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The never-abating excitement for targeted therapies

In combining technical innovation with foundational research, targeted therapies remain at the forefront of oncology drug discovery efforts.

Achieving the ultimate goal of discovery cancer research, namely the discovery of new and improved ways to target cancer, requires a deep understanding of the underlying biology and genetics of a tumor combined with innovation in drug development. This interdisciplinary way of thinking has led to the expansion of targeted drug discovery efforts over the past few decades to include classic small-molecule inhibitors such as kinase inhibitors and small molecules that block key interactions in oncogenic pathways, but also cancer-targeting macromolecules, such as monoclonal antibodies, polypeptides and nucleic acids. Recent work published in *Nature Cancer* highlights preclinical efforts on several such fronts.

In this issue of *Nature Cancer*, Dong et al.[1] report the development of a peptide against a potassium channel that disrupts the communication between tumor and neuronal cells in glioblastoma. The authors found that the voltage-gated potassium channel EAG2 and its auxiliary β-subunit Kvβ2, were enriched in glioblastoma and observed specifically at the interface between the tumor and the brain. Delving deeper into biological function, they showed that this potassium channel localized at glioblastoma and neuronal cell contact sites where it regulated calcium transients known to drive the proliferation and migration of glioblastoma cells. Having validated these tumor-promoting effects of EAG2 and Kvβ2 in vitro and in vivo, the authors demonstrated that they required the physical interaction of the two subunits. They went on to develop a peptide that disrupted the interaction of EAG2 and Kvβ2 in glioblastoma cells, showing that it was able to suppress tumor growth in vivo without overt toxicity in patient-derived xenograft and orthotopic mouse models. Moreover, the peptide had specific efficacy against glioblastoma models resistant to the standard-of-care drug temozolomide. The accompanying News & Views article by Robbins and Senger[2] provides a deeper discussion of the implications of these findings on glioblastoma therapy and cancer neuroscience research.

In our previous issue, Chitty et al.[3] focused on targeting a different aspect of the tumor microenvironment, the tumor stroma. After verifying the association of lysyl oxidase enzymes with poor outcome in pancreatic cancer and their role in the formation of the fibrillar collagen-rich extracellular matrix found in such tumors, they developed a first-in-class selective and irreversible small-molecule pan-lysyl-oxidase inhibitor. They went on to show that this inhibitor was active against the desmoplastic stroma and pancreatic tumor stiffness in three-dimensional organotypic models in vitro and genetically engineered mouse models and patient-derived xenograft models in vivo. They further showed that the co-administration of the inhibitor with gemcitabine was able to increase the anti-tumor efficacy of the latter. These findings provide a basis for testing this pan-lysyl-oxidase inhibitor in pancreatic cancer clinical trials.

Contributing to the field of kinase inhibitors, Miyazaki et al.[4] recently reported the development of a next-generation RET inhibitor. Activation of the transmembrane receptor tyrosine kinase RET is responsible for driving several cancers, with RET kinase inhibitors becoming standard-of-care. However, their efficacy is hampered by the development of resistance and brain metastases. Miyazaki et al.[4] developed vepafestinib, a small molecule with a distinct binding mode from other RET inhibitors, that they showed was able to block proliferation of several RET-driven cancer cell lines in vitro and in vivo with higher selectivity and superior or similar efficacy to other RET inhibitors. Verifying these effects in patient-derived xenograft models, the authors also showed that their inhibitor was active against RET mutations known to be acquired after treatment with existing inhibitors. Moreover, this drug could cross the blood–brain barrier with improved penetrance compared with other RET inhibitors, remaining active against brain metastatic tumor growth. As also discussed in the accompanying Research Briefing article[5], a phase 1–2 clinical trial is currently underway to investigate the potential of this inhibitor in patients with RET-rearranged solid tumors.

Staying on the theme of kinase inhibitors, Rialdi et al.[6] presented a multi-kinase inhibitor that they showed is active against hepatocellular carcinoma driven by mutant β-catenin. Harnessing the power of tumor organoids, the authors conducted chemical screens that led them to the identification of WNTinib, an inhibitor that targets the KIT receptor tyrosine kinase upstream of the MAPK signaling cascade and reducing the engagement of anti-targets therein, such as the BRAF and p38α/β kinases. The authors found that this compound led to the transcriptional suppression of the Wnt pathway by impaired phosphorylation of the EZH2 transcriptional repressor, which resulted in nuclear localization of EZH2, increased chromatin engagement and suppression of Wnt target genes. They further showed that WNTinib had superior efficacy in mouse models of hepatocellular carcinoma in vivo, compared to four US Food and Drug Administration (FDA)-approved kinase inhibitors, strengthening the argument for clinical testing of this compound.

Taking a different approach, Hagenbeek et al.[7] targeted the well-known interaction of TEAD transcription factors with YAP/TAZ cofactors. They developed an allosteric inhibitor against all TEAD isoforms that bound to the TEAD lipid pocket and blocked the binding of YAP and TAZ, thereby suppressing the induction of their transcriptional programs. Application of this small-molecule inhibitor to YAP/TAZ-dependent cancer cell lines in vitro and in vivo inhibited cell proliferation and tumor growth. Given the known crosstalk of the KRAS-driven MAPK pathway and YAP/TAZ in cancer, the authors showed that their pan-TEAD small-molecule inhibitor was efficacious against lung cancer cell lines resistant to the KRAS(G12C) inhibitor sotorasib in vitro and in vivo. They further demonstrated that combination of these two agents in vivo had improved anti-tumor

efficacy compared with monotherapy and was well tolerated in mice. Although direct comparisons in additional models are needed to demonstrate this conclusively, these findings argue for further clinical testing of this pan-TEAD inhibitor, in light of the limited preclinical efficacy of previous agents that target the TEAD lipid pocket. The companion News & Views article by Mira and Ambrogio[8] provides a broader discussion on the clinical implications of this TEAD-targeting effort in light of YAP/TAZ-mediated resistance to KRAS inhibitors.

The above findings provide a small but exciting snapshot of some of the directions of targeted therapy discovery and development. Interest remains very high in the wealth of ongoing preclinical and translational research that aims to tackle the complexity and context-dependence of different cancer types, to provide new and improve existing targeted therapies for clinical testing.

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