Multimodal foundation model of human lung tumors identifies tertiary lymphoid structures (TLS) and reveals novel therapeutic targets that promote anti-tumor immune response

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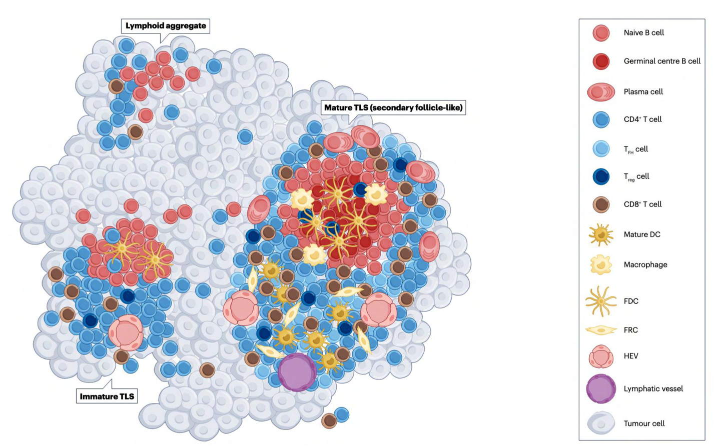
[1] Noetik Inc., South San Francisco, CA

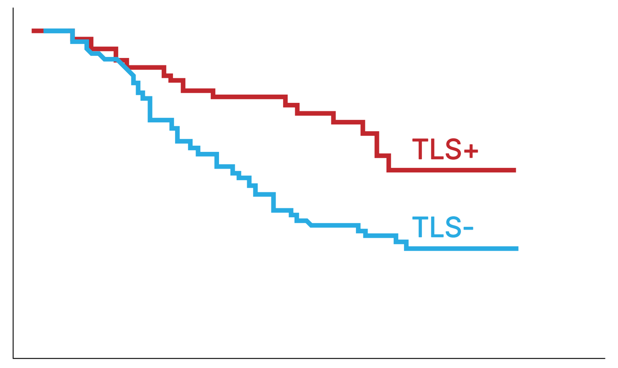
Tertiary lymphoid structure (TLS) induction is a promising therapeutic strategy in NSCLC

TLS development



Teillaud et al., Nat Rev Cancer (2024)

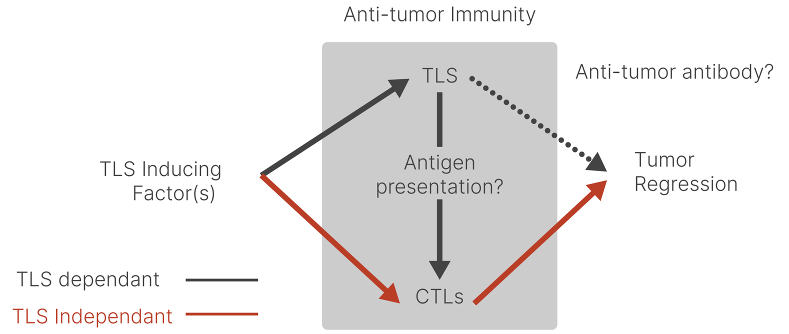
NSCLC survival



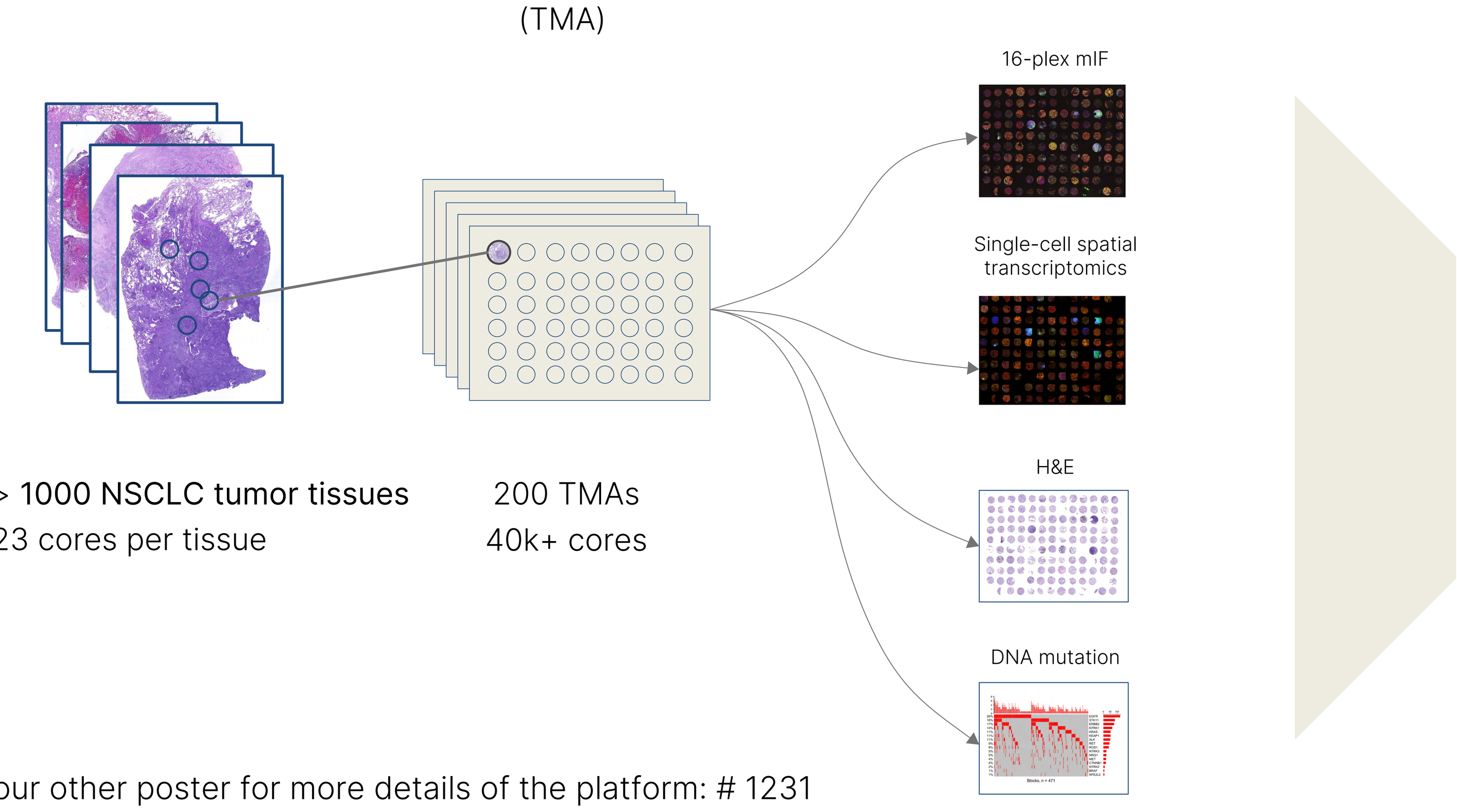
Patil et al., Cancer Cell (2022)
Srivastava et al., SITC (2023)

TLS develop to different maturation stages. Mature TLS with germinal centers were shown to be predictive of survival in phase 3 clinical trials of checkpoint inhibition in NSCLC.

Based on these results, We hypothesized that TLS inducing factor(s) can drive anti-tumor immunity via 1) inducing TLS that promote immune response 2) directly boosting cytotoxic T cell (CTLs) function independent of TLS.



1000 NSCLC tumor multimodal spatial atlas for dissecting TLS and tumor microenvironment



See our other poster for more details of the platform: # 1231

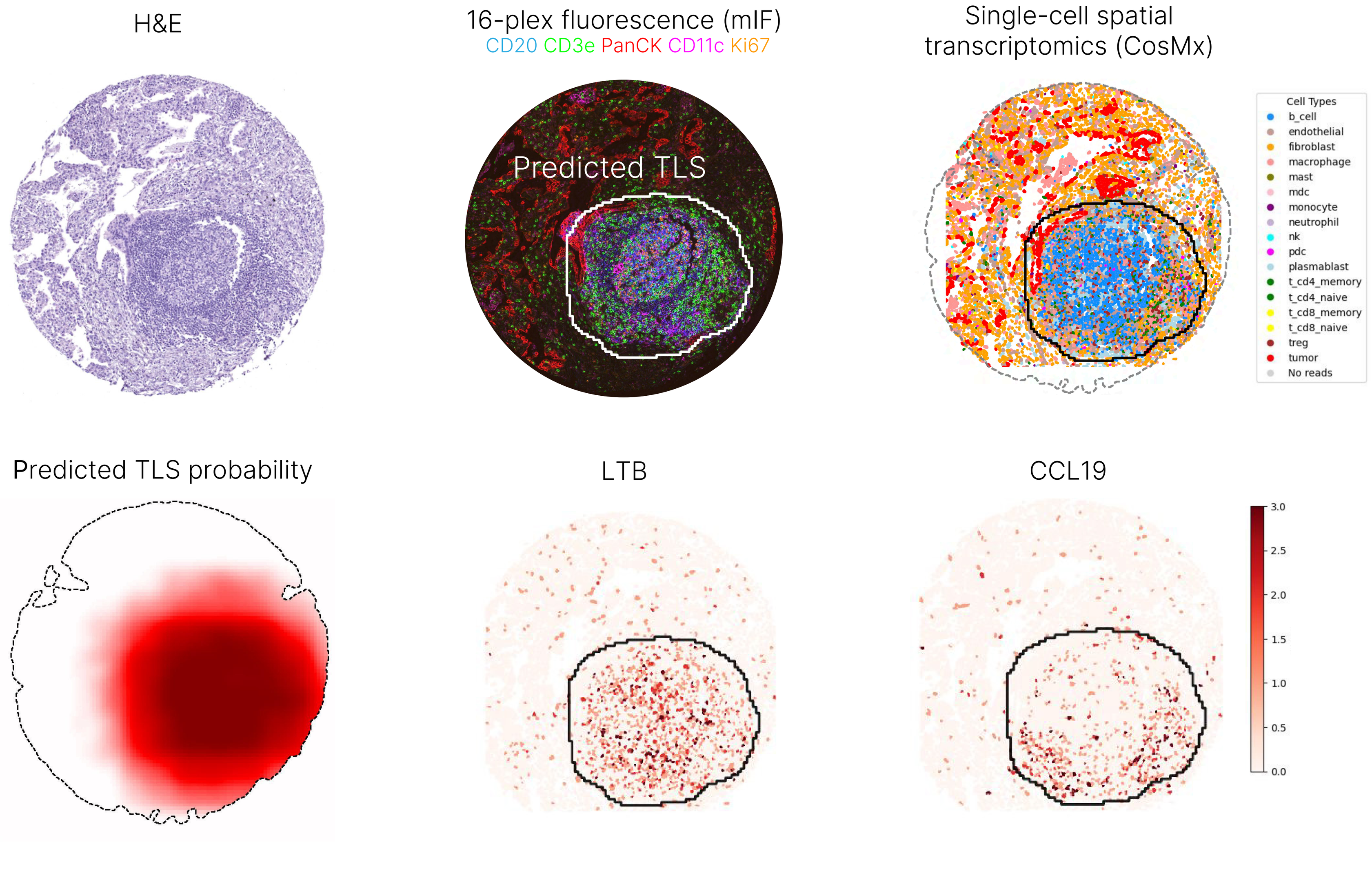
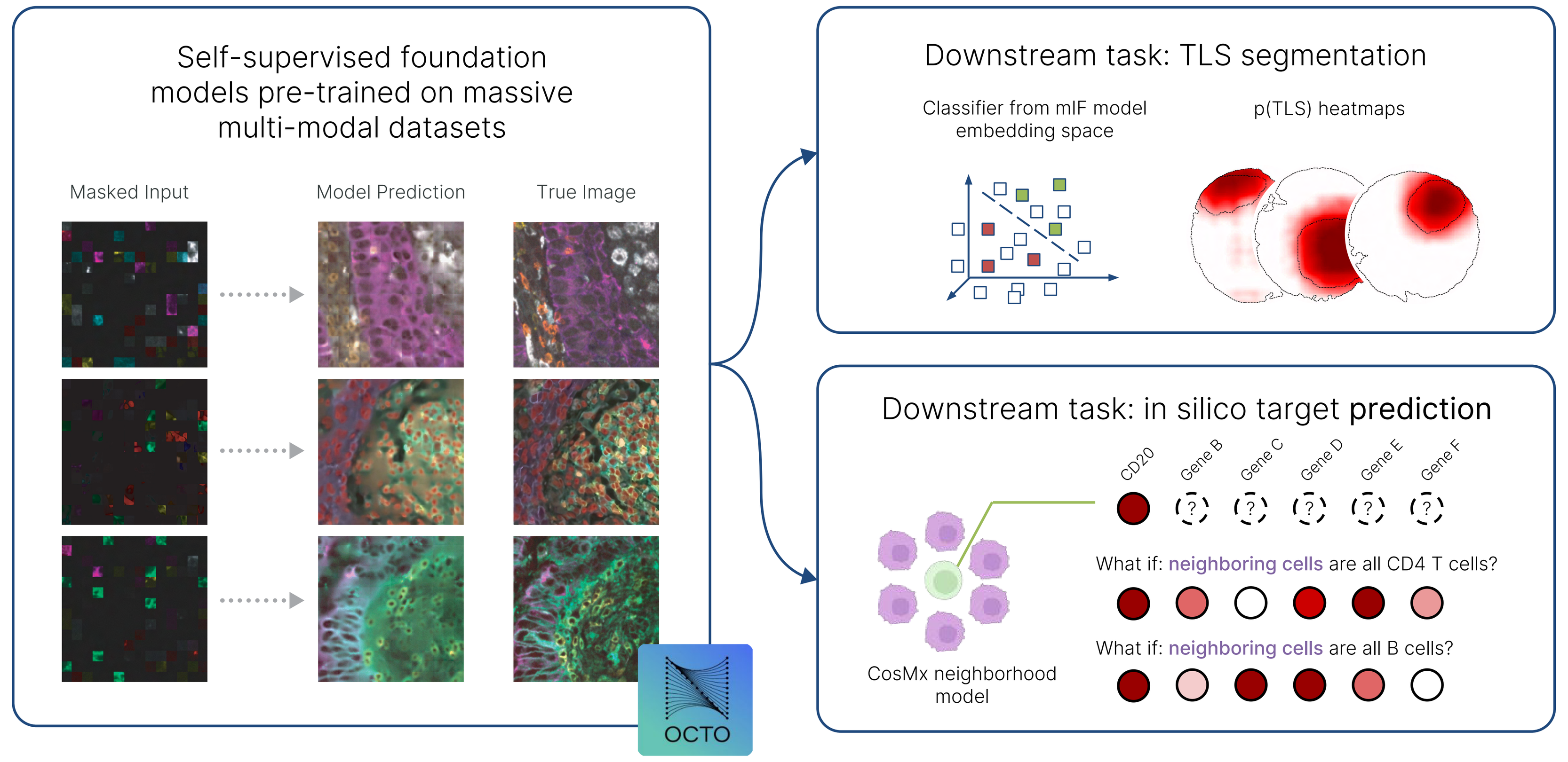
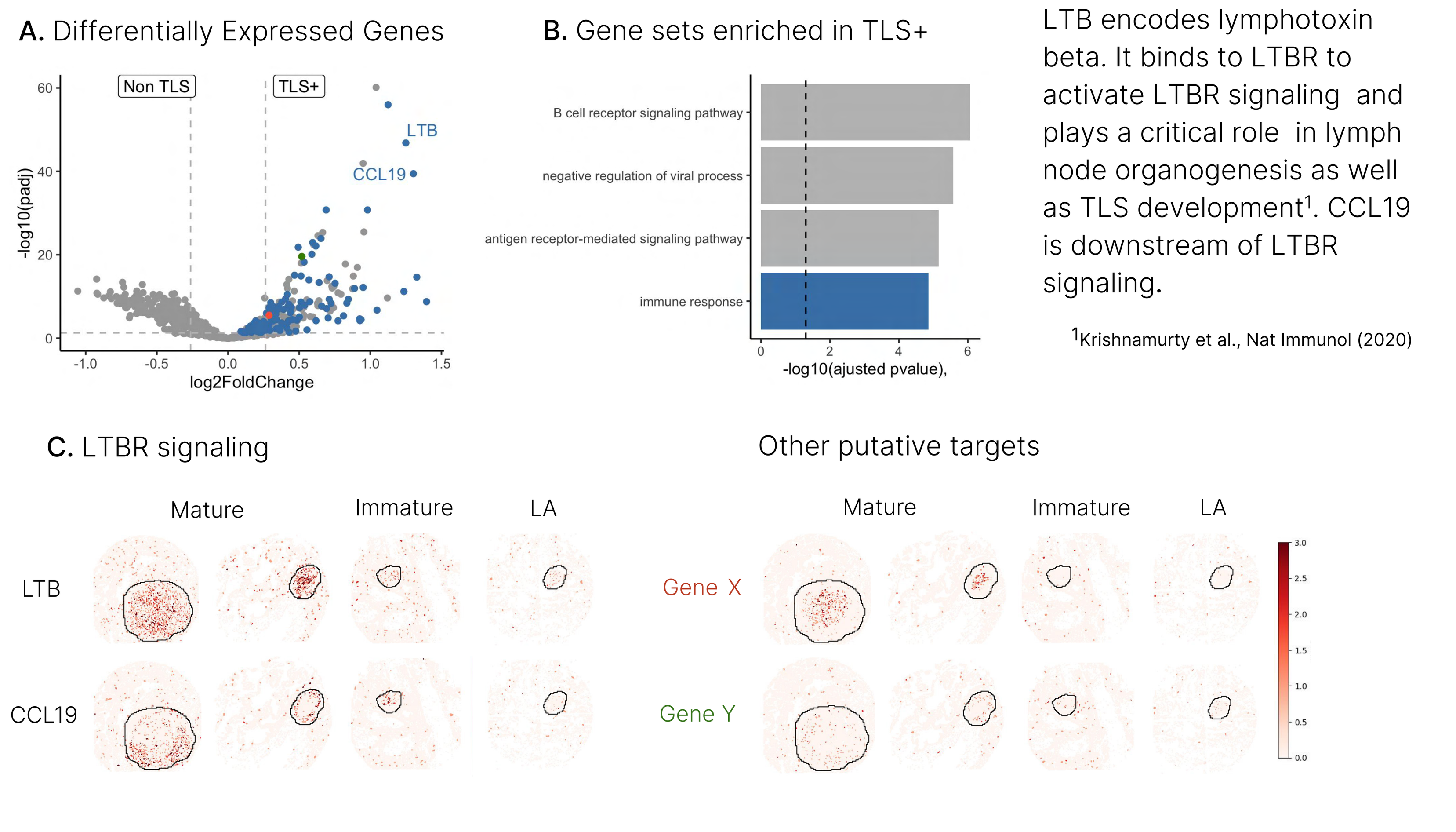


Fig 1. A core with a mature **germinal center** TLS. Top row are paired data with predicted TLS annotated. Bottom row from left: Model predicted TLS probability, LTB and CCL19 gene expression in CosMx cells

Multimodal foundation models enable TLS target identification



Immune response genes are enriched in TLS gene correlates

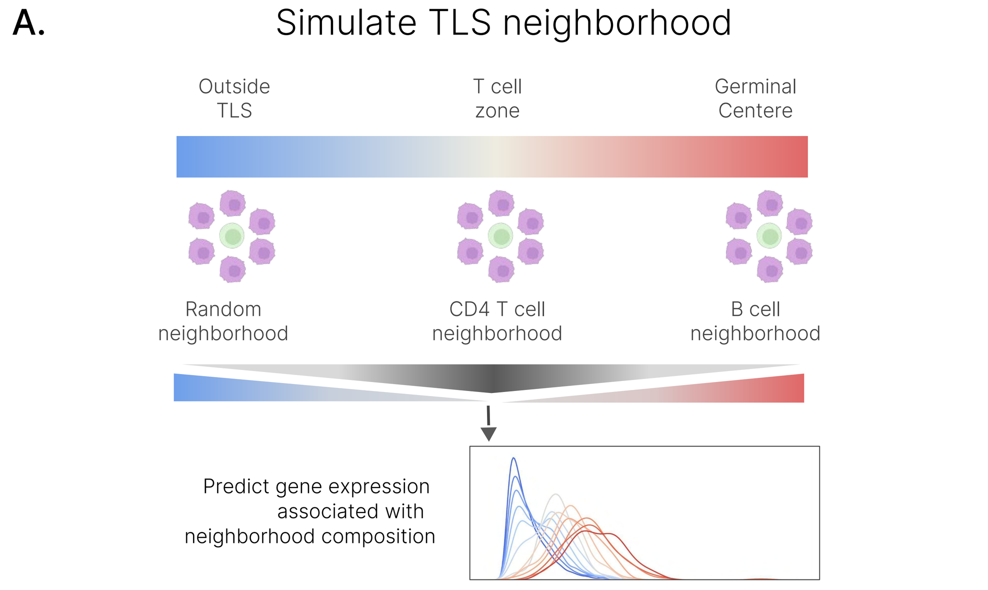


LTB encodes lymphotoxin beta. It binds to LTBR to activate LTBR signaling and plays a critical role in lymph node organogenesis as well as TLS development[1]. CCL19 is downstream of LTBR signaling.

[1]Krishnamurty et al., Nat Immunol (2020)

Fig 2. *A.* Volcano plot of genes upregulated in TLS+ cores vs Non TLS cores. *B.* Gene ontology biological process gene sets that are over represented in the TLS associated genes. X axis is the significance of enrichment. *C.* LTB, CCL19, Gene x and Gene Y expression in cores with mature, immature and lymphoid aggregate cores measure by CosMx

Model of spatial gene expression predicts genes associated with B cell maturation



We simulated TLS maturation by changing the cell type composition of the 6 nearest neighbors of a virtual CD20+ B cell using a transformer model, and inferring changes in expression of the virtual B Cell. We simulated neighborhood changes from randome background to CD4 T cells, then to all B cells, giving us us a pseudo-trajectory that mimics B cells outside of TLS to the T cell zone of TLS, then to the germinal center. This allowed us to look for genes whose expression associates with B cell maturation and TLS development.

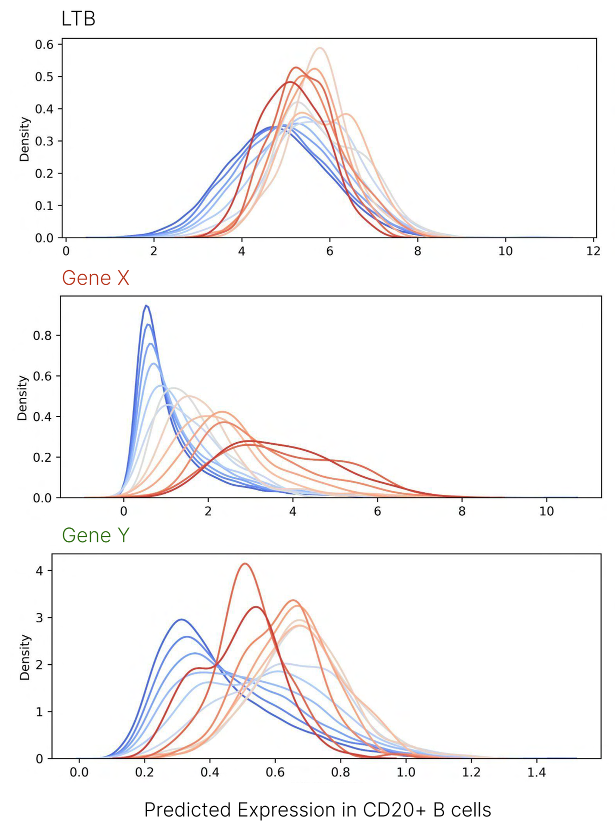


Fig 3. *A.* Illustration of TLS neighborhood set up. Each **neighborhood composition is simulated** 100 times. *B.* Model predicts gene expression colored by the neighborhood composition.

Conclusion and Future Direction

We developed a robust AI/ML computational workflow for TLS segmentation and spatial neighborhood based gene expression prediction. This enabled target nomination for TLS inducers. Analysis and modeling of spatial transcriptomic atlas of 1000 NSCLC tumors revealed:

- LTB > LTBR signaling as a known causal factor and clinical stage target[2] that may drive TLS formation and contribute to anti-tumor immunity.
- Additional putative targets that are immune response related genes and associated with TLS. These putative targets are predicted to promote B cell maturation.
- Going forward we are running Perturb-Map[3], a high high throughput phenotypic mouse platform to validate putative targets in vivo.

[2] ClinicalTrials.gov ID: NCT06448364
[3] Dhainaut et al., Cell (2022)

Society for Immunotherapy of Cancer (SITC) Annual Meeting 2024: Houston, TX.
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