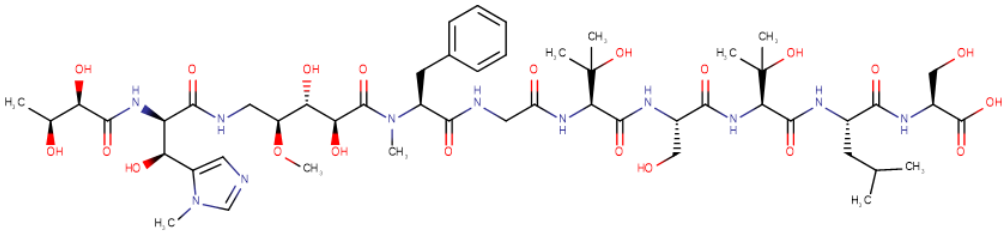
CORRAMYCIN: A NOVEL CLASS OF NATURAL ANTIBACTERIALS FROM MYXOBACTERIA

Eric Bacqué[a], Corinne Leroi-Geissler[b], Anouchka Fievet[b], Nelly Dubarry[b], Sandra Silve[b], Veronique Cazals[b], Astrid Rey[a], Sylvie Sordello[c], Erwin Sentausa[b], Thierry Vermat[b], Patrice Nordmann[d], Marie Attwood[e], Alan Noel[e], Alasdair McGowan[e], Shampa Das[f], Alexander von Tesmar[g], Rolf Müller[g], Jean-Christophe Carry[h], Odile Angouillant[h], Sylvie Monget[h], Thierry Gouyon[h], Isabelle Terrié-Vacher[h]; Karine Vilet[h], Fabienne Thompson[h], Gilles Lebourg[h], Audrey Louboutin[h], Claire Muller[h], Jerome Leroux[h], Victor Certal[h], Nicolas Lebreton[h], Esther Arranz[h], Gilles Doerflinger[h], Francois Bretin[h], Stephanie Versluys [c], Thomas Taillier[a], Stephane Renard [b], **Cédric Couturier*** [a]

[a] *Evotec, 1541, Avenue Marcel Mérieux, 69280 Marcy L'Etoile, France ;* [b] *Evotec, 40 avenue Tony Garnier 69007 Lyon, France ;* [c] *Evotec, 195, route d'Espagne, 31100 Toulouse, France ;* [d] *Université de Fribourg, Section de médecine, Ch. du Musée 8, CH-1700 Fribourg, Switzerland ;* [e] *Bristol Centre for Antimicrobial Research & Evaluation, Department of Medical Microbiology; University of Bristol & North Bristol NHS Trust, Southmead Hospital, Westbury-on-Trym, Bristol BS10 5NB, U.K.;* [f] *Institute of Systems, Molecular and Integrative Biology, University of Liverpool, Biosciences Building, Crown Street, Liverpool, L69 7BE, UK.;* [g] *Helmholtz Institute for Pharmaceutical Research Saarland (HIPS), Helmholtz Centre for Infection Research,* Saarland University Campus, 66123 Saarbrücken, Germany.; [h] *Sanofi, 3 Quai Jules Guesde, 94400 Vitry-sur-Seine, France*

Natural products and their derivatives have played (and will continue to play) a key role in drug discovery. They account for a significant proportion of the marketed drugs currently used to treat a variety of human diseases, such as cancer, diabetes, and infectious diseases.[1] Despite the natural products' major contributions as antibiotics, AMR (particularly the emergence of multidrug-resistant bacteria) still constitutes a global health problem. [2] Finding novel antibiotics that are active against resistant bacteria makes the task even more challenging.

In this context, researchers at Sanofi used an activity-guided approach to isolate corramycin from a culture of the myxobacterium *Corallococcus coralloides*. The compound's structure was determined by combining NMR with total synthesis. Corramycin is a peptide compound with a novel scaffold containing eight α-amino acids (including the previously unknown histidine analogue δ-N-methyl-β-hydroxy histidine) and an unusual sugar moiety. The compound displayed a moderate level of activity (minimum inhibitory concentrations (MICs): 4 to 64 µg/mL) against several multidrug-resistant, Gram-negative bacteria, including *E. coli* ATCC25922, *K. pneumoniae* 13883, and *A. baumannii* ATCC1906, but was not active against Gram-positive bacteria. Corramycin exhibited good physicochemical and ADME properties, poor PK parameters, and remarkable *in vivo* efficacy in a model of *E. coli* septicaemia – making it a very attractive starting point for a lead optimization programme.



Multiparameter lead optimization was initiated by Sanofi and Evotec and led to the synthesis of more than 800 corramycin analogues. Of these, a new analogue of Corramycin was found to be at least 300 times more potent than native corramycin against *E. coli* 25922, *K. pneumoniae* 13883, and *A. baumannii* ATCC1906 (MICs: from 0.015 to 0.031 µg/mL). It showed good ADME-PK properties and reasonable activity against *E. coli* and *K. pneumoniae* in vivo. Overall, Corramycin is a promising candidate for the development of a new series of antibiotics against Gram-negative multidrug-resistant bacteria.

References

1/ Tackling Drug-resistant infections globally: final report and recommendations. The review on antimicrobial resistance chaired by Jim O'Neill, 2016.

2/ Rossiter SE, Fletche MH, Wuest WM. Natural Products as Platforms To Overcome Antibiotic Resistance. *Chemical Reviews* **2017**, 117, 12415. https://doi.org/10.1021/ACS.CHEMREV.7B00283.