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From stromal barrier to immune anchor: A translational view of FAP×CD3 engagement with OMTX305

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Bispecific T-cell engagers have expanded the therapeutic vocabulary of oncology, but their translation into solid tumors remains constrained by problems that are only partly antigenic. T cells must reach the relevant compartment, remain functional in an inhibitory microenvironment, and sustain cytotoxicity despite spatial and phenotypic heterogeneity. In this setting, Thiel and colleagues take a notable detour from the conventional tumor-cell target and use the stroma itself as an immunological entry point. Their molecule, OMTX305, is a trivalent 2+1 Fab-eIg bispecific antibody that couples fibroblast activation protein (FAP) to CD3 and redirects T cells toward FAP-expressing cancer-associated fibroblasts (CAFs).[1] This design is conceptually attractive because the target is not simply a marker on malignant cells; it is embedded in a compartment that helps determine whether immune cells can productively engage the tumor at all.[2]

The experimental progression is one of the study's strengths. OMTX305 was first evaluated in matched patient-derived CAF and normal-fibroblast cultures, then in three-dimensional CAF spheroids and heterotypic CAF-tumor spheroids, and finally in precision-cut tumor slices (PCTSs) from 15 primary tumors, including 10 high-grade serous ovarian cancers (HGSOCs) and five non-small cell lung cancers (NSCLCs).[1] Across these systems, cytotoxicity depended on both FAP expression and T-cell engagement. In CAF spheroids, treatment increased T-cell activation and apoptosis of FAP-positive fibroblasts. In heterotypic spheroids containing FAP-negative tumor cells, the effect extended beyond the intended stromal target: neighboring malignant cells also underwent apoptosis, indicating a local bystander effect rather than simple stromal depletion.[1]

The PCTS experiments make this observation more persuasive because they preserve native spatial relationships that are lost in conventional cocultures. OMTX305 activated tissue-resident T cells, increased granzyme B, perforin, granulysin, interferon-γ and Fas ligand, and reduced the FAP-positive stromal area. Apoptotic tumor cells were enriched near FAP-positive regions, typically within tens of micrometers, supporting the idea that a FAP-directed immune synapse can create a cytotoxic field that reaches antigen-negative tumor cells.[1] This is an important mechanistic distinction. In solid tumors, a stromal antigen does not need to be expressed by every malignant clone if it can serve as a spatial anchor for local immune activation.

The same data also caution against treating CAF depletion as a uniformly beneficial endpoint. Fibroblasts are heterogeneous, and their biological effect depends on state and position. Spatial profiling in human lung tumors has shown that FAP-positive, αSMA-positive CAF programs can organize dense matrix structures associated with T-cell exclusion.[3] Consistent with that framework, single-cell RNA sequencing in the OMTX305 study showed preferential effects in FAP-high stromal populations, with reduced collagen-associated transcripts and increased matrix metalloproteinase expression after treatment.[1] These ECM-related transcriptional changes are compatible with a shift in matrix programs, but the short ex vivo window does not establish durable architectural remodeling. The distinction matters because acute CAF killing and sustained immune permissiveness are not synonymous.

Perhaps the most informative result is the degree of interpatient heterogeneity. In HGSOC, the immune-desert sample showed little T-cell activation or apoptosis, whereas immune-excluded and immune-inflamed tumors were more capable of mounting a response. In NSCLC, all five tumors were classified as immune-inflamed, yet responses still varied; the sample with the highest PD-L1 expression did not show clear granzyme B or cleaved caspase-3 induction.[1] The cohort is too small to validate immune phenotype or PD-L1 as predictive biomarkers, but the heterogeneity suggests a two-gate translational framework (Figure 1): Gate 1 is target availability (sufficient FAP-positive stroma), and Gate 2 is immune competence (a resident T-cell compartment that can still be activated). Neither gate alone should be treated as sufficient. Future stratification will likely need to integrate FAP abundance, T-cell infiltration and activation state, spatial immune phenotype, and other microenvironmental features rather than rely on a single biomarker.

FAP has an unusual advantage in this context because target distribution can be assessed noninvasively. In a prospective study of 89 patients with platinum-sensitive recurrent HGSOC, Feng and colleagues reported an overall diagnostic accuracy of 96.3% for ^{68}Ga-FAPI PET/CT compared with 86.9% for ^{18}F-FDG PET/CT.[4] The same study linked FAPI-positive/FDG-negative lesions after PARP inhibitor maintenance to CAF accumulation and activation, hypoglycolytic tumor features, and resistance to PARP inhibitor rechallenge in patient-derived organoids.[4] Although these observations do not establish FAPI uptake as a biomarker of OMTX305 sensitivity, they show that FAP-directed imaging can identify clinically relevant stromal phenotypes that conventional metabolic imaging may underrepresent. FAPI PET should therefore be viewed as a target-mapping tool rather than a validated predictor of OMTX305 response.

Figure 1 therefore presents a translational framework rather than a validated clinical selection algorithm. FAPI PET could map FAP-rich disease and heterogeneity across lesions (Gate 1); tissue profiling could assess whether T cells are present, spatially positioned and activation-competent (Gate 2); and PCTS testing could provide a functional readout of whether OMTX305 activates resident lymphocytes and induces apoptosis. These layers are complementary: target abundance alone does not establish therapeutic susceptibility. In the recurrent ovarian cancer series, false-positive FAPI findings occurred in previously operated regions with scar tissue or adhesions, underscoring that FAP imaging reports fibroblast biology rather than malignancy per se.[4] Prospective studies should test integrated models combining imaging, tissue-based FAP quantification, immune phenotyping and functional response assays rather than rely on a single threshold.

PCTSs are particularly well suited to this translational question because they retain tumor cells, stromal cells and tissue-resident immune cells in their native arrangement. The OMTX305 study shows that this platform can capture cell type-specific apoptosis, cytokine release and spatial relationships.[1] At present, however, PCTS is best positioned as a functional translational research platform or candidate-response assay; routine clinical screening would require standardized tissue handling, assay reproducibility, predefined response criteria and prospective validation. A three-day ex vivo culture cannot reproduce systemic pharmacokinetics, trafficking from lymphoid organs, repeated dosing, cytokine-release physiology, or delayed on-target effects in normal tissues. Nor can it determine whether early T-cell activation persists. The observed fall in CD3-positive T-cell density after treatment, despite continued production of cytolytic mediators, may reflect activation-induced loss, inadequate costimulation, or simply the constraints of the slice system.[1]

The transcriptional response provides a hypothesis-generating rationale for combination therapy, but combinations should be tested mechanistically rather than added empirically. OMTX305 increased effector programs in CD4-positive and CD8-positive T cells while also inducing inhibitory receptors and regulatory feedback pathways, including CTLA4, TIGIT and LAG3 in selected T-cell populations.[1] The FAP-targeted 4-1BB agonist RO7122290 produced peripheral and intratumoral T-cell activation in a first-in-human study, including increased intratumoral CD8-positive and Ki67-positive CD8-positive

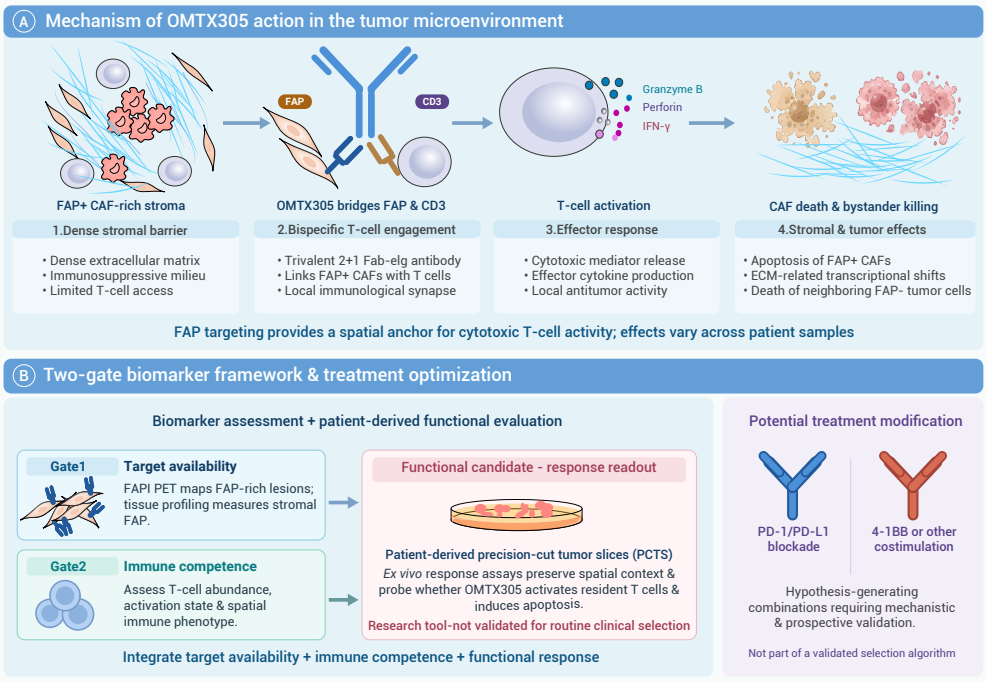


Figure 1. OMTX305 mechanism and a proposed biomarker-guided framework for FAP×CD3 therapy (A) Mechanism of action. (1) FAP-positive cancer-associated fibroblasts (CAFs) contribute to an immunosuppressive stromal barrier. (2) OMTX305 bridges FAP-positive CAFs and CD3-positive T cells. (3) T-cell activation promotes cytotoxic mediator release. (4) These responses induce CAF apoptosis, extracellular matrix (ECM)-related transcriptional changes, and bystander tumor-cell killing. (B) Proposed translational framework. Gate 1 assesses FAP target availability using FAPI PET and tissue profiling; Gate 2 evaluates T-cell abundance, activation state, and spatial phenotype. Patient-derived precision-cut tumor slices (PCTSs) provide an exploratory functional response readout. Potential combinations with PD-1/PD-L1 blockade or 4-1BB costimulation require prospective validation. This framework remains hypothesis-generating rather than clinically validated.

cells.[5] Together, these data justify prospective evaluation of FAP×CD3 engagement with checkpoint blockade or spatially restricted costimulation, particularly when baseline T cells are present but functionally constrained; they do not establish either strategy as an effective OMTX305 combination. The key question is whether such combinations widen the therapeutic window or merely intensify systemic immune activation.

Safety will ultimately determine whether the stromal-anchor concept is clinically useful. The tissue cross-reactivity experiments reported for the OMTX305 anti-FAP sequence did not show specific binding in the examined normal human tissues, which is reassuring at the preclinical level.[1] Nevertheless, an ex vivo efficacy platform cannot substitute for in vivo evaluation of exposure, cytokine kinetics and tissue effects. Early clinical development should therefore integrate pharmacodynamic sampling with target mapping rather than treat toxicity and efficacy as separate workstreams. Serial FAPI imaging, baseline and on-treatment biopsies, circulating cytokines, intratumoral T-cell state and spatial CAF/ECM state could together reveal whether target engagement is occurring in the intended compartment and whether biological activity remains localized.

The principal contribution of the study is therefore broader than the preclinical activity of one bispecific antibody. It offers a testable model in which the tumor stroma is converted from a passive barrier into an immune anchor. The next step is not simply to ask whether OMTX305 kills FAP-positive cells, but to determine which FAP-rich tumors contain a recoverable T-cell response and whether that response can be sustained without unacceptable toxicity. Future stratification should test whether an integrated model combining whole-body target mapping, spatial immune phenotyping and patient-derived functional testing outperforms any single biomarker. If prospectively validated, such an approach could move FAP from a descriptive stromal marker toward a clinically actionable address for microenvironment-directed immunotherapy.

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AUTHOR CONTRIBUTIONS

H.W. and Z.F. conceived and designed the analysis; Y.W. and S.L. wrote the manuscript. All authors contributed to the manuscript and approved the final version.

DECLARATION OF INTERESTS

The authors declare no competing interests.