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Development of polymer-based combination therapeutics for the treatment of Castration-Resistant Prostate Cancer (CRPC)

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Introduction: Prostate cancer (PCa) is the most prevalent malignancy diagnosed in males and the second most common cause of male cancer deaths.[1] Therefore, identification of biomarkers for aggressive PCa could facilitate the identification of therapeutic targets. The presence of a fusion gene between TMPRSS2 (androgen-dependent serine protease) and ERG (transcription factor belonging to the ETS family), causing overexpression of TMPRSS2-ERG (T2E) transcript, represents a chromosomal rearrangement that is present in 50% of diagnosed PCa.[1,2] The androgen receptor (AR) and phosphatidylinositol 3-kinase (PI3K) signaling pathways play an important role in PCa. Preliminary results demonstrated that these pathways regulate each other by reciprocal negative feedback.[3] Interestingly, the combination of an IGF1R inhibitor (monoclonal antibody mAb) with an anti-androgen drug results in synergistic anti-tumor effects in T2E positive cells.[4]

Objective: To improve this therapeutic strategy, our final aim is to construct a polymer-based combination therapy composed of a polymer-antibody conjugate (PGA-mAb) combined with anti-androgen drug (Abiraterone) to produce a T2E-targeted treatment for aggressive PCa.

Methodology: To evaluate the mAb and PGA-mAb response in PCa cell models the cells were seeded in 96 well plate, after 48h the cells were treated with the compounds and 72h later the cell viability was analyzed by 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium (MTS) assay. To determine the selectivity against T2E fusion gen the cells were seeded in 24 well plate 2 days prior transfection. ERG siRNA and non-silencing siRNA were added to cells for 24 h. Following this time the medium was replaced and after another 24h cells were incubated with mAb, PGA-mAb alone and in combination with Abiraterone along 72 h, in this point the activity was measured by MTS assay. To check the mAb and PGA-mAb localization cell trafficking studies were performed, both compounds were labeled with a fluorophore Cyan 5.5. The compounds were incubated in VCaP cells for 30min and then was studied the cellular fate by immunofluorescence using confocal and STORM microscopy (Fig.1). To determine the cellular pathways related with treatments, we checked different proteins by Western Blot assay. To optimize in vivo model, VCap cell line was virally infected with Lentis pRNA tin Luc 2 vector to express luciferase, 24 h later the medium was replaced and the cells were selected by G-418 antibiotic. Cells were implanted into C.B-17/IcrHanHsd-Prkdc-scid male prostate gland and tumor growth was measured twice a week by IVIS spectrum along 7weeks. PGA-mAb and mAb treatments were administered intravenously instead antiandrogen drug was given orally.

Results: We synthesized, fully characterized, and evaluated an antibody-drug conjugate (poly-L-glutamic acid (PGA)-mAb) in a panel of PCa cell lines (VCaP, LNCaP, PC3, 22RV1, DU145 and RWPE1). Only the VCaP cells, which express the T2E fusion gene, responded to both the conjugated and unconjugated forms of the mAb. To assess the potential of the combinatorial approach, we evaluated the mAb and the PGA-mAb with and without anti-androgen drug in the VCaP cell line. This study found that the antitumor activity of the combination therapy (mAb or PGA-mAb + anti-androgen drug) relied on the expression of the ERG gene (and hence the

fusion gene). However, the PGA-mAb in combination with anti-androgen drug displayed enhanced selectivity for T2E fusion gene presence when compared to the combination employing the unconjugated mAb. To understand this difference, we are currently exploring potentially different mAb/PGA-mAb cellular trafficking mechanisms and we are also testing the activity of the combination therapy in an optimized orthotopic PCa model employing luciferase-expressing VCaP cells. Our *in vivo* results showed higher PGA-mAb antitumoral activity compared with mAb treatment.

Conclusions: Our results suggest that a combination of the PGA-mAb conjugate with anti-androgen drug could represent a promising therapeutic strategy for enhanced treatment of the T2E PCa patient subtype.

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