





Fig. S2. Poorly-differentiated PDX-derived spheroids as monocultures and iMSCs co-cultures. CCA tissues (CCA2 (A), CCA4 (B), CCA5 (C) and CCA6 (D)) were enzymatically dissociated, and the cells were mono- or iMSCs co-cultured at 1:2 ratio (cancer cells:iMSCs) into an ULA 96-well round bottom plate at a final cell density of 1000 cells per well with 300µg/mL of basement membrane extract (BME). The effect of co-culture with iMSCs was assessed using brightfield microscopy at day 0, 3, 5 and 7 at 10x magnification. Live/dead cell staining was carried out using Calcein acetoxymethyl (AM) (green - live cells staining) and EthD-1 (red - dead cells staining) at days 3, 5 and 7. Representative spheroids are shown. Scale bar 100µm. Viability was monitored by PrestoBlue at day 3, 5 and 7 (Mean ± SEM).



Fig. S3. Well-differentiated PDX-derived spheroids as monocultures and iMSCs co-cultures. CCA tissues (CCA1 (A), CCA7 (B) and CCA11 (C)) were enzymatically dissociated, and the cells were mono- or iMSCs co-cultured at 1:2 ratio (cancer cells:iMSCs) into an ULA 96-well round bottom plate at a final cell density of 1000 cells per well with 300µg/mL of basement membrane extract (BME). The effect of co-culture with iMSCs was assessed using brightfield microscopy at day 0, 3, 5 and 7 at 10x magnification. Live/dead cell staining was carried out using Calcein acetoxymethyl (AM) (green - live cells staining) and EthD-1 (red - dead cells staining) at days 3, 5 and 7. Representative spheroids are shown. Scale bar 100µm.

Ingenuity Canonical Pathways	-log(p-value)	Ratio	z-score
S100 Family Signaling Pathway	14.9	0.28	9.54
FAK Signaling	11.7	0.27	9.70
PD-1, PD-L1 cancer immunotherapy pathway	8.25	0.40	-3.53
Tumor Microenvironment Pathway	6.39	0.31	5.98
Molecular Mechanisms of Cancer	6.38	0.22	9.99
Breast Cancer Regulation by Stathmin1	4.74	0.23	8.63
Cachexia Signaling Pathway	4.5	0.24	4.57
HOTAIR Regulatory Pathway	2.43	0.24	2.83
Role of Tissue Factor in Cancer	2.34	0.22	6.03
SPINK1 Pancreatic Cancer Pathway	2.31	0.33	-3.05
ID1 Signaling Pathway	1.71	0.21	2.60
Colorectal Cancer Metastasis Signaling	1.7	0.20	5.28
PTEN Signaling	1.53	0.21	-2.68
BEX2 Signaling Pathway	1.46	0.24	2.00
Thyroid Cancer Signaling	1.45	0.24	3.15
PCP (Planar Cell Polarity) Pathway	1.42	0.25	2.31
HEY1 Signaling Pathway	1.3	0.21	2.41

Table S1. Canonical pathways associated with cancer that were significantly dysregulated comparing patient tissues to PDXs.

Table S2. List of upstream regulators identified through Ingenuity Pathway Analysis (IPA) analysis, including growth factors (GF), cytokines, kinases, and transcription regulators (TR).

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Upstream Regulator	Expr Log Ratio	Expression (PDX vs PT)	Molecul e Type	Predicted Activation State	Activation z-score	p-value of overlap
EPHA2	-1.94	3.85	kinase	Activated	2.16	6.34E-05
MET	-1.88	3.69	kinase	Activated	3.19	3.60E-08
MST1R	-1.72	3.29	kinase	Activated	2.80	6.54E-03
MAP3K21	-1.66	3.16	kinase	Activated	2.00	2.26E-02
TYRO3	-1.52	2.87	kinase	Activated	2.41	3.72E-06
PRKCZ	-1.35	2.55	kinase	Activated	3.39	6.32E-04
EIF2AK2	-1.05	2.07	kinase	Activated	3.21	1.54E-02
RET	-0.97	1.95	kinase	Activated	2.28	2.15E-07
СНИК	-0.87	1.83	kinase	Activated	6.10	6.93E-19
CDK6	-0.82	1.76	kinase	Activated	2.24	7.59E-02
CAMK2D	-0.66	1.58	kinase	Activated	2.00	2.56E-02
CDK5	-0.62	1.53	kinase	Activated	2.76	1.11E-05
EPHB4	-0.47	1.38	kinase	Activated	3.19	2.77E-03
PTK2	-0.44	1.35	kinase	Activated	3.45	2.42E-07
PAK1	-0.31	1.24	kinase	Activated	2.21	2.55E-01
IRAK1	-0.31	1.24	kinase	Activated	2.36	4.68E-04
TBK1	-0.29	1.22	kinase	Activated	3.03	7.47E-04
PDK1	-0.27	1.20	kinase	Activated	4.23	6.01E-03
MAP2K3	-0.23	1.17	kinase	Activated	3.26	3.58E-03
MAP2K1	-0.18	1.13	kinase	Activated	3.51	1.29E-11
RIPK2	-0.11	1.08	kinase	Activated	5.39	1.54E-04
MAPK8	-0.08	1.05	kinase	Activated	4.22	2.22E-08
МАРК9	-0.03	1.02	kinase	Activated	2.90	1.33E-06
MAPK14	-0.02	1.01	kinase	Activated	4.48	1.51E-18
PRKACA	0.07	0.95	kinase	Activated	2.03	2.18E-04
HK2	0.09	0.94	kinase	Activated	2.24	1.52E-01
IKBKG	0.10	0.93	kinase	Activated	4.97	1.34E-13
SRC	0.10	0.93	kınase	Activated	2.29	1.94E-07
RPS6KA5	0.11	0.93	kınase	Activated	2.12	3.34E-04
MAPK11	0.12	0.92	kinase	Activated	2.81	1.25E-02
RAFI	0.15	0.90	kinase	Activated	2.94	3.33E-06
	0.16	0.90	kinase	Activated	4.12	7.18E-06
PRKCD	0.19	0.88	kinase	Activated	3.61	3.43E-08
	0.20	0.87	kinase	Activated	3.02	4.09E-08
	0.23	0.85	kinase	Activated	2.79	2.00E-09
AKII MADV2	0.23	0.84	kinase	Activated	2.00	2.81E-18
MAPK5 DOCK1	0.20	0.84	kinase	Activated	4.07	3.93E-08
KUCKI IVDVD	0.28	0.85	kinase	Activated	5.97	9.44E-08
MAD2K14	0.31	0.00	kinase	Activated	2.12	1.23E-20
	0.37	0.78	kinase	Activated	2.12	1.00E-07
PRKCF	0.39	0.77	kinase	Activated	2.31	1.10E-05
MAD3K1	0.40	0.72	kinase	Activated	2.00	1.37E-07
MKNK1	0.49	0.71	kinase	Activated	<u> </u>	5.03E-04
ROP1	0.03	0.04	kinase	Activated	3 20	3.95E-05
	0.77	0.58	kinase	Activated	2 77	1.77F_03
CAMA4	0./7	0.30	KIIIdSC	Activated	2.11	1.7712-03

Table S3. Inhibited cancer-associated kinases (ICAKs) identified in PDX models.

Upstream Regulator	Expr Log Ratio	Expression (PDX vs PT)	Molec ule Type	Predicted Activatio n State	Activation z-score	p-value of overlap
ACVR1C	4.72	26.32	kinase	Inhibited	2.43	9.12E-02
RET	1.91	3.76	kinase	Inhibited	3.13	2.15E-07
HK2	1.71	3.27	kinase	Inhibited	2.00	3.72E-01
TYRO3	1.65	3.13	kinase	Inhibited	2.20	2.79E-03
CAMK2D	1.38	2.61	kinase	Inhibited	2.00	4.02E-02
CHUK	1.29	2.44	kinase	Inhibited	5.13	5.97E-15
PRKCZ	1.24	2.36	kinase	Inhibited	2.60	1.40E-02
CAMK4	1.06	2.09	kinase	Inhibited	3.23	1.24E-03
RIPK2	1.04	2.06	kinase	Inhibited	2.94	4.52E-05
MAPK11	0.94	1.92	kinase	Inhibited	2.16	7.27E-03
CDK5	0.90	1.87	kinase	Inhibited	2.27	2.13E-04
PDK1	0.76	1.69	kinase	Inhibited	3.13	2.10E-03
PTK2	0.71	1.64	kinase	Inhibited	3.17	1.25E-06
IKBKG	0.71	1.63	kinase	Inhibited	4.76	1.44E-11
EPHB4	0.59	1.51	kinase	Inhibited	2.85	6.43E-04
PRKACA	0.53	1.44	kinase	Inhibited	2.44	3.82E-05
MAP2K1	0.53	1.44	kinase	Inhibited	2.69	3.60E-14
MAPK8	0.49	1.41	kinase	Inhibited	2.87	8.35E-10
PAK2	0.48	1.39	kinase	Inhibited	2.14	5.61E-04
IRAK1	0.46	1.38	kinase	Inhibited	2.46	8.17E-03
MAP3K14	0.45	1.37	kinase	Inhibited	3.29	5.94E-06
MAP2K3	0.43	1.35	kinase	Inhibited	3.04	7.86E-04
TYK2	0.16	1.12	kinase	Inhibited	3.58	1.86E-05
MAPK9	0.11	1.08	kinase	Inhibited	3.11	8.74E-05
ROCK1	0.08	1.05	kinase	Inhibited	3.45	4.83E-07
MAPK14	0.07	1.05	kinase	Inhibited	3.86	3.85E-16
AKT1	0.05	1.04	kinase	Inhibited	2.50	1.31E-17
IPMK	0.05	1.04	kinase	Inhibited	3.18	2.86E-03
PRKCD	0.05	1.03	kinase	Inhibited	3.38	3.94E-09
DYRK1A	0.04	1.03	kinase	Inhibited	2.44	3.40E-03
PRKCE	-0.13	0.91	kinase	Inhibited	2.73	2.21E-04
ROR1	-0.19	0.88	kinase	Inhibited	2.20	6.10E-03
FGFR2	-0.34	0.79	kinase	Inhibited	2.31	2.45E-08
MAP3K1	-0.35	0.79	kinase	Inhibited	2.22	7.86E-04
IRAK4	-0.46	0.73	kinase	Inhibited	2.12	4.36E-03
MAPK3	-0.48	0.72	kinase	Inhibited	2.57	3.04E-05
MAP3K3	-0.62	0.65	kinase	Inhibited	2.39	5.41E-06
IKBKB	-0.64	0.64	kinase	Inhibited	5.93	1.52E-18
MKNK1	-0.67	0.63	kinase	Inhibited	2.44	6.20E-04
NEK6	-0.84	0.56	kinase	Inhibited	2.00	3.35E-02
JAK1	-0.92	0.53	kinase	Inhibited	2.68	1.24E-02

Table S4. Upstream regulators and inhibited cancer-associated kinases (ICAKs) identified in the well-differentiated group.

Upstream	Expr Log	Expression	Molec ule	Predicted Activation	Activatio	p-value of
Regulator	Ratio	(PDX vs PT)	Туре	State	n z-score	overlap
ERBB3	2.67	6.38	kinase	Inhibited	2.154	5.73E-13
MST1R	2.21	4.62	kinase	Inhibited	2.449	3.81E-03
MAP3K21	2.15	4.45	kinase	Inhibited	2	1.46E-03
EGFR	2.14	4.41	kinase	Inhibited	2.213	5.51E-06
ERBB2	2.11	4.33	kinase	Inhibited	3.731	1.01E-11
PRKCZ	1.57	2.97	kinase	Inhibited	2.774	1.75E-03
TYRO3	1.44	2.71	kinase	Inhibited	2.412	2.30E-06
PLK4	1.16	2.24	kinase	Inhibited	2.449	5.06E-03
MET	1.16	2.24	kinase	Inhibited	4.548	2.48E-06
BMPR1A	0.90	1.86	kinase	Inhibited	2.207	1.31E-02
РІКЗСВ	0.75	1.68	kinase	Inhibited	2.216	4.11E-04
SRC	0.46	1.38	kinase	Inhibited	2.619	8.84E-10
PRKCA	0.42	1.34	kinase	Inhibited	2.674	1.09E-03
СНИК	0.40	1.32	kinase	Inhibited	5.426	3.62E-15
EPHB4	0.39	1.31	kinase	Inhibited	2.764	4.37E-03
IKBKB	0.32	1.25	kinase	Inhibited	5.692	3.33E-22
IRAK1	0.19	1.14	kinase	Inhibited	2.036	1.03E-03
РТК2	0.16	1.12	kinase	Inhibited	3.063	9.14E-09
МАРК3	0.15	1.11	kinase	Inhibited	2.742	1.67E-06
TBK1	0.05	1.03	kinase	Inhibited	3.575	1.67E-06
MAP2K3	0.04	1.02	kinase	Inhibited	2.95	1.28E-04
MAPK14	0.03	1.02	kinase	Inhibited	4.766	3.86E-18
RAF1	-0.05	0.97	kinase	Inhibited	3.985	1.27E-02
RIPK3	-0.07	0.95	kinase	Inhibited	2.4	2.01E-03
MAP2K4	-0.14	0.91	kinase	Inhibited	2.8	4.73E-02
MAP2K1	-0.20	0.87	kinase	Inhibited	4.861	6.11E-11
CAMK2D	-0.25	0.84	kinase	Inhibited	2	1.05E-02
PDK1	-0.29	0.82	kinase	Inhibited	3.162	3.84E-02
IPMK	-0.35	0.78	kinase	Inhibited	3.742	4.75E-05

Table S5. Upstream regulators and inhibited cancer-associated kinases(ICAKs) identified in the poorly differentiated group.

MAPK8 -0.42 0.75 kinase Inhibited 2.244 2.47E-06 PRKCD -0.43 0.74 kinase Inhibited 2.78 9.99E-03 BRD4 -0.44 0.74 kinase Inhibited 4.838 8.29E-09 MAP2K6 -0.52 0.70 kinase Inhibited 2.183 1.30E-08 MKNK1 -0.53 0.69 kinase Inhibited 4.214 5.90E-05 AKT1 -0.56 0.68 kinase Inhibited 4.292 1.15E-12 MAP3K1 -0.59 0.67 kinase Inhibited 2.488 2.08E-06 CDK9 -0.61 0.65 kinase Inhibited 2.415 2.95E-07 STK40 -0.63 0.65 kinase Inhibited 3.138 7.79E-08 ROCK1 -0.64 0.64 kinase Inhibited 3.719 3.41E-09 BMPR2 -0.81 0.56 kinase Inhibited 2.236 2.30E-02							
PRKCD -0.43 0.74 kinase Inhibited 2.78 9.99E-03 BRD4 -0.44 0.74 kinase Inhibited 4.838 8.29E-09 MAP2K6 -0.52 0.70 kinase Inhibited 2.183 1.30E-08 MKNK1 -0.53 0.69 kinase Inhibited 4.214 5.90E-05 AKT1 -0.56 0.68 kinase Inhibited 4.292 1.15E-12 MAP3K1 -0.59 0.67 kinase Inhibited 2.477 4.20E-04 TYK2 -0.61 0.65 kinase Inhibited 2.415 2.95E-07 STK40 -0.62 0.65 kinase Inhibited 3.138 7.79E-08 ROCK1 -0.64 0.64 kinase Inhibited 2.413 2.62E-02 PLK2 -0.81 0.57 kinase Inhibited 2.413 2.62E-02 PLK2 -0.83 0.56 kinase Inhibited 3.264 1.13E-02	MAPK8	-0.42	0.75	kinase	Inhibited	2.244	2.47E-06
BRD4 -0.44 0.74 kinase Inhibited 4.838 8.29E-09 MAP2K6 -0.52 0.70 kinase Inhibited 2.183 1.30E-08 MKNK1 -0.53 0.69 kinase Inhibited 4.214 5.90E-05 AKT1 -0.56 0.68 kinase Inhibited 4.292 1.15E-12 MAP3K1 -0.59 0.67 kinase Inhibited 2.477 4.20E-04 TYK2 -0.61 0.65 kinase Inhibited 2.415 2.95E-07 STK40 -0.63 0.65 kinase Inhibited 3.138 7.79E-08 ROCK1 -0.64 0.64 kinase Inhibited 3.719 3.41E-09 BMPR2 -0.81 0.57 kinase Inhibited 2.236 2.30E-02 PLK2 -0.83 0.56 kinase Inhibited 3.264 1.13E-02 IKBKG -0.88 0.54 kinase Inhibited 4.302 9.31E-07	PRKCD	-0.43	0.74	kinase	Inhibited	2.78	9.99E-03
MAP2K6 -0.52 0.70 kinase Inhibited 2.183 1.30E-08 MKNK1 -0.53 0.69 kinase Inhibited 4.214 5.90E-05 AKT1 -0.56 0.68 kinase Inhibited 4.292 1.15E-12 MAP3K1 -0.59 0.67 kinase Inhibited 2.477 4.20E-04 TYK2 -0.61 0.65 kinase Inhibited 2.415 2.95E-07 CDK9 -0.62 0.65 kinase Inhibited 2.415 2.95E-07 STK40 -0.63 0.65 kinase Inhibited 3.138 7.79E-08 ROCK1 -0.64 0.64 kinase Inhibited 3.719 3.41E-09 BMPR2 -0.81 0.57 kinase Inhibited 2.236 2.30E-02 PLK2 -0.83 0.56 kinase Inhibited 3.264 1.13E-02 IKBKG -0.88 0.54 kinase Inhibited 2.201 8.79E-08	BRD4	-0.44	0.74	kinase	Inhibited	4.838	8.29E-09
MKNK1-0.530.69kinaseInhibited4.2145.90E-05AKT1-0.560.68kinaseInhibited4.2921.15E-12MAP3K1-0.590.67kinaseInhibited2.4774.20E-04TYK2-0.610.65kinaseInhibited2.6882.08E-06CDK9-0.620.65kinaseInhibited3.1387.79E-08STK40-0.630.65kinaseInhibited3.7193.41E-09BMPR2-0.810.57kinaseInhibited2.2362.30E-02PLK2-0.830.56kinaseInhibited3.2641.13E-02IKBKG-0.880.54kinaseInhibited3.2018.79E-08	MAP2K6	-0.52	0.70	kinase	Inhibited	2.183	1.30E-08
AKT1-0.560.68kinaseInhibited4.2921.15E-12MAP3K1-0.590.67kinaseInhibited2.4774.20E-04TYK2-0.610.65kinaseInhibited2.6882.08E-06CDK9-0.620.65kinaseInhibited2.4152.95E-07STK40-0.630.65kinaseInhibited3.1387.79E-08ROCK1-0.640.64kinaseInhibited3.7193.41E-09BMPR2-0.810.57kinaseInhibited2.2362.30E-02PLK2-0.830.56kinaseInhibited3.2641.13E-02IKBKG-0.880.54kinaseInhibited4.3029.31E-07	MKNK1	-0.53	0.69	kinase	Inhibited	4.214	5.90E-05
MAP3K1-0.590.67kinaseInhibited2.4774.20E-04TYK2-0.610.65kinaseInhibited2.6882.08E-06CDK9-0.620.65kinaseInhibited2.4152.95E-07STK40-0.630.65kinaseInhibited3.1387.79E-08ROCK1-0.640.64kinaseInhibited3.7193.41E-09BMPR2-0.810.57kinaseInhibited2.2362.30E-02PLK2-0.830.56kinaseInhibited3.2641.13E-02IKBKG-0.880.54kinaseInhibited4.3029.31E-07JAK2-0.880.54kinaseInhibited2.2018.79E-08	AKT1	-0.56	0.68	kinase	Inhibited	4.292	1.15E-12
TYK2-0.610.65kinaseInhibited2.6882.08E-06CDK9-0.620.65kinaseInhibited2.4152.95E-07STK40-0.630.65kinaseInhibited3.1387.79E-08ROCK1-0.640.64kinaseInhibited3.7193.41E-09BMPR2-0.810.57kinaseInhibited2.2362.30E-02PLK2-0.830.56kinaseInhibited3.2641.13E-02IKBKG-0.880.54kinaseInhibited4.3029.31E-07JAK2-0.880.54kinaseInhibited2.2018.79E-08	MAP3K1	-0.59	0.67	kinase	Inhibited	2.477	4.20E-04
CDK9-0.620.65kinaseInhibited2.4152.95E-07STK40-0.630.65kinaseInhibited3.1387.79E-08ROCK1-0.640.64kinaseInhibited3.7193.41E-09BMPR2-0.810.57kinaseInhibited2.4132.62E-02PLK2-0.830.56kinaseInhibited2.2362.30E-02PRKCE-0.840.56kinaseInhibited3.2641.13E-02JAK2-0.880.54kinaseInhibited4.3029.31E-07	ТҮК2	-0.61	0.65	kinase	Inhibited	2.688	2.08E-06
STK40-0.630.65kinaseInhibited3.1387.79E-08ROCK1-0.640.64kinaseInhibited3.7193.41E-09BMPR2-0.810.57kinaseInhibited2.4132.62E-02PLK2-0.830.56kinaseInhibited2.2362.30E-02PRKCE-0.840.56kinaseInhibited3.2641.13E-02IKBKG-0.880.54kinaseInhibited4.3029.31E-07JAK2-0.880.54kinaseInhibited2.2018.79E-08	CDK9	-0.62	0.65	kinase	Inhibited	2.415	2.95E-07
ROCK1 -0.64 0.64 kinase Inhibited 3.719 3.41E-09 BMPR2 -0.81 0.57 kinase Inhibited 2.413 2.62E-02 PLK2 -0.83 0.56 kinase Inhibited 2.236 2.30E-02 PRKCE -0.84 0.56 kinase Inhibited 3.264 1.13E-02 IKBKG -0.88 0.54 kinase Inhibited 4.302 9.31E-07 JAK2 -0.88 0.54 kinase Inhibited 2.201 8.79E-08	STK40	-0.63	0.65	kinase	Inhibited	3.138	7.79E-08
BMPR2 -0.81 0.57 kinase Inhibited 2.413 2.62E-02 PLK2 -0.83 0.56 kinase Inhibited 2.236 2.30E-02 PRKCE -0.84 0.56 kinase Inhibited 3.264 1.13E-02 IKBKG -0.88 0.54 kinase Inhibited 4.302 9.31E-07 JAK2 -0.88 0.54 kinase Inhibited 2.201 8.79E-08	ROCK1	-0.64	0.64	kinase	Inhibited	3.719	3.41E-09
PLK2 -0.83 0.56 kinase Inhibited 2.236 2.30E-02 PRKCE -0.84 0.56 kinase Inhibited 3.264 1.13E-02 IKBKG -0.88 0.54 kinase Inhibited 4.302 9.31E-07 JAK2 -0.88 0.54 kinase Inhibited 2.201 8.79E-08	BMPR2	-0.81	0.57	kinase	Inhibited	2.413	2.62E-02
PRKCE -0.84 0.56 kinase Inhibited 3.264 1.13E-02 IKBKG -0.88 0.54 kinase Inhibited 4.302 9.31E-07 JAK2 -0.88 0.54 kinase Inhibited 2.201 8.79E-08	PLK2	-0.83	0.56	kinase	Inhibited	2.236	2.30E-02
IKBKG -0.88 0.54 kinase Inhibited 4.302 9.31E-07 JAK2 -0.88 0.54 kinase Inhibited 2.201 8.79E-08	PRKCE	-0.84	0.56	kinase	Inhibited	3.264	1.13E-02
JAK2 -0.88 0.54 kinase Inhibited 2.201 8.79E-08	IKBKG	-0.88	0.54	kinase	Inhibited	4.302	9.31E-07
	JAK2	-0.88	0.54	kinase	Inhibited	2.201	8.79E-08

Table S6. Genes differentially expressed in the co-culture model associated with overall survival. The adjusted p-values were derived from Kaplan-Meier survival analysis using Cox proportional regression. Additionally, the log2 difference in expression in the co-culture is provided for each gene.

Cono Symbol	Adjusted n-value	Log2 Fold Change in
Gene Symbol	Aujusteu p-value	Expression in Co-culture
SPOCD1	0.024	2.241128
CAPRIN2	4.95E-04	1.233663
FAM109B	0.024	9.388593
SERPINE2	8.43E-03	2.074787
SCEL	0.019	-1.55945
VSTM2L	0.024	6.567292
C16ORF45	1.30E-03	6.774376
ANGPTL4	3.20E-05	1.230297

Table S7. Differentially expressed genes identified by DESeq2 in KKU-M213-derived spheroids (monoculture vs co-culture). Gene ID, name, adjusted p-value, and log2-fold change are provided for each gene.

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Upstream Regulator	Expr Log Ratio	Expression (PDX vs PT)	Molecule Type	Predicted Activation State	Activation z-score	p-value of overlap
EPHA2	-		-	-	-	-
MET	0.01	1.00	kinase	Activated	3.39	2.68E-06
MST1R	-		-	-	-	-
MAP3K21	-0.27	0.83	kinase			6.63E-03
TYRO3	-		-	-	-	-
PRKCZ	-0.18	0.88	kinase		1.98	4.50E-02
EIF2AK2	-		-	-	-	-
RET			kinase	Activated	2.39	3.33E-05
СНИК	-0.01	0.99	kinase	Activated	3.06	2.57E-08
CDK6	-0.13	0.91	kinase		1.89	1.72E-01
CAMK2D	-		-	-	-	-
CDK5	-		-	-	-	-
EPHB4	-		-	-	-	-
РТК2	0.05	1.04	kinase	Activated	2.39	9.84E-08
PAK1	-		-	-	-	-
IRAK1	0.09	1.06	kinase		0.72	3.02E-02
TBK1	-		-	-	-	-
PDK1	-		-	-	-	-
MAP2K3	0.08	1.05	kinase		1.98	3.86E-06
MAP2K1	0.01	1.01	kinase	Activated	2.30	7.77E-07
RIPK2	-		-	-	-	-
MAPK8	-0.15	0.90	kinase		0.96	1.41E-04
МАРК9	-		-	-	-	-
MAPK14	0.14	1.10	kinase		1.71	3.27E-04
PRKACA	-		-	-	-	-
HK2	-0.82	0.57	kinase	Activated	2.22	1.06E-03
IKBKG	0.04	1.03	kinase	Activated	2.68	7.10E-06
SRC	0.08	1.05	kinase		1.41	1.58E-06
RPS6KA5	-		-	-	-	-

Table S8. Inhibited cancer-associated kinases (ICAKs) activated in MSC co-cultures identified from whole PDX analysis.

MAPK11	-		-	-	-	-
RAF1	-		-	-	-	-
ІРМК	-0.26	0.84	kinase		1.22	7.53E-03
PRKCD	-0.19	0.88	kinase	Activated	2.47	7.00E-04
ТҮК2	-		-	-	-	-
CDK9	0.06	1.04	kinase			8.52E-03
AKT1	0.46	1.38	kinase	Activated	3.03	1.44E-06
МАРК3	-		-	-	-	-
ROCK1	0.20	1.15	kinase	Activated	3.44	1.98E-09
IKBKB	0.14	1.10	kinase	Activated	3.29	3.05E-10
MAP3K14	0.17	1.12	kinase	Activated	2.56	1.95E-04
DYRK1A	-		-	-	-	-
PRKCE	-0.22	0.86	kinase	Activated	2.60	1.05E-02
MAP3K1	-0.28	0.82	kinase	Activated	2.00	8.52E-03
MKNK1	-0.12	0.92	kinase	Activated	2.16	2.71E-03
ROR1	0.27	1.20	kinase	Activated	2.76	1.58E-03
CAMK4	-		-	-	-	-

Upstream Regulator	Expr Log Ratio	Expression (PDX vs PT)	Molecule Type	Predicted Activation State	Activatio n z-score	p-value of overlap
ERBB3	-1.07		kinase	Activated	2.10	7.66E-11
MST1R	-	1.00	-	-	-	-
MAP3K21	-0.27		kinase			6.63E-03
EGFR	-0.10	0.83	kinase	Activated	2.73	9.69E-06
ERBB2	-0.29		kinase	Activated	2.75	1.92E-21
PRKCZ	-0.18	0.88	kinase		1.98	4.50E-02
TYRO3	-		-	-	-	-
PLK4	-		-	-	-	-
MET	0.01	0.99	kinase	Activated	3.39	2.68E-06
BMPR1A	-0.17	0.91	kinase		0.56	1.55E-03
РІКЗСВ	-		-	-	-	-
SRC	0.08		kinase		1.41	1.58E-06
PRKCA	-		-	-	-	-
СНИК	-0.01	1.04	kinase	Activated	3.06	2.57E-08
EPHB4	-		-	-	-	-
IKBKB	0.14	1.06	kinase	Activated	3.29	3.05E-10
IRAK1	0.09		kinase		0.72	3.02E-02
РТК2	0.05		kinase	Activated	2.39	9.84E-08
МАРК3	-	1.05	-	-	-	-
TBK1	-	1.01	-	-	-	-
MAP2K3	0.08		kinase		1.98	3.86E-06
MAPK14	0.14	0.90	kinase		1.71	3.27E-04
RAF1	-		-	-	-	-
RIPK3	0.15	1.10	kinase			4.10E-02
MAP2K4	-		-	-	-	-
MAP2K1	0.01	0.57	kinase	Activated	2.30	7.77E-07
CAMK2D	-	1.03	-	-	-	-
PDK1	-	1.05	-	-	-	-
IPMK	-0.26		kinase		1.22	7.53E-03

Table S9. Inhibited cancer-associated kinases (ICAKs) activated in MSC cocultures identified from well-differentiated PDXs.

MAPK8	-0.15		kinase		0.96	1.41E-04
PRKCD	-0.19		kinase	Activated	2.47	7.00E-04
BRD4		0.84	kinase	Activated	3.50	7.45E-07
MAP2K6	-0.79	0.88	kinase		1.69	3.20E-04
MKNK1	-0.12		kinase	Activated	2.16	2.71E-03
AKT1	0.46	1.04	kinase	Activated	3.03	1.44E-06
MAP3K1	-0.28	1.38	kinase	Activated	2.00	8.52E-03
ТҮК2	-		-	-	-	-
CDK9	0.06	1.15	kinase			8.52E-03
STK40	-0.06	1.10	kinase		1.16	2.71E-04
ROCK1	0.20	1.12	kinase	Activated	3.44	1.98E-09
BMPR2	1.70		kinase		1.13	3.87E-02
PLK2	-	0.86	-	-	-	-
PRKCE	-0.22	0.82	kinase	Activated	2.60	1.05E-02
IKBKG	0.04	0.92	kinase	Activated	2.68	7.10E-06
JAK2	0.35	1.20	kinase		1.73	3.65E-03

Upstream Regulator	Expr Log Ratio	Expression (PDX vs PT)	Molecule Type	Predicted Activation State	Activatio n z-score	p-value of overlap
ACVR1C	-1.32		kinase	Activated	2.61	2.94E-04
RET		1.00	kinase	Activated	2.39	3.33E-05
HK2	-0.82		kinase	Activated	2.22	1.06E-03
TYRO3	-	0.83	-	-	-	-
CAMK2D	-		-	-	-	-
СНИК	-0.01	0.88	kinase	Activated	3.06	2.57E-08
PRKCZ	-0.18		kinase		1.98	4.50E-02
CAMK4	-		-	-	-	-
RIPK2	-	0.99	-	-	-	-
MAPK11	-	0.91	-	-	-	-
CDK5	-		-	-	-	-
PDK1	-		-	-	-	-
PTK2	0.05		kinase	Activated	2.39	9.84E-08
IKBKG	0.04	1.04	kinase	Activated	2.68	7.10E-06
EPHB4	-		-	-	-	-
PRKACA	-	1.06	-	-	-	-
MAP2K1	0.01		kinase	Activated	2.30	7.77E-07
MAPK8	-0.15		kinase		0.96	1.41E-04
PAK2	-0.06	1.05	kinase		0.45	1.64E-02
IRAK1	0.09	1.01	kinase		0.72	3.02E-02
MAP3K14	0.17		kinase	Activated	2.56	1.95E-04
MAP2K3	0.08	0.90	kinase		1.98	3.86E-06
TYK2	-		-	-	-	-
МАРК9	-	1.10	-	-	-	-
ROCK1	0.20		kinase	Activated	3.44	1.98E-09
MAPK14	0.14	0.57	kinase		1.71	3.27E-04
AKT1	0.46	1.03	kinase	Activated	3.03	1.44E-06
IPMK	-0.26	1.05	kinase		1.22	7.53E-03
PRKCD	-0.19		kinase	Activated	2.47	7.00E-04

Table S10. Inhibited cancer-associated kinases (ICAKs) activated in MSC co-cultures identified from poorly-differentiated PDXs.

DYRK1A	-		-	-	-	-
PRKCE	-0.22		kinase	Activated	2.60	1.05E-02
ROR1	0.27	0.84	kinase	Activated	2.76	1.58E-03
FGFR2	-0.49	0.88	kinase		-0.08	4.77E-07
MAP3K1	-0.28		kinase	Activated	2.00	8.52E-03
IRAK4	-	1.04	-	-	-	-
МАРК3	-	1.38	-	-	-	-
MAP3K3	0.46		kinase			3.98E-03
IKBKB	0.14	1.15	kinase	Activated	3.29	3.05E-10
MKNK1	-0.12	1.10	kinase	Activated	2.16	2.71E-03
NEK6	-	1.12	-	-	-	-
JAK1	0.40		kinase	Activated	2.80	2.71E-03