Converging technologies in the design and the development of novel aminoglycoside antibiotics

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Evolutionary selection pressures resulted in bacteria able to kill other bacteria by the synthesis of complex carbohydrates. The pharmacological optimization of these natural products has resulted in semisynthetic derivatives that have in some cases been developed into efficacious medicinal products. But no matter how great an antibacterial therapeutic is, evolutionary forces remain in power and bacterial resistance to chemotherapy emerges soon after a new drug is launched, demanding continuous and relentless efforts in designing the next generation of antibacterial carbohydrates. Developing a 21st-century aminoglycoside antibiotic of high clinical utility requires substantial improvements to patient safety and bacterial resistance when compared to existing drugs, without compromising its potent and rapid bactericidal activity, broad-spectrum coverage, or stability. Here, we present a multidimensional approach in aminoglycoside drug design integrating technology platforms that assess or predict activity in a specific host environment, selective affinity for bacterial over mitochondrial ribosomes, drug safety, and evasion of resistance due to aminoglycoside modifying enzymes, RNA methyltransferases, and efflux. The carbohydrate chemistry required to synthesize complex new chemical entities is complemented by chemoenzymatic catalysis and metabolic engineering of biosynthetic pathways to achieve scalability in manufacturing and acceptable cost of goods, warranting availability to patients and communities that are affected the most by drug-resistant bacteria.