High DDR1 mRNA and protein expression across human tumor types correlate with epithelial composition of the tumor microenvironment

Laura A. Dillon[1], Xinwei Sher[1], Fredrick D. Gootkind[1], Thomas Schürpf[1], Jordan D. Berlin[2], G. Travis Clifton[1]

[1]Incendia Therapeutics, Boston, MA, USA; [2]Vanderbilt University Medical Center, Nashville, TN, USA

INCENDIA THERAPEUTICS

2309P

Background

- Discoidin Domain Receptor 1 (DDR1) is a collagen-binding receptor tyrosine kinase expressed by tumor cells. It has been implicated in cancer invasion, progression, and immune exclusion.
- A first-in-human trial of PRTH-101, an α-DDR1 monoclonal Ab, is underway.
- The relationship between *DDR1* mRNA, DDR1 protein, and the epithelial composition of the tumor microenvironment across tumor types has not been established and has the potential to influence indication and patient selection for DDR1-targeted therapies.

Methods

- Human tumor samples (n= 93) from a range of epithelial and mesenchymal tumor types were evaluated by bulk RNA-sequencing and multiplex immunofluorescence microscopy (mIF) of DDR1 and pan-cytokeratin (CK) using the Ultivue platform (**Figure 1**).

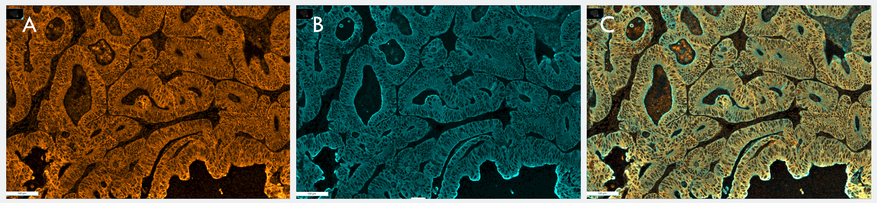

Figure 1. *Representative mIF staining on a CRC tumor sample. A. DDR1 in orange. B. CK in cyan. C. Overlay of DDR1 (orange) and CK (cyan).*

- DDR1+ cell density was determined for each sample by image analysis.
- For epithelial tumors, tumor-stromal segmentation was performed by image analysis with tumor epithelium defined by CK positivity in the pathologist-annotated tumor bed. Percentage of epithelium was calculated per sample.
- Correlative analyses were done to relate *DDR1* mRNA expression to DDR1+ cell density (all tumor types), proportion of tumor cells expressing DDR1 (epithelial tumors only), and percentage of tumor epithelium (epithelial tumors only).

Disclosures

- Drs. Dillon, Sher, Schürpf, and Clifton and Mr. Gootkind are employees of Incendia Therapeutics.
- Dr. Berlin is on the advisory boards of Mirati, Insmed, Oxford Biotherapeutics, Biosapien, EMD Serono, Ispen, Merck Sharpe & Dohme, Merus, BMS, and Bexion and DSMBs for AstraZeneca, Novocure, BI, and I-SPY. He receives research support from Abbvie, Astellas, Atreca, Bayer, Dragonfly, I-Mab, Lilly, Incyte, EMD Serono, Pfizer, BMS, Transcenta Tx, Tyra, Totus, Sumitomo Dainippon Pharma Oncology, 23 and me, Incendia Tx, and Hibercell.

MADRID 2023 ESMO congress

Contact: laura.dillon@incendiatx.com

Results

- DDR1+ cell density was significantly higher in tumors of epithelial origin than in tumors of mesenchymal origin (median 2803 vs 9 cells/mm^2) (**Figure 2, Table 1**).
- Moderate correlation was observed between *DDR1* mRNA expression and DDR1+ cell density across all tumor types (R=0.48 p<0.0001) (**Figure 3, Table 1**).
- Within the epithelial tumors, a high proportion of tumor cells expressed DDR1 (median of 0.76) (**Figure 4, Table 1**).

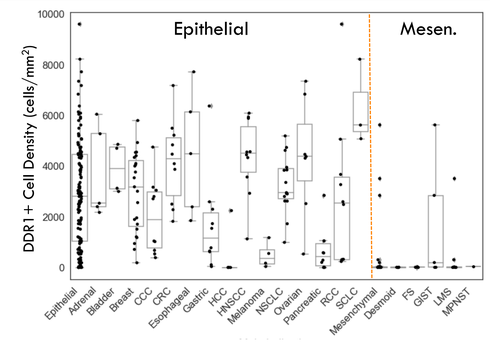

Figure 2. *Density of DDR1+ cells within the tumor bed by tumor type.*

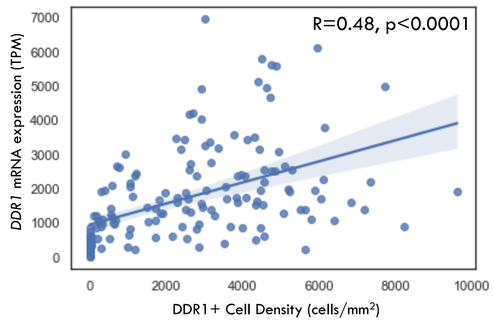

Figure 3. *Relationship between DDR1 mRNA expression and DDR1+ cell density across all tumor types.*

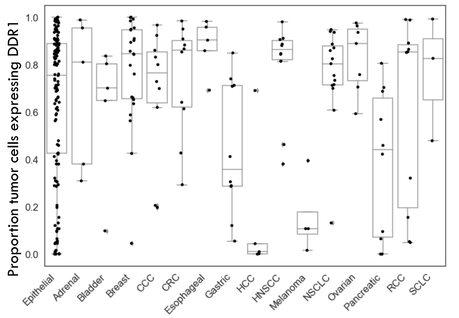

Figure 4. *Proportion of tumor (CK+) cells within the tumor bed that are DDR1+ by tumor type (epithelial tumors only).*

- In epithelial tumors, both *DDR1* mRNA and protein were correlated with the percentage of epithelium (R=0.37 and 0.56, respectively; both p<0.0001), with significant variance between tumor types (**Figure 5, Table 1**).

Table 1.

Tumor type	DDR1+ cell density		Proportion tumor cells expressing DDR1		Percentage of Epithelium		
	Median (cells/mm^2)	Corr. with mRNA (R)	Median (Prop.)	Corr. with mRNA (R)	Median (%)	Corr. with mRNA (R)	Corr. with Protein (R)
All tumors	**2521**	**0.48**	**0.76**	**0.46**	**55**	**0.37**	**0.56**
Epithelial	**2803**	**0.38**	**0.76**	**0.46**	**55**	**0.37**	**0.56**
Adrenal	2536	0.86	0.81	0.68	67	-0.06	0.01
Bladder	3915	-0.04	0.75	0.85	72	0.03	0.36
Breast	3183	0.19	0.84	0.28	43	0.29	0.33
CCC	1877	0.45	0.76	0.19	41	0.56	0.77
CRC	4284	-0.17	0.86	-0.41	52	0.36	-0.03
Esophageal	4493	0.69	0.90	0.98	56	0.52	0.50
Gastric	1161	0.16	0.36	0.29	49	0.22	0.49
HCC	1	1.00	0.01	1.00	4	0.84	0.82
HNSCC	4502	0.18	0.86	0.59	63	-0.03	0.11
Melanoma	361	0.99	0.11	0.98	56	0.34	0.42
NSCLC	2954	0.62	0.80	0.57	65	0.30	0.48
Ovarian	4378	0.44	0.89	0.27	60	0.72	0.72
Pancreatic	430	0.14	0.44	0.15	18	0.52	0.42
RCC	2540	0.25	0.85	0.52	63	0.08	0.49
SCLC	5621	-0.82	0.83	-0.08	81	-0.99	0.72
Mesen.	**9**	**-0.05**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**
Desmoid	2	-0.19	N/A	N/A	N/A	N/A	N/A
FS	10	0.72	N/A	N/A	N/A	N/A	N/A
GIST	195	-0.48	N/A	N/A	N/A	N/A	N/A
LMS	9	0.00	N/A	N/A	N/A	N/A	N/A
MPNST	46	0.00	N/A	N/A	N/A	N/A	N/A

CCC: Cholangiocarcinoma; CRC: Colorectal Cancer; HCC: Hepatocellular Carcinoma; HNSCC: Head & Neck Squamous Cell Carcinoma; NSCLC: Non-Small Cell Lung Cancer; RCC: Renal Cell Carcinoma; SCLC: Small Cell Lung Cancer; Mesen: Mesenchymal; FS: Fibrosarcoma; GIST: Gastrointestinal Stromal Tumor; LMS: Leiomyosarcoma; MPNST: Malignant Peripheral Nerve Sheath Tumor

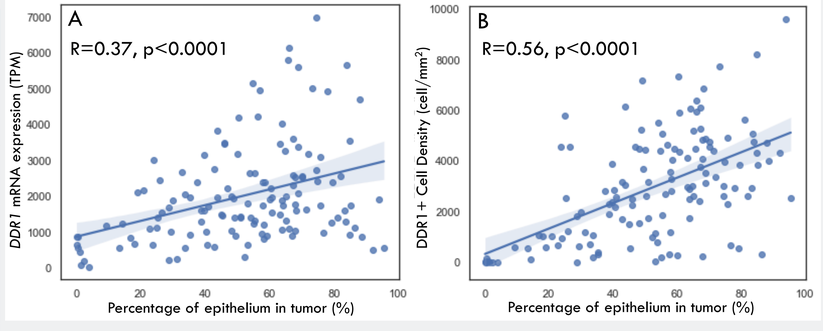

Figure 5. *Relationship between percentage of epithelium and DDR1 expression as assessed by mRNA (panel A) or protein (panel B) (epithelial tumors only).*

Conclusions

- DDR1 is expressed in a high proportion of tumor cells across a range of epithelial tumor types, suggesting potentially broad application of DDR1-targeted therapies.
- As expected, since DDR1 is primarily expressed by tumor cells, both mRNA and protein expression levels are correlated with the proportion of tumor epithelium.
- Correlation between DDR1 mRNA and protein appears to be tumor type specific, possibly due to differences in DDR1 protein density in DDR1+ cells and/or contamination of bulk RNA with adjacent tissue.
- Assessment of DDR1+ cell density may be more accurate for patient selection in certain tumor types.