Ref: OT-44

Title:

Useful new molecules for the treatment of liver cancer.

Summary:

The present invention provides p38 protein kinase (MAPK) inhibitors which are useful for the treatment and prophylaxis of liver cancer.

In particular, the present invention provides compounds capable of inhibiting the intracellular expression of the p38 gamma and/or delta protein in the hepatocytes of a subject relative to that observed in the absence of the compound for use in the therapeutic treatment of liver cancer.

The compounds given in the patent application are selected from p38 gamma or delta gene silencer compounds such as siRNAs or shRNAs, a peptide and a list of different chemical compounds, some of which are described in this invention for the first time. The invention also claims methods of treatment, a screening method for obtaining compounds capable of inhibiting p38 gamma or delta intracellular expression and a biomarker used as indicative of a positive response to the therapy in a subject.

Mitogen-activated protein kinase (MAPK) signalling has a critical role in cell processes whose deregulation leads to cancer development and progression. MAPK pathways link extracellular signals to the machinery that controls fundamental cell activities such as growth, proliferation, differentiation, migration and apoptosis.

Innovative aspects:

Whereas most studies of the p38MAPK pathways to date focused on p38alpha function in the cell transformation process, there are few and contradictory reports on the role of p38gamma and p38delta. Our results are the first to provide evidence on the relationship between the inhibition of p38gamma/p38delta MAPK and the therapy of hepatic cancer or liver cancer.

The key scientific findings that confer an innovative approach for the treatment of liver cancer are 1) p38gamma is essential for liver proliferation and regeneration after partial hepatectomy (PHx). 2) p38γ/δ positive cells exhibit stronger tumorigenicity than p38gamm/delta negative cells; 3) Lack of p38gamma or p38delta protected against DEN-induced liver cancer (a liver carcinogenesis model whose gene expression profile correspond closely to that of Human hepatocellular carcinoma (HCC) with unfavourable

outcome); 4) comparative effects of p38gamma inhibitors protects against DEN-induced liver tumour showing a pronounced inhibitory effect on tumor volume and number; 5) determining a useful biomarker for p38 gamma and delta inhibition in vivo.

Competitive advantages:

HCC is the fifth most common cancer in the world and overall, the incidence and mortality rates are ranging from 67% to 91%. Currently, surgical resection is the only effective treatment for HCC if the tumor is resectable. Small molecules, biologics and siRNAs as anti-cancer drugs have been explored for the treatment of HCC. Selective targeting to tumor tissue rather than normal liver in HCC patients is still a challenge. For that reason to find specific proteins that are over expressed in HCC is very important in order to achieve a specific treatment and to reduce secondary effects.

Based on the results obtained by inventors, new drugs to specifically target p38 gamma or delta have been obtained; these molecules are classified in 3 different categories: Phenylpirazole-derived compounds, urea-derived compounds and Phenylhydrazine-derived compounds.

The finding that p38 gamma and delta are good candidates for treating liver tumour open the possibility to further look for new inhibitors.

Key words: liver cancer, hepatic cancer, liver tumours, p38 protein kinase (MAPK), p38 gamma, p38 delta, p38 inhibitors, Human hepatocellular carcinoma (HCC).

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