DUX4 partnership

By Lauren Martz, Staff Writer

Researchers at the **Fred Hutchinson Cancer Research Center** have identified a mutation that induces expression of the transcription factor *double homeobox 4* and could be targeted in facioscapulohumeral muscular dystrophy.¹ Based on this and previous research, the team has partnered with **GlaxoSmithKline plc** to develop small molecule inhibitors against this target, or its downstream effectors, to treat the disease.

The collaboration is the company's third partnership as part of the Discovery Partnerships with Academia program and the first with a U.S.-based institution.

Facioscapulohumeral muscular dystrophy (FSHD) is an inherited disease that causes muscle weakness and loss of function beginning in the muscles of the face and upper extremities. Although researchers have started to uncover FSHD's genetic causes and underlying mechanisms, there are no approved therapeutics to treat or even slow disease progression.

In 2009, a Fred Hutchinson group led by Stephen Tapscott found that mutations causing expression of *double homeobox 4* (*DUX4*) mRNA and protein in skeletal muscle tissues could be responsible for FSHD pathology.² *DUX4* is a transcription factor that normally is expressed in germline tissues and repressed in somatic tissues.

Tapscott, a member of the Division of Human Biology at Fred Hutchinson and professor of neurology at the **University of Washington**, built on work from a group at **Leiden University**. In 1990, the Leiden team mapped FSHD to a mutation in chromosome 4q.³ Three years later, the same group found that the mutation caused a reduction in the number of *D4Z4* macrosatellite repeat units in the subtelomere of the chromosome.⁴

Whereas healthy individuals express 11–100 unit repeats of *D4Z4*, patients with FSHD express 1–10.

The Hutchinson team showed that *D4Z4* represses transcription of *DUX4* in somatic tissues of healthy controls. When fewer *D4Z4* repeats are expressed than normal—as is the case in most patients with FSHD—*DUX4* repression is lower than that in healthy individuals, leading to decreased levels of *DUX4* mRNA and protein expression in skeletal muscle.

In the current paper, published in late 2012, the team found that a mutation in *structural maintenance of chromosomes flexible hinge domain*

containing 1 (*SMCHD1*) decreased epigenetic repression of *DUX4* in somatic tissues compared with no mutation and thus helped cause the disease.

Tapscott and his team identified mutations in *SMCHD1* that reduce protein levels and cause *D4Z4* CpG hypomethylation. They found that a subset of patients with FSHD, classified as patients with FSHD2, carry mutations in *SMCHD1* that cause *DUX4* expression despite normal numbers of *D4Z4* repeat units.

Data were published in *Nature Genetics*.

Prior to this study, Tapscott and colleagues also used *in vitro* models of FSHD based on their mechanistic data in order to examine the link between *DUX4* expression and disease pathology. Indeed, expression of *DUX4* in the FSHD model upregulated genes involved in RNA processing, ubiquitin pathways and immunity.⁵ These upregulated genes could be new targets to help treat the disease.

GSK collaboration

Based on the new mechanistic insights, the next steps for the Hutchinson team are to choose the best target and develop a therapeutic. To do so, Tapscott partnered with GSK under the pharma's first Discovery Partnerships with Academia (DPAC) collaboration with a U.S.-based institution.

DPAC started in 2011 and involves partnerships with academic researchers to develop early stage projects and facilitate their translation to the clinic by combining academic expertise with GSK's drug discovery and development capabilities.

Under the DPAC agreements, GSK provides financial support for a project based on the achievement of milestones, and the academics are eligible for royalties.

GSK already has formed DPAC collaborations with academics from the

University of Cambridge and the **University of Dundee**.

Tapscott's team will work with GSK to identify new small molecule therapeutics for FSHD. He told *SciBX* that they will be testing both direct inhibitors of *DUX4* and inhibitors of the transcription factor's downstream targets.

"We know many of the genes regulated by *DUX4*, and they suggest different possible mechanisms for the disease. Future work will need to determine which of the candidate mechanisms are dominant contributors to the disease phenotype, and those could be targeted individually," he said.

Tapscott said a therapeutic that blocks *DUX4* or its downstream targets should be able to treat most, if not all, patients with FSHD. "These are the only known genetic causes for the condition, and we know that while there may be other causal factors, these mutations account for the vast majority of cases," he said.

He added, "It is also important to note that both *DUX4* and *SMCHD1* mutations are involved in the same pathway, so if there is

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Fred Hutchinson Cancer Research Center**

another mutation responsible for the disease, it would also most likely be expressed in this pathway. These patients should also respond to a drug developed to block the pathway.”

Additionally, Tapscott said, “inhibitors of DUX4 should prevent disease progression if our model of the disease is correct.” He said that the patent status of the work and any development timelines are undisclosed. GSK declined to comment.

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COMPANIES AND INSTITUTIONS MENTIONED

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