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► **COVER:** 'Stress-free' by Lara Crow, inspired by the review on p537.



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As we map signalling pathways more accurately in normal and cancer cells, the opportunities for effectively targeting specific tumours are becoming apparent. In this month's issue we have two Reviews that are focused on well-defined and crucial signalling pathways in cancer cells — the PI3K–Akt pathway and the LKB1–AMPK pathway.

On page 550 Jeffrey Engelman discusses PI3K inhibitors that are currently in preclinical development and clinical trials. Some of these inhibitors target all isoforms of PI3K, as well as the downstream PI3K target mTOR, whereas others specifically target one PI3K isoform. It is currently unclear whether the pan-PI3K inhibitors will prove more effective than the specific inhibitors, or whether toxicity issues are likely to be greater with the pan-specific inhibitors and so restrict their use. Inhibitors targeting the PI3K pathway might prove most useful as adjuvant therapy to circumvent resistance to targeted therapies, such as trastuzumab.

The LKB1–AMPK pathway can also regulate mTOR, as outlined on page 563 by David Shackelford and Reuben Shaw. However, what is particularly interesting about this pathway is the evidence that links it to both diabetes and cancer. AMPK is the target of some diabetes drugs, such as metformin, and epidemiological studies indicate that the incidence of tumour development is lower in patients with type 2 diabetes who are treated with metformin. Moreover, mouse models of cancer in which the LKB1 pathway is disrupted indicate that targeting AMPK could be an effective strategy.

Interestingly, the take-home message from both Reviews is that although targeting these pathways looks promising, a clear understanding of how other signalling pathways are disrupted and regulated in a tumour will be needed to make the most of these agents.

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