

Proposed Training

The two year postdoctoral training program is aimed at physicians (MDs, D/PhDs or DOs) completed clinical training in neurology, neurosurgery, or psychiatry, or individuals with other doctoral degrees who have a genuine interest in translational neuroscience research. It is anticipated that many of the MDs will have little or no research training. Indeed, these are the type of individuals we wish to recruit for research training. Other candidates may have had considerable research experience and will be attracted to our program because of the translational research emphasis. For this reason, the training program is adaptable to individual trainees.

The program is designed to encourage postdoctoral research training of MD, MD/PhD and DO degree holders in an interdisciplinary research environment that includes as mentors both PhD and MD scientists in basic science and clinical departments. The major emphasis of the program will be on laboratory research under the tutelage of a faculty sponsor. We anticipate beginning with a smaller project that is an offshoot of the sponsor's major work (in order for the trainee to acquire the appropriate technical skills) and then quickly encourage the trainee to design and craft his/her own major, original, and independent project. The faculty participating in this training grant all have close clinical ties and are pursuing research that has direct clinical applicability. Prior to initiation of the project, the trainee will present a proposal to the mentors of the T32 training program for approval and suggestions. This second tier of review will provide the trainee with feedback regarding the clinical value of the translational study. It is recognized the term 'translational' is broadly defined and that any type of neuroscience research could be considered translational by some. However, as described in the background section, we will strive to follow the definition of translational research used by the NINDS, i.e. the process of applying ideas, insights, and discoveries generated through basic scientific inquiry to the treatment or prevention of human disease.

As a translational training program we will strive to strengthen the already strong bonds between the basic sciences and clinical disciplines. The participating faculty includes both MDs and PhDs. The strategy of the program will be to combine the strengths of an apprenticeship, i.e. a close affiliation with a faculty member for professional guidance, within the broad academic milieu of a major university with strengths in teaching, clinical care, and research. Regimentation and requirements will be kept to a minimum and we will not permit a firmly directed, laboratory-centered assistantship in which the trainee works mainly at the sponsor's bidding. Trainees will emerge from the program having designed and developed their own, independent niche in translational research. All trainees will be expected to commit to our program for two years. During the second year of the program the trainees will receive guidance in preparing NIH grants and encouraged to apply for independent funding.

All trainees will participate in a weekly graduate level course in neuroscience, the Pathophysiological Basis of Brain Diseases course, which is currently offered bi-weekly to neurology, neurosurgery, and psychiatry residents as well as other postgraduate fellows within the NCD. This year's syllabus is appended in Appendix II. The course, under the direction of Dr. Gregory L. Holmes, consists of a didactic session followed by discussion. Faculty members are chosen from the NCD and provide a list of three key articles or chapters to be read prior to the session, a pre-test, and a post-test. The primary objective of the course is to understand the neurobiology of neurological, neurosurgical, and psychiatric disorders, and is highly interactive, providing the opportunity to review recent advances in the understanding of the pathophysiological basis of brain disorders. Trainees are required to supply a written evaluation for each lecture.

All trainees will be required to take a course in the ethical conduct of research and biostatistics. In addition, depending on the background and goals of the trainee, other courses can be taken during the two year fellowship. Our goal is to have each trainee have a tailored training program based on their individual needs. The individual trainee and their mentor will design the individual curriculum. For example, selected trainees may elect to take courses in advanced biostatistics, computer science, neurobiology, genetics, or neuropharmacology, to name a few.

In addition, the NCD has developed a new neuroscience curriculum in combination with the Program in Experimental and Molecular Medicine (PEMM) which is recruiting PhD and MD/PhD graduate students. PEMM at Dartmouth is a new, translational umbrella program that encompasses five broad disciplines: "Cancer Biology & Molecular Therapeutics", "Molecular Pharmacology, Toxicology & Experimental Therapeutics", "Neuroscience", "Systems Biology", and "Vascular Biology". This new graduate program will train the next generation of scientists and physician-scientists to engage in genomic, proteomic, cellular, and systems biology for the purpose of translating this knowledge into disease treatment and prevention. Depending on the scope of the trainees' research and their course background, these courses will also be available to the trainees. Since it will be 4-6 years since the trainees would have had formal basic neuroscience instruction these neuroscience course options will provide the necessary background.

All trainees will participate in the journal club for postdoctoral neuroscience fellows and will be required to review and critique a research paper at least once a year. In addition, trainees will participate in journal clubs which are typically held in the individual laboratories on a weekly to monthly basis. Our relatively small training program will preserve a tutorial atmosphere and promote a close working relationship among all participants in the program.

An example of activities outside the trainees' laboratory research during a typical week is shown below. Most of the laboratories meet weekly for 1-2 hours to review methodology, work flow and results. Mentors will meet with trainees individually at least weekly, although this typically occurs on a daily basis. The courses and Grand Rounds listed here are examples and will vary from trainee to trainee.

	Monday	Tuesday	Wednesday	Thursday	Friday
8:00 - 9:00	Laboratory Meeting	Psychiatry Grand Rounds		Trainee/Mentor meeting	
9:00 - 10:00	Neuroscience Core Course		Biostatistics Course		Laboratory Journal Club
10:00 - 11:00					
11:00 - 12:00					
12:00 - 1:00	Pathophysiological Basis of Brain Diseases (PBBB) (bi-weekly)	Ethics Course			Neurology/Neurosurgery Grand Rounds
1:00 - 2:00					
2:00 - 3:00					
3:00 - 4:00					
4:00 - 5:00		Postdoctoral Fellow Journal Club (monthly)			

Trainees will be encouraged to attend a minimum of one national meeting and present a poster. While most trainees will likely attend the Society for Neuroscience meeting, attendance at other conferences such as the Gordon Research Conferences, will also be encouraged. In addition, the Neuroscience Center at Dartmouth sponsors an annual Neuroscience Day at Dartmouth which will allow trainees an opportunity to present their research either at oral or poster sessions during the day's events.

To maintain clinical skills, postdoctoral fellows may elect to attend a maximum of one half day outpatient clinic weekly. Trainees will not be permitted to take clinical call during the fellowship program.

Trainee Candidate

Selection of postdoctoral fellows will be primarily based on educational background, recommendations from residency directors and other faculty members, and a personal interview. The training program will emphasize translational research and we will make efforts to attract trainees who have completed clinical training in neurology, neurosurgery, or psychiatry. While it is expected that the trainees will have completed their clinical training, residents wishing to interrupt their clinical training to obtain translational research will be considered.

It is expected that most applicants will have formulated ideas about the type of research they would like to pursue before their interview. However, in cases where the applicants are uncertain as to research direction, we will encourage meeting faculty members from a number of laboratories during their visit. The postdoctoral fellow will be expected to choose a laboratory in which to work three months prior to the start date. This time period will allow the trainee to read key articles related to the laboratory research and register for the necessary course work.

Background

As defined and discussed in the NIH Roadmap, translational research is the process of applying ideas, insights, and information generated through basic scientific inquiry to the modification, cure, or prevention of human disease. The understanding of the etiology, genetics, and pathophysiology of neurological and psychiatric disorders has grown dramatically in the last decade. As our understanding of the biology of neurological and psychiatric disorders continues to grow there are incredible opportunities for developing early biomarkers of disorders and novel disease-specific therapies. Indeed, opportunities for further discovery and progress in the treatment of neuropsychiatric diseases have never been greater. However, from the patient's viewpoint the translation of basic discoveries to effective therapeutics has been agonizingly slow. The challenge now is for basic, applied, and clinical scientists to combine and coordinate their efforts in translating basic discoveries to the bedside.

By uniting investigators from basic and clinical neuroscience, new perspectives and insights can be brought to bear on research findings. To accomplish this, it will require that innovative clinicians join forces with basic neuroscientists with an interest in applying their work to human disease. Neuroscience programs that catalyze the development of partnerships between basic and clinical investigators are in an ideal position to develop neuroscience translational research programs. Just as importantly, such centers also provide an excellent environment for training neuroscientists who wish to acquire skills in translational research.

We have proposed the establishment of a new translational neuroscience postdoctoral training program. It is our strong belief that the Neuroscience Center at Dartmouth (NCD), a comprehensive, highly interactive and inter-departmental program, is in a unique position to develop a new training program in translational research in neuroscience. This proposal has received strong institutional support.

The NCD is composed of a dedicated group of investigators and teachers that have been assembled to pool their talents and provide instruction to pre-doctoral and postdoctoral fellows, and medical school students in the fundamentals of neuroscience. Members of the NCD come from Dartmouth College and Dartmouth Medical School (located on the Hanover campus and Lebanon campus at the Dartmouth-Hitchcock Medical Center). The NCD draws from the strengths in three key areas: clinical, cognitive/behavioral, and molecular/cellular/systems neuroscience. It is the vision of the NCD faculty members to produce and disseminate new knowledge and, in so doing, train and educate the next generation of neuroscientists. By promoting multidisciplinary efforts above basic and applied research, the faculty of the NCD contributes to human health and well-being by increasing our understanding of the mechanisms underlying nervous system function, both in health and disease. This partnership will lead to valuable discoveries that translate into biomarkers of disease progression, novel pharmaceutical agents, and therapeutic approaches for the treatment of a variety of central nervous system diseases and disorders.

Although the development of a neuroscience training program at the NCD is new, it should be recognized that Dartmouth Medical School and Dartmouth College have a long history of training neuroscientists within departments and programs such as the departments of Physiology, Pharmacology, Psychological and Brain Sciences and the Molecular and Cellular Biology Program. The application for a training program through the NCD should, therefore, not be considered as a totally new program, but rather as an extension of highly successful ongoing neuroscience training. The development of an unusually strong and broad neuroscience program at Dartmouth has arisen from the convergence of several favorable factors. It is due in part, of course, simply from the coincidence of recruitment of multiple individuals with interest and experience in neuroscience research. This has been greatly facilitated, however, by the nature of Dartmouth. Unlike many institutions, Dartmouth has a long and effective tradition of cross-disciplinary interactions involving engineering, mathematical, computing, and basic scientists with medicine. It also has one of the leading centers in the world for outcomes research [the Center for the Evaluative Clinical Sciences (CECS), directed by Jack Wennberg} and the Norris Cotton Cancer Center; a National Cancer Institute designated Comprehensive Cancer Center (directed by Mark Israel).

Our training program is designed to capitalize on the special strengths at Dartmouth to have a training program that can accommodate candidates that have backgrounds suitable to specialized translational research in neuroscience over a full range of opportunities that are available, while also being exposed to the full range of concepts and knowledge. We wish to capitalize on the range of potential trainees that are already available at our institution: residents in neurology, neurosurgery, and psychiatry, and postdoctoral researchers who wish to obtain training in translational neuroscience research. We also have a vigorous outreach program to inform potential pools of students about the opportunities at Dartmouth in neuroscience. We are particularly interested in attracting minority applicants to the neuroscience community at Dartmouth. The training program will include both rigorous training in the student's area of specialization and individually-designed curriculum that will provide all students with an introduction to the full range of concepts that are involved in neuroscience at Dartmouth.

The training program will afford trainees the opportunity to investigate a wide variety of topics in neuroscience, with a clear emphasis on translational neuroscience. An enriched learning experience for all is provided by a close scientific collaboration among faculty, a one-to-one ratio between trainees and faculty, active and daily participation by virtually all faculty in the NCD, opportunities for interactions with students and undergraduates, close interaction with clinicians in psychiatry, neurology, and neurosurgery, and the juxtaposition of all physical components of the training program on the Lebanon and Hanover campuses. Our trainees will learn numerous skills in the program including critical thinking, the scientific approach, and numerous technical skills including all the most advanced experimental approaches in neuroscience research and the ethical conduct of research.

The Neuroscience Center at Dartmouth has provided an opportunity to identify and integrate members of the Dartmouth community engaged in neuroscience research across departmental lines. Over 100 faculty members at Dartmouth College, Dartmouth Medical School, the Thayer School of Engineering and Veterans' Affairs Medical Center (White River Jct., VT), identify themselves as neuroscientists and/or as having neuroscience related interests, and are members of the NCD. Faculty members selected as mentors for this T32 application represent 11 different departments, and were chosen for their mentoring skills, collaborative abilities, publication record, diversity of interest and expertise in translational research, and success at obtaining National Institute of Health funding.

The NCD provides a fertile ground for training of postdoctoral fellows and it is for that reason that this center has now requested NIH funding for postdoctoral training for a broadly based interdisciplinary research training program, which, as defined by NINDS, supports the training of: basic neuroscientists who are broadly educated in modern biology; basic scientists who study the mechanisms of disease; and clinical neuroscientists who conduct basic research or study patients and apply advances in basic science to the diagnosis, treatment, and prevention of brain diseases. We will train MD, MD/PhD and DO degree holders in an interdisciplinary research environment that includes as mentors both PhD and MD scientists in basic science and clinical departments.

Program Plan

Program Direction: Gregory Holmes, M.D., the program director, has been involved in the teaching of medical students and postdoctoral fellows since 1979 when he became Assistant Professor of Neurology at the University of Connecticut Health Center. In 1986 he moved to the Medical College of Georgia for two years, during which time he maintained an active clinical and basic neuroscience research program. From 1988 to 2002, he was at Harvard Medical School and Director of the Clinical Neurophysiology Program and, subsequently, Director of the Center for Research in Pediatric Epilepsy. He became Professor of Neurology at Harvard Medical School in 1996. During his tenure at Children's Hospital Boston and Harvard Medical School, he trained many pre-doctoral students and postdoctoral fellows in the area of developmental epilepsy. Currently, he is Chief of Neurology at Dartmouth Medical School, and is in a strong position to guide a translational neuroscience research training program over the next decade.

Dr. Holmes has been mentor to 30 clinical fellows and 24 basic neuroscience postdoctoral fellows. He has been involved in neuroscience teaching at the pre-doctoral level to medical students at Harvard Medical School and Dartmouth Medical School. Dr. Holmes has a very extensive bibliography with 238 peer-reviewed papers in journals such as Journal of Neuroscience, Journal of Comparative Neurology, Neurology, Nature, Nature Neuroscience, New England Journal of Medicine, and Annals of Neurology, and multiple books, book chapters, review articles, and abstracts. He has received extensive NIH funding and currently is PI on two NIH grants and co-PI one other. He also has funding from the Tuberous Sclerosis Alliance and multiple pharmaceutical companies. His laboratory is heavily involved in translational research, studying the cognitive effects of seizures in the developing brain. Dr. Holmes and his staff has extensive experience in using behavioral measures and *in vivo* and *in vitro* electrophysiological techniques. He has been widely recognized for his research efforts and has received many awards including the Sidney Farber Research Award from the United Cerebral Palsy Association, Inc, the Michael Prize awarded by Stiftung Michael, Bonn, Germany, the American Epilepsy Society Basic Scientist Award, and the Pierre Gloor Award for outstanding achievements in research from the American Clinical Neurophysiology Society. He has lectured widely on both clinical and basic topics and is known for his ability to integrate basic science with clinical issues.

Dr. Holmes has been on many editorial boards including the Annals of Neurology, Electroencephalography and Clinical Neurophysiology, Epilepsy Research, Brain & Development, Epilepsy & Behavior, Pediatric Neurology, Clinical Neurophysiology, and Journal of Child Neurology. He has served on the executive committees of the Child Neurology Society, American EEG Society, American Epilepsy Society, and is president-elect of the American Epilepsy Society (2005-2006). He currently is a permanent member of the CND1 study section of NINDS and has previously served on a number of other NIH study sections. He was a co-organizer of a recent highly successful NIH workshop on animal models for epileptogenesis and refractory epilepsy and the organizer of a Tuberous Sclerosis Alliance workshop on the pathophysiology of epilepsy in tuberous sclerosis.

The translational aspects of his research, his leadership role in a clinical section, his close ties with both basic and clinical neuroscientists, and his mentoring skills makes him an ideal person to direct this translational neuroscience research training program.

Program Co-Director: Joyce DeLeo, PhD has mentored numerous undergraduate students, graduate students, post-doctoral fellows, and residents over the last 17 years while at Dartmouth Medical School. Following two post-doctoral fellowships, Dr. DeLeo was promoted to Assistant Professor of Anesthesiology and Pharmacology in 1991. She was recently promoted to Full Professor in 2003. Dr. DeLeo was appointed as the first Director of the Neuroscience Center at Dartmouth in 2002 by the Dean of Dartmouth Medical School and the Provost of Dartmouth College. She also is the Vice-Chair of Pharmacology and Toxicology, the Molecular Biology and Cytokine Core Director of the Center of Biomedical Research Excellence (COBRE) Immune Mechanisms Controlling Inflammation and Cancer grant, and Co-course Director of Dartmouth Medical School Year II Medical Pharmacology course.

Dr. DeLeo has been the recipient of numerous awards including a Fulbright Scholarship to conduct PhD research in the Department of Neuromorphology, Max Planck Institute for Psychiatry, Martinsried, West Germany under the direction of Dr. Peter Schubert and Dr. Georg Kreuzberg, Young Investigator Award, American Pain Society, Sofamer-Danek Award for Best Basic Science Oral Presentation, "The Role of Cytokines in Chronic Pain", International Society for the Study of the Lumbar Spine; Elected to Alpha Omega Alpha Medical Society; Dartmouth Medical School; Member of the 2001-2002 class of Fellows in the Hedwig van Ameringen Executive Leadership in Academic Medicine (ELAM) Program; Sofamer-Danek Award for Best Basic Science Oral Presentation, "An in vivo approach to characterizing local biomechanics in a radiculopathy model," International Society for the Study of the Lumbar Spine.

Dr. DeLeo is actively involved in teaching at all educational levels from junior high student community teaching of the neurobiology of addiction to undergraduate, graduate, medical student, resident and faculty teaching on topics of neuroscience and pain. She served as the Chair of a vertical integration group to bring a curriculum on pain physiology and management to all four years of medical school training at Dartmouth. Her research is very translational with the ultimate goal to develop novel targets for the treatment and prevention of chronic pain. The neuroimmunology of chronic pain laboratory team has extensive experience in *in vivo*, *in vitro* and *ex vitro* methods including: behavioral pharmacology, animal model development of chronic pain, gene array analyses, assessment of genes/mRNA using real time Reverse Transcription- Polymerase Chain Reaction (PCR), RNase Protection assays, and conventional PCR, ELISAs, immunohistochemistry, Western and Northern blot analyses, Fluorescent Activated Cell sorting (FACs), and glial cell cultures.

Dr. DeLeo served on the NIH Somatosensory Chemosensory Systems study section for 5 years and has been an *ad hoc* reviewer for numerous other NIH and VA study section and special emphasis panels. She is an associate editor for the journals Spine and Pain and regularly reviews for Journal of Neuroscience, Proceedings of the National Academy of Science, Journal of Neurochemistry, Neuroscience, Brain Research, Life Sciences, Physiology and Behavior, Journal of Neuroscience Methods, Pain, Journal of Pain, Journal of Orthopaedic Research, Journal of Pharmacology and Experimental Therapeutics, Experimental Neurology, Journal of Comparative Neurology, British Journal of Pharmacology, and Annals of Neurology.

The translational aspects of her research, her ability to mentor basic scientists and clinicians, her enthusiasm for neuroscience, her administrative skills in leadership roles, and her close relationships with Dr. Holmes and her directorship of the NCD make Dr. DeLeo an excellent Co-Director for this training program.

Program Administration: Dr. Holmes and DeLeo, as program Director and Co-Director, have ultimate responsibility for the scientific leadership and administrative execution of this training program. In administering the Translational Neuroscience Postdoctoral Training Program, Drs. Holmes and DeLeo will have assistance from Barbara Atherton, Manager of the Neuroscience Center at Dartmouth. Ms. Atherton benefits from many years of experience with federal research and training grants. She will be responsible for oversight of the administrative matters involving the training grant's budget, account reporting, and records management. She will assist with trainee recruitment, and is the primary liaison with the Office of Sponsored Research.

The breadth of expertise of the NCD is quite extensive and involves participation from eighteen departments, including the departments of Psychiatry, Medicine (the Section of Neurology), Surgery (the section of Neurosurgery), Anesthesiology, Pharmacology, Psychology, Pathology, Physiology, Biochemistry, Genetics, Psychological and Brain Sciences, and Radiology. The membership and environment provides an exciting, interactive atmosphere that fosters the exchange of ideas and approaches, cultivates collaborations, enhances research activities, and promotes bi-directional translational research opportunities for both basic science and clinical faculty. For a trainee, our educational environment is ideal.

The listing below provides representative areas of research strengths within the NCD.

Neuroscience Center at Dartmouth ~ Representative Areas of Research

<u>Clinical Neuroscience</u>	<u>Cognitive & Behavioral Neuroscience</u>	<u>Molecular/Cellular/ Systems Neuroscience</u>
Multiple Sclerosis	Behavior and Mental Illness	Neuroimmunology
Neuroimmunology	Cognitive Development	Neurogenesis
Behavioral Neurology	Hemispheric Specialization	Mechanisms of Neurodegeneration
Psychopharmacology	Social Cognition and Brain Science	Ion Channels: Structure, Development and Disease
Neuro-oncology	Learning and Action	Electrophysiology of Learning and Memory
Psycho-oncology	Functional Localization and Brain Mapping	Neurobiology of Learning and Memory
Neuroimaging	Language Development	Epileptogenesis
Pain Management	Multisensory Integration	Neural Control of Breathing

All mentors variously assume responsibility for one or more aspects of the program such as the recruitment and interviewing of postdoctoral fellows, participating in didactic sessions, research seminars, and career guidance. While trainees will pick a laboratory for research concentration, trainees will be invited to visit and learn techniques in the laboratories of participating faculty. When visiting scientists are invited to speak in the NCD, one of the faculty members of the training program, along with the trainee, will organize and host the event. All trainees will be encouraged to meet individually with the visiting scientists.

In addition to the daily interactions among faculty and trainees, the faculty and trainees will meet quarterly (or more frequently as needed) to discuss all aspects of the training program. In addition, the faculty will meet separately to discuss evaluations of the trainees, to enable the director and co-director to obtain continuing advice with respect to the operation of the program. If problems arise in the program, such as poor performance of trainees or mentors, the NCD Advisory Board will discuss the problem and decide on a course of action.

Dr. Holmes and DeLeo will solicit advice and suggestions from trainees on a yearly basis, conduct exit interviews with all trainees, and solicit advice from former trainees on how they would improve the training program. However, it should be noted that because of interactive nature of the program there is usually weekly, or even daily, contact with the trainees. We will also elicit the help of prior trainees in recruiting new applicants.

Program Faculty

Faculty members representing the faculty at Dartmouth College and Dartmouth Medical School will serve as mentors for this T32 application. As noted in the background, all faculty members were chosen for their mentoring skills, collaborative abilities, publication record, interest in translational research, and success at obtaining National Institute of Health funding. In addition to their close ties with the NCD the core faculty members are knowledgeable about training opportunities within their primary departments, and have established interactions among colleagues who are noted in their fields of expertise and can enhance the training experience.

Gregory L. Holmes, MD (Professor of Medicine [Neurology] and Pediatrics and Chair, Section of Neurology)

The research focus of the Holmes laboratory is on the pathophysiological basis of epilepsy, how seizures affect brain development and the development of neuroprotective agents that can be used to treat epilepsy patients. Approximately 2.1 million people in the United States have active epilepsy; nearly 9 million will have epilepsy at some point during their lifetime and approximately one in 11 will have at least one seizure. The consequences of epilepsy are many, including a substantial risk for cognitive impairment, particularly if seizures occur during early childhood. The Holmes laboratory has investigated the biological basis of this seizure-induced cognitive impairment. The laboratory uses a variety of *in vivo*

animal models including flurothyl inhalation, kindling, and status epilepticus induced by lithium-pilocarpine, kainic acid, and bicuculline. Using these models, the investigators have found that seizures in young animals result in a number of morphological and physiological alterations including mossy fiber sprouting, decreases in dendritic spines and neurogenesis, and altered synaptic responses. The cognitive effects of seizures in rodents are assessed with a number of behavioral studies including the water maze and radial-eight arm maze. To study the electrophysiological bases of these morphological and behavioral changes, the laboratory utilizes *in vivo* and *in vitro* techniques including hippocampal slices, the intact hippocampal preparation, and place cell recordings in freely running animals. There are also a number of ongoing studies looking at novel therapeutic interventions to prevent these seizure-induced changes. Goals of the laboratory are to find surrogate markers for cognitive impairment and epileptogenesis and develop strategies to prevent seizure-induced brain damage in children.

Trainees in the Holmes laboratory will receive excellent training in the design and implementation of experiments closely related to the human condition of epilepsy. Following acquisition of basic skills in neurobehavioral testing and electrophysiology the trainee will work independently on a project of their choice.

Joyce A. DeLeo, PhD (Professor of Pharmacology and Anesthesiology)

The mission of the DeLeo laboratory is to understand central nervous system (CNS) mechanisms that lead to chronic pain and to build a scientific foundation for developing new approaches in the treatment, and even prevention, of chronic pain syndromes. Neuropathic and radicular pain (pain caused by nerve or root injury) is prevalent, persistent, and debilitating. There is no effective treatment for chronic pain syndromes that afflict an estimated 8 million patients including patients with diabetes, the elderly, and young people who experience trauma. Chronic pain is often refractory to standard treatments such as opioids, non-opioid analgesics, and surgical interventions. Research performed by the laboratory has provided substantial data to support the role of CNS cytokines, chemokines and other immune mediators in chronic pain using neuropathic and radicular pain animal models developed by the group at Dartmouth. They began by characterizing spinal protein expression of cytokines in nerve injury and in acute inflammatory animal models. Separate studies then addressed the question of the origin of these spinal cytokines using *in situ* hybridization, axonal transport blockade, radiation bone marrow chimeric rats and peripheral macrophage depletion. Additionally, specific pharmacological tools have been used to test the therapeutic potential of cytokine/immune/glial manipulations as treatments to alter sensory processing. Recognizing that no single class of molecules work in isolation to produce or propagate chronic pain, current studies address the unifying hypothesis that chronic pain following peripheral nerve injury is maintained by central neuroimmune/neuroinflammatory and neuroprotective autoimmunity mechanisms. The entire DeLeo Neuroimmunology of Chronic Pain Laboratory, consisting of students, post-doctoral fellows, research and administrative assistants, meets weekly to discuss data and relevant literature.

These studies outlined provide opportunities for training in molecular/cellular and systems behavioral neuroscience with the ultimate goal to translate the preclinical data into the development of novel targets for the treatment and prevention of chronic pain. The laboratory works closely with clinicians and pharmaceutical companies to realize this goal and thus, the potential for high impact results to improve the quality of patient care is clearly evident.

Ann-Christine Duhaime, MD (Professor of Surgery [Neurosurgery])

Approximately 2 million head injuries occur each year in the United States, producing a brain injury rate of 175 to 200 per 100,000 population and causing as many as 56,000 deaths per year. The economic and emotional toll of this public health burden is staggering. The outcome is even more devastating when the trauma occurs in children. Traumatic brain injuries are a leading cause of morbidity, mortality, and disability in children. Dr. Duhaime is a pediatric neurosurgeon who has an active clinical program in Children's Hospital at Dartmouth. Dr. Duhaime has started the pediatric neuroscience program at Dartmouth, a multidisciplinary clinical and research program. Her laboratory is focusing on age-related differences in brain recovery following head trauma. Her laboratory has developed a highly reproducible cortical contusion model scaled for brain growth during maturation in Yorkshire piglets. Using serial magnetic resonance imaging studies in piglets of different ages, her group has found that despite comparable injury inputs, the youngest animals had lesions whose volumes peaked earlier and resolved more quickly than those in older animals. The intermediate-age piglets (toddler) had the most pronounced swelling of any age group, and the oldest piglets (adolescent) had the latest peak in lesion volume. This model is being developed further using functional MRI and neurophysiological studies. Dr. Duhaime collaborates with a number of individuals within the NCD including Dr. Holmes and Saykin. The laboratory goal is to mimic head trauma in children, study the mechanisms of recovery and discover novel therapeutics to prevent the sequelae of head trauma.

Trainees working in the Duhaime laboratory will be exposed to animal models of head trauma, functional MRI, electrophysiological techniques, and immunohistochemistry techniques. A major strength of the laboratory is the high degree of interaction with other investigators within NCD.

Alan I. Green, MD (The Raymond Sobel Professor of Psychiatry and Chair of the Department of Psychiatry)

Dr. Green's research group, the Psychopharmacology Research Group within the Department of Psychiatry, focuses on psychotic disorders, primarily schizophrenia and schizoaffective disorder, and the relationship of these disorders to co-morbid substance use disorder. The work of his group over many years has characterized the biochemical mechanisms of action of typical and atypical antipsychotic medications and the potential use of the atypical antipsychotic agents (particularly clozapine) early in the course of schizophrenia to improve the long-term outcome of patients. The focus on co-morbid substance use disorder is based on the common occurrence of substance abuse in schizophrenia and other psychotic disorders, its negative effect on the outcome of these patients, and on the ability of clozapine (unique among the antipsychotics) to decrease alcohol/substance use in these patients. Clozapine's noradrenergic actions (its potent antagonism of norepinephrine alpha 2 adrenergic receptors and its ability to dramatically elevate norepinephrine in the plasma and the cerebrospinal fluid) have been a particular area of study. Three of Dr. Green's on-going NIH-supported studies are characterizing the role of clozapine in patients with comorbid substance use disorder, including those within the first episode of schizophrenia. Dr. Green has proposed that dysfunction of dopamine mediated mesocorticolimbic brain reward circuits in patients with schizophrenia underlie the substance abuse in this population, and that clozapine ameliorates this reward circuit dysfunction and thereby limits substance abuse. One of these NIH studies seeks to further study this issue by characterizing reward circuit functioning with functional magnetic resonance imaging both before and after treatment with clozapine. In addition, NIH-funded studies in alcohol-preferring rodents are also underway to fully elucidate the mechanism behind the group's finding that clozapine also decreases alcohol drinking in these animals. And lastly, the group is also studying alcohol drinking in adult rats who have undergone a ventral hippocampal lesion as neonates (NVHL rats). NVHL rats are proposed as an animal model of schizophrenia; Dr. Green's group is also assessing whether the NVHL rat will also be useful as an animal model of schizophrenia and substance use disorder.

Rich and diverse training opportunities are available within the clinical trials, the neuroimaging/brain reward studies, and the animal studies for predoctoral and postdoctoral trainees. Dr. Green and members of his group collaborate extensively with members of the Department of Psychiatry Brain Imaging Laboratory and with members of the Department of Pharmacology and Toxicology.

Leslie P. Henderson, PhD (Professor of Physiology and Biochemistry)

Anabolic-androgenic steroids (AAS) are synthetic derivatives of testosterone originally designed for therapeutic uses to provide enhanced anabolic potency with negligible androgenic effects. Although AAS continue to be used clinically today, the medical benefits of low therapeutic doses of AAS stand in sharp contrast to the potential health risks associated with the excessive doses self-administered not only by elite athletes and body builders, but by a growing number of recreational users, including adolescent boys and girls. The deleterious effects of AAS on peripheral organs and the incidence of altered behaviors, such as aggression and sexual behavior, in AAS abusers are now well documented. The long term goals of the Henderson laboratory are to understand how steroids alter the expression and function of ion channel proteins involved in synaptic signaling. Recent studies are focused on determining how anabolic AAS act in the mammalian brain to regulate the expression and function of γ -aminobutyric acid type A (GABA_A) neurotransmitter receptors. Neural transmission mediated by forebrain GABA_A receptors plays a pivotal role in the expression of aggression and sexual behaviors, and changes in forebrain GABAergic transmission may contribute to the AAS-induced changes in these behaviors. The GABA_A receptor is a major target of a wide range of endogenous and exogenous psychoactive drugs. Recently, the laboratory discovered that commonly abused AAS can induce rapid and reversible allosteric modulation of GABA_A receptor-mediated currents in the mammalian forebrain, that is dependent upon subunit composition of the receptor. The laboratory has also determined that chronic exposure to AAS in a regime that mimics human abuse of these illicit steroids alters GABA_A receptor subunit expression and synaptic responses in the forebrain, but that these changes are greater in adolescents than in adults and greater in female than in male subjects. These data are particularly timely as recent reports that the most significant increases in AAS use are in adolescents, especially young girls, and that adolescents may be particularly vulnerable to the deleterious effects of AAS. Current studies are therefore also directed towards understanding the signaling mechanisms that underlie the changes in the forebrain GABAergic system in chronic AAS abuse. The laboratory has a long-standing collaboration with Dr. Ann Clark in the Department of Psychology and Brain Science integrating experiments on how AAS modulation of synaptic transmission is reflected in changes in aggression and sexual behaviors. The Henderson laboratory has also maintained a long-standing interaction and collaboration with Dr. Robert Maue's lab, and joint lab meetings are held weekly. Three MD/PhD students have completed their thesis work in this laboratory, one of the current postdocs is a Neurology fellow from University of Sao Paulo, and the laboratory participates in summer research opportunities for DMS medical students.

Mark A. Israel, MD (Professor of Pediatrics and Genetics and Director of the Norris Cotton Cancer Center)

Primary malignant tumors of the central nervous system account for about 16% of all childhood malignancies. These tumors are the second most common type of childhood cancer and the most frequent of the solid tumors. The Israel lab studies the differentiation of nervous system precursor cells and the disordered regulation of proliferation and differentiation that characterizes tumors arising in the brain. All tumors, including brain tumors, are invariably characterized by inappropriate growth and a lack of mature cellular characteristics which are typical of cells found in the brain. The regulation of cellular differentiation within the nervous system is therefore critical for understanding the pathogenesis of brain tumors. Towards this end the laboratory studies the role of Id gene family members in regulating the maturation of neural stem cells and proliferating cells of the developing nervous system. The Israel laboratory is interested in understanding which of the different growth regulatory pathways expressed in normal nervous system precursor cells are important for the pathogenesis of tumors, and how it is that tumor cell proliferation becomes unresponsive to regulatory mechanisms that normally inhibit proliferation. Towards that end the laboratory is seeking to identify and characterize both the regulatory signals and the pathways over which such signals are mediated in normal cells of the central nervous system and in malignant brain tumors. These studies provide opportunities for training in molecular neuroscience and neuro-oncology, molecular biology, cell biology, and biochemistry. The experimental strategies and technologies they employ are translatable to many fields, and a key goal of the laboratory is to translate our scientific progress into improved patient care, especially the care of patients with brain tumors.

Trainees in the Israel laboratory would have exposure to cutting-edge technology in molecular genetics and animal modeling of human tumors necessary to study the biology of brain tumors. The research laboratory is based in the laboratories of the Norris Cotton Cancer Center; an NCI designated comprehensive Cancer Center. For the trainee interested in cellular differentiation and growth the laboratory offers an incredibly rich educational experience.

James C. Leiter, MD (Professor of Physiology and Medicine)

Respiratory abnormalities based on central nervous system pathology are common, and unfortunately often fatal. Mechanisms responsible for disorders such as Sudden Infant Death Syndrome (SIDS) and Sudden Unexplained Death in Epilepsy (SUDEP) remain unclear. The laboratory of Dr. Leiter is interested in the neurophysiology of respiratory control. Recent proposed studies and interests include, examining the mechanisms whereby seizures may contribute to sudden, unexplained death in epilepsy, and the interactions between astrocytes and neurons in chemosensory areas of the brainstem. His laboratory conducts studies elucidating the nature of brainstem abnormalities underlying the Sudden Infant Death Syndrome and is interested in respiratory control of the upper airway during wakefulness and sleep. Drs. Leiter and Holmes are currently conducting a joint research project examining respiratory function during seizures in the hope of gaining insight into the mechanisms responsible for SUDEP. In addition, studies on the ontogeny and cellular basis of carbon dioxide sensitivity in the central nervous system are underway in his lab. Additional interests include comparative neurophysiology and adaptations to hypoxia. The laboratory uses a variety of innovative neurophysiological techniques including use of an in situ perfused preparation of the decerbrate rat to assess neurological control of respiration.

As a result of the interests of a recent trainee (Kendall Lee), studies of the mechanism of action of deep brain stimulation in Parkinson's disease and epilepsy are currently underway. This is a new area for Dr. Leiter, but a translational research topic that may be particularly fruitful for future research and for future training opportunities. For example, Dr. Lee is an MD/PhD in the Neurosurgery training program and this topic is ideally suited to his clinical and research interests.

A major advantage of this laboratory for trainees in translational neuroscience research is the close collaboration of basic neuroscientists and clinicians in the investigation of disorders of respiratory control.

Dean R. Madden, PhD (Associate Professor of Biochemistry and Genetics)

The goal of the Madden laboratory is to understand the function and regulation of transmembrane ion channels in terms of their molecular structures. The focus is on the glutamate receptor ion channel family (iGluR). Glutamate receptors are essential for excitatory synaptic signalling in the brain and for the synaptic plasticity that is thought to underpin learning and memory. These receptors are implicated in a variety of neuropathologies, including stroke, epilepsy and brain cancer. A major problem in the design of iGluR-specific therapeutics has been difficulty in selectively targeting subsets of these widely distributed molecules. This research has helped to elucidate the molecular assembly and mechanisms of these channels. Electron microscopic studies are now underway to dissect the detailed molecular architecture of the iGluR, in order to better understand how their components interact to produce regulated transmembrane ion fluxes. In particular, the laboratory is focusing attention on the structure of the transmembrane pore domain, which provides an attractive target for treatment of glioblastoma. Existing homology models of the domain have been shown to be incomplete, and Electron Microscopy analysis provides the only current structural information on this key functional site. Complementing

these basic studies, efforts are being initiated to screen for compounds that selectively target disease-associated structures. A second effort is aimed at determining the atomic resolution structure of subunit-subunit interactions within the glutamate receptors, which may provide regulatory targets for modulatory compounds with greater subunit selectivity than those currently available.

Dr. Madden's primary expertise is in the application of biophysical techniques to study the molecular basis of physiological processes. The techniques and approach are thus highly complementary to those of other participating faculty. Equipment and expertise in the lab include X-ray crystallography, electron microscopy, isothermal titration calorimetry, surface plasmon resonance, and stopped-flow fluorescence techniques. The projects provide a foundation for translational efforts aimed at the identification and design of lead compounds for treatment of various iGluR-associated neuropathologies that are the research focus of other groups in the program.

Robert A. Maue, PhD (Professor of Physiology and Biochemistry)

Sodium (Na^+) channels play a major role in signalling in the mammalian brain, and abnormal Na^+ channel function and expression have been implicated in a number of neurological disorders, including multiple sclerosis, chronic pain, and epilepsy. The Maue lab is interested in the regulation of neuronal excitability and growth during normal and abnormal development of the brain. They have focused on identifying mechanisms that govern the expression of voltage-gated Na^+ channels, key proteins in the generation and propagation of action potentials. Although the members of the Na^+ channel gene family exhibit temporal, spatial, and region-specific differences in their expression in the brain, the mechanisms underlying these differences and the functional consequences arising from them are unknown. As an approach to this, the Maue laboratory has recently been examining the impact of "misplaced" Na^+ channel isoform expression on neuronal hyperexcitability. In parallel studies they are investigating neuronal function in Niemann Pick Type C (NPC) disease, a fatal genetic disorder affecting young children that is associated with progressive neurodegeneration and seizures. In both lines of research, the laboratory has recently focused on cerebellar Purkinje neurons, due to their experimental advantages and well-characterized development, as well as their preferential loss during NPC disease. Purkinje cell function is measured in primary cultures, cerebellar slice preparations, and in vivo, taking advantage of mouse models of NPC disease and a variety of transgenic and "knockout" mice, including novel mouse models they have developed. In addition, the laboratory utilizes the ability to acutely modify gene expression via viral-mediated gene delivery. For analyses of gene expression Northern blots, RNase protection assays, real-time, quantitative RT-PCR, and single-cell RT-PCR are utilized, and analyses at the level of protein expression include immunocytochemistry, Western blotting, and viral-mediated expression of epitope-tagged proteins in vitro and in vivo. Functional analyses include patch clamp recording of electrical activity and ion channel function, as well as behavioral measures of motor coordination, ataxia, and gait.

In their recent work the investigators have found that factors crucial for nervous system development, such as brain-derived neurotrophic factor (BDNF), appear to play an important role in both Na^+ channel gene regulation and NPC disease. In particular, identification of biochemical signaling pathways by which these factors induce Na^+ channel gene expression have been identified, and they are determining their relative importance to Purkinje neuron development and eventual electrical properties in vivo, as well as to the deficits in growth and Na^+ channel function they have uncovered in the Purkinje neurons of NPC mice. Investigation of the potential of adenoviral-mediated gene expression to overcome the in vitro and in vivo deficits in Purkinje cell growth and excitability they have discovered in NPC disease are underway. Overall, the results will provide insight to the mechanisms underlying normal and abnormal neuronal development in the brain.

Trainees in the Maue laboratory will have the opportunity to use behavioral, electrophysiological, biochemical, and molecular biological techniques to analyze animal models of human neurological disorders associated with abnormal electrical activity, development, and neurodegeneration. In doing so, they will acquire valuable experience with disease-oriented research in a laboratory group that typically includes a mixture of clinicians, basic scientists, and clinician/scientists. As such, the laboratory provides an outstanding training opportunity and intellectual environment for translational research, as well as an excellent platform for establishing independent research programs relevant to neurological disorders such as Alzheimer's disease, multiple sclerosis, chronic pain, autism, ataxia, and epilepsy.

Thomas W. McAllister, MD (Professor of Psychiatry and Director of the Section of Neuropsychiatry)

Memory deficits represent a major problem to patients following head trauma. Understanding the neural circuitry and neurochemistry of memory is an important first step in developing therapeutic agents that can reduce or eliminate these problems. The McAllister laboratory has found that catecholamines play a central role in the activation and regulation of working memory and thus lays a framework in which to consider the use of catecholaminergic agents (dopaminergic and alpha-2 adrenergic agonists) in the treatment of specific cognitive deficits after traumatic brain injury. The investigators combine methods of cognitive neuroscience, functional brain imaging and neuropharmacology in their study of working memory deficits.

Training opportunities involve the use of functional MRI and psychopharmacological probes to understand the mechanisms underlying cognitive deficits following neurotrauma. In addition to being a member of the Neuroscience Center at Dartmouth, he is part of the multi-disciplinary Brain Imaging Lab and group of investigators in the department of Psychiatry.

Jeffrey S. Taube, PhD. (Professor of Psychological and Brain Sciences)

Learning and memory are affected in a variety of brain disorders. Understanding the neurobiological mechanisms underlying learning and memory is essential as we begin treating disorders such as Alzheimer's Disease. Dr. Taube's research interests are centered around two main themes: understanding 1) the biological basis of spatial cognition and 2) the neurobiological mechanisms underlying learning and memory.

One cognitive function often taken for granted is the knowledge of where we are in our environment. Many investigators believe that we maintain a mental representation (or cognitive map) of our environment and that we depend on this representation to navigate our environment. How is this spatial information organized and processed in the brain? To pursue these questions, Taube's laboratory is using electrophysiological recording techniques to record from neurons in freely-moving, behaving rats. His previous work identified a population of cells in the rat hippocampal formation that discharged as a function of the animal's head direction in the horizontal plane, independent of its behavior and location in the environment. For example, a particular neuron would discharge only when the animal's head pointed northeast, while another neuron might discharge whenever the animal pointed its head south. Current research is designed to determine how the head direction signal is derived and processed from known sensory inputs. The question asked is: how is primary sensory information transformed into a signal which represents the animal's directional orientation with respect to its environment? A second aim of their research is to determine the functional significance of the head direction cell signal to the organism; that is, how does an animal use these cells for orientation and navigation? In order to analyze the discharge characteristics of spatial cells using quantitative methods, an automated video/computer system is used to monitor neuronal discharge while simultaneously tracking the location and directional orientation of the animal.

In addition to these studies, the laboratory is also studying the properties of cells in the hippocampus whose primary behavioral correlates are often location-specific (i.e., hippocampal neurons discharge as a function of the rat's location in the environment and are mainly independent of the animal's head direction). His laboratory is also conducting experiments that investigate how the vestibular system interacts with the spatial processing system in the hippocampus. Finally, the nature of the head direction signal makes it very conducive for modeling and future studies will use neural networks to try and simulate how neurons encode such a signal given the known sensory inputs. Trainees in the Taube laboratory will learn electrophysiological techniques that have also been applied to humans. For example, it is known that human, like rodents have location-specific cells and that these cells may fire abnormally in pathological states. Understanding the processes responsible for normal firing of these cells is important in understanding how visual-spatial memory is encoded in humans. They will also be testing the effectiveness of a vestibular prosthesis for restoring spatial orientation functions in a rodent model.