Supplemental Table S1: A list of cell types expressing MIF and/or DDT as well as their upstream signals and stimuli.

Stimuli	Cell Type	Effect on MIF and/or DDT
Hypoxia, LPS, Reactive Oxygen Species, IFN-Gamma, TNF-alpha, Glucocorticoids[1,2]	Immune Cells (Macrophages; Monocytes, Neutrophils, Eosinophils, Lymphocytes)	Increased MIF and DDT expression and secretion
LPS, CNS Insult (Stroke, Spinal Cord injury, Traumatic Brain Injury)[3-5]	Central and Peripheral Neuronal Cells (Astrocytes, microglia, neuronal cell bodies, oligodendrocytes, Schwann cells)	Increased MIF and DDT expression and secretion
Glucose[6]	Pancreatic islet beta cells	Increased MIF secretion
TNF-alpha[7]	Insulin-targeted cells (myocytes, cardiomyocytes, adipocytes)	Increased MIF secretion
LPS[8-10]	Hepatocytes	Increased MIF and DDT expression and secretion
Direct Injury[11]	Corneal tissues, Aqueous humor	Increased MIF expression and secretion
Lipopolysaccharide (LPS), UVB[12-15]	Fibroblasts, keratinocytes, Basal layer of epidermis	Increased MIF and DDT expression and secretion
TNF-alpha, LPS[16,17]	Endothelial Cells, Epithelial Cells	Increased MIF Secretion

Supplemental Table S2: A list of MIF and DDT inhibition strategies evaluated in murine cancer models .

Inhibition Strategy	Murine Model	Outcome
Anti-MIF antibody	Prostate Cancer in MF-1 nude mice[18]	- Reduction in tumor growth rate
	B cell Lymphoma in C3H/HeN mice[19]	- Reduction in tumor vascularization
	Esophageal squamous cell carcinoma in BALB/c nude mice[20]	- Reduction in tumor growth rate

		- Reduction in tumor vascularization
	Colorectal Carcinoma in BALB/c mice[21]	- Reduction in tumor mass and hepatic metastases
Anti-DDT antibody	Melanoma in C57Bl/6 mice[1]	- Reduction in tumor growth rate
4-IPP (MIF and DDT inhibitor)	Osteosarcoma in nude mice[22]	- Reduction in tumor burden and metastases - Suppression of osteoclast formation, and induction of osteoblast differentiation
	Bladder Cancer chemically induced by BBN in MIF -/- C57Bl/6 mice[23]	- Reduction in tumor burden, bladder weights, and tumor stages
	Neuroblastoma in athymic mice[24]	- Decreased tumor growth and improved overall survival
4-IPP + anti-CTLA-4, 4-IPP + anti-CTLA-4 + anti-PD-L1	Melanoma in C57Bl/6 mice[25]	- Reduction of lung metastases in combination treatments compared to anti-CTLA4 alone - Increased M1 and decreased M2 macrophages in the TME - Increase in CD3+, CD4+, and CD8+ tumor infiltrating lymphocytes in the TME
CPSI-1306 (Chemical Based MIF inhibitor)	Bladder Cancer chemically induced by BBN in C57Bl/6 mice[26]	- Reduction in bladder weight, tumor mass, tumor growth rate, and tumor vasculature
	Triple Negative Breast Cancer in NSG mice[27]	- Reduction in tumor volume and weight - Reduction in proliferation and angiogenic markers
ISO-1 (MIF ~~and DDT~~ inhibitor)	Colorectal Carcinoma in BALB/c mice[21]	- Reduction in tumor growth, weight, vasculature, and hepatic metastases
SCD-19 (MIF inhibitor)	Lung Cancer in C57BL/6 mice[28]	- Reduction in tumor volume
MIF Knockdown	Acute Myeloid Leukemia in lentiviral mediated MIF KD in NSG mice[29]	- Improved overall survival

	Colorectal Carcinoma in siRNA-mediated MIF KD in BALB/c mice[30]	- Reduction in tumor growth - Upregulation of apoptotic markers in tissue - Reduction in hepatic metastases
	shRNA mediated MIF KD of Triple Negative Breast Cancer in NSG mice[27]	- Reduction in tumor volume, weight and pulmonary metastases
	shRNA mediated MIF KD of Breast Cancer cells in BALB/c mice[31]	Increase in tumor-infiltrating CD8+ T cells
MIF and DDT Knockdown	shRNA mediated MIF, DDT, and MIF/DDT KD of Renal Cell Carcinoma transplanted in athymic BALB/c nude mice[32]	- Reduction in tumor vasculature
MIF Knockout	Bladder Cancer chemically induced by BBN in C57Bl/6 mice[33]	- Decrease in tumor vascularization
	Pancreatic Cancer in C57Bl/6 mice[34]	- Reduction in tumor size, weight, and vascularization - Reduction in Tregs, IL-10, and TGF-beta1 in the TME
	MIF KO in MMTV-PyMT (Spontaneous breast cancer) transgenic mice[31]	- Reduction in tumor growth rate and tumor mass
	Pancreatic Cancer in LSL-$Kras^{G12D}$;LSL-$Trp53^{R172H/+}$;Pdx-1-Cre (MKPC) generated mice[35]	- Improvement in overall survival - Reduction in metastasis

BBN: N-butyl-N-(4-hydroxybutyl)-nitrosamine (BBN)

Supplemental Table S3: A list of anti-cancer therapeutics targeting the MIF/DDT/CD74 axis evaluated in Clinical Trials.

Clinical Trials for use in Cancer

Inhibitor	Mechanism	Patient Enrollment	Findings	Study
Imalumab (BAX69)	Recombinant anti-oxMIF antibody	Advanced solid tumors (metastatic colorectal adenocarcinoma, non-small cell lung or ovarian cancer)	- 13/39 (33%) of patients exhibited stable disease - Terminated early due to poor study design, and concerns with safety and efficacy	Phase I NCT01765790

Ibudilast	PDGE2 and allosteric MIF inhibitor	Newly diagnosed and recurrent glioblastoma	- Results not yet published	Phase I/II NCT03782415
Milatuzumab	Anti-CD74 antibody	Relapsed or Refractory Multiple Myeloma	- 5/19 (26%) of patients had stable disease - Moderate reduction of serum B cell levels (median decrease 34%) - No evidence of dose-limiting toxicity - No evidence of rapid drug clearance from the serum	Phase I NCT00421525
		Relapsed or Refractory Chronic Lymphocytic Leukemia	- Overall modest response - Reduction in spleen size, BCL2 levels in malignant cells, and WBC counts	Phase I/II NCT00868478

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