

**Testimony for “Stem Cell Science: The Foundation for Future Cures” before the Subcommittee on Health of the Committee on Energy and Commerce**

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Chairman and members of the Committee, thank you for inviting me to testify before you. My name is Amit Patel. Please note that the testimony I am giving today is my own opinion and not necessarily that of the institution where I am currently employed. I am a translational scientist for cardiovascular diseases where my research is focused on working with regenerative therapies taking the science from the lab bench to the patients. I am also a cardiovascular surgeon who on daily basis sees patients who have exhausted all medical and surgical options available who may benefit from the science of stem cell research.

My goal today is to give both a scientific and real life perspective of the impact that cardiovascular disease has in the United States and potential use of stem cell therapies.

**Cardiovascular Disease**

Heart disease is the leading cause of death in the United States. Nearly 930,000 Americans die of cardiovascular diseases each year, which amounts to one death every 33 seconds. About 70 million Americans have some form of cardiovascular disease, which is responsible for more than 6 million hospitalizations each year. There are over a one million patients with heart attacks every year, along with six million patients with chronic angina (chest pain), and five millions patients with heart failure. In 2005, the cost of heart disease and stroke in the United States exceeded \$394 billion: \$242 billion for health care expenditures and \$152 billion for lost productivity from death and disability. Patients with end-stage cardiovascular disease have over \$30 billion dollars in health care expenditures per year. Also, up to 20% of patients over the age 70 have limb ischemia.

**Problem:** The patients with end stage cardiovascular disease have at least one of two major problems:

1. Heart failure, where there is inadequate pumping function of heart due to decreased blood supply or lack of sufficient muscle.
2. Critical limb ischemia, where there is inadequate blood supply to the leg.

**Current Treatment Options:** Heart failure management involves optimal treatment with oral and/or intravenous medications along with surgical therapies. As patients continue to deteriorate the use of artificial hearts and heart transplantation remain the gold standard for end-stage therapy. There are many problems with the surgical options such as infection, stroke, rejection, and the overall costs associated with treatment. However,

even with all these options there are limited organs for transplant and fifty percent of end-stage heart failure patients die within five years.

Critical limb ischemia management involves oral medical therapy followed by surgical revascularization by bypass grafts. If the graft fails and further reoperative therapy is not possible, then amputation of the leg is performed. This problem is more severe in patients who also have diabetes.

### **The Role of Stem Cells:**

Based on the current science, human stem cells have been shown both in a lab dish and in the pre-human work to make new blood vessels and in rare cases new heart muscle.

### **Current Clinical Therapies**

Human stem cell therapies for cardiovascular disease have been performed under legitimate clinical trials since early 2000. The first group of patients had cells from thigh muscle (skeletal myoblasts) injected into their heart at the time of coronary bypass surgery hoping to grow new heart muscle in Europe. The early data demonstrated some issues with the therapy but larger trials were performed which also did not show significant improvement in heart function. This was truly an example of too rapid translation which could have destroyed the field. However, when these cells were used in a heart failure population and delivered via a catheter in U.S., the results were positive and have led to a large scale clinical trial. Also, using bone marrow cell therapy for the same patient population, both surgically and catheter based delivery has been performed in over one thousand patients in registered trials demonstrating no safety issues. This is the most important issue when performing translational therapies even though all the mechanisms of action have not been defined. As patient safety has been established, the next goal is to identify the patient population which may benefit the most from this therapy, which in the lab dish and pre-human work has shown to grow blood vessels and may improve cardiac muscle function. In these early clinical trials there has been modest improvement in heart function but there has been a significant decrease in adverse events, readmission for heart failure and new heart attacks in the randomized controlled studies. It is true that improvement in overall pumping has not been as large as most people had anticipated but that is most likely related to baseline function of the patient being enrolled in the studies. The analysis of the more severely impaired patients has shown a very dramatic increase which could not be attributed to medical therapy alone. The problem is, that most of these trials have been conducted in Europe or South America.

Similarly, the use of bone marrow stem cells for critical limb ischemia has also been studied since 2000. Most of the early clinical work was performed in Japan, with later translation to Europe and then most recently to the U.S. There has been a decrease in the rate of amputations which has been significant enough that the German government has approved certain centers of expertise which perform the therapy on patients as standard of care and obtain reimbursement from the equivalent of CMS.

Both of these examples are of the first generation of cardiovascular cell therapy. There are many other multi- and pluri-potent stem cells which also have potential for clinical use in cardiovascular disease but the safety still needs to be established before large scale clinical trials are performed such as adipose (fat), amniotic, menstrual, umbilical cord, cardiac stem cells, fetal, and embryonic. Some of these cells are in phase I safety trials both here in the U.S. and Europe. I have attached a table below which shows some of the larger cardiovascular studies in the U.S. and the rest of the world based on the international registry [clinicaltrials.gov](http://clinicaltrials.gov).

<b>Phase III</b>	Country	# Patients	Funding	Results
Acute Myocardial Infarction	Germany	200, 800 pending	Government/ Private/ Corporate	Safe, Mild improvement in heart function and decrease mid term adverse events
Acute Myocardial Infarction	Brazil	300	Government	Ongoing
Heart Failure	Brazil	300	Government	Ongoing
Limb Ischemia	Germany	90	Government	Ongoing
<b>Phase II/III</b>				
Heart Failure-myoblasts	USA	390	Corporate	Ongoing
CABG + cells	Germany	100	Government	Pending
<b>Phase II</b>				
Chronic Angina	USA	120	Corporate	Completed – awaiting results

### **Problems in Clinical Use:**

There are a number of clinical issues related to translation into reliable therapy. I have listed them below but also have attached a supplement which goes into further detail for each question: 1. What is the best source of stem cells? 2. Is a variety or combination of cells required for different types of heart disease? 3. What are the doses of cells required in humans compared to animals? 4. Are therapeutic doses available? 5. If so, what will be necessary to acquire them? 6. What is the best delivery method for the cells into the heart? 7. When is the best time after myocardial injury to deliver the cells? 8. Are the cells going to stay in the heart and, if not, where do they go and will they cause any harm? 9. How do we follow applied cells over time? 10. Will a tissue engineered scaffold be required to enhance effect? 11. Is it worth the risk to the patient?

### **Roles of the National Institutes of Health & Food and Drug Administration**

The NIH has done a great job in terms of supporting cardiovascular cell based therapies by developing Cell Therapy Network, Heart Failure Network, and the Cardiac Surgery Network. They will all play a significant role in answering the above questions and advancing clinical cardiac cell therapy and the science that is needed to make it a reliable, safe and reproducible therapy.

The FDA has also been very helpful in approving clinical trials with adult based cell therapies. However, the use of both outside basic and clinical scientists in the field early

in the development and approval of the trials may expedite approval but more importantly help in ensuring safety to the patients, which is most important.

### **Summary**

Cardiovascular cell therapies using the first generation adult stem cell have great potential to help our patients today. The science needs to continue to improve and help support the safety and efficacy of the therapies. Continued development of other multipotent stem cells along with tissue engineering to make new large blood vessels, heart valves, and the entire heart are the future of cardiac cell therapy. However, significant improvement in the amount of funding is required to keep pace with other countries but most importantly help our patients here in the U.S. I am a realist that these early therapies are a treatment for cardiovascular disease and not a cure. They are experimental but without our current work, the future cures that everyone hopes for and needs will be very difficult if not impossible to achieve.