4al Strategies for Overcoming Drug Resistance

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The selective pressure of a drug on any rapidly proliferating population of cells or organisms results in drug resistance, a medical problem that is often observed in bacterial infections, cancer cells, and HIV. In both my graduate and postdoctoral studies, I have used a wide array of techniques to focus on two complementary strategies for overcoming drug resistance.

One approach is the development of new drugs. During my graduate work in Chaitan Khosla's lab at Stanford University, I investigated polyketide synthases, multidomain enzyme systems that are tractable for combinatorial biosynthesis of bioactive compounds in the polyketide class of natural products. In particular, I quantified the substrate specificity of acyl transferase domains, the key gatekeeper that determines which building blocks are incorporated by polyketide synthases. A fundamental understanding of these domains will allow us to rationally engineer polyketide synthases to produce novel polyketides.

During my postdoctoral work in Patrice Courvalin's lab at the Institut Pasteur in Paris, I pursued a complementary approach to overcoming drug resistance by delving into the molecular mechanisms of resistance. In particular, I studied a clinically novel mechanism of resistance to aminoglycoside antibiotics. The aminoglycoside class includes streptomycin, gentamicin, and amikacin, and are used clinically to treat gram-negative, aerobic bacilli infections. This high-level, broad resistance resulted from methylation of 16S rRNA by the product of the armA gene. I characterized the ArmA's mechanism of methylation, identifying the precise target of methylation, establishing the necessity of ribosomal proteins for methylation, and demonstrating the role of methylation in conferring resistance. This detailed understanding of resistance mechanisms lays the groundwork for developing inhibitors for this clinically relevant antibiotic resistance mechanism.