Yale Center for Molecular Discovery

Fall 2014 Newsletter

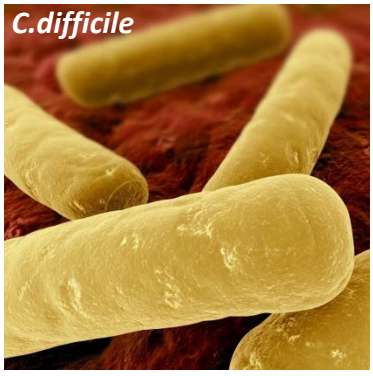
Contents

Featured Project

Breaker Lab: Synthesis and Evaluation of Riboswitch-targeting antibiotics to treat CDI

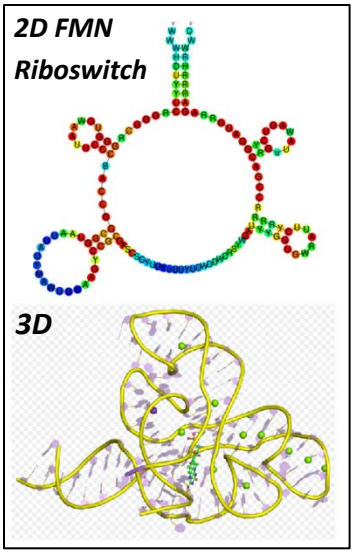
This issue features guest writer, Kenneth Blount, who has been investigating RNA targeting antibiotics for over 10 years.

Clostridium difficile infections (CDI) are severe intestinal bacterial infections that most frequently occur in hospitalized or long-term care patients as a side-effect of broad-spectrum antibiotic therapy [1]. The incidence and severity of CDIs has not only increased dramatically, the recent emergence of more virulent *C. difficile* strains is projected to further increase the recurrence rate and the severity of CDI [2,3]. To address this challenge, our research focuses on optimization of a new class of CDI antibiotics that target messenger RNA (mRNA) structures called riboswitches.



Riboswitches are mRNA-based gene regulators that sense the concentration of essential metabolites and regulate metabolic homeostasis [4]. Ligand binding to a riboswitch receptor causes a conformational change that modulates the expression of the adjacent gene(s) [4]. Novel small molecules can be identified and optimized that mimic the natural ligands of riboswitches, thereby functioning as bacteriostatic or even bactericidal agents. A riboswitch target of particular interest is a class that responds to the coenzyme flavin mononucleotide (FMN) [5] and regulates genes involved in riboflavin biosynthesis and transport.

Based on the validation of FMN riboswitches and other classes as antibacterial targets, Drs. Breaker and Blount cofounded BioRelix—a biotech company that optimized and developed new riboswitch-targeting antibiotics. A major focus was the discovery and optimization of a new class of antibiotics that rapidly kill *C. difficile* and can cure mice of a CDI. These compounds are more selective than currently prescribed CDI antibiotics and are predicted to have a lower infection recurrence frequency in humans. Moreover, our preliminary data suggests that the compounds kill *C. difficile* by dysregulating FMN riboswitch-regulated genes.



In collaboration with the Yale Center for Molecular Discovery, our focus is to synthesize and complete the evaluation of several advanced leads whose efficacy in animal models of CDI is predicted to be superior to currently marketed antibiotics.

Upcoming Open House

Four West Campus Core Facilities are hosting an Open House on Wednesday, **November 12, 12 - 1PM**, at Yale's West Campus Conference Center, 800 West Campus Drive, Room 220. Please join us for presentations of services, pizza, & a $25 Eli Bucks raffle!

Training by Request

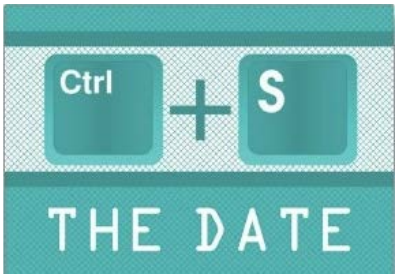
Based on the popularity of the General Nanocourse, we are introducing **Training by Request**. We've noticed that members of the Yale community have **timely needs** for **relevant, hands-on training** in the areas of **enzymatic assays** and **cell-based assays**. We'll schedule you to visit the Center, often shadowing us while we are conducting similar projects, to build confidence in the skills you need to further your research. For Image Analysis, we can come to your laboratory to work with you and teach pipeline creation in the freeware program CellProfiler. Contact us ☺.

Group Meeting Presentations by Request

If you are interested in learning more about YCMD, or in discussing a specific idea or a project, YCMD staff can do a presentation in your lab. **Presentations will be customized based on your specific needs.** They can cover general YCMD capabilities, or specific biology and/or chemistry services relevant to your project. These presentations are offered as part of our education mission to all interested members of Yale community. Contact us.

Upcoming Nanocourse

Save the date: details for the upcoming popular General Nanocourse on December 4, 2014 will be distributed soon. Don't miss out!



Recent Center Publications

Kinch MS, **Patridge E**. An analysis of FDA-approved drugs for infectious disease: HIV/AIDS drugs. Drug Discov Today. 2014 Oct: 19(10):1510-3. doi: 10.1016/j.drudis.2014. 05.012

Kinch MS, **Patridge E**, **Plummer M**, **Hoyer D**. An analysis of FDA-approved drugs for infectious disease: antibacterial agents. Drug Discov Today. 2014 Sep; 19(9):1283-7. doi: 10.1016/j.drudis.2014.07.005

Kinch MS, **Surovtseva Y**, **Hoyer D**. An analysis of FDA-approved drugs for cardiovascular diseases. Drug Discov Today. 2014 September 15. doi: 10.1016/j.drudis.2014.09.001

Kinch MS, **Patridge E**. An Analysis of FDA-approved drugs for psychiatric disorders. Drug Discov Today. 2014 September 6. doi: 10.1016/j.drudis.2014.08.013

Pirruccello M, Nandez R, Idevall-Hagren O, Alcazar-Roman A, **Abriola L**, Berwick SA, Lucast L, Morel D, De Camilli P. Identification of inhibitors of inositol 5-phosphatases through multiple screening strategies. ACS Chem Biol. 2014 Jun 20; 9(6):1359-68. doi: 10.1021/cb500161z

Kinch MS, **Merkel J**, **Umlauf S**. Trends in pharmaceutical targeting of clinical indications: 1930-2013. Drug Discov Today. 2014 May 29. doi: 10.1016/j.drudis.2014.05.21

Sztuba-Solinska J, Shenoy SR, **Gareiss P**, Krumpe LRH, Le Grice SFJ, O'Keefe BR, Schneekloth Jr. JS. Identification of Biologically Active, HIV TAR RNA-Binding Small Molecules Using Small Molecule Microarrays. J Am Chem Soc. 2014 May 12; 136, 8402-8410. doi: 10.1021/ja502754f

YCMD Web Links

See what resources YCMD has to support your research:

Screening Collections Instrumentation Software
Feedback or questions

Featured Project: References

1. http://www.cdc.gov/hai/organisms/cdiff/cdiff_infect.html
2. Cookson, B. 2007. Hypervirulent strains of *Clostridium difficile*. *Postgrad Med J.* **83**: 291-5.
3. Marsh JW, et al. 2012. Association of relapse of Clostridium difficile disease with BI/NAP1/027. *J Clin Microbiol.* **50**: 4078-82.
4. Roth A, Breaker RR. 2009. The structural and functional diversity of metabolite-binding riboswitches. *Annu Rev Biochem.* **78**: 305-34.
5. Winkler WC, Cohen-Chalamish S, Breaker RR. 2002. An mRNA structure that controls gene expression by binding FMN. *PNAS.* **99**: 15908-15913.