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A potent next-generation glycopeptide with best-in-class potential

The discovery and development of new antibiotics with enhanced activity, reduced toxicity, and the capacity to overcome resistance is a challenge of growing societal significance. In addressing this challenge, the Martin group applies chemistry-based strategies to enhance the properties of structurally diverse naturally occurring antibacterials. To this end we recently reported a novel class of highly potent semisynthetic glycopeptide antibiotics with enhanced activity against a range of Gram-positive pathogens including clinically relevant strains of methicillin-resistant *Staphylococcus aureus* (MRSA) and *Clostridium difficile*.[1,2]

This lecture will cover the design and synthesis of these next-generation glycopeptides as well as the biochemical and biophysical techniques used to characterize their mechanism of action. In addition, assessment of the *in vivo* activity of these new antibacterial agents in established infection models will be presented.

References:

[1] van Groesen, E.; Mons, E.; Kotsogianni, I.; Arts, M.; Tehrani, K.; Wade, N.; Lysenko, V.; Stel, F. M.; Zwerus, J. T.; De Benedetti, S.; Bakker, A.; Chakraborty, P.; van der Stelt, M.; Scheffers, D. J.; Gooskens, J.; Smits, W. K.; Holden, K.; Gilmour, P. S.; Willemse, J.; Hitchcock, C. A.; van Hasselt, J. G. C.; Schneider, T.; Martin, N. I., Semisynthetic guanidino lipoglycopeptides with potent *in vitro* and *in vivo* antibacterial activity. *Science Translational Medicine,* **2024,** *16* (759), eabo4736.

[2] Mons, E.; Henderickx, J.G.E.; Sanders, I.M.J.G.; Rader, A.G.; Perkins, C.E.; Stel, F.M.; van Groesen, E.; Smits, W.K.; Theriot, C.M.; Martin, N.I., Experimental glycopeptide antibiotic EVG7 prevents recurrent *Clostridioides difficile* infection by sparing members of the *Lachnospiraceae* family. *Nature Communications*, **2025**, *16*, 9017.