

MONOUBIQUITINATION LINKED TO REGULATION TRANSCRIPTIONAL MECHANISM IN BREAST CANCER

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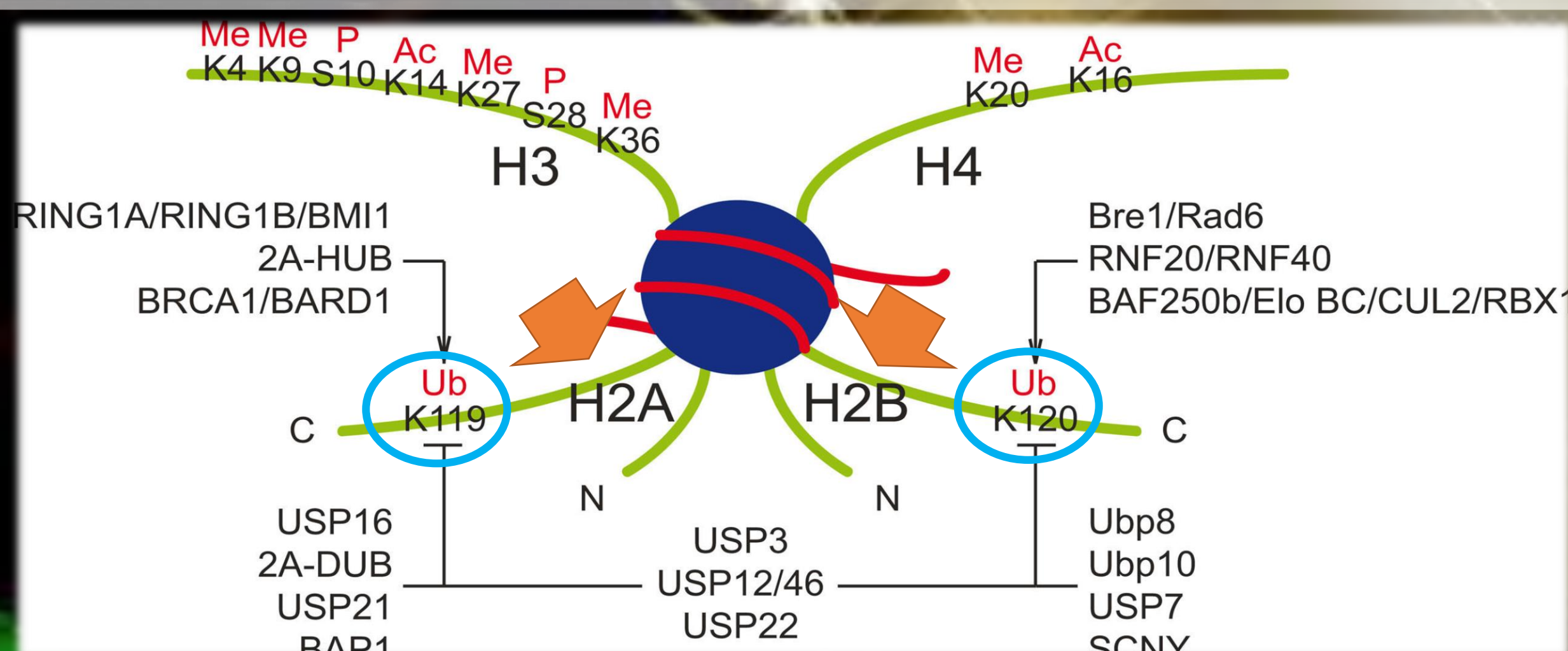
Research Proposal

Background:

Histone post-transcriptional modifications play essential roles in regulation of all DNA related processes. Recent advances have defined critical roles of histone ubiquitination in transcriptional regulation (epigenetic) and DNA repair.

It knows that there is a level epigenetic deregulation in the process of breast cancer and several cases have been reported related to the process of histone monoubiquitination.

The roles of histone ubiquitination in transcription processes of breast cáncer seems to have great importance in expression of genes mutagenic and linking great risk in developing breast cancer.



Edited from: Histone ubiquitination and deubiquitination in transcription, DNA damage response, and cancer. Jian Cao; et al.

Hypothesis:

Confirm and establish the monoubiquitination process as an alternative way of studying and understanding the development of breast cancer in the epigenetic process and determination of possible targets of action of anticancer drugs that can stop the development of breast cancer.

Specific aims:

- Establish a direct relationship between breast cáncer genes and monoubiquitination H2A and H2B histones.
- Establish the monoubiquitination as important epigenetic regulator in breast cancer.
- Find Possible drug targets against cancer development.

Material and Methods:

- MDA-MB-231 Tumoral Cells (culture in vitro).
- Immunoblot to see levels of monoubiquitination in histones of tumotal Cells.
- Condicional Knock-Out mice (Stock BRCA1), control mice (C57BL/6J) and CRE-mice.
- PCR:Determination of correct transgenic mice.
- ChIP-seq: Use specific antibody to H2A and H2B monoubiquitinated
- Microarrays and Analisis Bioinformatics to see differences between control mice and Brca1 KO mice.

Societal Significance:

Cancer is a disease with a high social impact today by the lack of a cure or treatment. Our study will focus on the possibility of finding a new alternative way of action of drugs in genetic processes such as the monoubiquitination providing a new way of action against cancer with greater specificity in comparison with existing therapies.

Budget:

Research costs (euros)				
	Year 1	Year2	Year 3	Total
Personal	20.000	20.000	20.000	60.000
Equipment	10.000	15.000	7.500	32.500
Animals	16.000	16.000	16.000	48.000
Total	46.000	41.000	43.500	140.500

Expected Results:

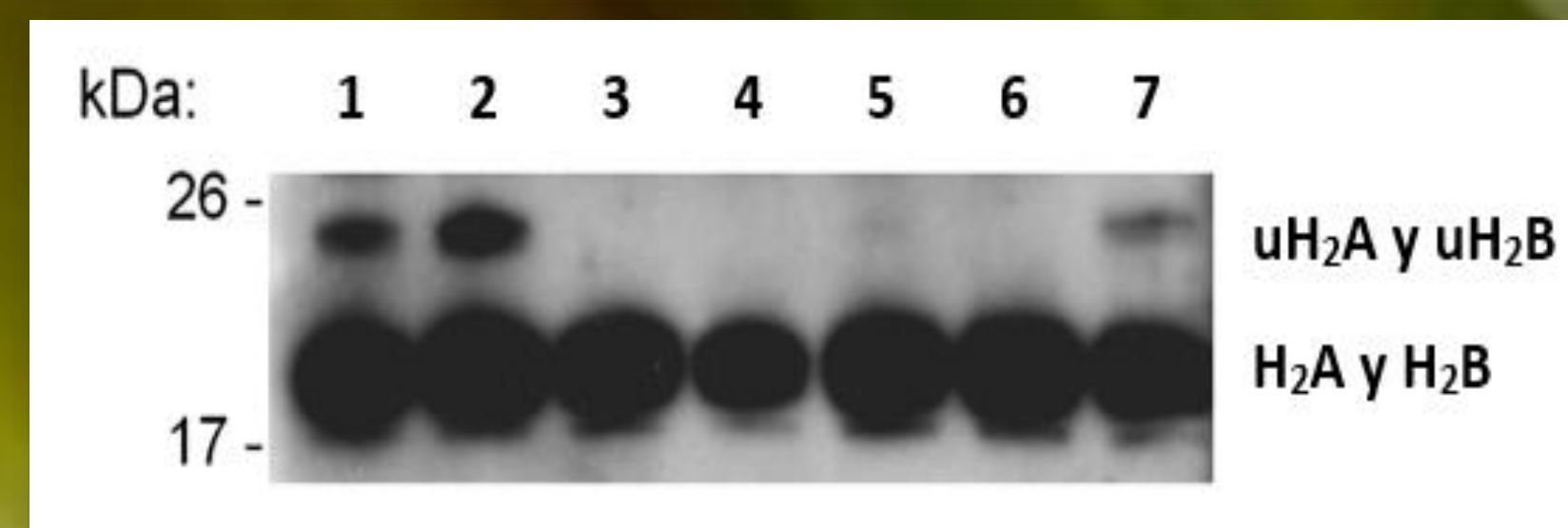


Fig A Edited from Histone H2B Monoubiquitination Facilitates the Rapid Modulation of Gene Expression during Arabidopsis Photomorphogenesis Ratonos: Clara Bourbousse et al.

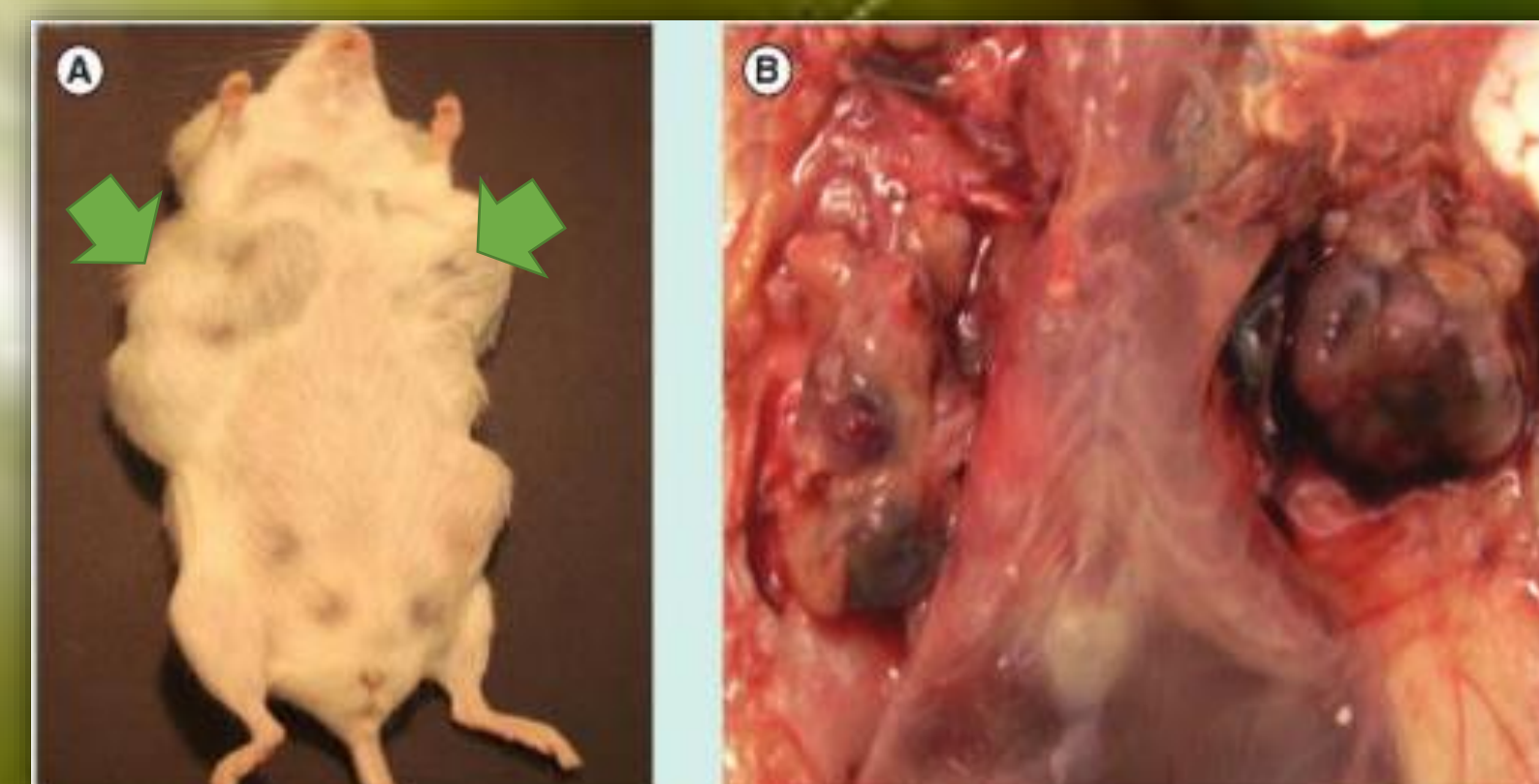
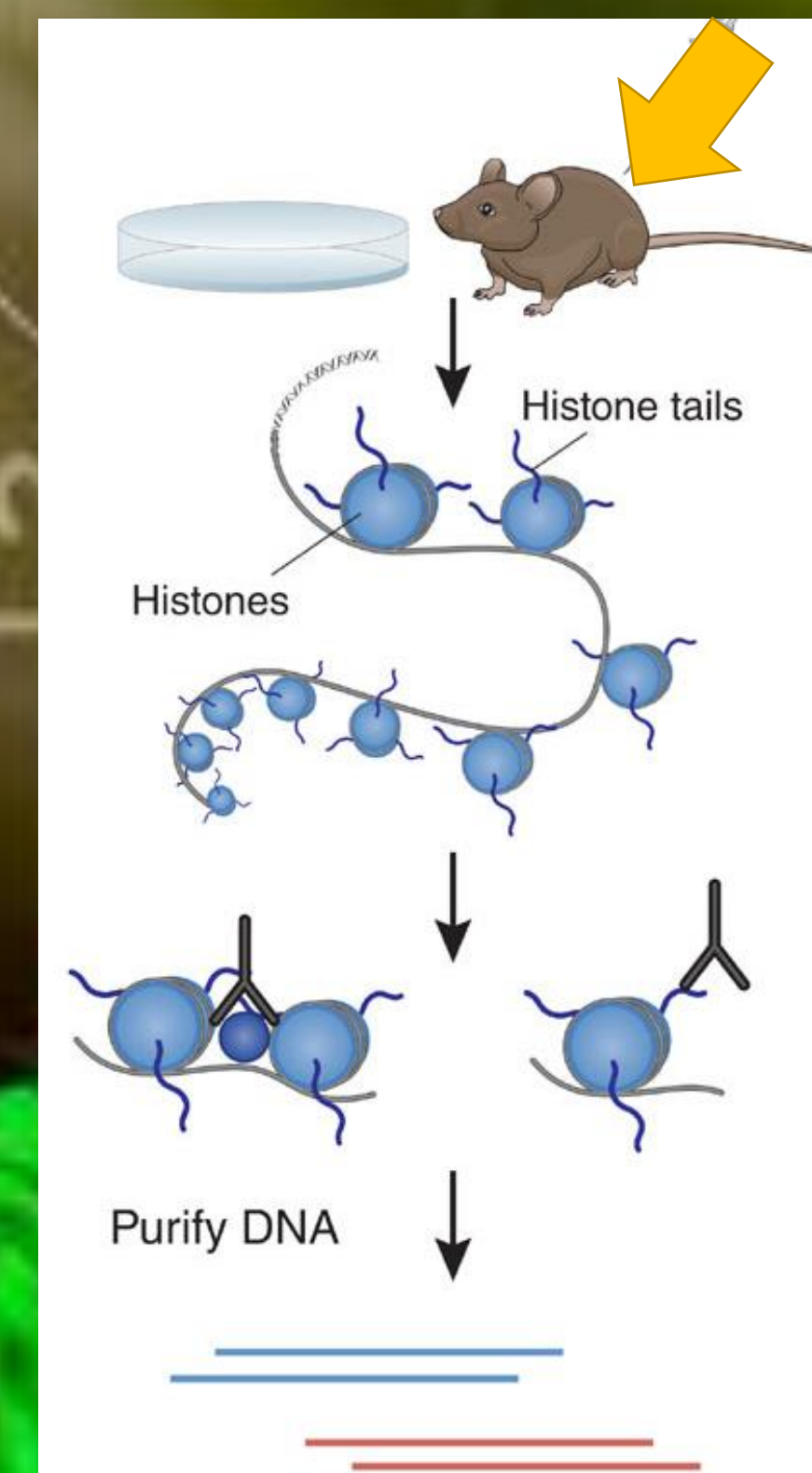
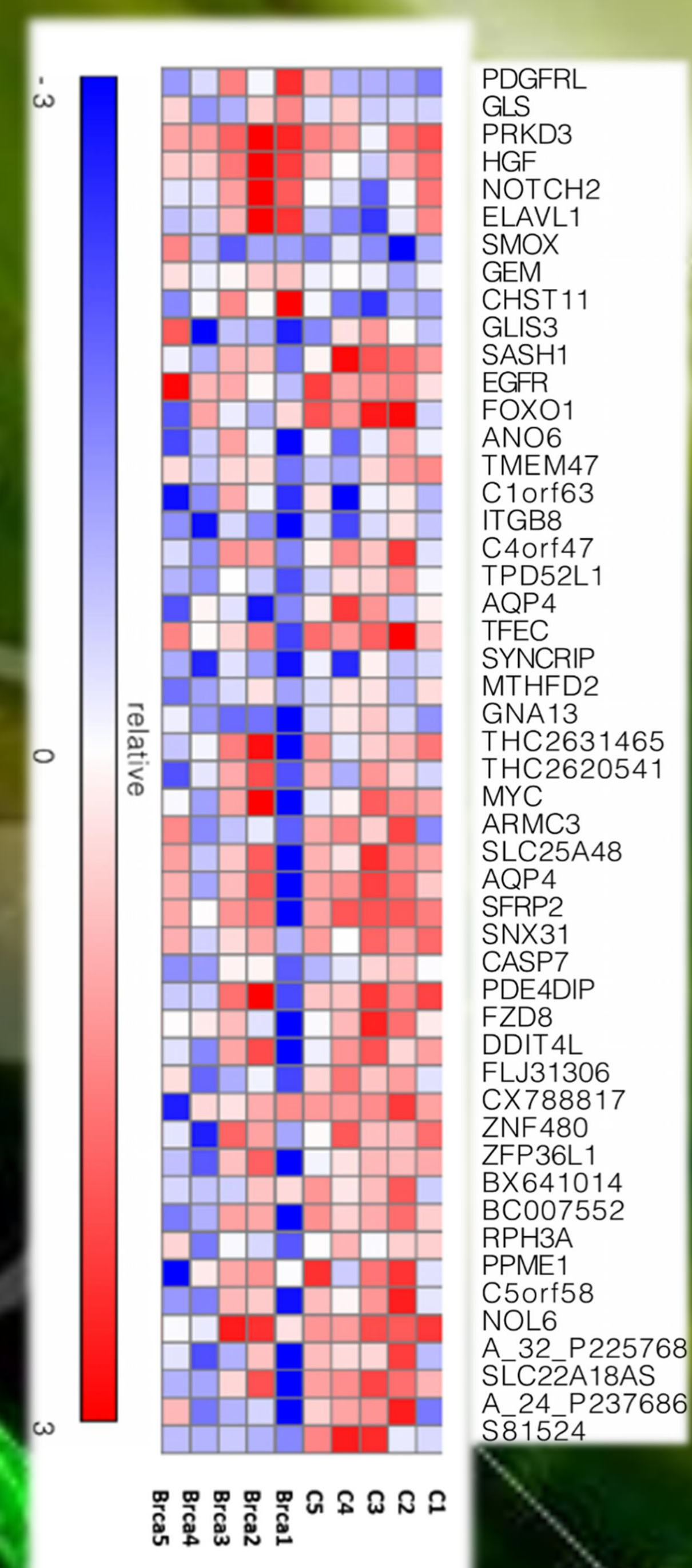
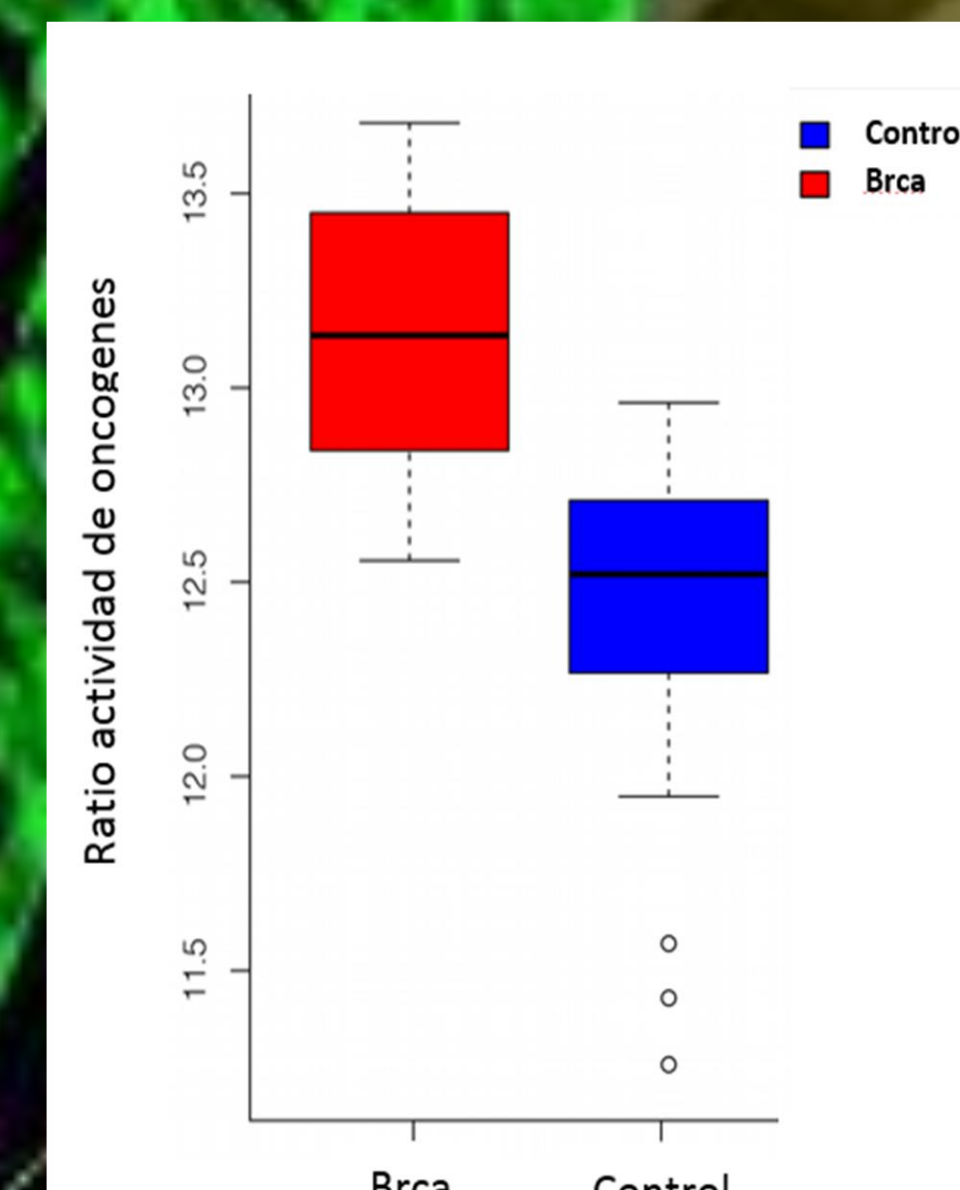


Fig B Edited from MMTV mouse models and the diagnostic values of MMTV-like sequences in human breast cancer; Pankaj Taneja, et al.



Determination of sequences of DNA bound to modified histones with ubiquitins

High differences between gens of control Cells and gens of Brca cell: comparison oncogenes



Timetable of the Project:

Project	1º Year		2º Year		3º Year
Objetivos	1º Semester	2º Semester	1º Semester	2º Semester	1º Semester
Inmunoblot Analisis	X				
obtaining animals		X			
PCR		X	X		
ChIP-Seq.			X		
Microarrays			X	X	
Results					X

References:

- Histone ubiquitination and deubiquitination in transcription, DNA damage response, and cancer Jian Gao* and QinYan*
- The ubiquitous nature of cancer: the role of the SCFFbw7 complex in development and transformation. KM Crusio; Et al.
- Targeting the ubiquitin-proteasome system for cancer therapy; Yili Yang Et al
- Breast Cancer Linkage Consortium Pathology of familial breast cancer: differences between breast cancers in carriers of BRCA1 or BRCA2 mutations and sporadic cases. Lancet 349(9064):1505-10
- Depletion of BRCA1 impairs differentiation but enhances proliferation of mammary epithelial cells. Furuta S, Jiang X, Gu B, Cheng E, Chen PL, Lee WH.