Science Will Win
Season 3, Episode 3

Imagine this hypothetical scenario: You're a research chemist at a university hospital in a metropolitan area. Your specialty is finding molecular compounds that could become antibiotics.

And for the first time in years, you're bursting with excitement to go to work. Your team just got access to an invaluable new tool.

On your commute this morning, the weather is an uncomfortable mix of humid and rainy. Since you left early, the train to the lab is a bit sparser than usual. You manage to snag a seat.

As soon as you relax into your spot, your mind wanders to your greatest concern: the rising prevalence of antibiotic resistant infections in your area.

You have access to local microbiology surveillance data that suggests drug resistant bacterial infections, and in particular, a dangerous strain of MRSA, are rising sharply. These predictions accelerated work that your lab had already been doing for years, trying to discover a new antibiotic that could treat infections caused by this kind of bacteria more specifically and effectively.

Over the course of those years, your fellow chemists have been doing painstaking research to narrow the pool of potential treatment options to about one thousand compounds, when your initial models started at five thousand. But work has been slowing down. You and your colleagues have had to choose the most likely options and run experiments or simulated tests to determine which one should move forward with development.

Fifty potential compounds have been ruled out so far, as many of these prospective treatments would be too toxic for the human body.

You feel immense pressure to work harder, better. All the while, you've been hearing from your physician friends about the increasing number of patients dealing with multidrug-resistant superbugs in the hospital. Though a viable treatment is likely years away, you're reminded nearly every day how important your work is.

And that brings your mind back to why you're excited today. Your lab just got access to a new tool, powered by artificial intelligence. It's been trained on a large volume of data – like molecular structures, or information about the activity and function of molecules and

their potential for therapeutic activity as antibiotics. You'll be able to screen those one thousand compounds for the most likely potential treatments.

When you get to the research center, you nod to the receptionist and hurry straight to the lab. You're still shrugging on your lab coat when you make it to the computer, meet the computational scientist, and run the AI program.

You chat excitedly with the computational scientist as you run the algorithm together, and it only takes 15 minutes to deliver the results.

Your heart stutters a beat.

Already, the AI has suggested *three* compounds that match your criteria. What could have been a labor-intensive, manual slog through one thousand options, or months of narrowing down that number further, has become a targeted look at the most promising three options.

You don't know yet if any of these options will be successful. But for the first time in years, you feel hope.

[MUSIC]

Jeremiah:
This is season three of Science Will Win. I'm your host, Jeremiah Owyang. I'm an entrepreneur, investor, and tech industry analyst. I'm passionate about emerging technologies and the ways they can shape our world.

This season we're talking about artificial intelligence and how it can help the scientific community overcome one of the greatest challenges facing humanity: antimicrobial resistance, or AMR.

Now the scenario you just heard at the top of this episode is hypothetical. It takes place in a not-too-distant, potential future where the problem of AMR that we're currently facing has worsened slightly. But the technology mentioned is based on technology that we're going to be talking about today. Technology that researchers are using to help solve the problem of AMR, among many other big challenges in healthcare.

[MUSIC]

In our last episode, we learned how artificial intelligence is helping us understand the medical and biological problem of AMR. In particular, because it helps researchers make sense of *a lot* of data.

This episode, we're talking about using data from molecular diagnostic tests to get faster, more precise diagnoses of infection. And we're talking about using a combination of biological and molecular data to help scientists discover new drugs. Artificial intelligence may be key for both.

[MUSIC]

So, let's think back to the hypothetical from episode one, where our patient was diagnosed with antibiotic resistant MRSA. How does a doctor determine what is causing an infection? We're going to take a look behind the scenes.

Adrian Egli:
What I do as a medical microbiologist. So I do a bit both diagnostics and research.

Jeremiah:
That's Dr. Adrian Egli again. He's a professor of medical microbiology at the University of Zurich in Switzerland.

Someone like Adrian comes in when doctors swab a sample from a wound to gather a bit of the bacteria, then they can send that to the lab to help with the diagnoses.

Adrian:
So basically, very often they call the lab, they ask us, uh, what kind of samples should they take? What is the, the right sample material, and so on.

Jeremiah:
Once the sample reaches the lab, the technicians start to grow – or "culture" – the bacteria in a small dish. When enough of the bacteria grows, they can look at it under a microscope to actually identify what species it is.

It's not as simple as just looking at it and knowing what it is. Lab technicians have to look at all the bacteria's characteristics: its shape, growing pattern, and structure. Traditionally, this has been a very laborious process.

Adrian:
The classical way how we, how we work in the lab, it's a lot of labor. So you would need to stain the slide, uh, apply the, uh, gram stain potentially manually nowadays, we would also have robots who do that, but let's assume we do this manually.

Jeremiah:
The stain helps technicians figure out whether the bacteria are "gram positive" or "gram negative." That's essentially a classification for differences in the cell wall of the bacteria. That can also help technicians begin to identify the species.

Adrian:

Then you put the slide under the microscope, you have to focus yourself so there's no auto focus done by the robot, so it's really on your own. Look through the slide, you know, slowly scanning through the slide. It takes ages and then maybe it's, uh, you know, you're right after lunch, you are tired, actually you're more feeling like a nap or your thoughts are somewhere else. Maybe you think about your holidays. So there are lots of reasons how a human being can be distracted.

Jeremiah:
That's where artificial intelligence comes in: by helping to increase productivity around these tasks.

Adrian:
And I think that's the beauty of AI. So it's, it's consistent. And humans can also do more exciting jobs than screening a microscopy slide. So if we have a sample and we, for example, look, uh, under the microscope and we do a gram staining, then automated image analyzes using AI can recognize gram-positive and gram-negative bacteria. It can separate rods and cocci and it can really do this in a very consistent way, um, and very precisely, and there are commercial systems around which can do that. So AI-based microscopy, that's one, one way how AI can, can be applied.

Jeremiah:
Once the lab techs determine what species they're looking at, that's when you know what's causing your infection.

The scientists also then culture the bacteria in the presence of antibiotics, to see which ones can kill the bacteria.

The scientists are also able to analyze the bacteria using molecular characterisation or whole genome sequencing to learn more about the genetic sequence of that particular bacteria, and if it holds any mutations that could cause resistance to current antibiotics.

The combination of drug susceptibility and genetic resistance data may be used to help doctors choose the right medicine to use against a tricky infection.

Adrian:
And then we have a result. So we very often do a profile of different antibiotic drugs and then we have to communicate this profile. And that's very often a quite complex, you know, table of information. And we do this electronically. But what is also very important is the personal discussion with the treating colleagues. So I would, for example, call the infectious disease specialist and really discuss the results and say, and say, how good do the individual drugs work?

Jeremiah:

Using artificial intelligence is about *augmenting* human intelligence and ability, not replacing humans altogether. Training AI to take over tasks streamlines the process. That allows doctors and researchers to work on solutions more efficiently.

So, using artificial intelligence techniques, lab teams like Adrian's can help doctors find the right diagnoses more quickly. But as we've discussed on the show already, it's becoming increasingly common for *none* of the antibiotics we have right now to be effective against any given bacteria. So what do we do then?

[MUSIC]

To pinpoint potential new antibiotics, researchers first need to understand what they're up against. In the last episode, we talked about a lot of ways AI plays a role in that.

Scientists like Adrian are working on sequencing the genomes of these resistant bacteria to find patterns because a bacterial genome can be up to *14,000,000* base pairs long. Base pairs are the building blocks that make up DNA. A small change in even *one* of these pairs can potentially lead to antibiotic resistance.

Adrian:
And this is like comparing two books versus each other. Let's say you have a book, um, which you read, and then you have the exact same book, um, again, then all the letters are the same. That's the comparison of two genomes. But if there's a single, um, letter changed, you have a typo basically in one of the books, that can have, uh, quite some consequences. And if you have a series of these typos, you would even say this is a different book or a different book chapter.

Jeremiah:
The more genomes researchers sequence, the more data points there are over time to paint a picture of how certain bacteria might be changing. Which is where artificial intelligence plays a crucial role. AI is great at taking massive amounts of data and finding trends inside it, the kind of trends that humans wouldn't be able to find. At least, not without a *lot* of looking.

Adrian:
The amount of data we can nowadays produce is so massive that we need artificial intelligence to actually make sense out of that. There are too many data points. So it's no longer a matter of producing large amount of data. Nowadays we have the technology that you can sequence a bacterium within 10 minutes. So, to generate the information is not a problem. The problem is to actually make sense out of it.

Jeremiah:
Identifying changes and trends in bacterial genomes can help researchers understand the mechanisms of resistance at play. They might even help the scientific community find weaknesses in bacteria, or predict the rise of new resistances.

Because one important goal is to find new potential antibiotics that will avoid these same issues of resistance. Some extra help from artificial intelligence along the way could also make the process more efficient.

> Marinka:
> It can cost two to 3 billion dollars to develop a new drug from scratch and design it, develop it, and eventually deliver it to the market so that patients can actually benefit from it.

That's Dr. Marinka Zitnik. You may remember her from the previous episode. She's at the forefront of bringing machine learning into drug discovery and development, to help researchers and labs around the world. In 2020, Marinka founded the Therapeutic Data Commons.

> Marinka:
> It's the largest open science initiative that serves a submitting point between on one end drug designers, biomedical researchers who work in the broad area of drug discovery and development, and on the other end, the community of AI experts and machine learning specialists who can develop powerful new deep learning and machine learning models.

Jeremiah:
Marinka thinks that machine learning and AI in drug discovery and development can significantly speed up the process, allowing patients to potentially get more effective antibiotics faster.

For a drug to go from an undiscovered concept to a pill in a bottle at a pharmacy takes years – often over a decade – of time and effort. What starts as an idea for a drug has to go through a process of screening and design. Then it has to be synthesized and developed before it can even start being tested for safety and effectiveness.

So, to explore how artificial intelligence might help that process along, let's start at the beginning: screening and design.

> Marinka:
> This process is concerned really with finding and optimizing candidate molecules. Most typically, those are small molecules that are chemicals that might have drug-like properties. At that stage, we don't yet know if they are safe for human patients, where we simply have information about the chemical structure. And we want to figure out is the chemical structure of this molecule that we're currently looking at, similar to the structure of molecules that are approved drugs and safe and effective for humans. And that's the step one and stage one.

Jeremiah:

But finding potential chemicals that could become drugs, and then choosing the best ones to actually move forward with, is a lot harder than it might seem. On the surface, the possibilities are essentially endless.

> Marinka:
> The size of the chemical space, which is the number of chemical compounds that could potentially be synthesized in labs, is estimated to be close to the 10 to the power of 60, which is one followed by 60 zeros.

Jeremiah:
Just to put that into perspective, 10 to the power of 60 is about one trillion *more* possibilities than there are atoms on Earth.

> Marinka:
> The sheer number of possible compounds is so, um, big that there is no way we can experimentally just go and in a brute force approach test and try each and every one and see whether it has certain desirable, uh, biological antibiotic properties.

Jeremiah:
These numbers feel unfathomable. Researchers have long had scientific methods to narrow this pool. Otherwise, how could they choose any compound to develop? But even so, AI can quickly and effectively sort through that massive library of possibilities. Then, it can prioritize the compounds that seem most likely to have antibiotic properties, based on what has worked in the past.

> Marinka:
> And that, effectively then means that downstream biological experiments in the wet lab and and elsewhere could focus on those, uh, highly scored, uh, candidate compounds first rather than experimentally exhaustively trying out each and every chemical compound in a collection of, uh, compounds that, um, that that can potentially be generated.

Jeremiah:
The full drug development process is labor intensive, expensive, and time consuming. Many of those potential drugs are not going to turn out to be viable options – whether that means they are ineffective against the disease they're meant to target, or they are too toxic for the human body. Getting a better chance at picking a promising option from the start could go a long way.

Pfizer, for example, already uses artificial intelligence to help with the screening and design process.

> Lei:
> There are, you know, several different ways we're using AI to, um, help in this particular phase.

Jeremiah:
That's Dr. Lei Zhang, Executive Director of Medicinal Chemistry in Medicine Design at Pfizer. He doesn't work on antibiotics specifically. But, he has been working on discovering new small molecule medicines at the company for two decades.

Lei and his team use artificial intelligence technology during the screening process to narrow down their options before selecting a chemical compound for development.

> Lei:
> This process can help us to sample a much greater chemical space, uh, and identify potential hits without the need of physical screening of every single compounds, right? So this is a way for us also save time and cost as well.

Jeremiah:
Once a potential molecule has been identified, the drug has to actually be designed. To do that, Lei's team turns to artificial intelligence and machine learning once again.

> Lei:
> We do have, uh, machine learning tools that is knowledge-based. And, um, we couple that with extensive computational modeling and simulation to generating new design ideas that prospectively give us, uh, hopefully better potency and selectivity.

Jeremiah:
So, Lei and his team create these simulations as computer models to help them find the right molecular structure, determine the right or best dose for therapeutic effect, and see how the molecule will be metabolized in the human body.

After the design process, those candidate molecules move on to the next stages: synthesizing and testing out those molecules in the lab. Synthesizing is a part of the development process that turns these designed molecules into an actual drug. Because designing the molecule is only beneficial if it can become a safe, effective drug that you can produce at scale.

Think about the development of penicillin, which we talked about in episode one. The roadblock that stalled the development of the drug was *not* whether or not it was effective – it was whether or not researchers could find the right way to make it. It took over a decade for that to happen.

This is where AI's ability to find trends can help out again. Chemists have a better shot at getting those production methods right the first time when AI can provide suggestions based on a long history of experience. Lei has found AI to be particularly helpful with designing something called a synthetic route – basically the directions for building the chemical compounds of drugs.

> Lei:

When you design a synthetic route, you, you sort of, you know, disconnect them into different building blocks. You may think about what is the transformation to connect those building blocks together. And there are many different options for you, uh, particularly around the reagent choices and the reaction choices. And there's extensive chemical literature up there. And once AI model was trained over there, they can look at the knowledge base, the, you know, the knowledge extracted from those database and give you suggestions. This is the reagent, this is the reaction condition, most likely will make the reaction go well and give you the best yield so that then you can incorporate that into your work and, and which in turn can improve your success rate of overall synthetic route.

Jeremiah:
Once drugs have been synthesized, they need to be tested for safety and effectiveness. First, that happens in the lab – testing potential drugs on human and bacterial cells in a petri dish. AI can even help during this process. Data from around the world can be used to train AI to perform safety screenings *digitally*. That way, scientists can focus on key experiments to test their hypotheses.

Eventually, after many tests and trials, the few potential medicines that are deemed safe and effective will move on to human clinical trials to confirm their safety and effectiveness.

[MUSIC]

Understanding all of the work that goes into developing new viable drugs might feel like it's at odds with the urgency of this situation. But, just a few years ago, we saw the real benefits of artificial intelligence partnering with scientists to find a much-needed new drug.

Recently, Pfizer used AI to support development of an oral antiviral medicine following the onset of the COVID-19 pandemic. Remarkably, the treatment was developed and made accessible to eligible patients in just over a year.

This was possible for two reasons. One, Pfizer had existing and relevant institutional knowledge related to the development of potential treatments for similar viruses. In 2003, there was an outbreak of SARS, a virus very familiar to Pfizer scientists. The learnings from that outbreak helped scientists identify ways they could similarly combat the virus responsible for COVID-19.

And two was artificial intelligence.

Some members of Dr. Lei Zhang's team at Pfizer helped create that medicine.

Lei:
AI, machine learning, pharmacokinetic and human dose prediction tools are absolutely used at every single step of designing that molecule as well.

Jeremiah:
Now, this medicine is not an antibiotic. It's an antiviral treatment. New classes of antibiotics are notoriously more difficult to develop. So, we are quite a ways from creating a novel antibiotic within the span of a year.

But this story is a meaningful demonstration of AI's ability to speed up the drug discovery and development process, without compromising safety and efficacy.

Much like how the COVID-19 pandemic required an urgent response and timely solutions, our fight against AMR, too, is reaching a crisis point. For Lei, artificial intelligence is a vital part of his work. He sees it as an enabling tool that helps scientists make better decisions more quickly.

> Lei:
> I view them as, uh, extremely knowledgeable partners sitting in the room saying, you know, together with you, enable you and make you more efficient and make you, you know, make the better decisions that move the project faster. So that's how I view it. And I certainly have, you know, worked in the days of without AI. And, uh, I feel that with AI, you can make your work less about trial and error, less empirical, uh, be more focused and more rational, uh, right. So as I, as I mentioned in some of these examples, I think there's certain process that can accelerate and really, you know, sometimes scientists, um, require a bit of patience and sometime you've got less patience when you're waiting for data to come back around, with the AI, they can address that. You can get your data faster, you make decisions faster and make your job more fulfilling.
>
> *[MUSIC]*

Jeremiah:
Next week on Science Will Win. Where is all this research into AMR and artificial intelligence going? What's next?

We'll dive into potential future use cases for this technology. Plus, we'll talk about the movements for better policy, advocacy, and stewardship for the antibiotics we do have.

> Subha:
> It would be a shame if we don't leverage all of that data to improve medicine. And, um, you know, if we don't actually make use of that, uh, you know, what are we doing,

Jeremiah:
Science Will Win is created by Pfizer and hosted by me, Jeremiah Owyang. It's produced by Wonder Media Network. Please take a minute to rate, review and follow Science Will Win wherever you get your podcasts. It helps new listeners to find the show. Special thanks to the responsible AI and anti-infective teams at Pfizer. And thank *you* for listening!