Novel target for the promotion of healthy cartilage in osteoarthritis

Key benefits

- Novel experimental treatment that eliminates pain and reverts structural changes in a murine model of osteoarthritis
- Unique therapeutic potential: non-redundant target with limited expression in adult tissues offering the advantage of fewer side effects compared to current anti-inflammatory therapies
- Inhibition of the proposed novel target can be developed into an effective therapy that can cure the cause of osteoarthritis, unlike current treatments that only ameliorate symptoms

Background

Osteoarthritis (OA) is a debilitating joint disease characterized by breakdown of the articular cartilage and bone changes, including thickening of the bone supporting the cartilage and excessive bone formation at the margins of the joint (osteophytes).

The Problem

There are no disease modifying therapies to treat the cause of osteoarthritis. Current treatment consists of symptom management with non-steroidal-inflammatory drugs, eventually joint replacement\(^1\). Hence, there is an urgent unmet need for a new therapeutic approach targeting and resolving the etiology of the disease.

The solution

- A novel cell-surface receptor specifically upregulated in cartilage as a result of local inflammation and mechanical stress, expressed in minimal level in physiological condition.
- Blockage of this receptor promotes cartilage repair which correlates with sustained pain relief, Fig 1A and 2A

Cartilage repair is achieved by:

Preventing cartilage degradation
- inhibition of expression of key cartilage degrading enzymes
- reduction in cartilage breakdown in vivo, Fig. 2A

Inducing cartilage formation
- in vitro chondrogenic differentiation of a mesenchymal stem cell line
- reduction in pathological growth of the medial tibia, Fig. 1B
- increase in size and differentiation of human cartilage organoids, Fig 3

We are seeking collaborators to develop preclinical studies to progress towards clinical trials and develop a new therapeutic approach.

Fig. 1. siRNA-silencing treatment of skeletally mature mice with surgically-induced meniscocartilage injury (MCI) to one hind limb resulted in significantly reduced pain on weight bearing as compared to control mice (A) and prevention of pathological growth of the medial tibia (B)

\(^1\) NICE. (2012). Centre for Clinical Practice
Additional results

- si-RNA silencing of the target receptor in-vivo reduces cartilage breakdown in the meniscal/ligamentous injury model of osteoarthritis

Fig 2. Degradation of glycosaminoglycans (GAGs, which have a primary role in regulating and supporting cartilage formation) contribute to the reduction of tibial cartilage, which is considered an early feature in developing OA.
A) A significant reduction in degradation of GAGs was observed in skeletally mature mice injected with siRNA inhibiting the target receptor. B) Correlation between density of the cartilage and percentage of body weight carried on the limb with meniscal/ligamentous injury: The extent of cartilage breakdown correlates with pain.

- Target receptor silencing supports formation of human cartilage organoids in vivo

Fig 3. Human articular chondrocytes form cartilage organoids when implanted ectopically in nude mice. RNA-silencing of the target receptor resulted in significantly increased GAG content in human cartilage organoids.

Link to inventor’s website: [http://www.whri.qmul.ac.uk/staff-all/staff-research/220-dell-accio-francesco](http://www.whri.qmul.ac.uk/staff-all/staff-research/220-dell-accio-francesco)