Supplementary Information

Supplementary Table 1. Participant characteristics

Strata	PCa[a]		Family History Controls		Family History Cases		Risk - case only			Advanced[b]	
	controls	**cases**	**No**	**Yes**	**No**	**Yes**	**High**	**Intermediate**	**Low**	**No**	**Yes**
PRACTICAL Consortium											
Australia	1557	3996	798	114	768	618	1162	2102	118	169	132
Belgium	103	166	0	0	28	12	112	44	4	3	8
Bulgaria	89	192	89	0	192	0	108	77	6	0	0
Canada	455	668	338	77	486	155	96	314	143	0	0
Croatia	149	146	149	0	118	0	75	57	9	2	10
Denmark	1031	2057	0	0	766	87	802	1017	95	91	75
Finland	1183	2421	0	62	0	70	675	1021	543	79	148
France	691	923	606	85	629	294	417	501	3	8	13
Germany	493	781	484	9	578	203	308	424	7	64	33
Multi_Center	693	877	0	0	0	0	161	331	94	21	28
Nederland	65	71	0	0	0	0	0	0	0	0	0
Norway	0	1443	0	0	0	0	51	484	0	182	761
Poland	317	484	0	0	432	5	241	175	56	0	0
Portugal	180	374	0	0	181	190	182	161	29	0	1
Spain	819	1322	434	34	659	122	359	689	223	60	34
Sweden	2834	5976	750	79	1436	294	1599	2473	1380	539	624
UK	10854	17565	4881	1156	9129	3543	6396	5302	1566	1073	2307
USA	10488	10479	7410	1060	5977	1599	1303	3936	1766	1313	579
Total	**32001**	**49941**	**15939**	**2676**	**21379**	**7192**	**14047**	**19108**	**6042**	**3604**	**4753**

[a]Prostate Cancer; [b]Identification of advanced disease cases was based on Gleason score 8+, metastatic disease, PSA>100 or death from PCa.

Supplementary Table 2. Risk of prostate cancer for rs17632542 SNP

Analysis	OR (95% CI)[a]	P-value
All prostate cancers	0.70 (0.67-0.73)	9.6E-69
Positive family history status	0.75 (0.71-0.79)	2.7E-26
Age of disease onset	0.75 (0.71-0.79)	5.2E-29
High risk[b] vs Low[c]	1.58 (1.42-1.76)	1.23E-17
High risk vs Low/Intermediate[d]	1.42 (1.33-1.51)	1.41E-26
Risk lethal vs controls	1.33 (1.16-1.51)	2.29E-05

[a]Odds-ratio and (95% confidence interval); we defined [b]High risk as tumour stage T3/T4 or N1 or M1 or Gleason score ≥8 or PSA >20 ng/mL; [c]low risk as tumour stage ≤T1 and Gleason score ≤6 and PSA <10 ng/mL; and [d]intermediate risk as tumour stage T2 or Gleason score=7 or PSA=10-20 ng/mL. Association between the rs17632542 SNP and PCa risk was analysed using the per-allele trend test, adjusted for study relevant covariates using logistic regression and seven principal components derived from analysis of the whole iCOGS and OncoArray dataset. Odds Ratios and 95% confidence intervals were derived using SNPTEST or an in-house C++ program. Tests of homogeneity of the ORs across strata were calculated using a likelihood ratio test. In a case-only analyses, Cox proportional hazards regression was used to estimate associations of SNP.

Supplementary Table 3: Frequency distribution for the rs17632542 SNP

Category	Coding	TT	CT	CC	Total	Genotype Frequency		
						p(TT)	p(CT)	p(CC)
T-Stage	T0	19	4	0	23	0.826087	0.173913	0
	T1	13433	1408	38	14879	0.902816	0.09463	0.002554
	T2	13496	1543	45	15084	0.894723	0.102294	0.002983
	T3	6317	926	41	7284	0.867243	**0.127128**	0.005629
	T4	686	103	8	797	0.860728	**0.129235**	0.010038
Total		33951	3984	132	38067			
GLEASON score_Range	1	306	38	1	345	0.886957	0.110145	0.002899
	2	7697	890	32	8619	0.893027	0.10326	0.003713
	3	1182	203	8	1393	0.848528	**0.145729**	0.005743
	4	3	0	0	3	1	0	0
Total		9188	1131	41	10360			
N-Stage	N0	11883	1402	43	13328	0.891582	0.105192	0.003226
	N1	1001	182	12	1195	0.837657	**0.152301**	0.010042
Total		12884	1584	55	14523			
M-Stage	M0	13839	1709	55	15603	0.886945	0.10953	0.003525
	M1	1413	215	8	1636	0.863692	**0.131418**	0.00489
Total		15252	1924	63	17239			
SEER Staging	Local	27928	3056	85	31069	0.898902	0.098362	0.002736
	Regional	6454	948	43	7445	0.866891	**0.127334**	0.005776
	Distant	1421	216	8	1645	0.86383	**0.131307**	0.004863
Total		35803	4220	136	40159			

Significant frequencies for the genotype highlighted in bold.

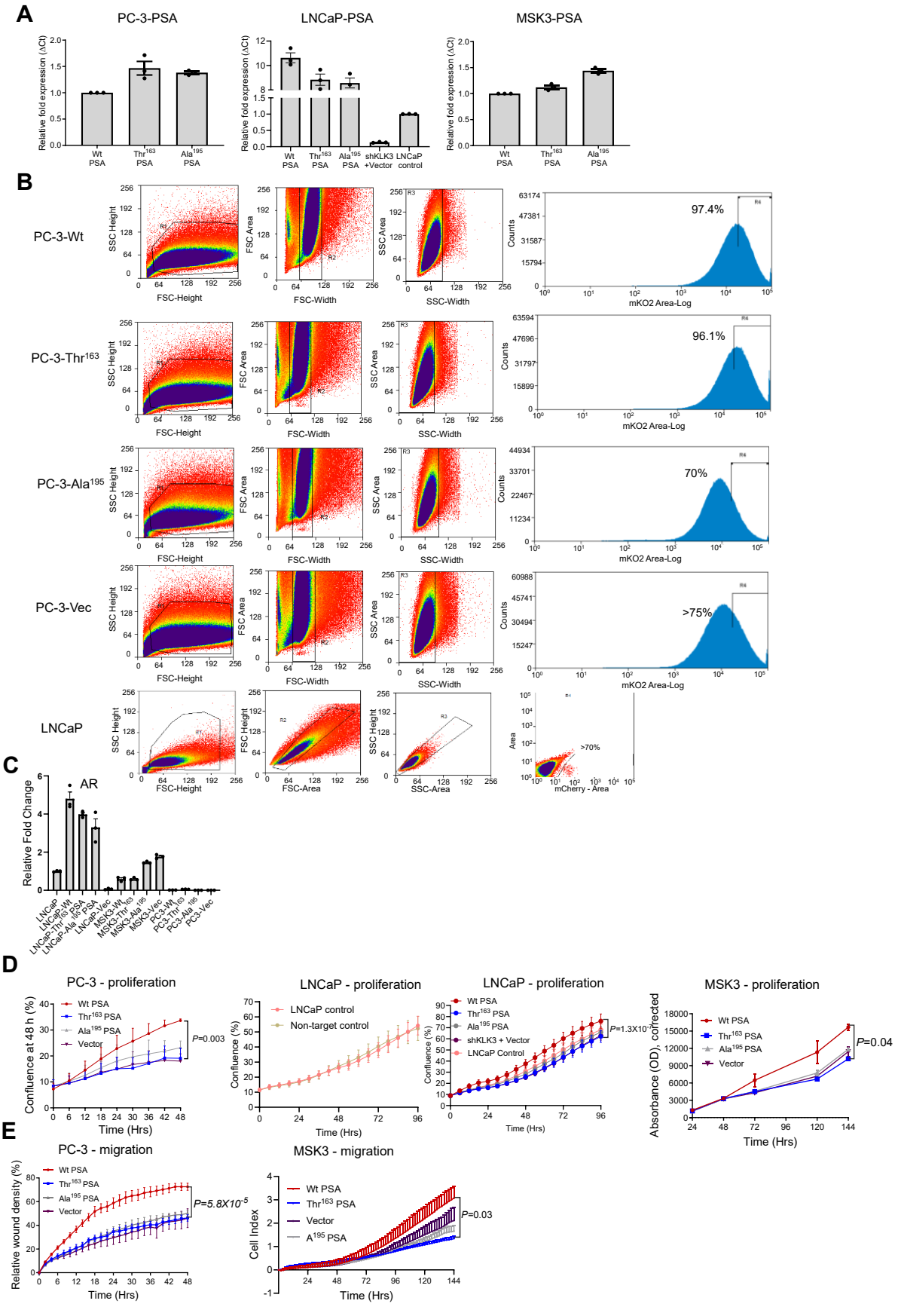
Detailed description for each “Category”

Category	Variable name	Description	Coding
Cancer Stage	T-Stage	T-Stage: Size or direct extent of the primary tumour ('T')	T0=no evidence of tumour, T1=tumour present, but not detectable clinically or with imaging, T2=the tumour can be felt (palpated) on examination, but has not spread outside the prostate, T3=the tumour has spread through the prostatic capsule, T4=the tumour has invaded other nearby structures
Gleason	Gleason score_Range	Range based on Gleason score	1=Gleason score<5. 2=Gleason score 5,6,7. 3=Gleason score 8, 9, 10. 4=undifferentiated.
	N-Stage	Degree of spread to regional lymph nodes ('N')	N0=there has been no spread to the regional lymph nodes, N1=there has been spread to the regional lymph nodes
	M-Stage	Presence of metastasis ('M')	M0=there is no distant metastasis, M1=there is distant metastasis
	SEER Staging	Prostate cancer SEER staging	Local=Confined to the prostate, Regional=Direct extension involving adjacent local structures and local lymph node, Distant=Direct extension or metastasis

Supplementary Table 4. Primers used for the study

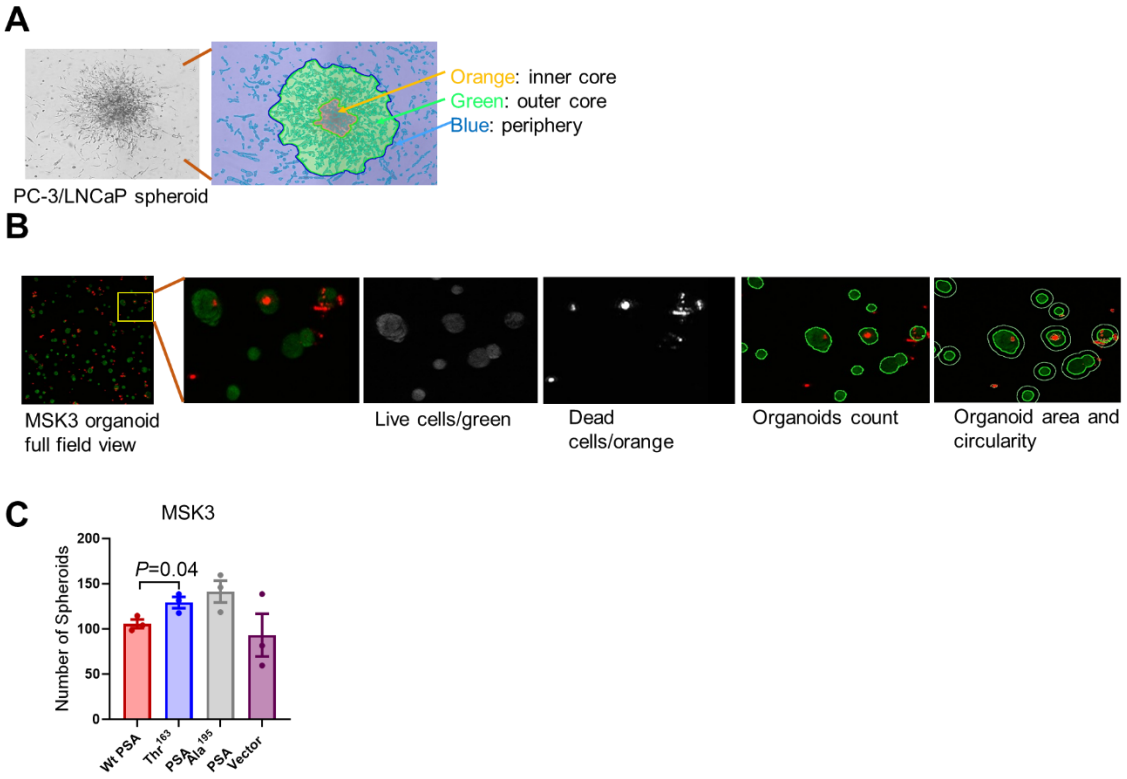
Gene	Primer sequences (5' to 3')	Reference/Source
KLK3 (Exon 2-3)	F1-AGTGCGAGAAGCATTCCCAAC R1-AACAAAAGCGTGATCTTGCTGG	[1]
GAPDH	F-GCAAATTCCATGGCACCGT R- TCGCCCCACTTGATTTTGG	[2]
pcDNA3.1 vector sequencing primers	F-TAATACGACTCACTATAGGG R-TAGAAGGCACAGTCGAGG	(Invitrogen™)
7SL	F-ATCGGGTGTCCGCACTAAGTT R-CAGCACGGGAGTTTTGACCT	(Life Technologies)
Alpha-signal	GGACGGATCCAAACGATGAGATTTCCTTCA	Sigma Aldrich, Australia
PSA mature	F-CTCTCGAGAAAAGAATTGTGGGAGGCTGGGAGT R-CAGCCTCCCACAATTCTTTTCTCGAGAGATACC	Sigma Aldrich, Australia
Site-directed mutagenesis primers for PSA-inactive mutant Ala[195]	F-GCACCTGCTCGGGTGATGCTGGGGGCCCACTTGTC R-GACAAGTGGGCCCCCAGCATCACCCGAGCAGGTGC	(Primer X)
Site-directed mutagenesis primers for rs17632542	F-GTGGACCTCCATGTTACTTCCAATGACGTGTG R-CACACGTCATTGGAAGTAACATGGAGGTCCAC	(Primer X)

Supplementary Figure 1



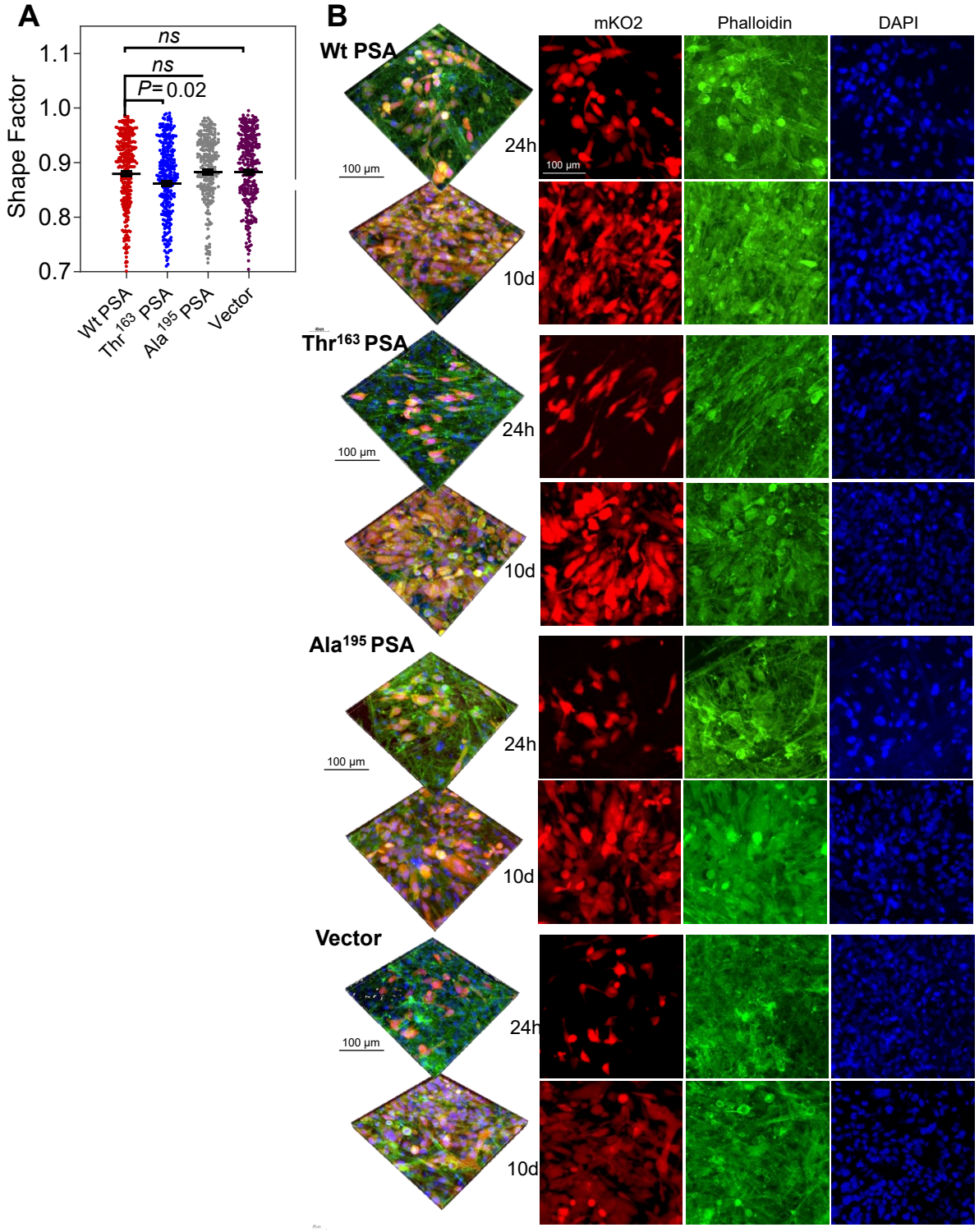
Supplementary Figure 1. *KLK3* expression in overexpression models.

A) Representative mRNA analysis demonstrating the expression of PSA in PSA transfected PC-3, LNCaP and MSK3 clones: Wt PSA, Thr^{163} PSA and inactive mutant Ala^{195} PSA. For LNCaP cells, PSA expression in vector (PSA knock-down (shKLK3) and transfection with vector pLEX307-GFP) and control non-transfected LNCaP cells are shown (*n*=3 independent experiments). **B)** FACS analysis showing mKO2 positive cells in PC-3 cells and mCherry positive cells in LNCaP cells. The % of transfection efficiency is indicated. **C)** *AR* expression in LNCaP (non-transfected) and PSA transfected PC-3, LNCaP and MSK3 clones: Wt PSA, Thr^{163} PSA and inactive mutant Ala^{195} PSA (*n*=2 independent experiments). **C)** Proliferation rate (confluence %) monitored in the IncuCyte live cell imaging system for PC-3, LNCaP and MSK3 cells expressing PSA variants, vector control and non-target control (LNCaP) (*n*=3 independent experiments). **D)** Migration rate (relative wound density %) measured by IncuCyte live cell imaging system for PC-3 cells and migration (Cell index) for MSK3 cells measured using the xCELLigence system, expressing PSA variants and vector control (*n*=3 independent experiments). All error bars represent mean ± SEM. Statistical analyses were determined by one-way ANOVA followed by Dunn's multiple comparison test (D, E). Source data are provided as a Source Data file.



Supplementary Figure 2. Digital spheroid analysis of PC-3, LNCaP and MSK3 cells.

A) A gray channel image generated from the original image was corrected to reduce the background. A density image was generated for the detection of spheroids as cell agglomerations with high cell numbers per area and their separation from isolated cells distributed across the wells. Positive objects (confirmed spheroids) were split into three areas, with the green contour indicating the outer core, the orange contour labelling the inner core and the blue contour highlighting the regions with detectable cells in the periphery. Quantitative analyses for the area and circularity of PC-3 or LNCaP spheroids were determined by the StrataQuest™ software. **B)** Dead (red) and live (green) cells count and mean intensity within the spheroid was detected based on setting thresholds, spheroid number, and event area for spheroid area were measured for the MSK3 spheroids. **C)** Number of MSK3 spheroids in selected field (average number from two images; *n*=3 independent experiments). See also Figure 2A–J. All error bars represent mean ± SEM. Statistical analyses were determined by two-sided Unpaired *t* test with Welch's correction. Source data are provided as a Source Data file.

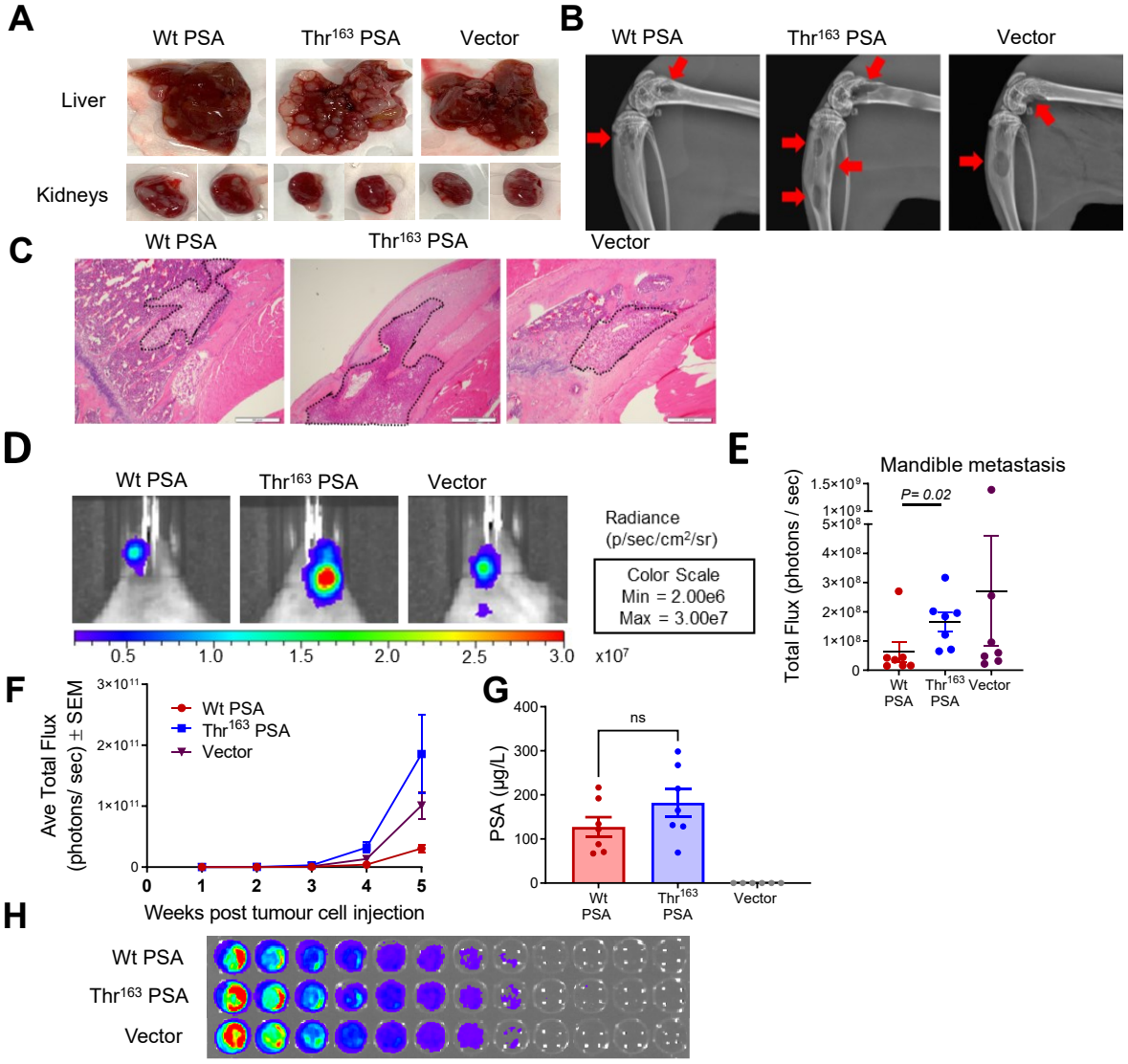


Supplementary Figure 3. Confocal Microscopy for PSA and vector transfected PC-3 cells on OBM constructs.

A) Shape Factor of PC-3 cells to OBM constructs after 12 h co-culture. **B)** Confocal laser microscopy images from PC-3/OBM constructs after 1 day and 10 days co-culture showing, from left to right, a volume snapshot of all channels and the maximum projections of z-stacks (mKO2 (red) for PC-3, GFP (green) for Phalloidin, and DAPI channel (blue) showing nuclei of

both cancer cells and osteoblasts. For **A-B**, 2 technical replicates were used, 4-5 fields of view/replicate, for a total of 120-230 cells per condition. *P* values on all groups were evaluated by one-way ANOVA followed by Games-Howell post hoc analysis. See also Figure 2H-J. Source data are provided as a Source Data file.

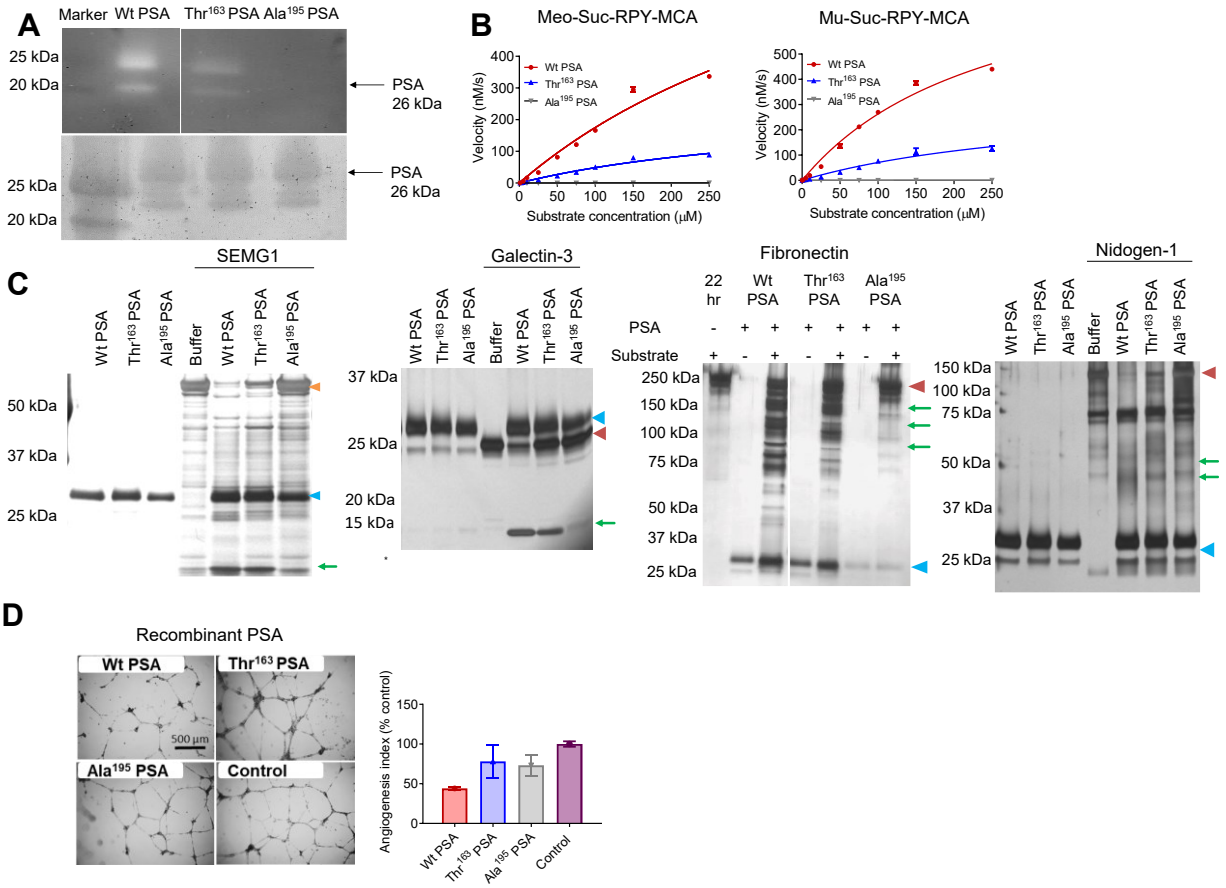
Supplementary Figure 4



Supplementary Figure 4. Effect of rs17632542 SNP on PC-3 cell metastasis in an experimental metastasis mouse model.

A) Representative photographs of resected liver and kidneys from mice following cardiac injection of PC-3-Wt/Thr^{163} PSA (*n*=7 mice/group). Increased tumour lesions are observed in the livers of Thr^{163} PSA injected mice. **B)** X-ray images of tumour-bearing hind legs of mice; red areas indicate areas of bone degradation, suggesting presence of tumour. **C**) H&E staining of tumour-bearing hind leg bones. **D**) Representative bioluminescence images of tumour-bearing mandibles of mice (week 4) post cardiac inoculation. **E**) Scatter plots of tumour bioluminescence based on region of interest (ROI) drawn over the jaw; horizontal line indicates median value. Statistical analysis was Dunn's multiple comparisons test. **F**) Mean bioluminescence values from ROI drawn over entire animals from each group, over multiple weeks. **G**) Serum concentration of total PSA at endpoint from mice injected intracardiac with tumour cells. All error bars represent mean ± SEM. Statistical analyses were determined by two-sided Student's *t* test (*n*=7 mice/group). **H**) *In-vitro* bioluminescence images of cell lines seeded by 2-fold serial dilution, starting at 50,000 cells per well. Also see Figure 2N-O.

Supplementary Figure 5

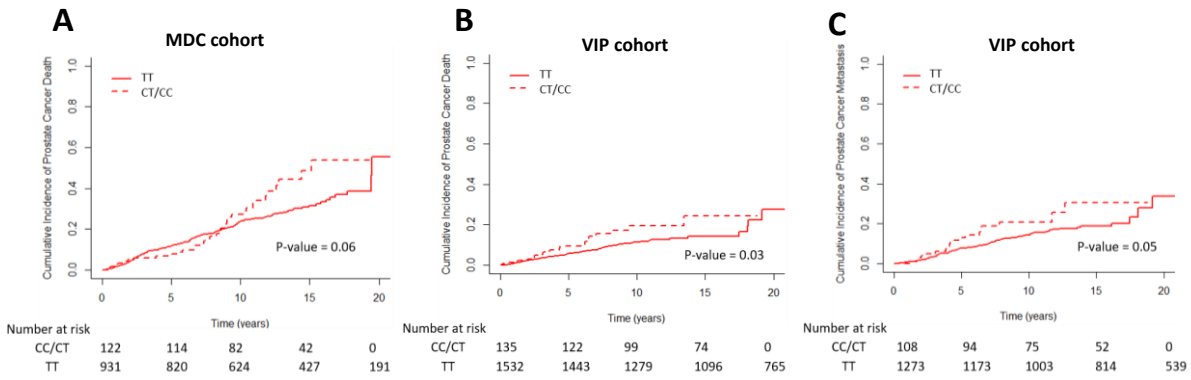


Supplementary Figure 5. Proteolysis of peptide and full-length protein substrates by mature PSA protein variants.

A) Casein zymography of Wt PSA and Thr^{163} PSA: One µg of Wt PSA, Thr^{163} PSA and inactive mutant Ala^{195} PSA (from left to right) were resolved on a 10% casein zymogram Protein Gel (Invitrogen) followed by Coomassie brilliant blue R-250 (0.25% w/v) staining. Clear zones due to protease activity were observed in the Wt PSA and Thr^{163} PSA lanes only. The bottom gel represents the silver stain analysis to indicate equal protein loaded into the wells. **B)** Michaelis-Menten kinetics for PSA protein variants: Michaelis-Menten kinetic analysis of Wt PSA (red), Thr^{163} PSA (blue) and inactive mutant Ala^{195} PSA (grey) for two substrates MeO-Suc-RPY-AMC and Mu-HSSKLQ-MCA. Kcat values showed the Thr^{163} PSA protein variant had decreased substrate activity in comparison to Wt PSA (mean ± SEM; *n*=3 independent experiments). Also see legend to Figure 3B. (**C)** Silver stain analysis of mature PSA variants (0.2 µM) incubated for 22 h with full-length substrates (semenogelin-1, galectin-3, fibronectin, nidogen-1, and laminin α-4) (0.5 µM) at 37°C, indicated that the Thr^{163} PSA isoform exhibited lower proteolytic activity compared to the wild type (Wt) PSA. Ala^{195} PSA had less effect. Wt PSA efficiently cleaved full-length fibronectin and laminin α-4, while partial proteolysis was observed with nidogen-1. The full-length proteins (orange arrow), PSA band (blue arrow) and their corresponding molecular weights are indicated. Cleaved products of the substrates (green arrows) due to PSA proteolytic activity are indicated to the right. High molecular weight bands that may correspond to the dimers of the full-length protein or their aggregates were observed above their expected size bands. Molecular weight of the protein standard (kDa) is indicated to the left. Also see Figure 3C-D. **D)** HUVECs treated with different recombinant PSA

protein variants (250 nM) (Wt, Thr^{163} and Ala^{195} PSA) and the graph to the right represents the angiogenesis index. Thr^{163} PSA exhibited lower anti-angiogenic potential compared to Wt PSA (*n*=2, mean ± SEM). Scale bar is 500 µm. Also see Figure 3F.

Supplementary Figure 6



Supplementary Figure 6. Overall- and metastasis-free survival of MDC and VIP cohorts for the rs17632542 SNP.

A-B) Overall survival as measured by cumulative incidence of death from PCa for the rs17632542 SNP in **A)** MDC (*n*=1,053), HR= 1.39, 95% CI=0.98-1.98, *P*=0.06; and **B)** VIP cohorts (*n*=1,644), HR=1.69, 95% CI=1.07-2.65, *P*=0.03. **(C)** Metastasis free survival analysis estimated by Kaplan Maier plot in the VIP cohort of 1,381 prostate cancer cases. rs17632542 is associated with metastasis-free survival time in VIP cohort (HR=1.65, 95% CI=1.03-2.62, P=0.05).

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