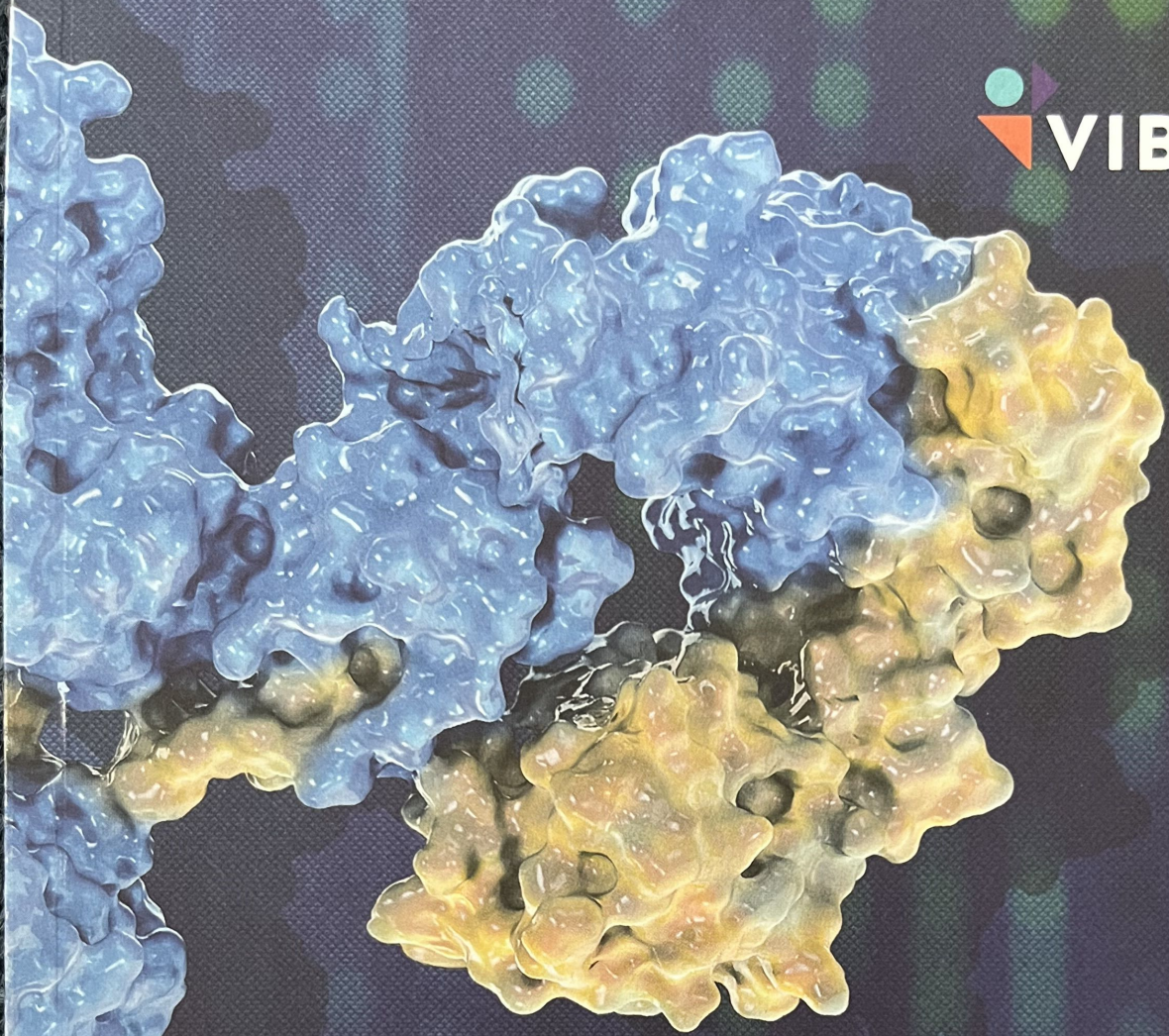


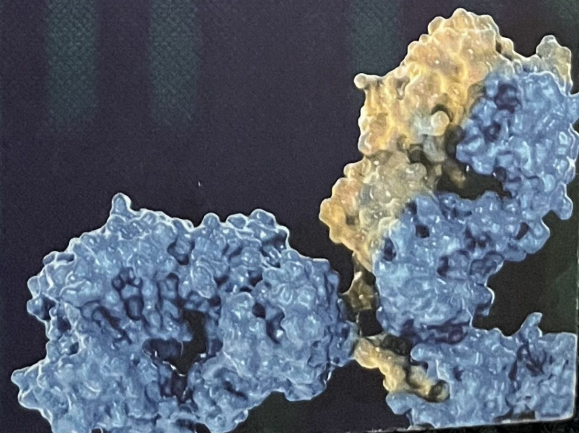


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SPATIAL MOLECULAR PROFILING OF ALK-REARRANGED LUNG CANCER

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Introduction: Around 3-5% of non-small cell lung cancers carry a chromosomal rearrangement of the ALK gene, defining a diverse molecular subset of lung cancer with peculiar biology and distinct clinical behavior. Both inter- and intratumoral heterogeneity need to be better understood to further improve therapeutic response in this relatively rare cancer type.

Methods: Seven FFPE lung cancer samples with ALK-rearrangement were spatially profiled combining GeoMX digital spatial profiling and label-free shotgun proteomics. In total, 84 transcriptomic and 23 proteomic regions of interest (ROIs) were selected for molecular profiling (an average of 12 ROIs for RNA, and 3.2 ROIs for proteomics were selected on each tumor slide; each proteomic region contained on average 3.1 RNA regions). Tumor regions were also evaluated for varying levels of lymphocytic infiltration, and histopathological properties (solid, tubular, papillary morphology, and normal tissue).

Results: 1,812 genes and 2,318 protein groups were confidently identified in the samples. Moderate correlation between the transcriptomic and proteomic profiles across the ROIs was observed. Pathway-level differences between tumors and normal tissues and high vs low immune infiltrated tumor regions were outlined on both omic layers. The extent of molecular heterogeneity varied substantially across the seven examined cases, and also within tumor samples.

Conclusions: To the best of our knowledge, this is the first study that tackles the spatial heterogeneity of ALK-rearranged lung cancers on a multi-omic level. We envision that our work contributes to a better understanding of this type of gene aberration driven malignancy.

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