### Background and objective
Bone mass is often negatively affected in autoimmune diseases such as rheumatoid arthritis. It has generally been assumed that bone mass is controlled by endocrine mechanisms and/or the local bone environment. Recent findings demonstrate that central pathways are involved in the regulation of bone mass. Estrogen is involved in the regulation of bone mass and the central nervous system is also a target for estrogen actions.

The aim of this study was to investigate in vivo the role of central estrogen receptor-α (ERα) expression for bone mass.

### Methods
Nestin-Cre mice were crossed with ERα<sup>flox</sup> mice to generate mice lacking ERα expression specifically in nervous tissue (nestin-ERα<sup>−/−</sup>). Mice homozygous for ERα-loxP, but lacking Cre expression, were used as controls. Phenotyping of the bone was performed using pQCT, μCT, histomorphometry and three-point bending. Gene expression analyses were performed using real-time PCR and serum analyses with commercial kits.

### Results
Bone mineral density was increased in both the trabecular and cortical bone compartments in nestin-ERα<sup>−/−</sup> mice compared to controls. Femoral bone strength was increased in nestin-ERα<sup>−/−</sup> mice as demonstrated by increased stiffness and maximal load of failure. The high bone mass phenotype in nestin-ERα<sup>−/−</sup> mice was mainly caused by increased bone formation. Serum leptin levels were elevated as a result of increased leptin expression in white adipose tissue (WAT) and slightly increased amount of WAT in nestin-ERα<sup>−/−</sup> mice. Leptin receptor mRNA levels were reduced in the hypothalamus but not in bone. Furthermore, nestin-ERα<sup>−/−</sup> mice displayed disturbed regulation of T cells with reduced proliferation and decreased frequency in bone marrow.

### Conclusions
In summary, while peripheral ERα activation increases bone mass, the authors here demonstrate that central ERα activation decreases bone mass. Thus, the balance between peripheral stimulatory and central inhibitory ERα actions is important in the regulation of bone mass. The authors propose that the increased bone mass in nestin-ERα<sup>−/−</sup> mice is mediated via decreased central leptin sensitivity and thereby increased secretion of leptin from WAT which, in turn, results in increased peripheral leptin-induced bone formation. In addition, an altered T cell regulation might contribute to the high bone mass phenotype in the nestin-ERα<sup>−/−</sup> mice.