National Academies Keck *Futures Initiative* Launches a Genomic Attack on Infectious Diseases

By Kiryn Haslinger

One of the biggest questions on everyone's mind each winter is the how to avoid getting the flu. Influenza and its fellow infectious diseases—which range from moderately troublesome bugs such as the common cold to lethal assassins like HIV—are collectively the most potent source of illness and mortality across the world. Just as understanding the criminal mind may be the most effective way to deter human villains, a similarly penetrating approach could be applied against these microbial bad guys.

This broad imperative provided the impetus to bring together 150 researchers, policy makers, foundation representatives, and members of the science media during November 10-13, 2005, at a conference to discuss solutions to the growing problem of infectious diseases using the field of genomics. The third annual conference of the National Academies Keck *Futures Initiative* (NAKFI), "The Genomic Revolution: Implications for Treatment and Control of Infectious Disease," invited its participants to develop creative ways to attack dangerous microbes through understanding their fundamental genomic compositions.

The Rise of Genomes

At the intersection between advances in molecular biology and genetics and advances in computing, techniques have been developed to rapidly and efficiently read genome sequences. This research area, which applies computational methods to large-scale genetic analysis, is known as “genomics.”

Genomics is a tool scientists, engineers, and medical clinicians use to gain a detailed understanding of the biological roots of health and disease. A genome is the collection of chromosomes in an organism, which carries all its genes. It is the instruction book for creating a paramecium, pea plant, or person—written in DNA. Possessing the recipes for the Earth's creatures is extremely valuable. Knowing these chemical codes is a clue to figuring out how organisms function.

Nearly every human ailment is genetically based, at least to some degree, and knowing the ins and outs of genomes will be vital for the next phase of medical diagnosis and treatment of a wide variety of diseases. The goal of the third annual NAKFI conference was to bring to the table bold, innovative ideas about harnessing genomic science to mitigate the spread of infectious disease.

Facilitating Collaboration

The focus of the *Futures Initiative* is interdisciplinary research. "Discovery comes at the interstices of disciplines," said National Academy of Engineering President Wm. A. Wulf as he kicked off the four-day conference. Genomics is itself an interdisciplinary field, the progeny discipline born from the marriage of genetics and computer science. A primary objective of the meeting was to present a fertile ground for additional cross-disciplinary collaborations: stimulating alliances between biochemistry and engineering, immunology and economics, pharmacology and politics, science and communication. "I hope that by the end of this session," said Dr. Wulf, "you will establish lifelong relationships with people from fields you don't normally interact with."

To foster such relationships, Dr. Wulf introduced a series of tutorial sessions intended to explain the state of the science of various specialties, so that researchers could communicate clearly with one another across disciplines. In one tutorial, Gary Nabel, director of the Vaccine Research Center at the National Institute of Allergy and Infectious Diseases, discussed genomics, structural biology, and rational vaccine design. Using genomics, he asked, "How can we create new paradigms to create highly effective vaccines?" He stressed that the key would be gaining a better understanding of gene function and evolution.

In another session, to emphasize the dynamic interplay between humans and microbes Stanford University Professor David Relman declared, "We are 10 parts microbial and one part human," as though he were a bartender mixing up a biological cocktail. He then led conference participants on a tour of disease epidemiology, highlighting the importance of studying the genomes of pathogens as well as that of the human host, a point that was continually revisited throughout the conference.

Michael Waterman, a professor at the University of Southern California, in his talk attempted to demystify the technical work involved in computational biology and bioinformatics. These highly mathematical specialties form the core of genomics, and it is becoming increasingly vital for researchers to learn about automated sequencing, microarray technology, and optical mapping.

Interspersed with other technical tutorials on topics such as human genetic variation were talks about the societal impact of infectious disease. Austin Demby, a senior staff fellow at the Global AIDS Program of the Centers for Disease Control and Prevention, discussed the needs of developing countries and the unique delivery and implementation issues that face parts of the world most affected by infectious diseases, such as sub-Saharan Africa.

Drilling for Oil in Orange County

The tutorials served as a stepping-off point for the participants to address concrete problems in small working groups. Each of 11 groups was presented with an outstanding challenge in the area of genomic approaches to infectious disease and asked to develop a scientific plan to address it. As conference chair, Robert Waterston, a professor at the University of Washington and head of one of the genome-sequencing centers that led the Human Genome Project, announced his charge to the working groups, and emphasized the value of problem-oriented thinking. Dr. Waterston also encouraged the group members to connect with researchers in other disciplines, joking that the real challenge of the working groups would be to figure out “how to have fun locked in a room with 10 of your newest colleagues.”

Throughout eight hours of intense discussion spread over the four-day meeting, conference participants brainstormed about potential plans for designing technology to improve rapid response to disease, developing an inexpensive diagnostic test for pathogens, preventing the next pandemic flu, creating a device to detect and identify pathogens, and sequencing an individual's genome for under $1,000. Other groups focused on such vital topics as determining the role of public health in integrating genomics into disease control and devising new therapies by harnessing natural genetic variation in disease resistance.

The groups were not expected to solve these pressing scientific conundrums during the conference, but rather they were asked to assess the related advances that already exist and identify the gaps that must be filled. Their primary objective was to outline a method of attack for their problem. Richard Foster, a board member of the W. M. Keck Foundation, which funds the $40 million 15-year NAKFI program, spoke to the assembled groups about the life and spirit of W. M. Keck, an oil pioneer who drilled 23 dry holes before he hit his first gusher. “We expect you all to drill dry holes,” he stressed. “We want you to get in there and start drilling right away. That’s what this meeting is all about.”

Drill the groups did, intensely digging into their individual areas of expertise to drive discussions about potential solutions to the problems presented. Each group, complete with strong personalities that ranged from open-minded and optimistic to imperious and despairing, was a microcosm for real-world research groups who work everyday to explore possible solutions to substantial scientific problems. Group members debated how best to phrase the questions they would set out to answer and then traded expertise in hopes of generating innovative ideas. At the end of the meeting, each group reported to the others what they had come up with.

One group outlined a detailed framework for governments to react rapidly to emerging disease, providing details for the key stages of surveying and monitoring pathogens, identifying infectious agents, and treating infected individuals. Another group developed blueprints for a device to monitor the environment (either air or biological fluids like mucus, where infectious agents may reside) by rapidly sequencing microbial genomes. Using a combination of microarray methods and nanotechnology, the group conceptually designed a disposable chip to search for malaria or HIV by sequencing DNA. A third group also incorporated nanoscience in their plan to engineer a laboratory incubator for culturing and crystallizing microbes to expedite vaccine research. Still another group devised a detailed budget for dispersing $100 million to prevent a pandemic flu, theoretically allotting $50 million to create an international flu research center and the remaining funds for supporting competitive grants for vaccine and antiviral research.

These working groups provided a fertile environment for communication among scientists, engineers, and medical researchers, many of whom discovered a valuable opportunity for interdisciplinary collaboration. The *Futures Initiative* aims to spark such relationships and offers a rewarding incentive for researchers to do so: up to $75,000 to fund innovative research and continue collaborative dialogues that emerged from the conference. The initiative supplies $1 million annually for such seed grants, awarded competitively to conference participants.

Communicating Science

Another major goal of the initiative is to encourage communication of scientific discoveries and ideas to the public. Effective communication, particularly on the topic of genomics, not only educates the public about scientific progress but also empowers individuals to make informed decisions about their own health. If you understand the basics of genomics and your genome indicates that you are predisposed to, say, high blood pressure, you know that it is particularly important to avoid cigarettes and limit the amount of salt in your diet. Genomic sequencing can also tell you if you have been exposed to a disease like malaria, which can help you expedite treatment and prevent spreading it to others. The working groups that were charged with outlining the role of public health in integrating genomics came to the realization that clear communication about this subject is itself a weapon against infectious disease.

Clear, accessible writing and broadcasting can serve to interest and excite people about genomic discovery and to dilute the mainstream sensationalism that asserts the utility of the field lies in ethically questionable applications like designer babies and cloned pets. A core feature of the *Futures Initiative* is the presentation of the National Academies communication awards, given to an author, a journalist, and a television or film producer. The $20,000 awards recognize excellence in reporting and communicating science, engineering, and medicine to the general public, and the winners were selected from more than 200 entries. At the conference, one award was given to John M. Barry for his book *The Great Influenza: The Epic Story of the Deadliest Plague in History*. Gareth Cook, a journalist for *The Boston Globe*, was presented an award for his coverage of the national debate on stem cells. An additional prize was given to Thomas Levenson for his television program on the evolution of life in the cosmos, WGBH NOVA's "Origins: Back to the Beginning."

By inviting graduate student science writers to attend its meetings and write articles describing the progress of the working groups, NAKFI encourages young writers to communicate science effectively to a diverse audience. Eleven students, selected from universities from around the country, had the opportunity at November's conference to attend the same tutorials as the researchers and participate in the working groups. Their articles have been collected here to create a comprehensive summary of the working groups' conclusions.

The Revolution Continues

The devastation wreaked by infectious disease spurred the conference participants to have valuable discussions and consider novel genomic solutions to controlling disease. In an era of fast-mutating deadly viruses like SARS and avian flu, and persistent killers like malaria, tuberculosis, and HIV, there is certainly a compelling reason to focus modern developments in genomics while trying to treat infectious diseases. Throughout the conference, discoveries about genomics and infectious disease permeated the Arnold and Mabel Beckman Center, even when the working groups were on hiatus. Poster sessions were held each afternoon, allowing researchers to present relevant unpublished work from their laboratories and providing ample opportunity for networking. In several cases, meeting participants took inspiration from these informal sessions back with them to the working groups.

Perhaps because of the striking relevance of the problems at hand, there was a great deal of overlap among the discussions by various groups and consensus on recommendations for future research. The overarching theme of the conference was the need for individualized approaches to medicine, which, because of genomic variation, will be the vital next step in advancing medical treatment.

At the end of the four days, working group members announced their progress and recommendations for future research (see the write-ups that follow for specific summaries). Some recommendations were made by multiple groups. For instance, several groups projected that rapid, inexpensive sequencing would dramatically boost the progress toward their goals. Such a revolution in sequencing would advance the capability of diagnostic tests, enable efficient environmental monitoring for pathogens, and spur new technologies that we cannot even envision at present. The group responsible for outlining a path to the $1,000 genome vigorously debated the ethical issues that this cheap technology would introduce, while all the other groups took the value of such technology for granted.

There are risks, technical and ethical, inherent in pursuing this type of research. In a tutorial on conducting team science, Mary E. Lindstrom, vice-provost of research at the University of Washington, warned, "If you're going to take risks, you cannot expect 100 percent success."

The *Futures Initiative* has made valuable investments in scientific risk taking since it was launched in 2003, lauding and supporting bold efforts in both scientific research and communication. And the payoff may be very high: helping to mitigate the ravages of infectious disease.