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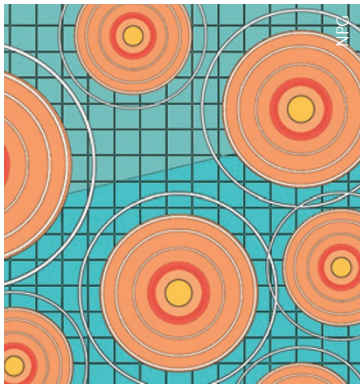
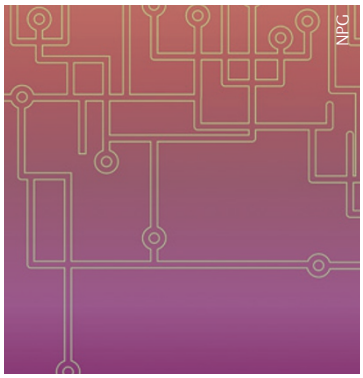


Virus-encoded GPCRs as targets p123



Intervening in the PI3K network p140

Although G protein-coupled receptors (GPCRs) are one of the most common and successful classes of drug targets, the potential of modulating virus-encoded GPCRs has largely been neglected. In their Review, Smit and colleagues discuss how herpesviruses can hijack the GPCR-mediated cellular signalling networks of their host to subvert cellular signalling, a strategy that has important roles in virus survival, replication and pathogenesis. They focus on the roles of specific herpesvirus-encoded chemokine receptors in certain inflammatory and proliferative diseases, including Kaposi's sarcoma and glioblastoma, and assess their potential as novel therapeutic targets. The most frequently altered pathway in human cancer is the phosphoinositide 3-kinase (PI3K) signalling network. However, despite significant efforts, most agents targeting individual pathway components have so far shown only limited activity in the clinic. Fruman and Rommel review the complexity of the PI3K signalling network in cancer and address the key challenges associated with therapeutically intervening in this pathway. Priorities to guide future efforts in translational and clinical research are discussed, including biomarker identification, increased understanding of immune modulation and the use of rational drug combinations. Finally, in an Analysis article, Hopkins and colleagues discuss the application of ligand efficiency metrics — which quantify the molecular properties of small molecules that are required to gain binding affinity to a drug target — to guide hit and lead optimization. By analysing data on the ligand efficiencies of compounds for particular targets and of recently marketed oral drugs, they illustrate that optimizing ligand efficiencies based on molecular mass and lipophilicity, in the context of a specific target, could help to increase the quality of drug candidates.

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