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Unlocking the genes behind antibiotic resistance: an interview with Professor Romesberg

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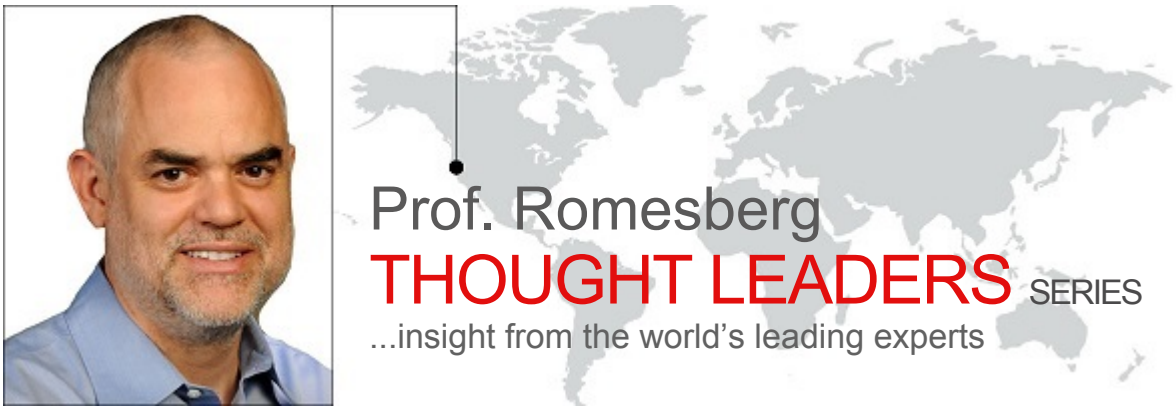
Interview conducted by April Cashin-Garbutt, MA (Cantab)



How much do antibiotic resistance rates vary in different bacteria and what was previously known about the reasons why some bacteria have higher antibiotic resistance rates than others?

Bacteria are very, very diverse. This is why their susceptibility to different antibiotics can be very different. It also makes the tools they have to evolve resistance in many cases different.

Some bacteria have to do a lot to become resistant, so it takes a long time. In addition, their biology may not be compatible with some forms of resistance that are common with other bacteria so they will have to find other ways to be resistant.

Having said this, it remains true that the actual mechanisms that many bacteria use to evolve resistance are common. This may be because there are only a few ways to easily evolve resistance to a given antibiotic.

It may also be because bacteria have been fighting with each other for eons, and since they have been using the same antibiotics, or evolved derivatives thereof, the resistance mechanism have had eons of time to evolve.

When we watch the evolution of resistance today, it is actually just the process of selecting for those members of the bacterial population that already had or were able to acquire the resistance mechanism (meaning the DNA that encodes the proteins that confer resistance).

How did your research on arylomycin antibiotics help you to unlock the genes behind antibiotic resistance in *Staphylococcus aureus?*

We are involved in optimizing the arylomycins as antibiotics. Part of this is to understand how sensitive different bacteria are to the arylomycins.

When we were surveying different strains of the bacterium *Staphylococcus aureus* (often just called "staph," and the origin of the bacteria called MRSA, which stands for methicillin resistant *Staphylococcus aureus*) we found that some were sensitive and some were resistant.

When we looked at their DNA, we found out that the only consistent difference was that the ones that were sensitive had mutations in a certain operon (an operon is a cluster of genes that are transcribed into RNA together, and often also into protein together).

We then forced sensitive *S. aureus* to evolve resistance to the arylomycins and found that they evolved resistance by mutating the gene that controlled the expression of the operon. So we suspected that the expression of the operon conferred resistance, which turned out to be the case.

Were you surprised that *S. aureus* could survive without SPase?

Very. The single thing that took us the longest during all of this research was convincing ourselves that SPase was

not essential when the operon was upregulated.

We confirmed it about four times independently. It seems crazy, SPase is one of the best characterized genes/proteins and everyone knew (thought) it was essential for survival.

What impact will the discovery of this new step in protein secretion have?

It has important implications for our understanding of fundamental bacteria physiology. Secretion is a central process and understanding how it is accomplished, including backups that exist to make sure it is accomplished even when the primary mechanism are failing.

It will also have important implications for the development of the arylomycins as antibiotics (the arylomycins are currently under development as antibiotics at a major pharmaceutical company).

All antibiotics eventually succumb to resistance with use, and understanding when, where, and how resistance arises, and how that resistance is mediated is important for their development. It might tell you which other antibiotics it might be really helpful to pair with your antibiotic or it might tell you which types of diseases will be most effectively treated.

What further research is needed to increase our understanding of the genetics behind antibiotic resistance?

A lot of new and powerful scientific tools have become available since the golden era of antibiotic development (1950-1970s), and these should all be used to understand the evolution of resistance to available antibiotics, as well as those in development (like the arylomycins).

Society as a whole needs to understand the threat poses by bacteria in the past and that resistance threatens to make this the case again.

How many new antibiotics are in the pipeline?

At early stages of development, no one really knows because companies don't always disclose everything that they are doing. But everyone knows that it is only a handful, and much less than in the past.

In late stages of development (at or past what is called "phase I," which is the first time you give the antibiotic to people), it is somewhere between 30 and 40. These studies cost millions and take years to complete, and based on historical standards, most will fail.

Where can readers find more information?

http://www.scripps.edu/romesberg/

About Professor Romesberg

Prof. Romesberg received his Ph.D. in physical organic chemistry from Cornell University. After completing postdoctoral research at UC Berkeley, he joined the Department of Chemistry at The Scripps Research Institute in La Jolla, California.

Prof. Romesberg's lab at Scripps uses a broad range of interdisciplinary techniques to study different aspects of evolution, including femtosecond spectroscopy, organic chemistry, microbiology, and molecular biology.

The Romesberg lab has worked to develop unnatural base pairs (UBPs) for the expansion of the genetic alphabet, including the generation of a semi-synthetic organism that stably maintains a UBP in its genome; to develop novel antibiotics; to develop and implement new methods to determine how evolution tailors protein dynamics; and to elucidate how cellular stress and DNA damage induce cell cycle checkpoint responses and mutation.