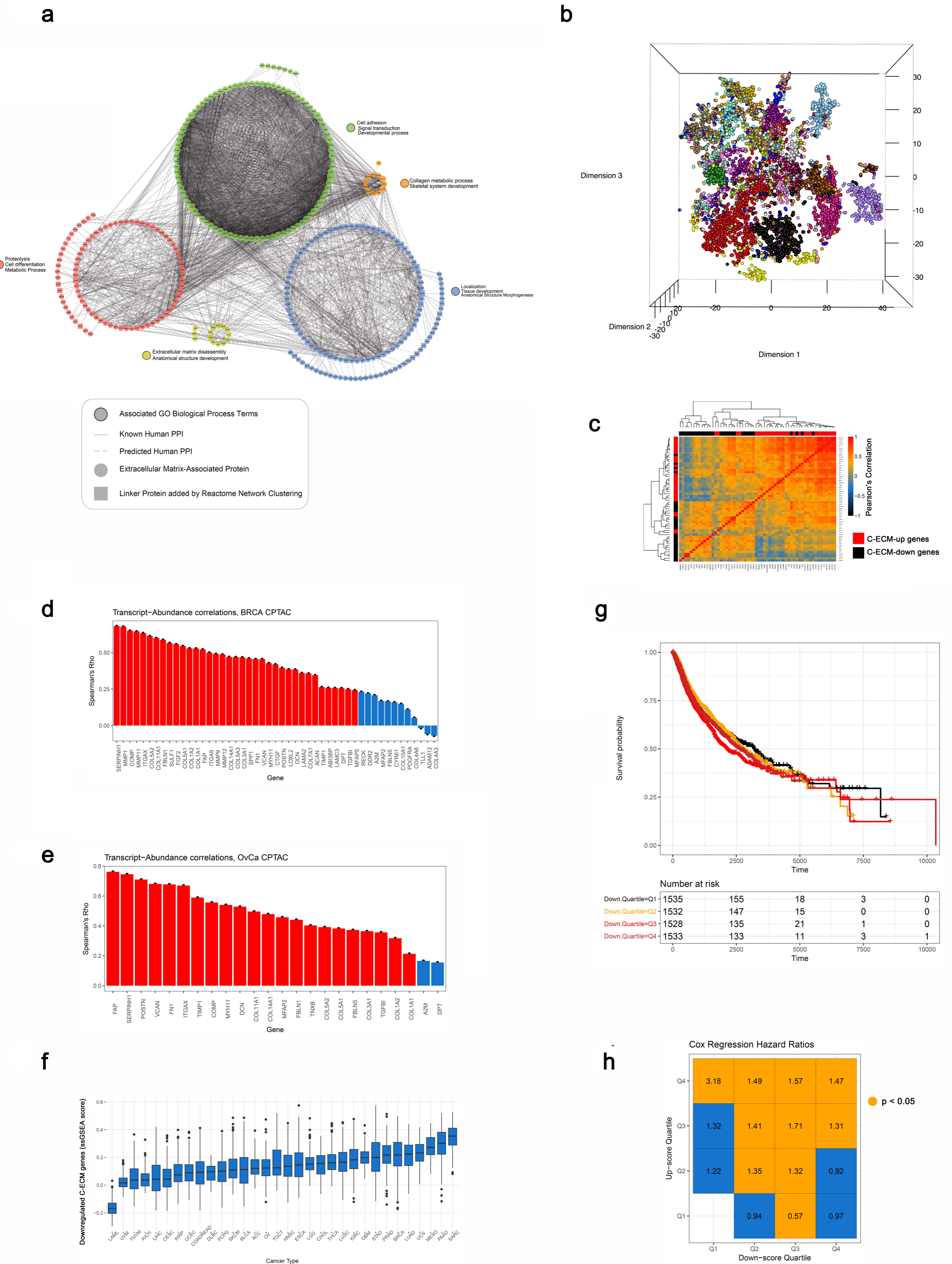
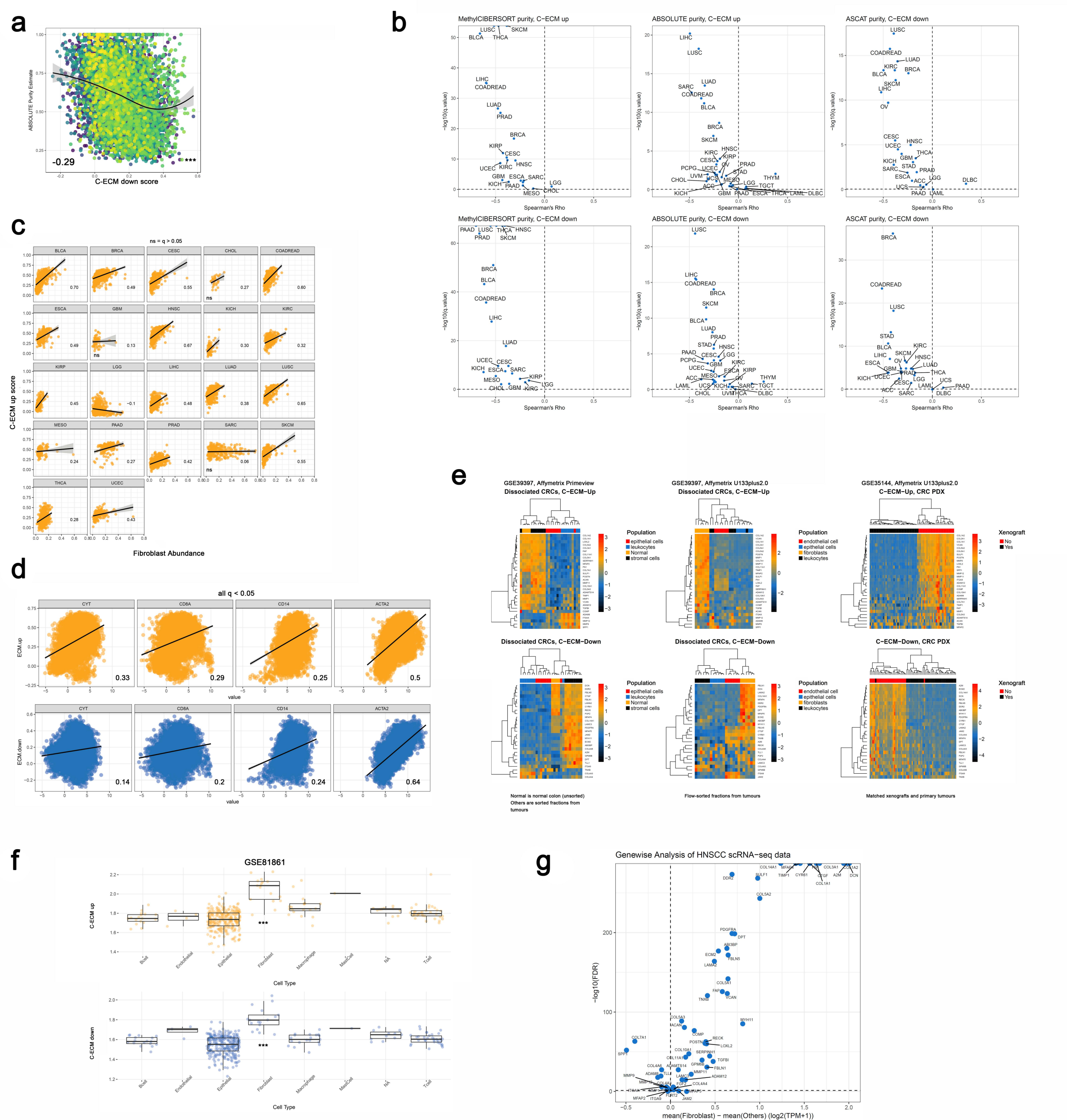


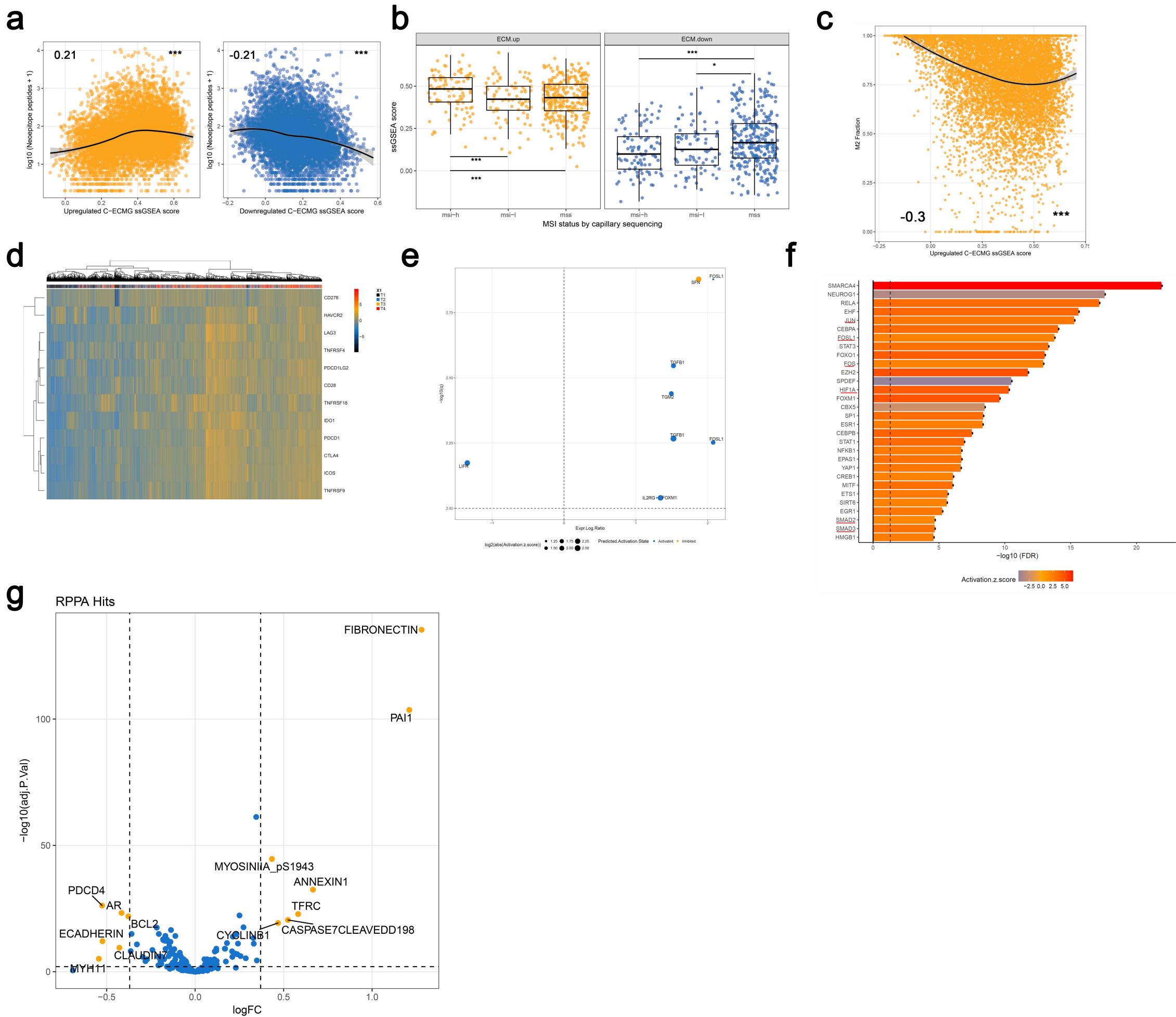
Supplementary Information for Chakravarthy et al, TGF-B associated extracellular matrix genes link cancer associated fibroblasts to immune evasion and immunotherapy failure.



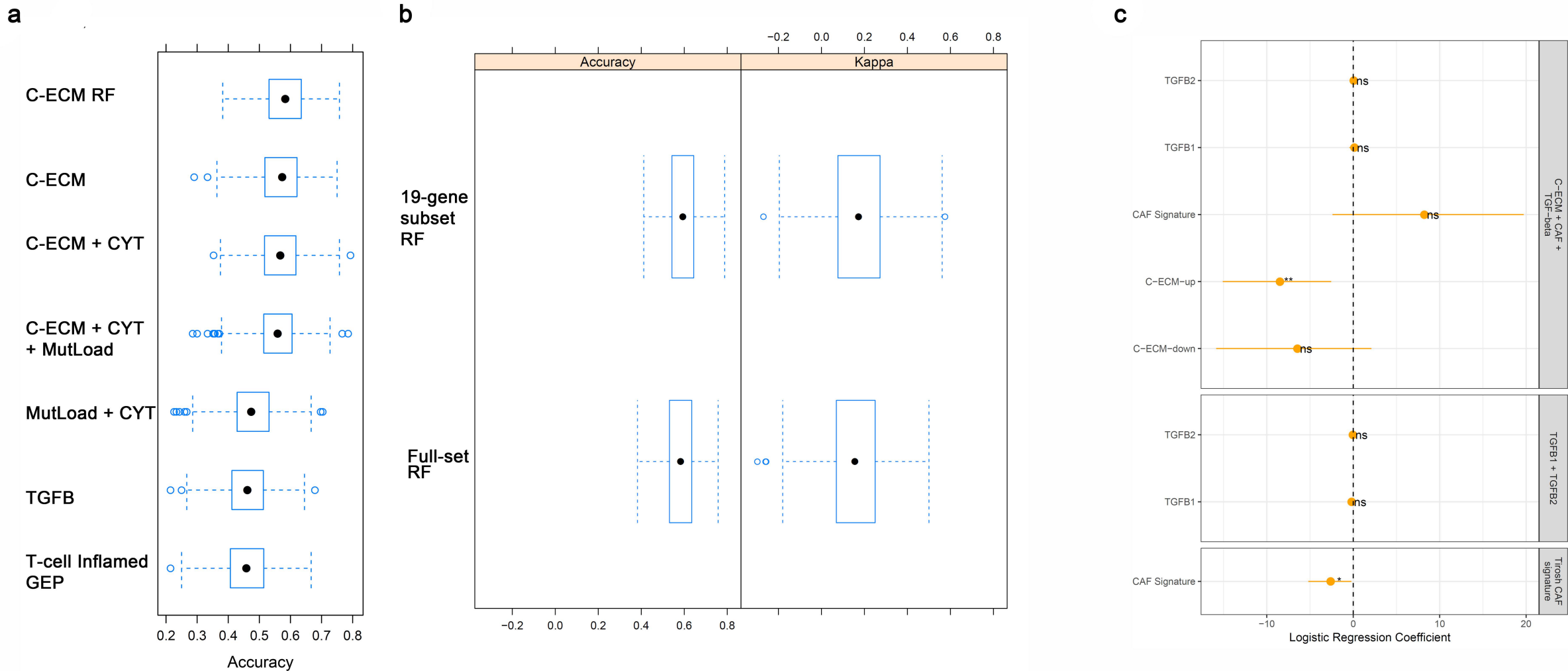
Supplementary Figure 1: a. Reactome ontology analysis for genes in the ECM gene set. b. tSNE visualisation of all ECM genes, suggesting variation across cancer types, which led us to focus on developing a pan-cancer signature after accounting for tumour type. c. Heatmap of inter-gene Pearson correlations between C-ECM genes. d. and e. Validation of C-ECM signature at the protein level in matched proteome/transcriptome data from TCGA/CPTAC for Breast Cancer. Each bar represents a gene and the y-axis represents the Spearman's Rho between transcript and peptide levels. Red indicates correlations at FDR < 0.05. f. Distribution of C-ECM-Down-scores by tumour type on a tSNE plot, g. K-M curves based on quartiles of C-ECM-down scores. h. Hazard ratios from Cox regression modelling based on combinations of up-score quartile and down-score quartile. Associations significant at $p < 0.05$ are coloured in orange. For boxplots, box-ends represent upper and lower-quartiles, centerlines represent medians, and whiskers represent 1.5x interquartile range (IQR).



Supplementary Figure 2: a. Inverse correlation between ABSOLUTE purity estimate and C-ECM-down score. b. Correlation breakdown by tumour type based on ABSOLUTE, ASCAT and MethylCIBERSORT between purity estimates and C-ECM ssGSEA scores. All plots show correlation coefficient on the x-axis and $-\log_{10}(\text{FDR})$ on the y-axis. c. Correlations between C-ECM-up score and MethylCIBERSORT fibroblast estimates across cancer types. d. Plots showing correlations between marker gene expression and C-ECM scores, confirming correlations inferred using MethylCIBERSORT. e. Heatmaps showing stromal/fibroblast association of C-ECM genes in additional colorectal cancer microarray datasets. f. Validation of CAF-origin for C-ECM scores in an independent scRNAseq dataset from colorectal cancers. g. Volcano-plot showing mean difference in $\log_2(\text{TPM}+1)$ for C-ECM genes between CAFs and other cell-types in HNSCC scRNA-seq data (Mann Whitney Test). Y axis represents $-\log_{10}(\text{FDR})$. For boxplots, box-ends represent upper and lower-quartiles, centerlines represent medians, and whiskers represent 1.5x interquartile range (IQR)



Supplementary Figure 3: a. Correlations between numbers of Class I MHC neopeptides estimated using Topiary and C-ECM scores. **b.** C-ECM-scores show associations with microsatellite instability as inferred using capillary sequencing. **c.** Relationship between M1/M2 fraction and C-ECM-up score. **d.** Heatmap of immune checkpoints (ligands and receptors) different between cancers in upper and lower quartiles of C-ECM-up score. **e.** Volcano plot showing results from Causal Network Analysis of genes differentially expressed between C-ECM-up score upper and lower quartile cancers. **f.** Results of upstream regulatory analysis (y axis = regulator, x axis = $-\log_{10}(\text{FDR})$) based on genes differentially expressed between C-ECM-up score upper and lower quartile cancers. Barplot shows breakdown of hot and cold tumours by C-ECM-up score quartile. **g.** Volcano plot showing differentially abundant peptides/epitopes between C-ECM-up score upper and lower quartile cancers.



Supplementary Figure 4. **a.** Boxplots showing breakdown of performance using Accuracy instead of Cohen's Kappa for many of the models in Figure 4C. **b.** Boxplots showing Cohen's Kappa and Accuracy for random forests trained using all C-ECM genes and those trained with the subset differentially expressed between immunotherapy responders (CR/PR/SD) and nonresponders (PD). **c.** Logistic Regression Model coefficients and p-values for models regressing immunotherapy response against a CAF signature alone, TGFB1/2 expression alone, and a model consisting of C-ECM signatures, a CAF signature, and TGFB1/2 expression alone. For boxplots, box-ends represent upper and lower-quartiles, central lines or central points represent medians, and whiskers represent 1.5x interquartile range (IQR). Error bars represent 95% confidence intervals for logistic regression plots.

Supplementary Table 1

ITGA2	ERO1A	SH3PXD2A	FBN2
COL5A1	SFRP2	NF1	FBN1
LAMC3	ELN	COL4A4	HAPLN2
DCN	CTSS	C6orf15	BMP1
LAMA3	KDR	COL9A1	MFAP5
CPB2	KLK2	CST3	SERPINF2
ITGA11	SMOC2	TIMP1	ITGA5
PRSS2	NDNF	AGT	COL4A5
CYP1B1	FBLN5	ADAMTS14	ICAM3
COL6A3	VPS33B	LAMC1	CTSL
COL6A2	OPTC	TGFBI	FLRT2
COL6A1	SMAD3	POMT1	KLK7
COL11A1	SPINT1	ITGAV	ICAM1
FSCN1	PLG	SOX9	CAPNS2
CTRB2	PRSS1	CYR61	ADAMTS5
HSPG2	NR2E1	EGFLAM	RGCC
FAP	CREB3L1	TLL2	ITGAD
PLOD3	ICAM4	SERPINB5	COL4A3
GREM1	ITGB1	ADAMTSL4	DMP1
COL4A1	MMP14	EXOC8	FGG
COL3A1	LRP1	PDPN	FGB
COL2A1	P4HA1	CSGALNACT1	FGA
COL1A1	COL7A1	TNFRSF11B	ITGA1
FERMT1	ITGA4	PDGFRA	ADAMTS3
NPHS1	VCAN	HTRA1	CDH1
LAMA2	ADAM10	MMP16	WT1
THBS1	ABI3BP	MMP15	MMP10
LAMB1	DPT	LOXL3	MMP7
VCAM1	MELTF	COL10A1	
BCAN	DSPP	POSTN	
CTRB1	CD47	ETS1	
TNXA	NOX1	TIMP2	
ABL1	COL8A1	CAPNS1	
BCL3	HSD17B12	SCX	
DPP4	PTK2	TMPRSS6	
PRDX4	URS000024463E_9606	ITGA7	
OLFML2A	CRISPLD2	CHADL	
SPARC	PDGFB	NOTCH1	
FN1	LOX	MYF5	
CCDC80	HAS2	ITGB8	
MMP11	MMP19	ITGB7	
LOXL1	COL1A2	ADAMTSL2	
DDR1	SPOCK2	ITGA3	

CAPN2	COL16A1	FURIN	
TLL1	ITGA8	WNT3A	
CAPN1	IBSP	TNC	
MPV17	BGN	KAZALD1	
ANXA2	SCUBE3	LUM	
PDGFA	TCF15	NPNT	
CMA1	SERPINH1	VIT	
VTN	TTR	TNF	
CTSV	CD44	COL27A1	
MATN3	JAM2	WASHC1	
LAMA5	LCP1	TGFBR1	
ITGA10	VIPAS39	AGRN	
COL8A2	CFLAR	ADAM8	
COL18A1	GAS6	NID1	
ADAMTS20	ITGB2	SH3PXD2B	
ADAM19	MMP1	GPM6B	
LAMA4	KLKB1	MADCAM1	
RECK	APP	ADAM15	
COL5A2	FOXC1	JAM3	
MMP20	B4GALT1	TNR	
SPINK5	MYH11	COL14A1	
RIC8A	PHLDB2	ERO1B	
DDR2	LAMB2	TGFB1	
SPINT2	NFKB2	DAG1	
COMP	CTSG	RAMP2	
CTGF	ACAN	ITGB3	
CLASP2	ITGB6	BSG	
SERAC1	LAMB3	MYO1E	
FLOT1	ITGA9	FOXF2	
CARMIL2	TGFB2	FOXF1	
ICAM5	ELANE	LAMA1	
ENG	NPHP3	COL11A2	
ATXN1L	CLASP1	COL9A2	
MMP8	MFAP2	EGFL6	
SERPINE1	FBLN1	LAMC2	
FMOD	KIF9	PHLDB1	
NID2	PECAM1	ITGA2B	
FGF2	MATN1	ELF3	
ANTXR1	ITGAM	MMP9	
VWA1	HPN	COL4A2	
THSD4	VWF	MMP2	
TNXB	MMP12	MMP3	
ITGAX	COL12A1	HAPLN1	
ITGAL	FOXC2	MFAP4	

SPP1	HPSE2	SCUBE1	
COL19A1	A2M	ECM2	
GFOD2	TPSAB1	SULF1	
ATP7A	F11R	SULF2	
NOXO1	COL13A1	HAS3	
DNAJB6	HAS1	ITGB4	
ADAMTS4	CTSK	ITGA6	
ADAM12	ITGAE	PXDN	
FGFR4	APBB2	MMP13	
MATN4	LOXL2	ICAM2	
ADAMTS2	ITGB5	NCAN	
COL5A3	ERCC2	COL9A3	
IHH	MPZL3	COL4A6	

Supplementary Table 2

logFC	AveExpr	T	P.Value	adj.P.Val	B	ID	is.ECM	is.upSig	is.downSig	is.sig
3.88317	5.347023	53.7002	0	0	1202.634	MMP11	Yes	Yes	No	Yes
-2.85059	4.141546	-41.3598	0	0	758.196	TNXB	Yes	No	Yes	Yes
-3.66323	2.279534	-40.2158	0	0	720.3502	DPT	Yes	No	Yes	Yes
2.351311	1.420181	37.15318	1.9E-276	1.1E-274	622.4141	ADAMTS14	Yes	Yes	No	Yes
-1.86451	2.077423	-34.9136	9.3E-247	4.2E-245	554.1347	GPM6B	Yes	No	Yes	Yes
1.097931	7.643832	34.57119	2.5E-242	1E-240	543.9592	SERPINH1	Yes	Yes	No	Yes
-2.73276	4.770041	-34.3025	6.9E-239	2.8E-237	536.0226	MFAP4	Yes	No	Yes	Yes
3.506895	2.276359	33.83967	5.5E-233	2.1E-231	522.4597	COL10A1	Yes	Yes	No	Yes
-2.55413	7.175302	-33.5345	3.9E-229	1.4E-227	513.5883	DCN	Yes	No	Yes	Yes
3.941206	1.738904	33.38066	3.4E-227	1.2E-225	509.1396	COL11A1	Yes	Yes	No	Yes
-1.74214	4.897319	-33.2138	4.2E-225	1.4E-223	504.3316	FBLN5	Yes	No	Yes	Yes
-1.70129	2.060619	-33.0972	1.2E-223	4E-222	500.9813	JAM2	Yes	No	Yes	Yes
-2.78801	6.206148	-32.298	9.2E-214	2.7E-212	478.2518	MYH11	Yes	No	Yes	Yes

- 2.2934 8	3.4950 44	- 30.033 2	9.5E- 187	2.1E- 185	416.12 97	ABI3BP	Yes	No	Yes	Yes
3.1236 32	2.5425 82	29.835 22	1.9E- 184	3.9E- 183	410.86 34	MMP1	Yes	Yes	No	Yes
2.0620 79	10.007 93	29.623 13	5.1E- 182	1E-180	405.25 28	COL1A1	Yes	Yes	No	Yes
1.4124 55	5.1715 97	29.194 96	3.9E- 177	7.5E- 176	394.02 14	LOXL2	Yes	Yes	No	Yes
2.4105 89	4.5053 34	29.082 86	7.3E- 176	1.4E- 174	391.10 24	MMP9	Yes	Yes	No	Yes
2.0307 05	3.2886 21	28.662 73	3.9E- 171	6.8E- 170	380.24 07	ADAM1 2	Yes	Yes	No	Yes
2.0504 33	1.3467 64	27.739 49	6E-161	9.1E- 160	356.81 54	ACAN	Yes	Yes	No	Yes
- 1.1668 8	3.1055 98	- 27.739 2	6E-161	9.2E- 160	356.80 91	RECK	Yes	No	Yes	Yes
- 1.8824 8	4.4291 09	- 26.765 3	1.7E- 150	2.3E- 149	332.76 93	PDGFRA	Yes	No	Yes	Yes
2.3131 36	6.8619 16	26.741 55	3.1E- 150	4E-149	332.19 26	SPP1	Yes	Yes	No	Yes
1.9136 89	3.0888 95	26.440 05	4.6E- 147	5.8E- 146	324.89 83	FAP	Yes	Yes	No	Yes
- 1.7602	3.4906 71	- 25.762 8	4.8E- 140	5.5E- 139	308.76 23	LAMA2	Yes	No	Yes	Yes
- 1.4027	6.8533 13	- 25.606 1	1.9E- 138	2.2E- 137	305.07 9	CYR61	Yes	No	Yes	Yes
- 1.5927 9	2.6307 81	- 25.481 4	3.6E- 137	3.9E- 136	302.15 87	FGF2	Yes	No	Yes	Yes
- 2.3416	1.0195 02	- 25.316	1.7E- 135	1.8E- 134	298.30 83	COL4A6	Yes	No	Yes	Yes
1.3042 81	3.7436 98	25.237 11	1.1E- 134	1.1E- 133	296.47 73	ADAM8	Yes	Yes	No	Yes
1.3754 29	6.6260 83	24.567 44	5E-128	4.9E- 127	281.13 5	COL5A2	Yes	Yes	No	Yes
- 1.6532 1	1.9967 44	- 23.667 4	2.7E- 119	2.4E- 118	261.06 62	DDR2	Yes	No	Yes	Yes
1.1439 59	8.0431 02	23.423 33	5.7E- 117	4.8E- 116	255.73 39	TIMP1	Yes	Yes	No	Yes
- 1.2461 8	3.1607 57	- 23.406 8	8.2E- 117	6.8E- 116	255.37 34	ECM2	Yes	No	Yes	Yes
- 1.6042 8	5.1056 69	- 23.291 1	1E-115	8.3E- 115	252.86 42	COL14A 1	Yes	No	Yes	Yes
- 1.0643 4	9.0981 73	- 22.935 6	2.1E- 112	1.7E- 111	245.22	A2M	Yes	No	Yes	Yes

- 1.7900 6	0.7031 45	- 22.359 9	4.2E- 107	3.1E- 106	233.05 75	COL4A3	Yes	No	Yes	Yes
2.2257 36	1.0672 24	22.002 06	7.2E- 104	5.1E- 103	225.63 33	MMP12	Yes	Yes	No	Yes
- 1.3509 1	6.6708 97	- 21.507 4	1.8E- 99	1.19E- 98	215.54 28	FBLN1	Yes	No	Yes	Yes
- 1.2958 6	2.6151 76	- 21.348 5	4.38E- 98	2.88E- 97	212.34 37	ITGA9	Yes	No	Yes	Yes
1.1736 81	3.7960 73	21.259 01	2.64E- 97	1.72E- 96	210.55 14	ITGAX	Yes	Yes	No	Yes
1.2823 16	6.9123 91	20.554 7	2.9E- 91	1.73E- 90	196.67 8	COL5A1	Yes	Yes	No	Yes
- 1.3843 8	2.3246 23	- 20.344 1	1.71E- 89	9.95E- 89	192.61	COL4A4	Yes	No	Yes	Yes
1.6735 6	3.6413 77	19.596 27	2.47E- 83	1.32E- 82	178.46 82	COL7A1	Yes	Yes	No	Yes
1.1476 05	4.0913 71	19.522 56	9.73E- 83	5.16E- 82	177.1	COL5A3	Yes	Yes	No	Yes
- 1.0717 6	7.2244 62	- 19.136 8	1.19E- 79	6.03E- 79	170.01 61	CTGF	Yes	No	Yes	Yes
- 1.2913 2	2.7816 3	- 18.914 8	6.68E- 78	3.31E- 77	165.99 67	FLRT2	Yes	No	Yes	Yes
1.0738 81	7.4318 12	18.600 35	1.88E- 75	8.99E- 75	160.37 55	TGFBI	Yes	Yes	No	Yes
2.1950 06	2.4129 26	18.582 69	2.57E- 75	1.23E- 74	160.06 24	COMP	Yes	Yes	No	Yes
1.2543 4	3.8429 1	18.579 32	2.73E- 75	1.3E- 74	160.00 27	MFAP2	Yes	Yes	No	Yes
1.1812 32	6.5471 71	17.147 79	1.26E- 64	5.13E- 64	135.53 01	VCAN	Yes	Yes	No	Yes
1.0723 22	9.7022 56	16.995 39	1.55E- 63	6.21E- 63	133.03 09	COL1A2	Yes	Yes	No	Yes
- 1.1427 2	0.7853 9	- 16.988 5	1.73E- 63	6.95E- 63	132.91 77	TLL1	Yes	No	Yes	Yes
1.1265 95	9.6229 4	16.884 05	9.55E- 63	3.77E- 62	131.21 79	COL3A1	Yes	Yes	No	Yes
1.0754 76	6.3159 95	16.212 22	4.44E- 58	1.63E- 57	120.51 32	SULF1	Yes	Yes	No	Yes
1.2797 37	6.4464 11	15.889 76	6.69E- 56	2.37E- 55	115.51 85	POSTN	Yes	Yes	No	Yes
1.1275 48	10.369 94	15.792 89	2.96E- 55	1.04E- 54	114.03 63	FN1	Yes	Yes	No	Yes
- 1.0991 9	2.3542 47	- 15.489 5	2.97E- 53	1.01E- 52	109.44 89	LAMC3	Yes	No	Yes	Yes
- 1.3285	1.7200 66	- 14.003 8	5.6E- 44	1.65E- 43	88.192 67	MFAP5	Yes	No	Yes	Yes

Supplementary Table 3

Term	coef	HR	Std.Error	Z	p.value	Significance
ECM.up.qQ2	0.19453	1.21474	0.09347	2.081	0.03741	*
ECM.up.qQ3	0.30455	1.35601	0.1058	2.879	0.00399	**
ECM.up.qQ4	0.34764	1.41572	0.11941	2.911	0.0036	**
ECM.down.qQ2	0.01757	1.01773	0.0789	0.223	0.82376	
ECM.down.qQ3	0.0619	1.06385	0.09473	0.653	0.5135	
ECM.down.qQ4	0.02759	0.97278	0.12184	-0.226	0.82084	
NonECM.up.Q2	0.4312	1.53911	0.10313	4.181	2.90E-05	***
NonECM.up.Q3	0.77113	2.16222	0.12653	6.094	1.10E-09	***
NonECM.up.Q4	0.79609	2.21685	0.14612	5.448	5.09E-08	***
NonECM.down.Q2	0.04464	1.04565	0.07919	0.564	0.57294	
NonECM.down.Q3	0.10356	1.10912	0.10961	0.945	0.34473	
NonECM.down.Q4	0.20076	1.22233	0.14335	1.401	0.16136	

Supplementary Table 4

Microarray / Cancer vs Normal	ECM-up	ECM-down	Non-ECM-up	Non-ECM-down
Stroma-vs-Epithelium-up	17.89	9.13	0.7	4.18
Cancer-stroma-vs-normal-stroma-up	11.49	1.08	1.74	0.84

blue = $p > 0.05$

Supplementary Table 5

Antibody	Status	Phenotype	Reference
Fibronectin	Up	TGF- β induces Fibronectin synthesis through a transcriptional mechanism	1
PAI1	Up	TGF- β induces expression through SMADs	2
MYOSINIIA_pS1943	Up	TGF- β inhibits a decrease in phosphorylation at this site and permits retention.	3,4
ANNEXIN1	Up	Is known to potentiate TGF- β mediated activation of SMADs	5
TFRC	Up	The Transferrin receptor is known to be required for TGF- β activation	6
CCNB1	Up	TGF- β is known to reduce CCNB1 levels and inhibit cell cycle progression. This could be a compensatory event	7
CLAUDIN7	Down	TGF- β activation is known to reduce Claudin 7 expression.	8
E-CADHERIN	Down	TGF- β reduces E-Cadherin levels in a PI3 kinase and PTEN dependent manner.	9
BCL2	Down	TGF- β activation is known to reduce BCL2 levels	10
AR	Down	The Androgen Receptor is known to directly antagonise TGF- β signalling through colocalization with SMAD	11
PDCD4	Down	PD4-downregulation is known to abrogate TGF- β mediated apoptosis	12

Supplementary Table 6

Mutation/alteration	Association with TGF- β	Reference
<i>TP53</i>	needed for TGF- β cytotaxis	13
<i>SMAD4</i>	Key TGF- β transcription factor	
<i>BRAF</i>	confers dependence on TGF- β	14
<i>ACVR1B</i>	Potentiate SMAD activation	15
<i>NF1/NF2</i>	Prior associations recorded	16
<i>MYC (Amplified)</i>	In renal fibrosis, activates latent TGF- β through integrin signalling. Also, MYC is inhibited by TGF- β activation as part of the cytotstatic response, and amplification may therefore permit ability to withstand active TGF- β in the microenvironment.	17, 18

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