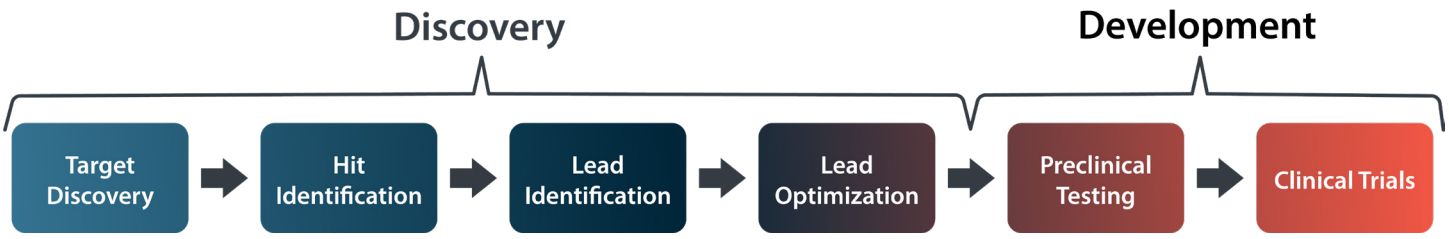
HALO® Image Analysis in Drug Discovery

From target identification to clinical development, digital pathology with the HALO® image analysis platform is contributing to the research and development of next-generation therapies for a range of diseases. Here, we list a selection of recent publications by their stage in the drug discovery pipeline and explore several applications in detail.

Although some publications describe work that spans multiple stages, papers are only listed once.



The drug discovery pipeline is a complex process with multiple stages spanning discovery and development. From target discovery to phase 3 trials, researchers are leveraging HALO to advance their image analysis and help accelerate findings.

Target Discovery

An M, Mehta A, Min BH et *al*. Early immune remodeling steers clinical response to first-line chemoimmunotherapy in advanced gastric cancer. *Cancer Discov* **14(5)**: 766-785 (2024). DOI: 10.1158/2159-8290.CD-23-0857.

Caramella-Pereira F, Zheng Q, Hicks JL et *al*. Overexpression of fibroblast activation protein (FAP) in the stroma of proliferative inflammatory atrophy (PIA) and primary adenocarcinoma of the prostate. *Pathology* **57(5)**: 592-604 (2025). DOI: 10.1016/j.pathol.2024.12.637.

Chen F, Byrd AL, Liu J et *al*. Polycomb deficiency drives a FOXP2-high aggressive state targetable by epigenetic inhibitors. *Nat Commun* **14**: 336 (2023). DOI: 10.1038/s41467-023-35784-x.

Flayer CH, Kernin IJ, Matatia PR et *al*. A γδ T cell–IL-3 axis controls allergic responses through sensory neurons. *Nature* **634**: 440-446 (2024). DOI: 10.1038/s41586-024-07869-0.

Larkin RM, Lopez DC, Robbins YL et *al*. Augmentation of tumor expression of HLA-DR, CXCL9, and CXCL10 may improve olfactory neuroblastoma immunotherapeutic responses. *J Trans Med* **22**: 524 (2024). DOI: 10.1186/s12967-024-05339-9.

Lu IN, Müller-Miny L, Krekeler C et *al*. The CXCL16/CXCR6 axis is linked to immune effector cell-associated neurotoxicity in chimeric antigen receptor (CAR) T cell therapy. *Genome Med* **17**: 71 (2025). DOI: 10.1186/s13073-025-01498-6.

Multi-omics and imaging mass cytometry characterization of human kidneys to identify pathways and phenotypes associated with impaired kidney function

Authors: Asowata EO, Romoli S, Sargeant R, Tan JY, Hoffmann S, Huang MM, Mahbubani KT, Krause FN, Jachimowicz D, Agren R, Koulman A, Jenkins B, Musial B, Griffin JL, Soderberg M, Ling S, Hansen PBL, Saeb-Parsy K, Woollard KJ

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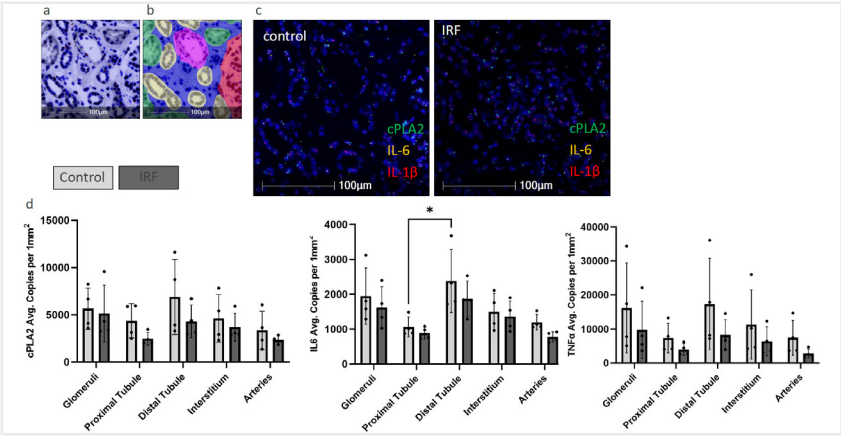

Science: Despite major progress in defining the molecular circuits underpinning human kidney disorders, new therapeutic strategies that can prevent progression to end-stage disease remain limited, in part due to the translational gap between traditional animal models and human pathology. In this study, Evans Asowata and colleagues leveraged human kidneys procured from deceased transplant donors with normal or reduced renal function to more accurately define the cellular and metabolic programs associated with kidney injury. Using a multi-omics approach, they characterized the cellular landscape and inflammatory milieu in impaired kidneys and found that eight metabolic pathways, including arachidonic acid metabolism, were elevated in injured tissue. The authors observed that inhibition of cytosolic phospholipase A2 (cPLA2)–arachidonic acid metabolism reduced injury and inflammation in human proximal tubular epithelial cells, suggesting that lipid metabolic dysregulation may be a key driver of kidney inflammation. These findings identify lipid-associated pathways as promising targets for therapeutic intervention and support the use of deceased donor kidneys as a human-relevant model of renal injury.

Technology: To observe the source of cPLA2 and inflammatory cytokines, the authors investigated RNA expression levels in human kidney sections using the HALO FISH module and a DenseNet V2 tissue classifier developed using HALO AI. The feature image shows AI-based classification of glomeruli (red), proximal (green) and distal (yellow) tubules, interstitium (blue), and arteries (pink) and RNA counts across tissue types. Imaging mass cytometry was performed to measure differences in kidney and immune cell populations and their proximity. Sections were segmented into glomeruli and cortical regions using another DenseNet classifier followed by cell phenotyping and spatial analysis using the HALO Highplex FL and Spatial Analysis modules, respectively.

Ridnour LA, Cheng RYS, Kedei N et al. Adjuvant COX inhibition augments STING signaling and cytolytic T cell infiltration in irradiated 4T1 tumors. *JCI Insight* **9(12)**: e165356 (2024). DOI: 10.1172/jci.insight.165356.

Vos JL, Traets JJH, Qiao X *et al*. Diversity of the immune microenvironment and response to checkpoint inhibitor immunotherapy in mucosal melanoma. *JCI Insight* **9(21)**: e179982 (2024). DOI: 10.1172/jci.insight.179982.

Wang J, Wei J, Pu T *et al*. Cholinergic signaling via muscarinic M1 receptor confers resistance to docetaxel in prostate cancer. *Cell Rep Med* **5(2)**: 101388 (2024). DOI: 10.1016/j.xcrm.2023.101388.

Hit Identification

Cerra C, Tancock MRC, Thio N et *al*. Exploiting dysregulated iron homeostasis to eradicate persistent high-grade serous ovarian cancer. *Cell Death Discov* **11**: 423 (2025). DOI: 10.1038/s41420-025-02716-1.

Senatorov IS, Bowman J, Jansson KH et al. Castrate-resistant prostate cancer response to taxane is determined by an HNF1-dependent apoptosis resistance circuit. *Cell Rep Med* **5(12)**: 17 (2024). DOI: 10.1016/j.xcrm.2024.101868.

Elucidating molecularly stratified single agent, and combination, therapeutic strategies targeting MCL1 for lethal prostate cancer

Authors: Jiménez-Vacas J, Westaby D, Figueiredo I, De Haven Brandon A, Padilha A, Yuan W, Seed G, Bogdan D, Gurel B, Bertan C, Miranda S, Lambros M, Montero-Hidalgo A, Coleman I, Yu I, Buroni L, Zeng W, Neeb A, Welti J, Rekowski J, Paravati R, Gabel F, Pandell N, Ferreira A, Crespo M, Riisnaes R, Das S, Taylor J, Waldron N, Hobern E, Valenti M, Ning J, Bernett I, Liodaki K, Persse T, Galipeau P, Wilkinson S, Trostel S, Karzai F, Chau C, Beatson E, Zhang X, Klumpp-Thomas C, Varkaris A, Luque R, Swain A, Raynaud F, Lack N, Thomas C, Ha G, Figg W, Bezzi M, Sowalsky A, Nelson P, Carreira S, Balk S, de Bono JS, Sharp A

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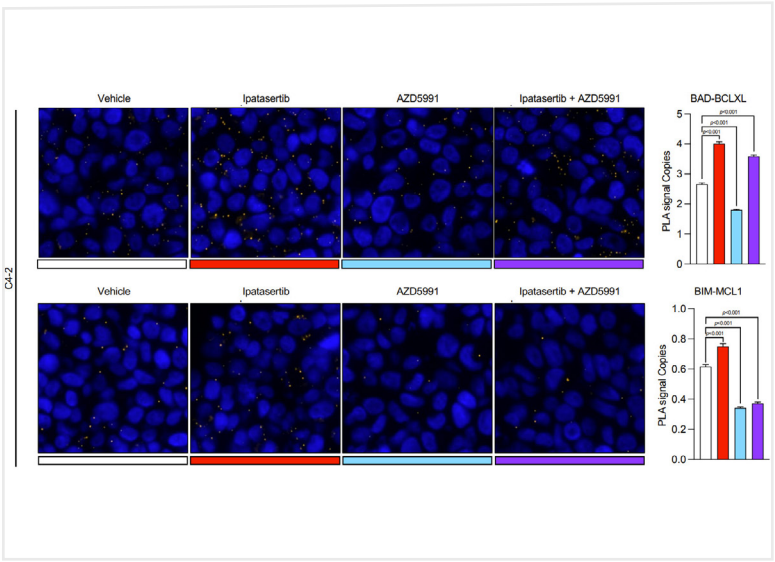

Science: Metastatic castration-resistant prostate cancer (mCRPC) remains highly lethal despite modern therapies, in part because tumor cells acquire mechanisms to evade apoptosis. In this study, Juan Jiménez-Vacas and coauthors investigated whether Myeloid Cell Leukemia 1 (*MCL1*), a frequently amplified gene with an anti-apoptotic product, could serve as a target in advanced prostate cancer. The authors found that *MCL1* copy number gain emerges early in aggressive disease evolution and is associated with poorer clinical outcome. Prostate cancer cell models with *MCL1* amplification were observed to exhibit heightened sensitivity to MCL1 inhibition. Subsequent screening of FDA-approved drugs for combination treatment showed that MCL1 blockade plus AKT inhibition yielded robust cancer-selective killing. These findings support the clinical investigation of MCL1-targeted strategies, either as monotherapy in *MCL1*-amplified disease or combined with AKT pathway inhibition in PTEN loss/PI3K-driven tumors.

Technology: To measure the correlation between *MCL1* copy number and expression, immunohistochemistry was performed on 30 mCRPC biopsies with matched RNA-seq data. HALO AI was used to differentiate cancer cells from stroma, followed by cellular and nuclear segmentation and quantification of cytoplasmic MCL1 optical density using the HALO Multiplex IHC module. The impact of MCL1 and/or AKT inhibition on interactions driving the intrinsic apoptotic pathway was investigated using proximity ligation assays of BAD-BCLXL and BIM-MCL1 in a prostate cancer cell model. Protein interactions (fluorescent dots) were quantified using the HALO FISH module. The feature image depicts representative images from PLA and quantification of dots under various inhibitory and control conditions.

Tedeschi A, Schischlik F, Rocchetti F et *al*. Pan-KRAS inhibitors BI-2493 and BI-2865 display potent antitumor activity in tumors with KRAS wild-type allele amplification. *Mol Cancer Ther* **24(4)**: 550-562 (2025). DOI: **10.1158/1535-7163.MCT-24-0386**.

Thatikonda V, Lyu H, Jurado S et *al*. Co-targeting SOS1 enhances the antitumor effects of $KRAS^{G12C}$ inhibitors by addressing intrinsic and acquired resistance. *Nat Cancer* **5**: 1352-1370 (2024). DOI: **10.1038/s43018-024-00800-6**.

Yoshinari T, Nagashima T, Ishioka H et *al*. Discovery of KRAS(G12D) selective degrader ASP3082. *Commun Chem* **8**: 254 (2025). DOI: **10.1038/s42004-025-01662-4**.

Yuan Y, Lin Q, Feng HY et *al*. A multistage drug delivery approach for colorectal primary tumors and lymph node metastases. *Nat Commun* **16**: 1439 (2025). DOI: **10.1038/s41467-025-56768-z.**

Zimmerman B, Dakin LA, Fortier A et *al*. Small molecule APOL1 inhibitors as a precision medicine approach for APOL1-mediated kidney disease. *Nat Commun* **16**: 167 (2025). DOI: **10.1038/s41467-024-55408-2**.

Preclinical Testing

Ma Y, Cai H, Smith J et *al*. Evaluation of antisense oligonucleotide therapy targeting Hsd17b13 in a fibrosis mice model. *J Lipid Res* **65(3)**: 100514 (2024). DOI: **10.1016/j.jlr.2024.100514**.

Müller M, May S, Hall H et *al*. Human-correlated genetic models identify precision therapy for liver cancer. *Nature* **639**; 754-764 (2025). DOI: **10.1038/s41586-025-08585-z**.

Clinical Testing

Champiat S, Garralda E, Galvao V et *al*. Nanrilkefusp alfa (SOT101), an IL-15 receptor βγ superagonist, as a single agent or with anti-PD-1 in patients with advanced cancers. *Cell Rep Med* **6(2)**: 18 (2025). DOI: **10.1016/j.xcrm.2025.101967**.

Eerkens AL, Brummel K, Vledder A et *al*. Neoadjuvant immune checkpoint blockade in women with mismatch repair deficient endometrial cancer: a phase I study. *Nat Commun* **15**: 7695 (2024). DOI: **10.1038/s41467-024-52098-8**.

Hong DS, Van Tine BA, Biswas S et *al*. Autologous T cell therapy for MAGE-A4+ solid cancers in HLA-A*02+ patients: a phase 1 trial. *Nat Med* **29**: 104-114 (2023). DOI: **10.1038/s41591-022-02128-z**.

Huang SW, Jiang W, Xu S et *al*. Systemic longitudinal immune profiling identifies proliferating Treg cells as predictors of immunotherapy benefit: biomarker analysis from the phase 3 CONTINUUM and DIPPER trials. *Sig Transduct Target Ther* **9**: 285 (2024). DOI: **10.1038/s41392-024-01988-w**.

Huyghe N, Benidovskaya E, Masoodi T et *al*. Impact of the tumor immune contexture in microsatellite-stable metastatic colorectal cancer treated with avelumab, cetuximab, and irinotecan. *Cell Rep Med* **6(7)**: 15 (2025). DOI: **10.1016/j.xcrm.2025.102201**.

Nederlof I, Isaeva OI, de Graaf M et *al*. Neoadjuvant nivolumab or nivolumab plus ipilimumab in early-stage triple-negative breast cancer: a phase 2 adaptive trial. *Nat Med* **30**: 3223-3235 (2024). DOI: **10.1038/s41591-024-03249-3**.

Ressler JM, Plaschka M, Silmbrod R et *al*. Efficacy and tolerability of neoadjuvant therapy with Talimogene laherparepvec in cutaneous basal cell carcinoma: a phase II trial (NeoBCC trial). *Nat Cancer* **6**: 51-66 (2025). DOI: **10.1038/s43018-024-00879-x**.

Tsimberidou AM, Vining DJ, Arora SP et *al*. Phase I trial of TTI-101, a first-in-class oral inhibitor of STAT3, in patients with advanced solid tumors. *Clin Cancer Res* **31(6)**: 965-974 (2025). DOI: 10.1158/1078-0432.CCR-24-2920.

Verschoor YL, van de Haar J, van den Berg JG et *al*. Neoadjuvant atezolizumab plus chemotherapy in gastric and gastroesophageal junction adenocarcinoma: the phase 2 PANDA trial. *Nat Med* **30**: 519-530 (2024). DOI: 10.1038/s41591-023-02758-x.

Nivolumab for mismatch-repair-deficient or hypermutated gynecologic cancers: a phase 2 trial with biomarker analyses

Authors: Friedman CF, Manning-Geist BL, Zhou Q, Soumerai T, Holland A, Da Cruz Paula A, Green H, Ozsoy MA, Iasonos A, Hollmann T, Leitao Jr. MM, Mueller JJ, Makker V, Tew WP, O'Cearbhaill RE, Liu YL, Rubinstein MM, Troso-Sandoval T, Lichtman SM, Schram A, Kyi C, Grisham RN, Andrieu PC, Wherry EJ, Aghajanian C, Weigelt B, Hensley ML, Zamarin D

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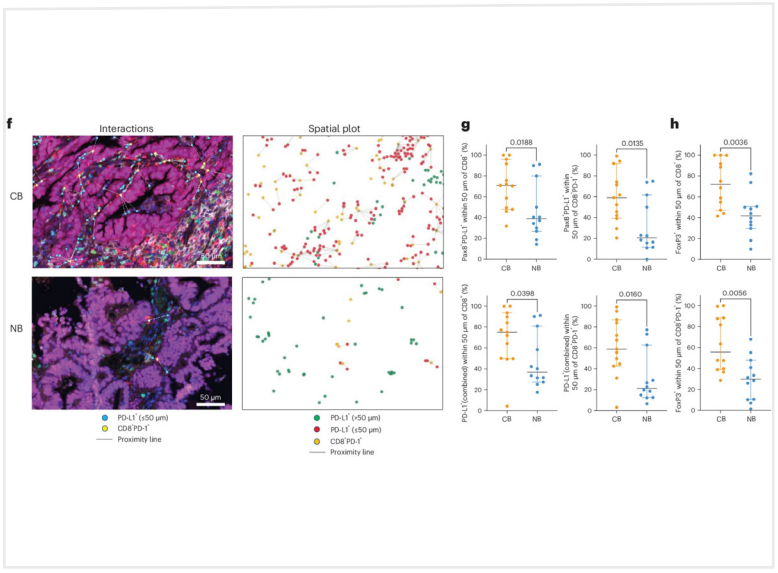

Science: Endometrial and ovarian cancers cause substantial mortality, and patients with advanced or recurrent disease experience limited benefit from standard chemotherapy or hormone therapy. Around 30% of endometrial cancers are classified as microsatellite instability (MSI) or DNA mismatch repair deficient (dMMR), characteristics that are associated with high mutational burden as well as durable response to PD-1/PD-L1 inhibition. In this phase 2 trial, Claire Friedman and coauthors evaluated nivolumab, a PD-1 antibody, in patients with advanced or recurrent dMMR/MSI-high gynecologic cancers to define predictors of response to PD-1 inhibition. Through clinical endpoints and exploratory analyses, the trial demonstrated the clinical activity of nivolumab and revealed tumor microenvironment features, specifically CD8+PD-1+ or CD8+PD-1+TOX+ subsets and their interaction with PD-L1+ cells, correlated with durable benefit. These results support further study of nivolumab for treatment of advanced or recurrent dMMR/MSI-high gynecologic cancers as well as these potential biomarkers of response to PD-1 blockade.

Technology: Exploratory analysis of the TME was performed using multiplex immunofluorescence of pre-treatment archival tissue from a subset of the trial patients. For each sample, cell segmentation and phenotyping was performed using the HALO Highplex FL module, followed by proximity analysis using the Spatial Analysis module. The feature image shows markup images, spatial plots, and quantification of proximity analyses of samples from patients who experienced clinical benefit (CB) and those who had no clinical benefit (NB).

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