Sunday Afternoon, October 14, 2007

Biomaterials Plenary

Room: 609 - Session BP-SuA

Biomaterials Plenary Session - Global Health Technologies

Moderator: B.D. Ratner, University of Washington

3:00pm **BP-SuA1 Paratransgenic Strategies for Control of Vector-borne Diseases: Rewards and Risks**, ***R.V. Durvasula***, *I. Hurwitz, S. Matthews*, University of New Mexico School of Medicine **INVITED**

The last decade saw vector-borne disease emerge as an urgent global health concern. Malaria, leishmaniasis, dengue fever, African trypanosomiasis, and Chagas disease place over sixty percent of the world's population at risk with nearly 740 million new cases. The mainstay of vector-borne disease control has been pesticide-based vector eradication. Pesticides were responsible for dramatic reductions of malaria in India during the 1950's and 60's. More recently, the Southern Cone Initiative against Chagas disease achieved spectacular reductions in South America. Unfortunately, such reductions may be temporary. Progress can be retarded by twinned factors: vector resistance and cost. In addition, pesticides pose a significant hazard to human health and the environment. These limitations have inspired new strategies for prevention and control, such as genetic modification of insect vectors to reduce their competence to transmit a target pathogen. This goal has been pursued via two approaches: modification of the vector genome and paratransgenesis, which involves genetic manipulation of symbiotic bacteria resident in vectors. Although proof of concept for both of these approaches has been achieved in laboratory studies, field application remains a possibility with many attendant risks. Paratransgenesis has been proposed as a strategy for the control of Chagas disease, a parasitic illness endemic to Central and South America. The WHO estimates that 8 - 11 million people are currently infected and 25 million are at risk for the disease. Chagas disease can be chronic and debilitating, with infected persons suffering cardiac, gastrointestinal, and neurological damage. Because neither vaccine nor treatment exists for the chronic stage of the disease, controlling transmission has been a priority. Chagas disease is transmitted to humans by obligate blood-feeding insects, the triatomines (order Hemiptera, family Reduviidae). The causative agent of the disease, the parasite Trypanosoma cruzi, lives in the gut of the triatomine and is transmitted via a fecal droplet deposited by the bug after a blood meal. In the paratransgenic strategy, the symbiotic bacterium, Rhodococcus rhodnii, which lives in the Chagas disease vector, Rhodnius prolixus, has been transformed with a series of expression plasmids to export molecules that are toxic to the parasite, T. cruzi. Laboratory lines of R. prolixus carrying cecropin A-producing symbionts have been reared which are refractory to T. cruzi infection. Field use of this approach will rely on natural coprophagic spread of symbionts by R. prolixus. A fake fecal preparation termed CRUZIGARD has been made and impregnated with engineered symbionts. Under closed cage and greenhouse conditions, CRUZIGARD- mediated delivery of transgenic bacteria to target populations of R. prolixus has been demonstrated. A paratransgenic approach to another important vector-borne disease, visceral leishmaniasis, is also under development. Soil-borne bacteria isolated from the sandfly vector, P. argentipes, in Bihar, India have been transformed to export molecules to larval and adult stages of sandflies with the aim of disrupting the cycle of Leishmania donovani. The paratransgenic approach has the potential to reduce pathogen transmission. Because it involves release of engineered microbes, aspects of field release impacting the environment merit investigation. An analysis of risks versus benefits of these strategies and the role for other delivery strategies of foreign genetic material will be presented.

3:40pm **BP-SuA3 Engineering New Diagnostics for Global Health**, ***W.R. Rodriguez***, Harvard Medical School **INVITED**

More than 70% of the 40 million people living with HIV infection worldwide do not know they are infected, and do not have access to the critical blood tests--CD4 cell counts and HIV RNA levels—essential for effective treatment. Diagnosis of tuberculosis, which kills 9,000 people per day, remains rooted in a 19th century test--light microscopy--and as a result, nearly half of TB cases go undiagnosed. Malaria diagnostics, also dependent on microscopes, are insensitive and difficult to implement. Are these engineering problems? How can advances in microfabrication, MEMS, microfluidics, and nanosensing be extended to global health problems? Are technical solutions to the unforgiving challenges of monitoring disease in poor countries within reach? Through a case history of a CD4 cell counting device, I will review the product specifications of the most urgently needed diagnostic devices for global health; review current efforts in microscale and nanoscale diagnostics, and their application to diseases like AIDS, TB and malaria; and discuss the biological, technical, product development, intellectual property, funding, and commercialization challenges to unleashing the potential of microscale technologies for global health.

4:20pm **BP-SuA5 Development of a Point-of-Care Diagnostics System for the Developing World**, ***P. Yager***, University of Washington, *G. Domingo*, PATH, *C.F. Battrell*, Micronics, Inc., *W. Mahoney*, Nanogen, Inc., *P. Stayton*, University of Washington **INVITED**

Microfluidics and related fields have progressed to the point that one can now tackle the technical challenges of miniaturizing complex bioassays for use in point-of-care diagnosis. The potential for improving health is great, but in the developing world the final system must be simple, robust, operable without the need for supporting infrastructure, and extremely inexpensive. We are engaged in a 5-year project for development of such a diagnostic system for use in the developing world. Supported by the Bill & Melinda Gates Foundation's Grand Challenges in Global Health initiative, this is a team effort led by the University of Washington that includes PATH, Nanogen, Inc., and Micronics, Inc. In many resource-limited settings, patients presenting with fever are treated on the basis of a presumptive clinical diagnosis due to unavailability of complex diagnostic assays, and the patients are, therefore, often treated incorrectly. The initial focus of this project is on a panel of tests for detection (from a few drops of blood) of a range of infectious agents that cause rapid-onset fever: malarial parasites, the bacteria Salmonella typhi and Rickettsia, and viruses including those that cause dengue, measles and influenza. The technical aim is to develop an integrated system that includes a portable battery-powered reader and small disposable single-use microfluidic cards; the cards allow the system to perform both immunoassays and nucleic acid amplification assays on this panel of infectious disease targets simultaneously and within a few minutes. The instrument itself remains dry; the disposable card is pre-loaded with all necessary reagents (in either dry or wet form) to perform in parallel both immunoassays for antigens and pathogen-specific IgM levels and amplification and detection of both RNA and DNA from pathogens. Optical imaging of absorption is used for the immunoassays, and fluorescence is used for the nucleic acids. After adding the sample, the card will be inserted into the reader, which activates the fluid movements, thermal cycling, and other preparatory and analytical activities. The disposable card will contain molecular systems for sample concentration and controlled delivery of reagents, and will be made of cost effective materials for low-cost volume production. All reagents on the card will be storable at ambient conditions for at least 1 year. This platform eventually is intended to ultimately accommodate a wide range of analytical panels tailored for region-specific and disease-specific diagnostic problems.

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