A Novel Disease Modifying Therapeutic for Osteoarthritis

BACKGROUND

Osteoarthritis (OA) affects 1 in 3 people who are aged 45+ in the UK (almost 9 million) and 50% of those aged over 65 worldwide.

The major pathological feature of OA is the loss of cartilage leading to impaired joint function (e.g. in the knee, hip and hand) and pain; ~25% of patients are unable to perform major activities of daily living.

There are no disease modifying therapies for OA and current treatments are limited to pain relief and surgical intervention - primarily joint replacement. Osteoarthritis patients are having joint replacements at ever-younger ages, necessitating greater numbers of revision surgeries that typically have poorer outcomes.

There is a pressing need for new treatments that can slow, halt or reverse the OA disease process and, thereby, eliminate or delay the requirement for joint replacement.

We are developing a protein-based biological (Link_TSG6) that has both disease modifying and analgesic properties in models of OA.

Arthritis Research UK, a charity dedicated to transforming the lives of people with arthritis, is supporting us with our efforts to progress our therapeutic to the clinic.

THE TECHNOLOGY - Link_TSG6

- TSG-6 is a multi-functional protein that is expressed during inflammation and protects tissues from inflammatory damage; see https://doi.org/10.1016/j.matbio.2018.01.011
- Many of the tissue-protective and immunomodulatory properties of mesenchymal stem cells (MSCs) are mediated by their production of TSG-6.
- Our focus is on the 11 kDa Link module from human TSG-6 (termed Link_TSG6).

We have discovered that Link_TSG6 has a unique combination of activities. It is:
- Chondroprotective
- Analgesic
- Anti-inflammatory
- Anti-resorptive
Link_TSG6 is a potential disease-modifying and pain-relieving therapeutic for osteoarthritis and other musculoskeletal indications.

Chondroprotective and analgesic effects:

- A hallmark feature of osteoarthritis is the loss of cartilage extracellular matrix
  - This occurs via (i) proteolytic breakdown of aggrecan by aggrecanase enzymes (ADAMTS4 and ADAMTS5) and (ii) irreversible damage to the collagen network by the collagenase MMP13.
- Link_TSG6 dose-dependently inhibits cytokine-induced and spontaneous aggrecan breakdown in cartilage explants from OA patients.
- Link_TSG6 inhibits cytokine-induced expression of aggrecanase and collagenase enzymes by human chondrocytes, e.g. reducing MMP13 to background levels.
- Link_TSG6 treatment reduces cartilage damage and pain in a rat model of surgically-induced OA, where these chondroprotective and analgesic effects are independent of each other.

Anti-inflammatory effects:

- OA is a disease of the whole joint, with synovial inflammation being a common feature.
- Expression of TSG-6 during inflammation suppresses pro-inflammatory pathways, i.e. providing endogenous tissue protection.
- TSG-6 is the first soluble chemokine-binding protein to be identified in mammals.
- Link_TSG6 has potent anti-inflammatory effects via its interactions with chemokines (e.g. CCL2, CCL5 and CXCL8) and the modulation of their activities.

Anti-resorptive effects:

- Altered bone turnover is a feature of OA, with pathological changes to the subchondral bone occurring early in the disease process.
- Link_TSG6 treatment inhibits bone breakdown in a mouse model of post-menopausal osteoporosis by impairing osteoclast adhesion to the bone matrix, rather than by inhibiting osteoclast formation.
- Unlike other anti-resorptive agents, Link_TSG6 does not suppress bone formation and does not perturb the normal cycle of bone remodelling.
- Thus, Link_TSG6 could likely be used long-term without deleterious effects on bone.
KEY BENEFITS

• We have a body of data showing that Link_TSG6 has a unique combination of activities (chondroprotective, analgesic, anti-inflammatory and anti-resorptive) relevant to the treatment of OA and other forms of musculoskeletal disease.
• We have a well-developed, scalable method for cost-effective production of the Link_TSG6 protein.
• We have identified solution formulations where Link_TSG6 is highly stable.

APPLICATIONS

• The technology is being developed as a biological therapeutic.
• Our target indication for Link_TSG6 is osteoarthritis since there is a lack of disease-modifying drugs for this disease.
• There is also scope to treat other musculoskeletal indications (e.g. osteoporosis and rheumatoid arthritis) as well as a broad-range of inflammatory and age-related conditions.

INTELLECTUAL PROPERTY

We have granted patents in Europe, Japan and USA that cover the use of Link_TSG6 as a treatment for bone disorders and osteoporosis (EP2001499 B1, JP_5346216_B2, US 9,066,908).

A ‘continuation in part’ to our US patent, covering the use of Link_TSG6 for osteoarthritis (application No. 14/481841) is due to grant in 2018.

All intellectual property is wholly owned by The University of Manchester.

OPPORTUNITY

The technology will be of interest to biotechnology and pharmaceutical companies. We would like to collaborate with an industry partner for further preclinical and clinical investigations with a view to licensing the technology.

CONTACT

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