Quarterly Report of Top Awards

UW School of Medicine

Based on awards received from October 2014 through December 2014

Health Metrics Institute Proposal — $12,088,740

PI: Murray, Christopher J

Sponsor: Bill and Melinda Gates Foundation

The goal of this proposal is to create an independent global institution that will monitor global health and health systems and evaluate health interventions, initiatives, policies, and reforms - the Health Metrics Institute. High quality information on health is needed by policymakers, researchers, funders, practitioners, local decision-makers, and other to help better allocate limited resources in a way that can have the mos beneficial impact. Multiple and sometimes competing global health efforts have sprung up over the past several decades in parallel with an unprecedented rise in health spending to 9% of total economic output. Tl result is a profusion of diverse and well-intensioned efforts - from disease control programs to direct care funding schemes to global frameworks for coordinating vaccine development efforts, amongst others-that operate with sub-optimal information about important areas of health information. Valid, reliable, and comparable information is needed on health outcomes, health services, and resource inputs. A set of cross-cutting themes that highlight particular attributes of these areas - such as inequalities in each of them vis a vis geography, population, or age - also require investigation. Finally multiple efforts in global health requ independent evaluation to objectively assess their progress.

International AIDS Education and Training Center — $8,330,483

PI: Holmes, King K.

Sponsor: Health Resources and Services Administration (HRSA)

GOALS and OBJECTIVES: The International AIDS Education and Training Center (I-TECH) is associated with the Dept. of Global Health at the University of Washington (UW). I-TECH works from program offices in 8 countries and from its headquarters in Seattle. Additionally, the University of California San Francisco (UCSF) is a key implementing partner for I-TECH. I-TECH provides training and technical assistance to support the goal of improving health in countries hardest hit by the AIDS epidemic. The strategic objectives include:

- Strengthening health care delivery systems;
- Improving quality of care; and
- Creating sustainable human and institutional capacity for health.

OVERVIEW: With a mandate to increase human and institutional capacity in health care, I-TECH is actively engaged in supporting Ministries of Health and other local partners to best serve their countries and regions. Critical to achieving these objectives are activities such as strengthening the recruitment, retention and training of students in universities and technical training schools; faculty development; secondment and professional development of staff to ministries; organizational and systems strengthening; production of educational materials in local languages; transfer of learning to practice settings through clinical mentoring and decision support mechanisms for clinicians; task-shifting from doctors to mid-level professionals; and measurement of program effectiveness through assessment and continuous quality improvemer activities. I-TECH works to build sustainable local capacity by engaging and mentoring local people and institutions, strengthening Ministries of Health, and rigorously monitoring for effective transfer of skills and capabilities to local partners. Local I-TECH offices use their strong linkages to UW, UCSF and local universities in order to enhance on-going technical assistance activities and maintain high performance standard EVALUATION: I-TECH implements a comprehensive monitoring and evaluation strategy to measure achievement of program goals and objectives, assure high quality of activities undertaken and materials produced, and measure program impact. I-TECH uses a tailored information collection system called TrainSMART. I-TECH also requires logical frameworks annually from every country program and uses an evaluation database to organize and store data. A dedicated team collects and disseminates continuous quality improvement data to assure that program improvements are integrated into routine country project monitoring and management.

Development of Nearest Neighbor Immunogens for HIV-1 Vaccines — $7,463,791

PI: Baker, David

Sponsor: Bill and Melinda Gates Foundation

Herein we describe the development of improved HIV-1 envelope glycoprotein (Env) immunogens based on the engineered SOSIP HIV glycoprotein trimer constructs developed by the Moore lab. The goal is to arrive at next generation “Nearest Neighbor (NN)” SOSIP Env immunogens that avoid restriction by autoimmune mimicry that may be the basis for sub-optimal immune responses to current HIV vaccines. The tean aims to do this by raising broadly neutralizing antibodies (bNAbs) against HIV gp41 and gp120 by priming with a designed NN antigen that avoids cross-reaction with potential tolerizing epitopes, followed by boost with the current or next generation SOSIP trimer immunogen. The work is a collaborative effort between the research labs of David Baker (UW), John Moore (Weill Cornell), Garnett Kelsoe (Duke), and Andrew Ward (Scripps) and CureVac GmbH and Kymab Ltd.

Evaluating effectiveness, efficiency and cost of ART service delivery models in Uganda and Zambia — $4,301,853

PI: Duber, Herbert C.

Sponsor: Bill and Melinda Gates Foundation

Over the past decade there has been tremendous scale-up of antiretroviral therapy (ART) in sub-Saharan Africa. However, more than 50% of people who would qualify for treatment based on updated World Healt Organization treatment guidelines are still not receiving ART. In order to meet national and international goals of universal ART coverage in an era of increased fiscal constraint and accountability, policymakers need to understand what factors are most important in developing highly effective, efficient and low cost systems of HIV treatment and care. Our prior work on ART delivery systems suggest wide variations in cost and effectiveness, with generally low levels of efficiency. Here, we propose expanding this effort, with the goal of understanding the determinants of observed variation in effectiveness, efficiency and cost. In this study we plan to evaluate different measures of facility performance, including retention and HIV RNA viral load (VL) suppression, to clarify their relationship and utility. In addition, we will collect information on a wi array of programs and characteristics within each facility-based ART delivery system, and use that data to assess the relative impact of these programs on overall performance. Together with cost estimates, we wi be able to develop more accurate estimates of facility efficiency, and ultimately more accurate estimates of the cost-effectiveness of different models of HIV treatment and care.

Development of a Nanoparticle RSV-MPV F Protein Vaccine Candidate — $2,697,432

PI: Baker, David

Sponsor: Bill and Melinda Gates Foundation

The work described in this proposal will provide an assessment of a novel and potentially transforming virus-like nanoparticle (VLNP) vaccine platform while simultaneously guiding the field toward identifying an optimal protein particle immunogen that may be used in a combined human RSV/human MPV formulation that may be suitable for maternal immunization. The work is a collaborative effort between the research lab of David Baker (UW), Antonio Lanzavecchia (IRB), Davide Corti (HuMabs), and CureVac GmbH.

Next Generation CD8 Directed Nanoparticle Vaccines for HIV — $2,358,606

PI: Baker, David

Sponsor: Bill and Melinda Gates Foundation

Although it has been demonstrated that peptides derived from non-cytosolic or secreted antigens can be presented to CD8+ T cells (called cross-presentation) in mouse models, cross-presentation in primates or humans is less well understood. For this reason we currently rely almost exclusively on intracellular or cytoplasmic viral vectors to drive CD8+ T cell (cytotoxic T cell) responses to vaccines. As all of the convention nanoparticle strategies have failed to optimally drive CD8+ T cell responses in humans, it is clear that the usual strategies for nanoparticles and adjuvant formulation are not sufficient. Therefore, we are proposing a novel approach informed by recently elucidated pathways of innate cell activation which combines designed non-porous self-assembling nanoparticles with novel adjuvant STING pathway agonists and T cell epitopes for the Group-specific Antigen of Simian Immunodeficiency Virus (SIV-Gag). We propose to construct, with atomic-level accuracy, novel nanoparticle / T cell epitope / STING pathway adjuvant combination that are optimized for the specific task of antigen cross-presentation by dendritic cells and optimal CD8+ T cell activation. These nanoparticles will be characterized in cell based immunobiological assays to demonstrate productive MHC-I cross-presentation of SIV-Gag T cell epitopes and the optimal activation of Gag-specific CD8+ T cells. Nanoparticles that meet the specified criteria will be candidates for further vaccination studies in non-human primates.

Treatment Options for Depression in Patients Undergoing Hemodialysis — $2,106,602

PI: Mehrotra, Rajnish

Sponsor: Patient-Centered Outcomes Research Institute (PCORI)

BACKGROUND
End-stage renal disease patients undergoing hemodialysis (HD) have to adjust to loss of bodily function, complex dialysis treatment regimens, high pill burden, restrictive diet, and are frequently hospitalized. This is compounded by a high prevalence of comorbid depression (22-39%), which is associated with poor patient-reported outcomes, non-adherence, cardiovascular events, hospitalizations, and mortality. Yet, depressio is often not diagnosed when present in HD patients, and even when detected frequently not treated. This is likely a result of lack of high-quality evidence for the efficacy of different approaches for the treatment of comorbid depression in HD patients.

OBJECTIVES
To conduct (1) an open-label, randomized controlled trial to compare the efficacy of 12 weeks of cognitive behavioral therapy (CBT) or anti-depressant drug therapy (sertraline) in HD patients with comorbid depression (n=180); and (2) ascertain the longitudinal evolution of depressive symptoms over 12 weeks in patients who refuse to accept any treatment (n=90).

METHODS
HD patients in 50 dialysis facilities in three regions (Albuquerque, NM; Dallas, TX; Seattle, WA) will be screened for the presence of significant depressive symptoms. In individuals who consent to participate in the clinical trial, a diagnosis of major depression or dysthymia will be confirmed prior to randomization. CBT will be administered in a dialysis facility and sertraline will be titrated to the maximum tolerated dose using shared-decision making. A single assessor, blinded to treatment assignment, will assess patient-reported outcomes for subjects at all sites. The primary efficacy measure will be a change in severity of depressive symptoms; secondary outcome measures will assess other patient-reported outcomes and adherence with dialysis treatment and diet. The association of patient preferences on the efficacy and tolerability of each the two interventions will also be examined. Individuals who refuse any treatment but consent to be evaluated periodically will be followed for 12 weeks to determine the change in depressive symptoms while assuring patient safety and constantly providing opportunity for treatment.

PATIENT OUTCOMES (PROJECTED)
This study will provide answers to three questions faced by HD patients with comorbid depression: (1) “Given my preferences, what should I expect will happen to me?”; (2) “What are my options, and what are the potential benefits and harms of these options?”; and (3) “What can I do to improve the outcomes that are most important to me?” The study has been developed with substantial input from patients and stakeholder Separate Patient and Stakeholder Advisory Boards will also provide support and oversight and assist in dissemination of the results of the study. This will allow us to generate high-integrity evidence guided by patients, caregivers, and the broader health care community.

Immunodominant Viral Memory CD4 Epitopes of Biosecurity & Geriatric Medicine Concern — $2,084,973

PI: Koelle, David

Sponsor: National Institutes of Health (NIH)

The scope of work includes a) the recruitment of appropriate human subjects who are immune at baseline to the viruses under study, b) the provision of active VV and VZV vaccination to obtain highly immune specimens, c) IRB and clinical activities associated with the above, d) an open reading frame (ORF)-level discovery phase in which VV or VZV-reactive T-cells will be polyclonally enriched from PBMC samples, expanded, and tested against every ORF (70-240 per virus) present in the relevant virus, and e) an epitope-level discovery phase in which the reactivity of these VV or VZV-reactive T-cells will be decoded to the level of 20 amino-acid epitopes. After initial epitope discovery, epitope validation will be performed by defining the precise HLA restricting locus and allele restricting each response, by truncation analyses to determine the minimal reactive epitope, and by dose-response assays to determine EC50 levels. Epitopes with unequivocal patterns of HLA restriction, fully active 8-12 amino acid short forms, and EC50 values of < 1 ?g/ml will be considered validated. After validation, a hypothesis-driven basic science phase will be integrated into the workflow that will include interrogation of un-manipulated PBMC directly ex vivo to measu the abundance, phenotype, and persistence after vaccination of epitope-specific T-cells.

Evaluation of New HIV Testing Technologies in Clinical Settings with High HIV Incidence — $2,023,237

PI: Stekler, Joanne D.

Sponsor: Centers for Disease Control and Prevention (CDC)

Early diagnosis increases the likelihood that HIV-positive individuals can receive the benefits of HIV treatment and change behaviors to reduce transmission to others. In particular, the identification of AHI could have advantages both for individuals and public health. ARV therapy during AHI could delay disease progression by preserving immune system function, limiting viral diversity and dissemination, and reducing the viral "set point" if treatment is discontinued, leading to the possibility of “functional cure.” From the public health perspective, persons with AHI are more likely to transmit HIV per sex act compared to persons with established infection, and cohort studies and mathematical models suggest that a large proportion of infections originate from persons who have also been recently infected. If HIV diagnosis leads to sustained behavior change, early diagnosis, especially during AHI, could avert greater numbers of infections.
In practice, there is growing evidence that detection of AHI has additional benefits. Partner services provided to persons with AHI is more likely to identify the source and other infected persons than partner service provided to persons with established infection. AHI impacts the effectiveness of serosorting, as it can only be protective if those who believe themselves to be HIV-negative are truly uninfected. Recognition of AHI (the failure thereof) is similarly relevant to “point-of-sex” testing. Finally, diagnosis of AHI is a priority for PrEP programs: in iPrEx, acquisition of drug resistance was associated with starting PrEP during AHI, when antibody tests were negative, HIV RNA levels were high, and PrEP provided only partial virologic suppression.

Continued Assessment of Nano-Fibers for Multi-Purpose Prevention Technology (MPT) Development — $1,991,719

PI: Woodrow, Kim A.

Sponsor: Bill and Melinda Gates Foundation

The project framework in our current application outlines a critical path to further evaluate and inform the development pathway of electrospun fibers for MPTs. Drug-eluting fibers constitute an entirely new dosage form for vaginal delivery, and exhibit unique materials and processing features that may distinguish them from existing products being developed for multipurpose prevention. Our previous work demonstrates that electrospinning is a powerful method to produce near 100% drug encapsulation of high drug-loaded fibers in composite materials produced by simultaneous spinning of multiple solutions and/or layering of multiple types of electrospun fabrics. However, the feasibility of this new platform technology to be designed for production robustness in support of variable design specifications that may need to be realized in an MPT ha not been demonstrated. We propose to employ an iterative process to design, test and evaluate fiber formulations delivering ARV drug and hormonal contraceptives alone and in combination to support the evaluation of critical aspects of the platform as a MPT drug delivery technology. To accomplish this goal, this proposal integrates three modules to be conducted in parallel for developing and testing ARV drug fiber (Module I) and hormonal contraceptive fibers (Module II) that are constrained by specifications related to biological safety/PK and user-guided preferences for on-demand MPTs (Module III). Module I and II include phase (Outcomes 1.2, 3.1) of iterating through formulation and electrospinning processing parameters that will challenge the platform to meet the range of possible performance specifications that could be require for biological efficacy and use of a MPT. Platform attributes for fiber electrospinning will support manufacturing robustness that satisfy USP specifications appropriate for clinical trial materials, and be compared to existing platforms for producing vaginal films by solvent cast and hot-melt extrusion methods. The electrospinning platform attributes will be assessed for formulations that are iterated and optimized to meet critical performance specifications related to safety/toxicity, PK and form features prioritized from user-preference evaluations. Formulations will be iterated and selected based on outcomes from in vitro biological evaluations to assess cell and tissue toxicity, as well as deployment, dissolution, spreading and local tissue/fluid drug concentrations using in vitro cell culture and ex vivo organ and tissue models (Outcomes 2.1-2 3.2). In vitro and ex vivo biological performance will be validated by measuring safety and drug PK using an established PM model. Module II also includes an exploratory science and engineering arm that allows u to develop novel fiber fabrics that may function as a physical barrier contraceptive alone and in combination with hormonal contraceptives (Outcome 3.3-3.4). To inform the feasibility and robustness of the electrospinning platform to realize form attributes and performance specifications required for promoting user adherence, we propose to conduct formative research on fiberbased MPTs by engaging relevant end-user populations through internet-based surveys and focus-group discussions (Outcomes 4.1-4.2). End-user feedback will be used to prioritize form attributes for on-demand MPTs, which will guide concepts for fib formulations and requirements for production of unit dosage forms. The modules will move forward synchronously in attempt to input constraints for the electrospinning platform that reflect realistic requirements of biological safety/PK and user adherence for an MPT. The scope of work and expected outcomes from these modules provide a framework for defining the range of performance specifications of an MPT that can b realized by the electrospinning platform, and is expected to support a gap analysis to evaluate further advancement of drug-eluting fibers in drug delivery system pipeline for MPTs.

Analysis of GSK Active Targets — $1,932,069

PI: Stamatoyannopoulos, John A

Sponsor: GlaxoSmithKline Biologicals SA

Scope of Work. The overall goal of the project will be to aggregate, review, and analyze the available functional genomic data deriving from the ENCODE, Epigenome Roadmap, and related Projects, as well as data from genome-wide association studies, with an aim of comprehensively annotating confidential GSK target genes.

Clinical sequencing in cancer: Clinical, ethical, and technological studies — $1,928,454

PI: Jarvik, Gail

Sponsor: National Institutes of Health (NIH)

his program is designed to investigate aspects of using exomic data clinically, considering clinical, technical, informatics, and bioethical components. Specifically, we propose a randomized controlled trial of exome testing vs. usual care in medical genetics clinic patients indicated for colorectal cancer/polyposis (CRC) genetic testing. We will return CRC gene test results and also incidental findings that are medically actionabl We will evaluate the effectiveness of this technology and also subject reporting on their own experiences. We will consider the input of referring physicians and patients using focus groups. We will also perform ger discovery studies for subjects without identifiable CRC mutations. An important component of our work is determination of which results to return and how best to incorporate these into the medical record. These studies will facilitate the future practice of genomic medicine.

Self Renewal and Differentiation of Human Embryonic Stem Cells — $1,773,008

PI: Blau, Carl

Sponsor: National Institute of General Medical Sciences (NIGMS)

This application seeks renewed support for a highly productive collaboration centered on human pluripotent stem cell research. The investigators of this P01 represent a highly interactive and collaborative group. Each of the projects interacts extensively with at least two of the other Projects and Cores. Project 1 (Blau) will dissect the molecular basis of stem cell quiescence using novel in vivo and in vitro models. Project 2 (Moon) will characterize context dependent changes in Wnt signaling in human pluripotent stem cells and their differentiated mesodermal and cardiomyocyte progeny (in collaboration with Project 3). In addition, Project 2 is developing a panel of signaling reporter human pluripotent stem cell lines and these lines will prove extremely valuable to Projects 1, 3 and 4 in understanding how signaling differs between distinct pluripotent states and during differentiation. Project 3 (Murry) will test novel candidate regulators of cardiomyocyte differentiation that they identified during the current funding period. Project 4 (Reh) will interact wit Projects 1 and 3 on the biology of microRNAs in quiescence and maturation.

Our Cores are designed to support the projects in essential aspects of their work. Our Stem Cell Core A (Ware) will work with Projects 1, 3 and 4 to examine whether metabolites can act as drivers of distinct state of pluripotency or to direct differentiation, and will work with Projects 3 and 4 to identify methods for positioning human pluripotent stem cell lines to generate cardiomyocytes or neuroretinal cells. Our Computationa Biology Core B (Ruzzo) will provide bioinformatics support for each of the projects as well as for Core A, and will integrate this information with existing genetic and medical datasets.

These extensive interactions between the Projects and the Cores assure that the aggregate knowledge to be gained from this Program Project vastly exceeds the sum of its parts.

Health Alliance International 8 (Moz. Health Comm.) — $1,767,782

PI: Wasserheit, Judith N.

Sponsor: Health Alliance International (HAI)

The purpose of this application is to extend the period and secure additional funds for the current contract to meet the scope of activities under the Global Health Projects of Health Alliance International (HAI). The UW will provide assistance in the following areas:
1) Health Services Research involving faculty, staff, and students, particularly in the areas of program planning and evaluation
2) Training for public health workers in Mozambique, Cote d'Ivoire, and Timor Leste
3) Community education in the United States to broaden the local community's knowledge and participation in public health issues of Mozambique, Cote d'Ivoire, and Timor Leste
4) To fund UW staff involved in the administrative component of the project.

Based on awards received from October 2014 through December 2014

Improving Biosurveillance and Response across Cambodia and Lao PDR — $1,736,119

PI: Martin, Robert

Sponsor: Defense Threat Reduction Agency (DTRA)

Functional laboratory systems are increasingly being recognized as a keystone of effective biosurveillance, biosecurity and of sustainable national health programs. Specifically, diagnostic microbiology laboratories significantly contribute to patient care, hospital infection control, national disease surveillance and outbreak investigations. Inaccuracies in diagnostic testing can lead to potentially devastating outcomes for patients systemic errors in surveillance data, and can ultimately affect health policy. Working together with the World Health Organization (WHO) in the Western Pacific Region, the Cambodian and Lao People's Democrati Republic (PDR) Ministries of Health, and other partners in Southeast Asia, the International Training and Education Center for Health (I-TECH) will implement a training program to strengthen the quality and capac of infectious disease diagnosis and surveillance in national and provincial public health laboratories across the Mekong Delta region.