

# DRUGGING THE CANCER GENOME: INHIBITORS OF PI3 KINASE AND HSP90

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Success in drugging the cancer genome relies on the simultaneous development of new therapeutic agents that exploit molecular abnormalities and dependencies in malignant cells together with biomarkers for proof of mechanism/concept and patient selection (1-3). Much work has focused on drugging protein kinases involved in cancer. There is a need to expand the druggable genome to access the therapeutic potential other classes of cancer targets. This presentation will describe our work on new inhibitors of the family of lipid kinases known as PI3 kinase (4) and of the HSP90 molecular chaperone (5). The PI3 kinase pathway is deregulated by multiple means in human cancers and the discovery of potent and isoform-selective inhibitors has benefited from high-throughput screening (HTS) and subsequent optimization by medicinal chemistry, guided by molecular modelling and X-ray crystallography (6-11). The molecular chaperone HSP90 is responsible for the stability and activation of a range of oncogenic client proteins and the discovery of new inhibitors acting at the N-terminal ATP site has been enhanced by chemical biology, HTS and structure-based design (12-17). An alternative approach is to inhibit the interaction between HSP90 and co-chaperones such as AHA1 (18). Identification of biomarkers is based on detailed mechanistic studies, together with gene expression microarray and proteomic profiling, magnetic resonance spectroscopy and imaging, and positron emission tomography (3). The combined use of gene expression profiling and proteomic analysis has recently proved very useful (19). These and other approaches to drugging the cancer genome are paving the way towards developing personalized molecular cancer medicine.

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