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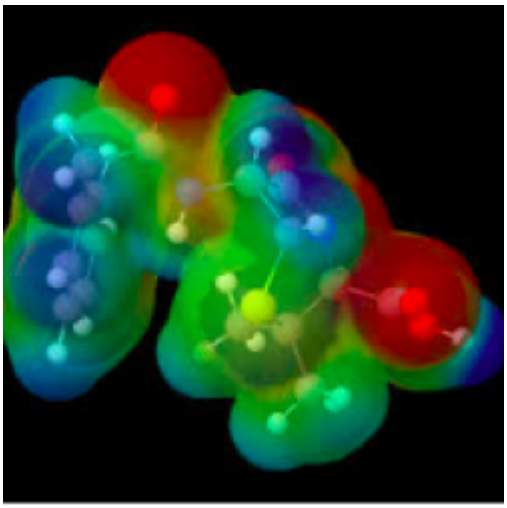
Antibiotics: Innovation or Clinical Utility?

By David Shlaes — November 25, 2019



Space-Filling Model of Penicillin G.
Credit: Flickr [1]

Lately I have become intrigued by the word, innovation. Innovation is used as a criterion for funding grants, for status in reviews of our antibiotic pipeline, for intelligence, imagination and many other great things. I want to explore the meaning and utility of innovation in the particular context of antibiotic discovery and development and of our antibiotic pipeline.

A story I tell frequently comes from my days as a practicing infectious diseases physician at the Cleveland VA Medical Center. In the early 1980s, our surgical ICU suffered an outbreak of bacteremia and pneumonia caused by *Serratia marcescens* resistant to all the antibiotics we tested at the time (colistin was not on that list). But imipenem was undergoing its phase 3 testing and I was able to obtain some under a compassionate use protocol that Merck had established. I am sure that we saved lives. But imipenem is really just a B-lactam – albeit a very special one. Is it innovative? I think so. But more importantly, its clinical utility was infinite for the care team and our patients.

To me, innovation stands for imagination, daring, intelligence and the ability to see things beyond what we know and think we understand. To innovate is to navigate to where we have not gone before, and, hopefully, to see a way to get there. So, yes, innovation can be a good thing. In the context of antibacterial discovery, Theuretzbacher et. al. note [2] that for many, innovation connotes a novel target or novel chemistry or novel mode of action. In the end, Theuretzbacher et. al. end up defining innovation as simply meaning that the therapy shares no cross-resistance with existing therapies.

I would like to introduce a more useful concept – clinical utility. Clinical utility clearly would include

a lack of cross-resistance, but also may include other advantages. A new therapy might avoid the need for monitoring drug levels, it might be safer than existing treatments, it might reduce the numbers of doses required, it might be orally bioavailable, or it might avoid the need for new, experimental diagnostic tests. All of these speak to the utility of any new therapy to the physicians who prescribe it and the patients they treat.

In my world, innovation also means risk. And risk in the pursuit of new and important therapies is fine as long as everyone understands that this is the case. Therapies directed at novel targets, those that use novel chemistry and those that exploit new modes of action all are subject to increased risk. The risks include the risk of scientific failure early in the discovery process, the risk of failure from non-clinical safety studies and the risk of clinical failure either because of safety or efficacy issues.

On the other hand, the use of known targets, known chemistries and known modes of action reduce risk. Sometimes, this lack of “innovation” might also lead to a lack of clinical utility. But, historically, while this does occur, there have been many very useful but not so innovative therapies to come forward over the last several decades. The B-lactamase inhibitors recently introduced to market (avibactam, vaborbactam) have a much broader spectrum of inhibition than their predecessors. They are innovative in that they utilize new chemistries to achieve their improved spectrum. Of greater importance to me, they have increased clinical utility based on this broad spectrum of activity and still avoid most cross-resistance. A major addition to our clinical armamentarium will be aztreonam-avibactam that will have activity against Class B B-lactamases, a group of enzymes that have so far eluded the BLI-BLA strategy. At this point, one could argue that this combination is not so novel or innovative and that would be true. But look at how clinically useful it might be. Another pipeline combination that achieves this goal is VNRX5133-cefepime from VenatoRx. In this case, the inhibitor is still based on boron chemistry like vaborbactam, but is able to assume different binding modes to inhibit class A and B B-lactamases – an innovative mode of action.

When I look at drug discovery and development plans and proposals, although I consider “innovation,” what I truly evaluate and value is potential clinical utility. These two characteristics do not always go together. I suggest that we all prioritize providing better (but not necessarily innovative) therapies to our patients with unmet medical needs as our ultimate goal.

This article is reprinted with permission from Dr. Shlaes' "Antibiotics, the Perfect Storm" blog. The original article can be found here [3].

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