# Discoidin Domain Receptor 1 (DDR1) expression is associated with degree of immune exclusion across epithelial tumors

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**Background**
Discoidin domain receptor 1 (DDR1) is highly expressed in epithelial cancers and has been implicated in tumor growth, invasion, and lack of response to therapy. DDR1 contributes to immune exclusion by promoting tumor collagen alignment in *in vivo* models. However, it is unclear how DDR1 expression impacts immune cell infiltration in human tumors. A first-in-human trial of PRTH-101, a DDR1-targeted therapeutic antibody, is underway. Establishing a correlation between DDR1 expression and immune infiltration in the tumor microenvironment (TME) will shed light on the role of DDR1 in the TME and inform indication and patient selection strategies for DDR1-targeted therapies.

**Methods**
Adjacent formalin fixed paraffin embedded slides from colorectal (CRC), non-small cell lung (NSCLC), ovarian (OC), pancreatic (PDAC), and triple-negative breast cancers (TNBC) were stained by H&E and a multiplex immunofluorescence (mIF) panel containing DDR1 and immune cell markers CD8 and CD45. Tumor-stromal segmentation and cell identification was done from H&E using AI-powered models developed by PathAI (PathExplore™) or from mIF by image analysis using QuPath. *DDR1* mRNA expression was measured by bulk RNA-sequencing, while DDR1 protein expression was measured by mIF. Immune Exclusion Scores (IESs) were calculated for each tumor based on lymphocyte density (from H&E), CD8+ T cell density (from mIF), or CD45+ cell density (from mIF). Each IES is the orthogonal distance between the coordinate of immune cell density in tumor epithelium and stroma, and the regression line representing equal density in epithelium and stroma. Correlations between lymphocyte, CD8, and CD45 IESs and DDR1 mRNA or protein expression levels were evaluated.

**Results**
Both DDR1 mRNA and protein expression levels were significantly correlated with all Immune Exclusion Scores (IESs) measured by the distribution of lymphocytes (H&E), CD8+, or CD45+ cells (mIF) in tumor epithelium and stroma (R: 0.31-0.55, adjusted p: <0.001-0.01) at a pan-cancer level. While the degree of the correlation varied between tumor indications by IES immune cell type, pancreatic cancer exhibited the strongest correlation between the lymphocyte-based IES and DDR1 mRNA and protein expression (R: 0.48-0.54, adjusted p:0.04-0.07). *DDR1* mRNA was also moderately correlated with lymphocyte IES in NSCLC and TNBC (R: 0.37-0.48, adjusted p: 0.12-0.14).

**Conclusions**
We developed a continuous scoring method to quantify the degree of immune exclusion in tumors based on the spatial distributions of lymphocytes, CD8+ T cells, and CD45+ immune cells from H&E and mIF images. DDR1 mRNA and protein expression are correlated with immune exclusion at both the pan-cancer and specific indication level. This adds additional

insight into the role of DDR1 in human cancers and may be useful in selecting indications and stratifying patients for DDR1-targeted therapies.