Association pour la Recherche sur les Tumeurs de la Prostate

Session V : Poster Session

TRPV6 CALCIUM CHANNEL TARGETING USING MAB82 INDUCES PROSTATE CANCER TUMOR REGRESSION IN VIVO

Clément Cordier[1], Aurélien Haustrate[1], George Shapovalov[1], Adriana Mihalache[2], Benjamin Soret[1], Alexandre Barras[3], Gautier Robin[4], Pierre Gosset[2], Natalia Prevarskaya[1], and V'yacheslav Lehen'kyi[1]

[1]Laboratory of Cell Physiology, INSERM U1003, Laboratory of Excellence Ion Channels Science and Therapeutics, Department of Biology, Faculty of Science and Technologies, University of Lille, 59650 Villeneuve d'Ascq, France

[2]Service d'Anatomie et de Cytologie Pathologiques, Groupement des Hôpitaux de l'Institut Catholique de Lille (GHICL), 59000 Lille, France

[3]Univ. Lille, CNRS, Centrale Lille, Univ. Polytechnique Hauts-de-France, UMR 8520 – IEMN, F-59000 Lille, France

[4]Mabqi SAS, F-34298, Montpellier, France

TRPV6 calcium channel is a prospective target in prostate cancer (PCa) since it is not expressed in healthy prostate while its expression increases during cancer progression. Despite the role of TRPV6 in PCa cell survival and apoptotic resistance has been already established, no reliable tool to target TRPV6 channel in vivo and thus to reduce tumor burden is known to date. Here we report the generation of mouse monoclonal antibody mAb82 directed against the extracellular epitope of the channel pore region as well as its mode of action on TRPV6-expressing prostate cancer cells in vitro and in vivo. mAb82 inhibited TRPV6 currents in a dose-dependent manner while decreasing store-operated calcium entry and thus PCa survival rate in vitro. The latter events induced cell death cascade via apoptosis by activation of the protease calpain, following bax activation, Cyt C release, pro-caspase 9 cleavage with the subsequent activation of caspases 3/7. In vivo, mAb82 showed a TRPV6-expression dependent organ distribution and virtually no toxicity in the same way as mAbAU1, a control antibody of the same IgG2a isotype. Mice bearing either PC3M$^{trpv6+/+}$ or PC3M$^{trpv6-/-}$+pTRPV6 tumors were successfully treated with mAb82 resulting in a significant reduction in tumor growth. The survival rate was markedly improved in mice treated with mAb82 compared to the control antibody mAbAU1. Overall, our data demonstrate for the first time the use of an anti-TRPV6 monoclonal antibody in vitro and in vivo in the treatment of the TRPV6-expressing PCa tumors.

Keywords: Prostate cancer; TRPV6 calcium channel; monoclonal antibody; tumor in vivo; metastasis; anti-cancer treatment

Contact: clement.cordier@inserm.fr

Establishment of patient-derived organoids for personalized prostate cancer therapy using smart nanoparticles targeting mRNA

Virginie Baylot[1,4], Thi Thom TRAN[1,4], Michael Baboudjian[1, 3], Quang Hieu DUONG[1,4], Thi Khanh LE[1,4], Laurence Colleaux[1], David Taïeb[1, 2, 4], Palma Rocchi[1, 4]

[1] Marseille Cancerology Research Centre, CRCM, Inserm UMR1068, CNRS UMR7258, Aix-Marseille University U105
[2] La Timone University Hospital, Aix-Marseille University;
[3] Department of Urology, Hospital Nord, Aix-Marseille University, Marseille, France
[4] European Center for Research in Medical Imaging (CERIMED), Aix-Marseille University, 13005 Marseille, France

Personalized medicine is the future of oncology, notably to efficiently treat patients with prostate tumors that are resistant to standard therapies. The development of mRNA-based therapeutics is particularly relevant and promising as they could be tailored to individual patients. The RNAnoTher lab develops oligonucleotide antisense (ASO)-based therapies that can be designed to specifically target disease-causing genes and can be loaded on nucleo-lipids based nano-vehicles to enable their internalization in prostate cancer (PCa) cells.

We hypothesized that the generation of an organoid bank derived from PCa clinic samples would provide the ideal platform to 1/identify key factors responsible for PCa progression and/or resistance in a patient-dependent manner, 2/ examine the dynamic changes that occur during PCa resistance and recurrence and 3/screen in a relevant model, that includes the 3D architecture of PCa tumors, the efficiency of our novel nanoparticles loaded with ASOs.

We have recently started the establishment of an organoid bank derived from fresh tumor specimens of both castration-sensitive (CS) and castration-resistant PC (CRPC) patients, as well as patients with benign prostatic hyperplasia (BPH). Fresh tumor tissues collected during transurethral resection were enzymatically digested, and cultured in droplets embedded in matrigel. The culture media was supplemented with growth factors and cytokines, according to the published method described by Drost J et al., (Drost et al., 2016). We will first characterize the organoids and corresponding tissue specimens using a combination of Western Blot analysis, qRT-PCR, Immunohistochemistry, and Immunofluorescence. Furthermore, we will determine which oncogenic drivers, related to the Hsp27 pathway, are overexpressed in each sample.

We successfully generated organoids derived from 6 patients: CS (N=1), CRPC (N=2), BPH (N=3). The expression of luminal (CK8) and basal (CK5) markers confirmed the presence of both prostate epithelial lineages in our established organoid cultures. The patient tumor-derived organoids (PTDOs) maintain the heterogeneity, gene expression profile, and histological architecture of the corresponding primary tumors. We interestingly found that the PCa derived PTDOs recapitulate the molecular diversity of PCa subtypes. Indeed, overexpression of the Androgen Receptor, Hsp27, and TCTP is commonly shared across our organoid lines while, PSMA overexpression or PTEN loss are tumor specific features. Our findings demonstrated the relevance of PTDOs ex vivo models to identify potential therapeutic targets on an individual level. Our nucleolipids-based carriers that can be loaded with ASOs will be further be used as a platform to develop personalized nanomedicine to treat advanced and refractory PCa.

IL6/JAK/STAT3-MEDIATED CROSSTALK BETWEEN CANCER ASSOCIATED FIBROBLASTS AND EPITHELIAL CELLS PROMOTES LINEAGE PLASTICITY AND PROSTATE CANCER PROGRESSION

Darya Yanushko[1], Beatriz German-Falcon[1], Rana El Bizri[1], Céline Keime[1], Tao Ye[1], Christelle Thibault-Carpentier[1], Gilles Laverny[1], Daniel Metzger[1]

1 Institute of Genetics and Molecular and Cellular Biology, CNRS UMR 7104, Inserm U1258, University of Strasbourg, France.

Prostate cancer is a heterogeneous disease with a slow progression and a highly variable clinical outcome. The tumor suppressor gene TP53 is frequently mutated in prostate cancer and predictive of an early metastatic dissemination and unfavorable patient outcome. However, the mechanism underlying TP53-loss induced disease aggressiveness is unknown.

The characterization of genetically engineered mice revealed that Trp53 deficiency in Pten-null prostatic epithelial cells does not impact prostatic intraepithelial neoplasia formation, nor growth arrest and senescence. However, with time, Pten- and Trp53-deficient tumors become invasive and acquire metastatic potential. Single-cell analyses of prostatic tumors revealed the presence of a cell population exhibiting a transcriptomic profile highlighting cell plasticity driven by Jak/Stat3 signaling, and further bioinformatic analyses suggested an interaction with cancer associated fibroblasts (CAFs). Experiments performed with conditioned medium from CAFs and prostate cancer organoids demonstrated that epithelial cell plasticity of Trp53-deficient tumors is induced by CAF-produced IL6, promoting Stat3 activation and metastatic dissemination.

Importantly, as the molecular signatures of Stat3-driven epithelial cells and IL6-producing CAFs identified in our mouse model are associated with prostate cancer aggressiveness and metastasis in patients, the pro-tumorigenic crosstalk between PTEN- and TP53-deficient prostatic epithelial cells and the tumor microenvironment is relevant in human disease and provides new vulnerabilities to counteract prostate cancer progression.

Development of novel models of aggressive variants of castrate-resistant prostate cancer

Ludovic Bigot [1], Jonathan Sabio[1], Loic Poiraudeau[1], Maxime Annereau[2], Naoual Menssouri[1], Carole Helissey [3], Olivier Déas[4], Marine Aglave[5], Tony Ibrahim[1], Cédric Pobel[1], Catline Nobre[1], Alice Da silva[1], Anne Chauchereau[1], Christophe Massard[1], Luc Friboulet[1], Karim Fizazi[1,6] , Benjamin Besse[1,6], Jean-Yves Scoazec[7,8] , Yohann Loriot[1,6,9]

AFFILIATIONS

1 Université Paris-Saclay, Gustave Roussy Cancer, Inserm U981, Biomarqueurs prédictifs et nouvelles stratégies thérapeutiques en oncologie, 94800, Villejuif, France.

2 Pharmacy, Gustave Roussy, Université Paris-Saclay, Villejuif, France.

3 Clinical Research Unit, Department of Oncology, Military Hospital Begin, Saint-Mandé, France

4 XenTech, Evry, France

5 Gustave Roussy, Plateforme de Bioinformatique, F-94805, Villejuif, France

6 Department of Medical Oncology, Gustave Roussy Cancer Campus, Villejuif, France

7 Experimental and Translational Pathology Platform (PETRA), Genomic Platform - Molecular Biopathology Unit (BMO) and Biological Resource Center, AMMICA, INSERM, Villejuif, France

8 Department of Medical Biology and Pathology, Gustave Roussy Cancer Campus, Villejuif, France.

9 Drug Development Department (DITEP), Gustave Roussy Cancer Campus, Villejuif, France

Background: Genomic studies have identified new subsets of aggressive prostate cancer (PCa) with poor prognosis (e.g., neuroendocrine prostate cancer (NEPC), PCa with DNA Damage Response (DDR) alterations or PCa resistant to androgen-receptor pathway inhibitors (ARPI). Development of novel therapies relies on the availability of relevant preclinical models.

Methods: NEPC (n = 5), DDR (n = 7), MSI-high (n=1) patient-derived xenografts (PDXs) were established from 51 patients with metastatic PCa enrolled in MATCH-R trial (NCT02517892). PDX-derived organoids (PDXO) (n=16) and patient-derived organoids (PDO) (n=6) were developed to perform drug screening. Histopathology and treatment response were characterized. Molecular profiling was performed by whole-exome sequencing (WES, n =13), RNA sequencing (n =13), and single-cell RNA sequencing (n = 14). WES and RNA-seq data from patient tumors were compared with the models.

Results: Our PDXs captured both common and rare molecular phenotypes as well as their molecular drivers, including alterations of BRCA2, CDK12, MSI-high status and NEPC. RNA sequencing profiling demonstrated broad representation of PCa subtypes. Single-cell RNA sequencing indicate that PDXs reproduce the cellular and molecular intra tumor heterogeneity. WES of matched patient tumors showed preservation of most genetic driver alterations. PDX, PDXOs and PDOs preserve drug sensitivity of the matched tissue and can be used to determine drug sensitivity.

Conclusion: Our models reproduce the phenotypic and genomic features of both common and aggressive PCa variants and capture their molecular heterogeneity. Successfully developed aggressive-variants PCa preclinical models provide an important preclinical tool to predict tumor response to anti-cancer therapy and study mechanisms of resistance.

Mouse LSC^{med} cells are a model of Club/Hillock Cells of the human prostate

[1]Manon BAURES, [1]Charles DARIANE, [2]Emilia PUIG LOMBARDI, [3]Florian RAMBOW, [4]Marc DIEDISHEIM, [5,6]Fred SAAD, [1]Jacques-Emmanuel GUIDOTTI, [1]Vincent GOFFIN

[1]INSERM Unit 1151 / Team 5 - Institut Necker Enfants Malades, Université Paris Cité, 75015 Paris, France
[2]Bioinformatics Core Platform, INSERM US24 / CNRS UAR3633 and INSERM UMR1163 / Imagine Institute, Université Paris Cité, 75015 Paris, France
[3]Institute for AI in Medicine (IKIM), Department of Applied Computational Cancer Research, University Hospital Essen.
[4]INSERM Unit 1151 / Immediab - Institut Necker Enfants Malades, Université Paris Cité, 75015 Paris, France
[5]CRCHUM, Institut du Cancer de Montréal (ICM), Montréal, QC H2X 0A9, Canada
[6]Department of Surgery, Université de Montréal, Montréal, QC H3C 3J7, Canada

Background
Club and Hillock cells have been recently identified by scRNAseq as rare epithelial cell types in the healthy human prostate, but are emerging as potential contributors to prostate pathogenesis and therapeutic resistance. In parallel, we recently identified LSC^{med} (Lin^{-}/Sca-1^{+}/CD49f^{med}) cells as luminal cells of the mouse prostate that exhibit castration-resistance and progenitor properties. The aim of this study was to evaluate their human relevance.

Methods
We combined phenotypic and functional analyses of LSC^{med} cells FACS-enriched from WT and Pten-null mice (an acknowledged model of castration-resistant prostate cancer, CRPC), bioinformatic analyses of public transcriptomic databases and immunostaining studies of retrospective human prostate cancer cohorts (n=285).

Results
We interrogated transcriptomic databases using a "LSC^{med} score" established from the transcriptomic signature of WT LSC^{med} cells. We found that LSC^{med} cells correspond to the Club/Hillock cells in the healthy human prostate. In scRNAseq datasets of naïve localized prostate cancer, we detected a small cell cluster enriched in LSC^{med} cell genes. Using KRT7 as a marker of LSC^{med}-like cells, we analyzed a cohort of localized prostate cancer and we found that KRT7 staining was predominant in benign peri-tumoral prostatic glands. Strikingly, KRT7 was associated with shorter bone metastasis-free survival. Mesenchymal stem-like prostate cancer (MSPC), a recently-identified prostate cancer subtype, is associated to castration-resistance and metastasis development. We found that MSPC is highly enriched in cells exhibiting high LSC^{med} score. Using CellPhoneDB, we identified EGFR, IGF-1R and MET as potential drivers of LSC^{med} proliferation, and we showed that pharmacological targeting of each receptor hampered organoid growth. However, the signaling redundancy of these receptors offers options to bypass receptor-targeted inhibition, as suggested in patient.

Conclusions
Thus, LSC^{med} cells represent a relevant preclinical model to investigate further the role of Club/Hillock cells in prostate cancer progression and to identify new therapeutic targets to prevent CRPC.

IN VITRO NEUROENDOCRINE DIFFERENTIATION OF BPH-1 CELLS UNDER BETA-ADRENERGIC STIMULATION

PIGAT N, GARRIDO L, LEFEVRE C, BAURES M, GOFFIN V, ARMAND A-S and CAPIOD T.

Recent studies have shown that adrenergic fibers from the sympathetic nervous system (SNS), acting through stromal b2-adrenergic receptors, play an important role in the initial phases of cancer development by promoting tumor cell survival. Recent epidemiological data suggest that b-blocker intake is associated with improved survival of prostate cancer patients. Hypertension and high blood pressure have been suggested to increase prostate cancer development suggesting that the use of b-blockers in these patients could also reduce prostate cancer risk. b-adrenoceptors signal through the cAMP/PKA pathway that is known to promote neuroendocrine differentiation (NED) in LNCaP prostate cancer cell line. While neuroendocrine (NE) cells expressing synaptophysin (SYN) represent a minor cell population in the epithelial compartment of normal prostate glands, the population of NE-like cells, exhibiting NE phenotypes and expressing NE markers, is increased in, and correlates with, cancer progression, androgen-independent state and poor prognosis. Expression of the routine tissue biomarker of prostate cancer AMACR in NE-like cells discriminates them from NE cells. Our aim was to investigate whether NED could also be associated with benign prostatic hyperplasia (BPH) as recent studies showed that an increase in neuroendocrine cell density occurred before development of BPH in hypertensive rats.

Our results showed that a 10-day treatment with 100µM IBMX (blocking cAMP degradation) and 10µM forskolin (FSK, adenylate cyclase activator) to trigger sustained activation of the cAMP/PKA pathway led to an increase in SYN and AMACR expression in BPH-1 cells (qPCR and WB). Similar results were observed by combining the effect of the b-adrenoceptor agonist isoproterenol (1µM) and FSK. The same treatments reduced BPH-1 cell proliferation rates by 40% and 60%, respectively, as expected for NED. Effects on AMACR and SYN expression and cell proliferation were fully reversed by the b-blocker carvedilol (5µM).

This data suggests that b-adrenoceptors could be linked to the development of NE-like cells in BPH, a non-lethal disease affecting the transition zone (TZ). As 20% of the prostate cancer occur in this TZ, this observation may need further investigation.

MENIN IMPLICATION IN PROSTATE CANCER PROGRESSION VIA MICRO-RNAS REGULATION

Souhaila Zaghdoudi[1-2-5], Thi Khanh LE[1-2], Pascal Finetti[1], Le Thi Thuy[1], Laurence Colleaux[3], Ahmed Sleheddine Masmoudi[5], David Taieb[1-2-4] and Palma Rocchi[1-2]

1 Centre de Recherche en Cancérologie de Marseille-CRCM, Inserm UMR1068, CNRS UMR7258, Aix-Marseille University U105, 13009 Marseille, France

2 European Center for Research in Medical Imaging (CERIMED), Aix-Marseille University,13005Marseille, France
3 Faculté de Médecine Timone, INSERM, MMG, U1251, Aix-Marseille University, 13385 Marseille, France
4 Department of Nuclear Medicine, La Timone University Hospital, Aix-Marseille University, 13005 Marseille, France

5 Laboratory of Biotechnology and Bio-Geo Resource Valorization, Tunisia

Background

Prostate cancer (PC) is one of the most common cancers in European and American countries. Menin, a scaffold protein that regulates gene expression and cell signaling, has previously been shown to be overexpressed in high-grade PC and Castration-resistant PC (CRPC). Furthermore, menin inhibition using ASO technology have been demonstrated to improve chemosensitivity in CRPC cells. Notably, menin acts as a tumor suppressor in normal prostate model PNT1A via microRNA regulation, implying the oncogenic role in PC aggressiveness and treatment resistance regarding microRNA dysregulation.

Objectives Here we will provide a whole human microRNA prolife that are regulated by menin in the normal and PC cells. We aim to investigate the implication of menin in prostate tumorigenesis that is mediated through crucial carcinogenic pathways associated with microRNAs. **Methods** Western blotting: To evaluate protein expression after siRNA transfection in 3 cell lines (PNT1A: normal prostate cells, LNCaP: castration-sensitive PC cells and PC-3: CRPC cells). HTG EdgeSeq miRNA whole transcriptome Assay: To measure the expression of whole human microRNA transcripts using next-generation sequencing (NGS) after menin knockdown. Functional analysis using KEGG pathway database: to identify functions or signaling involved by identified menin-regulated microRNAs in PC. **Results** The evaluation of microRNAs expression in PNT1A, LNCaP and PC-3 cell lines shows that menin plays a vital role in prostate cancer progression through microRNA regulation. Indeed, the gene suppressor role of menin is elucidated through the down-regulation of many key tumor suppressor microRNAs (miR1296-5p, miR183-3p) in normal prostate cells. In CRPC cells (PC-3), menin acts as an oncogenic factor and is related to CRPC development through the regulation of microRNAs regarding cell cycle regulation, apoptosis, proliferation, migration, metastasis and drug resistance. Menin inhibition in PC-3 cells downregulates onco-miRNAs (miR1179 and miR155) and upregulates gene suppressor miRNAs (miR122-5p, miR143-3p and miR155). **Conclusion** Taken together, our results suggest that the tumor suppressor Menin switches to an oncogene that play a key role in the CRPC progression via the regulation of microRNAs. This finding has the potential to ameliorate the effectiveness of targeted treatment strategies for PC.

EXPLOTIING SINGLE-CELL RNA SEQUENCING DATA TO OPTIMIZE PROSTATE CANCER PATIENT-DERIVED ORGANOID MODELS

Robin Dolgos[1,2,3]*, Raphaëlle Servant[1,2,3]*, Mariam Manawi[2], Renaud Mével[1,2], Romuald Parmentier[1,2,3], Lukas Bubendorf[2], Helge Seifert[1], Ashkan Mortezavi[1], Cyrill A. Rentsch[1], Clémentine Le Magnen[1,2,3]

[1] Department of Urology, University Hospital Basel, Basel, Switzerland

[2] Institute of Medical Genetics and Pathology, University Hospital Basel, University of Basel, Switzerland

[3] Department of Biomedicine, University of Basel, Basel, Switzerland

*Equal contribution

Introduction & objectives

Patient-derived organoids (PDOs) have been associated with low success rates in the context of prostate cancer (PCa). One hypothesis is that prostate tumor cells require signals which are lacking in the current culture conditions and may be specific to distinct PCa types. Therefore, we aimed at defining refined PDO culture conditions that are more adapted to the unique characteristics of PCa cells.

Materials & methods

Four single-cell RNA-sequencing (scRNA-seq) publicly-available datasets of the benign prostate and PCa were analyzed. Ligand-receptor interactions were inferred using the single-cell interactome tool CellPhoneDB. Identified candidate factors were integrated in distinct medium formulations and tested on five PCa organoid lines evaluating their viability using CellTiter-Glo 3D. Whole-mount immunofluorescence was performed on organoids using antibodies recognizing CK5, CK8 and AR markers.

R**esults**

We focused on cellular interactions involving receptors expressed by prostate epithelial cells and ligands expressed by any prostate cell type. These analyses led to the identification of putatively important ligands specific to epithelial prostate cells, including members of the TGFß and EREG/EGFR signaling pathways. Initial experiments identified groups of factors which improved organoid growth and viability. To identify the specific responsible factors, we next defined 11 medium formulations integrating several or single members of these families. Interestingly, NRG1 and MDK were associated with a significant increase in viability in castration-resistant (CRPC)-derived organoids but not in castration-sensitive (CSPC)-derived organoids. In addition, EGF improved the growth of certain CSPC organoids but not all, suggesting heterogenous factor-dependency within CSPC samples. Finally, high expression of CK8 and AR was maintained in CRPC organoids cultured with NRG1 and MDK, suggesting preservation of the luminal identity and androgen signaling.

Conclusions

We have identified factors that may improve viability of PCa PDOs, while maintaining their luminal phenotype and active androgen signaling. Our study paves the way towards advancing patient-derived organoids of PCa for translational studies.

PERIPROSTATIC ADIPOSE TISSUE: A NEW SOURCE OF ANDROGENS FOR CASTRATION RESISTANT PROSTATE CANCER

Yiyue Jia [1], Mathilde Lacombe[1], Cynthia Houël [1], Mathieu Roumiguié [1,2] David Estève [1], Stephanie Dauvillier [1], Mohamed Moutahir [1], Anne-Lise Royer [3], Maryline Morvan [3], Yann Guitton [3], Catherine Muller [1] and Delphine Milhas [1]

[1]: Institut de Pharmacologie et de Biologie Structurale, Université de Toulouse, CNRS, UPS, 205 route de Narbonne, 31077 Toulouse, France

[2]: Département d'Urologie, CHU Toulouse 1 Av. du Professeur Jean Poulhès, 31400 Toulouse

[3]: Laboratoire d'Etude des Résidus et Contaminants dans les Aliments, Oniris, Ecole Nationale Vétérinaire, Agroalimentaire et de l'Alimentation Nantes Atlantique, 101 Route de Gachet, 44300 Nantes, France

Androgen deprivation is the treatment of choice for locally advanced prostate cancer (PCa) and involves the inhibition of testosterone secretion by the testes. However, the disease will progress into castration resistant PCa (CRPC) after a few years. An emerging mechanism of CRPC involves the ability of cells to find other sources of androgens in the tumour microenvironment in order to produce active forms of androgens, as recently shown for gut microbiota and cancer-associated fibroblasts.

The aim of our study was to determine if periprostatic adipose tissue (PPAT), an adipose depot surrounding the prostate has a specific steroid metabolism that could favour CRPC occurrence. We characterized the sex steroid content and the steroidogenic enzyme expression profile of human PPAT and abdominopelvic adipose tissue (APAT, as control) from patients with PCa who underwent a radical prostatectomy, by Gas Chromatography–Mass Spectrometry (GC-MS) and RT-qPCR. The effects of PPAT/APAT-conditioned media (CM) on PCa cell growth and proliferation were evaluated by real-time imaging system Incucyte and Brdu incorporation.

We have demonstrated that PPAT contains more steroid metabolites such as 5α androstanedione and epiandrosterone compared to the APAT, involved in the alternate routes for 5α-DHT synthesis in CRPC. Within PPAT, mature adipocytes appear to be the main source of androgen metabolites. Regulation of the expression of steroidogenic enzymes could explain the higher content of 5α androstanedione and epiandrosterone in PPAT. Furthermore, we demonstrated that PPAT-CM can support cell growth and proliferation of an androgen-dependent cell line LNCaP cultivated in androgen-deprived medium but not in androgen containing medium. This effect is inhibited by an AR antagonist, bicalutamide, and PPAT-CM upregulates the expression of AR target genes (KLK3 and FKBP5). PPAT-CM reverses the acute regulation of steroidogenic enzymes in the absence of androgens. Altogether, these results bring arguments in favour of a functional effect of the steroid metabolites contained in PPAT on PCa cells and demonstrated that PPAT could represent a new source of androgens for CRPC.