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A SPATIAL PK/PD FRAMEWORK TO PREDICT ADC RESPONSE IN SOLID TUMORS BY INTEGRATING DRUG DELIVERY, TARGET ENGAGEMENT, AND MICROENVIRONMENTAL READINESS

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ALIRI BIOANALYSIS

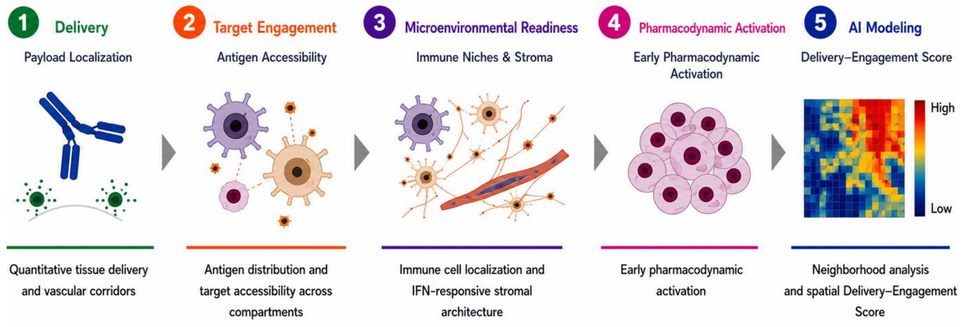
INTRODUCTION

Antibody-drug conjugates achieve therapeutic activity only when payload delivery, target accessibility, and microenvironmental readiness align within tumor tissue. Conventional biomarkers capture isolated components of this biology but fail to resolve the spatial coordination that ultimately governs pharmacodynamic activity.
To address this gap, we developed a translational spatial PK/PD framework integrating MSI, spatial proteomics/transcriptomics, and multiplex tissue imaging to spatially interpret coordinated ADC activity within solid tumors.

AIM

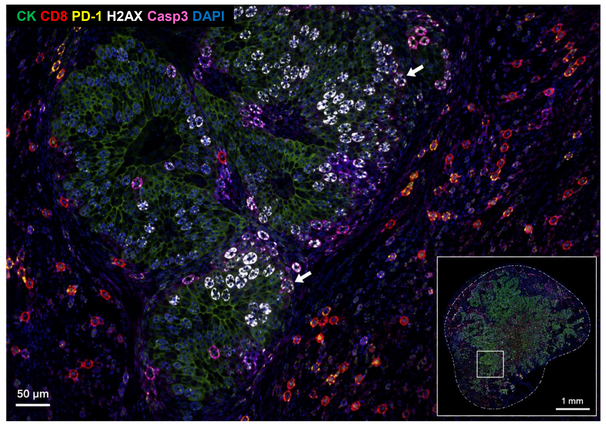
To establish an integrated spatial PK/PD framework enabling mechanistic spatial interpretation of coordinated ADC delivery, target engagement, tumor microenvironment organization, and pharmacodynamic activation in solid tumors.

Figure 1. Integrated Spatial PK/PD Workflow



Tumor biopsies from patients and PDX models treated with a clinically relevant ADC were analyzed using an integrated spatial PK/PD workflow. Quantitative payload imaging by MSI was combined with spatial proteomics and spatial transcriptomics to map antigen distribution, stromal architecture, vascular delivery architecture, immune niches, and pharmacodynamic activation. All data modalities were spatially co-registered and modeled using AI-based neighborhood analysis to generate a **Delivery–Engagement Score** reflecting the degree of coordinated tissue-level ADC activity within each tumor region.

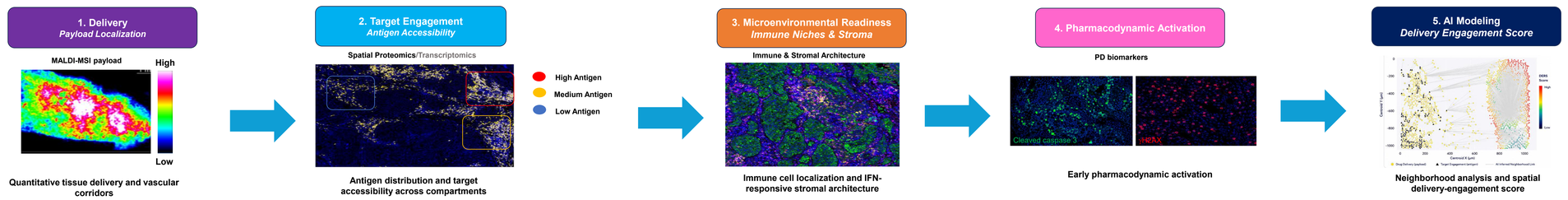
DIRECT VISUALIZATION OF ADC ACTIVITY IN HUMANIZED NSCLC XENOGRAFT



METHOD

Tumor biopsies from patients and PDX models treated with a clinically relevant ADC were analyzed using an integrated spatial PK/PD workflow. Quantitative payload imaging by MSI was combined with spatial proteomics and spatial transcriptomics to map antigen distribution, stromal architecture, vascular delivery architecture, immune niches, and pharmacodynamic activation. All data modalities were spatially co-registered and modeled using AI-based neighborhood analysis to generate a Delivery–Engagement Score reflecting the degree of coordinated tissue-level ADC activity within each tumor region.

KEY SPATIAL BIOLOGY FEATURES MEASURED



DELIVERY-ENGAGEMENT SCORE

Spatial integration of:
- payload localization
- target accessibility
- pharmacodynamic activation

to identify tumor regions associated with productive ADC activity.

HIGH SCORE
✓ Payload present
✓ Target accessible
✓ γH2AX / cCasp3 activation

→ Productive ADC activity

LOW SCORE
✗ Poor delivery or weak engagement
✗ Limited PD activation
→ Non-productive tumor region

.

WHAT THIS FRAMEWORK ENABLES

MECHANISTIC INTERPRETATION
Explains where and why productive ADC activity occurs within tumor tissue through spatial integration of delivery, engagement, and biological readiness.

IDENTIFICATION OF RESISTANT NICHES
Reveals spatial barriers associated with poor delivery, limited target accessibility, or insufficient pharmacodynamic activation.

TRANSLATIONAL SPATIAL PK/PD INSIGHT
Provides an interpretable tissue-level view of coordinated ADC biology across spatially heterogeneous tumor regions.

FOUNDATION FOR FUTURE PREDICTIVE BIOMARKER DEVELOPMENT
Establishes a translational framework supporting future development of predictive spatial biomarker strategies.

CONCLUSIONS

- Integrated spatial profiling enables direct visualization of coordinated ADC tissue activity within the tumor microenvironment.
- Spatial integration of payload delivery, target accessibility, microenvironment organization, and pharmacodynamic activation provides biologically interpretable insight into ADC mechanism of action.
- The Delivery–Engagement Score provides a quantitative estimate of regional tissue permissiveness for productive ADC activity and establishes a translational foundation for future predictive spatial biomarker development.

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