The "Odd Couple" of Virus Research

Their styles differ, but Dr. Peter Palese and Dr. Adolfo García-Sastre are focused on a common goal: a universal influenza vaccine.

By Philip Berroll

It would be hard to find two more sharply contrasting individuals than Adolfo García-Sastre, Ph.D. and Peter Palese, Ph.D. In appearance, Dr. Palese is every bit the sober, buttoned-down man of science; Dr. García-Sastre, bearded and long-haired, looks more like a rock musician, and in fact has several shelves of music cassettes – everything from Bach to Meat Loaf – stacked inside his desk. The Spanish-born Dr. García-Sastre is also an amateur entomologist with an extensive insect collection, while Dr. Palese, a native of Austria, cheerfully admits to having "very few" interests outside of medicine.

Yet for nearly 20 years, the two men have joined in a research partnership that has made them recognized leaders in their chosen field. Dr. Palese, who is Chairman of Mount Sinai's Department of Microbiology, and Dr. García-Sastre – a professor of Microbiology and Medicine (Infectious Diseases) who also serves as Director of Mount Sinai's Global Health and Emerging Pathogens Institute (GHEPI) – have both been in the forefront of efforts to understand and combat some of the world's most deadly viruses. And they are now at work on a project of global import: the development of a universal influenza vaccine that can be used against multiple strains of this persistent and sometimes fatal disease.

"We can say that we have different personalities – though it depends on how you define 'personality,' Dr. García-Sastre says with a smile. "But motivation-wise, we are very similar. What we have in common is that we are passionate about research."

A Vaccine for All Strains

The impact of a universal flu vaccine would be truly profound. At present, people need to be vaccinated every year at "flu season" because the virus evolves at a much faster rate than many other organisms, and pharmaceutical companies therefore have to keep updating their vaccines. And because that evolution has produced multiple strains of influenza, there is always a danger of targeting the wrong strain – resulting in an ineffective vaccine and an outbreak of epidemic proportions.

As Dr. Palese observes, “There is no other vaccine which has to be changed on a yearly basis, in contrast to things like measles or smallpox or mumps, whose vaccine strains from 50 years ago – or in the case of smallpox, *200* years ago – can still be used. So the hope is that we could get something which would be working and in use as an effective immune response against all strains of influenza.”

The two researchers and their teams have already made significant progress. “We have quite good evidence,” says Dr. Garcia-Sastre, “that when used for immunization, some types of influenza virus antigens provide the broader immune response that can protect against multiple strains, unlike the traditional vaccines. We need to come up with better immunogens to make this a reality. But the possibilities are there.”

At the same time, they are also researching the possible development of other types of broad-spectrum antiviral drugs which could be used against viruses such as dengue, West Nile and Ebola, for which specific drugs do not currently exist. If proven effective, these antivirals could have a dramatic impact on global health not seen since the introduction of broad-spectrum antibiotics to combat bacterial infections.

“We now have solid evidence that many different viruses all use particular cellular pathways,” Dr. Garcia-Sastre observes. “And it’s possible that broad-spectrum antivirals could be effective by inhibiting those pathways.”

In addition, their work has implications for the fight against other “ever-changing” viruses such as HIV and hepatitis-C. “It’s a slightly different scenario in that these viruses have many different variants coexisting at the same time, whereas with influenza, it is a change from year to year,” says Dr. Palese. “But if we are able to succeed in making better and longer-lasting influenza virus vaccines, we could possibly try to apply that to these others.”

Working Separately and in Tandem

Their partnership began as a student-teacher relationship. When Dr. García-Sastre came to Mount Sinai in the early 1990’s as a post-doctoral fellow, he worked in the laboratory of Dr.

Palese – who soon recognized his younger colleague as “a very able and very effective and successful, imaginative researcher.”

After getting his own lab, Dr. García-Sastre continued to collaborate with his mentor on numerous research initiatives while both men also pursued independent projects, an approach which has continued to the present day. For example, Dr. García-Sastre is currently “very focused” on the body’s innate immune responses and their effect on viral replication, while Dr. Palese is researching viral packaging – the ability of a virus to package, transport, and deliver its genome to a host cell, which involves the precise manipulation of DNA throughout the life cycle of the virus.

“But in the big, overreaching aspects of influenza biology – such as influenza virus vaccines or multivirals – we fully collaborate,” says Dr. García-Sastre, “because these areas require information from multiple, specific research initiatives, resulting in a more comprehensive program. And especially in the last year, the National Institutes of Health (NIH) has put more emphasis on intercollaborative grouping between different researchers, which makes things easier from the point of view of funding.”

What was perhaps the pair’s greatest achievement to date came in 2005, when they led a team that reconstructed the virus responsible for one of history’s most devastating pandemics: the 1918 Spanish flu outbreak, which resulted in at least 40 million deaths worldwide. Their efforts earned them the 2005 Paper of the Year award from the prestigious British medical journal *The Lancet*.

“We decided to focus on that subject in order to understand what made the 1918 virus so destructive – its mechanisms, its characteristics,” explains Dr. García-Sastre, “because by knowing that, we can be better prepared to fight future influenza viruses that may have the same traits.”

They began by taking the genetic material of the virus from human samples that were to some extent preserved from victims of the 1918 outbreak – “like *Jurassic Park,”* says Dr. Garcia-Sastre, “where they took the dinosaur DNA from mosquitos.” From there, they recovered the genetic information of the virus, which enabled them to reconstruct and study it.

Comparing the virus to that of a more recent global pandemic – the H1N1 (swine flu) outbreak of 2009 – they found enough similarities to determine that the vaccine developed to protect against H1N1 vaccine also worked against the 1918 strain. This discovery eliminated a serious concern among public health authorities about the possible use of the older strain in a bioterrorist attack.

"It was always one of our fears," Dr. Garcia-Sastre says, "that if someone had the genetic information that was generated from the 1918 virus, they could reconstruct it for evil purposes. But now we know that everyone who gets vaccinated with the newer vaccine not only becomes protected against the 2009 virus, but also against the 1918 strain. That makes the use of the 1918 strain as a bioterrorist weapon very difficult."

Between Complacency and Fear

Drs. Palese and García-Sastre often venture outside the lab to offer their expertise to a variety of government agencies – Dr. Palese is a member of the National Academy of Sciences (NAS), and Dr. García-Sastre is Director of the Center of Excellence in Influenza Research and Surveillance (CEIRS), which is funded by the NIH. In that capacity, both men have experienced the tendency of the public and the media to lurch between a false sense of security and unjustified panic regarding influenza outbreaks.

"It's a very interesting psychology," says Dr. García-Sastre. "When the first deaths from H-5 [avian flu] virus were reported, even though there were very few, it made people afraid to go to countries such as Hong Kong where the flu was found. It's very difficult to get infected with bird flu; you go to Hong Kong, you're more likely to die in a traffic accident than from H-5 infection. But the public has an inherent fear of infectious diseases. The same thing happened with Ebola and West Nile virus. It's the fear of the unknown, with the potential high mortality factor, which makes people very scared."

Dr. Palese speaks of the "hysteria" surrounding the 2009 pandemic, when he was part of a committee reporting to President Obama on best responses: "This report had a possible, non-predictive scenario to help plan for the fall flu season – that many people infected, that many people symptomatic, etc. And the next thing we know, the headline on page one of *USA Today*

reads ‘Flu Could Infect Half the USA; 90,000 Deaths, 2 Million Patients Possible.’ We made clear that this virus was probably not comparable to 1918, and that we were making vaccines for it – but that was not on page one of *USA Today*.”

Still, Dr. Palese does take seriously the possible use of viruses in bioterrorism: he has been on several panels advising government officials on dealing with potential bioterrorist threats. “I’m worried about nuclear proliferation and nuclear terrorism as well,” he says, “but I feel that the biological threats are even worse, because of how easily a virus can be developed. At this point, it’s really a catch-up situation where we’re trying to ramp up the production of vaccines and other anti-bacterial, anti-viral substances.”

But both men retain a sense of optimism – based in large part on the progress that has already been made against a number of once-deadly viruses. “The impact that vaccines have had in human health has been enormous,” notes Dr. García-Sastre. “You don’t see kids dying any more from poliomyelitis, except in very rare cases. You don’t see people dying any more from smallpox. And I think that hopefully we can come up with new vaccines against some of the other agents that are still making a big impact on human health, like influenza and HIV and tuberculosis and malaria.”

They have also come to see the humor in their odd-couple partnership. Dr. García-Sastre acknowledges with a laugh that compared to his colleague, he appears “relaxed.”

And when asked about their differing styles, Dr. Palese responds, “You mean that he never wears a necktie? Well, it’s a free country.”

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