



# Anti-tumoral Effect of a Cell Penetrating and Interfering Peptide Targeting PP2A/SET Interaction

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## Abstract

**Objective:** To test cell penetrating and interfering peptide Mut3DPT-PP2A/SET in interaction between serine threonine phosphatase PP2A and its physiological inhibitor, the oncoprotein SET.

**Materials and methods:** Adult male C3H/S-strain mice, 60 days old, were given a graft of breast adenocarcinoma cells (TN60) into subcutaneous tissue. Mut3DPT-PP2A/SET peptide was used to block PP2A and SET oncoprotein interaction. The graft-bearing animals were divided into a control group (injected with saline buffer), and an intervention group injected intraperitoneally with Mut3DPT-PP2A/SET peptide (5 mg/kg) every day from day 5 to day 37. The variables we used to compare the outcome in both groups were tumor size in mm (length×width) and histological changes. In the statistical analysis we used ANOVA and Student-Keuls multiple comparisons test and Tuckey for the post-test analysis.

**Results:** 48 mice were grafted at day 0 with breast UNLP-C3H/S tumor cells, and after randomization, they were assigned to one of the two study groups. At day 5 all mice were injected either with placebo or with the peptide. The treated group showed significant tumor reduction ( $p < 0.07$ ). Histological changes showed presence of apoptosis and necrosis of tumor in treated group.

**Conclusion:** The peptide Mut3DPT-PP2A/SET has demonstrated anti-tumor activity by reduction in vivo of tumor growth becoming a promising future in anticancer therapy.

## Keywords

apoptosis, cancer, drug research, peptide

## INTRODUCTION

Breast cancer is still a major public health problem worldwide and still poses significant challenges in relation to therapeutic options. Breast cancers are characterized by

uncontrolled growth of malignant cells in the mammary epithelial tissue. From the surgical resection introduced in the 18<sup>th</sup> century to novel options including hormonal, che-

motherapies and targeted drugs to certain cell's molecules like trastuzumab, many treatment alternatives have been developed in order to control this disease. However, breast neoplasms still remain as one of the leading challenges for public health, the most frequent cancer and unfortunately one of the major causes of decease in females of the 21<sup>st</sup> century. This fact requires actions to investigate new options tending to have new therapeutic options to treat this disease.

The protein phosphatase 2A (PP2A), one of the main serine-threonine phosphatases in mammalian cells, maintains cell homeostasis by counteracting most of the kinase-driven intracellular signalling pathways.<sup>1</sup> PP2A has been shown to be genetically altered or functionally inactivated in many solid cancers and leukaemias, characterised by aberrant activity of oncogenic kinases. Inhibition of PP2A activity is critical to promote cell transformation, tumor progression and angiogenesis, which indicates that PP2A has tumor suppressive role.<sup>2-4</sup>

Recent reports show that pharmacological restoration of PP2A tumor-suppressor activity effectively antagonises cancer development and progression.<sup>4</sup>

SET is a multitask oncoprotein that is critically involved in the initiation and progression of cancer cells. Over-expression of SET protein is a recurrent and clinically relevant event in many malignant diseases. SET is over-expressed in 97% of head and neck squamous cell carcinoma, in more than 90% of non-small cell lung cancer (NSCLC, associated with worse progression-free survival and overall survival), in 70.9% of colon cancer, in 60% of breast tumor tissues (regardless of known biological subtypes), and in 47.5% of prostate cancer among others. It was shown that the functional inactivation of PP2A was essential for BCR/ABL leukemogenesis and, required for blastic transformation in chronic myeloid leukaemia (CML).<sup>5</sup>

SET has also a critical role in promoting the development of therapeutic resistance and, therefore, may be a biomarker that predicts drug sensitivity and a therapeutic target to enhance current anticancer treatments.<sup>6</sup> The SET protein binds to PP2A and is a potent physiological inhibitor of PP2A phosphatase activity PP2A.<sup>7</sup> Accumulation of SET in cancer cells, especially haematological cancers, accounts for decreased PP2A activity.<sup>8,9</sup>

Through direct association, SET affects the function of its interacting proteins, such as PP2A inducing the appearance of tumor phenotype.<sup>7</sup> Consequently, targeting and disrupting the SET-PP2A interaction would result in a recovered PP2A activity and reduced tumor activity. Recent data have shown that antagonizing SET restores sensitivity to anticancer effects of chemotherapies of previously resistant models. Three novel compounds, the small molecules FTY720 (Fingolimod, Gilenya) and EMQA (TD-x series), and the apolipoprotein-E mimetic peptides (COG112, OP449), targeting the SET-PP2Ac interface inhibit tumor growth and overcome therapeutic resistance in many different malignant diseases. We have experimentally identified the sequence of PP2A binding to SET using a PEP-scan

approach.<sup>10</sup> This sequence is exposed at the surface of the protein PP2A and is associated to a cell penetrating peptide in order to generate the peptide Mut3DPT-PP2A/SET.

The peptide Mut3DPT-PP2A/SET has been tested chronic lymphocytic leukemia xenograft models showing an increase in the survival of the mice. In order to prove the activity of the peptide Mut3DPT-PP2A/SET against aggressive breast cancer cells, we performed the present preliminary study in a breast cancer xenograft model developed in our laboratory (Histology A, School of Medicine, National University of La Plata).<sup>11</sup> The chimeric peptide blocking PP2A/SET interactions showed an important tumor growth inhibition, suggesting that it can be used as therapeutic tool for breast cancer treatment.

## MATERIALS AND METHODS

**Mice:** adult male C3H/S-strain mice of 60 days of age raised in the bioterium of Cytology, Histology and Embryology "A" of the Faculty of Medical Sciences of the National University of La Plata were included in the experience. Mice were weighed at the beginning of experiment and each day until the end of the experiment. Animals were sacrificed at day 37 because at this stage of the study the tumor begins to ulcerate and become severely infected.

**Breeding conditions:** mice were subjected to the following standard conditions: water and food available *ad libitum*, ambient temperature maintained at 22±2°C, alternating light and dark periods restricted to 12 h each with illumination by fluorescent lamps beginning at 06:00 a.m.<sup>11</sup>

**Tumor Cell Line:** After an appropriate period of synchronization, the C3H/S-breast adenocarcinoma labeled as TN60-UNLP-C3H/S, was grafted into the subcutaneous tissue of each animal's flank. This is a breast carcinoma that was spontaneously originated in January 2003 in a C3HS mouse of 16 months of age and it is currently in its passage number 131. Macroscopically, it is a well-defined tumor, of yellowish color and elastic consistency. Morphologically, it is categorized as a solid neoplasm encapsulated with cells of medium to large size, vesicular nuclei with prominent nucleoli, scarce basophilic cytoplasm and abundant figures of mitosis and apoptotic forms. It is considered an aggressive tumor that ulcerates after 37 days and causes the death of the specimens affected at day 40 in average. The dose of the tumor injected subcutaneously on the flank of each mouse was 4×10<sup>5</sup> cells.

**Peptide synthesis and sequence:** Peptide was synthesized in an automated multiple peptide synthesizer with solid phase procedure and standard Fmoc chemistry by the company GL Biochem Ltd, Shanghai, China. The purity and composition of the peptides were confirmed by reverse phase HPLC and by mass spectrometry. The sequence of the peptide Mut3DPT-PP2A/SET is as follow: VKKKKIKAEIKI ETVTLLVALKVRERERIT. The sequence VKKKKIKAEIKI corresponds to the cell penetrating peptide and the sequence ETVTLLVALKVRERERIT corre-

sponds to the interfering peptide blocking the interaction between PP2A and SET.

## Experimental groups

The graft-bearing animals were divided into 2 groups: *group 1 (control)*: injected with saline buffer and *group 2* injected intraperitoneally with the Mut3DPT-PP2A/SET peptide (5 mg/kg) every day from day 5 to day 37.

## Variables

Tumor size and histological changes in optical microscopic analysis were selected as variables. Tumor growth was measured in mm (length×width), on alternate days, since the moment they become visible macroscopically until 30 days post tumor graft. Histological changes in tissue samples were performed after the sacrifice of the animals at day 37. The anatomopathological analysis consisted in a Hematoxylin and Eosin staining process. For determination of morphometric parameters, a digital image analyzer was used. Colored sections were observed under an optical microscope (Olympus BX-50, Tokyo, Japan) and the selected images were captured by a digital video camera and entered into a computer for quantitative analysis by ImagePro / ImageJ (NIH-USA)

## Statistical analysis

The data were statistically analyzed using ANOVA and Student-Keuls Multiple Comparisons test and Tuckey as a post-test.

## Ethical considerations

Conditions concerning animal management fully respected the policy and mandates of the Guide for the Care and

Use of Laboratory Animal Research of the National Research Council. We obtained the X±ES of each experimental group.

## RESULTS

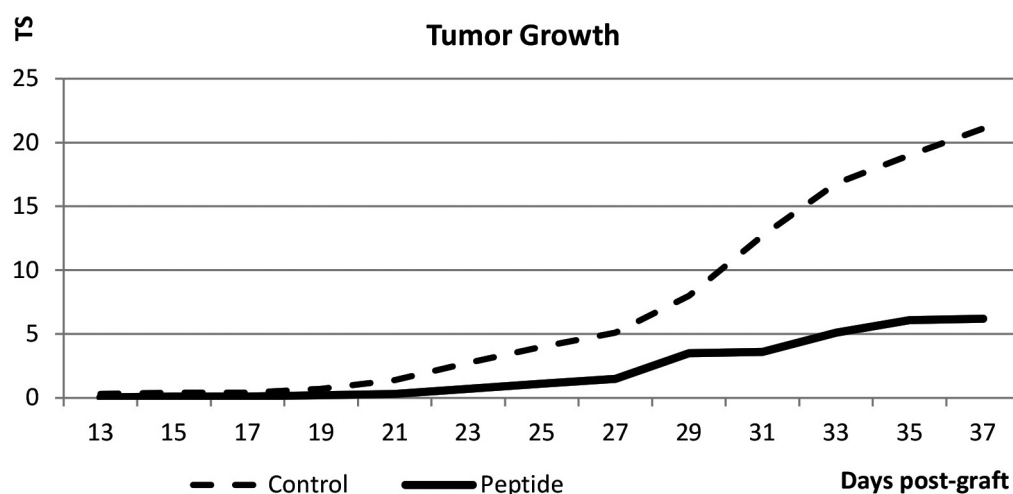
After the tumor graft, 48 mice were randomized and assigned to the two study groups: 24 specimens were included in the group 1 (controls) and 24 – in group 2 (the treatment group). All mice were injected at day 5 either with placebo or with peptide. As we can see in **Fig. 1** all animals (**Group 1 control and Group 2 treated mice**) showed the appearance of the tumor at approximately day 13 of the tumor graft.

Group 1 (controls mice) grew up faster and had a final size greater than that of group 2. However, we couldn't find statistically significant differences between the size of the tumors of groups ( $p < 0.07$ ).

### Peptide Mut3DPT-PP2A/SET has anti-tumoral effect in human xenograft models of breast cancer.

The in vivo efficacy of the peptide was evaluated in breast cancer xenograft models, made using the cell line C3H/S-UNLP. After the tumor graft, 48 mice were randomized and assigned to the two study groups: 24 specimens were included in the control group and 24 in the treatment group. All mice were injected at day 5 either with placebo or with peptide Mut3DPT-PP2A/SET at 5 mg/kg daily in preventive treatment. As shown in **Fig. 1**, the treated group show a strong delay in the tumor development when compared to non-treated control group. This tumor reduction was round 72%, being statistically significant in comparison with controls ( $p < 0.07$ ). Non-treated controls mice were sacrificed on day 35.

C3H/S strain mice were subcutaneously inoculated with  $10 \times 10^6$  C3H/S UNLP tumor cells and intraperitoneally (IP) treated with 5 mg/kg of the peptide Mut3DPT-PP2A/SET



**Figure 1.** Tumor growth by study groups. Tumor growth (TS) was assessed by size calculated by the following formula:  $TS = \text{length} \times \text{width}$  (mm). All animals were sacrificed at day 37.

daily. Control mice received NaCl. The average tumor volume of each group (24 mice per group) is shown in Fig. 1.

Tumor samples were histologically analyzed at day 37. Figs 2, 4 shows the histological status of the tumor in control group at different magnification and Figs 3, 5 – the effect of peptide treatment.

It is clear that in the tumor samples from control group there shows a higher degree of inflammation, apoptosis and necrosis compared to the treated group either at  $\times 10$  or  $\times 40$  magnification.

The tumor showed an expansive growth, with intense reddish coloration and central necrotic changes when treated with peptides. Histological analysis demonstrated a solid neoplasm composed of medium to large cells with vesicular nuclei and prominent nucleoli, with scarce basophilic cytoplasm and a large amount apoptotic forms in treated group.

## DISCUSSION

Apoptosis is a genetically programmed cell death procedure and its deregulation is associated among many malignancies including breast cancer. Apoptosis is known to rely on the Bcl-2 family members and caspases, however recent data suggested that two major families of serine/threonine phosphatases, PP1 and PP2A, are key factors involved in the cell life or cell death decision.<sup>12-14</sup> The Ser/Thre phosphatase PP2A has been implicated in both, induction and prevention of apoptosis, pointing to a complex interplay of phosphatase actions.<sup>15</sup> The only clinical drugs that target a phosphatase are the immunosuppressive cyclosporine A and FK506.<sup>16</sup>

Cell penetrating peptides (CPP) are either protein derived or artificially designed amino acid sequences with the ability to pass through cellular membranes and deliver different types of cargo.<sup>17</sup> CPP can translocate into cells without causing membrane damage, leading to their proposed use as vectors for delivering therapeutic cargo.<sup>18</sup> Hence, they have been applied from cell cultures to organisms with therapeutic purpose.<sup>19</sup>

Hence, peptides that penetrate cells have emerged as new modulators of protein-protein interactions that allow the delivery of biomolecules through biological barriers, thus overcoming the obstacles of internalization and delivery of these vectors to cells. A promising therapeutic use of these biomolecules are testing bi-functional peptides with penetration capability and protein/protein interfering properties like DPT-C9h<sup>20</sup>, targeted to the binding site of caspase-9 to PP2A. This type of peptides, has the ability to induce apoptosis *in vitro*. Since PP2A has been characterized as a tumor suppressor, the inhibition of PP2A activity increases tumorigenesis, and its modulation can be beneficial for cancer treatment<sup>21-22</sup>, suggesting that this protein can be considered as a therapeutic target. In the last years, several cellular inhibitory proteins of PP2A have been described, but one of the more exciting is the SET on-

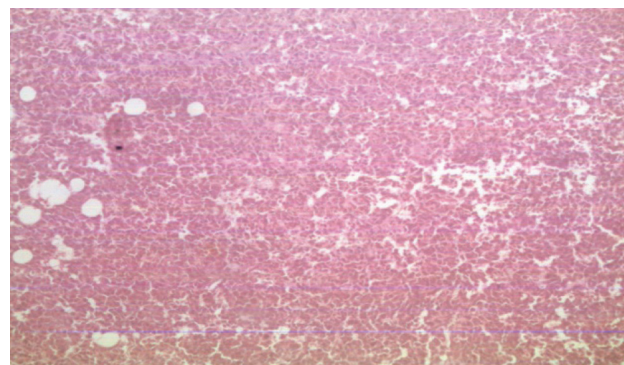


Figure 2. Tumor sample from control mice at day 37 ( $\times 10$ ).

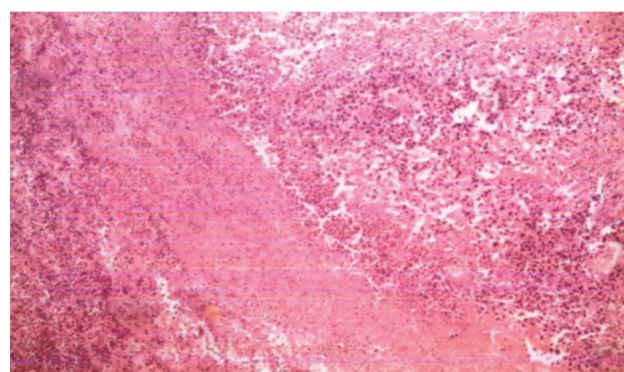


Figure 3. Tumor sample from Treatment Group at day 37 ( $\times 10$ ).

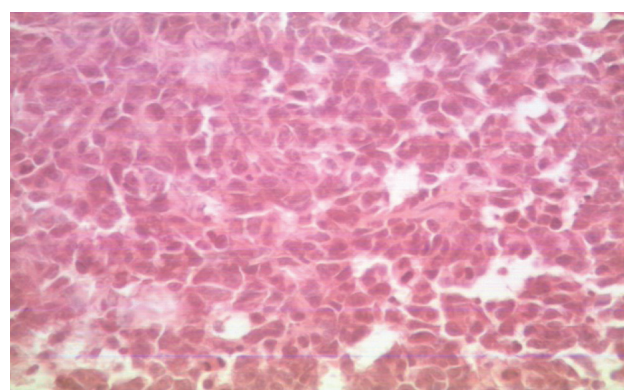


Figure 4. Tumor sample from control mice at day 37 ( $\times 40$ ).

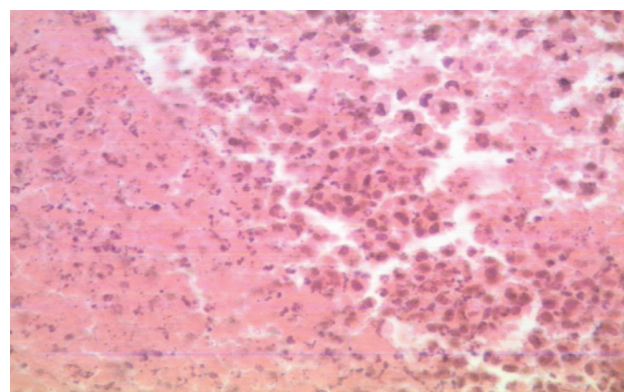


Figure 5. Tumor sample from Treatment Group at day 37 ( $\times 40$ ).

coprotein, which contributes to tumorigenesis, by forming an inhibitory protein complex with PP2A.<sup>23,24</sup> These SET oncoproteins are present as endogenous inhibitors PP2A and cancerous inhibitor of PP2A (CIP2A) that are in about 90% of breast cancers.<sup>25</sup> That is the reason we focused on assaying peptides like Mut3DPT-PP2A/SET containing sequences as ETVTLVALKVRYRERIT, with the capability to block the interaction between PP2A and SET.

The pro-apoptotic peptide we tested in this study specifically deregulates the interaction between caspase-9 and PP2A,<sup>20,26,27</sup> which becomes specifically interesting in aggressive breast cancer like UNLP-breast tumor line. The anti-neoplastic action was clearly demonstrated in the histological analysis that showed high level of tissue inflammation, apoptosis and necrosis of tumor images, as well as a reduction in tumor size when compared with non-treated mice of control group. These results give expectations for the study of highly aggressive tumors with expression of SET oncoproteins.

## CONCLUSION

Tumor growth and its evolution are complex phenomenon controlled by an intricate pattern of competing processes. Classical anti-neoplastic drug chemotherapy seems to reach its maximum profit. New therapeutic options are needed to obtain better results in the future. In this order, we tested a cell penetrating peptide Mut3DPT-PP2A/SET in a breast cancer xenograft model. The results of the study showed a significant tumor reduction and also several changes in the tumor histological analysis. We concluded that the peptide Mut3DPT-PP2A/SET has demonstrated anti-tumor activity by reduction *in vivo* tumor growth, suggesting the potential of this peptide as anti-cancer therapeutic agent.

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## Противоопухолевый эффект клеточно-проникающего и интерферирующего пептида, нацеленного на взаимодействие PP2A / SET

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### Абстракт

**Цель:** Исследовать клеточно-проникающий и интерферирующий пептид Mut3DPT-PP2A / SET при взаимодействии серин-треонинфосфатазы (PP2A) и его физиологического ингибитора, онкопротеина SET.

**Материалы и методы:** Взрослым самцам мышей линии C3H / S в возрасте 60 дней вводили суспензию, содержащую клетки аденокарциномы молочной железы (TN60) в подкожную клетчатку. Пептид Mut3DPT-PP2A / SET использовали для блокирования взаимодействия PP2A и онкопротеина SET. Животные были разделены на контрольную группу (инъекционную солевую буфером) и группу вмешательства, которой внутривенно вводили пептид Mut3DPT-PP2A / SET (5 мг / кг) ежедневно с 5 по 37 день. Переменные, использованные для сравнения результата в обеих группах были: размер опухоли в мм. (длина x ширина) и гистологические изменения. Для статистического анализа мы использовали тест ANOVA и тест множественных сравнений Student-Keuls и Tuckey для послетестового.

**Результаты:** 48 мышам была введена суспензия в день 0 с опухолевыми клетками UNLP-C3H / S из молочной железы и после рандомизированного отбора их разделили на две группы. На 5-й день всем мышам вводили либо плацебо, либо пептид. Обработанная группа показала значительное уменьшение опухоли (p.0.07). Гистологические изменения выявили наличие апоптоза и некроза опухоли в обработанной группе.

**Выводы:** Пептид Mut3DPT-PP2A / SET демонстрирует противоопухолевую активность, уменьшая рост опухоли in vivo, что представляет собой многообещающее будущее для противоопухолевой терапии.

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### Ключевые слова

апоптоз, лекарственное исследование, пептид, рак

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