Deep Learning–Based Model Augments Utility of Real-World Evidence

Radiology reports are a rich source of real-world evidence that may supplement trial data, but they take substantial time to interpret. Arbour, Luu, and colleagues developed a deep learning–based model relying on natural language processing and applied it to radiologic data from patients with non–small cell lung cancer treated using PD-1 blockade. As evaluated in the training cohort, the model identified best overall response and progression-free survival with high accuracy. The model also performed well when applied to an internal test cohort and a completely separate cohort. This model may enhance the utility of real-world data.

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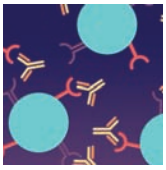
BCL2 Inhibition Synergizes with Immunotherapy in Preclinical Models



Some cancers are dependent on the antiapoptotic protein BCL2 and sensitive to its inhibition. Kohlhapp, Haribhai, Mathew, and colleagues investigated whether treatment with the BCL2 inhibitor venetoclax would affect immune checkpoint blockade, uncovering preclinical evidence of synergy between venetoclax and immunotherapy in mouse syngeneic tumor models. This was despite a reduction in numbers of lymphocytes, including T cells; one possible explanation is that effector T-cell function was not affected because activated T cells are BCL-X_L–dependent. Supporting evidence was obtained from human cells cultured *ex vivo* following venetoclax treatment. This work suggests that the combination of venetoclax and immune checkpoint blockade may not be contraindicated and, in fact, may be beneficial.

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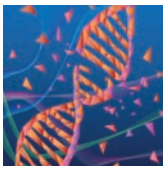
ATR Inhibitor Shows Early Evidence of Efficacy against Solid Tumors



ATR kinase is an essential DNA-repair protein that that is often hypomorphic in cancers; therefore, ATR inhibition may provide an opportunity for selective cancer cell killing. In a phase I, first-in human trial, Yap and colleagues tested the ATR inhibitor BAY 1895344 in 22 patients with advanced solid tumors. The most frequent adverse event was anemia. Of the 21 patients whose disease was evaluable for efficacy, four had partial responses and eight had stable disease; responses were more common in patients with loss of the DNA-repair protein ATM and/or *ATM* mutations, providing clinical proof of concept for a synthetic lethal relationship between ATR and ATM. Larger trials of this agent are justified.

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Inhibition of CDK4/6 and PI3K May Be Synergistic in Breast Cancer

Preclinical data indicate that there may be synergy between CDK4/6 inhibitors and PI3K inhibitors in *PIK3CA*-mutant, estrogen receptor–positive, HER2-negative breast cancer, potentially overcoming the limitations of either treatment alone. In a phase Ib trial, Pascual and colleagues evaluated the combination of the CDK4/6 inhibitor palbociclib plus the PI3K inhibitor taselisib with or without the estrogen receptor antagonist fulvestrant. Among the 25 patients receiving the triple combination therapy, the objective response rate was 37.5% and the median progression-free survival was 7.2 months. These results suggest that further investigation of a synergistic interaction between CDK4/6 inhibitors and PI3K inhibitors is warranted.

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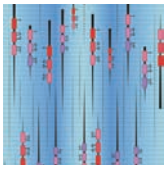
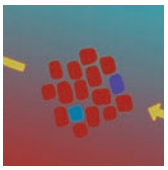
Secondary Kinase Domain Mutations Mediate PDGFRA Inhibitor Resistance



Activating mutations affecting either of the homologous receptor tyrosine kinases PDGFRA or KIT are present in most cases of gastrointestinal stromal tumor (GIST). Some resistance mechanisms to KIT inhibition are established, but less is known about resistance to recently approved PDGFRA inhibitors. Grunewald, Klug, Mühlenberg, and colleagues found that *PDGFRA*-mutant GISTs that progressed on the PDGFRA inhibitor avapritinib had secondary mutations affecting the PDGFRA kinase domain; importantly, these tumors were still dependent on oncogenic PDGFRA signaling. In addition to suggesting an on-target mechanism of action for avapritinib, these findings suggest that PDGFRA inhibitor resistance may be circumvented by the inclusion of additional agents that target PDGFRA or its pathway.

See article, p. 108.

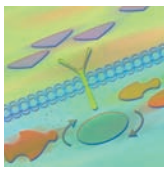
Type I TKI Resistance Mutations in TRK Cause Type II TKI Sensitivity



Mutations affecting the residue directly *N*-terminal to the conformation-determining DFG motif shared among many oncogenic kinases are known to cause resistance to type I tyrosine kinase inhibitors (TKI), which are ATP-competitive inhibitors. Using TRK fusion–positive cancers as a model, Cocco, Lee, Kannan, Schram, and colleagues found that the same mutations associated with type I TKI resistance cause sensitivity to type II TKIs by promoting the inactive "DFG-out" conformation of TRK, the conformation that is bound by type II TKIs. Because many oncogenic kinases share these escape mutations, these mutations may be broadly indicative of type II TKI sensitivity.

See article, p. 126.

Small-Molecule Drug Prevents KRAS–SOS1 Binding to Block KRAS Signaling



Although inhibitors targeting the most common forms of mutant KRAS have shown promise, inhibitors that broadly target oncogenic KRAS signaling have not achieved high efficacy. Hofmann, Gmachl, Ramharter, and colleagues developed a novel small-molecule drug, BI-3406, which prevents the interaction between KRAS and SOS1, a guanine exchange factor that activates KRAS. By reducing SOS1-mediated GTP loading, BI-3406 limited the ability of KRAS to adopt the active, GTP-bound state and thus reduced KRAS-driven tumor cell growth *in vitro* and *in vivo*. Further, BI-3406 sensitized KRAS-dependent cancers to MEK inhibitors by dampening feedback reactivation, suggesting the drugs could act synergistically.

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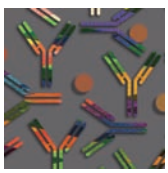
A CD137 Antibody Switched on by Extracellular ATP Activates T Cells



T-cell proliferation and survival can be enhanced by stimulating the surface receptor CD137, making it an attractive candidate for immunotherapy uses, but agonistic antibodies to CD137 have been limited by lack of specificity (leading to off-target toxicity) or low potency. Kamata-Sakurai, Narita, and colleagues designed an agonistic CD137 switch antibody, STA551, that is activated only in the presence of high extracellular ATP levels such as those found in many tumors. STA551 exhibited antitumor efficacy *in vivo*, and experiments in cynomolgus monkeys showed a lack of off-target toxicity. This work supports further investigation of STA551 and similar switch antibody–based treatments.

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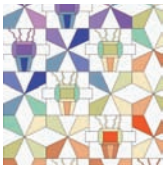
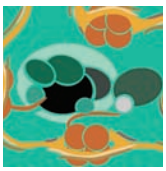
Blocking Nuclear Pore Complex Formation Selectively Kills Cancer Cells



Normal cells can maintain their nuclear pore complexes (NPC) for years or possibly even decades, but rapidly proliferating cells such as cancer cells depend on increased NPC assembly and greater NPC numbers. Sakuma and colleagues found that depleting components of NPCs caused selective cancer cell death, sparing normal cells. *In vivo*, depletion of NPC components caused regression of melanoma and colorectal cancer xenografts and inhibited leukemia cell proliferation. Mechanistically, depleting NPC components caused nuclear transport failure, altered the transcriptome, and induced DNA damage. In summary, inhibiting NPC formation may represent a useful strategy for anticancer therapies.

See article, p. 176.

The Epigenetic Protein PHF23 Mediates 17p Loss–Driven Tumorigenesis



Chromosome 17p deletion is common in many cancers, and its effects are more powerful than loss of *TP53* (which resides on 17p) alone. Chen, Chen, and colleagues identified loss of *PHF23*, encoding a protein that binds histone 3 trimethylated at lysine 4 (H3K4me3), as a previously unknown cause of 17p deletion–driven tumorigenesis. *In vivo*, *Phf23* depletion promoted lymphomagenesis, and mechanistic studies revealed that PHF23 colocalized with genomic regions bearing large amounts of H3K4me3, where it joined the SIN3–HDAC complex to block its deacetylase activity on H3K27ac. This work reveals PHF23 loss as important for promoting cancer associated with 17p loss.

See article, p. 194.

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