

## Micro-CT analysis in osteoporosis target validation research at Organon N.V.

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Until recently pQCT measurements of mouse and rat femurs were a crucial step in the validation of osteoporosis target genes in the mouse knockout model and compound testing in the rat. The introduction of the micro-CT at Organon N.V. has brought refinement to those measurements and has led to an exploration of new models.

An early step in the validation of a gene as a potential osteoporosis drug target is establishment of a bone phenotype in the mouse knockout model. The micro-CT apparatus is used to analyze trabecular bone parameters in the distal femur, proximal tibia and L4 vertebrae and cortical bone parameters in the diaphysis of the femur. If changes are found relative to the wild-type control mice these bone parameters give direction to further validation research (e.g. osteoblast and osteoclast functionality via histopathology, histomorphometry, microarray/Q-PCR, ex-vivo and in-vitro cell systems). If no changes are found relative to the wild-type control mice, osteoporosis is induced in the knockout mice to determine if their response to this is changed. Experimental setup includes an in-vivo micro-CT measurement at T=0, followed by ovariectomy or orchidectomy, and a second micro-CT measurement 4 weeks later, in order to evaluate changes in bone parameters in each individual mouse.

The micro-CT also has enabled us to use an ex-vivo mouse calvaria assay for compound testing. In this assay calvaria are isolated from 8 days old mice and cultured with or without inducers of bone resorption and components that block resorption. At different time-points, up to 14 days after isolation, the calvaria are analyzed in the micro-CT to determine bone volume and assess compound efficacy.