

## **INTRODUCTION AND RATIONALE**

Information from basic investigation on the biology of inflammation, injury and repair in the lung (and other organs) has burgeoned. Although there is a substantial body of work from clinical research on patients with acute lung injury, this has not kept pace with the output of basic investigations. Basic science advances, with few exceptions, have failed to be translated into clinical benefits to patients with acute lung injury (or other critical illness). Although the reasons for this failure of translation are likely multifactorial, a major component is likely to be a lack of training of translational investigators in this field. The usual situation has been that of basic investigators working in the laboratory with isolated systems or animal models and clinical investigators (trained in clinical epidemiology or outcomes research) working separately on clinical questions but with little cross communication between them. This has resulted in a lack of useful application of the basic work to humans with disease and a paucity of human studies that fully incorporate the sophisticated and detailed information available through basic research concerning the cell and molecular biology of lung injury and repair.

An especially common scenario has been the development of a biochemical intervention in the laboratory, testing of this intervention in animal models with positive results, and then rushing the intervention to clinical trials – often by industry – with little of the translational research background performed which is necessary to enhance the chances of the human clinical trial being successful. Paramount in this scenario is a lack of information on the mechanisms, timing of those mechanisms, and interactions with other potential mechanisms operative in humans with disease. Examples of the sorts of fundamental questions which have usually not been answered prior to clinical trials include the following. Is the mechanism to be blocked an active mechanistic component in human lung injury? If so, is the timing of that component in the process known (i.e., was it active when the blocking agent was administered)? What are the interactions with the blocking agent and other pathways affecting injury and repair? Is the mechanism active to the same degree in various etiologies of the lung injury which are represented in the clinical population being studied? Answers to these and other questions are key to the successful testing of interventions and yet have seldom been studied prior to clinical testing. This is just one type of example of needed translational research to allow basic research findings to be translated into clinical benefit.

The proper study design and experimental work to answer questions like these require that the investigators have backgrounds that allow them to understand both basic biologic processes and methodology and clinical investigation methodology involving comprehensive data gathering and analysis from humans with acute lung injury. In addition, little attention has been paid to the appropriate training of clinical trialists, one particular type of translational investigator. We have developed a plan for training translational investigators to address this obvious need.

## **SPECIFIC AIMS**

Specific Aim 1: To train translational investigators in acute lung injury research

Specific Aim 2: To develop a comprehensive Translational Research Training Program (TRTP) by:

- a. Creating specific training elements needed to allow translational investigator training, and
- b. Providing the leadership and oversight to blend these elements with currently existing training opportunities.

## **DEFINITIONS AND STATEMENT OF PURPOSE**

The 1997 Report of the NIH Director's Panel on Clinical Research gave a three-part definition of "clinical research":

- a. Patient-oriented research. Research conducted with human subjects (or using material of human origin) for which an investigator directly interacts with human subjects. This area includes: 1) mechanisms of human disease; 2) therapeutic interventions; 3) clinical trials; and 4) development of new technologies.
- b. Epidemiologic and behavioral studies
- c. Outcomes research and health services research

We define translational research as a form of clinical research that involves both collection of data about human subjects (which includes the skills needed in epidemiologic and outcomes research encompassed under parts b. and c. of the above definition) and measurements made in the basic science laboratory on human specimens (as in part a. of the above definition). These two elements are integrated in our notion of translational research. The aims of this translational research are usually those defined under part a. of the above definition. One important goal of translational investigation is to take basic concepts, developed at a molecular or cellular level, and demonstrate their relevance in humans with disease. Such proof of concept is essential to translating knowledge of basic biological processes into meaningful interventional strategies in the clinical setting. The need for this approach is emphasized in Project 3 (Avery Nathens, PI). Thus, there are compelling reasons to view translational research as a pathway which is interrelated with the other two.

Our research training programs in the Division of Pulmonary and Critical Care Medicine, Department of Medicine, and in the Department of Surgery at the University of Washington currently have strong components for training basic research investigators (which may or may not involve measurements on human specimens) and training clinical investigators as described under parts b. and c. of the above definition. Although we have carried out considerable translational investigation on acute lung injury that would fit our definition, we have not specifically focused on the training of translational investigators. The training program described in this Core is specifically designed to do that.

In this grant application when we use the term “clinical investigator” we refer to the type of individual currently being trained in our Clinical Investigator Fellowship Research Training Track (or in the Harborview Injury Prevention and Research Center Surgical Critical Care Fellowship), that is an individual who is trained as a clinical epidemiologist or outcomes researcher with a Master’s degree, either as an MPH or an MSc in Epidemiology. We use the terms “basic investigator” or “basic scientist” to refer to the trainee with primary research training in basic laboratory based research, even though that individual may be working with human specimens (and therefore would technically fit the definition of “clinical research” proposed by the NIH Director’s Panel on Clinical Research, but would not necessarily have specific training in translational research). The purpose of this proposal is to develop a program specifically designed to train a third type of investigator, which we will call a “translational investigator”. The scope and training of this “translational investigator” will be described in detail below.

## **BACKGROUND AND PRELIMINARY WORK**

The Division of Pulmonary and Critical Care Medicine and the Department of Surgery (especially regarding trauma and critical illness) have national and international reputations for their strong research training programs. The Division of PCCM has been known for its research training since shortly after it was created in 1965. John Butler, MD, the first Division Head, was known for his research training in pulmonary physiology. Other early faculty with strong records in research training included Michael Hlastala, PhD, Claude Lenfant, MD, and Jack Hildebrandt, PhD. Hlastala and Hildebrandt remain active in research training within the Division. Lenfant, of course, is Director of the National Heart Lung and Blood Institute of the NIH. Butler was PI of the Division’s first NIH institutional NRSA research training grant in 1977. Leonard D. Hudson, MD, assumed the PI role on this training grant in 1982 and has been PI on all renewals since that time. He has been the second Division Head, taking over from Butler in 1985. In the 1980’s the Division focused on diversifying to build a strong cell and molecular biology research program, in addition to our already strong base in Physiology. Thomas R. Martin, MD, Program Director of the current SCCOR application, led that development. Early recruitments in this area included Joan Clark, MD, Section Head of PCCM at the Fred Hutchinson Cancer Research Center.

In the 1990’s, with a strong and productive cell and molecular biology research program and research training well established, Hudson focused on development of a clinical investigator training program. Although we and other Divisions of PCCM had trained clinical investigators, including the occasional individual who sought an advanced degree (usually an MPH), ours was the first program of which we are aware that formalized clinical investigator training into an organized training track. This track provided rigorous training including enrollment in a Master’s degree program in our nationally and internationally highly regarded School of Public Health and Community Medicine. Hudson hired Randy Curtis, MD, MPH, and Gordon Rubinfeld, MD, MSc,

to head up this new training track. Both had training in our own program and both had additional research training through the Robert Wood Johnson Clinical Scholars Program, Curtis at the University of Washington and Rubenfeld at the University of California, San Francisco. They and Hudson subsequently described this training track and its elements in a publication (Curtis JR, et al. *Am J Respir Crit Care Med* 1998; 157:1012-1015). This track has been highly successful, resulting in well-trained individuals entering academic positions; recently the program's reputation has attracted several applicants who already have some course work in a clinical research area, some with Master's degrees already.

A new recent addition to this track is the ability of trainees to receive training and graduate degrees in Genetic Epidemiology. A Master's degree program in Genetic Epidemiology, the first program of this kind in the country, has been established within the Institute of Public Health Genetics in the Department of Epidemiology. Karen Edwards, PhD, the coordinator of the Master of Science program in Genetic Epidemiology, is a member of the Steering Committee of our Translational Research Training Program. Three PCCM fellows are currently enrolled in this degree program, Jason Chien (with a research interest in sepsis), Ed McKone (with a research interest in cystic fibrosis), and Catherine (Terri) Lee (with a research interest in acute lung injury).

The PCCM research training program has several strong elements. The most important is a critical mass of experienced mentors in all three training tracks (Physiology, Cell and Molecular Biology, and Clinical Investigation) with an ample number of ongoing research projects in which the trainees can participate. Other elements include a strong mentoring program with a mentoring committee for each trainee, research resources including research funding, laboratories, support staff, and a research support infrastructure, and a rich and supportive research training milieu. This environment includes a weekly Division- and School-wide Pulmonary Research Conference as well as smaller conferences for each training track at which trainees are expected to present work in progress. The conferences for the Cell and Molecular Biology and Clinical Investigation training tracks are more completely described below in the description of the translational research training plan.

The Division's research has always had a strong focus on acute lung injury and repair and the inflammatory mechanisms involved in these processes. In addition to investigators within our own Division, we have cultivated research interactions with internationally prominent investigators in other disciplines who are working on related questions. John Harlan, MD, Professor of Medicine and Head, Division of Hematology, has been a project PI on our SCOR in ALI since its inception in 1983. His collaborator, Robert Winn, PhD, Research Professor of Surgery and co-PI of Project 5 in this SCCOR application, has also been a SCOR investigator since the program's beginning. Other prominent investigators outside our Division with whom we have had collaborative research and/or research training ties include Seymour Klebanoff, MD, Professor of Medicine, Division of Infectious Diseases (and a research mentor for Tom Martin), Russell Ross, PhD, former Professor and Chair, Department of Pathology, Chris Wilson, MD, Professor and Chair, Department of Immunology, Bill Henderson, MD, Professor of Medicine and Head, Section of Allergy, in the Division of Infectious Diseases and Allergy, Dennis Hickstein, MD, Division of Hematology (currently an investigator at the National Cancer Institute), Paul Bornstein, MD, Professor of Biochemistry and Medicine, and Pedro Verdugo, MD, Professor of Bioengineering and Biostructure. Our Division has also had close collaborative ties with investigators in the Department of Surgery interested in acute lung injury and multiple organ dysfunction. This collaboration began with Hudson and Jim Carrico as PIs of a project on ARDS in the NIH funded Burn and Trauma Research Center of which Carrico was PI and has continued to the present including strong ties with Ron Maier, MD. Maier is an investigator in the Seattle site of the NIH ARDS Clinical Trials Network and is acting PI of that center while Hudson is on sabbatical. The SCOR in ALI also provides human specimens of BAL constituents to Maier for his laboratory investigations.

The investigators who are mentors in the PCCM research training program (as named in the most recent NIH institutional NRSA training grant) are listed in Table 1. They are listed for each of the three training tracks with their major area of research interests.

**Table 1: Training Faculty – Pulmonary and Critical Care Medicine Research Training Program**

<b>Faculty</b>	<b>Research Area</b>	<b>Department</b>	<b>Title</b>
<b>Cell and Molecular Biology Training Track</b>			
Aitken, Moira L, MD	Cystic fibrosis; airway epithelial cell biology	Medicine/PCCM	Associate Professor (approved for Professor at department level)
Bornstein, Paul, MD	Biology of thrombospondins and growth factors in fibrogenesis	Biochemistry and Medicine	Professor
Clark, Joan G, MD	Repair of lung injury	Medicine/PCCM	Professor
Frevert, Charles W, DVM, ScD	Chemokines in ALI; animal models of inflammation and sepsis	Medicine/PCCM	Associate Research Professor
Goodman, Richard B, MD	Inflammatory mechanisms of ALI	Medicine/PCCM	Associate Professor
Harlan, John M, MD	Mechanisms of leukocyte adhesions; pathophysiology of sepsis	Medicine/ Hematology	Professor
Kavanagh, Terrance J, PhD	Molecular mechanisms in toxic environmental exposures	Environmental Health	Associate Professor
Madtes, David K, MD	Growth factors in lung repair	Medicine/PCCM	Associate Professor
Martin, Thomas R, MD	Inflammatory mechanisms of ALI; host defenses	Medicine/PCCM	Professor
Raghu, Ganesh, MD	Fibroblast biology; idiopathic pulmonary fibrosis	Medicine/PCCM	Professor
Skerrett, Shawn J, MD	Host pulmonary defense mechanisms	Medicine/PCCM	Associate Professor
Verdugo, Pedro, MD	Control of mucus secretion and rheology	Bioengineering and Biostructure	Professor
Wilson, Christopher B, MD	Inflammatory mechanisms of lung inflammation	Immunology	Professor
Winn, Robert K, PhD	Mechanisms of ALI; neutrophil apoptosis in ALI	Surgery/Physiology and Biophysics	Research Professor
<b>Respiratory Physiology Training Track</b>			
Domino, Karen B, MD	Hypoxic vasoconstriction in normal and diseased lungs	Anesthesiology	Professor
Glenny, Robb W, MD	Regulation of blood flow distribution	Medicine/PCCM	Associate Professor (approved for promotion to Professor at department level)
Hildebrandt, Jacob, PhD	Pulmonary mechanics	Medicine/PCCM and Physiology and Biophysics	Professor
Hlastala, Michael P, PhD	Control of ventilation/perfusion heterogeneity	Medicine/PCCM and Physiology and Biophysics	Professor
Lakshminarayan, S, MBBS, MRCP	Control mechanisms of the bronchial circulation	Medicine/PCCM	Professor
Robertson, H Thomas II, MD	Ventilation/perfusion heterogeneity	Medicine/PCCM	Professor
Schoene, Robert B, MD	High altitude and exercise physiology	Medicine/PCCM	Professor

Swenson, Erik R, MD	Carbonic anhydrase biology; CO <sub>2</sub> in acid-base control	Medicine/PCCM	Professor
<b>Clinical Investigation Training Track</b>			
Au, David, MD, MSc	Epidemiology and process of care in COPD	Medicine/PCCM	Assistant Professor
Benditt, Joshua O, MD	Neuromuscular lung dysfunction; clinical trials in COPD	Medicine/PCCM	Associate Professor (approved for promotion to Professor at department level)
Curtis, J Randall, MD, MPH	Health-related quality of life; health care delivery at the end of life	Medicine/PCCM	Associate Professor
Goss, Christopher, MD, MSc	Epidemiology of cystic fibrosis	Medicine/PCCM	Assistant Professor
Hudson, Leonard D, MD	Epidemiology of ALI; mechanisms of ALI	Medicine/PCCM	Professor
Kapur, Vishesh K, MD, MPH	Epidemiology of sleep disordered breathing	Medicine/PCCM	Assistant Professor
Martin, Diane P, PhD	Health care delivery; epidemiology and outcomes in ALI	Health Services	Professor
Pierson, David J, MD	Mechanical ventilation and respiratory care	Medicine/PCCM	Professor
Patrick, Donald L, PhD, MSPH	Health related quality of life and healthcare policy research	Health Services and Rehabilitation Medicine	Professor
Psaty, Bruce M, MD, PhD	Epidemiology of cardiovascular diseases	Medicine and Epidemiology	Professor
Rubinfeld, Gordon D, MD, MSc	Clinical epidemiology of ALI	Medicine/PCCM	Assistant Professor (approved for promotion to Associate Professor at department level)
Steinberg, Kenneth P, MD	Clinical epidemiology of ALI; clinical trials in ALI	Medicine/PCCM	Associate Professor
Tonelli, Mark R, MD, MA	Biomedical ethics	Medicine/PCCM and Medical History and Ethics	Associate Professor

The PCCM fellowship training program has been successful in training investigators with research careers. With our combined clinical and research fellowship program, well over 50% of trainees stay in full-time academic careers, a number which compares favorably with our peer training programs in major research universities. Since 1995, of those trainees who have completed training, 14 are in academic positions and 10 are in private practice. This recent record of placing trainees in academic positions is consistent with our experience over the prior 18 years of our training grant. A list of prior trainees and their current positions will be submitted as an appendix to this application.

The Department of Surgery research training programs are also known for their strong training records in Cell and Molecular Biology and in clinical outcomes research. These programs are funded by two NIH institutional training grants. Both have a major focus on trauma and sepsis related organ injury, including acute lung injury and the prevention and treatment of that injury. The DOS NIH institutional NRSA training grant for Trauma and Burn Research (Postdoctoral Training Grant) has been in continuous existence since 1975. Ron

Maier, MD, a former awardee of the training grant, has been PI of this grant and Director of the Trauma Research Program since 1990. Maier is Professor and Vice-Chair, Department of Surgery, and Surgeon-in-Chief at Harborview Medical Center. Maier has had continuous NIH R01 funding since 1982. Maier has published some substantial bodies of work in both basic cell and molecular biology, primarily dealing with alveolar macrophage function, and clinical epidemiology and outcomes of trauma. He also has experience in translational research involving ALI and multiple organ dysfunction syndrome in patients with sepsis and trauma. Maier has strong ties with PCCM investigators.

When the DOS postdoctoral training grant was first awarded in 1975, its focus was aimed at training surgical residents for academic careers and its investigators were all within the DOS. With broadening of the trauma research effort to involve multiple disciplines, there has been a broadening of scope of the training grant. Currently, investigators (mentors) include members from disciplines throughout the School of Medicine and the executive committee has members from the departments of surgery, medicine, physiology, pathology, and environmental health. The trainees now include individuals with a PhD degree. The nature of the research has also evolved to a current heavy focus on the cellular and molecular biology of inflammatory processes. Maier chairs the executive committee and Hudson serves as a member of this committee. The investigators available as mentors in this postdoctoral training grant and their areas of research interest are displayed in Table 2. Trainees from this program and their current positions will be submitted as an appendix to this application. The program has been highly successful in terms of the number of trainees who have gone on to productive academic careers.

**Table 2 – Training Faculty, Department of Surgery Post-Doctoral Research Training Program**

<b>Faculty</b>	<b>Research Area</b>	<b>Department</b>	<b>Title</b>
Bomsztyk, Karol, MD	Signal transduction and gene transcription mechanisms	Medicine/Nephrology	Associate Professor
Chi, Emil, PhD	Histology of pulmonary injury and ARDS	Pathology	Research Professor
Clark, Joan G, MD	Repair mechanisms of ALI	Medicine/PCCM	Professor
Clowes, Alexander, MD	Cellular mechanisms of vascular healing	Surgery/Vascular	Professor
*Cochrane, Charles, PhD	Inflammatory mediators of acute lung injury	Immunology (Scripps Clinic and Research Foundation, LaJolla, CA)	Member
Gibran, Nicole, MD	Skin biology and the contribution of the neuro-epithelial axis in wound healing	Surgery/Burns	Associate Professor
Harlan, John M, MD	Neutrophil - endothelial interactions; membrane adherence molecules	Medicine/Hematology	Professor
Heimbach, David M, MD	Burn wound healing	Surgery/Trauma and Burns	Professor
Henderson, William R, Jr, MD	Effect of leukotrienes in pulmonary dysfunction	Medicine/Infectious Diseases	Professor
Hildebrandt, Jacob, PhD	Pulmonary mechanics and circulation	Medicine/PCCM and Physiology and Biophysics	Professor
Hudson, Leonard D, MD	ARDS: epidemiology and acute cellular response	Medicine/PCCM	Professor
Kavanagh, Terrance J, MS, PhD	Cellular resistance to oxidants and environmental toxic agents	Medicine/PCCM	Research Associate Professor

Langdale, Lorrie, MD	Mechanisms of liver ischemia/reperfusion injury	Surgery/Critical Care	Associate Professor
Maier, Ronald V, MD	Immunomodulation of macrophage function following trauma	Surgery/Trauma and Critical Care	Professor and Vice Chair
Martin, Thomas R, MD	Lung humoral immunity; PMN function in ARDS	Medicine/PCCM	Professor
Pavlin, Edward, MD	Membrane receptor alterations following trauma	Anesthesiology	Professor
Pohlman, Timothy H, MD	Cytokine-endothelial cell interactions; endothelial cell function in sepsis	Surgery/Trauma and Critical Care	Associate Professor
Reidy, Michael, PhD	Vascular wall healing: matrix and myocytes	Pathology/Vascular Biology	Professor
Schwartz, Stephen, MD, PhD	Growth control of vessel wall cells; basis of cellular regulation	Pathology/Vascular Biology	Professor
Sharar, Sam R, MD	Neutrophil function in multiple organ failure	Anesthesiology/Pediatric Anesthesiology	Associate Professor
Tarr, Phillip I, MD	Bacterial adherence mechanisms; epidemiology of hemolytic-uremic syndrome	Pediatrics/ Gastroenterology	Professor
*Ulevitch, Richard J, PhD	Molecular mechanisms of LPS-induced toxicity	Immunology (Scripps Clinic and Research Foundation, La Jolla, CA)	Member and Chair
Vedder, Nicholas B, MD	Neutrophil-endothelial adherence following ischemia/reperfusion	Plastic Surgery	Associate Professor
Verrier, Edward, MD	Endothelial function following surgery and hypothermia	Surgery/Cardiothoracic Surgery	Professor
Winn, H Richard, MD	Adenosine and CNS microvascular perfusion	Neurological Surgery/Trauma	Professor and Chair
Winn, Robert K, PhD	Neutrophil adherence to endothelium in multiple organ failure, ischemia/reperfusion and hypothermia	Surgery/Physiology and Biophysics	Research Professor
Zager, Richard, MD	Sepsis induced acute renal failure	Medicine/Nephrology	Professor

\**Extramural Faculty*

The DOS has also established a strong clinical investigation training program, similar to that in the Division of PCCM. This program, the Harborview Injury Prevention and Research Center Surgical Critical Care Fellowship, is funded by a separate CDC grant. Fellows in this program receive formal in-depth training in clinical and epidemiologic investigation and the necessary background sciences including biostatistics, epidemiology and related fields through course work in the School of Public Health and Community Medicine. Trainees are expected to complete either the MPH or MSc in Epidemiology degree program. The trainee's theses are their research project, generally based at Harborview Medical Center. A list of mentors and their research interests available to training individuals enrolled in this program are shown in Table 3. Over the last ten years, nine fellows have completed their training in this program, eight are in full-time academic positions, and one is in the armed services (Head of the Surgical Critical Care Division and Co-Director of the ICU at the Naval Hospital in San Diego).

**Table 3. Training Core Faculty for the Harborview Injury Prevention and Research Center Surgical Critical Care Fellowship**

<b>Name</b>	<b>Injury Research Interests</b>	<b>Primary Affiliation</b>	<b>Title</b>
Bergman, Abraham B, MD	Prevention of bicycle injuries, falls, equestrian, pedestrian, alcohol related trauma	Pediatrics	Professor
Bynum, Christian, PhD	Occupational injuries, child abuse, falls in the elderly	Epidemiology	Assistant Professor
Cummings, Peter, MD, MPH	Firearms, poisoning, violence, acute care	Epidemiology	Associate Professor
Gentilello, Larry M, MD	Alcohol treatment, hypothermia	Surgery	Associate Professor
Grossman, David C, MD, MPH	Rural and minority populations, trauma systems, children, intentional injuries, motor vehicle injuries	Pediatrics/Health Services	Professor and Director of HIPRC
Jaffe, Kenneth M, MD, MS	Head injury rehabilitation	Rehabilitation Medicine/ Pediatrics/Neurological Surgery	Professor
Jurkovich, Gregory J, MD	Alcohol, trauma triage, acute care, trauma systems	Surgery	Professor
Koepsell, Thomas D, MD, MPH	Pedestrian, motor vehicle, injury methodology	Epidemiology/Health Services	Professor
Maier, Ronald V, MD	Acute care, trauma systems	Surgery	Professor and Vice Chair
Mueller, Beth A, DrPH	Pedestrian, motor vehicle, aviation	Epidemiology	Associate Professor
Quan, Linda, MD	Drowning	Pediatrics	Professor
Rivara, Frederick P, MD, MPH	Injury epidemiology and prevention	Pediatrics/Epidemiology	Professor
Tencer, Allan F, PhD	Orthopedic Biomechanics	Orthopedic and Sports Medicine and Mechanical Engineering	Professor

One aspect of the foundation for this application is the evolution of both PCCM and DOS research training into extremely strong tracks in cell and molecular biology basic research and in clinical outcomes research. This situation for both programs and the excellent working relations between the PCCM and DOS programs is unique. Another aspect of the preliminary work is the amount of translational research, using the definition given above that has taken place on acute lung injury and related problems including trauma and sepsis. Some of the publications resulting from these studies over the last ten years are listed in Table 4.

**Table 4. Partial List of Translational Research Publications in ALI or Related Critical Illnesses from Studies Conducted in Part or in Whole at the University of Washington in the Last 10 Years**

1. Martin TR, Pistorese BP, Hudson LD, Maunder RJ. The function of lung and blood neutrophils from patients with the adult respiratory distress syndrome: Implications for the pathogenesis of lung infections. *Am Rev Respir Dis* 1991; 144:254-262
2. Gregory TJ, Longmore WJ, Moxley MA, Whitsett JA, Reed CR, Fowler AA III, Hudson LD, Maunder RJ, Crim C, Hyers TM. Surfactant chemical composition and biophysical activity in acute respiratory distress syndrome. *J Clin Invest* 1991; 88:1976-1981
3. Cobean RA, Gentilello LM, Parker A, Jurkovich GJ, Maier RV. Nutritional assessment using a pulmonary artery catheter. *J Trauma* 1992; 33:452-456
4. Steinberg KP, Milberg JA, Martin TR, Maunder RJ, Cockrill BA, Hudson LD. Evolution of bronchoalveolar cell populations in the adult respiratory distress syndrome. *Am J Respir Crit Care Med* 1994; 150:113-122
5. Gubler KG, Hassantash SA, Gentilello LM, Maier RV. The impact of hypothermia on dilutional coagulopathy. *J Trauma* 1994; 36:847-851
6. Maier RV, Mitchell D, Gentilello L. Optimal therapy for stress gastritis. *Annals of Surgery* 1994; 220 (3):353-365
7. Dries, DJ, Jurkovich, GJ, Maier, RV, Clemmer, TP, Struve, SN, Weigelt, JA, Stanford, GG, et al.. Effect of interferon gamma on infection-related death in patients with severe injuries. *Arch Surg* 1994; 129(10):1031-1041
8. Clark JG, Milberg JA, Steinberg KP, Hudson LD. Type III procollagen peptide in the adult respiratory distress syndrome: association of increased peptide levels in bronchoalveolar lavage with increased risk for death. *Ann Intern Med* 1995; 122:17-23
9. Sutherland KR, Steinberg KP, Maunder RJ, Milberg JA, Allen DL, Hudson LD. Pulmonary infection during the acute respiratory distress syndrome (ARDS). *Am J Respir Crit Care Med* 1995; 152:550-556
10. Mock CN, Jurkovich GJ, Dries D, Maier RV. Clinical significance of antibiotic endotoxin-releasing properties in trauma patients. *Arch Surg* 1995; 130:1234-1241
11. Gentilello LM, Anardi D, Mock C, Arreola-Risa C, Maier RV. Permissive hypercapnia in trauma patients. *J Trauma* 1995; 39 (5):846-853
12. Goodman RB, Strieter RM, Martin DP, Steinberg KP, Milberg JA, Maunder RJ, Kunkel SL, Walz A, Hudson LD, Martin TR. Inflammatory cytokines in patients with persistence of the acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1996; 154:602-611
13. Mock CN, Maier RV, Jurkovich GJ, Dries D. Assessment of two clinical trials: Interferon-gamma therapy in severe injury. *Shock* 1996; 5(4):235-240
14. Mendez C, Jurkovich GJ, Garcia I, Wener M, Mays M, Maier RV. Effects of supplemental dietary arginine, canola oil, and trace elements on cellular immune function in critically injured patients. *Shock* 1996; 6(1):7-12
15. Mock CN, Jurkovich GJ, Dries D, Maier RV. The clinical significance of endotoxin released by antibiotics: what is the evidence? *J Endotoxin Research* 1996; 3(3):253-259
16. Martin TR, Rubenfeld GD, Ruzinski JT, Goodman RB, Steinberg KP, Leturcq DJ, Moriarty AM, Raghu G, Baughman RP, Hudson LD. Relationship between soluble CD14, lipopolysaccharide binding protein, and the alveolar inflammatory response in patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1997; 155:937-944
17. Gregory TJ, Steinberg KP, Spragg R, Gadek JE, Hyers TM, Longmore WJ, Moxley MA, Cai G-Z, Hite RD, Smith RM, Hudson LD, Crim C, Newton P, Mitchell BR, Gold AJ. Bovine surfactant therapy for patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1997; 155:1309-1315
18. Matute-Bello G, Liles WC, Radella II F, Steinberg KP, Ruzinski JT, Jonas M, Chi EY, Hudson LD, Martin TR. Neutrophil apoptosis in the acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1997; 156:1969-1977
19. Vedder N, Harlan J, Winn R, Heckbert S, Maier RV, Hudson L, Copass M, Sharar S, Yu A, Anardi D, Peterman S. Pilot phase 2 clinical trial of a humanized CD11/CD18 monoclonal antibody in hemorrhagic shock. Proceedings: 4th International Congress on the Immune Consequences of Trauma, Shock and Sepsis, Munich, Germany March 1997. Monduzzi Editore S.p.A, Bologna, Italy, 1997, pp. 941-943
20. Mendez C, Jurkovich GJ, Garcia I, Davis D, Parker A, Maier RV. Effects of an immune enhancing diet in critically injured patients. *J Trauma* 1997; 42(5):933-941

**Table 4. (Continued)****Partial List of Translational Research Publications in ALI or Related Critical Illnesses from Studies Conducted in Part or in Whole at the University of Washington in the Last 10 Years**

21. Heard SO, Fink MP, Gamelli RL, Solomkin JS, Joshi M, Trask AL, Fabian TC, Hudson LD, Gerold KB, Logan ED, The Filgrastim Study Group. Effect of prophylactic administration of recombinant human granulocyte colony-stimulating factor (filgrastim) on the frequency of nosocomial infections in patients with acute traumatic brain injury or cerebral hemorrhage. *Crit Care Med* 1998; 26:748-754
22. Madtes DK, Rubenfeld G, Klima LD, Milberg JA, Steinberg KP, Martin TR, Raghu G, Hudson LD, Clark JG. Elevated transforming growth factor- $\beta$  levels in bronchoalveolar lavage fluid of patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1998; 158:424-430
23. O'Keefe GE, Gentilello LM, Maier RV. Incidence of infectious complications associated with the use of histamine 2-receptor antagonists in critically ill trauma patients. *Ann Surg* 1998; 227(1):120-125
24. Arons MM, Wheeler AP, Bernard GR, Christman BW, Russell JA, Schein R, Summer WR, Steinberg KP, Fulkerson W, Wright P, Dupont WD, Swindell BB, for the Ibuprofen in Sepsis Study Group. Effects of ibuprofen on the physiology and survival of hypothermic sepsis. *Crit Care Med* 1999; 27:699-707
25. Greene KE, Wright JR, Steinberg KP, Ruzinski JT, Caldwell E, Wong WB, Hull W, Whitsett JA, Akino T, Kuroki Y, Nagae H, Hudson LD, Martin TR. Serial changes in surfactant-associated proteins in lung and serum before and after onset of ARDS. *Am J Respir Crit Care Med* 1999; 160:1843-1850
26. East TD, Heermann LK, Bradshaw RL, Lugo A, Sailors RM, Ershler L, Wallace CJ, Morris AH, McKinley B, Marquez A, Tonnesen A, Parmley L, Shoemaker W, Meade P, Thaut P, Hill T, Young M, Baughman J, Olterman M, Gooder V, Quinn B, Summer W, Valentine V, Carlson J, Bonnell B, deBoisblanc B, McClarity Z, Cachere J, Kovitz K, Gallagher E, Pinsky M, Angus D, Cohen M, Hudson L, Steinberg K. Efficacy of computerized decision support for mechanical ventilation: Results of a prospective multi-center randomized trial. *Proc AMIA Symp* 1999; 251-5
27. Matute-Bello G, Liles WC, Radella F II, Steinberg KP, Ruzinski JT, Hudson LD, Martin TR. Modulation of neutrophil apoptosis by granulocyte colony-stimulating factor and granulocyte/macrophage colony-stimulating factor during the course of acute respiratory distress syndrome. *Crit Care Med* 2000; 28:1-7
28. The ARDS Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000; 342:1301-1308
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## **HYPOTHESES**

We are basing our plan for training translational investigators on the following hypotheses. Since this is a Core and not a scientific project we will not be directly testing these hypotheses. Rather, they serve as explicit statements of the assumptions upon which we have based our training plan.

- 1) A major reason for the lack of successful translational research is that appropriate training and mentoring of translational investigators has not occurred.
- 2) It is unrealistic to think that a translational investigator can be simultaneously trained in the methods of basic science and clinical investigation in the time that it takes to train investigators in only one of these disciplines. Proper training of each of these two types of researchers takes years of dedicated training and experience.
- 3) Successful translational investigators will have primary training in either a) basic science research or b) clinical investigation, with a thorough working knowledge of the research principles and their appropriate application in the alternate research discipline. This knowledge will include familiarity with the research methodologies and familiarity with the literature, especially as it relates to acute lung injury, as well as having the ability to critically evaluate that literature in both disciplines.
- 4) Training of translational investigators based on hypothesis 3) will both stimulate these investigators to want to participate in translational research and provide these trainees with the skills to successfully collaborate with others in carrying out high quality translational investigation.
- 5) Appropriate training will markedly improve the translation of basic research advances to the clinical arena, enhancing the probability of the development of successful treatments for patients with acute lung injury and related conditions.

## **OVERALL TRAINING PLAN DESCRIPTION**

In this section we discuss the philosophy and reasoning behind our training plan and provide a description of the elements in that plan. We describe the elements that are already in place, the elements that would be developed with the resources available from this grant, and how they will be combined to create a new comprehensive program to train translational investigators.

It is our contention that we (and others) do well in training basic investigators and clinical investigators but that the major defect in training translational investigators is inadequate “cross-over” to the other research field. For example, this would require that a basic researcher understand the principles and research methodology of clinical epidemiology and biostatistics. For the clinical investigator this includes not only knowing what basic research methodologies are available and what sort of questions these methods can address but also having a working knowledge of the biology of inflammation, lung injury, and repair in order to better participate in the development of appropriate translational research questions. If this training were done, we believe that it would result in cross-fertilization of ideas, novel approaches to translational research, and better skills in being able to perform this type of research. The end result should allow basic research advances to be more rapidly translated into significant clinical benefits.

We think we have several training elements to allow this training already in place. However other training elements need to be developed. This grant and its resources will allow us to a) develop the elements we are missing and b) mold our current training components with the newly developed ones to create a cohesive program aimed at training translational investigators.

Our vision of a translational investigator is not that of the superstar trained fully in both basic and clinical investigative skills and single-handedly carrying out both sides of the investigation. Although a few individuals are capable of doing this (and a very few do exist now), this approach is not likely to result in developing large numbers of translational investigators, and we believe it is unnecessary and unrealistic. Our vision is that a translational investigator must have a primary discipline – either basic or clinical investigation – and then enhance that training with better knowledge of approaches, issues, and methods in the other discipline. Although this would require that translational research be collaborative, it would allow that collaboration to be more creative and yet realistic, and should allow it to be more successful. Each participant would be able to “speak the language” of the other and know the capabilities and the limitations of the research methods. We

think it should also allow development of better questions as well as encouraging collaboration when appropriate for the issues under investigation.

We believe that our program is ideally poised to develop a translational research training program focused on acute lung injury. We believe this is so because of our track record of successful training of both basic and clinical investigators, the heavy emphasis in our research program on questions addressing acute lung injury, and our considerable experience in acute lung injury translational research.

A number of Pulmonary and Critical Care Medicine research training programs are good at training basic investigators. We count ourselves as being in that group. Much of our basic research has been in the area of mechanisms of acute lung injury and repair and the role of perturbations of inflammation in both of these processes.

Only a few programs, on the other hand, have focused their efforts on rigorous training of the clinical investigator. Our program has been a national leader in this area (Curtis JR, Rubenfeld GD, and Hudson LD. Training pulmonary and critical care physicians in outcomes research: Should we take the challenge? *Am J Respir Crit Care Med* 1998; 157:1012-1015). We were among the first (if not the first) to develop an organized clinical investigator training track with dedicated faculty with backgrounds including Master's degrees in relevant fields, a formal curriculum leading to a Master's degree as an integral part of the program, appropriate mentoring, and practical research experience all aimed at developing clinical investigators. Like our basic research program, one of the foci of our clinical research has been acute lung injury, in both cases stimulated in part by our current SCOR in acute lung injury.

In addition we have had considerable experience with translational research in acute lung injury. This has included our research program centered around the study of constituents in serial bronchoalveolar lavage from patients with ALI and ARDS and their correlation with clinical variables. We also have extensive experience in clinical trials involving patients with acute lung injury, both as part of the NIH/NHLBI ARDS Clinical Trials Network (ARDSnet) and in independent studies. See Table 4 for a list of translational research publications in patients with ALI or critical illness in the last 10 years.

We do not believe, however, that the training we have provided has been optimal for the training of translational investigators in acute lung injury. We believe we can significantly enhance this training through the provision of limited but appropriate cross-training in the trainee's alternative area of research, providing opportunities for the trainee to participate in high quality collaborative translational research, and mentoring in translational research (the major hypothesis of this Core). Our experience in training investigators and in conducting acute lung injury translational research has allowed us to develop a training approach that we are highly confident will be successful.

### Proposed Translational Research Training Program (TRTP)

The proposed training program for translational investigators will be comprised of five components:

- Primary research training in trainee's primary discipline
- Cross-training in the alternate discipline
- Research project(s) – to include a translational research component
- Mentoring – to include a mentoring committee with membership reflecting translational research
- Research environment – to include participation in activities to enhance translational research training

The last three components are part of our current primary research training tracks. They will be modified, however, for trainees in the Translational Research Training Program to better support that training. None of the translational research training enhancement (cross-training in the alternate discipline) is currently being carried out. Some of the elements described are available but have not been adequately utilized and have not been integrated into a single training track. Other (most) elements are novel and will be built specifically for this program.

This proposed training program is divided into two tracks: translational research training for basic scientists and translational research training for clinical investigators. We will describe each of the above components for the two sections of the translational training track: primary basic science and primary clinical investigation.

*Primary research training.* Research training in the trainee's primary discipline (basic or clinical research) will continue as it is currently carried out. Trainees will either be fellows in Pulmonary and Critical Care Medicine or Critical Care Medicine in the Division of Pulmonary and Critical Care Medicine (D-PCCM), Department of Medicine, or in the Surgical Critical Care Fellowship Program and the Postdoctoral Training Program of the Department of Surgery (DOS). These fellows have the opportunity to have primary research training in either basic or clinical investigation. The majority of fellows will be in the D-PCCM which takes 6 fellows each year compared to 3 fellows each year in the Department of Surgery (1 in the clinical epidemiology based Harborview Injury Prevention and Research Center Surgical Critical Care Fellowship and 2 in the cell and molecular biology based Postdoctoral Training Program).

Table 5 shows the current training tracks of the PCCM and DOS Research Training Tracks and in italics also shows the novel training tracks and sections of these tracks proposed in this application.

**Table 5: Current (regular type) and Proposed (*italics*) Training Tracks**

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**Current PCCM Research Training Tracks**

- A. Basic Research
  - Cell and Molecular Biology
  - Physiology
- B. Clinical Investigation (includes enrollment in Master's degree program)

**Current DOS Research Program Training Tracks**

- A. Basic Research (Postdoctoral Training Program)
- B. Clinical Investigation (Harborview Injury Prevention and Research Center Surgical Critical Care Fellowship) (includes enrollment in Master's degree program)

**Proposed Training Tracks for both PCCM and DOS**

- Translational Investigation
  - A. Primary training in Basic Science
  - B. Primary training in Clinical Investigation

**Translational Research Training for Basic Scientists**

Primary Research Training in Basic Science Research

Primary research training at the University of Washington is extremely strong in both the Division of Pulmonary and Critical Care Medicine (D-PCCM) and the Department of Surgery. The training is primarily in Cell and Molecular Biology, although the D-PCCM has maintained a strong Physiology training track which is increasingly engaging in research integrating cell and molecular biology approaches with physiology research techniques. The D-PCCM has had an NIH institutional research training (NRSA) grant to support this training since 1977 and Hudson has been PI of this grant since 1982. The DOS has had an NIH institutional research training (NRSA) grant to support basic research training since 1975 and Maier has been PI since 1990. Both of these programs include high quality experienced research mentors in basic science, important and funded research projects, strong mentorship and a rich and supportive research environment in which to work.

The major focus of the basic science research training is the research project and direct mentoring within the laboratory. A partial list of research mentors and their areas of interest is given in the Background and Preliminary Work section (see Tables 1 and 2). This training is supplemented by didactic training with selected courses, especially Conjoint courses 501, 502, and 503 – the Molecular Basis of Cell Function – in the School of Medicine. Conjoint 501 covers the plasma membrane including membrane structure, ion channels, and transmembrane signaling. Conjoint 502 covers the nucleus including chromatin structure, recombination, RNA processing, and gene expression. Conjoint 503 covers the cytoplasm including protein synthesis, targeting and secretion, organelles, extracellular matrix, and high-order cell functions.

### Formal Research Cross-training in Clinical Investigation

Translational research includes testing for proof of biologic concept in humans of ideas generated in the basic laboratory and in animal models, studying mechanisms of injury in humans (based on basic research findings), and testing interventions in humans developed in the basic science laboratory. These require knowledge of clinical epidemiology, clinical research methods, biostatistics, and ethical issues related to human research. This background will be provided in two ways, first, through a didactic lecture series, and second, by participation in practical hands-on clinical research workshops.

*Lecture Series.* Translational investigators whose primary training is in basic science will benefit from a background in the core disciplines of biostatistics, clinical epidemiology, and health services research. Although translational investigators do not need to be statisticians or epidemiologists, they do need an understanding of these disciplines in order to design and conduct clinical research and collaborate with colleagues in these areas. These topics will be covered in didactic courses designed specifically for the translational investigator. Each trainee will attend three 3-week lecture series dealing with clinical research protocol design, clinical trial study design, and critical appraisal and application of evidence in health care. These courses are offered under the auspices of the University of Washington's K-30 Clinical Research Curriculum Award (PI: Jeffrey L. Probstfield, MD).

The courses developed in the K-30 grant are specifically designed for the clinician-scientist with a background in basic research who intends to participate in studies involving patients – translational research by our definition above. Thus, the content of these courses fits perfectly with the intent and needs of our Translational Research Training for Basic Scientists. The three courses are described below.

“Clinical Protocol Design” will be taught by Margaret Pepe, PhD, Professor of Biostatistics in the School of Public Health and Community Medicine and Biostatistician for the University of Washington General Clinical Research Center (GCRC). This course describes the key elements to be considered in designing a clinical research study. The following elements will be discussed: 1) Outcome measures (primary, secondary, precise definitions, clinical and biological relevance); 2) Selection of study subjects (choice of study population, biases in selection, inclusion/exclusion criteria); 3) Controls (randomization, historical controls, study subjects as their own controls, blinding); 4) Describing study procedures and evaluations (the study flow sheet); 5) Data analysis (simple comparisons to answer study questions, plotting data, interpretation for p-values and confidence intervals, more elaborate analyses, implications of results); 6) Sample size (enough data to make conclusion, statistical power, width of confidence intervals, determinants of precision/power, formulas for sample size). Consistent emphasis will be made throughout the course that these components need to be driven by and repeatedly tied to specific aims.

The phases of research will be discussed. The concepts of phase 1 (toxicity, dose finding), phase 2 (biological efficacy), and phase 3 (clinical efficacy) studies will be explained as well as the pre-clinical stages of research and the concept of the post marketing phase (phase 4) research. Basic classification of study designs will be defined including the notions of cohort versus case-control studies, cross section versus longitudinal studies, prospective versus retrospective studies and crossover versus parallel studies.

Several real examples of studies conducted at the GCRC will be used to illustrate specific points. In addition, students will be asked at the beginning of the course to formulate a real or hypothetical research question of interest to them. They will develop study designs to address these questions and write design proposals using six design components described in the lectures. For these exercises, students will work together in groups. Each group will include a biostatistician as a member.

“Clinical Trial Design” will be taught by Jeffrey Probstfield, MD, Professor of Medicine, Associate Program Director for Education of the UW GCRC, and PI of the K-30 Clinical Research Curriculum Award. This course will review selected topics in clinical trials and will build on the foundation of the Clinical Protocol Design course. The following topics will be covered: 1) Formulation of the Scientific Question for investigation (acceptability and alteration of natural history trials, intention to treat analysis); 2) Sample size consideration (adjustments for non-adherence and competing morbidity and mortality); 3) Outcome measures (primary, secondary and surrogate measures); 4) Issues of recruitment and adherence; 5) Big and simple trials

and meta-analysis; 6) Subgroups (proper identification and interpretation); 7) Data and Safety Monitoring Board (structure and function, monitoring guidelines); and 8) Proper reporting of findings from trials (let the data speak for themselves). The lectures will be supplemented by discussion of examples of clinical trials in a small discussion group setting.

“Critical Appraisal of Evidence” will be taught by Fredric M. Wolf, PhD, Professor and Chair, Department of Medical Education and Biomedical Informatics and Adjunct Professor of Health Services. This course will cover the following topics: 1) Literature appraisal skills for various articles (therapeutic effectiveness, diagnostic tests, literature reviews, clinical measurement, prognosis, quality of care, decision analysis, causation/etiology, guidelines, and economic evaluation); 2) Appraisal of clinical information from literature (strengths/weaknesses of data, analyses, study design/applicability to a specific patient’s problem); 3) Conceptual understanding of the qualitative methods used to synthesize evidence; and 4) Methods for pooling evidence across independent studies, pooling binary/continuous outcomes, differences between fixed and random effects models, and guidelines for appraising published systematic reviews/meta-analyses.

*Clinical Research Workshops.* In addition to this didactic lecture series, there will also be two practical clinical research workshops that will occur each year of the trainee’s research fellowship. These workshops will be 3 days in duration. These clinical research workshops will be developed and led by J. Randall Curtis, MD, MPH, and Gordon D. Rubenfeld, MD, MSc. Curtis and Rubenfeld are co-directors of the Clinical Investigation Training Track of the D-PCCM. Curtis has an NIH K-24 Mentoring Award and Rubenfeld is PI of the Clinical and Data Management Core of the current University of Washington SCOR in ALI and a project PI in this SCCOR application. The purpose of these workshops is to cover the practical aspects of clinical investigation. The workshops will involve both seminars and working sessions. During each workshop, the fellows will have a specific task they will be working on and the outcome of each workshop will include a specific written product.

During the fall workshop of each year, the topics that will be covered include: a) the principles of clinical research and study design; b) developing a clinical research question; ethics of clinical research concerning human subjects; the basics of writing a clinical grant application; and the basics of the funding sources and cycles. The outcome for 2nd year fellows will be a written 2-3 page research outline. The outcome for 3<sup>rd</sup> and 4<sup>th</sup> year fellows will be work on a grant application. During the spring workshop the topics will be: a) writing a research protocol; b) the basics of database management and data analysis; c) obtaining and maintaining grant funding; d) writing, submitting, and reviewing manuscripts; e) the ethical conduct of the clinical research enterprise. The outcome for all fellows from this workshop will be either work on a manuscript or work on data analysis, depending on the needs of the specific fellow.

These clinical research workshops are being developed and designed specifically for this translational research training program for basic scientists. We plan to also invite all clinical investigation trainees in our programs to these workshops as well. We believe this will provide a critical mass that will enhance the learning environment of the workshop. The basic scientists in the TRTP will benefit and learn from interacting with clinical investigator trainees. We will have an adequate number of clinical research faculty at the workshop to ensure individual attention and tutoring for each basic scientist translational research trainee. One outside consultant, expert in clinical research methodology, and experienced in translational research, will be invited to participate in each workshop.

The practical clinical research workshops are based on the Advanced Epidemiology Course that Drs. Rubenfeld and Curtis conduct each year as part of the American Thoracic Society’s International Respiratory Epidemiology Course. The Advanced Epidemiology Course of 2002 represents the third time that Drs. Rubenfeld and Curtis have directed this course and it has received very positive reviews from students of the course.

### Trainees’ research projects

Although coursework is extremely important, the most important component of any research trainee’s education is his/her research projects. Trainees should obtain experience in formulating a research question, designing a study to answer the question, completing the study, and writing the results for publication. They

can gain experience in these tasks early in their research training, provided they have sufficient guidance. Trainees in this division of the Translational Research Program will have a primary research mentor in the basic sciences and a secondary research advisor from the clinical investigation pathway (see mentoring committee description below).

We have a wide variety of translational research projects in which trainees can participate. Also, there are several paths by which a basic science trainee can become involved in a translational research project. In some cases the project, arising from basic laboratory origins, is designed as a translational research project. For example, this is the case for Project 1 - (Thomas R. Martin, PI) in this SCCOR application. In other cases a basic project may evolve with the findings indicating a relevant mechanism in animal models which leads to the development of specific interventions which may be relevant in humans. Projects 5 (Robert Winn, PI) and 6 (Conrad Liles, PI) are potential examples of a basic laboratory project which may lead to a translational project. Other examples in this category are the interventions proposed for study in Project 3 (Avery Nathens, PI), the Clinical Trials Incubator Unit. This project will have subprojects (pilot clinical trials primarily designed to test biologic proof of concept) in which a trainee could participate. Nathens has the perfect background to oversee such translational research; he is an MD with a PhD in basic science investigation and an MPH in Epidemiology. A role for a trainee is built into each of these clinical trials. Thus the Clinical Trials Incubator Unit is an ideal “laboratory” in which a basic science trainee can receive experience in translational research. This may represent a third path, a project in which the trainee had not participated in the basic work which led to the foundation of the trial. On the other hand, we expect that some of the pilot trials will result from local work in which a trainee might have participated.

A number of published translational research projects conducted in part or in whole at the University of Washington involving our faculty are listed in Table 4 in the Background and Preliminary Results section.

### Mentoring

Our current research training programs include a mentoring committee for each trainee. The mentoring committee generally meets once a year. It reviews the trainee’s self-stated short- and long-term training goals and his or her progress toward those goals. The committee provides overall career guidance and recommendations regarding any aspect of training. The committee is chaired by the trainee’s primary research mentor. The membership generally consists of two additional faculty members with areas of research interest and expertise that are similar to the trainee’s primary interest, one faculty member in an unrelated research field (to provide perspective) and one faculty representing the administration of the research training program (often Hudson for PCCM trainees and Maier for DOS trainees). Each trainee in the Translational Research Training Program will have a secondary translational research training mentor. This mentor will be a faculty member in the alternate research discipline, in this case a clinical investigator, who is involved in the trainee’s translational research project. The secondary mentor will serve on the monitoring committee and will be responsible for preparing an addendum to the committee’s report that specifically focuses on progress toward translational research training goals.

### Intellectual and Collaborative Environment

A translational research training program must provide the intellectual environment in which to develop experience collaborating with other investigators, giving and receiving constructive criticism, and learning to advance in the academic medicine system. Such an environment requires: 1) a “critical mass” of basic, clinical and translational investigators, usually both faculty and fellows, to provide a network of colleagues; and 2) a framework in which to teach collaboration. We already have a critical mass of faculty and research fellows. The framework to teach this collaboration exists in part through the “Works in Progress” sessions in which clinical investigation and basic science trainees present their research at various stages of development.

The research environment includes ongoing opportunities to present work in progress and to participate in discussions of the work of others. In addition to laboratory meetings, one of the important conferences aimed at hearing work in progress is the Cell and Molecular Biology Study Group, organized by the D-PCCM but with participants including trainees and faculty from the DOS. More formal presentations of more complete projects are expected at the weekly Respiratory Research Conference and the Department of Surgery Research

Conference. Regular seminars with local and invited speakers on topics relevant to the cell and molecular biology trainee are available and well advertised at the University of Washington Health Sciences Center, the Fred Hutchinson Cancer Research Center and the Veterans Affairs Puget Sound Health Care System.

Trainees enrolled in Translational Research Training for Basic Science Trainees will also participate in the Clinical Research Works in Progress (CRWIP) biweekly conference organized and led by Drs. Curtis and Rubenfeld. Work in progress is presented and clinical research methodology and its appropriate application is stressed in the discussions. The average attendance at the conference is 15 participants, on the average 8 trainees and 7 faculty. Basic science trainees in the Translational Research Training Program are expected to present their work in progress at least two times per year at this conference. The trainees prepare an outline which covers their presentation and which includes a series of questions on which they would like input from the conference participants. The CRWIP conference is purposely scheduled on alternate weeks to the Cell and Molecular Biology Study Group conferences, its counterpart for presentation and discussion of basic research work in progress. In this way, trainees in the Translational Research Training Program can (and are expected to) participate in both conferences.

## **Translational Research Training for Clinical Investigators**

### Primary Research Training in Clinical Investigation

Both the Division of Pulmonary and Critical Care Medicine and the Department of Surgery (through its Harborview Injury Prevention and Research Center Critical Care Surgery Fellowship) have unusually strong training programs in clinical investigation. Both have strong ties to the Departments of Epidemiology, Biostatistics, and Health Services in the School of Public Health and Community Medicine, all three departments being highly regarded nationally and internationally. Trainees in both programs are enrolled in a Masters degree program, usually obtaining a Master of Science (MSc) degree in Epidemiology, although occasionally this is an MSc in Health Services or a Master of Public Health (MPH) degree, depending on the trainee's primary research focus.

Our Clinical Investigation Fellowship Training Track was among the first, if not the first, in the country in a Division of Pulmonary and Critical Care Medicine to provide such rigorous organized training in clinical outcomes research. This novel training track includes a formal curriculum, a critical mass of trainees and faculty, appropriate research and mentoring opportunities, and a vehicle – the biweekly CRWIP Conference – to allow frequent presentation by the trainees with discussion of their work stressing the principles of research methodology and design. Trainees in this track have participated in the generation and publication of a substantive body of knowledge dealing with the epidemiology and outcomes of patients with ALI. The Department of Surgery has also been a national leader in clinical investigator training. Their clinical research training track, the Harborview Injury Prevention and Research Center Surgical Critical Care Fellowship, funded through a grant from the CDC, also includes enrollment in a Master's degree program in Epidemiology. This training track has also resulted in a significant body of work dealing with the epidemiology, prevention, and outcomes of trauma and surgical critical illness, including in patients developing the complications of ALI and multiple organ dysfunction.

### Formal Cross-Training in Basic Science Research

Translational research involves the demonstration and validation of basic biological concepts and the application of basic scientific discoveries in the clinical arena. Translational research also involves the generation of new scientific questions which are founded on clinical observations. Translational researchers whose primary training is in clinical investigation will benefit from a didactic curriculum specifically designed to introduce them to the basic concepts and biological processes relevant to acute lung injury, inflammation and repair. This will be accomplished through curriculum development and project-focused co-mentoring.

It is increasingly important that translational investigators whose primary training is in clinical research acquire an understanding of basic cell and molecular biology and laboratory methods to bridge the gap between the laboratory bench and patients. The curriculum is designed to expose clinical researchers to cutting edge laboratory science and provide the opportunity to develop meaningful partnerships with basic scientists. The

formal research training curriculum will be composed of two parts specifically designed for the translational investigator: a lecture series and a laboratory workshop.

*Lecture Series.* Each trainee will attend an intensive 2 month 3x/week lecture series covering the biology of inflammation, lung injury and repair and an overview of laboratory based methodologies and their appropriate application. Such a course does not currently exist. It will be developed and directed by Richard B. Goodman, MD and Lynn Schnapp, MD of our Cell and Molecular Biology Research Training Track. Goodman is Associate Professor of Medicine and Director of the Cell and Molecular Biology Training Track for the Division of Pulmonary and Critical Care Medicine. Schnapp is Associate Professor of Medicine and has a strong interest in research education and mentoring. Goodman will play the lead role in organizing the lecture series.

The lecture series will focus on selected topics in the following 6 core categories with 1-5 lectures in each category (Table 6). Each lecture is designed as an introduction or overview of the topic targeting translational research trainees with a background in clinical investigation. Topics are selected for their potential relevance to acute lung injury.

**Table 6. Introductory Lecture Topics for Translational Research Trainees with a Background in Clinical Investigation**

<b>Topic #</b>	<b>Topic Category</b>	<b>Lecture</b>
1.	Biology of acute inflammation and injury	a) Histopathology of acute lung injury and ARDS b) Pro- and anti-inflammatory cytokines c) Chemokines and their receptors d) Integrins, selectins and cell adhesion e) Apoptosis and cellular necrosis
2.	Biology of tissue repair	a) Growth factors in the lung b) Cellular and molecular components of fibroproliferation c) Lung matrix alterations
3.	Immunology and host defense	a) Antibodies – their clinical utility and limitations b) Cell signaling and potential interventional targets c) Innate and acquired immunity – interventional strategies d) Knock-outs and transgenics – limitations and opportunities for translational research
4.	Molecular diagnostics	a) RFLPs, SNPs, PCR, ELISA – applications and limitations
5.	DNA and protein technologies	a) Gene array technology b) Proteomics technology
6.	Genomics	a) Fundamental concepts b) Screening for the genetic basis of disease c) Mapping and cloning human disease genes

Each lecture will be supplemented with a pertinent translational research article from the literature selected by the course faculty. For example, the lecture on "Pro- and anti-inflammatory cytokines" could be supplemented by the following articles from our own group:

Park WY, Goodman RB, Steinberg KP, Ruzinski JT, Radella F, Park DR, Pugin J, Skerrett SJ, Hudson LD, Martin TR. Cytokine balance in the lungs of patients with the acute respiratory distress syndrome (ARDS). *Am J Respir Crit Care Med*, 2001; 164:1896-1903.

Goodman RB, Strieter RM, Martin DP, Steinberg KP, Milberg JA, Maunder RJ, Kunkel SL, Walz A, Hudson LD, Martin TR. Inflammatory cytokines in patients with persistence of the acute respiratory distress syndrome. *Am J Respir Crit Care Med*, 1996; 154:602-611

The lecture on "Cellular and molecular components of fibroproliferation" could be supplemented by the following articles:

Clark JG, Milberg JA, Steinberg KP, Hudson LD. Type III procollagen peptide in the adult respiratory distress syndrome. *Ann Intern Med* 1995; 122:17-23

Chesnutt AN, Matthay MA, Tibayan FA, Clark JG. Early detection of Type III procollagen peptide in acute lung injury. Pathogenetic and prognostic significance. *Am J Respir Crit Care Med* 1997; 156:840-845

The lecture on "Chemokines and chemokine receptors" could be supplemented by the following articles:

Cummings CJ, Martin TR, Frevert CW, Quan JM, Wong VA, Mongovin SM, Hagen TR, and Goodman RB. Expression and function of the chemokine receptors CXCR1 and CXCR2 in sepsis. *J Immunol* 1999; 162:2341-2346

Articles will be provided in advance of each lecture for review by the participants. Each lecture will close with a discussion of the relevant future applications of the topic in translational research. Thoughtful supplementation with pertinent translational articles and focused closing discussion are what distinguishes this from a simple lecture series. This innovative approach will demonstrate the relevance of each topic for translational researchers and introduce participants to the process of creatively applying these basic concepts to translational research projects. An outside consultant expert in basic cell and molecular biology research and experienced in translational research, will be invited to speak in the lecture series and to meet with trainees in years 3 and 5.

*Laboratory Workshop.* Each trainee will participate in a week long, hands-on laboratory based workshop which will provide the trainee with practical experience with commonly used cell and molecular biology lab techniques. This course will be developed and co-directed by Lynn Schnapp and Rick Goodman of our Cell and Molecular Biology Research Training Track. Schnapp will take the lead role in organizing the workshop. Each day will consist of a brief didactic session, with an overview of the day's experiments. The remainder of the time will be spent in the laboratory. Methods to be covered will include: polymerase chain reaction (PCR), introduction to plasmids and DNA isolation, analysis of protein and gene expression in cultured mammalian cells, introduction to protein/DNA databases and BLAST searching, and overview of proteomics and microarray technology.

The target audience for this "Introduction to Laboratory Techniques" workshop is clinical investigation fellows in the Translational Research Training Program who desire an understanding of laboratory basics that affect clinical research. Each morning will consist of a 1-hour didactic session, covering the rationale behind the procedures of the day. The rest of the day will be spent in the laboratory. All reagents/products will be prepared in advance so that if one step should fail, we will have the necessary templates to continue with the

next step. For example, we will have pre-made plasmid DNA, PCR products, protein lysates and RNA samples and probes for Northern analysis. The syllabus will contain an overview of techniques with protocols.

Sample schedule.

Day 1. Overview of safety issues, Introduction to plasmids and PCR

1. Isolate plasmid DNA from E. coli broth cultures.
2. Amplify plasmid DNA by PCR.
3. Lysates for protein analysis from cultured cells.
4. Measurement of protein concentration.

Day 2. Cloning/Introduction to cell culture and analysis of protein expression in cultured mammalian cells.

1. Run Western gel, transfer, block, set up primary antibody.
2. Analyze PCR products by restriction digest and agarose gel electrophoresis.
3. Set up ligation reaction.

Day 3. Analysis of gene expression in cultured mammalian cells.

1. Transformation of competent bacteria.
2. RNA isolation from cultured cells.
3. Spectrophotometric measurement of RNA.
4. Finish Western.

Day 4. Introduction to antibodies

1. ELISA
2. Northern analysis: prepare gel, make probe (non-radioactive), set-up hybridization
3. Pick colonies from transformation and grow O/N

Day 5.

1. Finish Northern
2. Complete any additional experiments (mini-prep from transformation)
3. Introduction to searching protein/DNA databases, BLAST searching.

### Trainees' Research Projects

Research projects will be the heart of the training experience. Trainees will gain experience collaborating with basic science investigators in projects that require a partnership with a basic laboratory. Early on, trainees will have the opportunity to join ongoing projects developed by our faculty members. Over time they will be encouraged to explore their own scientific creativity and develop novel directions to support the next level of funding and career development. The work they accomplish will serve as preliminary data for funding applications, which will be prepared by the fellows with the strong support of their research mentors. Fellows will present their work at national meetings, and prepare manuscripts of their work for publication. A variety of translational projects are available in which trainees may participate. These will include the clinical trials being carried out in the Clinical Trials Incubator Unit of Project 3 (Avery Nathens, PI). Table 4 (background and preliminary work section) contains a list of translational research projects resulting in publications.

### Mentoring

As described above under the Translational Research Training for Basic Scientists, the trainee's primary research mentor will be in the trainee's primary research discipline and a secondary mentor will be from the alternate discipline, in this case basic science, and involved in the trainee's translational research project. This secondary mentor will serve on the trainee's mentoring committee and will have the same responsibilities as described above in the Translational Research Training of Basic Scientists.

### Intellectual and Collaborative Environment

The translational research trainees with primary clinical research training are already working in a supportive and collegial environment. We plan to enhance their experience in giving and receiving constructive criticism by having them attend the Cell and Molecular Biology Study Group conferences and present their translational research in progress. These conferences are held on alternate Thursdays from the Clinical Research Works in Progress. Thus, these translational research trainees are expected to attend and participate in both of these conferences.

### Clinical Trialist Education and Experience

The trainee who is committed to a career as a clinical trialist will benefit from participation in the Translational Research Training for Clinical Investigators. They should particularly benefit from learning about the biology of lung inflammation, injury, and repair. Trainees who declare this intention to become a clinical trialist will be asked to enroll in Biostatistics 524 as part of their coursework toward their Master's degree. This course deals with clinical trial study design. This trainee will be assigned a mentor experienced in clinical trials. They will participate in the pilot clinical trials focused on showing biologic proof of concept carried out in the Clinical Trials Incubator Unit of Project 3 (Avery Nathens, PI) and also in the phase III trials conducted at our center under the auspices of the NIH ARDS Clinical Trials Network. We have several investigators experienced in clinical trials to serve as mentors, including Len Hudson (PCCM), Ron Maier (DOS), Ken Steinberg (PCCM), Margaret Neff (PCCM), Avery Nathens (DOS), Jerry Jurkovich (DOS), and Fred Rivara – Department of Pediatrics and former Director of the Harborview Injury Prevention and Research Center. The trainee is expected to gain practical experience in all aspects of preparation for and conduct of human clinical trials including development of an Informed Consent form and Institutional Review Board application.

### **Ethical Conduct of Clinical Research**

All translational research trainees will receive training in the ethical conduct of research and the ethics of research concerning human subjects. The didactic portion of this training will be provided through two avenues available at the University of Washington. Trainees will complete the training program in Ethical Conduct of Research Involving Human Subjects provided by the University of Washington and will attend the Seminar in Research Ethics offered each summer for research trainees. In addition, each of the Divisions will incorporate the ethical conduct of clinical research into the practical training sessions and the mentoring sessions.

### **Program Organization and Oversight**

The Translational Research Training Program (TRTP) will be organized and led by Len Hudson. He is in the process of stepping down as Division Head and will be focusing his efforts on the training of research fellows and his own clinical and translational research. Thus, this responsibility fits well with his major career emphasis at this time. His leadership has the added advantage of coordinating the Translational Research Training efforts with the current PCCM training, as he is the Research Coordinator for the PCCM fellowship program, working closely with Mark Tonelli, the overall training program director (a position Hudson held until recently), and is the PI of the Division's NRSA institutional research training grant. This will also help with coordination with the Department of Surgery Research Training Program as Hudson serves as a member of the Executive Committee of this program.

Hudson has had a long interest in fellowship and research training. He has been the Program Director for the PCCM Fellowship Program from 1975-2002. He has been the PI of the NIH NRSA institutional training grant for the Division of PCCM since 1982. He also is familiar with the research at the University of Washington dealing with ALI and ARDS; he has been PI of the SCOR on ALI (or, in previous cycles, on ARDS) for four consecutive five-year cycles. He has been PI for the University of Washington site of the NIH NHLBI ARDS Clinical Trials Network (ARDSnet) since 1994. He has had strong ties with investigators from the Department of Surgery interested in critical illness and ALI; he helped initiate a joint program on ARDS research with the late C. James (Jim) Carrico, then the Surgeon-in-Chief at Harborview Medical Center and subsequently Chair of the Department of Surgery at the University of Washington and University of Texas,

Southwestern. This program has continued with the subsequent Surgeons-in-Chief at HMC, formerly Charles (Chip) Rice and currently Ron Maier.

Hudson's duties as Director of the TRTP will include the following:

- 1) To meet with research trainees in both D-PCCM and DOS to describe the TRTP opportunities. He will meet with them annually at their orientation session.
- 2) To meet with any individual trainees interested in the TRTP. He will make suggestions on other faculty with whom they should consult to discuss translational research training and projects, depending on the trainee's specific research interests.
- 3) To meet with each trainee, once they commit to the TRTP. This will consist of a minimum of one meeting with each translational research trainee per year.
- 4) To supervise and monitor the Mentoring Committee Program, with the help of his administrative assistant and primary staff person for this program, Norma Jean Schwab. All primary research mentors will be contacted to assure that a mentoring committee has been appointed with a translational research representative and that annual meetings have been scheduled. Schwab will assist with committee meeting logistics. When possible, Hudson will attend Mentoring Committee meetings. If he is not in attendance, he will review the meeting report, the writing of which will be the responsibility of the primary research mentor with comments on translational research training by the secondary mentor. Schwab will be responsible for obtaining reports of all Mentoring Committee meetings.
- 5) To convene annual Steering Committee Meetings for program review and oversight. (See below for committee makeup.)
- 6) To meet as necessary with leaders of the major programs with which the TRTP will interact, including the K-30 Clinical Research Curriculum Award institutional grant, the PCCM research training tracks, the DOS Research Training Program, the SCCOR on ALI, the Clinical Trials Incubator Unit (Project 3 of the proposed SCCOR), and the Master's degree training programs of the School of Public Health and Community Medicine.

The Steering Committee of the Translational Research Training Program will meet at least annually to provide program review and oversight. Hudson will chair the committee. Members will include the following: Ron Maier, MD is Professor of Surgery, Surgeon-in-Chief at Harborview Medical Center, and PI of the DOS institutional training grant. Maier is also a co-investigator on the NIH ARDS Clinical Trials Network. Thomas R. Martin, MD, Professor of Medicine and Chief of the Medical Service at the VA Puget Sound Health Care System, will sit on the committee as the Program Director of the SCCOR. He is also an experienced translational investigator and will provide a valuable perspective. Avery Nathens, MD, PhD, MPH, is PI of Project 3, the Clinical Trials Incubator Unit. His presence on the committee will allow coordination of the participation of trainees in projects being carried out in this unit. Nathens is experienced and trained in both laboratory-based and clinical research and is involved in translational investigation. Richard Goodman, MD, Associate Professor of Medicine, directs the Cell and Molecular Biology Research Training Track for PCCM. He is responsible for the development of the lecture series for Translational Research Training for Clinical Investigators and will participate in the development and conduct of the Laboratory Techniques Workshop. Lynn Schnapp, MD, Associate Professor of Medicine, is responsible for development of the laboratory Techniques Workshop and will participate in the development of the basic science lecture series. Randy Curtis, MD, MPH, Associate Professor of Medicine, is co-director of the Clinical Investigator Research Training Track for PCCM and is PI of a K-24 mentoring award. He shares responsibility for developing and leading the clinical research workshops. Gordon Rubinfeld, MD, MSc, Assistant Professor of Medicine (and approved at the departmental level for promotion to Associate Professor), co-directs the Clinical Investigator Research Training track. Along with Curtis, he is responsible for developing and leading the clinical research workshops. Karen Edwards, PhD, Assistant Professor of Epidemiology, Institute of Public Health Genetics, Department of Epidemiology, School of Public Health and Community Medicine, is coordinator of the Master of Science degree program in Genetic Epidemiology. She also is PI of the University of Washington Center for Genomics and Public Health and is an expert in methodologies to study genetic susceptibility to complex diseases.

Edwards will provide contact with the Masters program in Epidemiology and especially in Genetic Epidemiology, and will be valuable as a consultant on the application of genomics methodology in our translational research projects.

Arthur S. Slutsky, MD, Professor of Medicine, Surgery and Biomedical Engineering and Director, Interdepartmental Division of Critical Care Medicine, University of Toronto, and Vice President, Research, St. Michael's Hospital, Toronto, Ontario, has agreed to be the external consultant for our TRTP. Slutsky is renowned for his integrated and translational research studies in acute lung injury. He is interested in and knowledgeable about research training. Slutsky will review the annual progress reports generated after the Steering Committee meets for its annual review and will discuss in detail the program's structure and progress with Hudson. Slutsky has agreed to perform an on-site in-depth review of the TRTP in its third year of existence. This visit will include his meeting with the leaders of each program element and meeting with each of the translational research trainees to review their research and their training progress. Slutsky will meet with Hudson and the Steering Committee at the conclusion of his visit to provide his assessment of the program and recommendations for improvement. Another external consultant will be invited to perform a similar review in our program's fifth year of existence.

### **LIMITATIONS AND STRENGTHS**

We have proposed a model for translational research training which emphasizes rigorous training in the primary research discipline with selected and limited cross-training to provide what we consider to be the necessary and relevant background in the alternative research discipline and which fosters the concept of collaborative translational research. This is in contrast to the model in which a translational investigator is equally trained in both basic and clinical research methodology and performs all aspects of the research single-handedly. It is possible that the latter model is superior to our model, a possible limitation of our training. We have given the reasons we think this is unlikely in the text of this application, including both theoretic and practical concerns and we are confident that our model will be successful. Any trainee, however, could choose to get more complete training in the alternate area to their primary discipline. We have the resources at the University of Washington to make this training available to any individuals. Even if that model were superior, however, we believe that our model will result in a significantly greater number of investigators trained in translational research than would be possible if more complete training in both research realms were carried out. We believe, therefore, that our model would still have a greater positive impact on stimulating quality translational investigation.

We are confident that we can carry out the training plan as described and we do not foresee any problems that would limit that. A successful program will depend on successful recruitment of trainees interested in participating in this track. Although it is possible that this will be a problem, we think that is doubtful. Many members of our training faculty are currently engaged in translational research. Our faculty has been enthusiastic about this training proposal. With the leaders of our current training programs and training tracks thoroughly committed to the concept of this new program and excited about putting it into reality, we believe that our trainees will share in this enthusiasm. Many of our trainees have a clinical background. We believe that the chance to make their basic research more relevant to clinical problems in a timely fashion will be a strong factor in convincing trainees to engage in the additional training entailed to allow higher quality translational research.

The current proposal builds on several existing strengths of our programs. This includes the unusually strong nature of both our basic research and clinical research tracks. Although other universities may match us in basic science training, we doubt that many can claim to have such rigorous training in both basic science and clinical investigation. Excellence in clinical research training is fundamental to our plan and our proposal directly builds on this strength.

This program brings together trainees with primary research training in basic science and clinical research and allows them to interact together, especially by participation of both types of primary trainees in the Cell and Molecular Biology Study Group and the Clinical Research Works in Progress conferences as well as the Clinical Research workshops. It also brings together trainees with backgrounds in Pulmonary and Critical Care Medicine and Internal Medicine and those with clinical training in Surgery. We believe this will result in

benefits in the questions generated and the approaches proposed to answer those questions. The range of the different backgrounds will bring a broader range of knowledge and experience to the table and we think will result in more creative research approaches.

This training plan utilizes the Clinical Trials Incubator Unit described in Project 3 (Avery Nathens, PI) in the training of translational investigators. This unit will be particularly beneficial to the training of individuals with a primary interest in clinical trials. However, it will also benefit the basic scientist trainee enrolled in the TRTP by providing an infrastructure which will allow them to more easily take ideas from their basic research results and begin to study them in a more clinical context. Thus, the TRTP provides another dimension to the Clinical Trials Incubator Unit.

Our training plan is based on a model with conceptual and practical rationale. We also believe the plan is achievable. We think we will be able to test this model; if it provides to be successful, we will be able to describe the model and its elements. It is our belief that this will allow this program to be expanded to other fields for translational research training at the University of Washington and allow the model to be exported to other universities.

## **SUMMARY AND FUTURE DIRECTIONS**

The proposed Translational Research Training Program is based on the concept of providing cross-training of a substantial yet limited extent in the alternate research discipline to the trainee's primary research training. Thus, we describe Translational Research Training for Basic Scientists and Translational Research Training for Clinical Investigators. The primary research training will remain as is currently carried out in our training programs. Cross-training for basic scientists will involve formal lectures in clinical research methods through the auspices of the University of Washington NIH K-30 Clinical Research Curriculum Award and clinical research workshops, newly developed for this program by PCCM faculty. They will work on a translational research project, attend the Clinical Research Works in Progress conference in addition to the Cell and Molecular Biology study group, and will have a secondary translational research mentor who will also serve on their mentoring committee. Cross-training for clinical investigators will include a formal lecture series on the biology of lung inflammation, injury and repair and basic laboratory techniques, specifically developed for this program by PCCM faculty. They will also participate in a Laboratory Techniques Workshop, also developed by PCCM faculty for this program. They will work on a translational project, attend Cell and Molecular Biology Study Group in addition to CRWIP, and have a secondary translational research mentor who will serve on their mentoring committee.

Oversight and administration of the program will be the responsibility of Len Hudson, with advice from a Steering Committee which will meet annually and as otherwise necessary. An outside consultant will do a thorough program review including meeting with all TRTP trainees in years 3 and 5.

Our plans are to test this program as it has been described limited to the PCCM and DOS trainees for the first three years. If the program is considered to be successful and well accepted at that time, we will explore expanding the program to other Divisions within the Department of Medicine. We have already had discussions with William Bremner, MD, PhD, Professor and Chair, Department of Medicine about this possibility. Bremner is enthusiastically supportive of our training plan and is very receptive to program expansion and identification of the necessary resources to allow that at some point in the future.

## **INTERACTIONS WITH CORES AND OTHER PROJECTS**

Core C, the Translational Research Training Core, will interact with the other SCCOR projects in several ways. First, it will enrich the training program for post-doctoral fellows recruited to participate in Project 1, Host Susceptibility (Thomas Martin, PI), and Project 3, Clinical Trials Incubator Unit (Avery Nathens, PI). The Clinical Trials Incubator Unit and the pilot trials it performs will serve as a training laboratory for translational research trainees. Additionally, as projects 4, 5, and 6 evolve generating questions that require translational validation, post-doctoral fellows recruited to those new directions will also benefit from this Core. Core C will coordinate the placement of translational research trainees with these projects as they reach a phase where translational research, by our definition, is involved. This will be coordinated through Hudson's membership on the SCCOR Steering Committee (which also includes all project PIs). Core C will benefit from participation

of several of the PIs (Martin, Rubens, Harlan, Liles) for support of the Basic Science Lecture Series for Translational Scientists who have trained in Clinical Investigation. Our recruitment of these participants to this Core will facilitate our focus on developing a program to train translational researchers interested in acute lung injury. Core C will interact with Core B, the Biotechnology Core, in facilitating use of the biotechnology available for inclusion in projects involving trainees, where that technology is appropriate.

**HUMAN SUBJECTS** - None

**VERTEBRATE ANIMALS** - None

**LITERATURE CITED**

Curtis JR, Rubenfeld GD, Hudson LD. Training pulmonary and critical care physicians in outcomes research: Should we take the challenge?. *Am J Respir Crit Care Med* 1998; 157:1012-1015

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<http://www.nih.gov/news/crp/97report/1report.htm>

**CONSORTIUM/CONTRACTUAL ARRANGEMENTS** - None

## CONSULTANTS

*Edwards, Karen, PhD:* Edwards will serve on the Steering Committee. Edwards is Assistant Professor of Epidemiology, Institute of Public Health Genetics, Department of Epidemiology, School of Public Health and Community Medicine, and coordinator of the Master of Science degree program in Genetic Epidemiology. She also is PI of the University of Washington Center for Genomics and Public Health and is an expert in methodologies to study genetic susceptibility to complex diseases. Edwards will provide contact with the Masters program in Epidemiology and especially in Genetic Epidemiology, and will be valuable as a consultant on the application of genomics methodology in our translational research projects.

*Maier, Ron V., MD:* Maier will serve on the Steering Committee. Maier is Professor and Vice-Chair of the Department of Surgery, Surgeon-in-Chief at Harborview Medical Center, PI of the Department of Surgery NIH NRSA institutional research training grant, and Director of the University of Washington Trauma Research and Surgical Critical Care Postdoctoral Fellowship Program. Maier will provide input from the Surgery research training programs and coordinate them with the TRTP.

*Slutsky, Arthur S., MD:* Slutsky will be the external consultant for the Translational Research Training Program. Slutsky is Professor of Medicine, Surgery and Biomedical Engineering and Director, Interdepartmental Division of Critical Care Medicine, University of Toronto, and Vice President, Research, St. Michael's Hospital, Toronto, Ontario, Canada. Slutsky will review the annual progress reports generated after the Steering Committee meets for its annual review and will discuss in detail the program's structure and progress with Hudson. Slutsky has agreed to perform an on-site in-depth review of the TRTP in its third year of existence. This visit will include his meeting with the leaders of each program element and meeting with each of the translational research trainees to review their research and their training progress. Slutsky will meet with Hudson and the Steering Committee at the conclusion of his visit to provide his assessment of the program and recommendations for improvement.

*Steinberg, Kenneth P., MD:* Steinberg will participate in the training of clinical trialists. Steinberg is Associate Professor of Medicine, Medical Director for Critical Care Services, Harborview Medical Center, and Investigator, University of Washington site for the NIH ARDS Clinical Trials Network. Steinberg is experienced as a clinical trialist. He will serve as a primary mentor for trainees interested in developing as a clinical trialist and assist Hudson in developing the clinical trialist training component.