



## New Therapeutic Approaches for Non-Muscle Invasive Bladder Cancer (NMIBC): Intravesical Use of OncoTherad Biological Response Modifier and Its Association with Platelet-Rich Plasma (PRP).

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### Abstract

This study characterized the effects of the immunotherapy using the nanostructured complex OncoTherad, either associated or not to Platelet-Rich Plasma (PRP) on the non-muscle invasive bladder cancer (NMIBC) chemically induced in mice. The treatment with OncoTherad inhibited the cancer's progression and promoted tumoral regression in 85.7% and the OncoTherad associated with PRP in 71.4% of the animals. Thus, the immunotherapy using OncoTherad associated to PRP raises as a new therapeutic strategy for NMIBC, which allows the treatment's personalization and the reduction of the immunogenicity to patients who either show recurrence, are resistant to the therapy using *Bacillus Calmette-Guérin* (BCG) or are ineligible to the radical cystectomy. The immune system modulation and the relation of OncoTherad with the activated platelets demand continuity of studies to detail the mechanisms of this association.

### Key words:

Bladder Cancer, OncoTherad, Platelet Rich Plasma

### Introduction

Non-muscle invasive bladder cancer's (NMIBC) primary treatment consists on the transurethral resection, followed by the intravesical immunotherapy with *Bacillus Calmette-Guérin* (BCG), which is associated with collateral effects and recurrence index of up to 30%. Aiming new, more effective and with less adverse effect therapies, our research group developed a synthetic nanostructured compound: Biological Response Modifier - Inorganic Phosphate Complex 1, or OncoTherad. In chemically induced CBNMI rats, OncoTherad showed a significant immunomodulatory and antitumor effect through the stimulation of the interferon signaling pathway Toll-like receptors (TLRs) 2 and 4-mediated<sup>1</sup>. Our research group investigated the importance of Platelet Rich Plasma (PRP) in the modulation of immune system receptors (TLRS) and demonstrated that PRP was able to exert antitumor effects<sup>2</sup>. Considering the importance of the modulation of these immune system receptors by the phosphate groups and its relation to the activated platelets, the objective of this study was to describe the effects of OncoTherad associated with PRP on the treatment of NMIBC chemically induced in C57BL/6J mice by the histopathological characterization of NMIBC and the comparison of the tumor progression after the treatments with either OncoTherad, PRP and OncoTherad+PRP.

### Results and Discussion

The different treatments did not alter animal's body weight, water and food consumption ( $p > 0.05$ ). After the induction using the *N*-ethyl-*N*-nitrosourea carcinogen (50mg/mL), the predominant diagnose was carcinoma *in situ* (pTis), which was characterized by marked cellular atypia and disorganization in a flat urothelium (Figure 1). Comparing the tumor progression after the treatments, PRP (0,1mL) decrease of bladder neoplastic lesions progression in 28.5%; OncoTherad (20mg/mL) 85.7% and OncoTherad+PRP in 71.4% of the animals. Benign lesions such as flat hyperplasia were present in 42.8% of the animals from Oncotherad group, as well as healthy urothelium (28.5%). The animals of the PRP group exhibited papillary urothelial carcinoma – pTa (57.1%) and pTis (14.2%); while in the OncoTherad+PRP group there

was a predominance of non-malignant histopathological lesions such as flat hyperplasia (42.8%) and low-grade intraurothelial neoplasia (28.5%).

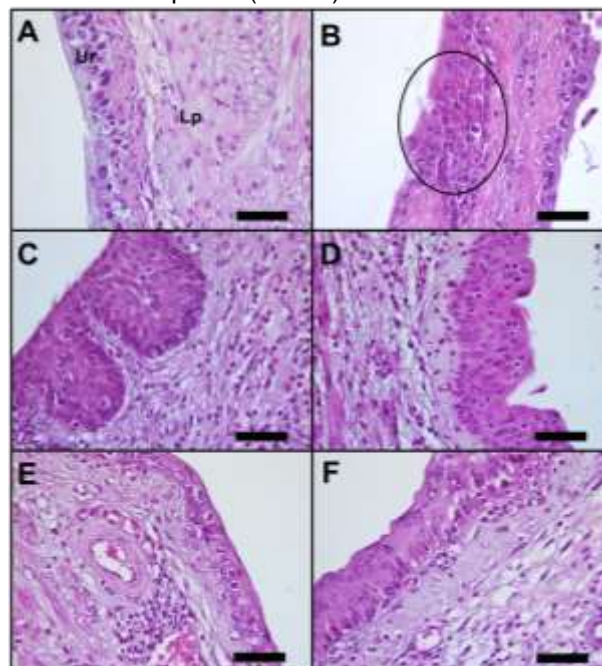


Figure 1: Photomicrographs of the urinary bladders from Control (A); Cancer (B); PRP (C); OncoTherad (D, E) and OncoTherad+PRP (F) groups. (A) Healthy urothelium (Ur) and Lamina propria (Lp). (B) pTis (circle): disordered arrangement and cellular atypia - enlarged nuclei, reduced cytoplasm and prominent nucleoli. (C) pTa: endo or exophytic papillary lesions and disordered proliferation of urothelial cells with loss of cellular polarity. (D) Flat hyperplasia: thickening of the urothelium without atypia. (E) Normal urothelium. (F) Low-grade intraurothelial neoplasia: few atypia, without loss of cellular polarity. HE. Bars = 50 µm.

### Conclusions

We concluded that the immunotherapy with OncoTherad either associated or not with PRP significantly promoted inhibition of tumor progression, constituting a new therapeutic strategy for refractory CBNMI patients who are resistant to BCG's therapy or ineligible to the cystectomy.

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