

PASTEUR PERSPECTIVES

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

A Message from the Chairman of the American Advisory Board

Elizabeth Fondaras retired in November 2006 as Chairman of the American Advisory Board after nearly 20 years of unparalleled service. She continues to be active on the Board, offering invaluable assistance in her position as Founding Chairman. Elected to succeed Mrs. Fondaras, Anne Cox Chambers is a founding Advisory Board member and recipient of the 2004 Pasteur Foundation Award.

Dear Readers:

This issue marks the 20th edition of Pasteur Perspectives which, over the last decade, has brought you news of breakthroughs from the Institut Pasteur laboratories. Today, in addition to reading about a promising cancer vaccine trial, you will learn of progress in fighting the plague, tuberculosis and childhood deafness.



In an attempt to provide an eclectic perspective, over the years we have unearthed lasting tributes to Louis Pasteur in the United States – from playgrounds to cathedral windows. To discover some of these stories, you can read all of our archived issues online. If you have a special Pasteur-U.S. connection, please write to us.

We are pleased to provide information in each issue about the opportunities we have created for Americans to work in the Paris facilities of the Institut Pasteur. Application deadlines for our Postdoctoral Fellowships and Zuccaire Undergraduate Internships may be found on page 3. Essential to the vitality of Pasteurian research, these programs would not be possible without our generous American donors.

There are many means to ensure the continuation of Pasteur's research programs by supporting the Pasteur Foundation, a 501(c)(3) organization. Please attend or contribute to our Annual Gala on May 3rd in New York City (see back panel for more information). Additionally, you can help by returning the enclosed gift envelope with your tax-deductible contribution. Your support will help to advance our research and create wonderful opportunities for American scientists in France.

We welcome your comments to improve this newsletter. In the meantime, we thank you for reading and hope you enjoy this 20th issue.

Sincerely,

Anne Cox Chambers
Chairman, American Advisory Board



THE CUTTING EDGE

by Caitlin Hawke

A CANCER VACCINE CANDIDATE: MAG-TN3

After 10 years of research, two Institut Pasteur teams, spearheaded by Professor Claude Leclerc, have developed a method to stimulate an immune response against antigens that are expressed by certain tumors. Tn, an antigen of particular interest to the teams, is strongly expressed on the surface of adenocarcinomas of the prostate, colon, breast and lung. By way of a synthetic compound, MAG-Tn3 (multiple antigenic glycopeptide), the scientists have been able to stimulate the immune system to attack and eliminate such tumors. Used as a vaccine, MAG-Tn3 was shown to protect mice against grafted tumors in 70% to 90% of cases, depending on the dose administered. Moreover, in mice already afflicted with tumors, MAG-Tn3 treatment produced a cure rate of 80%.

Encouraged by this outcome, the Pasteur teams are now laying the groundwork to apply the results to a vaccine for use in humans suffering from adenocarcinomas. Production of a GMP batch – Good Manufacturing Practice batch – is underway, and it is anticipated that a therapeutic vaccine will be in hand by 2011, when patient trials will be conducted to verify that it induces an antibody response in humans.



On the surface of a healthy cell, Tn is masked by other elements. On the surface of a cancerous cell, Tn is expressed; vaccination enables an antibody response directed at these cells.

How You Can Help

The overall budget for this project is \$5.75 million and depends significantly on public charitable giving. If you would like to support this work and learn more, please contact the Pasteur Foundation.

MEET THE FELLOWS: MELANIE HAMON

Dr. Hamon is a Florence Gould Scholar of the Pasteur Foundation Postdoctoral Fellowship Program. She joined Pascale Cossart's Bacteria-Cell Interactions Unit at the Institut Pasteur in 2004. Taking a break from the lab to write research articles and recover from childbirth-induced sleep deprivation, Melanie was kind enough to make time to share some thoughts about her favorite kind of microbes.

BACTERIA IN EIGHT EASY LESSONS

by Melanie Hamon, Ph.D.

When I introduce myself as a bacteriologist, I am often asked, "Just what does that mean?" To help explain my scientific discipline, I give you, in eight letters, some demystifying facts about bacteria.



Basic principles: Their average size is 1/25,000th of an inch. In other words, hundreds of thousands of bacteria fit into the period at the end of this sentence. In comparison, human cells are 10 to 100 times larger with a more complex inner structure. While human cells have copious amounts of membrane-contained subcompartments, bacteria more closely resemble pocketless sacs. Despite their simplicity, they are self-contained living beings, unlike viruses, which depend on a host cell to carry out their life cycle.

Astonishing: Bacteria are the root of the evolutionary tree of life, the source of all living organisms. Quite successful evolutionarily speaking, they are ubiquitously distributed in soil, water, and extreme environments such as ice, acidic hot springs or radioactive waste. In the human body, bacteria account for 10% of dry weight, populating mucosal surfaces of the oral cavity, gastrointestinal tract, urogenital tract and surface of the skin. In fact, bacteria are so numerous on earth that scientists estimate their biomass to far surpass that of the rest of all life combined.

Crucial: It is a little known fact that most bacteria in our bodies are harmless and even essential for our survival. Inoffensive skin settlers form a protective barrier against any troublesome invader while approximately 1,000 species of gut colonizers work for our benefit, synthesizing vitamins, breaking down complex nutrients and contributing to gut immunity. Unfortunately for babies (and parents!), we are born with a sterile gut and "colic" our way through bacterial colonization.

Tools: Besides the profitable relationship they maintain with us, bacteria have many other practical and exploitable properties, most notably, perhaps, in the production of cream, yogurt and cheese. Less widely known are their industrial applications as antibiotic factories, insecticides, sewage processors, oil spill degraders and so forth.

Evil: Unfortunately, not all bacteria are "good," and those that cause disease give them all an often undeserved and unpleasant reputation. If we consider the multitude of mechanisms these "bad" bacteria – pathogens – use to assail their host, it is no wonder that they get a lot of bad press. Indeed, millions of years of coevolution have shaped bacteria into organisms that "know" and "predict" their hosts' responses. Therefore, not only do bacterial toxins know their target, which is never missed, but bacteria can predict their host's immune response and often avoid it.

Resistant: Even more worrisome than their effectiveness at targeting their host is their faculty to withstand antibiotic therapy. For close to 50 years, antibiotics have revolutionized public health in their ability to treat bacterial infections. Unfortunately, overuse and misuse of antibiotics have led to the alarming fact of resistance, which promises to be disastrous for the treatment of such diseases.

Ingenious: The appearance of antibiotic-resistant bacteria is a reflection of how adaptable they are. Thanks to their large populations they are able to mutate their genetic makeup, or even exchange it, to find the appropriate combination that will provide them with resistance. Additionally, bacteria are able to form "biofilms," which are cellular aggregates covered in slime that allow them to tolerate antimicrobial applications that normally eradicate free-floating individual cells.

Along tradition: Although "little animalcules" were first observed in the 17th century, it was not until the 1850s that Louis Pasteur fathered modern microbiology. From this point forward, research on bacteria has developed into the flourishing field it is today. For many years to come, researchers will continue to delve into this intricate world, trying to understand how the good ones can help and how to protect ourselves from the bad ones. It is a great honor to be part of this tradition, working in the very place where it was born.

Bacteria depicted (top to bottom): *Escherichia coli*, *Mycobacterium tuberculosis*, *Mycobacterium leprae*, *Mycobacterium tuberculosis*, *Streptococcus*, *Yersinia pestis*, *Leptospira*, *Vibrio cholerae*

MELANIE HAMON

THE FACTS

DATE OF BIRTH: December 1, 1976

B.S. (1999):

Microbiology, Immunology and
Molecular Genetics
(University of California, Los Angeles)

PH.D. (2004):

Microbiology, Immunology and
Molecular Genetics
(University of California, Los Angeles)

LAST POSITION: Ph.D. student at UCLA

LAST ADDRESS: Westwood, California

MENTOR: Dr. Beth Lazazzera

IF YOU COULD BE PRESENT AT A GREAT SCIENTIFIC
DISCOVERY WHAT WOULD IT BE?

when man discovered how to fly

THE LIGHTER SIDE

HOME ARRONDISEMENT: I live in the *banlieue*,
just outside the Parisian circle.

FAVORITE METRO STATION:

any station with the Guimard
art nouveau entrance

FAVORITE GUILTY PARISIAN PLEASURE:

warm fresh bread

FAVORITE FRENCH TOURIST SITE:

the way the Eiffel Tower is
illuminated at night – *scintillante*

MOST ABUSED "FAUX AM": *excitant*

ARE YOU A FAN OF

WOODY ALLEN? in small doses

MICKEY ROURKE? Keanu Reeves was my
preferred teenage heartthrob.

JERRY LEWIS? I am embarrassed to say that
I probably would not recognize him.

FAVORITE WINE: Champagne

FAVORITE CHEESE: smelly ones

CURRENT BEDSIDE READING:

My Name Is Red by Orhan Pamuk

MAC OR PC: Mac

FAVORITE PIECE OF LAB EQUIPMENT:

the spectrophotometer

WHAT THE FRENCH DO BETTER THAN AMERICANS:

socialized medicine – I walked out of
the maternity ward after four days
with a new baby and paid nothing.

WHAT AMERICANS DO BETTER THAN THE FRENCH:

customer service

BEST THING ABOUT BEING AN AMERICAN IN PARIS:

not having to read subtitles at movies

WHAT YOU MISS MOST ABOUT THE U.S.:

Mexican food!

WHAT YOU THINK YOU'LL MISS MOST ABOUT FRANCE:

la joie de vivre

BECOME AN AMERICAN SCIENTIST IN PARIS!

Apply for our internship or fellowship positions.

APPLICATION DEADLINE REMINDERS

THE POSTDOCTORAL FELLOWSHIP PROGRAM

was launched in 2002 and, to date, has been funded with
nearly \$4 million, thanks to the generosity of our U.S.-based donors.

The fellowship positions award an annual package of \$60,000
for three years to outstanding American postdocs.

There are two annual calls for applicants –
in February and September –
for the Pasteur Foundation Postdoctoral Fellowships.

Next deadline: Friday, September 7, 2007

THE PAUL W. ZUCCAIRE SUMMER INTERNSHIP PROGRAM

is open to undergraduates who are independent,
have a developed interest in the biological sciences
and contemplate graduate studies in the field.
Annual applications are due in December.

Next deadline: Friday, December 14, 2007

Please consult our website for specific dates and
eligibility requirements. For all information, please visit:
www.pasteurfoundation.org

DID YOU KNOW THAT THE INSTITUT PASTEUR IS A PRIVATE, NONPROFIT RESEARCH FOUNDATION?

Since its inception nearly 120 years ago, the Institut Pasteur has
become one of the world's symbols of science and research,
remaining faithful to the spirit that drove Louis Pasteur
in his fight against infectious diseases. Today, it is a premier center
of biomedical research.

Americans may support
its work by donating to the
Pasteur Foundation, a 501(c)(3)
organization whose mission
is to raise funds to advance
the research conducted at the
Institut Pasteur, to foster specific
projects and to promote
scientific exchanges with
American researchers.



Institut Pasteur

To make a tax-deductible contribution,
please call Caitlin Hawke at the Pasteur Foundation in New York
at 212.599.2050 or return your donation in the enclosed envelope.

HONORING PASTEUR: THE U. S. PAYS TRIBUTE

LOUIS PASTEUR PARK, NEW YORK CITY

New York City boasts 1,700 parks and playgrounds spread over 28,000 acres throughout the five boroughs. One that caught our eye is located on 52nd Avenue between 248th Street and Marathon Parkway in Queens. Intimate in comparison to its well-known 840-acre Manhattan cousin, this 3.7-acre park is part of the New York City Department of Parks and Recreation, from which we learned that "this park honors the extraordinary achievements of pioneering French microbiologist Louis Pasteur." The land was acquired by the department in 1954, and four years later a playground was built on the site. In 1986, former Parks Commissioner Henry J. Stern named it Louis Pasteur Park. After a \$1 million restoration in 1987, which coincidentally marked the Centennial of the Institut Pasteur, the space became a natural haven for the neighborhood and, in particular, for the 1,000 students of the adjacent school, JHS 67, also known as Louis Pasteur Junior High School. It features a baseball field; playground equipment; and handball, basketball, boccie and tennis courts.

We asked Parks and Recreation Commissioner Adrian Benepe about this special New York tribute to Louis Pasteur, and he said, "The men and women of the past shaped what our country and the world have become today. One of the small things we can do to pay tribute to their great contributions is to name our streets, our buildings...and our parks in their honor. Parks and Recreation has a long tradition of naming the city's green spaces after important historical figures, and former Parks Commissioner Stern was one of the biggest supporters of this tradition."

There are at least two other American parks that bear Pasteur's name: one in Illinois and one in Massachusetts. Logo used with permission of City of New York Parks & Recreation

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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Pasteur Foundation

DÉJA VINGT?

This issue marks the 20th edition of our newsletter. We wish to acknowledge this occasion by asking readers to send in their remarks and suggestions for future issues.

Also, in preparation for the 120th anniversary of the Institut Pasteur in 2008, we plan to publish reminiscences from Americans who have worked in Pasteur labs over the course of its history.

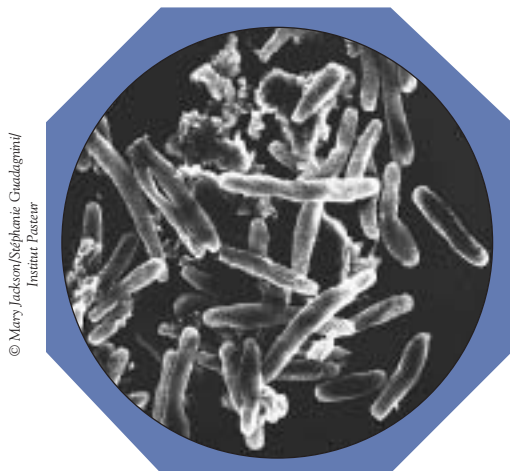
**IF YOU HAVE A PASTEUR STORY TO SHARE,
PLEASE LET US HEAR FROM YOU.**



MORE TO THE POINT: NEWS IN BRIEF FROM PASTEUR

FAT CHANCE FOR TB

Considered a global health emergency by the World Health Organization, tuberculosis kills nearly 2 million people each year. An Institut Pasteur team has recently shown that the TB bacillus hides from the immune system in its host's fat cells, where it is also protected from isoniazid, one of the main antibiotics used to treat it. However, the bacillus may reactivate, a probable scenario in immunocompromised individuals such as those infected with AIDS.



© Mary Jackson/Stephanie Gradadignil
Institut Pasteur

A scanning electron microscope image of the TB bacillus

The team's work helps to explain how, many years after first testing positive for tuberculosis, people with no trace of pulmonary TB may develop some other form in sites including the bones or genitals or again in the lungs. It also suggests that isoniazid treatment, prescribed for close friends and family of patients as a preventive measure, may in some cases not provide sufficient protection against the disease. The search for new targeted antibiotics able to reach the dormant bacillus in its hiding place is now clearly crucial to combating TB.

GENETIC DEAFNESS IN CHILDREN: REVERSING THE IRREVERSIBLE

A mutated gene that causes profound irreversible deafness in newborns has been identified by an Institut Pasteur team. The discovery, published in the journal *Cell* (October 20, 2006), led these researchers to uncover the role of its encoded protein, otoferlin. Otoferlin, necessary to stimulate the auditory nerve, is a protein of the synaptic vesicles required for the release of a neurotransmitter by the auditory sensory cells of the cochlea. As a result, children who carry a mutation in the otoferlin gene can be identified early and are likely to benefit from a cochlear implant – an electroacoustic device that substitutes for the function

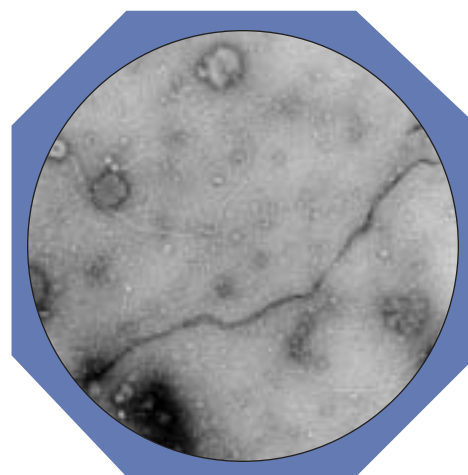
of the defective cochlea. Already in use is a molecular diagnostic tool developed by the Pasteur team to detect mutations in the otoferlin gene.

SNEAKY STOMACH BUG

Shigella flexneri is responsible for bacillary dysentery, or shigellosis, one of the most severe diarrheal diseases causing 600,000 to 1 million deaths per year. It invades intestinal cells to provoke an inflammatory response, our first line of defense. Researchers from the Institut Pasteur have now shown how the bacterium modulates this response by blocking signaling pathways at two levels. *Shigella* thereby weakens our ability to combat the disease and enables itself to survive in the intestinal lining. Deciphering the molecular mechanisms at play has led the way to new therapeutic targets and the search for new generations of anti-inflammatory drugs and immunomodulators. The study could eventually prove useful in treating diseases like ulcerative colitis and Crohn's disease.

A PLAGUING QUESTION

A re-emerging disease globally that continues to rage in areas of Africa and Asia, the plague is far from eradicated. In the Middle Ages, it decimated a third of the European population in less than three years. Why is the plague bacillus – *Yersinia pestis* – so pathogenic? Institut Pasteur researchers have just discovered one of the basic causes of this extreme virulence: the ancestral form of the bacillus encodes for the production of a filamentous phage. Phages, which are viruses that infect bacteria, are implicated in the pathogenicity of other microorganisms such as that which causes cholera. For plague specialists, this discovery is a key step in understanding the specific pathogenic mechanisms of the plague and eventually to the development of an effective means of combating it.



© Institut Pasteur

The filamentous phage produced by *Yersinia pestis*

PLEASE SAVE THE DATE

Pasteur Foundation Spring Gala



Daniel Vasella, M.D.

Thursday, May 3, 2007

Daniel Vasella, M.D.

Chairman and Chief Executive Officer
Novartis AG

Pasteur Foundation 2007 Award Recipient

Cocktails, Dinner & Dancing

To purchase tickets or to make a contribution
in support of the gala, please call 212.599.2050.

For more information about the annual gala, please visit our website:
www.pasteurfoundation.org

Pasteur Foundation Gala
Thursday, May 3, 2007
New York City
honoring
Dr. Daniel Vasella
See back panel for more information.

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