

P3.186-281: CCL2+ Cancer Cells Drive Intrinsic and Therapy-Induced LUAD Bone Metastasis:
An Integrated Single-Cell Analysis



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INTRODUCTION

Bone metastasis (BM) remains a primary cause of mortality in EGFR-mutant lung adenocarcinoma (LUAD), frequently emerging from the osimertinib-induced drug-tolerant persister (DTP) state. However, the elusive spatiotemporal clonal dynamics governing BM initiation severely impede the development of interceptive therapeutics.

METHODS

We integrated barcode-based single-cell lineage tracing in murine LUAD models (Lewis lung carcinoma (LLC) and KrasG12D;Trp53-/- (KP) cell lines) (Figure 1a) with comprehensive single-cell RNA sequencing (scRNA-seq) of two EGFR-mutant LUAD clinical cohorts: treatment-naïve matched primary and BM lesions (n=3 pairs) (Figure 1c), and longitudinal baseline versus osimertinib-induced DTP samples (n=4 pairs) (Figure 2b). Mechanistic insights and therapeutic targeting were validated through in vitro assays (qPCR and immunofluorescence) (Figure 2c-d) and an in vivo osimertinib-DTP murine model (Figure 2e) utilizing celecoxib, a PTGS2/COX-2 inhibitor acting upstream of the CCL2 axis.

RESULTS

In vivo lineage trajectories revealed highly bone-tropic, Ccl2-amplified cancer clones (KP5/KP20/LLC12) peaking precisely at the metastatic tipping point (Figure 1b). Clinical transcriptomics corroborated this, identifying a distinct CCL2+ cancer cell cluster (C8) driving treatment-naïve BM (Figure 1c,d), alongside an analogous CCL2+ subpopulation (C20) that markedly expanded to dominate the osimertinib-DTP state (Figure 2b). Mechanistically, interactome mapping demonstrated these advantageous clones orchestrate a pro-metastatic bone niche via robust Ccl2-Ccr2 crosstalk with macrophages and monocytes (Figure 2a). Pharmacological blockade with celecoxib significantly abrogated CCL2 expression (Figure 2c-d) and profoundly suppressed BM incidence in the DTP murine model (P = 0.001) (Figure 2e).

Figure 1

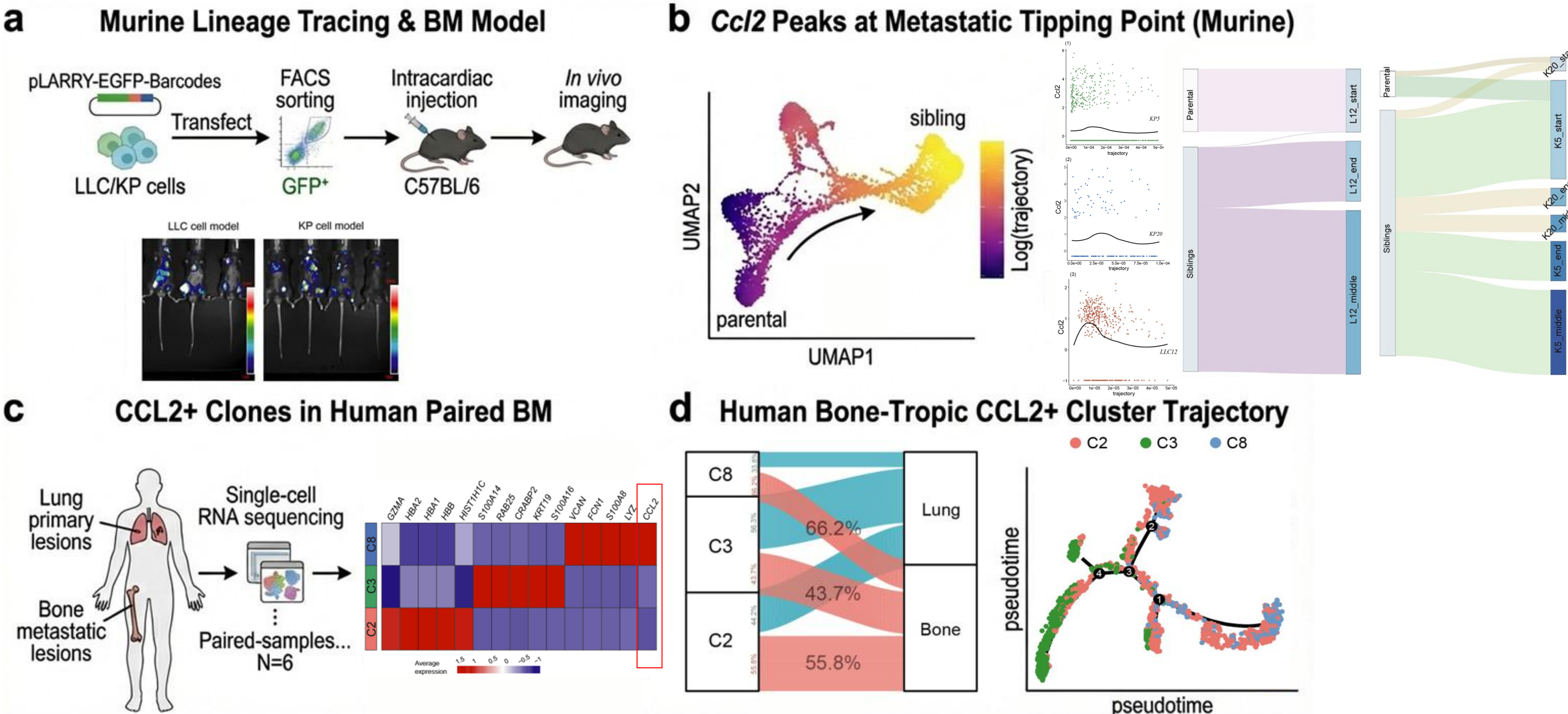
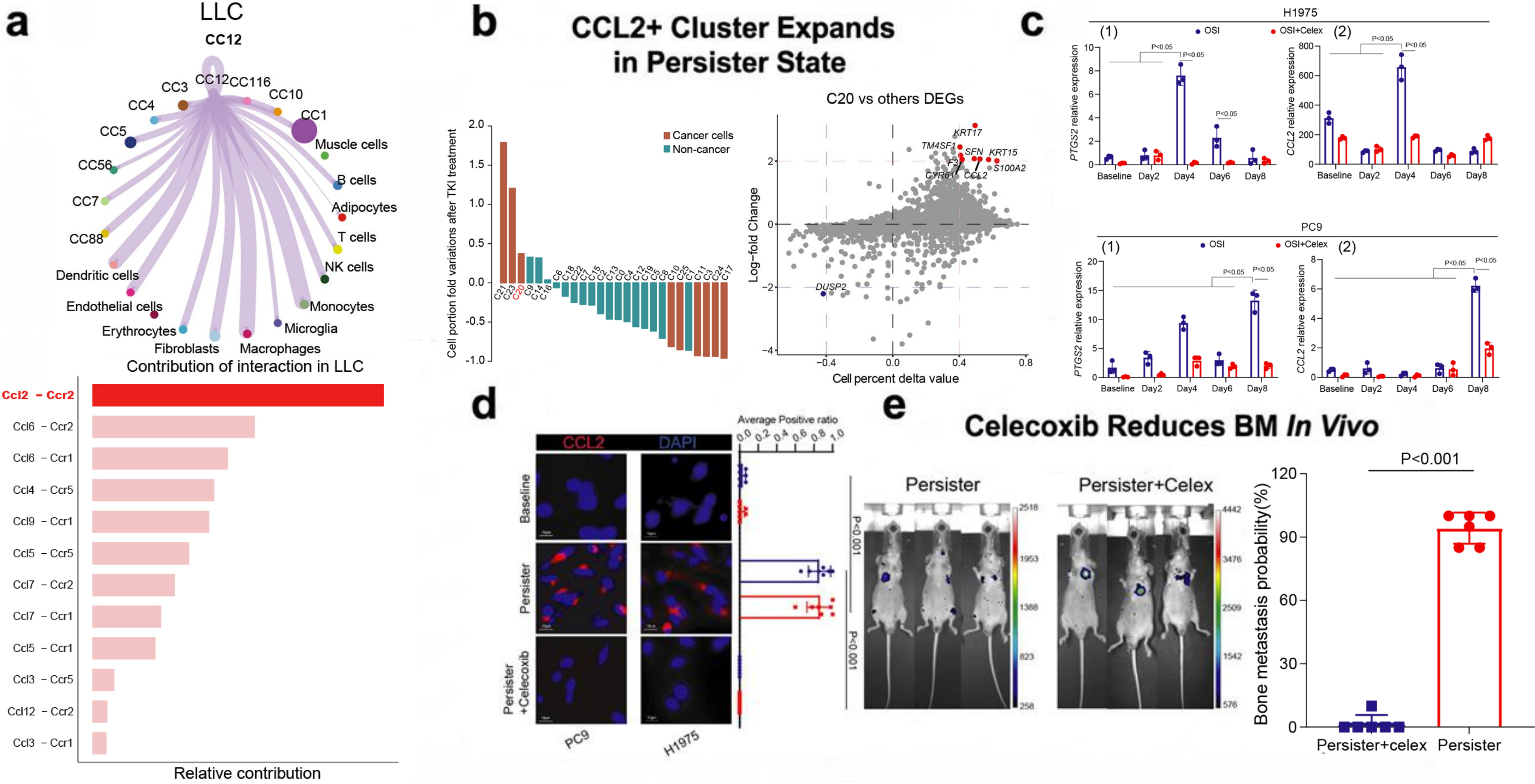


Figure 2



CONCLUSION

High-resolution lineage tracing and clinical transcriptomics unveil CCL2+ clones as pivotal spatiotemporal drivers of LUAD BM, governing both intrinsic and osimertinib-persistent dissemination.

Targeting the CCL2-CCR2 tumor-immune interactome with celecoxib presents a highly translatable, combinatorial strategy to eradicate DTPs and prevent BM in EGFR-mutant LUAD.

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