

## **CNIO Scientists Unveil a Therapeutic Strategy for K-Ras driven Non-small Cell Lung Carcinoma**

**Madrid, July 18th, 2010** - Researchers at the Spanish National Cancer Research Centre (CNIO) have unveiled a *synthetic lethal* interaction between K-*Ras* oncogenes and *Cdk4* in a mouse tumour model that closely recapitulates human non-small cell lung carcinoma (NSCLC).

Scientists from the CNIO's Experimental Oncology Group, led by Mariano Barbacid, have published a study in the latest issue of *Cancer Cell* that investigates the role of *Cdk4* as a therapeutic target for non-small cell lung cancers carrying K-RAS oncogenes.

### **Manuscript Reference:**

**Title:** "A synthetic lethal interaction between K-Ras oncogenes and *Cdk4* unveils a therapeutic strategic for non small cell lung carcinoma"

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### **Introduction: Synthetic lethality**

The phenomenon known as *synthetic lethality* occurs in situations in which two mutations or alterations that do not cause damage to the organism by themselves have lethal effects when combined. "When applying this concept to tumour cells," explains Mariano Barbacid, "we look for secondary alterations that are linked to existing oncogenic mutations in these cells, causing their death. These secondary alterations, according to the concept of synthetic lethality, do not show a negative effect by themselves and may exist in normal

cells. In clinical practice, this secondary alteration could be the inhibition of a particular cellular activity or a therapeutic target, without causing actual damage to normal cells.

### **The discovery: A synthetic lethal interaction between K-Ras oncogenes and genetic ablation of *Cdk4***

It is well known that 25% of lung adenocarcinomas are caused by the K-Ras oncogene. Using a mouse tumour model for NSCLC, the investigators in this study have discovered that the ablation of the interphase cell cycle kinase, *Cdk4*, but not of *Cdk2* or *Cdk6*, induced an immediate senescence response in lung cells expressing an endogenous K-Ras oncogene. No such response occurs in lungs expressing a single *Cdk4* allele or in other K-Ras-expressing tissues. More importantly targeting of *Cdk4* alleles in advanced tumours, detectable by computed tomography scanning, also induced senescence preventing tumour progression.

### **Cdk4 inhibitors**

CDK inhibitors have failed as anti-cancer agents due to their limited activity and significant toxicity. Whereas Cdk1 is essential for the mammalian cell cycle, interphase Cdks, Cdk2, Cdk4, and Cdk6, are only essential for proliferation of highly specialized cells. In this study, under the supervision of Mariano Barbacid, the scientists also provide pharmacological evidence that Cdk4 is essential for proliferation of lung cells, providing they express a K-Ras oncogene.

Once this unexpected connection between synthetic lethal-K-Ras oncogenes and Cdk4 enzyme was established in lung adenocarcinomas, Mariano Barbacid's team examined the antitumour activity of a selective Cdk4 inhibitor developed by *Pfizer*. In a similar fashion to the *Cdk4* genetic ablation studies, its enzymatic inhibition caused a pronounced overall antitumour effect; although this effect was not complete, perhaps due to the partial inhibition of the enzyme by this compound.

To date, selective CDK4 inhibitors have demonstrated no significant therapeutic benefit in clinical trials against leukemias and breast tumours. However, none of these tumours were bearing K-Ras oncogenes, an event that may explain their lack of activity in the clinic.

Based on the findings in this study, several clinical trials are now planned with the participation of the CNIO's Clinical Research Programme, under the supervision of its Director, Dr. Manuel Hidalgo. These trials aim at testing this compound as well as other, more powerful Cdk4 inhibitors, which are now in developmental stages by other pharmaceutical companies.

### **Future implications**

Mariano Barbacid wants to clarify that despite the interest aroused by these results, "these findings only represent an indication of a biological phenomenon and, at no time, guarantee that they can be extrapolated to patients with lung cancer."

Moreover, Mariano Barbacid cautions "tumours used in this study, are less aggressive than those observed in patients with lung cancer. Therefore, in order to observe a therapeutic benefit in the clinic, Cdk4 inhibitors will have to be used in combination with other therapies."

In summary, this study illustrates that without experimental research, this *synthetic lethal* interaction between K-Ras oncogene and Cdk4 inhibition would not have been discovered. In addition, studies such as this one open the door to the systematic application of synthetic lethal interactions to other tumour models to identify additional molecular targets that eventually should help to improve existing anti-cancer therapies.