Candidate's Statement
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Research

Humans are exposed to potentially pathogenic micro-organisms every moment of every day. The air we breathe, the things we touch, the food we eat, even our natural microflora harbours potential pathogens and yet we are healthy most of the time. My overarching research goal is to uncover how our body, and specifically our innate immune response, successfully manages to control these constant threats to our health and how as we age pathogens are able to evade what was once effective immune surveillance. To achieve this goal, my research focus is on a specialized innate immune cell called a macrophage.

Macrophages are the sentinel cells of the immune response; their role is to detect pathogens via expression of surface receptors. Generally, they are effective in clearing the pathogen without mounting an inflammatory response; however, when a pathogen evades detection or clearance, macrophages are instrumental in mobilizing an appropriate immune response. In some cases, an unsuccessful attempt to resolve infection or an inappropriate response to non-infectious stimuli can result in tissue damage and sterile inflammation. Since macrophage receptors are crucial to this initial interaction with pathogens and shape the downstream immune response, factors that alter the rate or magnitude of receptor expression (e.g. slight genetic variations in receptor genes, age associated changes in receptor expression) can have profound effects on an individual's susceptibility to infection. I have received NSERC funding (5yrs) to discover how a specific class of macrophage receptors, the class A scavenger receptors, have evolved in vertebrates (Whelan et al BMC Evol Biol, 2012) and how they send signals to the cell once the detect a foreign agent (Tu et al., manuscript in progress).

A key focus of my research program is the role of macrophages in the control of infection in the upper respiratory tract. The upper respiratory tract (e.g. nose, sinuses, trachea) is the gateway to respiratory infections such as influenza and pneumonia. Despite the crucial importance of the upper respiratory tract in controlling access of these life-threatening pathogens to the lung and blood-stream, very little is known about mechanisms of immune control therein and how these mechanisms deteriorate with age. In order to study this, in collaboration with Prof. Jeff Weiser (University of Pennsylvania Medical School) we have developed a mouse model of *Streptococcus pneumoniae* colonization of the upper respiratory tract. *S. pneumoniae* is the major cause of pneumonia yet it generally lives transiently and asymptomatically in the upper respiratory tract ("colonizes") and infection (i.e. bacteria in the lungs or blood) only occurs when immune mediated control of colonization fails. Prof. Weiser and I have received NIH funding (5 yrs) to discover which macrophage mediated receptors are key for recognition and immune control in the upper respiratory tract and have published our findings in the *Journal of Immunology.* In addition, Drs. Mike Surette, Jennie Johnstone and I have received a CIHR Emerging Team Grant (5 yrs) to dissect the interplay between the innate immune response and the complex microbiota of the upper respiratory tract, and how this changes with age. Together Dr. Surette and I supervise two graduate students and two post-doctoral fellows, and have made some exciting discoveries regarding how the microbiota changes with age. We are currently pursuing whether these are a result of a changes in the aging immune system and whether changes in the microbiota might contribute to the increased susceptibility of the elderly to respiratory infections.

We know that the most common but most complicated cause of loss of immune control to *S. pneumoniae* is aging. At 55-65 years an individual's susceptibility to pneumonia increases dramatically and in fact, 90% of pneumonia deaths in Canada occur in the elderly, in large part because vaccination is ineffective in this population. This is a major scourge of our aging population yet surprisingly little research addresses the molecular and cellular mechanisms of immune control that breakdown with age and leave us susceptible to infection. To address this question, I have developed a mouse model of *S. pneumoniae* colonization and infection in aged mice, which to my knowledge is unique in the world.

Although logistically difficult since mice must be housed at great expense for up to 2 years and many are lost due to age-related diseases, by working closely with the staff and veterinarians at the Central Animal Facility, we have a small colony of aged mice, a unique resource in Canada, which I am planning to expand. Because there is no avenue for obtaining aged mice in Canada, this has led to a number of collaborations locally (Drs Jonanthan Schertzer (Biochemistry)& David Rollo (Biology)) and will be a valuable resource as McMaster expands its focus on research in aging and couples epidemiological and population level studies in humans (e.g. the Canadian Longitudinal Study on Aging) with basic research. Using this model has been phenomenally informative and has provided many novel hypotheses on why the elderly are unable to control colonization of the upper respiratory tract and subsequently become infected. Due to the novelty and clear translational potential of this model, I was awarded a prestigious New Investigator Award from Pfizer (ASPIRE-Pfizer) to further develop an aged mouse model of post-influenza pneumonia and the Pfizer-Ontario Lung Association Research Award to discover how initial recognition of bacteria by aging macrophages is impaired. In addition, I have been invited to present this work at nationally (McGill, Queen's, Calgary, Guelph) and at international meetings (e.g. Society for Leukocyte Biology).

This mouse model has enabled us to translate observations on age-associated defects in immunity to humans. One of the goals of my research program is to translate discoveries in basic science to human studies. To do this, I actively collaborate with a number of clinicians including Drs. Param Nair and Mark Loeb. Dr. Nair is a collaborator on my CIHR Operating Grant (5 yrs) in which we collaborate to elucidate how chronic age-associated inflammation contributes to the impaired anti-bacterial response of macrophages. With Drs Mark Loeb and Jennie Johnstone, we have studied the dynamics of colonization and infection in a cohort of local nursing home patients, who are at extremely high risk for developing pneumonia. We are discovering blood based markers for susceptibility to infection and performing functional assays on monocytes/macrophages to determine which age-associated defects predispose them to *S. pneumoniae* infection. This has resulted in two submitted publications. Since there may be diagnostic potential for this work a provisional patent application is in progress (Monocyte biomarkers of dementia in the elderly. D.M.E. Bowdish & C. P. Verschoor). The long-term aim of my research program is to follow these age-related changes in a larger population and to determine which are linked to increased risk in infectious disease in general. As an investigator with the Canadian Longitudinal Study on Aging, the world's largest longitudinal study on aging with upwards of 20,000 participants donating biological materials over the course of decades, I have developed protocols that allow us to test these observations at the population level. My PhD work resulted in a number of patents for novel anti-infective therapies and the formation of the company Inimex. I continue to be committed to developing novel immunomodulatory therapies, with emphasis on those that will benefit the elderly. To pursue this goal I am spearheading a clinical trial, funded by the Labarge Initiative, in collaboration with Drs. Loeb, Bramson, Johnstone, Nair and Surette to determine if probiotics will reduce the incidence of respiratory infections in the nursing home elderly.

In summary, I have built a strong and diverse research program that tackles research questions that are of fundamental importance to Canadians and incorporates training of highly qualified personnel (undergraduate and graduate students, post-doctoral fellows, technicians). By incorporating basic science, clinical collaborations and translational studies, I will elucidate the basic mechanisms of bacterial recognition by macrophages, how these mechanisms change with age and how the health of Canadians can be improved by discovering novel immunotherapies.

Education

I chose to build my research career within academia, and specifically at McMaster, because I believe that innovative, ambitious and important research is performed by those with an undergraduate and graduate background that fosters these qualities. My philosophy is that scientists have a responsibility to foster the next generation of creative and bold scientific thinkers and to share our enthusiasm for our work, which we do by 1) formal teaching, using dynamic examples of the application of our work, 2) mentorship, providing our trainees ample opportunities to excel and 3) public engagement, sharing both our knowledge and the relevance of our work to the broad public.

Although my primary appointment is research (80%), I am strongly committed to incorporating teaching into my research portfolio. As such I supervise undergraduate thesis students, graduate students and post-doctoral fellows. In addition to teaching basic laboratory skills, critical thinking, creativity and ambition, I expect them to take ownership for their projects and to become independent and integrated members of our department. I am available to my students in a number of capacities, weekly scheduled meetings, instant messaging, and our lab Google+ site which we use for broader conversations on new data and recent publications. I encourage my trainees to attend local, regional and international venues to promote their research and to date each of my undergraduate and graduate students have won local or regional awards for poster presentations or been invited to speak at conferences. (For a complete list of distinctions awarded to my trainees, see my website http://www.bowdish.ca/lab/people/). This recognition of their hard work and success is inspiring to both them and to me. In order to obtain feedback on my performance as a mentor I encourage all thesis and graduate students to fill out an evaluation form in which they are encouraged to provide candid feedback on areas of improvement.

I am co-ordinating the HTHSCI 4II3 course and use a number of innovative educational initiatives (e.g. social media) to engage students in both the course material and immunology in a larger social context. I have also lectured in a graduate seminar course MS715. Because I find one-on-one mentorship very fulfilling I also teach the graduate independent study course (MS779), which, although time consuming, allows me to mentor students directly. In addition, I am an Area Co-ordinator for the Medical Sciences Graduate Program (Infection & Immunity). I serve on a number of graduate committees and take these mentorship opportunities very seriously, often meeting with the students outside of formal meetings and provide them with “at-the-bench” training, career support and networking opportunities. I also participate in “Career Day” at the University of Guelph to discuss what an academic career entails. From my own experience, I know how often the post-doctoral fellows, feel that they “slip through” many of the support systems that the undergraduate and graduate students have access to, especially with regard to career mentorship. I have taken special interest in mentoring our post-doctoral fellows who have questions about combining careers and family or starting their own independent careers as either faculty or in other avenues such as science journalism.

Beside the conventional model of teaching, I am also involved in engaging the public in my science, science in general, and careers in science. My motivation for this is two-fold. First, I was motivated to begin a career in science by an inspiring post-doctoral fellow at McMaster who participated in a high school outreach program and I would like to inspire other young people to choose science as a career. As such, my trainees and I are involved with the YES (Youth Engaging in Science) Mentorship program. We have hosted and will continue to host “at-risk” youth (i.e. a student chosen from one of Hamilton’s underperforming high schools where the average family income is at or below the poverty line) with an aptitude for science in our lab to provide them with a project suitable for presentation at the Bay Area Science & Engineering Fair (BASEF). In addition my trainees and I participate as judges in the science fair. Since the bacteria we study, *S. pneumoniae*, causes ten times the disease in First Nation populations compared to non-Aboriginal populations, my lab is developing a proposal to host a First Nations high school student as a summer intern to involve them in what we hope will be research that is particularly beneficial to First Nations people.

My second motivation for public engagement is that as my work has always been funded by the Canadian taxpayer, I believe that they have the right to know what I work on and how that contributes to health science research in Canada and how the work we are doing at McMaster is ultimately relevant and important to the well-being of Canadians. In order to promote my work and McMaster I have given interviews and written articles for the lay public and am participating in public outreach such as Café Scientifique (April 2013) designed to have a constructive dialogue with the community on controversies in vaccination. I also manage the McMaster Immunology Research Centre website and our social media presence on Facebook and Google+ page, which together have over 1000 followers, primarily from the lay public.

I believe that one of my unique strengths as an educator is that I embrace teaching opportunities that encompass the entire spectrum of the educational process and promote independence, creativity and ambition at all levels of the educational spectrum.

January 2, 2013