Future MICROBIOLOGY

Interview

Anti-infectives derived from botanical natural products: an interview with Cassandra Quave

Alice Greenway[1] & Cassandra Leah Quave*,[2]
[1]Future Science Group, London, N3 1QB, UK
[2]Emory University, Atlanta, GA, USA
*Author for correspondence: cassandra.leah.quave@emory.edu

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The editor of Future Microbiology, Alice Greenway, speaks to Cassandra Quave from Emory University (GA, USA) following her talk entitled 'Discovery of Anti-infectives and Virulence Inhibitors from Botanical Natural Products' at American Society for Microbiology (ASM) Microbe 2018 (7–11 June).

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Q Could you introduce yourself & tell us a bit about your background?

My name is Cassandra Quave, I have a PhD in Biology from Florida International University and a bachelor's degree in Biology and Anthropology from Emory University. I am currently an Assistant Professor of Dermatology and Human Health at Emory University and I curate the Emory University Herbarium – a museum of plant specimen records.

Q What is your current research focus & what inspired you to work in this area?

My current research focuses around natural product drug discovery for escape pathogens. I am most interested in applying an interdisciplinary lens to understanding how natural compounds can be leveraged to deal with antibiotic-resistant organisms. I am very interested in compounds that potentiate or restore activity of antibiotics, are effective in blocking biofilm formation or those that interfere with cell-to-cell communication or quorum sensing. One of the unique aspects of my group's work is that we focus on plants that have been used in indigenous medicine from different parts of the world for infectious disease for many years.

Q Please can you give me an overview of the research you will be presenting here at ASM microbe?

I was really excited to be invited to speak in the symposium entitled 'Natural products in microbiology'. I will be focusing on the way that we approach drug discovery through the lens of ethnobotany. I will provide examples of how we identify which plant species to collect and how we go about extracting those compounds from these species. I will then give some examples, several of which focusing on quorum sensing inhibition and biofilm inhibition in *Staphylococcus aureus*, as a case study of how we leverage this approach to understanding how traditional medicines work.

Q What types of natural anti-infectives are most promising & which are the most difficult?

Some of the biggest challenges in working with natural products stem from the isolation of individual components, because within every plant tissue, a single plant leaf may contain hundreds of different molecules. There is a lot of work that goes into isolating and identifying new molecules that are unknown to science – and unreported – so that takes a bit of time. But that is also the exciting and fun thing about our science; it is the discovering of new things.

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The most exciting natural products we are working with at the moment are the ones that could have interesting utility in the future as adjuvants to existing therapeutics. The idea being that we could combine these with existing classes of antibiotics to either enhance their effectiveness, reduce risk of resistance development or reduce morbidity in the infectious process by targeting virulence cascades. I think the challenging aspects besides isolating and identifying compounds in these mixtures also has to do with the regulatory framework in which we operate today – there is no clear drug development path for a virulence inhibitor or a biofilm inhibitor. On the other hand, within the scientific community, more and more people are starting to see the value of what such an inhibitor could have in improving patient outcomes.

Q What are the possible real-world applications? Which are the most developed?

We are currently working on pulling together data for an investigational new drug application for our quorum-sensing inhibitors from chestnut and pepper tree. The idea being that there could be potential applications for the management of atopic dermatitis, which is driven in many ways through staphylococcal virulence. We are also collaborating with an industry partner to integrate our biofilm inhibitor into a wound devise, so I am looking forward to seeing the results of our animal studies; hopefully we have developed an innovative way of developing bandages for these natural products.

The three plants that I am most excited about and that are the most developed in our current studies would be *Rubus ulmifolius*, an elm leaf blackberry from the Mediterranean, *Castanea sativa*, also known as the European chestnut and the Brazilian pepper tree or *Schinus terebinthifolia*. These have all yielded some interesting chemistry and bioactivity that could show some promise as the basis for new therapies moving forward.

Q What are the next steps in your research?

The next steps are multifold. On one hand the joy of my work comes from the early discovery process, so I am continuing to work on expanding our library of natural products, we currently have over 1400 extracts derived from 500 species of plants. This summer we will continue to expand upon our chemical library by collecting additional species that have been historically used for treatment of skin ulcers, nonhealing wounds and other kinds of infection. I am interested in continuing to screen and look for new leads against multidrug-resistant pathogens. Beyond these discovery aims, we are going full force forward trying to develop our existing projects regarding quorum-sensing and biofilm inhibition.

Q Would you say you have one of the biggest database of natural products?

The National Cancer Institute also has a natural products library, but what is unique about ours, is that we have heavy representation of the Mediterranean, something that the National Cancer Institute does not have. Our database also ties together the traditional uses of products, specifically for inflammatory disease. We are really fishing from a stocked pond as these are plants that people have been using for centuries, if not millennia, to address the infectious process. But what is different about what we bring to the table, is that we are starting to develop a scientific understanding as to how these compounds work, if they work, why they work and what is their safety?

Q What are the key hurdles to overcome in the field?

I think one of the key hurdles in the field is mindset, I am going to argue this in my talk; what we really need in infectious disease drug discovery is a paradigm shift. If you look at the history of how medicine has shifted and changed over time, it has not always been an area of rapid change. For example, look at the theory of spontaneous generation – the theory that living organisms can emerge from nonliving matter – it took 300 years of experiments to overthrow that theory. However, we are still in the infancy of the antibiotic era, we have been using antibiotics for less than a century and we are already encountering all these problems with emergence of resistance to multiple antibiotic classes. Meanwhile, you have this vast history and knowledge from across the globe of people that have been using plants to treat infections for generations. The challenge really is that we do not know how they work, or in some cases, if they work. What I tell my students, is to not just think outside the box when we are trying to ask the right questions to understand how these plants work, but to remember there is no box. We cannot just limit ourselves to checking minimum inhibitory concentrations and minimum bactericidal concentrations, we also need to think of what other potential pathways might these compounds be working on, whether it be pathogen or host targeted.

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