Transgenic Mice Over-Expressing Human RANKL

Application Area
Novel genetic model of osteoporosis for use in pre-clinical trials

Background
RANKL is a central regulator of bone remodeling by mediating osteoclast-induced bone resorption. Disruption of RANKL function leads to recessive osteopetrosis due to failure of osteoclast formation whereas overproduction of RANKL is implicated in a variety of degenerative bone diseases such as osteoporosis. Clinical trials with denosumab, a fully human monoclonal antibody against RANKL, showed increased bone mass and reduced incidence of fractures in postmenopausal women with osteoporosis and in prostate cancer patients receiving androgen-deprivation therapy. This antibody has been recently approved in the USA and EU for the treatment of patients with osteoporosis and in prostate cancer patients undergoing hormonal ablation therapy. Therefore, RANKL is considered the major therapeutic target for the suppression of bone resorption in bone metabolic diseases such as osteoporosis, rheumatoid arthritis and cancer metastasis.

Technology
Transgenic mice overexpressing human RANKL (TghuRANKL) have been generated by using a 200kb genomic fragment containing the whole human RANKL gene as a transgene to achieve a physiological relevant pattern of RANKL overexpression.

There are two mouse lines: (i) low copy Tg5516 mice expressing human RANKL at low levels displayed a mild osteoporotic phenotype as shown by trabecular bone loss and reduced biomechanical properties and (ii) high copy Tg5519 mice overexpressing human RANKL developed severe early-onset osteoporosis characterized by trabecular bone loss, destruction of the growth plate, increased osteoclastogenesis, bone marrow adiposity, increased bone remodeling, severe cortical bone porosity, and decreased bone strength. The observed phenotypes developed in both sexes and the levels of human RANKL expression were correlated with bone resorption and disease severity. Model validation was further established by evidence that denosumab, an antibody that inhibits human but not murine RANKL, fully reversed the osteoporotic phenotype of Tg5519 mice.

Summary
Our TghuRANK mice constitute the first transgenic models of early-onset osteoporosis due to human RANKL overexpression and thus offer a unique system for understanding the pathogenesis of high-turnover bone diseases and for the preclinical evaluation of novel inhibitors that target human RANKL and/or osteoclast activity.

Reference

Key Scientist
Dr Eleni Douni, BSRC Al Fleming, Vari, Greece.