CANCER DISCOVERY

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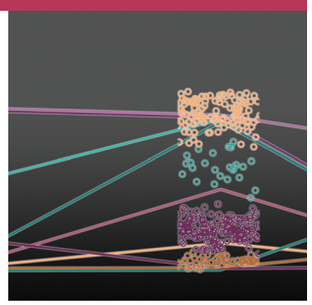

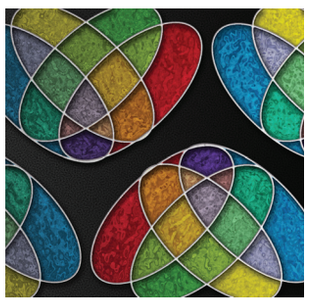

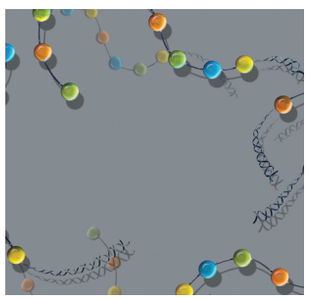

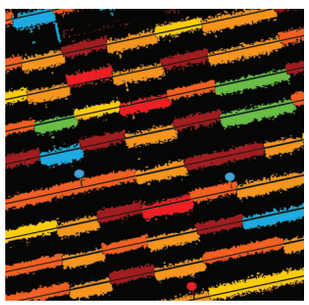

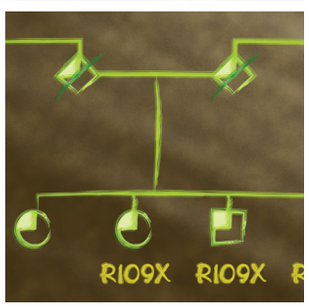

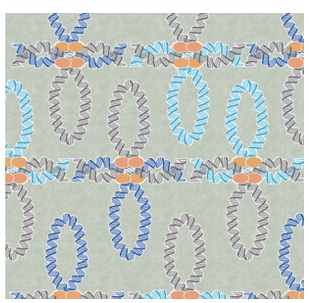

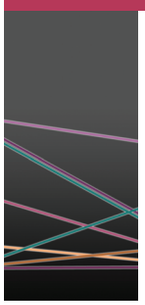

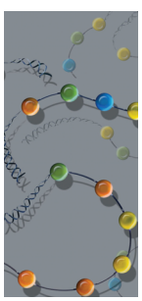

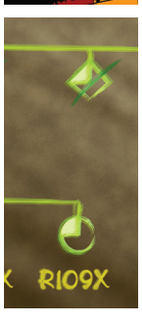

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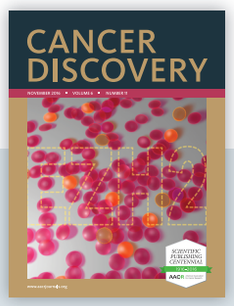

ON THE COVER Tyrosine kinase inhibitors (TKI) successfully target BCR–ABL1 in chronic myelogenous leukemia (CML), but the cure rate is low due in part to the resistance of leukemic stem cells (LSC) to TKIs. In two related studies, Xie and colleagues and Scott, Korfi, and colleagues discovered a dependence of CML LSCs on EZH2 that might be targeted to eradicate LSCs. CML LSCs exhibited upregulation of EZH2 and deregulation of polycomb repressive complex 2 target genes, and suppression of EZH2 reduced colony-forming ability and induced apoptosis in LSCs alone and in combination with TKIs. *In vivo,* genetic inactivation or pharmacologic inhibition of EZH2 reduced the LSC population and prolonged survival. These studies indicate that EZH2 inhibition may eliminate CML LSCs and support further clinical investigation of EZH2 inhibitors in combination with TKIs in patients with CML. For details, please see the article by Xie and colleagues on page 1237 and the article by Scott, Korfi, and colleagues on page 1248.