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Commentary

Rethinking the Antibiotic Discovery Paradigm

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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 particular approach has almost certainly favoured the development of the current antibiotic resistance crisis. The paper of Nizet and colleagues (Lin et al, 2015) shows clearly that we need to rethink this approach.

We are facing a potentially catastrophic failure of our most valuable and successful medical asset, antibiotics. A lack of useful antibiotics would lead to difficulties with major surgeries, cytotoxic therapy, transplantations, and early-term births, etc, and even minor injuries would have the potential for serious complications. This is a real concern since resistance of most pathogenic bacteria to essentially all antibiotics, and especially multiple-antibiotic resistance, is rising steadily, with rates of almost-untreatable "Superbug" infections reaching proportions where they seriously impact on outcome in the clinic. Although estimates of deaths from antibiotic-resistant infections are often estimated to be moderate (e.g. 23,000 annually in the USA), these estimates fail to account for the annual 210,000 deaths in the USA from sepsis, which is triggered by infection and for which antibiotics are the front line (and clearly often unsuccessful) treatment.

When dealing with bacteria that do not respond to treatment, the major tactic utilized is antibiotic stewardship, whereby the physician switches the patient to a new class of antibiotics with different underlying mechanisms of action, and thus mechanisms of resistance. Unfortunately there has been a serious void in the discovery of truly novel antibiotics and especially of new chemical classes (Singh, 2014). There are at least three possible reasons for this: (a) conventional antibiotics are a very hard act to follow since they are inexpensive, often broad in the spectrum of activity, and tend to be very safe to use — this might explain the dearth of new discovery despite billions of dollars of investment in Pharma over the past 20 years; (b) it might be that we have already exploited all of the available excellent targets, especially given the requirements for selectivity for bacteria and uptake without efflux; and (c) little of antibiotic discovery has been directed to those clear problem areas in which antibiotics have never proven very successful, namely sepsis (with an ~30% death rate and 5 million deaths worldwide), chronic infections especially biofilms (representing 65% of all infections in the clinic and leading to adaptive resistance to essentially all antibiotics), and infections in individuals, with disturbed immune systems due to chemotherapy, immunosuppressive disease, or massive injuries/burns, who are unable to provide immune support for antibiotic therapy.

It is clear when viewing the frightening impact of resistance and the deficit in new discovery that we need to rethink the current discovery paradigm. In particular, it is important to consider novel, alternative approaches for creating anti-infectives (e.g. host-directed and immunomodulatory treatments, phage-based therapies, anti-virulence strategies, therapeutic antibodies, and adjustment of the microflora by faecal transplantation or probiotics; Hancock et al., 2012; Nigama et al, 2014). Other "new" approaches include directly addressing the above described "problem areas" (e.g. antibiofilm therapies, correcting host deficits, treating 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.

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 above organisms, this antibiotic had a clear therapeutic effect in lung and catheter infection models in mice, increasing survival in one instance by 4 fold to ~90%. Another major observation regarding this antibiotic when evaluated in tissue culture medium was the clear synergy with cationic antimicrobial peptides including the human cathelicidin LL-37 (which was otherwise inactive), and the cationic peptide antibiotic colistin. This indicates the potential for therapeutic adjuvant approaches in which azithromycin could be administered with an agent

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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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