**How Inflammation Begets Pathology**

Most pathology involves inflammation. Acute inflammation is obvious, but most chronic diseases—and especially their symptoms—are due to inflammation that is continuing to be stimulated, failing to resolve, or self-directed. The Damage Associated Molecular Patterns (DAMPs) and Pathogen Associated Molecular Patterns that induce the inflammatory response are more similar than they are different—as are the receptors that respond to them and the stereotyped inflammatory response by the vasculature and circulating leukocytes. What, then, dictates whether some inflammation heals with complete restoration of tissue structure and function, while other inflammatory events heal with scarring and loss of function? Spoiler alert: It isn't just whether or not the tissue can regenerate.

To get everyone on the same page, we will review what is known about how inflammation is initiated, and the cellular and molecular events that lead to *tumor, rubor, calor,* and *dolor.* We will then review the coordinated interactions between molecules expressed on leukocytes and those presented on endothelial cells that serve in essentially a combination lock fashion to allow the leukocytes to adhere to endothelial cells in the vasculature selectively at the site of inflammation.

All of that is pretty amazing, but it is all reversible. Most leukocytes summoned to the site of inflammation do not roll on the endothelium; most leukocytes that role do not adhere, and most of the ones that adhere let go and return to the bloodstream. However, once a leukocyte commits to migrating across the endothelium, with rare exceptions, it does not return. And, as I am fond of saying, "All the Good, the Bad, and the Ugly of inflammation takes place after leukocytes enter the tissues." (A movie reference that is lost on almost all of you born after 1966.) Therefore, the final part of the talk will cover the latest developments, from my lab and others, on the process of transendothelial migration (TEM). We will discuss the relevant adhesion and signaling molecules, membrane movements, cytoskeletal rearrangements, signaling pathways, and soluble mediators that regulate TEM. We will also discuss some alternative pathways of TEM, exceptions that prove the rules, and unanswered questions for future research.