Experience is a valuable asset in scientific discovery. It enables the researcher to understand what has and has not worked in the past, and the way that problems can or should be addressed. However, sometimes experience becomes enmired in dogma, and we must become careful as scientists not to think that what has been done previously is the only meaningful route forward. A strong object lesson is provided by the antibiotic discovery paradigm. With few exceptions, since the very first investigations we have considered that the gold standard for discovery of a useful antibiotic is its ability to kill or prevent the growth of serious bacterial pathogens using standard laboratory protocols that have been enshrined as the Clinical and Laboratory Standards Institute (CLSI) guidelines (Wiegand et al, 2008). However this single-minded faith in a gold standard approach (Lin et al, 2015). The paper of Lin et al in this issue of *EBioMedicine* (2015) addresses many of these paradigm-breaking approaches but, in particular, points to how our thinking about antibiotics has been muddied by clinging to the old ways.

Lin et al. demonstrate that the most commonly prescribed antibiotic in the USA, azithromycin, lacks activity when assessed using CLSI methods vs. the serious MDR Gram negative pathogens *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and *Acinetobacter baumannii* (three of the most concerning antibiotic resistance pathogens in our society). However they reasoned that laboratory medium used for CLSI testing is quite distinct from the in vivo environment. Thus they tested and demonstrated excellent bactericidal activity for these pathogens in tissue culture medium that mimics the host environment and is normally used for growing human cells in culture. Furthermore, although current clinical guidelines do not recommend the use of azithromycin for the treatment of the immune deficit underlying sepsis; Fuente-Núñez et al., 2013; Pena et al., 2014), using therapeutic adjuvants that make antibiotics work better (Gill et al, 2015; Lin et al, 2015), and redefining the gold standard approach (Lin et al, 2015). The paper of Lin et al in this issue of *EBioMedicine* (2015) addresses many of these paradigm-breaking approaches but, in particular, points to how our thinking about antibiotics has been muddied by clinging to the old ways.

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to promote penetration into bacteria as well as the potential synergy of azithromycin with host derived factors (LL-37).

Overall this study provides a powerful argument that we need to break out of the suffocating limitations of dogma and start to rethink all aspects of antibiotic discovery if we are to stave off an antibiotic resistance crisis.

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