

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



PRINCIPE FELIPE  
CENTRO DE INVESTIGACION

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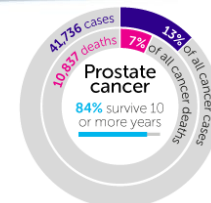
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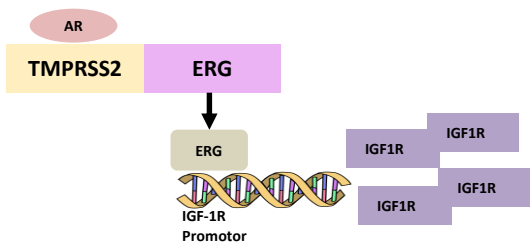
Second most common cancer in men and leads to 10% of cancer deaths in Europe.

PCa presents a high molecular heterogeneity both intratumoral and intertumoral. Association with different clinical behavior.



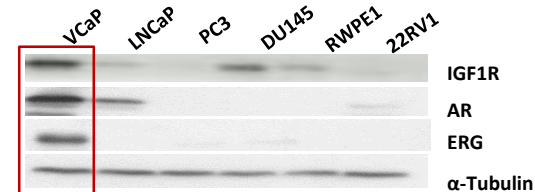
Adapted from <http://www.cancerresearchuk.org/>

**POTENTIAL BIOMARKER:** FUSION GEN between **TMPRSS2** (androgen-dependent serine protease) and **ERG** (transcription factor) = **T2E**

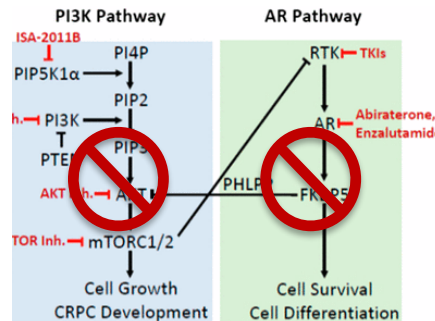
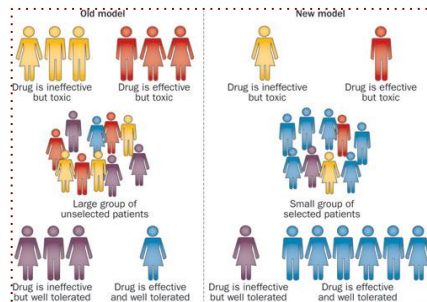


- **TMPRSS2-ERG (T2E)** is present in **50%-70%** PCa
- **Overexpression of ERG transcript**
- **Increase IGF1R levels**

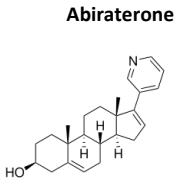
Vertebral- Cancer Prostate (VCaP) cell line



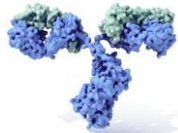
**FINAL AIM**  
Design Personalized Medicine for PCa



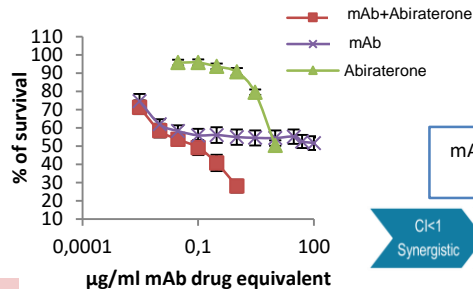
Preliminary studies and Aim



IGF1R  
inhibitors



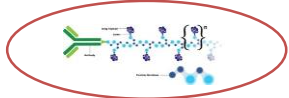
Need for better/safer therapies  
NANOMEDICINE







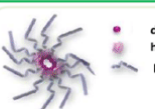
mAb:Abiraterone  
CI: 0.03

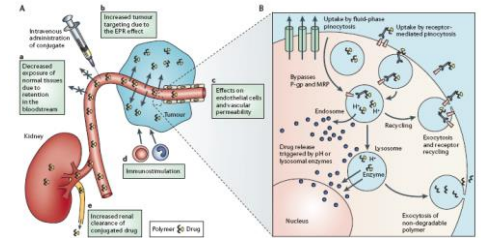


Immunoconjugate



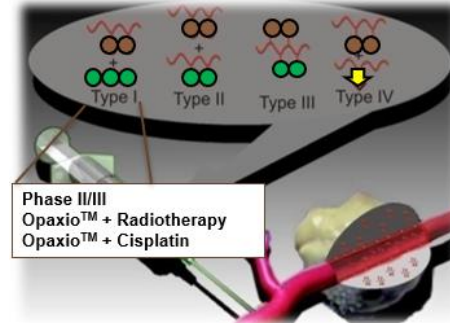
- Increase stability and solubility of the antibody
- Long blood circulation time
- Decrease immunogenicity
- Decrease toxicity
- Specific drug delivery (EPR effect) + Active targeting
- Possibility to use multivalent carriers to allow combination therapy

Polymeric drug	Polymer-protein conjugate	Polymer-drug conjugate
 2-20nm Random copolymer L-alanine, L-lysine, L-glutamic acid and L-tyrosine (COPAXONE®)	 10-20nm PEG-Asparaginase (ONCASPAR®)	 3-20nm Poly(glutamic acid)-PTX (OPAXIO®)
Polyplex	Polymeric micelle	
 30-100nm PEG-Poly(aspartic acid)/siRNA	 60-100nm PEG-Poly(aspartic acid)-DOX (NK911)	

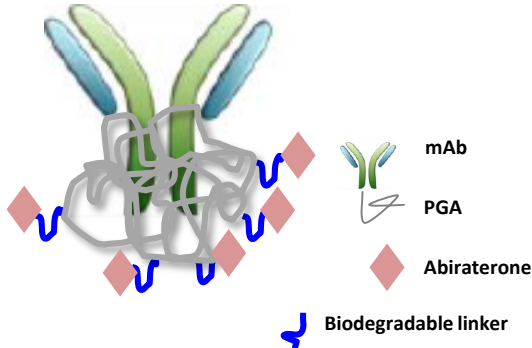


Duncan R. Nature Rev. Cancer 2006

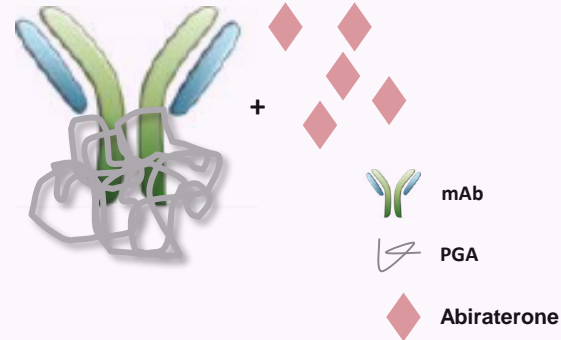
A polymer-based combined therapy using two targetable drugs such as Abiraterone and mAb would produce a more effective and safer compound for the treatment of advanced PCA positive for T2E fusion gene



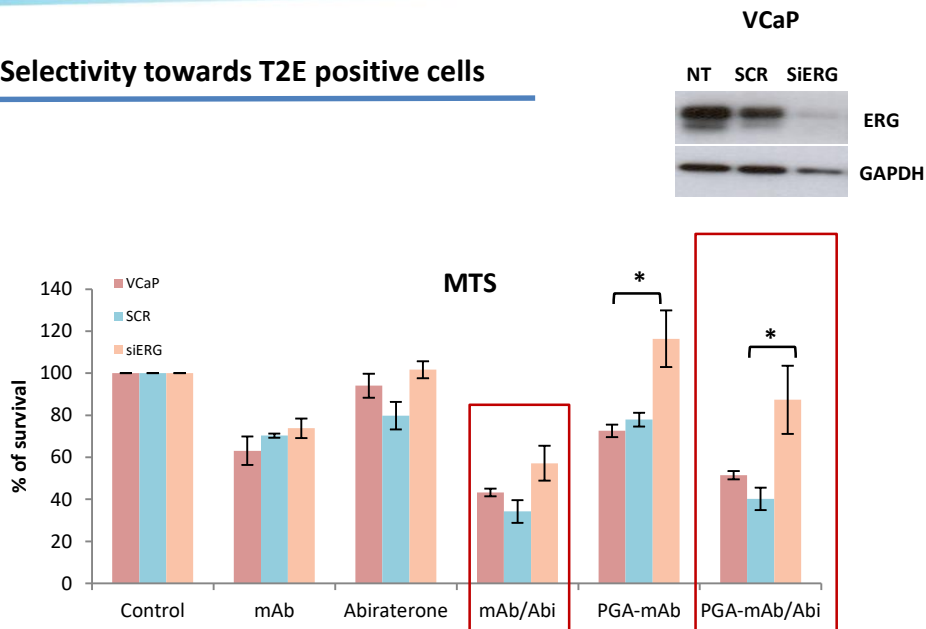
PGA-mAb-Abiraterone combination conjugate



PGA-mAb conjugate + free Abiraterone

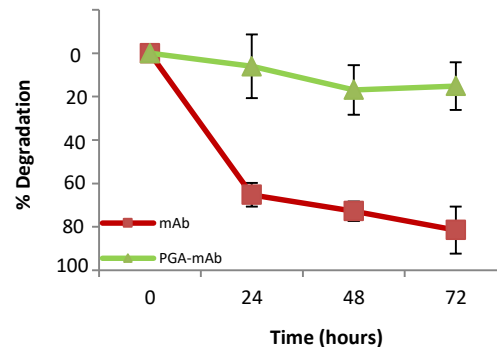


### Selectivity towards T2E positive cells



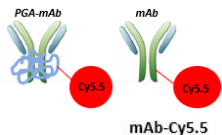
Greater selectivity towards T2E+ models upon PGA-mAb/Abiraterone conjugation

### Stability studies (Activated serum)

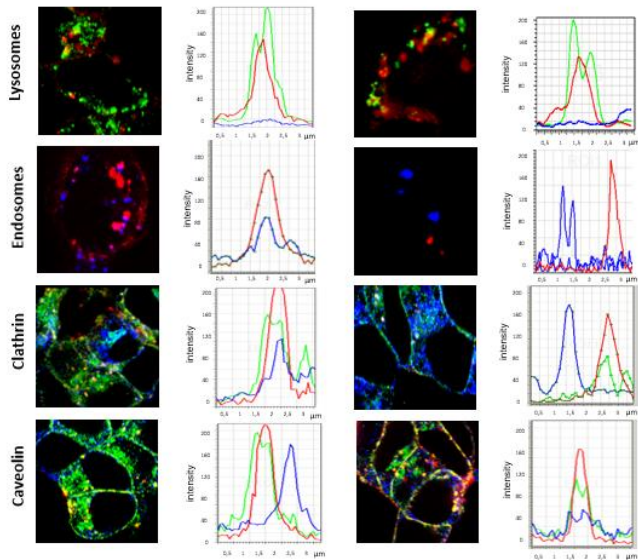


Polymer conjugate stability is maintained along the time but the antibody is decreased 65% after 24 hours

Study of the cellular uptake of the combination polymer conjugates (VCaP cell line)

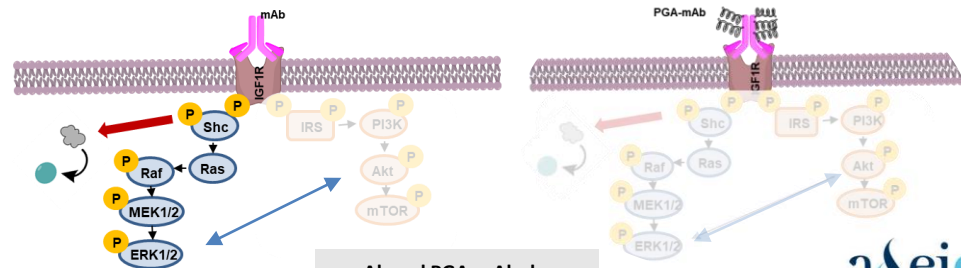
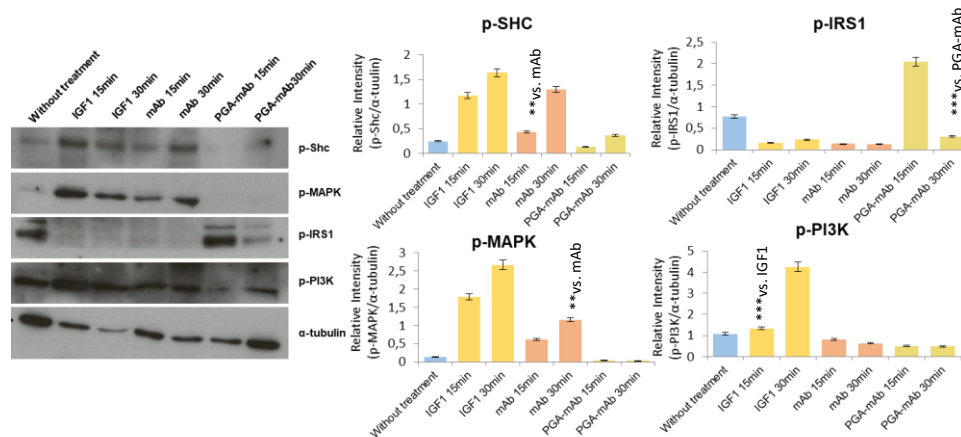


- Lysosomes, Clathrin, Caveolin-1
- Endosomes
- mAb, PGA-mAb



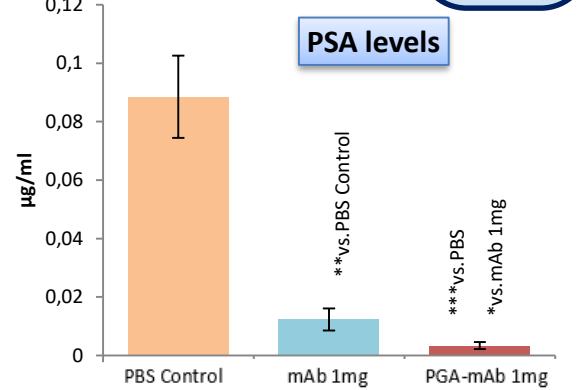
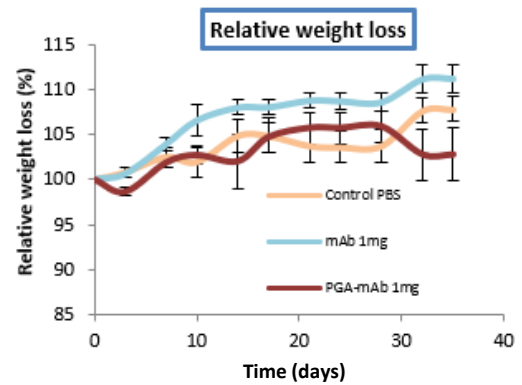
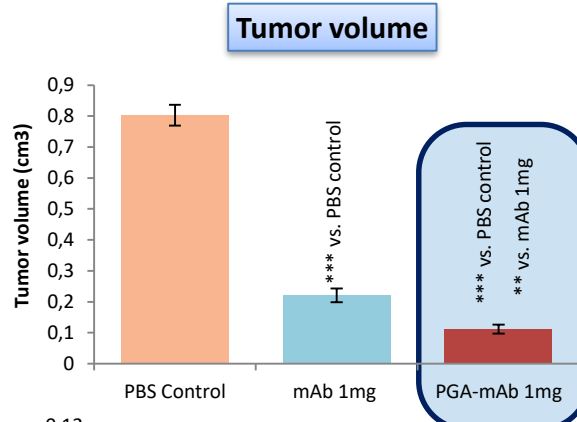
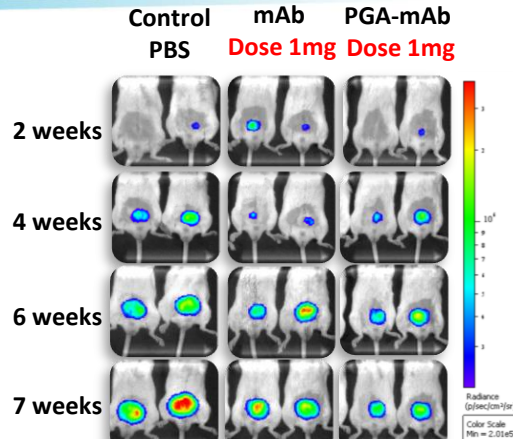
The mAb mostly colocalizes with Clathrin and the PGA-mAb mainly with Caveolin-1

mAb and PGA-mAb show different cellular trafficking



mAb and PGA-mAb show different inhibition pathways

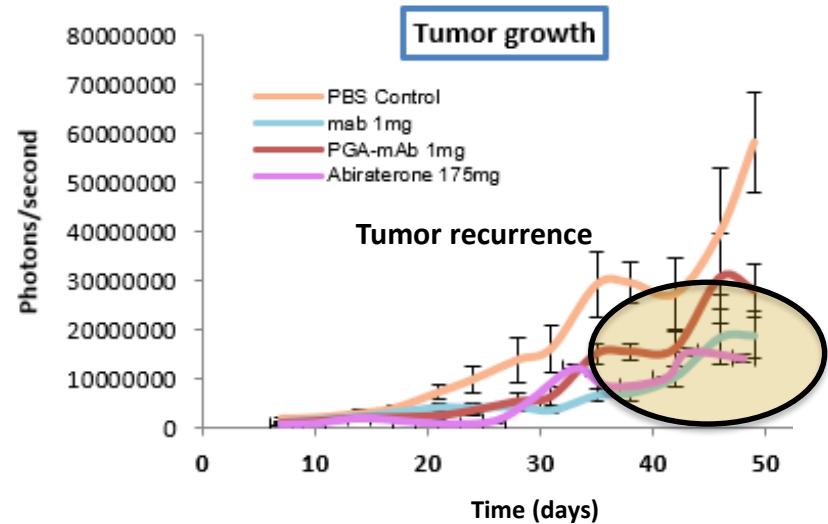
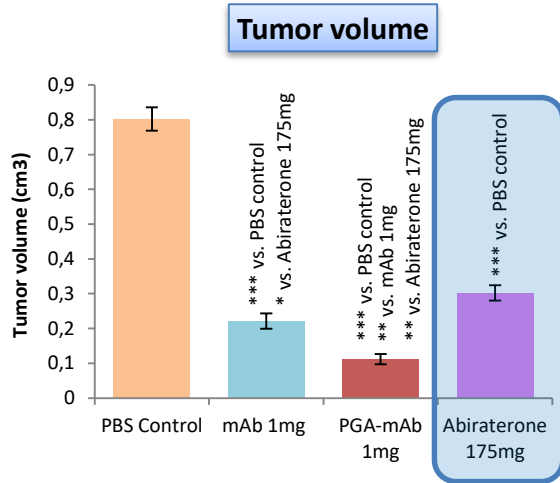
## Orthotopic Prostate Cancer mice model



### Concluding Remarks

PGA-mAb could be a better IGF-1R inhibitor since it shows different inhibition pathway and cellular trafficking comparing with mAb

*In vivo* studies shows promising results upon conjugation using an equivalent dose



ONGOING

Combination therapy *in vivo* with polymer conjugate and free Abiraterone to delay tumor recurrence.

# 16<sup>th</sup> ASEICA INTERNATIONAL CONGRESS

Valencia, 6<sup>th</sup> - 7<sup>th</sup> - 8<sup>th</sup> November 2018



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**SAF2013-44848-R**

**FPI grant BES-2014-068439**



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