

## A Novel Disease Modifying Therapeutic for Arthritis

### BACKGROUND

Osteoarthritis (OA) is the most common form of arthritis worldwide. It affects almost 9 million people aged 45+ in the UK and is one of the 10 most disabling diseases affecting developed countries worldwide. The World Health Organization estimates that 9.6% of men and 18% of women aged over 60 years have symptomatic OA.

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.

Multiple factors can contribute to the development of osteoarthritis; for example age, gender, obesity, genetic factors and prior joint injury or joint disease, such as gout or rheumatoid arthritis.

There is no disease modifying therapy 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, both impairing an active lifestyle and necessitating greater numbers of revision surgeries, which typically have poor outcomes.

Therefore 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.

### THE TECHNOLOGY - Link\_TSG6

- TSG-6, the 35 kDa secreted protein product of TNF-Stimulated Gene-6, is a multi-functional protein that is expressed in response to inflammatory mediators and protects tissues from inflammatory damage.
- TSG-6 is composed of two protein domains (modules).  
**Our focus is on the 11 kDa Link module from human TSG-6 (Link\_TSG6).**
- Link\_TSG6 mediates binding to polysaccharides (hyaluronan and sulphated glycosaminoglycans), protein components of the extracellular matrix and signalling molecules (e.g. chemokines).



We have discovered that Link\_TSG6 has a unique and potent combination of activities. It is:

- Chondroprotective
- Anti-inflammatory
- Anti-resorptive

**Link\_TSG6 is a potential disease-modifying therapeutic for arthritis**

#### Chondroprotective effects:

- A hallmark feature of arthritis is the loss of cartilage extracellular matrix
  - In OA, this occurs via (i) proteolytic breakdown of aggrecan by ADAMTS4 and ADAMTS5 (aggrecanase enzymes) and (ii) irreversible damage to the collagen network by the collagenase MMP13.
- We have identified a new chondroprotective mechanism for TSG-6, whereby it inhibits cytokine-induced expression of the proteases ADAMTS4, ADAMTS5 and MMP13 by human chondrocytes
- **Link\_TSG6 is more potent than the full-length protein**, e.g. it reduces MMP13 gene expression to background levels.
- Link\_TSG6 inhibits cytokine-induced aggrecan breakdown in cartilage explants from OA patients.
- **Link\_TSG6 reduces cartilage damage and pain** in a rat model of surgically-induced OA.

#### Anti-inflammatory effects:

- OA is a disease of the whole joint, with synovial inflammation being a common feature of the disease.
- TSG-6 is secreted by neutrophils (and other cell types) in response to inflammation, forming part of an endogenous anti-inflammatory feedback loop.
- **Link\_TSG6 is a potent inhibitor of neutrophil migration *in vivo* via its binding to the chemokine CXCL8.**

#### 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 inhibits bone breakdown in a mouse model of osteoporosis by impairing osteoclast adhesion to the bone matrix, rather than by inhibiting osteoclast formation.
- **Unlike other anti-resorptives, Link\_TSG6 does inhibit bone formation.**

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## KEY BENEFITS

- We have a body of *in vivo*, *ex vivo* and *in vitro* data showing that Link\_TSG6 has a unique combination of activities (chondroprotective, anti-inflammatory and anti-resorptive) relevant to the treatment of OA and other forms of arthritis.
- We have a well-developed, scalable method for Link\_TSG6 production in *E. coli*.

## APPLICATIONS

- The technology is being developed for therapeutic application.
- Our ultimate goal is to develop Link\_TSG6 as a treatment for osteoarthritis (OA) as there is a complete lack of disease-modifying drugs for OA.
- However, there is also scope to target mono-arthritis, rheumatoid arthritis and septic arthritis.

## INTELLECTUAL PROPERTY

A 'continuation in part' application has been filed in the US on 9/9/14 (Application Serial No. 14/481841) to our granted US patent application on the use of TSG-6 for the treatment of bone loss (which has also been granted in Europe and Japan). 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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