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ANTICANCER DRUGS

# Compartmental solution

Owing to the large number of deregulated genes that are associated with cancer, interest is increasingly shifting from a target-centric to a pathway-oriented approach to anticancer drug discovery, whereby inhibition of 'nodal' proteins affects multiple cancer signalling pathways. One such protein is the chaperone heat shock protein 90 (HSP90), which controls the folding of various proteins that are involved in tumour growth. However, clinical results with HSP90 antagonists have not fulfilled the promise of preclinical studies. Now, in the *Journal of Clinical Investigation,* Altieri and colleagues describe how targeting HSP90 antagonists specifically to mitochondria can dramatically increase their anticancer activity in mice.

The key roles of mitochondria in the regulation of energy metabolism, reactive oxygen species production and apoptosis, and their emerging implication in disease, makes them an attractive drug target. In this study, the authors used the fact that mitochondria in normal tissues do not contain HSP90 to selectively target tumour tissue. They describe the synthesis and properties of gamitrinibs, which are small molecules that are based on the established HSP90 inhibitor 17-AAG conjugated to a mitochondria-targeting moiety of 1–4 tandem repeats of cyclic guanidium (gamitrinibs-G1–G4) or triphenylphosphonium. In addition to displaying no effect on cytosolic HSP90 — no changes in the levels of 'client' proteins or compensatory upregulation of HSP70 were observed — these compounds were shown to be selective for cancer cells over normal cells.

When added to isolated tumour mitochondria, gamitrinibs induced a fast and irreversible loss of mitochondrial membrane potential, leading to the rupture of the outer mitochondrial membrane and the release of cytochrome *c*, which are hallmarks of mitochondrial permeability transition and apoptosis. These effects were attenuated by inhibiting or silencing the mitochondrial permeability transition pore protein cyclophilin D, and seem to be independent of the pro-apoptotic protein BAX, indicating a different mode of action from pro-apoptotic B cell lymphoma protein 2 (BCL2) modulators.

Gamitrinib-G3 and gamitrinib-G4 were found to induce apoptosis in a range of cancer cell lines at concentrations at which 17-AAG only partially reduced cell viability and proliferation. Moreover, systemic administration of gamitrinib-G4 inhibited xenograft tumour growth in mice, without causing any obvious toxicity.

This study suggests that the targeting of existing drug-like compounds to specific subcellular compartments might represent a useful strategy for increasing their potency. This could be particularly effective in the development of cancer drugs, for which differences in this signalling compartmentalization between diseased and healthy cells can be exploited.

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**ORIGINAL RESEARCH PAPER** Kang, B. H. *et al.* Combinatorial drug design targeting multiple cancer signaling networks controlled by mitochondrial Hsp90. *J. Clin. Invest.* **119**, 454–464 (2009).