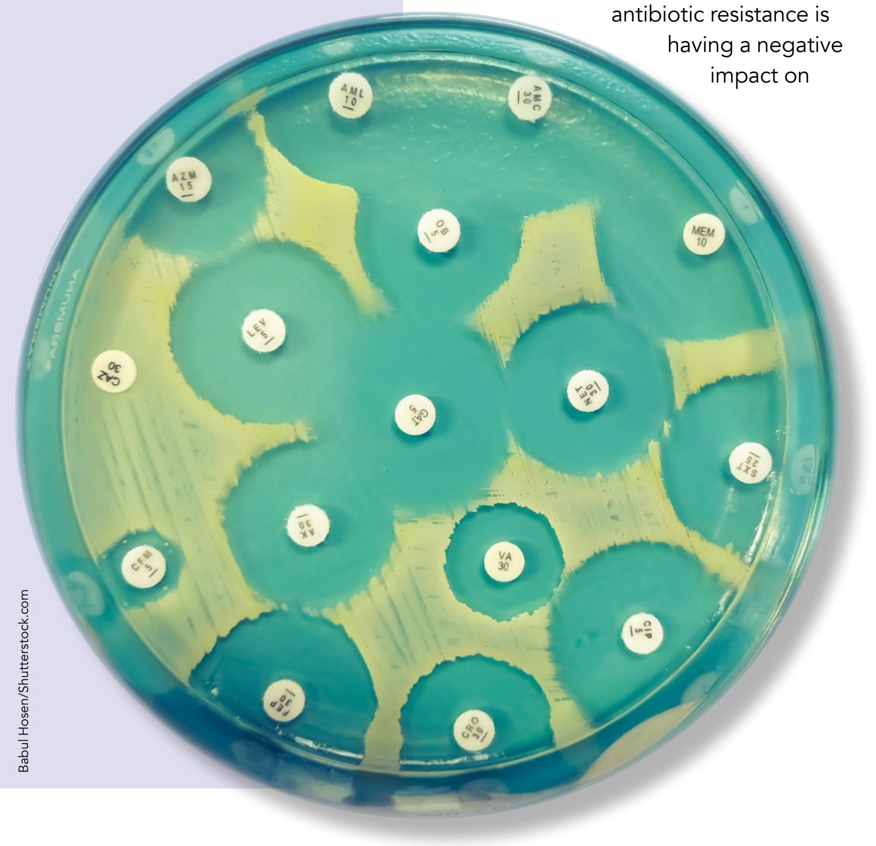
Antimicrobial metals

A recycled weapon against bacteria

Antibiotics are one of the key factors facilitating the increase of life expectancies by nearly 30 years in the US, and they have been since the 1920s. Before the development of antibiotics, even a seemingly innocuous cut could have fatal results when a bacterial infection took hold. However, with the growing use of these wonder drugs, bacterial resistance has become an increasing problem, and one that Professor Raymond J Turner at the University of Calgary, Canada, is working to solve, through revisiting and developing metal-containing antimicrobials.



Babul Hosen/Shutterstock.com

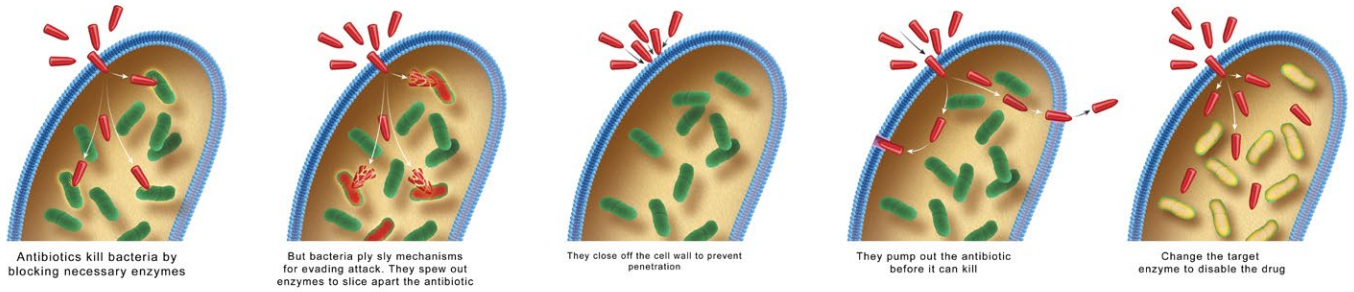
Antibiotic and antimicrobial resistance has the potential to become one of the biggest threats to global health and we find ourselves entering an antimicrobial resistance (AMR) era. Already, many microbes are developing partial or have developed complete antimicrobial resistance leading to the rise of the so-called 'superbugs' – resistant strains of microbes that are invulnerable to some or all of our treatment options.

The consequences of antimicrobial resistance can be severe. Even very minor surgeries would become almost intolerably risky as any post-operative infection could prove fatal. Life expectancies would decrease dramatically as there would be no way of controlling the development of initially minor infections. There is already some evidence to suggest that antibiotic resistance is having a negative impact on life expectancy, and diseases such as urinary tract infections, gonorrhoea, and tuberculous are already becoming increasingly difficult to treat with available therapies.

Why has the problem become so bad? One theory is that the over-prescription and misuse of antibiotics, particularly in the agriculture industry as a prophylaxis and in mismanagement of infections, has helped bacteria develop resistance to common therapies. This is because unless the bacterial population is completely annihilated by the treatment, the bacteria that remain tend to be those with the highest levels of tolerance against the drug. These then go on to multiply, passing on the genetic information that gave them a higher level of resistance. If this cycle continues, the problem worsens until treatments become completely ineffective.

One way of circumventing resistance issues is to try treating with different classes of antimicrobials, in the hope that the bacteria will not have developed resistance to all of them. Unfortunately, this strategy is also becoming less effective as there have been no new major classes of antibiotics developed in the last 30 years, so trialling different antibiotic classes as part of treatment has also led to the development of greater resistance.

Professor Raymond J Turner at the University of Calgary, Canada, has been investigating how metal ions might help us in the fight against bacteria. Many metal species, including copper and silver, have known antimicrobial properties, and Turner has been investigating which metals might be the best at destroying biofilms and other bacterial growth forms.



Aldona Griskeviciene/Shutterstock.com

AMR is leading to the rise of the so-called 'superbugs'.

MAGIC METALS

The amazing antimicrobial properties of metals have been known since 4BC, when Hippocrates, often considered the father of modern medicine, was using ointments of metals in his treatments. The ability of metals to kill bacterial species is why some bandages and sports equipment have silver infused into their fibres. These textiles can help keep wounds sterile or kill the bacteria that feed on our sweat to prevent odours.

Understanding why metals make good antimicrobials and how they work has been a long unanswered question.

Turner and his team have been systematically investigating which metals – silver, gold, copper, titanium, gallium, nickel, aluminium, tellurium, selenium, zinc, and others – would offer the best antimicrobial activity against different strains of bacteria. They wanted to discern which metals would be most efficient at eradicating already established biofilms of the bacteria and which would prevent any future growth in the region.

Biofilms are the consortium of bacteria that form and stick to surfaces as the bacterial community grows. They are often slimy to the touch and can stick to surfaces and other areas, including the cells of wounds. The biofilm can help protect the bacteria as some films can even prevent treatments such as antibiotics entering the bacterial cells, stopping the treatment from working.

Turner's group found that, if they combined certain metal salts, some combinations proved to be synergistic. That means the bacterial killing or prevention activity of the combination was greater than the sum of the two individual components. The combination could also reduce or even prevent resistance from developing. Finding the right synergistic combination was dependent on the bacteria being targeted, with several metals (either as salts or nanomaterials) proving particularly promising.

Turner and his group are keen to highlight the nuances of resistant bacteria. They point out that there are already silver-resistant bacteria, for example, arising because of misuse of silver within the textile industry (one might develop silver resistance as a result of silver used in garments, meaning in future, silver used in a bandage after a burn will offer little protection).

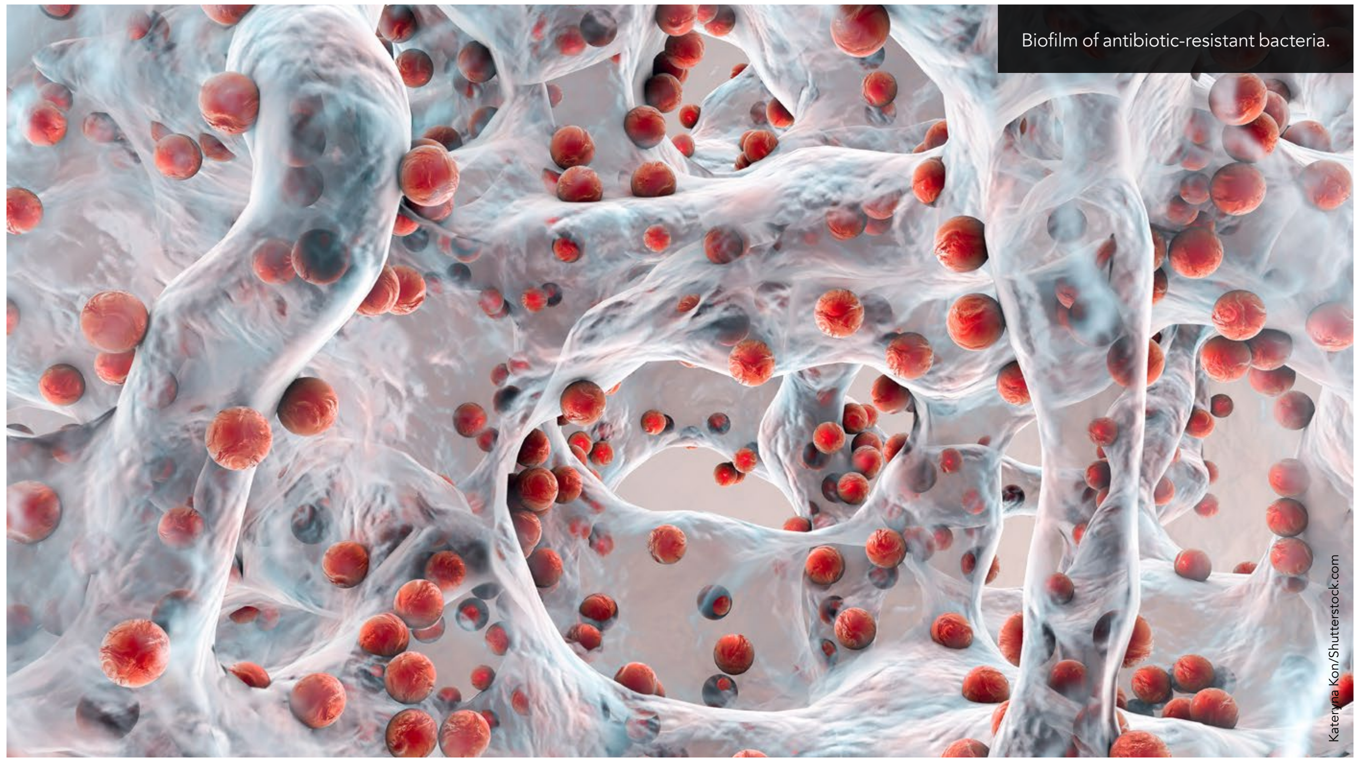
While we might have been reaping the antimicrobial benefits of metals since the time of Hippocrates, understanding why metals make good antimicrobials and how they work has been a long unanswered question.

HIDDEN WORLD

There are a number of different ways metals can destroy bacteria. These

Silver used in a bandage after a burn will offer little protection if a patient has developed silver resistance.

Africa Studio/Shutterstock.com


Biofilm of antibiotic-resistant bacteria.
Kateryna Kon/Shutterstock.com

include the generation of reactive oxygen species that can lead to cell death – a similar mechanism that is used in many cancer treatments to kill the unwanted cancerous cells. This can be via depletion of the antioxidant concentrations that would normally control the concentration of the reactive oxygen species to prevent cell damage.

Other routes include substitution of the natural metal in an enzyme, which can disrupt and inhibit its function. Some metals can also interfere with cell nutrient uptake so the cell essentially starves to death. More severe disruption can be caused by direct damage to the bacteria's genetic material which can prevent reproduction, growth and function, or by damage to the cell membranes that act as both a safety barrier and a container for the cell contents.

Turner has been investigating not just the more standard mechanisms of metal-bacterial interactions, but also the origins of the synergistic effects of multiple metals on bacteria. While there are some concerns that the inherent cell toxicity of many metals will make them challenging for human use as antibiotic treatment, new abilities to specially manufacture nanomaterials doped with just the right amount of metal may help overcome some of these challenges.

Tackling antimicrobial resistance is an urgent challenge for scientists, and finding new and novel families of compounds with antimicrobial activity is part of addressing that challenge. Turner's work shows the many possibilities of individual or combination metal-based therapies, and how they can be used to fight even the most stubborn of pathogens.

The amazing antimicrobial properties of metals have been known since antiquity.


Destruction of bacteria with silver nanoparticles.
Kateryna Kon/Shutterstock.com

Behind the Research

Raymond J Turner

E: turnerr@ucalgary.ca **T:** +1 403 220 4308 ca.linkedin.com/in/raymondjturner
ResearchGate: https://www.researchgate.net/profile/Raymond-Turner
Publons: https://publons.com/researcher/2354952/raymond-j-j-turner/
Department web page: https://profiles.ucalgary.ca/raymond-j-turner

Research Objectives

Professor Raymond J Turner explores metal-containing antimicrobials to target bacteria.

Detail

Address
Department of Biological Sciences
447 Biological Sciences Building
University of Calgary
2500 University Drive NW
Calgary
Alberta
Canada T2N 1N4

Bio
Biochemistry/chemistry BSc (1985) and biophysical chemistry PhD (1990). Post-doc (1990–94) in molecular and microbiology. Joined University of Calgary in 1998 and is currently Faculty Professor. Past roles include Associate Department Head, and chair of various units. Research interests in multiple fields.

Funding
NSERC, CIHR, MITACS

Collaborators
- Dr Joe Lemire
- Dr Natalie Gugala
- Dr Ali Pormohammad
- Dr Joe Harrison

References

Lemire, JA, Kalan, L, Gugala, N, Bradu, A, Turner, RJ, (2017) Silver oxynitrate – an efficacious compound for the prevention and eradication of dual-species biofilms. *Biofouling*, 33(6), 460–469. doi.org/10.1080/08927014.2017.1322586

Lemire, JA, Harrison, JJ, Turner, RJ, (2013) Antimicrobial activity of metals: Mechanisms, molecular targets and applications. *Nature Reviews Microbiology*, 11(6), 371–384. doi.org/10.1038/nrmicro3028

Pormohammad, A, Turner, RJ, (2020) Silver antibacterial synergism activities with eight other metal(Loid)-based antimicrobials against *Escherichia coli*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*. *Antibiotics*, 9(12), 1–19. doi.org/10.3390/antibiotics9120853

Gugala, N, Vu, D, Parkins, MD, Turner, RJ, (2019) Specificity in the susceptibilities of *Escherichia coli*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* clinical isolates to six metal antimicrobials. *Antibiotics*, 8(2), 1–12. doi.org/10.3390/antibiotics8020051

Gugala, N, Lemire, JA, Turner, RJ, (2017) The efficacy of different anti-microbial metals at preventing the formation of, and eradicating bacterial biofilms of pathogenic indicator strains. *Journal of Antibiotics*, 70(6), 775–780. doi.org/10.1038/ja.2017.10

UNIVERSITY OF CALGARY

Personal Response

Do you think metals in antimicrobials will become more commonplace?

" We will need multiple approaches (bacteriophage, antimicrobial peptides, microbiome health, novel chemistries and coatings, etc), and although metals will be an important player, there will be no perfect 'silver bullet'! We now recognise our follies that led to AMR, thus we must build effective stewardship of use into any and all new antibiotic alternatives, regardless if used in industries controlling biofouling, in agriculture pest and disease control, or human healthcare. "

wacomka/Shutterstock.com

www.researchfeatures.com