MedicalXpress

Scientist develops gene therapy for muscle wasting

July 27 2016, by Seth Truscott

A discovery by Washington State University scientist Dan Rodgers and collaborator Paul Gregorevic could save millions of people suffering from muscle wasting disease.

The result of the team's four-year project is a novel gene therapeutic approach. The work was published July 20 in *Science Translational Medicine*, a journal of the American Association for the Advancement of Science.

"Chronic disease affects more than half of the world's population," said Rodgers, professor of animal sciences and director of the Washington Center for Muscle Biology. "Most of those diseases are accompanied by muscle wasting.

"It occurs with chronic infection, muscular dystrophy, malnutrition and old age," he said. "About half the people who die from cancer are actually dying from muscle wasting and there's not one single therapy out there that addresses it.

Family history inspires search for treatment

"I have a strong motivation to do something about this, to do more than simply publish results," said Rodgers, who teamed with Gregorevic of Baker IDI Heart and Diabetes Institute in Australia. "My father died from cachexia," the wasting disease caused by cancer, "and my nephew

has Duchenne muscular dystrophy, an incurable, fatal disease that could claim his life in his teens.

"Others have tried and failed to develop treatments for muscle wasting," Rodgers said, "and some drugs have even caused serious safety problems. Our targeted approach only affects muscle and completely avoids these problems, which is why we think we have a solution."

In the paper, lead author Catherine Winbanks, a postdoctoral fellow of Gregorevic, details how researchers built muscle in healthy mice and prevented the loss of skeletal and heart muscle in mice with tumors.

Hormone's muscle-wasting effect blocked

In cachexia, tumors secrete hormones that cause muscle deterioration; in effect, the body eats its own muscles, causing weakness, frailty and fatigue.

"What kills a lot of people isn't the loss of skeletal muscle but heart muscle," said Rodgers. "The heart literally shrinks, causing heart failure."

Researchers have long sought to stop this process, but failed to find a safe way. That's because the hormones that cause wasting - in particular, a naturally occurring hormone called myostatin - play important roles elsewhere in the body.

Rodgers and Gregorevic needed a way to stop myostatin, but only in muscles. Their solution: an adeno-associated virus - a benign virus that specifically targets heart and skeletal muscle.

The virus delivers a small piece of DNA - a signaling protein called Smad7 - into muscle cells. Smad7 then blocks two signaling proteins

called Smad2 and Smad3, which are activated by myostatin and other muscle-wasting hormones. By blocking those signals, Smad7 stops the breakdown of muscles.

"Smad7 is the body's natural break and, by inhibiting the inhibitor, you build muscle," Rodgers said.

For cachexia patients, such a therapy could massively increase their chances of survival.

"Instead of having one year to fight cancer, you'd have 10 or 15," Rodgers said.

Startup works to develop commercial drug

In 2015, Rodgers launched AAVogen, a company that will develop this discovery into a commercial drug, AVGN7.

He has been working with Norman Ong, a technology licensing associate at WSU's Office of Commercialization, on patents, startup funding and recruitment for AAVogen. Using the funds from WSU's commercial gap fund award, Rodgers' lab will determine the minimum effective dose for AVGN7.

"We want to turn WSU discoveries into real-world uses that benefit the public," said Ong. "Dan is a very busy scientist, so we're proud to help him and AAVogen connect with the right people."

"I formed this company for one purpose: to move the science into society, to see it applied," Rodgers said. "WSU's Office of Commercialization has been instrumental and invaluable to this endeavor.

"Now we have a company with the potential to save a lot of lives," he said.

More information: C. E. Winbanks et al, Smad7 gene delivery prevents muscle wasting associated with cancer cachexia in mice, *Science Translational Medicine* (2016). DOI: 10.1126/scitranslmed.aac4976

Provided by Washington State University