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Project Title: Cellular factors that promote pro-MMP9 activation in chronic wounds
Year Awarded: 2001

My name is Yuan-Ping Han, Professor of Biochemistry and Cell Biology, College of Life Sciences, Sichuan University, China. I was a recipient of Recognition Grant (3M Health Care, Research Recognition Award), by Wound Healing Foundation and Wound Healing Society, in 2001, and a plaque was given in the Wound Healing Society meeting in Albuquerque, New Mexico. Time flies fast, and it has been many years since then, but the initial award to me is so important that it has continued to help my career development and achievement for many years since then. The award was based on my post-doctoral work with Dr. Warren Garner, my mentor and a plastic surgeon at the University of Southern California. The topic of the award was our work on the mechanism of MMP activation and inhibition in human skin wound healing. It is well documented that chronic wound healing is associated with persistent inflammation and MMP activation. But it was not very clear how particular types of proMMPs are activated in chronic wounds. Through the human specimens collected from patients under IRB supervision, we found the converting enzymes for proMMP9 in human skin is a chymotrypsin like proteinase, while the activation of the enzyme is controlled and inhibited by alpha-anti-chymotrypsin, an acute response factor secreted from liver. We published six papers to report the issue, two in *Journal of Biological Chemistry (2001, and 2002)*, one in *Surgery* (2005), one in *Journal of Investigative Dermatology (2008),* one in *Journal of Surgical Research (2002),* one in *Wound Healing and Regeneration (2009).* The initial 3M Recognition Award also helped me to get my first R01 award in 2004, to address the molecular mechanism for controlling MMP activation in wound healing of human skin. Since then, I set up my lab in USC and recruited graduate students and post-doctoral fellows. We reported for the first time about EMT features in human skin wound healing in *American Journal of Pathology* in 2010 (also, one image of the paper was used as the cover page for the issue).

Based on the Lab in USC, I also expanded my efforts to study tissue fibrosis including the cirrhosis in the liver. By comparison the fibrosis in the skin and liver we know the common mechanisms governing tissue fibrosis in general. In particular, we are interested to know how MMP genes are silenced or permanently turned off by myofibroblasts, which favors ECM accumulation in fibroplasia. The work brought me my second R01 grant, through which we addressed epigenetic suppression of MMPs in fibrosis. The work was published in another issue of *American Journal of Pathology* in 2010. Formation of scar or fibrosis is contributed not only by myofibroblasts and accumulation of ECM, but also the immune tolerant environment. In fact, fibrosis is almost always associated with tumor, namely tumor environment. Recently, we are addressing how immune tolerance is built in tissue fibrosis. In particular, we are addressing how regulatory T cells, called T-regs, and alternatively activated macrophages, or type-II macrophages contribute to tissue fibrosis. Our paper, published recently in *Journal of Molecular Cell Biology*, showed that MMP-9/13 mediated activation of TGF-beta may contribute to induction of iT-regs in liver wound healing.

In 2011, I left University of Southern California, in part because of lack of sustained funding support. I returned to my birthplace, Chengdu City in China. Through its Oversea Faculty Recruiting Program, I was appointed as a faculty in the College of Life Sciences, Sichuan University, my alma mater. Sichuan University is the biggest college in west China, which has 100,000 students. And its University Hospital has more than 20,000 beds, the biggest in China. In addition teaching undergraduates in Biochemistry in English, I launched my research lab, joined by eight graduate students and a few undergraduate students. Similar to USA, metabolic syndrome is prevalent in China. About 20-30% total population suffers varying levels of metabolic syndromes, which may not kill the subjects, but sets risk factors for diabetes, cardiovascular diseases, and stroke. Moreover, wound healing for diabetic patients is a big clinical challenge, which can also be categorized in metabolic syndrome. We started the project two years ago in collaboration with clinicians in Beijing YouAn Hospital. The initial work has been drafted into a manuscript, currently under revision. We are interested to know the systems biology of the high-fat-diet-induced metabolic syndrome.