Research Project Proposal
Academic year 2019-2020

Project Nº 13

Title: *Study of the implication of an oncogenic domain in cell biology of primitive eukaryotic cells*

Department/ Laboratory: *ISTUN, CIMA and Dpt. of Microbiology and Parasitology* .

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Summary:
Eukaryotic BRCT (BRCA C-Terminal) domains come from prokaryotic BRCT domain through horizontal transfer (1). It contains four beta sheets, surrounded by three alpha helices (2). At least 23 proteins of the human genome have BRCT domain. Most are implicated in DNA Damage Response (DDR) (3-5). BRCT also plays a role in cell cycle checkpoints. It is thought to be implicated in the transmission of DDR signalling from sensors to cycline-dependent protein-kinases. It is usually a 95-amminoacids sequence, and normally located at the C-terminal end of proteins. The number within the protein can vary from a single copy up to six copies. The distance between repetitions is variable.
We recently identify these oncogenic domains in the proteome of Leishmania, parasites and primitive eukaryotic cells. *Leishmania* spp. cause Leishmaniasis and according to the World Health Organization (WHO) data, these infections are endemic in 98 countries worldwide, with more than 350 million people at risk and few drugs are currently available (6).
BRCT structures are DNA and protein-binding domains related to DNA damage repair (DDR), cell cycle progression, ribosomal biogenesis and protein interaction among others.
Our aim is to characterize the implication of this oncogenic domain in cell biology. We'll study its role in the resistance to treatment of Leishmania parasites. For this purpose, we will test the leishmanicidal activity of genotoxic compounds in parasites overexpressing this oncogenic structure. Also, we will assess the cellular localization of molecule bearing such domain using fluorescent fusion protein technology. We'll finally analyze the implication of this domain and protein harboring this domain in different processes such as infectivity, cell cycle or proliferation of primitive eukaryotic cells.

References

(1) Sheng *et al.*, 2011. Functional evolution of BRCT Domains from Binding DNA to protein. *Evolutionary Bioinformatics*, *7*, 87.

(2) Zhang *et al.*, 1998. Structure of an XRCC1 BRCT domain: a new protein–protein interaction module. The EMBO journal, 17(21), 6404-6411.

(3) Gerloff et al., 2012. BRCT domains: A little more than kin, and less than kind. FEBS letters, 586(17), 2711-2716.

(4) Nguewa et al., 2003. Pharmacological modulation of Poly(ADP-ribose) polymerase-mediated cell death: exploitation in cancer chemotherapy. Mol Pharmacol., 64(5):1007-14.

(5) Nguewa et al., 2005. Poly(ADP-ribose) polymerases: homology, structural domains and functions. Novel therapeutical applications. Prog Biophys Mol Biol., 88(1):143-72.

(6) Fernandez-Rubio et al., 2015. Leishmanicidal activities of novel methylseleno-imidocarbamates. Antimicrob Agents Chemother. 59(9):5705-13.

yes	**X**	**Does the project include the possibility of supervised animal manipulation to complete the training for animal manipulator?**
no		