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Responding to the superbug alarm [1]

From Our Labs [2]

Don Ganem witnessed first-hand the devastating impact of drug-resistant bacteria while working as an infectious disease doctor at the University of California, San Francisco Medical Center. One young woman, for example, was forced to return to the operating room just weeks after undergoing surgery for a deformed spinal column when she developed a serious infection that did not respond to treatment. Although the patient had a straight back for the first time in her life, she developed redness and swelling at the wound site, followed by a persistent fever. The new hardware supporting her spine had become infected with a potentially deadly bacterium. She required an arduous treatment regimen that included additional surgeries and many weeks of intravenous antibiotics.

Although Ganem saw that drug-resistant infections were becoming more common and treatment options more limited, as an academic physician-scientist he was not in a position to develop new solutions. That's one reason he accepted a position with the Novartis Institutes for BioMedical Research in 2011. As Global Head of Infectious Diseases, he leads a unit that's responsible for developing new drugs against tenacious microbes [3]. Here is an excerpt from a conversation with him about the threat of so-called "superbugs" and the scientific challenges associated with fighting them.

Should we be worried about drug-resistant bacteria?

Ganem**:** I would say we're at the point where the siren is going off, like the warning before the tornado. Most infections can still be treated by the available drugs, but increasingly you hear

horror stories about superbugs, bacteria that are resistant to many or all current therapies—and these are not imaginary. In the clinic we see the emergence of bacteria that are resistant to most of the antibiotics routinely used to fight a broad range of infections, including drugs like carbapenems, a potent antibiotic class that is typically used when everything else has failed. When resistance develops to these drugs, there are very few options left—an alarming situation. And the number of carbapenem-resistant infections jumped significantly [4] in the United States over the last decade. So the siren is sounding, and medicine must respond.

Why are so few companies tackling this problem?

Don Ganem, Global Head of Infectious Diseases at the Novartis Institutes for BioMedical Research

Ganem**:** The storyline in the lay press is that companies are walking away from making antibiotics because they're not profitable. It's true that most antibiotics do not command the kind of premium prices that, say, anticancer drugs do. And they are typically used for much shorter periods of time. These are significant economic issues. But what's missing from that narrative is that antibiotics are very difficult to make. I didn't appreciate just how difficult when I was working at UCSF. When I came to Novartis three years ago, I started hanging around medicinal chemists, and I learned that they have a saying: "Antibiotic research is where drug discovery goes to die." It's just plain hard to do.

If antibiotics are hard to discover, then why are they so ubiquitous?

Ganem: Most antibiotics were discovered in the middle of the last century, when scientists hunted for compounds that microbes produce to kill other microbes as they seek to maintain a competitive advantage in Mother Nature's endless evolutionary struggle. Scientists screened thousands of soil bacteria for substances of interest and isolated most of the chemicals that we currently use to control infections. But by 1960, they'd plucked all of the low hanging fruit. It's proving incredibly difficult to find or design additional compounds that kill these bugs.

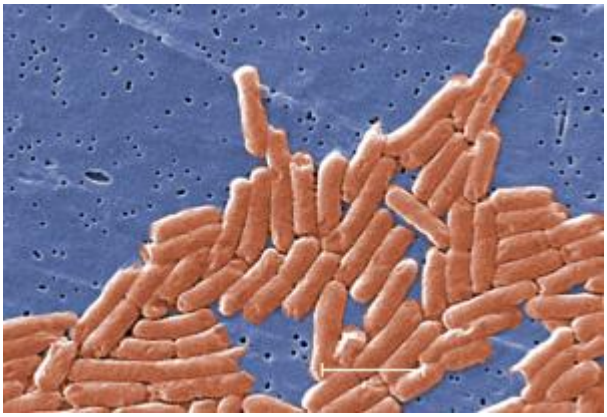
What are the biggest challenges?

Ganem: The scientific challenge begins with bacterial membranes. We don't understand how small molecules—including drugs—get through them. Bacteria can be divided into two

groups—gram negative and gram positive. Gram negative bacteria, in particular, seem to be plated with armor for combat. They have two membranes—an inner membrane and an outer membrane, and many (though not all) antibiotics need to make it past both. In addition, the outer membrane is both impermeable and equipped with numerous efflux pumps—molecules whose function is to pump stuff out of the cell.

Bacteria have spent millions of years making sure that they're not killed by substances in the environment, and we don't really understand the first thing about how they do it. Academic microbiologists largely ignore this problem because it's just not sexy. And it's not as though this is something for which you could propose a "Manhattan Project" and solve within three years; there's a generation's worth of work to do.

If we understood bacterial membranes, could we design drugs that would cross them and cripple the bugs?



There are hundreds of species of gram negative bacteria, including one to two dozen that are medically relevant, meaning that they frequently cause infections in humans. (Photo © CDC, Janice Haney Carr)

Ganem: It would help, but there's still another challenge. Modern compound libraries aren't optimized for antibiotic discovery. The average pharmaceutical company has a collection of more than a million compounds, which provide starting points for new drugs. You'd think that some of these chemicals would kill bacteria, and there are a few that do, but not many. Our libraries are made up of things that were designed to get into human cells and hit human proteins. They are compounds that are very different from most known antibiotics. In addition, as I mentioned, the majority of our current antibiotics come from natural products, things made by other microorganisms to kill off their neighbors. The complex structures of natural products are also underrepresented in most compound libraries.

You're attempting to design antibiotics that will be effective against multiple species of bacteria. Does that complicate the drug discovery process?

Ganem: Yes. There are hundreds of species of gram negative bacteria, including one to two dozen that are medically relevant, meaning that they frequently cause infections in humans. These bacteria have diverged from one another over many millions of years of evolution. That means that a given bacterial protein will differ from species to species. If you target that

bacterial protein, then you need to make sure that the drug you make blocks every version of it present in common human pathogens.

Is the problem of drug resistance conquerable?

Gram negative bacteria

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Gram negative bacteria are plated with armor for combat. They have two membranes, and antibiotics need to make it past both. (Photo © Wellcome Images, David Gregory and Debbie Marshall)

Ganem: Not in the traditional sense of the word “conquest,” which implies that a decisive victory can resolve the issue for all time. The need for new antibiotics will never go away. Bacteria will continue to evolve in response to treatment. In fact, people have started to use the word “resistome” to describe the collection of all the genes that could confer resistance to antibiotics. Resistance elements exist out there in the universe of microorganisms and it’s just a matter of time before they make their way into patients. Infectious diseases are an intrinsic part of human evolution and a great shaper of human evolution. They’ll never be eradicated. The goal is not to eliminate this problem, but to manage it. And part of that management is to develop new antibiotics that stay ahead of mutational drug resistance. Another part, of course, is to avoid inappropriate use of existing drugs, so as to minimize the selection for resistant bugs.

It sounds like the odds are stacked against you. Why are you—and by extension Novartis—committed to developing new antibiotics?

Ganem: These are dramatic and important infections that threaten not only the lives of individual patients, but also many aspects of contemporary clinical practice. You can’t do cancer chemotherapy if you can’t bail people out of the consequences of losing white blood cells, which are the body’s natural mechanism for fighting infections. You can’t do organ transplantation if you can’t deal with the infectious consequences of the immunosuppression required to prevent transplant rejection. People will not agree to hip replacements if they fear untreatable bacterial infections of the implant. So I think it’s perfectly rational for the industry to stay in the game to protect the gains that we’ve made in many areas.

And then there’s the moral argument, which carries a great deal of weight with me. I signed up for this career as a physician and a scientist to help people. I left UCSF and came to Novartis

because I wanted to make therapies that patients need. I've spent my entire career preparing myself to approach this problem—and now, at Novartis, I get to do it. For me, it's a personal imperative.

Tags:
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