Written responses to open questions of the webinar 'Discovery of new antibacterials using artificial intelligence (computational chemoinformatics)' by James J. Collins, Cesar de la Fuente, Henriette Willems and Fredrik Svensson, originally broadcast on 17 November 2020. See webinar recording here: https://revive.gardp.org/discovery-of-new-antibacterials-using-artificial-intelligence-computational-chemoinformatics/

	Question asked	**Response from the speakers**
1	Since the membranes are different between gram positive and Gram-negative bacteria, how does one get a broad-spectrum membrane targeting antibacterial with a specific mode of action?	We have not studied the mechanism of action of halicin against Gram-positive bacteria. You could have a molecule that generally targets bacterial membranes (both Gram-negative and positive).
2	How do you fund the wet lab work you have done? Taking the in silico work into the real world. I ask because grants/investors in my experience can be put off without solid 'real world' data.	We have received funding the Audacious Project at TED to launch the Antibiotics-AI Project. Mostly through a combination of federal funding (e.g., NIH, DoD) and funds from companies. Such funds help generate the data needed for AI approaches.
3	Knowing the mechanisms of resistance to antibiotics, could the antibiotic be designed in a single molecule together with the factor that inhibits resistance?	Yes. Some drugs are known to have dual pharmacology (see for example DOI: 10.1111/j.2042-7158.2010.01236.x) One strategy for designing dual pharmacology is to combine the pharmacophore features required for both pharmacologies in to one molecule. It may be possible to do something similar for antibiotics by combining features known to inhibit resistance with features that give antibiotic potency, possibly at different ends of the molecule. I have successfully used this approach, but not applied to antibiotics.
4	Can you successfully run virtual screens on very large compound databases, such as Zinc or Enamine REAL, with limited resources?	We have successfully run virtual screens on Enamine REAL, but not by docking the whole REAL database. We selected a subset of REAL compounds using Infinisee from BioSolveIT, based on FeatureTree similarity to known actives. This set of around 40,000 ligands was then docked in Glide and scored and a small subset selected for purchase. The Infinisee software can screen the whole EnamineREAL in minutes, but this is a 2D method, it cannot use protein information.
5	Have you looked at Metagenomics for microbial peptide antibiotics and compared it to human derived peptides?	We have looked at genomes and proteomes searching for antibiotics. We have not yet done a side-by-side comparison of microbial vs human molecules.
6	Can this approach be applied to natural products or is it restricted to small molecule drug discovery?	Yes

Remaining audience questions from the webinar 'Discovery of new antibacterials using artificial intelligence (computational chemoinformatics)', broadcast on 17 November 2020