CANCER DISCOVERY

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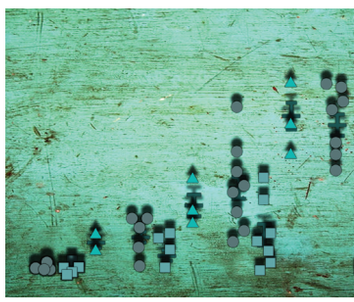

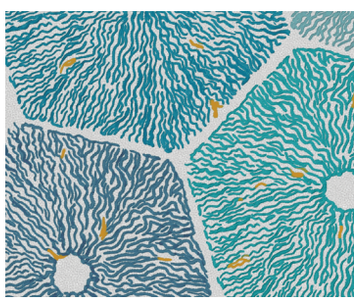

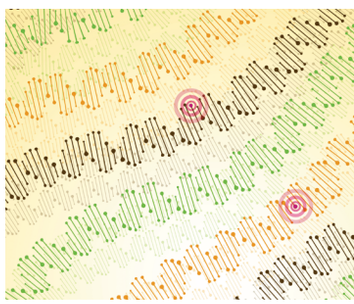

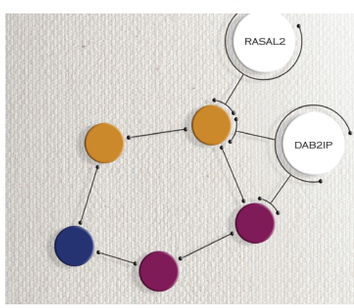

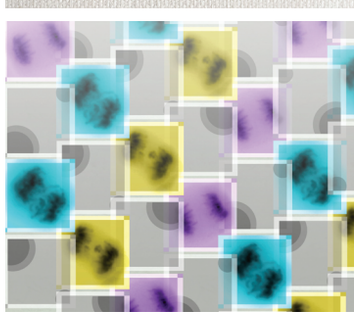

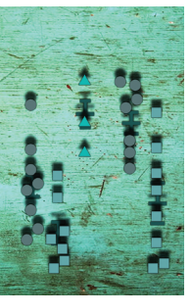

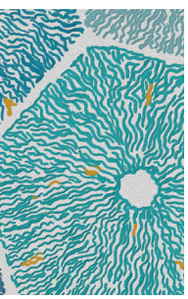

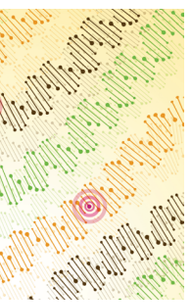

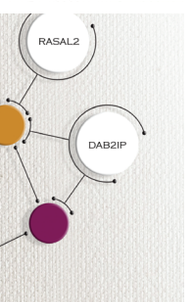

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ON THE COVER

Shin and colleagues performed whole-exome sequencing of pretreatment biopsies from 23 patients with metastatic melanoma and 16 patients with metastatic colon cancer treated with anti–PD-1 therapy and identified a concomitant loss-of-function *JAK1* mutation and amplification of the *JAK* locus in one of the patients with melanoma and a concomitant homozygous truncating *JAK1* mutation and LOH at the *JAK1* locus in one of the patients with colon cancer. Loss-of-function *JAK1/2* mutations abrogated IFNγ-mediated signaling and subsequent upregulation of PD-L1 in patient-derived melanoma cell lines. Analysis of the Cancer Cell Line Encyclopedia and The Cancer Genome Atlas databases revealed that truncating *JAK1/2* mutations occurred in multiple types of cancer and were associated with significantly decreased overall survival in patients with melanoma or breast, prostate, and lung cancers. These findings describe the mechanism by which loss-of-function kinase mutations induce primary resistance to anti–PD-1 therapy. For details, please see the article by Shin and colleagues on page 188.