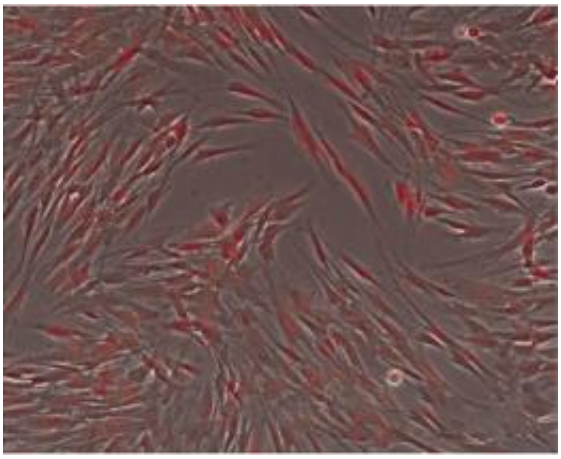
Study describes first proof of principle for treating rare bone disease

November 7 2011



Microscopic image of tooth-derived stem cells from an FOP patient acquired through the "Good Tooth Fairy" program at the Perelman School of Medicine at the University of Pennsylvania. Credit: Josef Kaplan. PhD, Perelman School of Medicine, University of Pennsylvania

(Medical Xpress) -- Scientists at Penn's Perelman School of Medicine Center for Research in FOP and Related Disorders have developed a new genetic approach to specifically block the damaged copy of the gene for a rare bone disease, while leaving the normal copy untouched.

Lead author Josef Kaplan, PhD, postdoctoral fellow; and senior authors Eileen M. Shore, PhD, and Frederick S. Kaplan, MD, both from the Department of Orthopaedic Surgery, published this new proof-of-

principle approach for treating the disease, called FOP, in the online edition of Gene Therapy.

FOP, fibrodysplasia ossificans progressiva, is a rare genetic disorder of progressive extra bone formation for which there is presently no cure. It is caused by a mutation in the gene for ACVR1/ALK2, a bone morphogenetic protein (BMP) receptor that occurs in all classically affected individuals. Individuals who have FOP harbor one normal copy and one damaged copy of the ACVR1/ALK2 gene in each cell. The mutation increases the amount of BMP in cells to greater than normal levels, which initiates the transformation of muscles and cartilage into a disabling second skeleton of bone.

Using a special type of RNA molecule engineered to specifically silence the damaged copy of the gene rather than the normal copy -- a process known as RNA interference, or RNAi -- the scientists restored the cellular function caused by the FOP mutation by ridding cells of the mutant ACVR1/ALK2 mRNA. Cells were essentially left with only normal copies of ACVR1/ALK2 mRNA, thus adjusting the protein's activity to normal, similar to that of cells without the FOP mutation.

The human cells used in the experiments were adult stem cells obtained directly from discarded baby teeth donated by FOP patients. These contained the exact combination of damaged and normal ACVR1/ALK2 receptor proteins found in all classically affected FOP patients worldwide. The discarded teeth were obtained from FOP pediatric patients and normal controls, usually non-affected siblings, in the ongoing "FOP Good Tooth Fairy Program."

The authors caution that the utility of the RNAi approach must be confirmed in mouse models of classic FOP prior to its consideration for human use. Additionally, other hurdles stand in the way of human application at the present time, most notably safe delivery of the small

RNA molecules to cells in the human body.

The authors acknowledge that they have a long way to go, but have taken a big first step. “Improvements in RNAi design are advancing at a rapid rate and will enhance the stability, potency, and specificity of inhibitory RNAs, allowing for long-term experiments both in vitro and in vivo,” says Shore.

Provided by University of Pennsylvania School of Medicine