Table 1 | Mechanisms of resistance (and sensitivity) of hypoxic cells to cytotoxic therapy

Effect of hypoxia	Resistance/ sensitivity	Mechanism	Agents affected	Example	Ref
Lack of oxidation of DNA free radicals by O_2	Resistance	Failure to induce DNA breaks	Ionising radiation	2-3-fold increase in radiation dose required for equivalent cell kill	1
			DNA-breaking antibiotics	Bleomycin	2
Cell cycle arrest in G1 or G2 phase	Resistance	Repair before progression to S or M phase	Cycle-selective chemotherapy drugs	5-fluorouracil	3
Cell cycle arrest in S-phase	Sensitivity	Collapse of stalled replication forks	PARP-1 inhibitors[a]	ABT-888	4
Distance from vasculature (indirect)	Resistance	Compromised drug exposure	Drugs extensively bound in tumour cells	Taxanes	5
Extracellular acidification (indirect)	Resistance	decreased uptake	Basic drugs	Doxorubicin	6
	Sensitivity	Increased uptake	Acidic drugs	Chlorambucil	7
Resistance to apoptosis	Resistance	Genetic selection of TP53 mutants	Multiple		8
		Downregulation of Bid,Bax	Multiple	Etoposide	9
Genomic instability	Resistance	Mutagenesis [10]	Multiple	DHFR amplification and methotrexate	11
Suppression of DNA repair	Resistance	Downregulation of MMR	DNA methylating agents		12
	Sensitivity	Downregulation of NER	Bulky DNA monoalkylating and crosslinking agents		13
		Downregulation of HR	DNA crosslinking agents	Cisplatin	114
HIF-1 stabilisation	Resistance	Expression of ABC transporters	ABC transporter substrates	MDR1 and doxorubicin	15
		Downregulation of NHEJ	DNA double strand breaking agents	Etoposide	16

[a]Also sensitised by downregulation of HR under hypoxia. DHFR, dihydrofolate reductase; NHEJ, non-homologous end joining; HR, homologous recombination repair; MMR, mismatch repair; PARP, poly(ADP-ribose) polymerase

Table 2 | Representative examples of the prognostic and predictive significance of hypoxia in human cancer

Measure of hypoxia	Probe	Clinical setting	Outcome for hypoxic tumours	Ref
Oxygen concentration	Eppendorf oxygen electrode	Chemoradiation of advanced HNSCC	Worse OS	17
		Irradiation of soft tissue sarcomas before surgery	Worse DFS due to higher rate of distant metastasis	18
		Brachytherapy irradiation of localised prostate cancer	Decreased biochemical control (PSA)	19
		Cervical carcinoma	Worse DFS in node negative patients due to higher rate of distant metastases	20
Endogenous markers	HIF1α	Lymph node negative breast cancer	Worse OS	21
	HIF1α	BRCA-1 mutant breast cancer	Worse DFS	22
	HIF2α, CA-9	CHART trial in HNSCC	Worse local control and OS	23
	CA-9	Adjuvant chemotherapy of breast cancer	Worse OS	24
	Osteopontin	Radiotherapy for HNSCC	Nimorazole (hypoxic radiosensitiser) improved local control and OS	25
	Lysyl oxidase (LOX)	Breast cancer	Worse metastasis-free survival	26
	Hypoxic gene signature	HNSCC, breast cancer	Worse outcome, multiple endpoints.	27
	Hypoxic gene signature	Hepatocellular carcinoma	Worse OS	28
Exogenous probes	Pimonidazole	Radiotherapy for advanced HNSCC	Worse local control	29
	EF5	Post-surgical irradiation of HNSCC	Worse DFS	30

CHART, continuous hyperfractionated accelerated radiotherapy; DSF, disease-free survival; EF5, pentafluorinated etanidazole; HNSCC, head and neck squamous cell carcinoma; OS, overall survival; PFS, progression free survival; PSA, prostate specific antigen

Table 3 | Bioreductive prodrugs of DNA-reactive cytotoxins recently or currently in clinical development.

Prodrug	Clinical status	Company/ Institution	Chemical class	Mechanism of activation[a]	Mechanism of cytotoxicity	One-electron reductases	Two-electron reductases	K_{O2} (μM)	Ref
Tirapazamine (SR 4233)	Phase III, cervix (Closed)	SRI International/NCI	Aromatic *N*-oxide	1, 3 [R•]	Complex DNA damage	CYPOR, iNOS	NQO-1[b]	~ 1	31
Apaziquone (EO9)	Phase III, bladder (Closed)	Spectrum	Quinone	1,4 [X,Y]	ICL	CYPOR	NQO-1		32
TH-302	Phase I/II , multiple (active)	Threshold	Nitro	1, 3 [D]	ICL	CYPOR		~10[c]	33
PR-104	Phase I/II, leukaemia (active)	Proacta/U. Auckland	Nitro	1/2, 4,5,6 [Y,Z]	ICL	CYPOR, iNOS,MTRR, NDOR1	AKR1C3	~0.1	34
Banoxantrone (AQ4N)	Recent Phase I/II	Novacea	Aliphatic *N*-oxide	2, 5 [Y]	TopoII	iNOS	CYP3A4, CYP2S1		35
Prolarix (CB 1954 + EP-0152R)	Phase II, HCC (discontinued)	BTG	Nitro	1 /2,4,5,6 [Y,Z]	ICL	CYPOR, iNOS	NQO-1, NQO-2		36
RH1	Recent Phase I	CRUK	Quinone	1,4 [X,Y]	ICL		NQO-1, NQO-2		37
NLCQ-1	Preclinical	Evanston Hospital	Nitro	1,4,5	TopoII or Multiple?	CYPOR		~1[c]	38
SN30000 (CEN-209)	Preclinical	Centella/U. Auckland	Aromatic *N*-oxide	1,3 [R•]	Complex DNA damage	CYPOR		~ 1	39
SN29730	Preclinical	U. Auckland	Nitro	1, 4,5,6 [Z]	Adenine *N*3 alkylation	CYPOR			40
KS119W	Preclinical	Yale U.	Nitro	1,4,5,6 [D]	Guanine O6 ICL	B5R, CYPOR			41

See FIG. 2B for additional chemical structures. [a]Reaction numbers refer to FIG. 2A. Active cytotoxins (X,Y etc in FIG. 2A) are shown in square brackets. [b]Detoxifying. [c]Gas phase O_2 concentration [42] (K_{O2} values of 2-nitroimidazoles are typically much lower based on solution oxygen concentrations). AKR, aldo-keto reductase; B5R, NADH:cytochrome b5 reductase, CYP, cytochrome P450; CYPOR, NADPH:cytochrome P450 oxidoreductase; HCC, hepatocellular carcinoma; NDOR1, NADPH-dependent diflavin oxidoreductase-1; ICL, DNA interstrand crosslink; iNOS, inducible nitric oxide synthase; MTRR, methionine synthase reductase

Table 4 | Representative examples of pharmacological approaches to molecular targets in hypoxic cells.

Pathway	Target	Agent	Class	Ref
HIF-1a expression.	HIF antisense mRNA	EZN-2698	RNA oligonucleotide	43
	Topoisomerase I	Topotecan	Camptothecan analogues	44
	Multiple	PX-478	Melphalan N-oxide	45
	Translation	Digoxin	Cardiac glycoside	46
	HSP90	Geldanamycin, 17-AAG	Benzoquinone ansamycin antibiotics	47
HIF-1 transcription	HIF-p300 binding	Chetomin and analogues	Dithiodiketopiperazine	48
	Thioredoxin-1	PX12	Imidazole disulfide	49
		PMX290	Indoloquinol	50
	DNA binding	Echinomycin	DNA intercalator	51
HIF-1 target genes	CA-9/CA-12	Aryl sulfonamides	Sulfonamide zinc binders	52
	GLUT-1	Glufosfamide	Glucose isophosphoramide mustard	53
		2-GLU-SNAP	Glucose SNAP conjugate	54
		Fasentin	Oxobutanilide	55
		STF-31154	Unknown	56
	Hexokinase II	5TDG, 2DG, 2FDG	Glycolysis inhibitors	57-59
	MCT1	α-Cyano-4-hydroxycinnamate	Lactate transport inhibitor	60
Receptor tryosine kinases	VEGFR	Bevacizumab	Monoclonal antibody	61

	EGFR	Gefitinib, erlotinib	ATP competitive kinase inhibitors	62
		Cetuximab	Monoclonal antibody	63
Ras-MAPK signalling	BRAF	Sorafenib	ATP competititive kinase inhibitor	64
mTOR	mTORC1	Rapamycin, everolimus	Allosteric binders of FKBP12-rapamycin binding domain	65
		WYE-125132	ATP-competitive mTOR kinase inhibitor	66
	Autophagy	Chloroquine	Lysosomal pH	67
UPR	HSP90	Geldanamycin, 17-AAG	Benzoquinone ansamycin antibiotic	68
	IRE1 endonuclease	Salicaldehydes	IRE1 inhibitor	69
	26S proteosome	Bortezomib	Boronic acid tripeptide	70
		Nelfinavir, ritonavir	HIV protease inhibitors	71
	SERCA	2,5-Dimethyl celecoxib	Celecoxib analogue	72

Abbreviations: CA-9, carbonic anhydrase 9; EGFR, epidermal growth factor receptor; FKBP12, FK506 binding protein-12; HIV, human immunodeficiency virus; HSP90, heat shock protein 90; IRE1, inositol requiring endonuclease 1; MAPK, mitogen-activated protein kinase; MCT1, monocarboxylate transporter 1; mTOR, molecular target of rapamycin; ; SERCA, sarco/endoplasmic reticulum Ca2+-ATPase; SNAP, S-nitroso-acetyl-penicillamine; VEGFR, vascular endothelial growth factor receptor.

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