A. Personal Statement

My overall aim is to probe the social ecology of early childhood using hair cortisol concentrations (HCC) and hair oxytocin concentrations (HOC) as summative measures of stressful vs. supportive experiences in their environment. In subsequent projects, these measures will be used to investigate the long-term physical health and mental health outcomes following childhood trauma and critical illness. First, we will establish the normative ranges for hair cortisol and hair oxytocin in healthy preschool children and identify the demographic and psychosocial factors that explain the variability in these biomarkers. Second, we will quantify protein biomarkers in hair, including inflammatory cytokines and other mechanistic proteins that reflect illness vs. wellness in early childhood. Third, we will measure these neurohormones and candidate cytokines in specific patient populations to reveal specific molecules and expression profiles with diagnostic value, or those that change with specific therapies. My research training occurred as a Rhodes Scholar at University of Oxford studying stress responses to surgery, and continued in a postdoctoral fellowship at Harvard Medical School, where I proposed the first scientific rationale for pain-related stress in newborns. Over 30 years, my research has contributed extensive knowledge about early development of pain/stress, established novel approaches for analgesia/anesthesia, investigated the long-term effects of pain/stress, and the mechanisms underlying opioid tolerance and anesthetic neurotoxicity in the immature brain. I have designed multiple randomized clinical trials and other clinical cohort studies, including the International NEOPAIN trial funded by NICHD, the NeoOpioid Consortium funded by the European Commission, and studies funded via collaborative research networks launched by NIMH, NINDS, and NICHD. With my clinical training and decades of experience in pediatric critical care, extensive research experience, track record of previous NIH and other competitive funding, and history of successful collaborations, I feel that I am qualified to serve as Principal Investigator for the proposed project. Publications relevant to the proposed research project include:

C. Contributions to Science

1. Current controversy exists regarding normative references ranges for cortisol in children. We developed a novel assay measuring hair cortisol concentrations (HCC) in children and proposed that diurnal variations, or changes related to age, or sex, or puberty do not affect HCC values, therefore, measuring hair cortisol may represent an alternative approach to defining the normative cortisol values for children. We examined the relationship of maternal variables to hair cortisol levels and the social-emotional development of 1 year-olds, suggesting that hair cortisol mediates the effects of early adversity on social-emotional development. We recently found that maternal exposures to prenatal traumatic life events were associated with increased hair cortisol levels in preschool children. We identified a clinical profile of nervous system dysregulation in children and found it was associated with multiple adverse childhood experiences (ACEs), mediated possibly via neuroendocrine, neuroimmune and neurenteric pathways (including HPA axis dysregulation).


2) In the 1980’s, surgical operations were being performed in infants and young children with minimal or no anesthesia. We investigated the hormonal-metabolic stress responses of infants undergoing surgery and proposed the mechanisms by which early adverse experiences can lead to the long-term changes in brain development and behavior.


3) We designed, executed and reported the first randomized, placebo-controlled clinical trials to show that adequate anesthesia can reduce the hormonal-metabolic stress responses of newborns and thereby decreasing their morbidity and mortality following surgery in the neonatal period.


4) Results from the randomized clinical trials listed above led to the first scientific rationale for development of the pain system in early life. This presented a framework for pain assessment in neonates, which allowed us to launch some of the pivotal multicenter randomized clinical trials of neonatal analgesia / anesthesia.


5) Changes in clinical practice led to indiscriminate opioid use with an increasing incidence of opioid tolerance and withdrawal. We examined the mechanisms underlying opioid tolerance and their impact on early brain development; documented the prevalence of opioid tolerance and withdrawal in critically ill children in a multicenter study and its relationships to the variability of clinical practices for opioid analgesia.


**D. Additional Information: Research Support and/or Scholastic Performance**

My scholarly contributions include more than 300 papers, chapters and books, with an H-index of >60. Many of my publications are listed in Scopus: [http://www.scopus.com/authid/detail.url?authorId=7101749758](http://www.scopus.com/authid/detail.url?authorId=7101749758)

**Ongoing Research Support:**

1 K08 HL118118 (Schwingshackl) 02/01/2014 – 05/31/2019
National Heart, Lung & Blood Institute (NIH/NHLBI)
*The role of 2-pore domain potassium channels in Acute Lung Injury*

Major goals of this project are to develop novel therapeutic targets including stretch-activated ion channels for treating ARDS in children and adults.
Role: Co-Mentor

5 K23 HD082782 (Chidambaran) 09/01/2014 – 06/30/2019
*Eunice Kennedy Shriver National Institute for Child Health & Human Development (NIH/NICHD)*
*Morphine Pharmacogenomics to Predict Risk of Respiratory Depression in Children*

Major goals of this project are to identify specific genetic biomarkers that can increase the risks of opioid side effects including respiratory depression after postoperative analgesia.
Role: Co-Mentor

Stanford University School of Medicine (Anand) 10/01/2015 – 09/30/2020
Child Health Research Institute
*Identifying potential biomarkers for measuring pain and stress in critically ill children*

Major goals of this grant are to set up the Pain/Stress Neurobiology Laboratory focused on investigating the mechanisms, measurements, and outcomes of pain/stress in infants and children.

Child Health Research Institute (Anand) 01/01/2018 – 06/30/2019
*Biomarkers of Risk and Resilience in Preschool Children*

Major goals of this project are to develop and validate a novel ELISA-based assay for measuring hair oxytocin concentrations (HOC) and to collect pilot data from preschool children and their parents currently living in Santa Clara County.

1 R41 DA046983 (Gholami, Anand) 09/01/2018 – 08/30/2019
*National Institute for Drug Abuse (NIH/NIDA)*
*Measuring Infant Pain Objectively using Sensor Fusion & Machine Learning Algorithms*

Major goals of this project are to differentiate acute pain from baseline or non-painful events in hospitalized infants and newborns and to develop sensor fusion frameworks for integrating the physiological data from multiple clinical and non-clinical sensors.

1 S10 OD026962-01 (Chien) 02/01/2019 – 01/31/2020
*NIH Office of the Director (Priority Score=10 from ZRG1 BCMB-T(30), awaiting notice of grant award)*
*Xevo TQ-XS Triple Quadrupole Mass Spectrometer System*

Major goals of this project are to fund a Triple Quadrupole Mass Spectrometer for supporting a range of funded projects involving targeted peptide and small molecule quantitation, including the hair cortisol and hair oxytocin proposed for this project.
Role: Co-Investigator.