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Proteoglycans on the knee

By Tim Fulmer, Senior Writer

Baylor College of Medicine researchers have shown that delivering the gene encoding proteoglycan 4 directly to the knee prevented and treated osteoarthritis in mice.[1] **GeneQuine Biotherapeutics GmbH** has exclusively licensed the findings and is developing a similar gene therapy to treat osteoarthritis in animals and patients.

Proteoglycan 4 (PRG4; HAPO) is a protein secreted by joint cartilage cells that helps synovial fluid dissipate joint strain. Loss-of-function mutations in PRG4 cause early onset osteoarthritis (OA) associated with the rare condition camptodactyly-arthropathy-coxa vara-pericarditis syndrome.[2] *Prg4* knockout leads to early development of OA in mice.[3,4]

Based on those prior results, the Baylor team hypothesized that increasing levels of PRG4 in knee cartilage might help protect against or treat OA associated with aging and traumatic injury, the two most common forms of the disease. The team was led by Brendan Lee, professor and chair of molecular and human genetics.

The researchers first generated mice that overexpressed *Prg4* in cartilage cells. At 10 months, the animals had lower levels of markers of cartilage hypertrophy and degradation and overall lower OA severity than their equally aged wild-type counterparts.

The team next subjected the *Prg4*-overexpressing mice to knee cruciate ligament transection to generate a model of post-traumatic OA. The resulting animals showed less overall OA development following injury than similarly injured wild-type controls.

To translate the genetic overexpression findings into a potential therapy, the researchers tested direct delivery of *PRG4* to the knee in mice. Because long-term expression of *Prg4* might be needed to treat a potentially chronic condition like OA and a recombinant protein could have a short half-life in knee tissue, the researchers relied on gene therapy to deliver a gene overexpressing recombinant *Prg4*.

They used a helper-dependent adenoviral vector (HDV) to deliver the gene because HDVs trigger a mild host immune response compared with first-generation adenoviral vectors, which can trigger a potent immune reaction. HDVs may therefore be better for long-term expression of a recombinant protein.[5]

In mice, intra-articular injection of the HDV-Prg4 gene therapy protected joints from development of OA following injury.

Results were published in *Science Translational Medicine*.

Getting a leg up

The Baylor researchers will next study the HDV-Prg4 construct in a horse model of OA, corresponding author Lee told *SciBX*.

That model "is much more meaningful than mouse models since equine joint volumes are closer to human ones and clinical parameters such as lameness, pain and joint effusion can be determined," said coauthor Kilian Guse, a former postdoctoral researcher in Lee's lab and CEO and cofounder of GeneQuine.

Lee said the Baylor researchers also plan to build on the paper's findings by using HDV technology to deliver *PRG4* in combination with other proteins that may show efficacy in OA, such as *IL-1 receptor antagonist* (*IL-1RA*). "We must approach OA like treating cancers or infectious disease using combinatorial therapy" because the pathogenesis of OA is multifactorial, he said.

In 2011, Guse founded GeneQuine to develop OA therapies. The company is developing the gene therapy approach to treat animals before going into patients. "We will first focus on horses and dogs since regulatory requirements for veterinary drugs are significantly lower and, therefore, development is markedly cheaper and faster," said Guse.

> **"High levels of therapeutic protein can be achieved in joints over a long period of time after a single injection of vector."**
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> ***—Kilian Guse, GeneQuine Biotherapeutics GmbH***

GeneQuine's lead gene therapy product for humans, GQ-203, is in preclinical development to treat OA. The construct uses the HDV platform but delivers an undisclosed therapeutic gene distinct from the *Prg4* gene used in the paper, said Guse.

The company thinks gene therapy is ideal for OA because "high levels of therapeutic protein can be achieved in joints over a long period of time after a single injection of vector," Guse told *SciBX*.

GeneQuine has an exclusive worldwide license from Baylor to HDVs for the delivery of therapeutic genes and is in the process of licensing the *PRG4*-expressing vector from Baylor, said Guse.

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COMPANIES AND INSTITUTIONS MENTIONED

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