Name: Catherine B. Anders
Title: Postdoctoral Research Fellow
Institution: Idaho Veteran's Research and Education Foundation at the Boise VA Medical Center
Project Title: Longitudinal, In Situ Profiling of Wound-Associated Macrophage Phenotypes by Q-IHC
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What do you hope to/did you learn through this research?
As of 2013, there were nearly 30 million Americans with diabetes or one in ten adults, but by 2050, estimates from the American Diabetes Association indicate that one in three adults (~350 million Americans) will be diabetic. At current rates of amputation (~25%) due to non-healing wounds, this 2050 population will have to absorb the social and economic burden of over 85 million diabetic amputees. In healthy, non-immunocompromised individuals, the normal wound healing process initiates quickly and proceeds through well-characterized, iterative steps; however, in chronic wounds, the healing process appears stalled at the resolution of inflammation and initiation of tissue re-organization. This stalled wound-healing process and chronic inflammatory state can most clearly be observed in patients with diabetic foot ulcers (DFUs). We contend that, in the diabetic patient, the inflammatory potential of infiltrating MΦs is elevated and recalcitrant to localized signals mediating wound transition into the inflammation-resolution phase and that diverse MΦ phenotypic plasticity mediated by metabolic immunomodulation is required for efficient wound healing. As a first step toward establishing the functionality and metabolic immunomodulation of diverse MΦ phenotypes within the primary wound, we intend to utilize longitudinal, quantitative immunohistochemistry (qIHC) to directly profile wound associated MΦs *in situ*.

What can you tell us about the progress made in this area since you first began your research?
The MΦ effector functions needed to facilitate the wound healing process is often ascribed to M1 or M2-like phenotype; however, the spatial and temporal dynamics that exist in wound resolution suggests this paradigm is an oversimplification of the *in vivo* MΦ populations and overlooks the unique MΦ potential for phenotypic plasticity. To address MΦ phenotypic plasticity within the metabolic complexity of the wound environment, we utilize a quantitative Complex Systems Biology (qCSB) approach based on the integration of metabolomic, microbiome, and innate immune variables. In previously published work from our group, we established the feasibility of integrating metagenomic profiling with global metabolomics to identify correlations between bacterial community composition and metabolic landscape within the wound environment. Additionally, our group has demonstrated a strong correlation between wound-derived metabolite profiles and predictability of chronic wound response to treatment indicating the important contribution of the metabolic landscape to wound resolution. More recently, using an *ex vivo* human MΦ polarization model, we have developed quantifiable biometrics by which we can distinguish functionality between classically-activated/pro-

inflammatory M1 MΦs and an expanded set of alternatively activated phenotypes including M2a, M2b, M2c, and M2d MΦs. In this *ex vivo* MΦ model, we have not only comprehensively defined cellular functionality, but also mapped the unique metabolic shifts associated with each of these phenotypes and identified unique biological markers that may be useful in identifying these phenotypes *in situ*.

How can this research help patients, clinicians and/or scientists?
By exploring the complex interplay between pathogenic bacterial community composition and metabolic landscape within the wound environment with the phenotypic characteristics of the macrophages present within the wound tissue, we hope this project will generate the groundwork necessary to develop an algorithm of diagnostic and prognostic indicators applicable to predictive modeling for healing versus non-healing in DFUs and evidence-based protocols that can be tailored to each patient's needs at the bedside.

How did this award help your career?
This award came at a critical point in my research. The completion of the NIH-funded Histology/Pathology/Imaging Core facility at the Boise VA provided an excellent opportunity for investigating this unresolved question and the WHF 3M Fellowship will provide the necessary funds to implement the project.

How did you get interested in wound healing and this area in particular?
As the daughter of a US veteran, I care deeply about the healthcare of US service members and veterans. In the veteran population alone, approximately 1 in 3 veterans has Type 2 diabetes and DFUs result in the highest percentage of new lower extremity amputations with an average cost of ~$51,000 per patient. Addressing these health issues is critical to the health and well-being of our veteran population.

What are your future plans for your work in wound healing?
My long-term career objective is to pursue research opportunities that explore regulatory mechanisms in innate immune system cells during the wound healing process and how these processes are dysregulated by the chronic wound microenvironment in patients with Type II diabetes and other metabolic disorders. During my master's work in physical analytical chemistry and my doctoral work in biomolecular sciences, I explored the mechanistic disruption of nanoparticle therapeutics in complex infection and disease processes. By integrating my experience with non-conventional therapeutics with our complex system biology approach to wound healing, I hope this research will lead to innovative translational opportunities in the development of novel therapeutics and diagnostics.

Who do you consider your mentors and your close associates in this project? How did you start working with them?
I was blessed with the opportunity to join the research team of Mary Cloud Ammons, PhD in collaboration with the wound clinic at the VA in 2018. Her extensive experience in the field of innate immunology, metabolomics, bacterial biofilms and complex systems biology has profoundly impacted my approach to translation research.

Tell us about your life away from the lab and/or clinic?
I am the mother of four amazing children, ages 20-26, and the wife of an incredibly supportive husband. In my spare time, I am active in my church community and enjoy hiking, reading, gardening, playing games with my family and hanging out with friends.