Name: David James Sharp, Ph.D.
Title: Professor of Physiology and Biophysics
Institution: Albert Einstein College of Medicine
Project Title: Development of a Concentrated Poloxamer-siRNA Technology to Promote Full-Thickness Excisional and Burn Wound Healing via Depletion of the Novel Microtubule Regulatory, Fidgetin-like 2.
Year awarded: 2016

What do you hope to learn through this research? Poloxamers have emerged as a safe drug delivery platform with a favorable irritation and toxicity profile. By using poloxamers as a siRNA delivery system in the treatment of wounds and burns, we may be able to expedite healing by combing the intrinsic therapeutic activity of poloxamers through maintenance of membrane integrity, with efficient delivery of therapeutic siRNAs *in vivo*. Using high concentrations of poloxamer may also contribute to Phase 1 of wound healing by helping keep the wound clean and protecting wounded tissue, in the same way that many commercial topological antiseptic creams do. Results from this study will lead to the development of a novel siRNA/poloxamer based delivery system for the treatment of dermal wounds and burns. At the end of this project we will be able to directly compare this poloxamer based siRNA treatment regimen to an established silica nanoparticle based siRNA formulation in two wound healing models

What can you tell us about the progress made in this area since you first began your research? We have identified new and unique functions in this process for a number of microtubule severing and depolymerizing enzymes and are currently testing the hypothesis that the differential localization and regulation of these allows the microtubule cytoskeleton to selectively tune and coordinate different parameters of cell movement. Additionally, we have found that these enzymes can be targeted *in vivo* using nanoparticle encapsulated siRNA to predictably alter cellular motility in a variety of clinical contexts related to tissue regeneration and repair. Tested applications include cutaneous wound healing, cardiovascular repair after myocardial infarction, and neural regeneration in both the CNS and PNS.

How can this research help patients, clinicians and/or scientists? This research will help patients, clinicians and scientists. Firstly, by investigating new treatment regimens using a combination of poloxamers and siRNA targeting FL2 for wounds and burns, wound care management will become easier, meaning more productive clinicians and better outcomes for patients.

Secondly, developing new siRNA delivery systems to work *in vivo* will help scientists with their research. *In vivo* transfections are always problematic, and novel systems continuously need to be developed.

Has your work thus far yielded any surprises? The discovery of Fidegtin-like 2 was the greatest surprise. It was identified in a siRNA screen of putative microtubule regulatory proteins. We had no idea that knockdown of this undiscovered gene would have such a dramatic phenotype, and have such great potential as a therapeutic target.

In vivo, knockdown of FL2 in injured skin tissue resulted cells moving into the wounds faster. Not only that, but we observed normal, well-orchestrated regeneration of tissue, including hair follicles and the skin's supportive collagen network. These initial results prompted us to continue investigating this astonishing protein.

How did this award help your career? This award will help develop the basic cell biology we have done in the lab into a real treatment. It will allow us to communicate our research and help establish my lab in the wound healing research community.

How did you get interested in wound healing and this area in particular? My lab has always focused on understanding the regulation of microtubules and microtubule associated processes. The cytoskeleton is known to play an important role in cell migration, with a large research emphasis focused on understanding actin's role. However, recently emerging evidence suggests microtubules also play a crucial role in this process. My lab identified multiple microtubule based regulators of cell migration *in vitro,* and we naturally began to "move" our findings into *in vivo* work (mice, rats, and now most recently pigs).

Tell us about some of the outcomes of your research you are most proud of and what it means for patients, clinicians and/or scientists. My career-long research objective has been to elucidate the molecular machinery that assembles and regulates the functions of the microtubule cytoskeleton, and I have co-authored ~60 papers on this topic to date. Therapeutic translation of our basic NIGMS-funded science has led to the issuance of three US patents with three patents pending. It has also led to the formation of the biotech spinout, MicroCures Inc., as a commercialization vehicle for our technology (I am co-founder and Chief Scientific Officer).

Our technology strategically alters the activity of select microtubule "regulatory" proteins, thereby controlling cell motility and growth to promote healing in different therapeutic contexts. I am incredibly proud of the research we have done, and of the biotech start-up that has resulted.

What are your future plans for your work in wound healing? Our goal is to move through an IND and get our technology into the clinic as soon as possible. In some cases, we have made it through pig wound healing studies and hope submit our IND application within the year.

Who do you consider your mentors and your close associates in this project? How did you start working with them? My Ph.D mentor Dr Peter Baas and postdoctoral advisor Dr. Jonathan Scholey have obviously had and continue to have a major impact on my views about science. Indeed, we remain close friends to this day and collaborate on various projects. In terms of close associates, Drs Joshua Nosanchuck, Joel Friedman and Adam Friedman – all colleagues here at Einstein-- have been instrumental in the development of our wound healing project. Oddly enough, this project really came about through discussions among Drs Nosanchuk, Friedman and myself in the locker room at the school gym.

Tell us about your life away from the lab and/or clinic? I am happily married with 2 children (a son, age 12, and daughter, age 9) and a 125 pound German shepherd. They all keep me pretty busy in my spare time. I love sports, specifically football and am a die-hard Michigan fan. I work out regularly and maintain a small gym in my office.