NOVEL TREATMENT FOR OSTEOSPOROSIS

BACKGROUND

Osteoporosis, which affects a large proportion of the elderly population, frequently results in fragility fractures due to uncontrolled bone loss; 50% of women and 20% of men over the age of 50 will experience an osteoporosis-related fracture during their lifetime. This severely impacts on quality of life and 20-30% of hip fractures lead to death within 12 months. Although a number of effective treatment options are available (e.g. bisphosphonates, strontium ranelate and teriparatide), none of these is ideal due to issues such as intolerance and inconvenient dosing regimes. Furthermore, the long-term use of existing therapies is not advised (e.g. due to over-suppression of bone loss that can result in atypical fractures) and sequential use of multiple drugs is recommended. Thus, there is a pressing need for new treatments to enable the effective management of osteoporosis over many decades in an aging population.

Bone loss in osteoporosis arises from an age-related shift in the balance of normal bone remodeling to favour bone degradation (by osteoclasts) over bone formation (by osteoblasts). Controlling the activity of osteoclasts is, therefore, an important target in the development of anti-osteoporotic drugs. Our research has revealed that a human protein, TSG-6, which is produced at sites of inflammation and has anti-inflammatory properties, is also a novel and potent inhibitor of bone resorption by osteoclasts. The properties of this protein make it an attractive candidate for the treatment of osteoporosis and other conditions associated with bone loss.

THE TECHNOLOGY

We have identified the human TSG-6 protein (typically expressed in response to inflammatory stimuli such as TNF) as a novel and potent inhibitor of bone resorption by osteoclasts. TSG-6 is, thus, applicable to the development of improved treatments for conditions associated with bone loss.

Using a cell culture system, where osteoclast precursors undergo differentiation and activation in response to the protein RANKL, we have shown that TSG-6 substantially inhibits bone erosion in a dose-dependent manner (see Figure 1; Mahoney et al., 2008). Our data suggest that TSG-6 does not prevent osteoclasts from forming, but acts at the point of osteoclast activation; TSG-6 inhibits the formation of F-actin rings, which are associated with the attachment of osteoclasts to the bone surface (see Figure 2; Mahoney et al., 2011). Furthermore, we have shown that TSG-6 can significantly reduce bone loss in a mouse model of post-menopausal osteoporosis.
We have well-established protocols for the expression and purification of recombinant human TSG-6 (both the full-length protein and individual domains). We are working towards the development of a GMP-compliant E. coli-based system that will allow scale-up of protein production for pre-clinical evaluation and clinical trials.

APPLICATIONS

This technology is relevant to the development of a novel treatment for osteoporosis and other diseases associated with abnormal rates of bone erosion, e.g. Paget’s disease, periodontal disease, bone cancers and bone lesions associated with metastatic cancer. It could also have applications in improved bone fracture healing (e.g. in the elderly) and in aseptic loosening of joint replacements.

KEY BENEFITS

TSG-6 represents an excellent target for the development of a novel treatment for osteoporosis, with the advantages of anti-inflammatory and other beneficial (e.g. chondroprotective) activities in addition to its potent inhibition of bone resorption. Importantly, TSG-6 has been found to be an autocrine

Figure 1: Recombinant human TSG-6 (rhTSG-6) inhibits bone resorption by human primary osteoclasts. Peripheral blood mononuclear cells (PBMCs) were cultured with RANKL and M-CSF, in the absence or presence of rhTSG-6 for 21 days on dentine slices (as a model of bone). Data are expressed as mean percentage lacunar resorption (n=9) ± S.E.M, compared to RANKL/M-CSF alone, where **, *** = p < 0.01, p < 0.001 respectively; for further details see Mahoney et al., 2008.

Figure 2: TSG-6 inhibits osteoclast activation by preventing F-actin ring formation. PMBCs were cultured with RANKL and M-CSF (R), in the absence or presence of rhTSG-6 (250 ng/ml) for 21 days. F-actin was visualised by staining with phalloidin (red); for further details see Mahoney et al., 2011.
regulator of osteoclast function (Mahoney et al., 2011) and we have data to indicate that its anti-resorptive activity might be regulated in vivo (i.e. to limit its suppression of bone resorption).

Prolia, a monoclonal antibody that was recently approved (e.g. in Europe and USA) for the treatment of osteoporosis, is based on OPG, a naturally occurring inhibitor of RANKL-mediated osteoclastic resorption. Our in vitro data indicate that TSG-6 is likely to be as potent as OPG in inhibiting bone erosion, but that these two proteins act through different mechanisms (Mahoney et al., 2008; 2011). OPG has effects on the immune system (in addition to bone) and use of Prolia can be associated with increased incidence of infections (e.g. cellulitis). This undesirable off-target effect of Prolia would not be expected for TSG-6.

At the very best TSG-6 could provide effective inhibition of bone loss without the side effects of existing treatments; at the very least it could represent an important addition to the panel of anti-osteoporotic drugs that are required for the long-term management of this multi-decade disease. Furthermore, the ability to produce TSG-6 at low cost in E. coli represents an economic advantage over antibody-based therapeutics.

PATENT STATUS

OPPORTUNITY
The technology is currently at an early-stage with very promising in vivo data. We seek discussion, under confidentiality agreement, with a potential licensee/collaboration partner to assist in the development, scale-up and commercialisation of this technology.

REFERENCES


CONTACTS
SCIENTIFIC CONTACT:
Prof. Anthony J. Day, University of Manchester  ☉: anthony.day@manchester.ac.uk ☏: +44 (0)161 275 1495

COMMERCIAL CONTACT:
Dr Sonia Nikolovski, UMIP. ☉: sonia.nikolovski@umip.com ☏: +44 (0) 161 606 7297