TRKA was identified as an oncogene in colon carcinomas. It triggers proliferation and promotes survival. An oncogenic role has been found in several types of cancer. Evidence suggests that TRKA signaling play a role in AML, as >40% of AML samples have TRKA expression, 30% may carry activating TRKA mutations, and a patient-derived, constitutively-active TRKA variant induces AML in mice. However, neither the importance of TRKA signaling nor the efficacy of TRK inhibition has been explored in AML.

TRKA mRNA and protein expression was detected in all AML cell lines. NGF (5ng/mL) stimulation enhanced proliferation in all lines (mean 28% increase, 16-93%), which was abrogated with 25nM of AZ23. NGF stimulation induced phosphorylation of PI3K/AKT and ERK1/2. In contrast, AZ23 blocked these effects and activated MEKK5, JNK1/2, p53 and BAX. Importantly, AZ23 induced apoptosis in all AML cell lines. Three cell lines (HL60, KG1 and U937) were highly sensitive (IC50s <40nM), suggesting that a subset of AML may be dependent on constitutive TRKA signaling. Human AML-engrafted mice treated with AZ23 had significantly decreased AML burden (18% vs. 70%) and experienced prolonged survival (p=0.004).

We report a critical role and mechanism for TRKA signaling in AML. TRKA activates proliferative pathways (PI3K/AKT and ERK1/2), while inhibition via AZ23 activates apoptosis via MEKK5, JNK1/2, p53 and BAX. Importantly, we demonstrate the therapeutic potential of AZ23 in vitro and in vivo, especially in a subset with TRKA dependence, suggesting that TRK inhibition may serve as a novel approach for AML.

REFERENCES
