



[URMC](#) » [Publications](#) » [Rochester Medicine - Summer 2010](#)

Sensing a Breakthrough

Unique International Collaboration Advances Understanding and Treatment of a Muscular Dystrophy

By Michael Wentzel

When researchers pinpointed the genetic mutation that leads to the disease known as facioscapulohumeral dystrophy (FSHD) in 1992, hopes rose that the discovery not only would result in better treatments but also eventually a cure for the disease.

But FSHD, which was first described by French physicians in 1884, is an atypical genetic disease. While the discovery of the genetic defect on chromosome 4 opened new areas of research, it also added to the disease mysteries. This genetic defect involves the loss of a critical number of repetitive pieces of DNA, a sequence called D4Z4. At least 11 copies of the sequence are required for normal health. Those who have fewer than 11 get the disease.

"Usually we find a mutation in a particular gene," said Rabi Tawil, M.D. (R '91, FLW '93), professor of neurology at the University of Rochester Medical Center who has treated and investigated FSHD for two decades. "In FSHD, the genetic defect did not seem to derange the sequence of a particular gene. We did not know why the loss of a certain number of copies of the DNA repeat caused FSHD. There were many conflicting theories that could not be resolved very easily."

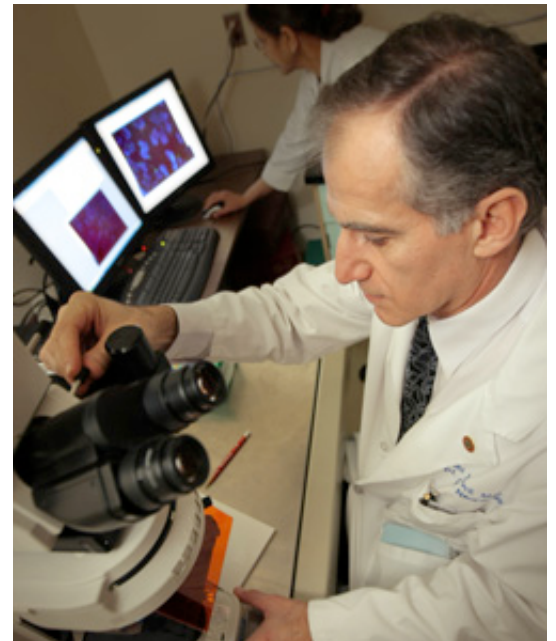
After the excitement of the 1992 discovery, research only inched forward. But for Tawil and others, a turning point occurred in October, 2007, when New York developer and philanthropist Richard T. Fields donated \$7.1 million to the Medical Center to establish the Fields Center for FSHD and Neuromuscular Research.

"We have accomplished more in the last two years than in all the years since 1992," said Tawil, who is director of the Fields Center.

The Fields Center began as an international collaboration between Tawil at the Medical Center's Department of Neurology and Silvere van der Maarel, Ph.D., professor of medical genetics at Leiden University Medical Center in the Netherlands. The center now also includes Stephen Tapscott, M.D., Ph.D., a research scientist at the Fred Hutchinson Cancer Research Center in Seattle.

The resources and the collaborative nature of the Fields Center have created a potent momentum.

"There is a synergy between the three centers," Tawil said. "There are open relationships between investigators, not competitive relationships. We have one aim and we work very well together because we are all dependent on each other. The center is more than the sum of the parts, and our work has grown exponentially. For the first time since 1992, we have a target gene. We still have work to do. We have to flesh out the consequences of the abnormal expression of the DUX4 gene, but, for the first time, we



Rabi Tawil, M.D.

have a therapeutic target to work on. That's where we are heading next."

Van der Maarel, the Fields Center's co-director, said the center's strength comes from the highly complementary expertise of the institutions and the drive to advance the understanding of FSHD.

"It has been a privilege and joy to work with the Rochester team and I find it personally incredible how much we have accomplished in only two years and the advances we are still making," he said. "We are both fortunate to be supported by an incredible team. Stephen Tapscott's joining us only further strengthens this unique collaboration. For me and my team, the past two years have been a revolution from which, in the end, the patients will benefit. For more than a decade, I have presented our progress at annual patient meetings and last year was the first in many years that we could really bring a positive story to the patients."

Deciphering a DNA deletion

The exact path to facioscapulohumeral dystrophy, as with many diseases, has remained elusive. After the discovery of the link between the missing sequences of DNA and FSHD, some researchers suggested that the loss of the DNA sequences influenced how nearby genes functioned. In particular, they focused on a gene called FRG1.

One laboratory demonstrated that the loss of the DNA resulted in an abnormally high level of expression of FRG1. However, "many subsequent studies were done to show that getting rid of copies of DNA turns on FRG1 and that causes a muscle disease," Tawil said. "But none could confirm the initial data. In a study done in 2004, based on samples of muscles we had taken from patients, we showed that FRG1 was not increased in patients who had FSHD versus unaffected individuals."

The Fields Center researchers turned to a different gene called DUX4, a copy of which is present in each of the repeated DNA sequences. They saw DUX4 as a possible culprit in FSHD, even though some wondered whether DUX4 is a working gene that actually codes for a protein.

"In combining our resources with our collaborators in Holland, we were able to look at a large number of patients and we have been able to identify patients with unusual combinations in their DNA that actually predicted or helped us confirm that the disease emanates from one of the remaining copies of the repetitive DNA," Tawil said. "If you lose a certain number of copies, the chromosome unfolds in such a way that this gene, DUX4, which is normally turned off, becomes activated."

Each facet of the Fields Center has a different role. Van der Maarel and his lab in Holland are experts at genotyping, or determining the genetic makeup of a chromosome. They probe the fine differences and sequences between affected individuals and those not affected by FSHD and compare different families with FSHD.

In Seattle, Tapscott and his group are experts in epigenetics, focusing on the structure of a chromosome, or the bundles of DNA that form a chromosome, and how changes in the chromosome structure can cause disease.

In Rochester, Tawil and his team take cell samples from FSHD patients, determine the severity of the disease and send the samples to the labs in Leiden and Seattle. For 10 years, Tawil and those at the Medical Center who treat dystrophy patients have collected samples from patients who enthusiastically help with research. Many have donated cells and tissues more than once. This work has generated several hundred samples.

"Patients come to us from across the country because we are not only a research center, we are a clinical center," Tawil said. "We understand their disease. We can provide them with feedback. We can provide feedback on a genetic level and a practical level. We have developed techniques for taking cells and maintaining muscle cell lines."

This well-developed Rochester pipeline is a rich resource for researchers.

"Researchers often get samples from anonymous sources or big repositories where there is not a clear understanding where the



Research team in Leiden

sample came from," Tawil said. "We correlate their findings of the DNA sequence with what we see in the patient clinically and with the severity of the disease. We can give Leiden and Seattle information from the patient. We can correlate what we see in the patient with what they see in test tube or Petri dish. We have not been able to do this in the past with such magnitude."

The result of this collaboration is a significant new insight on the role of DUX4 in FSHD. The missing sequences of DNA appear to be associated with unraveling of the structure of the chromosome.

"That bigger structure of the chromosome is important to how the individual genes on the DNA function. Change the structure of the chromatin and you change how individual genes work," Tawil said. "The DUX4 gene is turned on in patients with FSHD and we have reason to believe that it produces a protein that, even at low levels, may damage the muscles enough to cause a progressive muscular dystrophy.

"We already have published work that shows preliminarily that the protein is selectively expressed in cells and muscles of patients who have FSHD and not in those who don't have FSHD. We expect to publish soon work led by Stephen Tapscott that confirms this in a much more definitive way. Our big collaboration brings all the pieces together into one entity. It is having all the right people and all the right resources that have made this happen."

Tawil and Fields Center investigators enthusiastically share resources with other researchers, including scientists at the University of California at Irvine, Tulane University and University of Minnesota.

"We are not exclusive," Tawil said. "We have generated enough biological resources that we can share with others who may not be working directly with us. I had loose connections with these researchers in the past but the Fields Center solidified these small collaborations and they are very helpful. Too bad more people don't work this way."

Closing in on a breakthrough

The Fields Center is about more than genetic and molecular research. The center's ultimate focus is the person, the patient who eventually might benefit from research accomplished at each step along the way.

Fields Center investigators have organized a meeting that will bring FSHD experts from around the world to Leiden in June to discuss diagnostic procedures and to develop a genetic testing protocol for FSHD. In January, the investigators met in Leiden to outline standards of clinical care for FSHD as well as develop outcome measures to be used in future clinical trials. These projects are designed to be useful to the medical and patient communities now while treatments are being sought.

"No one has looked at best practices in a systematic way for FSHD," Tawil said. "There is no one place where you can find what to do with patients. For example, surgery can help increase range of motion of the shoulders in FSHD, but there is no place that tells you who are the patients who should go for surgery or what kind of surgery is best. In some forms of dystrophy, exercise might not be the best thing. Who should exercise? Who needs to be screened for retinal problems? We need to document these topics based on the evidence. We have to bring multiple opinions to a consensus."

Guidelines will help standardize the care of patients with FSHD across the world. Tawil has written an article based on the consensus reached at a workshop and it currently is in press. The Fields Center also is preparing for clinical trials by developing outcome measures.

"We must develop relevant outcome measures for our patients for the time when we do clinical trials," Tawil said. "You must have measurable outcomes that can accurately measure the efficacy of an intervention. We are trying to determine what the best outcome measures are. We used to just measure strength in patients. If a patient's strength measure improved, we said it was an effective drug whether or not the patient noted an improvement.

"That is no longer acceptable to the Food and Drug Administration. The FDA wants outcome measures that are understandable to the patient and also any clinician who looks at the study. If I have a study that shows an intervention causes 10 percent increase in muscle strength, that does not mean very much. If I can say we did an intervention and a patient now can walk 50 yards instead of 10, that is more clinically pertinent and understandable to the general public and the patient."

The Fields Center is about more than genetic and molecular research. The center's ultimate focus is the person, the patient who eventually might benefit from research accomplished at each step along the way.

The advancements made by Fields Center investigators have attracted additional funding and donations and cemented collaborations.

Tapscott, who has wide-ranging research interests in diseases of muscle, initially served as an adviser to the Fields Center. But as his interest in FSHD grew, the center provided money to support a member of his lab. Tapscott leveraged the financial support and work with the Fields Center to win a National Institutes of Health grant of \$5 million that will fund research in Seattle, Leiden and Rochester.

The Fields Center received what Tawil describes as a "sizable donation" from Daniel Frenzel, a citizen of Germany. His gift supports a joint project conducted in Rochester, Leiden and at the Institut de Myologie in Paris to create immortalized cells lines that originate from muscle biopsy samples taken from individuals with FSHD. These cell lines are ideal to study the underlying mechanisms that lead to FSHD.

The center also received a gift of \$25,000 from the Geraldi Norton Foundation and the Eklund Family in Illinois that helped support Tapscott's investigation of multiple, novel genetic messages from the region on chromosome 4 implicated in FSHD. Early indications suggest that one or more of these messages may interfere with muscle growth and repair.

The support and the collaborations fostered by the Fields Center have pushed research closer to a treatment for FSHD.

"Right now, we think DUX4 probably is the primary cause of FSHD," Tawil said. "We do believe DUX4 is very toxic to muscle. But in FSHD, there are two other things that happen that are not related to the muscle and have to be explained—hearing loss and retinal vascular problems. They usually are not very clinically disabling but whatever we say is the primary cause of FSHD has to be able to explain what happens to the muscles, the eyes and hearing. DUX4 is our target and we're going to take what we have learned and try to translate that into a treatment."

"It will take a worldwide effort to solve this disease and the Fields Center wants to be a big part of the effort," said van der Maarel. "I am always cautious about making predictions for the future so not to mislead patients. What we would consider major breakthroughs likely will take years before it makes a difference to the patient. But yes, we are close to breakthrough and I am looking forward to the coming years in the Fields Center."

Tapscott also avoids predictions, but like Tawil and van der Maarel, he is optimistic.

"I do not think about this in terms of a breakthrough but rather in terms of steady progress," Tapscott said.

To comment on this article, [email us](#).