THE INCREDIBLE (SCIENTIFIC) JOURNEY OF PROF. KARIKÓ

While her work went unnoticed for years, Katalin Karikó continuted to push scientific boundries and make history.

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Photography courtesy of Katalin Karikó

You've probably never heard of Katalin Karikó, and if by chance her name does ring a distant bell, you may not know why.

And that's more than fine with her.

For decades, the biochemist has worked in obscurity, her pioneering research all but ignored, even by many of her colleagues in the scientific community.

But then the pandemic struck, and her work and that of her collegiate collaborator, Dr. Drew Weissman, on the therapeutic power of the synthetic genetic messenger RNA (mRNA) became the key to the production of the lifesaving COVID-19 vaccines.

Biotech company Moderna produced one vaccine based on the pair's work and Pfizer, in partnership with BioNTech, the German-based company that Karikó is a senior vice president of, developed the other.

Karikó, a modest, down-to-earth woman who hides behind gold wire-rim spectacles and who—characteristically—responded personally to all participants of the Pfizer-BioNTech vaccine trial who contacted her on social media, is 66 years young. Speaking with her via Zoom, she appears decades younger. She has all the energy and exuberance of a 26-year-old who is just discovering a shiny, new world.

She's never been one for the spotlight, and she's not quite sure how to react to her sudden fame. She's been the subject of several recent news stories that focus on her career-long scientific struggles and credentials.

What's more, Derrick Rossi, one of the founders of Moderna, has suggested that Karikó should be nominated for the Nobel Prize in chemistry. Other notable peers speak of the results of her work as "possibly the most significant breakthrough in the field of the past 100 years."

VACCINE PHOTO BY ARTEM PODREZ/PEXELS

Karikó in Hungary, 1984

But we're getting ahead of her story.

Everything starts in Kisújszállás, a tiny town with a population of 10,000 in Jász-Nagykun-Szolnok County, nearly 100 miles outside of Budapest, where Karikó spent the first 18 years of her life.

In her first decade, the family—Karikó's father, a butcher, her mother, a bookkeeper, and her older sister, Zsuzsanna—lived in a tiny adobe house with a reed roof and no running water, much less a television set or refrigerator. The heat came from a sawdust stove.

"What we had was enough," Karikó says. "I had a happy childhood—there was food to eat, and I had a loving family."

Hungary has a very impressive record: This landlocked Eastern European country has produced 18 Nobel Prize winners. And like many Hungarians who achieved extraordinary success in a variety of fields, early on, Karikó had teachers who inspired her to pursue science, and by eighth grade, she was nationally ranked in biology competitions.

At the age of 17, Karikó (or "Kati," as she is known to friends and colleagues) decided to make biology her career.

"The subject was exciting," she says. "It was difficult to get in, and it also was very difficult because I had never seen a scientist before."

She was among only 20 students—10 boys and 10 girls—who were accepted into the program at the University of Szeged, then called JATE. The school was, and still is, one of the top-rated universities in Hungary.

The move to the well-known school was a big step toward her future for the knowledge-hungry Karikó.

"My English wasn't good at that point," she notes. "And I had to catch up with all the other students. I had to constantly study, I was always catching up; everybody was better than me."

In 1978, Karikó got a position at the prestigious Biological Research Centre in Szeged, though at the time, virtually no one was conducting research on RNA there.

But serious research requires solid funding, and Hungary historically lacked in providing sufficient monetary support despite its history of thriving residents—that is why most of them moved on to places that offered more chances of success.

The trend was not new, as a significant number of Hungarian pioneers in science chose to immigrate to countries with stronger funding and better opportunities, including: Ignac Semmelweis, who uncovered a cause-effect link between handwashing in obstetrics clinics and infant sickness; Loránd Eötvös, a physicist who developed methods and tools to measure gravity and conducted experiments that helped inform Einstein's theory of relativity; and Mária Telkes, who pioneered the use of solar energy.

And the list goes on.

Hungary has been a fertile ground for extraordinary minds. The "Martians" was a term used to refer to a group of prominent Hungarians who immigrated to the United States in the early half of the 20th century. The Hungarian scientists were seemingly superhuman in intellect, spoke an incomprehensible native language, and came from a small obscure country. Because they all spoke English with a strong accent, they were considered outsiders in American society.

Karikó in 1989

"I wanted to work in Hungary, but I didn't get an answer about the jobs I applied for," she says. "I tried to settle in Europe: Montpellier, London, and Madrid, because they dealt with similar short RNA molecules there. I would have been accepted on the condition that I bring my scholarship, but I did not have a scholarship."

In 1985, when she was dismissed from her job on her 30th birthday, she, her engineer husband, Béla Francia, and their two-year-old daughter, Zsuzsanna (Susan), left Hungary when Karikó got an offer to continue her research and studies at Temple University in Philadelphia.

"We were only allowed to take $100 with us," she recalls. "It wasn't enough for a family even though I was going to start working the day after we arrived."

The couple sold their car and the proceeds—an illegal foreign currency of $1,200—were exchanged on the black market and bravely sewed into Susan's teddy bear.

"My first yearly salary of $17,000 wasn't much," Karikó remarks. "We gave up everything—our ticket was only in one direction. We had to adapt quickly to this strange world in order to survive—we had no credit card, and we didn't know anybody, not even the person at the university who hired me. My mother later joined us, and even though my husband is an engineer, he started cleaning and doing odd jobs."

A few years later, in 1989, Karikó became a research assistant professor at the University of Pennsylvania, where she "really learned molecular biology." In 1997, she started working with Weissman, who had just joined the university as an assistant professor. Weissman's primary focus was on developing a vaccine against HIV.

"In 1990, my yearly salary was only $40,000, and 20 years later, $60,000," Karikó says matter-of-factly. "I told my daughter that she would have to go to school at UPenn because employees got a 75 percent reduction in tuition."

In the beginning, Karikó and Weissman didn't get much support for their work.

"We tried to show other professors that our technology was useful, but they were happy in their own environments, and they didn't want to hear that mRNA would provide a solution for them," she says.

Securing financing, too, proved to be a monumental task.

"Research was my hobby," she explains. "I didn't spend money on anything. For my family's simple life, it was enough and then I had fun—work was my enjoyment."

Weissman received a grant from the NIH to develop mRNA for an HIV vaccine, so the pair used those funds as support to do more research.

Unlike many scientists who see applying for grants as a distraction from the real work, Karikó used the process—which requires a lot of reading—to hone her ideas.

"I liked writing them because I had to think through the whole process and research," she says, adding that she and Weissman eventually received from the NIH a $1 million small business grant for their fledging company, RNARx, which they established in 2006.

Karikó points out that it wasn't only mRNA that wasn't taken seriously; she, as a woman speaking with an accent, made some assume inferiority.

Karikó with her family at the 2012 Olympics in London

"When I presented at meetings, they asked me who my supervisor was because they thought that if there is a woman with an accent, then probably there must be somebody behind her who is giving her advice," she remembers.

Despite the obstacles, Karikó was determined to continue. "I didn't see it as a struggle—I enjoyed doing it, and that's what's important."

She saw mRNA as a silver bullet to fight disease and even thought of it as a replacement for surgery. But there was a huge stumbling block: mRNA was very immunogenic, causing a strong inflammatory reaction.

At the time, it seemed that such immunogenic mRNA might be ideal for a vaccine, but Karikó wanted to use mRNA for therapy and started research on how she could reduce the RNA immunity. She replaced one of the four building blocks of mRNA, uridine, with its modified version, pseudouridine, which is often found in the RNA of human cells, and Weissman showed that such mRNA is "silent"—it does not activate immune cells.

"To our surprise, such a 'silent' mRNA was also better for a vaccine," Karikó says.

The university patened a method called the Karikó-Weissman technique, which is the basis for the development of COVID-19 vaccines today. The article appeared in the well-known magazine *Immunity*. Two of the world's leading biotechnology companies, BioNTech and Moderna, have acquired the patent rights from another company, because in the meantime, the university has sold the right of use.

And yet their paper, published in 2005, was largely ignored by everyone except for the scientists who would subsequently found Moderna.

In 2005, the duo submitted their first patent application, which was awarded in 2012 and followed with nine more granted patents related to their mRNA technology.

"We didn't want to patent the nucleoside-modified mRNA," Karikó explains, "because we wanted everybody to use it. But we were told that if we didn't, nobody would develop it or invest in it. We wanted the science available to everybody—it wasn't about the money."

Karikó retired from the university in 2013, but states, "I could not be doing nothing."

Instead, she joined the German-based BioNTech as a senior vice president. At the present, BioNTech has 1,500 employees.

She and Weissman continued their research collaboration and together with Norbert Pardi, another Hungarian scientist working with the duo, produced a 2017 breakthrough paper that was the first to demonstrate the effectiveness of the modified mRNA vaccine: They had proven that a small amount of mRNA vaccine protected mice and monkeys against the Zika virus.

"It was interesting because the amount of mRNA used was the same for mice and monkeys—it didn't have to be scaled up for the bigger animal," she says.

As Karikó explains it, the vaccine science is simple and elegant.

While typical vaccines are made of an inactive or weakened version of the virus or some of its proteins, the two vaccines that build upon the research by Karikó and Weissman use the virus's synthetic genetic material, or its mRNA. Lipid wrapping protects and carries the mRNA into the cells, where spike protein of the coronavirus is produced from the encoding mRNA.

In essence, the mRNA vaccines come with a set of specific instructions that tell the body's cells to make copies of the coronavirus's spike protein. The immune system then reacts by generating antibodies, so when the real virus comes, the

TOP: Pardi Norbi and Karikó in 2012

BOTTOM: Drew Weissman and Karikó in London in 2015

body is protected.

Karikó says that mRNA can be tailored to fight a variety of diseases. Because the mRNA vaccines generate not only an antibody response but also a cellular one, "they eliminate cells infected with the virus," she says.

Of course, not everyone is sold on the vaccine, or vaccines in general. There are those who believe them to be dangerous and vocally oppose them. Karikó feels that the best way to address these concerns is to simply talk about them.

"I try to find out the reason for their fear and to give specific answers to the doubts and questions that arise in them," she says. "People's concerns need to be taken very seriously, they need to be helped to make a decision. Most people are afraid due to a lack of knowledge, but are open to listening to the professionals they trust. Of course, there are always those who can't or don't want to learn and have already decided not to ask for vaccinations."

Although Karikó is based in Mainz, Germany, during the pandemic, she has been staying in her home in Rydal, Pennsylvania, where her family has lived for the past 30 years. She and her husband began the long-distance commute when she started work at BioNTech in 2013.

"In the beginning, I didn't know whether I would like working there, so my husband stayed here," she says. "In my first week in Germany, I cried every night because I missed my family."

Eventually, the couple got into a workable routine: Karikó spends 10 months of the year in Mainz, and her husband and daughter visit from time to time.

Last year, Karikó decided to visit her husband for his birthday, not knowing that her Lufthansa flight on March 13, 2020, would be the last one allowed to enter into the United States before the pandemic lockdowns were implemented.

She quickly settled back into suburban life. She rises at five o'clock in the morning, works out on the

rowing machine in her living room, and works in her office all day long.

"I used to run in the morning," she says. "I have run marathons and half-marathons to challenge myself."

She notes that her morning routine is pretty much the same as it was in Germany, so it wasn't a huge adjustment.

"I talk with my colleagues every day," she says. "Most of my time at BioNTech has been spent in front of a computer, so I'm still doing that, but now I'm just doing it in my home."

She also cooks; when she first came to America, she experimented in the kitchen with some Italian dishes, but since then has stuck with Hungarian fare to the great delight of her family.

"We almost never go out to eat," she says.

While she's shy about her own accomplishments, she's more than willing to talk about all of her daughter's. Susan Francia, a two-time Olympic gold medalist in rowing, has a master's degree in criminology from UPenn and an M.B.A. from UCLA. She works at TriLink BioTechnologies in San Diego.

Karikó mentions that she and Susan have the same approach to life: Whether you're rowing or researching, never give up—keep trying.

Victorious and vindicated, Karikó is content to stay right where she is, continuing her groundbreaking mRNA research.

"There's no question of leaning back and quitting work," she says, smiling. "Researchers are like rock musicians. They play as long as they can."

She brushes aside the notion that she deserves special credit for the pivotal role she played in the creation of the vaccine. In characteristic modesty, she praises her many colleagues, who hail from a variety of ethnic and national backgrounds. All of them had one common focus: the advancement of science in the service of humanity.

"Hundreds and thousands of people worked on this problem," she says. "The tens of thousands of people who participated in the trials, they are the real heroes."

Over 35 years after leaving her homeland, culturally, Karikó is still deeply rooted in her Hungarian heritage. She is a ferocious reader of Hungarian literature and she still enjoys listening to Hungarian music, like performances of her favorite artist, Zorán Sztevanovity, a popular guitarist, singer, and composer.

"All three of us are also Hungarian and American citizens," she says about her family. "I work in Germany as a Hungarian citizen. We have always had Hungarian passports and we return home every year. I'm glad I was born Hungarian. My childhood, my student years, was happy and carefree. The richness of light music at the time, the better-sounding singers, the beautiful songs still fly me back into my youth in an instant."

One of Karikó's prized possessions is a personally autographed Zorán Sztevanovity album that she proudly showed during her interview with *Lifestyles Magazine*.

Life has its ways to create great ironies. Chances are that perhaps very soon, Zorán Sztevanovity, along with some of those left behind at the University of Szeged, will be asking Karikó to autograph one of her works for them. LM