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A Call to Arms: Unifying the Fight Against Resistance

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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-resistance “superbugs” have grabbed newspaper headlines. Crop yields are likewise imperiled as resistance develops to pesticides and herbicides. In many cancers, miracle drugs buy time, but outright cures remain elusive because resistance inevitably arises.

Resistance creates 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, while timelines are much 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, whereas the cost of goods 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 breakdown 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 amongst 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/herbicides.

The evolution of resistance:

How do mutations find their way to the relevant genes without massive collateral damage to the genome? Do resistance mutations pre-exist in a population, or are they generated in response to drug/pesticide/herbicide-induced stress (1)? What are the nature and kinetics of these stress responses? Does resistance evolve via a predictable sequence of events(2)? There is a growing awareness of the seminal importance of DNA amplifications around drug targets in all systems(3), both on chromosomes and extrachromosomally(4).

Population heterogeneity:

How do stochastic differences in gene expression influence the emergence of resistance (5)? 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(6, 7).

Treatment combinations:

Resistance can be avoided in the laboratory by employing multi-agent combinations, but translating combination therapy from the laboratory to real world applications is not straightforward(8). Regulatory policy creates another potential hurdle- combinations that prevent resistance do not necessarily improve efficacy, and may not gain FDA approval.

Target choice:

Are some targets more resilient than others? Can drugs/pesticides/herbicides be designed to be “resistance-resistant” by binding to conserved regions of the targets? Or by engaging multiple targets? Pathogens rely on host factors - are these host factors “resistance-resistant” targets(9)? Can we anticipate and/or model the emergence of resistance and prepare the appropriate next generation treatment(10–12)? Work is underway to address these questions in both agriculture and medicine.

A call to arms

The practice of agriculture and medicine, and treatment of infectious diseases and cancer, can mask commonalities in approaches and tools that can benefit all. Some shared recommendations of interest that emerged from the Drug Resistance GRC are:

- Cross-disciplinary long-term funding to develop strategies that avoid resistance
- Promotion of public-private partnerships to enable the flow of technology between fields
- Training and support for a cohort of collaborative scientists with interdisciplinary expertise in cellular processes (e.g., stress responses and resistance) rather than specific organisms
- Incentives for scientists to work in the anti-infectives space: lack of pharmaceutical involvement and limited funding has led to disincentives to apply cutting edge technologies and more challenges in attracting top talent.
- Drug approval policies that encourage products which 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, evolving pathogens and cells, and the tools to combat disease changing. For this reason, it is critical to reevaluate where we stand on a regular basis, which we will do at the Drug Resistance GRC – we next meet in 2020.

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