Research Proposal

A. Title

How could nerve stimulation/acupuncture treat inflammatory disorders including sepsis, arthritis, brain degeneration disorders?

B. Background and Significance

Many human diseases are caused by excessive inflammation. Take severe sepsis as an example, which developed in patients with infection, trauma, and cancer (Angu and van der Poll, 2013). A hallmark of sepsis is excessive release of inflammatory cytokines that could cause organ dysfunctions and death, whose treatment remains a major medical challenge. In addition, inflammation has been linked with cancer development and side effects of cancer treadtment, such as chemotherapy-induced peripheral neuropathy. Worldwide, one-third of people who develop sepsis die. In the United States alone, over 250,000 patients died annually from sepsis, and the survived half million suffer various organ damage. The total hospital cost for all patients with severe sepsis was estimated to be $24.3 billion in 2007. Another form of inflammatory disorders is severe arthritis, with annual cost estimated to be close to $100 billion in USA. In recent years, it has also been increasingly recognized that brain degeneration disorders are partly caused by neurogenic inflammation, with activated microglia (related to the peripheral macrophages) contributing to abnormal neuronal activity and cell death. Thus, developing new effective treatment for severe inflammation is urgent and the underlying business potential is enormous.

While no effective drugs are available to treat sepsis and other severe inflammatory disorders, new hope does emerge in the past decade and half. That is, excessive inflammation can be managed by direct vagal nerve stimulation or indirect acupoint stimulation. The vagal nerve exits from the hindbrain and carries brain signals to modulate most organ activity in our body. In papers published in Science and Nature, Dr. Kevin Tracey and his colleagues showed that vagal nerve stimulation can release neurotransmitters to suppress the release of inflammatory cytokines from macrophages and other immune cells (Borovikova et al., 2000; Chavan and Tracey, 2014). In a study published in Nature Medicine in 2014 (Torres-Rosas et al., 2014), Ulloa and his colleagues show that stimulation of the ST36 acupoint in the hindlimb can suppress sepsis symptoms and promote animal survival, through a mechanism that depends on the activation of the vagal nerve. Collectively, these anti-inflammation effects via direct or indirect activation of the vagal nerve can dramatically promote animal survival in experimental sepsis models, thereby offering a novel strategy to treat severe inflammatory disorders (Chavan and Tracey, 2014). Notably, it has also been suggested that vagal nerve stimulation can dampen the release of inflammatory cytokines from the activated osteoclast associated with osteoarthritis and the activated microglia in the brain, raising the hope that osteoarthritis and brain degeneration disorders might also be

managed by the vagal nerve stimulation or by acupoint stimulation. Thus, a further study to improve this therapeutic strategy is of enormous business potential.

C. Our general conceptual framework and the ways to test this

It should be first pointed out that the vagal nerve stimulation discussed above, which eventually leads to activation of parasympathetic nerves and immune suppression, only represents one branch of nerve stimulations in modulating body physiology. The other major branch is the activation of the sympathetic nerves that act to antagonize the activity of parasympathetic nerves, such as enhancing immune activity, rather than immune suppression, thereby providing Yin-Yang balance.

We have a general theoretical framework on what kinds of acupoints whose activation could preferentially activate one of two opposing branches of the nervous system and regulate opposing physiology, such as immune suppression versus immune enhancement. We will use the genetic tools created in the Ma and Chiu labs to validate our hypothesis. Based on our hypothesis and subsequent validation, we will determine the best acupoints used for treating various diseases, such as inflammatory disorders discussed above. Within the selected acupoints, we will also optimize the parameters of acupuncture or electric stimulation (such as the intensity, duration, frequency, and depth of tissues) to achieve the best effects. Clinically, Dr. Lu's oncology acupuncture team at Dana-Farber Cancer Institute has conducted a randomized clinical trial to test the effectiveness of chemotherapy-induced peripheral neuropathy; an inflammation related never damage caused by chemotherapy drugs, in breast cancer patients. The preliminary results of the study so far are extremely encouraging. Therefore, we not only study acupuncture mechanisms in animals but also test it in real patients for real clinical conditions. Our unique strength and capacity from bench-to-bedside hold great promise for developing new therapeutic options. We are confident our research will not only make a contribution to understanding the overall conceptual framework about how acupuncture works, but also come back to improve acupuncture practice for disease treatment.

D. The collaborative team

The above conceptual framework was built upon extensive discussion with several top TCM clinical doctors and basic acupuncture scientists in China (and also in USA), as well as the basic science and clinical investigators in USA who have deep understanding of the neural pathways and mind-body interactions in regulating human/animal physiology. The doctors with deep understanding of TCM theories and extensive clinical experience are critical for knowing what acupoints and acupuncture handling methods (i.e., different depth of needling) to treat different diseases. Such information is crucial for basic scientists to form the conceptual framework or theories to explain how acupuncture works. Finally, it needs basic scientists to create new modern tools to test the hypotheses. The findings from basic

scientists will be fed back to clinical doctors. Ultimately, acupuncture clinical trials in real patients should be carried out to confirm these findings. Thus, a deep interaction between TCM doctors/scientists in China and basic scientists and clinicians in USA is the key for making a fundamental breakthough.

The proposed team at Harvard:

Dr. Qiufu Ma, Professor of Neurobiology at Dana-Farber Cancer Institute and Department of Neurobiology of HMS. He has been mapping neural circuits responding to various somatic sensory stimuli, and his lab's creation of a large cohort of mouse lines in which individual sensory pathways have been removed will offer an unique opportunity to study the neural basis of acupuncture.

Dr. Isaac Chiu, an excellent young Assistant Professor at HMS who has been trained in both immunology and pain-related neurobiology, will be crucial for studying nerve-immune interactions, a key foundation for understanding how TCM/acupuncture works.

Dr. Weidong Lu, the Oncology Acupuncture team leader at Dana-Farber Cancer Institute, who also is the Chair of the Committee of Acupuncture in Massacussetts, a professor at The New England School of Acupuncture and Instructor in Medicine of HMS, will be critical in linking basic science and clinical research at HMS

Dr. Shing tung Yau of Harvard, in collaboration with Dr. Tse L Lai of Stanford University, will help to set up data analysis program in Tsinghua university to help the analysis the data that are related to traditional Chinese medicine.

The above HMS scientists/doctors have building active collaborations with the following top TCM/acupuncture doctors/scientists in China:

1) Dr. Bin Zhu and Dr. Xianghong Jing, the former President and the current vice President of Beijing Institute of Acupuncture and Moxibustion.

2) Drs Gengcheng Wu and Yanqing Wang, the former and current Chairs of Department of Integrative Medicine at Fudan Universities.

3) Dr Baixiao Zhao, President of Beijing Tui-Na Institute, and personal TCM doctor for Chinese top leaders

4) Dr. Hongsheng Lin, Department Chair of Integrative Oncology, Beijing Guang An Men Hospital, Chinese Academy of Tradiational Chinese Medical Sciences

5) Dr. Zhiqiang Meng, Department Chair of Integrative Oncology, Cancer Hospital at Fudan University

E, Potential requested funding

1) Support four postdoctoral fellows or students to work in four different HMS/Stanford labs (Drs. Ma, Chiu, Lu, Yau/Lai). A three-year support will need around $400,000.

2) Equipment for Lu's lab for acupuncture-related human physiology studies ($100,000) (This part has no indirect overhead cost)

3) Equipment for Ma's lab: In vivo electrophysiological recording system to determine what acupuncture activates ($150,000), and the ultrasound guided in vivo injection systems to activate specific neural pathways to mimic acupuncture effects ($250,000). (This part has no indirect overhead cost)

4) Equipment for Chiu's lab: in vivo physiology measurement in small animals (such as heart rate variability and gastrointenstinal movements reflected by activation of different amount of sympathetic and parasympathetic nerves: $100,000) (This part has no indirect overhead cost)

5) Animal housing for Ma plus Chiu Labs: $20,000/year/lab. Total: $120,000/3years (This part has no indirect overhead cost)

6) Pilot human clinical trials for Lu lab: Total: $120,000/3yrs

7) General supply cost for three labs (Ma, Lu and Chiu): $14,500/year/lab. Total: $130,000/3yrs

8) Overhead for items 1, 6, 7 (20%): $130,000 for all three years

In total: $1,500,000 for three-year support.

Optional: if the funding is large enough, a two-photo imaging system will be extremely useful for acupuncture studies ($500,000).