

## IL-17 and COX-2 inflammatory response in the prostate anterior lobe from TRAMP mice after Nintedanib treatment

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### Abstract

The aim of study herein is to evaluate the Nintedanib therapy effects on the morphology and in COX-2 and IL-17 imunoreactivity in the prostate anterior lobe in different tumor progression grades in TRAMP mice. Our results indicated that Nintedanib delayed the prostate carcinogenesis progression, with reduction of over 20% at the frequency of tissue injuries in the treated 16 week old mice in relation to control mice. Also, decreased COX-2 and IL-17 levels were verified in both groups treated with Nintedanib in the prostate anterior lobe. Thus, we concluded that Nintedanib was efficient in reducing the tumor progression and also, despite not directly being related to inflammation, Nintedanib may adversely affect inflammatory pathways, favoring prostate cancer delay.

### Key words:

*Cancer, Inflammation, Nintedanib.*

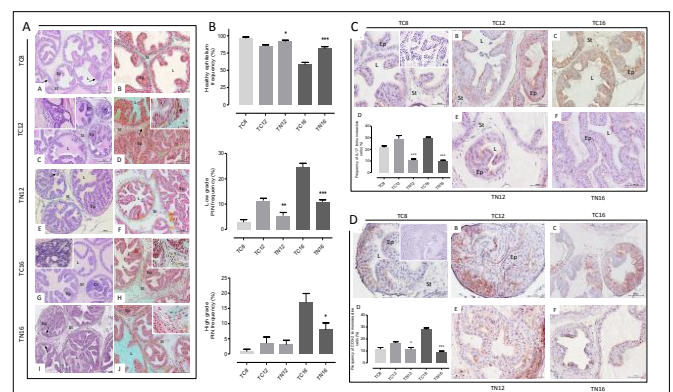
### Introduction

Different biological processes are involved in the development of prostate cancer such as inflammation which is responsible for over 20% of cancers<sup>1</sup>.

Different drugs have been evaluated for cancer treatment, including Nintedanib (which acts by inhibiting cell proliferation and apoptosis in three cell types involved in angiogenesis<sup>2</sup>). In addition to its antiangiogenic activity, Nintedanib has shown anti-inflammatory potential, presenting results in reducing cells such as lymphocytes and neutrophils in the tumor site beyond the reduction of cytokines such as IL-1 $\beta$ <sup>3</sup>. So the aim herein was to evaluate the potential anti-tumor and anti-inflammatory activity presented by Nintedanib in the anterior prostate lobe of TRAMP animals treated in different periods of lesion development.

### Results and Discussion

The experimental groups were divided into control and treated (10mg/kg/day Nintedanib) and sacrificed with 8 (only for control), 12 and 16 weeks of age. Nintedanib treatment showed significant results on delaying the advance of the carcinogenesis typical lesions in the anterior lobe of the prostate, especially in the intermediate grade group (16 weeks) where a reduction of 20% of the lesions was observed. Stromal changes were also noticed; the treatment reduced the thickening of the fibromuscular layer. IL-17 is a cytokine that appears to play a dual role in tumor development. It promotes cytotoxic response towards the tumor cells, resulting in tumor regression and it also promotes tumor progression by inducing the secretion of proinflammatory cytokines and neutrophils mobilizers chemokines<sup>4</sup>. The treatment reduced significantly the immunoreactivity of IL-17, the main difference was observed between the control and 16 weeks of age group. COX-2 is an enzyme that contributes to the inflammatory response and progression of cancer. Its gene is overexpressed in the presence of cytokines, growth factors and tumor stimulant factors, indicating their relation to inflammatory processes. By presenting these features, this enzyme has been targeted to identify inflammatory sites and cancer<sup>5</sup>. The immunoreactivity of the enzyme was also significantly diminished by treatment, mainly for the older group.



**Image 1.** A. Morphology results. B. Morphological analysis. C. IL-17 Immunohistochemical results. D. COX-2 Immunohistochemical results.

### Conclusions

Results showed that Nintedanib treatment have promising effects in delaying the tumorigenesis on the anterior prostate lobe in the TRAMP model in early and intermediate cancer development grades. The Nintedanib administration resulted in not only decreased tumoral lesions development but also in decreased levels of inflammatory molecules, indicating that the oncogenic and inflammatory pathways are so related this antiangiogenic drug can delay or even prevent the occurrence of chronic inflammation.

### Acknowledgement

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