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Infectious research

Consisting of 14 laboratories, Harvard School of Public Health's Department of Immunology and Infectious Diseases primarily focuses on diseases in developing countries. In this exclusive interview, Dyann Wirth discusses a new and fascinating approach which targets pathogens' resistance to drugs rather than the disease itself

Could you begin by introducing the Department of Immunology and Infectious Disease (IID) and the role it plays at the Harvard School of Public Health?

This is a department that focuses on applying the latest technologies in understanding infectious disease and human immunological responses for major public health problems. Our efforts centre on HIV, AIDS, TB, malaria, parasitic disease and the immunological and health consequences associated with the microbiome. We deal with all major health problems throughout the world – with a focus on basic science and human infections.

How has IID developed since it was established in 1997?

It grew out of two departments (Cancer Biology, Molecular & Cellular Toxicology, and Tropical Public Health) that converged around the topic of public health, namely infectious agents as major causes of global health problems – primarily parasitic, bacterial and viral disease. The Cancer Biology department focused much of its efforts on HIV and AIDS, which developed from an interest in viruses that cause leukaemia. Over time, the methods and strategies have become very much the same. We're all trying to understand how and why viruses, bacteria, parasitic organisms or other infectious agents cause disease and epidemics, why epidemics spread the way they do, and what we can do to check that spread.

Could you offer an example of some of the department's focus areas?

We have a range of scientific interests. A common feature is the blending of basic science lab research with an understanding of the natural infectious process and how that has an impact on disease. Our basic science research is very strong across the board, in terms of cell biology, molecular biology, pathogens and biochemistry. All the disciplines required to understand complex infectious diseases can be found in this department or among our local and international collaborators, and I think that this focus on natural infection really binds the department together.

Have there been any recent breakthroughs in IID's research that you would like to share?

There have been a number of important discoveries made in the field of tuberculosis. We are beginning to understand the fundamental differences in *Mycobacterium tuberculosis* biology and genetics that lead to different outcomes, for example, the emergence of drug resistant strains (which are a major public health problem). At the very fundamental level, with the advent of genomic biological approaches, we have begun to understand the intricacies of parasite biology as revealed by its genome. This is leading us in new directions for diagnostics, vaccines and for understanding disease pathogenesis.

How is IID helping to tackle the increasingly imminent threat of antimicrobial resistance?

This is a major area of interest; all of the research groups have an interest in understanding antimicrobial resistance.

Understanding it at its fundamental (genomic) level will be an important discovery, but in terms of moving to the next stage – ie. really understanding how drugs interact with an organism – we need a slightly different tactic. There are two different strategies: one is to understand how the pathogen interacts with the host and to attack the interaction between the host and parasite instead of directly attacking the pathogen (which is how resistance emerges); and the second is to approach the resistance as if it were a biological challenge and to target resistance in microorganisms.

Both of these approaches are potentially promising; they offer a different paradigm to the presumption that resistance won't occur, or that by combining unrelated drugs, resistance will be somehow reduced. A new concept is to target resistance, perhaps by developing drugs that hit both the sensitive and the resistant organism and administering them simultaneously. It is a novel idea which needs to be tested, but this concept and the experimental data that could support such an approach makes me very excited.

Can you tell us about IID's involvement with the Harvard School of Public Health's AIDS initiative? For instance, in terms of building and improving training programmes.

The Harvard AIDS Initiative is a very important component of the department. It is strong in fundamental research, as well as in intervention, education and advocacy. One of the major efforts that the initiative is involved in is our collaborations overseas – particularly the Botswana-Harvard AIDS Institute Partnership (BHP), which is probably the best example. We are collaborating with the Government of Botswana to bring cutting-edge research to the country to understand the HIV epidemic and to contribute to its management. This provides an opportunity for a diverse set of healthcare professionals in the country to use diagnostic and treatment modalities, and to understand the impact of new interventions (such as antiretroviral therapies) on the virus and spread of disease. It is also an opportunity to gain an insight into potential vaccines and supportive therapies because there is an integrated community effort to increase AIDS awareness.

The KITSO AIDS Training Program, which is part of the BHP, also trains healthcare professionals in Botswana on HIV/AIDS prevention, treatment and care. The Program has also expanded research and training efforts to include prevention of mother-to-child transmission (PMTCT), maternal health during and after PMTCT, and other multidisciplinary projects.

For me, the AIDS initiative has been extremely important in terms of bringing various groups of researchers across the university together with overseas collaborators, which ultimately affords great benefits to the department.



Could you shed some light on the Harvard Malaria Initiative?

The Harvard Malaria Initiative was also established in 1997. Two years ago, shortly after Julio Frenk

became Dean of the School of Public Health, he came to me with the idea that malaria – a complex, global health problem – could be examined from a variety of disciplines – all the way from the genetic level to the population level, and that Harvard was the right place to do that. In the past, the Harvard Malaria Initiative had concentrated only on the biomedical challenges of malaria, including promoting research, increasing human capacity through training and technology transfer activities. Julio encouraged me to broaden our horizons to include disciplines ranging from economics to government and business, and to more ethical concerns such as social and behavioural issues.

We first convened a leadership forum called 'Rethinking Malaria,' which brought people in from around the university and from the global malaria community. We met at the Harvard Business School with the notion of bringing a broader lens to the problem. Malaria eradication has been a world issue since the beginning of the last century, but the focus was primarily on biomedical public health. With the more recent call in 2007 to eradicate malaria by the Bill and Melinda Gates Foundation, which has been embraced by the world health community, there needs to be a widening of the knowledge base: businesses need to be involved, and people who have social, behavioural and economics backgrounds – all with a view to increasing communications and advocacy.

The meeting initiated the 'Defeating Malaria: From the Genes to the Globe' effort at Harvard, which spans the fundamental work conducted by our department as well as policy, governance and business expertise from across the university, to solve this complex problem. In some ways the tools that we have need to be better distributed, while others need to be improved. We are also going to need to understand a wide range of issues, ranging from the drivers that lead people to care about their health to the methods Coca-Cola, UPS or Amazon use to distribute their products to the peripheries of the world. A university is a good place to answer these questions because it generates ideas. As an academic institution we cannot solve malaria, but we can offer deep expertise to train the next generation and inspire knowledge; thus, Harvard is the perfect place to stimulate thinking about malaria as a complex but solvable problem.

What are your hopes for IID in the future? Are there any particular projects in the pipeline that you would like to highlight?

We are very interested in expanding our efforts into understanding the immune system and vaccine development. History tells us that vaccines are a powerful tool for controlling infectious disease and probably cancer



also. But the challenge is that unlike many of the infectious diseases that are currently controlled by vaccines, or in some cases approaching eradication (such as polio), the diseases we work on are much more evolutionarily sophisticated. They have mechanisms for abating natural infection.

Let's take malaria and measles as an example. Previously, before the availability of the measles vaccine, people contracted the infection and then, in the majority of cases, they were protected from measles for the rest of their lives. On the other hand, if a person becomes infected with malaria at a young age, he/she may be cured but they will not develop immunity. Obviously, there is partial immunity because people stop dying of the disease once they reach a certain age and have had a certain amount of exposure to malaria. But, this is a real challenge in terms of creating a vaccine: the vaccine has to be better than nature.

We have the same issue with HIV and TB. These organisms have evolved with humans, developing a mechanism for evading the human immune system. This presents yet another huge challenge to overcome, which requires fundamental understanding of human immune responses to infection and novel thinking on how we are going to use vaccination for both treatment and eradication. This is something we would very much like to expand.

There are other infectious diseases that are of major public health importance. In order to make progress, I feel that we will need a critical mass of people working on one problem. One person working on a problem does not make as much progress as a small group, so we have expanded the department organically. As the School of Public Health thrives, the next stage would be to expand research to other health concerns such as dengue fever or influenza. As mentioned before, the department is brought together by working on understanding the biology of organisms at the fundamental level and how it interacts with the host. This area will trigger real breakthroughs that can make a difference.

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