Taking 2 years out of the clinic to get research training in genetics was the bravest and most important decision made by Professor Silvia Priori, MD, PhD, scientific director and director of the Cardiology Department and Molecular Cardiology and Electrophysiology Labs at the IRCCS Fondazione Salvatore Maugeri in Pavia, Italy, associate professor of cardiology at the University of Pavia, and director of the Cardiovascular Genetics Program and professor of medicine at the Leon H. Charney Division of Cardiology, New York, NY, talks to Jennifer Taylor, BSc, MSc, MPhil.

"Discovering [That Mutations in the Ryanodine Receptor Gene Cause Catecholaminergic Ventricular Tachycardia] “Was a Lot of Fun Because It Stimulated Science in Other Groups on This Type of Protein”

Spotlight: Silvia Priori, MD, PhD

Making 2 years out of the clinic to get research training in genetics was the bravest and most important decision made by Professor Silvia Priori, MD, PhD, scientific director and director of the Cardiology Department and Molecular Cardiology and Electrophysiology Labs at the IRCCS Fondazione Salvatore Maugeri in Pavia, Italy, associate professor of cardiology at the University of Pavia, and director of the Cardiovascular Genetics Program and professor of medicine at the Leon H. Charney Division of Cardiology, New York, NY, talks to Jennifer Taylor, BSc, MSc, MPhil.

The urge to study genetics was an emotional drive stimulated by the discovery of the first gene for long QT syndrome by Professor Marc Keating, MD, an inspiring figure in Professor Priori’s career. For many years he and others had been studying this disease, which killed young children, and he found that it was caused by a genetic defect in cardiac ion channels. Professor Priori says, “It was such a breakthrough that the entire field was thrilled and revolutionised.” At that point the name of the game was to discover new genes. Professor Priori did not consider that she would discover a gene, but she definitely wanted a genetics background.

Professor Priori’s initial decision to study medicine was implanted at a young age by her grandmother, who on several occasions dressed her visiting granddaughter up in a doctor’s outfit and called a photographer. Until recently, when she came across the book of photographs, Professor Priori had thought the career had been her own idea. She started a premedical programme in bioengineering at University of California, San Diego in La Jolla, Calif, but after a few months her mother was diagnosed with cancer and she returned to Italy to study at the University of Milan, and she graduated in 1985.

At first, Professor Priori wanted to study excitable tissue and opted to specialise in neurology, but a series of 5 fainting episodes during her internship took her to the clinic of Professor Peter Schwartz, MD, who was studying long QT syndrome, to see whether she had the disease. The tests were negative, but she got so excited about his project that she decided to become a cardiologist. She knew the value of research training in the United States and wanted to return, so from 1988 to 1990, she worked as a research fellow of the American Heart Association at Washington University in St. Louis, Mo. She had already spent 2 years in Professor Schwartz’s group mapping arrhythmias in preparation for surgery and conducting biophysical studies with isolated cardiac cells. Professor Schwartz was interested in the sympathetic nervous system and arrhythmias, and she gained further insight into the relationship between the nervous system and the heart. Professor Priori chose St. Louis because she was fascinated by the work of...
Since 1997, the genes for different conditions have been identified by various groups, taking molecular cardiology beyond a field that found the genes of long QT syndrome. Professor Priori’s group identified the gene for catecholaminergic ventricular tachycardia and the gene for short QT syndrome. The first discovery was made in 2000, when they found the ryanodine receptor gene (hRyR2), the ion channel inside cells that controls the release of calcium. The gene had not been linked with arrhythmias previously, so the finding that it caused catecholaminergic ventricular tachycardia stimulated further research into the connection. The discovery won her the Outstanding Research Award in Pediatric Cardiology of the American Heart Association in 2001. Professor Priori says, “I am excited about this discovery, and it was a lot of fun because it stimulated science in other groups on this type of protein.”

In the 10 years since the discovery of the hRyR2 gene, Professor Priori’s group has continued to study the disease, making animal models, looking for a cure, searching for a risk stratifier to identify those at risk, and collecting a series of patients with the condition. They published a characterisation and description of the disease and a characterisation of the mouse model, which had exactly the same type of arrhythmias as the patients.

Next came the discovery of the gene for short QT syndrome. The research that Professor Priori had started in 1983 when she switched from neurology to cardiology all came together between 2000 and 2004. “It was in those 4 years that I started having the achievements that I had been dreaming of,” she says. In 2003, Professor Priori’s group published a study in the New England Journal of Medicine that established the first correlations between having a certain genetic disease and patient outcomes. In 2004, they published an article in JAMA on the response to therapy based on the different genetic subsets.

Identification of Afterdepolarisation in the Intact Heart in 1988

The discovery in 2000 was the perfect joy and the ultimate achievement, but some of the early work was enjoyable because it was more adventurous and done on a shoestring. One such study was done in the lab of Professor Schwartz with Carlo Napolitano, MD, a colleague for the past 20 years. They wanted to do a study recording monophasic action potentials, which meant recording the signal from the heart when a single cell is isolated. The method had been pioneered in the United States by Professor Michael Franz, MD. The young Drs Priori and Napolitano did not have money to buy the catheters, so they involved a young engineer in Parma and asked him to design an electrode from the methods section in an article by Professor Franz. After several months, he produced the catheters, which they then used to study the signal. The result was Professor Priori’s first important article, published in Circulation in...
1988. They showed that stimulating the nerve in the heart induced electrical signals in response to the release of excessive calcium. The electrical mechanism, called delayed afterdepolarisation, had never been identified in the intact heart before. It had always been identified in isolated cells. In the study they stimulated cats with sufficient catecholamine that produced the equivalent effect of a person being excited, frightened, or doing physical exercise. The catecholamine induced arrhythmias in the intact heart, and the idea was that the same type of event could occur in humans.

Twelve years later, when Professor Priori discovered the \textit{hRyR2} gene, she found that the mechanism by which the arrhythmias were induced was delayed afterdepolarisation. Today she is investigating how common variations of DNA modulate and influence the severity of genetic diseases. In other words, when 6 family members have the mutation that causes Brugada syndrome, why does only 1 have a cardiac arrest whereas the rest just have palpitations? A second area of interest is identifying new therapies for patients with genetic diseases, either new drugs or gene therapy to correct the disease.

Professor Priori’s most recent challenge has been establishing a lab in New York based on the same principles as the lab in Pavia: seeing patients in the clinics, genotyping, and studying basic mechanisms for arrhythmias in the lab. Professor Priori’s most important funding source has been the Telethon Foundation, which funds research on genetic diseases. In Italy, she is supported by government research funds provided for basic science, clinical science, and rare diseases. Collaborative work with U.S. colleagues has attracted funding from the National Institutes of Health, and the Leducq Foundation has also supported her work.

“Go Where There Is Still Dirt on the Gold and Discover the Gold Underneath Yourself”

Looking to the future, Professor Priori is concerned that young people worldwide are less interested in research, and she believes that funding has a big role to play in turning that around. She says, “They see that science is underpaid and poorly funded, and it is extremely difficult to become an established investigator if you start now. The clinician scientist is becoming an endangered species, and this is a matter of concern because I still believe that translational research, research done by clinicians who are able to go from the cell to the patients, is really [necessary] for advancement in the field.” The situation is compounded by the fact that today society is focussed on how careers in economics and management are important for the world economy. When Professor Priori was setting out in the 1970s, the focus was on doing something for humanity, curing people, and making discoveries for the common good.

For those young doctors who are considering a research career, she says: “If you really like it, do it. Follow your heart.” She admits, laughing, that it’s a funny statement coming from a cardiologist, but she has never regretted making decisions with her heart. When she decided to accept the challenge of setting up a lab in New York, many people said she couldn’t do it, she would be exhausted, and it would be disruptive. She says, “When you love something you find the energy. It’s like your body becomes so excited that you find the energy, you reason better, you function better when you’re really excited about something.” The message is not to be discouraged by the difficulties of life, particularly for women for whom it remains a difficult career. Professor Priori urges young people to be persistent.
with their research. A successful career in science requires intuition, mentors, and inspiring figures, a trusting sponsor, and the luck of being there at the right time. She also advises against going where the gold is already shining because there they are less likely to make their own contribution. She says, “Go where there is still dirt on the gold and discover the gold underneath yourself.”

“**When 1 Group Goes to Bed the Other Gets on With the Experiment, and When They Get Up the Others Have Already Sent Back the Results**”

The combination of a clinical group specialised in seeing patients with genetic diseases of the heart, together with a lab for genotyping and basic research on mechanisms of arrhythmias, has been such a success for Professor Priori in Italy that she was contacted by Professor Glenn Fishman, MD, at New York University, New York, NY, to establish the same setup in the cardiology division there. However, Professor Priori was not ready to leave Italy and the 11,000 DNA samples in the biobank she set up and that is owned by the Maugeri Foundation. “It’s hard to leave such a treasure,” she says.

Professor Fishman then suggested a partnership between the institutions in Pavia and New York, with sharing of science, research, and data. Lawyers worked on the agreement, and the collaboration between New York University and the Maugeri Foundation was established. Professor Priori says, “Now what I say is that I have 1 group located partially in Pavia and partially in New York because the people really work together.” The fact that it is 1 group means that Italian patients and American patients are merged in the same web-based database. Researchers can see the information in both locations. Research projects have seen mice being flown from Pavia to the United States and then after treatment being sent back to Pavia. Professor Priori spends 1 week each month in New York and 3 weeks in Pavia. Wherever she is, she communicates with researchers at the other location through Skype. The researchers also use it to discuss projects and results. She says, “It turns out to be very exciting because we really have 1 lab in 2 locations across the Atlantic Ocean. Now even the researchers think that it’s a great opportunity because when 1 group goes to bed the other gets on with
Around 25 people in Professor Priori’s Pavia team (made up of clinical, diagnostic, and basic science teams) of the Cardiology Department and Molecular Cardiology and Electrophysiology Labs, IRCCS Fondazione Salvatore Maugeri, Pavia, Italy are coordinated by Francesca Giovannoni, the administrative director. From left to right: Nian Liu, MD, cellular electrophysiologist; Rong Bai, MD; Tom Rossenbacker, MD; Elena Ronchetti, PhD, senior researcher; Professor Priori; Nicoletta Rizzi, BS, senior researcher; Jannì Astoli, PhD, senior researcher; front row, Mirella Menini, PhD, senior researcher; back row, Andrea Capoferrri, MD; front row, Marta Tomas, BS, junior researcher; back row, Giuseppe Celano, MD; front row, Raffaella Bloise, MD, clinical geneticist; back row, Luciana De Giuli, PhD, senior researcher; front row, Stefania Lugano, BS, junior researcher; back row, Juliane Theilade, MD; Barbara Colombi, PhD, senior researcher; front row, Francesca Giovannoni, BS, PA to Professor Priori; back row, Marina Raffaele Di Barletta, PhD, senior researcher; front row, YanFei Ruan, MD; Anna Maria Marangon, clinical staff secretary; Emilka Raycheva-Buono, MD; Carlo Napolitano, MD, PhD. Photographs courtesy of Professor Priori.

the experiment, and when they get up the others have already sent back the results.” The around-the-clock lab means that when Professor Priori is in Italy she works with the Italians in the morning. At around 3 p.m., when people arrive at the New York lab, she opens Skype so they can call with any questions. When in the United States, she connects to Skype at 9 a.m. to field questions from Italy.

The Italian and American groups are structured symmetrically, with a clinical team to see patients and take blood samples, a diagnostic team to conduct the genetic analysis and identify the mutations, and a basic science team to study the mutations. The work occurs in a loop, and the clinicians use the results to change a therapy or call in family members.

Professor Priori is proud of establishing a good clinical service for patients and introducing many young scientists to the field. The clinical service would not have been possible without these young doctors, who on a voluntary basis have had a mobile phone available for patients 24 hours a day, 7 days a week, 52 weeks a year. She says, “That becomes possible if there is a team spirit and you work well with your people. So that is something that I’m proud of.”

In both places, Professor Priori’s role is to identify projects, check and analyse data, help with writing manuscripts, and solve problems when people get “stuck.” When results do not fit or cannot be understood, it is Professor Priori’s job to interpret the findings. With the clinicians she oversees the clinical case review. They can handle 75% of the cases, but there are some cases where either they are not in agreement within the group or they are concerned about medicolegal implications and want to know what Professor Priori thinks they should write in the letter or what therapeutic decision should be taken.

Throughout the process, Professor Priori mentors individuals to provide increasingly greater contributions. Initially, she will have an idea and ask someone to do a specific project. Her more senior colleagues work out the details of the project based on her idea. The basic science team has criteria to decide whether it wants to work on a mutation. For those mutations that the team wants to study, it engineers a protein with that mutation. The team also creates computerised models or studies the ion channel using glass pipettes and records the current to see
whether the modified ion channel conducts more or less current.

When she set out to establish this cross-continental team, many people said it would be difficult, disruptive, and too tiring to travel across the world so frequently. Given these warnings, she is surprised that it works so well. The future is on her mind, and she is considering how long she can continue to split her month between Italy and New York. She may need someone to run the work in Italy so she can relocate to New York or vice versa. The decision is influenced by many factors, including where her children will want to live. Now would not be a good time to move to New York. Her 16-year-old son is in the middle of high school and wants to complete it in Italy, but he would like to go to medical school in the United States if he is accepted. Her other son, age 19, will finish an undergraduate engineering programme when the 16-year-old finishes high school. Then might be a good time to relocate to New York, but nothing has been decided yet.

Professor Priori has worked with the leaders in her team for many years, and she views the group as theirs collectively. She says, “These are the people who in a company would be the board of directors. They are the people who really think of the job not as going to work, but our operation, our activity, our team.”

References

Jennifer Taylor is a freelance medical journalist.