Development of novel antifungals against *Candida* based on an antifungal peptide produced by *E. faecalis*

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Secondary mentors: Dr. Michael Lorenz, Dr. William Miller, Dr. Timothy Palzkill

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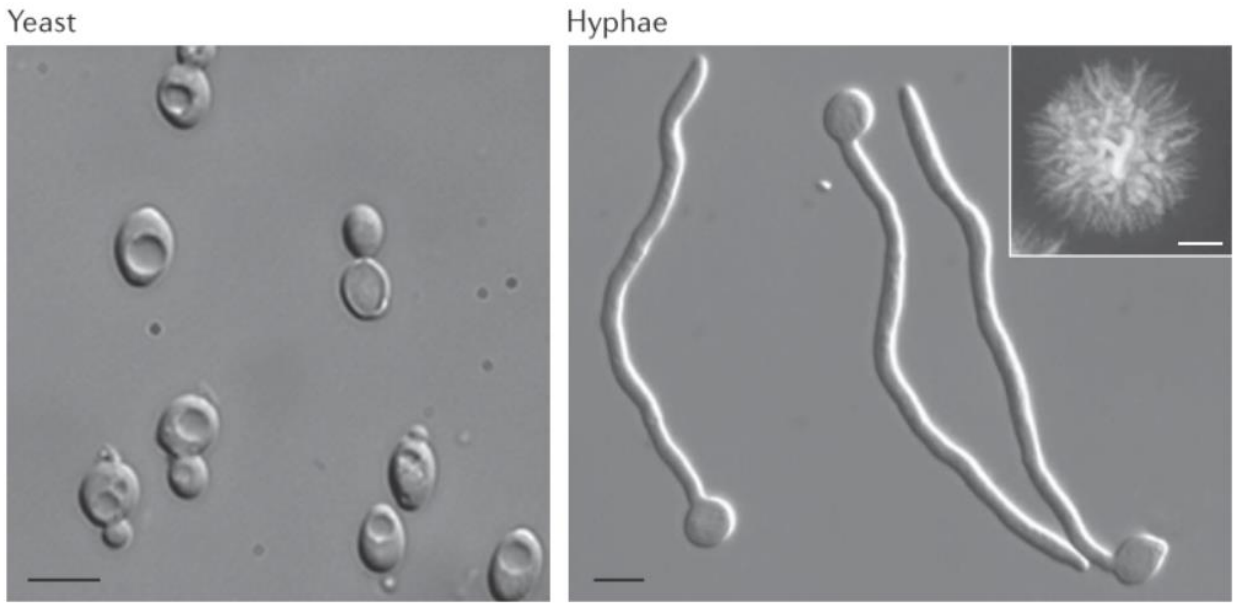

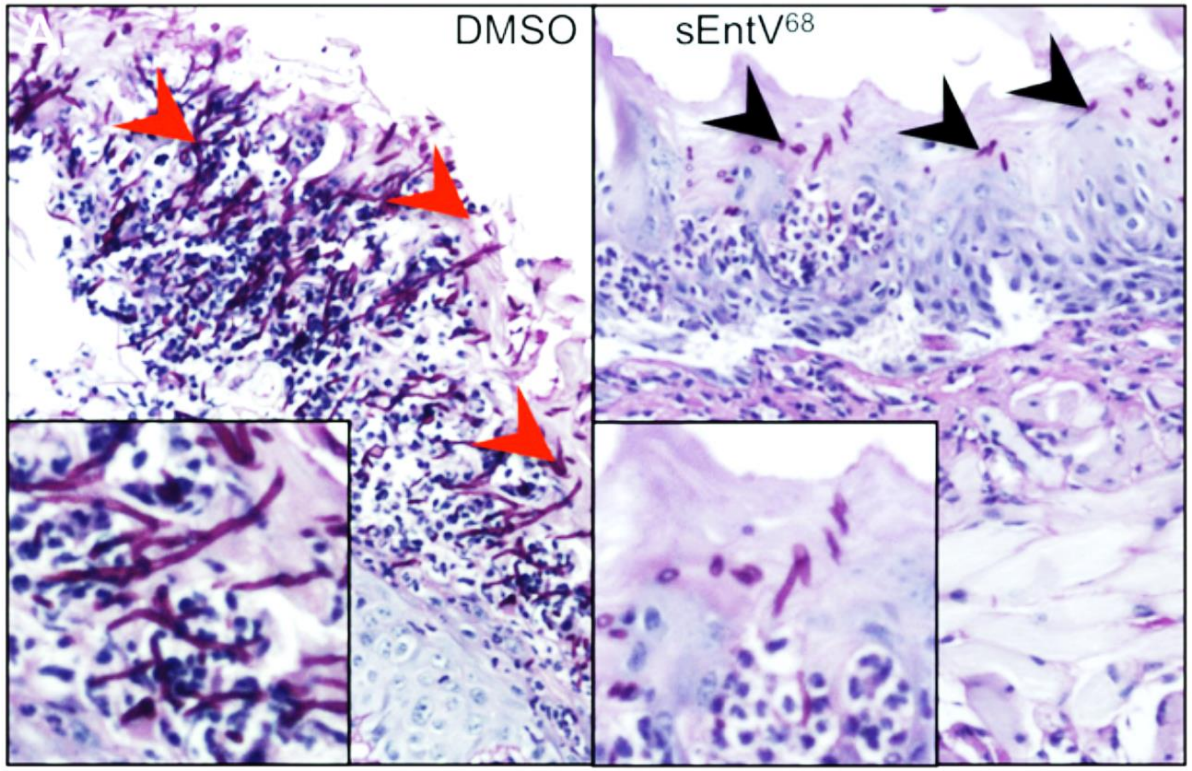

https://www.cdc.gov/drugresistance/pdf/threats-report/candida-508.pdf

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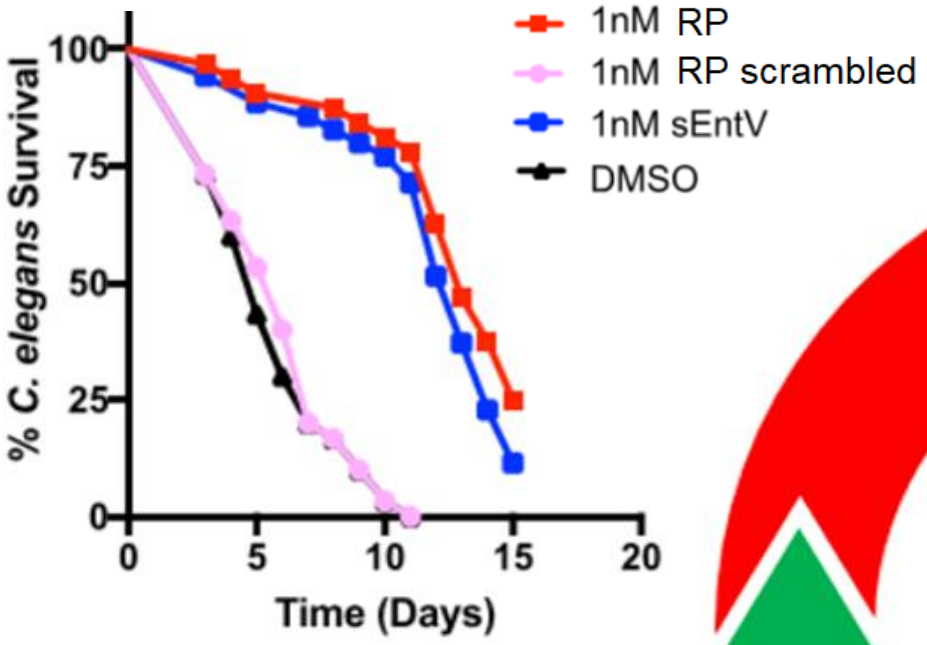
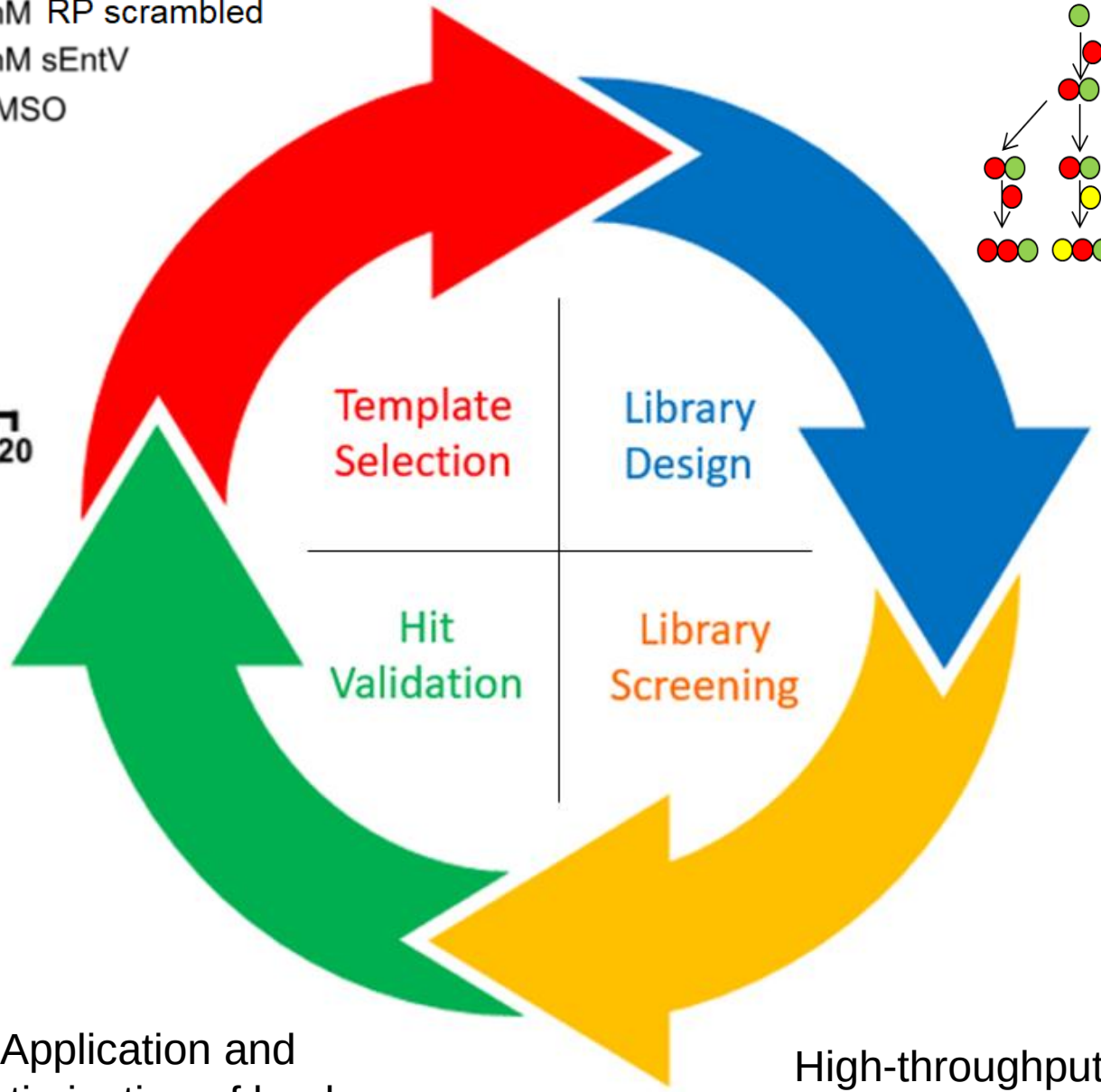
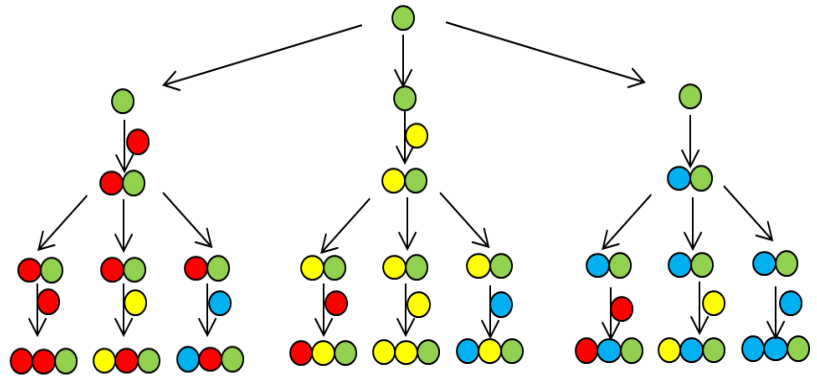
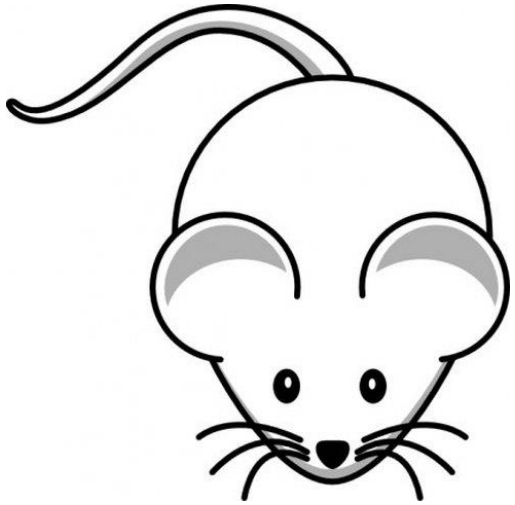


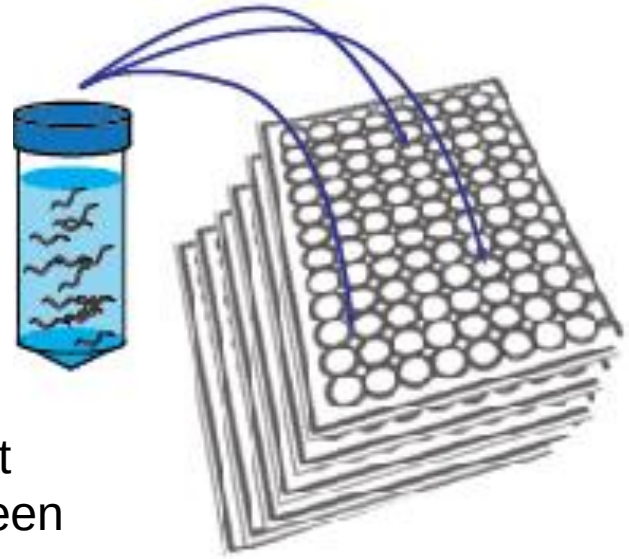




Peptide library synthesis using split-and-pool combinatorial chemistry

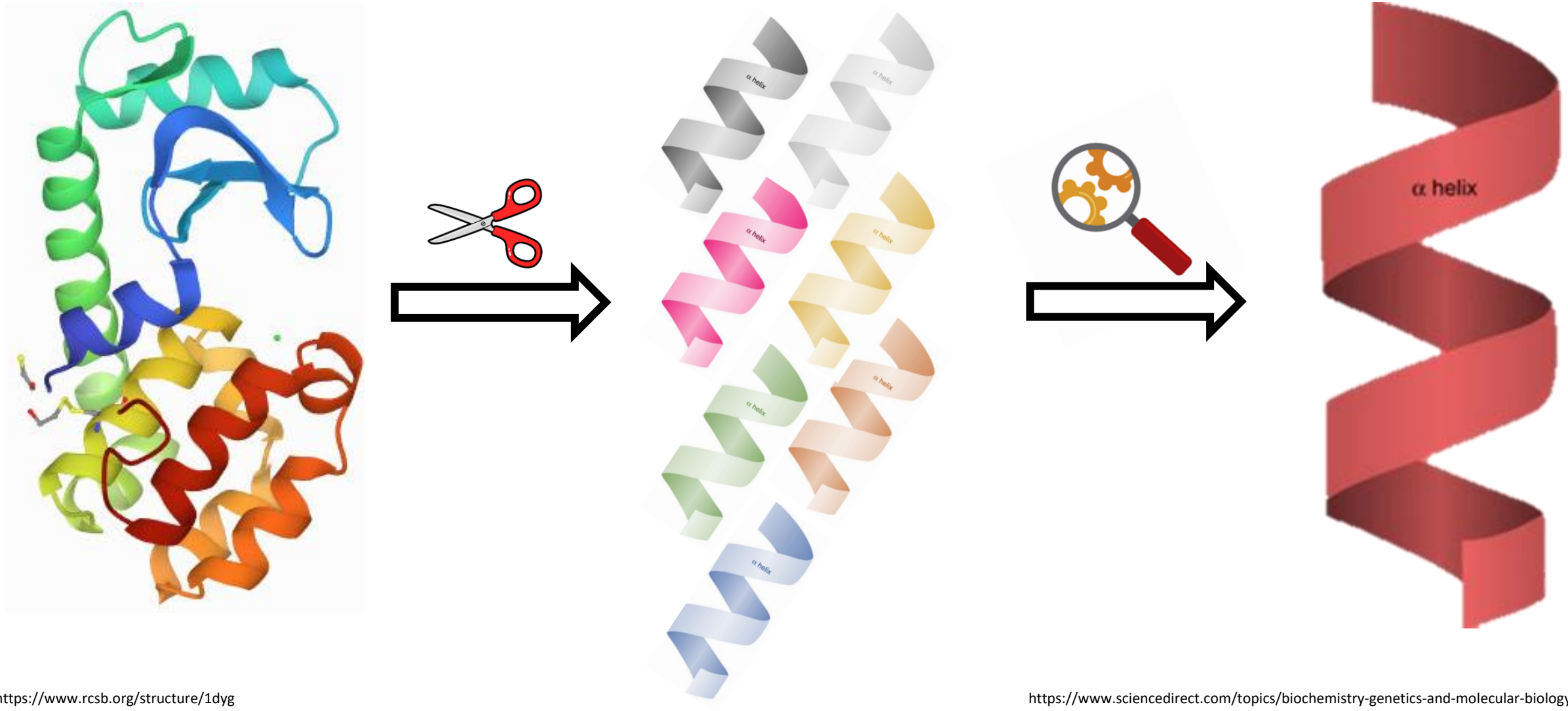


Application and optimization of lead candidates



High-throughput 96-well assay screen

Template Selection



https://www.rcsb.org/structure/1dyg

https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/alpha-helix

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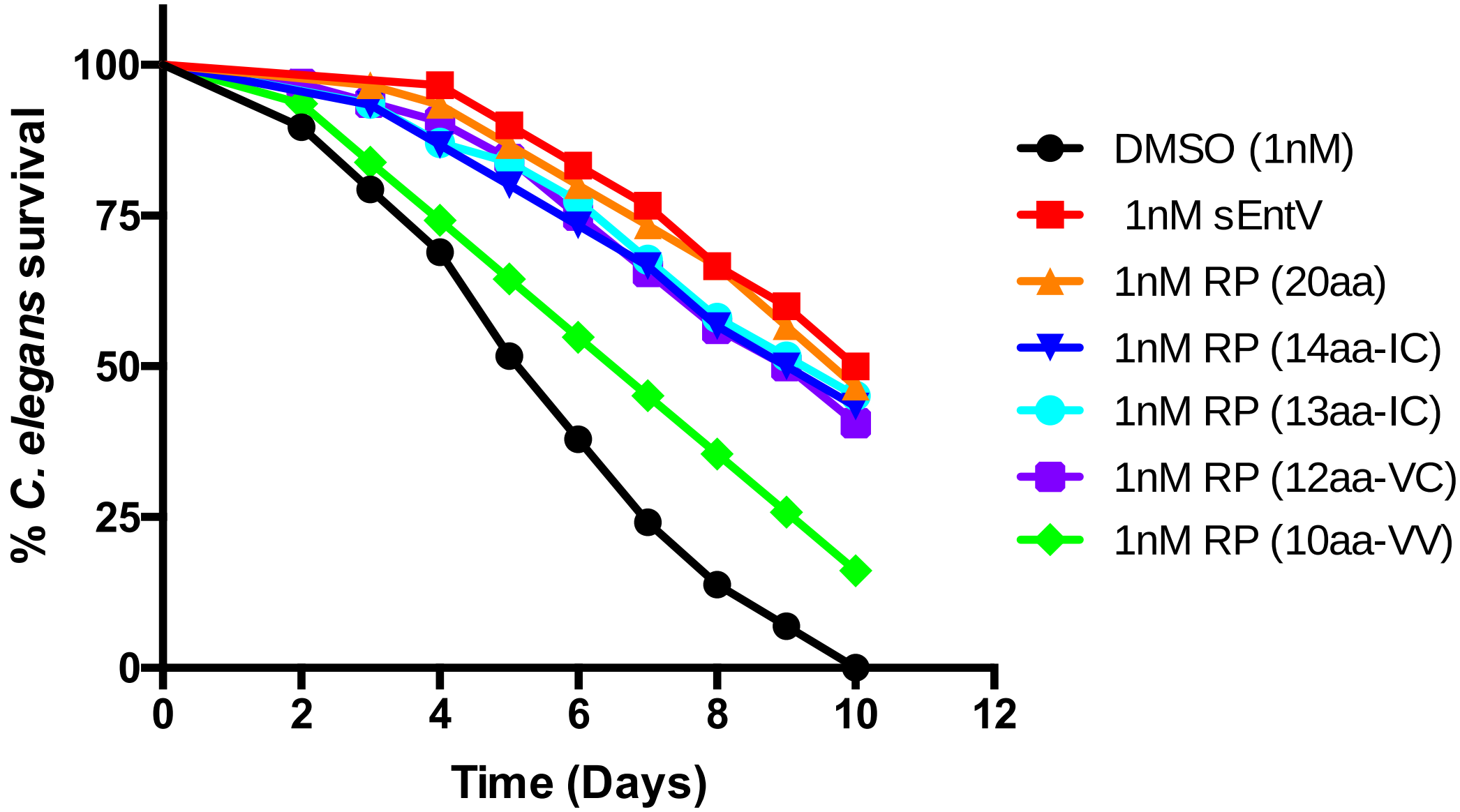

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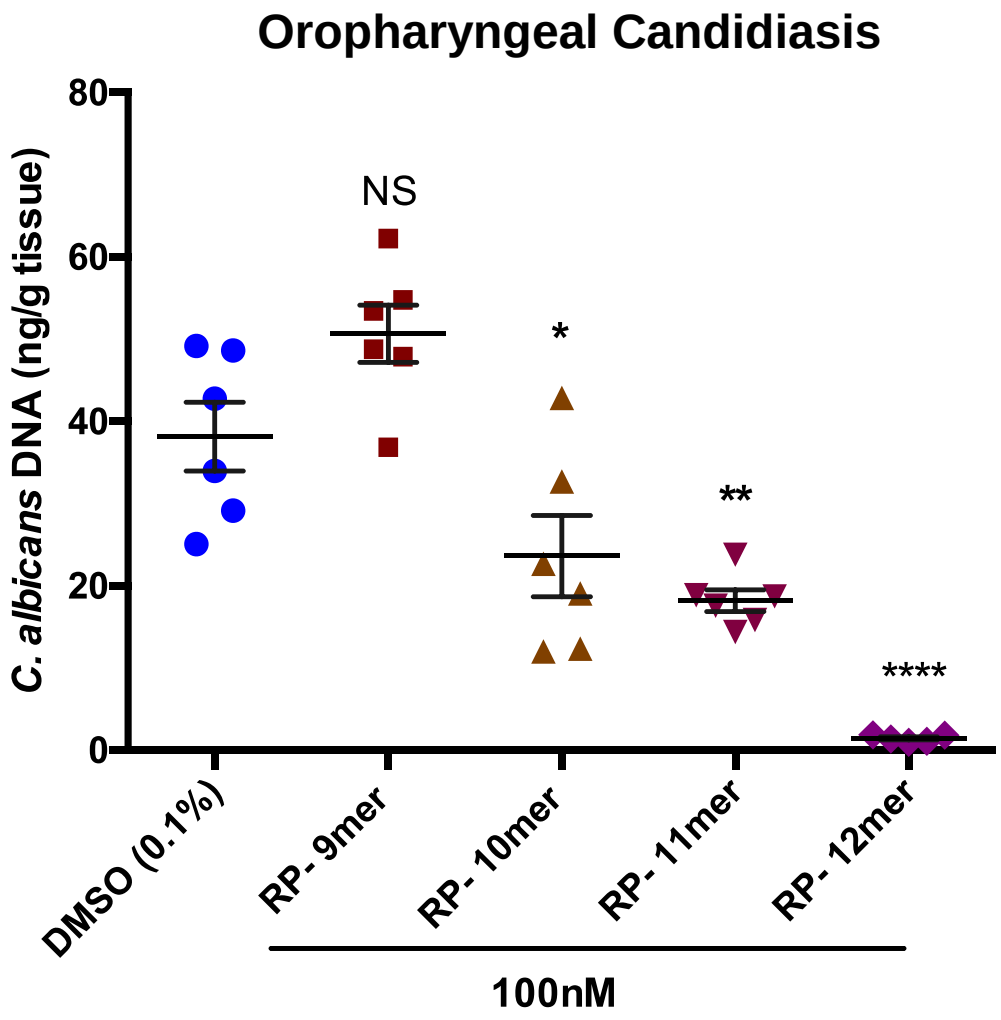
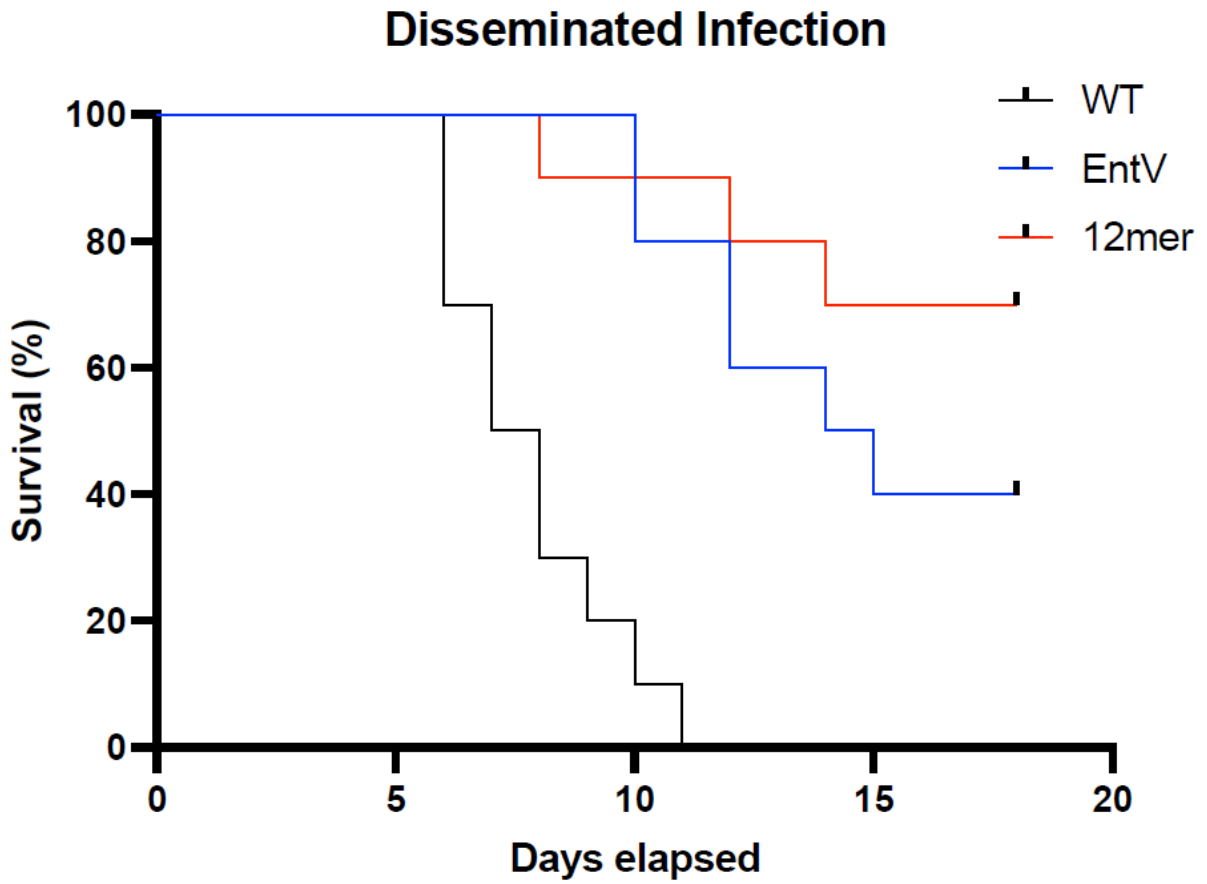
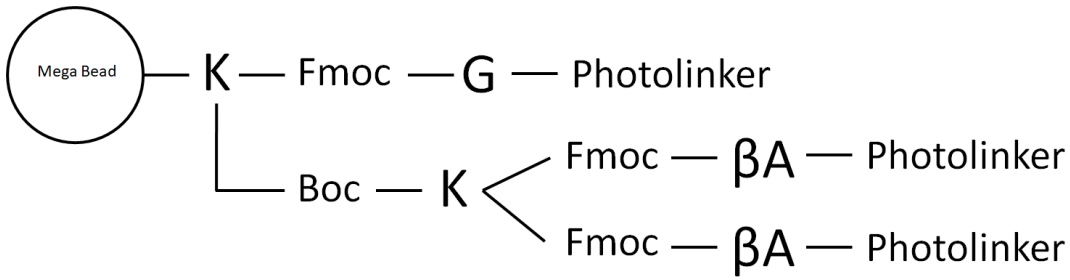
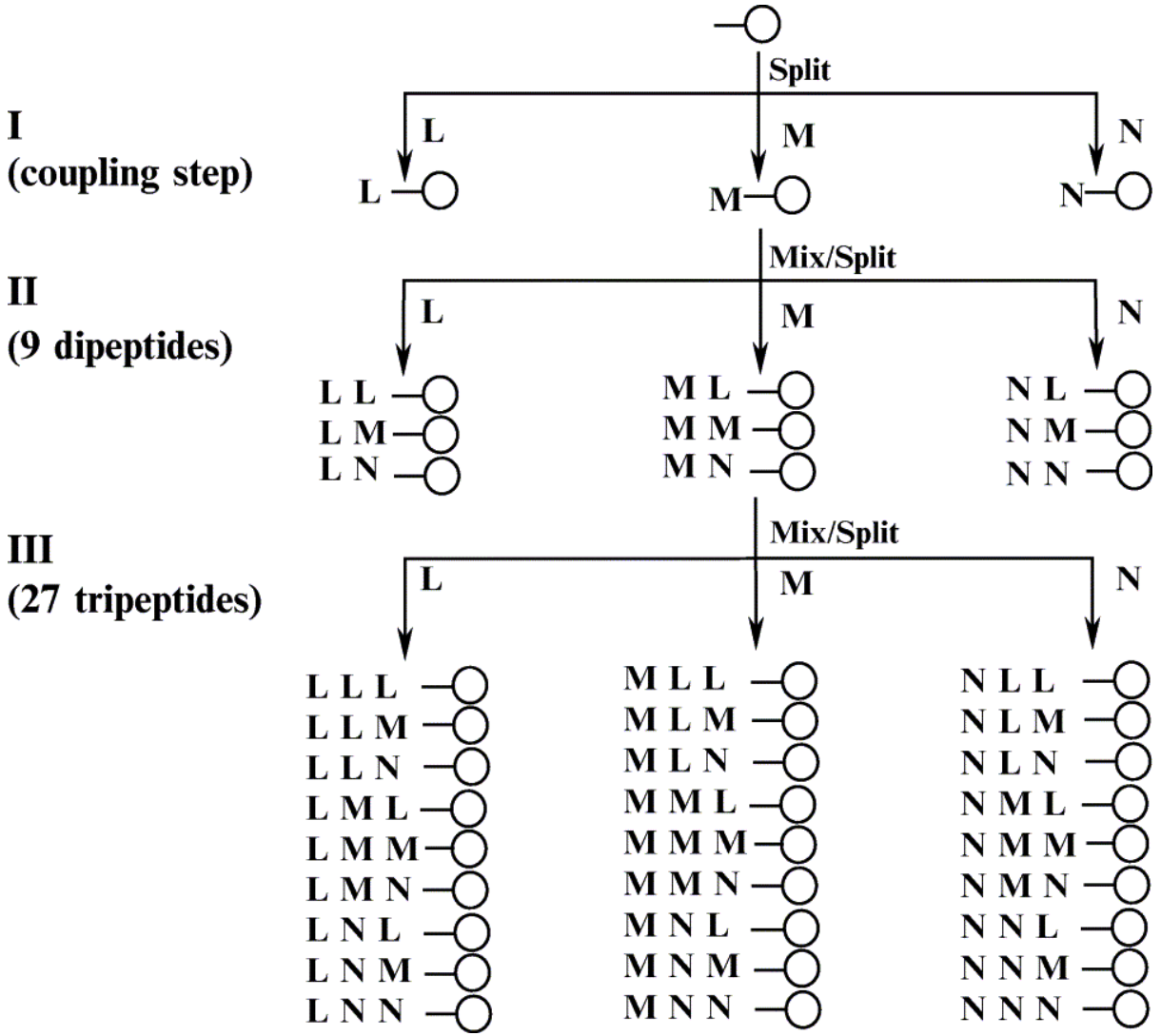




Library Synthesis – Combinatorial Chemistry

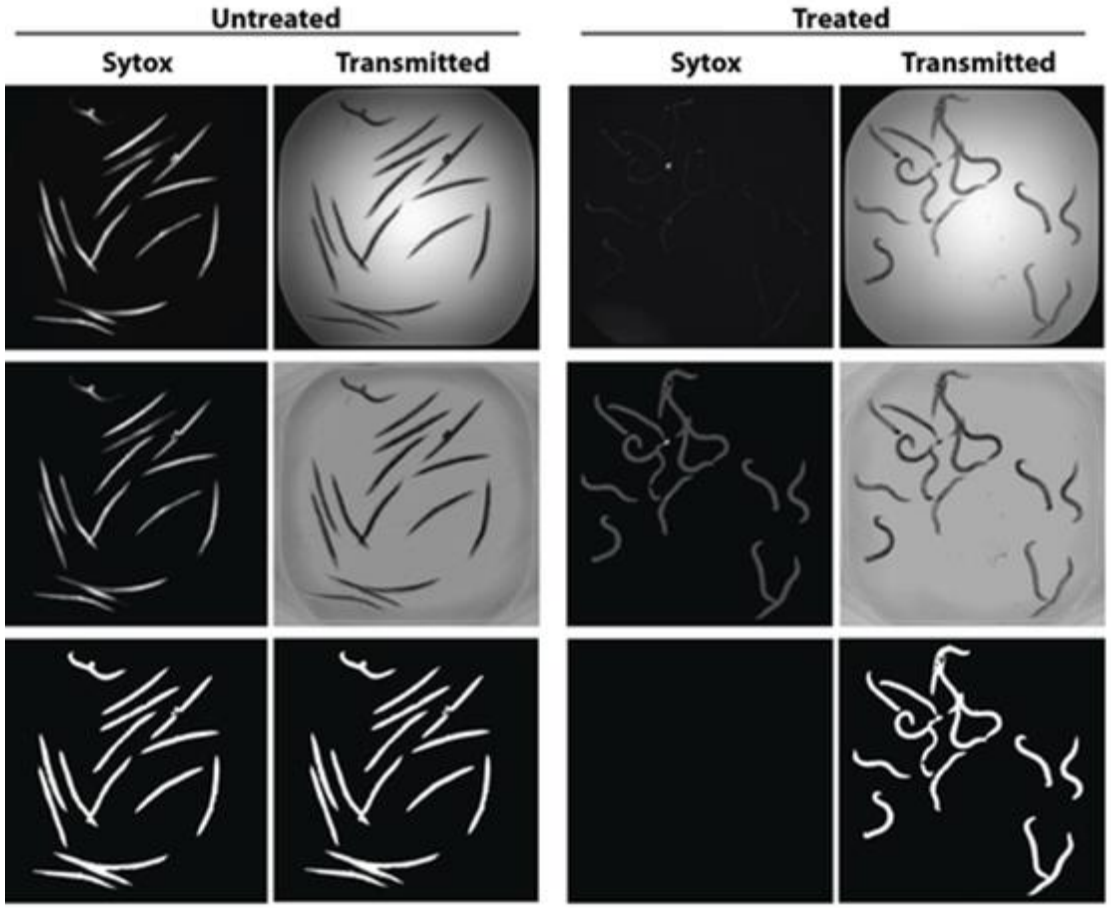
Bead branching to increase capacity

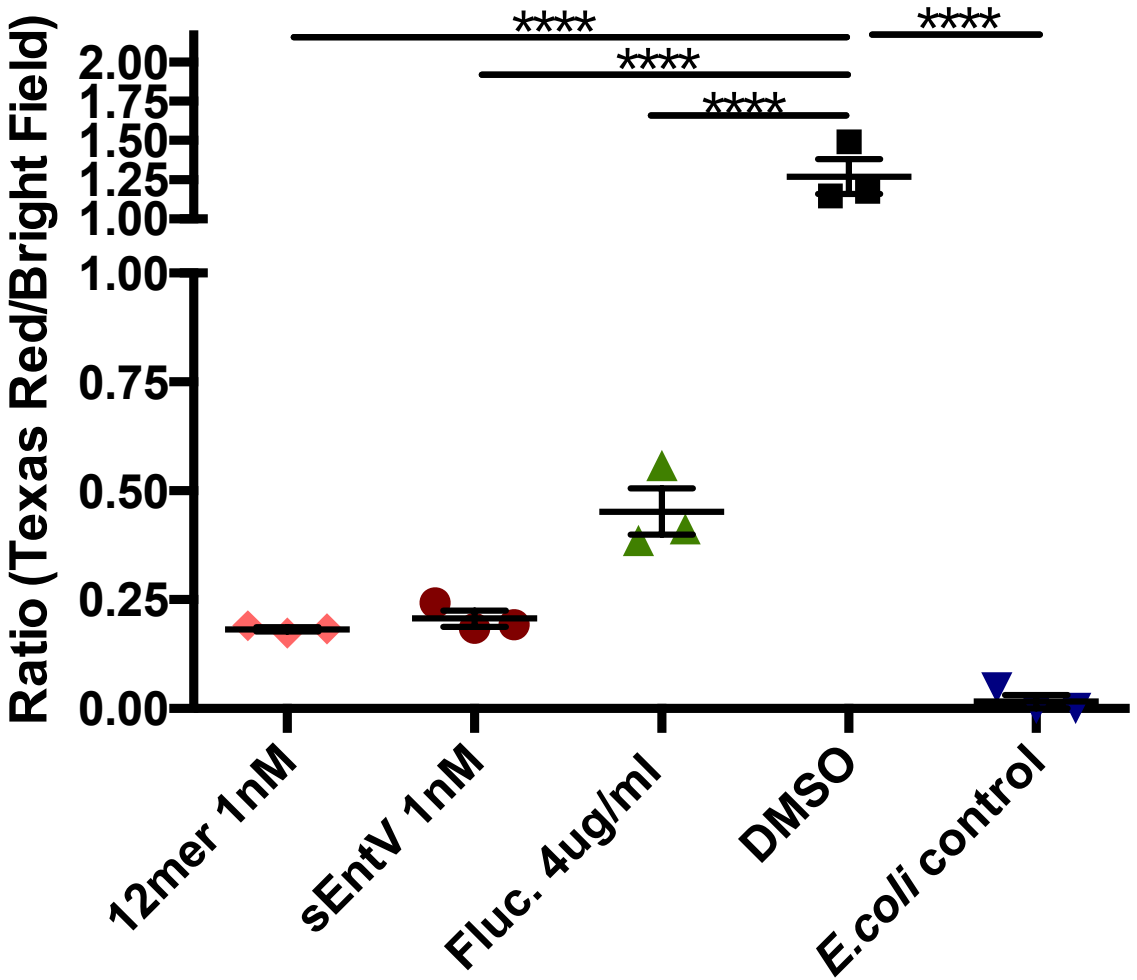




Kit S Lam, Alan L Lehman, Aimin Song, Ninh Doan, Amanda M Enstrom, Joeseph Maxwell, Ruiwu Liu, Synthesis and Screening of "One-Bead One-Compound" Combinatorial Peptide Libraries, Methods in Enzymology2003

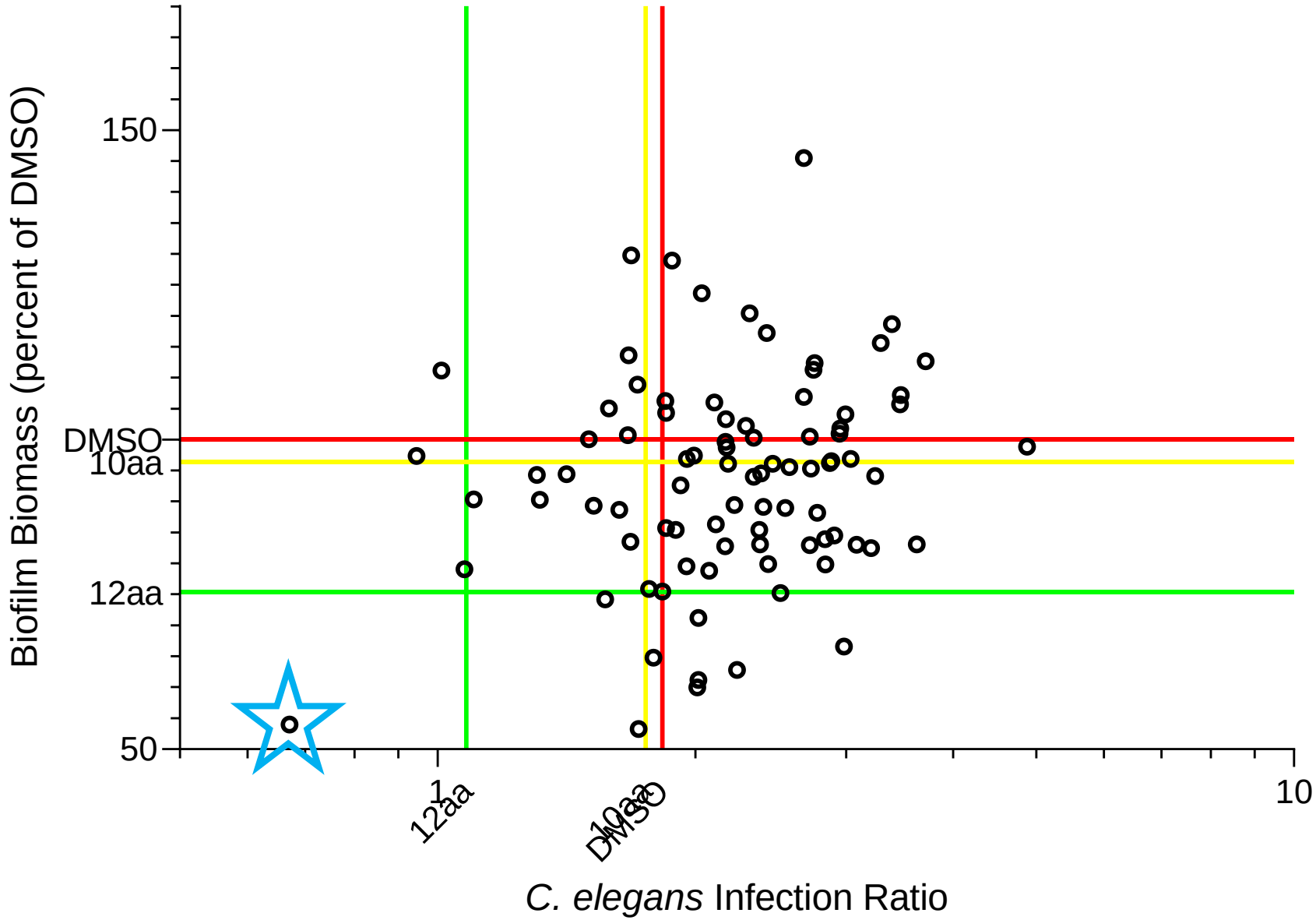
High-Throughput Library Screening





Rajamuthiah R, Fuchs BB, Jayamani E, Kim Y, Larkins-Ford J, Conery A, et al. (2014) Whole Animal Automated Platform for Drug Discovery against Multi-Drug Resistant *Staphylococcus aureus*. PLoS ONE 9(2): e89189. https://doi.org/10.1371/journal.pone.0089189

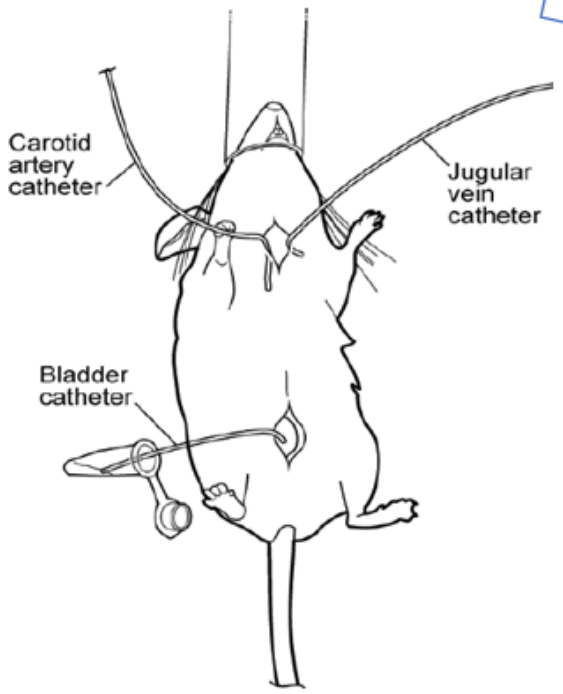
10AA Library Screening Results



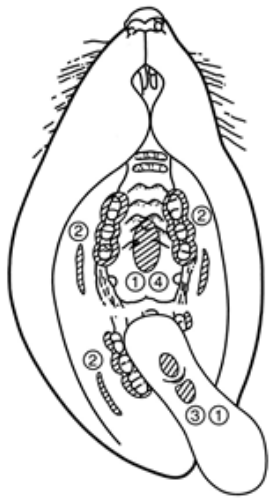
Hit Validation

Biofilm-based infection models

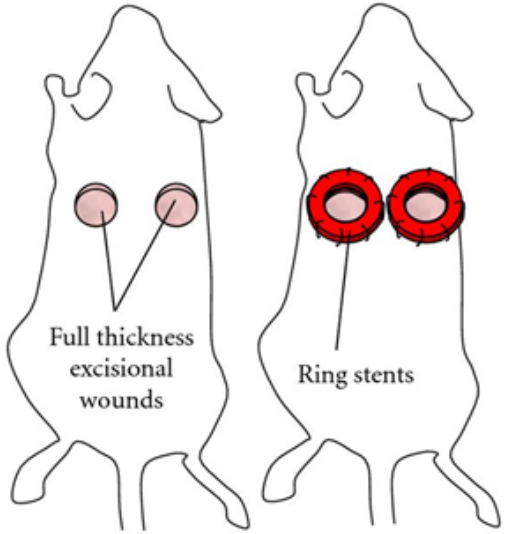
Systemic infection model



Catheter-based infection model



Oropharyngeal candidiasis model



Full thickness wound infection model

Systemic fungal infection model

https://www.hindawi.com/journals/bmri/2011/969618/
Yuthika H. Samaranayake, Lakshman P. Samaranayake Clinical Microbiology Reviews Apr 2001, 14 (2) 398-429

https://www.researchgate.net/publication/230717210_Managing_a_colony_of_spiny_mice
https://encapsula.com/intravenous-administration-tail-vein/

Conclusions & Future Directions

- We have determined that the 12AA peptide has strong antifungal efficacy
- The 12AA peptide has efficacy in two different mouse models of candidiasis
- I have generated a library of 2500 novel peptides and screening has revealed 5 mutant peptides with highly enhanced activity
- Stringently test the improved peptides in the *C. elegans* and mouse models we have chosen
- Look at antifungal efficacy of the 12AA and its variants against drug-resistant clinical isolates of *C. albicans* and other *Candida* species

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  - Dr. Timothy Palzkill
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  - **Melissa Martinez**
- Ah-Lim Tsai Lab
  - **Dr. Gang Wu**