

# Molecular characterization of STEAP1 and STEAP2 in advanced prostate cancer

Kevin K. Zarrabi<sup>1</sup>, Tolulope Adeyelu<sup>2</sup>, Andrew Elliott<sup>2</sup>, Daniel M. Geynisman<sup>3</sup>, David Y. Oh<sup>4</sup>, Carissa Chu<sup>4</sup>, Rana R. McKay<sup>5</sup>, Nicholas A. Zorko<sup>6</sup>, Emmanuel S. Antonarakis<sup>6</sup>, Lucia Languino<sup>1</sup>, Pedro C. Barata<sup>7</sup>, Daniel C. Danila<sup>8</sup>, Norm Smith<sup>2</sup>, Wm. Kevin Kelly<sup>1</sup>

1. Thomas Jefferson University Hospital, Philadelphia, PA; 2. Caris Life Sciences, Phoenix, AZ; 3. Fox Chase Cancer Center, Philadelphia, PA; 4. University of California, San Francisco, San Francisco, CA; 5. University of California San Diego, San Diego, CA; 6. University of Minnesota, Minneapolis, MN; 7. University Hospitals Seidman Cancer Center, Cleveland, OH; 8. Memorial Sloan Kettering Cancer Center, New York, NY;

## Background

- STEAP1 and 2 (six-transmembrane epithelial antigen of prostate) are metalloendopeptidase proteins involved in a variety of biologic processes.
- *STEAP1/2* are tumor-associated cell surface antigens highly expressed in prostate cancer (PC), although their role in cancer is poorly understood.
- *STEAP1/2* have emerged as potentially successful targets for adoptive T-cell therapy trials for PC.
- Ultimately, the involvement of STEAP proteins in prostate cancer pathogenesis is apparent; however, its regulation and specific role in driving cancer progression remain largely undefined.
- We employed a multi-omics approach to investigate the molecular features associated with *STEAP1* and *STEAP2* expression in PC

## Methods

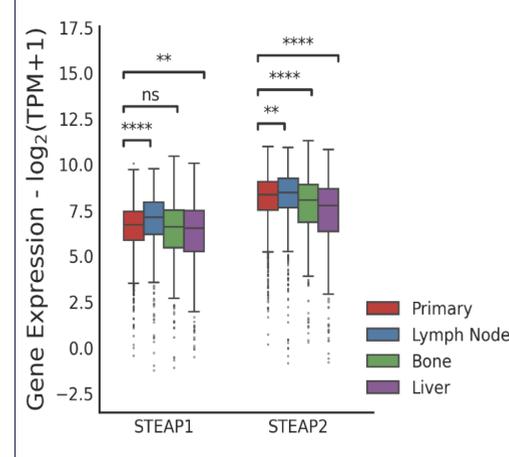
- NextGen Sequencing of DNA (592 genes or whole exome) and RNA (whole transcriptome) was performed for prostate tumors (n = 7089) submitted to Caris Life Sciences (Phoenix, AZ).
- Immune cell infiltration in the tumor microenvironment (TME) was inferred by quanTIseq.
- Transcriptomic signatures of androgen receptor signaling (AR), neuroendocrine classification (NEPC), and interferon gamma signaling (IFN) were calculated. Differentially regulated pathways were assessed by Gene Set Enrichment Analysis.
- Mann-Whitney U and X2/Fisher-Exact tests were applied where appropriate, with P-values adjusted for multiple comparisons (q < .05)

## Results

### Baseline Demographics

Samples	7089
<b>Median Age [Range]</b>	68 [35 – 89]
<b>Specimen Sites</b>	
Prostate	4477 (63.2%)
Genitourinary	422 (6.0%)
Gastrointestinal	125 (1.8%)
Liver	358 (5.1%)
Lymph node	827 (11.7%)
Bone	495 (6.9%)
Lung	144 (2.0%)
CNS	90 (1.4%)
Others	151 (2.1%)
<b>Histology</b>	
Adenocarcinoma	6975 (98.4%)
Neuroendocrine	50 (0.7%)
Mixed Histology	64 (0.9%)
<b>Castration Status</b>	
nonCS-PCa	1912 (31.8%)
CS-PCa	4106 (68.2%)

### STEAP Gene expression Across Tumor Sites

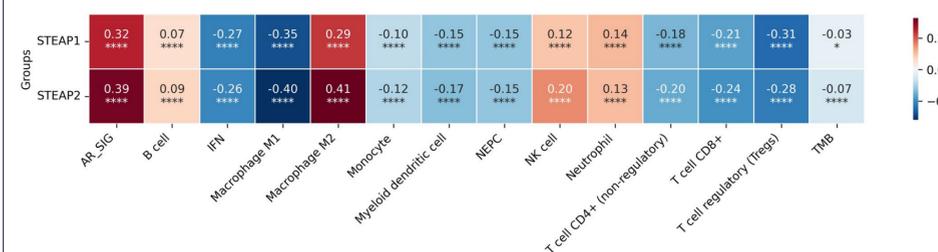


### Genomic Alterations Associated with STEAP 1/2 Expression Quartiles

Biomarkers	STEAP1				q-value		STEAP2				q-value
	Q1	Q2	Q3	Q4			Q1	Q2	Q3	Q4	
AR - IHC	92.00%	99.81%	99.68%	99.88%	****		92.00%	99.69%	99.81%	99.87%	****
TMPRSS2-Fusion	30.15%	34.11%	31.47%	32.30%	ns		27.40%	34.56%	33.95%	32.11%	ns
PIK3CA	7.03%	6.10%	3.15%	2.71%	****	High	7.59%	5.42%	3.71%	2.31%	****
APC	10.76%	7.32%	5.85%	5.53%	****		10.99%	6.93%	6.68%	4.90%	****
RB1	6.42%	3.17%	2.95%	2.81%	****		7.06%	3.83%	2.16%	2.46%	****
PIK3R1	2.07%	1.68%	1.13%	0.49%	****		2.20%	1.63%	1.14%	0.42%	****
CTNNB1	4.85%	4.66%	3.74%	2.47%	****		5.17%	4.20%	3.71%	2.67%	****
AR	1.94%	3.29%	3.27%	3.80%	***		2.74%	3.37%	2.64%	3.56%	***
KDM6A	2.18%	2.42%	2.71%	4.15%	****		2.45%	2.66%	2.48%	3.82%	*
TP53	37.95%	31.81%	31.40%	32.69%	***		41.30%	35.08%	30.86%	26.70%	****
PTEN	10.54%	8.94%	7.71%	7.40%	***		11.55%	8.48%	8.39%	6.21%	****
SPEN	2.79%	1.79%	1.72%	1.33%	***		3.04%	1.74%	1.61%	1.25%	****
SMARCA4	0.61%	0.06%	0.24%	0.06%	**		0.49%	0.24%	0.06%	0.18%	ns
PIK3CB	3.53%	3.24%	1.19%	0.37%	*		3.98%	3.17%	1.14%	0.00%	****
JAK1	3.95%	2.70%	2.86%	2.37%	*		4.70%	2.83%	2.70%	1.68%	****
PALB2	1.21%	0.60%	0.83%	0.42%	*		1.34%	1.02%	0.36%	0.36%	****
PTCH1	0.96%	0.57%	0.56%	0.26%	*		0.96%	0.63%	0.56%	0.19%	****
SPOP	8.37%	10.75%	10.99%	10.86%	*		8.82%	10.63%	10.84%	10.68%	ns
BRC1A1	1.03%	0.96%	0.36%	0.36%	*		1.04%	0.84%	0.66%	0.18%	****
SMAD2	0.91%	0.60%	0.42%	0.30%	*		0.79%	0.54%	0.66%	0.24%	*
ERBB2 (Her2/Neu)	0.31%	0.06%	0.12%	0.00%	*		0.25%	0.12%	0.12%	0.00%	ns
BAP1	0.79%	0.36%	0.18%	0.24%	*		0.67%	0.42%	0.12%	0.36%	ns
PBRM1	0.55%	0.48%	0.71%	0.12%	*		0.55%	0.60%	0.60%	0.12%	*
ARV7	10.45%	14.68%	17.74%	22.96%	****		14.29%	16.37%	17.51%	17.64%	**
LOH	25.89%	25.27%	24.34%	30.94%	****		30.36%	26.03%	25.32%	24.48%	****
TMB	6.14%	3.95%	5.35%	4.19%	*		6.70%	5.21%	4.58%	3.10%	****
MMRd	4.64%	3.43%	4.57%	4.03%	ns		5.12%	3.88%	4.26%	3.40%	*
PD-L1 (SP142)	2.48%	1.59%	3.87%	4.10%	*		2.31%	2.60%	2.87%	4.26%	**

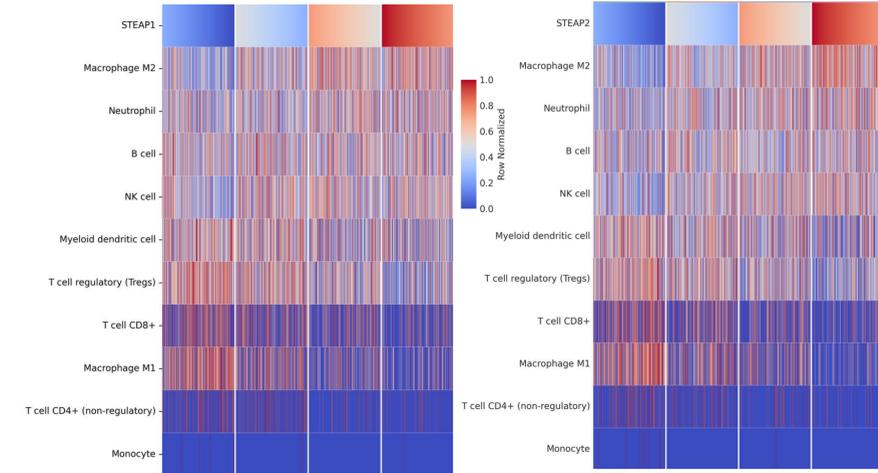
- AR -IHC/splice variant correlates positively with STEAP1/2 expression
- AR (Mut) significantly higher in STEAP1 Q4.
- Similarly, LOH and PD-L1 shows a positive correlation
- TMB on the other hand negatively correlates with STEAP1/2 expression

### STEAP Gene expression and Transcriptional Biomarkers



- STEAP1/2 correlates negatively with TMB/IFN and immune cell fractions.
- It however correlates positively with AR signaling

### Immune Cell Infiltrate Within the Tumor Microenvironment



- B Cells, NK Cells, M2 Macrophage and Neutrophil higher in STEAP1/2 Q4 compared to Q1
- Tregs and dendritic cells higher in STEAP1/2 Q1 compared to Q4

## Conclusions

- PC tumors expressing high *STEAP1/2* display distinct genomic and transcriptomic profiles compared to *STEAP1/2*-low PC, and *STEAP 1/2* expression varies across sites of metastases.
- Immune biomarkers and immune cell infiltration data suggest that *STEAP1/2* may be associated with a cold TME.
- The recent success of STEAP1-targeting T-cell redirecting therapies in PC suggests mechanisms by which adoptive T-cell strategies may overcome immunosuppressive factors within the TME.
- Ongoing development of T-cell immunotherapeutics targeting STEAP1 may account for the differential expression profiles in guiding patient selection and combination strategies