Pathway modeling to translate the 27-gene immuno-oncology algorithm into bladder cancer

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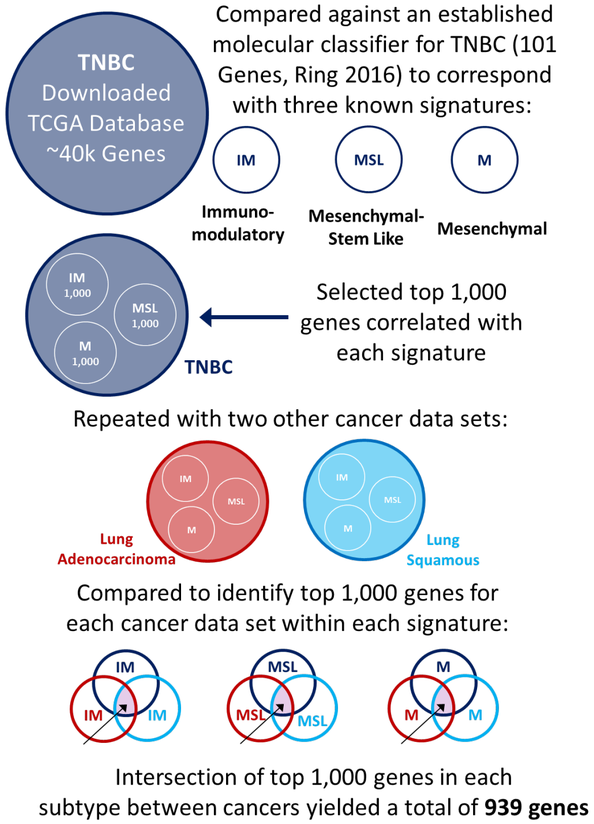
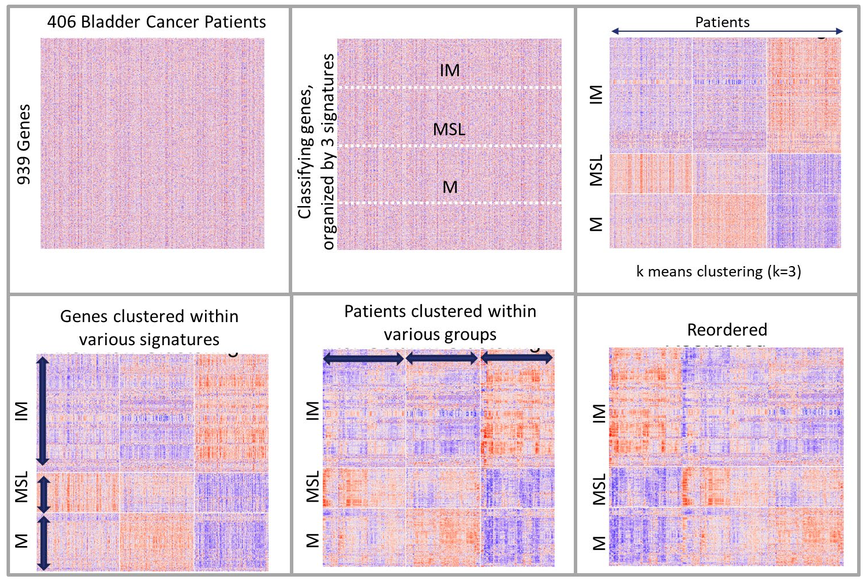
Introduction

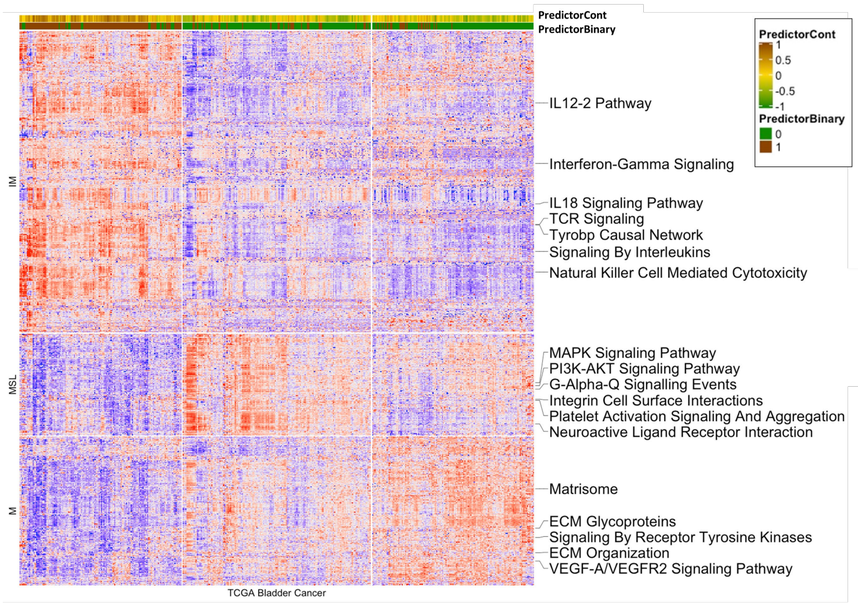
- The 27-gene immuno-oncology (IO) algorithm was trained, and threshold established for distinguishing immune response to checkpoint inhibitors (ICI's) based on distinguishing immunomodulatory, mesenchymal, and mesenchymal stem-like signatures in TNBC.
- The IO algorithm and assay have previously demonstrated significant association with clinical response to ICI's in TNBC and NSCLC.
- Based upon biologic recognition of inflammatory and tumor microenvironment phenotypes, the classification function and thresholds were assessed as immune micro-environment classifiers in bladder cancer (mUC) prior to correlative studies in ICI treated trials.

Methods

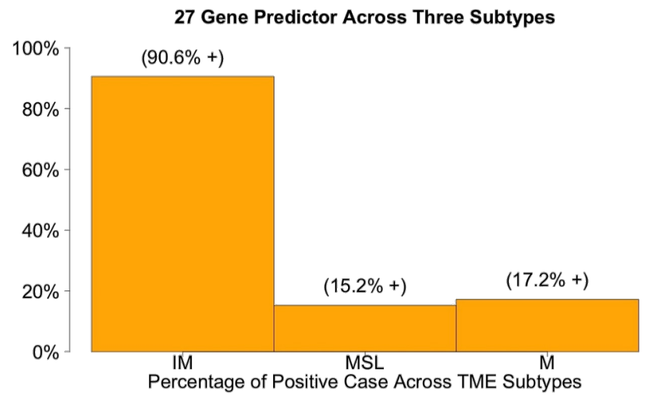


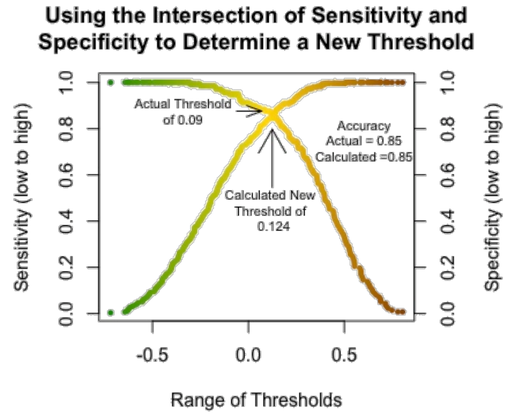
Results





- **(Above Left)** The combined 939-gene set representing the known IM, MSL, and M signatures were k-means (k=3) clustered by gene and patient ID.
- **(Above Right)** The 27-gene predictor was then calculated for the 406 patients and binary score overlaid on the heatmap (top bar) with IO algorithm positivity showing a clear association with the IM, "Immune Hot" cluster classification.
- **(Above Right)** The biologic pathways of 939 genes were explored by assigning to the three signatures as "phenotypes" (GSEA analysis from UCSD/Broad), linking biologic pathways to the IM, M and MSL cluster-based classification.





- **(Above Left)** Positive IO score was highly correlated to the IM "hot" classification.
- **(Above Right)** AUC was applied to the IO score threshold and the original threshold established in TNBC of 0.09 was found to be near optimal for distinguishing the IM, "hot" inflammatory phenotype from the M and MSL "cold" phenotypes.

Conclusion

- The IO algorithm, using a threshold previously established in TNBC and NSCLC was highly effective at appropriately classifying bladder cancer into positive, likely responder, and negative, likely non-responder classes.
- This supports the utilization of the 27-gene IO algorithm unmodified for examining the association with ICI response in treated mUC cohorts (AACR #23, 2021).
- This 27-gene signature, discerning tumor immune microenvironment physiology and associated with ICI response, appears to be relevant in multiple solid tissue types and warrants study as a pan-cancer ICI biomarker test.

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