**Efflux Pump Inhibitors: from Tools to Drugs**

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Recent research confirmed and expanded upon the clinical role that efflux pumps play in antibiotic resistance validating inhibition of efflux pumps in combination with antibiotic therapy as a strategy to significantly improve products for treating resistant bacterial pathogens. At least one class of broad-spectrum bacterial efflux pump inhibitors (EPIs) has been previously reported and extensively characterized both *in vitro* and *in vivo.* While these efforts demonstrated a significant potential for developing small molecule inhibitors of efflux pumps with acceptable serum pharmacokinetics and efficacy and no mechanism-based toxicities, they could not overcome unfavorable tissue accumulation and concomitant local organ toxicity of these compounds. We have initiated an EPI discovery program and conceived of the approach to avoid the tissue accumulation toxicity. This resulted in synthesis of MP-01,003, which demonstrated a persistent serum level but due to specific enzymatic instability, rapidly degraded in tissues, thus avoiding tissue accumulation and concomitant local toxicity. Importantly, tissue-selective degradation did not have any impact on clearance and consequently, on efficacy of so-called soft-drug EPIs. Since then, MP-01,003 has been extensively characterized *in vitro* and *in vivo*, a medicinal chemistry program initiated and improved analogs identified.