

Sector: Pharmaceutical**Sub-sector:** antibacterial; resistance

Inhibitors of aminoglycoside acetyltransferases as agents to mitigate resistance to aminoglycoside antibiotics

Information Summary

Reference Code:	ROI 05040
Technology overview:	First in class inhibitors of Aminoglycoside 6'-N-acetyltransferasey
Applications:	resistant infections in acute care setting.
Validation:	Preclinical potentiation of Kanamycin activity against <i>E. faecium</i> C238 .
Inventors:	Auclair, Karine et al et. al
Opportunity:	<i>first-in-class</i> adjuncts to conventional aminoglycoside antibiotics
Deal terms:	Exclusive or non-exclusive license to issued U.S. patent application and continuations.
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potentiates the antibiotic activity of kanamycin against *E. faecium* C238.

Medical and market need:

Notwithstanding the documented potential for nephrotoxicity and ototoxicity, aminoglycosides antibiotics remain important and at times indispensable treatment options in human chemotherapy as well as veterinary medicine. There is now a global public health concern due to an exponential rise in bacterial resistance. The problem is particularly acute in critical care settings. The Centers for Disease Control and Prevention (CDC) estimate that over two million hospital-acquired infections occur each year causing extended hospital stays and approximately 88,000 deaths each year in the United States alone. The CDC further reports that in 2002 an estimated 102,000 cases (57%) of the *Staphylococcus aureus* found in U.S. hospitals were MRSA leading to 12,000 deaths and US \$9.5 B in hospital costs. The burden on U.S. healthcare stemming from such nosocomial infections is in the order of US \$5 billion. Accordingly there is a strong need to overcome the MDR phenotype

Technology Summary

This invention relates to novel competitive inhibitors of Aminoglycoside 6'-N-acetyltransferase. The compounds of the present invention possess inhibitory activity against the target enzyme and offer potential as drug candidates in the management of resistance to aminoglycoside antibiotics. The genus also forms the basis of compounds that exhibit dual action activity as both antibacterial agents and bacterial 6'-N-acetyltransferase inhibitors. The high resolution bimolecular crystal structure of some inhibitors complexed with the target enzyme has been solved thereby providing the opportunity for chemical optimization. Proof of concept has been demonstrated with a preferred compound that

Opportunity:

Aminoglycosides are widely used antibiotics for the clinical management of a variety of infections. The increasing incidence of antibiotic resistance is alarming. For example, *Enterococcus faecium* is one of the leading causes of hospital-acquired infections. Since aminoglycoside 6'-N-acetyltransferase type II (AAC6'Ii) is chromosomally encoded in *E. faecium*, infections caused by this Gram-positive bacteria resist aminoglycoside treatment. The compounds of the invention have the potential to become *first-in-class* adjuncts to conventional aminoglycoside antibiotics for the management of bacterial infections resistant to aminoglycosides or combinations of antibacterial agents where an aminoglycoside is indicated.



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Dr. Auclair research focuses on the study of enzymes with pharmaceutical and industrial applications, including enantioselective synthesis. Among the research projects are those relating to enzymes as targets for antibiotics or associated with antibiotic resistance or drug metabolism. The results of our investigations have implications in fields as varied as medicine, biotechnology, and industrial processing, agriculture and food science.

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