UNIVERSITY OF CALIFORNIA SAN FRANCISCO,

ONE-YEAR PACCTR APPLICATION

APPLICATION INSTRUCTIONS

Application Checklist. We must receive the application form electronically by 5:00 pm on JANUARY 15, 2009 in order for your application to be considered; we will acknowledge receipt of all electronic documents by email to you. In addition, we must receive your transcripts, mentor endorsement and letters of recommendation, by mail to the address above. (*Please note that Non-UCSF medical students APPLYING FOR THE ONE-YEAR FELLOWSHIP should apply through the Doris Duke foundation AND also complete this application form.)

- Personal Statement (should not exceed 700 words, or approximately one single-spaced page)
- Research Plan Title* (should not exceed 255 characters, including spaces)
- Research Plan Summary* (should not exceed 250 words, or approximately 1/3 of a single spaced page)
- Research Plan* (which is limited to 2,100 words or less or approx. three single-spaced pages. The plan should be divided into three sections: a) Research question, b) Background, and c) Study design) (You should work closely with your mentor on writing the research plan)
- Research Plan Citations* (should not exceed 700 words, or approximately one single-spaced page)
- Transcripts (professional school transcripts only, do not include undergrad transcripts)
- Dean’s Letter (The Dean should comment on your potential for scholarly achievement, elaborating, where appropriate, on such matter as scientific knowledge, performance as a student in independent study or in research-participation programs and ability to make sound judgments. In addition, the dean may describe pertinent personal characteristics such as perseverance, persistence in the face of obstacles, creativity, independence and motivation)
- Two letters of reference from persons (other than the mentor or co-mentor on this application or Dean) who are familiar with the applicant’s talents and abilities and could comment on the applicant’s promise and potential
- Mentor choice(s) (does not have to be from list provided on PACCTR Web-site)
- Mentor’s endorsement (and co-mentor’s if applicable, see below for details)

In addition to the application form below, the applicant is responsible for

- Providing the mentor, co-mentor (if applicable), dean and references with the information necessary for them to submit the required letters and other information. It is the
applicant’s responsibility to make sure that the mentor (co-mentor, if applicable), Dean and references have provided all required information by the application deadline.

- Obtaining academic transcripts: (please provide, professional school transcripts, undergraduate transcripts are not requested. Have transcripts mailed directly to address above.

- A mentor’s endorsement is required from the prospective mentor stating that he or she has read the proposal and is willing to supervise the research described if the project is selected for funding. This should include information on the mentor’s plans for training the applicant, training experience, grant support, a brief curriculum vitae, and an evaluation of the applicant. A copy of human or animal research approvals must also be submitted if necessary for the proposed research.
(1) Personal Statement: (should not exceed 700 words, or approximately one single-spaced page)

Imagine being an expecting parent and hearing the frightening news that your unborn child will have congenital heart disease (CHD). From my experience in the neonatal intensive care unit, I have found that the most daunting issue for parents in this situation is the uncertainty of the consequences of their baby’s condition. Now imagine being able to offer these parents a simple visual aid, much like a growth chart seen at well-baby check-ups, which could roughly predict their newborn’s future cognitive abilities based on a simple assessment of his brain volume. Although not a panacea, this knowledge could relieve much of the stress of uncertainty and allow parents to financially, medically, and mentally prepare for their child’s future. The latter part of this theoretical scenario can become a reality through the future research that I plan to conduct as a Doris Duke Clinical Research Fellow.

My past research projects have all been smaller parts of a larger medical jigsaw puzzle. During my summers as an undergraduate, I worked on basic laboratory research exploring the mechanisms of neuronal regeneration in mouse, rat, and monkey models. Huddled in a cold jail-cell of a room with no windows, it was hard for me to make the connection between the ELISA that I was running and the stroke patients that my work was supposedly going to help. My early research provided just enough pieces to fill in a single corner of the medical puzzle, but I still had no idea what the final picture would be.

When I arrived in medical school, I wanted to expand beyond the bench and work on finishing a puzzle rather than starting one; so, I joined a team of clinical researchers. Since the beginning of my first year, I have been going to families’ houses and sticking their arms with needles, prodding their noses with Q-tips, and swabbing their mouths with saltlicks to detect *Bordetella pertussis*. My goal is to work out the details – fill in the edges of the puzzle – of transmission and detection of this meddlesome bug. I love research in the clinical setting; obtaining data from patients is a very dynamic process, especially when the patient is 15 months old and is more likely to bite you than offer their antecubetals. I am also pleased that my preliminary conclusions have already helped to influence public policy on vaccinations in Massachusetts as well as the Dominican Republic and I hope the developing manuscripts will build on these successes. However, there has not been any revolutionary discovery; I started this research having already glanced at the picture on the front of the box to get an idea of what the puzzle is supposed to look like.

Half way into the second year of clinical research and medical school, I wanted to bridge the bench with the field and explore other realms of pediatrics by conducting translational research. After 6 exhaustive months of searching for promising projects, I finally met the perfect match; Dr. Patrick McQuillen, an intensive care pediatrician who heads a lab at UCSF, offered me the chance to explore the relationship...
between brain volume and neurodevelopmental outcomes in newborns with CHD. The rich research environment will expose me to all aspects of clinical research including human subjects protection, informed consent, data collection, storage, analysis and publication. And, I will have the opportunity and challenge of learning the complicated method of deformation morphometry, which could hopefully be used as the tool to provide parents – like the one’s mentioned earlier – the prognostic information they and their doctors need about their newborn with CHD. Through this project, I won’t be just laying the building blocks or putting on the finishing touches; rather, I will be inserting the missing piece between basic science and clinical principles to unify the seemingly disparate parts of the CHD puzzle into one cohesive and medically applicable unit.

In addition to filling in the gap between the basic and clinical science, this project will serve as a perfect stepping stone towards my career in pediatric research. Gaining the valuable experience of conducting a full-time project from start to finish will provide the foundation necessary to lead my own projects as I evolve into a clinician-scientist during residency and fellowship.

Additionally, I will be able to use clinical research as a conduit for addressing pressing issues in pediatrics that are of particular interest to me including health system reform and international medicine. For example, let’s assume I decide to focus my future research endeavors on infectious diseases; I can use my expertise in vaccinations to consult local governments on the most fiscally responsible and medically sound immunization practices. Or, I could go into the field of neonatal research where my expertise could be used in the international setting to design high-yield screening tools for newborn disease in low-resource settings. Since medicine is inextricably linked with economic and social factors, my involvement in clinical research can serve as a gateway to helping people in more than just medical terms.

Being a Doris Duke Fellow will help me realize these goals by introducing me to other clinician-scientists from whom I can learn how to balance clinical practice with research. And, the exposure to radiology, neurology, cardiology, and neonatology will widen my research base giving me more options from which to chose a research focus later in my career.

I kindly ask for your support of my effort to find the missing piece of the puzzle and help newborns and their families cope with the challenges of CHD. I greatly appreciate your consideration and welcome any questions that you may have. Thank you.

(2) Research Plan Title: (should not exceed 255 characters, including spaces)
Using Magnetic Resonance Imaging To Determine The Relationship Between Brain Volumes And Neurodevelopmental Outcomes In Newborns With Congenital Heart Disease.

(3) Research Plan Summary: (should not exceed 250 words, or approximately 1/3 of single-spaced page)
This research project will be performed at the University of California, San Francisco in the research group of Dr Patrick McQuillen. Dr McQuillen’s lab consists of groups focused on basic laboratory investigations into neonatal brain injury and repair and clinical investigation using advanced magnetic resonance imaging to understand and prevent acquired brain injury in newborns with congenital heart disease. The applicant will spend 12 months conducting research on the relationship between brain volume and neurodevelopmental outcomes in newborns with congenital heart disease (CHD). The project aims to 1) compare brain volumes in neonates with CHD to those of neonates with normal heart physiology, 2) examine the relationship between acquired brain injury and brain volumes before and after surgery in neonates with CHD, and 3) examine the relationship between brain volumes and neurodevelopmental outcome. Brain volume will be assessed using advanced magnetic resonance imaging techniques and deformation morphometry. Neurodevelopmental outcomes will be assessed through clinical exam of newborns at 12 and 30 months of age. Subjects will come from a previously
established cohort as well as from new patient recruitment. During the research period, the applicant will help in identifying and enrolling new patients UCSF Clinical and Translational Sciences Institute (CTSI); performing daily patient screening; collecting, entering and validating data; performing the morphometry analysis; and taking part in all relevant activities of the Pediatrics and Neuroradiology Departments at UCSF including Grand Rounds.

(4) Research Proposal: (is limited to 3 pages and should be divided into three sections: a) Research Question, b) Background, and c) Study Design and Methods). You should work with your mentor on designing the research proposal.

Introduction & Specific Aims

Congenital heart disease is the most common birth defect, occurring in almost 1/100 births in North America[1]. Although advances in surgical and intensive care have improved survival, CHD is associated with adverse school age neurodevelopmental outcome in up to 60% of survivors of neonatal surgery[2]. Methods to predict adverse neurodevelopmental outcome are needed to design and implement trials to improve outcome. The etiology of neurodevelopmental impairment in CHD is complex with both genetic and acquired components. Our group has performed advanced magnetic resonance brain imaging before and after surgery with outcome assessment at 12 and 30 months in an ongoing cohort of more than 75 newborns with CHD. These studies have led to new insights into the timing and mechanism of acquired brain injury associated with neonatal cardiac surgery[3-5]. Despite this new understanding of mechanism, no measurements to date have been validated to predict school-age neurodevelopmental outcome. In preterm infants, quantitative measurement of brain volumes (morphometry) has been successfully used to predict subsequent neurodevelopmental outcome[6, 7].

The goal of this project is to determine the relationship between quantitative brain volumes and neurodevelopmental outcomes in newborns with congenital heart disease. To accomplish this goal, we propose three specific aims:

Specific Aim 1: To compare brain volumes in neonates with CHD before surgery to brain volumes in healthy term neonates without CHD using deformation morphometry.

Hypothesis: Neonates with impaired brain development due to CHD will have smaller brain volumes compared to age-matched neonates without CHD.

Approach: A reference model for the normal term brain will be constructed from three-dimensional magnetic resonance image datasets from 20 normal newborns without CHD enrolled as part of a parallel study. Brain volumes will be measured with deformation morphometry and will include: total brain volume, cortical grey and white matter volume and deep grey nuclei volumes. We will compare preoperative brain volumes from an existing cohort of 74 infants with CHD to the reference dataset constructed for the normal term brain. To minimize variability among different forms of congenital heart disease, only patients with: (1) transposition of the great arteries (TGA) or (2) single ventricle physiology (SVP) will be studied. Separate comparisons will be made for each of the subgroups (TGA and SVP).

Specific Aim 2: To examine the relationship between acquired brain injury and brain volumes before and after surgery in neonates with CHD.

Hypothesis: Brain volumes will negatively correlate with the presence and extent of acquired injury in term newborns with CHD.

Approach: Acquired brain injury will be determined using high resolution conventional and diffusion-weighted MRI before and after surgery as described. Brain volumes will be compared between newborns with CHD with and without preoperative brain injury and with and without new postoperative brain
Taking advantage of serial imaging, we will also measure change in brain volumes from pre- to postoperative time points and compare change in brain volumes between infants with and without acquired brain injury on convention MRI.

**Specific Aim 3:** To examine the relationship between brain volumes and neurodevelopmental outcome.

**Hypothesis:** Decreased brain volumes and/or growth due to acquired injury in motor, language and associative brain regions results in motor, language and cognitive deficits in term newborns with TGA and SVP.

**Approach:** Neurodevelopmental outcomes are being determined at ages 12 and 30 months using standardized measures of function: gross and fine motor, language and cognition in our existing cohort of 74 infants with CHD and 20 normal term infants. We will determine the association of pre- and postoperative brain volumes and brain growth to one-year and 30 month outcomes in this existing cohort.

Assessing the predictive value of brain volumes for subsequent neurodevelopmental outcome will help improve the understanding of the pathophysiology of acquired brain injury in newborns with CHD and will aid in the design and implementation brain protective trials.

**Background**

**Brain Injury & Congenital Heart Disease:** Prior to corrective surgery, more than half of newborns with CHD have clinical evidence of neurological deficits[8, 9]. In addition to preoperative brain injury, neurodevelopmental impairments can be attributed to cardiopulmonary bypass and low cardiac output following corrective surgery[10, 11]. Despite efforts to normalize cerebral blood flow during surgical correction of transposition of the great arteries (TGA), a type of CHD, postoperative neurodevelopmental deficits are still observed[12]. In comparison to population norms, newborns with TGA are more likely to have abnormal neurological examinations, learning disabilities, and behavioral disorders[11, 13, 14]. Children with other types of CHD, including single ventricle physiology (SVP), also have developmental delays[8]. In addition to detection of neurological damage by clinical assessment, magnetic resonance imaging (MRI) has detected brain injury in up to 60% of newborns with CHD[3, 15]. While MRI studies have assessed ischemic brain injury through detection of structural lesions, they have not yet assessed brain injury by quantifying changes in brain volumes of infants with CHD.

**Advanced MRI, Morphometry & Premature Infants:** Brain volumes in preterm babies have been explored through several quantitative studies. These studies have proven to be very beneficial in establishing the functional significance of structural abnormalities on neurodevelopment[16]. Recent data reveal a strikingly high incidence of white matter injury in term infants with CHD, with imaging characteristics similar to those seen in preterm newborns[2]. Given the considerable evidence that newborns with CHD have impaired in utero brain development associated with microcephaly, discovering the relationship between CHD and brain volume would be useful in understanding the neurodevelopmental consequences of brain ischemia and white matter injury[17, 18].

**Deformation Morphometry:** Regional brain tissue volumes (cerebrospinal fluid (CSF), gray matter, and white matter) will be automatically derived from a two-step process: tissue labeling and then regional parcellation using a probabilistic tissue segmentation technique[19]. Both of these steps will make use of multi-channel MRI data co-aligned within subject and then spatially normalized to a reference atlas containing spatial statistical priors to assist the segmentation process. This methodology will follow a similar approach to that we are developing for fetal brain image analysis [Habas et al, MICCAI 2008], where an unbiased shape and intensity average anatomy is constructed from a set of training scans which have been manually segmented to form a high quality atlas for the specific age range being studied. The second component of the regional volumetry is the parcellation of the brain to provide regional measures of tissue volumes. This will again make use of a statistical prior derived from a set of manually
marked subjects to encode the spatial location of the main lobes and the cerebellum. This statistical map of the expected location of each region label will then be warped into the space of new individual scans to provide an automated parcellation of the tissue labels. The marked regions will include: cerebellum, cortex, ventricular volume, caudate, putamen and globus pallidus bilaterally. The resulting volumes of each tissue type in each defined anatomical region will then be analyzed using general linear modeling to examine the relationship between acquired perioperative injury and regional morphometry.

Specific Responsibilities of the Applicant During the Research Fellowship & Selected Methods

Environment: This research project will be performed at the University of California, San Francisco in the research group of Dr Patrick McQuillen. Dr McQuillen’s lab consists of groups focused on basic laboratory investigations into neonatal brain injury and repair and clinical investigation using advanced magnetic resonance imaging to understand and prevent acquired brain injury in newborns with congenital heart disease. Dr McQuillen’s group collaborates closely with and is a part of, the Neonatal Brain Disorders Center headed by Dr Donna Ferriero. Along with Dr James Barkovich in Neuroradiology, Dr Ferriero has established two successful clinical cohorts applying advanced magnetic resonance imaging to term newborns with birth asphyxia (BAMRI) and premature infants (PREMRI). The bioengineering group headed by Dr Dan Vigneron, whose lab has designed custom ‘birdcage’ head coils and sequences for imaging the neonatal brain, supports all three neonatal MRI studies. This group includes Dr Colin Studholme who has specific expertise in deformation morphometry.

Responsibilities: During the research period, the applicant will participate in all activities of the McQuillen and Neonatal Brain Disorders Labs. This will include weekly lab meetings of both groups, as well as weekly meetings of the CardiacMRI, BAMRI and PREMRI groups with Drs Barkovich and Vigneron (10%). The applicant will help in identifying and enrolling new patients into the cardiac MRI project (5%). This will include daily patient screening performed along with study nurses of the UCSF Clinical and Translational Sciences Institute (CTSI). The applicant will assist with data collection, entry and validation along with the cardiacMRI study coordinator (2%). The majority of the applicant’s time will be spent performing the morphometry analysis under the supervision of Drs Studholme and McQuillen (80%). This will include manual review of existing three-dimensional MR datasets (T1/SPGR, T2) to select studies free of motion artifact and subsequent deformation morphometry (reviewed below). In addition to lab meetings, the applicant will meet daily to weekly with Dr McQuillen, weekly with Dr Studholme and monthly with Dr Ferriero. The applicant will take part in all relevant activities of the Pediatrics and Neuroradiology Departments at UCSF including weekly grand rounds, MRI rounds and clinical teaching rounds (3%). Finally, the applicant will participate in educational activities of the Neuroscience training program at UCSF including weekly journal clubs and seminars.

Research Plan Citations: (should not exceed 700 words, or approximately one single-spaced page)

References