Anexo 1

Becas Complementarias para la promoción de jóvenes investigadores

Nombre de la Institución	Nombre del Proyecto	Nombre del Investigador Peruano Colaborador/ Principal	Email del Investigador Peruano Colaborador/Principal	Lugar de Ejecución	Fecha de Cierre	Abstract
Pontificia Universidad Católica del Perú	Measurement of Renal Viscoelastic Properties with Ultrasound	Roberto Lavarello Montero	lavarello.rj@pucp.edu.pe	Lima	31-Mar-23	Chronic kidney disease (CKD) encompasses a long-term decrease in function of the kidneys. CKD can progress to kidney failure or end-stage renal disease (ESRD), which is treated by hemodialysis or kidney transplant. Patient and renal graft survival rates have increased over the past two decades, but long-term survival of grafts is still an issue. Renal biopsy is the gold standard for diagnosis of kidney health, but is an invasive procedure, cannot be used frequently, and can cause complications. Noninvasive indicators of kidney disease including levels of serum creatinine, glomerular filtration rate, and classical medical imaging can provide certain insights into kidney disease state. Elasticity imaging methods can discriminate healthy versus diseased tissue based on different parameters measured in the tissue. We have found in the previous cycle of this grant that certain elastographic parameters are sensitive to different structural or physiological changes in renal allografts. Linear and nonlinear elastic mechanical properties were found to be sensitive to the presence of interstitial fibrosis while viscoelastic parameters were sensitive to inflammatory processes and tubular atrophy. Based on these findings, we propose the use of quantitative, noninvasive methods to perform a comprehensive multi-parametric elastographic evaluation of renal allografts to evaluate health of the transplanted kidney. Methods: Ultrasound shear wave-based methods use acoustic radiation force to “push” the tissue and create shear waves. Ultrasound-based methods are used to detect the propagation of the shear waves through the tissue. The propagation velocity of the shear waves can be modified by several parameters including the elastic, viscoelastic, and nonlinear, mechanical properties in the tissue. We will use shear wave elastography (SWE) to measure elastic properties in the kidney using time-of-flight methods. Viscoelastic properties will be measured using a model-based approach by fitting shear wave velocity dispersion to rheological models or a model-free approach that involves extracting measurements of shear wave velocity and attenuation at various frequencies. Lastly, we will use a method called acoustoelasticity, which combines compression of the renal allograft and SWE measurements to estimate the nonlinear elastic modulus from shear modulus data obtained at various levels of applied stress. The parameters extracted from these measurements will be compared with structural (biopsy) and functional measures of kidney health (serum creatinine, estimated glomerular filtration rate, and Doppler ultrasound results) to elucidate how allograft disease changes these parameters. Establishing these relationships will provide a strong foundation for translating these elastographic measurement methods forward for widespread clinical use for assessment of renal allografts. The noninvasive nature of SWE measurements, available on many clinical ultrasound scanners, make them a strong candidate as a tool for reducing the number of biopsies, and to be used for frequent quantitative assessment and monitoring of patients’ responses to treatment, which will lead to reduced healthcare costs and potentially improved patient outcomes. To accomplish these objectives, we propose the following Specific Aims. Aims: 1) Evaluate the use of SWE to measure elastic mechanical properties for the noninvasive assessment of structural and functional changes in renal allografts. 2) Evaluate the use of SWE to measure viscoelastic mechanical properties to assess renal allograft fibrosis, inflammation, and function. 3) Evaluate the use of acoustoelasticity to measure nonlinear elastic mechanical properties to assess pathology and functional changes in renal allografts.

Hospital Edgardo Rebagliati Martins	Caracteri-zación Fe-notípica e Genómica de Microsomia Craniofacial (CFM) en la Población An-dina	Milagros Dueñas Roque	milagrosmariasela@gmail.com	Lima	31-Ago-22	• Población en estudio: 315 niños con Microsomia Craniofacial (CFM)*, 189 niños y 126 niñas y sus progenitores • Diseño de estudio: Multicentrico, transversal, observacional, con recolección de datos y especímenes biológicos de forma prospectiva en individuos con CFM. • Objetivo Principal: Caracterizar el fenotipo y genotipo de individuos con CFM aislada provenientes de Colombia, Perú y España. • Objetivos Secundarios: Caracterizar ancestralidad en individuos con CFM aislada provenientes de Colombia, Perú y España. • Tamaño de muestra: 315 niños con CFM y 570 progenitores • Duración del proyecto: 10 años * CFM es una condición congénita caracterizada principalmente por microtia e hipoplasia mandibular. Se considera que los individuos con microtia representan el extremo más leve del espectro de CFM (Beleza-Meireles et al, 2014, Keogh et al., 2007). Estamos ampliando el estudio “Caracterización fenotípica y genómica de microtia en la población andina”, para incluir el espectro completo de esta condición. Con el propósito de usar lenguaje conciso, usaremos el término CFM.
Universidad Nacional Mayor de San Marcos	Diagnóstico novedoso de nanoparti-culas para Toxoplasmo-sis y Chagas cerebral en pacientes con VIH que viven en América Latina	Eduardo Ticona	eticonac@unmsm.edu.pe	Lima	16-Feb-24	El tratamiento antirretroviral (ART) reduce la inmunosupresión causada por la infección del VIH y puede limitar el progreso de enfermedades infecciones oportunistas. Sin embargo existe poca adherencia a este tratamiento, es por ello que las infecciones oportunistas siguen siendo prevalentes. Dentro de las enfermedades oportunistas más mortales asociadas al VIH se encuentran aquellas que afectan al sistema nervioso central (SNC). Su presentación inespecífica hace que el diagnóstico sea casi imposible. Por lo tanto, las enfermedades del SNC, tales como la encefalitis toxoplásmica (ET), meningitis tuberculosa (MTB) y Chagas neurológico, son tratadas de manera empírica con un alto riesgo de desarrollar una enfermedad neurológica severa en comparación con pacientes inmuno-competentes. En la actualidad, estas enfermedades oportunistas son de difícil diagnóstico, ya sea por ausencia de recursos, complejidad para realizar procedimientos diagnósticos y la baja sensibilidad/especificidad para aislar a los agentes causales. Este estudio busca utilizar nano partículas que pueden incrementar la sensibilidad de las pruebas diagnósticas. Nuestro equipo demostró que tintes moleculares orgánicos modificados en el núcleo de la nano-partícula, pueden adherirse a moléculas de gran afinidad y concentrar el antígeno objetivo, para asi poder detectar al agente causal de las enfermedades mencionadas anteriormente.
Socios En Salud Sucursal Perú	Bacterial Determinants of Treatment Response in Mycobacteria Tuberculosis	Leonid Lecca	llecca_ses@pih.org	Lima	31-Mar-24	The premise of this project is that Mycobacteria tuberculosis (MTB) drug resistance phenotypes as measured by standard in vitro DSTs on conventional media may not encompass the full range of responses to drug therapy that affect patient outcomes. In previous work, we have identified MTB mutations that confer drug tolerance and conditional drug tolerance among drug resistant clinical strains. We hypothesize that patients who do not manifest early and vigorous clinical responses to treatment may be infected with strains with mutations that confer these phenotypes. If this is shown to be true, the early detection of these mutations through the use of rapid diagnostic tools which would allow clinicians to modify drug treatment to achieve better outcomes. OBJECTIVES: The goals of this study are to identify bacterial genetic determinants of 1) sub-optimal patient response to TB treatment. We will further characterize strains from people who respond and do not respond to TB treatment in terms of their ability to be grown on alternate non-conventional media, their mean inhibitory concentrations on alternate media, and their transcriptional signatures. We expect to identify specific mutations and transcriptional signatures that are associated with different growth characteristics and that these will be related to antibiotic tolerance and resistance phenotypes. DESIGN: We will conduct this longitudinal study at two field sites in different countries (Peru and Mongolia), enrolling active TB patients whom we will follow for interim and final treatment outcomes as measured by clinical criteria. Almost all previous studies of clinical treatment outcomes have relied on microbiological assays to determine treatment response so there are no well established norms to assess treatment response that do not include microbiological results. We propose here a panel of clinical assessments designed to measure pulmonary function, inflammatory response and respiratory symptoms, all of which we expect to improve over the first two months of effective TB treatment. Once we identify and isolate TB strains from people with sub-optimal responses to treatment, we will sequence these strains and perform a genome wide association study to identify specific variants associated with these outcomes. Public health relevance: Project 1 Although many mutations have been identified in Mycobacterium tuberculosis (MTB) that are associated with drug resistance as measured in the clinical laboratory, it is unclear whether these are indicators of patient treatment outcomes. In this study, we will examine the association between genetic variants in MTB bacilli and poor clinical response to TB treatment.

Universidad Peruana Cayetano Heredia	Molecular Basis of Hypoxia-Induced Excessive Erythrocytosis	Francisco Villafuerte	francisco.villafuerte@upch.pe	Lima/ Cerro de Pasco	30-Jun-23	Up to twenty percent of individuals living at high altitude in the Peruvian mountains and, to a lesser degree in Tibet, suffer from Monge's disease or Chronic Mountain Sickness (CMS). These subjects die in early adulthood because of excessive erythrocytosis (Polycythemia, hematocrit>60%). It is estimated that there are over 100 million people who live at altitudes > 2500 m world-wide, who are at risk for CMS. We are particularly interested in patients with CMS because they constitute a unique population that allows us to study how mechanisms of erythropoiesis can become awry or get exaggerated based on environmental conditions. The uniqueness of this population is even more significant when we realize that there are subjects that live side by side at similar altitudes as those with CMS but do not suffer from this disease. We have already demonstrated through whole genome sequencing that there are several genome-wide regions (containing a number of genes) that are consistent with selective sweeps in Peruvian subjects with polycythemia. Further, with the use of skin biopsies and native blood cells from CMS and non-CMS subjects, we have obtained iPS cells and differentiated them into red blood cells. We will use in this application the results of our already analyzed whole genomes of >100 CMS and non-CMS subjects as well as other molecular and genomic tools to better understand the role of SENP1 in hypoxia and understand the mechanistic basis of protection in females. Based on our preliminary results, we have formulated the central hypothesis that the hypoxia-induced polycythemia of high altitude has a genetic basis and that SENP1 plays a critical role in this extreme trait of polycythemia in Monge's disease. **Our Specific Aims are:** **Specific Aim 1:** Elucidate the role of SENP1 single nucleotide polymorphisms (SNPs) in regulating the marked hypoxia-induced polycythemia in CMS and the lack thereof in non-CMS subjects. We hypothesize that specific SNPs regulate SENP1 up-regulation in CMS but not in non-CMS in response to hypoxia. **Specific Aim 2:** Determine the transcriptomic changes and pathways that play an important role in the hypoxia-induced polycythemia in CMS. We hypothesize that an up-regulation of SENP1 will induce specific transcriptional changes in CMS cells that lead to the CMS polycythemic phenotype. **Specific Aim 3:** Investigate the role of hormonal factors in the gender-dependent high altitude induced excessive erythropoiesis. We hypothesize that the effect of estrogen hormone on SENP1/GATA1 is responsible for protection of females from CMS polycythemia. **Public Health Relevance** We are interested in finding the reasons why some individuals make too many red blood cells (RBC, polycythemia) at high altitude and others do not when they sojourn at high elevations. The individuals who make a lot of RBCs can die early in adulthood because of the concentration of red blood cells in the blood and the danger that this increased RBC can lead to stroke or myocardial infarction. Another interesting observation is that females, by and large, are protected from this disease until after menopause. Since we have sequenced the genomes of such individuals, we have information that will enable us to determine the basis for polycythemia. Although we seem to focus on high altitude diseases, our research efforts will also give us clues for similar diseases at sea level.

Universidad Peruana Cayetano Heredia	Respiratory and genomic contributions to adaptive/ maladaptive hypoxia responses	Francisco Villafuerte	francisco.villafuerte@upch.pe	Lima/ Cerro de Pasco	31-Mar-24	"The ability to use oxygen effectively is essential for survival. Many significant human diseases, including cardiopulmonary disease, hypertension, sleep apnea, and cancer involve a disruption in oxygen homeostasis. Human populations at high altitude have been challenged by hypoxia for hundreds of generations and show both unique physiological responses to this environmental stress and extremely strong natural selection for genes involved in oxygen transport, which can be demonstrated in relatively small studies. For example, we were the first to demonstrate a relationship between genes in the hypoxia inducible factor (HIF) pathway under natural selection and relatively lower hemoglobin concentration, which is further associated with exercise capacity, in Tibetans. Here we propose a similar integrative and targeted approach to identify the genetic determinants of both adaptive and maladaptive cardiopulmonary responses to hypoxia in Andean natives, who show a wide range of cardiorespiratory phenotypes, including chronic mountain sickness (CMS) rare among Tibetans. CMS is characterized by excessive erythrocytosis, arterial hypoxemia, carbon dioxide retention, and blunted ventilatory chemoreflexes, which are also traits associated with poor outcomes in patients with chronic heart and lung disease. We propose to test the overarching hypothesis that individual differences in cardiopulmonary phenotypes (hemoglobin concentration, arterial oxygen saturation, hypoxic/ hypercapnic ventilatory and cardiovascular responses) are predicted by (1) a lack of adaptive variants and/or (2) altered epigenetic regulation at loci identified with powerful state-of-the-art genomic analyses of Andean men and women with and without CMS. We will also test the hypothesis that the severity of sleep apnea underlies epigenetic changes that further modify cardiopulmonary responses as previously demonstrated in animal studies of intermittent hypoxia. Finally, we will determine if genetic and epigenetic variants result in gain- or loss-of-function to pursue therapeutic options for mitigating maladaptive responses to hypoxia in patients at sea level with chronic heart and lung disease. **Public Health Relevance** Individuals with chronic cardiopulmonary diseases as well as populations living at high altitude as are challenge by limited oxygen availability and exhibit some of the same outcomes. Studies of a relatively small number of adapted Andean highlanders provide an exceptional opportunity to understand mechanisms of oxygen transport underlying adaptive or mal-adaptive traits that can be predicted by genetic factors. Such findings provide novel insights into the challenge of low oxygen inherent to many disease states (e.g., heart and lung disease, stroke, hypertension, and cancer) and have broad implications for disease treatment and prevention."
Universidad Peruana Cayetano Heredia	Implemen-tation of ring strategy for communi-ty-engaged contorl of Neurocysti-cercosis	Patricia J. Garcia	pattyjannet@gmail.com	Tumbes	31-Jul-24	**Neurocysticercosis (NCC)** is a common neurologic disease and a leading cause of preventable epilepsy in Asia, Africa, and Latin America. It is caused by central nervous infection with Taenia solium (the pork tapeworm). While there has been considerable recent progress in developing interventions to control transmission, programmatic adoption of these strategies has lagged far behind. There is an urgent need for sound implementation research to ensure that the most effective and practical strategies can be adopted. Over the past 7 years we developed, optimized, and tested a targeted approach known as ring treatment that takes advantage of the strong spatial clustering between human and pig hosts of this zoonotic disease. Surveillance and detection of pig infection (cysticercosis), which is visible in meat at time of slaughter and in the tongues of live pigs, leads to treatment for taeniasis (human intestinal infection) in nearby homes. This strategy provides a simple and practical method for surveillance leading to efficient treatment of those humans at highest risk of being infected with taeniasis. In a head-to-head cluster randomized trial over 2 years, ring treatment achieved the same robust level of reduced parasite transmission as mass treatment (69.3% vs. 64.7% reduction, respectively) but did so using only a small fraction of the drug (1791 vs. 11,186 doses). However, a number of barriers exist that must still be solved for ring treatment to adopted a control program. In this 5-year project, we use the Consolidated Framework for Implementation Research (CFIR) to develop an adoptable approach for ring treatment as a control program for T. solium. We first use formative evaluation with stakeholders to develop intervention protocols, then refine these protocols through a pilot study with iterative evaluation. We then evaluate ring treatment implementation as a government run and community-engaged program in a 3 year trial, following the cRE-AIM framework (cost, reach, adoption, implementation, and maintenance). We also evaluate the utility and effectiveness of integrating a new urine screening assay for cysticercosis in ring treatment intervention. Finally, we provide a series of didactic and applied implementation research training opportunities for trainees to advance capacity for implementation research in Peru.