Final Program Report: Genomes to Global Health; the Computational Biology of Infectious Disease

April 20, 2006

1. Summary

The main goals of the SAMSI Computational Biology of Infectious Disease program were to advance the use and understanding of statistical modeling and genomic approaches in the study of infectious diseases, to integrate mathematical and biological viewpoints and to stimulate new collaborations between statistical, mathematical, biological and biomedical researchers.

The program achieved these aims. High points of the program included:

- Several highly active working groups, leading to significant research, a number of publications, funded grants and proposals in progress.
- Significant mentoring activities that have guided several students, including a number from minority and traditionally under-represented backgrounds, towards successful completion of their theses.

2. Program Review

2.1. Introduction, Motivation and Initial Ideas

Infectious disease remains a major cause of suffering and mortality among people in the developing world, and a constant threat worldwide. The major killers are HIV, *Mycobacterium tuberculosis*, and the malaria parasites (eg *Plasmodium falciparum*)[1]. 45 million people worldwide are infected with HIV, and in 2003, three million people died from AIDS. One third of the world's six billion people are infected with latent tuberculosis (TB), and an estimated two million people die each year from the disease. Of the approximately 8.4 million new TB cases each year, 300,000 involve multi-drug resistant TB (MDR-TB), strains that are resistant to two of the four drugs used to cure TB. 79% of MDR-TB cases involve "super-strains" that are resistant to at least three of the drugs. Each year, the approximately 300 to 500 million malaria infections lead to over one million deaths. 75% of these deaths are in African children less than 5 years of age. 80% of malaria cases are not responsive to current treatments because of drug resistance.

The advent of genome science and the continuing rapid growth of computational resources together herald an opportunity for the mathematical and statistical sciences to play a key role in the elucidation of pathogenesis and immunity and in the development of the next generation of therapies and global strategies. We intend for this SAMSI program to spark interest in the study of infectious disease in the mathematics and statistics communities. The primary aims of this year of research and study are to identify

those areas where mathematical/statistical innovation may have the greatest impact on the basic science and medicine of infectious disease, to progress materially toward major research efforts in these areas, to establish a greater sense of community among the researchers with skills and interests in these areas, and to contribute to the training of the next generation of mathematically-literate biomedical researchers, originating in both the biological and mathematical sciences.

Goals of the program:

1. Determine what the essential problems are in the study of infectious disease.

2. Identify those problems to which mathematicians, statisticians and computer scientists can make significant contributions.

3. Catalyze the flow of ideas between researchers who would normally not communicate but whose contribution is necessary for real progress in the study of infectious disease (eg statisticians, applied mathematicians, computer scientists, epidemiologists, immunologists, microbiologists, infectious disease experts, and physicians.

4. Forge new collaborations.

5. Generate interest and participation in the program through workshops, working groups, courses, seminars and visits from senior researchers.

2.2. Program Leadership

The program was led by Tom Kepler (Biostatistics and Bioinformatics, Duke University Medical Center), Lindsay Cowell (Biostatistics and Bioinformatics, DUMC), Denise Kirschner (Microbiology and Immunology, University of Michigan), Alun Lloyd (Mathematics, NCSU) and H. Tom Banks (Mathematics, NCSU).

3. Working Groups

The program gave rise to three working groups: mathematical genomics for vaccine design (fall and spring), cell communication (fall) and modeling the immune system (spring). The principle function of the working groups was to identify relevant research questions and pursue at least one of them with the goal of publishing the results and writing a grant to fund continued work on the topic. The working groups met at least once per week to organize the research and ensure progress towards the stated goals.

A major concern of ours was to integrate the views revealed from the disparate perspectives named above to explore novel, multiscale approaches to the fundamental problems.

3.1. Mathematical Genomics for Vaccine Design

The members of this working group were Thomas B. Kepler (DUMC, leader), Michael Cahalan (UC-Irvine), Lindsay G. Cowell (DUMC), Joanna Fueyo (IBM), Andrew Nobel (UNC), Scott Schmidler (Duke), Cliburn Chan (DUMC), Jeff Frelinger (Immunology, UNC), Georgia Tomaras (Surgery, DUMC), Padraic Neville (SAS), Byron Goldstein (LANL), Surajit Ray (SAMSI), Ben Cooke (Duke), Karl Strohmaier (Duke), Abel Rodriguez (UNC), and Soyoun Park (UNC).

Two specific research foci of members of this group were *Amino Acid Biophysical Properties in the Statistical Prediction of Peptide-MHC class I Binding* and *Statistical Inference of Mechanisms of T Cell Motion from in vivo 3D Video Microscopy*. A key step in the development of an adaptive immune response to pathogens or vaccines is the binding of short--approximately 9 amino acids--peptides to molecules of the Major Histocompatibility Complex (MHC) for presentation to T lymphocytes, which are thereby activated and differentiate into effector and memory cells. The rational design of vaccines consists in part in the identification of appropriate peptides to effect this process. There are several algorithms currently in use for making such predictions, but these are limited to a small number of MHC molecules and have good but imperfect prediction power. We have undertaken an exploration of the power gained by taking advantage of a natural representation of the amino acids in terms of their biochemical properties. We used several well-known statistical classifiers using either a naive encoding of amino acids by name or an encoding by biophysical properties. In all cases, the encoding by biophysical properties leads to substantially lower misclassification error.

The work on *T Cell Motion* is important because the immune system consists of a multitude of motile cells know as *leukocytes*, that move independently through the blood, lymph and tissues, surveilling the environment for evidence of microbial pathogens, unfamiliar molecular patterns, and damage to the host. Once any of these signals has been received, the cells themselves begin signalling to each other, and thereby alter the trafficking patterns of the population as a whole. Understanding the motions of leukocytes is key to understanding the immune response and to the rational design of immune interventions, and in particular, to vaccine design. Remarkable advances in imaging technology have made it possible to visualize these cells in vivo at high spatio-temporal resolution and to study their motions over long periods of time.

While the motion of leukocytes under artificial conditions has been well characterized, the mechanisms of motility under natural conditions have not been elucidated. We developed Bayesian methods to study the trajectories of these cells, based on using a Langevin Process prior and computing the posterior mean trajectory, and analyzing the residuals with respect to this mean trajectory. We have thus analyzed the trajectories of several T cells moving in intact lymph nodes and here describe these methods as well as the results themselves. These results are consistent with earlier analyses, but provide more detailed insight, suggesting that lymphocyte motion is saltational, with intervals of rapid and relatively unidirectional motion interrupted by pauses and reorientation of the direction of motion.

3.2. Cell Signaling

The members of this working group were Tim Elston (UNC, leader), Jeff Butterworth (Alien Skin Software), Rory Conolly (CIIT Centers for Health Research), Sujay Datta (Northern Michigan University, Department of Math and Computer Science), Chuanshu Ji (UNC-CH, Department of Statistics and Operations Research), Julia Kimbell (CIIT Centers for Health Research), Delong Liu (CIIT/SAS), Kevin Thomas Morgan (Sanofi-Aventis), Abby Todd (UNC-CH, Math Department), Xiao Wang (UNC-CH, Department of Statistics and Operations Research), and Qiang Zhang (CIIT Centers for Health Research).

3.3. Modeling the Immune System

The members of this working group were Alun Lloyd (NCSU, leader), Brian Adams (NCSU), H.T. Banks (NCSU), Efrat Barzohar (ASU), Ariel Cintron (Cornell), Yun Kang (ASU), Grace Kepler (NCSU), Alun Lloyd (NCSU), Hoan Nguyen (SAMSI), Miriam Nuno (Cornell), Morgan Root (NCSU), John Samuels (NCSU), Alicia Shim (ASU) and Stephen Tennenbaum (Cornell).

Since many of the group's participants had little experience in this area, most of the initial activity took the form of literature surveys. A new class of models, based around the so-called "immune program", were of particular interest. The group has considered the ability of such models to describe acute infections. A draft manuscript critiquing this class of models is currently in preparation.

A subgroup of this group consisting of Banks, H. Nguyen and G. Kepler began, in January, 2005, a collaboration with a group in the Dentistry School at UNC-CH led by Dr. Jennifer Webster-Cyriaque. This began as weekly group meetings at SAMSI that continued into the Fall, 2005 and resulted in project (still continuing into 2006) on statistical and mathematical modeling of reactivation of latent oral viruses. A research paper written by the group is currently submitted to *J. Theoretical Biology*. Several papers on related sensitivity methodologies are in progress.

As a direct result of the working group discussions, Lloyd has been developing new models that can be used to study the impact of drug resistance on acute viral infections, such as the common cold. A Masters student (Lisa Soberano, NCSU Biomathematics) has been working on these models with Lloyd and is due to graduate this summer. (Although Soberano was not a participant in the working group, her interest in infectious disease modeling was stimulated by the SAMSI program, following her attendance at the infectious disease modeling course and at Alan Perelson's Distinguished SAMSI Lecture.) Lloyd is currently writing a grant application to develop models for drug resistance in acute viral infections (in collaboration with D. Wodarz, UC Irvine). This work will adopt a multi-scale approach, integrating the within-host models (i.e. ones that describe infection within a given individual) that were the focus of the working group with between-host (epidemiological) models that describe the spread of infection at the population level.

4. Workshops and Courses

4.1. Opening Workshop

The Opening Workshop, held on September 18-22, 2004, began with a day of tutorials. In the morning, there were three tutorials: statistics and data analysis (Tom Kepler, DUMC), mathematical modeling and and simulation (Tom Kepler, DUMC), and epidemiology (Alun Lloyd, NCSU). There were three additional tutorials in the afternoon: molecular evolution (Jeff Thorne, NCSU), microbiology (Denise Kirschner, UM), and immunology (Lindsay Cowell, DUMC). The tutorials were followed by three days of research talks and discussions. The first day of talks and discussion centered around the mathematical and statistical challenges in biostatistics and public health. The second and third days focused on the mathematical and statistical challenges in microbiology and immunology, respectively. A major goal of the opening workshop was to frame issues to be addressed by the programs working groups; the workshop concluded with a discussion of potential working-group topics and the formation of three groups.

4.2. Mid-Program Focused Workshop

A midterm workshop on *Modeling Infectious Diseases* was held from January 31 – February 1, 2005. External participants included Alan Perelson (LANL), Carlos-Castillo Chavez (Arizona State Univ.), Priscilla Greenwood (ASU), Zhilan Feng (Purdue), Alison Galvani (Yale), Gerardo Chowell (LANL) and Christopher Kribs-Zaleta (Univ. Texas at Arlington). The main aim of the meeting was to discuss potential topics for the working group and to give the local students a better idea of the breadth of the field.

The workshop was notable for the wide range of topics and approaches that were discussed. During the workshop, Alan Perelson delivered a SAMSI Distinguished Lecture, *Modeling Viral Dynamics*, discussing his important contributions to the field of virus dynamics, with more than 80 attendees.

4.3. Transition Workshop

A workshop marking the formal end of the program was held from May 22-24, 2005, organized by Tom Kepler, DUMC and Arti Rai, School of Law, Duke University (co-chairs); Stephen Maurer, School of Public Policy, Berkeley; Andrej Sali, UCSF; Lindsay Cowell, DUMC. This transitional workshop was entitled *Collective Computational Biology for Infectious Disease*, and involved legal and policy scholars as well as statisticians, computer scientists and biologists. The workshop was the occasion for the newly-formed *Tropical Disease Initiative* (TDI) to make the acquaintance of the Genomes to Global Health participants. The TDI is devoted to the development of an open-source community for the discovery of drug targets and therapies for diseases of the developing world, starting with malaria. New collaborations were thus formed, and several GGH participants worked on infrastructure development for the TDI. Dr. Kepler has become a member of the TDI, and as a result of the workshop now sits on the board

of directors for *The Synaptic Leap,* a non-profit open-source biomedical research development company that hosts the TDI (http://thesynapticleap.org).

The TDI has now grown to include researchers in Europe, Australia and India as well as at several US sites and is engaged in negotiations with other research groups, including those at IBM and the pharmaceutical company Pfizer, to provide results from their research to the research community at large for collective computational discovery of novel antimalarial drugs.

These seminal developments were made possible by SAMSI and the workshop that brought together for the first time the principal actors who are now working together to bring new, collective, ways of doing statistics, mathematics and computational biology to bear on the enormous problem of infectious disease in the developing world.

Note: Extensive information about these workshops of the program is available in the SAMSI Annual Reports for Years 2004-05 and 2005-06. In particular, these annual reports contain the programs, abstracts, and lists of workshop participants for each of the program workshops.

4.4. Courses

Three courses were offered as part of the program. Each was listed at Duke, NCSU and UNC for graduate credit.

4.4.1. Computational Immunology and Immunogenomics

This course was taught in Fall, 2004 by Thomas B. Kepler, Duke Departments of Biostatistics & Bioinformatics and of Immunology and Lindsay G. Cowell, Duke Department of Biostatistics & Bioinformatics. Twenty graduate students from the three universities took the course for creditor audited it. Several postdoctoral fellows and researchers from local companies attended regularly. Guest lecturers joined on several occasions.

The course integrated empirical and computational perspectives on immunology and host defense. Students were expected to have significant preparation in either biomedicine, or a quantitative science. The class had a diversity of backgrounds; individuals willing to contribute their own knowledge to the development of the topics as they learned those parts of the subject with which they were less familiar. The topics covered provided an entrée into the use of computational methods for research and practice in immunology and infectious disease, from basic science to medical applications.

4.4.2. Mathematical Modeling of Infectious Diseases

This course was taught in Spring, 2005 by Alun Lloyd (NCSU). Between 25 and 35 students and postdocs attended the course, and several local and visiting faculty attended one or more of the lectures.

The course focused on the simplest biological situations, namely directly transmitted infectious diseases. Discussion of more involved settings, such as indirectly

transmitted diseases (e.g. malaria and other vector-borne infections) and multi-strain infectious agents (e.g. HIV and influenza) was given, but with reduced emphasis. The main emphasis was on epidemiological dynamics, with a discussion of the links to ecological (predator/prey) theory. The importance of evolutionary dynamics were highlighted where appropriate.

One long-term outcome of the course was the production of a detailed set (150 pages+) of lecture notes, which will in due course be expanded into a complete textbook. Several other students have, as a result of the course, started, and in some cases, completed, research projects on infectious disease modeling. This includes three Masters students (all in the NCSU Biomathematics Program) who have completed M.BMA. projects or M.S. theses in this area.

4.4.3 The Biophysics of Cell Signaling

This course was taught by Byron Goldstein (SAMSI university fellow) in Spring, 2005. Approximately 10 graduate students took the course for credit or audited. Several postdoctoral fellows participated as well.

Description: Cells must constantly sense their environment and respond. The macromolecules (ligands) that cells detect, and the concentrations at which they detect them, are determined by the cell surface receptors they express. Once a particular ligand binds to a receptor this information must be transmitted across the cell membrane if the cell is to respond. When the information transfer is successful, a complex set of events is initiated (a signaling cascade) that culminates in the activation or suppression of one or more cellular responses. In many cases the binding of a ligand to a receptor is not sufficient to initiate signaling. Rather, for these ligands signaling is initiated by inducing receptors to aggregate with additional membrane proteins or among themselves. We will focus on receptor families that work in this way, including the growth factor receptors, the immune recognition receptors and the cytokine receptors. We will discuss models for ligand-receptor binding, ligand-induced receptor aggregation and ligand-initiated cell signaling. Two basic types of cell signaling models can be distinguished: simple cell signaling models which ignore the details of the signaling cascade, but give insight into how ligand-receptor binding properties affect signaling outcomes; and detailed models, which include specific molecular components and interactions beyond the ligand and receptor, and that are required to gain a mechanistic understanding of cell signaling cascades. Both types of models will be considered.

5. Personnel

5.1 Faculty Releases

Faculty releases for the program from the partner universities were Tom Kepler (Biostatistics and Bioinformatics, Duke University Medical Center), Lindsay Cowell (Biostatistics and Bioinformatics, DUMC), Scott Schmidler (Statistics, Duke), Andrew

Nobel (Statistics, UNC), Tim Elston (Applied Mathematics, UNC), and Alun Lloyd (Mathematics, NCSU)

5.2 Research Visitors

Long term research visitors to the program included:
- Sujay Datta, Department of Mathematics, Northern Michigan University, visited during the Fall semester.
- Byron Goldstein, Theoretical Biology and Biophysics, Los Alamos National Labs was the University Fellow for the program, visiting Spring semester.
- Cliburn Chan, was appointed the New Researcher Fellow for the program.
- Carlos Castillo-Chavez, Arizona State University
- Priscilla Greenwood, Arizona State University
- Katja Ickstadt, University of Dortmund

Targeted experts who visited the program for shorter periods were
- William Scott, Duke Center for Human Genetics
- Mark Miller, University of California, Irvine
- Arup Chakraborty, University of California, Berkeley
- Jason Stout, Division of Infectious Disease, Duke University Medical Center
- Georgia Tomaras, Department of Surgery, Duke University Medical Center
- Bette Korber, Theoretical Biology and Biophysics, Los Alamos National Labs
- Alan Perelson, Theoretical Biology and Biophysics, Los Alamos National Labs

5.3 Postdoctorals

The postdoctoral fellow in the program was Surajit Ray. A second postdoctoral fellow, Hoan Nguyen, participated in the second semester program on immune response modeling and has, in her second year of postdoc at NCSU, continued research efforts on latent oral virus modeling into 2006.

5.4 Graduate Fellows and Associates

The graduate fellows and associates were Karl Strohmaier, Ben Cooke, Morgan Root, Soyoun Park, Abel Rodriguez, Efrat Barzohar, Ariel Cintron, Yun Kang, Miriam Nuno, Alicia Shim, and Stephen Tennenbaum.

5.5 Efforts Towards Diversity

The Leadership of the program consisted of one man and two women. Several of the long-term visitors and targeted experts were women – including one who gave a SAMSI Distinguished Lecture – and one long-term visitor was Hispanic; six of his graduate students, of various ethnic backgrounds including Hispanic, spent the semester in the program. The class on computational immunology taught by Drs. Kepler and Cowell was attended by graduate students from NCSU, UNC and Duke, and consisted of

approximately one-half women (including an African-American woman) and one-half men.

6. Follow-On Activities

6.1 Dissertations

Several of the graduate fellows and associates who were supported by the program, and mentored by Banks and Lloyd, have since successfully completed and defended their Ph.D. theses. This includes Miriam Nuno (now a postdoctoral researcher at the Harvard School of Public Health) and Stephen Tennenbaum (now a postdoctoral researcher at the Mathematical and Theoretical Biology Institute, Arizona State University). Ariel Cintron-Arias has almost completed his thesis, and is due to defend this summer.

Many other students who participated in the program have also completed projects related to infectious disease modeling. Haojun Ouyang and Ji Zhang completed M.BMA. projects in the NCSU Biomathematics Program, and Lisa Soberano is shortly due to complete an M.S. in the NCSU Biomathematics Program.

Also growing from the activities of this group, and the SAMSI course *Computational Immunology*, taught by Drs. Cowell and Kepler, is the PhD thesis project on *Computational T-Cell Epitope Discovery*. Ms. Ana Paula de Oliveira Sales, a PhD student in the Duke Computational Biology and Bioinformatics program, was a student in the course and has now gone on to pursue her thesis work with Dr. Kepler and Dr. Georgia Tomaras, an immunologist who presented a guest lecture for Computational Immunology, and participated in the MAGVAD group activities. Dr. Tomaras will co-advise Ms. Oliveira Sales. Her thesis work is being supported by the NIH contract: *Large Scale Antibody & T Cell Epitope Discovery Program* to Kent Weinhold, on which Drs. Kepler and Tomaras are senior investigators.

6.2 Collaborations

During the period of the program, the program leadership, with collaborators visiting as part of the program, wrote a proposal to the NIH entitled *Multiscale Systems Immunology for Adjuvant Development* with Tom Kepler as the principal investigator and involving faculty from Biostatistics & Bioinformatics, Mathematics, ISDS, Computer Science, Engineering, Medicine, and the Human Vaccine Institute, Emory University Vaccine Center, University of California at Irvine, Vanderbilt University School of Medicine, and Vaxgen, Inc. The NIH awarded the 5-year research contract for just over $10M to the consortium. The project was awarded for the development of computational tools to aid in the rational design of vaccine adjuvants, which are essential for the generation of a robust immune response to vaccine antigens. These compounds have in the past been developed by trial and error, and only very few are suitable for human use; only one is licensed for non-experimental purposes. The understanding of the receptor-ligand interactions that initiate these responses, and the interactions among immune cells in response to these stimuli has advanced substantially in the last five years. The contract project aims to gather data from several information-rich methods, including vital video

microscopy, laser-capture microdissection, gene expression analysis, and serial immunohistology and develop the methods required to integrate these data into a coherent picture of the immune response to various adjuvant agents.

Other collaborations involved the estimation of epidemiological model parameters from data, using methodology from Inverse Problem theory (the subject of an earlier SAMSI program). For example, Alicia Shim and Tom Banks have been working on parameter estimation for rotavirus infections, and Ariel Cintron-Arias and Banks have collaborated on parameter estimation in two settings: models for the spread of ideas and models for the evolution and spread of influenza. Alun Lloyd and Ariel Cintron-Arias have collaborated on the development of network models for the spread of infectious diseases.

6.3 Publications and Technical Reports

- Ickstadt, Katja, Tina Mueller and Holger Schwender *"Clustering and Disrimination Methods for Single Nucleotide Polymorphism Data"* To appear in a special issue of CHANCE on Genomics.

- Kepler, T.B., H.K. Nguyen, J. Webster-Cyriaque and H.T. Banks *"A Dynamic Model for Induced Reactivation of Latent Virus, CRSC-TR05-44"* December 2005 J. Theoretical Biology, submitted.

- Lloyd, A.L, Valeika, S. & Cintron-Arias, C. *"Epidemic Dynamics on Small World Networks. In: Modeling the Dynamics of Human Disease: Emerging Paradigms and Challenges"* (2006)

- Rodriguez, Abel and Schmidler, Scott *"Bayesian Structural Alignment of Proteins"* ISDS Discussion Paper, Duke University (2006)

- Rodriguez, Abel and Schmidler, Scott *"Combining Sequence and Structure Information in Protein Alignments"* ISDS Discussion Paper, Duke University (2006)

- Rodriguez, Abel and Dunson, David and Taylor, Jack *"Analysis of DNA Repair Studies Through Bayesian Hierarchical Models for Mixtures"* ISDS Discussion Paper, Duke University. Submitted to JASA Applications and Methods. (2005)

- Schwender, Holger, Sya Rabstein and Katja Ickstadt *"Do you Speak Genomish?"* To appear in a special issue of CHANCE on Genomics.

- Shim, E., H.T. Banks, and C. Castillo-Chavez *"Seasonality of Rotavirus Infection with it's Vaccination"* SAMSI 2005-9, November 4, 2005

- Todd, M., Taylor, G., Renom, M.M., Rai, A., Kepler, T., and Maurer, S. *"Open Source Chemistry Research."* submitted to the *Australian Journal of Chemistry.*

Reports in Preparation

- Cintron-Arias, A., Castillo-Chavez, C., Bettencourt, L., and Banks, H.T. *"Analysis of Effective Susceptible Population Sizes for Influenza A H3N2"* In preparation.

- *He, M, Tomfohr, J.K., Devlin, B.H., Sarzotti M, Markert M.L., Kepler T.B.* "SpA: Web-Accessible Sprectratype Analysis: Data Management, Statistical Analysis and Visualization" *Bioinformatics, under review. (2005)*

- Kepler, T. and Cahalan, M. *"Statistical Inference of Mechanisms of T Cell Motion from in vivo 3D Video Microscopy,"* in preparation.

- Kepler T.B., He M., Tomfohr J.K., Devlin B.H., Sarzotti M, Markert M.L. *"Statistical Analysis of Antigen Receptor Spectratype Data"* Bioinformatics, under review (2005)

- *Lu J., Tomfohr J.K., Kepler T.B.* "Identifying Differential Expression in Multiple SAGE Libraries: An Overdispersed Log-Linear Model Approach" *BMC Bioinformatics, under review (2005)*

- Ray, S., Nobel, A., Schmidler, S., and Kepler, K. *"Amino Acid Biophysical Properties in the Statistical Prediction of Peptide-MHC class I Binding."* (2006)

- *Tomfohr J.K., Lu J, Kepler T.B.* "Pathway Level Analysis of Gene Expression Using Singular Value Decomposition" *BMC Bioinformatics, under review (2005)*

6.4 Monograph

Alun Lloyd is developing a textbook on Infectious Disease Modeling, based on his lecture notes for his modeling course. He is currently approaching publishers with a first draft version.

7. Governmental and Industrial Participation

The program enjoyed the participation of individuals from SAS in the Mathematical Genomics for Vaccine Design working group. The transitional workshop held at the end of the program involved the participation of key representatives of the Burroughs Wellcome Fund, which has a strong and active interest in the diseases of the developing

world, and of One World Health, a non-profit organization seeking to facilitate the development of drugs for the developing world.