	Condition	Effect	
1	+Forskolin (1-10 μM)	negative	Metabolic
2	+PPARγ agonists (25 μM)	neutral	
3	+PPARα agonists (1-50 μM)	neutral	
4	+Metformin (10 mM)	negative	
5	+AICAR (1 mM)	negative	
6	+Compound C (20 μM)	negative	
7	+Palmitic acid (100 mM)	neutral	
8	Low Glucose (1-10 mM)	neutral	
9	+Jag1 (1-10 μM)	neutral	Growth and Differentiation
10	+Wnt3a (0.5 μg/ml)	neutral	
11	+Wnt5a (0.5 μg/ml)	neutral	
12	+GDF15 (50-500 ng/ml)	neutral	
13	+IL11 (100 ng/ml)	neutral	
14	+IFNβ (0.1 U/ml)	neutral	
15	- Noggin	neutral	Standard Factors
16	- p38i	positive	
17	-NAC	neutral/positive	
18	-TGFβi	negative/neutral	
19	-p38i -TGFβi	negative/neutral	Combinations
20	-p38i -NAC	positive	
21	-p38i +palmitic acid	neutral	
22	-p38i +metformin	negative	
23	-p38i +AICAR	negative	
24	-p38i +IL11	neutral	
25	-p38i +IL11 +Jag1	neutral	
26	-p38i + PPARα agonists	neutral	
27	-p38i +IFNβ	neutral	

Supplementary Table S1.

Table of media conditions tested. All conditions, are modifications of PrENR media. (+) indicates that a given factor was added to the media, (-) indicates that a standard component was removed from the media. Effect columns indicate the observed or measured effect on growth and/or survival relative to PrENR. When the minus p38i condition is combined with the addition or subtraction of other factors, the effect is relative to the minus p38i-only condition.

Group	LuCaP	Optimal Media	Site	Type
A ≥10 generations	23.1	-p38i -NAC	lymph node	Adeno
	77*	-p38i -NAC (GSK3βi)	femur	Adeno
	77CR**	-p38i -NAC	femur	Adeno
	141	-p38 +GSK3βi +LSD1i/MAOi	prostate	Adeno
	145.2	-p38i	lymph node	NE
	147	-p38i -NAC	liver	Adeno
	167*	-p38i (GSK3βi)	liver	Adeno
	170.2	-p38i	rib	Adeno
	170.3	-p38i -NAC	liver	Adeno
	173.1	-p38i -NAC	liver	NE
	189.3	-p38i	adrenal	Adeno
B 1-3 generations	73	-p38i -NAC	prostate	Adeno
	92	-p38i -NAC	lymph node	Adeno
	96	-p38i -NAC	prostate	Adeno
	105	-p38i	rib	Adeno
	136	-p38i -NAC	acites	Adeno
	35†	-p38i -NAC	lymph node	Adeno
	35CR†	-p38i -NAC	lymph node	Adeno
	86.2	-p38i -NAC	bladder	Adeno
	145.1	-p38i -NAC	liver	NE

Supplementary Table S2.

Optimal media condition for each LuCaP. The LuCaPs were arranged into groups based on how long a given LuCaP proliferates *in vitro*. Group A: cultured for at least ten generations. Group B: cultured between 1-3 generations. * GSK3βi is not required, but enhanced growth in two-week assays when included. ** Grows for more than three generations but still testing for growth ≥ 10 generations. † Slow growth rate.

Site	Dx	Culture Start Date	Organoid ID	Gen	PSA	gain	loss
Spine	mCRPC adenocarcinoma	8/2015	NCI-PC44	23	+	X	3p, 6q, 8p, 10q 13q, 16q, 17p, 18q
Neck	Metastatic, poorly differentiated carcinoma with NE features	11/2015	NCI-PC35-1 & NCI-PC35-2	21	+	8q	8p, 6q
Liver	Metastatic, poorly differentiated carcinoma	6/2016	NCI-PC60	9	-	X, 7, 8q	2q, 8p, 13q, 16q

Supplementary Table S3.

Patient-derived biopsy samples, cultured as organoids. Copy number gains and losses determined by Oncoscan array.

Selected CNVs known to be associated with mCRPC are listed.

Organoid ID	PDX Histology	AR	CK8	CK5	P63	CHGA	SYP
LuCaP 23.1	AC	+	+	-	rare	-	-
LuCaP 73	AC	+	+	-	-	-	-
LuCaP 77	AC	+	+	-	-	-	-
LuCaP 92	AC	+	+	-	-	-	-
LuCaP 136	AC	+	+	-	-	-	-
LuCaP 141	AC	+	+	-	-	-	-
LuCaP 145.2	NE	-	+	-	-	+	+
LuCaP 147	AC	+	+	-	-	-	-
LuCaP 167	AC	+	+	-	rare	-	-
LuCaP 170.2	AC	+	+	-	-	-	-
LuCaP 189.3	AC	+	+	-	rare	-	-

Supplementary Table S5.

Expression status in organoids, determined by immunofluorescent staining, for the indicated markers. AC = adenocarcinoma; NE = neuroendocrine