

Cell DIVE Multiplex Imaging Solution Publication

Transforming tissue research with open multiplexing.

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Cell DIVE Selected Publications

Highlight 2022: Distinct fibroblast subsets drive inflammation and damage in arthritis

A. P. Croft, J. Campos, K. Jansen, J. D. Turner, J. Marshall, M. Attar, L. Savary, C. Wehmeyer, A. J. Naylor, S. Kemble, J. Begum, K. Dürholz, H. Perlman, F. Barone, H. M. McGettrick, D. T. Fearon, K. Wei, S. Raychaudhuri, I. Korsunsky, M. B. Brenner, M. Coles, S. N. Sansom, A. Filer & C. D. Buckley

[Nature volume 570, pages 246–251 \(2019\)](#)

Prostate cancer

Multiparametric MRI is an important tool for the diagnosis of prostate cancer. However, this technology fails to identify about 15% of clinically significant prostate cancers. Here, the authors used Cell DIVE, alongside gene expression profiling and AI-based analytic algorithms to explore the ecosystem of these tumors. Using these technologies, the authors uncovered deep molecular, cellular, and structural characteristics of prostate tumors, and found that the MRI-invisible examples tended to display a less complex tumor environment, contributing to their difficulty in detection.

[Single-cell Spatial Proteomic Revelations on the Multiparametric MRI Heterogeneity of Clinically Significant Prostate Cancer](#)

Pachynski RK, et al.

Clin Cancer Res. 2021 Jun 15;27(12):3478-3490. DOI: 10.1158/1078-0432.CCR-20-4217.

Breast cancer

Tumor cells that enter circulation are often the precursors of metastatic cancer. Previously, the authors of this work found that specific genomic regions in these cells are frequently subject to copy-number gains and used this information to identify tumors that share this genomic signature—bridging the gap between genomics and spatial biology. This study showed that these so-called circulating tumor cell (CTC)-associated tumors formed more frequently in breast cancer patients after multiple rounds of treatment, and often showed an increased level of

spatial heterogeneity. Cell DIVE analysis demonstrated that these, more heterogeneous tumors, have a high degree of B lymphocyte infiltration in triple-negative breast cancer. These data show how genetic subclones arise, how they are selected and how they ultimately shape the microenvironments around them.

Heterogeneity of Circulating Tumor Cell-Associated Genomic Gains in Breast Cancer and Its Association with the Host Immune Response

Kanwar N, et al.

Cancer Res. 2021 Dec 15;81(24):6196-6206. DOI: 10.1158/0008-5472.CAN-21-1079.

Colorectal Cancer

Colorectal cancer is a high incidence and high mortality cancer. Currently, postoperative chemotherapy benefits only a minority of patients, and thus, new tools are necessary to screen patients and identify those at increased risk. Tissue samples from hundreds of patients were analyzed using Cell DIVE to reveal the fine cellular determinants of survival following cancer treatment. By using multimarker analysis enabled by Cell DIVE and a unique analysis algorithm, the authors show that the recruitment of a particular T cell subtype, the PD-1 negative Treg, was most highly associated with disease-free survival. Thus, multiplex imaging and analysis of tumor samples may provide a future means to target clinical resources towards those patients with higher risk profiles.

Stratification of chemotherapy-treated stage III colorectal cancer patients using multiplexed imaging and single-cell analysis of T-cell populations

Stachte X, et al.

Mod Pathol. 2021 Nov 3. DOI: 10.1038/s41379-021-00953-0.

Melanoma

Cancer immunotherapies can yield powerful, lasting effects and tumor regression. However, identifying patients and tumors in which these therapies can be most effective remains challenging. In this study, the authors used Cell DIVE to explore the phenotypes of tumor cells in patients who had received and showed a strong response to immunotherapy, as well as in those patients who did not respond. In the case of “extreme responders” who featured complete eradication of tumor cells after IL2 injection immunotherapy, proliferating CD8+ T cells with a particular phenotype (PD-1+LAG-3+TIM-3+) and IFN γ and IL2 response gene expression characterized the tumors, while loss of membrane bound MHC class I typified lesions that resisted the therapy. This study indicates that antigen presentation from tumor cells is critical for an efficacious response to IL2 therapy and demonstrates the power of multi-marker phenotypic analysis enabled by Cell DIVE.

Tumor MHC Class I Expression Associates with Intralesional IL2 Response in Melanoma.

Pourmaleki M, et al.

Cancer Immunol Res. 2022 Mar 1. DOI: 10.1158/2326-6066.CIR-21-1083.

Cell DIVE technology development publications

1. **Highly multiplexed single-cell analysis of formalin-fixed, paraffin-embedded cancer tissue**
Gerdes MJ, et al.
Proc Natl Acad Sci U S A. 2013 Jul 16;110(29):11982-7. DOI: 10.1073/pnas.1300136110.
2. **A novel, automated technology for multiplex biomarker imaging and application to breast cancer**
Clarke, GM, et al.
Histopathology 64(2), pp.242–255 (2014). DOI: 10.1111/his.12240
3. **Microfluidic Tissue Mesodissection in Molecular Cancer Diagnostics**
Surrette C, et al.
SLAS Technol. 2017 Aug;22(4):425–430. DOI: 10.1177/2211068216680208
4. **Multi-modal imaging of histological tissue sections**
Can, A, et al. (2008)
IEEE International Symposium on Biomedical Imaging: From Nano to Macro pp. 288–291 (2008). DOI: 10.1109/ISBI.2008.4540989

Multiplexed image processing and single cell analysis

1. **GammaGateR: semi-automated marker gating for single-cell multiplexed imaging**
Xiong J, et al.
Bioinformatics 40 (2024).
2. **Evaluation of cell segmentation methods without reference segmentations**
Chen H, et al.
Mol Biol Cell 6 (2023)
3. **FLINO: a new method for immunofluorescence bioimage normalization**
Graf J, et al.
Bioinformatics 38 (2022).
4. **Autofluorescence removal using a customized filter set**
Pang Z, et al.
Microsc Res Tech. 2013 Oct;76(10):1007-15. DOI: 10.1002/jemt.22261.

5. **Dark pixel intensity determination and its applications in normalizing different exposure time and autofluorescence removal**
 Pang Z, et al.
 J Microsc. 2012 Apr;246(1):1-10. DOI: 10.1111/j.1365-2818.2011.03581.x.
6. **Autofluorescence removal by non-negative matrix factorization**
 Woolfe, F., et al.
 IEEE T Image Process 20(4), 1085–1093 (2011). DOI: 10.1109/TIP.2010.2079810
7. **Characterization of biological processes through automated image analysis**
 Rittscher J.
 Annu Rev Biomed Eng. 2010 Aug 15;12:315-44. DOI: 10.1146/annurev-bioeng-070909-105235.
8. **Techniques for Cellular and Tissue-Based Image Quantitation of Protein Biomarkers**
 Can, A. et al.
 Microscopic Image Analysis for Lifescience Applications, 1–8 (2008).
9. **Quantitative single cell analysis of cell population dynamics during submandibular salivary gland development and differentiation**
 Nelson DA, et al.
 Biol Open. 2013 Apr 18;2(5):439-47. DOI: 10.1242/bio.20134309.

Tumor heterogeneity

1. **Spatial molecular profiling of mixed invasive ductal and lobular breast cancers reveals heterogeneity in intrinsic molecular subtypes, oncogenic signatures, and mutations**
 Shah O, et al.
 Proc Natl Acad 121 (31), (2024). DOI:10.1073/pnas.2322068121
2. **Characterizing the heterogeneity of tumor tissues from spatially resolved molecular measures**
 Graf JF, Zavodszky MI
 PLoS One. 2017 Nov 30;12(11):e0188878. DOI: 10.1371/journal.pone.0188878
3. **Platform for Quantitative Evaluation of Spatial Intratumoral Heterogeneity in Multiplexed Fluorescence Images**
 Spagnolo DM, et al.
 Cancer Res. 2017 Nov 1;77(21):e71-e74. DOI: 10.1158/0008-5472.CAN-17-0676
4. **Optimized multiplex immunofluorescence single-cell analysis reveals tuft cell heterogeneity**

McKinley ET, et al.

JCI Insight. 2017 Jun 2;2(11):e93487. DOI: 10.1172/jci.insight.93487

5. **Pointwise mutual information quantifies intratumor heterogeneity in tissue sections labeled with multiple fluorescent biomarkers**

Spagnolo DM, et al.

J Pathol Inform. 2016 Nov 29;7:47. DOI: 10.4103/2153-3539.194839

6. **Emerging understanding of multiscale tumor heterogeneity**

Gerdes MJ, et al.

Front Oncol. 2014 Dec 18; 2014;4:366. DOI: 10.3389/fonc.2014.00366

7. **Multiscale, multimodal analysis of tumor heterogeneity in IDH1 mutant vs wild-type diffuse gliomas**

Berens ME, et al.

PLoS One. 2019 Dec 27;14(12):e0219724. DOI: 10.1371/journal.pone.0219724

Tumor microenvironment and immuno-oncology

1. **Multi-omic profiling of follicular lymphoma reveals changes in tissue architecture and enhanced stromal remodeling in high-risk patients**

Radtke A, et al.

Cancer Cell 42, 444-463 (2024).

2. **The efficacy of recombinant human adenovirus type 5 (H101) intra-tumor therapy in persistent/recurrent/metastatic gynecological cancer and the exploration of changes in tumor**

microenvironment.

Zhang Q., et al.

JCO 42, 5536-5536 (2024).

3. **Robust single cell quantification of immune cell subtypes in histological samples**

Santamaria-Pang, A. et al. (2017), February

IEEE EMBS International Conference on Biomedical & Health Informatics (BHI), (p. 121–124). IEEE. DOI: 10.1109/BHI.2017.7897220

4. **Stromal-Based Signatures for the Classification of Gastric Cancer**

Uhlik MT, et al.

Cancer Res. 2016 May 1;76(9):2573-86. DOI: 10.1158/0008-5472.CAN-16-0022

5. **Multi-channel algorithm for segmentation of tumor blood vessels using multiplexed image data**

Al-Kofahj, Y. et al. 2016, April

Biomedical Imaging (ISBI), 2016 IEEE 13th International Symposium on (pp. 213–216). IEEE. DOI: 10.1109/ISBI.2016.7493247

6. **Oncolytic Virotherapy Promotes Intratumoral T Cell Infiltration and Improves Anti-PD-1 Immunotherapy**
Ribas A, et al.
Cell. 2017 Sep 7;170(6):1109-1119.e10. DOI: 10.1016/j.cell.2017.08.027. Erratum in: Cell. 2018 Aug 9;174(4):1031-1032.
7. **Immune Profiling and Quantitative Analysis Decipher the Clinical Role of Immune-Checkpoint Expression in the Tumor Immune Microenvironment of DLBCL**
Xu-Monette ZY, et al.
Cancer Immunol Res. 2019 Apr;7(4):644-657. DOI: 10.1158/2326-6066.CIR-18-0439
8. **Efficacy and tolerability of anti-programmed death-ligand 1 (PD-L1) antibody (Avelumab) treatment in advanced thymoma**
Rajan A, et al.
J Immunother Cancer. 2019 Oct 21;7(1):269. DOI: 10.1186/s40425-019-0723-9
9. **Understanding heterogeneous tumor microenvironment in metastatic melanoma**
Yan Y, et al.
PLoS One. 2019 Jun 5;14(6):e0216485. DOI: 10.1371/journal.pone.0216485
10. **Characterization of the liver immune microenvironment in liver biopsies from patients with chronic HBV infection**
van Buuren, N, et al.
JHEP Reports. 2021 Oct 23. DOI: 10.1016/j.jhepr.2021.100388
11. **Antitumor immune effects of preoperative sitravatinib and nivolumab in oral cavity cancer: SNOW window-of-opportunity study**
Oliva M, et al.
J Immunother Cancer. 2021 Oct;9(10):e003476. DOI: 10.1136/jitc-2021-003476

Cancer characterization and prognosis

Lung Cancer

1. **Spatial profiling of non-small cell lung cancer provides insights into tumorigenesis and immunotherapy response**
Kim J, et al.
Commun Biol 7, 930 (2024). DOI: 10.1038/s42003-024-06568-w

Colorectal Cancer

1. **Integrated multiplex analysis of cell death regulators in stage II colorectal cancer suggests patients with 'persister' cell profiles fail to benefit from adjuvant chemotherapy**
Cho S, et al.
BMJ Oncol 3(1), (2024). DOI: 10.1136/bmjonc-2024-000362
2. **Spatial effects of infiltrating T cells on neighbouring cancer cells and prognosis in stage III CRC patients**
Azimi M, et al.
J Pathol, 264, 148-159 (2024). DOI: 10.1002/path.6327
3. **Identification of unique rectal cancer-specific subtypes**
Kisakol B, et al.
Br J Cancer 130, 1809–1818 (2024).
4. **Microenvironment in Mucinous Rectal Cancer Characterized by Increased Lymphocyte Infiltration and Enhanced Programmed Cell Death Protein 1 Expression**
Duggan W, et al.
Diseases of the Colon & Rectum 66, 914-922 (2023).
5. **Increased Fusobacterium tumoural abundance affects immunogenicity in mucinous colorectal cancer and may be associated with improved clinical outcome**
Duggan W, et al.
J Mol Med 101, 829–841 (2023).
6. **Apoptotic and Necroptotic Mediators are Differentially Expressed in Mucinous and Non-Mucinous Colorectal Cancer**
O'Connell E, et al.
Front Oncol 12, 815001 (2022).
7. **Epithelial TGF β engages growth-factor signalling to circumvent apoptosis and drive intestinal tumourigenesis with aggressive features**
Flanagan D, et al.
Nat Commun 13, 7551 (2022).
8. **An atlas of inter- and intra-tumor heterogeneity of apoptosis competency in colorectal cancer tissue at single-cell resolution**
Lindner A, et al.
Cell Death Differ 29, 806–817 (2022).

9. **Excess PLAC8 promotes an unconventional ERK2-dependent EMT in colon cancer**
Li C, et al.
J Clin Invest. 2014 May;124(5):2172-87. DOI: 10.1172/JCI71103
10. **The relative distribution of membranous and cytoplasmic met is a prognostic indicator in stage I and II colon cancer**
Ginty F, et al.
Clin Cancer Res. 2008 Jun 15;14(12):3814-22. DOI: 10.1158/1078-0432.CCR-08-0180
11. **Cytometry-based single-cell analysis of intact epithelial signaling reveals MAPK activation divergent from TNF- α -induced apoptosis in vivo**
Simmons AJ, et al.
Mol Syst Biol. 2015 Oct 30;11(10):835. DOI: 10.15252/msb.20156282. Erratum in: Mol Syst Biol. 2016 Aug 29;12(8):881.
12. **Stratification of chemotherapy-treated stage III colorectal cancer patients using multiplexed imaging and single-cell analysis of T-cell populations**
Stachte X, et al.
Mod Pathol. 2021 Nov 3. DOI: 10.1038/s41379-021-00953-0

Prostate cancer

1. **Deep learning-based automated pipeline for blood vessel detection and distribution analysis in multiplexed prostate cancer images**
Karageorgos G, et al.
Front Bioinform 3, 1296667 (2024).
2. **AZGP1 deficiency promotes angiogenesis in prostate cancer**
Wen R, et al.
J Transl Med 22, 383 (2024).
3. **Single-cell Spatial Proteomic Revelations on the Multiparametric MRI Heterogeneity of Clinically Significant Prostate Cancer**
Pachynski RK, et al.
Clin Cancer Res. 2021 Jun 15;27(12):3478-3490. DOI: 10.1158/1078-0432.CCR-20-4217

Hodgkin lymphoma

1. **Multiplexed Spatial Profiling of Hodgkin Reed–Sternberg Cell Neighborhoods in Classic Hodgkin Lymphoma**
Pourmaleki M, et al. Clin Cancer Res 30 (17), 3881–3893. DOI: 10.1158/1078-0432.CCR-24-0942

2. **A single slide multiplex assay for the evaluation of classical Hodgkin lymphoma**
Hollman-Hewgley D, et al.
Am J Surg Pathol. 2014 Sep;38(9):1193-202. DOI: 10.1097/PAS.0000000000000242

Pancreatic Cancer

1. **Dynamic immunoediting by macrophages in homologous recombination deficiency-stratified pancreatic ductal adenocarcinoma**
Hong W, et al.
Drug Resistance Updates 76, (2024). DOI: 10.1016/j.drug.2024.101115

Gastric Cancer

1. **Hyperactivation of mTOR/eIF4E Signaling Pathway Promotes the Production of Tryptophan-To-Phenylalanine Substitutants in EBV-Positive Gastric Cancer**
Zheng Z, et al.
Adv Sci 11, (2024). DOI: 10.1002/advs.202402284

Breast cancer

1. **Endothelial cell pY397-FAK expression predicts risk of breast cancer recurrences after radiotherapy in SweBCG91-RT cohort**
Drake R, et al.
Clin Cancer Res, (2025). DOI: 10.1158/1078-0432.CCR-24-2939
2. **Single-cell heterogeneity in ductal carcinoma in situ of breast**
Gerdes MJ, et al.
Mod Pathol. 2018 Mar;31(3):406-417. DOI: 10.1038/modpathol.2017.143
3. **Multiplexed immunofluorescence delineates proteomic cancer cell states associated with metabolism**
Sood A, et al.
JCI Insight. 2016 May 5;1(6):e87030. DOI: 10.1172/jci.insight.87030
4. **Taxonomy of breast cancer based on normal cell phenotype predicts outcome**
Santagata, S. et al.
J Clin Invest. 2014 Feb;124(2):859-70. DOI: 10.1172/JCI70941.
5. **Multi-protein spatial signatures in ductal carcinoma in situ (DCIS) of breast**
Badve SS, et al.
Br J Cancer. 2021 Mar;124(6):1150-1159. DOI: 10.1038/s41416-020-01216-6

6. **Heterogeneity of Circulating Tumor Cell-Associated Genomic Gains in Breast Cancer and Its Association with the Host Immune Response**
Kanwar N, et al.
Cancer Res. 2021 Dec 15;81(24):6196-6206. DOI: 10.1158/0008-5472.CAN-21-1079

Glioblastoma

1. **Regulatable interleukin-12 gene therapy in patients with recurrent high-grade glioma: Results of a phase 1 trial**
Chiocca EA, et al.
Sci Transl Med. 2019 Aug 14;11(505):eaaw5680. DOI: 10.1126/scitranslmed.aaw5680

Amyotrophic lateral sclerosis Neuroscience and Neurology

1. **Dementia with lewy bodies patients with high tau levels display unique proteome profiles**
Greally S, et al.
Mol Neurodegeneration 19, 98 (2024). DOI: 10.1186/s13024-024-00782-0
2. **Proteomic features of gray matter layers and superficial white matter of the rhesus monkey neocortex: comparison of prefrontal area 46 and occipital area 17**
Castro-Mendoza P, et al.
Brain Struct Funct 229, 1495–1525 (2024). DOI: 10.1007/s00429-024-02819-y
3. **Quantitative patterns of motor cortex proteinopathy across ALS genotypes**
Nolan M, et al.
Acta Neuropathol Commun. 2020 Jul 2;8(1):98. DOI: 10.1186/s40478-020-00961-2

Development and Organ Mapping

1. **Organ Mapping Antibody Panels: a community resource for standardized multiplexed tissue imaging**
Quardokus E, et al.
Nat Methods 20, 1174–1178 (2023).
2. **3D reconstruction of skin and spatial mapping of immune cell density, vascular distance and effects of sun exposure and aging**
Ghose S, et al.
Commun Biol 6, 718 (2023).
3. **Unsupervised Trajectory Analysis of Single-Cell RNA-Seq and Imaging Data Reveals Alternative Tuft Cell Origins in the Gut**

Herring CA, et al.
Cell Syst. 2018 Jan 24;6(1):37-51.e9. DOI: 10.1016/j.cels.2017.10.012

Immunology and Inflammation

1. **KLF2 maintains lineage fidelity and suppresses CD8 T cell exhaustion during acute LCMV infection**
Fagerberg E, et al.
Science 387, (2025). DOI: 10.1126/science.adn2337
2. **A longitudinal single-cell atlas of anti-tumour necrosis factor treatment in inflammatory bowel disease**
Thomas T, et al.
Nat Immunol 25, 2152–2165 (2024). DOI: 10.1038/s41590-024-01994-8
3. **Pathogenic role for CD101-negative neutrophils in the type I interferon-mediated immunopathogenesis of tuberculosis**
Saqib M, et al.
Cell Reports 44(1), (2024). DOI: 10.1016/j.celrep.2024.115072
4. **A single cell atlas of frozen shoulder capsule identifies features associated with inflammatory fibrosis resolution**
Ng M, et al.
Nat Commun 15, 1394 (2024).
5. **Pathobiology of Candida auris infection analyzed by multiplexed imaging and single cell analysis**
Chadwick C, et al.
PLoS One (2024).
6. **Post-resolution macrophages shape long-term tissue immunity and integrity in a mouse model of pneumococcal pneumonia**
Feehan K, et al.
Nat Commun 15, 4326 (2024).
7. **Ultrasound Neuromodulation of an Anti-Inflammatory Pathway at the Spleen Improves Experimental Pulmonary Hypertension**
Zafeiropoulos S, et al.
Circ Res 135, 41-56 (2024).
8. **3D deconvolution of human skin immune architecture with Multiplex Annotated Tissue Imaging System**

Scholaert M, et al.
Sci Adv 9 (2023).

9. **TSPO expression in a Zika virus murine infection model as an imaging target for acute infection-induced neuroinflammation**
Victorio C, et al.
Eur J Nucl Med Mol Imaging 50, 742–755 (2023).
10. **LAT1 enables T cell activation under inflammatory conditions**
Ogbechi J, et al.
J Autoimmun 138, 103031 (2023).
11. **Cellular characterisation of advanced osteoarthritis knee synovium**
Mimpen J, et al.
Arthritis Res Ther 25, 154 (2023).
12. **Cross-tissue, single-cell stromal atlas identifies shared pathological fibroblast phenotypes in four chronic inflammatory diseases**
Korsunsky I, et al.
Med 3, 481-518 (2022).



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