Title of the Contribution:
Exome sequencing of osteosarcoma reveals mutation signatures reminiscent of BRCA deficiency.

Abstract:
Osteosarcomas are aggressive bone tumours with a high degree of genetic heterogeneity, which has historically complicated driver gene discovery. Here we sequence exomes of 31 tumours and decipher their evolutionary landscape by inferring clonality of the individual mutation events. Exome findings are interpreted in the context of mutation and SNP array data from a replication set of 92 tumours. We identify 14 genes as the main drivers, of which some were formerly unknown in the context of osteosarcoma. None of the drivers is clearly responsible for the majority of tumours and even TP53 mutations are frequently mapped into subclones. However, >80% of osteosarcomas exhibit a specific combination of single-base substitutions, LOH, or large-scale genome instability signatures characteristic of BRCA1/2-deficient tumours. Our findings imply that multiple oncogenic pathways drive chromosomal instability during osteosarcoma evolution and result in the acquisition of BRCA-like traits, which could be...
therapeutically exploited.