The Role of Innate Tumor Immunity in Prostate Cancer

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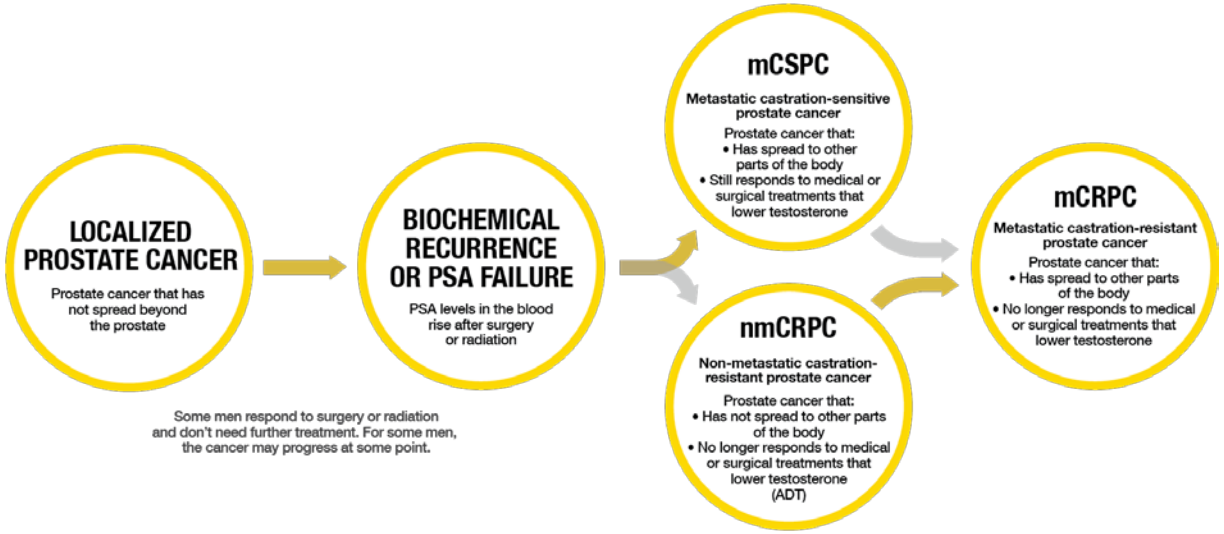
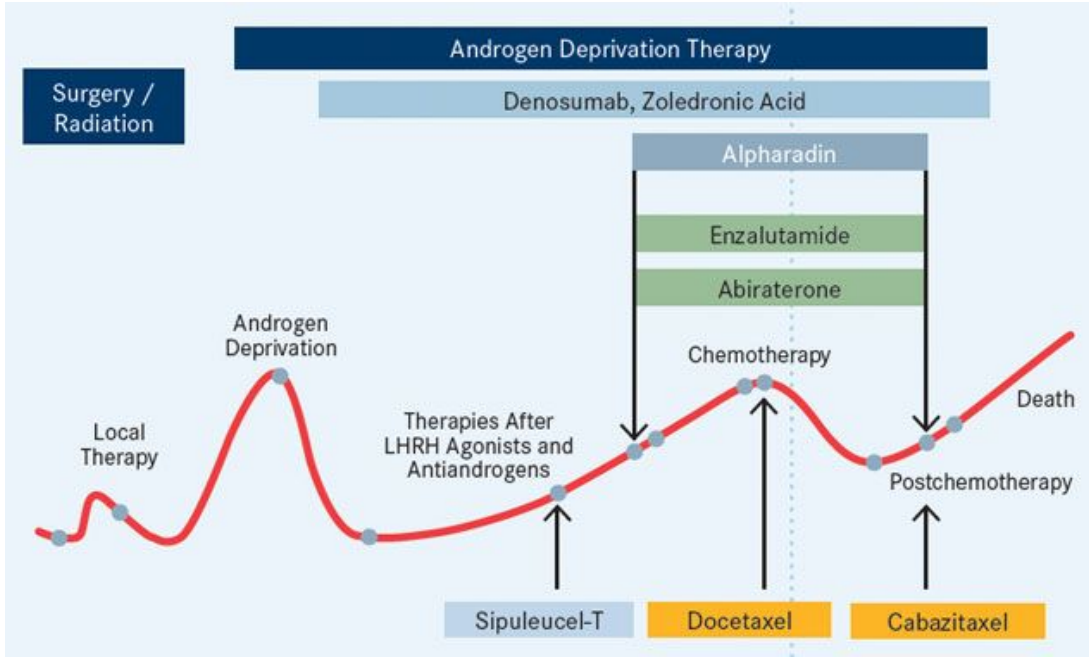
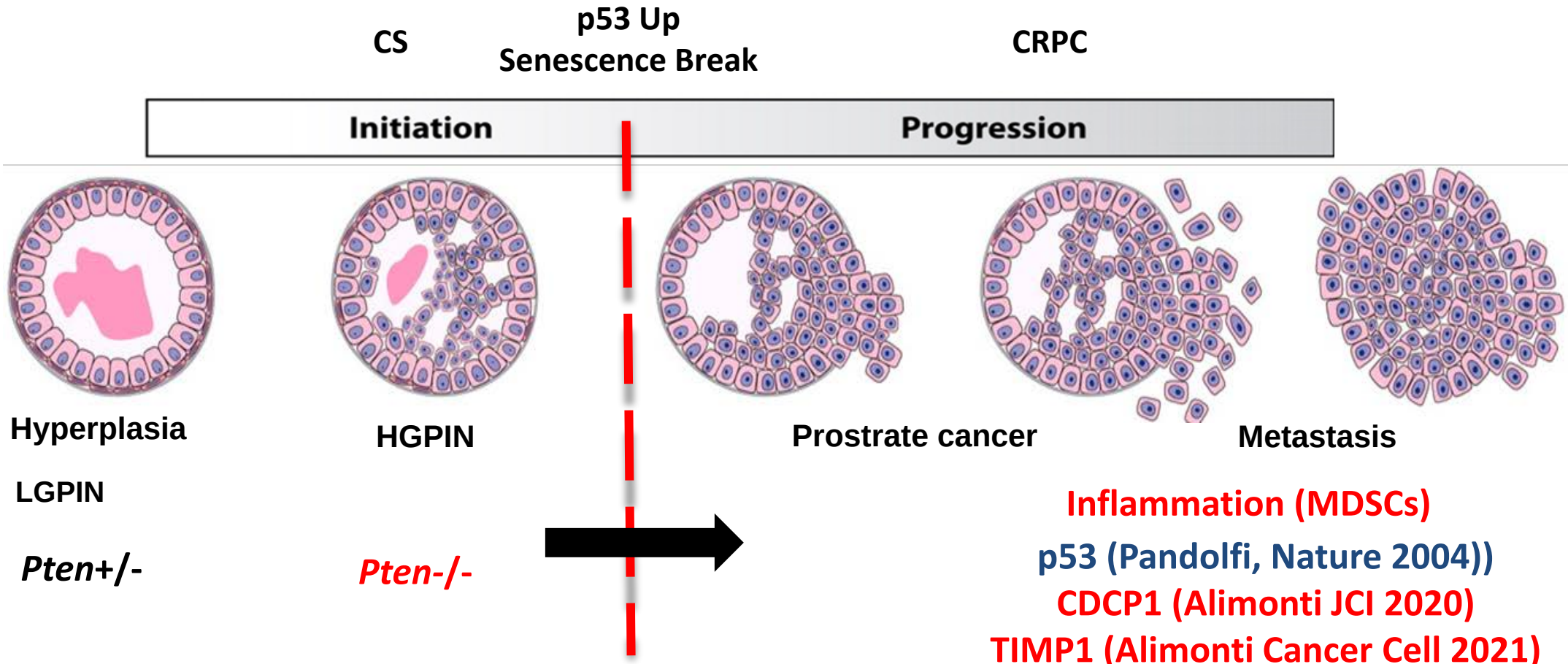
Prostate cancer is the second most frequently diagnosed cancer





Molecular drivers of castration-resistant prostate cancer



Alimonti, Nature Genet. 2010
Alimonti, JCI 2010

Metabolic Rewiring
(Alimonti team, Nature Genet. 2018)
(Pandolfi team, Nature Genet. 2018)

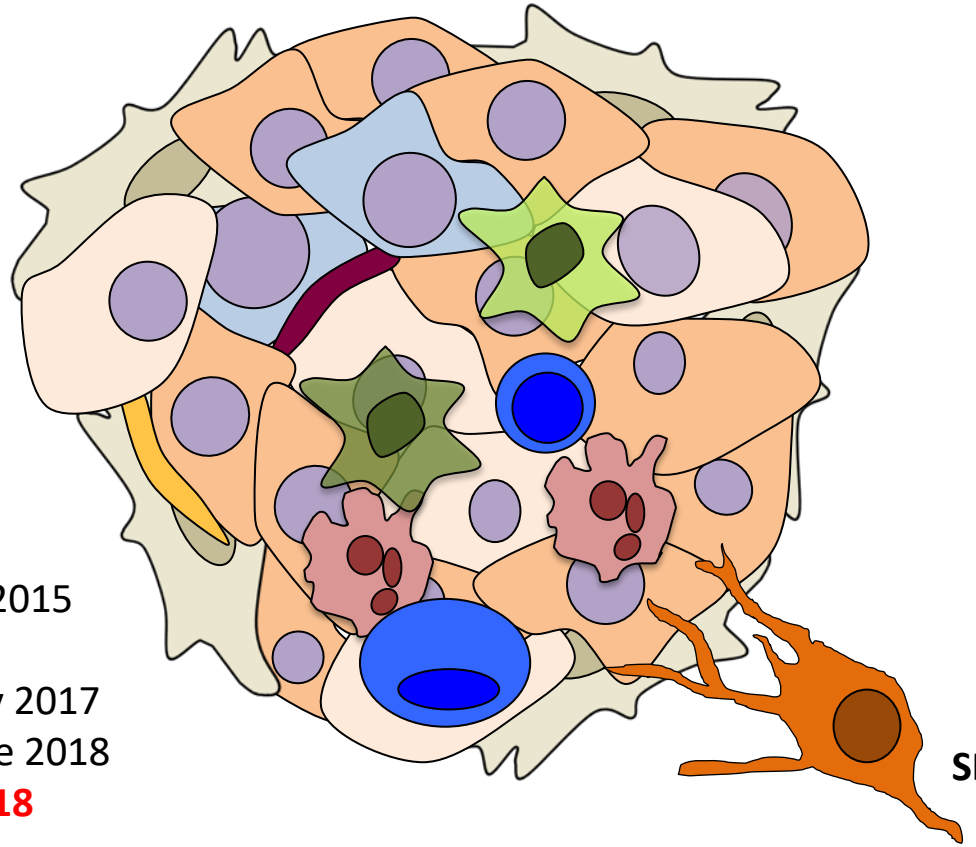
The tumour microenvironment in PTEN null prostate cancer

Tumor-Associated Macrophages

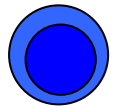
Escamilla, Cancer Res 2015
Di Mitri, Cell Reports 2019

Myeloid-derived Suppressor Cell

Di Mitri, Nature 2014
Wang, Cancer Discov 2015
Lu, Nature 2017
Patnaik, Cancer Discov 2017
Bezzi, Nature Medicine 2018
Calcinotto, Nature 2018

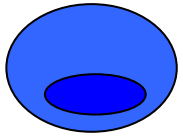


B cell



Ammirante M, Nature 2010

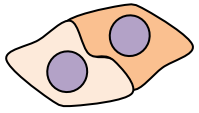
Plasma cell



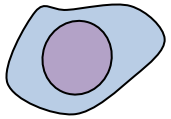
Shalapour S, Nature 2015

SNS Adrenergic nerve fiber
Magnon, Science 2013

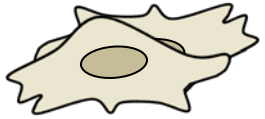
Tumor cells



Senescent tumor cell



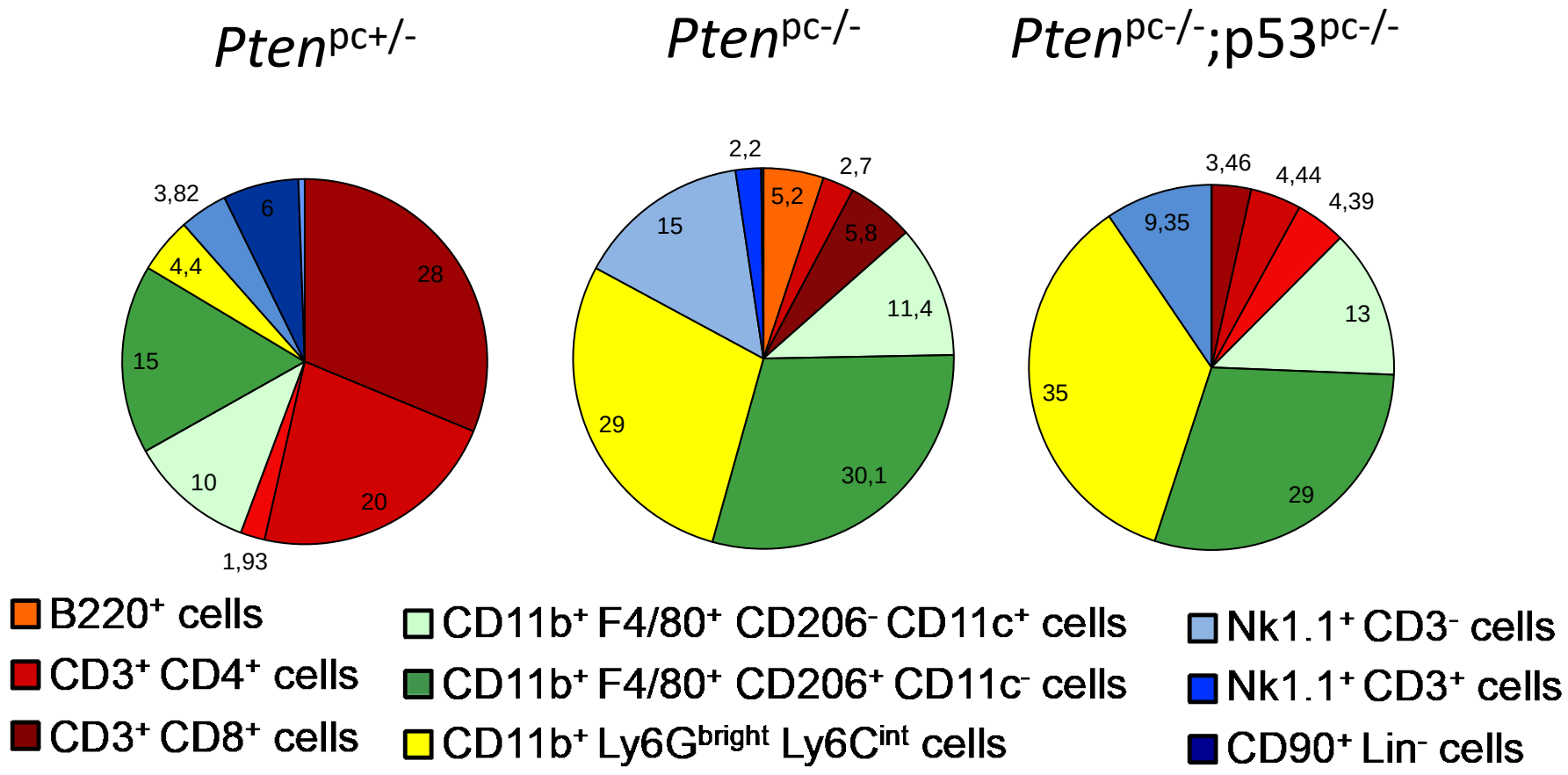
Stromal cells



Blood vessel

Lymphatic vessel

Pathologically activated neutrophils (PMN), termed myeloid-derived suppressor cells (PMN-MDSC), are enriched in the prostate tumor microenviroment of $Pten^{pc}$ null mice



Calcinotto A.

PMN-MDSCs infiltrate the tumours of CRPC patients

Castration Sensitive Prostate Cancer
(**CSPCs**)

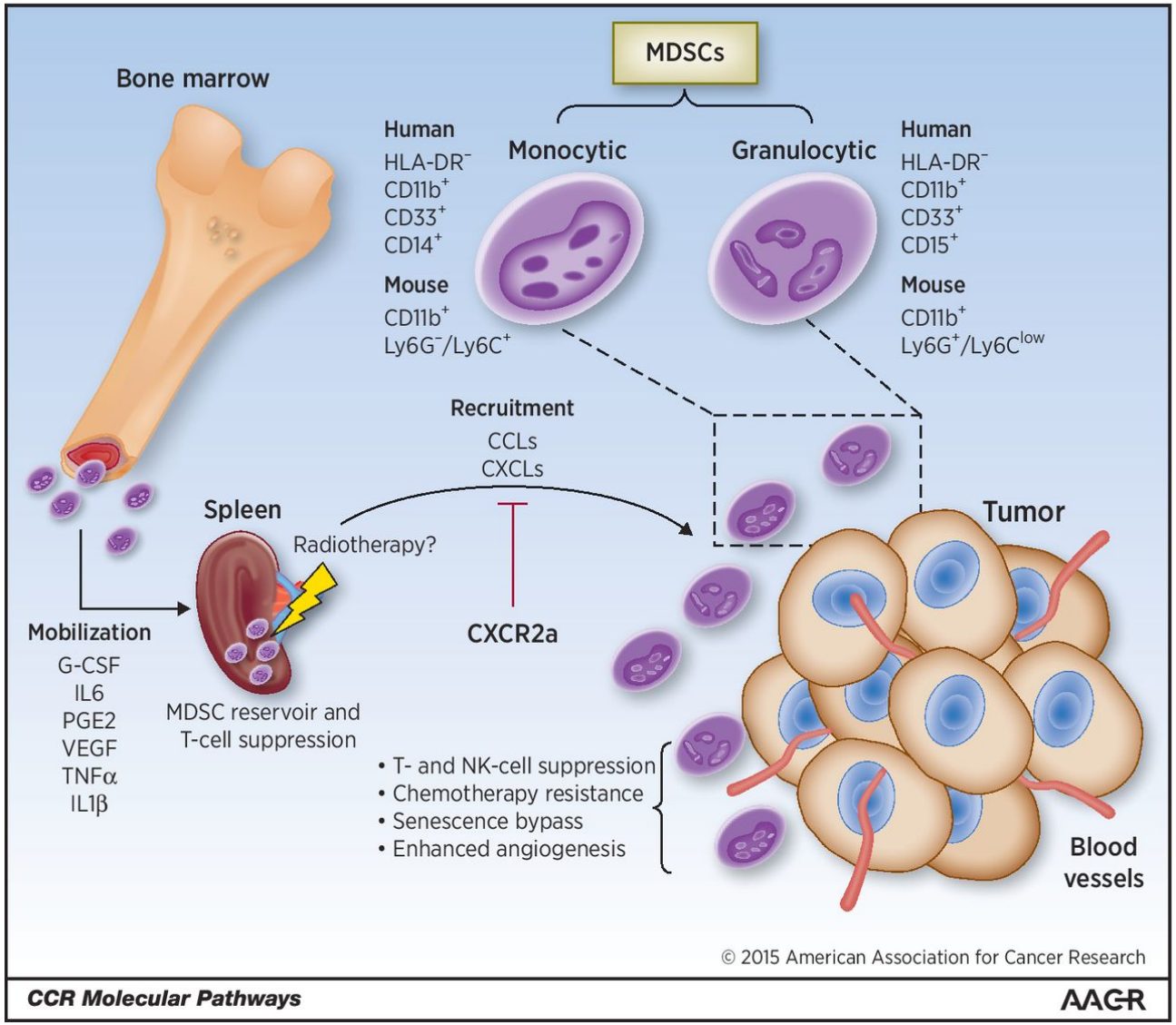
Castration Resistant Prostate Cancer
(**CRPCs**)

Alimonti/ De Bono teams, Nature 2018

Prognostic relevance of the Neutrophil-Lymphocyte ratio (NLR) in prostate cancer (Pca)

- Pca patients **having high NLR** have a worst DFS and **OS** than patients with low NLR (De Bono J, Annals of Onc 2014; Confirmed by a metanalysis on **16.266 patients**, Wang, Sci Reports 2016)
- Poor response to chemotherapy and androgen deprivation treatments in patients having high NLR (De Bono J, Annals of Onc 2015)

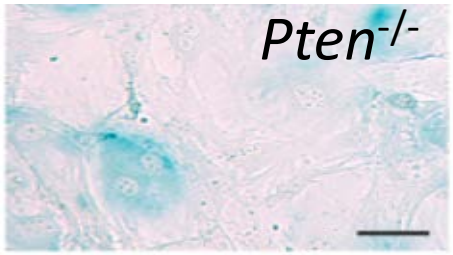
A fatal attraction: PMN-MDSCs are mobilized from the bone marrow and attracted in the tumor



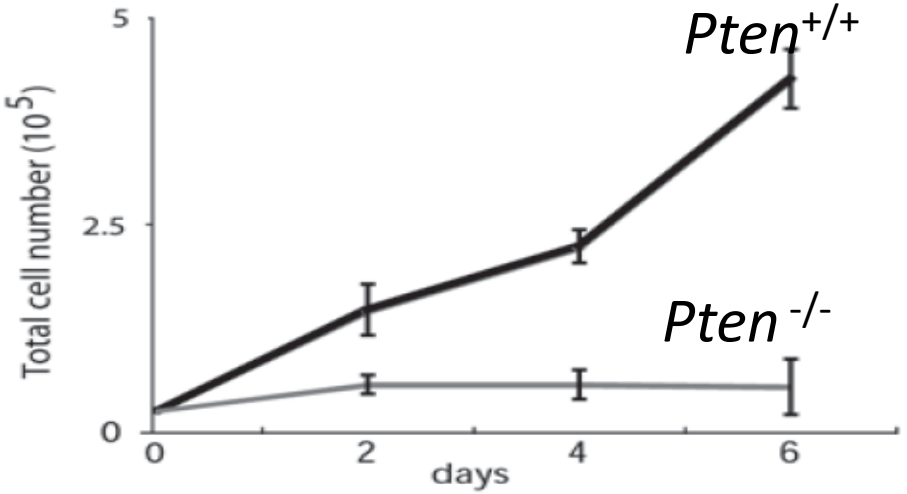
Alimonti, Clin. Can. Res 2015

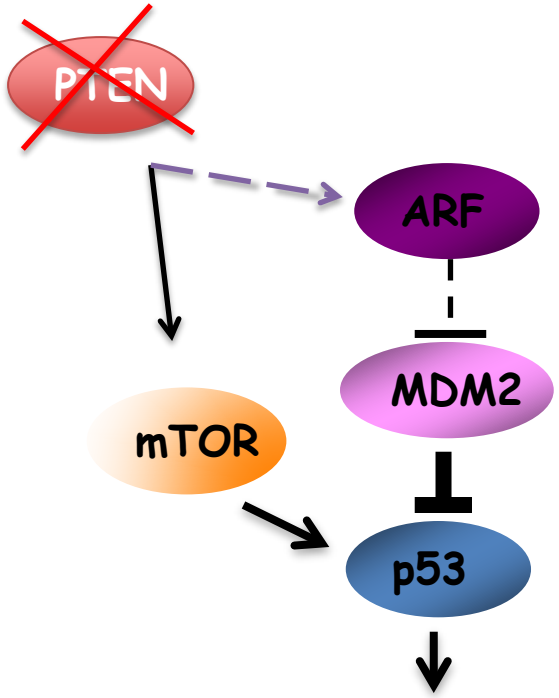
How MDSCs control prostate tumor growth?

Complete loss of *Pten* promotes cellular senescence



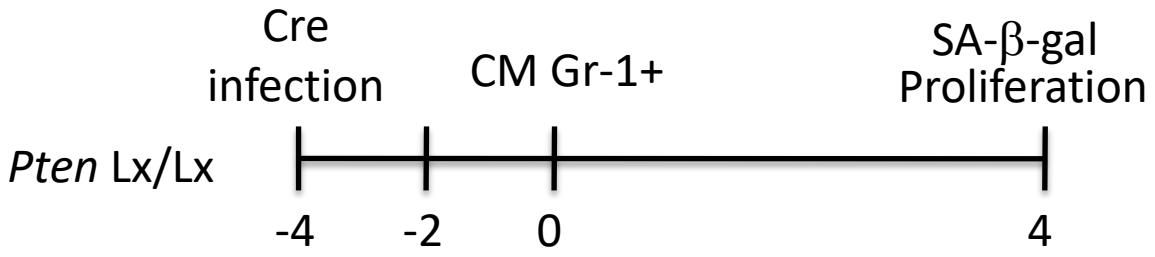
SA-β-gal staining

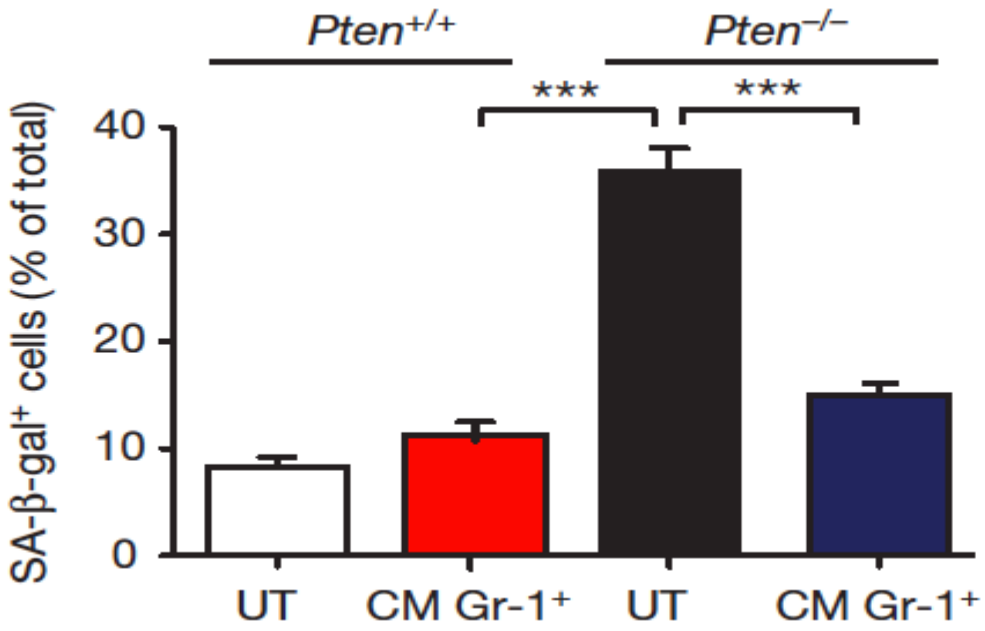


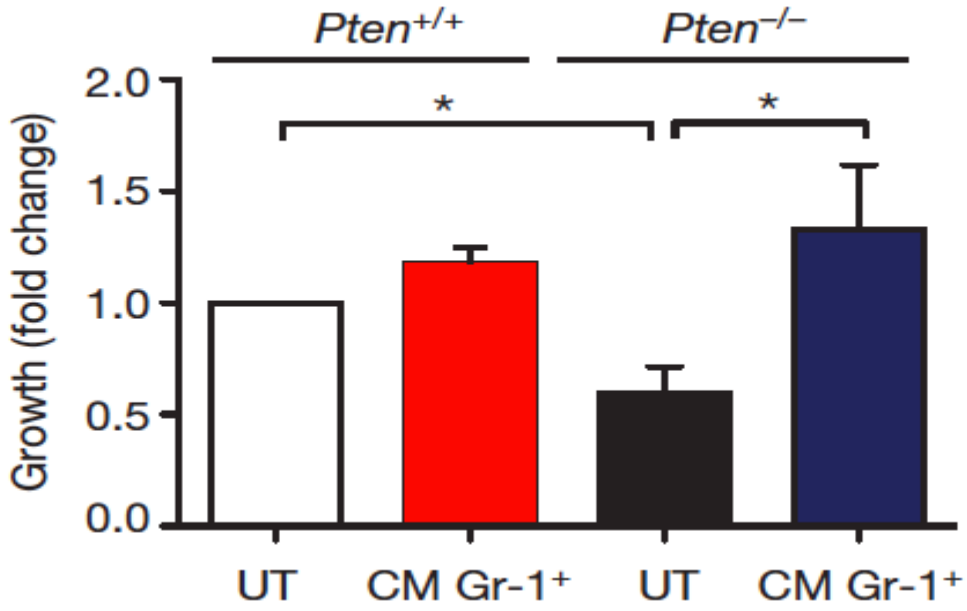


Alimonti, JCI 2010

Gr-1^{+} myeloid cells oppose *Pten*-loss-induced cellular senescence

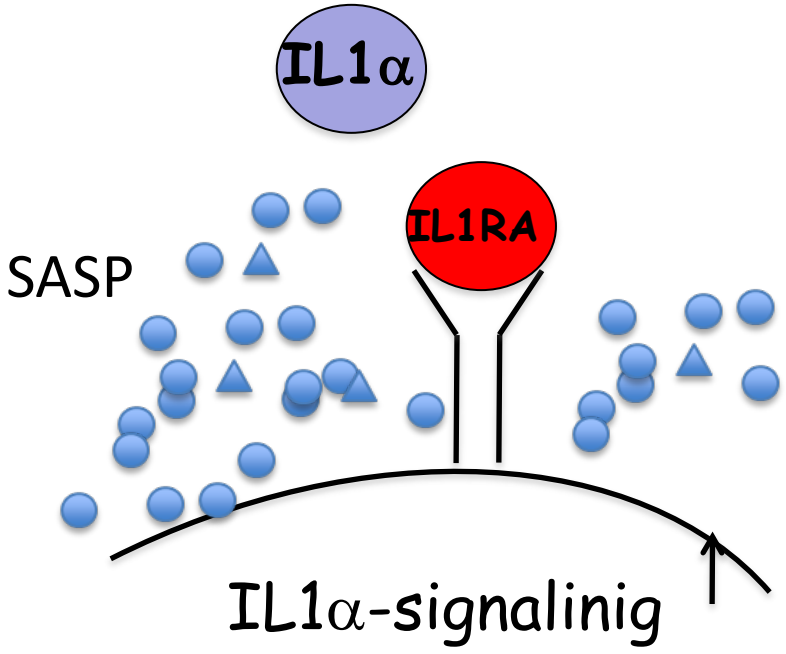






Di Mitri/Toso, Nature 2014

Senescence in *Pten* null cells depends on the SASP that is regulated by IL1α



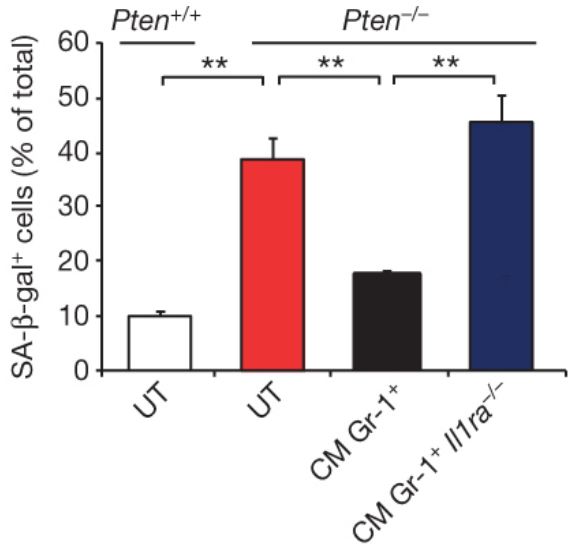
Conditioned medium

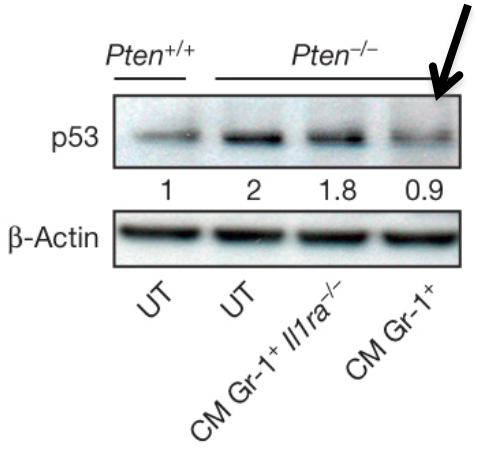
ILRA +/+ Gr-1+

ILRA -/- Gr-1+

Pten$^{-/-}$

Senescence ?

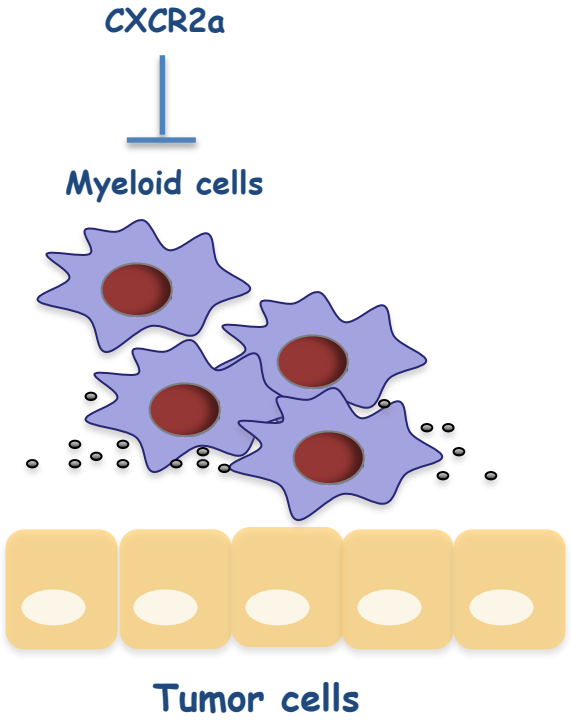


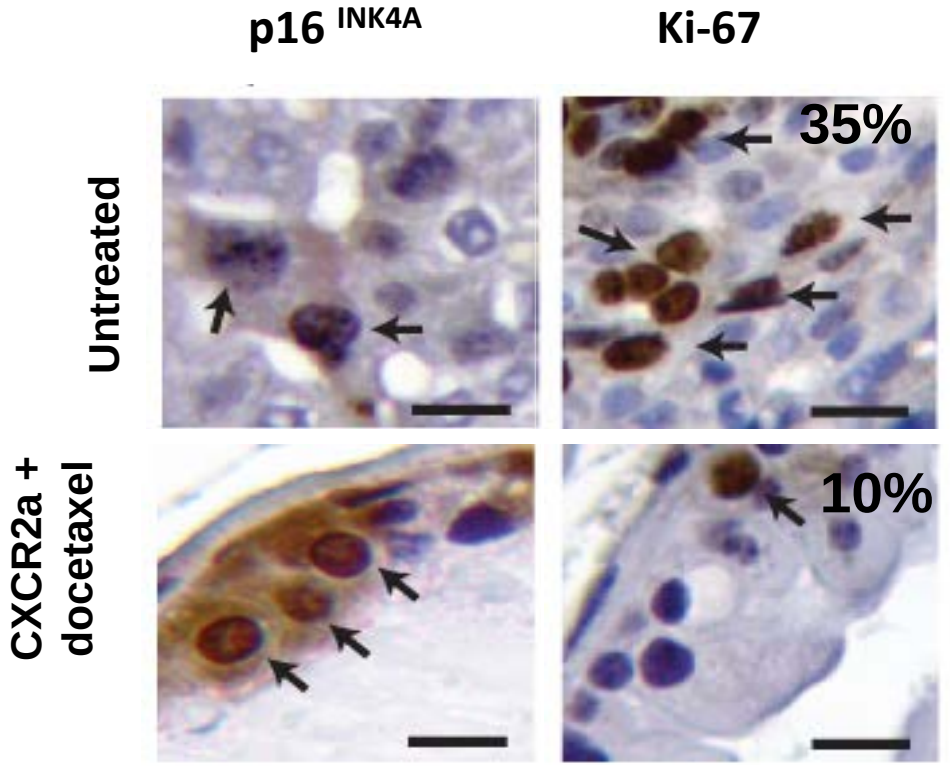


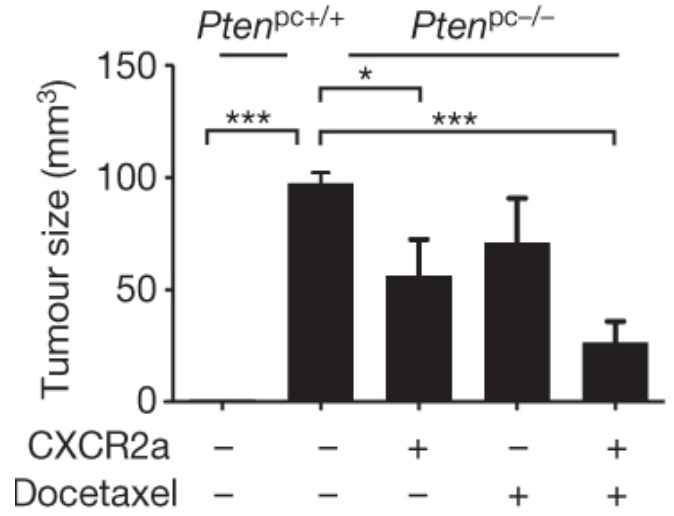
J. Gil, Nature Cell Biol. 2013

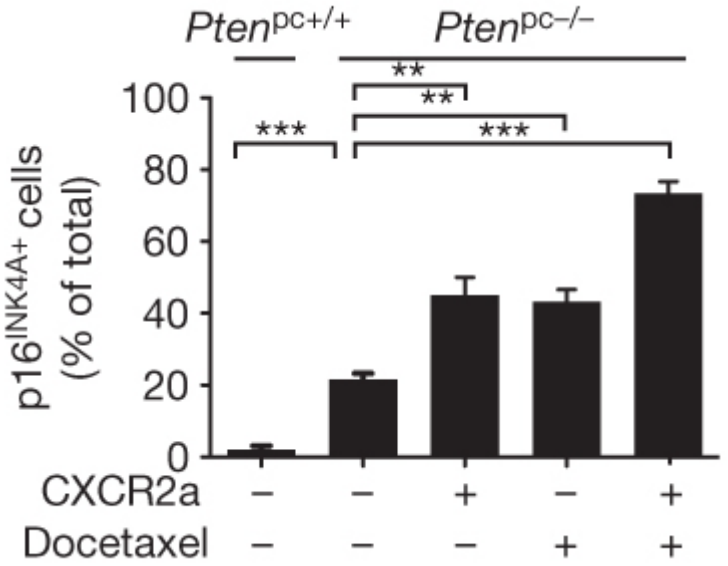
Di Mitri/Toso, Nature 2014

Impaired recruitment of Gr-1+ cells enhances chemotherapy-induced senescence







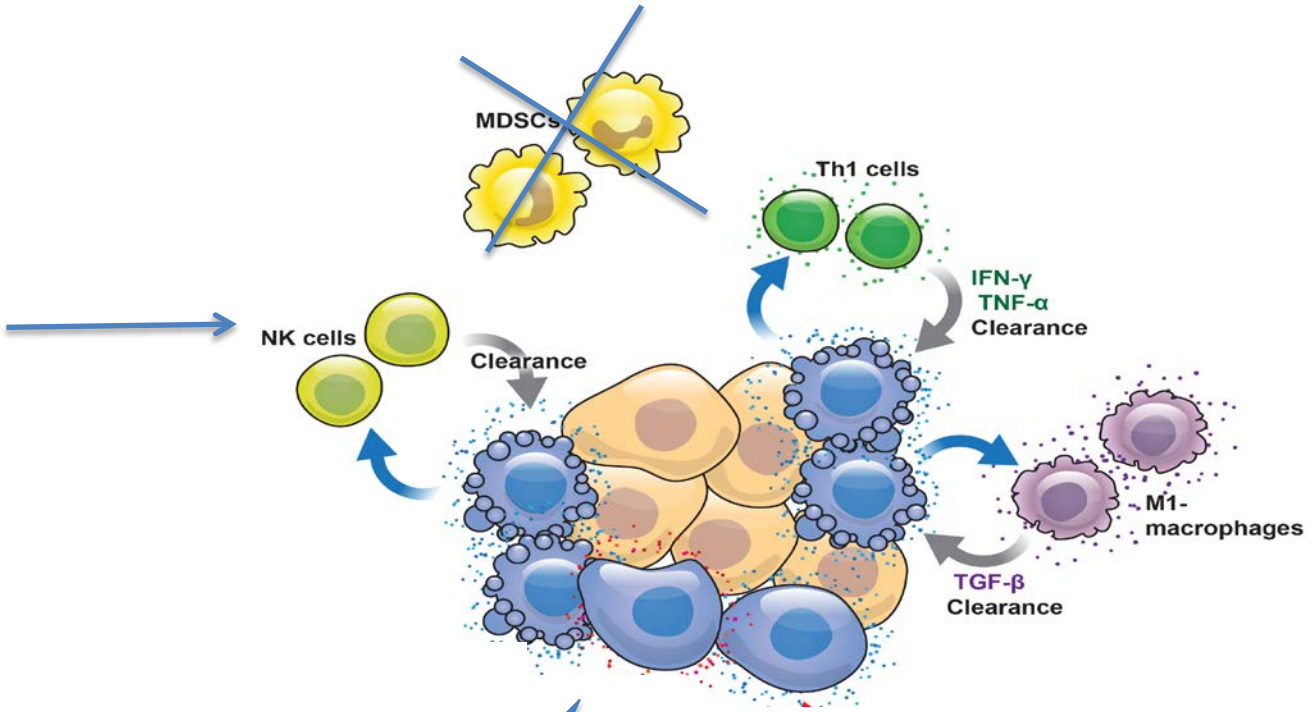


Di Mitri/Toso, Nature 2014

Enhancing senescence and immune surveillance by targeting tumor-infiltrating MDSCs

Maladaptive senescence

Positive senescence response

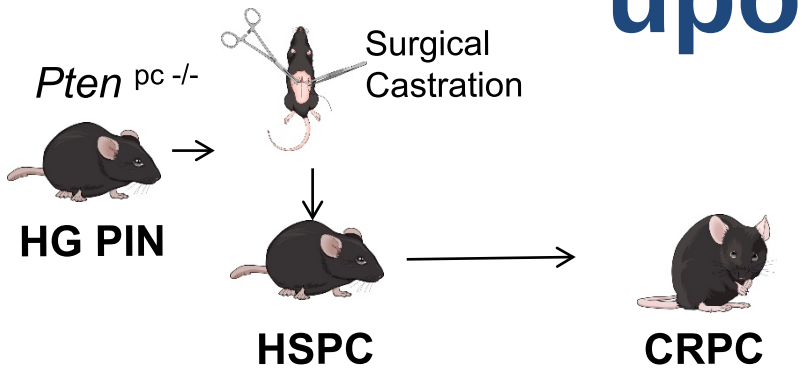


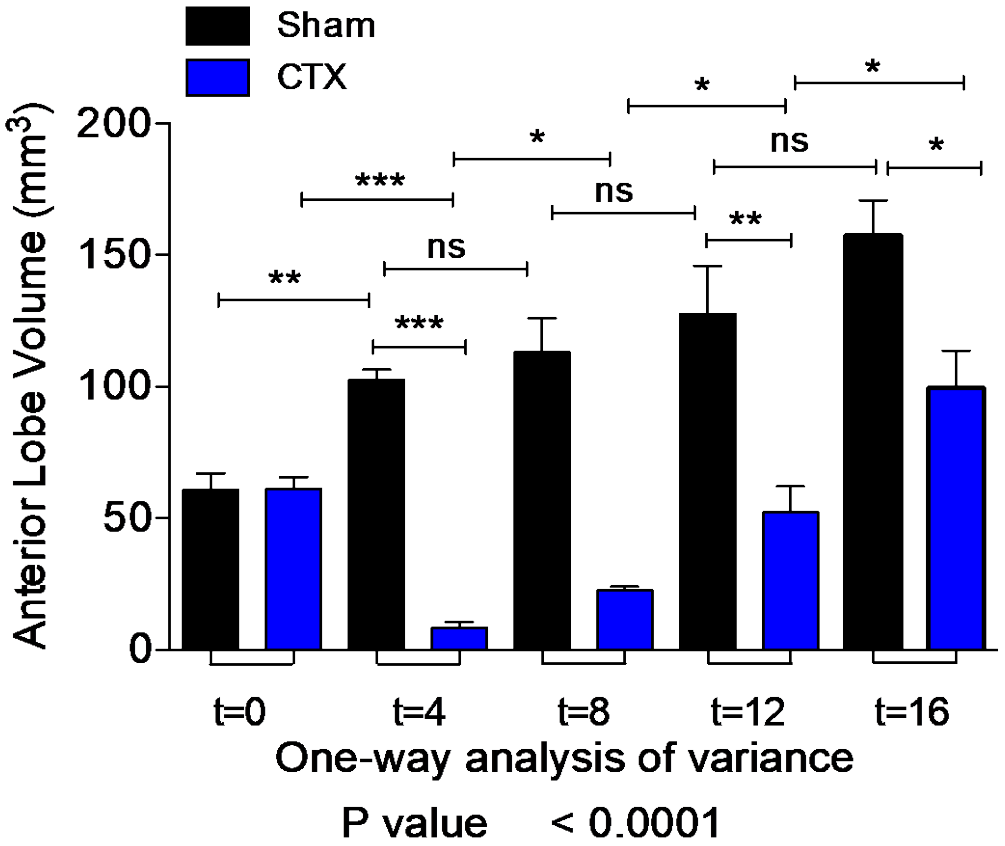
Chemoterapy

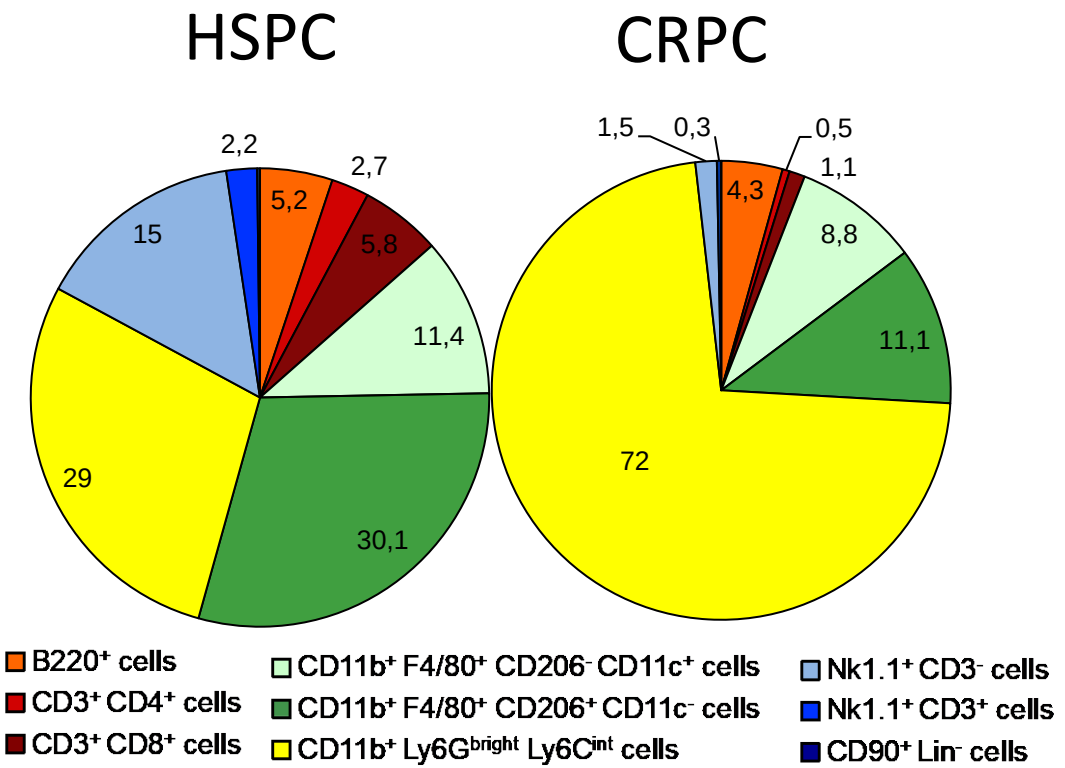
Chemoterapy

Di Mitri/Toso, Nature 2014;
Calcinotto Swiss Med Wkly 2016

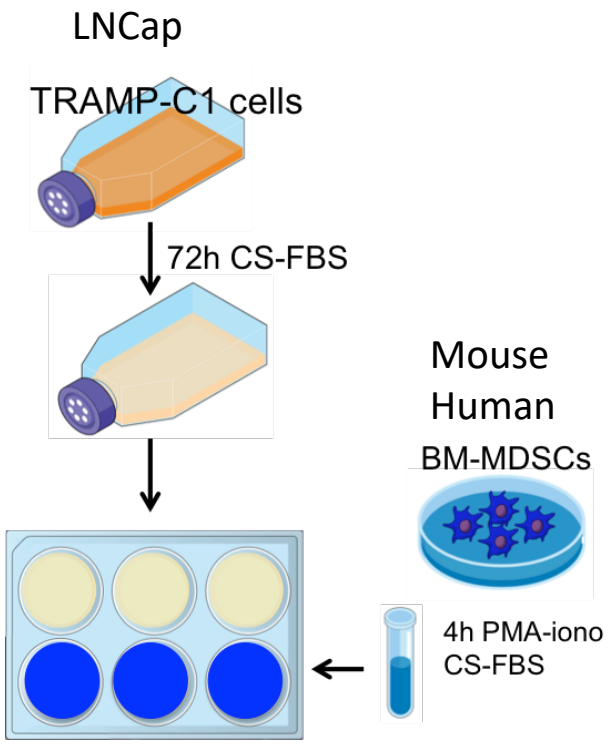
PMN-MDSCs expand in prostate tumors upon castration

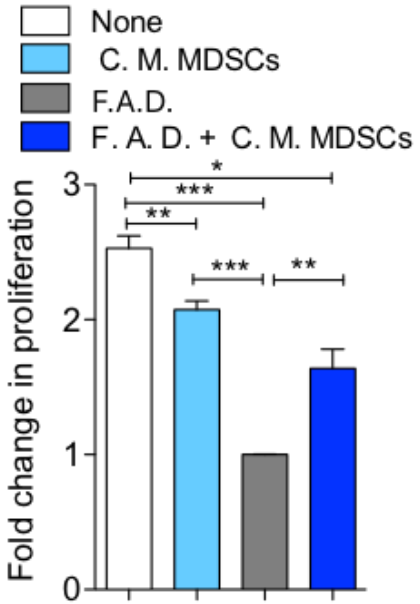


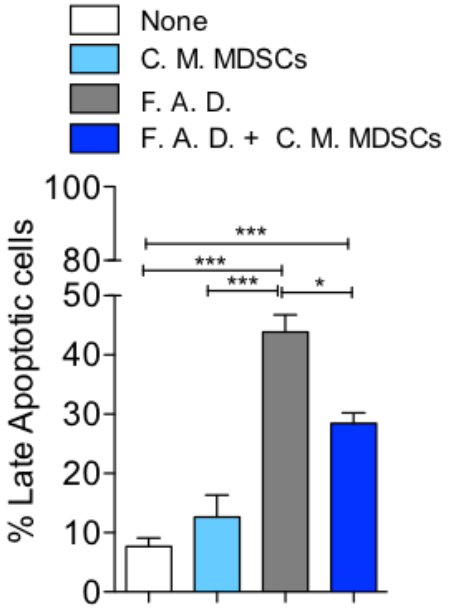


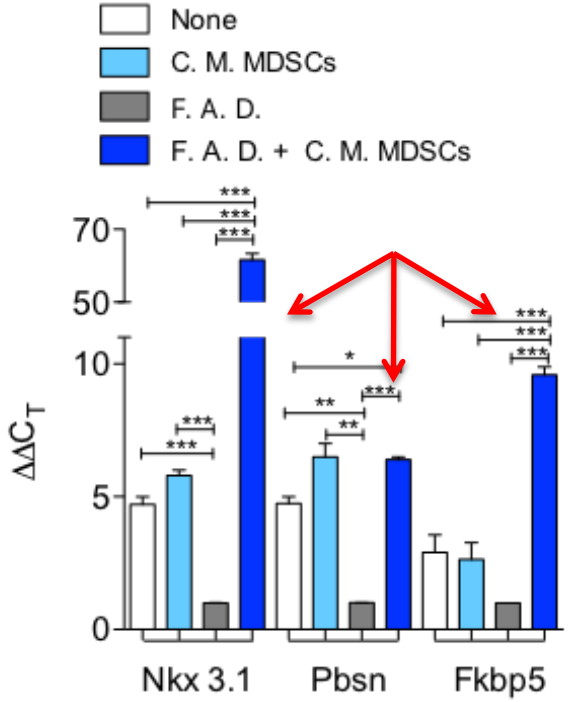


Factors secreted by MDSCs promote resistance to androgens deprivation in prostate cancer cells



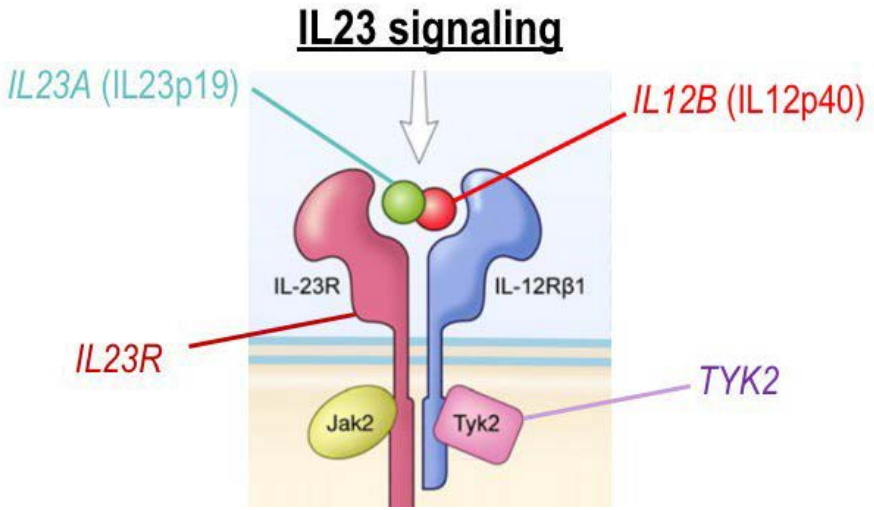


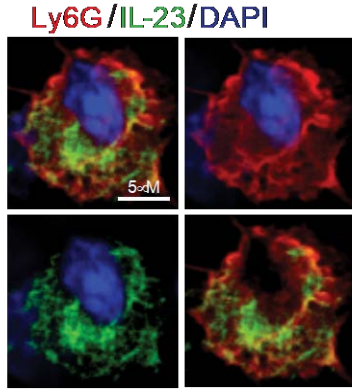


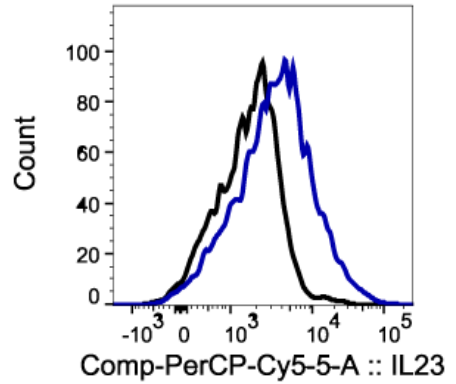


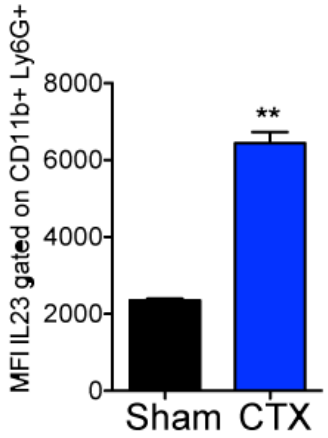
Calcinotto, Nature 2018

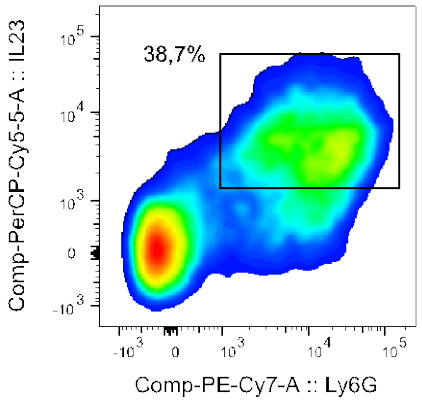
Castration drives the up regulation of IL23 in MDSCs and IL23R in prostate tumour cells

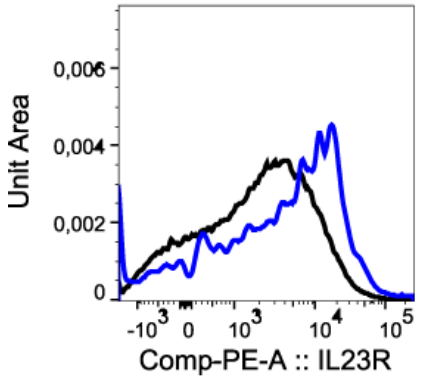


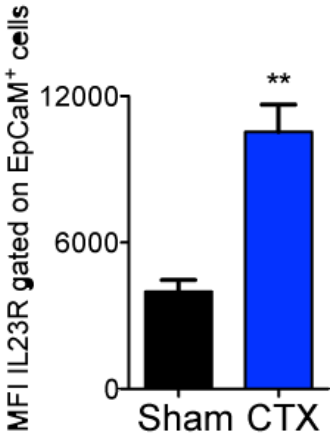






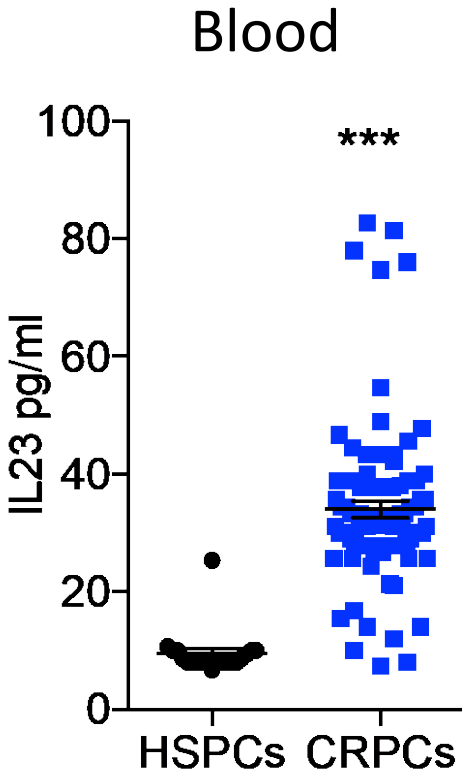


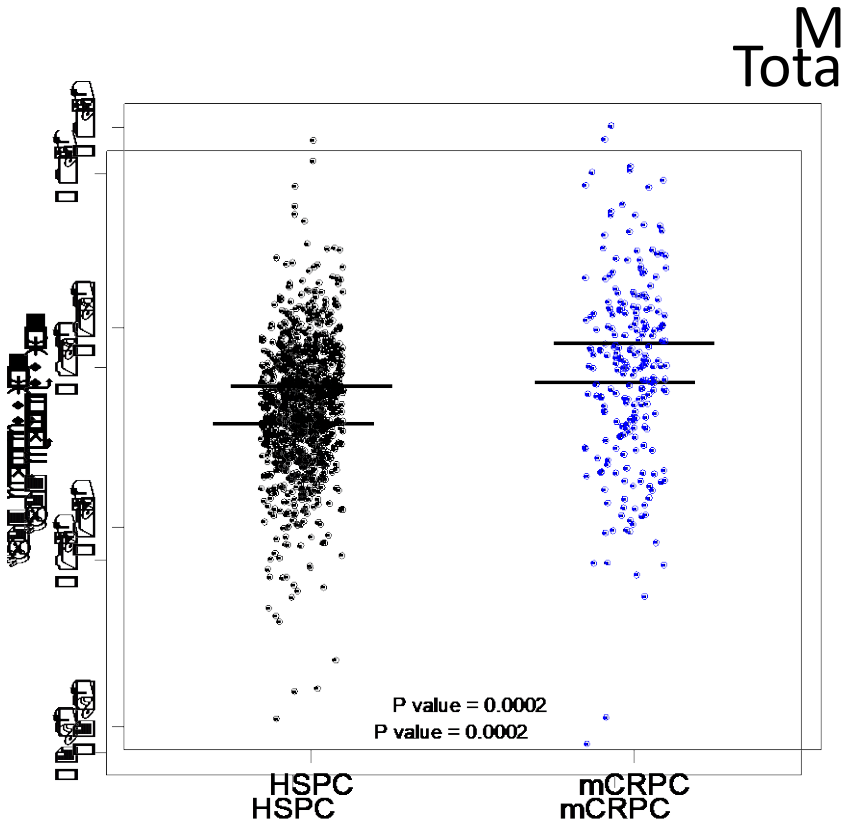


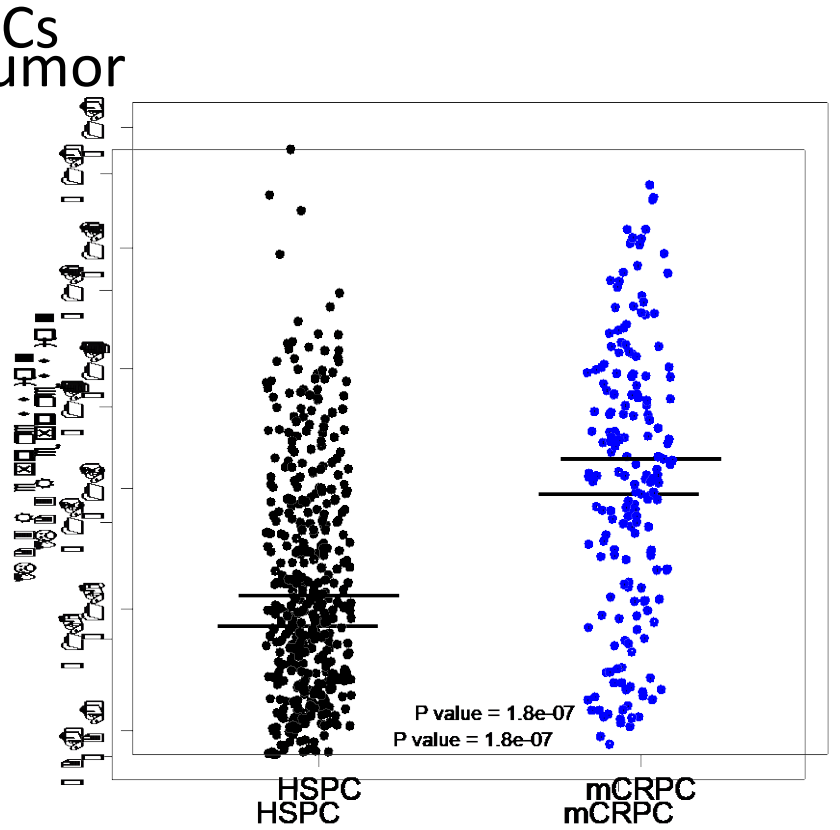


Calcinotto, Nature 2018

IL23 and IL23 receptor levels increase in mCRPC patients

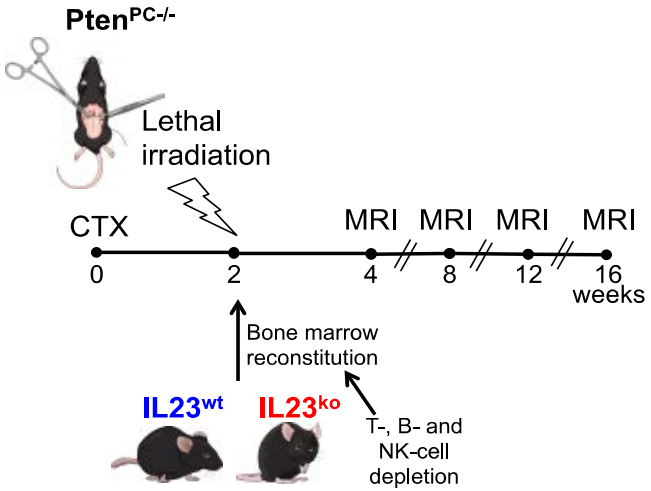


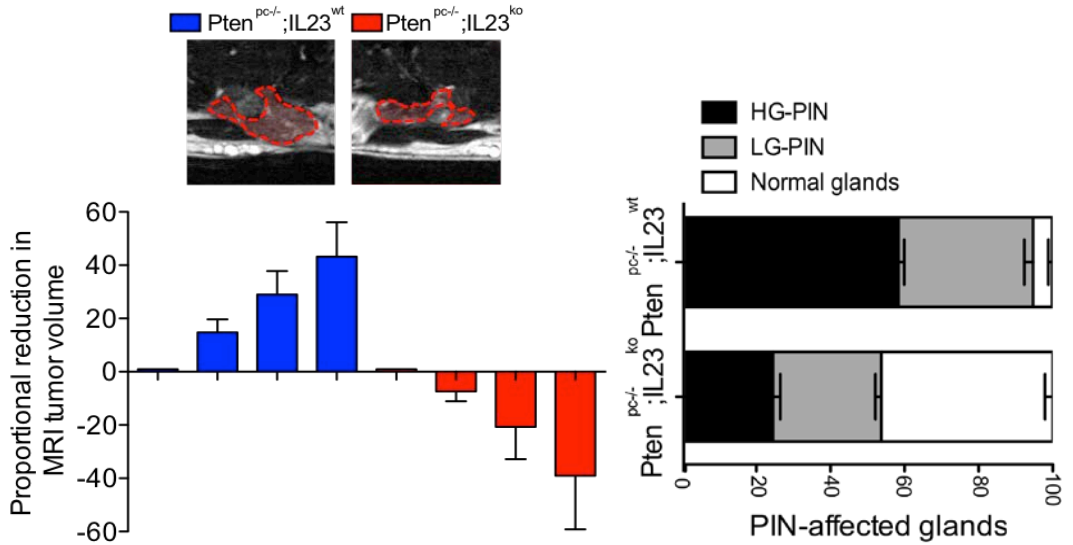


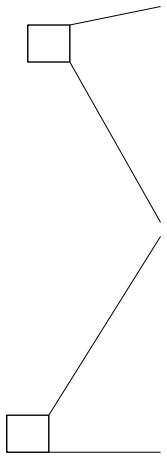


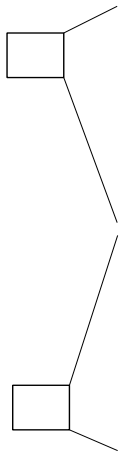
Calcinotto, Nature 2018

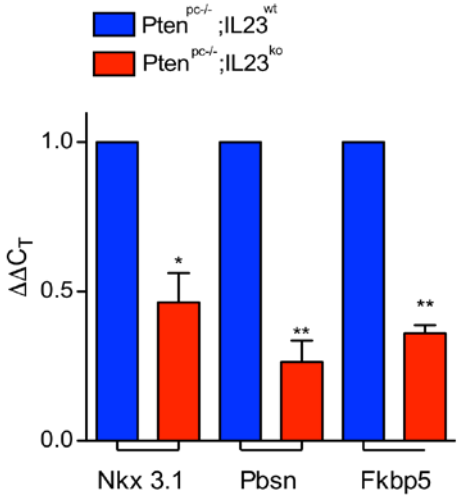
PMN-MDSCs promote castration resistance through IL23 *in vivo*



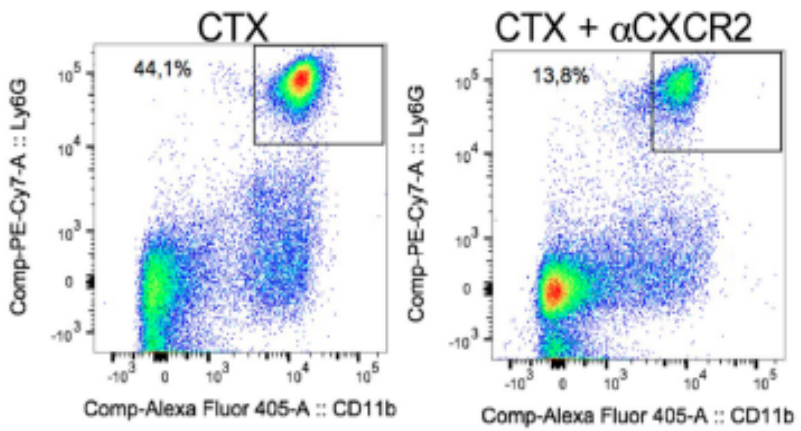


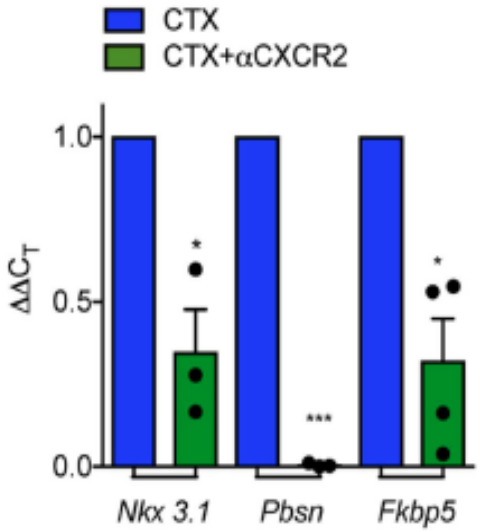


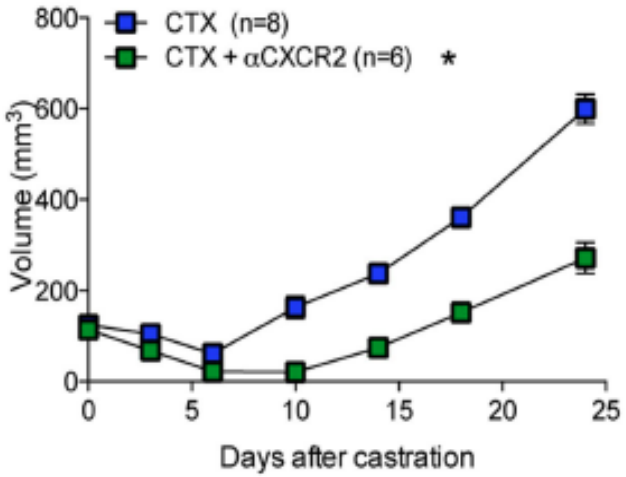


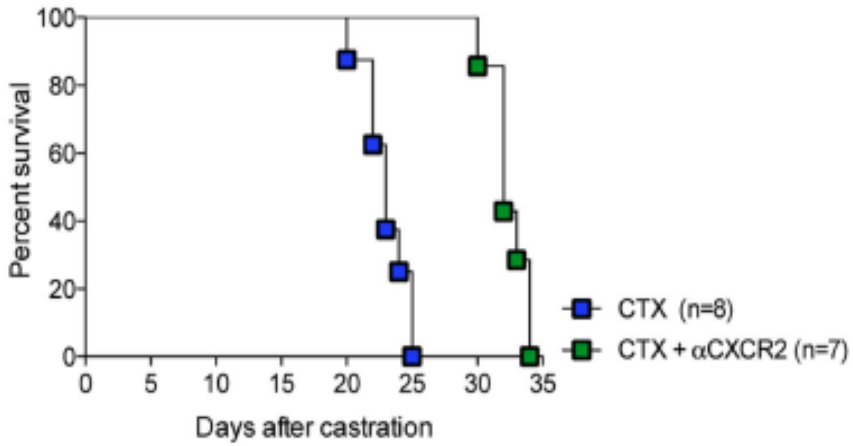


Treatment with an anti-CXCR2i enhances the efficacy of ADT *in vivo*

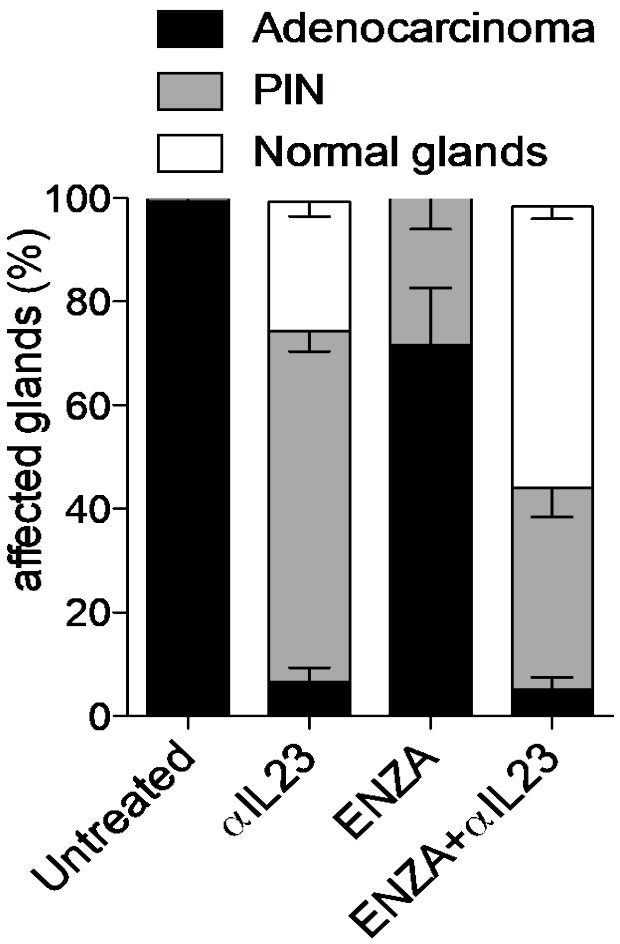


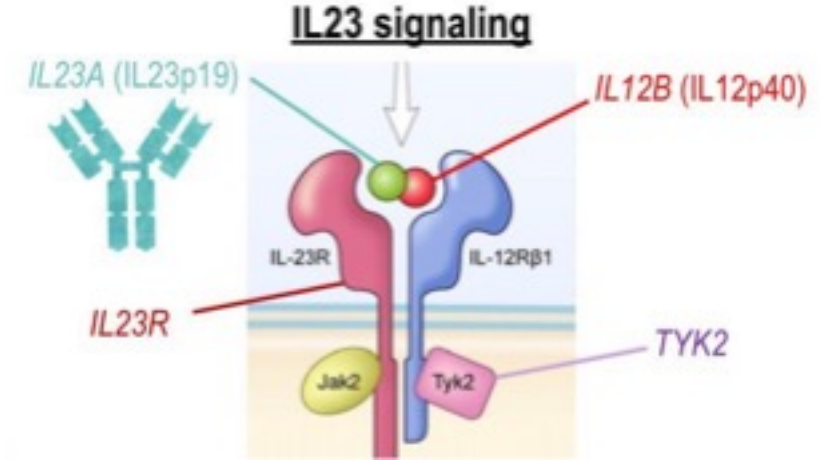


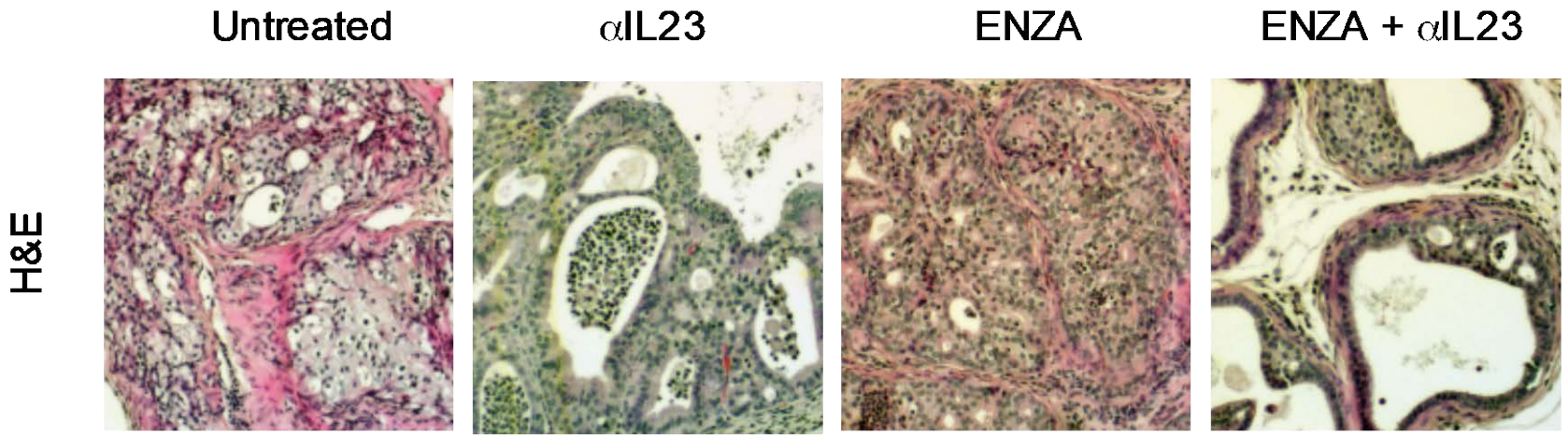




Treatment with an anti-IL23 antibody enhances the efficacy of standard androgen deprivation therapy (ADT)

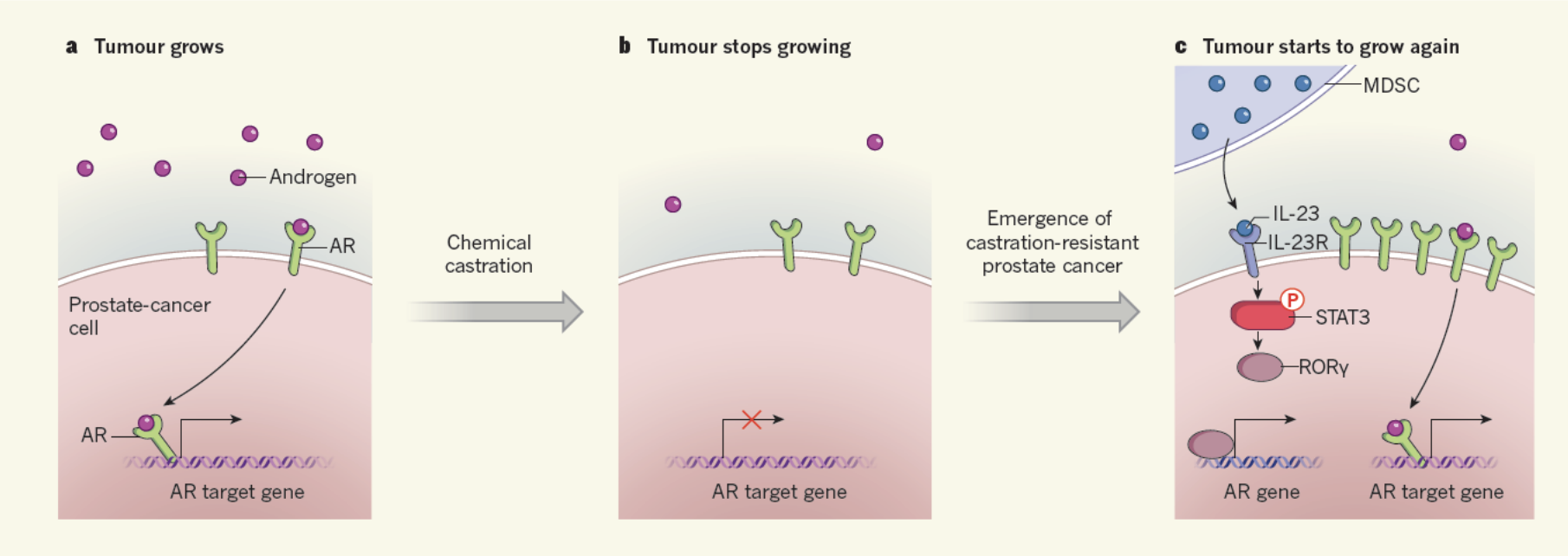






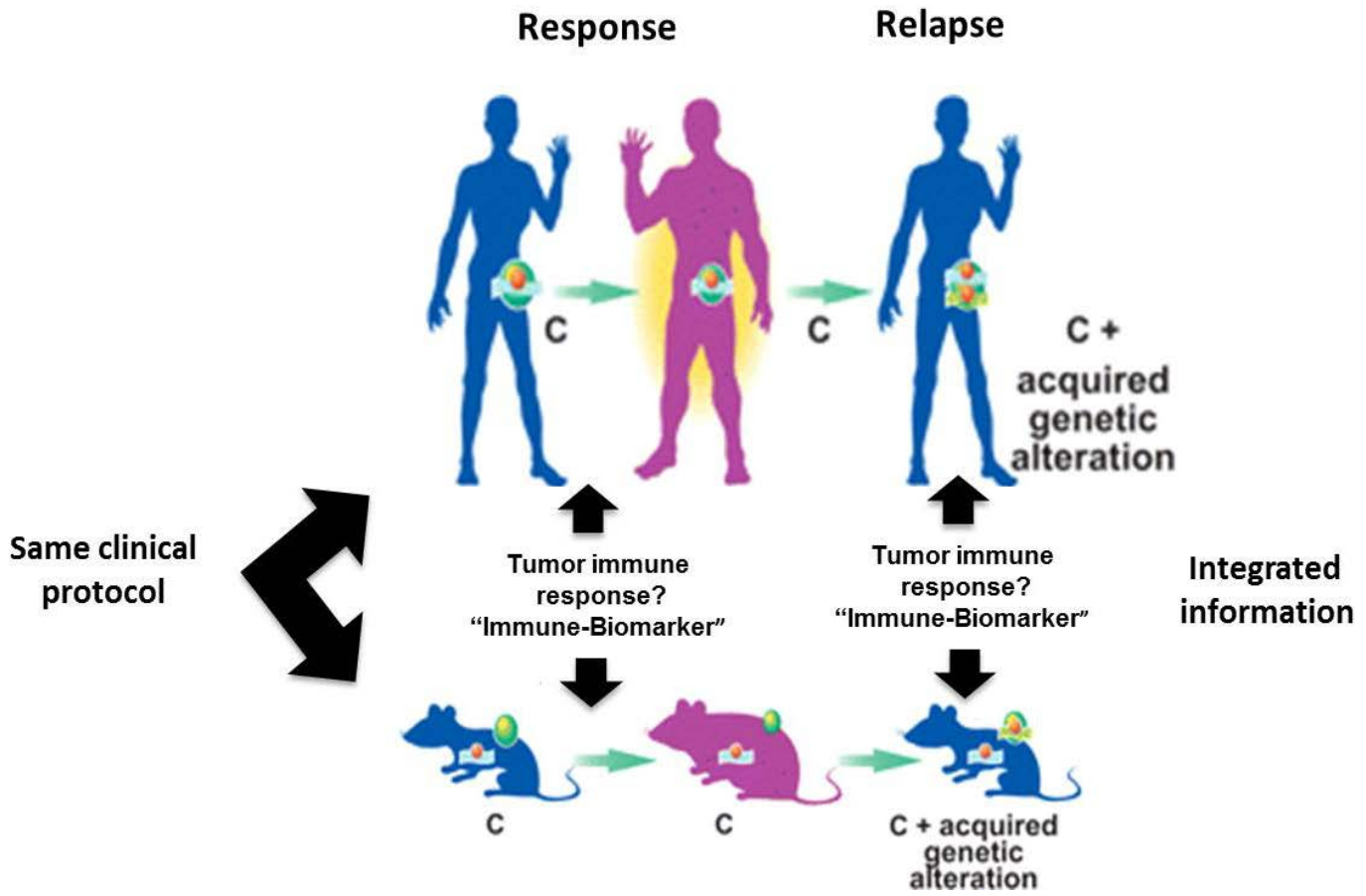
Calcinotto, Nature 2018

MDSCs promote CRPC by activating the IL23/STAT3/ RORγ pathway



Calcinotto, Nature 2018
M. Galsky, Nature 2018

Moving novel immunotherapies from bench to bedside



CO-CLINICAL PROGRAME IN PROSTATE CANCER

1. A clinical trial (Phase I/II) in mCRPC patients assessing the safety and efficacy of CXCR2a in combination with ADT
2. A POC trial prior prostatectomy to assess the efficacy of a JAK2 inhibitor in blocking MDSCs
3. An exploratory study to assess the prognostic relevance of circulating MDSCs in different stage of prostate cancer
4. A clinical trial (Phase I/II) in mCRPC patients assessing the safety and efficacy of IL23a in combination with ADT
5. A Phase I/II Trial to Assess the Safety, Tolerability and Preliminary Anti-tumour Activity of Oral Combination antibiotic therapy to modulate the microbiome in combination with enzalutamide with metastatic castration resistant prostate cancer (mCRPC)

Prostate Cancer Foundation
Curing Together.

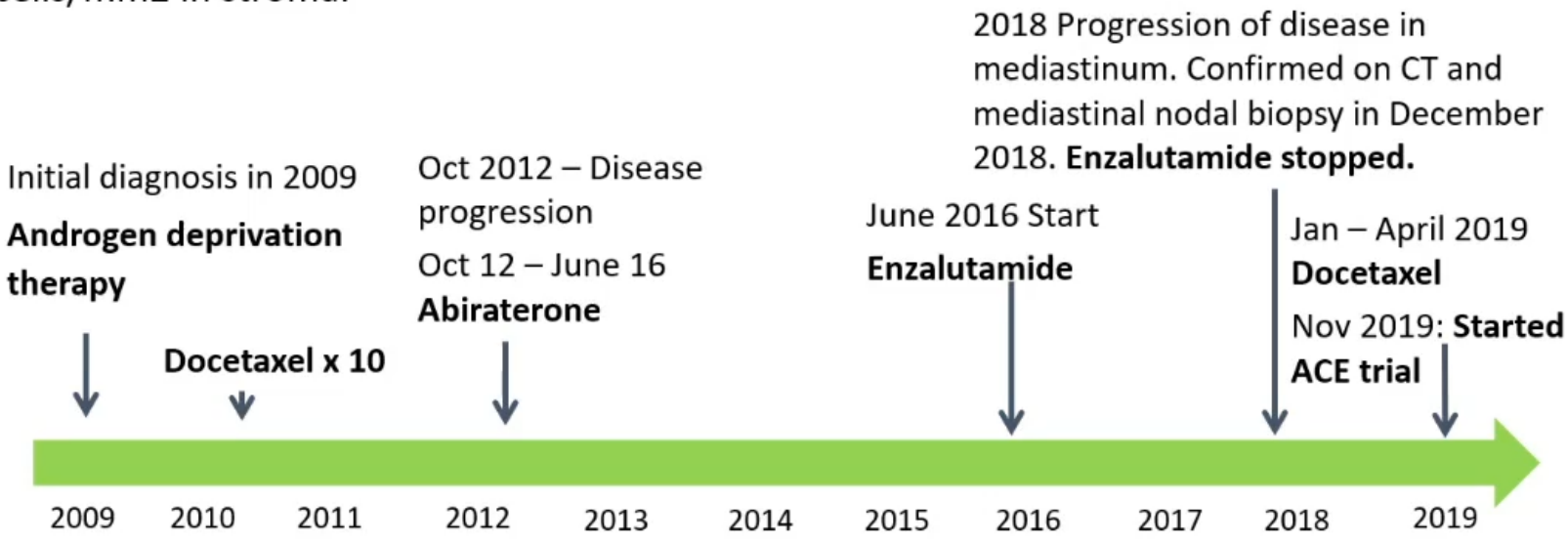
Therapeutic targeting of MDSCs in mCRPC

ACE is a multi-centre proof of concept Phase I/II trial of the CXCR2 antagonist AZD5069 in combination with Enzalutamide in mCRPC (NCT03177187)

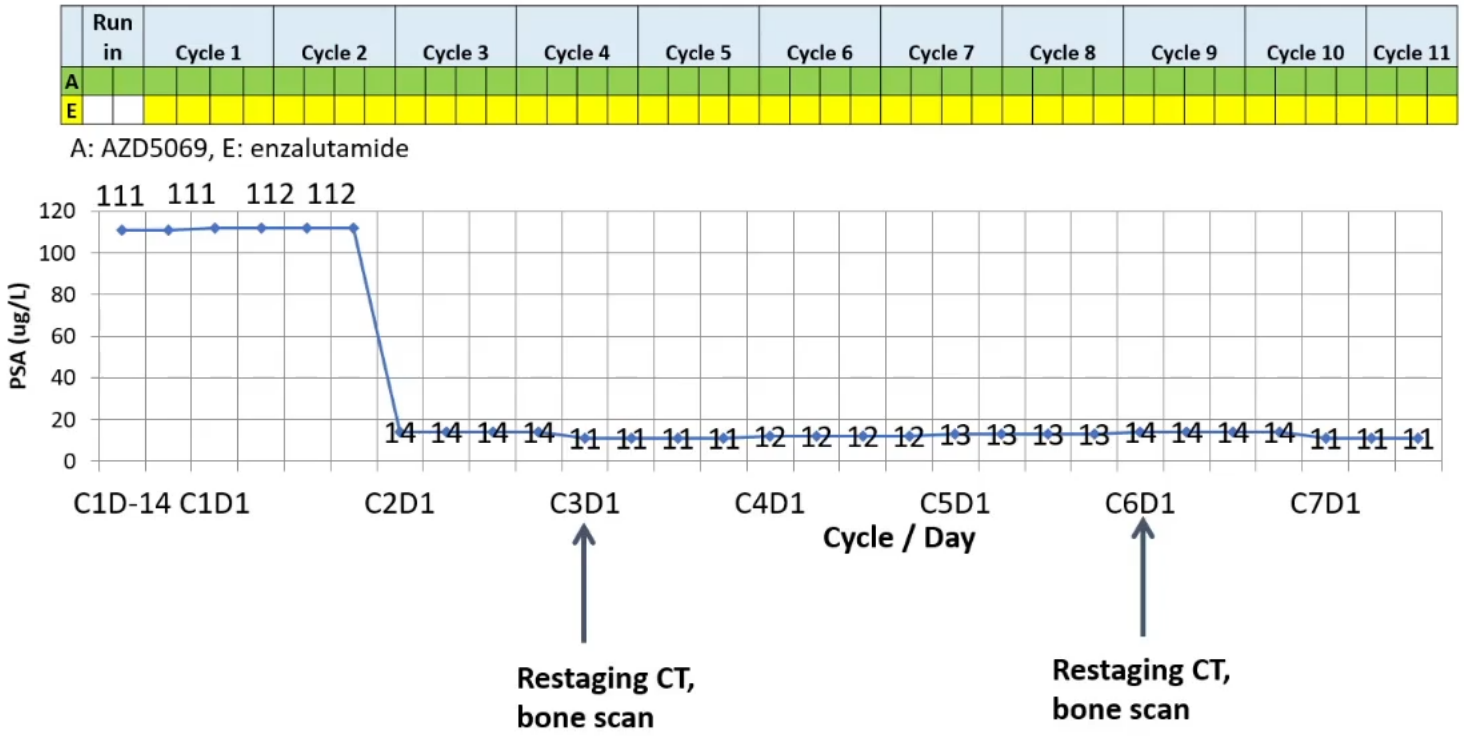
Action is a multi-centre proof of concept Phase I/II trial of the anti-IL23 targeting monoclonal antibody tildrakizumab in combination with abiraterone acetate in mCRPC (NCT04458311)

74 Male mCRPC

- Sites of disease: bone, lymph node, and primary tumour
- Molecular profile: PTEN intact, ATM intact, CD3 count 21 cells/mm2 in tumour and 148 cells/mm2 in stroma.



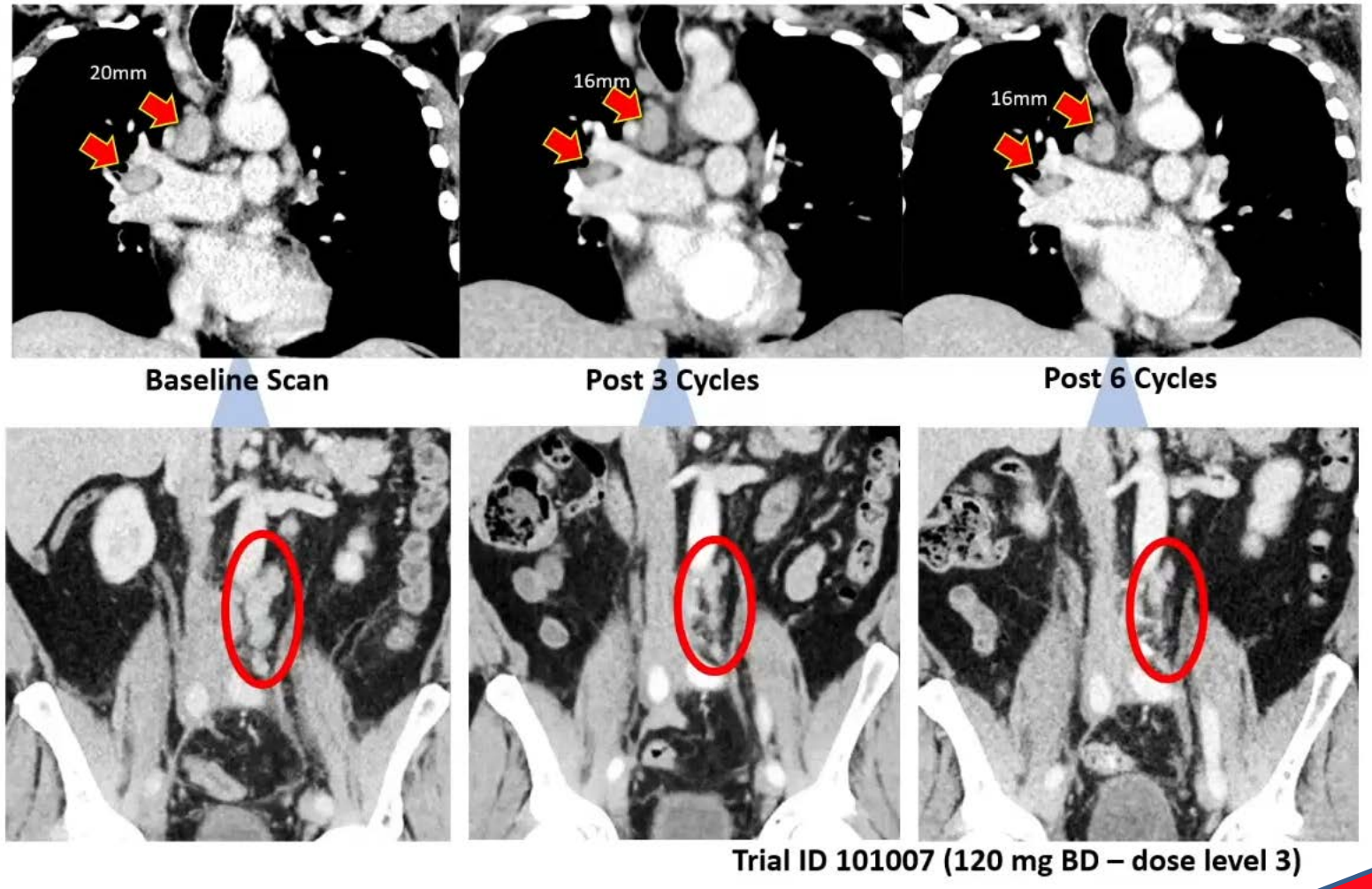
PSA Response to AZD5069 + enzalutamide



Trial ID 101007 (120 mg BD – dose level 3)

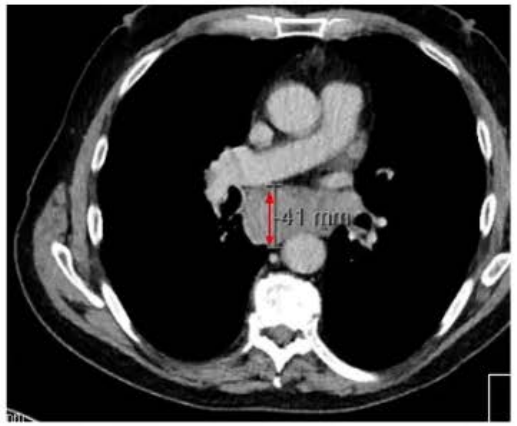
CONFIDENTIAL

Radiologic tumor shrinkage – AZD5069 + enzalutamide

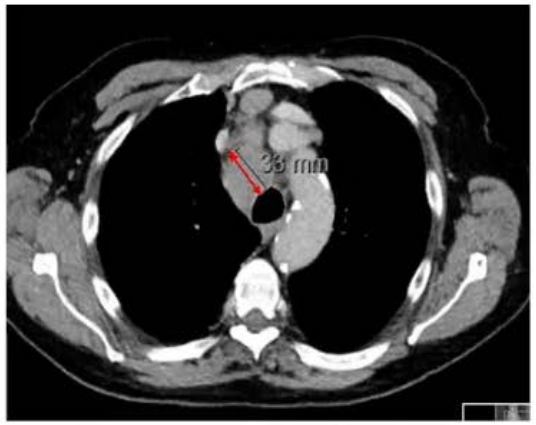


Trial ID 101007 (120 mg BD – dose level 3)

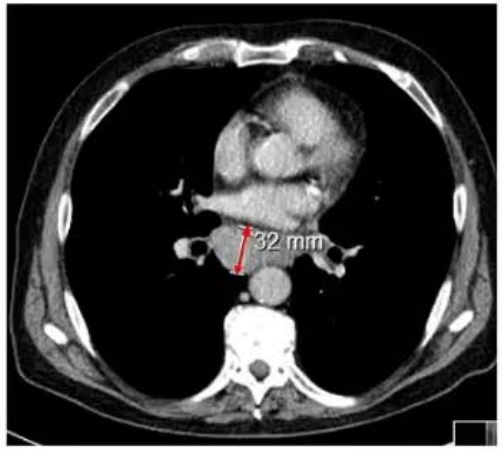
Radiologic Response - AZD5069 + enzalutamide



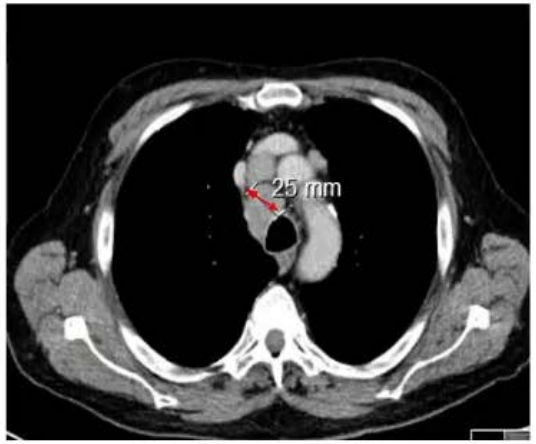
Baseline Scan – Mediastinal LN
41 mm



Baseline scan – Mediastinal LN
38 mm



Post 3 cycles
32 mm

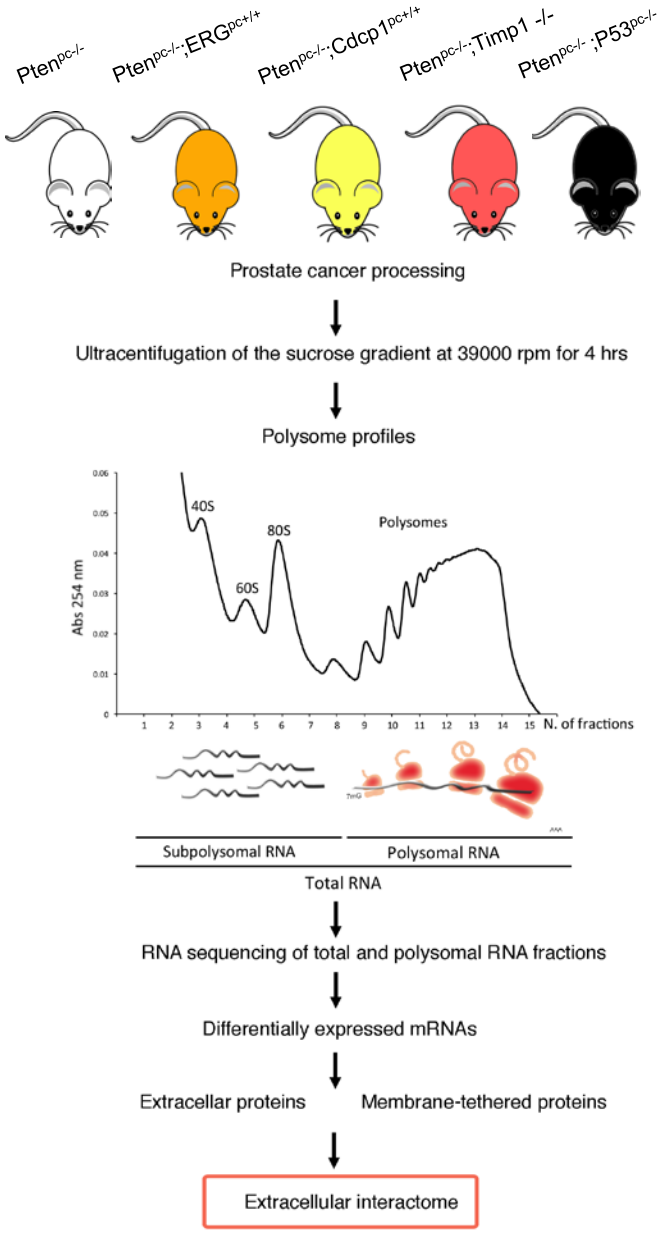


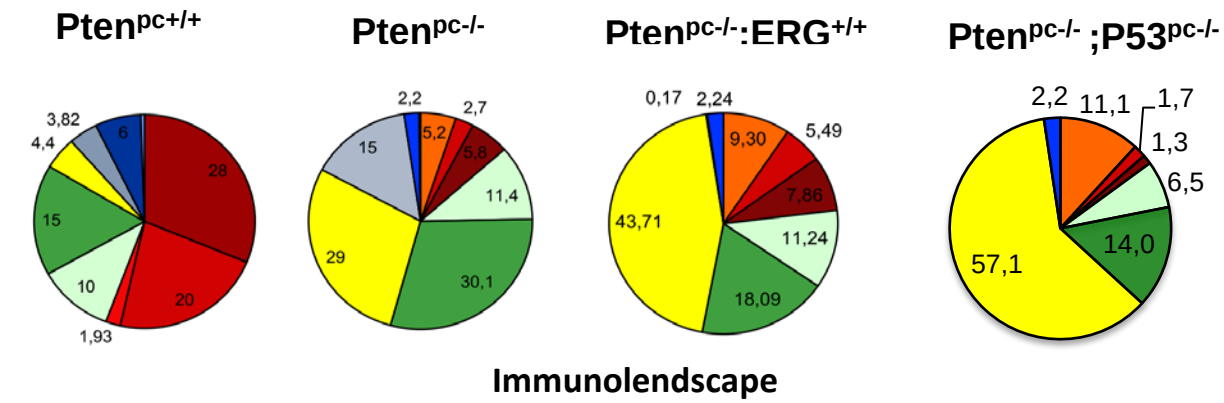
Post 3 Cycles
25 mm

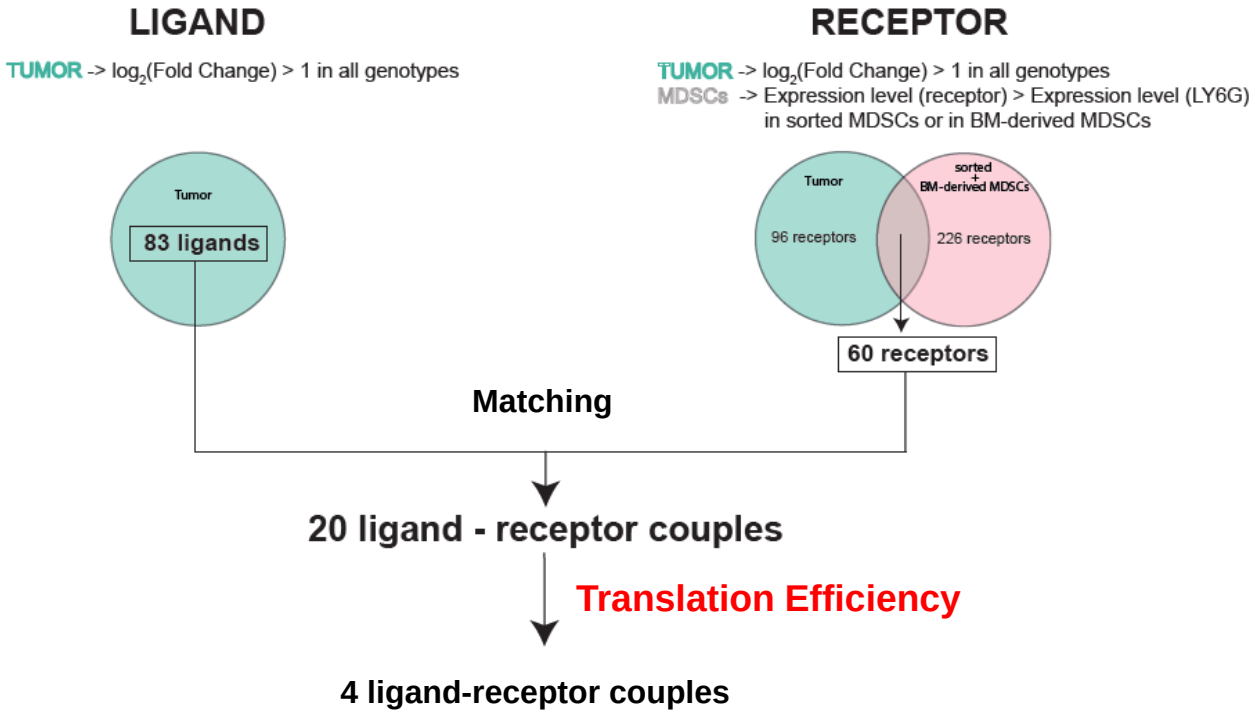
Target lesion Decrease by 20% as per RECIST 1.1

Why some patients do not respond to CXCR2i?

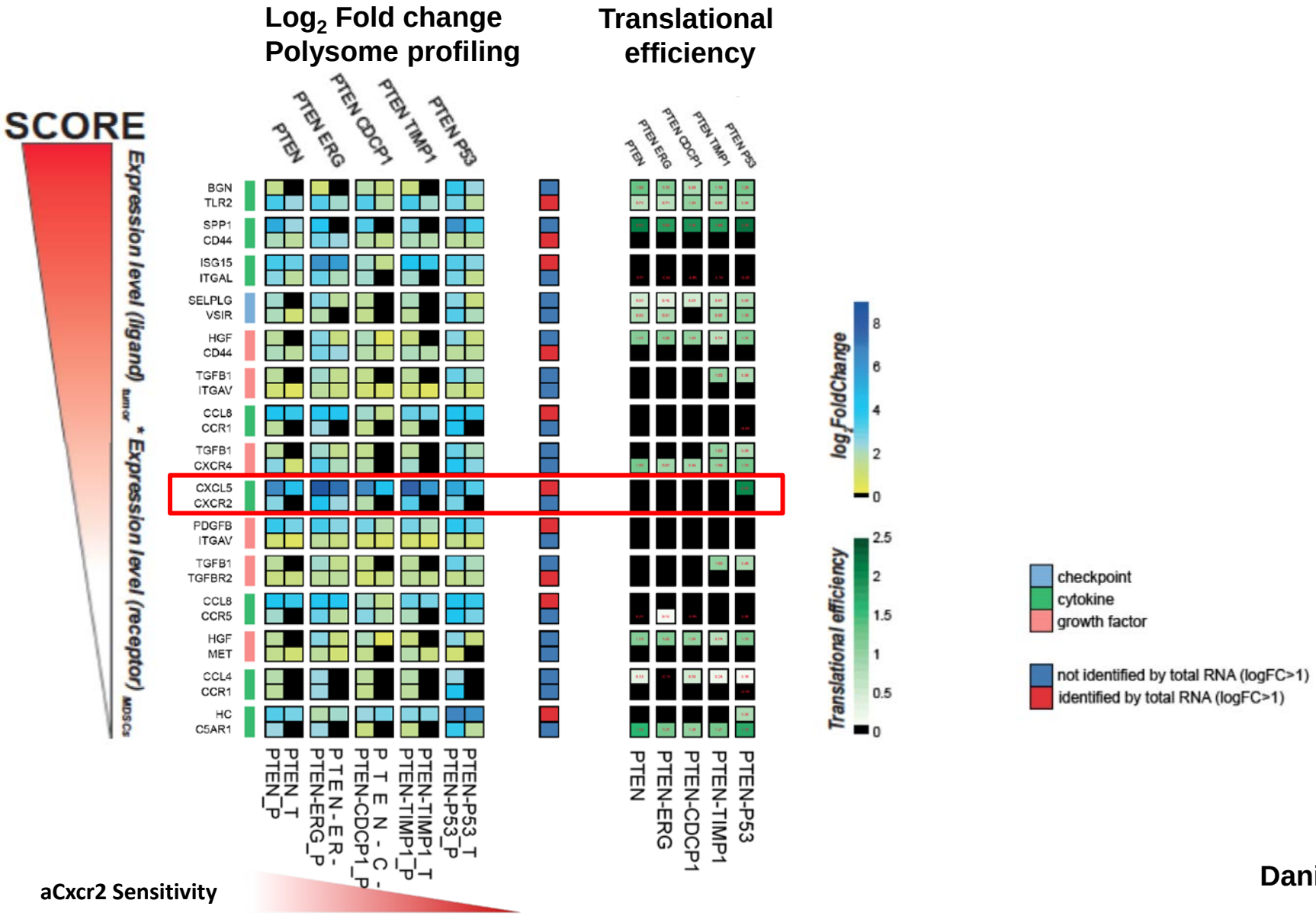
The extracellular interactome of prostate cancer





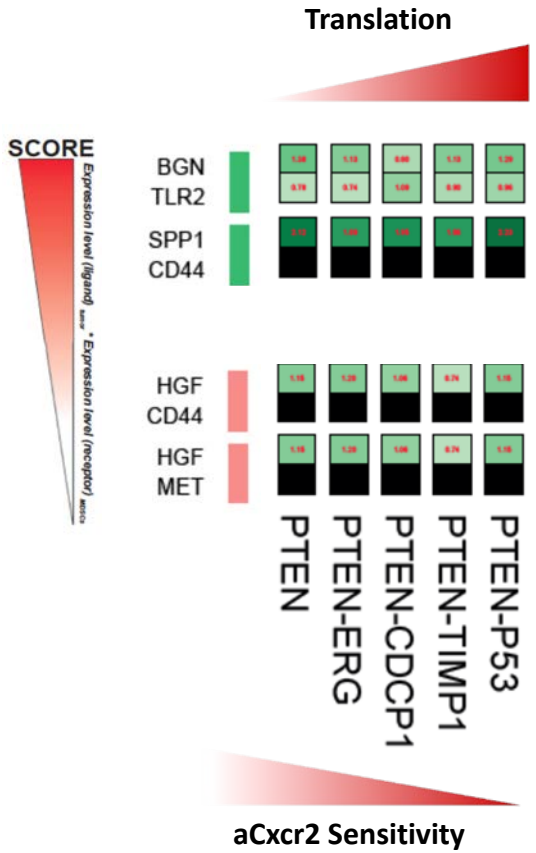


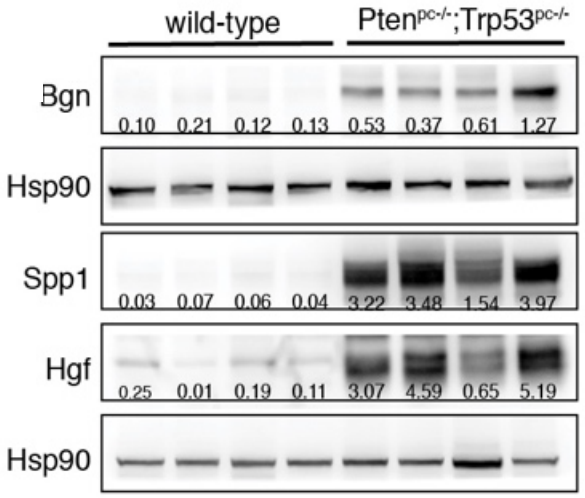
The extracellular interactome of prostate cancer

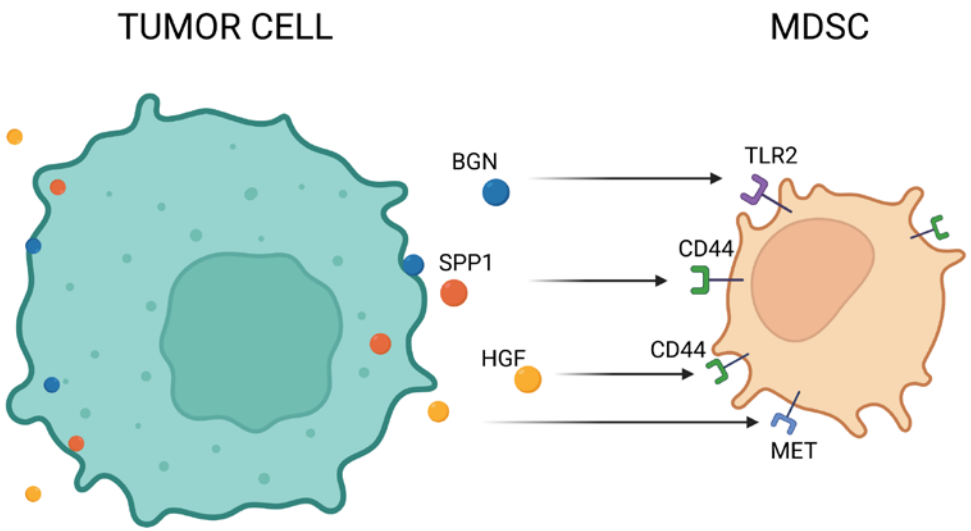


Daniela Brina, submitted

Identification of translationally regulated MDSCs targets

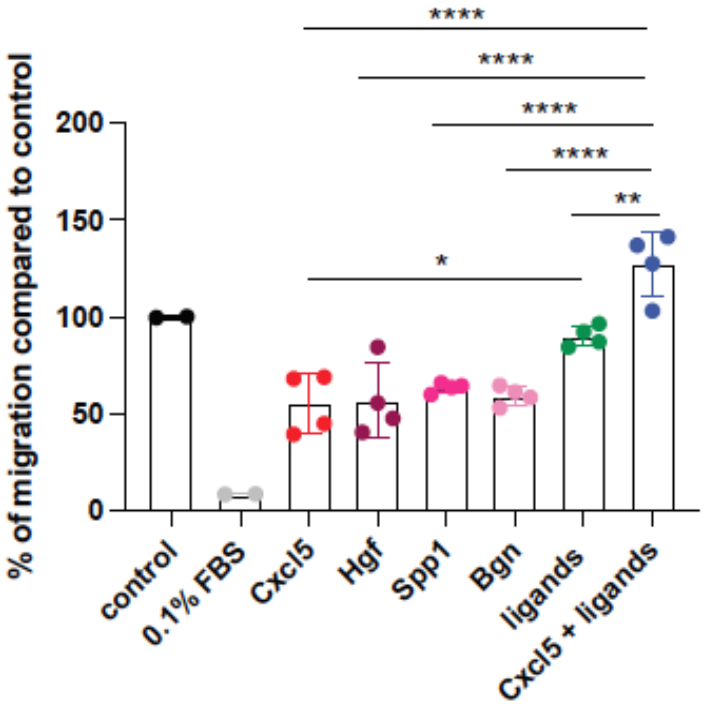


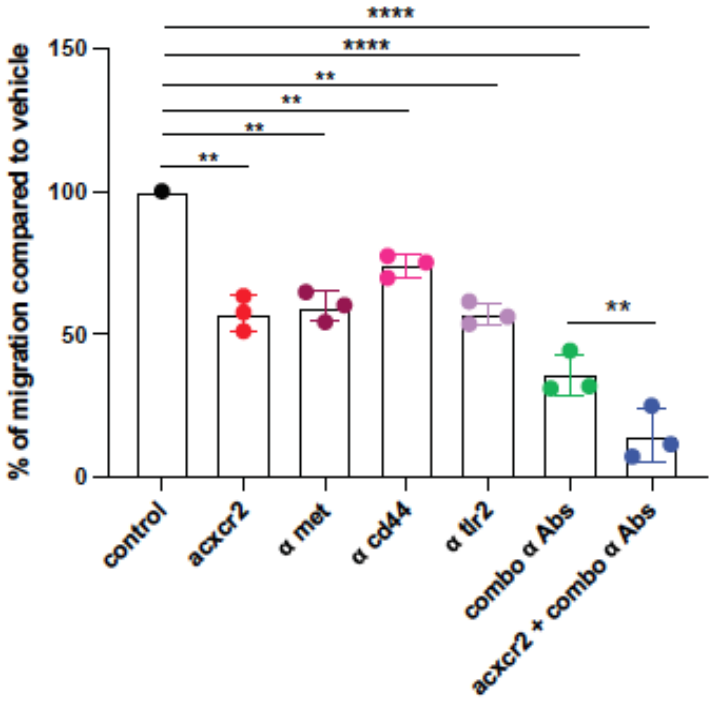


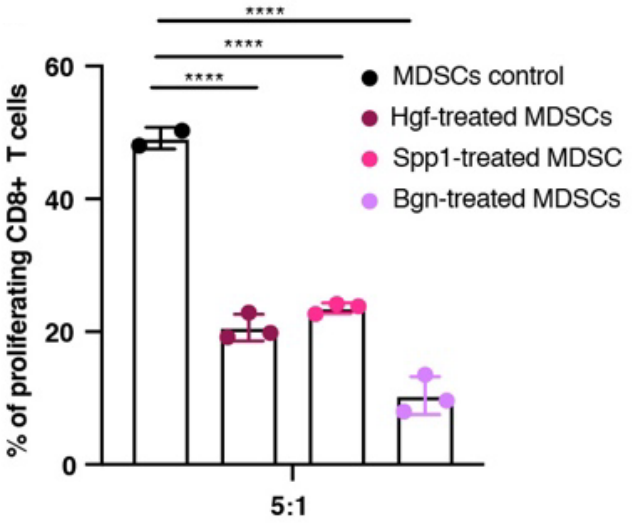


BGN=Biglycan
SPP1=Osteopontin
HGF= Hepatocyte growth factor

BGN,SPP1 and HGF modulate MDSCs migration and function

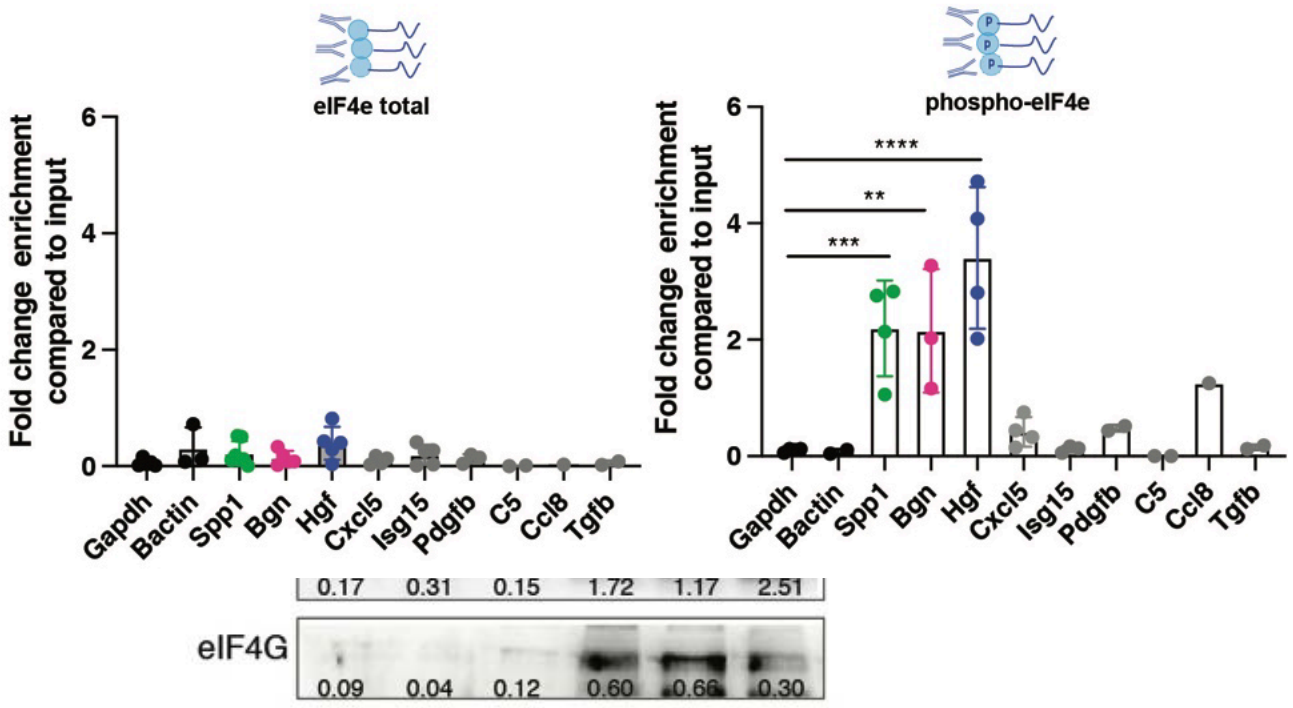


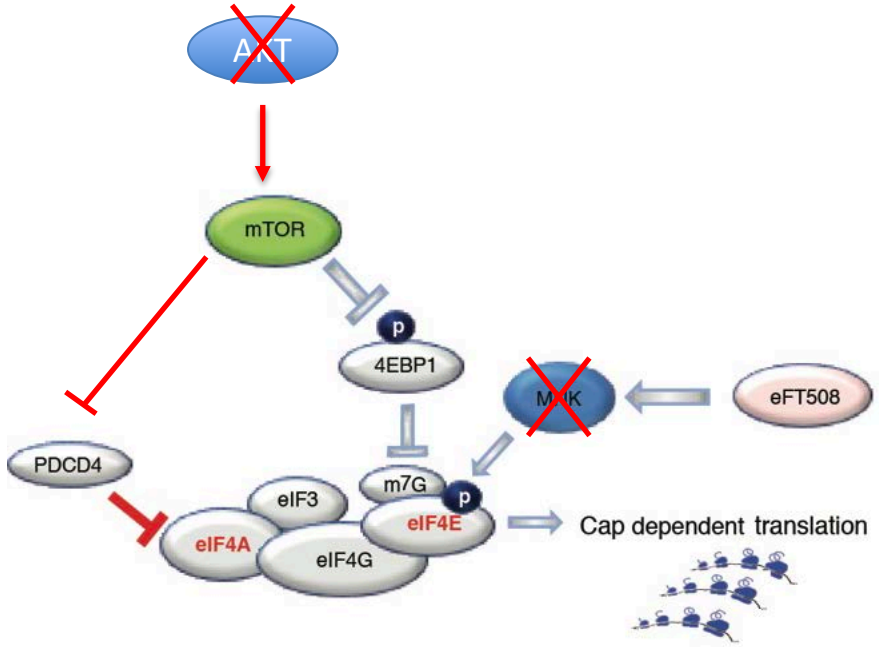




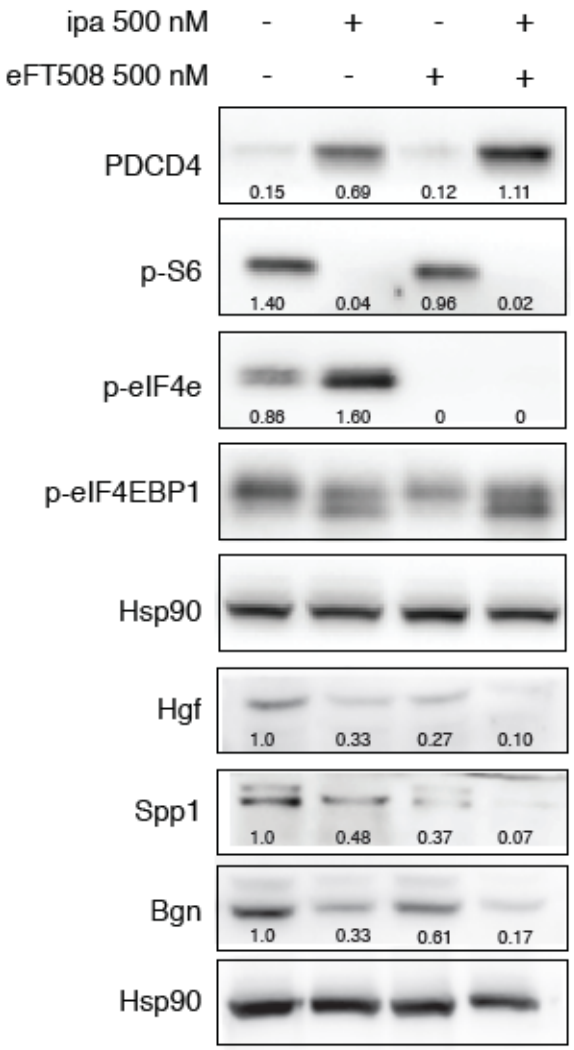
Daniela Brina, submitted

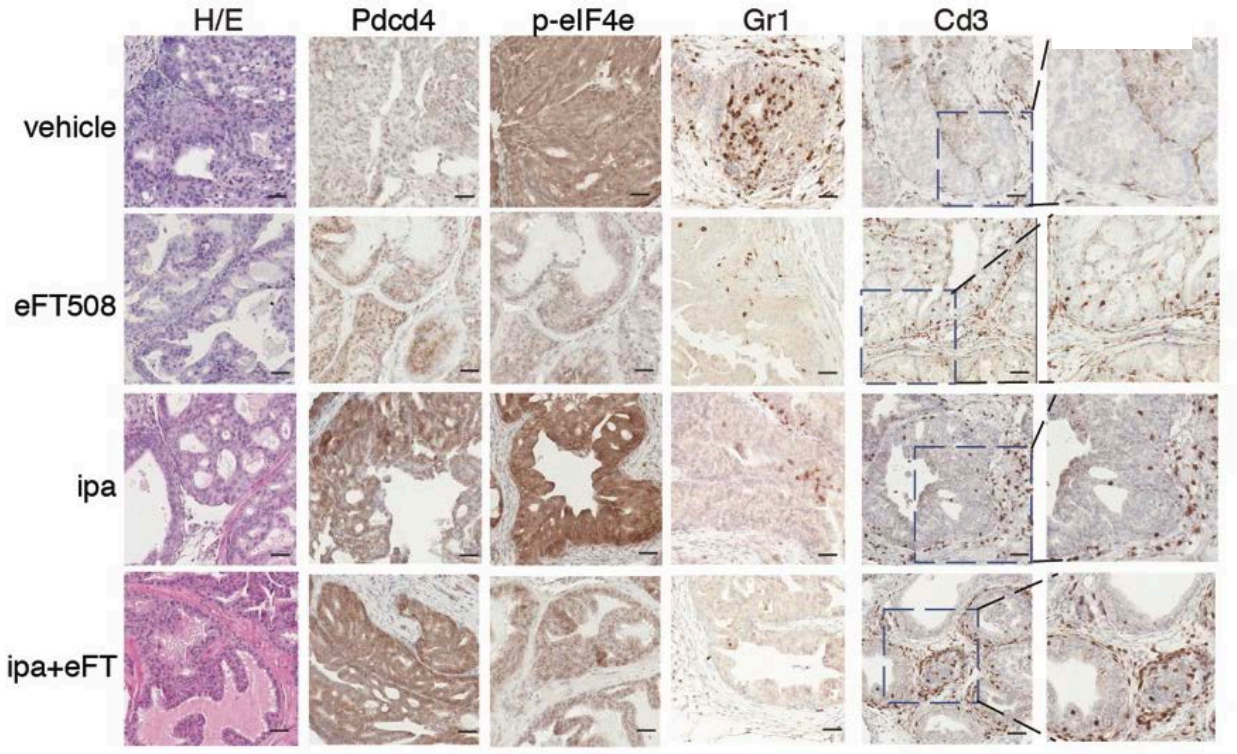
Translation of Spp1, Bgn and Hgf is controlled by MNK/peIF4E

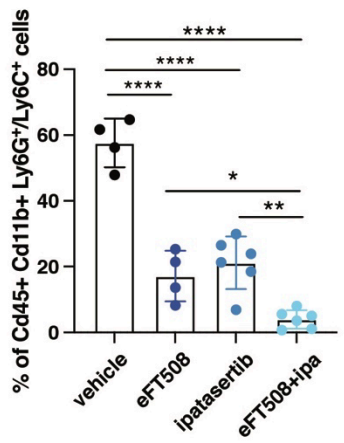


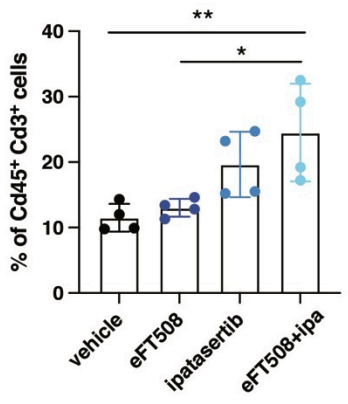


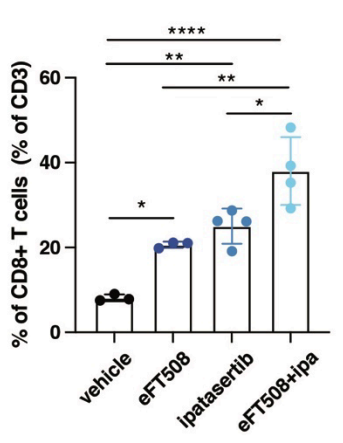
Dual eFT508(MNKi) and ipatasertib (AKTi) treatment dampens tumor-growth in *Pten*$^{pc-/-}$;*Trp53*$^{pc-/-}$ prostate cancers by blocking PMN-MDSCs











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Angelica Varesi

Prostate Cancer Foundation
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EMBO Young Investigator

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lega svizzera contro il canc

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