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PROFILES IN SCIENCE
SHARIF TABEBORDBAR

# Determined Yet Patient, He Looks for a Cure

A scientist is motivated by the muscle-wasting disease that has debilitated his father.

By GINA KOLATA

CAMBRIDGE, MASS. — When Sharif Tabebordbar was born in 1986, his father, Jafar, was 32 and already had symptoms of a muscle-wasting disease. The mysterious illness would come to define Sharif's life.

Jafar Tabebordbar could walk when he was in his 30s, but he stumbled and often lost his balance. Then he lost his ability to drive. When he was 50, he could use his hands. Now he has to support one hand with the other.

No one could answer the question plaguing Sharif and his younger brother, Shayan: What was this disease? And would they develop it the way their father had?

As he grew up and watched his father gradually decline, Sharif vowed to solve the mystery and find a cure. His quest led him to a doctorate in developmental and regenerative biology, the most competitive ranks of academic medical research, and a discovery, published in September in the journal Cell, that could transform gene therapy — medicine that corrects genetic defects — for nearly all muscle-wasting diseases. That includes muscular dystrophies that affect about 100,000 people in the United States, according to the Muscular Dystrophy Association.

Scientists often use a disabled virus called an adeno-associated virus, or AAV, to deliver gene therapy to cells. But damaged muscle cells like the ones that afflict Dr. Tabebordbar's father are difficult to treat. Forty percent of the body is made of muscle. To get the virus to those muscle cells, researchers must deliver enormous doses of medication. Most of the viruses end up in the liver, damaging it and sometimes killing patients. Trials have been halted, researchers stymied.

Dr. Tabebordbar managed to develop viruses that go directly to muscles — very few end up in the liver. His discovery could allow treatment with a fraction of the dosage, and without the disabling side effects.

Dr. Jeffrey Chamberlain, who studies therapies for muscular diseases at the University of Washington and is not involved in Dr. Tabebordbar's research, said the new method "could take it to the next level," adding that the same method also could allow researchers to accurately target almost any tissue, including brain cells, which are only beginning to be considered as gene therapy targets.

And Dr. Francis Collins, the director of the National Institutes of Health, which helped fund the research, said in a blog post that it holds "potential for targeting other organs," thereby "possibly providing treatment for a wide range of genetic conditions."

Dr. Tabebordbar's small office at the Broad Institute has a glass door that opens directly to his lab bench. It is not homey. There are no photos, no books, no papers strewn about on the white counter that serves as a desk. Even the whiteboard is clean. There, fueled by caffeine, he typically works 14 hours a day, except on the days when he plays soccer with a group at M.I.T.

"He is incredibly productive and incredibly effective," said Amy Wagers, who was Dr. Tabebordbar's Ph.D. adviser and is a professor and co-chair of the department of stem cell and regenerative biology at Harvard. "He works all the time and has this incredible passion and incredible dedication. And it's infectious. It spreads to everyone around him. That is a real skill — his ability to take a bigger vision and communicate it."

Dr. Tabebordbar likes to cook Persian food and hosts a feast in his small apartment every Thanksgiving for about a dozen friends. While he works at his lab bench he listens to Persian music, podcasts or audiobooks. He loves biographies, and made mention of a passage he found meaningful in the autobiography of one of his heroes, the former English soccer player Michael Owen.

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Sharif Tabebordbar of the Broad Institute at M.I.T. works on treatments for debilitating muscular diseases.

Mr. Owen writes that when he learned he had been voted European soccer player of the year, his reaction was muted. "All I wanted to do was score the next goal, the next hat-trick and lift the next trophy," Mr. Owen wrote. "Looking back, I was relentless in that respect and I've no doubt that that mind-set was key to my success."

Dr. Tabebordbar said: "That is like me. It is amazing that we achieved this but now" — he snaps his fingers — "we need to get to work. What's next?"

Dr. Tabebordbar was born in Shiraz, Iran, but moved to Rasht when he was 9.

Based on his score on a national test,

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Sharif Tabebordbar who said of the patience required to do his work, "I will do 100 experiments, and 95 will not work."

he was admitted to a high school that is part of Iran's National Organization for the Development of Exceptional Talents. There, motivated by his drive to help his father, he focused on the biological sciences. His mother, Tahereh Fallah, who had yearned to be a doctor but was unable to continue her education in Iran, pushed Sharif and his brother to excel and celebrated their successes.

After high school, Sharif was determined to be one of the eight to 10 students in the country admitted to an accelerated program at the University of Tehran. It leads to a bachelor's degree, a master's degree and a doctorate in only nine years.

"This was my dream," he said. "I had to study really hard for that exam — English, Arabic, science." It paid off — he placed seventh out of 1.3 million.

At the University of Tehran, he majored in biotechnology. After four and a half years, he had a master's degree but began applying to Ph.D. programs at top international universities doing research on muscular dystrophies, hoping that would lead to a discovery that could help his father. He ended up in Dr. Wagers's lab at Harvard.

All along the question hovered over him: What caused his father's illness?

When his father came to Harvard to attend the 2016 graduation ceremony, Dr. Tabebordbar seized the moment to have Jafar's genes sequenced and figure out the mystery. No mutations were found.

"How is that even possible?" Dr. Tabebordbar asked.

**The wider world will benefit from a scientist's lifelong quest to figure out his father's muscle-wasting disease.**

More detailed and sophisticated testing finally revealed the answer: His father has an extraordinarily rare genetic disorder, facioscapulohumeral muscular dystrophy or FSHD, that affects an estimated four to 10 out of every 100,000 people. It is not caused by a mutation in a gene. Instead, it is caused by a mutation in an area between genes, resulting in the excretion of a toxic chemical that kills muscle cells.

To Dr. Tabebordbar's horror, he learned that he had a 50-50 chance of inheriting the mutation from his father. If he had it, he would get the disease.

He was tested by a friend, who called him with the result.

Dr. Tabebordbar had inherited the mutation but — amazingly — the mutated gene was missing the last piece of the toxic DNA, which prevented the condition from emerging.

"You are the luckiest guy among the unlucky," he recalled his friend saying.

In Dr. Wagers's lab, Dr. Tabebordbar worked on muscular dystrophy, using CRISPR, the gene editing technique. He attempted to use AAV to transport the CRISPR enzymes to muscle cells where it might correct the mutation. As others found before him, that was not so simple.

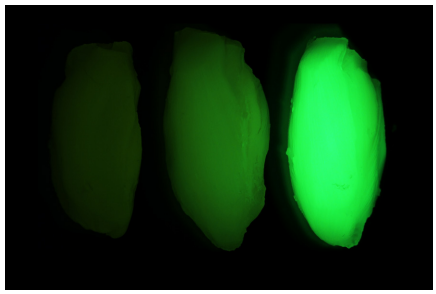
In 2004, Dr. Chamberlain of the University of Washington reported that AAV could deliver gene therapy to muscles of mice. But treatment required "astronomical doses" of the disabled virus, Dr. Chamberlain recalled.

"At these very high doses, you are right on the edge of other problems," Dr. Chamberlain said, and the liver gets overwhelmed.

Despite the risk with high AAV doses,

PHOTOS BY SHARIF TABEBORDBAR

Dr. Tabebordbar, left, with his father, Jafar; mother, Tahereh Fallah; and brother, Shayan, in 2016.



Mouse tissue from on of Dr. Tabebordbar's experiments, from left: a muscle injected with saline, a muscle injected with AAV9 and a muscle injected with an evolved AAV.

gene therapy clinical trials are underway for patients with muscle diseases, but only in children. Their smaller bodies can get by with lower doses that contain fewer viruses.

Gene therapy with AAV has been approved for one fatal muscle disease, spinal muscular atrophy.

"It's a horrific disease," said Dr. Mark Kay, a gene therapy researcher at Stanford. Even with the child-size doses, some children have died from the medicine meant to save them.

"But if you don't treat them they will die from the disease," Dr. Kay said.

Dr. Tabebordbar's project at Harvard suffered from the high dose problems, too. Although he managed to correct muscular dystrophy in mice — a feat reported at the same time by two other labs — that was no guarantee the gene therapy would work in humans.

A disease like the one Dr. Tabebordbar's father suffers from is especially difficult. More common muscular dystrophies are caused by a mutation that leaves patients lacking a particular protein. Gene therapy has to replenish that protein in some, but not all muscle cells.

The disease afflicting Dr. Tabebordbar's father involves a toxic substance produced by about one percent of muscle cells that then spreads through the muscle fibers. To rid muscles of that toxin, gene therapy has to get to every muscle cell.

"It's a much higher bar," Dr. Tabebordbar said.

After he graduated from Harvard, Dr. Tabebordbar thought he had a chance to develop a gene therapy for muscular dystrophy at a biotech company. But after about a year, the company dropped the muscular dystrophy program. Dr. Tabebordbar knew he had to go somewhere else.

He got a position in the lab of Pardis Sabeti at the Broad Institute and set to work. His plan was to mutate millions of viruses and isolate those that went almost exclusively to muscles.

The result was what he had hoped — viruses that homed in on muscle, in mice and also in monkeys, which makes it much more likely they will work in people.

As scientists know, most experiments fail before anything succeeds and this work has barely begun.

"I will do 100 experiments, and 95 will not work," Dr. Tabebordbar said.

But he said this was the personality that was required of a scientist.

"The mind-set I have is, 'This is not going to work.' It makes you very patient."

Dr. Chamberlain said that with all the pre-clinical work Dr. Tabebordbar had done, the new viruses could move into clinical trials soon, within a year.

Now Dr. Tabebordbar has moved on to his next step. His life, other than his brief stint in biotech, has been in academia, but he decided that he wanted to develop drugs. About a year ago, he co-founded the drug company Kate Therapeutics. It will focus on gene therapy for muscle diseases, and he will move there for the next phase of his career.

He hopes his work will spare others from suffering. Yet his father's fate hangs over him. Jafar Tabebordbar has missed the window when it might still be possible to help him.

"He was born too soon," his son said.