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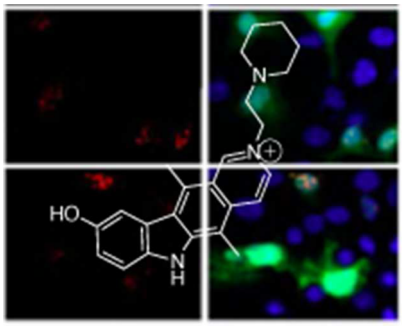
TARGETING RNA REPEAT OFFENDERS

Defects in RNA function are the cause of numerous diseases including Fragile X-associated Tremor Ataxia Syndrome (FXTAS), a neurodegenerative disorder characterized by problems with cognition and movement. FXTAS is caused by the presence of expanded repeats of the RNA sequence CGG, referred to as r(CGG)^{exp}, which leads to the aberrant splicing of various pre-mRNAs and the subsequent expression of defective proteins. Now, Disney *et al.* (DOI: 10.1021/cb300135h) report the discovery of a small molecule that specifically binds to r(CGG)^{exp}.

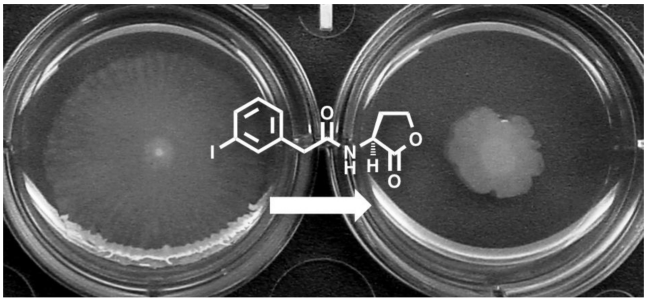


To tackle the notoriously difficult challenge of targeting expanded RNA repeat motifs, the authors created a library of small molecules with features likely to promote RNA binding. They then employed a high throughput protein-displacement assay to screen for those capable of binding to r(CGG)^{exp}. Using this strategy, they identified a promising new compound capable of improving pre-mRNA splicing defects and reducing the size and number of r(CGG) nuclear foci, a hallmark of cells expressing r(CGG)^{exp}. The compound is an effective new tool for probing FXTAS and also serves as a jumping off point for the development of drugs targeting the disease.

MAKING SENSE OF QUORUM SENSING

Bacteria use a process called quorum sensing to get a sense of their population density. This allows them to promote activities that help their community thrive, such as the formation of biofilms, sporulation, and virulence. Quorum sensing is mediated by *N*-acyl-L-homoserine lactone derivatives. The enzymes responsible for synthesizing these small molecules are members of the LuxI-type synthases, which interact with LuxR-type receptors to initiate gene transcription programs supporting various quorum sensing phenotypes. The LuxI–LuxR interaction is an appealing target for drug discovery strategies aimed at pathogenic bacteria such as *Acinetobacter baumannii*, and to this end, Stacy *et al.* (DOI: 10.1021/cb300351x) report the discovery of new small molecule modulators of a quorum sensing system in *A. baumannii*.

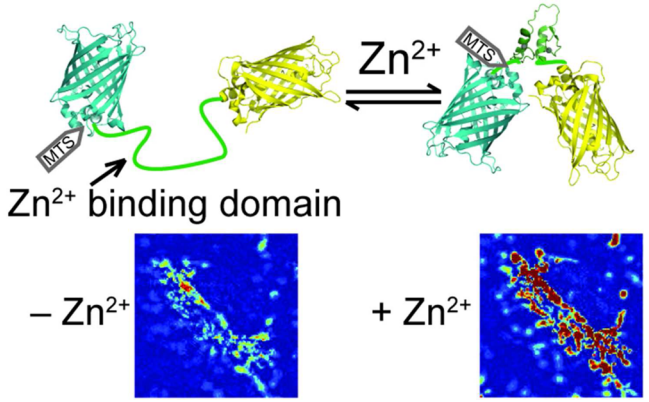
The authors subjected focused libraries of non-natural *N*-acetyl homoserine lactones to screens designed to identify antagonists and agonists of AbaR, a LuxR receptor in *A. baumannii*. They discovered numerous compounds capable of either promoting or preventing AbaR activity, providing



important molecular tools for exploring quorum sensing in this menacing bacteria.

GETTING A SENSE FOR MITOCHONDRIAL ZINC

Zinc is an essential mineral involved in diverse biological processes including the immune response, protein and DNA synthesis, and cell division. Zinc levels in the cell are tightly regulated, and either too little or too much can have various detrimental effects. However, methods to quantitate intracellular levels of zinc are limited. Park *et al.* (DOI: 10.1021/cb300171p) now report the development of three molecular sensors capable of detecting zinc that is present in the mitochondria of the cell.



Building on previously designed, genetically encoded mitochondrial zinc sensors comprising a zinc binding protein component and a small fluorescent molecule, the authors tweaked the affinity of the sensors for zinc to improve their dynamic range. Using the optimized sensors, they were able to determine that zinc is buffered at much lower concentrations in mitochondria than in the cytosol and that different cell types have strikingly varied mitochondrial zinc concentrations. These new and improved molecular sensors are valuable additions to the toolkit available for investigating zinc biology.

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