# Lack of CD45 in FLT3-ITD mice results in a myeloproliferative phenotype, cortical porosity, and ectopic bone formation.

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## Abstract

The receptor-tyrosine kinase FLT3 is expressed in myeloid and lymphoid progenitor cells. Activating mutations in FLT3 occur in 25 – 30 % of acute myeloid leukaemia (AML) patients. Most common are internal tandem duplications of sequence (ITD) leading to constitutive FLT3- ITD kinase activity with altered signalling quality promoting leukaemic cell transformation. Recently we observed an attenuating role of the receptor-like protein-tyrosine phosphatase (RPTP) CD45/Ptprc for FLT3 signalling *in vitro*. Low level expression of this abundant RPTP correlates with poor prognosis of FLT3-ITD positive AML patients. To get further insight into the regulatory role of Ptprc for FLT3-ITD activity *in vivo*, *Ptprc* knock-out mice were bred with FLT3-ITD knock-in mice. Inactivation of the *Ptprc* gene in FLT3-ITD mice resulted in drastically shortened life-span and development of severe monocytosis, a block in B cell development and anaemia. The myeloproliferative phenotype was associated with extramedullary haematopoiesis,

splenohepatomegaly and severe alterations of organ structures. The phenotypic alterations were associated with increased transforming signalling of FLT3-ITD including activation of its downstream target STAT5. These data reveal the capacity of Ptprc for regulation of FLT3-ITD signalling activity *in vivo*. In addition, histopathology and computed tomography (CT) revealed an unexpected bone phenotype: The FLT3-ITD *Ptprc*$^{-/-}$ mice, but none of the controls, showed pronounced alterations in bone morphology, and in part apparent features of osteoporosis. In spleen ectopic bone formation was observed. The observed bone phenotypes suggest a previously unappreciated capacity of FLT3-ITD (and presumably FLT3) to regulate bone development/remodelling, which is under negative control of CD45/Ptprc.

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