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Artificial Intelligence's Role in Combating the Antibiotic Resistance Crisis

Dr. Doghramji:
As a prevalence of antibiotic resistant continues to increase at an alarming rate, driven in part by the lack of new antibiotics being developed, researchers around the globe are working to identify potential antibiotic candidates to help combat this global crisis. And now, one such candidate has been found by an unexpected source: artificial intelligence. And how this discovery came about and what this means for AIs potential role in combating the antibiotic-resistant crisis, will be the focus of today's discussion.
Welcome to the Clinician's Roundtable on ReachMD, I'm Dr. Paul Doghramji and joining me today is Johnathon Stokes, a Post-Doctorate Fellow at the Board Institute of MIT and Harvard. He's also the lead author of the study that identified this powerful – and – new antibiotic compound. Thanks so much for joining us today, Johnathon.

Dr. Stokes:
Hello.

Dr. Doghramji:
So, before we jump right into the study, I'd love to learn more about how you started exploring the use of artificial intelligence to identify new antibiotic candidates.What sparked this line of research for you, Johnathon?

Dr. Stokes:
Yeah, so it was kind of interesting how it happened., Professor Collins and Professor Barzilay are the two corresponding authors on this manuscript, and they are faculty co-leads at J-Clinic at MIT. And J-Clinic is an effort to leverage AI approaches in healthcare. So being faculty co-leads, they both come from quite different academic backgrounds as well. Professor Collins is a bioengineer and Professor Barzilay is an expert in natural language processing. When they started working together as faculty co-leads, they wanted to work on a collaborative project, and given our labs interest in antibiotics and her labs relatively recent interest in applying natural language processing and approaches to chemistry, it seemed like an interesting collaboration to potentially use both of our expertise towards the discovery of new antibacterial molecule.

Dr. Doghramji:
Wow, that was very interesting background, thanks for that information. So, let's dive into some of the details here. What approach did your team take to reveal this new antibiotic compound?

Dr. Stokes:
For AI and machine learning models, in general, you have to provide them with training data. Examples of something that you want to see so they can make predictions on new things. So, what we did is we took one of Professor Barzilay's lab's models that they have used previously for molecular property prediction as it relates to physical chemical properties, so things like solubility. So we took that general frame work and instead of asking the model to predict physical chemical properties, we asked it to predict biological properties. And in our case, this was antibacterial activity. In the Collins' lab, we have a collection of about 2,500 small molecules. These include FDA approved drugs. So we have 1,700 or so of those and then we also have a collection of about 800 natural products compounds that are purified, which have been isolated from a variety of microbial and plant sources. So we have this library of 2,500 molecules. So at the start of the project, we screened those 2,500 molecules for those that inhibited the growth of E. coli. Just in a 96-well plate. So then we had this growth inhibition data of these 2,500 molecules and then we showed the model, the structure of every molecule, as well as its corresponding growth inhibition activity. And that was binarized, so we have the molecule. Did it inhibit growth, yes or no? So we have 2,500 molecule activity pairs. That's what we used to train the model on. And then with that model, we were able to run predictions

for antibacterial activities specifically across different chemical libraries, both housed here at The Broad and the virtual chemical library that is the ZINC 15 data base.

Dr. Doghramji:
Okay, and the results? What exactly did you find?

Dr. Stokes:
After we trained our model on the 2,500 molecules, we first applied it to the drug repurposing hub housed at the Broad Institute, and the drug repurposing hub contains both drugs that are used in the clinic for a variety of diseases, as well as the molecules in phase one, two, and three clinical trials and those that are in preclinical development. So, when we applied our model to the drug repurposing hub, we are looking for molecules that were both highly likely to be antibacterial, meaning that they had a high prediction score, the model strongly predicted that they were antibacterial, but the other constraint that we put was we only were interested in molecules that were structurally dissimilar from known clinical antibiotics. And that is measured in something called a tanimoto score. So, tanimoto similarity is a way of comparing two different structures of antibiotics and saying how similar are they? So, when we were looking for molecules, we wanted molecules that had a low tanimoto similarity to any clinical antibiotic. And the molecule that fit those two criteria, right, structurally dissimilar from known clinical antibiotic and strongly predicted to be antibacterial, was this molecule that we ended up naming halicin.

Dr. Doghramji:
Very interesting. So, now as I understand it, several other potential antibiotic candidates were also found using this machine learning algorithm and they show potential for new drugs based off of their chemical structures, so what components make up these particular molecules and what makes them so much more powerful than current antibiotics?

Dr. Stokes:
Right, so after we had ran our predictions on the drug repurposing hub, discovered halicin, we then leveraged our model to predict molecules from the ZINC 15 database. And the ZINC 15 database is a virtual chemical library that's composed of about 1.5 billion molecules. So, instead of applying our model to all 1.5 billion molecules, we selected a subset of around 107 million on which to run prediction. And just for reference, in a wet lab, your upper limit of molecules that can reasonably be screened is on the orders of a few million. You're not going to find very many screens that are beyond that. So, us being able to analyze the structures of 107 million molecules, I put this at two orders of magnitude greater than that, which we thought was quite exciting. Anyway, from the 107 million molecules, again, we prioritize those that were highly likely to be antibacterial, as well as structurally dissimilar from known antibiotics. So, with those constraints, we were able to curate 23 of such molecules for testing in the laboratory, and 8 of those 23 displayed antibacterial activity and at least one of the tested species, and we tested these molecules against just lab-strained E. coli, MRSA, Klebsiella pneumonia, Acinetobacter baumannii, and pseudomonas aeruginosa. Of these 8 molecules, we were particularly interested in 2 of these 8 because they displaced quite broad-spectrum activity.

Dr. Doghramji:
So for those just tuning in, this is the Clinician's Roundtable on ReachMD. I'm Dr. Paul Doghramji, and today I'm speaking with Johnathon Stokes from the Board Institute of MIT and Harvard about the recent discovery of a powerful new antibiotic compound that was identified using this artificial intelligence. So, Johnathon, now that we've covered what the study entailed and what was found, let's talk about its potential impact and based on the results, how do you think this may affect the global crisis around antibiotic resistance and its costly measures?

Dr. Stokes:
Yeah, so halicin is a really interesting molecule. It has a number of biological properties that we found quite exciting. First, it is a bactericidal, meaning it kills bacteria, but it's not only bactericidal against metabolically active and growing bacterial cells. It displays bactericidal activity against metabolically dormant cells. What's interesting is the vast majority of our currently used bactericidal antibiotics and they display great efficacy against metabolically active cells, those that are active growing and dividing let's say, but they fail to eradicate cells that are metabolically dormant. However, we showed that, halicin was able to retain this bactericidal activity against dormant cells. And there's quite a lot of recent evidence showing that these metabolically dormant antibiotic tolerance cells they're called, are responsible for chronic and recurrent infections in humans. So, the fact that halicin was able to eradicate these cells irrespective of their metabolic state suggest that it may have the capability of doing this in as well, which would prevent chronic and recurrent infections. The second thing that we tested was its ability to overcome various antibiotic resistance determinants. So we tested a small collection of antibiotic resistance determinants in E. coli and showed that halicin was able to retain activity in the presence of different antibiotic resistance genes and we also tested halicin against panels of carbapenem-resistant Enterobacteriaceae, Acinetobacter baumannii, and pseudomonas aeruginosa. And we observed that halicin retained activity in the vast majority of CRE isolates we tested and Acinetobacter we tested. We observed that it did not display strong efficacy against pseudomonas aeruginosa,

and we don't have empirical evidence for this, but getting molecules into pseudomonas remains a challenge. So we think it's just a permeability issue that we're dealing with. And the last phenotype that we observed is the frequency of resistance to halicin in the laboratory appears to be very low. So we ran an experiment. It was a 30-day long experiment where we tried to evolve spontaneous resistance to halicin in the lab using E. coli. So, we had halicin and then we compared it to how easily E. coli could evolve resistance to ciprofloxacin. And we observed E. coli began to evolve resistance to ciprofloxacin anywhere between like one to three days. However, over the 30-day experiment that we performed, we were unable to evolve resistance to halicin at all. And that's exciting because if the evolutionary barrier to evolving resistance is very, very high, as it appears to be, it may suggest that a molecule like this could have a prolonged shelf life in the clinic.

Dr. Doghramji:
It's a very interesting way of inventing a new medication. So how do you think this might impact the future of biotech and pharmaceutical industries for new antibiotics?

Dr. Stokes:
Yeah, I feel like the adoption of machine learning approach is beginning to permeate all aspects of our life, right? You know, we all get a different Amazon page when we open it up based on our previous buying history. All this stuff. So, I feel like it's natural about these approaches will strongly influence the future of biotech and pharma. Not only toward the discovery of new antibiotics, which we desperately need, but I feel like these approaches will also be leveraged, you know, to find new cancer drugs or hypertension medication. I'm very confident actually that these approaches will become more widespread in therapeutics discovery and development in general.

Dr. Doghramji:
Well, in line with that and looking at the future, what's next on the horizon for you and your colleagues? Will there be another line of investigations extending from this study sometime down the road?

Dr. Stokes:
Yeah, so the project that we're working on right now is leveraging very similar ML approaches to discover narrow spectrum antibiotic. So, you know, most antibiotics are fairly indiscriminate. You take them, and they'll treat, hopefully your infection, but they'll also kill your microbiome, which then leads you open to opportunistic infections like C. difficile. However, with a narrow spectrum agent, in theory you'd be able to take such an antibiotic, it would eradicate your infection, but spare your microbiome. So that's the project that I am immediately working on right now.

Dr. Doghramji:
That seems like a very nice way of approaching infectious diseases and in treating specific infections. Well I certainly hope to have the chance to speak with you again, Johnathon, once those future developments are underway, but for now, I want to thank you for joining me and shedding light on how artificial intelligence is being used to usher in new antibiotics. It was great having you on the program today.

Dr. Stokes:
Thank you very much for having me.

Dr. Doghramji:
I'm Dr. Paul Doghramji and you've been listening to the Clinician's Roundtable on ReachMD. To access this episode and others in the series, visit ReachMD.com/cliniciansroundtable where you can be part of the knowledge. Thanks for listening.