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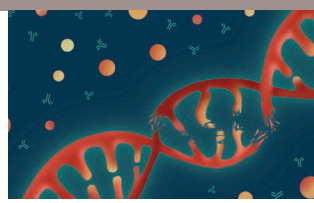
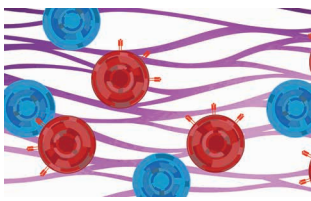
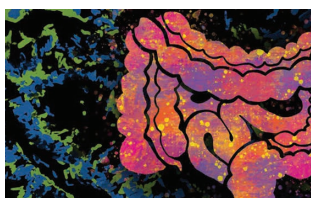
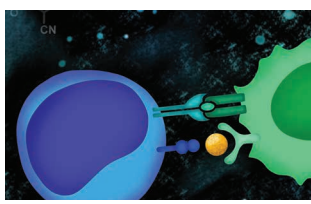
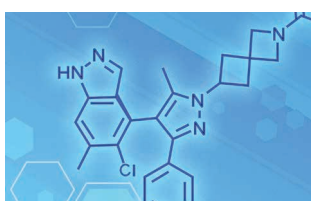
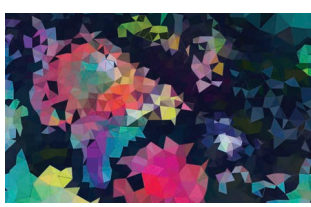
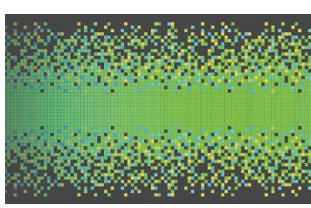

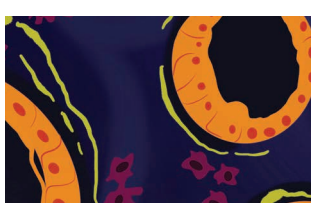

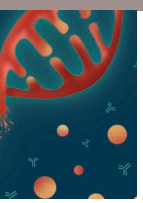
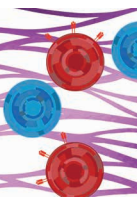

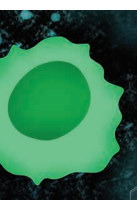


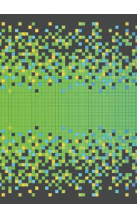

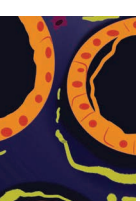

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ON THE COVER Mutations in *KRAS* span many cancer types and had been considered undruggable until the development of small-molecule inhibitors of the KRAS^{G12C} mutant protein. Several covalent inhibitors targeting this mutation have entered clinical development and have demonstrated antitumor activity; however, acquired resistance has emerged, and combination strategies have been suggested. Weiss, Lorthiois, and colleagues developed JDQ443, a structurally unique, potent, and covalent KRAS^{G12C} inhibitor capable of inhibiting downstream signaling and proliferation, including in KRAS^{G12C}-mutant cells with secondary *KRAS* mutations associated with KRAS^{G12C} inhibitor resistance, and with antitumor activity in preclinical models as both a monotherapy and in combination with inhibitors of SHP2, MEK1/2, and CDK4/6. Clinical activity was also demonstrated for JDQ443 both alone and in combination with the SHP2 inhibitor TNO155 in patients with KRAS^{G12C} mutations. For more information, see the article by Weiss, Lorthiois, and colleagues on page 1500.

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