Reversing (heart) failure in Friedreich's ataxia

By Michael J. Haas, Senior Writer

Heart failure accounts for over half the deaths in patients with Friedreich's ataxia, but no therapies exist to treat this neurodegenerative disease or its associated cardiomyopathy. Now, a team of French researchers has shown that i.v. *frataxin* gene therapy could prevent or even reverse heart failure in a mouse model of Friedreich's ataxia.¹

AAVLife, a new company founded by several team members, has licensed the findings and will test dosing and safety of direct cardiac injection of the gene therapy in healthy pigs.

Friedreich's ataxia (FRDA) is caused by inherited loss-of-function mutations in *frataxin* (*FXN*; *FRDA*), which encodes a mitochondrial protein involved in the assembly of iron-sulfur clusters that are essential to mitochondrial energy production.

FXN deficiency leads to degeneration of the spinal cord, resulting in progressive loss of motor function in the limbs, scoliosis, impaired vision and hearing, and speech problems. *FXN* deficiency also causes iron overload in cardiac mitochondria and impairs bioenergetics, thus contributing to heart failure.

There are no disease-modifying therapies to treat FRDA. Instead, disease management can include physical therapy to aid motor control, surgery to correct scoliosis and angiotensin-converting enzyme (ACE) inhibitors or other drugs that treat heart failure.

Thus, a team led by Hélène Puccio set out to test whether an adeno-associated virus serotype 10 (AAV10) vector encoding human *FXN* could treat cardiomyopathy in conditional *Fxn* knockout models of FRDA.

Puccio is director of **Institut National de la Santé et de la Recherche Médicale** (INSERM) research and head of the Department of Translational Medicine and Neurogenetics at the **Institute of Genetics and Molecular and Cellular Biology**.

In 2001, a group led by Puccio developed a conditional *Fxn* knockout mouse model—*Fxn*^{-/-} mice are nonviable because of embryonic lethality—that recapitulated key features of human FRDA, including cardiomyopathy and large sensory neuron dysfunction.²

In 2012, a team led by Ronald Crystal, chair of genetic medicine and a professor of internal medicine at **Weill Cornell Medical College**, showed that AAV10 exhibited significant tropism for the heart and liver—and to a lesser degree the dorsal root ganglia (DRG)—of nonhuman primates.³

The two groups connected after Crystal began collaborating on a different AAV-related project with Patrick Aubourg, who was familiar with Puccio's work on the *Fxn* knockout models.

Aubourg is co-director of INSERM's research unit at Le Kremlin-Bicêtre and head of pediatric neurology at the **University Hospital of Bicêtre** and the **University of Paris-Sud**.

The new team was led by Puccio and included Crystal and Aubourg. The group showed that prophylactic i.v. injection of the AAV10-*FXN* therapy in the mouse models, before the onset of cardiomyopathy, prevented the mitochondrial proliferation and iron accumulation in cardiomyocytes, left ventricular hypertrophy (LVH), loss of cardiac function and death from heart failure that were seen in untreated mice.

In models showing the first signs of cardiomyopathy, the gene therapy decreased mitochondrial proliferation and levels of iron deposits in cardiomyocytes, decreased LVH and cardiac fibrosis and increased cardiac function and survival compared with no treatment.

"Our study demonstrates that frataxin-deficient cardiomyocytes have severe mitochondrial dysfunction but retain the capacity to recover rapidly once their levels of frataxin are normalized," Aubourg told SciBX. This in turn suggests "that the cardiomyocytes of Friedreich's ataxia patients are still present and could be rescued" with the gene therapy.

The team included a researcher from the **University of Strasbourg**. Data were reported in *Nature Medicine*.

Heartfelt delivery

Last year, Aubourg, Puccio and Crystal cofounded AAVLife to develop the AAV10-*FXN* gene therapy. Last week, the company raised \$12 million in a series A round to help fund a Phase I trial. AAVLife expects to begin the trial in 2015.

"This is an exciting therapy that we would want to see in the clinic," said Guy Miller, chairman and CEO of **Edison Pharmaceuticals Inc.** "Even though it doesn't affect CNS symptoms of Friedreich's ataxia, reversing the cardiomyopathy is reason enough to move it forward. On a scale of 1–10, we give it a 20."

Edison has two compounds in the clinic to treat FRDA. Vatiquinone (EPI-743), an oral small molecule targeting NAD(P)H dehydrogenase quinone 1 (NQO1; QR1) that augments endogenous glutathione biosynthesis, is in Phase IIb testing. EPI-A0001, a coenzyme Q10 analog that enhances electron flux and increases ATP synthesis, is in Phase IIa trials.

Susan Perlman agreed. "Improving cardiac function would be a great help in increasing energy levels and endurance in these patients, which would certainly improve their quality of life," she said.

Perlman is a clinical professor of neurology, director of the Ataxia Center and director of the **Huntington's Disease Society of America's** Center of Excellence at the **University of California, Los Angeles**.

"The study results are impressive and highlight a promising therapeutic approach for a difficult disease," but the findings would need to be confirmed in larger animals such as pigs, whose hearts are similar in size to humans, said Hina Chaudhry, an associate professor of medicine and director of cardiovascular regenerative medicine at the **Icahn School of Medicine at Mount Sinai**.

Chaudhry also is the founder of **VentriNova Inc.**, which has VN-100, an adenoviral vector encoding *cyclin A2* (*CCNA2*), in preclinical development to treat myocardial infarction (MI).

Chaudhry and Perlman also said that additional studies will have to determine the safety of the therapy.

Perlman wanted to see follow-on studies of the treated mice to examine the effects of the therapy on tissues outside the heart. “Viral vector-based therapies have a risk of carrying their gene payloads to cells and tissues where they might prove harmful,” she said.

Roger Hajjar agreed that the effects of overexpressing *FXN* in liver and other organs were unclear. Also, “AAV10 is a relatively new vector and gene therapy; investigators have little experience in its use in the heart,” he said. “Its safety profile and efficacy as a vector in cardiac tissue need to be established.”

Thus, he would have liked to see the team use an empty AAV10 vector or one encoding a nontherapeutic marker protein as a control in the mouse models.

Hajjar is a professor of medicine in cardiology at **Mount Sinai Hospital** and director of the Cardiovascular Research Center at the Icahn School of Medicine. He also is a cofounder and scientific advisory board member of **Celladon Corp.**

Celladon and **AmpliPhi Biosciences Corp.** are developing Mydicar (AAV1/SERCA2a), a recombinant AAV vector encoding *ATPase Ca⁺⁺ transporting cardiac muscle slow twitch 2* (*ATP2A2*; *SERCA2A*) that is in Phase II testing to treat heart failure and in preclinical development to treat hypertension. Celladon also has CDN1163, a small molecule targeting SERCA enzymes, in preclinical development to treat diabetes and cardiovascular and neurological diseases.

Hajjar and Perlman said that the benefits of the gene therapy in treating cardiomyopathy in patients with FRDA clearly outweighed any potential risks associated with the vector or overexpression of *FXN* outside the heart.

“Since *frataxin* is expressed at low levels in all cell types, we are not worried about off-target effects,” said Amber Salzman, cofounder and CEO of AAVLife.

Crystal added that AAVLife plans to test the efficacy and safety of direct cardiac injection—not i.v. injection—of the therapy in pigs. “The issue will be whether we can genetically modify 40%–50% of cardiomyocytes, which we think will be sufficient” to prevent or treat cardiomyopathy in FRDA, he said.

The team will explore the number, size and spatial separation of direct cardiac injections of the AAV10-*FXN* therapy necessary to modify that fraction of cells in healthy pigs because there are no pig models of FRDA, he said.

Salzman added that the studies in pigs will compare two types of direct cardiac injection—into the myocardium and into coronary veins—to determine which route can modify the desired 40%–50% of cardiomyocytes.

“Our concern is that coronary injection will not get us there because the therapy will pass through the heart and get taken up by the liver,” she said. “We don’t want to have an overload of the vector in the liver because that could present a safety risk at high doses.”

Conversely, Chaudhry said that “as long as excess *frataxin* expression in the liver and other organs isn’t a problem, I think i.v. injection would be the way to go with this therapy” because direct cardiac injection is more complicated and invasive than i.v. injection.

In addition, she said, using a cardiac-specific promoter with the AAV10-*FXN* therapy could enhance the safety of i.v. injection by preventing unwanted expression of the gene outside the heart.

All the nerve

In addition to investigating the safety and delivery routes of the AAV10-*FXN* gene therapy, Perlman and Miller wanted to know whether it could be adapted to treat the neurological symptoms of FRDA.

“The team reported that the AAV10 vector not only has tropism for the heart but also for specific cell types in the CNS, including the DRG, that are among the primary sites of neuropathology in the disease,” said Jennifer Farmer, executive director of the **Friedreich’s Ataxia Research Alliance** (FARA). “The team also reported that they were able to detect expression of the *FXN* transgene in several CNS cell types in the mouse models.”

FARA provided funding for the *Nature Medicine* study.

“I hope that similar benefits with a gene therapy targeting the spinal cord or cerebellar structures of the CNS can be demonstrated” in mouse models with neurological symptoms of FRDA, Perlman said.

“A key question now is how to develop an analogous vector that would target the CNS to ameliorate neurological symptoms of Friedreich’s ataxia,” Miller said.

Crystal agreed that “the challenge with the nervous system is getting gene therapy into the right cells—especially the spinal cord and cerebellum. But we are working on a CNS-specific version of the gene therapy.”

Those studies will use a neurological mouse model of FRDA developed by the team, Aubourg said. “We will also use nonhuman primates to assess the best and safest route of vector delivery to target the populations of neurons in DRG, the spinal cord and cerebellum that are affected by the disease.”

But first, he said, the team is completing dose-response studies of the gene therapy in the cardiomyopathic mouse models, planning the studies of the therapy in healthy pigs and planning studies to confirm the cardiac tropism of the AAV10 vector in nonhuman primates.

Crystal and Farmer said that FARA would assist with patient recruitment once the therapy is ready for the clinic.

According to Aubourg, INSERM and **Cornell University** have filed a patent application covering the findings reported in *Nature Medicine*.

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COMPANIES AND INSTITUTIONS MENTIONED

AAVLife, Paris, France

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