

## PRESS NOTE

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# **New therapeutic target to fight liver cancer discovered**

- *Researchers from the Center for Cooperative Research in Biosciences, CIC bioGUNE (Bizkaia), led by Dr. Maria Luz Martínez Chantar, have found a close relationship between high levels of HuR protein and the malignancy of hepatocellular carcinoma through neddylation, a novel molecular process in the research of this pathology.*
- *The study, which was published in the journal Hepatology, has obtained a special mention in the Cancer section of the prestigious journal Nature Reviews Gastroenterology&Hepatology.*
- *This project opens new opportunities for the future development of potential personally-tailored therapeutic applications for the treatment of Hepatocellular Carcinoma.*

(Bilbao 13 January 2012).- Hepatocellular carcinoma (HCC) is responsible for most cases of liver cancer; it is the fifth most common cancer in the world and the third cause of death after lung and gastric cancer. HCC is a bad prognosis tumour, even in developed countries. Its incidence is similar to its mortality rate, which means that most patients die within several months, despite diagnosis and therapeutic breakthroughs. It is a heterogeneous tumour and therefore the scientific community is doubling their efforts to establish very precise and personalised therapeutic targets.

A group of researchers of the Metabolomics Unit of **CIC bioGUNE**, led by Dr. Martinez Chantar, has taken a new step in the study of liver cancer, revealing the molecular mechanism, which was unknown until now, involved in the development of HCC. They observed how the malignancy of this disease may be related with overexpression of a protein, HuR.

The paper, which was published in the journal **Hepatology**, and that has obtained a special mention in the Cancer section of the prestigious journal **Nature Reviews Gastroenterology & Hepatology**, has revealed the relationship between overexpression of the protein HuR and the malignancy of

Hepatocellular Carcinoma through a completely novel molecular mechanism called neddylation, which opens new opportunities for the future development of potential therapeutic applications. This new route is also applicable to colon cancer, due to the high correlation between both types of tumours.

"Neddylation is an enzymatic reaction that avoids protein degradation, in the biological context, of proteins that are modified by NEDD8 molecule. Just like ubiquitination marks proteins to be degraded, neddylation marks them to stabilise them. Therefore, we pose that these are key to tumour proliferation and development", explains Dr. María Luz Martínez Chantar, researcher at the Metabolomics Laboratory in bioGUNE and project leader.

In this sense, the strategy consisted on keeping the HuR at high expression levels modifying it by neddylation, thus promoting CHC proliferation and malignancy. Consequently, "when we block neddylation or regulate HuR protein levels in liver tumours and in vivo and in vitro hepatoma lines, cell death is induced leading to tumour regression", states Martínez Chantar.

Conventional oncological treatment options for Hepatocellular Carcinoma are limited, since it is a strong chemoresistant tumour, often developing in a cirrhotic liver. Around 40% of patients are diagnosed CHC at a late stage, and short-term prognosis is reserved (survival after 1 year in 29% of cases, and 2 years for 16%). This neoplasm is unique in Oncology, because in spite of its high incidence and bad prognosis, until recently an effective therapy had not been available. A possible explanation to this fact is the high heterogeneity of the molecular mechanisms involved in the development of this tumour.

The next step within this long and complex research process is to find a potential therapeutic application for the identified formula, for which Dr. Martínez Chantar, together with the pharmaceutical Millenium: The Takeda Oncology Company, will use new neddylation inhibitors marketed by the company and currently tested in other type of tumours, in "in vivo" Hepatocellular Carcinoma models (mice), exploring this new therapeutic solution.

"Now that we discovered that neddylation can play a key role in the development and progress of CHC, our next step is delving into a comprehensive study of its potential therapeutic applications" concludes Martínez Chantar.

### **References for the study:**

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