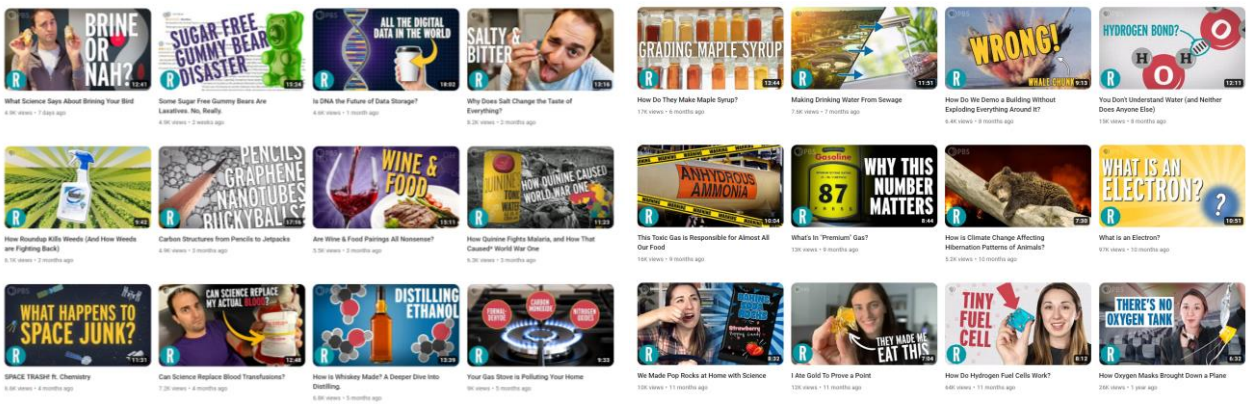

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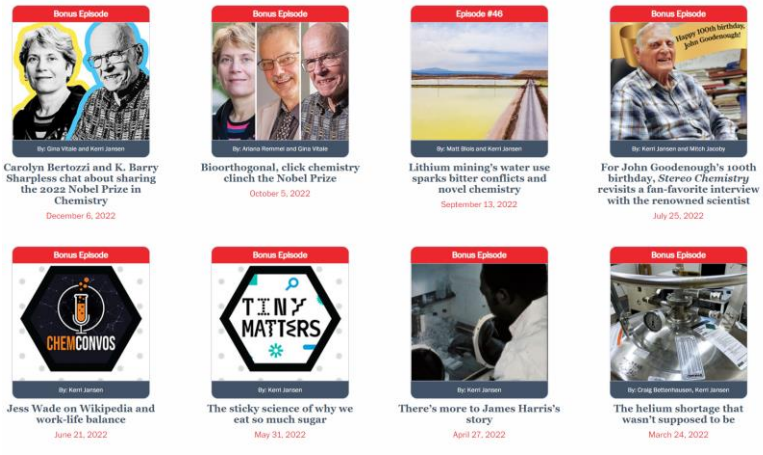

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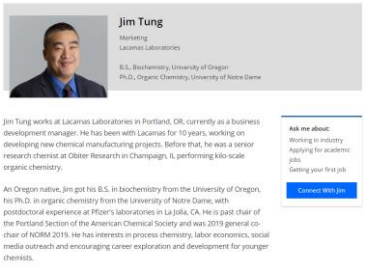

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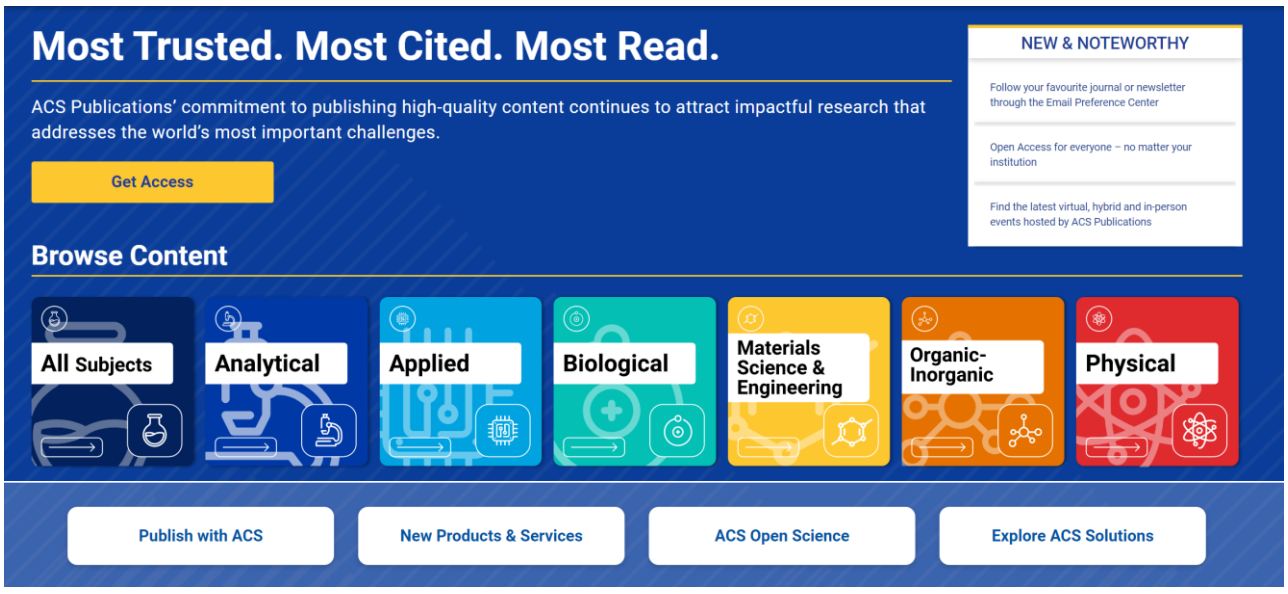

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Covering diversity and inclusion at the workplace

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Recommendations and best practices to ensure that your events can accommodate everyone.

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**Adapted from definitions from the Ford Foundation Center for Social Justice:

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Fungal Foes: Understanding the Challenges of Fungal Infections and New Treatment Options

HONGMIN LI, PhD

Professor, R. Ken and Donna Coit Endowed Chair in Drug Discovery, Department of Pharmacology and Toxicology, College of Pharmacy, University of Arizona, Tucson

SEAN EKINS, PhD, D.Sc.

CEO, Collaborations Pharmaceuticals, Inc.

REBECCA E. MOORE, PhD

Assistant Managing Editor, ACS Publications

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The Prp8 Intein as a novel Target for Inhibition of Pathogenic Fungi

Hongmin Li
Professor, R. Ken and Donna Coit Endowed Chair in Drug Discovery
Department of Pharmacology and Toxicology
College of Pharmacy

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- Background
- High throughput screening assay
- Inhibition of the prp8 intein by cisplatin
- Inhibition of *C. neoformans* by Prp8-inhibitors

Li et al. (2019), Emerging microbes & infections, 8(1): 895–908
Green et al (2019), Plos Biol, /doi.org/10.1371/journal.pbio.3000104
Li et al. (2021), PNAS, **118** (2), e2008815118
Anil et al. (2022), ACS Infect Dis, 8, 1851-68

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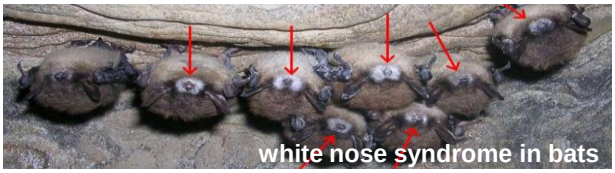
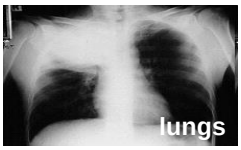
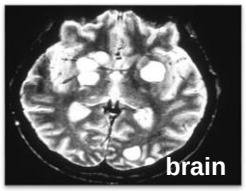
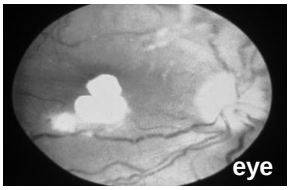


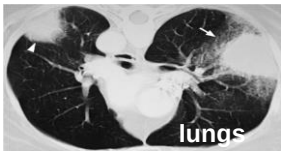
Fungal Infections

Cryptococcus









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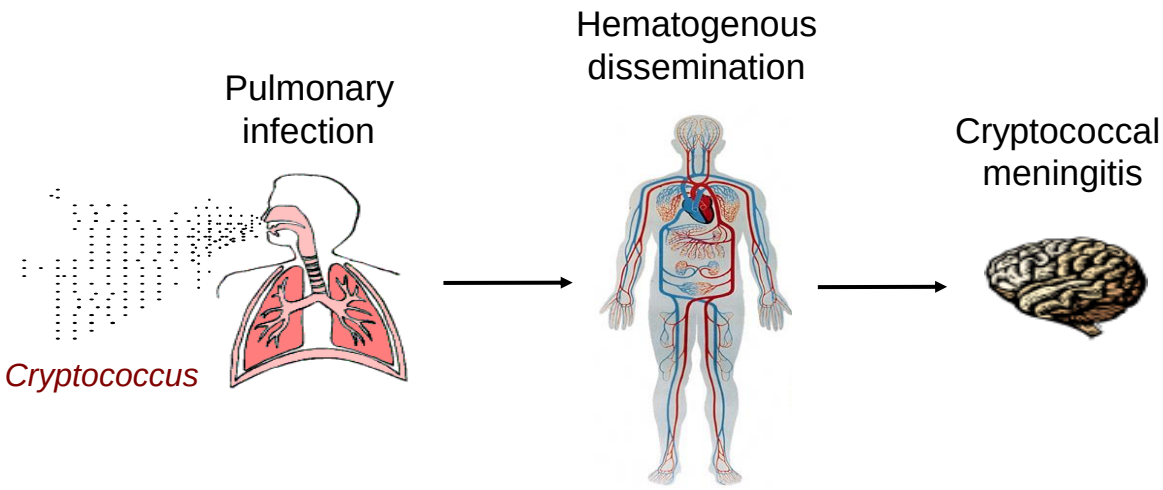
Cryptococcus infection



Lin and Heitman, *Ann Rev Microbiol* 2006, 60, 69-105

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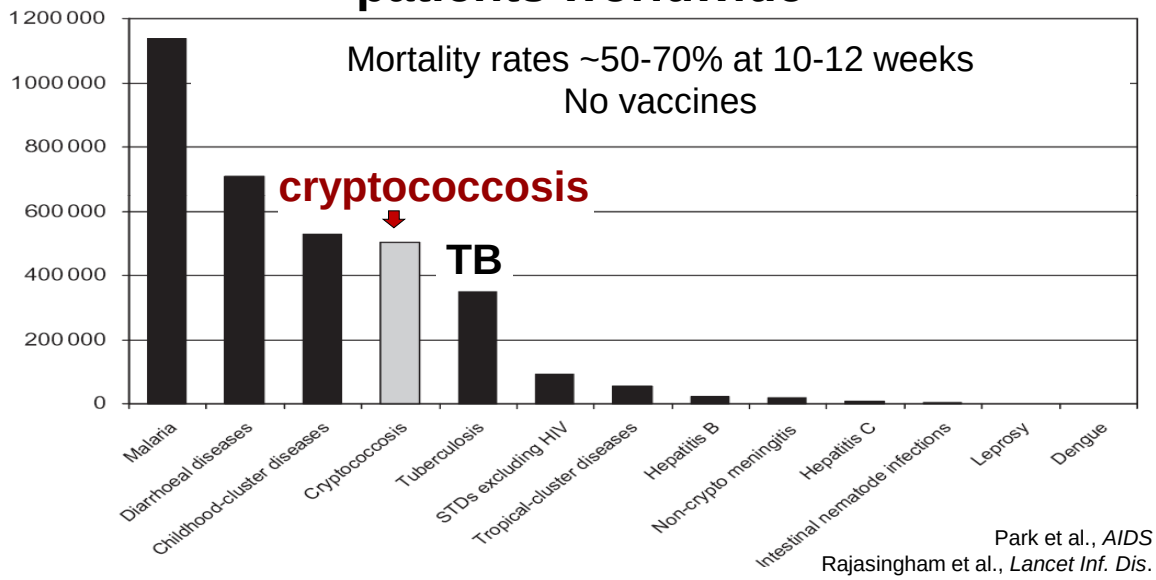
Cryptococcosis causes 15% of deaths in AIDS patients worldwide



Park et al., *AIDS* 2009
Rajasingham et al., *Lancet Inf. Dis*. 2017

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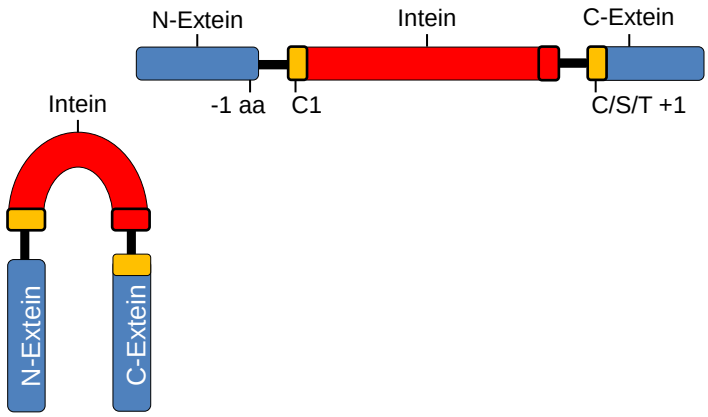
March 13, 2024 30

Microbial inteins as drug target

Intein is a mobile self-splicing element within a host protein similar to an intron between exons



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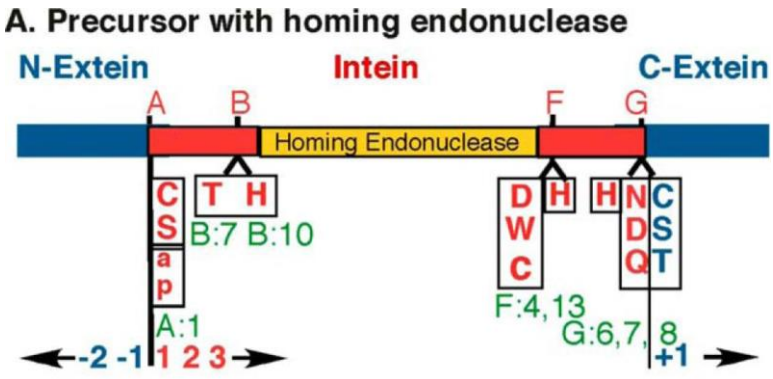
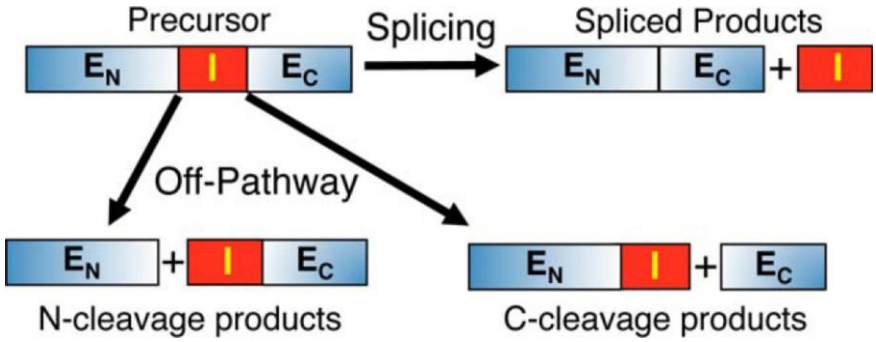


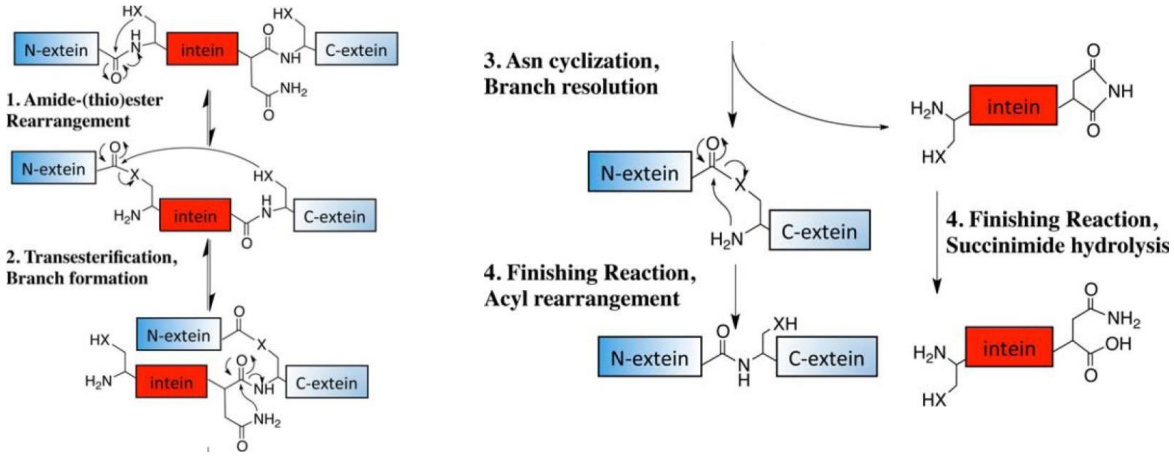
Mills et al (2014) JBC, *289, 14498-14505*

Potential intein reactions



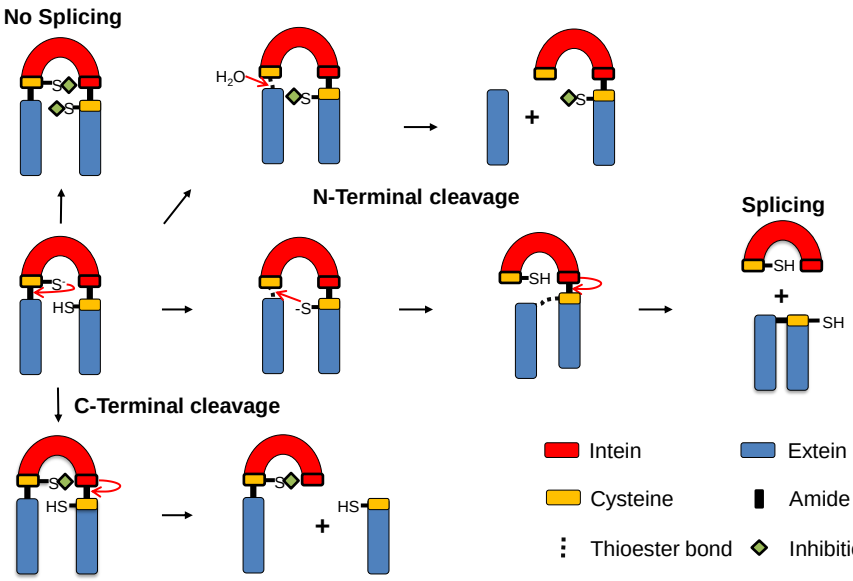
Mills et al (2014) JBC

Class I intein splicing mechanism

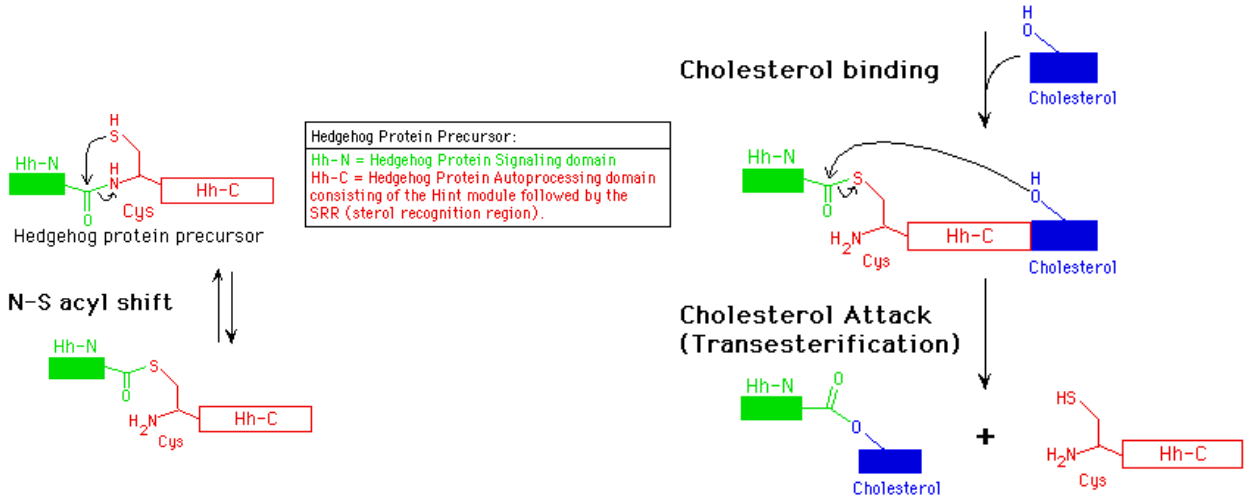


Mills et al (2014) JBC

Splicing mechanism and inhibition



Hedgehog protein autoprocessing mechanism



http://www.biocenter.helsinki.fi/bi/iwai/InBase/tools.neb.com/inbase/mech.html

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Pathogenic fungi contain the prp8 intein

- **Example Prp8 intein-containing pathogenic fungi:**
  - *Cryptococcus neoformans and C. gattii* - *Trichophyton rubrum*
  - *Aspergillus fumigatus* - *Blastomyces dermatitidis*
  - *Histoplasma capsulatum* - *Microsporum gypseum*
  - *Paracoccidioides brasiliensis* - *Trichosporon asahii*
  - *Neosartorya fischeri* - *Exophiala oligosperma*
  - *Microsporum canis* - *Fonsecaea pedrosoi*
  - *Botrytis cinerea* - *Rhinocladiella mackenziei*
  - *Emmonsia parva (formerly Chrysosporium parvum)*

- **Genes of human beings do not contain intein elements !**

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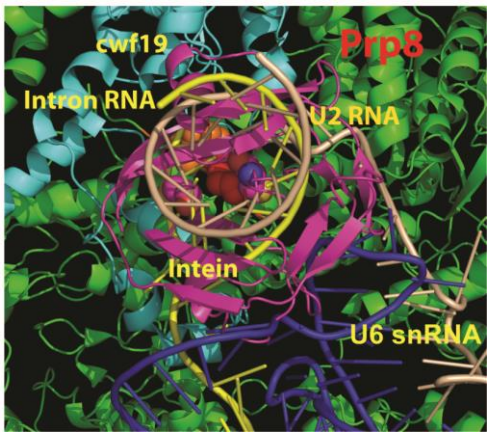
Prp8 is a critical component of the spliceosome

A
```
Cga Prp8    WEKAC...intein...HNSGFE
Cne Prp8    WEKAC...intein...HNSGFE
Afu Prp8    WERAC...intein...HNSGFE
Spo Prp8    WEKA---------------SGFE
```

B



Schizosaccharomyces pombe (*Spo*)

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Cis-Pt is specific for intein prp8-containing Cryptococcus fungi

Table 1. Inhibition of pathogenic fungi by cisplatin. (MIC_{50} and MIC_{80} were defined as minimum inhibitory concentration required to kill fungus at 50% and 80% in μg/ml, respectively)

	Prp8 intein ?	Strain	Group	MIC_{50}	MIC_{80}
C. neoformans	*Yes*	NIH H99	VN I	0.92	2.6
		WM148	VN I	2.0	8.0
		WM626	VN II	1.4	7.9
C. gattii	*Yes*	NIH444	VG IIa	1.1	2.6
		WM276	VG I	1.9	15
		CA1222	VG IIIa	1.5	3.5
		VM779	VG IV	1.5	12
Candida albicans	*No*	ATCC90028		25	100

Photo courtesy of Dr. Lesley McGee, CDC

Li et al (2019) Emerging Microbes and Infection, 8(1): 895–908

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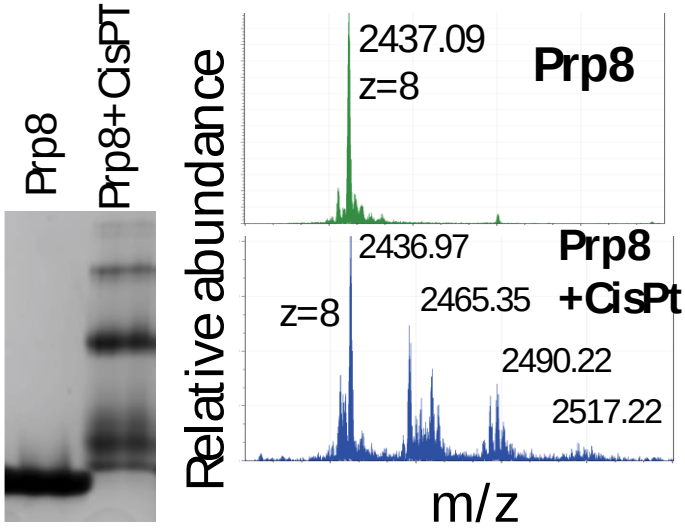
Binding of CisPt to the Prp8 intein



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Li et al (2019) Emerging Microbes and Infection

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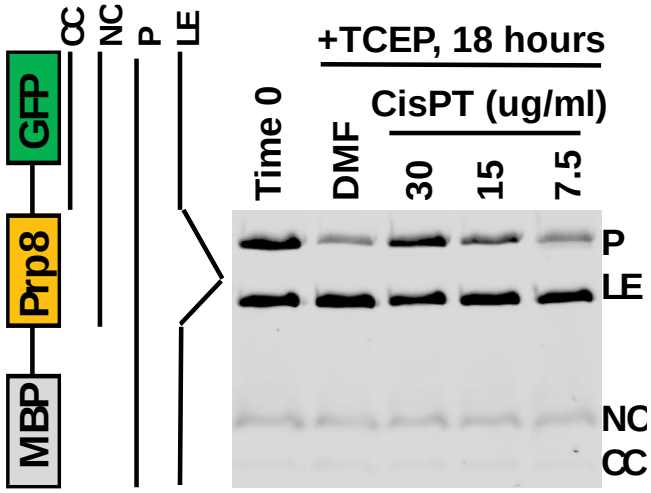
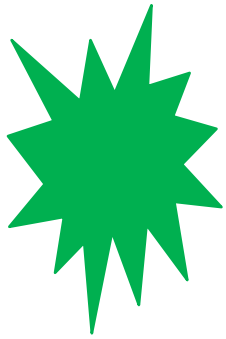
Inhibition of in vitro splicing of the Prp8 intein by CisPt





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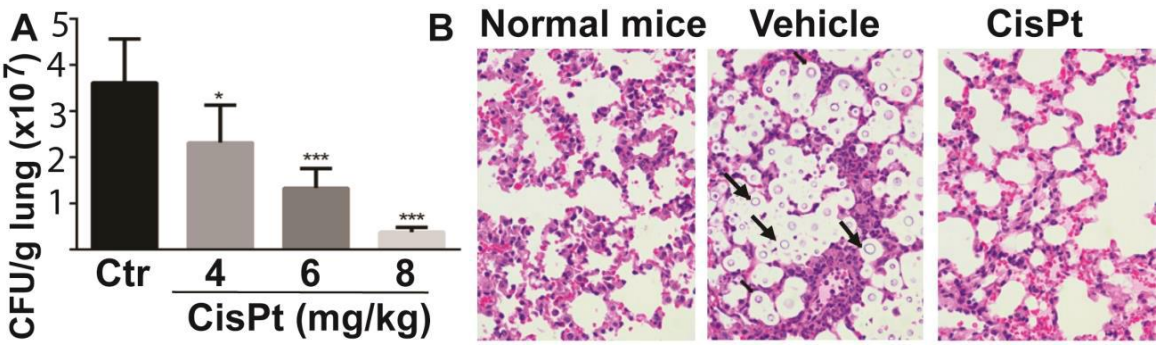
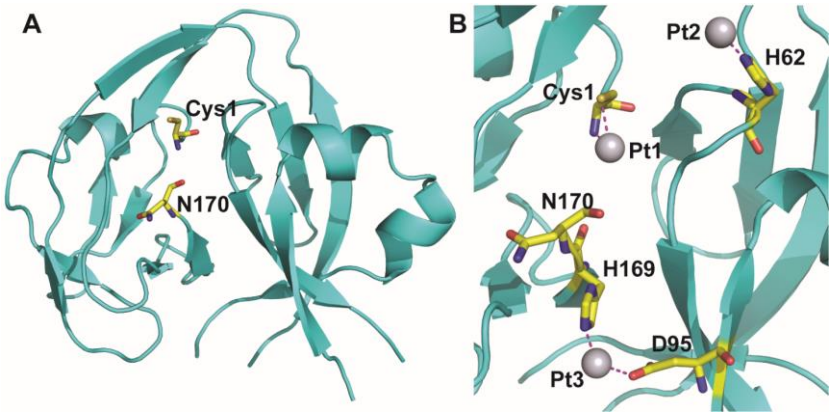
In vivo efficacy of CisPt in mouse model



Li et al (2019) Emerging Microbes and Infection

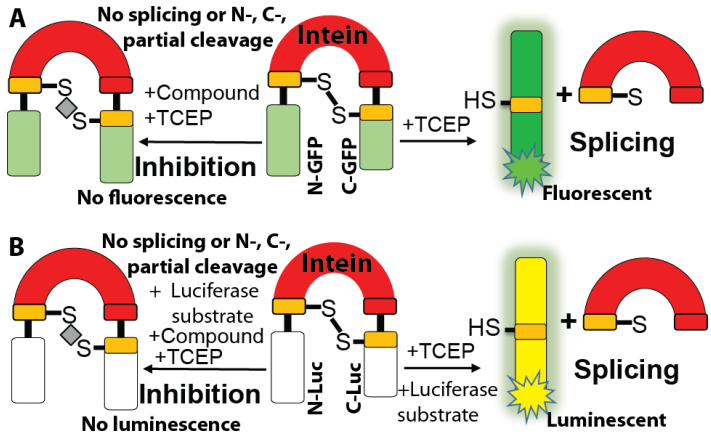
Cga Prp8-Cisplatin complex



Apo Complex

Li et al (2019) Emerging Microbes and Infection

Development of split luciferase-based or GFP-based HTS assays



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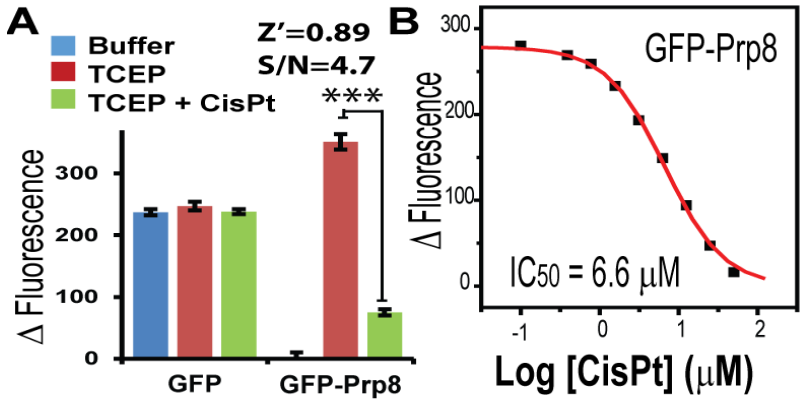
IC50 for cisplatin and HTS parameters



Li et al (2019) Emerging Microbes and Infection
Li et al (2021) PNAS, **118** (2), e2008815118

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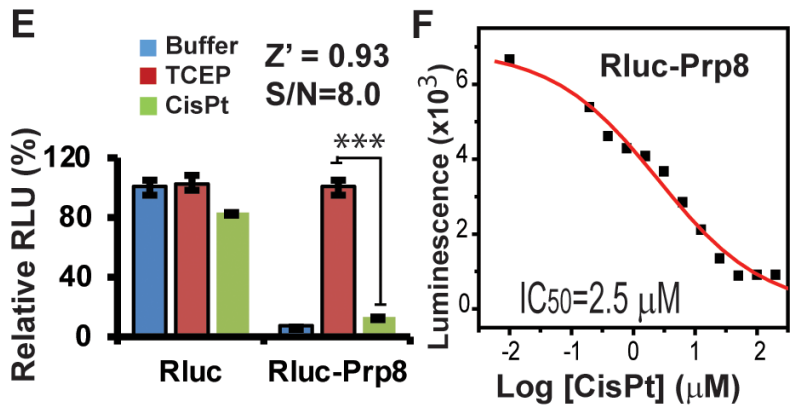
Split-Luc HTS assay



Li et al (2019) Emerging Microbes and Infection
Li et al (2021) PNAS, **118** (2), e2008815118

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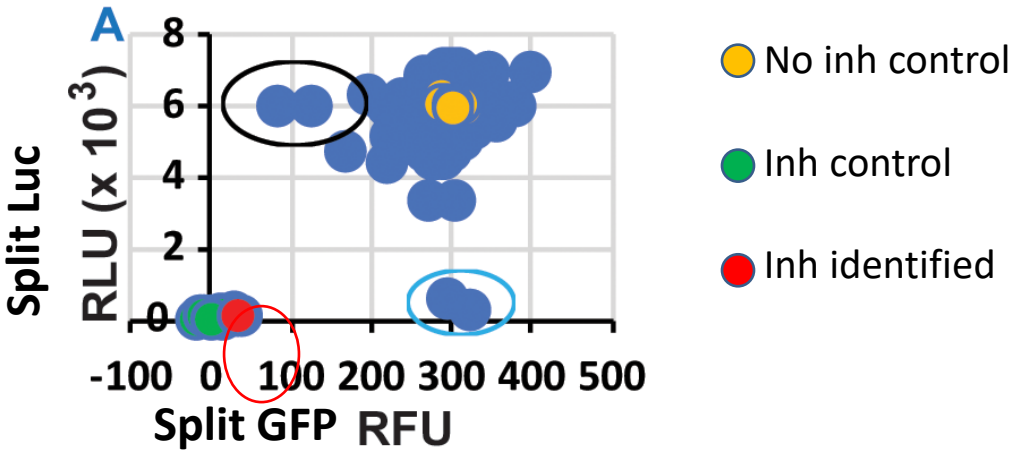
Pilot screen



Li et al (2019) Emerging Microbes and Infection
Li et al (2021) PNAS, **118** (2), e2008815118

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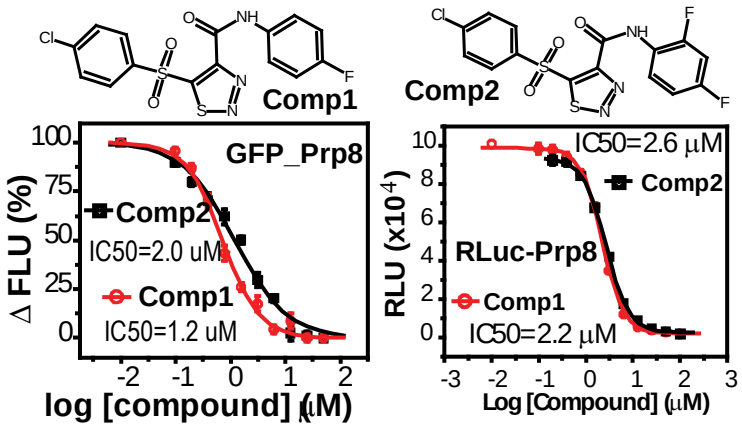
Inhibition of prp8 intein splicing by small molecule inhibitor



Li et al (2021) PNAS, **118** (2), e2008815118

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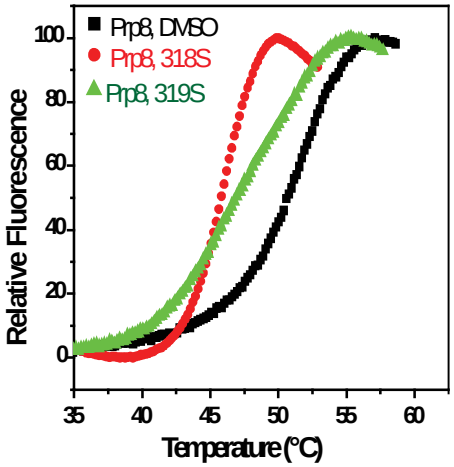
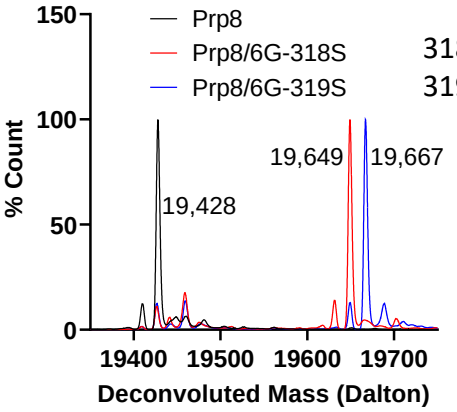
Binding of small molecule to the prp8 intein



Protein thermal shift assay



LC-MS/MS

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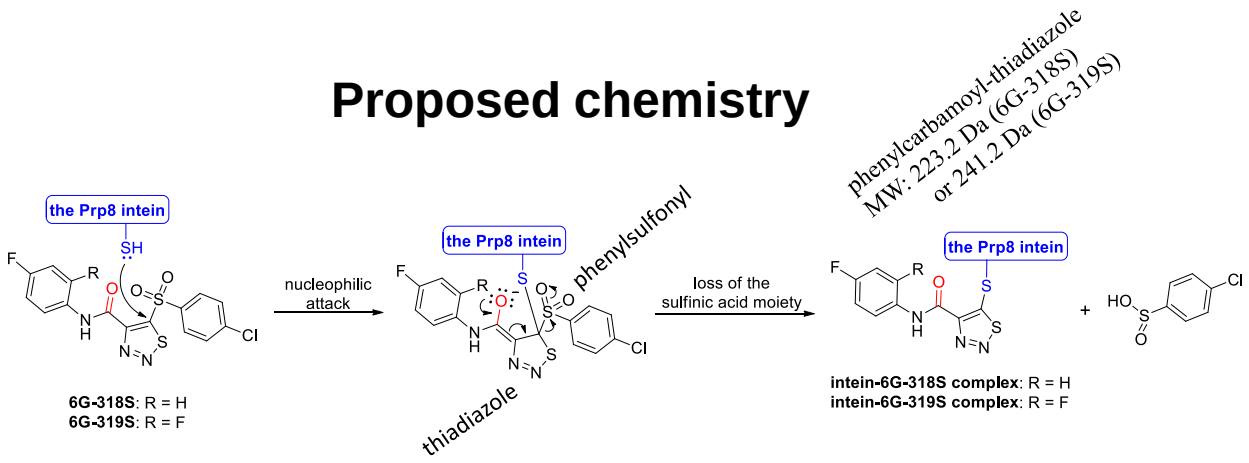
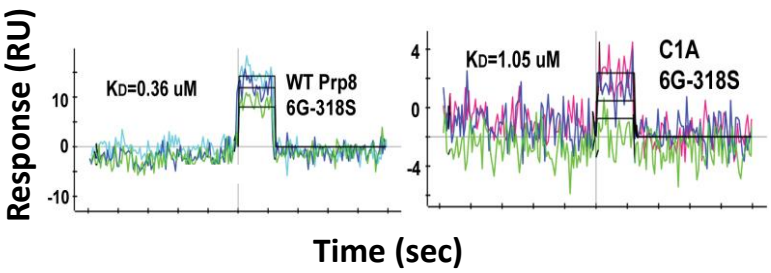
Proposed chemistry

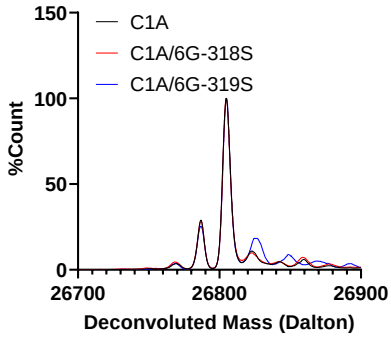


Li et al (2021) PNAS, **118** (2), e2008815118

49

C1A mutation led to loss of binding of 6G-318S to the Prp8 intein



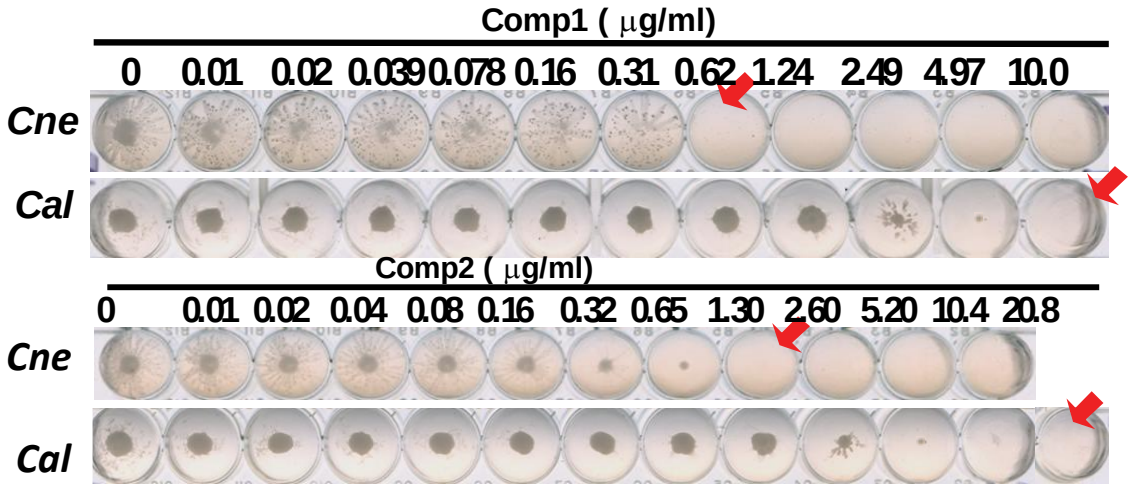


Suraface plasmon resonance binding studies

Li et al (2021) PNAS, **118** (2), e2008815118

50

Inhibition of Prp8 intein-containing Cne but not *Candida albicans* (Cal) (no intein)



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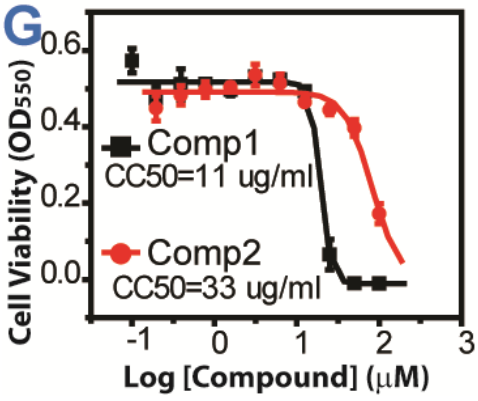
Cell viability on A549 lung carcinoma cell



Li et al (2021) PNAS, **118** (2), e2008815118

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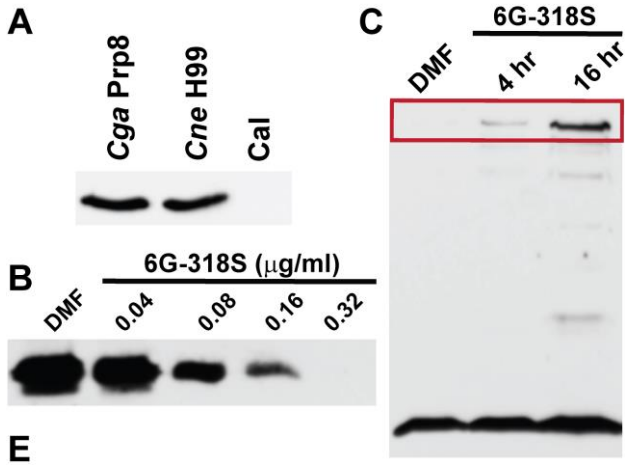
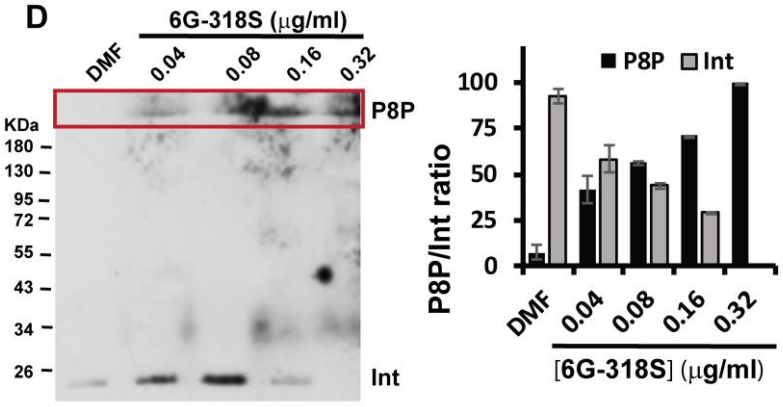
Inhibition of the Prp8 intein splicing *in vivo* by 6G-318S



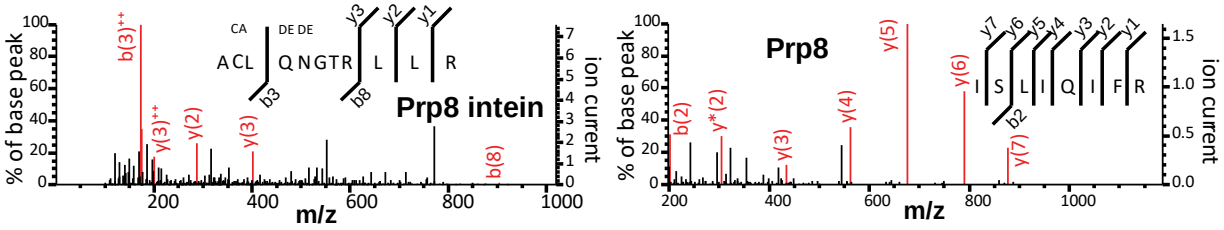
Li et al (2021) PNAS, **118** (2), e2008815118

Dose-dependent inhibition of the Prp8 intein splicing *in vivo* by 6G-318S



Li et al (2021) PNAS, **118** (2), e2008815118

Identification of the Prp8 precursor by Mass Spectrometry



Li et al (2021) PNAS, **118** (2), e2008815118

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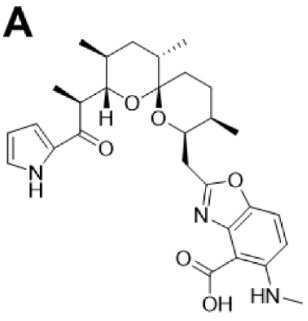
Calcimycin (CMN) specifically inhibits intein-containing but not intein-free C. neoformans

A



Calcimycin (CMN)

Species-Strain	MIC µM (µg/ml)
C. neoforman (Cneo-WT)	3.0 (1.5)
C. neoforman (Cneo-Mut)	>24 (12.0)
C. gatti	3.0 (1.5)
C. amylolentus	>50
A.funigatus	>25

Anil et al. (2022), ACS Infect Dis, 8, 1851-68

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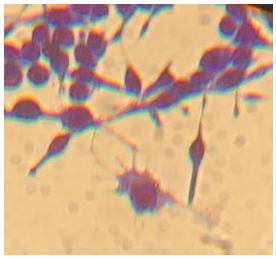
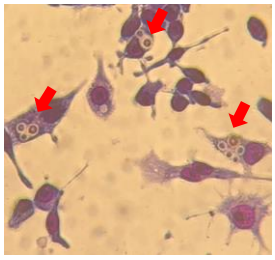
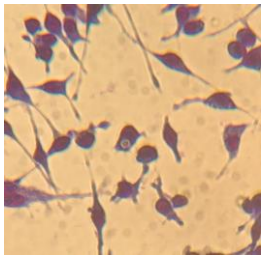
CMN reduces macrophage intracellular infection of C. neoformans



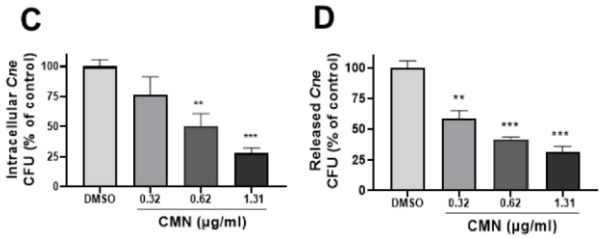
Uninfected-DMSO



Infected-DMSO



Infected-CMN- 0.419 ug/ml



Anil et al. (2022), ACS Infect Dis, 8, 1851-68

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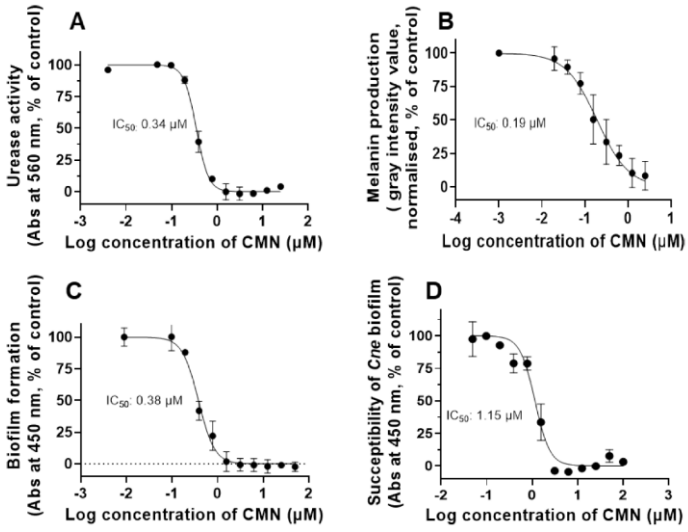
CMN reduces Cne virulent factors



Anil et al. (2022), ACS Infect Dis, 8, 1851-68

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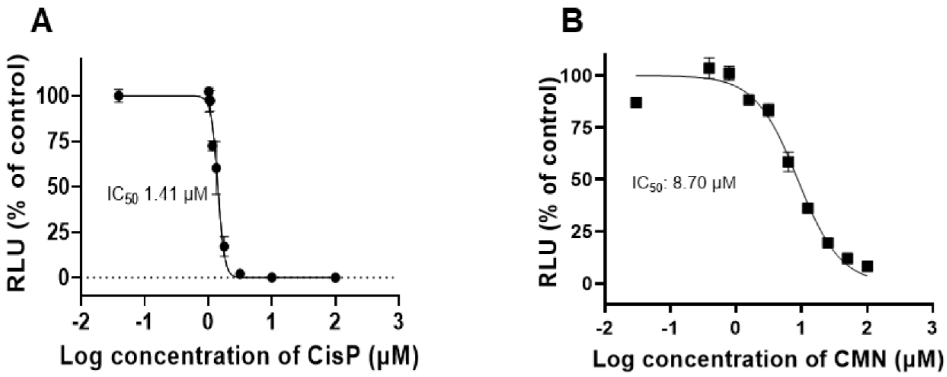
CMN reduces the Prp8 intein splicing



Anil et al. (2022), ACS Infect Dis, 8, 1851-68

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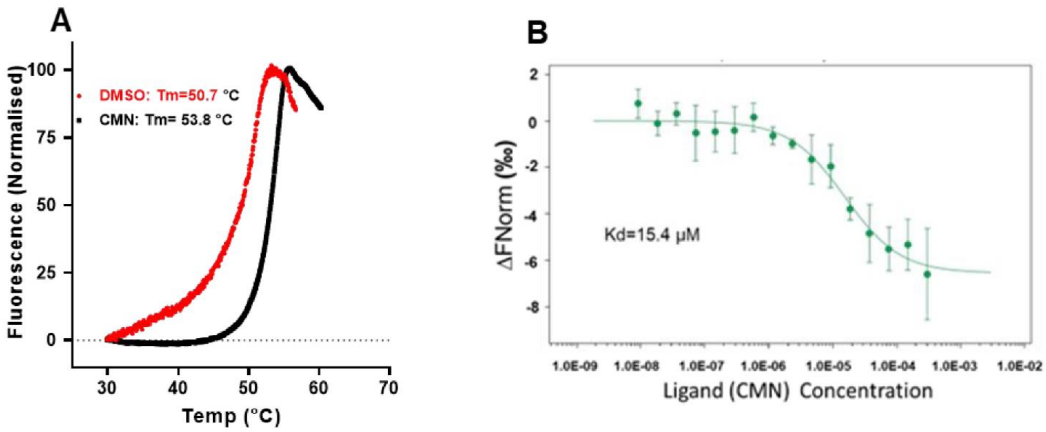
CMN directly binds the Prp8 intein



Anil et al. (2022), ACS Infect Dis, 8, 1851-68

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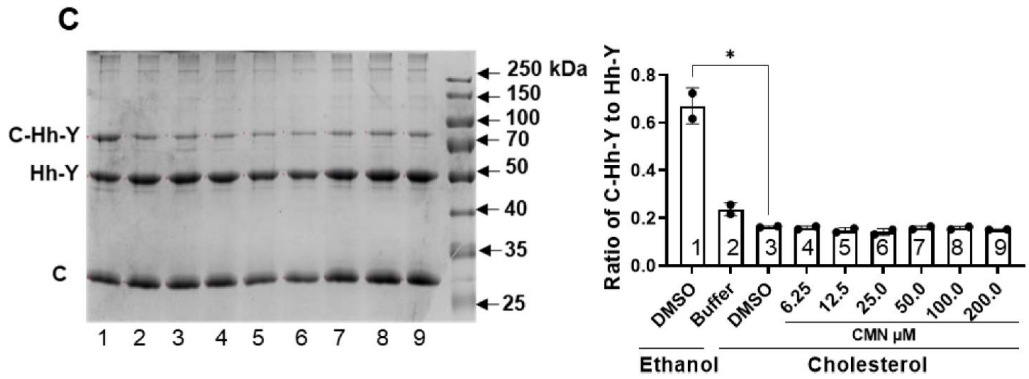
CMN does not interfere hedgehog cholysterolysis



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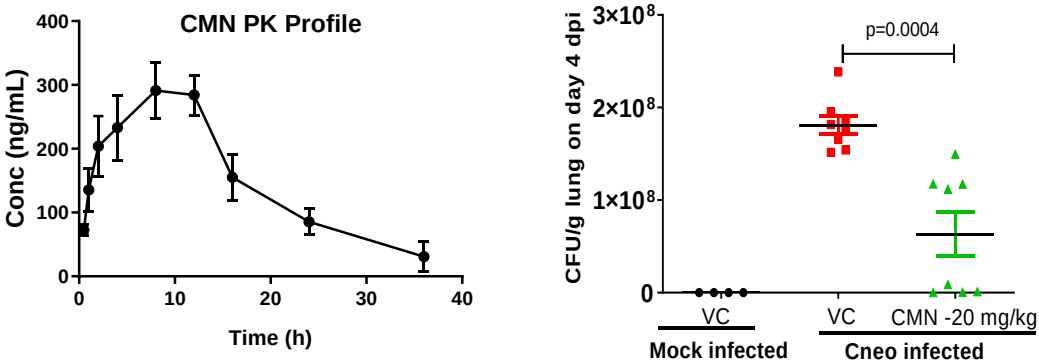
CMN treatment reduces fungal burden in the lung in mouse model



Anil et al. (2022), ACS Infect Dis, 8, 1851-68

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Acknowledgement

- Li's lab
  - Zhong Li
  - Jing Zhang
  - Fengshan Gao
  - Anil Tharappel

Marlene Belfort's lab
Cathleen Green
Hon Chan
Seth Pearson

- Qing-Yu Zhang's lab
  Xiangmeng Wu

Jia Zhou, UTMB
Jimin Xu

- Sudha Chaturvedi (Wadsworth Center)

Guojian Liao, Southwest University China
Bin Fu

Funding from NIH R01 AI140726 & R21 AI141178, R Ken & Donna Coit endowed chair fund, and COP start-up fund

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Drug discovery for *Cryptococcus neoformans* and *Cryptococcus gattii*

Sean Ekins Ph.D., D.Sc.
CEO
Collaborations Pharmaceuticals, Inc.
Raleigh, NC, USA

sean@collaborationspharma.com

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Collaborations Pharmaceuticals, Inc.

Founded in 2015

Pre-clinical stage company

Develops software for drug discovery and consumer product applications

>20 grants funded (~$21.3M) since 2016

Private company

3 Labs ~2,000 sqft incubator space at NC State University

9 orphan drug designations for rare & neglected diseases

3 pediatric rare disease designations

1 patent issued, multiple patents filed, 7 trademarks

>150 publications

Our work has been highlighted by:

The Economist · FINANCIAL TIMES · The Washington Post · NETFLIX · SCIENTIFIC AMERICAN · WIRED

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OUR MISSION

Transforming Chemistry, Enriching Lives

We use real intelligence alongside artificial intelligence to develop clinical candidates for rare, neglected and unmet therapeutic needs, as well as new molecules for consumer product applications.

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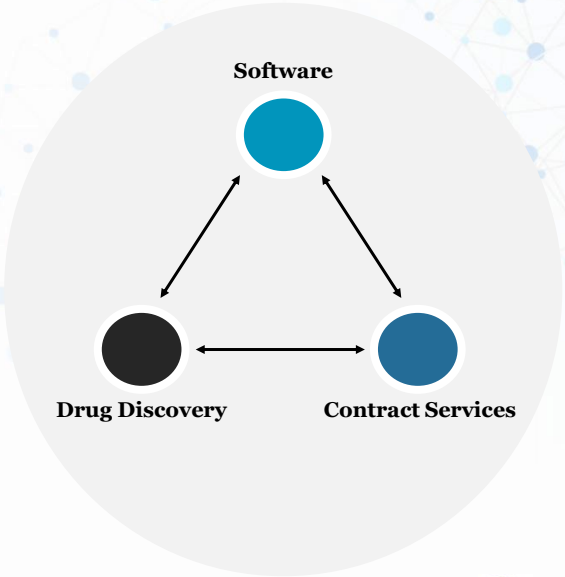
Company overview

- **We are a molecule discovery company**
  - We use *artificial intelligence* to develop molecules for consumer product and therapeutic needs. e.g. molecule design, sustainable chemistry, toxicology applications
- **We are a software company**
  - We license our internally-developed suite of machine learning tools allowing for the generative design and evaluation of molecules and the building/validation of brand new models.
- **We are a contract services organization**
  - Using our machine learning tools, we bring our AI expertise to your enterprise. We do the work, you keep your data.



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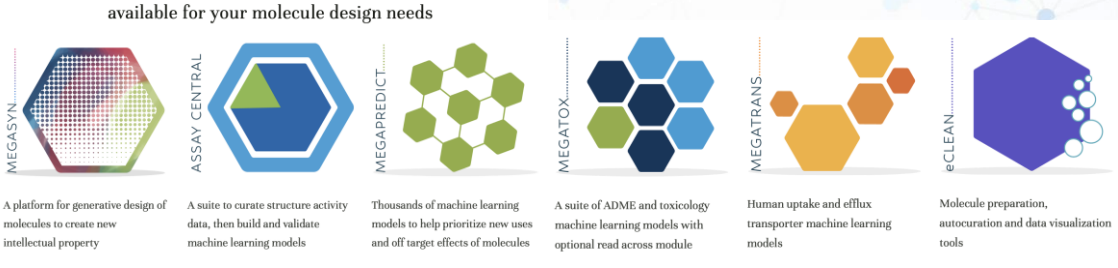
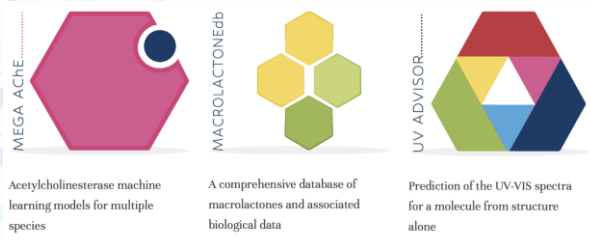
Company Developed Software Tools

Our suite of machine learning and generative design tools is available for your molecule design needs





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Company Pipeline

Assets available for licensing, partnering, spin outs.

Category	Disease	Target(s)	Preclinical in vitro	Preclinical in vivo	Pre-IND	Clinical	Rare Disease Designation	Orphan Designation	NIH/DOD Funding	Machine Learning	Patent Filing
Viruses	Ebola virus disease	Entry / Glycoprotein						* * *	*	*	*
	HIV-1	NNRTI, CCR5							*	*	*
	Enteroviruses	Capsid							*		*
	COVID-19	PI**, Lysosome, Kinases (CAMK1, MELK)								*	*
	Hepatitis B disease	?								*	
	Nipah virus disease	?									*
	Yellow Fever	?								*	*
	Chikungunya	?								*	
	Marburgvirus disease	?								*	*
	H1N1	Neuraminidase								*	
Rare Diseases	Malaria	Hemozoin Formation						*		*	
	Chagas Disease	?					*	* *	*	*	
	S. aureus	?								*	
	C. neoformans/gattii	?								*	*
	Tuberculosis	Various							*	*	*
	M. abscessus	?								*	*
	Neisseria gonorrhoeae	?								*	
	Batten CLN1 (chaperone)	PPT1							*	*	*
	Sialidosis	Sialidase-1								*	
	Batten CLN1 (ERT)	PPT1					*	*	*		
	Pitt Hopkins Syndrome	Nav1.8					*	*		*	*
Cancer	Multiple Cancers	FLT3, KIT, LRRK2, CLK2									
	Neuroblastoma	?								*	
	Chordoma	?						*		*	
Various	Alzheimer's Disease	AChE, BChE, GSK3β							*	*	*
	Psychoplastogens	$5HT_{2A}$							*	*	
	Countermeasures	AChE							*	*	
	Stroke	CCR4								*	*

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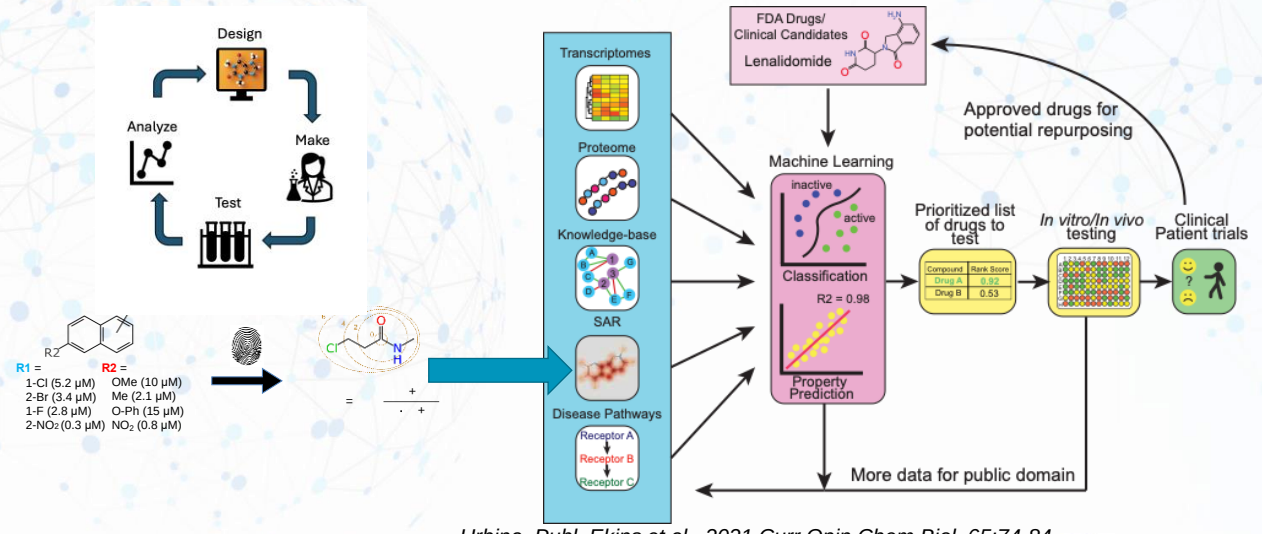
Finding new molecules or repurposing using machine learning



Urbina, Puhl, Ekins et al., 2021 Curr Opin Chem Biol, 65:74-84

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Audience Survey Question

ANSWER THE QUESTION ON THE INTERACTIVE SCREEN IN ONE MOMENT

What is considered true about Cryptococcus neoformans?

(Select all that apply)

- Identified in the 1860s
- 3rd Leading cause of infections in solid organ transplant
- Currently not treatable
- None of the above

* If your answer differs greatly from the choices above **tell us in the chat!**

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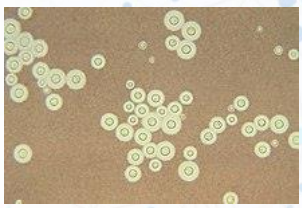
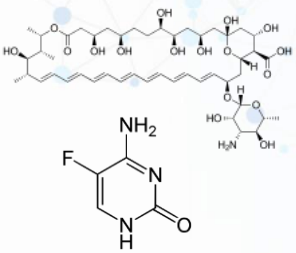
Cryptococcus neoformans

- Identified in the 1960s
- 3rd leading cause of infections in solid organ transplant
- 3% develop in the 1st yr and mortality = 25-40%
- Remain susceptible for 5 yrs





- It is treatable with Amphotericin B (binds ergosterol) and Flucytosine (pyrimidine biosynthesis)
- Treatment is long and toxic
- Mortality 15-30% in those with HIV
- Sub-Saharan Africa: cryptococcal meningitis prevalence is 25-45%

Donlin et al., ACS Med. Chem. Lett. 2021, 12, 774−781

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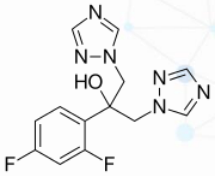
Cryptococcus gattii

- Lives in soil and trees
- Affects lungs and nervous system
- Infects immunocompetent
- Endemic in tropical areas
- Antifungals are insufficient to cure it
- No new antifungals approved since 2003
- Need to be safe and effective
- Fluconazole is only fungi static – potential for relapse
- Newest class of molecules is echinocandins but they are not active against cryptococcus
- VT-1129 CYP51 inhibitor –
- Some repurposing and clinical studies – nothing promising.



Donlin et al., ACS Med. Chem. Lett. 2021, 12, 774−781

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Our collaborators

Dr. Vadim Makarov
Federal Research Centre "Fundamentals of Biotechnology" of the Russian Academy of Sciences (Research Centre of Biotechnology RAS)

Inventor of BTZ043 and PBTZ169 for TB. He is an expert in medicinal chemistry and rational drug design with special interest in developing antimicrobial and antiviral agents.
We have worked on several TB and antiviral projects (HIV, HepB, SARS-CoV-2, YFV, HepB, EV-D68)

Dr. Maureen Donlin
Saint Louis University School of Medicine

Studies the cell wall integrity signaling pathway in the human fungal pathogen Cryptococcus neoformans. Works on identification of small molecule antifungals.

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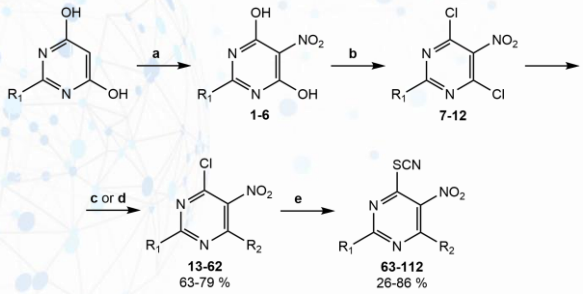
General synthetic scheme of 5-nitro-6-thiocyanatopyrimidines

- Reagents and conditions: a) HNO_3, H_2SO_{4cat}; b) $POCl_3$, Et_3N, HCl; c) corresponding amine solution, AcOH, dioxane or d) corresponding sodium alkoxide, alcohol; e) KSCN, alcohol



Donlin et al., ACS Med. Chem. Lett. 2021, 12, 774−781

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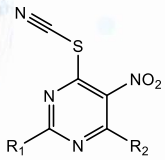
C. Neoformans & C. gattii

- Collaborated with Dr. Maureen J. Donlin, Saint Louis University School of Medicine
- Initially screened 121 compounds – Whole cell phenotypic assay
- Measured MIC_{80} against C. neoformans strain KN99
- 17 of the 121 compounds had MIC_{80} < 50 μM
- 5-nitro-6-thiocyanatopyrimidines were the most interesting
- Performed SAR

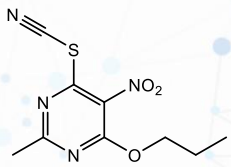
Core selection



MIC_{80}s (*C. neoformans* KN99) ~ 12.5-50 μM

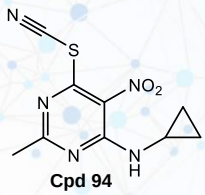
Predicting with a machine learning model and *in vitro* testing

Hit 4-thiocyano-5-nitropyrimidines



Cpd 89

MIC_{80} (*C. neoformans* KN99) ~ 0.6 μM
MIC_{80} (*C. gattii*) ~ 0.78-1.56 μM
MIC_{80} (FLC-resist. *C. neoformans*) ~ 0.78-1.56 μM



Cpd 94

MIC_{80} (*C. neoformans* KN99) ~ 0.6 μM
MIC_{80} (*C. gattii*) ~ 0.39-0.78 μM
MIC_{80} (FLC-resist. *C. neoformans*) ~ 0.78-1.56 μM

Donlin et al., ACS Med. Chem. Lett. 2021, 12, 774−781

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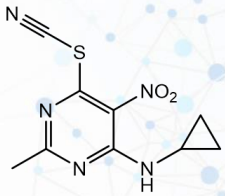
Checkerboard assay and ADME properties

- Cpd 94 tested with Amphoteracin B and flucytosine
- FICIs 1.25 and 1.5
- Indifference, but not antagonistic
- **Poor metabolic stability**



Hit compound – Cpd 94

MIC_{80} (*C. neoformans* KD99) ~ 0.6 µM
MIC_{80} (*C. gattii*) ~ 0.39-0.78 µM
MIC_{80} (FLC-resist. *C. neoformans*) ~ 0.78-1.56 µM

In vitro ADME properties for compound 94	
Solubility	< 0.2 µM pH 7.4
CYP inhibition	1A2 (4.78µM), 2C9 (40.2µM), 2C19 (50µM), 3A4 & 2D6 (>50µM)
Mouse liver microsomes	$t_{1/2}$ <5 min, CL_{int} 277.3 µL/min/mg protein
Human liver microsomes	$t_{1/2}$ <5 min, CL_{int} 277.3 µL/min/mg protein

Donlin et al., ACS Med. Chem. Lett. 2021, 12, 774−781

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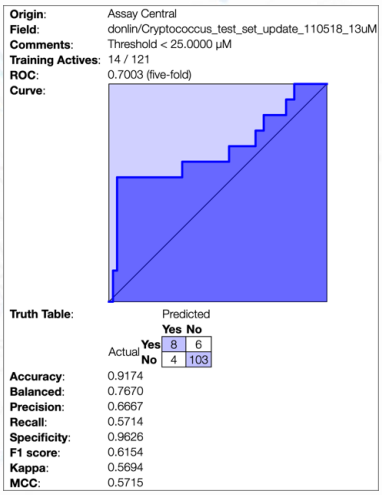
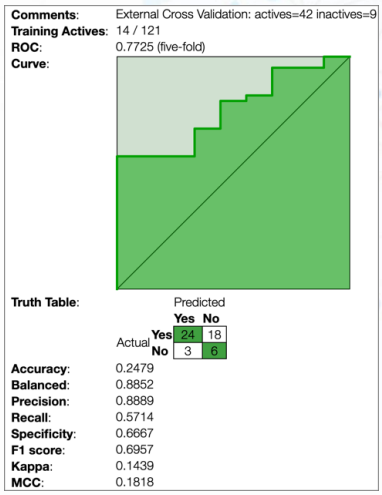
Machine learning

- Early version of Assay Central was used
- Bayesian algorithm with ECFP6 fingerprints
- N= 121 cpds – active threshold MIC_{80} 12.5-25uM
- Training 5 fold cross validation ROC 0.70
- Tested on additional 51 molecules
- ROC 0.77





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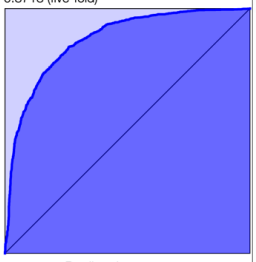
Literature cryptococcus neoformans model

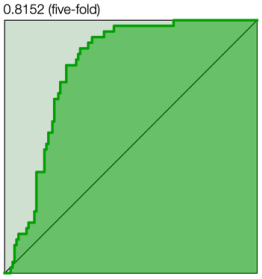
- Data from NIAID ChemDB HIV Opportunistic Infection and Tuberculosis Therapeutics Database
- Threshold MIC_{80} 10μM – 5-fold ROC 0.87
- Use our data to test this model
- ROC 0.81
- Models were also developed with *C. gattii* data
- Models could be used for virtual screening

Origin:	Assay Central
Comments:	Threshold < 10.0000 μM
Training Actives:	1424 / 3246
ROC:	0.8718 (five-fold)
Curve:	

Truth Table:

Actual \ Predicted	Yes	No
Yes	1202	222
No	475	1347

Accuracy:	0.7853
Balanced:	0.7917
Precision:	0.7168
Recall:	0.8441
Specificity:	0.7393
F1 score:	0.7752
Kappa:	0.5723
MCC:	0.5793

Comments:	External Cross Validation: actives=45 inactives=12
Training Actives:	1424 / 3246
ROC:	0.8152 (five-fold)
Curve:	

Truth Table:

Actual \ Predicted	Yes	No
Yes	36	9
No	31	96

Accuracy:	0.0407
Balanced:	0.0390
Precision:	0.5373
Recall:	0.8000
Specificity:	0.7559
F1 score:	0.6429
Kappa:	0.4801
MCC:	0.5010

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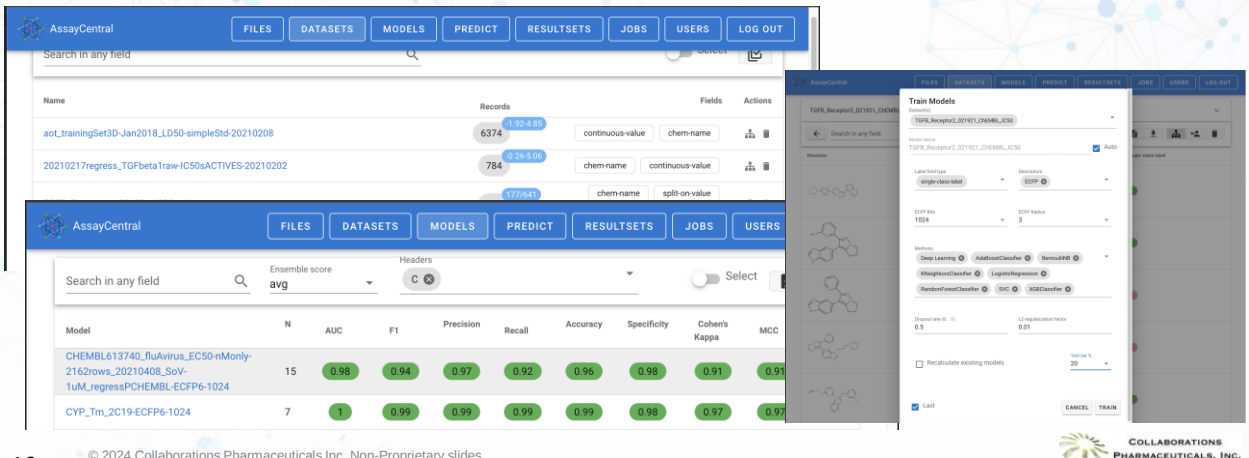
ASSAY CENTRAL

- **www.assaycentral.org**
- Web-app based, QSAR model automated model-building platform (no code required)
- We can host on AWS, our servers or your own.



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New Assay Machine Learning Models

- More algorithms and all the data generated (191 compounds 53 active, 138 inactive)
- 10 μM MIC_{80} cutoff 5-fold cross validation

Method	AUC	F1	Precision	Recall	Accuracy	Specificity	Cohen's Kappa	MCC
ada	0.9	0.7	0.66	0.76	0.82	0.84	0.57	0.58
bnb	0.92	0.74	0.72	0.83	0.84	0.84	0.63	0.66
knn	0.9	0.75	0.64	0.91	0.83	0.8	0.63	0.65
lreg	0.92	0.78	0.75	0.84	0.87	0.88	0.69	0.7
DL	0.89	0.73	0.66	0.83	0.83	0.83	0.61	0.62
rf	0.94	0.78	0.71	0.91	0.85	0.83	0.68	0.7
svc	0.94	0.79	0.68	0.95	0.85	0.82	0.68	0.71
xgb	0.92	0.73	0.72	0.76	0.84	0.88	0.62	0.63

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Assay Central Machine Learning Models

- 5 μM MIC_{80} cutoff (191 compounds 33 active, 158 inactive)

Method	AUC	F1	Precision	Recall	Accuracy	Specificity	Cohen's Kappa	MCC
ada	0.88	0.24	0.31	0.21	0.83	0.96	0.19	0.2
bnb	0.87	0.53	0.52	0.55	0.83	0.89	0.43	0.43
knn	0.89	0.59	0.56	0.64	0.84	0.88	0.49	0.5
lreg	0.89	0.56	0.59	0.59	0.85	0.91	0.48	0.5
DL	0.89	0.3	0.34	0.28	0.84	0.96	0.24	0.24
rf	0.9	0.65	0.5	0.94	0.82	0.8	0.54	0.6
svc	0.9	0.66	0.51	0.94	0.83	0.8	0.56	0.61
xgb	0.89	0.64	0.7	0.67	0.88	0.92	0.57	0.6

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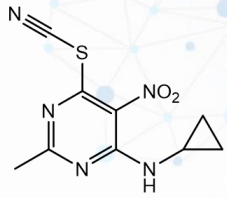
Next steps

- Need to generate more ADME/Tox data, Caco-2, MDCK
- BBB penetration
- Identify target – identify genes
- Perform directed evolution studies and or gene deletion screening
- Develop alternative scaffolds as back ups
- Test versus other fungi such a *C. auris*
- Access to data in public domain is limited
- Could use generative AI approaches to develop analogs
- Could use our approach with other Fungi



Hit compound – Cpd 94

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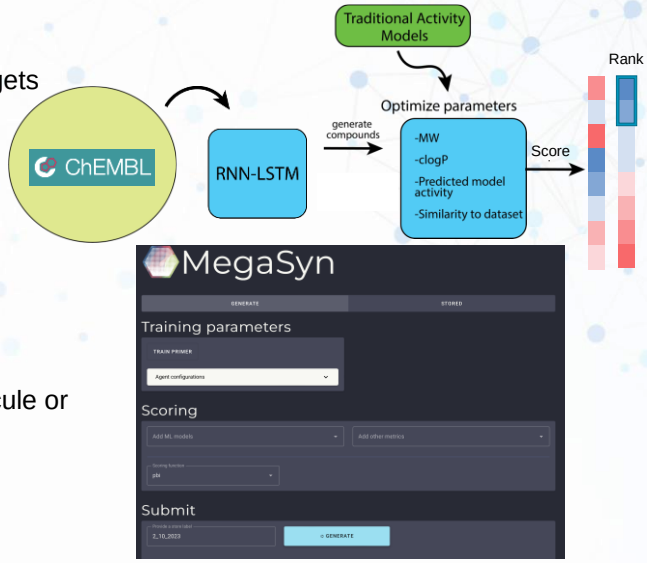
MegaSyn- Generative AI

- Integrated ML models for targets and off-targets
- Property prediction
- An easy-to-use interface
- Also command line version
- Enables rapid molecule generation
- Starting point for run could be a target molecule or guided by optimal parameter scores



Urbina et al., ACS Omega 2022 May 27;7(22):18699-18713

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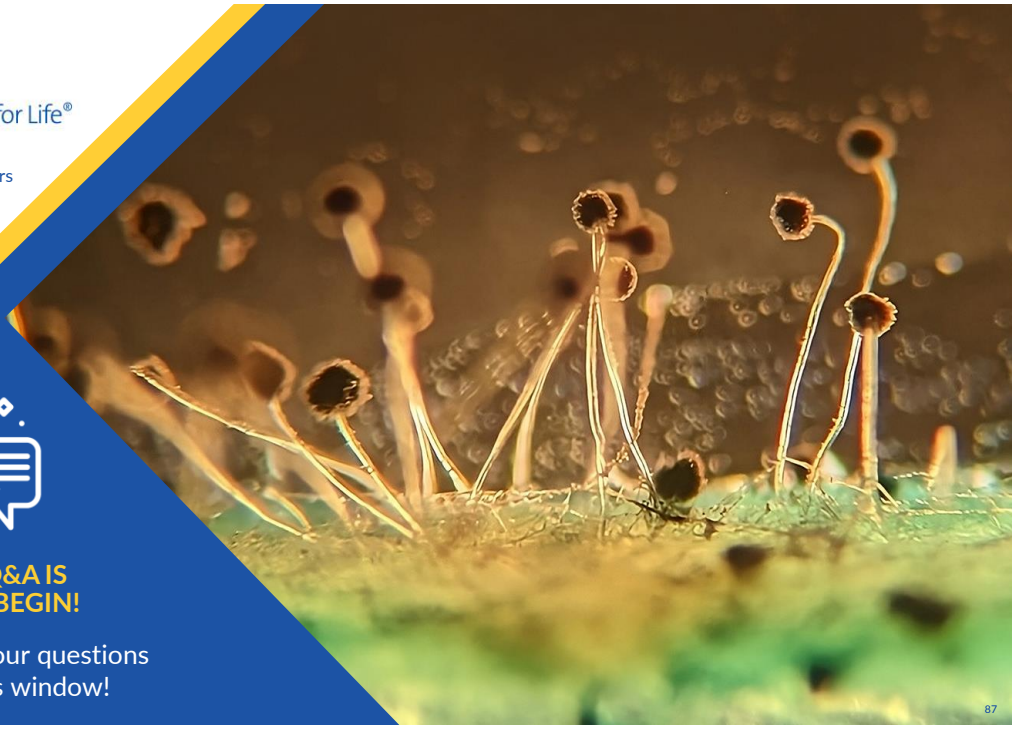

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