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EDITORIAL

Winners of the 2013 JA Medals for excellence

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The Editorial Board of *The Journal of Antibiotics* has changed the terms for the JA Medal, and this prestigious award will now be presented annually to two articles, an original article and a review. The articles must have been published in the journal in the past 24 months.

The 2013 JA Medal for an original article goes to an outstanding paper entitled 'Production of novel lipopeptide antibiotics related to A54145 by *Streptomyces fradiae* mutants blocked in biosynthesis of modified amino acids and assignment of *lptJ*, *lptK* and *lptL* gene functions' by Dylan Alexander, Richard H Baltz and colleagues at Cubist Pharmaceuticals.[1] In this article, the authors report the mutational analysis of lipopeptide antibiotics A54145 biosynthetic genes, *lptJ*, *lptK* and *lptL*, revealing their molecular function and their application in the production of novel antibiotics showing potent activity even in the presence of lung surfactant.

Daptomycin is a cyclic lipopeptide that has been approved for the treatment of complicated skin and skin structure infections caused by Gram-positive bacteria, and for the treatment of bacteremia and right-sided endocarditis. However, its efficacy against community-acquired pneumonia has been insufficient for clinical use, due to the sequestration of daptomycin in the lung surfactant. Therefore, chemical modification or derivatization of daptomycin has been conducted to develop new compounds with potent activity in the presence of surfactant, but none of the compounds were active enough to carry forward into clinical studies.

A54145 is a complex of cyclic lipopeptide antibiotics related to daptomycin, produced by *S. fradiae*. A54145 factors contain modified amino acids, L-3-methyl-Glu_{12} ($3mGlu_{12}$), L-hydroxy-Asn_3 ($hAsn_3$), sarcosine (Sar_5) and L-methoxy-Asp_9 ($moAsp_9$). The *lpt* gene cluster dedicated to the biosynthesis of A54245 has been cloned and analyzed, in which LptI was involved in the biosynthesis of $3mGlu_{12}$. The authors constructed strains containing combinations of deletions of *lptJ*, *ltpK* and *lptL* genes as well as the *lptI* deletion. Determination of the chemical structure of their products demonstrated the molecular functions of LptJ, LptK and LptL in the amino-acid modifications, providing novel information for genome mining of cryptic secondary metabolite pathways.

The Cubist group has discovered that the antibacterial properties of A54145 can be altered by simply changing the modified amino-acid composition. Whereas the fully modified A54145E was the most active antibiotic, several compounds lacking one or two amino-acid modifications were nearly as active as A54145E in the absence of surfactant and more active in the presence of surfactant. The best compound (CB-182,390) displayed only a twofold increase in MIC over A54145E in the absence of surfactant, with no change in potency in the presence of surfactant. The success in producing unnatural natural products with unique biological activity from inactivating the various amino-acid modification enzymes described herein should help in developing a clinically useful new antibiotic.

The 2013 winner of the JA Medal for reviews is for a comprehensive and insightful overview on 'Antibiotics in the Clinical Pipeline in 2011' authored by Mark Butler and Matthew Cooper.[2] In this well-researched paper, the authors not only outline antibiotics in various stages of clinical trials, they also describe the recent history of antibiotics brought to market since 2000. The review begins with a description of the clinical need for new antibiotic drugs and of the drug discovery process, both of which are challenges that new drugs must address and negotiate. The paper presents an accurate snapshot of antibiotic discovery at this juncture: a woefully meager number of compounds in late-stage clinical trials and correspondingly very few approved drugs. This situation has not improved since publication of this review.

The current alarming state of affairs means that we have little in the pipeline to address the growing clinical need for new drugs in the short term. In other words, there are no quick fixes to the problems of resistance on the near horizon. Nevertheless, there is some room for hope, which is another message from this paper. There is a growing interest in the area of antibiotic discovery, in particular in academic and small biotech institutions, and an increasing number of compounds in Phase I and II trials and in preclinical development. The authors' survey shows that natural product and synthetic compounds are roughly equally represented in various stages of development. While most of these are derivatives of known chemical scaffolds already in clinical use, a few are novel structures and this is encouraging. This review nicely describes the state of antibiotic development that is accessible to anyone interested in the area of antibiotic discovery and development and as such is a worthy recipient of the 2014 JA Medal for review.

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1 Alexander, D. C. *et al.* Production of novel lipopeptide antibiotics related to A54145 by *Streptomyces fradiae* mutants blocked in biosynthesis of modified amino acids and assignment of *lptJ*, *lptK* and *lptL* gene functions. *J. Antibiot. (Tokyo)* **64,** 79–87 (2011).
2 Butler, M. S. & Cooper, M. A. Antibiotics in the clinical pipeline in 2011. *J. Antibiot. (Tokyo)* **64,** 413–425 (2011).

Dylan Alexander received his PhD in 1988 in Microbiology and Molecular Biology from the University of Alberta, for his study on the regulation of cephamycin and clavulanic acid biosynthesis in *Streptomyces clavuligerus* under the supervision of Dr Susan Jensen. From 1999 to 2001, he then went on to work with Dr Tom Hosted at the Schering Plough Research Institute, studying novel integrative plasmid systems and characterization of the chloramphenicol and everninomicin biosynthetic gene clusters in *Micromonospora*. In 2001, he joined Cubist Pharmaceuticals to develop the molecular biology tools for the combinatorial biosynthesis of cyclic lipopeptides related to daptomycin in *Streptomyces*. His current research is focused on the discovery and characterization of novel antibiotics, with special interest in antibiotics with activity against multidrug-resistant Gram-negative pathogens.

Richard H Baltz, PhD, received a BS degree in Microbiology from The Ohio State University in 1966 and PhD in Microbiology from the University of Illinois, Urbana-Champaign, in 1971. After completing Postdoctoral research at the University of Illinois, he joined Eli Lilly and Company in 1974. At Lilly, he worked on projects directed at genetic manipulation of secondary metabolite production in actinomycetes, and expression of human peptides in *Escherichia coli* and other microorganisms. He helped build a molecular genetics department in the 1980s, and advanced to the level of Research Advisor. He helped establish Lilly as a world leader in genetic engineering of industrial actinomycetes. His group developed many synthetic biology tools in common use today, and they were the first to generate novel macrolide, glycopeptide and β-lactam antibiotics by genetic engineering. He retired from Lilly in 1998, and founded CognoGen Biotechnology Consulting. He consulted for several biotechnology or pharmaceutical companies, then joined Cubist Pharmaceuticals in 2001 to help develop and launch daptomycin, and to lead the Natural Products group as Executive Director. His group developed synthetic biology methods to generate derivatives of daptomycin, and developed ultra-high throughput natural product screening methods. He retired from Cubist in 2009, reactivated CognoGen, and currently consults for WarpDrive Bio and Dow AgroSciences. He serves on the Scientific Advisory Boards of WarpDrive Bio and SynBERC, and is Senior Editor for Reviews for the *Journal of Industrial Microbiology and Biotechnology (JIMB)*, and Section Editor for *The Journal of Antibiotics*. His current interests include the applications of genome mining and synthetic biology to discover and develop new and novel secondary metabolites for pharmaceutical and agricultural markets. He has presented his work in over 250 publications, book chapters and abstracts, and has 38 issued US patents.

Prof Matthew Cooper completed his PhD in 1995 and then spent 13 years in the United Kingdom, first at the University of Cambridge, then 9 years in start-ups and biotechnology companies. He returned to Australia in 2009 as a NHMRC Australia Fellow, at the University of Queensland, where he is currently driving new antibiotic and bacterial diagnostic R&D. He was founder and Managing Director of Cambridge Medical Innovations (part of Alere Inc.) and CSO and co-founder of Akubio. He has more than 130 scientific articles, 2 books and 20 patents.