DRUG RESISTANCE

A call to arms: Unifying the fight against resistance

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This Editorial discusses the state of research on drug resistance in the fields of cancer, infectious disease, and agriculture. Reaching across the aisle for a more cross-collaborative approach may lead to exciting breakthroughs toward tackling the challenges of drug resistance in each field.

A PERSISTENT THREAT

We live in an age of unrivaled global prosperity, though far from perfect. Many deadly infectious diseases have been tamed by antimicrobials, antivirals, and vaccines. Food production has kept apace with human population booms, thanks in part to pesticides and herbicides. Even cancer, that most pernicious disease, is being slowed by new therapies. Yet, all of these achievements face an ancient, unyielding threat—the emergence of resistance. The impending crisis is well recognized in infectious disease, where antibiotic-resistant "superbugs" have grabbed newspaper headlines. Crop yields are likewise imperiled as resistance develops to pesticides and herbicides. In many cancers, miracle drugs buy the patient time, but inevitable resistance makes outright cures elusive.

Resistance creates different challenges between agriculture and medicine and, indeed, even within medicine between infectious disease and cancer. Resistance can spread regionally or even globally in agriculture and infectious disease but is confined to a single patient in cancer. Bacterial infections require treatments within hours, whereas timelines are typically less urgent in viruses, cancer, and agriculture. All areas require new agents to replace those rendered obsolete by resistance, but there is little overlap in drug, pesticide, and herbicide targets. The cost of new cancer therapy is notoriously high (and generally accepted as such), whereas the cost of interventions must be low in agriculture and infectious disease. Rather than respond to the consequences of resistance, perhaps shared strategies to avoid resistance can be developed if agriculture and medicine worked together. How do we break down the siloes and promote cross-field collaborations?

COMMON THEMES AND LESSONS

The Gordon Research Conference (GRC) on Drug Resistance met in July 2018 with the goal of bringing together scientists, clinicians, and regulators from agriculture, infectious disease, and cancer to share experiences and insights. Common themes were readily apparent among the questions each field is asking with respect to the evolution of resistance, the role of population heterogeneity, the use of multi-agent combinations, and the design of "resistance-resistant" drugs, pesticides, and herbicides.

The evolution of resistance

How do mutations accumulate in relevant genes without massive collateral damage to the genome? Do resistance mutations preexist in a population, or are they generated in response to drug-, pesticide-, or herbicide-induced stress? What are the nature and kinetics of these stress responses? Does resistance evolve via a predictable sequence of events? There is a growing awareness of the seminal importance of DNA amplifications of drug targets in all systems, both on chromosomes and extrachromosomally.

Population heterogeneity

How do stochastic differences in gene expression influence the emergence of resistance? How do quiescent cells tolerate agents that are toxic to proliferating cells? Both agriculture and medicine are struggling to develop strategies to address such "persister" cells.

Treatment combinations

Resistance can be avoided in the laboratory using multiagent combinations, but translating combination therapy from the laboratory to real-world applications is not straightforward. Regulatory policy creates another potential hurdle—combinations that prevent resistance do not necessarily improve efficacy and may not gain U.S. Food and Drug Administration approval.

Target choice

Are some targets more resilient than others? Can drugs/pesticides/herbicides be designed to be robust and "resistance-resistant" by binding to conserved regions of the targets? Or by engaging multiple targets? Pathogens rely on host factors—are these host factors robust targets? Can we anticipate and/or model the emergence of resistance and prepare the appropriate next-generation treatment? Work is under way to address these questions in both agriculture and medicine.

A CALL TO ARMS

Commonalities in approaches and tools exist throughout agriculture and medicine that, if translated, can benefit all in the treatment of infections, cancer, and pests. Some shared recommendations of interest that emerged from the Drug Resistance GRC are

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(i) cross-disciplinary long-term funding to develop strategies that avoid resistance; (ii) promotion of public-private partnerships to enable the flow of technology between fields; (iii) training and support for a cohort of collaborative scientists with interdisciplinary expertise in cellular processes (such as stress responses and resistance) rather than specific organisms; (iv) incentives for scientists to work in the anti-infectives space, as lack of pharmaceutical involvement and limited funding have led to disincentives to apply cutting-edge technologies and more challenges in attracting top talent; (v) and drug approval policies that encourage products that slow the development or reverse resistance in medicine and agriculture.

The drug resistance landscape is in flux, with academic and industry partners moving in and out of the space, with ever-evolving pathogens and cells, and with the emergence of new tools to study and combat disease. For this reason, it is critical to reevaluate where we stand on a regular basis. We look forward to these reflections and the opportunity to explore new ways to cross-collaborate toward common goals when we meet again in 2020 and points in between.

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