VEGF signaling in adventitial stem cells in vascular physiology and disease

Grant Award Details

VEGF signaling in adventitial stem cells in vascular physiology and disease

Grant Type: New Faculty II

Grant Number: RN2-00909

Project Objective: The overall goal of the award is to understand the biology of adventitial cells and their role in restenosis and graft atherosclerosis, two processes that are roadblocks to interventional cardiology.

Investigator:

Name:	Ching-Pin Chang
Institution:	Stanford University
Type:	PI

Disease Focus: Heart Disease

Human Stem Cell Use: Adult Stem Cell

Award Value: $3,005,695

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Reporting Period: Year 4

View Report

Reporting Period: Year 5 (partial)

View Report

Grant Application Details

Application Title: VEGF signaling in adventitial stem cells in vascular physiology and disease

Public Abstract: Coronary heart disease is the leading cause of death in the developed world. This disease results from atherosclerosis or fatty deposits in the vessel wall that causes blockage of coronary arteries. Blockage of these arteries cut off supplies of nutrients and oxygen to the heart muscle, causing heart attacks, heart failure or sudden death. To restore coronary blood supply, physicians use guide-wires to position an inflatable balloon at the blockage site of the artery, where the balloon is inflated to open up the artery. This procedure is called percutaneous transluminal coronary angioplasty or PTCA, which is usually accompanied by the placement of a metal tube (or stent) at the diseased site to maintain vessel opening. PTCA is the dominant procedure to restore blood flow in coronary arteries- in the United States alone nearly 1.3 million PTCA procedures were performed in 2004. However, as a response to PTCA-related vessel wall damage, cells from the vessel wall are activated to divide and grow into the vessel lumen, causing re-narrowing or restenosis of the artery. Restenosis of the vessel lumen is the major hurdle limiting the success of PTCA. It occurs in 20-50% of cases within six months of the initial PTCA procedure and requires repeated PTCA to open up the re-narrowed artery, leading to tremendous human and social expenses. Stents which contain drug inhibitors of cell growth (drug eluting stents, or DES) reduce restenosis; however, considerable concerns have emerged regarding the safety of DES due to an increased risk of sudden stent occlusion by platelet aggregates (or thrombosis). This sudden occlusion is caused by a concomitant drug inhibition of cells that cover the raw surface of metal stents to prevent platelet aggregation. This complication is frequently lethal, resulting in death or heart attack in 85% of cases. The safety concerns over DES have created an urgent need to define the mechanisms underlying the biology of restenosis. A population of cells resident in the vessel wall consists of progenitor cells that divide and grow into the vessel lumen when vessels are injured. The repair process mediated by these cells directly contributes to vessel restenosis. Our goal is to understand the biology of these stem cells in the repair of injured arteries- how vessel injury signals these cells to divide and invade the vessel lumen, what molecular effectors control the cellular responses, and how to intercept these signals and effectors to prevent vessel restenosis. This will provide a solid scientific basis for new therapeutic targets and strategies for vessel restenosis after PTCA. The proposal is a targeted response to CIRM New Faculty Awards II. It seeks to extend my research expertise into the field of stem cell biology related to clinically important vascular diseases. We are confident that our proposed studies will generate significant progress in this field, in both scientific knowledge and useful therapies.

Statement of Benefit to California:	Coronary heart disease is the leading cause of death in California. This disease results from atherosclerosis or fatty deposits in the vessel wall that causes blockage of coronary arteries of the heart, causing heart attacks, heart failure or sudden death. Physicians use wires and balloons to open up the blocked artery (angioplasty) and a metal tube (stent) to keep the artery open and restore blood flow. Although effective, angioplasty and stenting cause some damages to the blood vessel, which leads to a recurrent blockage (or restenosis) of the vessel in 20-50% of patients within 6 months of the procedure. This vessel restenosis requires repeated angioplasties and stenting for restoration of blood flow. Given the large number of patients with coronary heart disease in California, the need for repeated surgical procedures has resulted in tremendous human, social and economic costs in our state. An attempt to reduce vessel restenosis is the placement of drug-eluting stents (or DES) in angioplastied vessels. Although drugs released from the stents reduce vessel restenosis, this approach creates a new and frequently fatal complication- sudden occlusion of the stented arteries. This complication is because drugs in the stents delay the repair of inner lining of the artery, whose function is to prevent platelet aggregation within the lumen of the artery. Sudden platelet aggregation (or thrombosis) within the vessel lumen causes instantaneous obstruction of the artery, leading to acute heart attacks or death. Thus, the safety concerns over DES have created an urgent need to define the mechanisms underlying the biology of restenosis. A population of cells present at the vessel wall possess stem cell characteristics. After vessel injury, these cells increase in number and turn into different kinds of cells, which then migrate from the vessel wall into the lumen, causing blockage of the vessel. Thus, understanding how these cells behave will inspire new ideas for treating recurrent vessel blockage or restenosis. We propose to study how and what molecular signals activate these cells when vessels are injured. Our goal is to provide a scientific strategy of intercepting these signals for the treatment of vessel restenosis. We believe that understanding the biology of vascular stem cells will lead to significant advances in the research and novel therapies of vessel injury and restenosis. Given the scope of this problem , an improved therapy of vessel restenosis will have a significant economic and social impact. We have proposed to use modern methods in genetics, cell biology, and molecular biology to attack the challenges of this project. At the same time, we will train a new generation of bright students and junior scientists in the areas of stem cell biology highly relevant to human disease. This ensures that an essential knowledge base will be preserved, passed on and expanded in California for the foreseeable future.