



Five Major Areas of Study Are Available to Fellows

Molecular Biology/Gene Therapeutics:

Specific areas of research in this area include examining the role of the mitogen activated protein kinase cascade in a number of injury and disease states. Other areas of research include the role of transforming growth factor-Beta (TGF- β) signaling in the regulation of organ homeostasis, while other projects use genomics to discover how regulatory proteins transduce signals to the cell's transcriptional machinery. Other areas of research include endotoxin signaling and detoxification and the application of adenoviral vectors using specific promoters to drive the expression of enzymes, anti-endotoxin agents and anti-cytokines. A number of research projects are directed to examine the actin cytoskeleton which assembles and unfolds to support the motile machinery of the cell; these studies focus on how extracellular signals are transduced into reorganization of the actin filament network in proliferating and apoptotic cells.

Cytokine/Mediator Biology:

A number of studies are directed to determine tissue-specific regulation and expression of proinflammatory and anti-inflammatory cytokines. In addition, the role of cardiac cytokine expression and the pathogenesis of cardiac dysfunction after burn, sepsis, cardiopulmonary bypass or in disease states such as myocardial hypertrophy are explored. A number of transgenic animals have been characterized in which either inflammatory cytokine expression or upstream regulation of cytokine signaling is driven by promoters specific to the myocardium. In this setting, the development of transgenic systems allows cytokines and/or their antagonists to be targeted directly to cardiomyocytes using inducible and repressible genetic systems, allowing the examination of precise mechanisms of cytokine-induced cardiac dysfunction.

Neurobiology:

Differentiation among many of the cell types in the nervous system result from the expression of a specific set of genes in response to multiple extracellular-intracellular signals. Transcription factors of the basic loop-helix family are involved in the development of neuronal lineages in both invertebrates and vertebrates. Several studies available to trainees in this NIH Burn Trauma Fellowship include examining specific aspects of early stages of neuronal development where the decision to proliferate or differentiate is made. Other studies are directed to identify upstream regulators of these genes and to determine the molecular mechanisms underlying the decision of proliferating precursor cells to differentiate to a specific type of neuron. Other studies available to trainees include those examining the function of the trk gene family which encodes tyrosine kinases that act as receptors for the nerve growth factor family of neurotrophin ligands. Gene targeted knockout mutations in mice by homologous recombination for the genes encoding the neurotrophins have been developed, allowing the function of neurotrophins to be examined.

Tissue Engineering-Repair/Biomaterials:

One area of research available to trainees includes studies examining cell-signaling mechanisms that regulate cell motility and cell proliferation during wound repair. Fibroblasts in resting tissue are quiescent and the cells are engaged in minimal biosynthetic activity. With wounding, the cells become

proliferative and migrate into the wounded region where they synthesize and contract a new connective matrix. After healing is completed, the wound fibroblasts become quiescent and regress through apoptosis. The use of fibroblasts cultured in three dimensional collagen matrices provide an in vitro model that mimics many of the features of repair including matrix contraction. The availability of these in vitro models allow the study of signal transduction pathways involved in cell quiescence and apoptosis after contraction, the regulation of contraction by several growth factors as well as the role of MAP-kinase signaling in wound healing.

Other areas available to the trainees include projects directed toward the development of biomaterials, derivatized polymers with high albumin affinity, pulse plasma polymerization of adhesion peptides and other biologicals, and cell anesthesia to increase biocompatibility. Biomaterials are evaluated by gamma scintigraphy and the availability of numerous in vitro models allows evaluation of biomaterials by examining surface analysis or protein sorption by TIRF and TEM replica methods. Other projects include developing new technologies to exploit the massive amount of emerging sequence from the human genome project; these projects include development of genomic analysis software, digital optical chemistry to produce oligonucleotide arrays, spotted array technology, high performance hyperspectral imaging microscopy and the latest techniques in sequencing technology.

Applied Cardiac, Pulmonary and Microvascular Physiology:

Studies in this area include in vitro models of pulmonary capillary leak as well as in vivo model of burn and sepsis mediated alterations in pulmonary endothelial function. Applied cardiac physiology studies include the use of numerous technologies to assess cardiac output and cardiac function in the intact animal; echocardiography is used to assess systolic and diastolic defects in vivo while the use of Langendorff perfusion techniques allows in vitro assessment of left ventricular contractility. In addition, the ability to perfuse isolated hearts within a nuclear magnetic resonance system allows assessment of left ventricular function concomitant with measures of cell sodium/calcium levels, as well as measures of intracellular pH and energy availability (ATP, Pi, CP). Studies of contracting cardiomyocytes allow assessment of burn and sepsis mediated changes in myocyte shortening paralleled by measures of intracellular sodium, calcium and pH through the use of fluorescent indicator techniques. Strategies available allow assessment of cardiac function both in the intact animal and human subject, as well as assessment of myocardial contractility using isolated perfused organs or single cell preparations.