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Mechanistic study of NVP-CGM097: A potent, selective and species specific inhibitor of p53-Mdm2

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An effective strategy to restore p53 activity in cancer cells containing wild type p53 is to inhibit the Mdm2-p53 protein-protein interaction (PPI). NVP-CGM097 is a novel PPI inhibitor under evaluation in a Phase I clinical trial. It binds to the p53 binding-site of the Mdm2 protein, disrupting the interaction between both proteins, leading to an activation of the p53 pathway.

The main biophysical and biochemical inhibitory characteristics of NVP-CGM097 are presented here. These include affinity constants for Mdm2 & Mdm4, and the binding kinetics of NVP-CGM097.

Moreover, biochemical studies have revealed the species specificity of NVP-CGM097 with human Mdm2 being inhibited more strongly than the dog, mouse or rat forms of the protein. This was confirmed in cellular assays where NVP-CGM097 treatment resulted in induction of p53 target gene expression (p21, PUMA and Mdm2) only in human, but not in dog, mouse or rat cell lines.

Biography

Therese Valat is currently Lab-head in oncology research at Novartis (Basel, Switzerland). She completed her in Enzymology in 1995 at the University of Compiegne (France). She has 17years of experience in drug discovery for oncology and anti-infectives, with an advanced expertise in biochemistry and biophysics, assay development, compound profiling, in both large multinational pharmaceutical (HMR, Sanofi-Aventis, Novartis) and small VC-funded environments (Novexel). She has been involved in more than 20 different projects from target validation to Phase II clinical trials working on low molecular weight molecules that target enzymatic reactionsor protein-protein binding.

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