DISCOVER — ENGAGE — IMPACT

SO LONG, SUPERBUGS – CROWDSOURCING IS HERE

By creating the world's first molecule bank, UQ scientists are working with industry and institutional partners to crowdsource antibiotic compounds, aiming to seek out new antibiotics and prevent the proliferation of drug-resistant superbugs.

In 1928, Scottish pharmacologist Alexander Fleming returned from a holiday and found that his poor housekeeping had the potential to save lives. On a petri dish containing colonies of bacteria was a blob of mould – a mould that was killing the Staphylococcus it was sharing a plate with.

This was the birth of penicillin –which was developed into the first antibiotic medication by a team of researchers, including Australian Howard Florey – an antibiotic that has since saved millions of lives. Fleming's discovery was the first of many, with major new antibiotics being discovered in 1948 (cephalosporin), 1976 (carbapenem) and 1980 (fluoroquinolones).

And then, for more than 30 years – nothing. No approved new classes of antibiotics have been discovered.

We've managed to invent wireless internet, the smartphone and revolutionary pain medications, but this particular area of science has come to a standstill. The average first-world citizen might not see this as a problem; after all, we have plenty of antibiotics to treat diseases, why do we need more? But for those in the know, the fact that no new classes of antibiotics have been approved is a growing concern.

The creation of the first antibiotic led to the discovery of antibiotic-resistant bacteria. In an interview shortly after winning the Nobel Prize in 1945 for discovering penicillin, Fleming said, "The thoughtless person playing with penicillin treatment is morally responsible for the death of the man who succumbs to infection with the penicillin-resistant organism."

The diseases we take for granted as being 'cured' are actually still killing people, and gaining strength from the very products we use to treat them. It's an issue affecting doctors and patients globally, which is why the Community for Open Antimicrobial Drug Discovery (CO-ADD) decided to take a global approach to finding the next antibiotic.

"A superbug is a bacterium that's become resistant to drugs, and occurs from over-using antibiotics that are often inappropriately prescribed for things like viral infections, for which they don't work."

"Since the 1930s we've taken antibiotics for granted because they can kill bacteria. Over time we've misused them and we've used them too much. And so now these bacteria – which are bugs – become superbugs: bugs that don't respond to antibiotics so the infection can then progress and lead to, unfortunately, loss of limbs and loss of life."

The CO-ADD team considered the way antibiotic compounds were discovered in the past.

"We'd assay soils in Borneo and weird fungi – these are natural products that are made in a variety of ways and they're very, very diverse in structure," says Professor Cooper.

"The problem is again, with that, we've mined all of those. All the low-hanging fruit is gone. So we thought, how can we access chemical diversity?

"Every day, mankind makes 15,000 new compounds. Every single day. There are more than 90 million compounds on the planet. If you analyse those, they're really diverse."

CO-ADD's group of scientists had figured out where they needed to look, but they needed access to these compounds, and funding to test them.

"These compounds are all in laboratories around the world. Individually they have no value, but collectively, they could be incredibly powerful," says Professor Cooper.

"We could create the world's largest, most diverse bank of molecules. We have a world bank of money, we have sperm banks and blood banks and tissue banks. They're community-based resources. At the moment, we don't have a molecule bank. Instead, the people who control this space are very powerful: they're big pharma companies and they're interested in making a profit. They're privileged banks of molecules, and they don't get let out. But we're challenging that paradigm and, working collectively as the CO-ADD, we can create the world's first molecule bank and have a better chance at finding the world's next antibiotic."

The team came up with a five-year plan and, using Professor Cooper's National Health and Medical Research Council Principal Research Fellow funding, created a website calling for chemists around the world to send in their compounds for testing. This project, dubbed the Worldwide Antibiotic Discovery Initiative, became the year-long pilot for CO-ADD, which the group used to prove that they had the capabilities to screen the compounds.

The goal was to convince chemists to send their discarded compounds to the team for screening – for free – and to assure the original owners of the compound that if something was found, they would still own the intellectual property and potential to develop the compound into an antibiotic.

"We just started doing it. We had the audacity to ask for forgiveness and not permission," he says.

"These are very large collections, millions of compounds, so you think – great; the more we screen, the bigger the numbers are, the more likely we are to find a drug. But what's happened is that the chemical space they occupy – the diversity and the shape and size of the molecules in those collected compounds is actually very, very small. And so we're screening this tiny portion of the potential chemical space, and in the last 20 or 30 years, no approved new class of antibiotic has been discovered.

"We have second, third and fourth generation compounds, but they're just tweaks on the same parent compound we found back in the '70s or the '80s. Unfortunately, the bacteria now have all these resistant mechanisms and so when we have a new drug it's sometimes only weeks or months until we see the superbug return.

"What we're doing isn't working. Even Einstein said there's no point trying to create a solution with the same thing that created the problem.

"What we desperately need is a completely new type of antibiotic.

"We screened 114,000 compounds in the pilot phase with no funding."

With a year of experience under their belts, and a proven track record, the team began to seek a funding source. They eventually secured $3.1 million from the Wellcome Trust to launch CO-ADD as a not-for-profit initiative in February 2015. Since then, CO-ADD has received over 110,000 compounds. The program has screened more than 50,000 of these compounds, identified 3000 possible new antimicrobial compounds of which 260 look promising for further studies.

The team tests compounds for their ability to inhibit any one of five different types of bacteria and two fungi. Positive 'hit compounds' undergo additional confirmation and validation testing to show they are not toxic and are suitable for development. The researchers who originally sent in the compound can publish or patent their findings, and can also request further advice on compound development.

"We aim to pioneer a new open-access model of drug discovery through the curation of a community-owned library of compounds," says Professor Cooper.

"We will strive to find at least five novel, potent and non-toxic antimicrobial compounds in the next five years. We hope that at least one of these will progress to clinical trials.

"It's early days. From where we are now to where we get a drug that's ready for phase one clinical trial is, at best case, three years and normally four years. It's really simple – we're just trying to get shots on goal. The more hits we have the more chance we have that one of those will actually become a candidate antibiotic compound.

Based at The University of Queensland's Institute for Molecular Bioscience, CO-ADD includes a team of scientists and researchers with expertise in chemistry, microbiology, genetics, and pharmacology.

Project instigator Professor Cooper – who was inspired to focus on fighting antibiotic resistance after travelling through less developed countries, such as Indonesia, India, Pakistan and Nepal, where he saw many young children and mothers succumb to such bacterial infections known as superbugs – says that it's a big experiment.

"It's probably a five-year experiment – that said, what's the alternative? Doing nothing?"

But perhaps somewhere in the world right now, a chemist is returning from holiday and deciding to clean out their compounds, sending them to be screened. And perhaps, in one of those rejected compounds, lies the potential to save lives, break the 30-year antibiotic discovery drought, and take on the superbugs.

We can only hope.

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The journey so far:

2013: Professor Cooper and his team develop five-year plan to battle superbugs

2014: Worldwide Antibiotic Discovery Initiative pilot program begins

February 2015: The team secures funding from Wellcome Trust and forms CO-ADD

June 2015: Queensland Minister for Health The Hon Cameron Dick officially opens CO-ADD lab

July 2015: Professor Cooper meets Professor Victor Semenov, who agrees to send CO-ADD 150,000 compounds from his Nuclear Magnetic Resonance spectroscopy project in Russia

August 2015: First shipment of compounds arrives from Russia

September 2015: UQ IMB's Centre for Superbug Solutions officially launches

February 2016: CO-ADD partners with EU's Innovative Medicines Initiative

April 2016: CO-ADD signs agreement to screen French National Chemical Library (50,000 compounds)

April 2016: CO-ADD signs a Memorandum of Understanding to facilitate drug discovery in Africa

May 2016: CO-ADD lab receives its 100,000th compound to screen

May 2016: CO-ADD wins UK Antibiotic Guardian Award for Research

June 2016: The team wins UQ Award for Excellence in Innovation

July 2016: Wellcome Trust agrees to fund CO-ADD for another 12 months

April 2017: CO-ADD and IMB Centre for Superbug Solutions hosts first Asian-Pacific conference on Solutions for Drug-Resistant infections (SDRI 2017)

November 2017: So far more than 500 researchers from 200 institutes in 45 countries have joined CO-ADD's network and submitted more than 210,000 compounds for testing

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