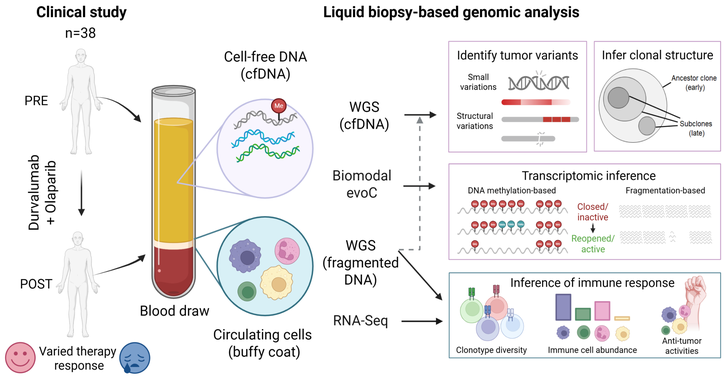
Mechanisms of resistance to PD-L1/PARP1-targeted therapy in metastatic castration-resistant prostate cancer inferred by liquid biopsy

Chennan Li, Anna Baj, Clara C. Y. Seo, Nicholas T. Terrigino, John R. Bright, S. Thomas Hennigan, Isaiah M. King, Scott Wilkinson, Shana Y. Trostel, William D. Figg, William L. Dahut, Jung-Min Lee, David Y. Takeda, Fatima Karzai, and Adam G. Sowalsky

Genitourinary Malignancies Branch; Women's Malignancies Branch, National Cancer Institute, Bethesda, Maryland, USA

Research hypothesis

Genetic, epigenetic, and immunological activities that are embedded in liquid biopsy inform mechanisms to therapy responses and failures.



Baseline clinical characteristics of the cohort studied

Characteristics	Unit	Median (range)
Age (on-study)	years	64 (45-88)
Hemoglobin	g/dL	12.4 (7.8-14.4)
Alkaline Phosphatase	U/L	108 (40-747)
LDH	U/L	204 (146-1997)
WBC	K/µl	5.58 (3.39-15.3)
Lymphocytes	%	25.2 (5.5-51.8)
Monocytes	%	8.4 (4.9-14.3)
Neutrophils	%	63.2 (36-88.4)
PSA	ng/dL	65.6 (1.6-5000)
Gleason score		9 (6-10)

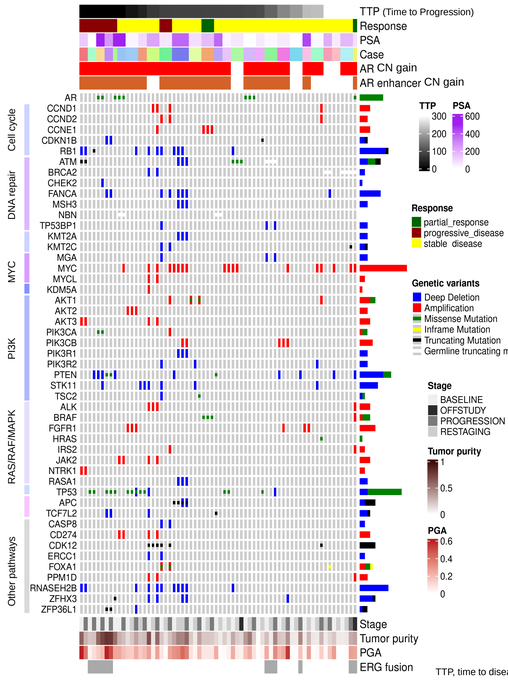
Ethnicity	n
White	30
Black	6
Asian	1
Hispanic	1

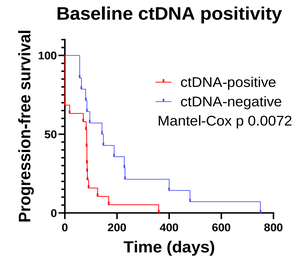
Prior Treatment	38
ADT	36
Enzalutamide	27
Abiraterone	26
Chemotherapy	27
Radiotherapy	19
Prior immunotherapy	14

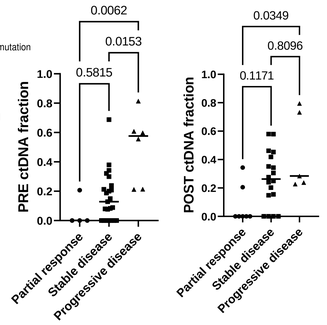
WGS coverage and fragment length

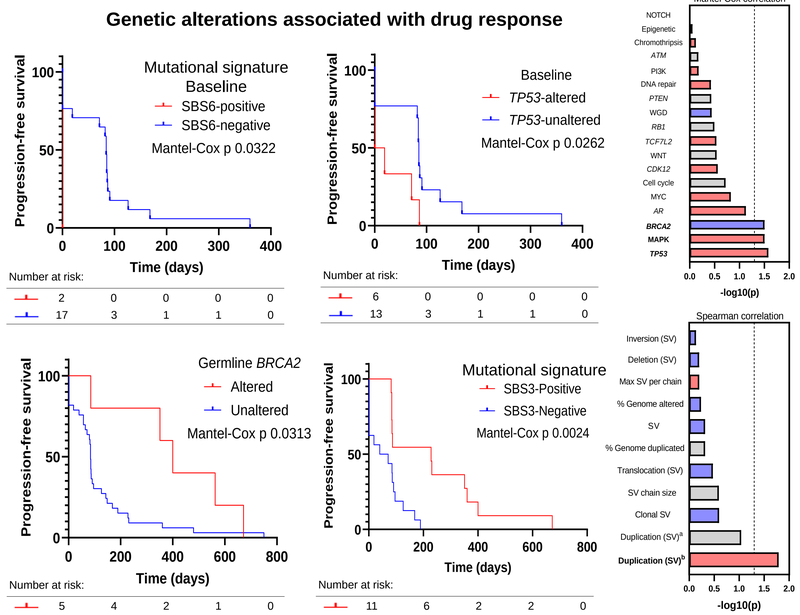
Category	Mean coverage	Range
Normal DNA	**153.2**	185.5-126.6
cfDNA	**139.2**	164.8-118.7
Category	Mean insert length (nt)	Range
Normal DNA	**180**	191-166
cfDNA	**165.6**	172-158

Circulating tumor DNA (ctDNA) purity and DNA repair genes are associated with therapy response





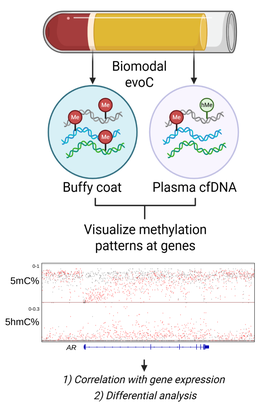


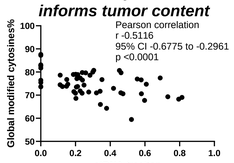


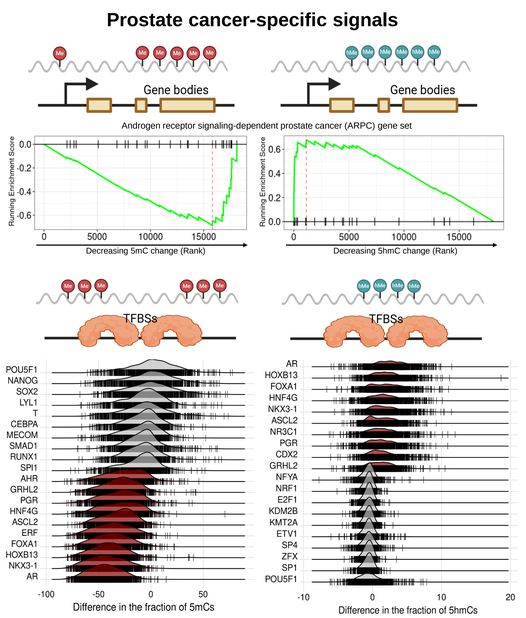
PRE, pre-treatment (baseline). MID, restaging. POST, post-treatment.
TTP, time to disease progression (in days). PSA, prostate-specific antigen. PGA, the percentage of the genome altered.

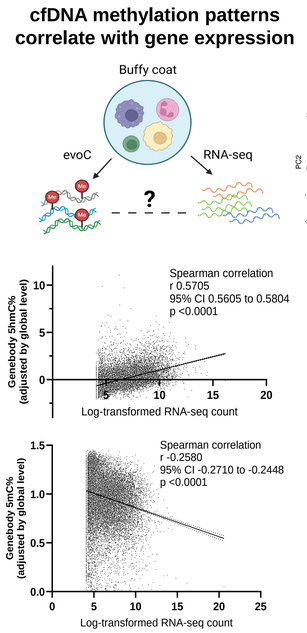
Alterations/increased event count correlates with shorter (red) or longer (blue) TTP.
WGD, whole-genome duplication. SV, structural variant.

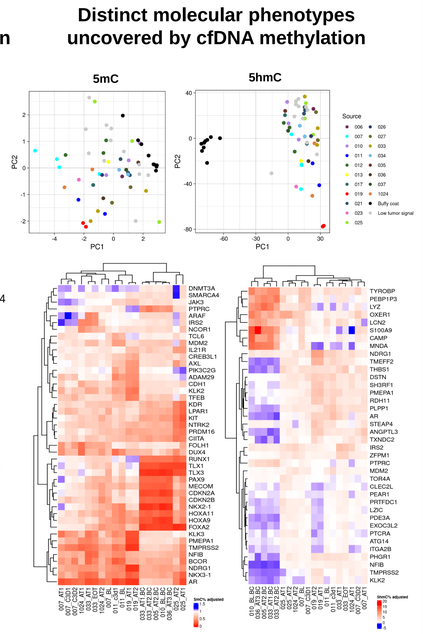
cfDNA methylation profiling reveals disease phenotypes and various therapy responses



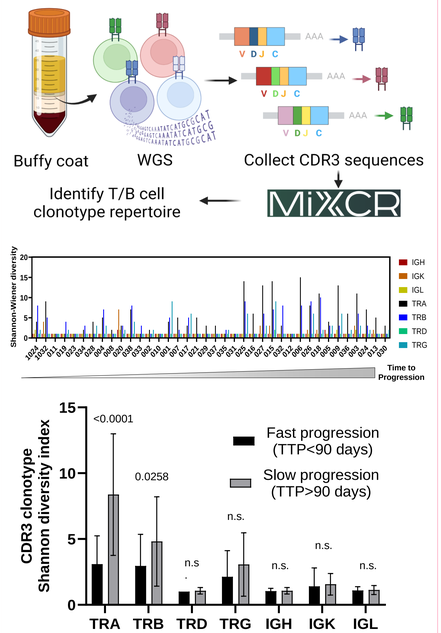








T/B cell clonotype inference



Conclusions

- Circulating tumor DNA (ctDNA) purity can be used to predict therapy response of metastatic castration-resistant prostate cancer (mCRPC) to PD-L1/PARP1 inhibition.
- Aberrant DNA repair signatures inform PD-L1/PARP1 inhibitor therapy resistance.
- cfDNA methylation pattern correlates with gene expression and allows for identification of gene signatures specific to prostate cancer and distinct tumor phenotypes.
- Therapy response also associated with a greater diversity of TCRα/β CDR3 V(D)J recombination, implicating the capability of T cells in antigen recognition and differentiation.

Future Directions

- To define mechanisms of therapy resistance against the PD-L1/PARP1 inhibition, we are evaluating interactions between genomic, epigenetic, and immunological alterations from each case.
- Select plasma specimen are also being analyzed for histone modification patterns, which will be integrated with the evoC cfDNA methylation data to obtain critical insights about drug resistance mechanisms
- We are investigating the use of cfDNA fragmentation patterns for gene expression/activity inference, which will potentially assist in validation of our results.
- Ultimately, we wish to validate the identified genetic mechanisms from similar clinical studies and through histopathological studies or in relevant human cell lines or animal models.

Acknowledgement

The authors wish to thank the patients and their families for participating in this study. Also, the study cannot be done without the assistance from the NIH High Performance Computing (HPC) team. This project was funded by the Intramural Research Program of the National Institutes of Health.