

**Discovery of RG6006, a Tethered Macrocyclic Peptide
Targeting *Acinetobacter baumannii***

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In the light of the rapidly rising number of people dying from bacterial infections and the lack of effective antibiotics, the Abx MCP project addresses the urgent need to fight multi-drug resistant bacteria.

The tethered macrocyclic peptides (MCPs) represent a structurally distinct compound class of antibiotics, which possesses a differentiated mode of action. Phenotypic high-throughput screening of a library of MCPs identified a hit, which was selectively targeting *Acinetobacter baumannii*. Medicinal chemistry efforts rapidly resulted in potent compounds, which were able to cure bacterial infections in mice, where established antibiotics failed.

However, these compounds suffered from poor intravenous tolerability and multi-organ toxicity in rats. The lead optimisation was guided by consideration of the antibiotic drug-like space and supported by a customised plasma compatibility assay, producing highly efficacious compounds with improved intravenous tolerability and no organ toxicity. The development compound RG6006 is currently in phase 1 clinical trials, and if approved it would become the first antibiotic of a new class in more than 50 years to be used against infections caused by gram-negative bacteria.