melanoma cells to discover gene products that sensitize tumors to immunotherapy. The screens were carried out in vivo by transplanting the CRISPR^{ed} B16 tumors to mice treated with or without inhibitors of the immune checkpoint programmed cell death 1 (PD-1). One key sensitizer identified in the screen was RIPK1 (*Nature*, **547**, 413–418, 2017). Dosing mice with an oral RIPK1 inhibitor protected mice against the melanoma by shifting the population of tumor-associated macrophages to a mixed phenotype of immunosuppressive and immunostimulatory cells. The effect, moreover, was enhanced when the RIPK1 inhibitor was combined with either a PD-1 blocker or an inducible T-cell co-stimulator agonist (*Cancer Cell* **34**, 757–774, 2018).

GSK is now testing GSK3145095 alone and in combination with Merck's PD-1 inhibitor Keytruda (pembrolizumab) in the

hope that RIPK1 inhibition will sensitize tumors to the antibody. Pancreatic cancer is notoriously difficult to treat, and immune checkpoint inhibitors, now approved in over a dozen oncology indications, have failed to make headway against the condition. Any evidence of efficacy would, therefore, be a welcome advance. "The bar is very low—these patients have very few options," says Miller.

Drug developers' interest in RIPK1 inhibition stems from a much broader effort to understand the role of sterile inflammation in chronic inflammatory and neurodegenerative conditions. Intriguingly, RIPK1 signaling appears to intersect with the nucleotide-binding and oligomerization domain (NOD)-like receptor (NLR) family pyrin-domain-containing protein 3 (NLRP3) inflammasome signaling pathway, which

is also receiving considerable attention from drug developers (*Nat. Biotechnol.* **35**, 893–894, 2017). "The biology does overlap," says Vucic. "There are some instances, especially some inflammatory situations, where they do talk to each other and do cross-activate each other." Genentech has beefed up its inflammasome credentials recently by acquiring Jecure Therapeutics, a start-up developing NLRP3 inflammasome inhibitors for nonalcoholic steatohepatitis and liver fibrosis. Will convergence between these two signaling systems become an important theme in immunology? "This is an area we are trying to investigate," says Yuan. □

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Published online: 4 February 2019
<https://doi.org/10.1038/s41587-019-0023-4>

Around the world in a month

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Published online: 4 February 2019
<https://doi.org/10.1038/s41587-019-0018-1>