

How antibacterials really work: impact on drug discovery



“Why did target-based antibacterial drug discovery not deliver? Is there a way to reconnect modern genome-based biology and rational target-based medicinal chemistry?”

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Large-scale failure of target-based antibacterial drug-discovery programs has triggered a move back to empirical whole-cell screens for the identification of new chemotypes, which are urgently needed to keep drug resistance at bay. Lead finding and optimization using whole bacteria instead of molecular targets is possible. The price to pay is inefficient medicinal chemistry work owing to the ‘black box’ nature of this approach. Furthermore, many modern drug-discovery tools, such as structure-guided design or fragment-based screening, cannot be employed. Why did target-based antibacterial drug discovery not deliver? Is there a way to reconnect modern genome-based biology and rational target-based medicinal chemistry? Recently, a few papers have demonstrated, for the first time, how antibacterials work at the whole-cell level, and how they actually kill the organisms [1–10]. These initial findings suggest that antibacterials have an ‘extended’ mechanism of action beyond the well-known modulation of their primary targets. This could, at least in part, explain why we have failed in the past – our target selection criteria might have been too simplistic.

“In pathogens, the newly uncovered death pathways will deliver targets for the rational discovery of the urgently needed new drugs to control multidrug-resistant superbugs.”

If asked to think about how an antibiotic works, you will probably envisage the drug entering the bacterium, inhibiting an important biochemical function, such as protein, RNA, DNA or cell wall synthesis, and then the microbe dying. However, this is incorrect. Although antibacterials have been around for more than half a century – and are considered by many to have had the biggest

impact on medicine – we know surprisingly little about how they actually cause bacterial cell death. Recent studies on the mechanism of action of aminoglycosides, tetracyclines, chloramphenicol, fluoroquinolones and β -lactams show that antibacterials do not kill by simply inhibiting an enzymatic function, which prevents the synthesis of some cell components. In fact, inhibition of an individual enzyme appears to be insufficient in itself to cause rapid bacterial cell death. Death is achieved by complex intracellular ‘corruption’ events, which follow on from the initial target modulation of the drug, resulting, for instance, in accumulation of broadly toxic intermediates or suicidal derailing of signaling systems that ultimately cause collapse of central homeostatic systems within the bacteria [1–10].

Why is that important? It means that the pharmacological approach to antibacterial drug discovery over the past 15 years has been based on the wrong concept. We might have had the wrong biological target selection criteria. High-throughput screening for biochemical inhibitors against isolated bacterial enzymes shown to be genetically essential might not be the way to go. Enzyme inhibitors were found, but no antibacterials [11]. Not a single new antibacterial drug based on the reductionist paradigm from the 1990s has reached a patient.

Efforts to discover new drugs for TB – which kills 2 million people each year and has a huge problem with multidrug resistance – have followed the same pattern. Renewed interest and funding over the last decade triggered a series of target-based discovery programs, which have been frustrated by a failure to translate target inhibition into efficient killing of intact *Mycobacterium tuberculosis* [12,13].

Now, it appears that we have a working model explaining why we failed: antibacterials do not work in that simplistic way. Rather they make

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use of systems biology to kill. Real antibacterials work within the cellular context by corrupting metabolic and information networks, resulting in the breakdown of core homeostatic systems essential for maintaining viability.

What is the way forward? We need to learn how to select targets with cidal potential based on their place within cellular metabolic and signaling networks, rather than on their properties as isolated enzymes and their genetic essentiality. One attractive approach to identify such targets is, for instance, to apply the battery of existing and emerging 'omics', genetic, single-cell analysis and systems biology platforms (as pharmacodynamic tools) to determine the effect of cidal versus static compounds on the bacterial cell and cell population. Understanding the sequence(s) of molecular events triggered by cidal compounds after primary target interaction (i.e., identifying bacterial cell death pathways) could deliver a new category of targets. These could then be exploited for, preferentially parallel, biochemical and whole-cell reporter-based screening and optimization campaigns to identify new leads and candidates to feed into the desperately empty antibacterial development pipelines [14].

A new grammar for antibacterial drug discovery needs to be written. Industry cannot do this alone. Bacterial systems biology, cell death mechanisms and working definition of life pose

fundamental science questions that should interest academic researchers. The pharmaceutical industry can make drugs if it has the right targets.

Future perspective

We are experiencing a renaissance in prokaryote biology in the context of systems biology. What was true at the beginning of the molecular biology era in the middle of last century still holds true today: ease and speed of manipulations of bacterial cells provide a huge experimental advantage over mammalian systems. This, paired with the increasing application of chemical genetics for functional dissection of cellular networks, will result in the identification of compound/drug-induced bacterial cell death pathways. In pathogens, the newly uncovered death pathways will deliver targets for the rational discovery of the urgently needed new drugs to control multidrug-resistant superbugs.

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