Seattle Children's Research Institute
Eligible Diversity Supplement Grants
Updated: May 11, 2020

PI Last Name	SCRI Center	Project Title	Project Abstract	Project Number
ADEREM, ALAN A	Center for Global Infectious Disease Research (CGIDR)	Adminstrative Core	Abstract – Administrative CoreThe goal of the Administrative Core is to establish tightly interacting Projects that interface with Technology,Modeling, and Data Management and Bioinformatics Cores to achieve the scientific and administrative goals ofthe Omics for TB (OTB) consortium.The Core will organize and manage projects, their integration andprogress, as well as communication among the groups. The Core is also responsible for implementation of aTraining and Outreach Program, Systems Biology of Pathogens and Their Hosts Short-Course, to promote theuse of the systems biology approach in the study of infectious disease.The Administrative Core will: • Continuously monitor the scientific progress of each component of the program. • Facilitate communication across OTB program, other U19 Centers, and with NIH. • Administer the Training and Outreach Program. • Coordinate meeting scheduling and travel with the PI's and the NIH (Annual Programmatic Meeting). • Provide fiscal oversight to ensure that all financial resources are used appropriately. • Coordinate production of annual progress reports and updates to the Resource Sharing Plan.	5U19AI135976-04
ADEREM, ALAN A	Center for Global Infectious Disease Research (CGIDR)	Project 1: Mechanisms of Disease Progression	Abstract – Project 1Human Mtb infection results in a large variety of clinical outcomes, ranging from bacterial eradication, to controland latent infection, to progression and active disease with a range of clinical phenotypes. We recentlydiscovered a blood transcriptional signature that predicts TB risk in Mtb-exposed individuals up to 18 monthsbefore they exhibit clinical symptoms, a landmark contribution to the field. Still, the mechanisms that underlieTB disease progression remain poorly understood, in large part because the key immune responses within thehuman lung cannot be readily monitored. Furthermore, TB is a highly heterogeneous disease in whichindividuals progress to active disease due to a variety of mechanisms. In this project, we will conduct acomprehensive, multi-scale integration of transcriptomic, cytokine, chemokine and eicosanoid profiles fromlung and blood during Mtb infection in order to identify and model molecular mechanisms and pathways thatdetermine the outcome of infection. First, we will use multiple experimental strategies to recapitulate theheterogeneity of human Mtb infection in the mouse. These include a novel "ultra low dose" (ULD) infectionmodel that we have pioneered in which mice are infected with 1-3 bacteria and subsequently exhibit a broadrange of outcomes, ranging from immune control to progression. We will also employ mice from theCollaborative Cross project that have demonstrated extreme TB phenotypes and Mtb strains that span a rangeof pathogenicity. Second, we will interrogate and model the host-Mtb interaction in these mouse models usinga variety of systems biology approaches in order to uncover the molecular regulators, pathways, and networksin pulmonary innate and adaptive immune cells. We will test the predicted role of critical regulatory moleculesby genetically perturbing them in vivo and examining the impact on control of Mtb infection. We will also applymachine-learning approaches to define multi-omic blood based signatures in mice that predict TB progression.In our preliminary work, we have defined an early blood-based signature that predicts the late-time bacterialburdens in ULD-infected mice. We will correlate this signature with systems-level measurements of immunefunction in the lung to uncover mechanisms of Mtb control. Third, we will translate these findings to humandisease. Through the Africa Health Research Institute, we will leverage a large-scale program that will obtaingenomic sequence data as well as associated epidemiological and clinical metadata on 50,000 individualsliving in a TB-endemic region. We will conduct a candidate gene genetic association analysis to validateregulatory molecules identified in mice to determine whether mutations in human orthologs are associated withaltered risk of TB. In addition, we will use several existing non-human primate and human datasets to refinethe blood based multi-omic progression signatures defined in mice and test their ability to predict TBprogression in humans.	5U19AI135976-04
ADEREM, ALAN A	Center for Global Infectious Disease Research (CGIDR)	Omics for TB: Response to Infection and Treatment	Abstract – OverviewWith about 10 million new cases of active disease and 1.8 million deaths annually, TB is a global healthemergency. A distinguishing feature of TB disease is its biological heterogeneity, which manifests at the clinicallevel chiefly in 2 forms: disease progression and treatment response. The premise of this Program is that theheterogeneous outcomes of TB infection and treatment are determined by the interplay of competingregulatory networks between the pathogen and the host. Our primary goal is to apply systems biologyapproaches to elucidate the biological control underlying the variability of disease outcome and response totreatment. Our first specific aim is to define novel host regulators of TB disease progression in vivo, and theinnate and adaptive networks they control. We will also seek to define novel Mtb regulators of TB treatmentresponse, and the Mtb regulatory networks that they control. This work will allow us to produce and validatehost and Mtb models of TB disease progression and treatment response. Altogether, this program addresseskey unanswered questions that stymie efforts to combat the TB pandemic. Our team has perfected therequired platforms and scientific approaches to execute this ambitious research plan in a timely and cost-effective manner. All the participating investigators have strong records of interacting productively, and ofdisseminating their data and reagents to the scientific community.	5U19AI135976-04
AITCHISON, JOHN D.	Center for Global Infectious Disease Research (CGIDR)	Technology Core	Abstract - Technology CoreThis U19 proposes a novel and fully integrated approach to understanding disease progression and treatmentresponse in tuberculosis (TB). We will combine traditional approaches to understanding the pathophysiology ofTB, bacterial genetics and immunology, with systems biology approaches including genomics, transcriptomics,metabolomics, lipidomics, proteomics, and computational modeling. We will apply HTP "Omics" technologiesand systems analysis to murine and mycobacterial studies and to human field studies in tuberculosis. Datagenerated by HTP and targeted state-of-the-art approaches will be integrated through bioinformatic andmodeling approaches, which, combined with domain expertise, will lead to a deep understanding of themolecular networks that underlie the progression of TB infection and response to treatment, and predictcomplex biological behaviors that lead to either containment or active disease; treatment cure or relapse.Multiple innovative HTP technologies will be leveraged and enhanced through this program. Thesetechnologies have been established in multiple experimental systems and will be customized and furtherdeveloped for their application to this program and to clinical samples as appropriate. These developments willensure data quality,	5U19AI135976-04

			and maximize the efficiency of data generation. The approaches chosen are innovativeand state-of-the-art and will maximize our ability to complement and extend the existing comprehensivenetwork models and provide spatial perspective for models generated as part of the original OTB program. Wewill disseminate modifications and improvements to extant technologies and detailed protocols broadly toenable adoption and further development by the community.	
BEIER, DAVID R.	Center for Developmental Biology and Regenerative Medicine (CDBRM)	Screening for modifiers of PKD severity using ENU Mutagenesis	ABSTRACTThere is abundant evidence from the analysis of human populations and mouse models that the severity ofPolycystic Kidney Disease (PKD) can be modified by interacting genetic loci. The identification of these locishould provide insight into our understanding of the basic pathobiology of cystogenesis and diseaseprogression. Importantly, they can potentially reveal novel pathways of therapeutic intervention. We haveextensive experience in the characterization of a mouse model of cystic kidney disease, and specifically theinvestigation of strain-specific modifiers of its severity. However, the yield of proven causal genes in mousestudies of this type has been low. In contrast, we have been very successful using a different approach fornovel disease gene discovery, namely mutagenesis with the chemical ethyl-nitrosourea (ENU). We haverecently modified this method so that we can do our screen entirely on an inbred background, using WholeGenome Sequencing methodology for positional cloning. The recent characterization of the PKD1RC mutantmouse as having slowly progressive PKD, which is sensitive to strain-specific modifiers, compels our proposalthat we use ENU mutagenesis for the generation and discovery of modifiers of PKD1-induced cystic kidneydisease. To complement this phenotype-driven approach, we will also pursue an analysis of candidate loci thatmay modify PKD severity. We have data to suggest that Sonic Hedgehog (SHH) signaling plays a role incystogenesis, and we will test whether the deletion of genes in this pathway affects disease severity in thePKD1RC mouse model.	5R01DK111682-02
BJORNSON, KRISTIE F	Center for Child Health, Behavior and Development (CHBD)	Short-Burst Interval Treadmill Training to Improve Community Walking Activity and Mobility in Cerebral Palsy	Project Summary/Abstract:Ambulatory children with cerebral palsy (CP) walk predominately in low intensity stride rates with littlevariability, thus limiting their walking activity and ability to participate in daily life. In contrast, typicallydeveloping (TD) children engage in short bursts of intense walking activity interspersed with varying intervals oflow intensity walking within daily life. In order to optimize motor learning, active participation, task-specifictraining and multiple repetitions or massed practice is required to learn new motor skills. Short bursts ofvigorous intensity locomotor treadmill training (SBLTT) alternating with low/moderate intensity was specificallydesigned to mimic activity patterns of TD children in a massed practice format. Pilot data suggests that SBLTTis feasible and enhances walking capacity and performance in daily life for children with CP. The objective ofthis application is to examine the effect of SBLTT versus an equivalent dosage of traditional locomotortreadmill training (TLTT) on the primary outcomes of walking capacity and performance in children with CP.This protocol will also examine whether the effects of SBLTT on walking capacity and performance aremediated by improvements in in muscle power generation. The scientific premise is that SBLTT, thatapproximates the walking intensity patterns of typically developing (TD) children through a clinically feasiblemassed practice protocol, will be more effective than TLTT in improving walking capacity and performance. Wehypothesize that SBLTT strategies for children with CP modeled on activity patterns in TD children, will bepositively mediated by muscle power generation and subsequently improve walking capacity and communitywalking performance and mobility. We will test the following specific aims. Aim #1. Determine the immediateand retention effects of short-burst interval LTT (SBLTT) on walking capacity in ambulatory children with CP.Walking capacity will be measured by self-selected gait speed and the one minute walk test. Aim #2. Examinethe effects of treatment on community-based walking activity performance and mobility. Walking activityperformance will be captured by accelerometry. Community walking mobility individualized by home versuscommunity locations will be measured with a novel combination of global position system and accelerometry.Aim #3. Explore whether the effects of SBLTT on walking capacity and performance are mediated by musclepower generation. This project is innovative because it focuses novel task-specific approach for addressingwalking limitations in children with CP and implements an individualized community locations outcome. Theproposed research is significant because it will be the first step in a continuum of research that is expected todirect locomotor training protocols and rehab strategies across pediatric disabilities and positively effecting thecommunity walking performance and mobility for children with CP. Increased understanding of the musculermechanisms by which children with CP respond to SBLTT are expected. Such knowledge has relevance to thehealth and functional benefits of enhanced mobility and physical activity across the life span.	1R01HD098270-01
CHERRY, TIMOTHY JOEL	Center for Developmental Biology and Regenerative Medicine (CDBRM)	Non-Coding Genetic Vulnerabilities in Human Photoreceptor Function and Disease	PROJECT SUMMARY/ABSTRACTCis-regulatory elements (CREs) are critical sites of transcription factor (TF) binding to the genome thatorchestrate the expression of genes necessary for normal cellular function. Mutations within CREs can disruptTF binding and cause inherited human diseases including disorders of vision. The genomic location andfunction of CREs that are necessary for human vision is largely unknown. This gap in knowledge is asignificant obstacle toward understanding the genetic regulation of normal human vision and to identifyingdisease-causing mutations with CREs. The long-term goal for our research is to understand how geneticvariation within CREs shapes the structure and function of the retina and contributes to human vision. Thefocused objective of this proposal is to determine the mechanisms by which CREs regulate essential geneexpression in photoreceptor cells and to determine how genetic mutations within CREs lead to retinaldisease. The central hypothesis driving this work is that discrete DNA sequences within CREs are required toregulate essential photoreceptor gene expression and that CRE mutations that disrupt evolutionarily conservedTF binding sites contribute to inherited visual disorders. To test this hypothesis we are pursuing the followingspecific aims: 1) Determine the activity of human photoreceptor CREs in human retinal organoids using ATAC-Seq, ChIP-Seq and RNA-Seq to compare them to CREs we have previously identified from adult anddeveloping human retinas. This will demonstrate the utility of organoids for studying photoreceptor CREs intheir native cellular-genomic context. 2) Test the function of patient-derived variants in human photoreceptorCREs. Using high-throughput AAV-based reporter assays we will determine which CREs sequences aresufficient to drive cell-type-specific expression in the mouse retina and human retinal organoids and determinethe consequence of sequence variants on CRE activity. 3) Determine the mechanisms by which multiple CREsregulate the expression of a critical photoreceptor transcription factor, NRL. CRISPR/Cas9-based approacheswill target specific CREs at the NRL locus to reveal the contribution of each CRE to the expression of thisessential gene and to serve as a case study for the regulation of other essential genes. The contribution of thisresearch will be to elucidate the mechanisms by which CREs regulate genes that are necessary for humanphotoreceptor function and survival. This work will enable the systematic identification and interpretation ofgenetic variants within CREs and therefore improve genetic diagnostics for unexplained retinal disease. Byopening up the	5R01EY028584-02

			non-coding genome to functional analyses it will be possible for the first time to determine themechanisms by which individual CREs regulate specific genes that are critical for photoreceptor cell function ina high-throughput and comprehensive manner. This will enable discovery of genetic contributions to humanvision and inherited visual diseases that have thus far been inaccessible.	
CHRISTAKIS, DIMITRIA	Center for Child Health, Behavior and Development (CHBD)	Attentional attributes of early child media usage	PROJECT SUMMARY Increasingly, early childhood includes electronic media. It is not just the age at which children beginto view regularly that is concerning, but the content of the media and the context of the use. Recently,newer mobile and interactive media platforms (e.g. tablets) have changed the way media is consumed.Current viewing metrics suggest that tablet media is beginning to replace traditional TV viewing, but thatpassive content ("watching video") remains the primary component of early media use. Tablets allowseveral important differences in use. First, apps for tablets allow both passive viewing as well as interactivegame playing, providing a more diverse set of content choices. Second, the personalized use of thesesmaller devices allows the content to be delivered directly to the child, and adults are less likely to co-viewduring tablet use. On-demand access also allows programs to be controlled, changing patterns ofconsumption and use has extended out of the home into more environments. Observational studies of TVuse have linked excessive early media use with attention problems, language delay, and cognitivedetriments. It is unclear if the interactive nature of tables and apps might approximate more traditionalexchanges or even promote interactions. Given the changing media landscape, a better understanding ofhow tablet based media influences early learning is important for supporting better child outcomes, andpotentially identifying those with early risk. To address these issues, we will investigate: (1) the immediateimpact of different tablet media content on infant joint attention behaviors, engagement, andcardiophysiological responses related to regulation and attention. As well, we will explore parents ability topredict their child's difficulty disengaging from touchscreen technologies.	1R21HD099300-01A1
COKER, TUMAINI RUCKER	Center for Child Health, Behavior and Development (CHBD)	Well-Child Care Clinical Practice Redesign: A Parent Coach-Led Model of Care for Young Children	Project SummaryWell-Child Care (WCC) visits for child preventive health care during the first three years of life are criticalbecause they may be the only opportunity before a child reaches preschool to identify and address importantsocial, developmental, behavioral, and health issues that could have significant impact and long-lasting effectson children's lives as adults. Unfortunately, this opportunity is often missed for children in low-incomecommunities. The structure of WCC in the U.S. cannot support the vast array of WCC needs of thesevulnerable children and their families. Key structural problems include (a) reliance on physicians for basic,routine preventive care services, (b) limitation to a 15-minute face-to-face clinician-directed well-visit for thewide array of education and guidance services needed, and (c) lack of a systematic, patient-driven method forvisit customization to meet families' needs. These structural problems contribute to the wide variations inprocesses of care and preventive care outcomes, resulting in poorer quality of WCC and perhaps worse healthoutcomes. We previously used a rigorous, structured community-based participatory approach guided by keyWCC stakeholders and expert panel methods to develop and test a new, innovative model of WCC delivery tomeet the needs of children in low-income communities: Parent-focused Redesign for Encounters,Newborns to Toddlers (PARENT). PARENT is a team-based approach to care using a health educator("Parent Coach") to provide the bulk of WCC services, address specific needs faced by families in low-incomecommunities, and decrease reliance on the clinician as the primary provider of WCC services. In an initial pilotrandomized controlled trial of PARENT among 251 low-income families in two urban area pediatric practices,we found strong and consistent intervention effects on the quality of preventive care provided to families, andon reducing emergency department (ED) utilization. A larger trial of PARENT with multiple clinics isneeded to position PARENT as an evidence-based, financially sustainable model for WCC delivery thatcan be implemented by practices and clinics nationwide. In a clinic-randomized controlled trial of PARENT,we will examine parent-reported quality of care and healthcare utilization (e.g., ED utilization), conduct a costanalysis, and use direct observations to assess changes in physician time allocation with Parent Coach-ledwell-visits. The study will be conducted in partnership with 12 clinics and their health plan payers, and addressthe following Specific Aims:Aim #1: Measure the effect of PARENT on receipt of nationally-recommended WCC services and parentexperiences of care.Aim #2: Determine the effects of PARENT on WCC, urgent care, and ED utilization, and on net costs.Aim #3: Examine the effect of PARENT on physician time allocation for WCC and urgent care visits.Aim #4: Assess the effect of PARENT on parent-focused outcomes in an exploratory analysis.	5R01HD088586-04
FRENKEL, LISA M	Center for Global Infectious Disease Research (CGIDR)	Defining HIV reservoirs that rebound following suspension of ART	ABSTRACTIn the twenty years since effective HIV treatments became available, the lifespan of HIV-infected adults in high-resource settings has increased to within a decade of uninfected individuals. Nevertheless, antiretroviraltreatments (ART) fall short in restoring health, and if therapy is discontinued virus usually rebounds topretreatment levels due the persistence and reactivation of proviruses. Curative therapies are being sought,including therapeutic vaccines, chemotherapies paired with stem-cell transplant, chimeric antigen receptor Tcells, neutralizing and immune modulating antibodies, gene therapies, cytokines and initiation of ART duringacute infection. While some of these approaches have reduced the "reservoirs" of infectious viruses and in onecase may have cured HIV infection, a better understanding of the mechanisms underlying HIV persistence isneeded to develop an effective, safe and economical cure. HIV reservoirs are primarily established early ininfection, and while they decay and change in composition during ART, the mechanisms that sustain reservoirsare only partially known. We hypothesize that HIV reservoirs are maintained by: (1) Integrated proviruses thatmodulate gene expression to promote survival of these cells, allowing infected cells to persist by proliferationor latency; (2) HIV-specific immune responses become exhausted due to dysregulation of T-regulatory cellsresulting from provirus integration; and (3) Epigenetic marks repress expression of proviral DNA, allowinginfected cells to persist due to "deep" latency of proviruses. We propose studies to explore the role of thesemechanisms in sustaining HIV reservoirs using specimens collected prospectively from a unique Belgiancohort of chronically infected individuals sampled during ART-suppression as well as during and after ananalytical treatment interruption (ATI). Samples for this study include blood, cerebral spinal fluid, bone marrow,bronchioalveolar lavage fluid, lymph node, duodenum, ileum, and colon. The knowledge gained from theproposed studies should point to interventional strategies that could be tested and potentially contribute to thegoal of developing an intervention to cure HIV infection.	5R01AI134419-03
FRENKEL, LISA M	Center for Global Infectious Disease Research (CGIDR)	Drug Resistance Genotypic and Phenotypic Correlates of	AbstractAntiretroviral therapy (ART) is critical to improving the health of people living with HIV (PLHIV), to reducing HIVtransmission and to maintaining the effectiveness of the current ART programs in resource-limited settings(RLS). However, HIV antiretroviral drug resistance (HIVDR) can hamper global efforts to control the AIDSepidemic and achieve the UNAIDS 90-90-90 targets. Pre-treatment drug resistance (PDR) and on treatment-acquired drug resistance (ADR) are associated with virologic failure (VF) and increased morbidity andmortality. The correlates of PDR and ADR are not fully understood, and the level and breath of HIVDRmutations (DRM) circulating in	1R01AI147309-01

		Efavirenz and Dolutegravir based Treatment Outcomes across Non-B HIV-1 subtypes	individuals and populations, especially in RLS is lacking. Much of ourunderstanding of HIVDR genotype-phenotype-outcome correlations have been derived from developedcountries where the predominant circulating HIV strain is HIV-1 Group M subtype B. However, in communitieswith the highest prevalence of HIV-1 infection across the world, PLHIV are infected by non-B subtypes, suchas subtypes A, C, D and circulating recombinant forms CRF01_AE and CRF02_AG. HIVDR and the correlatesof viral suppression and outcome for these HIV-1 strains has been poorly studied. The success of modern ARTregimens in RLS such as TDF-3TC-EFV (TLE) and the planned roll-out of dolutegravir (DTG) based regimens(TLD) could be impeded by emerging evidence of widespread HIVDR. This proposal seeks to expand ourunderstanding of HIVDR and its correlates and consequences in low-and-middle income countries where HIV-1 non-B subtypes circulate. To accomplish these goals, we propose the following three Specific Aims:1. Determine the number and breadth of PDR mutations that correlate with virologic failure to TLE or TLD in adults and children infected with HIV-1 subtype A, C, D, CRF01_AE or CRF02_AG.2. Determine known and novel DRMs at the time of VF in adults and children, including DRM frequencies across cohorts by regimen (TLE and TLD) and by HIV-1 subtype.3. Determine the correlations between in vitro phenotypic drug resistance testing against genotypic DRMs across HIV-1 non-B subtypes (A, C, D, CRF01_AE and CRF02_AG).To address these aims we will use state-of-the-art and innovative assays to quantify the frequency of DRM inindividual's pre-ART quasispecies and use phenotypic assays to better understand DRM interactions. Ournovel studies will determine (1) the risks of specific PDR DRM and minority variants across HIV-1 non-Bsubtypes for VF; (2) interactions between DRM that determine phenotypic resistance associated with VF; and(3) mutations selected by TLE and TLD regimens at VF. The long-term goal of this proposal is to provide datato enable the best practices for HIV-1 care across a range of resource-limited settings.	
FRENKEL, LISA M	Center for Global Infectious Disease Research (CGIDR)	Mechanisms controlling the persistence of infectious HIV reservoirs in children	Project Summary/AbstractTwenty years ago effective treatments for HIV became available, and the lifespan of HIV-infected adults inhigh-resource settings has increased to within a decade of uninfected individuals. However, if therapy isstopped virus generally rebounds in the blood to pretreatment levels, due to viruses that persist and reactivatefrom the "HIV Reservoir". Curative therapies suitable for the millions of infected individuals have been sought,including strategies using therapeutic vaccines, chemotherapies paired with stem-cell transplant, chimericantigen receptor cells, gene therapies, cytokines and antiretroviral therapy during acute infection. While manyof these have reduced the HIV reservoir and in one case may have cured HIV infection, a better understandingof the mechanisms that allow persistence of the reservoir are needed to develop an effective, safe andeconomical cure. The HIV reservoir of perinatally infected children are primarily established early in infectionwhen their immune system is tolerogenic to foster a healthy gestation, postnatal colonization with commensalbacteria and tolerance of foods. We propose to examine four mechanisms that could contribute to sustainingthe HIV reservoirs and compare the contribution of each in children versus adults. We hypothesize that twomechanisms will be specific to children: (1) immune tolerance of HIV, due to "perinatal" infection (in utero orthe early weeks of life) when immune tolerance to non-self antigens including non-inherited maternal antigens(NIMA) and oral tolerance to foods are established; and (2) "cross immune tolerance" to HIV generated byincreased levels of maternal microchimerism (MMc), as observed with allografts.15 In both adults and children,we hypothesize that the HIV reservoir is maintained by (3) modulation of gene expression by HIV integration ingenes of Treg that promote survival of these cells, and/or through impairment of antiviral functions towards otherinfected cells; and (4) by the persistent loss of gut T-helper (Th)17 cells due to bacterial translocation elicitingpro-inflammatory cytokines that favor the development and persistence of Tregs instead of effective antiviralCD4+ T-cell help. Through studies of specimens collected prospectively from South African children known tohave acquired HIV perinatally, their mothers and uninfected controls, we will measure parameters of each ofthese mechanisms to gain insight into the roles of these mechanisms in sustaining the infectious HIV reservoir.The knowledge gained regarding the relative contribution of these four mechanisms in children vs. adultsshould point to mechanisms most relevant to children that we could test in non-human primates (NHP), withthe goal of developing interventions tailored to the unique mechanisms identified in children.	5R01HD094719-03
GUMBINER, BARRY M.	Center for Developmental Biology and Regenerative Medicine (CDBRM)	Regulation of cell junctions and cell contact dependent signaling in tissue development and physiology	Regulation of cell junctions and cell contact dependent signaling in tissue development and physiology.Classical cadherins are cell-cell adhesion proteins that regulate tissue morphogenesis and cell junctions duringphysiological processes. They are highly regulated at the cell surface, controlling dynamic interactions betweencells. Although much is known about the basic functions of cadherin-mediated adhesion, an understanding ofthe mechanisms underlying dynamic cell surface regulation, has not yet been achieved, nor is it wellunderstood how such regulatory mechanism control physiological processes in vivo. Cadherins also transducesignals into the cell to convey information about the state of the tissue. One way they do is by stimulation of theHippo-YAP signaling pathway to mediate contact inhibition of growth. This process is antagonized by growthfactor signaling, via the PI3-kinase (PI3K) signaling pathway, which inhibits the Hippo pathway and stimulatesnuclear YAP. We will investigate the mechanisms underlying the regulation of cadherin homophilic adhesivebinding at different levels of analysis, from basic biochemical/biophysical/structural mechanisms, through cellbiological process controlling adhesion (especially the role of p120-catenin), to evaluating the roles of adhesionregulation in physiological processes in vivo. We've found that cancer- and cleft lip-associated mutations in E-cadherin specifically interfere with the regulation of adhesion at the cell surface, and these will provide valuabletools for these studies. In vivo studies of cadherin regulation will focus on their roles in physiological control ofbarrier function in both epithelia and endothelia, especially during inflammatory processes where control ofthese functions are especially important. Studies on endothelial junctional regulation will require us to developtools for studying VE-cadherin regulation, including activating antibodies, and models for endothelial barrierfunction; these will be compared to our studies of E-cadherin in epithelia. We'll also investigate themechanisms by which cadherins transduce various signals into the cell. A major focus will be on the regulationof the Hippo-YAP pathway and associated TEAD transcription factors by cadherin-mediated contact and bygrowth factors and PI3K signaling. The goals are both to understand how they function and to enable us todevelop genetic approaches to selectively perturb these interactions in vivo to evaluate their importance. Hipposignaling by formation of cadherin contacts will be compared to signaling by tight junctions as well as signalsproduced by mechanical tension at the cadherins. The Hippo-YAP pathway may be an important new branchof the PI3K signaling pathway that regulates tissue growth in addition to the well-known Akt-TOR pathways.This hypothesis will be tested in vivo both by studies on tissue overgrowth diseases caused by somatic mosaicconstitutively active PI3K mutations and by studies of mouse models of mammary tumorigenesis. This projectshould reveal how	5R35GM122467-04

			cadherins work as bidirectional signaling proteins to transduce changes across themembrane and how these processes regulate the physiology and growth of tissues and organs in vivo.	
HORSLEN, SIMON	Center for Clinical and Translational Research (CCTR)	Continuation of the Childhood Liver Disease Research Network Seattle Clinical Center	Project Summary/Abstract Biliary atresia (BA) and the other childhood cholestatic liver diseases are significant causes of chronicliver disease in children, and the leading causes for liver transplantation in pediatrics. The initial fundingperiods leading to the current Childhood Liver Disease Research Network (ChiLDReN) have resulted inunprecedented collections of well phenotyped subjects and banked data and biological specimens. Althoughongoing recruitment of subjects with these rare conditions is needed to allow full attainment of many of theindividual study Aims, the collection of subjects, data, and biospecimens is now sufficient to supportmeaningful investigation into the pathogenesis of these diseases and allow thorough genomic screens toelucidate etiologies and modifiers of disease phenotypes. This next funding period will allow completion of theongoing studies and add study of primary sclerosing cholangitis. Furthermore, in conjunction with completingthe ongoing studies, such as PUSH, identification of predictors of liver disease development will be possiblevia the approved ancillary trial of non-invasive markers of disease (led by Dr. Murray). The Seattle ClinicalCenter (CC) has the experience, expertise, and proven track record to continue participation in ChiLDReN, andhas the expected patients over time to support the ongoing and new consortium trials. Dr. Murray and her CC team has additionally proposed a Pilot and Feasibility Trial to study the impactof parenteral nutrition, with standard intralipids versus Omegaven, on malnourished children with end-stageliver disease due to BA. This study has the potential to change the standard of care for these vulnerablepatients, improve their outcomes, and enhance our understanding of the pathogenesis of this obliterativecholangiopathy. Furthermore, to better understand the etiology of BA and potentially identify unique underlyingcandidate genes, Dr. Murray also proposes to perform whole genome sequencing and rare-variant analysis ona subset of the ChiLDReN BA trios to identify variants of both large and small effects in families with BA andductal plate configuration.	2U01DK084575-11
JACKSON, SHAUN WILLIAM	Center for Immunity and Immunotherapies (CIIT)	B cell costimulatory signals in the pathogenesis of SLE	Project abstractDespite modern immunosuppressive therapies, patients with systemic lupus erythematosus (SLE) remain athigh risk for progressive organ damage, emphasizing the need for better, targeted treatments for this disease.In addition to the production of pathogenic autoantibodies, recent studies have demonstrated that B cells canpromote lupus pathogenesis by initiating immune tolerance breaks and facilitating the generation ofspontaneous germinal centers (GC). In this context, distinct costimulatory receptor families have been linkedwith the pathogenesis of autoimmunity. However, despite compelling preclinical data in SLE and clinical benefitin other autoimmune diseases, costimulatory blockade with CTLA4-Ig (Abatacept) failed to control disease inlupus clinical trials. These data emphasize that our understanding of the cell-intrinsic mechanisms whereby B7:CD28 costimulatory signals impact autoreactive B cell activation in lupus is incomplete. In this project, wewill use well-characterized murine lupus models and the novel application of chimeric antigen receptor (CAR) Tcell technology to dissect the immune mechanisms underlying the initiation, propagation and cellular output ofextra-follicular (EF) vs. GC B cell activation pathways in SLE. In Aim 1, we will study whether pathogenicautoantibodies can be generated via an EF B cell activation pathway in a T cell-dependent, but CD28independent, manner. In Aim 2, we will test whether B cell costimulatory signals promote the initiation ormaintenance of autoimmune GC responses. Finally, in Aim 3, we will test whether another costimulatoryreceptor pair, ICOS:ICOS ligand, compensates for loss of CD28 signals during lupus pathogenesis. Together,these studies promise to advance our understanding of lupus pathogenesis and may inform the design offuture human clinical trials of costimulatory blockade in SLE and other humoral autoimmune diseases.	1R01AR073938-01A1
JAMES, RICHARD	Center for Developmental Biology and Regenerative Medicine (CDBRM)	Role of Dock8 in Mucosal Immunity	PROJECT SUMMARYDOCK8 deficiency in humans leads to severe immunodeficiency. The clinical manifestations of DOCK8immunodeficiency include recurrent infections, allergies, and malignancies. DOCK8 -deficient patients sufferfrom recurrent bacterial infections such as Staphylococcus aureus and fungal infections of the mouth or skinwith Candida, which are suggestive of TH17 cell dysfunction. Although it has been suggested that DOCK8might coordinate cytoskeletal arrangement, cellular detachment and regulate cell migration, the precise role ofDOCK proteins in the cell remains for the most part unknown. We have recently reported that DOCK8 isessential for the protective immunity against C. rodentium. DOCK8-deficient mice succumb rapidly to C.rodentium infection. DOCK8-deficient mice have very low numbers of IL-22-producing RORγt+ ILCs incomparison to WT mice. DOCK8-deficient RORγt+ ILCs are defective in IL-7-mediated signaling, more prone toapoptosis and produce less IL-22 than WT mice. We have also found that the generation of TH17 cells duringC. rodentium infection is selectively impaired, whereas the generation of TH1 cells is dramatically increased inDOCK8-deficient mice in comparison to WT mice. DOCK8 is a very large protein that has been shown tofunction as guanine nucleotide exchange factors (GEFs) that binds and activates small GTPases of theRho/Rac/Cdc42 family. In order to determine whether DOCK8 function in the generation of TH17 cells isdependent on its GEF activity for CDC42, or its interaction with WASp, a protein that plays an important role inthe organization and function of the actin cytoskeleton, we infected mice in which CDC42 or WAS wasspecifically eliminated in T cells. Whereas DOCK8-deficient mice were unable to mount a robust TH17 cellresponse upon infection, CDC42 T cell-deficient or WAS T cell-deficient mice developed a TH17 cell responseas robust as WT mice. From this study, we concluded that at least for the development of TH17 cells, DOCK8is likely acting as a scaffolding protein rather than a GEF for CDC42, or via its interaction with WASp. Thus, Itis possible that DOCK8 might act as a scaffolding protein that is important for the activation of unknown factorsnecessary for the differentiation of TH17 cells. Here we hypothesize that DOCK8 regulates the function ofTH17 cells by interacting with a specific set of proteins selectively expressed in TH17 cells and not in TH1cells. In order to identify proteins that interact with DOCK8 in vivo, we have generated a novel Knockin mousein which endogenous DOCK8 was fused to AVI tag, Flag and GFP reporter. The AVI tag technology will allowus to perform proteomics and Mass spectrometry analysis in a relatively small number of primary T cells,whereas the GFP will allow us to perform confocal microscopy and track DOCK8 subcellular localization inboth ILCs and TH17 cells. Overall, our proposed studies will help us understand why DOCK8 deficiency hassuch a profound effect on the immune system.	5R01AI140626-02
JOHNSON, SIMON C	Center for Developmental Biology and Regenerative	The role of mTOR in mitochondrial encephalopathy	Project Summary/AbstractOur overarching goal is to define the molecular mechanisms underpinning the pathogenesis ofmitochondrial disease. Our overall objective in the studies proposed here, which represent the next step inpursuing this goal, is to characterize the pathogenesis of subacute necrotizing encephalopathy and define therole of mTOR in this disease using the Ndufs4(KO) model.Genetic mitochondrial diseases include an array of symptoms, may affect one organ or present as amultisystem disorder, and are remarkably heterogeneous in severity. There are few good models for thesediseases and no effective treatment options for mitochondrial disease of	4R00GM126147-03

	Medicine (CDBRM)		any etiology. A clear understanding ofthe pathogenesis of individual mitochondrial diseases is severely needed; the molecular mechanismsunderlying their multiple distinct clinical manifestations are currently unknown.Subacute necrotizing encephalomyelopathy, or Leigh syndrome (LS), is a fatal pediatric mitochondrial disease.Characteristic features of LS include region specific necrotizing lesions of the brain. Though these lesions arethe major defining feature of LS, virtually nothing is known of initiating events, what underlies the spatial andtemporal specific aspects of the disease, or why some regions of the CNS are inexplicably spared. Our recentwork has shown that inhibition of the nutrient sensing signaling complex mTOR attenuates LS in a mousemodel, but the mechanisms underlying the benefit are unknown.The goal of this proposal is to define the pathogenesis of LS and the role of mTOR in this disease. Wehypothesize that the neurological lesions characteristic of LS result from region and cell-type specific effectsof mitochondrial dysfunction, and that mTOR inhibition acts through a discreet downstream neurotoxicpathway.Our experiments will take advantage of the Ndufs4(KO) mouse model of LS, a premier model of humangenetic mitochondrial disease which closely resembles human LS. Using this model, we will use characterizethe cellular and molecular pathogenesis of neurological lesions in LS by i) identifying the earliest type of celldeath and ii) the CNS cell types first lost in lesion formation, iii) defining the region, cell, and cell compartmentspecificity of phospho-proteome changes during CNS lesion formation, and iv) testing the role of key mTORregulated pathways in LS using pharmacological approaches. Ultimately, this work will expose basic molecularfeatures of LS and mitochondrial disease in general. In addition, the career development and trainingcomponents of this proposal will provide key elements for my successful transition to an independent career.	
KALUME, FRANCK K	Center for Integrative Brain Research (CIBR)	Mechanisms of epilepsy-related death in Leigh syndrome	Loss-of-function mutations in NDUFS4, the gene that encodes a subunit of the protein complex I in themitochondrial electron transport chain, are strongly associated with Leigh Syndrome (LS). LS, or subacutenecrotizing encephalopathy, is a debilitating progressive neurodegenerative disorder. It typically presents withmulti-systemic clinical symptoms which result in disability and ultimately death by 3 years of age.Mouse models of LS, generated by global or CNS specific Knock Out (KO) of Ndufs4, exhibit several keyclinical features of human LS, including failure to thrive, growth retardation, ataxia, hypotonia, visual problems,breathing irregularities, and spontaneous seizures and deaths. Our preliminary studies of conditional Ndufs4KO mice reveal that the epilepsy phenotype can be dissociated from most of the other features of LS, usinggenetic approaches. Selective KO of Ndufs4 in GABAergic (not glutamatergic) neurons causes spontaneousseizures and leads to sudden death in mice. Therefore, work in this proposal will explore the intriguingpossibility that Ndufs4 is a SUDEP gene and GABAergic neuron dysfunction, caused by its KO, is the principalcause of epilepsy and SUDEP in LS mice. Indeed, these mice present a unique opportunity for functionalstudies of SUDEP risks associated with LS-causing Ndufs4 mutation in particular and interneuron dysfunctionin general.Interestingly, current gene discovery studies have postulated that a SUDEP gene might be best identified as amutation or pathogenic variant that causes epilepsy and increases SUDEP risk via central or peripheralnervous system or end-organ effects on respiratory, cardiac, or other autonomic functions. The forebrainincludes regions known to be involved in seizure generation and the brainstem encompasses control centersfor autonomic functions, commonly affected in SUDEP. In this project, we will examine the role of interneurondysfunction in mechanisms SUDEP in Leigh syndrome epilepsy using mouse models. We will: (1) Comparethe contributions of Ndufs4 KO in excitatory (by Vglut2cre) and inhibitory (by Gad2cre) neurons to SUDEPsusceptibility in LS mice; (2) compare the contributions of Ndufs4 KO in forebrain (by Dlxcre12) and brainstem(by viral cre) GABAergic neurons to SUDEP susceptibility in LS mice; and (3) determine changes in intrinsicand synaptic functions of forebrain interneurons that contribute to epilepsy and SUDEP pathophysiology in LSmice. Findings from these studies will provide insights into the mechanisms of sudden death in Leighsyndrome, the most common form of mitochondrial disorder in children.	5R01NS102796-03
KAPPE, STEFAN HI	Center for Global Infectious Disease Research (CGIDR)	Molecular Determinants of Sporozoite / Host Cell Interactions	PROJECT SUMMARY/ABSTRACTMalaria, caused by Plasmodium parasites, continues to be a major global health problem, with more than 200million new infections and nearly 500 thousand deaths annually. Infection initiates when sporozoite stages areinoculated into the skin by the mosquito vector. Sporozoites then move in the skin tissue, enter the bloodstream and reach the liver. Sporozoites traverse cells before eventually infecting a hepatocyte within areplication-permissive parasitophorous vacuole (PV). Ensconced in the PV membrane (PVM), a singlesporozoite will transmogrify into a liver stage that replicates and then forms tens of thousands of merozoites.These are released from the liver and infect and replicate in blood cells, which causes all clinical symptoms ofmalaria and enables further parasite transmission. Targeting the pre-erythrocytic sporozoites thus representsan attractive intervention point since they are small in number, and successful disruption of the molecularinteractions required for infection would completely prevent disease and transmission. However, little is knownabout the critical molecular interactions leading to productive sporozoite entry into the host, infection of the liverand invasion of hepatocytes. In this proposal, using novel approaches, we will focus on elucidating themolecular map of infection that involves the sporozoite protein complexes containing P52, P36 and the TRAPcomplex, and their interactions with the host receptors EphA2, CD81 and PDGFRb, respectively. Currently weonly know that P36 and P52 are essential for establishing productive hepatocyte infection with a PVM and thatthe hepatocyte surface receptors EphA2 and CD81 are critical for PVM formation as well. In Aim 1, we willinvestigate the dynamics and conditions of release of P52 and P36 from sporozoites during interaction withhepatocytes. Following our preliminary isolation of a P52/P36 complex, we will proceed to determine theprecise molecular interactions within this complex and its interaction with EphA2, CD81 and any other novelputative receptor(s) identified. In Aim 2, we will focus on the hepatocyte surface to further study the functionalsignificance of EphA2 during hepatocyte invasion and PV formation as well as its relationship to CD81 andnovel receptors. In Aim 3, we will investigate a novel parasite-host interaction pair identified by us betweenhost protein PDGFRb and the sporozoite adhesin TRAP, and the importance of this interaction for hostinfection in the context of a large TRAP-containing sporozoite protein complex that we have recently identified.Upon completion of the proposed work we will have a clear molecular map of the interactions of criticalsporozoite invasion-related protein complexes and host receptor complexes. This data will be important todesign targeted interventions such as infection-blocking antibodies or small molecule inhibitors and as such willcontribute to the goal of preventing malaria infection.	5R01AI134956-03
KAPPE, STEFAN HI	Center for Global Infectious	Inducing durable, protective	Project Summary The goal of generating a licensed vaccine that can provide long-lived immunity against infection withPlasmodium falciparum, the protozoan parasite that causes the most lethal form of malaria, is yet unrealized.Currently, the malaria vaccine candidate that has undergone the most extensive clinical testing is RTS,S, asubunit vaccine based on the circumsporozoite protein (CSP), expressed on the surface of the infectioussporozoite stage of the parasite. Yet, as seen with many other vaccine strategies, protection induced	5U01AI142001-02

	Disease Research (CGIDR)	immune memory against malaria	byvaccination with RTS,S is not only suboptimal, it also wanes rapidly and there is negligible prevention of clinicaldisease measured four years after immunization. A critical bottleneck for the generation of a protective malariavaccine is therefore understanding how to generate long-lived, Plasmodium-specific immune memory, especiallyin people in malaria endemic countries. One promising approach is to gain greater insight into the immuneresponse to whole attenuated sporozoite vaccines, which can lead to the development of high levels(>60%) of sterile immunity in malaria naïve subjects when tested by challenge using controlled humanmalaria infection (CHMI) and has shown for the first time protection against infection in malaria-exposedsubjects in Africa. In this application, we will focus on three major questions that are critical to enhancing ourunderstanding of how immunity can be maintained after whole sporozoite vaccination: 1) how does the innateimmune response after sporozoite vaccination influence the development of long-lived adaptive memory, 2) howdoes previous malaria infection alter the generation of sporozoite vaccine-induced memory and 3) how can weharness recently characterized memory cell signatures in the blood to understand the maintenance of long-livedimmune cells in the tissues after sporozoite vaccination. Our team consists of experts in immunology, vaccinology, parasitology and collaborators that conductsporozoite vaccine trials, and will pursue a fully integrated approach to address these questions. To answerthese questions, we will use both relevant human samples obtained from malaria-naïve and malaria pre-exposedsubjects who received different modes of whole sporozoite vaccination, as well as murine malaria models, whichallow immune system perturbations and access to target organs. We will combine our unique expertise withnovel tools and techniques to provide key insights into how immunological memory can be maintained afterimmunization, which will broadly inform vaccination strategies for malaria, as well as other infectious diseasesfor which vaccines are not currently available.	
KAUSHANSKY, ALEXIS	Center for Global Infectious Disease Research (CGIDR)	Perturbations of host cell signaling by a complex hepatotropic pathogen	Pathogens must successfully navigate the complex interaction networks of their hosts to survive. Duringmalaria parasite liver stage infection, parasites protect their host hepatocyte by preventing its death andexploiting the host cell resources for growth and development. The host hepatocyte molecular signalinglandscape that facilitates successful liver stage replication has not been elucidated, yet it is highly medicallyrelevant. During the first award period of this grant, we have made significant strides towards elucidating anumber of signaling pathways upon which the malaria parasite relies and also identified the critical hostreceptor which parasites engage during entry to establish a permissive environment for intracellular replicationand optimal development. We have generated preliminary data that suggests that malaria parasites must notonly control conventional forms of host cell defense such as apoptosis, but also must carefully regulate an iron-dependent form of cell death called ferroptosis, which to our knowledge has never before been implicated inhost defense against pathogen. This proposal aims to fully delineate the pro-death milieu that the parasite canevade, and what perturbations lead to the demise of the wild-type parasite. We will test the hypothesis that thetumor suppressor P53 is the regulator of ferroptosis in infected cells. We will build on our data whichdemonstrates that P53 is suppressed by Plasmodium infection, and increasing P53 levels can eliminate liverstage parasites. Finally, we will build on our recent discovery that parasites select a subset of hepatocytes forinfection and determine the impact of this selection on establishing optimal host conditions for parasite survival.Throughout the proposed experiments, we will monitor hepatocyte signals not only in response to rodentmalaria infection, but also in response to the most deadly human malaria parasite, Plasmodium falciparum, inpart by using hepatocytes from a mouse with a humanized liver. The proposed studies will lead to a morecomprehensive understanding of the hepatocyte signaling landscape that regulates the success or demise ofthe Plasmodium liver stage. Accomplishing our aims opens the possibility of altering key host factors withsmall-molecules that could prevent a wild-type parasite from progressing to symptomatic erythrocyte infection.Such a host-based approach for prophylaxis is novel and will circumvent the massive problem of continuouslydeveloping resistance to standard antimalarial drugs. This approach is further fostered by the fact that manyhepatocyte proteins are already targets of known therapeutic inhibitors. A more detailed understanding of thecomplex perturbations elicited by this important intracellular pathogen might also reveal new aspects ofhepatocyte signaling.	5R01GM101183-09
KROSHUS, EMILY GRACE	Center for Child Health, Behavior and Development (CHBD)	Developing a tool to support shared decision making post-concussion between adolescents, parents and clinicians	PROJECT SUMMARYEvery year, more than one million U.S. youth sport participants ages 6 to 18 are diagnosed with a concussion.After acute post-concussive symptoms have resolved, clinicians often struggle with how to discuss returning tosport with families. The decision to cease sport is very individualized and cannot be reduced to a singlenumeric cut-off. Influential factors in this decision include clinical variability (e.g., injury severity, recoverytrajectory, type of functional impairment post-injury, the interval between prior injuries, the age at which injuriesoccurred, and premorbid health conditions), different family tolerance for the uncertain risk of harm associatedwith sustaining an additional concussion relative to what they see as the benefits of returning to sport, the risksand benefits of substitute activities, and psychosocial readiness for sport retirement. Further complicating thisconversation is the lack of definitive evidence about about the potential long-term risks of contact sport and theincremental increase in risk with subsequent concussions among youth. Addressing these challenges, we seekto develop and evaluate a decision aid that helps adolescents and their parents/guardians with their clinicianmake an informed and value-driven decision about sport participation post-concussion. We will focus onhelping shared decision making in two situations: (1) the clinician believes there is equipoise in the decisionabout whether to return to or cease participation in contact/collision sport, and (2) the clinician believescontact/collision sport cessation would be medically beneficial but sport disqualification is not mandatory basedon current consensus guidelines. This will be accomplished with a (1) a web-based module to be completedseparately by parents and adolescents pre-visit, sharing risk information and supporting values clarificationrelated to sport participation, and (2) implementation support for clinicians to facilitate within -visit discussion,prioritization and decision-making. To develop an optimally useful decision aid, we will engage a diverse groupof families and clinicians in the development process and will focus on meeting the needs of families with lowhealth literacy. Thus, the following aims will be addressed: (1) Develop a decision aid to support shareddecision-making about sport participation post-concussion using a process of user-engaged contentspecification and design; (2) Conduct usability testing of the decision aid in a clinical setting; (3) Conduct a pilottest of the efficacy of this decision aid in a diverse sample of families presenting to Seattle Children's Hospitalfor post-concussion care. The primary outcome of the pilot clinical trial will be decisional regret. Secondarily,the impact of the tool on sport participation, physical activity and psychosocial outcomes three months post-decision will be explored. Achieving the proposed aims will result in a decision aid that is acceptable to thetarget populations	1R21HD098355-01A1

			and that has preliminary evidence of its efficacy facilitating higher quality decision makingpost-concussion. This will provide the foundation for a subsequent R01 application to evaluate theeffectiveness of the tool in a multicenter cluster randomized controlled trial.1	
LAW, EMILY F	Center for Child Health, Behavior and Development (CHBD)	Enhancing Efficacy of Migraine Self-Management in Children with Comorbid Insomnia	PROJECT SUMMARY ABSTRACTMigraine is a major pediatric health problem impacting 10-12% of youth. Poor sleep is a common comorbidity,particularly insomnia symptoms, which are reported by 65-71% of adolescents with migraine. Insomniacontributes to greater headache-related disability, more frequent headache, higher pain intensity, greateranxiety and depressive symptoms, poorer quality of life, and increased health care use. History of childhoodmigraine places youth at risk for a lifelong pattern of migraine and disability and high health care costs inadulthood. Thus, finding effective methods that support youth in the self-management of migraine is a priority.Cognitive-behavioral therapy (CBT) for pain is an established treatment approach for youth with migraine;however improvements in sleep are inconsistent. In fact, our preliminary data suggest that poor baseline sleepis a risk factor for youth to achieve less improvement in pain outcomes with CBT for pain. Sleep and migraineshare a cyclical relationship, and data indicate that insomnia symptoms increase migraine severity in adultsand children. CBT for insomnia has demonstrated efficacy for improving insomnia symptoms in adults withmigraine and other pain conditions, however, effects on pain have been inconsistent. Post-hoc analysessuggest that changes in pain may occur only after there are sustained improvements in sleep, but this hasnever been empirically tested. In the proposed study, we will address these gaps in knowledge by using aninnovative 2-Phase trial design to: 1) test efficacy of CBT insomnia intervention for youth with migraine andcomorbid insomnia, and 2) investigate how changes in sleep may modify response to CBT pain intervention.We will study a cohort of 180 youth, ages 11-17 years, with migraine (with or without aura, chronic migraine)and comorbid insomnia. In Phase 1, youth will be randomly assigned to receive internet-delivered CBTinsomnia intervention or internet sleep education control over 4-weeks. In Phase 2, all youth will receiveinternet-delivered CBT pain intervention over 8-weeks. Assessments will occur at baseline, immediately afterPhase 1 intervention, immediately after Phase 2 intervention, and repeated 6 months post-intervention. Theprimary outcome for Phase 1 is insomnia symptoms. The primary outcome for Phase 2 is headache-relateddisability. Secondary outcomes are sleep quality and sleep patterns, headache frequency and pain intensity,anxiety and depressive symptoms, and quality of life. Sleep hygiene and pre-sleep arousal will be assessed aspotential mediators. We will use a comprehensive multidimensional assessment of sleep and headacheincluding self-report questionnaires, ambulatory actigraphy monitoring, and 14-day daily diaries. Given the highprevalence of insomnia in adolescents with migraine, extension of CBT insomnia intervention to this populationwill address an important gap in clinical practice and in conceptual understanding of the relationship betweensleep and migraine. By testing a separate CBT insomnia intervention, we will be able to apply this treatment inthe future to other pediatric populations (e.g., cancer, arthritis) who commonly experience comorbid insomnia.	1R01HD101471-01
MCELRATH, MARGARET JULIANA	Center for Global Infectious Disease Research (CGIDR)	Immune Responses to Malaria and HIV Infection and Immunization - Clinical Core	The Clinical Core, based within the Vaccine and Infectious Disease Division (VIDD) at Fred Hutchinson CancerResearch Center (FHCRC), will provide relevant expertise in clinical medicine, human subjects research,vaccine trials, and human immunology in support of the scientific aims of the Collaboration focused on theprevention and control of malaria and HIV. In order to most efficiently support the diverse aims of Collaborationprojects, the CC will utilize a variety of resources including: 1) archived samples (e.g., cryopreserved PBMC,serum, plasma) from study participants in relevant completed or ongoing clinical trials, which comprise theprimary source of clinical samples for Collaboration projects; 2) newly obtained samples from existing clinicalnatural history and control cohorts and from specifically designed sub-studies to enable more comprehensiveanalysis within ongoing or planned vaccine or treatment trials; and 3) samples acquired through the clinicalexpertise of collaborating clinicians accomplished in the safe sampling of specialized immunological reservoirs(e.g., bone marrow; lymph nodes; mucosa) using minimally invasive procedures in human volunteers.	5U19AI128914-04
MCELRATH, MARGARET JULIANA	Center for Global Infectious Disease Research (CGIDR)	Immune responses to HIV virus immunization - Project 2	Pre-exposure prophylaxis and treatment can lower HIV infection rates but nearly two million new infections stilloccur worldwide each year. A vaccine that can elicit long-lived protective immunity against HIV infection offersthe best prospect to end the AIDS epidemic. While no licensed HIV vaccine is available, the modest efficacyobserved in the RV144 Thai Trial raises hope that a preventive vaccine is possible. To improve on this efficacy,a deeper understanding of the underlying immune mechanism of vaccine protection is crucial. Our proposedstudies aim at generating critical insights on how to improve anti-HIV T cell function, induce enhanced immunepotency and durability, and develop paths to elicit broad neutralizing antibodies. We are in a unique position toaddress these topics with access to an exceptional set of samples from several HIV vaccine trials and well-characterized HIV infection cohorts. Our proposed studies include assessment of the kinetics of the vaccine-induced immune response in relevant anatomic compartments (lymph nodes, bone marrow and gut) andaccess to cutting edge analytical methods to generate linked datasets that are ideally suited for our proposed,comprehensive systems biology approach. Our project team is uniquely suited to conduct these studies, asleaders and well-established collaborators focused on HIV vaccine research, translational immunology,systems approaches to understand immunological memory, and immune correlates analyses. We expect thatour work will reveal testable hypotheses on the underlying mechanistic interplay between key components ofthe innate and adaptive immune response that are responsible for protection against HIV by vaccination.	5U19AI128914-04
MENDOZA, JASON A	Center for Child Health, Behavior and Development (CHBD)	Fit 5 Kids Screen Time Reduction Curriculum for Latino Preschoolers: A RCT	ABSTRACT Screen time is a major risk factor for childhood obesity and inadequate physical activity, both of whichare determinants of type 2 diabetes (T2D), cardiovascular disease, and multiple cancers. Latinos are thelargest and fastest growing minority in the US. Because US Latino children have more screen time and higherrates of obesity than their non-Latino White peers, interventions to reduce screen time adapted for Latinopreschoolers are necessary to reduce health inequities related to obesity and T2D in the US. However, asystematic review reported no successful screen time reduction interventions among Latino preschoolers. Our team's pilot study tested the culturally adapted Fit 5 Kids screen time reduction curriculum amongLatino preschoolers in Head Start. This short term cluster randomized controlled trial (RCT) is the onlysuccessful screen time reduction program for Latino preschoolers, having significantly reduced screen time byover 25 minutes/day. Our culturally adapted, multi-level intervention consists of lessons taught by study staffdirectly to preschoolers during Head Start, a weekly parent newsletter, child-tailored goal setting with parents,a lending library (books, games, arts/crafts, etc.) and parenting tips via text messages several times/week. Wewill use a social ecological model and consider multiple levels of influences for analyses: (1) individual-levelinfluences, e.g., acculturation and social cognitive theory, (2) families, e.g., screen time parenting practices, (3)schools, and (4) macro-environmental influences, e.g., neighborhood disorder. Building on this pilot work, wepropose a long term, efficacy, cluster RCT of the culturally adapted Fit 5 Kids among Latino preschoolers inHead Start from three US settings: Seattle,	5R01DK113005-03

			Houston, and the rural Central Valley of Washington State. Among280 Latino 3-5 year olds at 20 Head Start centers, our Specific Aims (SA) and Hypotheses (H) include:SA1) To conduct a cluster RCT of the culturally adapted Fit 5 Kids curriculum to evaluate its efficacy inreducing screen time and excessive weight gain over a school year (8-months) H1) Fit 5 Kids will decrease children's screen time (primary outcome), BMI z-scores and dietary energyintake, and increase MVPA compared to controlsSA2) To examine mediators and moderators associated with reducing Latino preschoolers' screen time H2) Parents' outcome expectations, self-efficacy, and screen time parenting practices will mediate therelationship between Fit 5 Kids and changes to preschoolers' screen time H3) Parents' depressive symptoms, stress, and social support will moderate changes to child screen time The proposed Fit 5 Kids cluster RCT will confirm the pilot's promising results, and the larger sample willallow for mediation analyses to better understand mechanisms. This research will provide justification for afuture community effectiveness trial with implementation by Head Start teachers, and the eventual widespreaddissemination of Fit 5 Kids in Head Start centers nationally.	
MIAO, CAROL H	Center for Immunity and Immunotherapies (CIIT)	Ultrasound-mediated gene delivery to achieve therapeutic correction of hemophilia A	Project SummaryThe goal of this proposal is to achieve long-term therapeutic correction of hemophilia A (HemA) via a noninvasiveprotocol of ultrasound (US) mediated gene delivery (UMGD) of factor FVIII (FVIII) plasmids in the dog model.HemA is a genetic disorder characterized by a deficiency of the blood clotting FVIII. Patients are treated acutelyor prophylactically by protein replacement therapy, which is very costly and inconvenient. Gene therapy is highlypromising for treating HemA patients by delivering hFVIII transgene into targeted cells to persistently producetherapeutic levels of FVIII protein. Recent clinical trials for HemA gene therapy using recombinant adeno-associated viral (rAAV) vectors have shown very promising results. However, significant obstacles remain toprevent treatment to a significant portion of patients especially patients who have high-titer anti-AAV antibodies.Repeated treatment is also prohibited. UMGD has emerged as an effective gene transfer approach with greatclinical relevancy and translational potential. In comparison to viral gene transfer, UMGD transfers plasmidvectors that are easier to prepare and more cost-effective; it also elicits less immune response and toxicity dueto specific tissue targeting, prevents random integration, and allows for repeated delivery of the vectors. Othernonviral gene delivery method such as DNA-packaged nanoparticle encounters the challenge of crossing thenuclear envelope for DNA transcription. We have established a minimally invasive, transhepatic venousapproach to efficiently deliver plasmid DNA (pDNA)/microbubble (MB) mixture into the target liver lobe combinedwith transcutaneous US applications in large animal models. We showed that high levels of luciferase reportergene expression were achieved in swine and therapeutic levels of FVIII expression was detected in canine0using the clinically feasible protocol. Only transient tissue damages were observed and repaired quickly andreturned to normal within short time. However, in order to translate this novel technology to clinics, we recognizethat several major problems need to be solved, (i) higher FVIII expression levels are needed to achieve a long-term therapeutic effect, (ii) persistence of therapeutic FVIII expression needs to be evaluated and maintained,(iii) consistently high efficiency of US treatment on targeted liver tissue is needed to achieve reproducible andefficient transfection. (iv) Better functional FVIII expression and reduced liver damage are desired. This may beachieved by targeting FVIII transfection in liver sinusoidal endothelial cells (LSECs), the native site of FVIIIsynthesis or by using newly synthesized nanobubbles (NBs). Thus, we propose to continue improving thetranscutaneous UMGD instrument, transducers, US protocols, FVIII plasmid constructs, and MBs/NBs in miceand swine. Furthermore, we will deliver FVIII gene using the best transcutaneous UMGD protocol combined withoptimal plasmid constructs and MBs/NBs to achieve persistent and therapeutic levels of FVIII expression innormal and HemA dogs. These progresses will promote the eventual translation of this novel technology intohuman application, bringing significant benefit for treating HemA patients, and potentially other genetic diseases.	1R01HL151077-01A1
PARK, JULIE R	Center for Clinical and Translational Research (CCTR)	Accelerate cellular immunotherapy development for treatment of life-threatening childhood disorders	Project Summary & AbstractDysregulated or dysfunctional immunity is well documented in human disease states ranging from auto-immunity to infection and cancer. A deeper understanding of the role of the immune system in human diseasebrings with it the real potential of immune-directed cellular therapies. However, the complexity and expenseassociated with the generation of cell therapies that are both patient- and disease-specific prohibit broadapplication at the current time. Progress in the setting of rare pediatric conditions is further hampered by thefact that the financial returns on investment are in many cases not considered favorable for industry-sponsoredresearch and development. This U01 Innovative Award application is designed to accelerate the translation ofcellular immunotherapies to treat disorders that affect children and adolescents through the establishment ofthe Consortium for Pediatric Cellular Immunotherapy comprised of quaternary care pediatric hospitalsaffiliated with their Clinical and Translational Science Award (CTSA) programs. We aim to accelerate theimplementation of engineered cellular therapeutic products for cancer (including chimeric-antigen receptor-Tcell therapy and NK cell therapy) or selected immune cellular therapies for treatment of lymphoproliferativedisorders, and viral diseases (viral-specific T cell therapy). In addition, we will also accelerate the novelimplementation of engineered regulatory T-cells to invoke immune tolerance as a therapeutic modality for awide range of disorders that include graft vs. host disease following allogeneic hematopoietic celltransplantation, rejection after solid organ transplantation and pediatric auto-immune diseases. We propose amulti-pronged approach to spearhead the development of cellular immunotherapy clinical trials inpediatric medicine. We aim to expand cGMP manufacturing programs with the capacity to supply productsthrough multi-center clinical trials, to establish a centralized clinical trials/regulatory affairs coordinating office toefficiently implement cellular immunotherapy clinical research for rare pediatric diseases, to increase efficiencyand reliability of analytic assays to monitor safety and clinical efficacy of cellular immunotherapy trials and todevelop collaborations necessary to sustain this infrastructure beyond the life span of the U01 grantmechanism. There will be a directed focus on training the translational workforce at each participating CTSAhub and establishing standard processes and procedures that can be easily disseminated to other hubs in thefuture. Moreover, within we will establish key collaborations between academia and pharma to ensure longterm sustainability and to broaden our advances towards applicable adult disease states. While our initial workwill develop a limited consortium of CTSA sites, our long-term goal is to expand these processes to enableexport of cellular immunotherapy trials to all CTSA sites and ultimately beyond.	5U01TR002487-02
PILIPONSKY, ADRIAN M.	Center for Global Infectious	Critical Role of Basophils in the Enhancement of	PROJECT SUMMARYThere are approximately 850,000 new cases of sepsis each year with mortality rates ranging from 240,000-375,000. An impaired innate immune response can aggravate the septic condition by compromising thepatient's ability to combat an infection. However, the cells and mediators that enhance the innate immuneresponse in sepsis are still unknown. Basophils account for less than 1% of peripheral blood leukocytes, whichmakes them the rarest known granulocytes. Basophils are evolutionarily conserved in many	5R01HL141094-02

	Disease Research (CGIDR)	the Innate Immune Response during Sepsis	animal species,suggesting a beneficial rather than deleterious role of basophils. Nevertheless, it is unknown whether basophilsplay any role in the host's defense against bacteria that can potentially prevent sepsis development. Ourpreliminary studies support such a role by showing that basophils are one of the very first cells to accumulateat the infection site at early stages of infection, and can improve survival and bacteria clearance in thepolymicrobial model of sepsis induced by cecal ligation and puncture (CLP). We think that our findings in themurine system may be translatable to humans because we observed that trauma patients show increasednumbers of basophils in circulation when a nosocomial infection was circumscribed to local tissues (earlystages of infection) while basophil numbers decreased or remain unchanged when a patient developed asystemic infection (bacteremia) and was therefore at high risk of developing sepsis. Based on these studies,we hypothesize that basophils play a protective role in sepsis by enhancing the innate immune responseagainst infection. Accordingly, we propose a research plan aimed at investigating the contribution of basophilsto the innate immune response against bacteria. In Aim 1, we will identify mechanisms involved in basophilactivation during an infection. We will use a genetic approach to investigate whether basophil stimulationthrough the TLR and MyD88 pathways is required to induce basophil activation and to confer protection duringan infection; and we will examine whether the epithelial cell-derived cytokine, thymic stromal lymphopoietin(TSLP), can enhance the ability of basophils to respond to an infection. In Aim 2, we will define themechanisms by which basophils confer protection against bacterial infections. Specifically, we will investigateinteractions between basophils, the endothelium, and circulating leukocytes in a microvessel system and wewill use mice with basophil-specific TNF deficiency to study these interactions during CLP. In Aim 3, we willestablish the relevance of basophils in human infections and sepsis. Specifically, we will use mass cytometry(CyTOF) to assess basophil immune functions in samples collected from patients that develop nosocomialinfections, mainly pneumonia, and we will establish whether these immune functions associate with clinicaloutcomes. We think that the studies proposed will expand our knowledge of sepsis physiopathology.Specifically, our studies will provide, for the first time, evidence for a critical role for basophils in theenhancement of the innate immune response against bacteria, an unexpected role for this rare cell population.	
PORTMAN, MICHAEL A	Center for Integrative Brain Research (CIBR)	Genetic Prediction for Treatment Resistance in Kawasaki Disease	PROJECT SUMMARY/ABSTRACTKawasaki Disease (KD) is a major contributor to cardiovascular morbidity in children. Poor response to IVIGremains one of the critical determinants of coronary artery risk in KD. The inability to predict this responseand the potential for developing persistent coronary artery aneurysms serves as a major impediment toprogress and development of intensified therapy. Currently available data indicate that KD susceptibility andtreatment response, as well as the propensity for coronary artery disease, depend on an individual patient'sgenetic background. Studies directed at identifying appropriate genetic biomarkers have been impaired by: 1)phenotyping lacking rigor, 2) use of genome wide association studies often employing chips or arrays fordetection of common variants rather than low frequency or rare variants, 3) lack of clarity for the mechanismsof IVIG anti-inflammation in KD (necessary for guiding most pharmacogenomics studies) 4) focus on genecandidates, which are impractical for clinical testing, and 5) vague racial assignment methodologyconfounding pharmacogenomics. Furthermore, exome sequencing and analyses likely would miss potentialimportant variants as IVIG anti-inflammatory mechanism includes transcriptional regulation at intergenicregions. We hypothesize that, by using improved and rigorous phenotyping techniques in combination withwhole genome sequencing (WGS) and analyses, we will be able to identify select biomarkers for accurateprediction of KD treatment response and development of coronary aneurysms. The Pacific NorthwestKawasaki Disease Data-Biobank, established mainly through funding via PI Portman, R21HL090558,Thrasher Research Foundation; and PI, Shrestha, Southeastern AHA has accumulated DNA and clinicaldata from over 800 KD patients, eligible for pharmacogenomics analyses. We will leverage this wealth ofDNA and clinical data along with recently updated AHA clinical KD criteria in order to identify rare andcommon variants, which determine IVIG treatment response. WGS will also allow a) identification ofindividual private SNPs (rare variants), b) identification of population-specific private SNPs, c) building acomplete picture of genetic variations including structural variants (CNVs and insertion/deletions), d) gene-based analysis of both common and rare variants, and e) identification of actual functional SNPs as opposedto common imputed or SNPs in linkage disequilibrium (LD). Additionally, we will account for race, animportant variant in KD, by rigorous racial assignment using ancestry information markers and principalcomponent analyses. We will use rigorous methodology to achieve the following specific aims 1) Performwhole genome sequencing to identify genetic variations, which could serve as clinical biomarkers for IVIGresistance in KD patients. 2) Determine novel genomic variants associated with giant coronary arteryaneurysms (GCA) among children with KD. 3) Prepare to assess if IVIG resistance is greater among AfricanAmericans and if this response depends on racial based differences in the frequency of genetic variations.	5R01HL146130-02
RABBITTS, JENNIFER	Center for Clinical and Translational Research (CCTR)	Mechanisms of transition from acute to chronic pain in youth undergoing musculoskeletal surgery	Chronic postsurgical pain (CPSP) has been recognized as a major health concern across the lifespan.Adolescents undergoing invasive musculoskeletal surgeries are particularly at risk for CPSP, which occurs inabout 20% of youth after surgery. CPSP is associated with significant functional disability and reduced physicaland psychosocial health-related quality of life. Chronic pain in adolescence also places individuals at risk forchronic pain in adulthood, as well as risk for substance use disorder, generating potential lifelongconsequences on functioning, productivity, and quality of life. In our own preliminary studies in a small sampleof adolescents having major surgery, we demonstrated that (1) youth who develop CPSP may follow distinctrecovery patterns that emerge within the first 2 weeks following surgery, and (2) baseline psychosocial riskfactors predict development of CPSP. However, further studies are needed to understand recovery during theinitial weeks following surgery when acute postsurgical pain begins to transition to CPSP. Although there isindication from prior studies that psychosocial factors may play a role in CPSP, there has been limited data onfurther biopsychosocial mechanisms that influence the transition from acute to chronic pain aftermusculoskeletal surgery in adolescents. These gaps in knowledge have limited the development andimplementation of perioperative interventions targeted at the mechanisms of the transition from acute to CPSPto positively alter the trajectory of postsurgical recovery. Thus, this project aims to 1) develop valid and reliableacute recovery indices using short-term trajectories of pain, sleep quality, mood, and physical function over thefirst 30 days following spinal fusion surgery, and 2) determine the psychosocial and psychophysicalmechanisms contributing to the transition from acute to chronic postsurgical pain. To address these aims, wepropose a 2-site prospective longitudinal cohort study in 160 youth aged 10 to 18 years undergoing spinalfusion surgery, and their parents. Prospective assessments of pain, health, and functional outcomes will becollected before surgery and at three time points during the 6 months after surgery. Immediately after surgery,adolescents will complete daily monitoring of pain, sleep quality, mood, and physical function in the first 30days following hospital discharge using ecological momentary	5R01AR073780-02

			assessment. These data will be used to developvalid and reliable acute recovery indices that predict CPSP at 3 and 6 months post-surgery. We will measuretwo potential sets of mechanisms underlying the transition from acute to CPSP, psychosocial variables andlaboratory-based psychophysical pain responses, before surgery and at 8-weeks post-surgery in order todetermine the temporal influence on subsequent development of CPSP. This study will increase understandingof the transition from acute to chronic postsurgical pain and the causal mechanisms involved. The long-termgoal of this research program is to develop effective perioperative interventions to reduce exposure to opioidsand decrease incidence of CPSP in adolescents undergoing musculoskeletal surgeries.	
RAJAGOPAL, LAKSHMI	Center for Global Infectious Disease Research (CGIDR)	Role of the hyaluronidase in GBS Virulence	PROJECT SUMMARYMorbidity and mortality of preterm and newborn infants remain significant public health concerns.Streptococcus agalactiae or Group B Streptococcus (GBS) are a leading cause of bacterial infectionassociated preterm births, stillbirths and early onset sepsis. We recently showed that increased expressionof the hyaluronidase can be associated with GBS invasive disease and induces fetal demise in pregnantmice. The objective of this proposal is to understand how the GBS hyaluronidase subverts the function ofmultiple host innate immune cells to induce fetal injury and systemic infection. Aim 1 will define mechanismsby which the GBS hyaluronidase subverts immune cell function and immune cell recruitment. Aim 2 willestablish how expression of the GBS hyaluronidase promotes microbial invasion of the amniotic cavity andfetal injury in the pregnant nonhuman primate model that closely emulates human pregnancy. Thesestudies will provide novel insight into mechanisms of immune evasion during GBS infections. These resultsare essential and invaluable for development of novel therapeutic approaches to reduce the risk of GBSinfection associated fetal injury, stillbirth, preterm births and neonatal infections.	5R01AI133976-03
RAJAGOPAL, LAKSHMI	Center for Global Infectious Disease Research (CGIDR)	Immune Control of Group B Streptococcal Placental	PROJECT SUMMARY/ABSTRACTIntra-amniotic infection and inflammation remain a significant cause of preterm birth, stillbirth and neonatalmorbidity and mortality. The objective of this proposal is to define early maternal and placental immuneresponses that are critical for resolution of bacterial infections at the maternal-fetal interface. Elucidation ofimmune events occurring at the maternal-fetal interface in human pregnancy is complicated by theinaccessibility of maternal and fetal compartments, which also imposes limitations on our understanding of thenature of the invading organism and cell types directing bacterial clearance. We have overcome thesechallenges by using a unique chronically catheterized pregnant nonhuman primate (NHP) model that closelyemulates human pregnancy. In this proposal, we will elucidate early immune mechanisms that result inbacterial clearance and define the key immune cell-types and host defense networks that protect the fetus frominvasive bacterial infections. We will use the established NHP model of GBS infection to study bacterialclearance at the maternal-fetal interface using innovative methods including: 1) multidimensional flowcytometry to quantitate immune cell populations at the maternal-fetal interface, 2) single cell RNA-Seq togenerate a transcriptional map of cell types and regulatory gene networks, 3) reverse phase protein array toanalyze signalling cascades and host translational networks and 4) sophisticated computational modelling tolink clinical metadata (e.g. bacterial burden, peak uterine activity) with single cell RNA-Seq and protein arraydata. The proposed aims will thus establish the temporal and spatial nature of immune responses and hosttranscriptional and translational networks essential for bacterial clearance at the maternal-fetal interface duringpregnancy.	1R01AI145890-01
RAMIREZ, JAN M.	Center for Integrative Brain Research (CIBR)	Unraveling respiratory rhythm generation in the medullary network	PROJECT SUMMARYBreathing is vital for survival, and failure to breathe is fatal. This has become tragically evident in the context ofthe current opioid crisis. Breathing disturbances are also the cause of sleep apnea, which is another healthissue of epidemic proportions. At the core of all these disturbances are neuronal networks located within thebrainstem. Two of these networks, the preBötzinger complex (preBötC) and the parafacial respiratory group(pFRG) are thought to give rise to inspiration and active expiration, respectively. During the initial fundingperiod of this grant, we identified a third excitatory microcircuit, the postinspiratory complex (PiCo), which givesrise to a third breathing phase: postinspiration – the expiratory phase that follows inspiration. Based on ourdiscovery, we proposed the triple oscillator hypothesis: i.e. three excitatory microcircuits (preBötC, pFRG,PiCo) give rise to the three phases of breathing. However, the discovery of PiCo raised an important,unresolved issue: what is the role of the so-called Bötzinger complex (BötC), a fourth region that containsrespiratory neurons, and that is located rostral of the preBötC?Here we test the overarching hypothesis that the preBötC is not a small microcircuit, as previously thought, butthat this network forms a dynamically regulated column contiguous with the BötC. The extent of this column isdynamically regulated by synaptic inhibition, chemo- and mechanosensory afferents. The project tests thishypothesis in three specific aims: Aim 1 maps the extent of respiratory activity along the medullary column. Wewill use electrophysiological, calcium imaging and optogenetic approaches to characterize the neuronaldischarge patterns within this column. Aim 2 investigates the cellular determinants that control the extent of thiscolumn using intracellular and optogenetic recordings. We specifically test the hypothesis that a balancebetween synaptic inhibition, and excitation regulates the regularity, frequency and spatial extent of the column.To conduct aims 1 and 2 we will employ horizontal brainstem slices that isolate the entire ventral medulla andthat are amenable to a rigorous cellular and network analysis. Aim 3 explores the dynamic regulation of thecolumn in alert and anesthetized in vivo animals. We test the hypothesis that vagal and chemosensoryafferents play a critical role in regulating the spatial extent of this column by activating inhibitory neurons thatare capable of shrinking and extending the inspiratory rhythmogenic network. The proposed research may leadto a better understanding of the fundamental question: how the brain generates rhythmic motor activity andhow it integrates sensory information. Insights gained will also have important implications for understandingthe cellular and systems level mechanisms underlying the mortality and morbidity associated with breathingdisorders.	2R01HL126523-05A1
RAMIREZ, JAN M.	Center for Integrative Brain Research (CIBR)	Unraveling the dynamic mechanisms underlying opioid respiratory depression	PROJECT SUMMARYThe opioid epidemic claims more than 50,000 lives every year and contributes to a significant drop in overalllife expectancy in the USA. The primary cause of death associated with opioid-based analgesics and drugs ofabuse is Opioid-mediated Respiratory Suppression (ORS). Although, the mortality risk increases in a dose-dependent manner, opioid use is particularly dangerous because it is unpredictable. Many conditions increasethe vulnerability to opioids, including sleep disordered breathing, which is very common among opioid users.Opioids cause respiratory depression and terminal apnea by inhibiting rhythmogenic networks within theventrolateral medulla. This project has 4 aims to explore the medullary mechanisms underlying ORS. Aim 1employs a variety of electrophysiological, pharmacological, and optogenetic approaches in vitro and in vivo toexplore how opioids inhibit the inspiratory rhythmogenic network. This opioid-sensitive network forms a columnthat dynamically extends beyond the well-known preBötzinger complex, a microcircuit that is essential forbreathing. Aim 2 will obtain horizontal slices from this rhythmogenic column to dissect the pre- and postsynapticmechanisms that are responsible for the cessation of inspiratory activity. Aim 3 will investigate how opioidsinhibit	5R01HL144801-02

			Postinspiration within the postinspiratory complex (PiCo), an excitatory network that is an order ofmagnitude more sensitive to opioids than the preBötC. The mechanisms revealed in aim 1-3 will provide thebasis for aim 4, which will explore combinations of substances capable of reversing ORS in alert animals. Thisproject introduces novel concepts of respiratory rhythmogenesis and describes multiple mechanisms of opioidactions, which could explain why opioid respiratory depression is so unpredictable. We test how opioidmodulation is sensitized by hypercapnic conditions and chronic intermittent hypoxia, both conditions are oftenexperienced by opioid users. The proposed research may lead to a better understanding of the mechanismsunderlying the mortality and morbidity associated with the opioid crisis.	
RAMSEY, BONNIE W	Center for Clinical and Translational Research (CCTR)	Administrative Core	The Administrative Core will continue to be responsible for the coordination and overall direction of the CysticFibrosis Research and Translational Core Center (CFRTC). It is responsible for all fiscal management of thebiomedical core facilities, pilot and feasibility projects and the enrichment program. The core fostersinteraction and cooperation among core directors and other investigators nationwide that utilize the centerprograms to enhance translational research. A web site for the Center is maintained by the core. In addition,the Administrative Core manages a shared resource database that can be used by each of the core directorsto facilitate tracking of projects and PIs that utilize core services, as well as publications that result fromprojects supported by the core. The core staff serves as the communication link between Seattle Children'sResearch Institute (SCRI), the University of Washington, and the NIDDK.	5P30DK089507-10
ROSENBERG, ABBY R	Center for Clinical and Translational Research (CCTR)	The Promoting Resilience in Stress Management (PRISM) Intervention: a multi-site randomized controlled trial for Adolescents and Young Adults with advanced cancer	PROJECT SUMMARYCancer among Adolescents and Young Adults (AYAs) is particularly difficult because age-relateddevelopmental challenges of identity, relationships, and vocation may add to the burden of cancer. Comparedto other age-groups, AYAs have poorer psychosocial outcomes. Among AYAs with advanced cancer, toomany miss opportunities to express their hopes, worries and end-of-life preferences, translating to both patientand parent distress. A potential barrier to improving these experiences may be that AYAs have fewopportunities to develop the personal resources needed to handle adversity and articulate their needs. Wehave previously described the "Promoting Resilience in Stress Management" (PRISM) intervention for AYAswith cancer. This manualized, brief intervention is delivered in 4, 30-60 minute, one-on-one sessions, followedby a family meeting. It targets skills in stress-management and mindfulness, goal-setting, positive reframing,and meaning-making. All of these skills are associated with improved patient well-being in other populations,and findings from a recent pilot randomized controlled trial among AYAs with newly diagnosed cancer suggestPRISM is associated with improved perceptions of resilience, lower psychological distress, and higher health-related quality of life (HRQOL). This application proposes to build on our prior experience and fill three criticalknowledge gaps: (1) PRISM's impact among AYAs with advanced (as opposed to early stage) cancer; (2)Associations between AYA-PRISM participation and parent outcomes; and, (3) Associations between PRISMskills and patient engagement in clinical decision-making. This funding opportunity seeks to test AYA-specificpalliative care interventions designed to positively impact HRQOL. Thus, we propose a multi-site randomizedcontrolled trial among N=144 AYAs (n=72 PRISM, n=72 Usual Care; ages 12-21) with the primary trialoutcome of patient-reported HRQOL 3 months following enrollment. Secondary outcomes will include patient-and parent-reported anxiety and depression, and family "palliative care activation" (advocacy on behalf ofAYA's hopes and worries, engagement in goals-of-care conversations, and utilization of formal palliative careand psychosocial services). We hypothesize that AYAs who receive PRISM and their parents will report higherHRQOL, lower anxiety/depression, and higher activation when compared to those who receive usual care.This application offers an opportunity to expand the body of knowledge regarding methodologically rigorousand evidence-based palliative care interventions and standards of care for AYAs with advanced cancer andtheir families. Ultimately, this research has the potential to reduce the burden of cancer in these vulnerablepopulations.	5R01CA222486-02
ROSENBERG, ABBY R	Center for Clinical and Translational Research (CCTR)	The Promoting Resilience in Stress Management (PRISM) Intervention: a multi-site randomized controlled trial for Adolescents and Young Adults receiving Hematopoietic Cell Transplantation	PROJECT SUMMARYThe experience of hematopoietic cell transplantation (HCT) for hematologic malignancy amongAdolescents and Young Adults (AYAs) is particularly difficult because age-relateddevelopmental challenges of identity, relationships, and vocation may add to the burden ofcancer. Compared to other age-groups, AYAs have poorer psychosocial outcomes includingincreased anxiety and depression and poorer adherence to oral immunosuppressivemedications. These outcomes may, in turn, predispose AYAs to disease-related morbidity andmortality such as graft-versus-host disease (GVHD) and/or cancer-relapse. A potential barrierto improving these experiences may be that AYAs have few opportunities to develop thepersonal resources needed to handle adversity. We have previously developed the "PromotingResilience in Stress Management" (PRISM) intervention for AYAs with serious illness. Thismanualized, brief intervention is delivered in 4, 30-60 minute, one-on-one sessions, followed bya family meeting. It targets skills in stress-management and mindfulness, goal-setting, positivereframing, and meaning-making. All of these skills are associated with improved patient well-being in other populations, and preliminary findings from a recently closed pilot randomizedcontrolled trial among AYAs with newly diagnosed cancer suggest PRISM is associated withimproved health-related quality of life. This application proposes to build on our priorexperience and fill a critical knowledge gap regarding PRISM's impact among AYAs receivingHCT. Thus, we propose a multi-site randomized controlled trial among N=70 AYAs (n=35PRISM and n=35 usual care; ages 12-24 years), with the primary trial outcome of patient-reported symptoms of anxiety and depression. Secondary outcomes will include patientadherence to oral GVHD prophylaxis and the cost-effectiveness of the intervention in thispopulation. We hypothesize that AYAs who receive PRISM will report fewer mixed affectivesymptoms and demonstrate better adherence. We also anticipate the intervention will be cost-effective. In sum, this application offers an opportunity to expand the body of knowledgeregarding methodologically rigorous and evidence-based psychosocial interventions andstandards of care for AYAs with hematologic malignancies. Ultimately, this research has thepotential to reduce the burden of cancer in these vulnerable populations.	5R01CA225629-03
ROTH, CHRISTIAN LUDWIG	Center for Integrative Brain Research (CIBR)	Brain systems and behaviors underlying response to obesity	PROJECT SUMMARY Given the high prevalence of childhood obesity in the U.S. and the lack of durable weight loss withexisting obesity interventions, new options that improve pediatric weight management are needed. Intensivefamily-based behavioral treatment (FBT) is the gold-standard intervention for children with obesity and isfocused on changing food environments and parenting around children's eating. The proposed research is arenewal of the Brain Activation and Satiety In Children (BASIC) study which used functional MagneticResonance Imaging (fMRI) to better understand if neurobiological factors impact success in FBT. In this study,55% of children with obesity treated with FBT showed clinically significant reductions in BMI z-score, and evenafter successful treatment, over two-thirds of children increased their BMI z-score 6–12 months after endingFBT. At baseline pre-FBT, children with obesity, compared to children of healthy weight, exhibited anattenuated central response to a satiating meal in which they did not reduce activation by high-calorie	2R01DK098466-05

		treatment in children	foodcues across a set of a priori appetite-regulating brain regions. This pattern also was associated with worse FBToutcomes among obese children undergoing FBT, specifically, less reduction in BMI z-score during treatment.Further, greater BMI z-score reduction during FBT was associated with a decreased neural satiety responseafter treatment. These findings implicate neurobiological factors as a negative input onto children's ability toachieve and maintain clinically significant improvement in weight status via FBT. The proposed follow-upproject builds upon these findings and investigates the hypothesis that adding a glucagon-like peptide-1receptor agonist (GLP-1RA) once weekly drug intervention to FBT will augment BMI z-score reduction, evenamong children who seem initially resistant to FBT, by promoting greater reductions in neural activation inresponse to a meal. In a double-blinded randomized placebo-controlled clinical trial among 64 children aged10-12 years old, Specific Aim 1 will test the effect of adding GLP-1RA to FBT on change in BMI z-score over atotal GLP-1RA treatment duration of 24 weeks and a subsequent 1-year observational follow-up period aftertreatment cessation. To provide mechanistic insight, Specific Aim 2 will test whether adding GLP-1RAintervention to FBT impacts neural activation by food cues. Finally, the proposed research will investigate therole of a cellular inflammatory process in the mediobasal hypothalamus –called gliosis– which might contributeto impaired hypothalamic function, attenuated satiety responsiveness, and potentially to worse weightmanagement outcomes. Specific Aim 3 will test if hypothalamic gliosis is modified by FBT and/or FBT plusGLP-1RA in children and if reduction of gliosis is associated with better long-term outcomes. This researchbuilds upon the team's prior findings to test a pharmacologic intervention with potential to modifyneurobiological barriers to treatment success. The long-term objective is to translate these findings to improveobesity interventions and sustain better long-term results.	
SARKAR, SUROJIT	Ben Towne Center for Childhood Cancer Research (BTCCCR)	Mechanisms of T Cell Memory Quiescence	ABSTRACT Cytotoxic T lymphocytes (CTLs) are a key element of adaptive immunity against intracellular infections andcancers. They are potent antigen-directed killer cells that specifically eliminate infected or diseased target cells.Following pathogen control, a subset of effector CTLs gradually shutdown their immediate cytotoxic functions,while retaining heightened responsiveness to future encounter with the same pathogen. Long-term persistenceof quiescent CTL memory sentinels is deemed a highly desirable outcome for vaccines and modern adoptivecell immunotherapies, to maintain durable protective immunity. The goal of this proposal is to gain mechanisticinsight into how functionally active effector CTLs convert into quiescent memory. The classic paradigm is that effector-to-memory conversion is the default differentiation pathway formemory precursor effector cells (MPECs) after antigen clearance. This is believed to occur simply because ofloss of T cell receptor (TCR) stimulation. However, recent studies from our group and others show that Tregsexert a critical role in the process of effector-to-memory transition following antigen clearance. Tregs promotethe development of quiescent, yet functionally poised memory cells by suppressing effector and proliferativeprograms in memory-fated CTLs. In the absence of Tregs during effector-to-memory transition, criticalmetabolic and transcriptional remodeling does not occur, thus leading to memory failure. Based on brightestexpression levels of CTLA-4 on Tregs (amongst all immune cells), and recent human studies notingdysregulation of Tregs and hyperactivation of T and B cells in CTLA-4 haploinsufficient individuals, we proposethat CTLA-4 is a critical mediator of Treg-dependent reprogramming of MPECs from effector-to-memory state.We further hypothesize that CTLA-4 mediates its effects through direct as well indirect effects on CD8 T cells.Our preliminary studies showing that exogenous administration of CTLA-4 restores homeostasis and fullyreverses the defects in CD8 T cell memory associated with Treg ablation, lend support to the notion that CTLA-4 is the primary initiating signal for Treg-mediated memory CD8 T cell quiescence. Using unique mousemodels, and high throughput cellular and biochemical readouts, the goal of this proposal is to rigorouslyinvestigate the interplay of cellular networks, and transcriptional and metabolic programs in orchestrating Treg-mediated help during memory CD8 T cell development. Over the last decade, there has been significant progress in understanding when and how memory fatecommitment occurs. However, less is known about how quiescent memory cells are formed from effector CTLsonce antigen is cleared, and how quiescent memory cells are maintained for life. Successful completion ofproposed studies will uncover novel strategies for augmenting CD8 T cell memory during immunization, andwill also afford newer immunotherapeutic approaches against cancers and for maintaining homeostasis inautoimmune disorders.	5R01AI132819-02
SATHER, D. NOAH	Center for Global Infectious Disease Research (CGIDR)	Development of a pre-erythrocytic P. vivax vaccine to prevent clinical relapse	ABSTRACTMore than 3 billion people are at risk for contracting malaria caused by Plasmodium vivax (Pv). Pv infectiondiffers from other Plasmodium species in that it develops dormant liver stage forms called hypnozoites.Hypnozoites can reactivate and cause blood stage malaria months to years after primary infection. It isestimated that nearly 90% of active blood stage Pv infections are due to relapse infection and not primaryvector-mediated infection. As such, the dormant form is a major driver of Pv transmission and accounts fornearly the entire clinical disease burden. Therefore, a vaccine that reduces or eliminates the formation ofhypnozoites, and hence reduces relapse infection, would have a significant impact on both disease burden andtransmission rates. Importantly, models suggest that this can be accomplished even in the absence ofsterilizing immunity, because hypnozoites only form in a fraction of the infected hepatocytes.Currently there are no clinically advanced vaccines to prevent Pv infection or relapse. Development effortshave been hampered by the inherent difficulty of working with Pv in the lab, the lack of non-CSP antigens, andthe lack of a biologically relevant model system that mimics Pv infection. Our long term goal is thedevelopment of a pre-erythrocytic vaccine against Pv by creating novel PvCSP vaccines and P. vivax/P.falciparum genetically attenuated parasite (GAP) vaccines that can reduce or prevent relapse infection. To thisend, we put together a research program that addresses all the major roadblocks of Pv vaccine development.We propose to evaluate the efficacy of PvCSP vaccines against relapse, and will study novel, non-CSPvaccine candidates that were recently identified to be part of the surface proteome. We will identify those thatcan augment anti-PvCSP-mediated immunity and reduce or block the formation of hypnozoites. Finally, we willengineer PvCSP (and potentially novel antigens) into the existing PfGAP platform that is under clinicalevaluation. Importantly, we have partnered with Mahidol University in Thailand to enable us to work with wildtype Pv sporozoites. Additionally, we propose to conduct our vaccine development in a completely humanizedmodel system. We will evaluate our vaccines in humanized immunoglobulin mice and test efficacy inhumanized liver mouse models of relapse infection, allowing for a more reliable translation of results in thisstudy toward the eventual deployment of the vaccine into the clinic. Our ultimate goal is the development of anear clinic-ready vaccine that is effective in reducing or eliminating Pv relapse infection.	5R01AI137234-02
SATHER, D. NOAH	Center for Global Infectious	Kinetics, evolution, and effector function	ABSTRACTA safe, effective vaccine remains the best hope for eradicating HIV-1, which now infects 37 million peopleworldwide and results in more than 1.2 million deaths and 1.8 million new infections each year. The only HIV-1vaccine clinical trial to show vaccine efficacy was RV144, which achieved 31% protection from infection.Follow-on analyses identified immunological correlates of reduced risk of infection,	5R01AI140951-02

	Disease Research (CGIDR)	of Fc repertoires during vaccination with native-like Env trimers	finding that vaccineprotection was not associated with neutralizing antibodies. Rather, protection was associated with non-neutralizing antibody activity, i.e., antibody effector function that is mediated through the constant Fc region.As such, there is intense interest in developing vaccines that can recapitulate and enhance the types offunctional antibodies that were found in RV144. However, a gap exists in our knowledge of how suchresponses can best be elicited by vaccination, and how Fc-mediated activity is induced, evolves and endures.It is not clear what effect vaccine modalities have on this process, nor how it can be optimized. In this proposal,we aim to discover the most optimal methods by which Fc-mediated activity can be elicited by vaccines. Wewill assess several vaccine parameters, including antigen, adjuvant, route of inoculation, and prime/booststrategies. Importantly, we will use novel cutting edge, high throughput technologies to define the ontogeny,kinetics, evolution and duration of Fc antibody responses in unprecedented detail and breadth. Further, we willdefine the relationship between vaccine-elicited Fc-mediated function and the antigenic landscape of Env. Ourgoal is to gain fundamental immunological insights into how vaccines drive Fc-related antibody responses, andhow vaccination modalities can be optimized to elicit highly functional, durable antibody responses againstHIV-1. If successful, these findings would guide the development of the next generation of vaccines movinginto the clinic, and would represent a significant step forward for HIV-1 vaccine development, and.	
SHERMAN, DAVID R	Center for Global Infectious Disease Research (CGIDR)	Project 2: Response to Treatment	Abstract – Project 2The responses of Mtb to individual drugs and regimens and their relationship to treatment outcome remainsvariable and poorly understood. Our premise is that knowledge of bacterial networks and their regulatorycontrols constitute a powerful but underexplored window to novel targets and treatment strategies.The major goal of this project is to identify strain-independent and strain-specific cellular networks associatedwith varying drug responses in Mtb, and their regulation. In Aim 1 this project will utilize carefully selectedclinical drug-sensitive Mtb isolates exhibiting varying responses to treatment to characterize the genetic,transcriptional, and metabolic differences revealed by exposure to important anti-TB drugs, and then to mapthose changes to condition-specific drug tolerance phenotypes. We will subject each strain to detailedanalyses including transcriptomics, metabolomics, and regulator-based genetic screens in response to frontline antibiotics and in conditions that promote tolerance. In Aim 2 we will employ the data from Aim 1 tobuild and refine regulatory network models that elucidate both common and strain-specific Mtb strategies tosubvert drug action. These models will be refined by testing model driven predictions through an iterativeseries of multi-omic analyses and perturbations including more focused experiments such as targetedprotein interaction studies, bacterial cell sorting and solid-phase time-lapse microscopy. Ultimately, in Aim 3we will test the extent to which the drug-response network models generated in Aims 1 and 2 predict clinicaltreatment outcomes, and identify potential strategies to interfere with adaptive drug-response network statesto improve the efficacy of chemotherapy. We will further test the relevance of identified drug responsenetworks in targeted studies of Mtb isolates from treatment failures in humans. The outcome of this projectwill be the identification and validation of the specific cellular networks associated with varying drugresponses in Mtb and their regulation.	5U19AI135976-04
SHIC, FREDERICK	Center for Child Health, Behavior and Development (CHBD)	Complex versus Essential Autism: A Developmental Study of Risk	PROJECT SUMMARY/ABSTRACTIn recognition of the developmental heterogeneity of ASD, Miles and colleagues divided ASD into two groups:'complex autism' and 'essential autism'. The label 'complex autism' grouped together children with ASD whohad overt evidence of abnormalities of early morphogenesis, e.g. as signaled by the presence of multipledysmorphic features and/or microcephaly and associated with lower IQs, more seizures, and higher incidenceof EEG and MRI abnormalities. Children with 'essential autism', by comparison, had fewer dysmorphicfeatures, had greater male to female ratios, and showed greater heritability of autism features within families.An implication of this work was that in complex autism, autism was expected to arise as the result of broaddevelopmental insult that also impacted social function, whereas essential autism was viewed as the result ofspecific social neural systems dysfunction. In this study, we use this conceptualization of complex versusessential autism to longitudinally track from 6 to 36 months of age two groups of infants with distinct etiologiesbut common elevation of autism symptoms: very low birthweight (VLBW, n=100) infants, who, like children withcomplex autism, are expected to evidence a broad range of delays in multiple domains, and high-risk infantsiblings of children with ASD (HR-Sibs, n=100), who, as in essential autism, show heightened heritability ofASD symptoms and greater risk for social and communicative challenges. These groups are compared againsta control group of low-risk typically developing children (LR, n=100). We take promising eye tracking (ET) andEEG paradigms that have been associated with the emergence of ASD in HR-Sibs in the first year after lifeafter birth, and which were primarily developed to capture social dimensions of function, and extend them inorder to investigate analogous nonsocial information processing. We hypothesize that VLBW infantsevidencing ASD symptoms will show decreased performance in both social and nonsocial tasks, highlightinggeneralized difficulty with information processing consistent with broader developmental risk, whereas wehypothesize that difficulties in HR-Sibs with similar ASD symptoms will show more specific social (c.f.nonsocial) atypicalities. By adapting and extending paradigms which have shown strong or unique signal forlater ASD in HR-Sibs, we will further our understanding of mechanisms underlying ASD risk and informpotential biomarker discovery; by pairing this with different etiological risk groups, we will elucidate multilevelvulnerabilities that can shape developmental trajectories and the emergence of the disorder. In summary, thiswork will advance our understanding of developmental trajectories of risk associated with ASD, elucidatemechanisms underlying later emergence of core autism features, and help to test and refine the sensitivity andspecificity of putative early neurobehavioral and neurocognitive biomarkers for ASD.	5R01MH115913-03
SHIH, ANDY Y	Center for Developmental Biology and Regenerative Medicine (CDBRM)	Deciphering the Cerebral Microinfarct and its Role in Vascular Cognitive Impairment	Project Summary.Numerous clinical studies have shown that cerebral microinfarcts are likely contributors to vascular cognitiveimpairment and dementia (VCID). However, the mechanism by which these small, but prevalent lesions lead tobrain-wide neural dysfunction remains unknown. Our central hypothesis is that microinfarct injury leads toneural impairments that extend well beyond the restricted lesion cores seen during histological and radiologicalexamination. These remote effects, when accumulated, are a mechanism by which microinfarcts cause large-scale disruption of brain function and cognitive decline. The rationale of the proposed research is to use amouse model where the timing and location of microinfarcts can be controlled in order to better understandhow they cause brain dysfunction. We plan to examine: i) the spatial extent and chronicity of functionalimpairments induced by individual microinfarcts, ii) the cumulative effects of multiple microinfarcts, and iii) thecellular/molecular changes that underlie their remote effects.Our model uses state-of-the-art methods for controlled optical occlusion of targeted cortical penetratingarterioles, individually and in multiples, to precisely and non-invasively form small regions of ischemic injurythat mimic human microinfarcts. The associated injury processes can	5R01NS097775-04

			then be studied in vivo over time usingparallel high-resolution two-photon fluorescence calcium imaging and 7T MRI to reveal detailed aspects ofbrain pathophysiology that are potentially invisible to MRI or histopathology. We further use behavioralparadigms that are sensitive to microinfarcts to uncover their effects on sensory perception and cognitivefunction. Aim 1 of the project tests the hypothesis that cortical microinfarcts induce sustained neuronal deficitsbeyond their lesion core following their strategic induction within the mouse vibrissa sensory system. It furtherexamines whether aberrant change in excitatory-inhibitory balance contributes to these deficits. Aim 2 of theproject tests the hypothesis that the accumulation of multiple microinfarcts, spatially distributed throughout thecortices of both cerebral hemispheres, is sufficient to cause subcortical white matter degeneration (assessed invivo with diffusion MRI tractography and ex vivo with histology) and impairment in cognitive tasks.This work will complement clinical research on VCID in several ways. First, it will provide detailed mechanisticinformation on how, and to what extent, microinfarcts impair remote brain tissues. Second, it will clarify whataspects of microinfarct injury are visible or invisible to MRI, the primary means to detect these lesions duringlife. Third, it will provide unique in vivo MRI-ex vivo histopathology comparisons to reveal the underlyingbiological processes that cause MRI signal change during gray and white matter injury. Fourth, it will establisha first-of-its-kind in vivo experimental platform to study mechanisms of microinfarct-induced pathology and togauge the utility of new therapeutic agents.	
SHNORHAVORIAN, MARGARETT	Center for Clinical and Translational Research (CCTR)	Testicular effects of modern chemotherapy regimens in osteosarcoma survivors	DESCRIPTION (provided by applicant): Among the most important challenges faced by male childhood and adolescent and young adult (AYA) cancer survivors is the reproductive toxicity of cancer chemotherapy. Cisplatin and Ifosfamide form the backbone of chemotherapy for some of the most common childhood and young adult cancers, but there is a gap in knowledge regarding the effects of cisplatin, and the effects of ifosfamide without cyclophosphamide, on spermatogenesis and steroidogenesis in male AYA survivors of childhood cancer and non-germ cell cancer populations. DNA methylation changes are a possible mechanism of action of these drugs on testicular function. A better understanding of these effects will allow for identificationof high risk patients and better prevention strategies for testicular toxicity to be developed for pediatric and AYA cancer treatment protocols. This study will comprehensively evaluate the effects of cisplatin with or without ifosfamide on spermatogenesis and steroidogenesis among childhood and AYA survivors treated with modern chemotherapies for osteosarcoma. Specifically, our aims are: 1) Determine whether infertility and/or biomarkers of spermatogenesis and steroidogenesis differ in male osteosarcoma survivors treated with cisplatin with or without ifosfamide compared to male controls without a history of cancer; 2) Evaluate whether cisplatin with or without ifosfamide for the treatment of osteosarcoma is associated with sperm DNA methylation patterns. Osteosarcoma survivors will be recruited from two COG therapeutic trials [COG AOST0331 and INT0133 (CCG7921 and POG9351)], and controls identified and recruited through address-based sampling. Subjects will complete questionnaires and provide blood, saliva, and semen samples through a mail protocol. Blood samples will be analyzed for testosterone, FSH, LH, Inhibin B; genomic DNA extracted from saliva and stored for future studies of host genetic variation in metabolism of chemotherapeutic drugs storage; and sperm DNA will be assayed using genome-wide methylated DNA immunoprecipitation followed by next generation sequencing. The assembled team and consortium brings together multi-disciplinary expertise in urology, andrology, oncology, epidemiology, biostatistics, and epigenomics. Completion of the proposed research will be a major step towards informing male childhood and AYA cancer patients receiving similar regimens about the adverse effects of their treatment and towards identifying high risk groups that would benefit from targeted strategies for fertility preservation.	5R01CA175216-03
SMITH, JOSEPH DOUGLAS	Center for Immunity and Immunotherapies (CIIT)	Molecular Mechanisms in Pediatric Cerebral Malaria Pathogenesis and Immunity	PROJECT ABSTRACTThe human malaria parasite Plasmodium falciparum remains one of the most important causes of childhoodmortality in the world. Cerebral malaria, the most severe complication of P. falciparum infection, is caused bythe sequestration of infected red blood cells in cerebral microvasculature. The var gene or P. falciparumerythrocyte membrane protein 1 (PfEMP1) is the major cytoadhesion ligand for the parasite. While progresshas been made in understanding the structure and function of PfEMP1 proteins, the key parasite ligand-receptor interactions involved in cerebral binding remain unestablished. Our recent studies have shown thatspecific parasite adhesion types are increased in the blood of cerebral malaria patients, and that parasiteadhesion to endothelial protein C receptor (EPCR) may impair a key anticoagulant and barrier protectivepathway. Moreover, we have shown that hyperlactemia increases fatality risk in pediatric cerebral malaria.However, large knowledge gaps remain in parasite sequestration in brain, in large part due to its inaccessibilityand the lack of appropriate in vitro models. We have recently developed an innovative technology using 3Dhuman brain microvessels that recapitulates physiological flow characteristics in health and disease. We areable to fabricate 3D microvessels with different geometries and lumen dimensions, which allow us to studyparasite adhesion across a range of flow velocities in a single device, as well as to investigate factors thatcontribute to microvascular obstruction in malaria. In this project, we will use 3D human brain microvessels incombination with parasite isolates from pediatric cerebral malaria cases to investigate parasite tropism forbrain, to identify the precise steps of infected red blood cell capture and firm adhesion on brain endothelialcells, to characterize potential interactions between lactemia and parasite adhesiveness, and to investigateantibody protective mechanisms in cerebral malaria. The proposed studies will advance our understanding ofthe molecular mechanisms of P. falciparum binding in cerebral malaria and immune mechanisms in anti-disease immunity.	1R01AI141602-01A1
SMITH, STEPHEN	Center for Integrative Brain Research (CIBR)	Quantitative protein network profiling to improve CAR design and efficacy	PROJECT SUMMARYThis grant is in response to PAR-18-206, Bioengineering Research Grants (BRG). Our goal is to adapt acutting-edge proteomic network analysis platform, Quantitative Multiplex co-Immunoprecipitation or QMI,to chimeric antigen receptor (CAR) T cell signaling. We will then use CAR-QMI to characterize signaltransduction network activation downstream of the CAR, to both understand how the CAR instructs a T cell toattack and destroy cancerous targets, and to make batch-specific predictions about efficacy and side-effectprofiles of CAR T cell products. CAR T cells are a breakthrough anti-cancer therapy that recently won FDAapproval for relapsed B cell lymphomas. A true “personalized medicine”, CAR T cells are manufactured foreach patient from that patient's own T cells by transducing T cells collected by leukopheresis with a viral vectorencoding a CAR. However, since each batch is unique, some batches perform better than others in terms ofproducing remissions and/or deleterious and sometimes fatal side effects including cytokine storms andneurotoxicity. The goal of this project is to develop a “personalized signal transduction network analysisplatform” that can screen each batch of CAR T cells and predict the efficacy and side-effect potential of thatspecific batch. Because signal transduction networks integrate information from multiple input sources- forexample costimulatory and immunosuppressive cell surface receptors, patient genetic background, and T-cellspecific history of activation- we hypothesize that this readout will be a powerful predictor of function.	1R01CA240985-01A1

			Ourpreliminary data show that small changes in CAR design parameters such as scFV binding domain affinityproduce measurable changes in signal transduction network state that correlate with functional variables suchas target killing ability and cytokine release. Further, we show that there exists considerable individual-to-individual variation in batches of CAR T cells produced from different donors. Therefore, the two prerequisitesfor an individualized predictive assay are present- variation in our measurement across the population, and thefunctional relevance of our measurement to outcome parameters. Our interdisciplinary team consists ofexperts in CAR development, signal transduction, proteomics, and bioinformatics. Our ambitious butachievable goals are to expand the QMI panel to include CAR-specific components; to understand how CARdesign parameters influence both signal transduction network states and functional performance measures;and to develop a predictive machine learning algorithm that translates QMI-derived signal transduction networkstates into a functional biomarker of in vivo clinical efficacy. Successful completion these aims will (1) identifyspecific proteins or protein interactions that determine clinically-relevant outcomes such as cytokine productionor cell killing ability, allowing CAR designers to rationally modify the design of CARs to target specific signalingoutcomes; (2) provide clinicians with a test to predict the clinical performance of CAR T cells on a batch-to-batch basis; and (3) provide the community with a novel analytical platform to measure CAR activity.	
SMITH, STEPHEN	Center for Integrative Brain Research (CIBR)	Investigating the synaptic pathology of Autism	PROJECT SUMMARYGenetic mutations that confer autism risk often occur in genes that are expressed at the glutamate synapse.The protein products of these genes form a highly interconnected protein interaction network (PIN), andrepresent attractive therapeutic targets since they are expressed throughout the lifespan and can be acutelytargeted with small molecule drugs. However, the dynamic, network-scale behavior of this PIN in normal ordisease states is poorly understood. Here, we apply a novel PIN-mapping technology, quantitative multiplexco-immunoprecipitation, to explore the input-output relationships of an autism-linked PIN at the glutamatesynapse as it responds to physiological inputs. Our target system is a 20-member PIN, consisting of glutamatereceptors, scaffolds, and signal transduction molecules; mutations in the genes encoding all target proteinshave been genetically linked to autism. We first show that, in wild-type animals, our target PIN changes itspattern of co-associations in a stereotyped manner in response to acute stimulation with KCl or glutamate,using cultured neurons or acute slices. We then model the input-output relationships of the PIN system, anddemonstrate that the PIN produces specific, recognizable signatures in response to stimulation through themGluR or NMDA receptors. In the context of physiological glutamate stimulation, the PIN integrates the twoinputs to produce a coordinated cellular response- potentiation or de-potentiation. Based on these and otherpreliminary observations and published data, we propose that mutations that contribute to autism risk disruptinformation flow through this PIN, such that the balance between LTP-like potentiation and LTD-likedepotentiaion is altered, ultimately leading to an organism-level imbalance between excitation and inhibition.We will test this hypothesis by modeling the PIN response to mGluR or NMDA stimulation in three distinct,well-characterized animal models of autism- the Fragile X knockout, Shank3 knockout, and Ube3aoverexpressing models. We will characterize the input-output relationships for mGluR or NMDA stimulation,and mathematically model their integration using a vector transformation model in principal component space.We will define specific mechanisms by which autism-linked mutations disrupt either input-output relationships,or disrupt signal integration in the context of physiological stimulation. In addition, we will treat two of ouranimal models (Shank3 and Fragile X) with drugs that have been previously demonstrated to rescue autism-like behaviors. We will model the response of the PIN to the drug with or without concurrent stimulation todefine a PIN signature associated with behavioral rescue. In summary we propose to (1) define normalinformation flow through a PIN consisting of the protein products of autism-liked genes; (2) define howinformation flow is disrupted in mouse models of autism, with the goal of understanding the system sufficientlyto design targeted drug treatments and (3) define how the PIN responds to drugs that correct behavior, whichcould serve as a template for the design of PIN-modifying treatments to restore normal synaptic function.	5R01MH113545-03
SODORA, DONALD L	Center for Global Infectious Disease Research (CGIDR)	Mediators of fatty liver disease during HIV/SIV and cART treatment	Liver disease is currently the most common cause of non-AIDS morbidity and mortality in developed countriesamongst HIV infected people. Indeed, non-alcoholic fatty liver disease (NAFLD) is more prevalent during HIVinfection compared to the uninfected population occurring in 30-40% of HIV-infected individuals. Critically,fatty liver disease is becoming an increasingly recognized precursor to non-alcoholic steatohepatitis (NASH),which can further develop into cirrhosis and liver failure. Progression toward NAFLD and steatohepatitis ismultifactorial, and includes metabolic changes, cytokine release associated with TLR stimulation and oxidativestress. With regards to HIV infection, the precise drivers and mechanisms of liver disease are not well defined.This proposal will utilize the pathogenic SIV infection of rhesus macaques and in vitro human cell cultures todelineate the early mediators that drive liver disease during SIV/HIV infection. Our previous study assessinglivers from SIV-infected and SIV-infected-cART-treated macaques (assessed at necropsy) identified increasedlevels of bacterial 16s DNA in the livers of both groups. Importantly, an unexpected finding from this studywas the enrichment of Mycobacterial 16s DNA in the liver of infected macaques, which we have subsequentlyidentified as Mycobacteria smegmatis, a commensal or potentially opportunistic pathogen. These data, as wellas published findings, have led to the hypothesis that translocation of bacteria and bacterialproducts to the liver (including Mycobacteria-associated dysbiosis) are key mediators of liverinflammation during cART-treated HIV/SIV-infection and can initiate the early events thattrigger fatty liver disease. This hypothesis will be tested through three specific aims the first two Aimsassess immune and microbiome changes within the liver, lymph node and blood in SIV-infected-cART-treatedmacaques. Aim 3 will evaluate the mechanisms underlying changes observed in human macrophages orhepatocytes utilizing in vitro experiments following exposure to HIV, cART and bacteria/PAMPs. Our goal isto delineate the role of bacterial translocation and microbiome dysbiosis in HIV/SIV-associated liverinflammation, with particular focus on mycobacteria. To undertake these aims, this study will be led by Dr.Sodora, who has 18 years of experience evaluating immune inflammation during HIV/SIV disease includingprevious studies assessing liver inflammation during SIV-infection and cART-treatment. In addition, the teamconsists of Drs. Burwitz, Sacha and Smedley at the Oregon National Primate Research Center who have thenecessary expertise to successfully undertake the outlined experiments. Collectively, these approaches willallow us to undertake a mechanistic assessment of the precise contributions of HIV/SIV virus, cART drugs andgut-derived microbes in liver inflammation as well as identify potential synergistic effects of these mediatorswhen combined in a macaque or in vitro. Our long-term goal is to identify an immune therapeutic strategy toreduce incidence and/or severity of liver disease in HIV-infected and cART-treated individuals.	5R01AI134630-04

STEIN, MARK A	Center for Child Health, Behavior and Development (CHBD)	1/2 Treating Mothers with ADHD and their Young Children Via Telehealth: A Hybrid Type I Effectiveness-Implementation Trial	ABSTRACT/PROJECT SUMMARYMaternal ADHD, present in 25-50% of families of children with ADHD and frequently untreated, interferes witheffective parenting and predicts poor child developmental and behavioral treatment outcomes. Based on theliterature and our own pilot data, we will randomly assign mothers with ADHD and their young at-risk childrento one of two conditions: (1) stimulant medication for mothers with ADHD followed by a child treatment strategy(CTS) beginning with behavioral parent training (BPT) with the added recommendation of child stimulanttreatment if the child remains impaired or (2) a CTS without treatment for maternal ADHD on parent, child, andfamily outcomes. We will examine target mechanisms including improvements in maternal ADHD-relatedimpairment and symptomatology (attention, impulsivity, emotional regulation), parenting skills, and BPTengagement, as well as treatment moderators (baseline maternal ADHD severity, maternal impairment, andparenting skills). Moreover, in an effort to develop a model of treatment that has potential for widespreaddissemination while also reducing barriers to receiving care, we will screen mothers for ADHD in primary care,where child ADHD is most often identified and treated, and co-located mental health providers will delivertreatments via telehealth. Development of an implementation plan and associated toolkit using a stakeholderparticipatory strategy will enhance the ability to move efficiently to adoption of this approach. In addition, wewill study the care delivery context, assessing procedures for and rates of screening and participation as wellas staffing, workflow, provider- and patient-level acceptability, readiness, and feasibility of implementationapproaches. This hybrid effectiveness-implementation project will be achieved via a collaborative R01 across 2research sites in the US (N = 240 families), with 4-5 primary care partners at each site.	1R01MH118313-01A1
STUART, KENNETH D	Center for Global Infectious Disease Research (CGIDR)	Mitochondrial DNA of Normal and Mutant Trypanosomes	AbstractThis project will determine how three closely related editosomes, precisely edit mRNAs and do so differentiallybetween life cycle stages in Trypanosoma brucei. We hypothesize that insertion and deletion editosomecompositional and structural differences enable differential binding and catalysis of specific gRNA/mRNAsubstrates during editing and the differential editing between developmental stages. We will: 1. Determine thehigh resolution structures of insertion and deletion editosomes, subcomplexes thereof, and RNA association bycryoEM. Samples for cryoEM will be purified from cells with one type of functional or catalytically arrestededitosome. This will determine detailed editosomes architecture, protein stoichiometry, RNA location anddifferences between these editosomes. 2. Determine the roles non-catalytic editosome proteins/domains. Wewill determine if endonuclease partner proteins function as heterodimers and if noncatalytic proteins function insubstrate RNA binding and positioning. The catalytic function of recombinant heterodimers will be assayed bycrosslinking, mutagenesis and sequencing and functional RNA-protein interactions will be identified in vivo. 3.Determine how editosomes progress from one editing site (ES) to the next and test whether editing is eitherprocessive or progresses non-sequentially 3' to 5' and if endonuclease subcomplexes exchange betweeneditosomes or not as they encounter different ESs. Cognate gRNA/mRNA pairs engaged in editing in cells withsingle or multiple types of functional editosomes will be identified and sequenced to resolve whether editing isprocessive or not. Proximal editosome specific proteins that will be tagged in vivo in cells that contain all three,combinations of two, one, or no functional editosomes that have specific tags and assayed to determine ifeditosome components exchange or not during editing. These results along RNAseq analysis of their editedRNAs will elucidate how the three different editosomes collaborate to edit multiple ESs specified by a singlegRNA, including gRNAs that specify insertion and deletion. 4. Identify key aspects of developmental regulationof RNA editing. We will determine the order in which differentially edited mRNAs arise during development, ifthese are accompanied by differences in the abundances and editosome associations, of specific 3' initiatinggRNAs and cognate gRNA/mRNA pairs, and if these are impacted by mutations that differentially affect editing.Selected structures of BF and PF editosomes will be compared by CXMS, SILAC and cryoEM based on Aim 1.These studies will determine whether specific cognate gRNA/mRNA pairs are differentially bound and utilizedas a result of stage specific editosome differences. The project will provide key insights into how three poly-protein complexes function in an integrated fashion to precisely edit mt mRNAs and differentially regulate thisprocess between life cycle stages which adapts energy metabolism to the different environments in the hostand the vector.	5R01AI014102-43
STUART, KENNETH D	Center for Global Infectious Disease Research (CGIDR)	Immune Responses to Malaria and HIV Infection and Immunization - Administrative Core	Within the context of this large multi-project and multi-center proposal it is imperative to establish a centralizedadministrative system necessary for tracking progress, documentation, communications and reporting andimportantly for enhancing synergies among the components of the project and with external partners. TheAdministrative Core (1) will allow for centralization of all the practical matters to be handled by an experiencedProject Manager in support of the scientific goals of Projects 1 and 2 and the Clinical (2), Data Managementand Analysis (3), and System Biology (4) Cores. The Administrative Core will facilitate exchange ofinformation, tools and analytical approaches between the projects and the cores. It will serve as the main hubwithin the structure of the overall project for all non-scientific and non-analytical aspects of this researchconsortium, as well as the scientific components that emerge from individual research projects. TheAdministrative Core Project Manager will work under the direct supervision of the program PI as guided by theScientific Leadership Committee, will act as a liaison for individual project managers or P.I.s of Projects 1 and2 and cores 2-4 and will ensure smooth operations and overall increased efficiency. This will entail assistancein managing budgets, organizing planning and discussions meetings, arranging necessary travel for projectPIs, and relaying communications to/from the Steering Committee, SLC, ESAC, HIPC and NIH officials.	5U19AI128914-04
STUART, KENNETH D	Center for Global Infectious Disease Research (CGIDR)	Immune Responses Associated with Malaria Infection and Immune Protection - Project 1	Scientific Project 1: Immune Responses to Preerythocytic MalariaThis project will comprehensively define human immune responses during the pre-erythrocytic stage ofPlasmodium falciparum infection and vaccination with attenuated sporozoites which prevents infection andthus target this stage. It will identify immune signatures during the pre-erythrocytic, immunization and postvaccination periods in complementary vaccine trials that assess protection by controlled human malariainfection (CHMI). The primary endpoint is a correlation of vaccine-induced protection from infection, secondaryendpoints are the effects of prior malaria exposure and differences in immunization protocols, vaccines andCHMI methods. The exploratory endpoints include the identification of signals that implicate immune processesthat contribute to protection. The approach combines formal statistical methods, well-defined endpoints andsystem biology analyses. It systematically integrates high-dimensional with diverse immunological analyses togenerate an expansive immunological view to identify and assess signals that are associated with protection. Itaims to: 1. Identify immune responses during the pre-erythrocytic stages of infection. Virtually nothing isknown about this stage the infection in the liver during which there is extensive parasite replication andsynthesis of new antigens. We will identify signals of infection and of immunization with attenuated SPZsduring this stage and compare variations among trials. 2. Determine immune response kinetics over theimmunization period. We will identify the	5U19AI128914-04

			kinetics of innate and adaptive immunological signals duringimmunization with attenuated SPZs and identify the development of those that correlate with protection andhow these differ among the trials. We will deduce molecular and cellular features from the signals that correlatewith each variable to provide insight into immune processes that are associated with each endpoint. 3.Compare responses at and following of malaria challenge infection. We will identify signatures in samplesfrom vaccinees prior to and following assessment by CHMI of protection from infection. We will compareimmune signatures that are associated with each endpoint. The results from all of the aims will be used toguide the selection and testing of specific hypotheses about the mechanisms that underlay each of theendpoints. Overall, the comprehensive and integrated immunological and systems biology analyses will identifyimmune signatures during the critical stage of infection by and immune protection against a complex protozoanpathogen. It will generate and analyze pooled data from multiple complementary vaccine trials in order toidentify correlates of protection from infection, how these are affected by variables among the trials. It willprovide insight into multiple aspects of immune processes that are operative during infection and affected byvaccination.	
STUART, KENNETH D	Center for Global Infectious Disease Research (CGIDR)	Immune Responses to Malaria and HIV Infection and Immunization	Malaria and HIV/AIDS are two of the most devastating infectious diseases, impacting millions of people world-wide. Effective vaccines against the pathogens that cause these diseases (HIV and Plasmodium falciparum)have proven elusive and traditional vaccine approaches are unlikely to succeed in eradicating either disease.In addition to our limited understanding of the desired immune responses to confer protection against thepathogens and our limited ability to elicit such responses, vaccine efficacy is also confounded by the diversityof pathogens, human populations, environmental exposures, and health status. The projects described hereinare designed to support the identification of immune profiles that correlate with vaccine efficacy and are ofpotential relevance to protection against HIV-1 and P. falciparum infection. Beyond the importance ofcombatting these diseases, the strategies for profiling immunity in response to infection and vaccination holdpromise for garnering fundamental insights into the complexity of the immune system as a whole. Such insightwill have potential for impacting strategies for vaccine development and for treating immune-related diseasesmore broadly.	5U19AI128914-04
URDAHL, KEVIN B	Center for Global Infectious Disease Research (CGIDR)	Eliciting lung-localized CD4 T cell responses against Mycobacterium tuberculosis in preventive and post-exposure settings	SUMMARYAn effective vaccination strategy is urgently needed to combat the global scourge of tuberculosis (TB). Due tothe known importance of CD4 T cells and IFNγ in immunity against TB, current vaccine efforts are focused onboosting bulk IFNγ-producing CD4 T cell numbers (i.e., Th1 cells). These efforts, however, have been onlymoderately successful in conferring protection against TB in animal models, and a recent human efficacy trialof a novel candidate vaccine failed to confer measurable protection despite significantly boosting a Th1response. Thus, there is growing concern that TB vaccines that target Th1 cells may not be adequatelyeffective. We, and others, have recently discovered that adoptive transfer of fully differentiated Th1 cells,expressing high levels of the Th1-promoting transcription factor T-bet, provide little or no protection againstmurine TB, at least in part because they localize poorly to the lung parenchyma, the primary site of infection. Incontrast, less-differentiated CD4 T cells, expressing intermediate levels of T-bet and sharing properties withTfh and central memory T cells, readily home to the M. tuberculosis (Mtb)-infected lung parenchyma andmediate superior protection. Importantly, however, we have also recently shown that Mtb infection itself drivesTh1 cells toward terminal differentiation and a non-protective state. This complicates vaccine approaches inregions of the world in which TB is endemic because most individuals who would benefit from immunizationhave already been exposed to Mtb or are persistently infected. The goal of this proposal is to elucidate themechanisms that enable protective CD4 T cell populations to enter and be maintained within the lungparenchyma and to evaluate the influence of pre-existing Mtb infection on these parameters during vaccinationin both animal models and human clinical trials. In Aim 1, we will determine the factors that govern thelocalization of CD4 T cells into the parenchyma, with the prime hypothesis that T cell KLRG1 binds N-cadherinon vascular endothelial cells, thus preventing entry. In addition, the role of key cytokines and glycolipidinteractions in granuloma-associated high endothelial venules will also be explored. In Aim 2, we will assesswhether vaccine-dependent CD103 expression serves to retain protective CD4 T cells within the parenchyma,and if so, whether this is beneficial or detrimental to immunity. Finally, in Aim 3, we will determine the impact ofvaccine dose on priming protective, lung-homing CD4 T cell responses and how previous Mtb exposureinfluences this priming. The access to clinical samples from dose escalation studies of infected individualsprovides a unique opportunity to compare human immune profiles to those observed in mice and to translateour murine findings into testable hypotheses for human TB. The proposed experiments will provide aframework for the future design of novel vaccine delivery strategies with the ability to induce and maintain lung-localizing T cells even in TB endemic regions.	5R01AI134246-04
WALKER, WILLIAM OTIS	Center for Child Health, Behavior and Development (CHBD)	Seattle Children's Urologic Management to Preserve Initial Renal Function Protocol for Young Children with Spina Bifida (UMPIRE Protocol) (Component C)	No abstract available.	1U01DD001284-01
YI-FRAZIER, JOYCE P	Center for Clinical and Translational Research (CCTR)	The Promoting Resilience in Stress Management	PROJECT SUMMARYAdolescents with type 1 diabetes (T1D) are at high risk for elevated diabetes distress, which greatly impactstheir adherence, glycemic control (A1C), and overall quality of life (QOL). A potential barrier to improving theseexperiences may be that adolescents have few opportunities to develop the personal resources needed tohandle adversity and manage stress. The “Promoting Resilience in Stress Management” (PRISM) interventionis a manualized, brief, skills-based intervention delivered in 2, 45-60 minute one-on-one sessions, followed bya family meeting and supplemented by booster sessions and a digital app. PRISM was developed from	5R01DK121224-02

		(PRISM) Intervention: a multisite randomized control trial in adolescents with Type 1 Diabetes	Stressand Coping theory and targets skills in stress-management and mindfulness, goal-setting, positive reframing,and meaning-making. All of these skills are associated with improved patient outcomes in diverse groups ofadolescent populations with chronic/serious illness, and findings from a feasibility trial in adolescents with T1Dshowed PRISM to be highly feasible and desirable in this population. Further, a recent pilot randomizedcontrolled trial among adolescents with cancer suggest PRISM is associated with improved perceptions ofresilience, lower psychological distress, and higher QOL. This application proposes to build on our priorexperience and fill three critical knowledge gaps: (1) PRISM's impact on A1C among adolescents with T1D; (2)PRISM's impact on diabetes distress, self-reported adherence, and other patient-reported outcomes includingresilience and QOL; and (3) the cost-effectiveness of PRISM compared to usual care in a prospectiveeconomic analysis. This funding opportunity seeks to test interventions targeting diabetes distress for impacton glycemic control. Thus, we propose a multi-site randomized controlled trial among N=120 adolescents(n=60 PRISM, n=60 Usual Care; ages 13-18) with the primary trial outcome of glycemic control 6-months post-enrollment. Time-in-range will be evaluated for participants on continuous glucose monitors as an exploratoryaim. Secondary outcomes will include diabetes-distress, and patient-reported adherence, resilience, andquality of life. Cost-effectiveness will also be assessed to address the potential for sustainability anddissemination. We hypothesize PRISM will promote better glycemic control, improved diabetes distress, andbe more cost-effective than usual care. This application offers an opportunity to expand the body of knowledgeregarding methodologically rigorous and evidence-based interventions for adolescents with T1D. Ultimately,this research has the potential to offer a practical, skills-based curriculum designed to improve outcomes forthis high-risk group.	