



**Friday September 10,  
12.00 pm  
CIC bioGUNE.  
Atrio Building 800**

**HOST:  
Dr. Malu Martínez-Chantar**

**SPEAKER:**

**Montse Sánchez-Céspedes, PhD**

**FROM:**

Institut Investigacions Biomediques Bellvitge-IDIBELL-PEBC. Barcelona

**TITLE:**

**LKB1 AND BRG1, TALES OF TWO TUMOR SUPPRESSOR GENES ON CHROMOSOME 19p  
AND HUMAN LUNG CANCER**

Lung cancer is the most common cause of cancer deaths worldwide, with over one million cases annually. In addition to preventing uptake and encouraging cessation of the smoking habit, it is important to invest in understanding the biology of this type of cancer. Several gene alterations contribute to the development of lung cancer, including activating mutations, gene translocation and gene amplification at oncogenes as well as inactivating point mutations, homozygous deletions or promoter hypermethylation at tumor suppressor genes. Losses of heterozygosity (LOH) at chromosome 19p are frequent in lung cancer, suggesting that one or more tumor suppressor genes are contained in this region. The *LKB1* gene, also called *STK11*, is somatically inactivated through point mutations and large deletions in lung tumors, demonstrating that *LKB1* is a target of the LOH of this chromosomal arm. The mutational signature of *LKB1* in lung tumors reveals high prevalence of CG:TA and CG:AT substitutions among the six types of nucleotide substitutions which may reflect the influence of polycyclic aromatic hydrocarbon (PAH) adducts from tobacco carcinogens, similar to what happens with *KRAS* and *TP53* mutations in lung tumors. Consistent with this explanation, most lung tumors with *LKB1* mutations are from smokers. *LKB1*-mutant tumors also carry concomitant mutations at other cancer genes such as *KRAS*, *TP53*, *EGFR* and *p16*, indicating that their role in carcinogenesis is not functionally equivalent. The critical involvement of *LKB1* in energetic control checkpoints highlights the importance of these processes in carcinogenesis and provides novel potential targets for gene screening in tumors and for therapeutic intervention. Interestingly, another gene on chromosome 19p, *BRG1* (also called *SMARCA4*), encoding a component of the SWI/SNF chromatin remodeling complex, has emerged as a tumor suppressor gene that is altered in lung tumors. The SWI/SNF complex can regulate transcriptional transactivation or repression by remodeling the chromatin structure, upon disturbing DNA-histone interactions at the nucleosomes in an ATP-dependent manner. The *BRG1* protein features a bromodomain and helicase/ATPase activity. Similarly to *LKB1*, *BRG1* is somatically inactivated by point mutations or large deletions in lung tumors. Simultaneous mutations at *LKB1* and *BRG1* are common in lung cancer cells, which exemplifies how a single event, LOH of chromosome 19p in this instance, targets two different tumor suppressors. However, alterations at *BRG1* always occurred in the absence of *MYC* amplification, suggesting a common role in lung cancer development. We have analyzed the capability of *BRG1* mutations to affect the biological function of *BRG1* and compared the efficiency of the wild type *BRG1* and that of the two mutants in reducing cell growth in cancer cells. Our data provide evidences for an important role for *BRG1* in lung cancer and highlight the need to further our understanding of the function of *BRG1* in cancer.