

Tuberculosis: in it for the long haul



Courtesy of Brigitte Gicquel

Prof. Brigitte Gicquel

Professor Brigitte Gicquel is head of the Mycobacterial Genetics unit at the Pasteur Institute in Paris, France. After completing her undergraduate and doctoral studies at the University of Paris VII, she joined the Pasteur Institute in 1973 and has spent much of her scientific career concentrating on the genetics of *Mycobacterium tuberculosis*. Gicquel coordinated both the European Commission's efforts to find a vaccine more efficient than bacille Calmette-Guérin (BCG) for tuberculosis and its TB Ethics project. She was editor-in-chief of the scientific journal *Tuberculosis*. In 2004 she was made a Chevalier of the Légion d'Honneur, France's highest order, and on World Tuberculosis Day in 2008 she was awarded the Georges, Jacques et Elias Canetti Prize for her research.

Tuberculosis is a disease that has come full circle. In the 1950s, as our cover poster shows, a treatment revolution prematurely downgraded its public health importance. The *Bulletin* spoke to Brigitte Gicquel about why there has since been a global resurgence and increased drug resistance and what the future holds for the control of the disease.

Q: The Pasteur Institute is 120 years old this year. How much does its history inspire and affect what you do today?

A: Many important historical findings are relevant to my work. Louis Pasteur's original discovery that diseases and microbes don't just appear spontaneously allowed the whole field of infectious diseases to develop. Since then, we have seen the development of molecular biology, work on gene expression and studies on the enzymatic properties of proteins. When I began working at the Pasteur Institute in 1973, the two worlds of infectious disease and molecular biology were quite separate. In 1986, I decided to bring the work I'd been doing on DNA-protein interactions to research a disease that wasn't very well studied – tuberculosis. We started a small group in the unit that was headed by Julian Davies and, in 1994, that became the Mycobacterial Genetics Unit.

Q: How is scientific progress linked to public health goals? What does your own research concentrate on today?

A: You can look at that from several different viewpoints, depending on the science in question.

The development of new drugs against tuberculosis, particularly ones that could shorten the current 6-month

treatment regimen, could allow us to be more ambitious with our treatment targets – possibly even aiming to treat 100% of patients.

Tied into that, advances in tuberculosis diagnosis over the past 20 years not only help us to diagnose cases more quickly but can also give us drug susceptibility tests. These allow health workers to target specific antibiotics against particular strains of tuberculosis which are resistant to different drugs.

Our own laboratory is working on molecular probes that can identify the particular tuberculosis bacillus causing an infection. That lets you work out how contagious a patient is and which drugs might be useful for treatment. The probes are increasingly being used in countries that were until recently only using microscopy to diagnose tuberculosis.

We're also working in collaboration with Carlos Martin's team in Zaragoza, Spain, to develop a new vaccine to replace BCG (which was also developed at the Pasteur Institute). The new vaccine is safer than BCG and tests in animals have also shown it to be more effective.

Lastly, molecular epidemiology has allowed us to identify the genetic markers that separate different strains of tuberculosis. With that, we can track

specific outbreaks of tuberculosis – particularly drug-resistant forms – and actively track down infected individuals and offer them free, supervised treatment. That approach has already been used in New York and other major cities.

Q: The Pasteur Institute is one of the world's foremost medical institutions. Can you tell us about your centres across developing countries, and are they all francophone?

A: Institutes belonging to the Pasteur Institute's international network focus on the public health problems of their own countries. To do that, it's very important for their laboratories to be in constant contact with scientists in industrialized countries. The scientists can, in turn, exchange information with front-line health-care workers and find out about the real problems in the field and how the tools are being used.

It used to be a French-speaking network because of the link with former French colonies. Now there are Pasteur Institutes in countries, such as Cambodia, China, the Republic of Korea and Uruguay, which communicate with each other in several languages, not just French.

Q: In France there has been a lot of discussion over the dominance of English as the language of science. Should more scientific writing and studies be in the French language?

A: In science, English happens to be the primary language. If we try to promote French, to the detriment of English, you may prevent people having access to the latest information and findings. The most important thing is to communicate, regardless of the language.

Q: An estimated two million people die of tuberculosis every year, particularly people with HIV/AIDS. Given that, why is it difficult to attract interest in research in an area such as tuberculosis, even though it causes a large burden of disease across the world?

A: First of all, *Mycobacterium tuberculosis* is difficult to work with. The bacillus grows very slowly. If you're a geneticist

working with the mycobacterium, it can take up to two years to complete an experiment. That's compared to just three weeks for a disease such as cholera. So when it comes to publishing, you have to submit studies in small pieces, which isn't very attractive to prestigious journals – so the research isn't attractive for ambitious young scientists.

The costs are also higher; not just because of the time taken, but the containment environments need to be quite stringent to prevent any accidental outbreaks of the disease. Because there's less financial return, industry makes less of an investment in the first place.

Q: Mycobacterium tuberculosis is becoming resistant to more and more drugs, cheap diagnosis leaves much to be desired, and the BCG vaccine has varying efficacy and is 80 years old. Why has it taken so long for control measures to be updated, and where do we go from here?

A: After the Second World War, antibiotics had just been developed and people thought they could solve any problem and kill any microbe. For

many bacteria, it was true. But after we had the antibiotics revolution, we had the revolution in microbial resistance to antibiotics. In recent years, scientists have come up with new research looking at the genetics of *M. tuberculosis*, but we've lost 20 years of research time because of the [over] confidence we had in antibiotics.

Increased drug resistance has meant that scientists and public health officials cannot act independently. We are hampered by the political and socioeconomic situation. Many people in need of improved tuberculosis control are in countries that lack political stability, resources and infrastructure. When the political system and infrastructure collapsed in the former Soviet Union, for instance, a new political system appeared but there was no new health system. That led to patchy drug distribution and patients not having the supplies to finish their treatment, which again led to drug resistance.

Q: WHO declared tuberculosis a global emergency 15 years ago in 1993. Has

progress been made since then in terms of tuberculosis control or are things getting worse?

A: The situation has been improving since 2003. After an initial increase in cases, we've now reached stabilization and even a small decline. It's not good, but it could be worse.

There have been major breakthroughs and more money is appearing, but a lot of it is going into specific tuberculosis research. Many scientific advances come from outside the field. For instance, the discovery of restriction enzymes, which cut DNA into small pieces, was made by Werner Arber and colleagues who were looking at the immune systems of bacteria but the work ended up having a big biotech impact. We need more basic research to acquire knowledge on the TB bacillus and its interactions with its host – if we only put the money into research specifically for precise goals like new antibiotics, vaccines or diagnostics, much of it will just be wasted. ■