Supplementary information

Clinical and therapeutic relevance of cancer-associated fibroblasts

Supplementary Table 1 │ Widely used biomarkers of CAFs and their clinical relevance

Gene	Marker	CAF subset	Expression in other cell types	Cellular location	Prognostic value based on HPA-TCGA[a]	
					Unfavourable	**Favourable**
ACTA2	αSMA[1-9]	Peritumoural myofibroblasts	Pericytes, smooth muscle cells and breast myoepithelial cells	Intracellular	Renal cancer	–
FAP	FAP[8-15]	A subset of myofibroblasts	Pericytes, smooth muscle cells, myocytes and glandular cells	Membrane and secreted	Head and neck cancer	–
S100A4	S100A4 (FSP1)[9,16-18]	Interstitial CAFs (apCAFs and some iCAFs)	Myeloid cells, some (EMT) cancer cells, haematopoietic cells, pneumocytes and urothelial cells	Membrane	Renal cancer	Head and neck cancer
TAGLN	Transgelin[5-7,19]	Myofibroblasts	Pericytes, smooth muscle cells and breast myoepithelial cells	Intracellular	Renal cancer	–
THY1	Thy1/CD90[5,20,21]	Myofibroblasts	T cells and neurons	Membrane and nucleoplasm	Renal cancer and glioma	–
LRRC15	LRRC15[10,22,23]	A subset of myofibroblasts	Glandular cells, smooth muscle cells and myocytes	Membrane	–	–
TNC	Tenascin C[5,24-27]	Myofibroblasts	Pericytes and cancer cells	Secreted	–	–
PDGFRB	PDGFRβ[5,9,28,29]	Myofibroblasts and some αSMA-low CAFs	Pericytes and neurons	Membrane	Renal cancer and urothelial cancer	–
PDGFRA	PDGFRα[5,6,28-33]	αSMA-low CAFs and some αSMA⁺ CAFs	Breast myoepithelial cells	Membrane	Renal cancer	Head and neck cancer
CAV1	Caveolin-1[34-36]	αSMA-low CAFs	Endothelial cells, some cancer cells, pericytes, pneumocytes, squamous epithelial cells, smooth muscle cells and myocytes	Membrane	Renal cancer and lung cancer	–
CLEC3B	CLEC3B[5,37-39]	αSMA-low CAFs	Renal tubule epithelial cells	Secreted	–	Pancreatic cancer, head and neck cancer and liver cancer
VIM	Vimentin[40,41]	Pan-CAF biomarker	Some (EMT) cancer cells, endothelial cells, pneumocytes, glandular cells, adipocytes, and haematopoietic and/or lymphoid cells	Intracellular	Renal cancer	Endometrial cancer
PDPN	Podoplanin[5,8,17,42,43]	Pan-CAF biomarker	Lymphatic endothelial cells, some myeloid cells, pneumocytes and breast myoepithelial cells	Membrane	–	–
DES	Desmin[44,45]	Pan-CAF biomarker, especially myofibroblasts	Pericytes, smooth muscle cells and myocytes	Intracellular	Renal cancer	–
DCN	Decorin[46]	Pan-CAF biomarker	Some epithelial and cancer cells and adipocytes	Secreted	Renal cancer	–
DDR2	DDR2[47,48]	Pan-CAF biomarker	Pericytes, smooth muscle cells and some cancer cells	Membrane	Renal cancer	–
LOX	LOX[49]	Pan-CAF biomarker	Some cancer cells	Secreted	Liver cancer, renal cancer, urothelial cancer	–

LOXL1	LOXL1	Pan-CAF biomarker	Pericytes and cancer cells	Secreted	Glioma	–
LOXL2	LOXL2[50]	Pan-CAF biomarker	Pericytes and cancer cells	Secreted	Lung cancer, renal cancer, cervical cancer, glioma and pancreatic cancer	–
MFAP5	MFAP5[7,51,52]	Pan-CAF biomarker	Smooth muscle cells	Secreted	Stomach cancer and urothelial cancer	–
MMP2	MMP2[7]	Pan-CAF biomarker	Some cancer cells and endothelial cells	Secreted	–	–
POSTN	Periostin[53]	Pan-CAF biomarker	Pericytes, neurons, glial cells, respiratory epithelial cells and glandular cells	Secreted and nucleoplasm	Renal cancer, lung cancer, stomach cancer	–
COL3A1	COL3A1[5]	Pan-CAF biomarker	Pericytes	Secreted	Renal cancer	–
SPARC	SPARC (osteonectin)[54]	Pan-CAF biomarker	Endothelial cells, cancer cells, haematopoietic cells and glandular cells	Secreted	Renal cancer	–
FGFR1	FGFR1	Pan-CAF biomarker	Endothelial cells, cancer cells, glandular cells, smooth muscle cells and myocytes	Membrane	–	–

apCAFs, antigen-presenting cancer-associated fibroblasts; cancer-associated fibroblast; CAF, cancer-associated fibroblast; EMT, epithelial-to-mesenchymal transition; iCAFs, inflammatory cancer-associated fibroblasts. [a]The prognostic values of indicated CAF biomarkers are based on the analyses by the Human Protein Atlas (HPA) based on the datasets from The Cancer Genome Atlas (TCGA) programme. A prognostic gene was defined with a log rank $P < 0.001$ in maximally separated Kaplan–Meier analysis (based on the RNA-sequencing fragments per kilobase million (FPKM) value of a given gene). Patients were classified into two expression groups and analyzed for the correlation between gene-expression level and survival.

Supplementary Table 2 │ Therapeutic strategies targeting CAFs in cancers and related clinical trials

Agent	Target	Therapeutic category	Mechanism of action	Development status	Clinical trials
PEGPH20	Hyaluronic acid	PEGylated enzyme	Enzymatic degradation of excessive stromal hyaluronan[55]	Phase III trials halted in Nov 2019	NCT02241187 and NCT03634332
Pamrevlumab (FG-3019)	CTGF	Human monoclonal antibody	Antagonizes the action of CTGF[56]	Phase III trials	NCT01181245, NCT02210559 and NCT03941093
Simtuzumab (GS-6624)	LOXL2	Humanized monoclonal antibody	Blocks fibroblast recruitment and collagen cross-linking functions of LOXL2[57]	Phase II trial for pancreatic cancer completed in 2014. Phase II trials for IPF and colorectal cancer terminated.	NCT01472198, NCT01769196, NCT01479465 and NCT02466516
Olaratumab	PDGFRα	Human monoclonal antibody	Antagonizes PDGFRα signaling[58]	Phase I and II trials	NCT03086369, NCT03994627, NCT03802071 and NCT03985722
Cabiralizumab (BMS-986227, FPA008)	CSF1R	Humanized monoclonal antibody	Inhibits CSF1R signalling; functional suppression of monocytes and macrophages[59]	Phase I and II trials	NCT03599362, NCT03336216, NCT04050462, NCT03502330 and NCT04331067
Istiratumab (MM-141)	IGF1R and HER3 (ErbB3)	Human tetravalent bispecific antibody	Blockade of the IGF-1R and HER3 (ErbB3) pathways in pancreatic cancer cells[60]	Phase I trial terminated	NCT02538627
Xentuzumab (BI 836845) or MEDI-573	IGF1 and IGF2	Humanized monoclonal antibody	Inhibits IGF1-stimulated and IGF2-stimulated activation of IGFRs[61]	Phase I and II trials	NCT02191891, NCT02204072, NCT02123823, NCT01446159 and NCT00816361
CAR T cell product	FAP	CAR T cells targeting FAP	Depletion of FAP-expressing CAFs and immune modulation[62-64]	Preclinical studies	NA
^{131}I-sibrotuzumab	FAP	Radioactive isotope-conjugated antibody	131I-labeled FAP-targeting antibody uptake in FAP-positive tumors[65]	Phase I trial for lung cancer terminated	NCT02209727
RO6874281 (FAP-IL2v, RG7461)	FAP	Antibody moiety linked to cytokine (immunocytokine)	Binding to FAP and targeting IL-2 (IL-2v) to FAP-expressing cells/tumours[66]	Phase I–II for multiple cancer types	NCT03875079, NCT02627274, NCT03386721 and NCT03193190
ATRA	Vitamin A metabolism	Metabolite	CAF normalization and restrained tumour growth[67,68]	Phase I–II trials for multiple cancer types	NCT03307148, NCT04113863, NCT04241276, NCT03999684, NCT03200847, NCT03572387 and NCT04433169
Paricalcitol (vitamin D analogue)	Vitamin D receptor	Small-molecule agonist	CAF normalization and improved chemotherapeutic efficacy[69]	Phase I–II for multiple cancer types	NCT03883919, NCT03415854, NCT03520790, NCT04054362, NCT02930902, NCT03519308, NCT02754726 and NCT03138720

Fresolimumab (GC1008)	TGFβ	Human monoclonal antibody	Blocks TGFβ signalling[70]	Phase I/II trial for lung cancer	NCT02581787
Galunisertib (LY2157299)	TGFβ receptor I kinase	Small-molecule inhibitor	Blocking TGFβ signaling and CAF activation[71]	Phase I–II for multiple cancer types	NCT01373164, NCT02688712, NCT02452008, NCT04031872, NCT03206177 and NCT02672475
Vismodegib (GDC-0449)	Hedgehog	Small-molecule inhibitor	Inhibition of HH–SMO signalling and tumour growth inhibition. Potential deactivation of CAFs[72]	Approved for basal-cell carcinoma (phase IV studies ongoing). Phase I–II trials for multiple cancer types.	NCT03610022, NCT02667574, NCT03052478, NCT02371967 and NCT00878163
LDE225 (Sonidegib)	Hedgehog	Small-molecule inhibitor	Inhibition of SMO and HH signalling pathway[73]	Approved for basal-cell carcinoma. Phase I for multiple cancer types	NCT04007744
Saridegib or patidegib (IPI-926)	Hedgehog	Small-molecule inhibitor	Inhibition of HH–SMO signalling, stromal depletion and facilitated drug delivery[74]	Phase II trials for basal cell carcinoma, phase III for basal cell nevus syndrome (as patidegib); phase I-II trials for multiple cancer types (as IPI-926 or saridegib)	NCT01130142, NCT04155190, NCT04308395, NCT00761696, NCT01383538 and NCT01310816
TP-0903	AXL	Small-molecule inhibitor	Inhibition of AXL on cancer cells, CAFs, and myeloid cells[75]	Phase I trial for solid tumours	NCT02729298
Plerixafor (AMD3100)	CXCR4	Small-molecule inhibitor	Blocks CXCL12(SDF1)–CXCR4 interaction and immune modulation[11]	Phase II–III trials for multiple cancer types	NCT03277209, NCT04177810, NCT04058145, NCT03746080 and NCT00103662
BL-8040	CXCR4	Small-molecule inhibitor	CXCL12-CXCR4 inhibition and immune regulation[76]	Phase II–III trials for multiple cancer types	NCT02826486, NCT04543071 and NCT02907099
Defactinib (VS-6063, PF-04554878)	FAK	Small-molecule inhibitor	Restrains tumour growth through FAK inhibition[77]	Phase I–II trials for multiple cancer types	NCT04201145, NCT03875820, NCT02758587, NCT03727880, NCT03287271, NCT04331041 and NCT04439331
Erdafitinib (JNJ-42756493)	FGFR1−4	Small-molecule inhibitor	Inhibits FGFRs expressed by cancer cells and antagonizing the signalling induced by FGF released from CAFs[78,79]	Approved for urothelial and bladder cancer. Phase I–III trials for multiple cancer types	NCT04083976, NCT03473743, NCT02699606, NCT02952573, NCT04172675, NCT04330248, NCT03238196, NCT03210714, NCT03390504 and NCT03999515
BGJ398, Debio-1347, AZD4547 or TAS120	FGFR1−3	Small-molecule inhibitors	Inhibit tumour growth. Induction of CAF senescence or inactivation[80]	Phase I–III trial for multiple cancer types	NCT02150967, NCT03773302, NCT04197986, NCT04228042, NCT04233567,

					NCT03344536, NCT01824901 and NCT04024436
AT13148	AGC kinases (ROCK, AKT, PKA)	ATP-competitive small-molecule iinhibitor	Inhibition of PI3K-AKT pathway signaling through AGC kinases[81]	Phase I trial for advanced-stage solid tumours	NCT01585701
Imatinib	PDGFR, BCR–ABL1 and KIT	Tyrosine kinase inhibitor	Inhibits tumour growth and angiogenesis. PDGFR inhibition in CAFs and pericytes[82]	Approved for CML, ALL and gastrointestinal stromal tumour	NA
Dasatinib	SRC and ABL1	ATP-competitive tyrosine kinase inhibitor	Inhibits cancer cells and CAFs[83]	Approved for CML and ALL	NA
PF-04136309	CCR2	Antagonist	Blocks CCL2–CCR2 signalling	Phase I/II trial for pancreatic cancer terminated	NCT02732938
Siltuximab or tocilizumab	IL-6 and IL-6R, respectively	Chimeric and humanized monoclonal antibody, respectively	Block IL-6–IL-6R signalling[84]	Approved for Castleman disease and arthritis. Phase I–II trials for multiple cancer types	NCT04191421 and NCT04375228
Danvatirsen (AZD9150)	STAT3	Antisense oligonucleotide	Inhibits STAT3 signalling[85]	Phase II trial for multiple cancer types	NCT02983578
Andecaliximab (GS-5745)	MMP9	Recombinant chimeric IgG4 monoclonal antibody	Inhibits MMP9[86]	Phase I/II/III for multiple cancer types	NCT02545504, NCT03631836, NCT01803282 and NCT02864381
S-3304	MMPs	Small-molecule inhibitor	Inhibits MMPs and ECM degradation[87]	Phase I–II trials	NCT00033566, NCT00078390 and NCT00033215
[131]I-m81C6	Tenascin	Radioactive isotope-conjugated antibody	^{131}I-labelled tenascin-targeting antibody for distribution to tumours[88]	Phase I–II trials	NCT00002752 and NCT00003478

ALL, acute lymphocytic leukaemia; ATRA, all-trans retinoic acid; CAF, cancer-associated fibroblast; CAR, chimeric antigen receptor; CML, chronic myeloid leukaemia; ECM, extracellular matrix; MMPs, matrix metalloproteinases; NA, not applicable.

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