Number 18/Spring 2006

PASTEUR FOUNDATION

PASTEUR PERSPECTIVES

THE NEWSLETTER OF THE PASTEUR FOUNDATION DEVOTED TO THE WORLD OF THE INSTITUT PASTEUR

THE WAITING GAME: A GLOBAL BIRD FLU VIGIL

by Caitlin Hawke

Identified for the first time in 1997 when it provoked six deaths in Hong Kong in what is thought to be its first epidemic, Avian Influenza A (H5N1) has reappeared recently and is in the midst of causing a global epizootic. The disease has killed hundreds of millions of birds in more than 30 countries and has led to the destruction of hundreds of thousands more. Both the public health and economic consequences are disquieting. Officials and scientists are all on heightened alert for the eventuality many fear: when this pathogen crosses over and a human-to-human transmissible strain appears.

Deputy Secretary Alex M. Azar of the U.S. Health and Human Services Department and Institut Pasteur President Professor Alice Dautry

While this subtype strain does not normally infect people, there have been some 186 cases identified in humans, over 100 of which have been fatal (as of March 2006). The majority of these cases resulted from close contact with diseased poultry.

Signs of infection include not only respiratory symptoms but also the traditional indication of flu: fever, achiness and sore throat. Deterioration in condition is typically rapid.

The Institut Pasteur is deeply involved both in the basic research of this pathogen and in the surveillance and ultimate prevention of its spread should a human strain arise. Its International Network provides a vivid example of cooperative vigilance, particularly in Southeast Asia where there are seven institutes spanning Cambodia, China, Korea and Viet Nam. This historic and strategic presence has recently led the United States government to call upon the expertise of the Institut Pasteur.

As a result, in February, the Institut Pasteur and the U.S. Department of Health and Human Services signed a Memorandum of Understanding to establish a joint HHS-IP working group to oversee projects including:

• Building capacity in terms of surveillance, epidemiological investigation, testing, diagnosis and

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MEET THE FELLOWS: IAN GLOMSKI

Dr. Glomski is the Judith P. Sulzberger Scholar of our Post-doctoral Fellowship Program. An eagle scout, Ian has always had great respect for nature. Neither that nor his thesis work on the infectious mechanisms of the microorganism that causes listeriosis, a food-borne illness, have prevented him from enjoying delicious raw milk cheeses such as Epoisses de Bourgogne! He joined Dr. Michèle Mock's Toxins laboratory at the Institut Pasteur in November 2003. We asked him to share his story with our readers.

A SCIENTIFIC CAREER IS NATURE'S CALLING

by Ian Glomski, Ph.D.

Unlike my French colleagues who needed to start focusing on a career in science at the age of fourteen, I had the American liberty to search for my calling well into adulthood. In short, I was a Religions and Philosophy major when I entered college. However after two years, I knew it wasn't for me. Needing time off to "soul search," I took a sabbatical year and motorcycled through the U.S., where I found my inspiration to be nature, which consequently led me to return to college to study biology and environmental sciences.

Ian Glomski

As I delved deeper into both modern molecular-level biology and the environmental sciences, I became more and more fascinated by interspecies interactions, in particular host-pathogen interactions. Ultimately, this interest brought me to pursue my doctorate in the lab of Daniel Portnoy at the University of California, Berkeley, to study the bacterium *Listeria monocytogenes*. At Berkeley, I focused

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my studies on the adaptations of *L. monocytogenes* that allowed it to live stealthily inside host cells. My work at the Institut Pasteur in the laboratory of Michèle Mock, on the contrary, focuses more on the adaptations of the host to counter bacterial infections.

Each microorganism that interacts with a host has a different method to achieve its ultimate goal – to multiply and spread so that it can multiply once again in the future. We can readily rationalize the course of some infectious diseases, if we keep evolution in mind. For instance, it is clear that the enteric pathogens, such as *Shigella* species, *Vibrio cholerae*, and *Salmonella enterica* species, which cause profuse diarrhea, have found a very efficient method of spreading to new hosts that is inconvenient to the host, but often not fatal. Other pathogens are not so benign, where host death is an integral part of their life cycle. Such is the case for my current research focus, *Bacillus anthracis* – the bacterium that causes the infamous disease anthrax.

B. anthracis spores (a durable and dormant form of the bacteria) that enter a host through inhalation, abrasions in the skin, or orally, quickly germinate and begin producing toxins and a bacterial cell-enveloping capsule. The toxins function to confuse the coordination of host defenses and the capsule prevents the bacterial cells from being cleared from the tissues of the host. The toxins and capsules allow the bacteria to multiply to incredibly high numbers (up to 10^8 bacteria/ml blood!). Upon death of the host, *B. anthracis* forms spores, which are released into the surrounding environment upon host decomposition and can remain viable for years while waiting for introduction into the next host.

My post-doctoral fellowship, funded by the Pasteur Foundation, focuses on exploring the means by which a host – in this case a mouse – can alter the balance of host-pathogen dominance in favor of the host. In particular, I am interested in the host defenses triggered in the mouse immediately after infection and the protective host responses that are induced through vaccination. We have found that defense cells recognize and react to spores to produce signaling molecules that further activate defenses to effectively counter infection. However, we also found that this host cell signaling is inhibited by bacterial toxins, suggesting that the defenses must activate and eliminate the spores before bacteria can begin secreting toxins.

One method to quicken the host response is to teach the immune system to recognize *B. anthracis* as a threat; this is achieved with a vaccine. To vaccinate mice, we inject killed spores that are incapable of causing an infection or secreting toxins, but are still recognized by the immune system as a potential threat. Subsequently, any particle that resembles spores will be immediately recognized as a threat and immune defenses will be rapidly deployed to more efficiently fight infection. Our studies have shown that this spore-based vaccine protects via the function of T lymphocytes, whereas the current human anti-toxin vaccine protects via the function of antibodies. Thus, our data suggest that the current human vaccine paradigm that focuses on the production of anti-toxin antibodies should be broadened to also target T lymphocyte activation as an additional mechanism of countering anthrax.

THE FACTS

NAME: Ian Glomski

DATE OF BIRTH: August 16, 1972

PLACE OF BIRTH: Park Ridge, Illinois, USA

B.S. (1995):
Biology and Environmental Studies (Tufts University, Boston, Massachusetts)

PH.D. (2002):
Molecular and Cell Biology (University of California, Berkeley)

LAST POSITION: graduate student researcher

LAST ADDRESS: Berkeley, California

MENTOR: Dr. Daniel A. Portnoy

IF YOU COULD BE PRESENT AT A GREAT SCIENTIFIC DISCOVERY WHAT WOULD IT BE?
when researchers discover how life became living

THE LIGHTER SIDE

HOME ARRONDISEMENT: 3rd

FAVORITE METRO STATION: Bastille

FAVORITE GUILTY PARISIAN PLEASURE:
hot chocolate from La Charlotte de l'isle

FAVORITE FRENCH TOURIST SITE:
Mont Saint Michel during a snowfall

FAVORITE RECENTLY LEARNED FRENCH EXPRESSION:
hypercool

MOST ABUSED "FAUX AMI": vegetable

FAVORITE FILM: *Ghost in the Shell*

ARE YOU A FAN OF

WOODY ALLEN: Too neurotic

MICKEY ROURKE: Eh, take him or leave him

JERRY LEWIS: No nutty professors, thank you

FAVORITE WINE: Page Springs Cellars "Old Vines Mourvedre" (from my family's winery)

FAVORITE CHEESE: Epoisses de Bourgogne

CURRENT BEDSIDE READING:
Leonardo: The Artist and the Man by Serge Bramly

MAC OR PC: Pac – I use one of each!

FAVORITE PIECE OF LAB EQUIPMENT:
the colony counter

WHAT THE FRENCH DO BETTER THAN AMERICANS:
ignore fat content

WHAT AMERICANS DO BETTER THAN THE FRENCH:
form proper waiting lines

BEST THING ABOUT BEING AN AMERICAN IN PARIS:
skipping the long lines of French people at the American Embassy

WHAT YOU MISS MOST ABOUT THE U.S.:
the wilderness

WHAT YOU THINK YOU'LL MISS MOST ABOUT FRANCE:
mandatory vacations

APPLICATION DEADLINE REMINDERS

Zuccaire Undergraduate Summer Internship applications are due in two parts beginning on **Friday, December 15, 2006**.

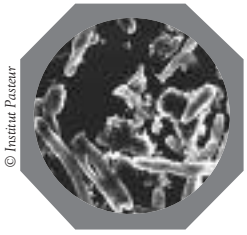
Postdoctoral Fellowship Program applications are due **Friday, February 2, 2007.**

Please consult our website for details: www.pasteurfoundation.org

More to the Point: News in Brief from Pasteur

TB or Not TB: A Key Genetic Factor Identified

Tuberculosis causes 2 million deaths annually. However, while some 2 billion people are infected by the causal agent *Mycobacterium tuberculosis*, only 10% of these people develop the disease. Scientists working at the Institut Pasteur have recently identified a new human genetic factor involved in TB susceptibility. They demonstrated that a variant of the gene, DC-SIGN, is over-represented in individuals who do not develop TB despite exposure to the bacterium. The variant of this gene may therefore play a role in protecting humans against TB and may provide avenues to develop new strategies to fight this disease.

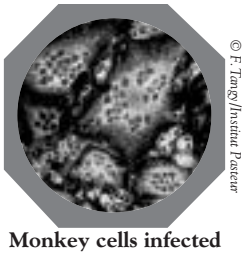


© Institut Pasteur

Mycobacterium tuberculosis

Measles Enlisted to Fight AIDS

Using an ancient scourge to combat a new one, in late 2005 researchers from the Institut Pasteur and GlaxoSmithKline Biologicals announced a new European collaboration to develop an AIDS vaccine by fusing genes from the human immunodeficiency virus (HIV) onto an existing measles vaccine. GSK Biologicals will license the measles vaccine vector technology from the Institut Pasteur and the two entities will jointly develop the AIDS vaccine. The measles vaccine, based on the Schwarz strain of the measles virus, is known to confer very long-lasting immunity. Scientists hope that using this vaccine as a carrier to deliver HIV proteins will allow them to produce a uniquely potent and long-lasting vaccine to prevent AIDS. AIDS research is one of the strategic objectives of the Institut Pasteur's research program. Some 15 teams are working on different approaches and several programs focus on potential vaccines.



© F. Tangy/Institut Pasteur

Monkey cells infected with an experimental recombinant measles vaccine express proteins from the HIV envelope.

Kidney Cyst Formation in PKD Decrypted

Researchers at the Institut Pasteur have unraveled the cellular mechanisms that are deregulated in polycystic kidney disease, known as PKD. A life-threatening genetic disease that impairs kidney function, PKD is one of the most widespread genetic diseases in the world – ahead of cystic fibrosis and muscular dystrophy; it currently affects 12.5 million people. New work has shown that the dilation of renal tubules leading to cyst formation is linked to a disorganized growth of tubular cells. This research, published in *Nature Genetics* (Dec. 11, 2005), permits a better understanding of the first stages of this genetic disease and is an important step toward new therapeutic approaches.

Honoring Pasteur: The U. S. Pays Tribute

American Poet Edgar Bowers Finds a Muse in Louis Pasteur

by Caitlin Hawke

"How shall a generation know its story if it will know no other?" queries the searching voice in Edgar Bowers's poem *For Louis Pasteur* from his 1989 collection of poems bearing the same title. Winner of the Bollingen Prize in Poetry and two Guggenheim fellowships, Bowers was an accomplished American poet and a professor admired by many of his contemporaries, but his name and work remain largely undiscovered.

Born in Georgia in 1924, he spent the first half of his life in the American south until he went to pursue his graduate studies at Stanford University. In 1945, his life took an abrupt turn when he left school to serve with the U.S. Army in Germany at the end of World War II.

His experience in the war would come to have a great impact on his creative work and perhaps explains his pursuit of meaning and perspective. The opening line of this article, a line from his poem in blank verse dedicated to Louis Pasteur, captures Bowers's search. His choice of Pasteur as a complex hero is a poignant one for it underscores a seemingly contradictory side of the brilliant scientist: a man who knew his generation's story and perhaps foretold that of the next generation, yet also a man who in spite of his great humanism was prone to feelings of nationalism.

Upon the publication of his final collection, Bowers was referred to by Harold Bloom as "one of the best living American poets these last 40 years." Edgar Bowers died in San Francisco in 2000 at the age of 75.

For Louis Pasteur

by Edgar Bowers

Two Excerpts

His mind was like Odysseus and Plato
Exploring a new cosmos in the old
As if he wrote a poem – his enemy
Suffering, disease, and death, the battleground
His introspection.

…

I like to think of Pasteur in Elysium
Beneath the sunny pine of ripe Provence
Tenderly raising black sheep, butterflies,
Silkworms, and a new culture, for delight,
Teaching his daughter to use a microscope
And musing through a wonder – sacred passion,
Practice and metaphysic all the same.

Princeton University Press, 1989

Very Special Thanks to the Grand Marnier Foundation

The Pasteur Foundation is pleased to announce the creation of the
Grand Marnier Foundation
American Guest Scientists Program
at the Institut Pasteur.

This three-year program to bring U.S. scientists to the Institut Pasteur as guest scholars and as scientists-in-residence fits aptly into the Pasteur Foundation's mission to promote scientific exchange between the Institut Pasteur and the American scientific community.

We look forward to bringing our readers further details in future issues.

The Waiting Game *continued from page 1*

control of infectious disease in countries affected by and at risk for the spread of this influenza strain;

• Exchanging technical expertise to enable rapid response to disease threats; and

• Disseminating effective public information on infectious disease, including information in local languages in developing countries.

HHS Deputy Secretary Alex M. Azar said that the United States was "very pleased to partner with the Institut Pasteur, an internationally respected research institute with such an impressive global network of institutes." Welcoming this French-American partnership, Institut Pasteur President Alice Dautry embraced this understanding as "a unique opportunity to join efforts to fight infectious diseases upfront."

For more information on this subject, please visit:
www.pasteur.fr and www.pandemicflu.gov

Pasteur Perspectives

A **501(c)(3)** organization, the Pasteur Foundation is the U.S. nonprofit affiliate of the Institut Pasteur. Located in New York City, the foundation works to introduce the research conducted at the Institut Pasteur to the American public, to develop exchanges between Pasteurian and U.S. scientists, and to raise funds for Pasteurian research. For more information, please contact the Pasteur Foundation.

A copy of the latest annual report may be obtained, upon written request, from the Office of the Attorney General, Charities Bureau, 120 Broadway, New York, New York 10271.

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❑ I have enclosed a contribution but do not wish to receive a gift so that 100% of my donation is tax deductible.

❑ Check enclosed ❑ Please charge my credit card: ❑ VISA ❑ MASTERCARD ❑ AMEX

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FOCUS ON BIRD FLU: A CONVERSATION WITH SYLVIE VAN DER WERF

Dr. Sylvie van der Werf heads the Molecular Genetics of Respiratory Tract Viruses Unit in the Institut Pasteur's Virology Department. An accomplished researcher, she is also a director of the National Influenza Reference Center in Northern France and of the World Health Organization's Collaborating Center for influenza and other respiratory viruses, both housed at the Institut Pasteur. In spite of the pressing situation of Avian Influenza now currently unfolding in Europe and demanding her full attention, she agreed to make time for our readers. Recently, Dr. van der Werf and Caitlin Hawke had the following exchange.

Caitlin Hawke: Before questions about a future human-to-human transmissible strain, is it a foregone conclusion that the current Influenza A (H5N1) strain will quickly become endemic to virtually every region of the world? Is it a virus with which we will co-exist forever? What does this mean for the world's bird population?

Sylvie van der Werf: Given the geographical extension in the bird population, the H5N1 virus is likely to become endemic. How quickly this could happen worldwide is not clear (for instance if and when the Americas might become infected remains to be determined). If the virus were to remain in the wild bird population, it might over the long term lose its high pathogenicity, but this scenario is not likely to happen as long as the virus is found in poultry.

CH: How much do scientists know about birds that carry the virus but do not die? Is this in anyway a key to the current epizootic?

SW: It is not totally clear at present whether wild birds are the main vectors of the virus or rather its victims. From available information to date, the prevalence in birds that do not die seems to be extremely low in favor of the second hypothesis. However, much more is to be done to have a clear picture and also to evaluate the prevalence according to bird species.

Dr. Sylvie van der Werf

CH: Public health experts seem to be preparing for the worst-case scenario – that in which a human-to-human transmissible strain appears and sparks a pandemic. Is it just a matter of time before this occurs? What specific molecular conditions need to be met for a human-to-human strain to appear?

SW: For a given probability for a pandemic virus to emerge, the possibility of the occurrence of such an event increases with the increased number of persons exposed to the virus parallel to the increase and geographic extent of the epizootic. It is not known which combination of changes would be needed for the virus to adapt to humans although some determinants that could contribute to such adaptation are known.

CH: Your lab serves both as a French National Reference Center as well as a WHO Collaborating Center. Given the sophisticated methods you employ for epidemiological surveillance and detection and the international cooperative spirit to monitor and prevent the spread of this strain of bird flu, is a pandemic on the scale of the Spanish flu of 1918 (40 million deaths) even possible today?

SW: All efforts today are directed at trying to follow the evolution of the virus as closely as possible in order to identify as quickly as possible any changes (both epidemiological and virological) that may suggest the onset of human-to-human transmission, in order to try to contain or at least slow down the progression of such virus if it were to emerge. Nevertheless, the possibility of a pandemic with a high mortality rate such as that seen during the Spanish flu in 1918 cannot be excluded. But a scenario like that of the previous pandemics (1957 or 1968) is equally possible.

CH: The optimist in me would like to ask if it's possible that, after undergoing the mutation process that would bring about a human strain of H5N1, this much-anticipated strain could actually be weaker in virulence and have a lower mortality rate than the avian strain?

SW: This is what would indeed be expected. Viruses that are well adapted to their host are usually less pathogenic.

CH: Could one say that the ultimate Darwinian success would be for a virus to co-habit with its host but not kill it?

SW: Yes, definitely.

CH: What are your views on the co-existence of viruses and humans in general?

SW: We have probably been living with viruses ever since mankind exists. Human activities and changes in our environment contribute to perturb the delicate equilibrium between viruses and their hosts offering opportunities for unprecedented contacts and interspecies transmissions. It is likely that many more viruses which might have the potential to infect and eventually establish in the human population remain to be discovered.

CH: We like to think of ourselves as victorious, but aren't viruses, in fact, adaptively far more successful?

SW: Just as viruses, human beings also constantly adapt to their environment. Adaptation for viruses – especially for RNA viruses like influenza virus – is extraordinarily fast.

CH: In a worst-case scenario, the cost in lives and in economic losses of such a plague is almost unfathomable. Is it nihilistic to think that fighting viruses is ultimately a losing battle? Or does your perspective as a scientist help you to believe that one day we will indeed fully understand these pathogens that render us so vulnerable?

SW: Eradication of smallpox shows that the fight against viruses can be successful. With increasing knowledge we will combat viruses more efficiently in the long run but new viruses will arise and the existing ones will adapt. As a parallel, antibiotics have been a tremendous boon to the fight against bacterial pathogens, but antibiotic resistance is today a major issue.

Please Save The Date

Pasteur Foundation Spring Gala

At one of our first galas, Elizabeth Fondaras is pictured here in 1992 with French star Gérard Depardieu at the premiere of his film *Tous les matins du monde*. As Chairman of the Pasteur Foundation American Advisory Board, Mrs. Fondaras has lent her savoir-faire to over fifteen of our galas as well as to each of our programs. We are thrilled to present the 2006 Pasteur Foundation Award to her on June 7th.

Wednesday, June 7, 2006

Elizabeth Fondaras

Founding Chairman
of our American Advisory Board
Pasteur Foundation 2006 Award Recipient

Award Gala
Cocktails, Dinner & Dancing

For gala invitations, reservations or
for more information about purchasing tickets
and tables or contributing to this event
please call 212.599.2050.

SAVE THE DATE

Pasteur Foundation Gala
Wednesday, June 7, 2006
New York City
honoring
Elizabeth Fondaras
See back panel for more information.

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