Supplemental Table 1 - Metabolic targets for cancer therapy

Targets	Pathways	Agents or approaches (company)*	Development stage	Observations	Refs
Bioenergetic metabolism					
CPT1	β oxidation	Etomoxir Oxfenicine Perhexiline RNAi	Perhexiline is approved for use an antianginal agent in Asia, Australia and New Zealand	Inhibition of CPT1 exerts anticancer effects in *vitro* and *in vivo*, yet it remains unclear whether these stem from the blockage of β-oxidation	1-3
Complex I	Mitochondrial respiration	Metformin Phenformin	Metformin is prescribed for the treatment of type 2 diabetes	The antineoplastic activity of metformin is independent of glycaemia and may reflect its capacity to inhibit mitochondrial respiration	4,5
GAPDH	Glycolysis	3-BP Koningic acid	Preclinical data	In glycolytic cancer cells, GAPDH inhibition leads to ATP depletion and caspase-independent cell death, hence suppressing *in vivo* growth	6,7
GLUD1	Glutamine metabolism	EGCG RNAi	EGCG is in clinical development	The safety and therapeutic potential of EGCG is being tested in cohorts of patients affected by multiple neoplasms	8
GLUT1	Glycolysis	WZB117 RNAi	Preclinical data	Pharmacological or genetic inhibition of GLUT1 exerts antineoplastic effects, both *in vitro* and *in vivo*	9,10
GLUT4	Glycolysis	Dehydrosilybin Silybin	Preclinical data	Both these flavonoids reduce the viability of cultured cancer cells in a GLUT4-dependent manner	11
GLS1	Glutamine metabolism	968 BPTES RNAi	Preclinical data	Malignant cells expressing mutant IDH1 may be particularly sensitive to GLS1-targeting agents	12,13
Glutamine	Glutamine metabolism	Phenylacetate Phenylbutyrate	Prescription drugs for the treatment of hyperammonaemia	Phenylacetate rapidly reacts with circulating glutamine to form phenylacetylglutamine, which is readily excreted in urine	14
HADHA	β oxidation	Ranolazine Trimetazidine	Prescription drugs for the treatment of angina	The actual antineoplastic potential of HADHA-targeting interventions remains to be elucidated	2,15,16
Hexokinases	Glycolysis	2-DG 3-BP Lonidamine Methyl jasmonate RNAi	The clinical development of 2-DG, 3-BP and lonidamine has been discontinued	It remains to be determined whether the anticancer effects of 3-BP and lonidamine stem from the inhibition of HKs	17-22

LDHA	Glycolysis	3-BP FX11 Galloflavin RNAi	Preclinical data	Targeting LDHA limits *MYC*-driven carcinogenesis, and – coupled to NAMPT inhibitors – mediates robust antineoplastic effects *in vivo*	23-25
MCT1	TCA cycle	AR-C155858 AR-C117977 AZD3965 (AstraZeneca) CHC RNAi	AZD3965 is in clinical development	AZD3965 is currently being tested in a phase I clinical trial enrolling patients with advanced solid tumours; these agents may be incompatible with the use of MCT1-transported drugs, such as 3-BP	7,26
MCT4	Glycolysis	*CD44* RNAi *CD147* RNAi	Preclinical data	Silencing CD44 and/or CD147 results in the downregulation of MCT4 coupled to the inhibition of tumour progression	27,28
PC	TCA cycle	RNAi	Preclinical data	Targeting PC exerts antineoplastic effects, especially when glutamine cannot be used by cancer cells	29
PDK1	TCA cycle	DCA	DCA is a prescription drug for the treatment of lactic acidosis	DCA is well tolerated by patients with glioblastoma multiforme and provokes profound mitochondrial defects in cancer cells	30
PDK2	TCA cycle	AZD7545 (AstraZeneca) Radicicol	Preclinical data	The anticancer effects of radicicol may be independent from its capacity to inhibit PDHK2, while the antineoplastic potential of AZD7545 remains entirely unexplored	31,32
PFKFB3	Glycolysis	3PO PFK15 *Pfkfb3*$^{+/-}$ mice RNAi	Preclinical data	Inhibition of PFKFB3 exerts anticancer effects in tumour-bearing mice and prevents *HRAS*-driven carcinogenesis; in part, these effects may result from the ability of PFKFB3-targeting interventions to inhibit vessel sprouting	33-36
PKM2	Glycolysis	TLN-232 (Thallion) RNAi	The clinical development of TLN-232 has been discontinued	Inhibition of PKM2 reverses the Warburg effect (at least in some tumour models), yet may favour anabolism	37-39
Anabolic metabolism					
ACC	Lipid biosynthesis	Soraphen A	Preclinical data	ACC inhibition blocks fatty acid synthesis and stimulates β oxidation, thus limiting cancer cell growth *in vitro*	40
ACLY	Lipid biosynthesis	SB-204990 (SmithKline Beecham) RNAi	Preclinical data	Irrespective of encouraging results, no ACLY inhibitor is currently being tested as an anticancer agent in clinical trials	41
Arginine	Arginine metabolism	Arginine deiminase (Polaris)	Arginine deiminase is in clinical development	Intensively investigated for the treatment of several different tumours, with promising results	42,43
Asparagine	Asparagine metabolism	*L*-asparaginase	*L*-asparaginase is a prescription drug for the treatment of ALL	*L*-asparaginase reduces the circulating availability of asparagine, which is strictly required by some ALL types	44

CK	Lipid biosynthesis	CK37 TCD-717 (TCD Pharma) RNAi	TCD-717 is in clinical development	The safety and therapeutic profile of TCD-717 is currently being tested in patients with advanced solid tumours	45,46
DHFR	Folate metabolism	Methotrexate Pemetrexed	Methotrexate and pemetrexed are prescription drugs for the treatment of several tumours	Methotrexate and pemetrexed are routinely used against various solid and haematological neoplasms	47
DNA polymerases	Nucleid acid synthesis	Fludarabine Gemcitabine	Fludarabine and gemcitabine are prescription drugs for the treatment of several tumours	Fludarabine and gemcitabine are employed against haematological cancers and carcinomas, respectively	47
HMGCR	Mevalonate pathway	Statins	Statins are prescription drugs against hypercholesterolemia	The antineoplastic potential of statins is being investigated in multiple prospective clinical trials	48,49
IDHs	Lipid biosynthesis	AGI-5198 (Xcessbio) AGI-6780 (Xcessbio) RNAi	Preclinical data	Inhibition of both wild-type and mutant IDH results in multipronged antineoplastic effects, presumably reflecting a decrease in 2-HG levels as well as an interference with glutamine metabolism	50-53
FASN	Lipid biosynthesis	C75 C247 Orlistat	Orlistat can be purchased over-the-counter as a support for the dietary management of obesity	In spite of promising preclinical data, no FASN inhibitor is being tested for its anticancer effects in clinical trials	54,55
MGLL	Lipid biosynthesis	JZL184 RNAi	Preclinical data	MGLL promotes migration, invasion and survival of malignant cells, as well as *in vivo* tumour growth	56
PGAM1	PPP	PGMI-004A RNAi	Preclinical data	Pharmacological or genetic inhibition of PGAM1 attenuates tumour growth *in vitro* and *in vivo*, presumably owing to the 3PG-mediated inhibition of the PPP	57
PHGDH	Anaplerosis	RNAi	Preclinical data	PHGDH inhibition fails to affect serine availability, yet limits that of multiple intermediates of the TCA cycle	58,59
PKM2	PPP	TEPP-46 SAICAR Serine	Preclinical data	PKM2 activators reportedly limit the diversion of glucose towards the PPP, hence mediating antitumour effects	60-63
RNR	Deoxynucleotide synthesis	Fludarabine Gemcitabine Hydroxyurea	Fludarabine, gemcitabine and hydroxyurea are prescription drugs for the treatment of several tumours	Hydroxyurea is currently employed for the treatment of myeloproliferative disorders, psoriasis and CML	47
TKTL1	PPP	RNAi	Preclinical data	Depletion of TKTL1 limits the proliferation of gastric cancer cells *in vitro* and *in vivo*	64
TYMS	Thymidine synthesis	5-FU	Prescription drug for the treatment of several tumours	5-FU is routinely employed for the treatment of colorectal, pancreatic and breast carcinoma	47

Other metabolic circuitries					
CAs	Extracellular pH regulation	Acetazolamide Indisulam RNAi	Acetazolamide is a prescription drug for the treatment of glaucoma and several neurological disorders	Inhibition of CAs results in the normalization of extracellular pH, therefore limiting local invasion and metastasis	65
CPT1	NADPH metabolism	Etomoxir RNAi	Preclinical data	Inhibition of CPT1 results in the accumulation of ROS, ATP depletion and cell death	1-3
HIF-1	Hypoxic responses	Acriflavine PX-478	Preclinical data	Most, if not all, HIF-1-targeting agents have failed (or never reached) clinical development	66
IDO	Tryptophan metabolism	RNAi	Preclinical data	IDO-derived kynurenine promotes tumour progression via cell-intrinsic and cell-extrinsic mechanisms	67
mTOR	Cell growth Autophagy	Rapalogues Torins	Rapalogues are prescription drugs for the treatment of graft rejection and several tumours	Although mTOR inhibitors may limit tumour growth, they may also favour chemoresistance or neocarcinogenesis	68,69
NAMPT	NADH metabolism	FK866	Clinical development Preclinical data	Associated with dose-limiting thrombocytopenic effects	70-72
NHE1	Extracellular pH regulation	Amiloride Cariporide RNAi	Amiloride is a prescription drug for the treatment of hypertension and congestive heart failure	Clinical development of cariporide has been stopped owing to an unexpected incidence of stroke	65
PTGS2 AMPK?	Cell growth Autophagy	Aspirin	Over-the-counter non-steroidal anti-inflammatory drug	Although aspirin has been shown to activate AMPK, its antineoplastic activity appears to stem from on-target effects	73-75

2-DG, 2-deoxy-*D*-glucose; 2-HG, *R*(-)-2-hydroxyglutarate; 3-BP, 3-bromopyruvate; 3PG, 3-phosphoglycerate; 3PO, 3-(3-pyridinyl)-1-(4-pyridinyl)-2-propen-1-one; 5-FU, 5-fluorouracil; 968, 5-[3-bromo-4-(dimethylamino)phenyl]-2,2-dimethyl-2,3,5,6-tetrahydrobenzo[a]; ACC, acetyl-CoA carboxylase; ACLY, ATP-citrate lyase; ALL, acute lymphoblastic leukaemia; AMPK, 5'-AMP-activated protein kinase; BPTES, bis-2-(5-phenylacetamido-1,2,4-thiadiazol-2-yl)ethyl sulfide; C75, 4-methylene-2-octyl-5-oxotetrahydrofuran-3-carboxylic acid; CA, carbonic anhydrase; CHC, α-cyano-4-hydroxycinnamate; CK, choline kinase; CK37, *N*-(3,5-dimethylphenyl)-2-[[5-(4-ethylphenyl)-1H-1,2,4-triazol-3-yl]sulfanyl] acetamide; CML, chronic myelogenous leukaemia; CPT1, carnitine palmitoyltransferase I; DCA, dichloroacetate; DHFR, dihydrofolate reductase; EGCG, epigallocatechin gallate; FASN, fatty acid synthase; FK866, N-[4-(1-benzoyl-4-piperidinyl)butyl]-3-(3-pyridinyl)-2E-propenamide; FX11, 3-dihydroxy-6-methyl-7-(phenylmethyl)-4-propylnaphthalene-1-carboxylic acid; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; GBM, glioblastoma multiforme; GLS1, glutaminase 1; GLUD1, glutamate dehydrogenase 1; GLUT, glucose transporter; HADHA, trifunctional protein, α subunit; HIF-1, hypoxia-inducible factor 1; HK, hexokinase; HMGCR, 3-hydroxy-3-methyl-glutaryl-CoA reductase; IDH, isocitrate dehydrogenase; IDO, indoleamine-2,3-dioxygenase; JZL184, 4-nitrophenyl-4-[bis(1,3-benzodioxol-5-yl)(hydroxy)methyl]piperidine-1-carboxylate; LDHA, lactate dehydrogenase A; MCT, monocarboxylate transporter; MGLL, monoacylglycerol lipase; mTOR, mammalian target of rapamycin; NAMPT, nicotinamide phosphoribosyltransferase; TEPP-46, 6-[(3-aminophenyl)methyl]-4,6-dihydro-4-methyl-2-(methylsulfinyl)-5h-thieno[2',3':4,5]pyrrolo[2,3-d]pyridazin-5-one; NHE1, Na^+/H^+ exchanger 1; PC, pyruvate carboxylase; PDK1, pyruvate dehydrogenase kinase 1;

PDK2, pyruvate dehydrogenase kinase 2; PFK15, 1-(4-pyridinyl)-3-(2-quinolinyl)-2-propen-1-one; PFKFB3, 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3; PGAM1, phosphoglycerate mutase 1; PGMI-004A, PGAM1 inhibitor 004A; PHGDH, phosphoglycerate dehydrogenase; PKM2, pyruvate kinase, muscle, M2 isoform; PPP, pentose phosphate pathway; PTGS2, prostaglandin-endoperoxide synthase 2; PX-478, S-2-amino-3-[4'-*N*,*N*,-bis(2-chloroethyl)amino]phenyl propionic acid N-oxide dihydrochloride; RNAi, RNA interference; RNR, ribonucleotide reductase; ROS, reactive oxygen species; SAICAR, succinylaminoimidazolecarboxamide ribose-5'-phosphate; SB-204990, (2*R*)-2-[(2*S*)-8-(2,4-dichlorophenyl)-2-hydroxyoctyl]-2-hydroxybutanedioic acid; TCA, tricarboxylic acid; TKTL1, transketolase-like protein 1; TLN-232, *D*-Phe-Cys-*D*-Trp-Lys-Cys-Thr-NH_2; TYMS, thymidylate synthase; WZB117, 3-hydroxy-benzoic acid 1,1′-(3-fluoro-1,2-phenylene) ester. *Where company name is not indicated, this is not applicable, the agent is an academic compound or it is a generic drug.

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