Written responses to remaining audience questions of the webinar 'Journal Club: Key findings from recent publications in antimicrobial R&D' by David Paterson, Melis Anahtar and Nicole Scangarella-Oman, moderated by Florian Maurer.
Originally broadcast on 26 March 2026. See webinar recording here: https://revive.gardp.org/journal-club-key-findings-from-recent-publications-in-antimicrobial-rd/

Question asked	**Response from the speakers**
What is the clinical efficacy of Aubaucin, the antibiotic developed using AI?	Melis: Abaucin was discovered in Jonathan Stokes' lab, he would be the best person to ask about whether they have plans to advance the compound into clinical studies. The first AI-discovered antibiotic candidate, halicin, which Jon found when he was a post-doctoral fellow in Jim Collins' lab, is being further developed by a non-profit antibiotic development company called Phare Bio.
We are so focused on working on new drugs, rather than trying to enhance the ones we already have. Between working on a new drug and enhancing the existing ones, which of them takes more time? What were the tools that you used for prediction?	Melis: Working on a new hit molecule takes more time and resources, but has the advantage of discovering new mechanisms of action to which bacterial resistance has not yet formed. We developed graph neural network models using a package called Chemprop. We trained our models on a set of nearly 39,000 molecules that we tested for growth inhibition activity against Neisseria gonorrhoeae or Staphylococcus aureus.
You validated only few compounds as active, but your pipeline rejected millions of candidates based on computational filters alone. How can you be confident you haven't discarded potentially superior antibiotics simply because your AI scoring functions couldn't recognize them? In other words, what is the false negative rate of your model, and is it even measurable?	Melis: It's quite possible that we discarded some potential active compounds. Model performance is lower on chemical structures that are vastly different from the training set, so those would be the most likely false negatives. We have not fully quantified the false negative rate of the model, and it would vary dramatically based on the chemical library being screened.
Is it possible to add a rule regarding potential resistance development (or an existing resistance mechanism)? - I do not think we need new antibiotics, we need to use what we have in a better/ more clever way (bacteria will	Melis: This model does not predict the effect of antibiotic combinations or potential resistance development. We test those two properties once we have a promising hit, through checkboard assays (to look for synergy/antagonism) and in vitro assays to measure sponanteous mutation frequencies and serial passaging experiments (to assess for potential resistance development.)

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always outsmart us/AI). Does the model predict the effect of a combination? It does not have to be two antibiotic molecules. Molecules from other therapeutic classes could have a positive effect.	
Can these small molecules penetrate the outer membrane of Gram-negative bacteria?	Melis: We think that NG1 is able to penetrate the outer membrane of *Neisseria gonorrhoeae*. We're not sure if it's able to penetrate other gram negative outer membranes because it does not have activity in those organisms, either because it cannot penetrate the outer membrane to access the target or the target is sufficiently different to preclude binding. The de novo compounds DN1-3 gained activity in E. coli when we tested the lptD mutants, which indicatses that the lack of activity on wild-type E. coli was due to inability to penerate the outer membrane (see Figure 6B).
Have you had a case where the compound had no activity at all? Or was promoting the growth of the pathogen? If yes, what was the problem during the design?	Melis: Yes, many compounds had no activity (MIC >128 µg/mL), like NG2 in the fragment-based design approach, all 16 compounds based on fragment F2', and 16 of the fully de novo designed compounds (see Figure 5F).
Are there any training programs or courses available that teach how to use AI tools for designing and developing new antibiotic molecules?	Melis: Not to my knowledge, but there are great resources like Wong et al., Nature Protocols, Dec. 2024, that walk you through the process we have used.
Very nice data!!! Would you expect efficacy to remain as strong in more complicated UTI settings, recurrent infections, or patients with prior antibiotic exposure, where bacterial populations may be more heterogeneous than in uncomplicated UTI?	Nicole: Gepotidacin's indication (and associated prescribing information) is limited to uUTI. Due to it's low systemic PK, it is not expected to be efficacious in the treatment of complicated UTI (e.g. UTI infections outside the bladder). However, as shown from the published data from the EAGLE-2 and EAGLE-3 clinical trials, it has demonstrated efficacy in the treatment of uUTI in different subgroups of patients, those with recurrent uUTI or uUTI's caused by drug-resistant pathogens.

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What is the main difference between gepotidacin and other antibiotics? Why is it better than other antibiotics? What makes it special?	Nicole: Gepotidacin's novel chemical structure, distinct binding site and unique mechanism of action makes it different from other antibacterials. This provides activity against isolates resistant to other antibacterial classes, and it's well balanced inhibition of 2 enzymes leads to a lower propensity for development of resistance