

PASTEUR PERSPECTIVES

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

MEET THE FELLOWS: DOUGLAS MACDONALD

Dr. MacDonald, a Pasteur Foundation Fellow and Florence Gould Scholar, is a structural biologist in the Biochemistry and Biophysics of Macromolecules Group at the Institut Pasteur. His current focus is discovering the shapes of enzymes responsible for the spread of antibiotic-resistant genes among bacteria. The proliferation of these genes has resulted in the resistance to commercially available drugs of formerly manageable bacterial infections. The goal of Dr. MacDonald and his colleagues is to understand the mechanisms of these enzymes in order to facilitate the design of drug inhibitors to thwart the transfer of antibiotic-resistant genes. We asked Dr. MacDonald to describe the current relevance of one of Louis Pasteur's seminal discoveries: molecular asymmetry.

CRYSTALLIZING IDEAS FOR NEW THERAPIES

By Douglas MacDonald

More than 150 years ago in the laboratories of the Parisian university, the École Normale Supérieure, the young Louis Pasteur suggested that two molecules composed of identical atoms could vary if their atoms were arranged differently in space. Although the term was yet to be defined, Pasteur had discovered the importance of “stereochemistry,” the spatial arrangement of atoms within a molecule. His breakthrough was even more impressive because it was based on the size and shape of simple salt crystals 30 years before the identification of carbon asymmetry, the principle that would eventually confirm his discovery.

Pasteur had begun to formulate his hypothesis two years earlier, when he learned of the observations of Eilhardt Mitscherlich, a German chemist who had noticed that during the fermentation of wine, two types of crystals formed in the “tartar.” The normal tartrate, or crystalline acid, coated the inside of wine barrels, and occasionally a second,

smaller, needlelike crystal was formed, which Mitscherlich called “paratartrate.”

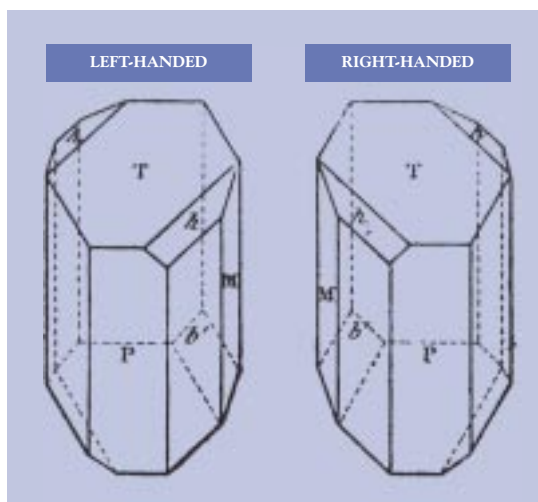
Pasteur's interest arose because Mitscherlich showed that although both of these acids shared the same chemical composition, their solutions behaved differently when placed in front of polarized light: the tartrate rotated the plane of polarized light to the right, while the paratartrate produced no rotation. (Source: a note sent by Mitscherlich to J.B. Biot and presented to the French Académie des Sciences in 1844.) This led Pasteur to question why two chemically equivalent compounds could possess different optical activities.

The young scientist's response demonstrated one of his most notable attributes: the ability to apply faultless logic to his scientific endeavors, to create a relevant set of experiments to unravel the mystery at hand. Pasteur thought that the difference between these two solutions would reveal itself in the shape of their crystals, and he

devised a procedure that proved the validity of his assumption. All the crystals he prepared from the paratartrate solution, the compound with no optical activity, demonstrated two types of facets that were, in fact, mirror images (see crystal illustration). In contrast, the facets from the tartrate crystals showed only one orientation. Further investigation revealed that the original paratartrate crystals taken from the wine barrel were actually a mixture of two compounds: the first

rotated the plane of polarized light to the left and the second rotated the plane to the right, together producing no optical activity.

Pasteur had discovered what are now called “enantiomers,” certain molecules that are non-superimposable images of each other. The most



Pasteur's drawings of crystals from the “tartar” of wine. Crystals from the paratartrate solution produce both left- and right-handed crystals. The tartrate solution yields only right-handed crystals. Note that the two crystal types are mirror images.



simple example of this concept is a set of human hands: the left hand cannot be superimposed on its mirror image, the right hand. Today we know that enantiomers are chemically distinguishable only through the use of special techniques.

We can only speculate whether Pasteur truly understood the magnitude of his discovery. Regardless, we are all beneficiaries of this work, as the study of molecular shapes is one of the bases for contemporary science and has resulted in significant contributions to modern medicine. The latter is readily apparent as we consider the human body. At any given time in every person, millions of reactions occur simultaneously, controlled by special proteins called enzymes and the molecules that bind to them, all individual in shape and size. Every enzyme fits uniquely with its molecule, like a key into a lock. If there is a problem with the reaction – if the lock and key do not fit well together – significant health concerns could result for those affected.

However, stereochemistry, begun by Louis Pasteur, allows these special shapes to be more easily identified and successfully imitated by pharmaceutical products. Therefore, even if the reactions in our bodies do not quite work the way they should, a drug may be available or in development that could remedy our problem. For example, scientists recently developed what are commonly referred to as “super aspirins,” or “cox-II inhibitors.” By knowing the shape or structure of both proteins with which traditional aspirin reacts, investigators were able to develop a more advanced version that works selectively with one of these proteins, thereby eliminating stomach upset and pain.

As a structural biologist, I determine the shapes of the enzymes and molecules that work together to make the human body run smoothly. Each of the molecular shapes or structures identified in our laboratory at the Institut Pasteur is made available to scientists and companies worldwide via an extensive database available on the Internet. These structures are often used to create pharmaceutical

THE FACTS

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MOST PERSONALLY MEANINGFUL DISCOVERY: new people
IF YOU COULD BE PRESENT AT A GREAT SCIENTIFIC DISCOVERY,
WHAT WOULD IT HAVE BEEN OR WILL IT BE?
the discovery of DNA

THE LIGHTER SIDE

HOME ARRONDISEMENT: 15th
FAVORITE METRO STATION: Montparnasse
FAVORITE PARISIAN/FRENCH TOURIST SITE/REGION:
the Seine
FAVORITE GUILTY PARISIAN PLEASURE: Where do I
start? But the holy trinity will do:
cheese, bread and wine.
FAVORITE FRENCH WINE: Bordeaux for winter
and Alsace for summer.
FAVORITE CHEESE:
Roquefort will always be king.
FAVORITE RECENTLY LEARNED FRENCH WORD:
Absolument
MOST ABUSED FRENCH EXPRESSION: *faux ami*
FAVORITE FILM: *Scarface*
ARE YOU A FAN OF
WOODY ALLEN: But of course.
MICKEY ROURKE: I'm luke warm.
JERRY LEWIS: I just don't get this guy.
CURRENT BEDSIDE READING:
A book on Haussmann's Paris
WHAT THE FRENCH DO BETTER THAN AMERICANS:
enjoy life
WHAT AMERICANS DO BETTER THAN THE FRENCH:
work too much
WHAT YOU MISS MOST ABOUT THE U.S.:
family and pizza by the slice
WHAT YOU THINK YOU'LL MISS MOST ABOUT FRANCE:
The people. I can import
everything else.



Douglas MacDonald and his wife Kim Cayz, with MacGregor

therapies that ultimately provide significant health benefits to people around the world.

Of course, there are still millions of molecular shapes that have not yet been identified, but without the foresight of Louis Pasteur, the world could not enjoy the health and well-being that many people take for granted today. Pasteur made a great leap for modern science and, hopefully, through the work of the scientific and medical community at the Institut Pasteur and elsewhere, these disciplines will keep moving forward, finding more keys to continue unlocking their mysteries.

Do you own an apartment in Paris?

If you own a Parisian apartment that you would like to rent, please contact us. We are organizing an informal network of U.S.-based apartment owners to help our American post-doctoral fellows in their quest for medium-term housing. The advantage to you? You can arrange to collect your rent in dollars and be secure in the knowledge that your renters are dependable, gifted American scientists working at the Institut Pasteur.

Contact Caitlin Hawke for more information: 212.599.2050 or e-mail: PasteurUS@aol.com

MORE TO THE POINT: NEWS IN BRIEF FROM PASTEUR

AIDS RESISTANCE VIA NATURAL KILLERS:

Despite repeated exposure to HIV1, some individuals remain seronegative. A study conducted by Institut Pasteur scientists suggests that “natural killer” cells found in our immune system play a role in this resistance to AIDS virus transmission. This is the first time that these cells have been associated with this phenomenon. Published in the *Journal of Immunology* in November, this work opens the way to new vaccination strategies and the study of protection against infection.

THE INSTITUT PASTEUR STRENGTHENS ASIAN TIES:

In keeping with the Institut Pasteur’s international scope, as defined by Louis Pasteur himself over 100 years ago, its global presence continues to develop.

- On January 29th, the Vice President of the Academy of Sciences of China and the Director General of the Institut Pasteur in Paris signed a letter of intention to create an Institut Pasteur in Shanghai. The mission of the Shanghai institute will be to respond to the primary public health issues in China and to develop research and training in the area of infectious diseases with particular emphasis on virology, vaccination and epidemiology.
- The Korean Institute of Science and Technology and the Institut Pasteur in Paris have created the Institut Pasteur of South Korea. The aim of this private nonprofit institution is to develop new therapeutic approaches to infectious diseases and cancer by harnessing post-genomic data. Financed by the Korean government in the amount of 100 million euros over 10 years, the Seoul-based institute will employ 250 people.

SARS ONE YEAR LATER:

A little more than a year after its appearance in China, SARS is back on the public health radar with at least three new cases identified in December. The Institut Pasteur continues its investigation of this emerging virus. In addition, Bio-Rad and the

Institut Pasteur have launched a collaborative effort to develop a diagnostic test for SARS. On the prevention front, GlaxoSmithKline Biologicals and the Institut Pasteur have combined forces to work toward a SARS vaccine. A joint research program between the Institut Pasteur and the University of Hong Kong is aimed at elucidating the molecular and cellular mechanisms that the SARS virus employs to infect its host and cause the illness.

FIGHTING ULCERS ONE GENE AT A TIME:

In January 2004, an international group of scientists, including teams from Knoxville and Nashville, Tennessee, and led by Institut Pasteur researchers, published results in the February 3rd issue of *Proceedings of the National Academy of Sciences* that represent a major advance in the fight against Buruli ulcers. These scientists demonstrated that the genes that permit the synthesis of mycolactone—the toxic factor—are carried by a giant plasmid (a group of genes separate from the bacterium’s chromosome that can easily jump from one bacterium to another).



Mycobacterium ulcerans

Credit: Laurent Morslière – Institut Pasteur

Buruli ulcer is the third most common mycobacterial infection, following tuberculosis and leprosy. Caused by the organism *Mycobacterium ulcerans*, this affliction leads to serious ulcerations of the skin, muscles and bones, leaving its victims both disfigured and incapacitated. Buruli ulcer is an emerging disease considered dangerous by the World Health Organization. Deciphering the

method of toxin synthesis should open avenues of treatment for these currently intractable infections.

HOW TO SPELL RELIEF? S-I-A-L-O-R-P-H-I-N:

Institut Pasteur scientists have observed the powerful analgesic effect of sialorphin in rats. Sialorphin is a molecule secreted by rats in certain stressful situations. Its discovery is an example of successful post-genomic work; scientists at the Institut Pasteur identified the sialorphin gene before its function was known. A powerful inhibitor of pain perception, this molecule is potentially the leader in a new class of natural pain relievers.

**2005 APPLICATION
DEADLINES ANNOUNCED**

Paul W. Zuccaire
Undergraduate Summer 2005 Internships:
Friday, January 7, 2005

Pasteur Foundation Post-Doctoral Fellowships:
Friday, February 4, 2005

For guidelines, please visit our website: www.pasteurfoundation.org

**RECEIVE OUR DVD
IN RECOGNITION OF
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Pasteur: A Contemporary View is now on DVD. If you make a donation of \$25 or more, you will receive this DVD as our gift to you. It is a wonderful 30-minute film that demonstrates simply and elegantly the brilliance of Pasteur's insights. You will also receive a bonus CD-ROM, so why not send in your contribution today? Please fill out the form below and check the DVD box.



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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- Please send information on how to support Pasteurian research by naming the Pasteur Foundation a beneficiary (*please check*): in my will in my trust in my insurance policy in my retirement plan
- I would like to help support the research conducted at the Institut Pasteur to improve worldwide public health by making a tax-deductible gift to the *Pasteur Foundation* in the amount of:
- \$1,000 \$500 \$100
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- I have enclosed a contribution of \$25 or more and would like to receive your thank-you gift: the 30-minute DVD *Pasteur: A Contemporary View*.*
- I have enclosed a contribution but do not wish to receive a gift so that 100% of my donation is tax deductible.
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The Pasteur Foundation is a 501(c)(3) organization. *NB: If you choose to receive the DVD, it will limit the deductibility of your donation.

**A LETTER
FROM THE
DIRECTOR
GENERAL**



INSTITUT PASTEUR

Le Directeur Général

March 2004

Dear Friends:

One cannot read a newspaper without feeling the urgency to protect and improve public health. Emergent and, indeed, re-emerging diseases are brought to our notice almost every day; avian influenza and SARS are among recent examples. In America, you have also read recently about foodborne diseases such as the hepatitis outbreak traced to green onions used in certain restaurants and, of course, the appearance of bovine spongiform encephalopathy. These illnesses, when added to the crippling effects of Third World epidemics of malaria, tuberculosis, diarrheal diseases and AIDS, affect every individual on the planet.

Our scientists are hard at work on infectious disease research. Thanks to your help, we have enhanced our efforts by the creation of 15 positions for young U.S. researchers to join us in the battle.

This summer we will launch a program for American undergraduates to enter Institut Pasteur laboratories and experience science at the bench as interns. Our hope is that this exposure will encourage these students to pursue careers in the basic sciences. This program exists thanks to the generosity of the Paul W. Zuccaire Foundation.

Because international collaboration and exchange are essential today to advancing research that benefits global health, these two Pasteur Foundation programs are vital to the Institut Pasteur. For your support, I thank you and warmly invite you to visit the Institut Pasteur Museum the next time you are in Paris. Please contact the Pasteur Foundation for a complimentary pass.

Sincerely,

Philippe Kourilsky
Director General
Institut Pasteur

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“AS LOUIS PASTEUR SAID....”

Please Send Us Your Favorite Quote of Louis Pasteur

Although it has been more than a century since his death, many people can still recite the words of Louis Pasteur. Below is one of our favorites.

“Science does not belong to any one country for knowledge is the heritage of humanity, the torch that lights the world.”

Please send us your favorite quotation and, if possible, the circumstances that led to Pasteur saying or writing it and why it is meaningful to you. We encourage teachers to ask their students to submit their best-loved quotations.

READERS, SEND US A PASTEUR QUOTE:

(NB: Teachers, why not ask your students to send us their choicest quotes from Louis Pasteur?)

Please submit answers to the following questions by mail or e-mail:

- What is your favorite Pasteur quote?
- What is the source of the quote (if you know it)?
- When did you come across it?
- Why is this quote meaningful to you?

Please provide the following information with your submission: your name, school and teacher (if applicable), address and e-mail.

Pasteur: A Contemporary View

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SAVE THE DATE: WEDNESDAY, APRIL 28, 2004

Do not miss this special opportunity to support the Pasteur Foundation.

Spring Gala



Gala art inspired by the painting "Tango" by Marina Malino. Used with the artist's kind permission.

The Pasteur Foundation Gala
Honoring
Anne Cox Chambers and Judith P. Sulzberger

Wednesday, April 28, 2004

Dinner and Dancing  Black Tie

This year at our annual gala, the Pasteur Foundation salutes Anne Cox Chambers and Judith P. Sulzberger, founding board members, lovers of science, philanthropists and friends of France. Please save the date and help us honor their commitment to public health.

GALA TICKETS: \$750 & \$1,500  TABLES: \$7,500, \$15,000 & \$25,000

To reserve corporate or benefactor tables or for ticketing information, please contact Caitlin Hawke at 212.599.2050.