



## **CF102 for the Treatment of Hepatocellular Carcinoma (HCC): From Bench to Bedside**

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The A<sub>3</sub> adenosine receptor (A<sub>3</sub>AR), a Gi protein associated cell surface receptor, was suggested as a target for cancer treatment. In this study we present the anti-cancer effect of the A<sub>3</sub>AR agonist CF-102 on growth of hepatocellular carcinoma (HCC) in experimental animal models and the clinical development program, currently conducted to develop this molecule as a drug candidate.

RT-PCR, western blot analysis and Immuno-histochemistry were used to evaluate the level of A<sub>3</sub>AR and cell growth regulatory proteins in tissues and peripheral blood mononuclear cells (PBMCs) derived from patients or rats with HCC. The anti-cancer effect of the A<sub>3</sub>AR agonist, CF102 was examined utilizing a rat orthotopic model of N1S1 HCC tumor.

A<sub>3</sub>AR was found to be highly expressed in tumor tissues derived from patients and rats with HCC. A<sub>3</sub>AR over-expression was also found in the PBMCs, reflecting receptor status in the remote organ. The high expression level of the receptor was directly correlated to over expression of NF-κB, known as a transcription factor of A<sub>3</sub>AR. CF102, a synthetic highly selective agonist at the A<sub>3</sub>AR, induced growth suppression of rat HCC in an orthotopic and xenograft models when given orally. Mechanistically, CF102 de-regulated the NF-κB and the Wnt signal transduction pathways and induced apoptosis of tumor cells manifested in the up-regulation of BAD, BAX and Caspase-3. CF102 was found to be safe and well tolerated in pre-clinical and Phase I human clinical studies. The drug is currently tested in Phase I/II patients with HCC to explore safety and efficacy.

Taken together, A<sub>3</sub>AR is highly expressed in tumors and PBMCs of HCC patients and tumor bearing rats. Oral administration of CF102 induced tumor growth suppression and apoptosis of HCC. The drug is safe and well tolerated in humans and is suggested as a potential targeted therapy to combat HCC.