Letters to the Editor

Harnessing Ferroptosis-Inspired Iron Chemistry to Combat Antimicrobial Resistance

Nalin Abeydeera, Ph.D.
Postdoctoral Scholar, Medicine,
School of Medicine,
University of California, San Francisco,
San Francisco, CA,
United States.

Antimicrobial resistance (AMR) has become a global healthcare threat due to the widespread use and misuse of antibiotics (Blaskovich et al 2018; Fish et al 2006). In response to this crisis, the current medicinal chemistry community favors the approach of modifying the structures of existing antibiotics through organic chemistry derivatization, hoping that the derivatives can evade resistance mechanisms in pathogenic bacteria. The reason for such an approach, as opposed to searching for completely unknown classes of compounds for new drugs, is that it is easier to produce "hits" rather than look for needles in a haystack. This strategy has been quite successful in the past but has become less effective in recent years. On the other hand, even if a new drug is discovered and marketed for treating bacterial infections, it would not take long for bacteria to mutate and express enzymes that defeat the drug. Hence, the development of drug resistance through bacterial mutations and the chemical modification of drug structures is almost like a cat-and-mouse game, figuratively speaking. Ideally, designing drug molecules from scratch to target different cellular and molecular components has become crucial.

Metal-based compounds may offer a unique opportunity to end such cat-and-mouse games in the sense that bacterial mutations may not keep up with the race to rapidly develop drug resistance if completely new cellular or molecular components are targeted by the metal compounds (Frei et al 2023). Metallo-antimicrobials have already seen extensive clinical use for the treatment of various diseases, exerting their effects through diverse mechanisms such as binding to biomolecules, redox activity, and radioactivity. Among the many antimicrobial metals studied for therapeutic use, such as Cu, Ag, Zn, Cd, Bi, and Ga, Fe stands out for its potent antimicrobial activity against *Staphylococcus aureus* due to its unique redox behavior, particularly through the production of reactive oxygen species (ROS) via the Fenton reaction (Frederick et al 2009).

Iron is an essential micronutrient necessary for the survival, growth, and propagation of bacteria, but iron is also known to be a double-edged sword in biology because of its catalytic role in the cellular environment to produce reactive oxygen species (ROS) (Schaible et al 2004). Excessive iron in the body accelerates aging, causes neurodegenerative diseases, and even heart failure. Iron is also known as a bacterial growth promoter. For these reasons, iron uptake is tightly regulated in bacteria, which makes the delivery of iron into bacterial cells very difficult. Recently, iron-based metallo-antimicrobials have been regaining attention and are considered one of the promising strategies to address the current AMR crisis due to their unique geometry, distinct physical properties, and multiple mechanisms of action. One emerging strategy focuses on disrupting bacterial iron homeostasis by using lipophilic, non-siderophore chelators with high affinity for Fe(III) but low affinity for Fe(II). Such chelators can transport iron across bacterial membranes independent of receptor-mediated pathways. Increasing evidence supports the potential of neutral octahedral Fe(III) complexes formed with bidentate chelating ligands containing hard Lewis donor atoms of O and/or N, such as maltol, hinokitiol, 8-hydroxyquinoline, and their derivatives, as potent antimicrobial agents. These complexes

can disrupt iron uptake regulation and deliver iron into bacterial cells (Abeydeera et al 2022; Abeydeera et al 2023). Their idealized D_3-symmetric structure eliminates molecular polarity and shields the ionic character of the metal within an octahedral coordination sphere, giving the complexes a hydrophobic, "greaseball-like" property that facilitates membrane permeability. Once inside the cell, Fe(II) is released via ferric reductase activity or by intracellular antioxidants (Schröder et al 2003), increasing the labile iron pool and triggering the Fenton reaction to generate ROS, ultimately leading to bacterial death (Imlay et al 1988). In eukaryotic cells, iron and ROS are closely linked through the Fenton reaction, which can mediate apoptosis via a recently recognized cell death pathway known as ferroptosis (Abeydeera et al 2023; Abeydeera et al 2024). Although ferroptosis itself may not occur in bacteria, recent experimental evidence suggests that the iron-triggered ROS signaling pathway leading to bacterial cell death represents a highly promising therapeutic target for the development of iron-based antibacterial agents (Abeydeera et al 2025).

These advances highlight the potential of iron (Fe)-based antimicrobials as a novel and effective approach to combat multidrug-resistant pathogens, offering a much-needed alternative in the ongoing fight against AMR. Through sustained innovation and interdisciplinary collaboration, iron-based therapeutics could broaden the arsenal of antimicrobial agents and help address the critical threat of multidrug-resistant infections.

References

Abeydeera, N.; Yu, B.; Pant, B. D.; Kim, M.-H.; Huang, S. D., Harnessing the toxicity of dysregulated iron uptake for killing Staphylococcus aureus: reality or mirage? *Biomaterials Science* 2022.

Abeydeera, N.; Benin, B. M.; Mudarmah, K.; Pant, B. D.; Chen, G.; Shin, W. S.; Kim, M.-H.; Huang, S. D., Harnessing the Dual Antimicrobial Mechanism of Action with Fe (8-Hydroxyquinoline) 3 to Develop a Topical Ointment for Mupirocin-Resistant MRSA Infections. *Antibiotics* 2023, *12* (5), 886.

Abeydeera, N.; Stilgenbauer, M.; Pant, B. D.; Mudarmah, K.; Dassanayake, T. M.; Zheng, Y.-R.; Huang, S. D., Lipophilic Fe (III)-Complex with Potent Broad-Spectrum Anticancer Activity and Ability to Overcome Pt Resistance in A2780cis Cancer Cells. *Molecules* 2023, *28* (13), 4917.

Abeydeera, N.; Mudarmah, K.; Pant, B. D.; Krause, J. A.; Zheng, Y.-R.; Huang, S. D., Transferrin-inspired iron delivery across the cell membrane using [(L 2 Fe) 2 (μ-O)](L= chlorquinaldol) to harness anticancer activity of ferroptosis. *Dalton Transactions* 2024, *53* (7), 3206-3214.

Abeydeera, N., Recent Development of Exploring Ferroptosis-Inspired Effect of Iron as a Feasible Strategy for Combating Multidrug Resistant Bacterial Infections. *Applied Microbiology* 2025, *5* (3), 73.

Blaskovich, M. A., The fight against antimicrobial resistance is confounded by a global increase in antibiotic usage. *ACS infectious diseases* 2018, *4* (6), 868-870.

Fish, D. N.; Ohlinger, M. J., Antimicrobial resistance: factors and outcomes. *Critical care clinics* 2006, *22* (2), 291-311.

Frederick, R. E.; Mayfield, J. A.; DuBois, J. L., Iron trafficking as an antimicrobial target. *Biometals* 2009, *22* (4), 583.

Frei, A.; Verderosa, A. D.; Elliott, A. G.; Zuegg, J.; Blaskovich, M. A., Metals to combat antimicrobial resistance. *Nature Reviews Chemistry* 2023, *7* (3), 202-224.

Imlay, J. A.; Linn, S., DNA damage and oxygen radical toxicity. *Science* 1988, *240* (4857), 1302-1309.

Schaible, U. E.; Kaufmann, S. H., Iron and microbial infection. *Nature Reviews Microbiology* 2004, *2* (12), 946-953.

Schröder, I.; Johnson, E.; De Vries, S., Microbial ferric iron reductases. *FEMS microbiology reviews* 2003, *27* (2-3), 427-447.