INTERVIEW

Illustration by Shonagh Rae

"You learn more from failure—when things are not working well."

Biochemist Katalin Karikó won the Nobel Prize for research that laid the groundwork for effective COVID-19 vaccines. She talks about how hard work and focus—rather than innate talent—led to her scientific success, and about the joy of solving interesting puzzles.

Katalin Karikó is a pioneer in research on messenger RNA (mRNA) and its medical possibilities, which were revealed on a global scale during the COVID-19 pandemic. With her colleague Drew Weissman, she developed the type of mRNA that eventually made possible the Pfizer-BioNTech and Moderna vaccines, which saved millions of lives worldwide. For their breakthrough, they received the 2023 Nobel Prize in Physiology or Medicine.

Karikó is an adjunct professor of neurosurgery at the University of Pennsylvania. She recently authored the memoir *Breaking Through: My Life in Science*, and is a member of the National Academy of Medicine. Karikó spoke with editor Sara Frueh about her childhood in Hungary, the joys and challenges of bench science, her struggle to find support for her RNA research, and the experience of finding herself suddenly in the spotlight.

What drew you to science as a young person?

Karikó: In Hungary, we started to learn biology in fifth grade. In the fall we went outside and the teacher picked up leaves and said, "Isn't that interesting? Why is it falling down? Why is it not growing very big?" And you just wonder. Science is not about being in a special place like a lab—it is just noticing what is right around you and asking, "Isn't that interesting?"

Even in elementary school, we did this little experiment over a saturated salt solution. We put a thread in it, and over a couple of weeks we checked to see if a crystal is growing. And later here at Penn, when sometimes I would see a little crystal form in the bottom of a bottle, I remember how happy I was.

You grew up in rural Hungary, and you emerged as a world-class scientist. Were there things about the Hungarian education system that helped that happen?

Karikó: It was the '50s and '60s. We didn't have phones, we didn't have television, so we just played outside. We didn't have special toys, so we had to figure out something we can use as a tool to play with. When you have fewer resources, you have to be more inventive. Our parents hadn't gone to high school—they had no resources, and they had to earn their living. My father was a butcher. Even when he was five, six years old, he was already working, herding animals, so that he could earn the food he ate.

By the time my sister and I entered school, the Hungarian system tried to say, "You can be anything—you just have to study."

The first time I saw a university building and a professor was at a summer program for high school students at the University of Szeged. We stayed in the dormitory, one room with 30 kids in metal beds. So that's how the system provided. At five in the morning, we would get up and go to lectures until the late evening. Later we came back during winter vacation for more lectures and testing, and eventually we got accepted to the university, which was very difficult. Many times I thought, *How many kids couldn't come here and study because maybe their parents thought that they shouldn't, or it never even occurred to them?*

What first appealed to you about studying mRNA and drew you to that line of work? It sounds like working with RNA, especially back then, was really difficult.

Karikó: When I started working with RNA, it was not a visionary thing. As an undergrad, I worked in a team at the Biological Research Center in Szeged studying lipids, and we happened to make liposomes that helped us to deliver DNA into cultured cells.

Then the organic chemist Jenő Tomasz said he had an opening in his team researching RNA, and did I want to do my PhD there? I said, "OK." At that time, getting a degree was not very organized in Hungary—you just worked for somebody, and whether it is good or bad, that is your luck.

So I started to work with RNA and, you know, you learn to do something, you enjoy it, so you read all about it. And then you are good at it, and then you enjoy it even more. This is how it happened with RNA. And I have to say, I have no special talent, no special memory, nothing. It is just that I can focus and work hard.

I continued to work with RNA when I came to the United States to work at Temple University in Philadelphia. I came to realize that maybe messenger RNA would be a better way to deliver therapies to cells than DNA.

When I went to Penn in '89, I looked up how we could make mRNA and that's where I started. Most laboratories at the time had difficulties working with RNA—it is very fragile and degrades easily. So they felt sorry for me when I said that I'm working with mRNA: "Oh my God, poor Kati."

Douglas Melton, who first reported how to make mRNA in a tube, never thought that it could be used as medicine; he thought it would be useful as laboratory research tool. At the beginning, only a very small amount of protein could be produced from the mRNA, and people questioned whether it would ever be therapeutically useful. But as I worked at the bench, I constantly improved the mRNA, the quantity of protein produced from it.

How did you develop the type of mRNA that was eventually used in the COVID vaccines?

Karikó: I didn't set up my career path so that I would make noninflammatory mRNA. In fact, I didn't even realize that RNA was inflammatory until I met and worked with Drew Weissman at Penn.

In an experiment where we introduced mRNA into immune cells, we could see inflammatory molecules were being generated. And we asked, "Why is that?" It was curiosity-driven research; we tried to understand the inflammation, and thought, maybe because the mRNA is coming from outside into the cells, it is a danger signal to the cell. We also wondered if all types of RNA trigger inflammation.

By that time, I had already worked with mRNA for 10 years, and I had a repertoire of different RNA isolates that we could test. So we did the experiment, and it turned out that one type of RNA called transfer RNA did not cause inflammation; it was nonimmunogenic. Considering that transfer RNA contains a lot of modified nucleosides, we suspected that those were making the RNA noninflammatory. We then generated a kind of mRNA with similar modifications, which was not only noninflammatory but also produced ten times more protein. Both these qualities were important in creating effective vaccines.

For a long time, you found it difficult to get grant funding or institutional support for your work on mRNA. Why do you think the potential of mRNA went unseen for so long?

Karikó: In 1992, Floyd Bloom and colleagues published a paper in *Science* about successfully treating sick animals by injecting vasopressin mRNA into their brain. It was an important work, but they never published anything on mRNA again. Another group of scientists who were using mRNA to try to develop a cancer vaccine told me that they couldn't get funding. My experience was similar—for two years at Penn, I wrote at least one grant application a month and not one of them came through.

I think what happened is what my Hungarian colleague Csaba Szabó describes in his forthcoming book, *Unreliable*. A scientist who gets a grant becomes a member of the National Institutes of Health committee to evaluate grant applications by fellow scientists working in the same field. They might get 10 grant applications and have to read all of them. They try to absorb them when a zillion things are going on in their life—they have to write their own grants, publish their papers, manage their lab, and so on.

And when they evaluate the grant applications, in some case they understand it immediately because it's similar to what they are doing. And in other cases, they think, "What? mRNA? And who is this person?" They think less of those applications because the science—and the scientist—is unfamiliar to them, and they do not have time to learn more. That's what I think happens, even if everybody is trying to do their job the best they can.

There was an article in the *Harvard Business Review* that described how there is a center where the money and the prestige are, and if you are not there, you are in the periphery, like me, and can get lost. And the article said the only benefit you have in the periphery is the freedom that you are doing what you think is important.

But you need a connection. You need somebody channeling at least enough money to survive, because otherwise your work will be lost. If you have enough funding to continue, at least you can advance the research. I didn't get grants, but Elliot Barnathan and David Langer helped me to survive at Penn until I met Drew Weissman, so thanks to them every time.

> "Science is not about being in a special place like a lab—it is just noticing what is right around you and asking, 'Isn't that interesting?'"

One thing that comes through in your memoir is your unwavering commitment to meticulousness and rigor in research, and to prioritizing quality over the number of publications and external rewards. Should academic science be doing more to impress those priorities on researchers?

Karikó: I did not pay attention to what others are doing in terms of getting promotions and grants. So that's what I tell the students: don't compare yourself to others. If I would have compared myself, I would have left the whole field a long time ago.

> "You try many things and you don't know whether something is doable or not. But this is being a scientist. We are doing things that nobody has done before, and we don't know whether it is possible."

But if your focus is always the science—"I want to understand this biological mechanism"—you never get disappointed. Not even when somebody else publishes something about what you are investigating, because you want to understand, and that person contributed to the knowledge.

Everybody starts by focusing on science, and somehow they shift to, "Oh, we should do more experiments. We need more people, so we need more money." They start to write grants, and more people come to work in the lab. Now those people have to publish to get to their PhDs. Then you are submitting more and more grant applications because you have to keep the lab running, and your promotion is coming up, and your tenure. And the goal has now became *that*, and performing experiments becomes a tool to reach *that*—not a tool for understanding.

Your memoir notes an idea, I think by the endocrinologist Hans Selye, that deeply resonated with you: that a scientific experiment asks a question of nature, to which nature answers "yes" or "no." And you've always been patient with the "noes"—the negative results. Why are they important, and should the scientific community be attaching more value to them?

Karikó: When you do an experiment and don't get what you expected, you think, "Oh, it didn't work." But the reality is that you just don't understand what's going on yet. It is very well known that you learn more from failure—when things are not working well.

With failure, you ask, "What's going on? I didn't get the result I thought I would. Maybe there is another approach I can try." And then you start to study. And then you figure out, "Oh, probably if I add this, then this will happen."

It is very important not to focus on success—it's so rare. If you want instant gratification, don't be a scientist, because you won't get that. You try many things and you don't know whether something is doable or not. But this is being a scientist. We are doing things that nobody has done before, and we don't know whether it is possible.

During the pandemic, what was it like to find out that the vaccines you'd been working on actually worked? And what was the most satisfying part about all of that?

Karikó: I have to say that I expected that the vaccines would work. BioNTech signed an agreement with Pfizer in 2018 to develop an mRNA-based influenza vaccine. And by end of 2019 we had already seen the results of animal trials. We were ready for the human trial with the nucleoside-modified mRNA. So in 2020 we just had to change the template so the generated mRNA coded for coronavirus-specific protein. Considering all the prior results, I expected that this new vaccine would work.

What I did not expect was that I would be recognized. One day at the end of 2020 CNN called me, and I was so scared that I had to say something. I was watching CNN, and I got a call from CNN, which could be seen right on the screen, "call from CNN," and I thought, "Oh my God, oh my God."

It was just so stressful. I could hardly say anything because I was not used to giving interviews. Later when I received awards, I felt the same way. It took time to realize: OK, the prize is for science; the spotlight is on the science. This is a good thing that people are talking about science. And I have to help the public to understand better what the scientists are doing. And I have to inspire the next generation. And I started to talk about these topics.

What advice do you have for young scientists, and students who are thinking about becoming scientists?

Karikó: Whatever you do, you have to enjoy, and love it, and then you will be good at it. And if you like to solve puzzles, then you should consider science as something that you could pursue in life. And it can be a fulfilling life. You won't be rich; it's not that kind of life. It is hard work, but the fun is there, as solving puzzles of science is fun.

Also, your physical and mental health is very important. Exercise regularly and learn how to handle stress. It is important to focus on things that you can change. Ask yourself what you can do, and not what others should do. And please do not compare yourself to others, it takes away your attention from those things that you can have influence on.

You have to believe in yourself—that with hard work you can achieve your goals. It is not easy, nothing is easy. But if you are working in a laboratory, you are already in a great place to have a wonderful and fulfilling life.