GHDx Course 4 Fellowship Projects

Opportunities for Fully-funded Fellowships in Laboratory Point-of-Care Diagnostics for Global Health

As an international participant in our Point-of-Care Diagnostics Course 1 in 2008, 2009, or 2010, we invite you to apply for a nine-month, fully-funded fellowship in point-of-care diagnostics for global health. We have listed several projects below proposed by mentors who would like you to participate in their projects. However, you also have the opportunity to propose your own project if you have identified a mentor in Seattle who has agreed to collaborate on your proposal. Unless otherwise indicated, all projects include a six-month, fully-funded fellowship in the mentor's laboratory followed by a three-month distanced mentorship in your home country. If you would like to apply, please send us a completed application form indicating the project of interest to you. An announcement on these fellowship opportunities and the application form can be found on the course website: http://www.path.org/dxcenter/training-developers-and-users.php.

We look forward to seeing our returning GHDx Course 1 alumni participate in the exciting projects listed below. If not indicated, the start time of these projects will be negotiated between the mentor and the fellow.

Project 1

Mentor: Geoffrey Baird, MD, PhD, Assistant Professor, Department of Laboratory Medicine, University of Washington, Project laboratory: Harborview Medical Center.

Project goal: To incorporate aptamers as reagents on lateral flow strip tests, as a step towards creating assays that would be useful in the developing world.

The fellow would develop a test system for a specific protein analyte, using both competitive and noncompetitive designs and a lateral flow format. For this proof-of-concept assay, the target would be a protein that can be purchased commercially and is safe to work with, such as a cytokine. Should this assay development prove successful, we will move on to developing assays for diarrheal diseases, incorporating aptamers for toxins from pathogenic organisms (such as cholera toxin or Panton-Valentine Leukocidin). PATH has offered the use of their BSL2 facility and their expertise in lateral flow assay design for this project. All of the aptamers needed for this work are already "on-the-shelf" reagents present at Dr. Baird's collaborator, SomaLogic's facilities.

Timeline: Start in fall, 2011

Project 2

Mentor: Tom Hawn, MD, PhD, Associate Professor, Department of Medicine, University of Washington

Project goal: To determine genetic determinants of immunity to tuberculosis for diagnostic development.

Despite the discovery of the tuberculosis (TB) bacillus over 100 years ago and the availability of effective drugs for over 50 years, formidable challenges for controlling *Mycobacterium tuberculosis* (MTb) remain. Understanding the mechanisms of variation in host resistance is one of these key challenges. Central among these is the conundrum of clinical outcome. Individuals exposed to MTb exhibit a wide spectrum of clinical outcomes including resistance to infection, rapid progression to active disease, or establishment of latent infection with substantial variation in the potential for and timing of reactivation. In immunocompetent individuals, the factors that determine clinical outcome are largely unknown and critical for achieving effective control of TB. With currently available tools, clinicians are unable to identify the subset of latently infected patients who will develop active TB disease. Studies in this area could lead to diagnostic tests that could alter treatment algorithms with more accurate prognostic information.

The primary goal of this research project is to discover which macrophage pathways mediate resistance or susceptibility to tuberculosis. We hope to identify which subjects with latent tuberculosis are at highest risk for developing active TB. To do this, we are examining the immune response of macrophages from individuals who are resistant or susceptible to MTb infection. We are infecting macrophages with MTb and comparing the response in individuals with different levels of resistance to MTb (resistant to infection versus latent infection versus active infection). The goal is to identify the pathways which define TB resistance and can be developed into a diagnostic assay to aid clinicians in their treatment of latent tuberculosis. Primary methodology includes development and execution of immune (ELISA, flow cytometry, mRNA, infection of cells) and genotyping (isolating genomic DNA, genotyping polymorphisms, analyzing data) assays. Potential studies include projects with collaborators in Vietnam, Uganda, and South Africa.

Project 3

Mentor: Bernhard Weigl, PhD, Group Leader, Diagnostics Development Teams and Leader of the Center for Point-of-Care Diagnostics for Global Health

Project Goal: Development and evaluation of a screening test for gestational diabetes (GDM).

Opportunities for alternate GDM screening and treatment monitoring approaches that are amenable to low-resource settings may result in a new generation of noninvasive or minimally invasive, rapid diabetes screening technologies that measure biomarkers of sustained hyperglycemia. As current type-2 diabetes methods can only identify slow changes in physiology due to elevated glucose levels, new, faster-responding biomarkers are needed. One promising area is determining the level of glycation of serum proteins with shorter half-lives than glycated hemoglobin, the most promising candidate being glycated albumin (GAlb). Glycated albumin—produced by a similar mechanism to A1c—is an emerging marker that may eventually become useful in GDM screening due to its shorter latency, but investigations are still in the research

stage, and no consensus has emerged. GAlb remains in circulation approximately one third as long as A1c, and thus integrates the effects of elevated glucose over approximately one month, long enough to average out the effects of recent nutritional intake, but short enough to allow identifying the changes within the gestational period. Human serum albumin has a clinical range of 3.4 to 5.4 g/dL, making it the most prevalent protein in serum. A fraction of it is glycated under normal and abnormal conditions, and a cutoff at 15% glycation rate appears to allow differentiation between normal individuals and those with gestational diabetes. The gold standard for GAlb quantification is HPLC, with several ELISAs available as well.

In order to determine if GAlb can be a useful marker to screen for GDM in low-resource settings, PATH will be working on an instrument-free rapid strip test to detect elevated GAlb. We would like to select a Core 4 fellow who is currently involved in diabetes and/or antenatal screening. The fellow would participate in both development and evaluation of the test at PATH, as well as to be able to also perform an evaluation at his or her home institution.

Project 4

Mentor: Matthew Steele PhD, MPH, Senior Program Officer, PATH

Project goal: Development of a technology for molecular detection of sexually transmitted diseases.

PATH is working with a private-sector partner to develop a simple (specimen in, results out) multiplex diagnostic for molecular detection of sexually transmitted diseases (gonorrhea, chlamydia infections, and trichomoniasis) and bacterial vaginosis. We are interested in a fellow who would participate in the development of this technology and adaptation of our standard PCR assays to an integrated all-in-one cassette. Applicants must have experience in molecular assay development and expertise in STD diagnosis would be welcomed. With this opportunity, we will offer an applicant an experience that includes technical, lab-based development of a cutting-edge technology, interaction with multinational partners in strategic planning for eventual prospective evaluation and regulatory submission, and user interface validation of intermediate prototypes.

Project 5

Mentor: Lisa Frenkel, MD, Professor, Pediatrics, Infectious Diseases, and Laboratory Medicine, University of Washington

Project goal: Optimize an economical, simple and sensitive HIV drug-resistance genotypic assay.

Dr. Frenkel's group is keenly interested in the development and transfer of practical and economical assays to detect drug-resistant mutations in HIV and hepatitis B virus. They developed an economical assay (US$2/codon) that is highly sensitive and specific. This high-throughput oligonucleotide ligation assay (OLA) can detect genotypic HIV-1 resistance to nucleoside, non-nucleoside reverse transcriptase inhibitors and protease inhibitors. They have been validating the OLA using pyrosequencing. At present this is not a point-of-care assay, rather it uses PCR and an EIA. Dr. Frenkel's lab staff are experienced in optimizing the OLA to regional variants of HIV, transferring the OLA technology to laboratories in South Africa, Thailand, and Zimbabwe, and using the OLA in multiple translation studies.

Dr. Frankel proposes to work with interested laboratory scientists to optimize HIV drug-resistance testing to your regional HIV variants and train you to test specimens that you supply on filter paper. They propose to train you in the development of an OLA, including the use of genetic databases and design of primers and probes to develop new assays; and to work together to optimize an OLA to detect drug-resistance mutations to hepatitis B. They propose to develop a collaborative relationship to work on projects of mutual interest. To learn more about Dr. Frankel's laboratory please refer to:
http://depts.washington.edu/idimmweb/facultyMember.php?sort=8

Project 6

Mentor: Mark Wener, MD, Professor and Director of Immunology, Department of Laboratory Medicine, University of Washington Clinical Laboratories and Director of the Dried Blood Spot (DBS) laboratory

Project goal: To develop DBS technology and bring a DBS assay on line.

Over the last few years, the University of Washington has become a large reference laboratory for epidemiologists around the country, measuring cholesterol, C-reactive protein, HbA1c, Epstein-Barr serology, hemoglobin, and glucose. The laboratory is expanding the menu of tests available to include tests of apolipoproteins, cytokine messenger RNA, autoantibodies, steroid hormones, cystatin C (an alternative to creatinine for measurement of renal function), perchlorate, selected virus RNA or DNA, and other analytes. Up to two students could be accommodated in the DBS laboratory to develop these assays. Students will learn about DBS technology (including punching of spots, storing, obtaining specimens, etc.), and will devote most of their time to bringing a DBS assay on line. Within the range of tests under development, students will be given latitude regarding their choice of an assay to develop. Dr. Wener's laboratory is located together with the Nutrition and Obesity Research Center laboratory in new facilities at the Ninth and Jefferson Building at Harborview Medical Center and most of the fellow's time will be spent at that laboratory site.

Project 7

Propose your own project

This is your opportunity to learn the skills you really need, collaborate with the group that you have always wanted to work with, and receive continued mentoring when you return to your home country. Using the application form on the course website (http://www.path.org/dxcenter/training-developers-and-users.php), describe the needs and impact of your project in your home country, outline of project activities, proposed timeline, and proposed mentor. Be sure to contact your mentor to make sure he/she is willing to participate in this project and has space in his/her laboratory.