Biophysical Determinants of Early Embryonic Stem Cell Fate Specification

Grant Award Details

Biophysical Determinants of Early Embryonic Stem Cell Fate Specification

Grant Type: Basic Biology V

Grant Number: RB5-07409

Project Objective: To analyze cell movements and forces during early human development and their effect on mesoderm differentiation, using hESC as a model.

Investigator:

Name:	Valerie Weaver
Institution:	University of California, San Francisco
Type:	PI

Disease Focus: Other

Human Stem Cell Use: Embryonic Stem Cell

Award Value: $1,186,500

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 4 (NCE)

View Report

Grant Application Details

Application Title: Biophysical Determinants of Early Embryonic Stem Cell Fate Specification

Public Abstract: Regenerative therapies require effective differentiation of stem cells to cell types that are functionally identical to those found in vivo. Many current differentiation protocols merely involve optimization of proteins added to the culture media, but do not consider the microenvironmental context in which cells differentiate during development or tissue repair. When we include the biophysical parameter of substrate stiffness, we are able to enhance differentiation of human embryonic stem cells to multipotent mesodermal progenitors, cells that can go on to form muscles, cartilage, and bone. We observe that this differentiation is accompanied by colony-wide organization and coordinated movements. Mesoderm forms during the developmental process known as gastrulation, and we also see aspects of this complex process recapitulated in our system. For example, we observe cells migrate and ingress into a region with similarities to the gastrulation-initiating structure called the primitive streak. We can therefore use this system to optimize directed differentiation protocols, to characterize and manipulate the forces and mechanisms required for coordinated differentiation, and to identify signals involved in primitive streak formation. Together, these studies will allows us to answer questions about the signals required for cell type specification and migration during spontaneous self-organization in the developing embryo.

Statement of Benefit to California: Regenerative medicine requires efficient generation of cells that are identical to their respective population in the human body, but traditional protocols often lead to inefficient or incomplete directed differentiation. By optimizing biophysical parameters such as substrate stiffness and colony geometry, we show that we are able to efficiently differentiate human embryonic stem cells to mesoderm progenitors, indicating that we can use engineering principles to design more efficient directed differentiation strategies. In addition to providing tunable parameters for any type of differentiation, this system also allows us to probe the molecular basis of early mesoderm differentiation. This will enable us to gain valuable insight into how physical parameters regulate this process in vivo, which is crucial for establishing robust tissue regeneration techniques. In our system, mesoderm commitment is accompanied by cell movements and colony-wide organization representative of some aspects of early embryogenesis, which we will study in more detail to understand how biophysical forces initiate and reinforce key signaling pathways required during morphogenesis. By tracking and manipulating cells during these gastrulation-like movements, we will be able to identify relevant proteins and knock them down to mimic disease states with the ultimate goal of rectifying human embryologic defects and informing the future of regenerative medicine.