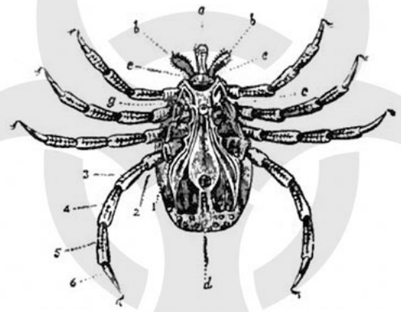
The unifying theory of collaborative research

Dr Karsten Hazlett of the Albany Medical Centre is a living example of how research collaboration can produce results impossible for individual researchers. Drawing together diverse investigators to tackle the problems involved in understanding the physiology and pathogenesis of bacterial pathogens, Dr Hazlett shows how this approach brings benefits for all involved.

The conceptual underpinnings for much of Dr Hazlett's work were forged during his postdoctoral training with Dr Justin Radolf at the University of Connecticut where he gained an understanding of bacterial physiology that has driven his subsequent research. The first of these tenets is that zoonotic bacteria (those which are passed from animals to infect humans) change composition in response to their immediate environment and these changes can impact efforts to understand microbial pathogenesis, immunology & vaccine-development. The second foundational point is that a correct understanding of bacterial proteins (structure, function, localisation and regulation) is a prerequisite to understanding bacterial physiology, as well as to developing vaccines.



COMING TO AN UNDERSTANDING

Dr Hazlett says his lab is driven by a singular guiding principle – "that understanding a bacterial disease, from the bacterium's perspective, will reveal translatable therapeutic opportunities". This has been their goal throughout their recent research, which has consequently drawn in other groups with a similar aim to combat bacterial pathogens and better understand the underlying mechanisms of their activity.

BACTERIAL AGENT AT LARGE

In 2009, the group started work on a project to assess the dynamic composition of *Francisella tularensis* (*Ft*), the causative agent of tularemia. This bacterium is an intracellular pathogen which has been found in many different wild animals. Infection of humans occurs through contact with these animals or via vectors (such as ticks and lice) – no human-to-human infection has ever been recorded. The pulmonary form of the disease (affecting the lungs) is often fatal and the bacterium has a low infectious dose, high virulence, and is readily spread by aerosol. For these reasons, the bacterium is a Tier 1 Select Agent meaning the US government believes it to have, "the potential to pose a severe threat to public health and safety".

Because of this potential for use as a biological weapon, the group set about investigating how to discriminate between naturally-occurring *Ft* and those which had been cultured with the specific intention of infecting the public (i.e., bioterrorism). Simulating these differing conditions in the lab, the team used mass spectrometry to analyse the lipids and proteins of

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fractionated bacteria. Collaboration was once again a key feature of this research, with Drs Bob Ernst and Steve Kron, from the universities of Maryland and Chicago respectively, bringing their expertise to bear on the lipid and protein fractions respectively.

THE ADVANTAGES OF TEAMWORK

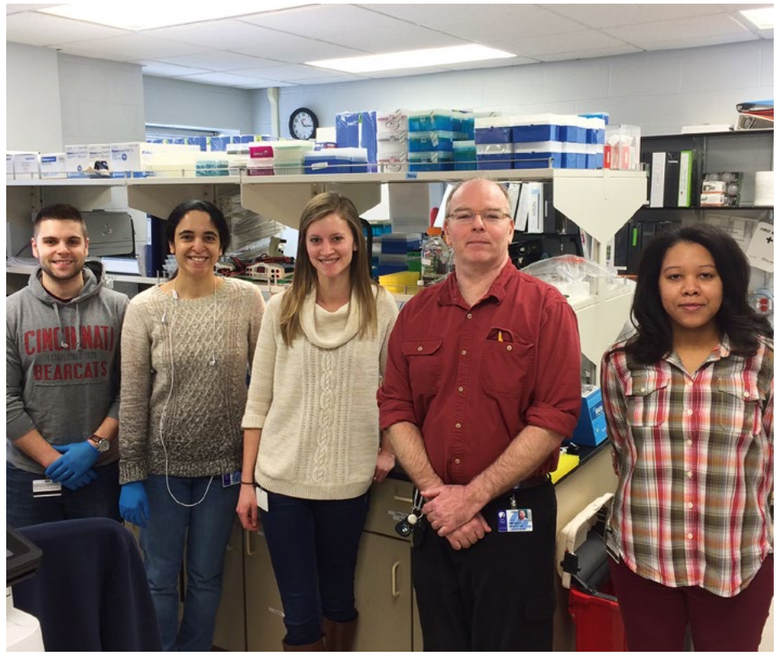
Convinced it is possible to develop a vaccine against this disease, Dr Hazlett and a second group focussed on three specific methods for improving vaccine efficacy. Firstly, maximising antigenic similarity, and ensuring that the vaccine composition is sufficiently similar to that of the bacterium during an infection. Secondly, optimising the capacity of this vaccine to stimulate an immune response in the individual. And thirdly, maximising the ability of the body's cells to present the vaccine to the immune system for effective targeting.

All of these approaches are also relevant to vaccine production more generally, so finding the answers for *Ft* would reap benefits for a host of other situations and organisms. Dr Hazlett, with his experience in the study and genetic manipulation of microbes, was well placed to get started, but once again it was bringing in the expertise of others which accelerated progress.

Dr Tim Sellati, an Immunologist and expert in the study of immune stimulation and microbial pathogenesis, and Dr Ed Gosselin, a Vaccinologist skilled in the development and testing of immunogens which provoke protective immune responses, made it possible to apply a unique multidisciplinary approach to vaccine research, unifying and streamlining the development of inactivated bacterial vaccines.

EXPANDING THE MODEL

Their current research programme draws these strands together to further develop vaccine candidates, through testing in outbred animal models. The standard practice of using inbred strains in biomedical research has advantages in ease of use, but also has its limitations when considering its relevance to human disease. By assessing the efficacy of vaccines in both outbred models and immunologically manipulated inbred models, it is possible to identify so-called 'correlates of protection' – elements of both the physical vaccine and the host immune response which are crucial for effective protective responses to vaccination.



The Hazlett Lab – Anthony (student), Prachi (post-doc), Kristen (student), Karsten, and Sarah (lab manager)

Once again Dr Hazlett has brought together a group of collaborating investigators who are able to progress the research using their diverse skills and experience. Alongside Dr Hazlett's microbiological expertise, Dr Eileen Barry, a Vaccinologist, and the Immunologist/Aerobiologist Dr Doug Reed (who re-established the outbred rabbit model of tularemia used in current aerosol infection scenarios), will uncover protection mechanisms for aerosolised, virulent *Ft* in an outbred animal model that will be applicable to prevention of the human disease.

A STAUNCH PROPONENT OF COLLABORATION

Dr Hazlett believes it is this ability to collaborate on scientific investigations which is the key to unlocking the complex mechanisms of action involved in vaccination research specifically, and biomedical research generally. To underline this concept he recently stated that, "My most enjoyable (and most successful) professional scientific experiences have been those in which a small group of like-minded investigators with differing backgrounds have come together for a focused, unified goal".

It is this unity of purpose which Dr Hazlett believes makes the small collaborative model such a productive and exciting way to work. His career to date has certainly shown how it can benefit not only the individual researchers, but also the wider scientific community, as the fundamental principles underlying observed phenomena are characterised and disseminated.

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Q&A

What excites you about researching bacterial pathogens?

Since the bacteria keep evolving, we have to keep learning. On top of this, folks keep finding out more about how the immune system functions and how the pathogens and hosts interact. With each new piece of knowledge, opportunities for novel insights or practical interventions avail themselves. Chasing these developments/ideas can be fun; ultimately, catching them is very intellectually satisfying.

How has working collaboratively benefitted your research?

Collaboration allows one to cast a broader net than most individuals (including me) can do by themselves. For me, collaboration has meant being able to think beyond isolated bacteria and individual bacterial proteins, and explore how bacteria operate in the context of a host and the multiple niches within the host environment. Moreover, as funding agencies have recently been encouraging well-constructed multidisciplinary grants, the "small team of experts" approach has become a valuable tool for academic medical researchers. For example, in 2006 the US National Institutes of Health implemented the Multiple Principal Investigator (MPI) funding mechanism specifically to *"encourage collaboration among equals"* and *"maximize the potential of team science efforts in order to be responsive to the challenges and opportunities of the 21st century"*.

What advice would you give someone attempting to forge collaborative partnerships?

I have had the best experiences with small groups of people (~3) with distinct scientific backgrounds and flexible personalities. Larger groups seem to be prone to becoming unbalanced and suffering from domineering personalities and splintered sub-groups – to the detriment of the project. A group of three folks willing to interact as co-equals naturally fosters an "us" and tempers the elaboration of unnecessary "alpha-ness". If you find yourself in a putative collaboration with someone who always needs to be the boss (even in your area of expertise), walk away and find or generate another group. There are good folks out there to work with and you did not get to this point in life to become someone's beta.

***What is the next step in developing a vaccine for* Francisella tularensis?**

Currently the two most effective candidates (developed by Eileen Barry and Wayne Conlan respectively) are live attenuated forms of otherwise virulent *F. tularensis*. These candidates are each more effective than the current gold-standard, (Ft LVS), and are both in various stages of advanced, pre-clinical development in outbred animal models. The efficacy of inactivated and/or sub-unit vaccine candidates has lagged behind largely because the correlates of protection for tularemia are currently ill-defined. As a result, tularemia vaccinologists are operating in an incomplete immunological landscape. By using live vaccines in both effective and sub-effective formulations, we are probing outbred, protective immune responses to identify the correlates of protection. Identification of these correlates will accelerate development of sub-unit vaccines, predictive immune assays, and novel vaccination/therapeutic platforms.

What has been the most enjoyable aspect of your collaborations?

Chatting with folks who look at a problem from different perspectives, coming up with novel interdisciplinary solutions, and testing the idea(s) with a "soup-to-nuts" approach.

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Detail

RESEARCH OBJECTIVES

Dr Hazlett's research focuses on bacterial pathogenesis, gene regulation, and vaccine development. His laboratory's principle is: understanding a bacterial disease, from the bacterium's perspective, will reveal translatable therapeutic opportunities.

FUNDING

- National Institutes of Health (NIH)
- National Institute of Allergy and Infectious Diseases (NIAID)

COLLABORATORS

- Eileen Barry, PhD (University of Maryland-Baltimore)
- Douglas Reed, PhD (University of Pittsburgh)
- Edmund Gosselin, PhD (Albany Medical College)
- Timothy Sellati, PhD (Southern Research)
- Robert Ernst, PhD (University of Maryland-Baltimore)
- Stephen Kron, MD/PhD (University of Chicago)

BIO

Dr Hazlett was born in Honolulu and received his BS degree in Biology/Chemistry at Frostburg State University in 1993. He later obtained a PhD at Albany Medical College and a postdoctoral fellowship at the University of Connecticut Health Center. He returned to AMC in 2005 and is currently an Associate Professor.

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