Investigating the Biological Basis of Multimodal AI Predictions in Prostate Cancer Using Spatial Single-cell Proteomics

William S. Chen[1], Emmalyn Chen[2], Rikiya Yamashita[2], Mikhail Dias[1], Stefanie Engler[3], Sophie Deglise[3], Cornelia Ding[4,5], Julian C. Hong[1], Peter R. Carroll[4], Andre Esteva[2], Felix Y. Feng[1,4], Bernd Bodenmiller[3], Matthew R. Cooperberg[4]

Affiliations:
[1]Department of Radiation Oncology, University of California San Francisco, San Francisco, CA; [2]Artera Inc., Los Altos, CA; [3]University of Zurich, Department of Quantitative Biomedicine, Zurich, Switzerland; [4]Department of Urology, University of California San Francisco, San Francisco, CA; [5]Department of Pathology, University of California San Francisco, San Francisco, CA

Background: A multimodal artificial intelligence (MMAI) model (ArteraAI Prostate Test) was previously developed using digital histopathology and clinical information to predict long-term outcomes (e.g., 10-yr distant metastasis) in localized prostate cancer. In this study, we investigated the underlying biology of the models' predictions via single-cell spatial proteomics by evaluating the association between the image features used by the MMAI model and the spatial expression pattern.

Methods: Tissue microarray (TMA) cores were obtained from 170 localized prostate cancer patients at UCSF. H&E images of the TMA samples were digitized using a Aperio AT2 at 20x magnification. Attention heatmaps were generated for all 128 MMAI image features. In parallel, imaging mass cytometry (IMC) was performed on a FFPE section of the same TMA to quantify protein expression of 45 proteins with sub-cellular spatial resolution. The H&E and IMC images from the same patient were de-arrayed and spatially realigned using computer vision-based affine transformations. Spatial expression patterns of 12 select proteins (including AR, PSMA, Ki-67, CD20, and CD4) were studied. Spearman rank correlation coefficient was used to assess the relationship between the attention value and protein expression counts for each image patch.

Results: The cohort of 170 men with localized prostate cancer patients had a median age of 58 years and median PSA of 5.9 ng/mL at time of diagnosis. The majority of patients had Gleason score 6 (59%) or Gleason score 7 (28%) disease. Multiple MMAI image features were correlated with protein expression. For example, image feature #41 correlated with AR (rho=0.81, $p<0.001$), PSMA (rho=0.79, $p<0.001$), and CD20 (rho=0.82, $p<0.001$). Additionally, image feature #126 correlated with Ki-67 (rho=0.80, $p<0.001$).

Conclusions: We successfully applied attention heatmaps and paired spatial proteomics data to interpret the imaging features prognostic of clinical outcomes in localized prostate cancer. Significant correlations were observed between the MMAI image feature attention values and expression of canonical tumor markers (e.g. AR and PSMA) and immune markers (e.g. CD20). These findings suggest that the model's predictions are based on presence of tumor microenvironment features including both cancer cells and immune cells. More broadly, our findings suggest that pathologic features visible in H&E images of biopsy samples in localized disease may predict clinically relevant outcomes such as risk of metastasis.

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Conflicts of Interest and Disclosure Statement: F.Y.F. is an advisor to and holds equity in Artera, Inc and is a consultant for Janssen Oncology, Astellas Pharma, Serimmune, Foundation Medicine, Exact Sciences, Bristol-Myers Squibb, Varian Medical Systems (termed), Novartis, Roivant (termed), Myovant Sciences (termed), Bayer, BlueStar Genomics, Tempus, Genentech (termed). P.R.C. is an investigator for Artera clinical studies.

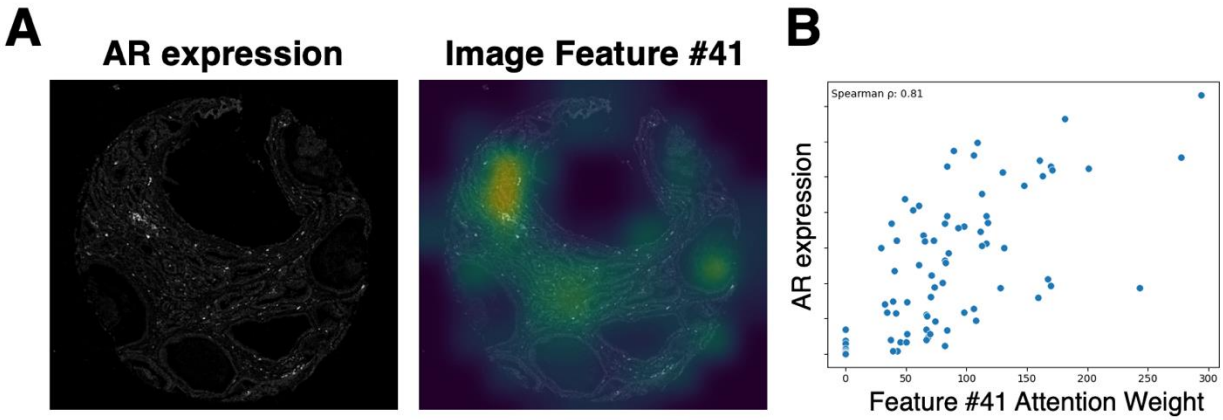

Figure 1. A) AR expression and MMAI attention heatmap of Image Feature #41 overlaid on AR expression of a primary prostate cancer tumor measured using Imaging Mass Cytometry. B) Spearman correlation between MMAI Feature #41 and AR expression ($\rho = 0.81$).

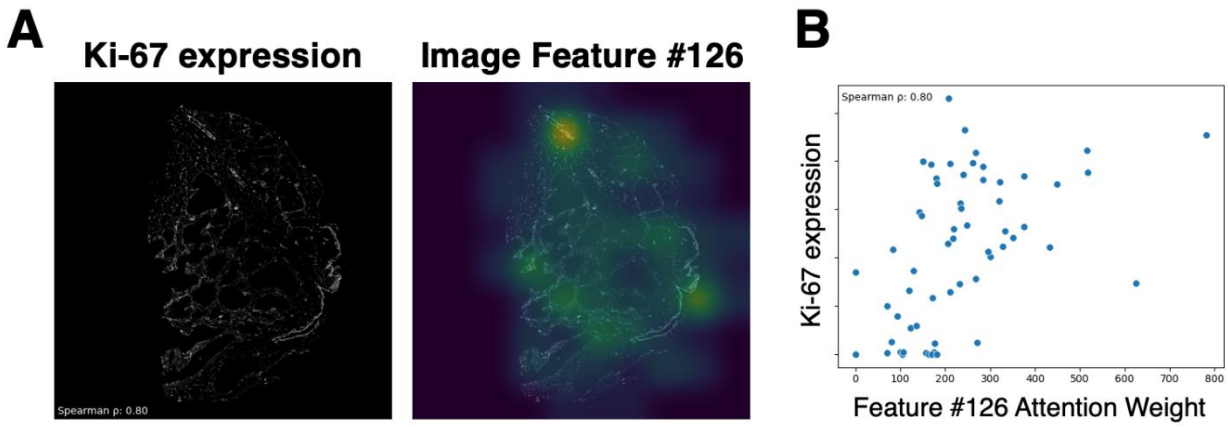

Figure 2. A) Ki-67 expression and MMAI attention heatmap of Image Feature #126 overlaid on Ki-67 expression of a primary prostate cancer tumor measured using Imaging Mass Cytometry. B) Spearman correlation between MMAI Feature #126 and Ki-67 expression ($\rho = 0.80$).