Quantifying hallmarks of ADC response and toxicity through AI-powered analysis of the Multi-Omics Spatial Atlas In Cancer (MOSAIC)

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Background

→ Antibody drug conjugates (ADCs) are a rapidly evolving class of cancer therapeutics.

→ The most prevalent type of ADC comprises a monospecific, tumour antigen-targeted antibody conjugated to cytotoxic payload via a molecular linker, yet bispecific, dual-antigen targeting ADCs are also advancing in the clinic.

→ Challenges remain in identifying novel targets, payload selection, patient selection and clinical development optimisation.

→ Few studies have extensively characterised known ADC targets pan-cancer across multiple omics modalities including spatial transcriptomics.

Objectives

→ Quantify hallmarks of ADC efficacy using multi-omics data, computational biology and AI.

→ Optimise ADC positioning relative to patient populations, indication selection and biomarker identification to improve efficacy.

Data

→ MOSAIC[1] data comprises 4 omics modalities (10X Visium spatial transcriptomics, 10X Chromium Flex scRNAseq, bulk RNA-seq and WES), H&E stained histology images, and clinical data including detailed treatment and response data from >2000 patient samples - a subset of which was analysed here.

→ Public datasets TCGA, CPTAC and GTEx also used.

Bulk RNA-seq | WES | sc RNA-seq | H&E | Spatial omics | Clinical data

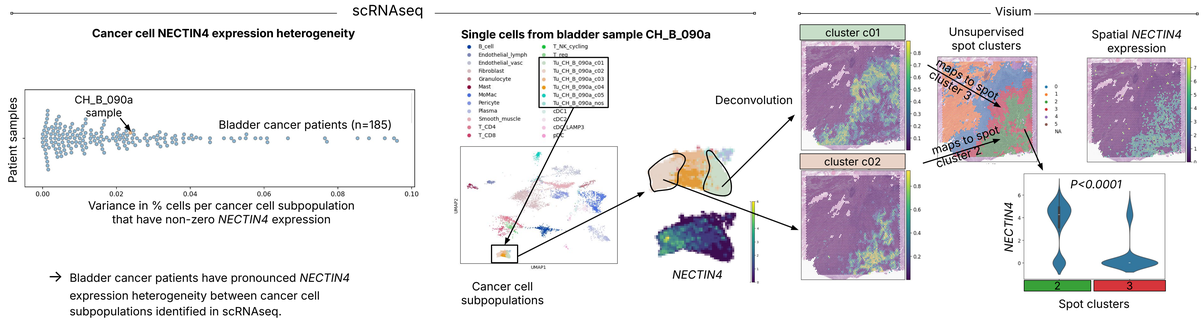
mosaic an owkin initiative

Multimodal patient data: Multiscale understanding of biology, from molecule to cell to tissue to organism

What information can each modality provide?

Hallmark of ADC benefit	H&E/ IHC	Bulk RNAseq	WES	scRNAseq	Spatial transcript- omics	MOSAIC & Multimodal AI
Protein function and subcellular localisation	Yes					Yes
Target expression level or amplification	Yes	Yes	Yes	Yes	Yes	Yes
Target expression hetero-geneity	Yes			Yes	Yes	Yes
Target specificity on cancer cells	Predicted			Yes	Predicted	Yes
Target co-expression				Yes	Yes	Yes
Payload sensitivity		Predicted		Predicted	Predicted	Predicted
Immune TME contexture				Yes	Yes	Yes
Bystander effect estimation					Yes	Yes

Cancer cell *NECTIN4* expression heterogeneity is concordant between scRNAseq and spatial transcriptomics with potential implications for patient response to treatment

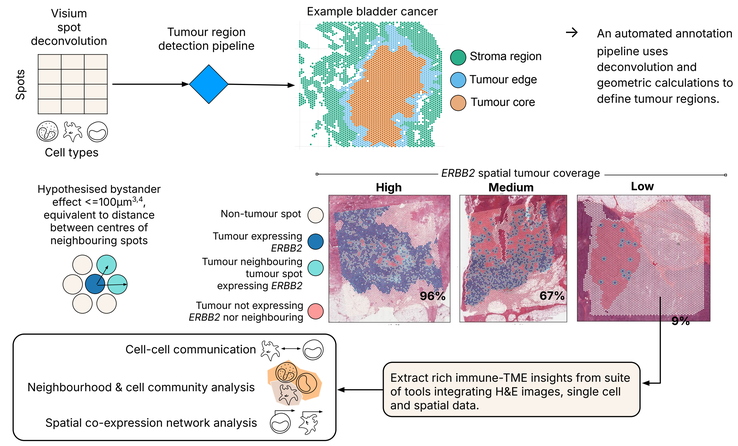


→ Bladder cancer patients have pronounced *NECTIN4* expression heterogeneity between cancer cell subpopulations identified in scRNAseq.

→ Embeddings of single cells from a bladder cancer sample (CH_B_090a) reveal 6 cancer cell subpopulations with distinct *NECTIN4* expression.

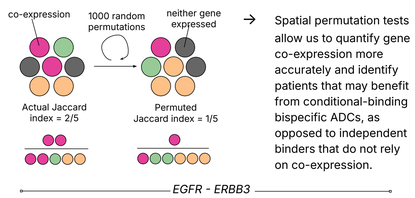
→ scRNAseq-derived cancer cell subpopulations map to distinct spatial locations and have concordant presence/absence of *NECTIN4* expression.

Spatial transcriptomics enables estimation of tumour payload exposure and the bystander effect

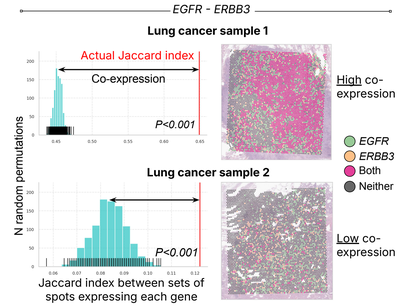


→ An automated annotation pipeline uses deconvolution and geometric calculations to define tumour regions.

Target co-expression across spots informs bispecific ADC assessment

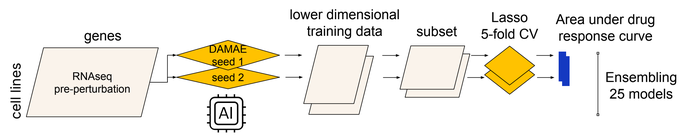


→ Spatial permutation tests allow us to quantify gene co-expression more accurately and identify patients that may benefit from conditional-binding bispecific ADCs, as opposed to independent binders that do not rely on co-expression.



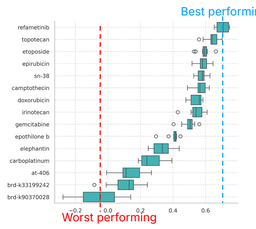
AI model trained on pre-clinical perturbation data predicts payload sensitivity of patient malignant cell populations

→ We trained the LEAP model[5] to predict the efficacy of >600 drugs including some with a shared mechanism-of-action to ADC payloads.



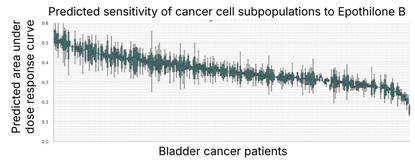
→ Test performance for many cytotoxic agents was strong

Model performance of payload-like drug molecules relative to the best and worst performing drugs



Test performance across splits: Spearman correlation

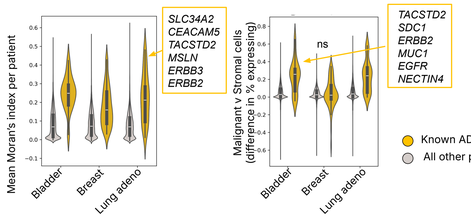
→ With pre-trained LEAP models we predicted sensitivity of patients cancer cell subpopulations to >600 drugs. This included Epothilone B; a microtubule inhibitor akin to MMAE that is a well established payload. In bladder cancer samples we noted inter- and intra-tumour heterogeneity in predicted sensitivity to Epothilone B.



Known ADC targets recovered by single- cell and spatial data derived features

→ Ground truth ADC targets were defined (data sources: AACT, ChEMBL, Citeline Trialtrove). Patient level features were computed for three indications and aggregated to the gene-level by for example taking the mean.

Cancer	Minimum pre-clinical		Minimum phase II	
	N drugs	N targets	N drugs	N targets
Bladder	39	14	21	10
Lung adeno	53	21	27	15
Breast	158	47	44	12



→ Known ADC targets across multiple indications have significantly higher mean Moran's index (left - representing spatial autocorrelation and target expression heterogeneity), and malignant-stromal expression fraction difference (right - ns= non-significant P>0.05). All differences are statistically significant by Mann Whitney test (P<0.01) unless marked ns.

Known ADC target entering clinical trials for the disease
All other protein coding genes

References

[1] MOSAIC Consortium, Hoffmann, C. (2025) 'MOSAIC: Intra-tumoral heterogeneity characterization through large-scale spatial and cell-resolved multi-omics profiling'. bioRxiv, p. 2025.05.15.654189. Available at: https://doi.org/10.1101/2025.05.15.654189.

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[3] Khera, E. *et al.* (2020) 'Quantifying ADC bystander payload penetration with cellular resolution using pharmacodynamic mapping', *Neoplasia (New York, N.Y.)*, 23(2), pp. 210–221. Available at: https://doi.org/10.1016/j.neo.2020.12.001.

[4] Burton, J.K., Bottino, D. and Secomb, T.W. (2019) 'A Systems Pharmacology Model for Drug Delivery to Solid Tumors by Antibody-Drug Conjugates: Implications for Bystander Effects', *The AAPS journal*, 22(1), p. 12. Available at: https://doi.org/10.1208/s12248-019-0390-2.

[5] Bodinier, B. *et al.* (2025) 'Predicting gene essentiality and drug response from perturbation screens in preclinical cancer models with LEAP: Layered Ensemble of Autoencoders and Predictors'. arXiv. Available at: https://doi.org/10.48550/arXiv.2502.15646.

Conclusions

We harnessed multimodal oncology data to quantify hallmarks of ADC response.

Integrating scRNAseq and spatial transcriptomics provides unprecedented insights on target expression heterogeneity, co-expression and bystander effects.

The analysis of the TME contexture can inform optimal combinations therapies for ADC + TME drugs like IO

Feature extraction from multi-omics data enables patients subtyping, novel target discovery, combination therapy selection and biomarker ID in a new era of more complex, dual payload, multi-target ADCs.