COLLEGE OF SCIENCE
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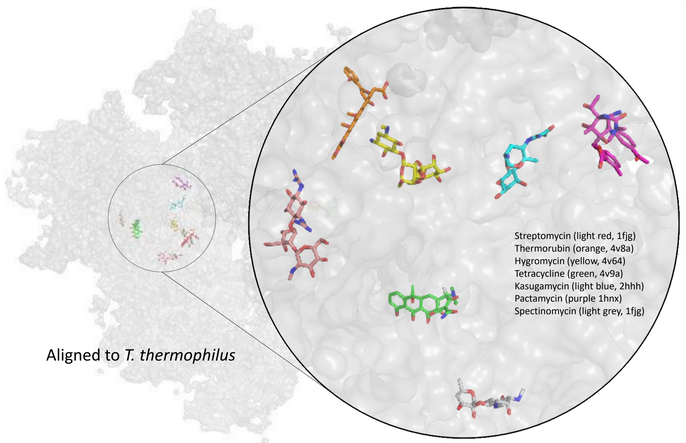
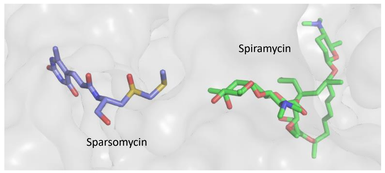
LOWELL GROUP RESEARCH

Bidentate Antibiotics

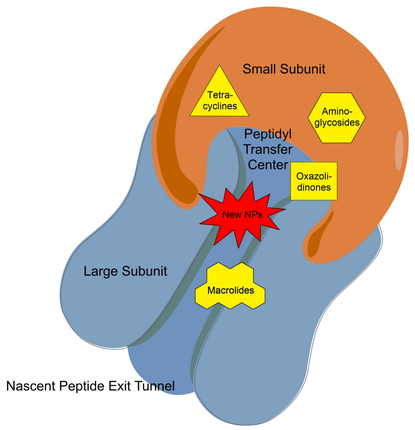
What happens if you link two drugs? Are they more effective? Do they overcome resistance? Scientists have previously investigated hybrid antibiotics where two drugs were linked, but selection was determined by ease of functionalization, not target compatibility. By rationally selecting drugs that inhibit the same cellular function, and connecting them via a flexible linker, we seek to create better drugs.

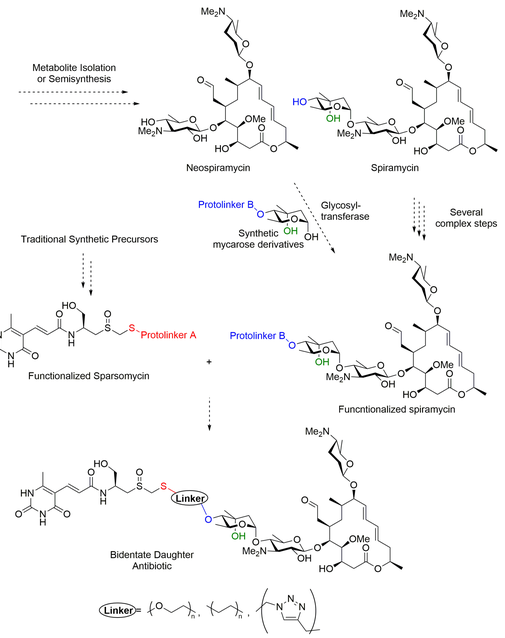


Antibiotics target two major regions of the bacterial ribosome, the tRNA binding sites and the peptidyl transfer center/nascent peptide exit tunnel (where peptide bonds are made and the protein emerges). These compound occupy proximal, but non-overlapping binding sites. Judicious functional group activation that keeps the relevant pharmacophores intact enables the installation of flexible linkers. Thus once connected, both antibiotics can still engage their target site.



Our primary target is the bacterial ribosome. Several different classes of antibiotics are known to inhibit protein synthesis through a variety of mechanisms. Importantly, resistance to one drug does not confer resistance to other classes of antibiotic.

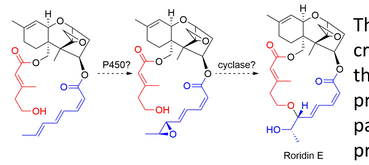




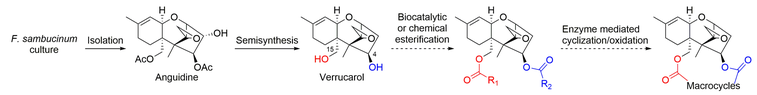
We can use chemoenzymatic methods to overcome issues with regiospecificity. The above example with sparsomycin and spiramycin illustrates how a biocatalytic method might be superior for regioselection (blue versus green alcohol) on a complex molecule.

Biocatalysis in Synthesis

Can we establish protein reactions as a legitimate subfield of catalysis? The central theme of our work is incorporating enzymes into organic synthesis. The interplay between synthesis and chemical biology enables creative approaches and insight into both fields.

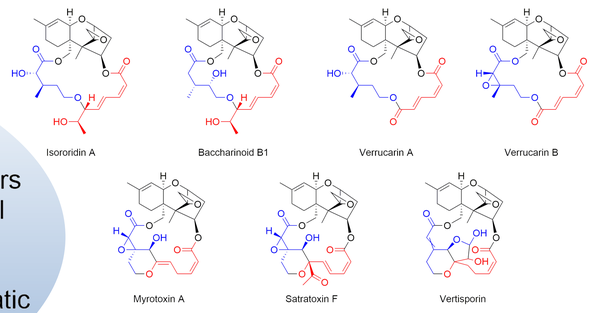


The lure of total synthesis is in its challenge: successfully create an extremely complex molecule. The difficulty is that some transformations are exceedingly difficult or presently unknown. By analyzing the *biosynthetic* pathway that an organism uses to produce a natural product, we can draw inspiration for *synthetic* strategies and also use proteins optimized by nature as catalysts. An excellent example of this approach is for the **trichothecene macrolactones**, a family of mycotoxins with a fascinating diversity of size, structure, and stereochemistry in the macrolactone (colored).



Our approach combines natural product isolation, semisynthesis, synthesis, and biocatalysis in order to achieve the desired natural products. Analysis of the macrocycle suggests it is created through the action of polyketide synthases and cytochrome P450 mono-oxygenases, two enzyme families common in natural product biosynthesis.

Through the interrogation of proteins encoded in the biosynthetic cluster with synthetic probes, we can identify the critical genes for cyclization. We can then use them in turn to effect the synthesis of the complex macrolactones (below) and additional derivatives. This is a particularly compelling approach to synthesis as catalysts that have natively evolved to have exquisite specificity are used for their designed transformation.

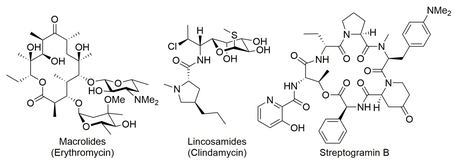


Adjunctive Therapy

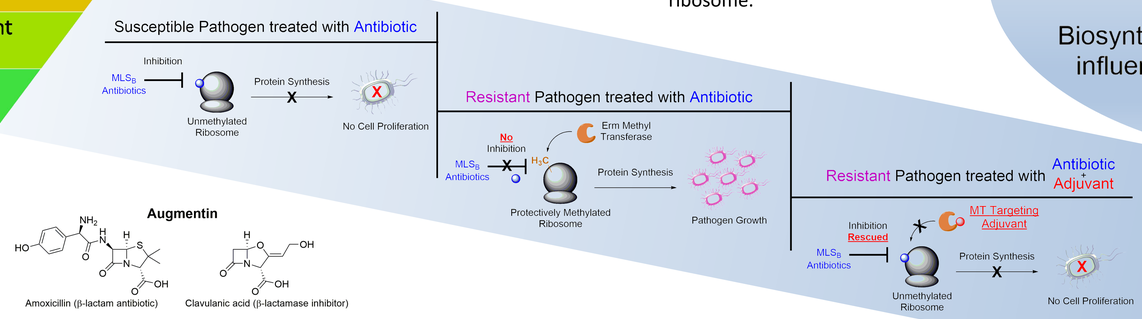
Can we make obsolete antibiotics effective again?

Primary Adjuvant Screen for Erm Inhibitors
Exclusion of Inherent Antibiotics
Hit Confirmation
Counter Screens
Top Hits

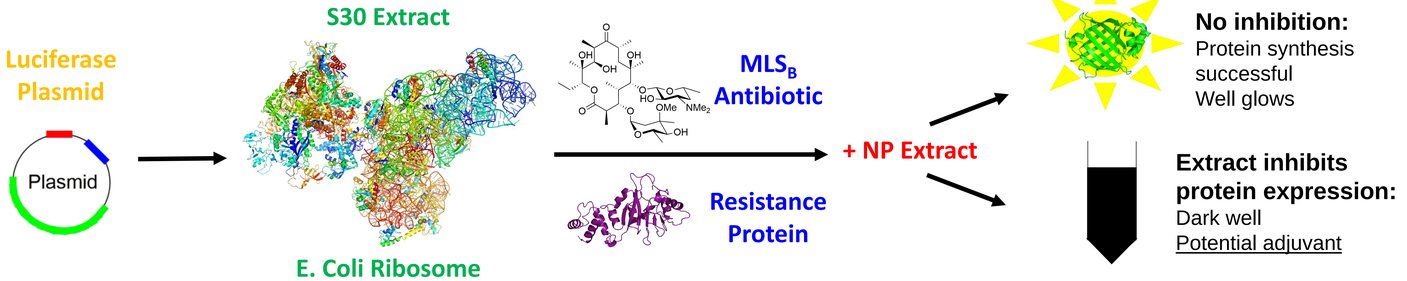
Beyond developing new antibiotics, finding creative ways to make old ones more effective is a critical and fruitful undertaking. Adjuvants, that is compounds that inhibit resistance mechanisms of bacteria, offer a compelling area for exploration. The classic example is Augmentin, where a β-lactam antibiotic, such as penicillin, is coadministered with a β-lactamase inhibitor.



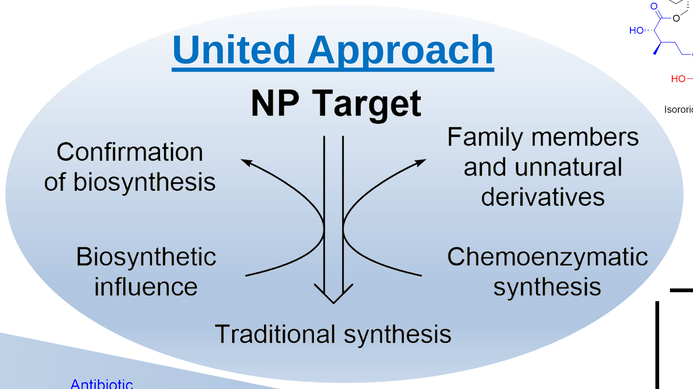
Our preliminary and understudied target is the Erm family of methyltransferases. These proteins protect the bacterial ribosome from being inhibited by the macrolide, lincosamide, streptogramin B (MLS_B) classes of antibiotics by methylating the adenosine 2058 of the *E. coli* ribosome.



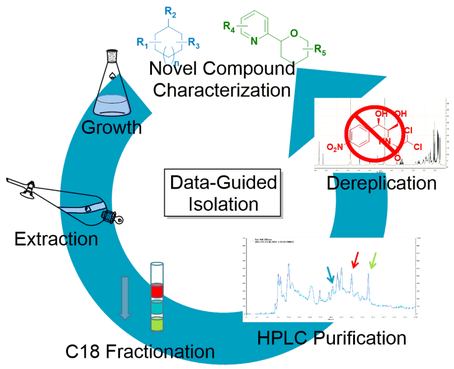
Our screening approach (below) adapts an in vitro transcription/translation assay originally designed to detect new antibiotics. By adding a methyltransferase and a macrolide antibiotic, we can shift the focus of the screen to compounds that inhibit the methyl transferase. Data- or activity-guided assays (above) enable us to follow and eventually identify the active substance from the natural product mixture. By co-administering these adjuvants with antibiotics, we can treat resistant bacterial infections.



United Approach



After confirming positive hits, we follow active hits through bioassay and data-guided isolation. We use natural products chemistry techniques (Extraction, HPLC, NMR, HRMS) to dereplicate and identify new compounds.



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