Interview

Web headline: Everyone dismissed Katalin Karikó's work. Until corona changed everything.

Newspaper headline: 'Nobody saw anything in mRNA. Just me.'

Katalin Karikó, biochemist

For forty years, no one valued Katalin Karikó's mRNA research. Until it led to a very effective vaccine against corona. Now her name is being mentioned for the Nobel Prize.

Niki Korteweg, April 22, 2022 NRC

https://www.nrc.nl/nieuws/2022/04/22/niemand-zag-iets-in-het-werk-van-katalin-kariko-nu-maakt-ze-kans-op-de-nobelprijs-2-a4116754

It has been raining awards for Katalin Karikó the last two years. She has been honored dozens of times, often with her research partner Drew Weissman, for the groundbreaking work that brought humanity the incredibly effective mRNA vaccines against Covid-19. On March 29, Karikó was awarded the prestigious Solvay Prize in Brussels, previously the duo received the Breakthrough Prize in Life Sciences (three million dollars from the founders of Facebook and Google, among others). Karikó's name has been circulating for the Nobel Prize for a year and a half.

She finds it baffling. “The John Scott Medal has been awarded for 200 years,” she says of yet another award. “And then I read the list of winners: Tesla, Marconi, all those names of great scientists I admire so much” (her hands go up) “and then suddenly there is also Katalin Karikó!” She shakes her head in disbelief and shrugs. “I never got a prize, not even a scholarship, for forty years.” All her life she worked on the large molecule mRNA while no one saw anything in it – she sometimes even slept in the lab. Invariably, her grant applications and publications were rejected, she was put in lower positions, and in 2013 she was even fired by her university. It took a pandemic to finally get recognition.

In a blue hoodie with a colossal University of Pennsylvania logo, Karikó (67) slid behind her laptop for the video call. She works at that university, but is now quarantined in a hotel in Tokyo, where she will receive the Japan Prize on April 13 in the presence of the Japanese emperor Naruhito and his wife. She still speaks English with a strong Eastern European accent and she supports her stories and jokes with hand movements. Her eyes twinkle behind her glasses, the smile doesn't leave her face throughout the interview.

Her life is a succession of coincidences, she says. For example, there is the letter from the famous stress researcher János Selye, in response to a letter from her high school class in Hungary. "Imagine, a village of ten thousand people, and someone like that sends a letter!" What he writes makes a deep impression on sixteen-year-old Kati. “He wrote: stress is positive, it makes you get out of bed and do things. It's not stress that kills you, but the way you deal with it.”

“If it hadn't been for him, I wouldn't be sitting here,” Karikó says. “People sometimes don't understand how I endured all those setbacks, but I lived a happy life. I don't hold a grudge,

not even against the people who wanted to send me back to Hungary, or who gave me a hard time. I focused on what I learned from them." If you see others get a promotion, or a higher salary, while you work much harder, you shouldn't get stuck in resentment, she says. "You can't change that. Focus on what you can do. Talk to someone, write a better grant application. And do things because they make you happy. Not to please your boss, or your child, husband or mother."

Cow brain

Katalin Karikó grows up in Kisújszállás in Hungary. The family has little to spend, her father is a butcher, her mother an accountant. As early as primary school she has been participating in science competitions – at 14 she placed third in a national biology competition. She studies biology at the University of Szeged and becomes captivated by the properties of RNA (ribonucleic acid) when she investigates its antiviral properties at a biological research institute.

As a young researcher, she is already resourceful. When, during an internship in a lab, she needs phospholipids, fatty substances that can't be bought behind the Iron Curtain, she gets cow brains from her father's butcher shop and mashes them to extract the fats. "I can also make good sausages, I worked in the butcher shop after school. Twice a month we made hundred kilos of sausages."

"I loved it: casting gels, seeding cells on growth plates, growing bacteria"

Throughout her career, she continues to do the work herself in the lab. "Also because I had no money to hire someone, I had no students. But I loved it: casting gels, seeding cells on growth plates, growing bacteria." She laughs. "That way I could also be sure that no mistakes were made."

When the research institute in Szeged runs out of money in 1985, she sells her car on the black market, hides the money in her two-year-old daughter's teddy bear and flies to the United States with her husband and child. She gets a position at the University of Pennsylvania and soaks up the knowledge. "I went to lectures at least twice a week. And then afterwards I thought: what could I use from this for RNA therapy? Nowadays you don't have to go to America for that, you can listen via YouTube. You just need to know who to listen to."

Inflammatory reactions

Early on, Karikó sees the potential of messenger RNA (mRNA). This is the molecule that copies the instructions from the DNA in a cell. Based on this copy, a cell makes proteins. In 1984, scientists succeed for the first time to make mRNA in the lab. Karikó wants to use lab-made mRNA to help cells to make missing proteins – many diseases are caused by a

deficiency of a protein, such as a hormone or enzyme. If it were possible to get self-made mRNA into cells, the body itself could make it own medicine.

In practice this turns out to be very challenging. The long mRNA molecules are very fragile, and they induce strong inflammatory reactions in laboratory animals. And a third problem: how do you get the molecule into a cell? Many scientists become discouraged and drop out in the 1990s. But Karikó carries on.

Thanks to grants from other people, she can do research. She works on blood vessel improvement with cardiologist Elliot Barnathan in Pennsylvania for six years. When he leaves, neurosurgeon David Langer brings her to his department in search of a treatment for stroke, but he too leaves.

Karikó: "We did a lot of work, but didn't publish anything, because we couldn't prove conclusively that it worked." She herself had still not secured any grants, and she had to clear the field – but for a short while she continued to work unpaid.

“I have never received an award in all these years, not even a scholarship”

Then, at the copy machine, she accidentally meets immunologist Drew Weissman. He wants to make a vaccine against HIV, and mRNA seems ideal for that. In the years that follow, they plod on, looking for ways to make the mRNA more stable, and to counteract the inflammatory response that mRNA induces.

Their greatest discovery they make by chance. In one of the experiments, they use tRNA (transfer RNA) as a control, another form of RNA with a different function in the cell. This does not appear to induce an inflammatory response. One of the four building blocks is different from mRNA. If they incorporate this building block, pseudo-uridine, into mRNA, the body accepts it without the immune system kicking in. This modified RNA (modRNA) also turns out to yield ten times as much protein. The leading scientific journal *Nature* does not want to publish their article on this, eventually it appears in the journal *Immunity*. "But no one was very interested."

Later they also discover together how the modRNA, packaged in tiny fat droplets, 'nanoparticles', can be delivered into cells. But even when they succeed in getting laboratory animals to make the hormone erythropoietin (Epo), which stimulates the production of red blood cells, and they set up a business, there is still no interest.

In fact, in 2013, Karikó even gets fired by the University of Pennsylvania. “I had not secured any funding for seventeen years. They offered me a position at the animal testing facilities. Unacceptable to me, it wasn’t a laboratory. So I was kicked out.”

Small power surges

With the words of stress researcher Selye in mind, Karikó, now 58 years old, changes her heading. She wants to join a biotechnology company that is already doing studies in humans with modified mRNA. She wants to make sure she is there when it finally leads to a medicine or treatment. “The pharmaceutical company Moderna offered me a position but it was not yet

doing human studies. It would take decades before there would be a working drug, by that time I would be long dead." She offers the German company Curevac to come and work with modRNA. "They didn't need that, they said."

Once again, an accidental event is decisive. She hears someone talking about BioNTech, a small biotech company that mainly focuses on mRNA as a cancer treatment. And they do clinical studies there. She decides to apply there. Only to discover that even Uğur Şahin, director and founder of BioNTech, thinks that modRNA is not necessary to get mRNA into cells. After all, he thinks, this can be done in another way: with electroporation, small electric pulses. "They didn't see the difference," says Karikó. "But for a vaccine to work properly, the lipid droplet must end up in endosomes, small vesicles in the cell. You can't do that with electroporation." Şahin liked her, she says, so she could come and work on modRNA in a small corner of the lab at BioNTech. "Nobody thought it was important," she chuckles, "just me!"

Chocolate-covered peanuts

Then the tables turn. Soon after the outbreak of the corona pandemic, Uğur Şahin decides to make and test a vaccine against Covid-19 with mRNA, together with manufacturer Pfizer. On November 8, 2020, they reveal the first results: the vaccine turns out to be safe and extremely effective. Karikó is not surprised. "Oh, it works," she said to her husband. "I thought so." To celebrate, she empties an entire bag of chocolate-covered peanuts. That same year, the rain of awards begins.

After forty years of scraping, Karikó now boasts millions of dollars in prize money. She gave away the money she received in Hungary and Spain to local schools and charities. "For children who have lost their parents to Covid, or for less privileged children like I was myself", she says. But of course she will mainly use the money for research. "Now I can finally do what I want myself! After this year, I will not accept any speech invitations, nothing at all. In 2023 I want to get my time back and do research again."

"I don't hold a grudge, not even against the people who wanted to send me back to Hungary"

She has many ideas: for years she has kept a list of diseases that might be treated with mRNA. "I don't want to say exactly what I'm going to do, because then I immediately get a lot of e-mails from people who want to have it. That also happened when it was announced that I would be working at BioNTech on epidermolysis bullosa, a hereditary skin disease that causes blisters. But we still have so much to figure out. We are still working on the best chemical composition, so that parents can simply take it out of the freezer to help their child."

The future of RNA therapy lies in the *delivery*, she says: "How do you get it where you want it, to a specific cell type, a specific organ?" Right now, the RNA remains locally, near the puncture site. "Particularly the immune cells take up the lipid particles, that is their function. If you inject it in the bloodstream, it can also reach the liver cells. And earlier this year, Drew

Weissman and his colleagues succeeded, in test mice, in sending nanoparticles containing modRNA to T-cells, a type of white blood cells, thus making CAR-T cells.” Those CAR-T cells have been reprogrammed in such a way that they can recognize and clean up damaged cells in the heart.

Malaria, tuberculosis and HIV

Karikó foresees many applications of mRNA in the near future. “Vaccines against diseases for which we do not yet have a vaccine, such as malaria, tuberculosis and HIV. And new vaccines to replace existing, expensive vaccines. Pfizer/BioNTech and Moderna will start a clinical trial with an mRNA vaccine against shingles in the second half of this year. That will be more affordable than the existing one because RNA is cheap and easy to make.”

In addition, Karikó expects to see mRNA treatments against diseases. “AstraZeneca and Moderna are already testing a drug against heart failure in a large clinical trial in patients, injecting modRNA into the heart to create new blood vessels. At BioNTech we test mRNA treatments against tumors.” And the company Intellia succeeded in repairing a genetic defect in 2020 with an mRNA treatment in patients with amyloidosis, a disease in which proteins accumulate in cells, she says. "So even the promise of gene therapy will be fulfilled with RNA."

Karikó is now allowed out of quarantine in Tokyo, she heard shortly before the interview. "Because I have had three injections." Three shots, with the Covid vaccine that would not have existed without her.

[SIDEBAR]:

CV

Katalin Karikó (Kisújszállás, Hungary, 1955) is a biochemist. She is a senior vice president at the German biotech company BioNTech and is affiliated with the University of Pennsylvania. After obtaining her PhD in RNA research in 1982, she started working at the Biological Research Center in Szeged. In 1985 she emigrated to the US.

In 1997, she teamed up with immunologist Drew Weissman at the University of Pennsylvania. Their discoveries are at the basis of the highly effective mRNA vaccines against Covid-19 from Pfizer/BioNTech and Moderna.

Kati Karikó is married to engineer Béla Francia. They have a daughter, two-time Olympic rowing champion Susan Francia.

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