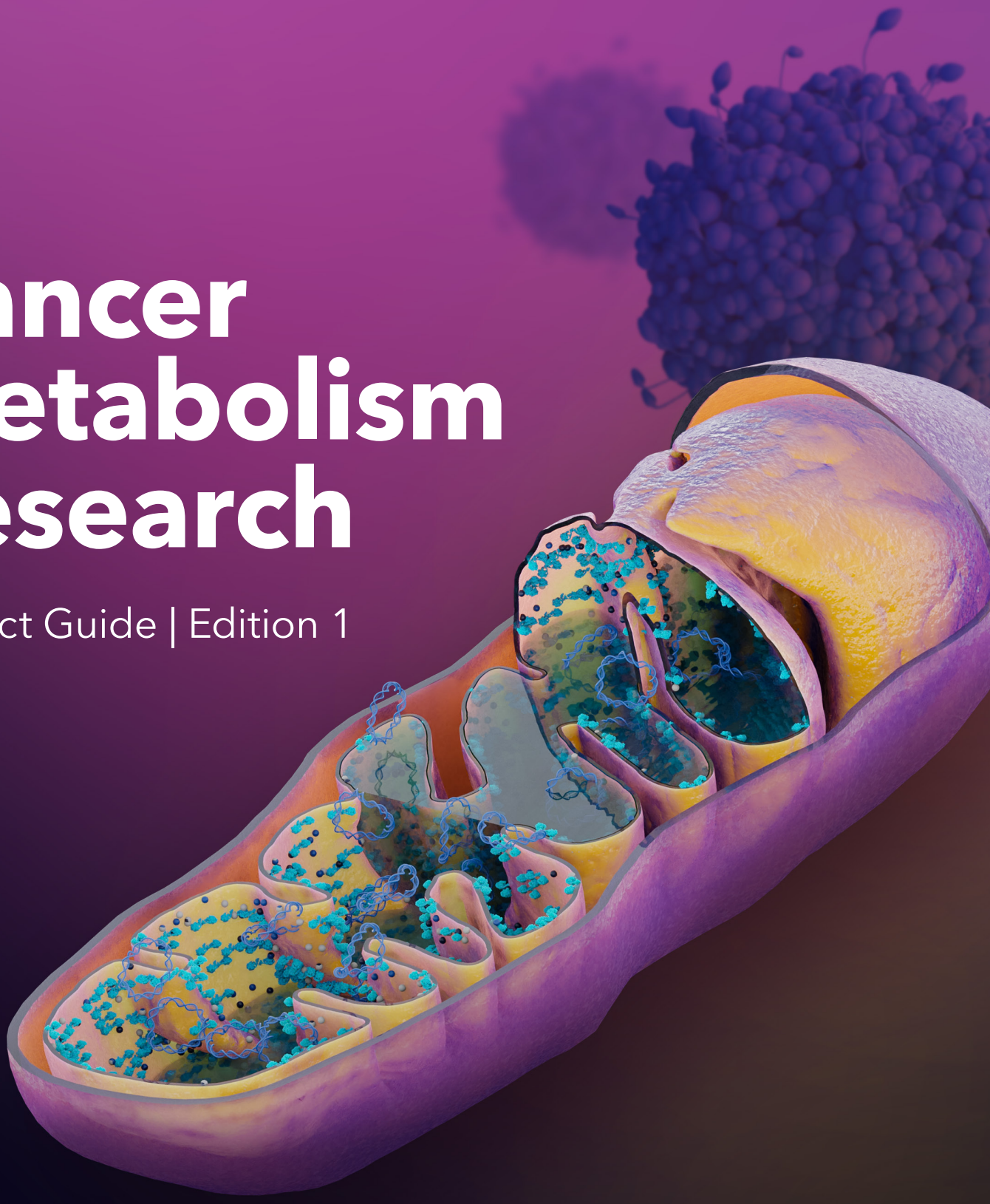
Cancer Metabolism Research

Product Guide | Edition 1



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Introduction

The discovery that cancer cells generate a large proportion of their ATP by metabolizing glucose via aerobic glycolysis, as opposed to mostly through oxidative phosphorylation (OXPHOS) in normal cells, was made by Otto Warburg in 1924. This Warburg effect was initially thought to be a cause of cancer, but it was subsequently established that the shift to glycolytic metabolism was an effect of cancer cell transformation. Malignant transformation and altered metabolism go hand in hand, because the rapid increase in proliferation places increased demand on metabolic processes that cannot be met by conventional cellular metabolism. Metabolic rearrangement has been associated with inactivation of tumor suppressor genes and activation of oncogenes, as well as with mutant enzyme (oncoenzyme) activity and the accumulation of tumorigenic metabolites (oncometabolites). Owing to the fundamental role of abnormal metabolism in cancer, metabolic reprogramming has been recognized as a hallmark of cancer and provides multiple therapeutic vulnerabilities that can be exploited in cancer research and treatment. This guide provides a background to cancer metabolism and highlights products to aid research in this field.

Cancer Metabolic Reprogramming

Genetic alterations and epigenetic modifications in cancer cells result in the abnormal regulation of cellular metabolic pathways compared with non-cancerous cells. Cancer cells require three crucial metabolic adaptations in order to rapidly proliferate and survive: Increased ATP production to fuel their high energy needs; increased biosynthesis of the three major classes of cellular building blocks, i.e., proteins, lipids and nucleic acids; an adapted redox system to counteract the increase in oxidative stress.

Malignant transformation is associated with the following:

- a shift from oxidative phosphorylation (OXPHOS) to glycolysis as the main source of ATP
- an increase in glucose metabolism through the pentose phosphate pathway (PPP)
- an increase in lipid biosynthesis; high glutamine consumption
- alterations in pH and redox regulation (**FIGURE 1**).

While metabolic reprogramming is a cancer hallmark, tumors display metabolic heterogeneity, with the tissue of origin and the nature of the transforming oncogene both influencing the metabolic profile of the cancer.

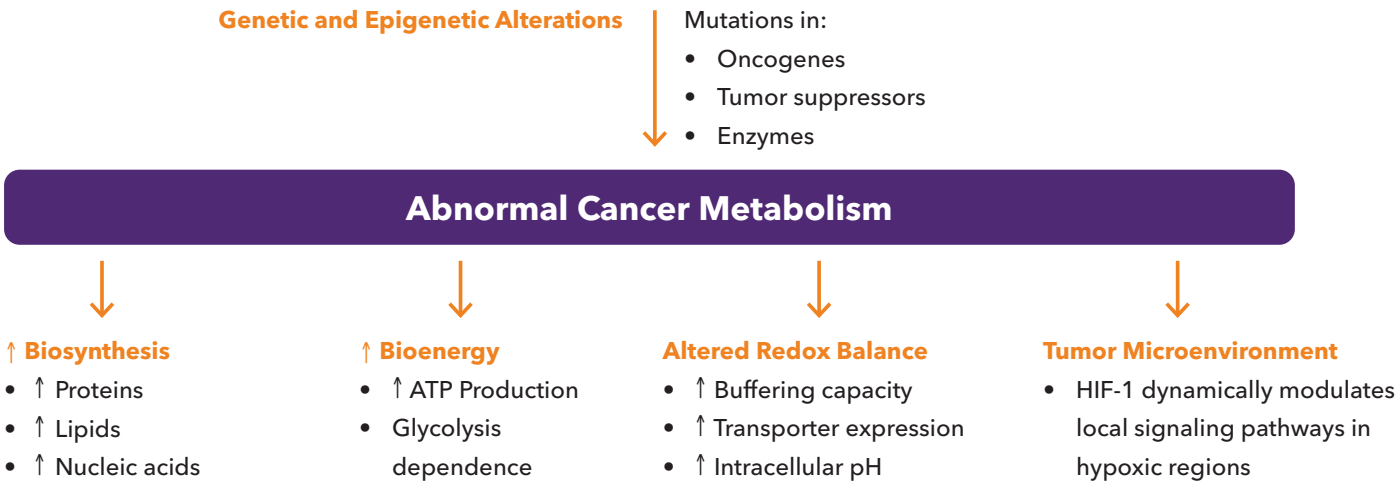


FIGURE 1: Metabolic Alterations in Cancer. Genetic and epigenetic mutations in cancer cells can alter the regulation of metabolic pathways. This results in increased biosynthesis, abnormal bioenergy production and an altered redox balance, which together promote cell proliferation and survival. Furthermore, microenvironments within large tumors can dynamically alter metabolic pathways creating heterogeneous populations of cells.

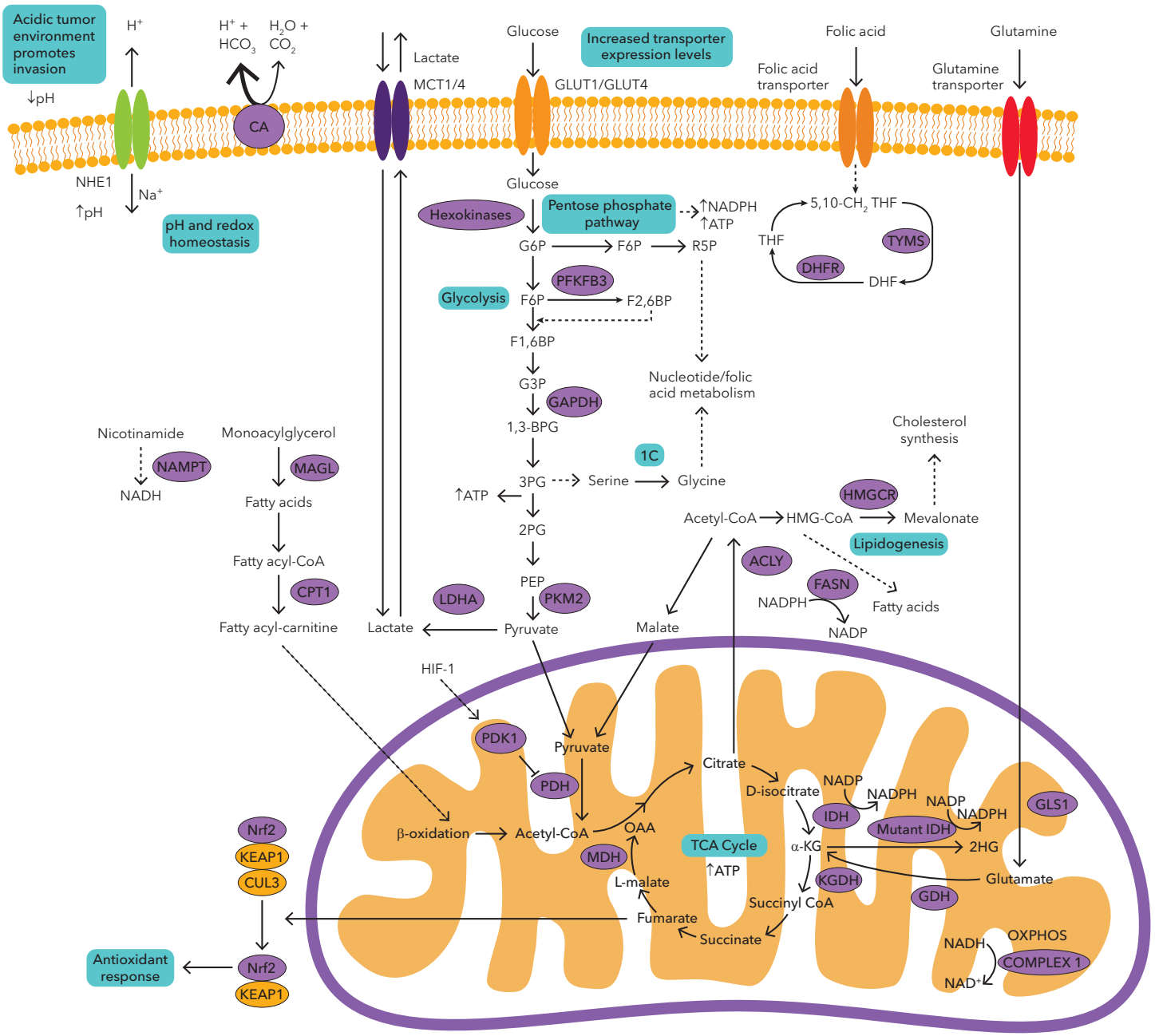


FIGURE 2: Main Targets in Cancer Metabolism. In cancer cells, increased transporter expression facilitates an increased uptake of substrates for metabolic pathways including glycolysis, PPP, OXPHOS and lipidogenesis. Mutant enzymes and abnormal regulation of these key pathways, drive cellular proliferation and promote cell survival. Furthermore, alterations in pH and the redox balance provide cytoprotective advantages and promote invasion and cell survival. ACLY, ATP citrate lyase; ATP, adenosine triphosphate; 1,3-BPG, 1,3-bisphosphoglyceric acid; 1C, one-carbon metabolism; CA, carbonic anhydrase; CPT1, carnitine palmitoyltransferase; CUL3, cullin 3; D2HG, D-2-hydroxyglutarate; DHF, dihydrofolate; DHFR, DHF reductase; FASN, fatty acid synthase; F1,6BP, fructose-1,6-bisphosphate; F2,6BP, fructose-2,6-bisphosphate; F6P, fructose 6-phosphate; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; GDH, glutamate dehydrogenase; GLUT, glucose transporter; GLS1, glutaminase; G3P, glyceraldehyde-3-phosphate; G6P, glucose-6-phosphate; HIF-1, hypoxia-inducible factor 1; HMGCR, HMG-CoA reductase; IDH, isocitrate dehydrogenase; α-KG, α-ketoglutarate; KGDH, α-ketoglutarate dehydrogenase; LDHA, lactate dehydrogenase A; MAGL, monoacylglycerol lipase; MCT, monocarboxylate transporter; MDH, malate dehydrogenase; NAD+/NADH, nicotinamide adenine dinucleotide (oxidized/reduced forms respectively); NADPH, nicotinamide adenine dinucleotide phosphate; NAMPT, nicotinamide phosphoribosyltransferase; Nrf2, nuclear factor (erythroid-derived 2)-like 2; OXPHOS, oxidative phosphorylation; PDH, pyruvate dehydrogenase; PDK, pyruvate dehydrogenase kinase; PEP, phosphoenolpyruvate; PFKFB3, 6-phosphofructo-2-kinase/fructose- 2,6-bisphosphatase; 2PG, 2-phosphoglycerate; 3PG, 3-phosphoglycerate; PKM2, pyruvate kinase M2 isoform; PPP, pentose phosphate pathway; ROS, reactive oxygen species; R5P, ribose-5-phosphate; 5,10-CH_2-THF, 5,10-methylene tetrahydrofolate; THF, tetrahydrofolate; TYMS, thymidylate synthase.

Broken arrow = additional intermediate steps not shown; Solid arrow = direct step

Enhanced rates of glycolysis (approximately 200-fold) place a large burden on cancer cells, which needs to be overcome in order for the cells to survive. Glucose metabolism via the glycolytic route produces ATP more rapidly than OXPHOS, but the process is far less efficient, so there is increased glucose demand. Glucose transporter expression is frequently increased in cancer cells to accommodate this. Furthermore, the enhanced rate of glycolysis produces large quantities of lactate which needs removing from the cell, so increased expression of lactate transporters is also often observed in cancer cells.

In addition to increased rates of glycolysis in tumor cells, there is an increase in the flux through the PPP. The PPP is required to generate ribose-5-phosphate (a precursor for purines and pyrimidines) and NADPH (Cat. No. 5515) (required for lipid and nucleotide synthesis, as well as redox homeostasis). Depending on the requirements of the cancer cell, glucose can be directed into the PPP or glycolysis pathway or both. For example, during high oxidative stress, cancer cells divert the flux of glucose away from glycolysis into the PPP to produce more NADPH.

Another commonly seen adaptation is an increase in the number of glutamine transporters. These are required to facilitate the increased demand for glutamine (termed glutamine addiction) in lipid biosynthesis and NADPH production. In addition, there is an increase in uptake of glycine and serine for amino acid biosynthesis and the replenishment of tricarboxylic acid (TCA, also known as the Krebs cycle) cycle intermediates. These altered pathways allow for the sufficient supply of nucleic acids, proteins and membrane lipids required to sustain the increased demands of proliferating cells.

Glucose and Glutamine Transporters

Glucose and glutamine can be broken down into the precursors of many cellular building blocks, as well as facilitating ATP production. Increased glucose and glutamine catabolism also leads to abundant NADPH production, which has cytoprotective effects and allows the cancer cell to buffer oxidative damage sustained through rapid proliferation.

The glucose transporter (GLUT) family of transporters and amino acid transporter 2 (ASCT2 or SLC1A5) are responsible for the increased uptake of glucose and glutamine respectively, making them promising targets for anticancer drugs. Overexpression of RAS or BRAF is associated with increased expression of GLUT1. Renal cell carcinomas (RCCs) have mutations in the von Hippel-Lindau (VHL) tumor suppressor gene with associated increases in glucose dependence. Selectively targeting GLUT1 with inhibitors such as STF 31 (Cat. No. 4484) has shown some promising results, selectively killing RCCs over normal cells *in vivo*, by causing necrotic cell death in VHL-deficient RCC cells. Ovarian cancers overexpress GLUT1 and exhibit high basal glycolytic activity. Inhibition of GLUT1 with the potent and selective inhibitor BAY 876 (Cat. No. 6199) reduces glycolysis rates and ATP production and suppresses ovarian cancer cell proliferation *in vitro* and *in vivo*.

The first step in glutamine catabolism is the hydrolysis of glutamine into glutamate and ammonia by glutaminase (GLS1). The essential nature of this process in cancer cell survival and proliferation makes GLS1 another potential target for cancer therapy. Inhibition of GLS1 with CB 839 (Cat. No. 7591) has been shown to attenuate tumor growth in patient-derived triple-negative breast cancer xenograft models, while BPTES (Cat. No. 5301) kills hypoxic tumor cells *in vitro*, together providing evidence of the crucial role of GLS1 in cancer cell survival. Furthermore, a study has shown that inhibiting ASCT2 with compounds such as the selective estrogen receptor modulators Tamoxifen (Cat. No. 0999) and Raloxifene (Cat. No. 2280) has resulted in reduced glutamine uptake and suppressed cell growth, as well as increasing apoptosis in breast cancer cells that are estrogen insensitive. A selective inhibitor targeting ASCT2 could make a useful research tool or possible treatment for cancer.

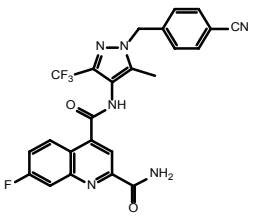
Another glutamine transporter, LAT1 (large neutral amino acid transporter 1, SLC7A5), exports glutamine in exchange for branched-chain amino acids, particularly leucine. Expression of LAT1 is upregulated in many cancers. It has been suggested that the activity of LAT1 and ASCT2 are linked, whereby the latter drives glutamine uptake, which then acts as an exchange substrate for the uptake of leucine by LAT1. Leucine is a regulator of mTORC1 (mammalian target of rapamycin complex), which has an important role in tumor cell growth. Inhibitors of LAT1 such as BCH (Cat. No. 5027) and KYT 0353 (Cat. No. 5026) could be used to further elucidate the role of this transporter in cancer cells.

Glycolysis

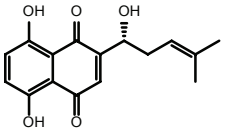
Many cancer cells rely on switching from OXPHOS to glycolysis as their main source of ATP. Glycolysis is the metabolic pathway by which glucose is converted to pyruvate and generates fuel in the form of ATP. The process also provides building blocks for lipid biosynthesis, as well as nucleotide synthesis via 1C (one-carbon) metabolism.

Small molecules that target glycolytic enzymes and transporters are being investigated as selective anticancer therapies. These targets include hexokinase, 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase (PFKFB3), monocarboxylate transporter (MCT) and lactate dehydrogenase A (LDHA). Several *in vitro* and *in vivo* models

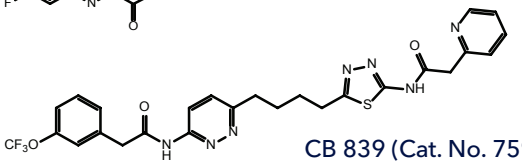
BOX 1 Glucose Metabolism and Glycolysis Products



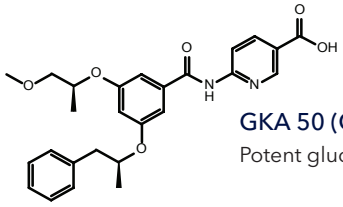
BAY 876 (Cat. No. 6199)
Potent and selective GLUT1 inhibitor; reduces glycolysis rates and ATP production in ovarian cancer cells



(R)-Shikonin (Cat. No. 6829)
Inhibitor of tumor-specific pyruvate kinase M2 (PKM2); suppresses glycolysis in cancer cells and inhibits tumor proliferation



CB 839 (Cat. No. 7591)
Potent non-competitive glutaminase (GLS1) inhibitor; reduces glutamine consumption and glutamate production in breast cancer cells



GKA 50 (Cat. No. 5133)
Potent glucokinase activator

of cancer have shown that small molecule inhibitors of these targets can limit the growth and survival of certain types of tumor (**BOX 1**).

Following the uptake of glucose by GLUT, the enzyme hexokinase catalyzes the conversion of glucose into glucose-6-phosphate. Glucose-6-phosphate is converted into pyruvate via multiple steps in the glycolytic pathway, or enters the PPP, which provides NADPH and intermediates for nucleotide synthesis.

The phosphorylation of glucose directly couples extramitochondrial glycolysis to intramitochondrial oxidative phosphorylation. In addition to glucose metabolism, mitochondrial hexokinases have been implicated in antiapoptotic signaling. Key compounds for studying hexokinases include Lonidamine (Cat. No. 1646) and GKA 50 (Cat. No. 5133), which inhibit and activate mitochondrial hexokinases respectively.

HIF-1-induced PFKFB3 expression is a critical adaptation in some cancer cells because it elevates concentrations of fructose-2,6-bisphosphate, a key glycolysis stimulator. PFKFB3 inhibitor PFK 15 (Cat. No. 5339) suppresses Fru-2,6-BP levels, which in turn suppresses glycolysis and attenuates cell growth. Another PFKFB3 inhibitor, 3PO (Cat. No. 5121) reduces glycolytic flux and suppresses glucose uptake. It also inhibits endothelial cell proliferation and amplifies the antiangiogenic effect of VEGFR blockade resulting in impaired vessel formation.

Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) catalyzes the conversion of glyceraldehyde 3-phosphate to 1,3-bisphosphoglycerate in the glycolytic pathway, concomitantly converting NAD^+ to NADH. GAPDH is overexpressed in many cancers and is more highly expressed in more rapidly growing cancers. The inhibitor CGP 3466B (Cat. No. 2966) reduces tumor proliferation and could be used to explore the role of GAPDH further.

Several oncogenes have been observed to drive metabolic changes in cancer cells. For example, cells expressing Myc mutants display an increase in glucose uptake, and an increase in expression of the M2 isoform of pyruvate kinase (PKM2). PKM2 is involved in the last step of glycolysis and reduced activity diverts glycolytic intermediates to anabolic metabolism through the PPP and promotes glutamine addiction (see **FIGURE 2**). Activating PKM2 has been suggested as a potential therapeutic strategy as it could promote glycolytic flux at the expense of the PPP, which is essential for nucleotide biosynthesis. However, the PKM2 inhibitor (R)-Shikonin (Cat. No. 6829) has been shown to decrease glucose uptake and aerobic glycolysis in cancer cells, promoting apoptosis and suppressing tumor proliferation *in vitro* and *in vivo*. In addition, it has been found that PKM2 is not a requirement for tumor growth in a range of models.

Pyruvate is either transported into the mitochondria, where it is converted to acetyl-CoA by pyruvate dehydrogenase and enters the TCA, or can be converted to lactate by LDHA. The LDHA inhibitor GSK 2837808A (Cat. No. 5189) inhibits lactate production from pyruvate in some cancer cell lines, reducing glucose uptake and enhancing mitochondrial oxygen consumption in a hepatocellular carcinoma cell line. The increased metabolic rate is often associated with an increase in expression of MCT, to either remove the waste product lactic acid or to import lactic acid to fuel the reverse Warburg effect. Preclinical data have shown that the use of MCT inhibitors, such as AR-C155858 (Cat. No. 4960), decrease glycolytic metabolism and glutathione synthesis and reduce proliferation of cancer cells.

Useful tools for studying the metabolic profile of cancer cells are the Scotfluor probes, SCOTfluor glucose probe 510 (Cat. No. 7447) and SCOTfluor lactic acid probe 510 (Cat. No. 7448). These fluorescent probes enable the real-time tracking of glucose and lactic acid, respectively, in live cells.

Researchers are investigating ways to reverse the metabolic change from OXPHOS to glycolysis. DCA (Cat. No. 2755) is an inhibitor of mitochondrial pyruvate dehydrogenase kinase (PDK), an enzyme that is often hyper-activated in cancer cells as a result of aberrant Myc, RTK or HIF-1 signaling. DCA shifts pyruvate metabolism from glycolysis and lactate production to glucose oxidation in the mitochondria.

Tricarboxylic Acid (TCA) Cycle

Glucose is broken down into pyruvate, which is then transported into the mitochondria. It is converted into acetyl-CoA which then enters the TCA cycle. This produces energy in the form of ATP, precursors for amino acid synthesis and the reducing agent NADH (**FIGURE 2**).

One of the major enzymes that feeds into the cycle is glutamate dehydrogenase (GDH), which converts glutamate to α-ketoglutarate (α-KG), an essential intermediate in the TCA cycle. Inhibition of GDH has been shown to suppress the use of glutamine in the TCA cycle and sensitizes glioblastoma cells to glucose withdrawal. EGCG (Cat. No. 4524), a GDH inhibitor, increases the sensitivity of glioblastoma cells to drugs that inhibit glycolysis. α-KG is a substrate for the mutant form of isocitrate dehydrogenase (IDH), which has been linked to oncogenesis. In hypoxic cancer cells or in those with defects in the electron transport chain, HIF-1 mediates signaling that upregulates PDK1 and Myc. This in turn drives IDH1-mediated reductive metabolism of glutamine, a process that is integral to lipogenesis in cancer cells. Mutant IDH converts α-KG to D-2-hydroxyglutarate (D2HG) resulting in high intracellular levels of D2HG. D2HG competitively blocks α-KG binding at a family of enzymes called 2-OG-dependent dioxygenases, which are regulators of important epigenetic events. IDH enzyme mutants are strongly associated with hypermethylation of CpG islands in acute myeloid leukemia (AML) and glioblastomas. Furthermore, IDH mutations also impair cell redox capacity. The mutant IDH selective inhibitor AGI 5198 (Cat. No. 7087) reduces production of the oncometabolite D2HG and suppresses growth of tumors bearing mIDH1. Another mIDH1 inhibitor, Ivosidenib (Cat. No. 7761) reduces intracellular levels of the oncometabolite 2-HG (Cat. No. 6122) and impedes tumor growth, invasion, and metastasis (**BOX 2**).

Targeting multiple points in cancer metabolic pathways is becoming a key strategy in investigational cancer treatment. An early example of this is the lipoate analog CPI 613 (Cat. No. 5348), which inhibits both pyruvate dehydrogenase (PDH) and α-ketoglutarate dehydrogenase (KGDH). This disrupts tumor cell mitochondrial metabolism and increases mitochondrial reactive oxygen species (ROS) production in lung carcinoma cells, while displaying no effect on KGDH activity in normal bronchial epithelial cells.

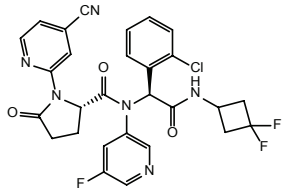
Lipidogenesis

Evidence suggests that in certain types of cancer, such as prostate cancer, the initiation of proliferation relies more on lipid metabolism than glycolysis. Targeting fatty acid synthesis can impair a cell's ability to proliferate and survive, because it limits lipid membrane production, which is essential for cellular expansion, as well as blocking β-oxidation of fatty acids in mitochondria. (R)-(+)-Etomoxir (Cat. No. 4539), a carnitine palmitoyltransferase (CPT1) inhibitor blocks β-oxidation in mitochondria and suppresses the synthesis of cardiolipin – a major membrane phospholipid in the mitochondria. Orlistat (Cat. No. 3540) (**BOX 3**) blocks lipid synthesis and inhibits fatty acid synthase (FASN), an enzyme that has been linked to tumor progression. Furthermore studies have shown that when used together, (R)-(+)-Etomoxir and Orlistat act synergistically to decrease the viability of prostate cancer cells.

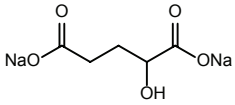
ATP Citrate Lyase (ACLY) is a key enzyme linking glucose metabolism to lipidogenesis. It catalyzes the conversion of citrate from the TCA cycle to cytosolic acetyl-CoA, which can subsequently be used in the generation of fatty acids. The ACLY inhibitor SB 204990 (Cat. No. 4962) decreases cholesterol and fatty acid synthesis and reduces proliferation of cancer cells showing anaerobic glycolysis both *in vitro* and *in vivo*.

Acetyl-CoA carboxylase 1 (ACC1) is the dominant ACC isozyme expressed in tumor cells and as such represents a potential cancer therapeutic target. ACC catalyzes the first step in the conversion of acetyl-CoA to fatty acids. Inhibition of ACC1 using the small molecule PF 05175157 (Cat. No. 5790), is associated with significant disturbances in cancer cell metabolism and transcription, with accompanying suppression of tumor growth.

BOX 2 TCA Cycle

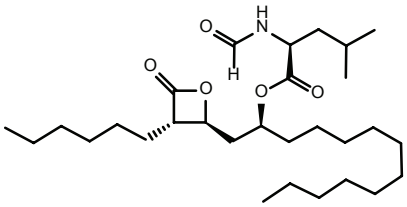


Ivosidenib (Cat. No. 7761)
Potent inhibitor of mIDH1; reduces intracellular 2-HG levels

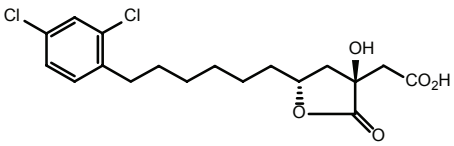


(RS)-2-Hydroxyglutaric acid (Cat.No. 6122)
Oncometabolite; synthesized by mIDH1 and TCA enzymes

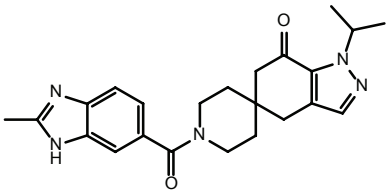
BOX 3 Fatty Acid and Lipid Metabolism



Orlistat (Cat. No. 3540)
Fatty acid synthase inhibitor; inhibits the thioesterase domain and leads to cell cycle arrest



SB 204990 (Cat. No. 4962)
ATP citrate lyase inhibitor; inhibits fatty acid and cholesterol synthesis in liver cancer cells



PF 05175157 (Cat. No. 5790)
Potent acetyl-CoA carboxylase (ACC) 1 and 2 inhibitor

The lipolytic enzyme monoacylglycerol lipase (MAGL) plays an important role in lipid metabolism and has been implicated in the pathogenesis of various cancers. It is highly expressed in various aggressive human tumors and has been shown to promote cancer cell migration and invasion *in vivo*. Highly selective and potent MAGL inhibitors, like JZL 184 (Cat. No. 3836) reduce levels of free fatty acids in primary tumors and suppress migration and invasion of xenograft tumor growth in mice.

Nucleotide Synthesis, 1C Metabolism and the PPP

De novo nucleotide synthesis is required by cancer cells for continued proliferation. New nucleotides can be derived from ribose-5-phosphate in the PPP, via one-carbon (1C) metabolism or from intermediates in the TCA cycle.

1C metabolism is a series of metabolic pathways that are essential for the biosynthesis of nucleotides and amino acids and entails the folate-mediated transfer of one-carbon or methyl groups. Tetrahydrofolate (THF) is an essential 1C carrier and once bound to THF, 1C units can switch between different oxidation states including 5,10 methylene-THF and 5-methyl-THF.

Several approved cancer treatments, known as antimetabolites, target 1C metabolism, such as 5-Fluorouracil (Cat. No. 3257), Methotrexate (Cat. No. 1230), and Pemetrexed (Cat. No. 6185), which are inhibitors of thymidylate synthase. Thymidylate synthase (TS) converts dUMP to dTMP by transferring a 1C unit from 5,10 methylene-THF with the resulting formation of dihydrofolate (DHF). DHF is then recycled into tetrahydrofolate (THF) by the NADPH-dependent dihydrofolate reductase. Methotrexate and Pemetrexed also inhibit dihydrofolate reductase.

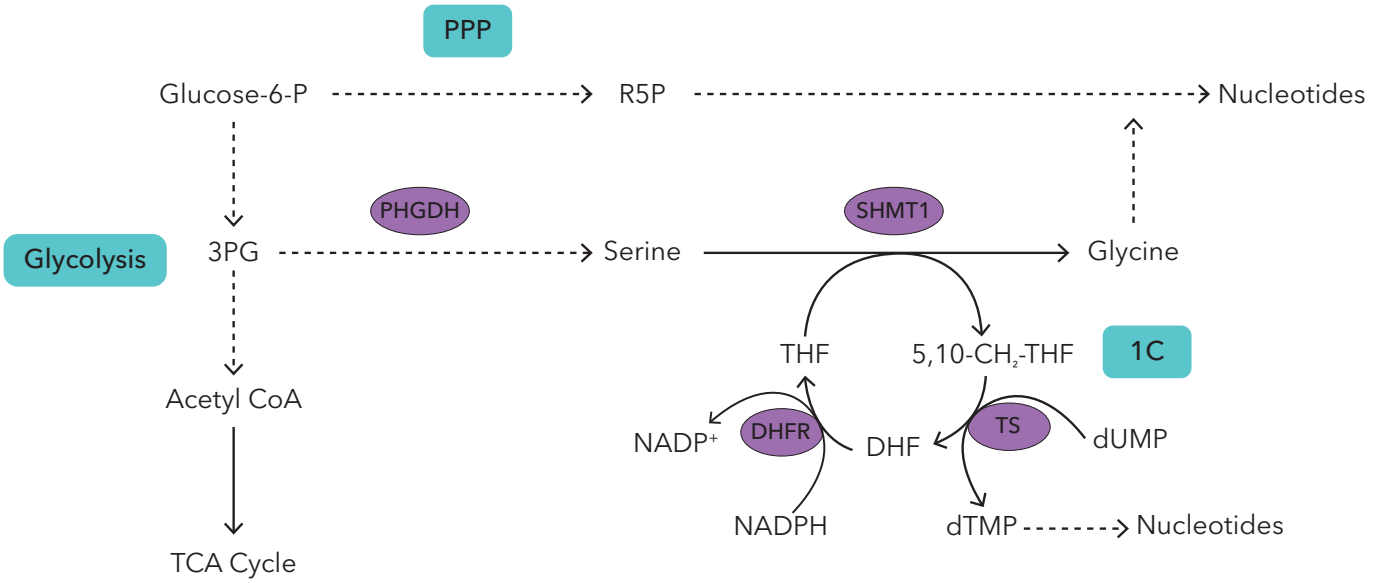


FIGURE 3: Schematic highlighting the role of 1C metabolism in nucleotide synthesis.

Serine is critical for providing 1C units for nucleotide biosynthesis, and can be derived from 3-phosphoglyceric acid (3PG) in the glycolytic pathway. The first and rate-limiting step in this process is the conversion of 3PG to 1,3-bisphosphoglycerate (1,3BPG), which is catalyzed by phosphoglycerate dehydrogenase (PHGDH). This is a target of interest as its expression is increased in cancers. The PHGDH inhibitor CBR 5884 (Cat. No. 5836) reduces *de novo* serine biosynthesis and inhibits growth of tumor cell lines in which PHGDH expression is upregulated (**FIGURE 3**).

The next step is the synthesis of serine from 1,3BPG which is catalyzed by phosphoserine aminotransferase 1 (PSAT1). Serine hydroxymethyltransferase (SHMT) then uses 5,10-methylene-THF to convert serine into glycine, donating a methyl group to THF in the process, and thereby mediating 1C metabolism. Since 1C units are a requirement for nucleotide generation, SHMT has been explored as a possible target for cancer therapy and the inhibitor SHIN 1 (Cat. No. 6998) has been found to reduce growth of colorectal cancer cells *in vitro* (**BOX 4**).

Drivers of Metabolic Reprogramming

PI 3-K/AKT/mTOR Signaling Pathway

Growth factors regulate the balance between cell proliferation and death, by binding to transmembrane receptors and activating intracellular signaling pathways, including phosphoinositide 3-kinase (PI 3-K) and mitogen-activated protein kinase (MAPK) pathways. Growth factor receptors have intrinsic kinase activity and in human cancers these receptor tyrosine kinases (RTK) frequently carry mutations, which results in upregulation of these signaling pathways.

One of the signaling pathways activated via RTKs is PI 3-K/Akt/mTOR (**FIGURE 4**). Growth factors activate RTKs resulting in recruitment of PI 3-K. Activated PI 3-K then catalyzes PIP2 into PIP3 which in turn activates Akt (protein kinase B); Akt in turn activates mTOR signaling and NRF2 translocation to the nucleus. PI 3-K/Akt/mTOR signaling dysfunction is frequently observed in cancers. The most common cause of PI 3-K/Akt/mTOR pathway dysfunction in human cancers is aberrant RTK regulation, although mutations in the tumor suppressor PTEN and N-RAS have also been shown to cause hyperactivation of this pathway. Aberrant PI 3-K activation, from mutations in the genes

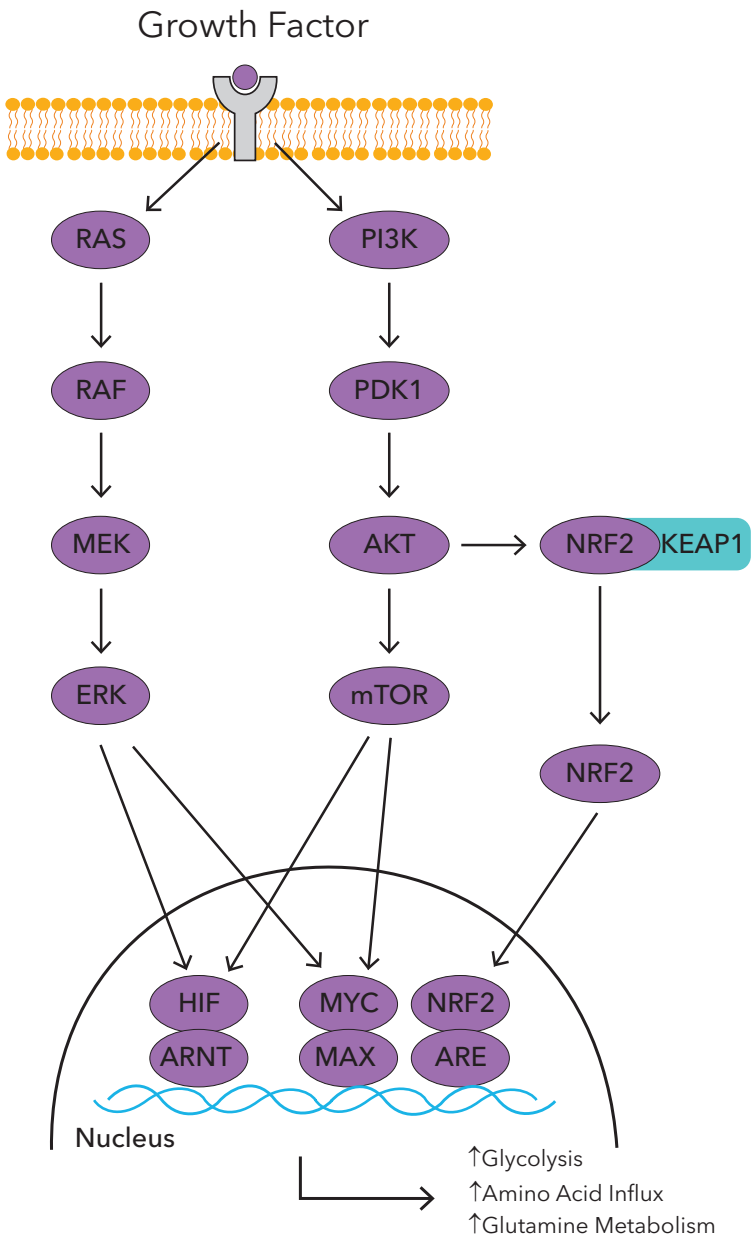
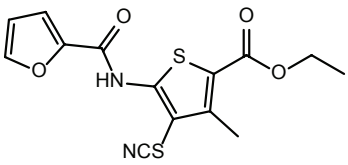


FIGURE 4: Schematic highlighting key signaling pathways involved in cancer metabolic reprogramming.

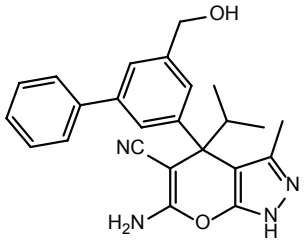
encoding downstream components of the PI 3-K pathway, has been linked to the development of malignancies such as lymphoma (p85 PI 3-K regulatory subunit), glioma (PTEN), breast cancer (S6K1) and gastric cancer (Akt1). Inhibition of this pathway with PI 3-K inhibitors such as LY 294002 (Cat. No. 1130) can reduce proliferation and induce apoptosis of colon cancer cells.

Akt (protein kinase B) is a mediator of PI 3-K signaling. Research has revealed that aberrant Akt signaling is instrumental in malignant transformation by promoting metabolic reprogramming. In particular, Akt induces

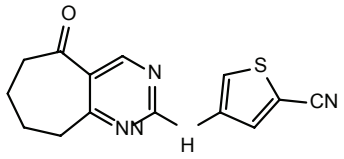
BOX 4 Nucleotide Metabolism



CBR 5884 (Cat. No. 5836)
Phosphoglycerate dehydrogenase (PHGDH) inhibitor; decreases serine synthesis in cancer cells



SHIN 1 (Cat. No. 6998)
Potent SHMT inhibitor; inhibits cancer cell growth



G6PDi 1 (Cat. No. 7561)
Potent and reversible inhibitor of glucose-6-phosphate dehydrogenase; decrease 6-PG levels and inhibits flux through the PPP

expression of GLUT1 and GLUT3. The inhibition of Akt by the selective inhibitor 10-DEBC hydrochloride (Cat. No. 2558) suppresses downstream activation of mTOR, while the potent and selective compound Akti-1/2 (Cat. No. 5773) sensitizes prostate cancer cells to apoptotic stimuli.

The mechanistic target of rapamycin (mTOR; mammalian target of rapamycin; FKBP12) is a highly conserved serine/threonine protein kinase. In cells, mTOR exists as two functionally distinct multiprotein complexes, mTORC1 and mTORC2, and integrates nutrients, growth factors, stress, and energy signals. In cancer cells mTORC1 is an important regulator of glycolysis, and inhibition of PI 3-K/Akt/mTOR signaling has been shown to reduce aerobic glycolysis in cancer cells. HIF-1 and MYC are downstream mediators of mTOR signaling, which in turn regulate expression of glycolytic enzymes. Interestingly it has been found that when the glycolytic pathway is inhibited, glucose metabolism is redirected through the PPP under control of mTORC1, allowing cancer cells to escape glycolysis dependency. Combined inhibition of glycolysis and mTORC1 signaling can disrupt this metabolic reprogramming and inhibit tumor cell growth.

Rapamycin (Cat. No. 1292) is a classical inhibitor of mTOR, which complexes with FKBP-12 and binds to mTOR, suppressing its activity, including inhibiting IL-2-induced phosphorylation and p70 S6 kinase activation. The ATP-competitive mTOR inhibitors, Torin 1 (Cat. No. 4247) and Torin 2 (Cat. No. 4248) are useful tools for elucidating the function of the mTOR/PI 3-K axis in cancer cell biology. Torin 2 inhibits both mTORC1 and mTORC2 and has been shown to display cytotoxic effects across multiple cancer cell lines, inducing both apoptosis and autophagy, as well as suppressing the activation of PI 3-K/Akt. PP 242 (Cat. No. 4257) is a selective ATP-competitive inhibitor of mTOR that has been shown to reduce oncogenic K-RAS and PI 3-K - induced lipogenesis in breast cancer cells.

The PI 3-K/AKT pathway also interacts with NRF2/KEAP1 signaling. Activation of PI 3-K/AKT signaling increases NRF2 translocation to the nucleus and promotes metabolic reprogramming and increased cancer cell proliferation.

c-MYC

c-MYC is a member of the MYC family of transcription factors that integrates signals from multiple pathways including PI 3-K and MAPK, and is involved in the control of cell proliferation and death. In cancer cells, mutations in c-Myc or in upstream pathways result in increased expression and activity of this transcription factor. c-Myc has numerous target genes, some of which have a role in aerobic glycolysis, including hexokinase 2 (HK2) and glutamate transporters. The histone deacetylase (HDAC) inhibitor Sodium Butyrate (Cat. No. 3850) downregulates expression of c-Myc which in turn inhibits expression of HK2 and aerobic glycolysis in hepatocellular carcinoma cells. 10058-F4 (Cat. No. 4406) inhibits dimerization of c-Myc and Max and has also been shown to reduce glucose uptake, expression of glycolysis-associated genes and viability of lymphoma cells. KJ Pyr 9 (Cat. No. 5306) is another inhibitor of the interaction between c-Myc and Max and a potential tool for further exploration of the role of c-Myc in cancer metabolic reprogramming.

RAS

RAS GTPases transduce signals from growth factor receptors and are integral mediators in regulating differentiation and proliferation in many cell types. RAS is mutated in approximately 25% of human cancers and these mutations enable RAS activation in the absence of growth factor-RTK binding. RAS-signaling helps establish the metabolic reprogramming that supports cancer growth, so inhibitors targeting the molecules involved in the RAS-RAF-MEK-ERK cascade are of potential therapeutic significance.

In humans there are three RAS genes, *HRAS, KRAS* and *NRAS*. K-RAS mutations are a major driver in pancreatic, colon and lung cancer; N-RAS mutations in melanomas; and H-RAS mutations in cervical and bladder cancers. Mutations in K-RAS or B-RAF, a mediator of RAS function, have been

shown to upregulate glutamate transporter expression leading to increased glucose uptake and glycolysis. K-RAS also upregulates glycolytic enzymes including hexokinases, phosphofructokinase 1 and lactate dehydrogenase A.

A range of inhibitors is available to investigate the role of RAS mutants in cancer metabolism reprogramming including the $KRAS^{G12C}$ mutant selective inhibitors, AMG 510 (Cat. No. 7713) and MRTX 849 (Cat. No. 7488) and the inhibitor of the KRAS/SOS1 interaction, BAY 293 (Cat. No. 6857). A different approach to investigating RAS signaling is to use a small molecule Degrader (PROTAC®) such as LC 2 (Cat. No. 7420), which triggers the selective degradation of $KRAS^{G12C}$ in cancer cells and inhibits ERK signaling.

KRAS mutant pancreatic ductal adenocarcinoma (PDAC) exhibits increased glutamine-dependency. Glutamine is converted by glutaminase in mitochondria to glutamate, which in turn is converted to aspartate by GOT2. Aspartate is ultimately converted to pyruvate with a concomitant increase in NAPDH production. The glutaminase inhibitor BPTES (Cat. No. 5301) has been found to inhibit PDAC proliferation *in vitro*.

Post-translational modifications are important in the activation of RAS. Prenyltransferases upstream of RAS, such as farnesyltransferase (FTase) and geranylgeranyltransferase I (GGTase I), are involved in the association of RAS with the plasma membrane and have been targeted by small molecules. Inhibition of H-RAS by FTase inhibitors has been shown to be effective in blocking signaling. However, K-RAS and N-RAS are able to bypass FTase inhibition by utilizing the related GGTase. FTase and GGTase inhibitors, such as Lonafarnib (Cat. No. 6265) and GGTI 298 (Cat. No. 2430), respectively, are therefore also useful tools for studying RAS and its associated oncogenic signaling.

pH and Redox Balance in Cancer Metabolism

One way that cancer cells are able to survive in the hostile tumor microenvironment is through increased expression of proton pumps and ion transporters. Aberrant regulation of hydrogen ions leads to a reversal of the pH gradient across tumor cell membranes, resulting in an increased basic intracellular pH (pHi) and a more acidic extracellular pH (pHe). It is critical to cancer cell survival that the intracellular environment does not become acidified because this could induce apoptosis. Under hypoxic conditions, HIF-1 induces expression of carbonic anhydrase IX (CA IX), which regulates cellular pH. Protons generated by CA IX activity decrease pHe, potentiating extracellular matrix destruction and tumor cell invasiveness. U 104 (Cat. No. 4540), a CA IX inhibitor, has been shown to suppress tumor growth and formation of metastases in *in vivo* models. Inhibition of the Na^+/H^+ exchanger (NHE1, SLC9A1) and monocarboxylate transporters (MCT) with compounds such as Zoniporide (Cat. No. 2727) and UK 5099 (Cat. No. 4186), respectively, also have a catastrophic effect on cellular pH and induce apoptosis.

Redox dysfunction is common in cancer cells owing to their altered metabolism. This results in excess production of reactive oxygen species (ROS). Mitochondria are a major source of ROS, which are generated in the electron transport chain (ETC) in response to hypoxia. Metformin (Cat. No. 2864) is an inhibitor of Complex I of the ETC. It inhibits ROS formation in cancer cells and reduces hypoxic activation of hypoxia-inducible factor 1 (HIF-1). In addition, in the presence of glucose, Metformin inhibits tumor cell proliferation, but induces cell death upon glucose deprivation, indicating that cancer cells rely on glycolysis for survival in the presence of Metformin.

Maintenance of ROS level in a steady state is essential for continued tumor growth and HIF activation. Elevated ROS levels may damage free nucleoside triphosphates (dNTPs). During DNA replication, these dNTPs become incorporated into DNA, resulting in mutagenesis and cell death. MutT homolog-1 (MTH1) is an enzyme that hydrolyzes oxidized dNTPs, preventing them from becoming incorporated into DNA. It has been suggested that cancer cells, unlike normal cells, depend on MTH1 activity for survival, making it an attractive therapeutic target. Inhibition of MTH1 with the small molecules TH 588 (Cat. No. 5334) and (S)-Crizotinib (Cat. No. 6025) has been shown to result in the incorporation of oxidative dNTPs into DNA, causing cell death in selected cancer cell lines *in vitro* and in patient-derived mouse xenografts. SCH 51344 (Cat. No. 5280) is a high affinity MTH1 inhibitor that inhibits Ras-induced malignant transformation, blocks anchorage-independent growth of Ras-transformed tumor cell lines, and induces DNA damage in a colon cancer cell line. However, it was found that the potent and selective MTH1 inhibitor BAY 707 (Cat. No. 6562) has no effect on cancer cell proliferation, indicating that MTH1 may not be essential for survival in all cancers.

The increased oxidative stress in cancer cells, also requires pathway adaptations in order to maintain the redox balance. The NRF2/KEAP1 signaling pathway is a key regulator of the antioxidant response, coordinating the expression of metabolic enzymes and antioxidant genes in response to stress. For example, NRF2 regulates expression of enzymes involved in glutathione (GSH) homeostasis, which has a key role in modulating oxidative stress, as well as expression of components of the thioredoxin system including

thioredoxin 1, thioredoxin reductase and NADPH. CDDO Im (Cat. No. 4737), a NRF2 activator, elevates expression of genes encoding antioxidant proteins and suppresses ROS formation. The NRF2 inhibitor ML 385 (Cat. No. 6243) blocks expression of NRF2 downstream targets and is cytotoxic in non-small cell lung cancer cells when used in conjunction with Doxorubicin (Cat. No. 2252).

NRF2 also influences the expression of the cystine/glutamate antiporter xCT (SLC7A11), which is overexpressed in several cancers. xCT has a key antioxidant role through the importation of cystine. Cystine is reduced to cysteine, which in turn serves as a precursor for glutathione biosynthesis. xCT is a target of interest, as inhibition of this transporter has been shown to increase intracellular ROS and induce cancer cell death. In addition, overexpression of xCT is associated with glucose-dependence in cancer, which sensitizes cells to glucose starvation-induced death, while pharmacological inhibition of the transporter using Sulfasalazine (Cat. No. 4935) attenuates this effect.

Another significant pathway with a role in responding to metabolic stress is the nicotinamide adenine dinucleotide (NAD) pathway. Depletion of NAD through the inhibition of nicotinamide phosphoribosyltransferase (NAMPT) leads to apoptosis. This has been shown using the NAMPT inhibitor FK 866 (Cat. No. 4808), which brings about apoptosis in a human liver carcinoma cell line. Whilst NAMPT inhibition has limited therapeutic benefit, selective degradation of NAMPT using the NAMPT PROTAC® A7 (Cat. No. 7842) could have interesting metabolic effects versus inhibition alone. NAD can also be converted into NADPH, which is a major product of the PPP and is one of the most abundant cellular antioxidants. Inhibition of the PPP therefore leaves cells vulnerable to oxidative stress and promotes apoptosis. G6PDi-1 (Cat. No. 7561) could be a useful tool for studying the role of the PPP in the generation of NADPH. This compound inhibits glucose-6-phosphate dehydrogenase, which catalyzes the first step in the PPP, the conversion of glucose-6-phosphate to fructose-6-phosphate and is frequently upregulated in tumor cells.

Tumor Microenvironment and Cancer Metabolism

Hypoxia inducible factors (HIF) are transcription factors that are considered to be the "master regulators of hypoxia" because they control the expression of hundreds of genes that help cells to survive at low oxygen levels. HIFs are heterodimers comprising an oxygen-sensitive α subunit and an oxygen-insensitive β subunit, also known as aryl hydrocarbon receptor nuclear translocator (ARNT). Under normoxic conditions HIF-1α is rapidly degraded by the ubiquitin-proteasome system (UPS), whereas under hypoxia, HIF-1α is stabilized and translocated to the nucleus where it activates HIF target genes (**FIGURE 4**). Small molecules that could be useful for further exploration of the role of HIF include Echinomycin (Cat. No. 5520), a highly potent and selective HIF-1α inhibitor, and VH 298 (Cat. No. 6156), an inhibitor of the ubiquitin E3 ligase VHL, which blocks the degradation of HIF-1α by the UPS leading to increased expression of HIF target genes. In addition, directly targeting HIF is a possible therapeutic strategy. Compounds targeting HIF-2α have been found to have therapeutic effect in patients with renal cell cancer and glioblastoma. Upstream regulators of HIF such as ERK are also potential targets for cancer treatments (**FIGURE 4**).

The glucose transporter GLUT1 and pyruvate dehydrogenase kinase 1 (PDK1) are both known to be upregulated by HIF. Upregulation of GLUT1 enables increased uptake of glucose and flux through the glycolytic pathway. Glycolysis generates pyruvate, which is converted into acetyl-CoA by pyruvate dehydrogenase (PDH) complex in mitochondria, and enters the TCA cycle. However, hypoxia inhibits this process by upregulation of pyruvate dehydrogenase kinase 1 (PDK1), an inhibitor of PDH, and lactate dehydrogenase A (LDHA) resulting in the conversion of pyruvate to lactate. Lactate accumulation leads to a reduction in pH in the TME. PDK and LDH inhibitors such as DCA (Cat. No. 2755) and GSK 2837808A (Cat. No. 5189), respectively, reduce lactate production and glycolysis and decrease tumor growth. The combination of high glucose consumption by proliferating tumor cells leading to reduced glucose availability in the TME, plus high lactate levels, both result in immunosuppression and promote tumor progression.

Cancer-associated fibroblasts (CAFs) are a key component of the TME and are chronically activated. They have an important role in cancer initiation and growth, and like tumor cells have altered metabolism, including increased aerobic glycolysis rates, to meet the nutritional demand of tumors. CAFs harness carbon from various sources to provide glutamine for tumor cells, and as such CAFs could be a target for future anticancer therapies.

Concluding Remarks

Through exploration of unique mutant enzymes, aberrant metabolic pathways and oncogenic drivers associated with cancer metabolic reprogramming, it is hoped a better understanding of these processes can be gained and new methods and medicines for treating cancer can be developed.

Cancer Metabolism Research Products

Pathways

Target Protein	Product Name	Catalog #	Action
Autophagy			
Autophagy	Hydroxychloroquine	5648	Autophagy inhibitor; also TLR9 inhibitor
	SMER 28	4297	Positive regulator of autophagy
Other ER Stress/UPR	Ceapin A7	6955	Selective inhibitor of ATF6α; sensitizes cells to ER stress
Glucose Metabolism/ Glycolysis			
GAPDH	CGP 3466B	2966	GAPDH inhibitor; neuroprotective
Glucose Transporters	BAY 876	6199	Potent and selective GLUT1 inhibitor
	Fasentin	6100	GLUT1/GLUT4 inhibitor; also Fas-sensitizer
	WZB 117	6143	GLUT inhibitor
Glycogen Synthase Kinase 3	CHIR 98014	6695	Highly potent and selective GSK-3 inhibitor
	CHIR 99021	4423	Highly selective GSK-3 inhibitor; acts as Wnt activator
	SB 216763	1616	Potent, selective GSK-3 inhibitor
Hexokinases	GKA 50	5133	Glucokinase activator
Lactate Dehydrogenase A	Galloflavin	4795	Lactate dehydrogenase inhibitor; impairs aerobic glycolysis
	GSK 2837808A	5189	Potent and selective LDHA inhibitor
	NHI 2	5363	LDHA inhibitor
Monocarboxylate Transporters	3-Bromopyruvate	7512	MCT1 inhibitor; also inhibits hexokinase II
	AR-C 141990	5658	MCT1 inhibitor
	AR-C155858	4960	MCT1 and MCT2 inhibitor; inhibits glycolysis in cancer cells
	BAY 8002	6817	Potent dual MCT1/2 inhibitor; orally bioavailable
	SR 13800	5431	Potent MCT1 inhibitor
	UK 5099	4186	MCT inhibitor; also inhibits pyruvate transport
NAMPT	CHS 828	6753	NAMPT inhibitor; active *in vivo* and cytotoxic
	FK 866 hydrochloride	4808	Potent and non-competitive NAMPT inhibitor; induces apoptosis and autophagy
	NAMPT PROTAC® A7	7842	Potent and selective NAMPT Degrader; reduces NAMPT levels in tumor cells
	P7C3	4076	NAMPT activator; also proneurogenic and neuroprotective

Target Protein	Product Name	Catalog #	Action
NAMPT	STF 118804	5207	NAMPT inhibitor; depletes leukemia stem cells
	STF 31	4484	NAMPT inhibitor; also GLUT1 inhibitor
PFKFB3	3PO	5121	PFKFB3 inhibitor
	AZ PFKFB3 26	5675	Potent and selective PFKFB3 inhibitor
	AZ PFKFB3 67	5742	Potent and selective PFKFB3 inhibitor
	PFK 15	5339	Selective PFKFB3 inhibitor
Phosphoglycerate Dehydrogenase	CBR 5884	5836	Phosphoglycerate dehydrogenase (PHGDH) inhibitor
	PKUMDL WQ 2101	6580	Negative allosteric modulator of 3-phosphoglycerate dehydrogenase (PHGDH)
	PKUMDL WQ 2201	6581	Negative allosteric modulator of 3-Phosphoglycerate dehydrogenase (PHGDH)
PKM2	(R)-Shikonin	6829	Tumor-specific pyruvate kinase M2 inhibitor; also PTEN and inflammasome inhibitor
Pyruvate Dehydrogenase	6,8-Bis(benzylthio) octanoic acid	5348	PDH and KGDH inhibitor
	Ranolazine	3118	Activates pyruvate dehydrogenase; antianginal
Pyruvate Dehydrogenase Kinase	DCA	2755	Mitochondrial pyruvate dehydrogenase kinase (PDK) inhibitor
SHMT	SHIN1	6998	Potent serine hydroxymethyltransferase (SHMT) inhibitor
Glutamine Metabolism			
Ceramidases	Ceranib 1	4448	Ceramidase inhibitor; antiproliferative
Glutamate Transporters	Dihydrokainic acid	0111	EAAT2 (GLT-1)-selective non-transportable inhibitor of L-glutamate and L-aspartate uptake
	DL-TBOA	1223	Selective non-transportable inhibitor of EAATs
	GT 949	6578	Potent and selective positive allosteric modulator of EAAT2
	TFB-TBOA	2532	High affinity EAAT1 and EAAT2 blocker
	UCPH 101	3490	Selective non-substrate EAAT1 inhibitor
	WAY 213613	2652	Potent, non-substrate EAAT2 inhibitor
Glutaminase	968	5460	Allosteric inhibitor of glutaminase
	BPTES	5301	Selective allosteric glutaminase (GLS1) inhibitor
	CB 839	7591	Potent glutaminase inhibitor
L-type Amino Acid Transporter 1	JPH 203	5026	Potent and selective inhibitor of L-type amino acid transporter 1 (LAT1); active *in vivo*

Target Protein	Product Name	Catalog #	Action
Lipid Metabolism			
Acetyl-CoA Carboxylase	PF 05175157	5790	Acetyl-CoA carboxylase (ACC) 1 and 2 inhibitor
ATP Citrate Lyase	BMS 303141	4609	ATP citrate lyase inhibitor; orally bioavailable
	SB 204990	4962	ATP citrate lyase (ACLY) inhibitor
Farnesyl Diphosphate (FPP) Synthase	Risedronate	3504	Farnesyl diphosphate (FPP) synthase inhibitor
	Zoledronic Acid	6111	Potent farnesyl diphosphate (FPP) synthase inhibitor
Fatty Acid Amide Hydrolase	JZL 195	4715	Dual FAAH and MAGL inhibitor
	PF 3845	4175	Selective FAAH inhibitor
	TC-F 2	4355	Potent, reversible and selective FAAH inhibitor
	URB 597	4612	Potent and selective FAAH inhibitor
Fatty Acid Desaturase 2	SC 26196	4189	Selective fatty acid desaturase 2 inhibitor
	T 3364366	6106	Potent and reversible fatty acid desaturase 1 inhibitor; orally bioavailable
Fatty Acid Synthase	C 75	2489	Potent fatty acid synthase inhibitor; proapoptotic
	GSK 2194069	5303	Potent human fatty acid synthase (hFASN) inhibitor
	Orlistat	3540	Inhibits the thioesterase domain of fatty acid synthase; also carboxylester lipase inhibitor
HMG-CoA Reductase	Fluvastatin sodium	3309	Potent HMG-CoA reductase inhibitor
	Lovastatin	1530	Potent HMG-CoA reductase inhibitor
	Rosuvastatin calcium	6343	Potent HMG-CoA reductase inhibitor
	Simvastatin	1965	HMG-CoA reductase inhibitor
	SR 12813	2969	Pregnane X receptor agonist; promotes degradation of HMG-CoA reductase
MAGL	JW 642	4906	MAGL inhibitor
	JZL 184	3836	Potent MAGL inhibitor
	JZP 361	5851	Potent and selective reversible MAGL inhibitor
	NF 1819	5956	Potent and selective irreversible MAGL inhibitor; membrane permeable and brain penetrant
Other Lipid Metabolism	LDN 193188	5631	Inhibitor of phosphatidylcholine transfer protein (PC-TP)
	Lomitapide	7492	Potent microsomal triglyceride transfer protein (MTP) inhibitor
	Ro 48-8071	5389	2,3-Oxidosqualene cyclase (OSC) inhibitor; blocks cholesterol synthesis
	Triacsin C	2472	Inhibitor of acyl-CoA synthetase

Target Protein	Product Name	Catalog #	Action
Mitochondria			
ATP Synthase	Bz 423	5791	ATP synthase inhibitor; proapoptotic
Hexokinases	Lonidamine	1646	Mitochondrial hexokinase inhibitor
Malate Dehydrogenase	LW 6	6322	Malate dehydrogenase-2 (MDH2) inhibitor; also inhibits HIF-1α
Mitochondria Complex 1	Metformin	2864	Mitochondrial complex I inhibitor; also activator of LKB1/AMPK; antidiabetic agent
Mitochondrial ATPase	Oligomycin A	4110	Inhibitor of mitochondrial ATPase
Monoamine Oxidase	Lazabemide	2460	Selective MAO-B inhibitor
	Moclobemide	4395	Reversible MAO-A inhibitor
	Pirlindole	0724	MAO-A inhibitor
Nucleotides			
Dihydrofolate Reductase	Phototrexate	7362	Photoswitchable inhibitor of human dihydrofolate reductase
	Pyrimethamine	3918	DHFR inhibitor; also inhibits STAT3 and multidrug and toxin extrusion (MATE) transporters
Dihydroorotate Dehydrogenase	Brequinar sodium	6196	Potent and selective DHODH inhibitor
	Teriflunomide	5069	Inhibitor of DHODH; active metabolite of Leflunomide
FTO	Ethyl LipotF	5950	Selective FTO inhibitor
	Rhein	6867	FTO (mRNA N6-methyladenine demethylase) inhibitor; also inhibits ALKBH2 and ALKBH3
	MO-I-500	6871	FTO inhibitor; anticonvulsant
G6PD	G6PDi	7561	Potent, reversible glucose-6-phosphate dehydrogenase (G6PD) inhibitor
Inosine Monophosphatase Dehydrogenase	BMS 566419	5492	Inosine monophosphatase dehydrogenase (IMPDH) inhibitor
	Mycophenolic acid	1505	Inosine monophosphatase dehydrogenase (IMPDH) inhibitor
MTHFD2	TH 9619	7719	Potent inhibitor of methylenetetrahydrofolate dehydrogenase/cyclohydrolase (MTHFD2); inhibits purine synthesis from serine
MutT Homolog-1	(S)-Crizotinib	6025	MTH1 inhibitor
	BAY 707	6562	Potent and selective MTH1 inhibitor
	SCH 51344	5280	Potent MTH1 inhibitor
	TH 588	5334	Potent MTH1 inhibitor
Other Oxygenases/ Oxidases	Bobcat339	6977	Ten-eleven translocation methylcytosine dioxygenase (TET) inhibitor
	Febuxostat	4427	Xanthine oxidase inhibitor
Ribonucleotide Reductase	3-AP	5962	Ribonucleotide reductase inhibitor; also an iron chelator
	Cladribine	5292	Deoxyadenosine analog; pro-apoptotic

Target Protein	Product Name	Catalog #	Action
Thymidylate Synthetase	5-Fluorouracil	3257	Thymidylate synthetase inhibitor
	Floxuridine	4659	Thymidylate synthetase inhibitor
	Methotrexate	1230	Thymidylate synthetase inhibitor also inhibits dihydrofolate reductase
	Pemetrexed	6185	Thymidylate synthetase inhibitor, also inhibits dihydrofolate reductase, GARFT and AICART
	Trifluorothymidine	4460	Thymidylate synthetase inhibitor
Oxphos			
Oxidative Phosphorylation	BAM 15	5737	Mitochondrial protonophore uncoupler
	BAY 87-2243	6980	Mitochondrial complex I inhibitor
	CCCP	0452	Oxidative phosphorylation uncoupler
	FCCP	0453	Oxidative phosphorylation uncoupler
	Rotenone	3616	Inhibits complex I of the mitochondrial electron transport chain
TCA Cycle			
Glutamate Dehydrogenase	EGCG	4524	GDH inhibitor; also β-secretase and DNMT1 inhibitor
Isocitrate Dehydrogenase 1	AGI 5198	7087	Potent and selective inhibitor of mutant isocitrate dehydrogenase 1 (mIDH1)
	Ivosedinib	7761	Potent and selective inhibitor of mutant isocitrate dehydrogenase 1 (mIDH1)
Other Dehydrogenases	6,8-Bis(benzylthio) octanoic acid	5348	PDH and KGDH inhibitor
	(*RS*)-2-Hydroxyglutaric acid	6122	Oncometabolite; synthesized by mIDH1
	Methylmalonate	4979	Succinate dehydrogenase inhibitor
Other Metabolism			
Aldehyde Dehydrogenase	673 A	6934	ALDH1A inhibitor; depletes CD133+ cancer stem cells (CSC)
	A37	5802	ALDH1A1 inhibitor
	CM 10	6933	ALDH1A inhibitor; depletes CD133+ cancer stem cells
	NCT 501	5934	Potent and selective ALDH1A1 inhibitor
	WIN 18446	4736	ALDH1A2 inhibitor
Carbonic Anhydrases	STX 64	7341	Potent steroid sulfatase inhibitor; also inhibits carbonic anhydrase II
	U 104	4540	Potent carbonic anhydrase (CA) IX and XII inhibitor
DNA, RNA and Protein Synthesis	Cycloheximide	0970	Inhibitor of protein synthesis
	Gemcitabine	3259	DNA synthesis inhibitor
	Homoharringtonine	1416	Inhibitor of protein synthesis; antileukemic agent

Target Protein	Product Name	Catalog #	Action
Hypoxia Inducible Factors	Echinomycin	5520	Highly potent and selective HIF-1α inhibitor
	VH 298	6156	High-affinity inhibitor of E3 ubiquitin ligase VHL; blocks interaction between VHL and HIF-α downstream of HIF-α hydroxylation
Na^+/H^+ Exchanger	BIX NHE1 inhibitor	5512	Potent and selective NHE1 inhibitor
	Cariporide	5358	Selective NHE1 inhibitor; cardioprotective and antitumor
	EIPA	3378	Inhibits TRPP3-mediated currents; also inhibits the Na^+/H^+ exchanger (NHE)
	Zoniporide	2727	Selective NHE1 inhibitor
NADPH Oxidase	Apocynin	4663	NADPH-oxidase inhibitor
	GSK 2795039	6848	NADPH oxidase 2 (NOX2) inhibitor
	VAS 2870	6654	NADPH oxidase (Nox) inhibitor
Nrf2	CDDO Im	4737	Nrf2 signaling activator; induces expression of genes encoding antioxidant proteins
	ML 385	6243	Nrf2 inhibitor; blocks expression of Nrf2 downstream targets
Other Dehydrogenases	SW 033291	5759	High affinity 15-hydroxyprostaglandin dehydrogenase (15 PGDH) inhibitor; promotes hematopoiesis and hepatocyte proliferation
Other Oxygenases/ Oxidases	Carbazeran	4420	Aldehyde oxidase substrate; PDE inhibitor
	Nitazoxanide	7234	Pyruvate flavodoxin/ferredoxin oxidoreductase inhibitor; also inhibits Wnt signaling; broad spectrum anti-infective
	PF 06281355	6004	Selective myeloperoxidase (MPO) inhibitor
Other Synthases/ Synthetases	AT 56	3531	Prostaglandin D synthase (L-PGDS inhibitor)
	Borrelidin	4706	Antiangiogenic; inhibits threonyl-tRNA synthetase
	C3	5957	Selective microsomal prostaglandin E synthase 1 (mPGES-1) inhibitor
	Halofuginone	1993	High affinity competitive prolyl-tRNA synthetase inhibitor
	HQL 79	3530	Human hematopoietic prostaglandin D synthase (H-PGDS) inhibitor
	N^1,N^{12}-Diethylspermine	0500	Polyamine synthase inhibitor
	TFC 007	5108	Potent hematopoietic prostaglandin D synthase (H-PGDS) inhibitor

Drivers

Target Protein	Product Name	Catalog #	Action
Akt (Protein Kinase B)	10-DEBC	2558	Selective inhibitor of Akt/PKB; suppresses downstream activation of mTOR
	Akti-1/2	5773	Potent and selective dual Akt1 and 2 inhibitor
	LY 294002	1130	Prototypical PI 3-kinase inhibitor; also inhibits other kinases
	MK 2206	7850	Potent and selective allosteric Akt inhibitor
	SC 79	4635	Akt activator

Drivers

Target Protein	Product Name	Catalog #	Action
mTOR	AZD 8055	7840	Highly potent and selective mTOR inhibitor
	PP 242	4257	Dual mTORC1/mTORC2 inhibitor
	Rapamycin	1292	mTOR inhibitor
	Torin 1	4247	Potent and selective ATP-competitive mTOR inhibitor
	Torin 2	4248	Potent and selective mTOR inhibitor
Myc	10058-F4	4406	Cell permeable inhibitor of c-Myc-Max dimerization; decreases glucose uptake and expression of glycolysis-associated genes
	KJ Pyr 9	5306	High affinity Myc inhibitor; disrupts Myc-Max interaction
	Sodium Butyrate	3850	Downregulates expression of c-Myc; histone deacetylase inhibitor
Ras GTPases	AMG 510	7713	Potent and selective covalent $KRAS^{G12C}$ inhibitor
	BAY 293	6857	Potent KRas/SOS1 interaction inhibitor; negative control (Cat. No. 6906) also available
	GGTI 298	2430	Geranylgeranyltransferase I (GGTase I) inhibitor
	LC 2	7420	Selective KRAS PROTAC® Degrader; induces selective degradation of $KRAS^{G12C}$; negative control (Cat. No. 7421) also available
	Lonafarnib	6265	Potent farnesyltransferase inhibitor
	MRTX 849	7488	Selective covalent $KRAS^{G12C}$ inhibitor

Detection

Product Name	Catalog #	Action
2-NBDG	6065	Glucose uptake probe
L 012 Sodium Salt	5085	ROS and RNS indicator
Mito-HE	7641	Mitochondrial superoxide indicator
MitoBrilliant™ 646	7700	Fluorescent mitochondrial stain; suitable for use in both live and fixed cells
MitoPY1	4428	Mitochondrial hydrogen peroxide indicator
Pimonidazole	6182	Hypoxia detection agent
SCOTfluor Glucose Probe 510	7447	Glucose uptake probe
SCOTfluor Lactic Acid Probe 510	7448	Lactic acid metabolism probe

A Selection of Related Products Available from our Sister Brands

Product Name	Catalog #	Action
ATG5 Antibody	NB110-53818	Autophagy Marker
AMPKα1 Antibody	NB100-239	AMPK1 antibody
ATP5A Antibody	NBP2-15515	Mitochondria ATP Synthase Antibody
COX4 Antibody	NB110-39115	Cytochrome C Oxidase - Electron Transport chain
COX5b Antibody	H00001329-M03	Cytochrome C Oxidase - Electron Transport chain
Glutamate Dehydrogenase Antibody	NBP2-16679	Mitochondria marker
LC3B Antibody	NB100-2220	Phagosome marker
mTOR Antibody	NB600-607	mTOR pathway activation
PDK4 Antibody	NBP1-07047	Mitochondria matrix enzyme

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