TOCRIS
a bio-techne brand

Cancer Research

Product Guide | Edition 3

Autumn Crocus
Colchicum autumnale
A source of Colchicine

Contents by Research Area:

- Cancer Metabolism
- Epigenetics in Cancer
- Receptor Signaling
- Cell Cycle and DNA Damage Repair
- Angiogenesis
- Invasion and Metastasis

Cancer Research

Contents

	Page
Cancer Metabolism	3
Epigenetics in Cancer	8
Receptor Signaling	13
Cell Cycle and DNA Damage Repair	22
Angiogenesis	27
Invasion and Metastasis	29
Related literature	32
Cancer Research Products	33
Chemotherapeutics	59
Index	61
Further Reading	62

Introduction

Cancer is a major focus of research activity throughout the world. Often defined as a multifactorial disease, with genetic, epigenetic and environmental factors influencing its progression, cancer usually develops over many decades from relatively benign collections of cells into malignant tumors. In seminal papers written by Hanahan and Weinberg, a number of consistently observed characteristics displayed by cancer cells have been defined and were termed the 'Hallmarks of Cancer'. These hallmarks are: sustained proliferative signaling; evasion of apoptosis and growth suppression; genomic instability; resistance to cell death; and the ability to induce angiogenesis and to metastasize.

Over the last decade the concept of primary tumors as a collection of abnormally proliferating cells, has expanded to include important elements of the host tissue architecture and tumor microenvironment, the influence of the immune system and the presence of tumor stem cells. The mechanism by which energy metabolism is subverted in tumor cells and the study of epigenetic modifications in tumor cells are two rapidly expanding areas, which are being intensely investigated. It is with these established and emerging hallmarks of cancer in mind that we have updated the Tocris Cancer Research Product Guide.

As cancer research progresses, the mechanisms behind malignancy are more clearly understood and additional mechanisms continue to come to light. Cancer researchers require both established standards and new cutting edge pharmacological tools to identify and study targets involved in these processes. Tocris provides a wide range of industry leading, high purity life science reagents for use in cancer research. Featured in each section are new and established key products, as well as a product finder, which gives a larger selection of the compounds available.

Key Cancer Research Products

Box Number	Title	Page
Box 1	Cancer Metabolism Products	6
Box 2	Epigenetics Products	10
Box 3	Growth Factor Receptor Products	14
Box 4	Intracellular Signaling Products	18
Box 5	Nuclear Receptor Products	20
Box 6	Cell Cycle and DNA Damage Repair Products	24
Box 7	Angiogenesis Products	27
Box 8	Invasion and Metastasis Products	30

Cancer Metabolism

Cancer Research Target	For Products See Page
ATP-citrate Lyase (ACLY)	33
Carbonic Anhydrases (CA)	33
Carnitine Palmitoyltransferase (CPT)	33
Dihydrofolate Reductase	33
Fatty Acid Synthase (FASN)	33
GAPDH	33
Glucose Transporters (GLUT)	33
Glutamate Dehydrogenase (GDH)	33
Glutaminase	33
Glutathione	33
Hexokinases	33
HMG-CoA Reductase (HMG-CoA)	33
Hypoxia Inducible Factor 1 (HIF-1)	55
Lactate Dehydrogenase A (LDHA)	33
Monoacylglycerol Lipase (MAGL)	33
Monocarboxylate Transporters (MCTs)	34
MutT homolog-1 (MTH1)	34
NAMPT	34
Na^+/H^+ Exchanger (NHE)	34
Oxidative Phosphorylation (OXPHOS)	34
PFKFB3	34
Pyruvate Dehydrogenase (PDH)	34
Pyruvate Dehydrogenase Kinase (PDK)	34
Pyruvate Kinase M2 (PKM2)	34
Ribonucleotide Reductase	34
Thymidylate Synthetase	34

Genetic alterations and epigenetic modifications of cancer cells result in the abnormal regulation of cellular metabolic pathways that are different when compared to normal cells. These distinct metabolic circuits could provide viable cancer therapeutic targets. In 1924 Otto Warburg first discovered that cancer cells generated a large proportion of their ATP by metabolizing glucose via aerobic glycolysis (as opposed to mostly through oxidative phosphorylation (OXPHOS) in normal cells). Initially it was thought that this Warburg effect was a cause of cancer, but it was later established that this 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 the activation of oncogenes, as well as with abnormal mutant enzyme (oncoenzyme) activity and the accumulation of tumorigenic metabolites (oncometabolites).

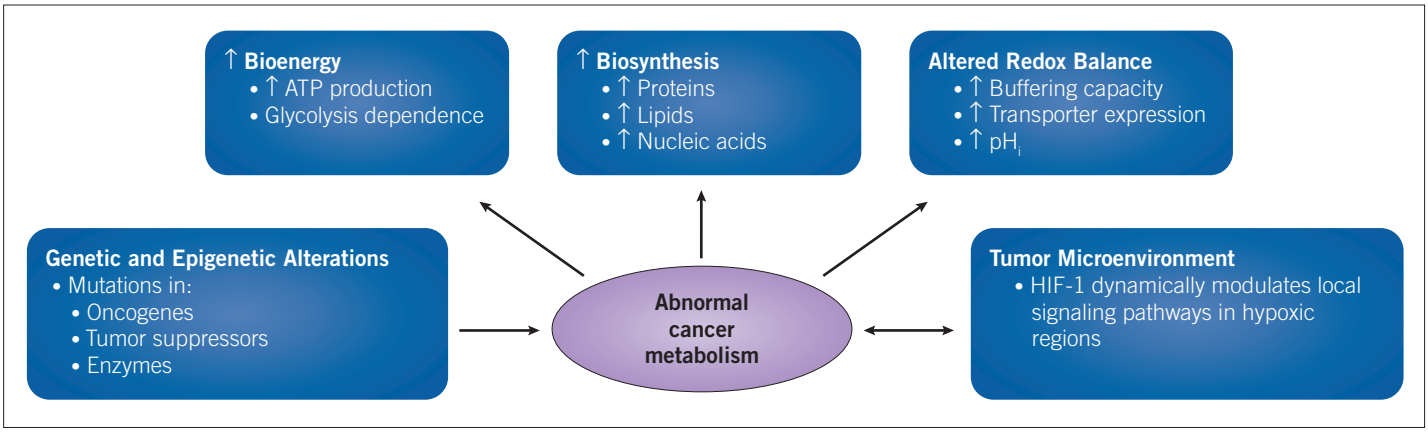
Cancer cells require three crucial metabolic adaptations in order to rapidly proliferate and survive: an increase in ATP production to fuel their high energy needs; an increased biosynthesis of the three major classes of cellular building blocks: proteins, lipids and nucleic acids; and an adapted redox system to counteract the increase in oxidative stress (Figure 1).

Metabolic Alterations in Cancer Cells

Malignant transformation is associated with the following: a shift from 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, and alterations in pH and redox regulation (Figure 2).

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. Glycolysis produces ATP more rapidly than OXPHOS, but this process is far less efficient, so there is an increased demand for glucose. As such, glucose transporter expression is frequently increased in cancer cells

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, all of which promotes cell proliferation and survival. Furthermore microenvironments within large tumors can dynamically alter metabolic pathways creating heterogeneous populations of cells.

to accommodate this need. 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, 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) (an integral component in lipid and nucleotide synthesis, as well as redox homeostasis). Depending on the requirements of the cancer cell, glucose is directed into either 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** (Cat. No. 0219) and **serine** (Cat. No. 0227) for amino acid biosynthesis and the replenishment of Krebs cycle intermediates. These altered pathways allow for the sufficient supply of nucleic acids, proteins and membrane lipids required to sustain the increased demands of highly proliferative 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 extra oxidative damage sustained through rapid proliferation.

The glucose transporter (GLUT) family of transporters and amino acid transporter 2 (ASCT2) are responsible for the increased uptake of glucose and glutamine respectively, thus making them promising targets for anticancer drugs. Overexpression of RAS or BRAF is associated with an increased expression of GLUT1. Renal cell carcinomas (RCCs) have mutations in their 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.

The first step in glutamine catabolism is the hydrolysis of glutamine into glutamate and ammonia by glutaminase (GLS1). Inhibition of GLS1 with compound **968** (Cat. No. 5460) has been shown to attenuate tumor growth in xenograft models and suppress invasive activity of breast cancer cells, 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.

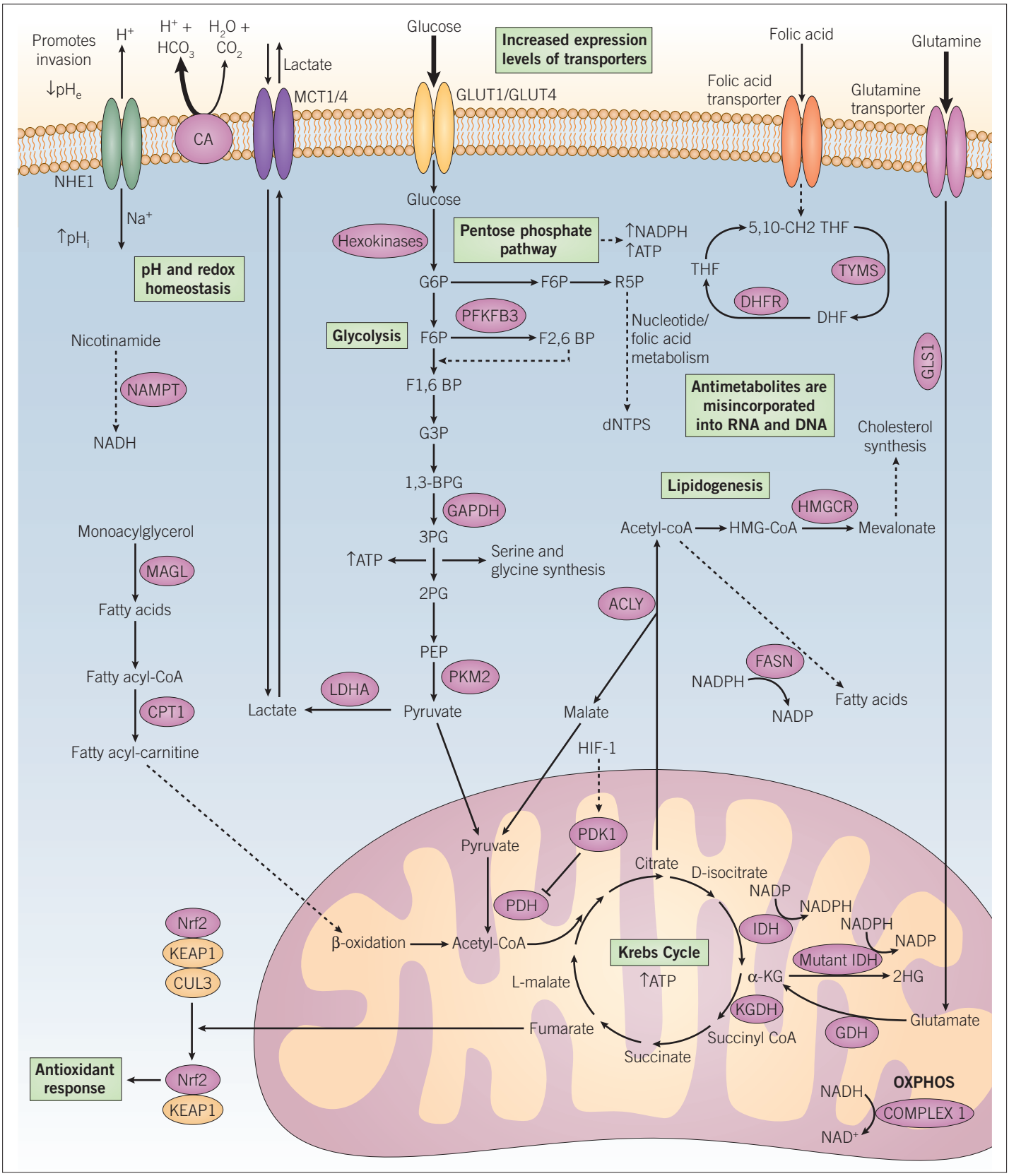
Glycolysis and the Pentose Phosphate Pathway

As the Warburg effect describes, cancer cells display significantly enhanced rates of glycolysis (Figure 1). Therefore 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 of cancer have shown that small molecule inhibitors of these targets can limit the growth and survival of certain types of tumor (Figure 2).

Hexokinase is the enzyme that catalyzes the first step of glucose metabolism, the conversion of glucose into glucose-6-phosphate. This phosphorylation event 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. **GSK 2837808A** (Cat. No. 5189) is an LDHA inhibitor that inhibits lactate production in selected cancer cell lines, as well as 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 indeed to import lactic acid to fuel the reverse Warburg effect. Preclinical data have shown that the use of MCT inhibitors, including **CHC** (Cat. No. 5029) and **AR-C155858** (Cat. No. 4960), decreases glycolytic metabolism, glutathione synthesis, cell migration and invasion *in vitro* and exhibits antitumor and antiangiogenic activity in gliomas *in vivo*. HIF-1-induced PFKFB3 expression is a critical adaptation in some cancer cells because it elevates Fru-2,6-BP concentrations, a key glycolysis stimulator. PFKFB3 inhibitors **PFK 15** (Cat. No. 5339) and **YZ9 (**Cat. No. 5048) suppress 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 (Box 1).

Many cancer cells rely on switching from OXPHOS to glycolysis as their main source of ATP and therefore researchers are investigating ways to reverse this metabolic change. **DCA** (Cat. No. 2755) is an inhibitor of mitochondrial pyruvate

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

dehydrogenase kinase (PDK), an enzyme that is often hyperactivated 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.

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) which diverts glycolytic intermediates to anabolic metabolism through the PPP and promotes glutamine addiction (see figure 2 for details of the PPP). Activating PKM2 using compounds such as **ML 202** (Cat. No. 4859) is one potential therapeutic strategy being investigated. **ML 202** promotes glycolytic flux at the expense of the PPP, which has been shown to suppress tumor growth in xenograft models.

Krebs Cycle

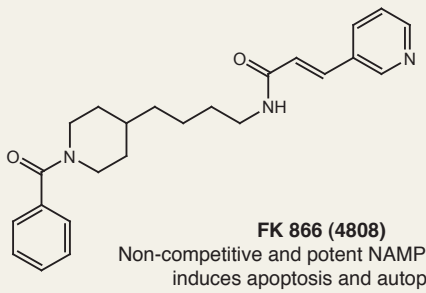
Glucose is broken down into pyruvate which is then transported into the mitochondria. It is converted into acetyl-CoA which then enters the Krebs cycle. This produces energy in the form of ATP, precursors for amino acid synthesis and the reducing the agent NADH (Figure 2).

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 Krebs cycle. Inhibition of GDH has been shown to suppress the use of glutamine in the Krebs cycle and sensitizes glioblastoma cells to glucose withdrawal. **ECGC** (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.

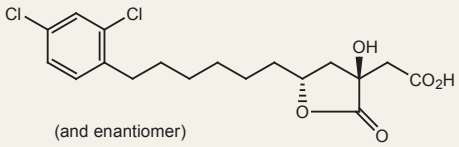
Targeting multiple points in cancer metabolic pathways is becoming a key strategy in investigational cancer treatment. An early example of this is the lipoate analog **CPI 613** (Cat. No. 5348), which inhibits both pyruvate dehydrogenase (PDH) and α-ketoglutarate dehydrogenase (KGDH). This disrupts tumor 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.

Box 1: Cancer Metabolism Products

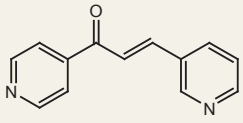
A full list of targets and related products is available on pages 33-60



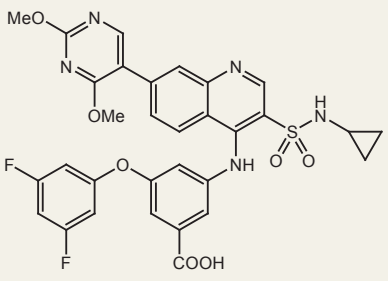
FK 866 (4808)
Non-competitive and potent NAMPT inhibitor; induces apoptosis and autophagy



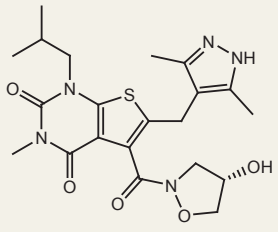
SB 204990 (4962)
ATP-citrate lyase (ACLY) inhibitor



3PO (5121)
PFKFB3 inhibitor; antiangiogenic



GSK 2837808A (5189)
Potent and selective LDHA inhibitor



AR-C155858 (4960)
MCT1 and MCT2 inhibitor

Lipidogenesis

Recent evidence suggests that in certain types of cancer such as prostate cancer, the initiation of cancer cell proliferation relies more on lipid metabolism than glycolysis. Targeting fatty acid synthesis can cripple 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) 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.

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.

pH, and Redox Balance in Cancer Metabolism

Cancer cells are able to survive in their hostile microenvironments because of 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 (pH_i) and a more acidic extracellular pH (pH_e). 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 carbonic anhydrase IX (CA IX) expression which subsequently regulates cellular pH. Protons generated by CA IX activity decrease pH_e, 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 of metastasis. Inhibition of the Na^+/H^+ exchanger (NHE1) 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 an excess production of ROSs, which 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. Cancer cells, unlike normal cells, are proposed to depend on MTH1 activity for survival, making it an attractive therapeutic target because it is cancer phenotypically lethal. Small molecule inhibition of MTH1 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, which has been shown to inhibit Ras-induced malignant transformation, block anchorage-independent growth of Ras-transformed tumor cell lines, and induce DNA damage in a colon cancer cell line.

With the increased oxidative stress in a cancer cell, metabolic pathways must adapt to maintain the redox balance. NRF2 is key regulator of the antioxidant response. **Oltipraz** (Cat.No. 5294), a Nrf2 activator, elevates expression of genes encoding antioxidant and multidrug resistance-associated proteins. Another significant pathway being investigated for its 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. For example, the NAMPT inhibitor **FK 866** (Cat. No. 4808) causes apoptosis in a human liver carcinoma cell line. 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 this pathway leaves cells vulnerable to oxidative stress and promotes apoptosis.

Antimetabolites in Cancer Metabolism

Antimetabolites have long been used clinically as standard components of chemotherapy; key compounds include **5-fluorouracil** (Cat. No. 3257), **methotrexate** (Cat. No. 1230) and **gemcitabine** (Cat. No. 3259). However, the similarities between metabolic pathways in malignant cells and healthy cells that have high proliferation rates result in a small therapeutic window. Therefore identifying therapeutic targets that selectively kill tumor cells is a major challenge of cancer metabolism research.

Through exploiting therapeutic windows for antimetabolites, targeting unique mutant enzymes and aberrant metabolic pathways, it is hoped that new tools will be found to add to the arsenal of cancer treatments.

Epigenetics in Cancer

Cancer Research Target	For Products See Page
14-3-3 Proteins	35
Aurora Kinases	48
Bromodomains (BRDs)	35
DNA Methyltransferases (DNMTs)	35
Histone Acetyltransferases (HATs)	35
Histone Deacetylases (HDACs)	35
Histone Demethylases (KDMs)	36
Lysine Methyltransferases (KMTs)	36
MBT Domains	37
Poly(ADP-ribose) Polymerase (PARP)	52
Protein Arginine Methyltransferases (PRMTs)	37
Protein Ser/Thr Phosphatases	44
Protein Tyrosine Phosphatases	44
RNA/DNA Polymerase	37

Epigenetics can be defined as acquired changes in chromatin structure that arise independently of a change in the underlying DNA nucleotide sequence. Epigenetic modifications such as acetylation, methylation and ubiquitination amongst others, can alter the accessibility of DNA to transcription machinery and therefore influence gene expression (Figure 3).

The dysregulation of these epigenetic modifications has been shown to result in oncogenesis and cancer progression. For example the cell cycle, as well as proliferation and metastasis can be regulated by histone modification, DNA methylation and chromatin remodeling. Unlike genetic mutations, epigenetic alterations are considered to be reversible and thus make a promising therapeutic target.

Proteins that carry out these epigenetic modifications can be thought of as being either "writers", "readers" or "erasers".

- **Epigenetic writers** catalyze the addition of epigenetic marks onto either histone tails or the DNA itself.
- **Epigenetic reader domains** are effector proteins that recognize and are recruited to specific epigenetic marks. "Writer" and "eraser" enzymes may also contain such reader domains, leading to the coordination of "read-write" or "read-erase" mechanisms.
- **Epigenetic erasers** remove epigenetic marks to alter gene expression.

This chapter reviews some of the main areas in cancer epigenetic research, including histone methylation and acetylation, which are the most frequently mutated epigenetic pathways in cancers.

Histone Methylation

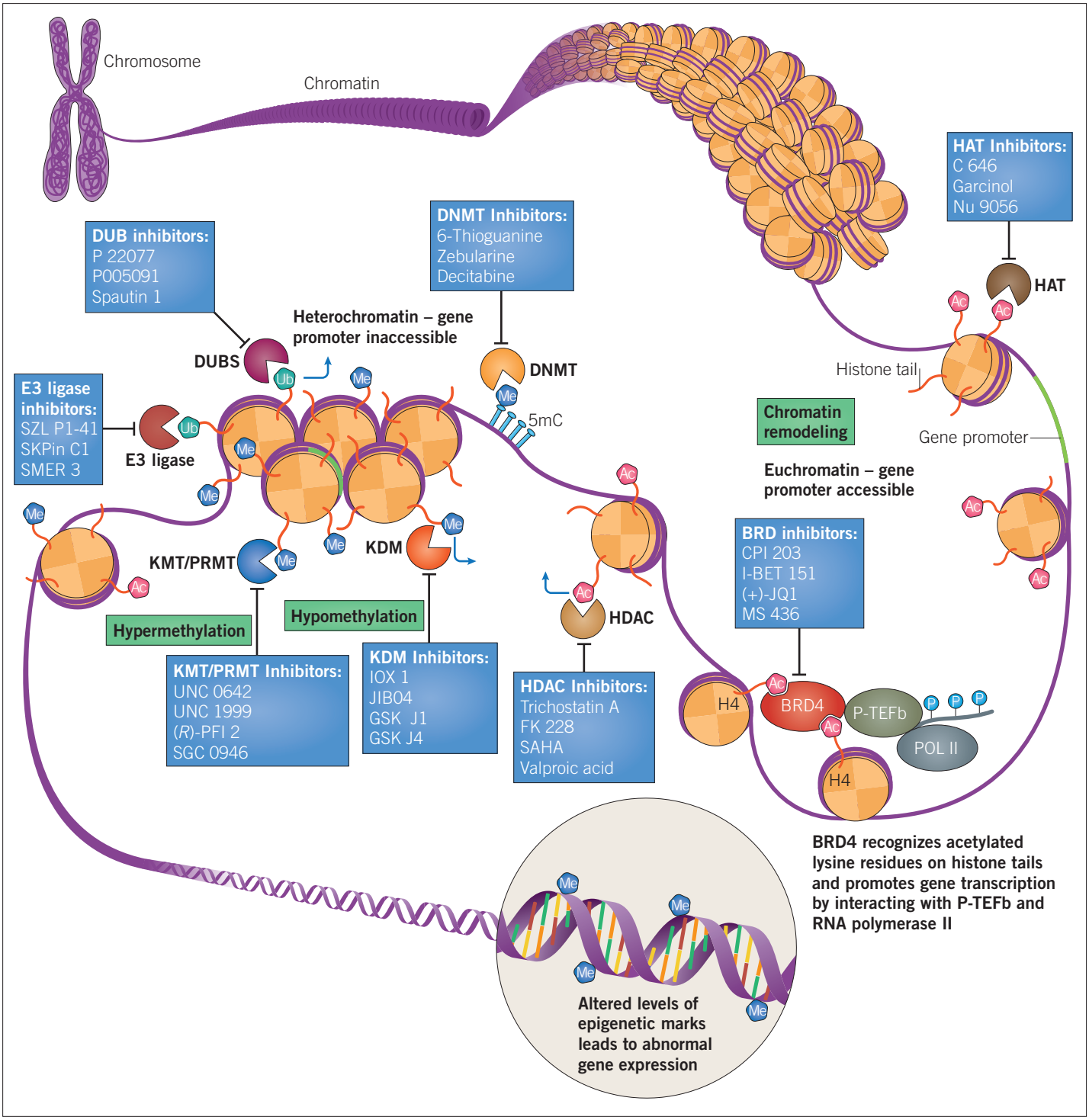
One of the most studied post-translational histone modifications is methylation. Histone methylation is carried out by histone methyltransferases (HMT), which are subdivided according to their target residue: those that methylate the arginine histone tail are known as protein arginine methyltransferases (PRMT), and those that methylate the lysine histone tail are known as lysine methyltransferases (KMT). PRMTs and KMTs regulate both transcriptional activation and repression, as well as DNA repair.

Dysregulation of the histone modifying enzyme enhancer of zeste homolog 2 (EZH2) is associated with tumor aggressiveness and is upregulated in breast and prostate cancer, as well as lymphoma and glioblastomas. The EZH2/EZH1 lysine methyltransferase inhibitor **UNC 1999** (Cat. No. 4904), has been shown to inhibit the growth of mixed-lineage-leukemia (MLL)–rearranged leukemia cells and prolongs survival in a mouse model of leukemia. **3-deazaneplanocin A** (Cat. No. 4703) inhibits both EZH2 histone methyltransferase and s-adenosylhomocysteine hydrolase activity, decreasing global histone methylation. This selectively causes apoptosis in multiple cancer cell lines, while having no apoptotic effect on normal cells.

Other HMTs under investigation as cancer targets include DOT1L and SET domain containing (lysine methyltransferase) 7 (SETD7). Recent studies have found that aberrant methylation by DOT1L is a fundamental step in the development of MLL-rearranged leukemia, and preclinical studies have shown that the inhibition of this enzyme increases survival in a mouse model of leukemia. The DOT1L inhibitor **SGC 0946** (Cat. No. 4541), selectively kills cells transformed with the MLL-AF9 fusion oncogene *in vitro*, and lowers levels of MLL target genes *HOXA9* and *Meis1*. The highly potent DOT1L inhibitor **EPZ 004777** (Cat. No. 5567) has also been shown to selectively inhibit proliferation and induce apoptosis of MLL-rearranged cells *in vitro*, as well as prolonging survival in a MLL xenograft mouse model. Two other useful research tools for studying MLL are **OICR 9429** (Cat. No. 5267) and **MM 102** (Cat. No. 5307). **OICR 9429** is a high affinity WDR5 antagonist, which disrupts WDR5/MLL interactions and reduces the viability of acute myeloid leukemia cells *in vitro*, as well as disrupting MLL1-RbBP5 interactions. **MM 102** is a potent WDR5/MLL interaction inhibitor, which induces *HoxA9* and *Meis-1* gene expression, two key genes involved in leukemogenesis (Box 2).

SETD7 has a large and diverse number of substrates and has been implicated in multiple cancer pathways. Research suggests that in addition to histone methylation, SETD7 plays an important role in nonhistone methylation of transcription factors and chromatin regulatory complexes, which also leads to changes in gene expression. The exact role of SETD7 is still not fully understood. It is hoped that the recently developed probe **(*R*)-PFI 2** (Cat. No. 4892) may help shed some light on the exact role and function of SETD7. This compound is a potent and selective SETD7 KMT inhibitor, which suppresses yes

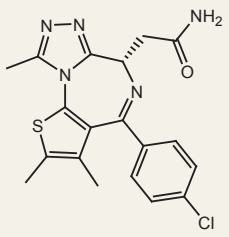
Figure 3 | Epigenetic Alterations in Cancer



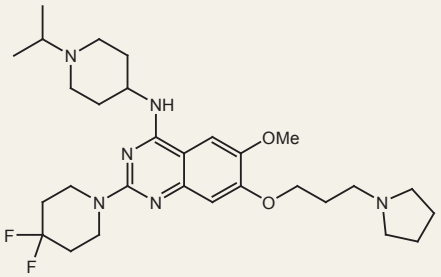
The fundamental unit of chromatin is the nucleosome, which consists of an octamer of the histone proteins H2A, H2B, H3 and H4 (two of each) tightly bound by DNA. Alterations in chromatin structure by post-translational modifications can regulate gene expression through the formation of heterochromatin or euchromatin, which usually repress or activate gene transcription, respectively. Post-translational modifications include DNA methylation and the covalent methylation (Me) and acetylation (Ac) of histone tails. DNA methylation represses transcription by blocking the binding of transcription complexes to the gene promoter. The acetylation of histone tails usually loosens the DNA from around the nucleosomes, increasing the accessibility of gene promoters to transcription complexes, therefore promoting transcription. Alternatively histone tail methylation can repress or promote gene expression, depending on the site and extent of methylation, as well as the presence of other histone modifications in the vicinity. The pattern of these post-translational modifications on a nucleosome determines the transcriptional profile of nearby genes. Abbreviations: BRD: bromodomains, DNMT: DNA methyltransferases, DUB: deubiquitinating enzymes, HAT: histone acetyltransferases, HDAC: histone deacetylases, KDM: histone demethylases, KMT/PRMT: lysine methyltransferases/protein arginine methyltransferases, UPS: ubiquitin proteasome system

Box 2: Epigenetics Products

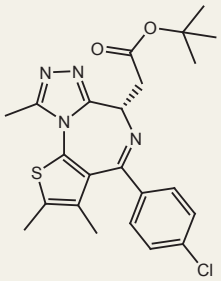
A full list of targets and related products is available on pages 33-60



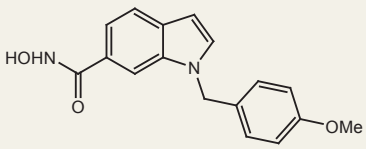
CPI 203 (5331)
BET bromodomain inhibitor;
arrests cell cycle at G_1 phase



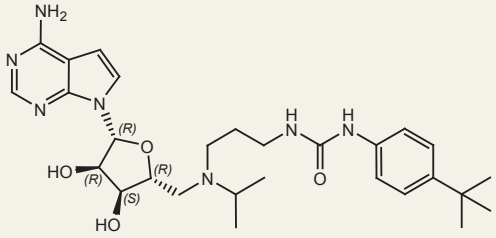
UNC 0642 (5132)
Potent and selective G9a and GLP inhibitor



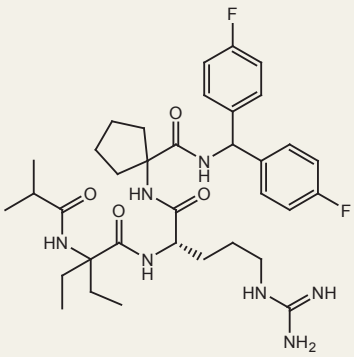
(+)-JQ1 (4499)
Potent, selective BET bromodomain inhibitor;
cell permeable



PCI 34051 (4643)
Potent and selective HDAC8 inhibitor



EPZ 004777 (5567)
Highly potent and selective DOT1L
inhibitor; cell permeable



MM 102 (5307)
WDR5/MLL interaction inhibitor

Ac-Ser-Gly-[N^5-(2-Chloro-1-iminoethyl)]-Orn-
Gly-Lys-Gly-Gly-Lys-Gly-Leu-Gly-Lys-Gly-
Gly-Ala-Lys-Arg-His-Arg-Lys-Val

C 21 (5128)
Selective PRMT1 inhibitor

associated protein (YAP) nuclear translocation and function following activation of the Hippo signaling pathway in breast cancer cells.

The methyltransferases G9a and GLP are involved in the dimethylation and consequent inactivation of the tumor suppressor p53. Overexpression of G9a and GLP has been found in many different types of cancer and thus, there is a need for small molecule inhibitors to investigate the effects of these proteins. Several G9a/GLP histone lysine methyltransferase inhibitors including **UNC 0638** (Cat. No. 4343) and **A 366** (Cat. No. 5163), have been shown to attenuate dimethylation of histones in cancer cells *in vitro*, as well as **UNC 0642** (Cat. No. 5132), which has sufficient properties to be used *in vivo*. This compound is a potent and selective G9a and GLP histone lysine methyltransferase inhibitor, which reduces histone dimethylation levels in cancer cells and displays modest brain penetration in mice.

Histone Demethylation

Histone demethylases (HDMs) catalyze the removal of methyl groups from histones and are involved in transcriptional regulation and DNA repair. **JIB 04** (Cat. No. 4972) is a pan Jumonji histone demethylase inhibitor, which diminishes tumor growth in mouse lung cancer xenograft models and prolongs survival in a mouse model of breast cancer. Another notable pan Jumonji histone demethylase inhibitor is **IOX 1** (Cat. No. 4464), which inhibits JMJD2A-mediated demethylation in cervical cancer cells. More selective histone demethylase inhibitors include the potent HDM inhibitor **GSK J1** (Cat. No. 4593); this compound inhibits the H3K27 histone demethylases JMJD3 (KDM6B) and UTX (KDM6A), as well as KDM5B, KDM5C and KDM5A. **GSK J4** (Cat. No. 4594) is the cell permeable ethyl ester derivative of **GSK J1**.

Histone Acetylation

Histone acetylation occurs on lysine residues and is predominantly associated with transcriptional activation. Acetylation increases transcription by neutralizing the histone's positive charge, making the attraction between the negatively charged DNA weaker and thus exposes gene promoters on the DNA for transcription. Chromatin conformation is regulated by histone acetyltransferases (HATs) and histone deacetylases (HDACs), which catalyze the addition and removal of acetyl groups, respectively.

There are three HAT families: Gen5, p300/CREB-binding protein (CBP) and MYST. Studies have found that 51% of cancer cells lines tested have a mutation at p300 and 35% show a mutation at the CBP, suggesting that these two genes are important tumor-suppressors. The selective p300/CBP inhibitor, **C 646** (Cat. No. 4200), suppresses histone H3 and H4 acetylation in fibroblast cell lines and **garcinol** (Cat. No. 4827) inhibits PCAF and p300 histone HAT activity, causing the reversal of epithelial–mesenchymal transition (EMT) in some breast cancer cell lines.

Acetyl transferase KAT5 (Tip60) is an interesting target because it plays a key role in chromatin remodeling, which regulates multiple levels of gene transcription and DNA repair. Furthermore, KAT5 acetylation is crucial for the p53-dependent apoptotic pathway. Selective KAT5 inhibitor **NU 9056** (Cat. No. 4903), inhibits protein acetylation in prostate cancer cell lines and blocks the DNA damage response. The compound decreases proliferation of LNCaP cells and induces apoptosis via caspase activation.

Histone Deacetylation

HDACs catalyze acetyl group removal from lysine residues on histones and oncoproteins including p53, YY1 and STAT3. Many cancer cell lines and primary tumors have shown hypoacetylation profiles, in comparison with normal cells. This combined with the observation that HDACs are upregulated in many types of cancers, including prostate colorectal and breast cancer, make HDACs an attractive target. Several HDAC inhibitors have shown promising results, including **NSC 3852** (Cat. No. 2521), **FK 228** (Cat. No. 3515), **valproic acid** (Cat. No. 2815) and **trichostatin A** (Cat. No. 1406), which have shown antiproliferative and antitumor activity *in vivo*. Furthermore the class I and II HDAC inhibitor **SAHA** (Cat. No.4652), induces an accumulation of acetylated histones H2A, H2B, H3 and H4 and suppresses cell growth in a range of cancer cell lines , while inducing apoptosis in cutaneous T cell lymphoma cells *in vitro*.

Bromodomains

Bromodomains (BRDs) are epigenetic "readers" that selectively recognize acetylated lysine residues on histone protein tails. Of particular interest is the BET (bromodomain and extra-terminal) bromodomain family, which comprises the ubiquitously expressed proteins BRD2, BRD3, BRD4; and the testis-specific protein, BRDT. BET proteins are epigenome readers that play a key role at the interface between chromatin remodeling and transcriptional regulation, and are integral in the regulation of transcriptional elongation and the cell cycle.

Inhibition of BET downregulates Myc in many malignant hematopoietic cell lines and exhibits therapeutic effects in mouse models of myeloid leukemia. **CPI 203** (Cat. No. 5331) is a BET bromodomain inhibitor, that downregulates Myc expression, causing G_1 cell cycle arrest and attenuating cell proliferation in pancreatic neuroendocrine tumors. It has also been shown to arrest the growth of T cell acute lymphoblastic leukemia cells *in vitro*. Furthermore, **CPI 203** enhances the antitumor effect of **rapamycin** (Cat. No. 1292).

BRD4 influences mitotic progression and is a critical mediator of transcriptional elongation because it binds to transcriptional sites of genes expressed during the M/G_1 cell cycle transition. BRD4 increases expression of genes that promote growth by recruiting p-TEFb to mitotic chromosomes. Furthermore, it has been observed that BRD4 is significantly upregulated in both primary and metastatic melanomas. *In vivo* studies have shown that inhibition of BRD4 impairs tumor growth and metastasis. Key BRD4 inhibitors include the potent, high affinity and selective, archetypical BET bromodomain inhibitor **(+)-JQ1** (Cat. No. 4499), which induces squamous cell differentiation and arrests tumor growth in BRD4-dependent carcinomas, including tumor growth in midline carcinoma cell xenograft models. **I-BET 151** (Cat. No. 4650) potently blocks recruitment of BRD3/4 to chromatin, inducing apoptosis and cell cycle arrest in MLL-fusion leukemia cell lines. This compound has also been shown to improve survival in rodent models of MLL-fusion leukemia. Another potent and selective BRD4 bromodomain inhibitor is **MS 436** (Cat. No. 5173). This compound has been shown to cause fast acting cytostatic effects and attenuates the proliferation of three melanoma cell lines *in vitro*.

While most BRD research has historically focused on BET domains, the roles of other BRD-containing proteins are starting to generate intense interest. The bromodomain adjacent to zinc finger domain (BAZ) family includes BAZ1A, BAZ1B, BAZ2A, and BAZ2B. BAZ2A, and BAZ2B are involved in chromatin remodeling and the regulation of non-coding RNA. BAZ domains form an interesting research target because BAZ2A has been shown to be involved in prostate cancer growth, and high expression levels of BAZ2B are correlated with B cell acute lymphoblastic leukemia. The selective BAZ2 bromodomain inhibitor **BAZ2-ICR** (Cat. No. 5266), demonstrates a 15-fold selectivity for the BAZ2 bromodomain over the CERC2 bromodomain and over 100-fold selectivity over a range of other bromodomains. Furthermore, **BAZ2-ICR** demonstrated a good *in vivo* profile and was suitable for oral administration, making it an ideal tool for investigating the BAZ2 bromodomain.

Plant homeodomain (PHD) fingers are readers that recruit transcription factor and chromatin modification complexes. Proteins that contain bromodomains and PHD fingers (BRPF) form scaffold complexes in the HAT MYST family. The BRPF family includes BRPF1, BRPF 2 and BRPF3. MYST complexes are involved in transcription activation and DNA repair and are often translocated in acute myeloid leukemia (AML). **OF 1** (Cat. No. 5289) is a selective BRPF1B/2 inhibitor, which exhibits 39-fold selectivity for BRPF1B and BRPF2 over BRD4. Another key BRPF compound is the potent and selective BRPF1 inhibitor **GSK 5959** (Cat. No. 5385). This is a cell permeable compound that inhibits BRPF1 interaction with histone H3.3 (a histone associated with reshaping the epigenome and several pediatric cancers).

Ubiquitination

Compared to other histone modifications, the functions of histone ubiquitination are less well understood. However increasing evidence points to an important role for this epigenetic modification in the DNA damage response.

One ubiquitin E3 ligase currently under investigation is Skp2, which promotes ubiquitination and degradation of p27, as well as triggering the ubiquitination of Akt. Skp2 is upregulated in many types of cancer, playing an integral role in apoptosis, cell cycle control, cancer progression and metastasis. In addition, Skp2 has been shown to regulate the self-renewal capability of cancer stem cells. **SZL P1-41** (Cat. No. 5076) selectively suppresses Skp2 Skp, Cullin, F-box (SCF) containing complex E3 ligase activity but exhibits no effect on the activity of other SCF complexes. Furthermore, it inhibits Skp2-mediated p27 and Akt ubiquitination *in vitro* and *in vivo*. This compound suppresses the survival of cancer cells and cancer stem cells by triggering cell senescence and inhibiting glycolysis. It also exhibits antitumor effects in multiple animal models and cancer cell lines. **SKPin C1** (Cat. No. 4817) is an inhibitor of Skp2-mediated p27 degradation, which has been shown to induce p27 accumulation in a metastatic melanoma cell line and promote cell cycle arrest in several other cancer cell lines.

The SCF family of ubiquitin ligases is involved in transcription and cell cycle control (specifically the control of G_1/G_2 transition). They catalyze the ubiquitination of proteins which then undergo proteasomal degradation. **SMER 3** (Cat. No. 4375) is a selective inhibitor of a yeast SCF family E3 ubiquitin ligase (SCFMet30), and studies have demonstrated its ability to block cell proliferation *in vitro* and *in vivo*, as well as enhancing the inhibition of mTOR by **rapamycin**.

Histone Deubiquitination

The removal of ubiquitin groups from histone lysine residues is catalyzed by proteases known as deubiquitinating enzymes (DUBs). Ubiquitin-specific protease (USP) and JAMM family members have been shown to regulate transcription, DNA repair, gene expression and cell cycle progression.

USP7 is a master regulator of p53-mediated apoptosis, modulating the effects of KAT5, Mdm2 and p53. USP7 deubiquitinates and stabilizes KAT5 and Mdm2; Mdm2 then ubquitinates p53, which leads to its destruction, therefore maintaining normal p53 levels. The USP7 inhibitor **P 22077** (Cat. No. 4485) destabilizes KAT5 and suppresses the p53-dependent apoptotic pathway. It also inhibits USP47 and HDM2. Selective USP7 inhibitor **P005091** (Cat. No. 4733) increases p53 levels and induces apoptosis in cancer cell lines, as well as displaying antiangiogenic activity *in vivo*.

Beclin 1 and p53 are two important tumor suppressors, which are frequently mutated in cancer. Beclin 1 regulates the activities of USP10 and USP13, which in turn regulate p53 levels. The autophagy inhibitor **Spautin 1** (Cat. No. 5197), inhibits USP10 and USP13 activity and selectively promotes apoptosis of cancer cells under starvation conditions. This compound also promotes the degradation of the Beclin1/Vps34 complex.

Other Histone Modifications

Other enzymes involved in histone posttranslational modification include kinases, phosphatases and proteases, see the product finder on page 8 for products relating to these categories.

DNA Methylation

DNA methyltransferases (DNMTs) are a family of enzymes that catalyze the transfer of a methyl group from S-adenosyl methionine (SAM) to the target DNA. DNA methylation usually occurs on the 5' position of the cytosine (5mC) ring within CpG dinucleotides. Widespread DNA hypomethylation and hypermethylation have been observed at CpG islands and short CpG-rich DNA regions in gene promoters, and is thought to promote tumorigenesis. Key research compounds for studying DNA methylation includes a synthetic analog of cytidine, **zebularine** (Cat. No. 2293), an orally active DNA methyltransferase inhibitor, which attenuates tumor cell proliferation and reactivates silenced genes in bladder carcinoma cells. **Decitabine** (Cat. No. 2624) is a cytosine analog that is incorporated into DNA and acts as a suicide substrate for DNA methyltransferase, resulting in DNA hypomethylation and activation of silent genes. This compound is a widely used chemotherapeutic agent that suppresses growth of human tumor cell lines. Another commonly used anticancer and immunosuppressive agent is **6-thioguanine** (Cat. No. 4061); this compound disrupts cytosine methylation by DNA methyltransferases after incorporation into DNA, and displays cytotoxic and antineoplastic properties.

Receptor Signaling

Cancer Research Target	For Products See Page
Growth Factor Receptors	
Anaplastic Lymphoma Kinase (ALK)	37
EGFR	37
FGFR	38
FLT3	38
Insulin and Insulin-like Receptors	38
PDGFR	38
Sphingosine-1-phosphate Receptors	38
TGF-β Receptors	39
VEGFR	56
Intracellular Signaling	
Abl Kinase	39
Akt (Protein Kinase B)	39
AMPK	40
Broad Spectrum Protein Kinase Inhibitors	40
Glycogen Synthase Kinase 3	40
G-protein Signaling	40
Heat Shock Proteins	41
Histone Deacetylases	35
LIM kinases (LIMKs)	41
MAPK	41
MEK	42
Mnk	42
Monopolar Spindle 1 Kinase	42
mTOR	42
Other Kinases	43
PKR-like ER kinase (PERK)	43
PI 3-Kinase	43
Protein Kinase D	43
Protein Ser/Thr Phosphatases	44
Protein Tyrosine Phosphatases	44
Raf Kinase	44
Rho-Kinase (ROCK)	44
Ribosomal S6 Protein Kinases (RSKs)	44
Sir2-like Family Deacetylases	45
Sphingosine Kinase	45
Src Family Kinases	45
Transferases	45
Translocation, Exocytosis & Endocytosis	45
Trk Receptors	46
Wnt Signaling	46
Nuclear Receptors	
Androgen Receptors	46
Aromatase	47
Aryl Hydrocarbon Receptor	47
Estrogen and Related Receptors	47
Estrogen (GPR30) Receptors	48

Cellular signaling pathways control the proliferation, differentiation, survival and migration of normal cells. However their dysregulation can result in tumor formation and progression. The overexpression or mutation of cell surface receptors and intracellular enzymes, as well as the altered expression of growth factors, cytokines and steroid hormones can drive the proliferation of malignancies, and recruit parenchymal cells to support tumor formation. Furthermore mutations of components within intracellular signaling pathways can result in activated pathways that are insensitive to external antiproliferative and proapoptotic signals.

Growth Factor Receptors

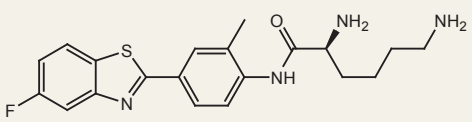
Under normal physiological conditions, growth factor availability regulates the balance between proliferation and cell death. This role in cellular homeostasis is often subverted in cancer. Tumor cells can acquire the ability to produce and secrete growth factors to ensure their own survival, as well as recruit non-malignant cells in order to support growth and evade detection by the immune system. Growth factors bind transmembrane receptors, which contain intrinsic kinase activity. When activated they stimulate intracellular signaling pathways including phosphoinositide 3-kinases (PI 3-K) and mitogen-activated protein kinase (MAPK) pathways (Figure 4).

In many human cancers, receptor tyrosine kinases (RTKs) are commonly affected by mutations resulting in upregulation of their signaling output (Figure 4). For example, the amplification or overexpression of the HER2/Neu/ERBB2 gene is frequently found in breast cancer (Figure 5). HER2 is part of the ErbB family of RTKs, which consists of four members: epidermal growth factor receptor (EGFR or ErbB1), HER2 (ErbB2), ErbB3 and ErbB4. Intracellular signaling from ErbB homo- and heterodimers occurs through the PI 3-K and MAPK signaling pathways (Figure 4). Compounds that selectively target EGFR or ErbB2 such as **iressa** (Cat. No. 3000) or **TAK 165** (Cat. No. 3599) respectively, are both clinically relevant and important tool compounds for the study of ErbB family signaling. **HKI 357** (Cat. No. 3580) is a potent inhibitor of both ErbB2 (HER2) and EGFR that suppresses ligand-induced EGFR autophosphorylation and cell proliferation. This compound has also been shown to circumvent mechanisms of resistance to **iressa** in lung cancer cells. **AG 490** (Cat. No. 0414) also inhibits both EGFR and ErbB2 as well as JAK2, JAK3/STAT, JAK3/AP-1 and JAK3/MAPK pathways, demonstrating potent inhibition of cytokine-independent cell growth *in vitro* and tumor cell invasion *in vivo*. Furthermore, this compound selectively induces apoptosis of leukemia cells over normal hematopoietic cells (Box 3).

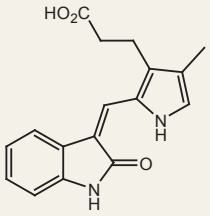
Type I insulin-like growth factor receptor (IGF1R) is important in the development and survival of many cell types and is ubiquitously expressed throughout the body. Dysregulation of IGF1R expression and signaling has been shown to drive

Box 3: Growth Factor Receptor Products

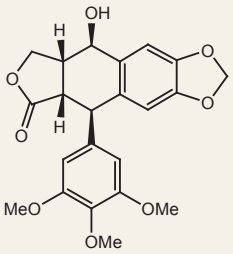
A full list of targets and related products is available on pages 33-60



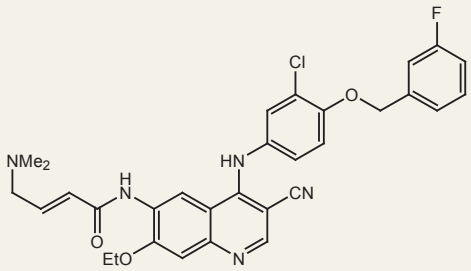
Phortress (4995)
Prodrug of the antitumor agent 5F 203



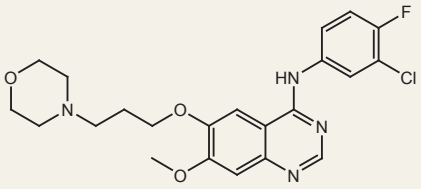
SU 5402 (3300)
Potent FGFR and VEGFR inhibitor



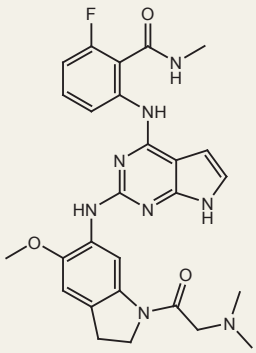
Picropodophyllotoxin (2956)
Selective IGF1R inhibitor



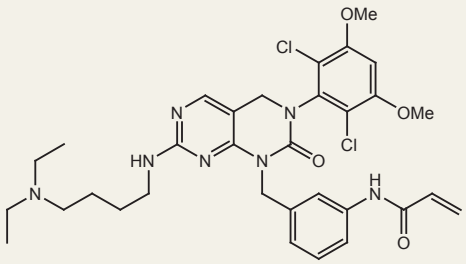
HKI 357 (3580)
Dual irreversible inhibitor of ErbB2 and EGFR



Iressa (3000)
Orally active, selective EGFR inhibitor



GSK 1838705 (5111)
Potent IR and IGF1R inhibitor; also inhibits anaplastic lymphoma kinase (ALK)

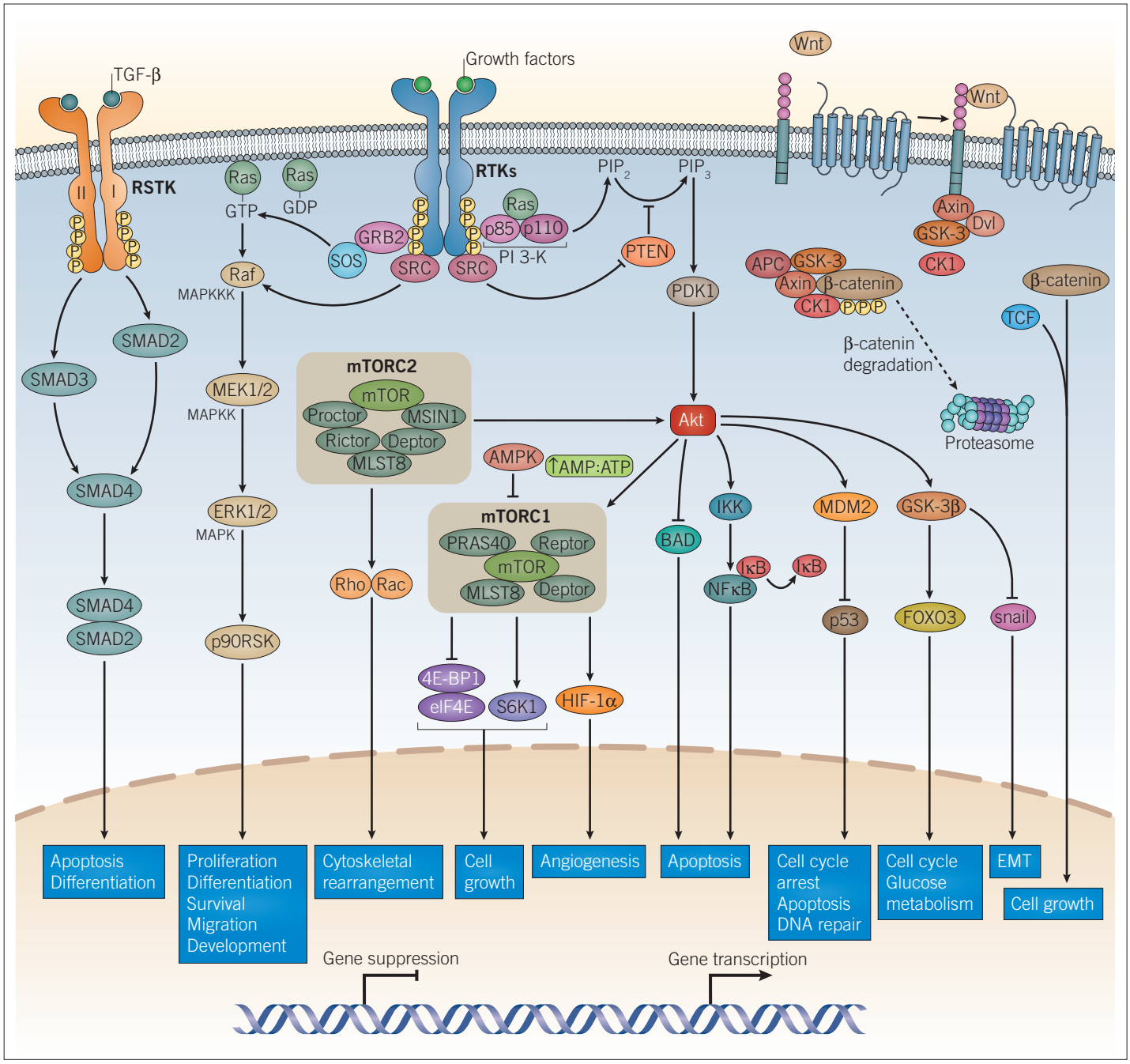


FIIN 1 hydrochloride (4002)
Potent, irreversible FGFR inhibitor

oncogenesis and progression. For example, studies have shown that overexpression of IGF1R promotes tumorigenesis in mouse models of cancer and prevents apoptosis in prostate cancer cells. Key IGF1R inhibitors include **BMS 536924** (Cat. No. 4774), a dual inhibitor of the insulin receptor (IR) and IGF1R, which has been shown to inhibit receptor autophosphorylation and downstream MEK1/2 and Akt signaling. **BMS 536924** induces G_1 arrest and apoptosis in acute myeloblastic leukemia (AML) cells and also inhibits cell proliferation in multiple other tumor types. Furthermore, this compound suppresses Snail mRNA expression in breast cancer cells overexpressing IGF1R, this leads to increased levels of E-cadherin and the reversal of epithelial to mesenchymal transition (EMT) (Figure 4). **GSK 1838705** (Cat. No. 5111) is another IR and IGF1R inhibitor that blocks proliferation of cancer cell lines *in vitro*, and causes complete regression of ALK-dependent tumors *in vivo*. The orally active IGF1R inhibitor **picropodophyllotoxin** (Cat. No. 2956) is an *in vivo* tool, which inhibits IGF1R autophosphorylation, increases the fraction of cells in the G_2/M phase, and induces apoptosis. This compound exhibits antiproliferative effects in multiple cancer cell lines and has anticancer and antineovascularization activity *in vivo*.

Anaplastic lymphoma kinase (ALK) is a RTK that was first identified in anaplastic large cell lymphoma (ALCL) as part of the fusion protein NPM-ALK. Downstream effectors of ALK tyrosine kinase activity have been shown to include the Ras-ERK, PI 3-K-Akt, JAK-STAT and NF-κB signaling pathways. In the absence of ligand binding ALK is inactive, with

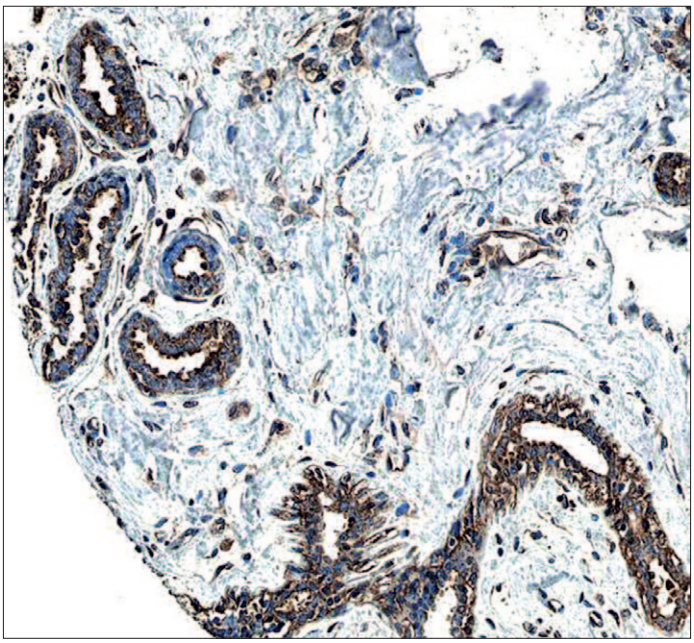
Figure 4 | Intracellular Signaling Pathways in Tumorigenesis and Cancer Progression



RTK growth factor receptors, TGF-β receptors and Wnt signaling all play a role in tumorigenesis and cancer progression. Dimerization of growth factor receptors and TGF-β receptors occur upon ligand binding, enabling activation of the intracellular kinases on each receptor, leading to autophosphorylation. The phosphorylated residues on the cytoplasmic domain of the RTK bind adaptor proteins to initiate PI 3-K signaling and MAPK signaling. TGF-β binds the TGF-β receptor I/II dimeric complex and causes the activation of SMAD2 and SMAD3, which results in the association of SMAD2/SMAD4 and upregulation of TGF-β-responsive gene transcription. β-catenin undergoes proteasomal degradation in the absence of Wnt; upon Wnt binding, β-catenin is released from its complex and combines with TCF to promote Wnt-responsive gene transcription. These pathways regulate a wide range of cellular processes and encompass many of the major targets studied in cancer research. Abbreviations: RSTK: receptor serine threonine kinase, RTK: receptor tyrosine kinases.

its expression promoting apoptosis. Conversely, when ALK is activated through either ligand binding or as part of an ALK fusion protein, apoptosis is decreased. ALK promotes oncogenesis through overexpression and gain-of-function mutations. ALK is overexpressed in lung cancer, melanoma and certain types of breast cancer, amongst others, whilst point mutations in the ALK kinase domain have been implicated in neuroblastoma development. Inhibition of ALK using small molecules

Figure 5 | ErbB2/Her2 in Human Breast Cancer Tissue



ErbB2 expression detected in paraffin-embedded sections of human breast cancer tissue. The ERBB2/HER2 gene is commonly amplified or overexpressed in breast cancer. The receptor is visualized here as brown staining using a Rabbit Anti-Human Phospho-ErbB2 Affinity-purified Polyclonal Antibody (R&D Systems, Catalog #AF4438). Hematoxylin counterstain in blue.

has shown some promising preclinical results in models of lung cancer. The potent and orally active ALK inhibitors **ASP 3026** (Cat. No. 5310) and **KRCA 0008** (Cat. No 5098), have been shown to reduce tumor growth in hEML4-ALK transgenic mice, and attenuate xenograft lung cancer tumor growth in mice respectively. **Crizotinib** (Cat. No. 4368) is a potent dual inhibitor of ALK and mesenchymal-epithelial transition factor (c-MET), which displays antitumor efficacy in multiple tumor models and inhibits c-MET-dependent proliferation, migration and invasion of human tumor cells *in vitro*. The high affinity and selective ALK and ROS1 inhibitor **PF 06463922** (Cat. No. 5640) has been shown to inhibit proliferation of a non-small lung cancer cell line containing a **crizotinib**-resistant ROS1 mutation *in vitro*. This compound is also orally available and brain penetrant and has been shown to suppress tumor growth in relevant mouse models.

Fibroblast growth factor (FGF) signaling is mediated by FGF receptors (FGFR). This signaling pathway is regulated by FGFR expression levels and the affinity of FGF for the different FGFR isoforms. In normal cells FGF plays a regulatory role in tissue homeostasis, tissue repair and angiogenesis. Dysregulation of this pathway has been shown to be involved in carcinogenesis. Two useful compounds for studying the role of FGFR in cancer are **PD 173074** (Cat. No. 3044) and **FIIN 1** (Cat. No. 4002). **PD 173074** is a selective FGFR1 and FGFR3 inhibitor, which has been shown to inhibit FGF- and VEGF-induced angiogenesis in a mouse cornea model of angiogenesis, and to block tumor growth in lung cancer xenograft models. Derived from **PD 173074** the potent, irreversible FGFR inhibitor **FIIN 1** exhibits antiproliferative activity in FGFR3- and FGFR1-transformed Ba/F3 cells.

TGF-β is a growth factor that plays an important role in several pathways involved with cell adhesion, differentiation, motility and death. In normal cells, TGF-β binds the serine/threonine kinase TGF-β receptors and suppresses the ability of cells to progress through the cell cycle, as well as promoting apoptosis. Disruption of the TGF-β/SMAD pathway has been implicated in a multitude of human cancers (Figure 4). TGF-β is therapeutically beneficial in the early stages of cancer because it inhibits cell growth; however in the later stages of cancer, cells become refractory to TGF-β-mediated growth inhibition and instead promotes tumor progression. *In vitro* studies have suggested that TGF-β enhances the invasiveness of cells by upregulating proteases such as MMPs and downregulating protease inhibitors. As a tumor grows, the environment becomes hypoxic and inflammation occurs, this increases TGF-β secretion by macrophages and has been linked to metastasis. Furthermore, TGF-β is involved in the induction of angiopoietin in pre-metastatic breast cancer cells, which encourages the retention of those cancer cells in other tissues such as the lungs. TGF-β receptor kinase inhibitors have shown promising preclinical results. The potent and selective TGF-β receptor kinase inhibitor **SB 431542** (Cat. No. 1614), has been shown to inhibit TGF-β-induced EMT, migration, invasion and VEGF secretion in several human cancer cell lines, as well as displaying antitumor activity in a mouse model of colon cancer. Another potent compound is the TGF-β type I receptor inhibitor **A 83-01** (Cat. No. 2939), this compound blocks phosphorylation of Smad2 and inhibits TGF-β-induced EMT.

While some clinically relevant inhibitors are selective for individual RTKs or RTK families, others have proved effective by targeting multiple receptors. For example, **sunitinib** (Cat. No. 3768), targets, amongst others, PDGFRb, VEGFR, FLT3 and RET. Other compounds, such as **lestaurtinib** (Cat. No. 3395), are more broad-spectrum inhibitors that target both the receptor and intracellular kinases. By combining EGFR inhibitors with inhibitors for other clinically relevant receptors such as IGF1R, TGF-β or c-MET, it may be possible to overcome the resistance to selectively targeted agents that occurs in some cancers. Looking to the future, personalized/precision medicine will focus on creating tailor made combinations of relevant drugs, depending on the genetic makeup of an individual.

Intracellular Signaling

One of the first intracellular kinases to be elucidated as a proto-oncogene was c-Src, an upstream mediator of both the PI 3-K

and MAPK pathways. Increased c-Src activity has been linked to a number of gastrointestinal malignancies, including pancreatic cancer. The Src family of kinases (Src, Fyn, Yes, Lck, Lyn, Hck, Fgr and Blk) are nonreceptor tyrosine kinases that interact with the intracellular domains of growth factor receptors, cytokine receptors, G protein-coupled receptors (GPCRs) and integrins. Src kinase activity is regulated by phosphatases, through binding to adaptor proteins, and proteasomal degradation.

The potent Src inhibitors **A 419259** (Cat. No. 3914) and **KB SRC 4** (Cat. No. 4660) have been shown to suppress the proliferation of several types of malignant cells *in vitro*. Furthermore **A 419259** has demonstrated inhibition of AML stem cell proliferation *in vitro* and *in vivo.* Another interesting compound that targets Src function is **pyridostatin** (Cat. No. 4763), which reduces Src protein levels and decreases Src-dependent motility in breast cancer cells by targeting the SRC gene directly (Box 4).

The oncogenic Bcr-Abl fusion protein (caused by a t(9,22) translocation) is linked to the development of chronic myeloid leukemia and has been successfully targeted by tyrosine kinase inhibitors. The potent multi-kinase and pan-BCR-ABL inhibitor **AP 24534** (ponatinib, Cat. No. 4274) may offer insights into overcoming mutated forms of BCR-ABL, e.g. BCR-ABL^{T3151}, whilst **bosutinib** (Cat. No. 4361), the dual Src and Abl kinase inhibitor, has been shown to control the proliferation and migration of certain breast and colon cancer cell lines.

PI 3-K/Akt/mTOR signaling dysfunction is frequently observed in cancers and thus is an intensely investigated pathway. 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. In normal cells, 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; Akt in turn activates mTOR signaling. Dysregulation of this pathway has been shown to cause oncogenesis and promotes cancer progression.

Signaling through all classes of PI 3-K play a role in cell proliferation, however cancer research is primarily focused on mutations in the *PIK3CA* gene that encodes the catalytic subunit of p110α of the class 1A PI 3-K. This has been shown to be frequently mutated in human cancers such as lung and cervical malignancies. Aberrant PI 3-K activation, from mutations in the genes 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). Key compounds for PI 3-K research include **LY 294002** (Cat. No. 1130), a prototypical PI 3-K inhibitor, which has been shown to inhibit proliferation and induce apoptosis in human colon cancer cells *in vitro* and *in vivo*. Studies have demonstrated that the potent and selective PI 3-K p110α inhibitor **A66** (Cat. No. 5595), inhibits Akt signaling and tumor growth in ovarian cancer xenografts in mice. Other key compounds include dual ATP-competitive PI 3-K/mTOR inhibitors such as **PF 04691502** (Cat. No. 4820) and **PF 05212384** (Cat. No. 4823), which potently inhibit tumor cell growth and exhibit antitumor activity in multiple cancer xenograft models.

Akt (protein kinase B) is an integral mediator of PI 3-K signaling; it stimulates glycolysis, promoting cell growth and inhibiting apoptosis. Preclinical research reveals that aberrant Akt signaling is instrumental in malignant transformation by promoting cell survival, angiogenesis and migration. Furthermore, Akt has been shown to have a role in chemoresistance. The inhibition of Akt by the small molecule inhibitors **API-1** (Cat. No. 3897) and **API-2** (Cat. No. 2151), results in antitumor activity *in vitro,* as well as selectively inhibiting cell growth in mouse models of human cancers overexpressing Akt.

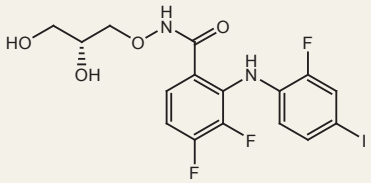
AMPK functions in contrast to Akt1, it acts as an energy sensor and is stimulated under energetic stress, when the ratio of AMP:ATP is increased, or in hypoxic conditions (Figure 4). AMPK activation inhibits mTOR, inducing apoptosis and autophagy. Tumor cells often suppress AMPK signaling, subverting the cellular metabolic shift to oxidative metabolism normally mediated by AMPK. Potent AMPK activators and inhibitors such as **A 769662** (Cat. No. 3336) and **dorsomorphin** (Cat. No. 3093) respectively, are useful tools for studying the role of AMPK in cancer.

The mechanistic target of rapamycin (mTOR; mammalian target of rapamycin) is a highly conserved serine/threonine protein kinase. In cells, mTOR exists as two functionally distinct multiprotein complexes mTORC1 and mTORC2 (Figure 4). mTORC1 is involved in autophagy and cellular proliferation, and is a key mediator of protein synthesis, by regulating the eukaryotic translation initiation factor 4F (eIF4F) complex. mTORC2 plays a major role in mediating cell proliferation and survival by phosphorylating Akt, as well as being a key regulator of glucose and lipid metabolism.

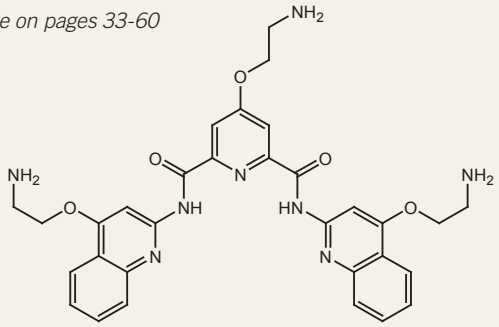
Rapamycin (Cat. No. 1292) is a classical inhibitor of mTOR, which complexes with FKBP-12 and binds to mTOR suppressing its activity, including inhibiting IL-2-induced phosphorylation and p70 S6 kinase activation. The ATP-competitive mTOR inhibitors **torin 1** (Cat. No. 4247) and **torin 2** (Cat. No. 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. The potent mTOR inhibitor **temsirolimus**

Box 4: Intracellular Signaling Products

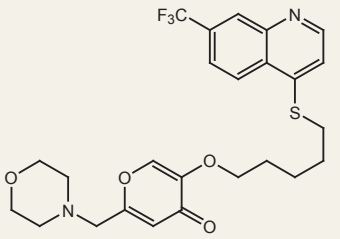
A full list of targets and related products is available on pages 33-60



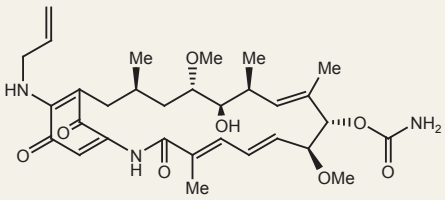
PD 0325901 (4192)
Potent inhibitor of MEK1/2



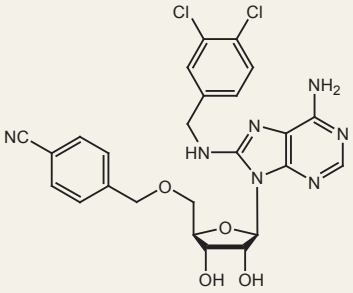
Pyridostatin (4763)
Stabilizes G-quadruplexes; induces DNA damage and cell cycle arrest



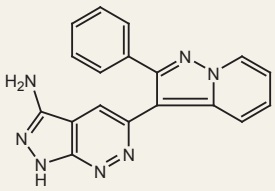
EHT 1864 (3872)
Potent inhibitor of Rac family GTPases



17-AAG (1515)
Selective Hsp90 inhibitor



VER 155008 (3803)
Hsp70 inhibitor



FR 180204 (3706)
Selective ERK inhibitor

(Cat. No. 5264) has displayed multiple antitumor effects in preclinical studies. This compound has been shown to inhibit tumor growth and HIF-1α-mediated VEGF production in breast cancer cell lines, as well as suppressing blood vessel formation *in vivo*. **Temsirolimus** also causes G_1/S cell cycle arrest in multiple cancer cell lines.

mTORC1 regulates the assembly of the eIF4F complex and transcription of the genes transcribing rRNA and tRNA. Activation of the mTOR pathway leads to the dissociation of 4E-binding proteins (4E-BP) from the eIF4G binding sites on eIF4E resulting in the assembly of the eIF4F complex. The small molecule **4E1RCat** (Cat. No. 4215) inhibits protein translation by blocking eIF4E:eIF4G and eIF4E:4E-BP1 interactions, furthermore it exhibits chemosensitizing properties. **4EGI-1** (Cat. No. 4800) also inhibits eIF4E:eIF4G interactions and has displayed activity against leukemia and lung cancer cells.

The other major pathway that has been extensively studied for therapeutic intervention in cancer is the MAPK pathway. MAPKs are serine-threonine kinases that regulate a wide variety of cellular functions. There are four major mammalian MAP kinase cascades involving: ERK1/2, p38, JNK and ERK5/BMK1. MAPK pathways transduce signals from growth factors and are integral mediators in regulating differentiation and proliferation in many cell types. Mutations in critical components of these cascades have been linked to many types of cancer. Consequently, inhibitors targeting the molecules involved in the Ras-Raf-MEK-ERK cascade are of potential therapeutic significance (Figure 4).

Ras is a small GTPase that is subject to activating mutations in a large proportion of cancers and is the most frequently activated oncogene. These mutations enable Ras activation in the absence of ligand-RTK binding. K-Ras mutations are common in colon and pancreatic cancer; N-Ras mutations in melanomas; and H-Ras mutations in cervical and bladder cancers. 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 to reduce their activity. Inhibition of H-Ras by FTase inhibitors has been shown to be effective in blocking its signaling. However, K-Ras and N-Ras are able to bypass FTase inhibition by utilizing the related GGTase. FTase and GGTase inhibitors such as **FTI 276** (Cat. No. 2406) and **GGTI 298** (Cat. No. 2430) are useful tools for studying Ras and its associated oncogenic signaling. Studies have shown that the CAAZ peptidomimetic GGTase I inhibitor **GGTI 298**, strongly inhibits the processing of geranylgeranylated Rap1A, with little effect on processing of farnesylated Ha-Ras and causing G_0-G_1 cell cycle arrest. This compound

also causes apoptosis in lung cancer cells, as well as inhibiting cell invasion and migration in colon cancer cells. **FTI 276** is a selective inhibitor of FTase that displays >100-fold selectivity over GGTase I, however, it still exhibits a potent effect on the function of both enzymes (IC_{50} values are 0.5 and 50 nM respectively). This compound blocks the growth of human lung carcinomas expressing oncogenic K-Ras in nude mice.

Raf kinases are activated by GTP-bound Ras and recruited to the cell membrane upon growth factor stimulation. There are three Raf family members – A-Raf, B-Raf and C-Raf. Activating mutations in the B-Raf proteins have been linked to a range of cancers including skin, thyroid, ovarian and pancreatic. In melanomas, *BRAF* is the most commonly mutated gene, with *BRAF* mutations evident in over 65% of malignant melanomas. A high proportion of these *BRAF* mutations contain a missense substitution which generates the B-Raf^{V600E} protein – a constitutively active kinase. A number of small molecule B-Raf inhibitors have shown promising preclinical results. Among these are the potent B-Raf inhibitors **AZ 628** (Cat. No. 4836), **GDC 0879** (Cat. No. 4453) and **SB 590885** (Cat. No. 2650), which have all demonstrated inhibition of ERK signaling, as well as inhibiting cell growth in a range of cancer cells harboring the B-Raf^{V600E} mutation *in vitro*. Furthermore the potent Raf kinase inhibitor **ML 786** (Cat. No. 5036) is a useful *in vivo* research tool, having been shown to attenuate tumor growth in melanoma cell xenografts expressing the B-Raf^{V600E} mutation in mice.

Signal transduction through Raf is also dependent on a number of proteins that are important in cancer research, including 14-3-3 and Hsp90. Hsp90 (90 kDa heat shock protein) is a molecular chaperone that aids protein folding and quality control for a large number of 'client' proteins, and acts in concert with other chaperones such as Hsp70. Other notable tumor-associated clients include estrogen receptors and p53. Hsp90 plays an important role in some tumor cell types by stabilizing mutated oncogenic proteins. Inhibition of heat shock proteins has shown promising preclinical results, for example **17-AAG** (Cat. No. 1515), an inhibitor of Hsp90 inhibited the activity of oncogenic proteins such as p185^{ErbB2}, N-Ras, Ki-Ras and c-Akt, and displayed antitumor effects *in vivo*. Furthermore, the Hsp70 inhibitor **VER 155008** (Cat. No. 3803) suppresses proliferation of multiple human tumor cell lines *in vitro*.

MEK, also known as mitogen-activated protein kinase kinase or MAP2K, is a dual specificity kinase that phosphorylates both the tyrosine and threonine residues required for the activation of the mitogen activated protein kinases, ERK. Although there have been few oncogenic mutations for this kinase reported, the frequent activation of the MAPK pathway in cancer has meant that MEK has been extensively studied as a therapeutic target. Research has shown that inhibiting MEK displays promising antitumor effects in cancer models. For example, the potent MEK1/2 inhibitor **PD 0325901** (Cat .No. 4192), inhibits the growth of melanoma cell lines *in vitro* and *in vivo*, induces cell cycle arrest and apoptosis in a mouse tumor xenograft, and inhibits the production of proangiogenic growth factors such as VEGF. Another notable MEK inhibitor is the selective MEK5 inhibitor **BIX 02189** (Cat. No. 4842), which induces apoptosis in leukemia tumors.

There is a growing body of evidence showing that inhibitors of other MAPK signaling pathways, may prove to be useful in cancer therapy. For example, in some cancers, activation of p38 and JNK is associated with suppression of apoptosis, with correlations found between increased phosphorylation of p38α and malignant transformation in lymphoma, glioma, lung, breast and thyroid cancers. Similarly, activation of the JNK pathway by the leukemia-associated Bcr-Abl protein has been observed in hematopoietic cells. The activation of ERK leads to the phosphorylation of many transcription factors and other kinases, which can modulate cell cycle progression, protein translation, cell differentiation and apoptosis. Furthermore, ERK activation upregulates the expression of EGFR ligands, promoting an autocrine growth loop which facilitates continued tumor growth. Essential research compounds for studying MAPK pathways include the selective ERK inhibitor **FR 180204** (Cat. No. 3706); the selective ERK5/BMK1 inhibitor **XMD 8-92** (Cat. No. 4132) and the highly potent and selective p38α inhibitor **VX 745** (Cat. No. 3915).

In addition to PI 3-K and MAPK signaling, several other signaling pathways have been found to be involved in the progression of cancer, particularly those associated with cell growth and proliferation. Wnt proteins are secreted glycoproteins that regulate diverse developmental processes, such as differentiation, cell migration and proliferation, during embryogenesis and in adult tissues. Wnt is known to be proto-oncogenic and promotes tumorigenesis and metastasis. Inactivation of the *APC* gene (a suppressor of the Wnt/β-catenin pathway) or constitutive action of β-catenin, is frequently observed in colon cancer and is thought to be important in malignant transformation. The TCF/β-catenin-mediated transcription inhibitor **ICG 001** (Cat. No. 4505), suppresses tumor growth in colon carcinoma cell lines and in an *APC* mouse xenograft model. It has also been reported that **ICG 001** suppresses TGF-β1 induction of EMT as well as α-SMA induction *in vitro*. Two other types of small molecules have been used to modify Wnt signaling in cancer cells; inhibitors of Wnt response (IWR) and inhibitors of Wnt production (IWP) compounds. ***Endo*-IWR 1** (Cat. No. 3532) inhibits Wnt signaling by inducing an increase in Axin2 protein levels, promoting β-catenin phosphorylation by stabilizing axin-scaffolded destruction complexes. **IWP 2** (Cat. No. 3533) and **IWP 4** (Cat. No. 5214) inhibit Wnt processing and secretion by inactivating PORCN and inhibiting palmitoylation of Wnt.

Sphingosine-1-phosphate receptors (S1PR) are involved in the proliferation, migration, differentiation and survival of cancer cells. Sphingosine-1-phosphate (S1P) signaling is mediated by five subtypes of related G-protein-coupled receptors of the S1PR family; $S1P_1$, $S1P_2$, $S1P_3$, $S1P_4$ and $S1P_5$. Due to the complex nature of S1PR signaling, the role that S1PRs play in different types of cancer can vary considerably. For example overexpression of $S1PR_1$ has been linked to the progression of certain types of hematological malignancies, where increased levels of $S1PR_1$ in glioblastomas are linked to a positive prognosis. All the S1PR subtypes have been linked with tumorigenesis or cancer progression including $S1PR_4$, which interacts with HER2 and is linked to breast cancer progression through stimulation of the ERK pathway. Compounds that antagonize S1P receptors are of interest in the attenuation of hyperproliferative, migratory and inflammatory phenotypes observed in cancer cells. There are a range of compounds available for investigating the action of S1P receptor signaling in cancer, including the potent $S1P_4$ antagonist **CYM 50358** (Cat. No. 4679), the highly selective and potent $S1P_2$ antagonist **JTE 013** (Cat. No. 2392), and the high affinity $S1P_1$ and $S1P_3$ receptor antagonist **VPC 23019** (Cat. No. 4195). In addition, there is the $S1P_3$ allosteric agonist **CYM 5541** (Cat. No. 4897), which occupies a different space within the ligand binding pocket of $S1P_3$ than S1P, and may prove to be a useful compound for elucidating the myriad effects resulting from S1P signaling.

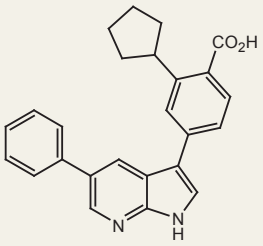
Nuclear Hormone Receptors

Nuclear hormone receptors bind sequence-specific promoter elements on target genes and modulate gene expression. Altered expression patterns in these receptors have been linked to many different cancers.

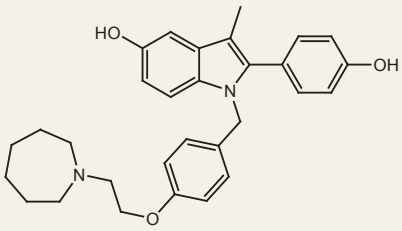
Both normal and cancer prostate cells need androgen to grow and divide. Actions of androgens are mediated by the androgen receptor (AR), a member of the steroid hormone super-family of nuclear receptors. The AR is a ligand-dependant transcription factor, which binds to specific androgen response elements (ARE) on the promoter regions of target genes, thereby inducing/repressing transcription of the gene. Androgen receptor signaling is the central regulator of tumor cells even after androgen ablation therapy. In light of this, the AR signaling axis has become a major focus in therapeutic development for castrate-resistant prostate cancer. AR activation promotes the growth and differentiation of prostate cancer cells, and AR signaling has also been implicated in breast cancer. In addition, the transcriptional activity of androgen receptors can be influenced by growth factors, prompting prostate cancer cell proliferation in the absence of androgens. There is a varied range of compounds available for investigating the role of ARs in cancer, including classic agonists, antagonists and modulators, as well as compounds that regulate the level of hormone release. Key compounds for prostate cancer research include

Box 5: Nuclear Receptor Products

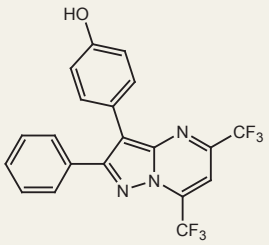
A full list of targets and related products is available on pages 33-60



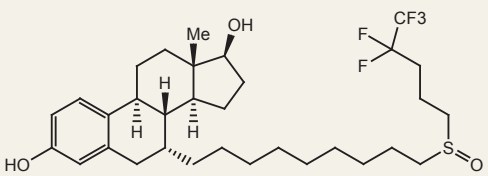
GSK 650394 (3572)
Serum- and glucocorticoid-regulated kinase (SGK1) inhibitor



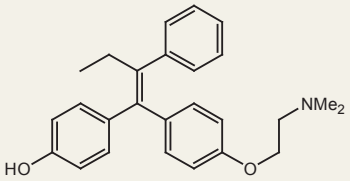
Bazedoxifene (5263)
Potent and selective estrogen receptor modulator (SERM)



PHTPP (2662)
Selective ERβ antagonist



ICI 182,780 (1047)
Estrogen receptor antagonist



(*Z*)-4-Hydroxytamoxifen (3412)
Metabolite of tamoxifen (Cat. No. 0999)

Receptor Signaling – continued

the endogenous AR agonist **testosterone** (Cat. No. 2822), the potent and selective androgen receptor modulator (SARM) **TFM-4AS-1** (Cat. No. 3813), and the serum- and glucocorticoid-regulated kinase 1 (SGK1) inhibitor **GSK 650394** (Cat. No. 3572), which has been shown to suppress androgen-stimulated growth of a human prostate carcinoma cell line (Box 5).

Estrogen plays an essential role in breast cancer cell growth, and estrogenic signal transduction pathways often become dysregulated in this disease. Breast cancer is classified into ERα positive (ER^+) or ER negative (ER^-). Key estrogen receptor (ER) compounds include the ER antagonist/partial agonist **tamoxifen** (Cat. No. 0999) and its metabolite **(*Z*)-4-hydroxytamoxifen** (Cat. No. 3412), which is used as a chemotherapeutic agent; the high affinity ER antagonist **ICI 182,780** (Cat. No. 1047) and the potent selective estrogen receptor modulators (SERM) **bazedoxifene** (Cat. No. 5263) and **raloxifene** (Cat. No. 2280). In addition, the Tocris range of ER compounds includes the highly potent and selective ERβ agonist **DPN** (Cat. No. 1494), with a 70-fold selectivity over ERα, and the selective ERβ antagonist **PHTPP** (Cat. No. 2662), which displays 36-fold selectivity over ERα (Box 5).

While ER^+ breast tumors often respond well to antiestrogen therapies, ER^- tumors do not, and these tumors are aggressive with a poor prognosis. As ER^- tumors account for ~30% of all breast cancers there is an urgent need for other viable targets. GPR30 has been reported to be expressed in ER^- tumors and is being investigated for its antitumor effects. GPR30 activation induces MAPK and PI 3-K signaling pathways, and has been shown to modulate the growth of cells in hormonally responsive cancers. Therefore it is postulated that GPR30 could modulate the estrogen response in ER^- tumors. Current studies report conflicting results, with some suggesting that GPR30 activation facilitates tumor cell proliferation, while others suggest that it inhibits proliferation. Thus, further studies are required to answer this question. In addition to their roles as ER ligands **ICI 182,780** and **tamoxifen** also act as high affinity agonists for GPR30, however their lack of selectivity for GPR30 limits their use in elucidating GPR30 function. **G-1** (Cat. No. 3577) is a potent and selective GPR30 receptor agonist, which displays no activity at ERα or ERβ (at concentrations up to 10 μM) and therefore may be a valuable tool for selectively studying GPR30. **G-1** has been shown to inhibit migration of breast cancer cells *in vitro* and block cell cycle progression at the G_1 phase. The high affinity and selective GPR30 receptor antagonist **G-15** (Cat. No. 3678), also displays no affinity for ERα and ERβ (at concentrations up to 10 μM) and has been shown to antagonize the effects of estrogen *in vivo*.

The mechanisms behind estrogen-related development of breast cancer are also being targeted for cancer therapies. For example, aromatase is a CYP450 enzyme involved in estrogen biosynthesis. Since estrogen is required for the growth of breast and ovarian cancers, inhibitors of aromatase exhibit anticancer activity by reducing estrogen levels. For example, **letrozole** (Cat. No. 4382), a potent, reversible, non-steroidal aromatase inhibitor displays antitumor effects in several animal models, and suppresses the endogenous aromatase-induced proliferation of breast cancer cells.

Aryl hydrocarbon receptors (AHRs) are cytosolic transcription factors that induce changes in gene expression upon ligand binding. AHR signaling is associated with malignant growth, and research has shown that tumor-derived ligands bind AHRs and suppress antitumor immune responses. The high affinity endogenous AHR agonist **ITE** (Cat. No. 1803) is just one of a range of compounds that demonstrate antitumor activity. **ITE** decreases the levels of the master pluripotency factor Oct4, inducing stem-like cancer cell differentiation in glioblastoma cells, as well as suppressing tumor growth in glioblastoma xenografts in mice.

Clearly, many signaling mechanisms can be dysregulated in cancer cells. By targeting critical receptors and signaling molecules using selective pathway inhibitors, cancer researchers can study one of the major hallmarks of cancer and its impact on tumorigenesis and progression.

Cell Cycle and DNA Damage Repair

Cancer Research Target	For Products See Page
ATM and ATR Kinase	48
Aurora Kinases	48
Calpains	48
Casein Kinase 1	49
Casein Kinase 2	49
Cdc25 Phosphatase	49
Cell Cycle Inhibitors	49
Checkpoint Kinases	49
Chemotherapeutics	59
Cyclin-dependent Kinases	49
DNA-dependent Protein Kinase	50
DNA, RNA and Protein Synthesis	50
Heat Shock Proteins	41
IRE1	50
Kinesin	50
Monopolar Spindle 1 Kinase	42
p53	51
PERK	43
Pim Kinase	54
Polo-like Kinase	51
Poly(ADP-ribose) Polymerase (PARP)	52
Telomerase	52
Translocation, Exocytosis & Endocytosis	45

In normal cells, each stage of the cell cycle is tightly regulated. In cancer cells, many genes and proteins that influence the progression of the cell cycle are mutated or overexpressed – they become oncogenes. The proteins/molecules involved in the regulation of the cell cycle, in particular DNA replication and DNA damage, have been of great interest to cancer researchers.

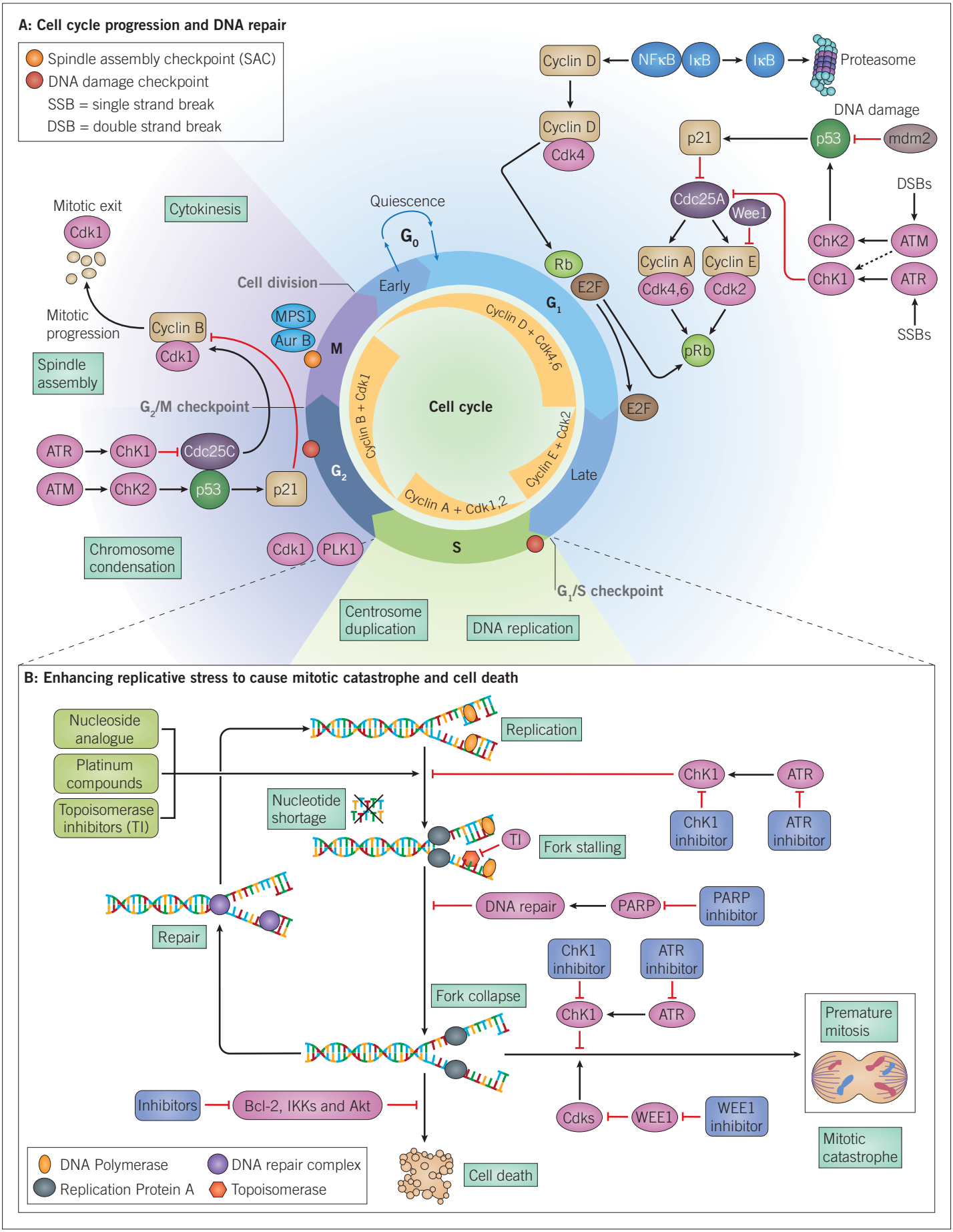
Cell Cycle and Mitosis

There are three major regulatory cell cycle checkpoints – G_1/S, intra-S phase and G_2/M phase. A cell can only pass through these checkpoints in the presence of stimulatory signals and in the absence of DNA damage. The cell cycle checkpoints are controlled by tumor suppressors and cyclin-dependent kinases (cdk). Cdks act in concert with their regulatory subunits cyclins, to control cell cycle progression through its four phases: G_1, S, G_2 and mitosis (M). Cdks are constitutively expressed and are regulated by several kinases and phosphatases, including Wee1 kinase and Cdc25 phosphatase. Such controls are necessary, since misregulation of cdk activity can induce unscheduled proliferation, resulting in genomic and chromosomal instability (Figure 6). Useful compounds for investigating cdks include **senexin A** (Cat. No. 4875), **ro 3006** (Cat. No. 4181) and **aminopurvalanol A** (Cat. No. 2072). **Senexin A** is a cdk8 inhibitor, which inhibits p21-induced transcription, and reverses **doxorubicin**-induced tumor-promoting paracrine activities *in vivo*. **Ro 3006** is a potent cdk1 inhibitor that suppresses cdk1/cyclin B1 and cdk1/cyclin A, inducing G_2/M phase cell cycle and apoptosis. **Aminopurvalanol A** inhibits cdk1/cyclin B, cdk2/cyclin A and cdk2/cyclin E, which causes cell cycle arrest at the G_2/M boundary (Box 6).

DNA replication occurs in five stages during the S-phase; initiation, unwinding, primer synthesis, elongation and termination. Helicase enzymes 'unwind' the DNA double helix, and telomerases reduce the resulting torsional strain, the single stands are now exposed and the replication fork is initiated. The leading strand of DNA is synthesized by Pol ε and the lagging strand is synthesized by Pol δ. PCNA is a cofactor for both DNA polymerase δ and ε, where it acts as a DNA clamp, which is important in both DNA synthesis and repair. At the end of the termination phase, DNA ligases form a phosphodiester bond which joins the DNA strands together, forming new doubled stranded DNA. There are many different compounds for targeting the enzymes involved in the replication of DNA including **T2AA** (Cat. No. 4723), **mithramycin A** (Cat. No. 1489), **NSC 617145** (Cat. No. 5340) and **L189** (Cat. No. 3561). **T2AA** is a PCNA inhibitor, which inhibits PCNA/PIP-box peptide interaction and causes DNA replication stress by stalling the DNA replication forks. It also inhibits PCNA interaction with DNA polymerase δ and arrests cell growth in S-phase. **Mithramycin A** binds to G-C-rich DNA and inhibits RNA and DNA polymerase action. **NSC 617145** is a Werner syndrome helicase (WRN) inhibitor, which acts synergistically with **mitomycin C** (Cat. No. 3258) to induce double-strand breaks and chromosomal abnormalities *in vitro*. **L189** is a DNA ligase I, III and IV inhibitor that blocks DNA binding and inhibits base excision repair (BER) and non-homologous end joining (NHEJ). In addition **L189** specifically sensitizes cancer cells to DNA damage and increases the cytotoxicity of DNA-damaging agents.

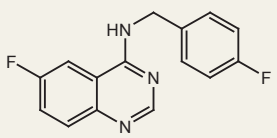
During mitosis, a small number of kinases coordinate a complex series of events. In particular, Aurora kinases, cdks and polo-like kinases (PLKs) work in concert to ensure chromosomes are segregated to daughter cells with high fidelity.

Figure 6 | Cell Cycle Progression and DNA Repair →
A) At specific points in the cell cycle, DNA damage is detected and repaired. The process is initiated by the DNA damage sensors, ATM and ATR kinase. Checkpoint kinases Chk1 and Chk2 initiate signaling cascades that activate DNA damage checkpoints in G_1 and G_2. The spindle assembly checkpoint (SAC) delays anaphase of mitosis until all chromosomes are properly aligned on the spindle, preventing aneuploidy. Kinases including aurora kinase B (Aur B), PLK1 and Mps1 are implicated at various control points in the cell cycle.
B) Enhancing replicative stress by targeting critical DNA replication checkpoints and replication machinery, as well as depleting nucleotides, encourages fork stalling and fork collapse, which leads to mitotic catastrophe and cell death.

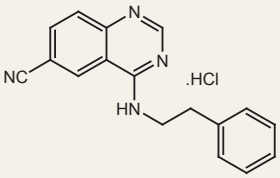

A: Cell cycle progression and DNA repair
Spindle assembly checkpoint (SAC)
DNA damage checkpoint
SSB = single strand break
DSB = double strand break
Cyclin D
NFκB
IκB
IκB
Proteasome
DNA damage
Cyclin D
Cdk4
p21
p53
mdm2
DSBs
Cdc25A
Wee1
ChK2
ATM
ChK1
ATR
SSBs
Cyclin A
Cyclin E
Cdk4,6
Cdk2
Rb
E2F
pRb
E2F
Mitotic exit
Cytokinesis
Quiescence
G0
Cell division
Early
G1
Mitotic progression
Cyclin B
Cdk1
MPS1
Aur B
M
Spindle assembly
Cyclin D + Cdk4,6
Cyclin B + Cdk1
Cell cycle
Cyclin E + Cdk2
G2/M checkpoint
ATR
ChK1
Cdc25C
ATM
ChK2
p53
p21
G2
Late
Cyclin A + Cdk1,2
Chromosome condensation
Cdk1
PLK1
S
G1/S checkpoint
Centrosome duplication
DNA replication
B: Enhancing replicative stress to cause mitotic catastrophe and cell death
Nucleoside analogue
Platinum compounds
Topoisomerase inhibitors (TI)
Replication
ChK1
ATR
ChK1 inhibitor
ATR inhibitor
Nucleotide shortage
TI
Fork stalling
DNA repair
PARP
PARP inhibitor
Repair
ChK1 inhibitor
ATR inhibitor
Fork collapse
ChK1
ATR
Premature mitosis
Inhibitors
Bcl-2, IKKs and Akt
Cdks
WEE1
WEE1 inhibitor
Mitotic catastrophe
DNA Polymerase
DNA repair complex
Replication Protein A
Topoisomerase
Cell death

Box 6: Cell Cycle and DNA Damage Repair Products

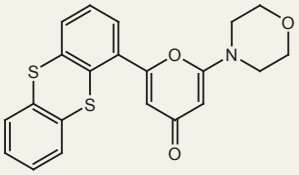
A full list of targets and related products is available on pages 33-60



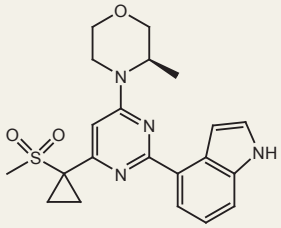
Spautin 1 (5197)
USP10 and USP13 inhibitor; inhibits autophagy



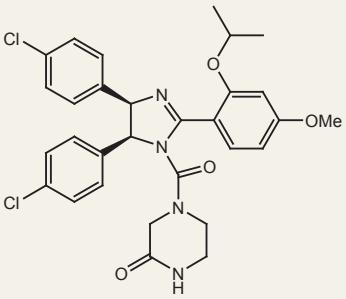
Senexin A (4875)
Cyclin-dependent kinase 8 (cdk8) inhibitor



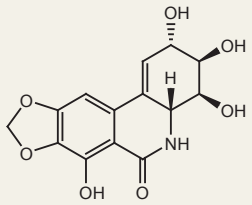
KU 55933 (3544)
Potent and selective ATM kinase inhibitor



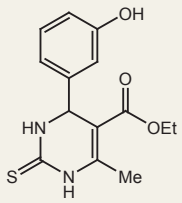
AZ 20 (5198)
Potent and selective ATR kinase inhibitor; antitumor



Nutlin-3 (3984)
MDM2 antagonist; inhibits MDM2-p53 interaction



Narciclasine (3715)
Antiproliferative agent; slows cell cycle progression



Monastrol (1305)
Selective inhibitor of mitotic kinesin Eg5

Improper chromosome segregation has significant effects on cellular function. It can contribute not only to decreased viability, but also to malignant transformation through the generation of genomic instability and aberrant cell division. A process known as mitotic catastrophe – a form of cell death which is initiated by disturbances in mitotic machinery – helps limit the risk of malignancy by eliminating potentially tumorigenic cells. Due to their role in chromosome segregation, Aurora kinases and PLKs are closely linked to mitotic progression. PLK1 promotes mitotic entry by inducing degradation of Wee1 and activation of cyclin B/cdk1, and has additional roles in chromosome segregation and cytokinesis. PLK2 and PLK3 are involved in checkpoint-mediated cell cycle arrest and help ensure genetic stability. Aurora A has been linked to centrosome maturation and spindle assembly, and is overexpressed in many human cancers. Aurora B is involved in the spindle assembly checkpoint and cytokinesis, amongst other mitotic processes. Inhibitors of these enzymes therefore inhibit critical mitotic processes, halting cell division. Key compounds for modulating mitosis includes the Aurora B kinase inhibitor **hesperadin** (Cat. No. 3988), which overrides the spindle assembly checkpoint and induces mitotic exit in **monastrol**- and **taxol**-treated cancer cells; **GW 843682X** (Cat. No. 2977), a selective inhibitor of PLK1 and PLK3 that inhibits proliferation of many tumor cell types *in vitro*; and **TAK 960** (Cat. No. 5403) a potent PLK1 inhibitor, which inhibits proliferation of a range of cancer cell lines *in vitro* and suppresses tumor growth of multiple human cancer cell xenografts *in vivo*.

Other mitotic spindle associated proteins being studied as potential therapeutic targets are the mitotic kinesin Eg5 and monopolar spindle 1 (Mps1). Eg5 is a motor protein essential for bipolar spindle formation, with inhibition of Eg5 by compounds such as **monastrol** (Cat. No. 1305) and **BRD 9876** (Cat. No. 5454) resulting in mitotic arrest. Mps1 is a mitotic checkpoint kinase involved in the spindle assembly checkpoint, where it ensures correct chromosome segregation. The selective Mps1 kinase inhibitor **Mps1-IN-1** (Cat. No. 5142), increases the frequency of multipolar mitosis and decreases cell viability in bone cancer cells *in vitro*.

DNA Damage and p53

DNA damage is a common occurrence in all cells, and must be repaired in order for proliferation to occur successfully and accurately. Several cellular DNA repair mechanisms exist to fix DNA damage and prevent its transmission to daughter cells. Genomic instability is a key characteristic of cancer cells, which results from DNA damage, inefficient DNA repair, and failure to stop the cell cycle, often through aberrant activity or expression of key checkpoint enzymes and proteins, such as cell cycle checkpoint kinases (Chks), Ataxia telangiectasia mutated (ATM) and Ataxia telangiectasia and Rad3 related (ATR) and p53.

If DNA damage is severe enough, apoptosis is induced in order to eliminate the cell and its tumorigenic potential. In cancer, the ability to evade apoptosis helps to promote the survival of malignant cells. Pro- and antiapoptotic proteins are involved

Cell Cycle and DNA Damage Repair – continued

in the complex network governing cell death. Mutations that activate prosurvival genes and/or disable proapoptotic genes are evident in many human cancers, providing evidence for the link between defective apoptosis and cancer development. There are many types of compounds that can induce apoptosis, such as **NQDI 1** (Cat. No. 4429), a selective inhibitor of apoptosis signal-regulating kinase 1 (ASK1); the Mcl-1 inhibitor **maritoclax** (Cat. No. 5368), which selectively induces apoptosis in a Mcl-1-dependent leukemia cell line; and **AEG 40730** (Cat. No. 5330), the potent inhibitor of apoptosis (IAP) antagonist, which has been shown to induce apoptosis in combination with TNF, and potentiate TRAIL-mediated apoptosis in a human colorectal carcinoma cell line. See page 52 for a full list of apoptosis inducers and apoptosis related compounds.

ATM and ATR kinases are DNA damage sensor proteins that are activated in response to DNA damage and induce cell cycle arrest by coordinating the initiation, amplification and activation of the DNA damage checkpoint. In cancer cells with DNA damage, inhibiting these enzymes could be therapeutically beneficial, because if the cell cycle continues in spite of significantly toxic DNA lesions, it will result in the death of the cell. **KU 55933** (Cat. No. 3544) is a potent and selective ATM kinase inhibitor, which decreases the viability of breast, lung and colon cancer cells, as well as decreasing p21 levels in vitro. **KU 55933** has also been shown to act as a radio- and chemotherapy-sensitizer. Furthermore, the potent ATM kinase inhibitor **KU 60019** (Cat. No. 4176) inhibits the migration and invasion of human glioma cells *in vitro*. The ATR-Chk1 kinase pathway plays a major cytoprotective role by reducing replicative stress. ATR phosphorylates Chk1 which upregulates its activity and thus is a viable target for modulating replicative stress. Inhibition of Chk1 and ATR have shown some promising preclinical results, especially in p53 mutant breast cancer. ATR inhibition also limits fork regression and suppresses replication fork collapse. The potent and selective ATR kinase inhibitor **AZ 20** (Cat. No. 5198) inhibits growth in cell lines with high baseline levels of replication stress and displays antitumor effects *in vivo*.

Chks are essential components in regulating cell cycle progression in normal and damaged cells, acting at all three cell cycle checkpoints. Chks and cdks act as control switches at various transition points in the cycle, ensuring that damaged DNA is not replicated. ATR kinase phosphorylates Chk1 in response to single strand DNA breaks, while ATM kinase phosphorylates Chk2 in response to double strand breaks. Chks phosphorylate Cdc25 phosphatase, which leads to Cdc25 sequestration in the cytoplasm, as well as phosphorylating p53 and Wee1, which in turn leads to the phosphorylation of cdk1 and progression of the cell cycle. Inhibition of Chk1 can be carried out through direct inhibition using selective Chk1 inhibitors or by inhibiting the kinase Wee1. If cdk activity is increased before the correct time, DNA can undergo inappropriate replication leading to fork stalling or collapse, meaning cells can enter mitosis prematurely. In addition, bursts of cdk activity promote increased rates of replication which can lead to nucleotide shortages (Figure 6). Several small molecule Chk1 inhibitors have shown promising results and some are currently in clinical trials. Useful research tools for studying Chks include **PF 477736** (Cat. No. 4277), a Chk1 inhibitor, which abrogates cell cycle arrest at S and G_2/M checkpoints, and sensitizes cells to DNA damage; as well as enhancing **docetaxel** (Cat. No. 4056) efficacy in tumor cells and xenografts. Another useful compound is **PD 407824** (Cat. No. 2694), a selective inhibitor of Chk1 and Wee1, which may also benefit from being used in combination with Hsp90 inhibitors such as **17-AAG** (Cat. No. 1515), because inhibition of Hsp90 has been shown to destabilize Wee1.

In response to DNA damage, tumor suppressor proteins such as retinoblastoma-associated protein (Rb) and p53, prevent cell cycle progression. p53 has been a thoroughly studied cancer target since its discovery over 30 years ago. It regulates a large number of genes involved in tumor suppression, including those with roles in cell cycle arrest, DNA repair and apoptosis. p53 is activated by several mechanisms, including phosphorylation by Chk1, and Chk2. These modifications inhibit its association with MDM2, an E3 ubiquitin ligase that targets p53 for degradation by the ubiquitin proteasome pathway (UPP). Phosphorylation prevents the turnover of p53, not only increasing its levels within the cell, but also increasing its affinity for the p53 DNA binding site. Inactivating mutations of p53 occur in a significant number of human cancers, making it a key target for gene and drug therapies. **Nutlin-3** (Cat. No. 3984) is an MDM2 antagonist sold by Tocris under license. It potently inhibits the interaction between MDM2 and p53, therefore inducing apoptosis in cancer cells. Other compounds, such as **PRIMA-1^{MET}** (Cat. No. 3710) and **SCH 529074** (Cat. No. 4240) bind p53 directly to reactivate its wild-type functions and suppress tumor growth.

Poly(ADP-ribose) polymerases (PARPs), are linked to base-excision repair (BER), and are investigated for their anticancer potential because they are involved in mediating the DNA damage response, as are tankyrases which also display PARP activity. Some PARP inhibitors have already been approved for the treatment of ovarian cancer. PARP has been shown to enhance the activation of Chk1 and it is hypothesized that the inhibition of PARP may increase replicative stress and induce apoptosis. PARP inhibitors also enhance the efficacy of radiation therapy and chemotherapy by preventing the repair of toxic DNA lesions. A valuable compound for probing the role of PARP in cancer cells is **PJ 34** (Cat. No. 3255), a potent inhibitor of PARP, which has been shown to potentiate the cytotoxic effects of the proapoptotic agent **cisplatin** (Cat. No. 2251).

Tumor cells can replicate in spite of incomplete DNA repair, in addition, most types of tumor cells seem to acquire the ability to proliferate endlessly, negating a barrier that normally limits

the number of times a cell can divide. This replicative potential is linked to the loss of protective nucleotide sequences at the ends of chromosomes, known as telomeres. Telomeres are progressively shortened during each round of cell division, to the point where they lose their ability to protect the ends of DNA – this gradual reduction in length is known as 'telomere attrition.' Consequently, the chromosome ends fuse and cell death occurs. The inhibition of telomerase, which adds telomeres, could therefore provide a mechanism through which unlimited cell proliferation is curbed. **BIBR 1532** (Cat. No. 2981) is one such telomerase inhibitor; it causes telomere shortening in rapidly proliferating cancer cells and induces growth arrest.

Ubiquitin Proteasome Pathway (UPP)

The UPP is essential for normal cell division and plays a critical role in cancer progression. The upregulation of cyclins necessary for the progression of the cell cycle is mirrored by the downregulation of cyclin dependent kinase inhibitors (CDKIs), which are responsible for the degradation of the cyclin/cdk complex. CDKIs are rapidly degraded by the proteasome contributing to the uncontrolled growth of cancer cells. Proteasomes are also involved in the degradation of tumor suppressor proteins such as p53, p27 and p21. Inhibition of the proteasome attenuates this degradation, which causes an accumulation of proteins in the cell. This induces the unfolded protein response (UPR), causing cell cycle arrest and if protein levels reach a cytotoxic level, apoptosis.

Compounds for studying the UPR or related integrated stress response (ISR) include **GSK 2606414** (Cat. No. 5107), **eeyarestatin I** (Cat. No. 3922) and **APY 29** (Cat. No. 4865). The UPR and ISR are initiated by ER stress, hypoxia and aberrant protein synthesis, which are all important factors in cancer. **GSK 2606414** has been shown to inhibit thapsigargin-induced PERK phosphorylation in a lung carcinoma cell line and attenuate pancreatic human tumor xenograft growth in mice. The potent inhibitor of endoplasmic reticulum associated protein degradation (ERAD) **eeyarestatin I**, selectively targets the p97-associated deubiquinating process (PAD) and inhibits ataxin-3 (atx3)-dependent deubiquitination. **Eeyarestatin I** has been shown to exhibit cytotoxic activity preferentially against cancer cells and induces cell death via the proapoptotic protein NOXA. **APY 29** is an allosteric modulator of IRE1α, which activates IRE1α ribonuclease activity, a key enzyme involved in monitoring the quality of synthesized proteins.

Another principal effect of proteasome inhibitors such as **MG 132** (Cat. No. 1748), is the suppression of NFκB. NFκB activates cyclin D, which binds cdk 4/6 in the G_1/S transition phase. This results in the phosphorylation of Rb and prevents p21 and p27 from inhibiting cyclin E/Cdk2. A potent cdk4/6 inhibitor **PD 0332991** (Cat. No. 4786), may prove a useful tool for studying this pathway. It has been shown to induce G_1 cell cycle arrest and block growth of glioblastoma xenografts in mice. Other useful compounds for investigating proteasomes in cancer are **PSI** (Cat. No. 4045) and **lactacystin** (Cat. No. 2267), which are proteasome inhibitors that also prevent activation of NF-κB (Figure 6).

Chemotherapy

Many chemotherapy treatments damage DNA directly or use nucleotide analogs to disrupt replication leading to cell death. Another strategy is to increase cell replication and replicative stress to such a degree that the cell cannot endure. When DNA replication is carried out in such an uncontrolled manner, the normal process of error checking is not carried out and essential stages are missed, so DNA damage accumulates – leading to apoptosis and cell death. Thus, it may be therapeutically beneficial to promote tumor cell proliferation, forcing immature cells through cell cycle checkpoints causing premature termination of the replication fork and premature progression into mitosis promoting cell death.

Chemotherapeutic agents commonly used include alkylating agents and platinum compounds, which form DNA intrastrand and interstrand crosslinking, and topoisomerase inhibitors, which cause DNA strand breaks. Platinum compounds include **carboplatin** (Cat. No. 2626), **cisplatin** (Cat. No. 2251) and **oxaliplatin** (Cat. No. 2623). These antitumor agents form platinum-DNA adducts and enhance radiation-induced single-strand DNA breakage. Another commonly used chemotherapeutic compound is the alkylating and methylating agent **temozolomide** (Cat. No. 2706), which binds to DNA and modifies the O^6 of guanine residues, leading to DNA cross-linking. This alkylation is readily reversed by the activity of O^6-methylguanine-DNA methyltransferase (MGMT). Inhibition of MGMT by compounds such as **lomeguatrib** (Cat. No. 4359) can therefore enhance the antitumor activity of these alkylating agents. Topoisomerase inhibitors, such as **etoposide** (Cat. No. 1226), **SN 38** (Cat. No. 2684) and **topotecan** (Cat. No. 4562), trap topoisomerases in complex with DNA, causing single and double strand breaks. Another DNA repair protein is DNA-dependent protein kinase (DNA-PK), which is involved in DNA double strand break (DSB) repair. Cells that exhibit defective DNA-PK activity are more sensitive to ionizing radiation (IR) than normal cells. **NU 7026** (Cat. No. 2828) is a DNA-PK inhibitor, which radiosensitizes both proliferating and quiescent fibroblast cells to IR and inhibits DSB repair.

Current therapeutic strategies rely on combinations of chemotherapy, but are going more towards targeted approaches which attack crucial points in replication pathways. By exploiting a cancer's phenotype and rapid cell proliferation, preclinical research shows therapeutic potential for multiple combinations of drugs that modulate cell cycle regulation and DNA damage, especially those involved in creating replicative stress.

Angiogenesis

Cancer Research Target	For Products See Page
Antiangiogenics	55
FGFR	38
Hedgehog Signaling	55
Hypoxia Inducible Factor 1 (HIF-1)	55
Matrix Metalloproteases	58
PDGFR	38
VEGFR	56
Wnt Signaling	46

Angiogenesis describes the generation of new blood vessels from pre-existing vasculature. This is a normal process in growth and development, being required for the formation of arteries, veins and capillaries. Proliferation of new blood vessels also has an essential role for the repair and regeneration of tissue during wound healing. Angiogenesis in normal tissues is a carefully regulated process, coordinated by pro- and anti-angiogenic factors such as VEGF and endostatin respectively, to produce well structured, uniform vasculature (Figure 7).

Angiogenesis is a hallmark of cancer and plays a key role in allowing tumor growth, progression and metastasis. As a consequence of their genetic instability, tumors are heterogeneous in nature. As such, tumor angiogenesis can differ significantly from physiological angiogenesis, producing poorly formed blood vessels with aberrant blood flow and differing permeability. In addition, factors such as a tumor's p53 status, can affect blood vessel formation because p53 regulates angiogenic cytokines.

A primary trigger for the growth of new blood vessels in a tumor is hypoxia. Hypoxia inducible factor 1 (HIF-1) is a heterodimer made up of the oxygen dependant α-subunit and the constitutively expressed β-subunit. In normoxic conditions HIF-1α undergoes prolyl hydroxylation, which facilitates ubiquitination and its destruction. In a hypoxic environment the expression of HIF-1 is stabilized; HIF-1α associates with HIF-1β, initiating transcription by binding to the response element of HIF-responsive genes, as well as binding the cofactors p300/CBP and pyruvate kinase isoform M2 (PKM2). This leads to the secretion of pro-angiogenic factors that encourage new vessel formation. As such, HIF-1 has been identified as a therapeutic target for the inhibition of angiogenesis. Small molecules that modulate HIF-1 expression include **KC7F2** (Cat. No. 4324), which down-regulates HIF-1α protein expression, as well as a prolyl 4-hydroxylase inhibitor, **DMOG** (Cat. No. 4408) and a thioredoxin-1 inhibitor, **PX 12** (Cat. No. 2954) both of which increase the expression of HIF-1α (Box 7).

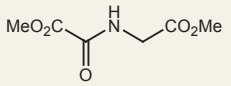
Tumors secrete several proangiogenic factors that induce endothelial cell proliferation and facilitate vessel patterning. Their receptors are very important in antiangiogenic research; key targets include vascular endothelial growth factor receptor 2 (VEGFR2), epidermal growth factor receptor (EGFR), fibroblast growth factor receptor (FGFR) and platelet-derived growth factor receptor (PDGFR). The most important and commonly secreted proangiogenic factor is VEGF, which binds VEGFR2 and neuropilin, increasing vasodilation and vascular permeability. Several notable broad spectrum receptor tyrosine kinase (RTK) inhibitors that have been well characterised over the years include **sunitinib** (Cat. No. 3768), **SU 5416** (Cat. No. 3037) and **XL 184** (Cat. No. 5422). All of these compounds have shown strong antiangiogenic activity *in vitro* and *in vivo* (as well as in the clinic). However, many cancers become resistant to the single agent RTK inhibitors, so there is a well defined need to broaden angiogenesis research to target several receptors and enzymes at once.

PDGFβR activation stimulates the attachment of pericytes along the new vessel branch forming cell-to-cell and gap junctions, followed by basement membrane formation. Pericyte attachment reduces endothelial cell proliferation and reduces their sensitivity to VEGF. The highly potent PDGFβR inhibitor **toceranib** (Cat. No. 3909) and selective PDGFβR inhibitor **SU 6668** (Cat. No. 3335) have been shown to induce apoptosis and antiangiogenic activity, respectively.

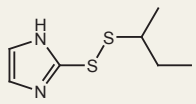
Other compounds used to study angiogenesis in cancer include broad spectrum matrix metalloprotease (MMP) inhibitors like

Box 7: Angiogenesis Products

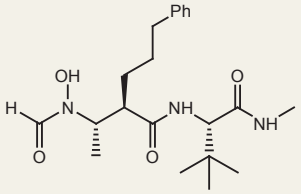
A full list of targets and related products is available on pages 33-60



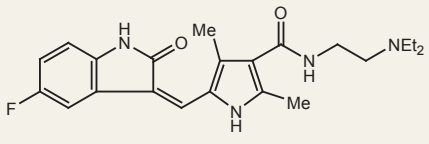
DMOG (4408)
Prolyl hydroxylase inhibitor



PX 12 (2954)
Thioredoxin-1 inhibitor

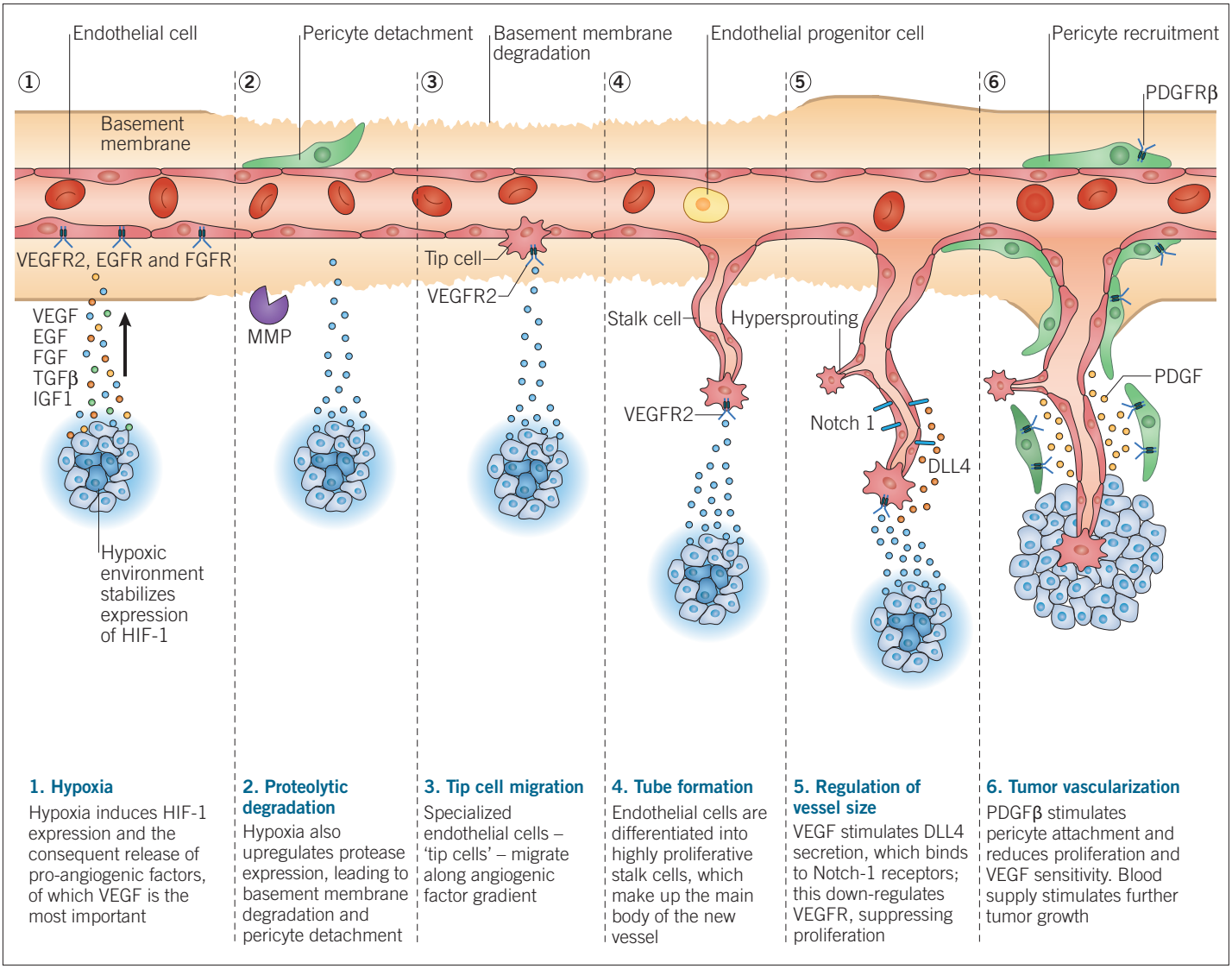


GI 254023X (3995)
Selective ADAM10 metalloprotease inhibitor



Sunitinib (3768)
Potent VEGFR, PDGFRβ and KIT inhibitor

Figure 7 | Tumor Vascularization



batimastat (Cat. No. 2961), **marimastat** (Cat. No. 2631) and **GM 6001** (Cat. No. 2983). MMPs are secreted from tumor cells and from VEGF-stimulated endothelial cells. They help break down the extracellular matrix (ECM) and mobilize proangiogenic proteins from the stroma.

In addition to broad spectrum MMP inhibition, selective MMP targets are the source of intense research. **WAY 170523** (Cat. No. 2633) is a potent and selective inhibitor of MMP-13, a collagenase, which is known to promote angiogenesis and is correlated with blood vessel density. MMP-13 inhibition forms a promising target in cancer due to its association with malignant cells, and its ability to promote the secretion of the pro-angiogenic factor VEGFA. Another promising therapeutic target is ADAM10, this MMP has been implicated in the pathology of angiogenesis, with increased expression linked to colon cancer. Furthermore ADAM10 cleaves several important angiogenic components including Notch collagen IV, VE-cadherin and c-Met. **GI 254023X** (Cat. No. 3995) is a selective ADAM10 inhibitor which could prove to be a valuable probe in elucidating the role of ADAM10 in angiogenesis.

Notch signaling plays a key role in differentiating and shaping the new vascular branch. VEGF stimulates the tip cell to secrete DLL4, which binds to Notch-1 receptors expressed on the stalk cells. This causes a down regulation of VEGFR which suppresses endothelial cell proliferation, regulating the size of the vessel. Inhibition of Notch signaling with the γ-secretase inhibitor **DAPT** (Cat. No. 2634), leads to increased tip cell formation and endothelial sprouting, which compromises the blood vessel patterns in model organisms such as the zebrafish.

It is hoped that by either inhibiting angiogenesis or by compromising blood vessel integrity, new treatments to prevent cancer progression may be found.

Invasion and Metastasis

Cancer Research Target	For Products See Page
Autotaxin	56
Chemokine Receptors	56
Dynamin	57
Focal Adhesion Kinase	57
G-protein Signaling	40
IκB Kinase	57
Integrin Receptors	57
JAK Kinase	58
Liver Receptor Homolog 1 (LRH-1)	58
Matrix Metalloproteases	58
MET Receptors	58
Microtubules	58
Other Kinases	43
Pim Kinase	54
Rho-kinase (Rock)	44
Urokinase	59
Wnt Signaling	46

Tumor metastasis is a multistep process involving the dissemination of tumor cells from the primary tumor to a distant organ or tissue. For metastasis to occur, the tumor has to invade the extracellular matrix (ECM) and surrounding stroma, and undergo a process known as epithelial-mesenchymal transition (EMT). EMT enables cell mobility and facilitates the migration of epithelial cells that have gained mesenchymal characteristics, notably the loss of adherins (specifically E-cadherins) and the loss of cell polarity. The cell then intravasates into blood or lymphatic vessels becoming a circulating tumor cell (CTC). The CTC eventually stops at a new site, for example in the liver or lung and undergoes mesenchymal-epithelial transition (MET), and adheres to the new tissue. Finally the tumor cell reinitiates proliferation, growing into a new tumor termed "metastatic colonization".

The degradation of the basement membrane, is carried out by matrix metalloproteases (MMPs), which are secreted by tumor cells themselves or by surrounding stromal cells stimulated by the nearby tumor. Numerous studies have linked altered MMP expression in different human cancers with poor disease prognosis. MMP-1, -2, -3, -7, -9, -13 and -14 all have elevated expression in primary tumors and/or metastases. Synthetic or natural inhibitors of MMPs result in inhibition of metastasis, while upregulation of MMPs leads to enhanced cancer cell invasion. Other proteases, such as urokinase (uPA), are also involved in ECM degradation (Figure 8). This breakdown in matrix integrity establishes a route for the tumor cells to enter the bloodstream or lymphatic system. See page 28 in the angiogenesis section for a full list of key MMP cancer research tools, including the broad spectrum MMP inhibitor **batimastat** (Cat. No. 2961) and selective MMP inhibitors such as the MMP-13 inhibitor **WAY 170523** (Cat. No. 2633).

Upregulation of certain receptor tyrosine kinase (RTK) signaling pathways, can promote invasion and metastasis. For example epidermal growth factor receptor (EGFR), transforming growth factor-β (TGF-β) receptor and the MET receptor, also known as hepatocyte growth factor receptor (HGFR), all mediate initiation signals that increase Snail transcription. Increased levels of the transcription factor Snail downregulate E-cadherin transcription, thus promoting EMT.

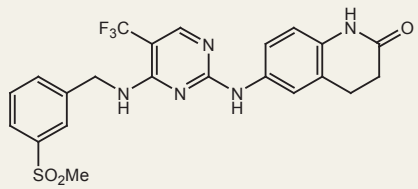
The endogenous ligand for c-MET is hepatocyte growth factor/scatter factor (HGF), a molecule produced predominantly by mesenchymal cells, hence MET receptor signaling is a key driver of invasive growth and EMT. Aberrant activation of the HGF/MET pathway leads to a variety of cancers and is associated with a poor prognosis as it can trigger tumor growth, angiogenesis and metastasis. Two key research tools for studying EMT include **crizotinib** (Cat. No. 4368) and **SU 11274** (Cat. No. 4101). **Crizotinib** is a potent inhibitor of c-MET (and ALK), which displays antitumor efficacy in multiple cancer models; selectively it inhibits c-MET-dependent proliferation, migration and invasion of human tumor cells *in vitro*. It may also be a useful *in vivo* tool as it is orally bioavailable. **SU 11274** is a selective inhibitor of MET tyrosine kinase activity, which reduces cell growth, and induces cell cycle arrest and apoptosis. Furthermore it abrogates cell motility and migration *in vitro* and tumor angiogenesis *in vivo*. See page 13 in the receptor signaling section for compounds targeting RTKs.

Disruption or loss of adhesive molecules such as cadherins, and integrins (which are integral in cell-cell adhesion and cell-ECM interactions, respectively) play a critical role in metastasis, as they allow tumor cells to begin metastatic colonies at a second site. Reduction in E-cadherin expression is a main driver of EMT and enhances the chances of metastatic cancer cell dissemination. Compounds such as **BMS 536924** (Cat. No. 4774), reverse EMT by inhibiting Snail-mediated downregulation of E-cadherin. Integrin receptors 'integrate' the extracellular environment with the cell interior by binding both the extracellular matrix (ECM) and the cytoskeleton. They are critical for cell attachment to the ECM, which is mediated through integrin-fibronectin, -vitronectin, -collagen and -laminin interactions. **BIO 1211** (Cat. No. 3910) and **BIO 5192** (Cat. No. 5051) are selective and potent $\alpha_4\beta_1$ integrin receptor inhibitors, which may be useful tools for studying the role of integrin receptors in metastasis (Box 8).

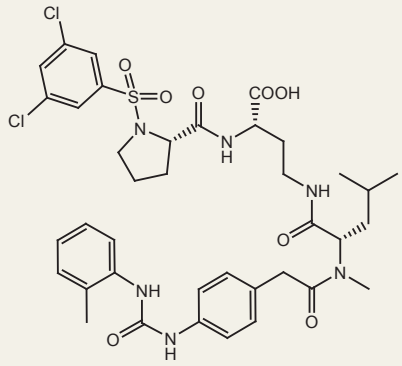
Focal adhesion kinase (FAK) also plays a part in cellular adhesion, it is activated in response to integrin-ECM interactions, becoming a critical focal point for numerous signaling components involved in cell growth and motility. There are several potent and selective FAK research compounds including **FAK Inhibitor 14** (Cat. No. 3414)**, PF 431396** (Cat. No. 4278) and

Box 8: Invasion and Metastasis Products

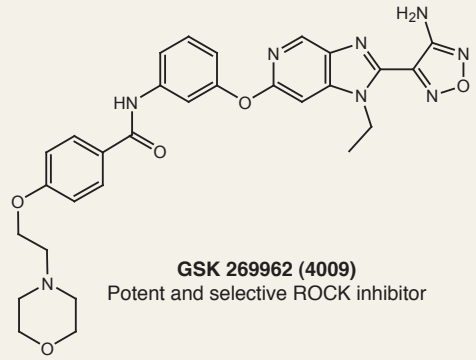
A full list of targets and related products is available on pages 33-60



PF 573228 (3239)
Potent and selective FAK inhibitor



BIO 5192 (5051)
Highly potent and selective inhibitor of integrin α4β1

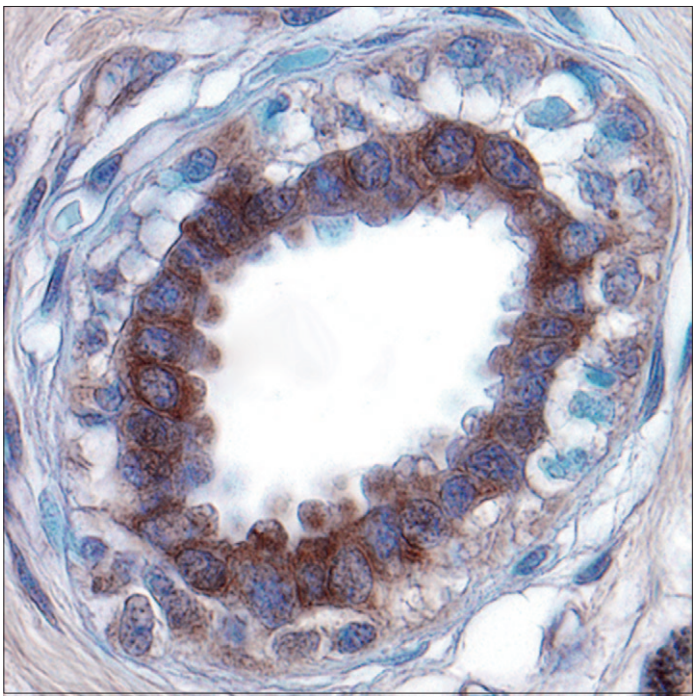


GSK 269962 (4009)
Potent and selective ROCK inhibitor

PF 573228 (Cat. No. 3239). **FAK Inhibitor 14** promotes cell detachment and inhibits cell adhesion *in vitro*, and exhibits antiproliferative activity in a variety of human tumor cell lines *in vitro* and in breast cancer cells *in vivo*. **PF 431396** is a dual (FAK) and proline-rich tyrosine kinase 2 (PYK2) inhibitor; it is a valuable probe for investigating cell migration because PYK2 is also an important mediator of cell migration and proliferation. **PF 573228** is a potent and selective inhibitor of FAK, which blocks serum and fibronectin-directed migration and decreases focal adhesion turnover *in vitro*.

FAK activates the Rho-family GTPases (Rac, RhoA and Cdc42), this family regulates actin assembly and the stability of microtubules involved in cell migration. There are many

Figure 8 | Extracellular matrix degradation



Urokinase-type Plasminogen Activator (uPA) expression detected in paraffin-embedded sections of human breast cancer tissue. uPA is a serine protease that is involved in ECM degradation, resulting in a loss of matrix integrity and a potential route through which tumor cells can to migrate to other tissues. Visualized here in brown using a Goat Anti-Human/Mouse uPA Affinity-purified Polyclonal Antibody (R&D Systems, Catalog #AF1310). Hematoxylin counterstain in blue.

direct inhibitors of the Rho-family GTPases including **EHT 1864** (Cat. No. 3872), while others such as **NSC 23766** (Cat. No. 2161), mediate their actions by interfering with Rac1 interactions. **NSC 23766** is a selective inhibitor of the Rac1-GEF (guanine nucleotide exchange factor) interaction; this compound prevents Rac1 activation by GEFs TrioN and Tiam1, without affecting Cdc42 or RhoA activation. Furthermore this compound has been shown to reverse tumor cell phenotyes in prostate cancer cells.

RhoA activates Rho-associated protein kinase (ROCK), which then regulates cell proliferation and mediates tumor cell migration by acting on the cytoskeleton. Preclinical studies have shown that combination treatment with RTK inhibitors can inhibit hematological malignancies, and early studies have demonstrated that classic ROCK inhibitors such as **Y-27632** (Cat. No. 1254) and **fasudil** (Cat. No. 0541) were able to inhibit metastasis in cancer models *in vivo*. **Fasudil** was also shown to suppress MMP-2 expression and induce apoptosis in glioblastoma cells *in vivo*. Other noteworthy ROCK inhibitors include the potent and selective ROCK inhibitors **GSK 269962** (Cat. No. 4009) and **GSK 429286** (Cat. No. 3726), which may prove to be valuable research tools for further probing the role of ROCK in cancer models.

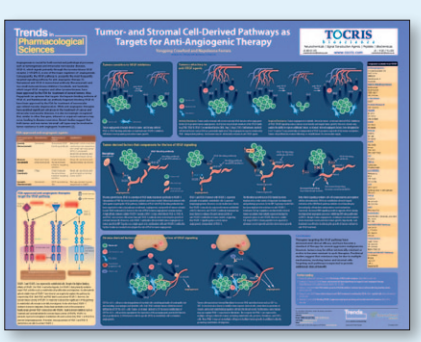
Invasion and Metastasis – continued

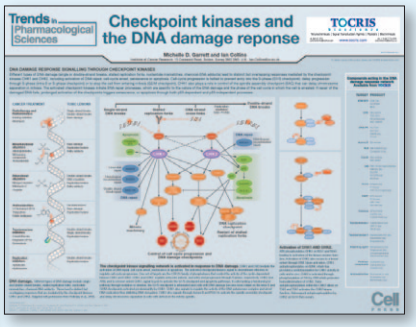
Downstream of Rac1 and Cdc42 lies group I p21-activated kinases (PAKs 1-4). These molecules link Rho GTPases with cytoskeletal remodeling and cell motility, and have recently been shown to promote cell proliferation and regulate apoptosis. Both overexpression and aberrant regulation of PAKs promote oncogenesis. **IPA 3** (Cat. No. 3622) promotes the inactive conformation of PAKs and inhibits PAK1-mediated signaling *in vivo*, exhibiting potential antitumor activity.

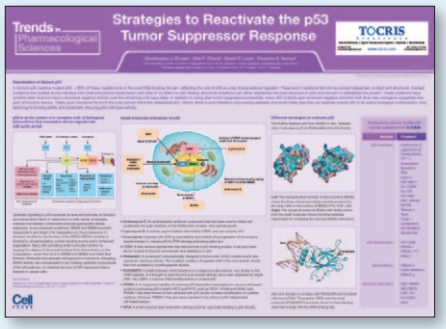
Overexpression of Liver receptor homolog-1 (LRH1) promotes motility and invasiveness in ER^+ and ER^- breast cancer cells by remodeling the cytoskeleton, and by facilitating post-translational modifications to E-cadherin, thus encouraging EMT. Overexpression of LRH1 has also been linked to a poor prognosis in liver, pancreatic and gastric cancer. Compounds such as the selective LRH1 inverse agonist **ML179** (Cat. No. 4957) and the selective agonist **DLPC** (Cat. No. 4378) may therefore prove useful investigational tools for studying tumor cell migration and invasion.

Metastasis is often closely linked to clinical prognosis. The mechanisms responsible for this process have consequently been of great interest in cancer research. In particular, the development of new pharmacological tools has helped elucidate the cellular changes and molecules involved in activating tumor cell invasion and metastasis. Future research may also take into consideration the roles of immune cells and tumor metabolism in the dynamics of metastasis.

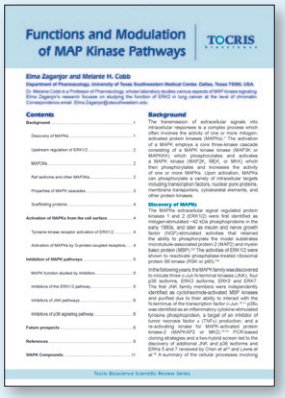
Related literature from Tocris







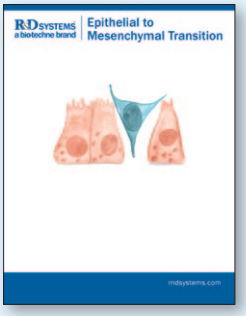
- Targets for Anti-Angiogenic Therapy
- Checkpoint Kinases and the DNA Damage Response
- Strategies to Reactivate the p53 Tumor Suppressor Response

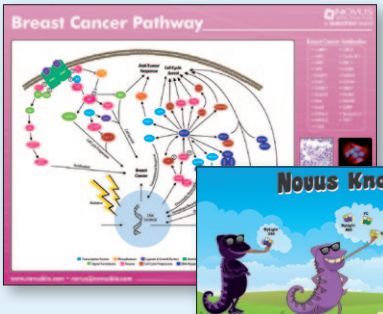


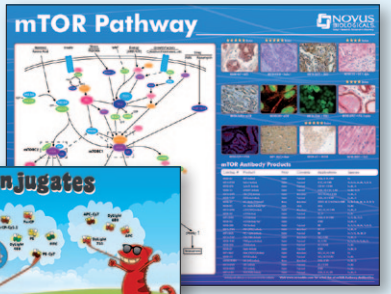
- MAPK Signaling Review
- Stem Cell Review
- Epigenetics Review

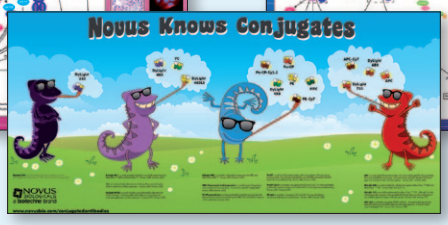
To download or request copies, please visit www.tocris.com/requestliterature

Related literature from other Bio-Techne brands









- Epithelial to Mesenchymal Transition Brochure (R&D Systems)
- Epithelial to Mesenchymal Transition Poster (R&D Systems)
- Breast Cancer Poster (Novus Biologicals)
- Novus Knows Conjugates Poster (Novus Biologicals)
- mTOR Pathway Poster (Novus Biologicals)

To download or request copies from:
- **R&D Systems; please visit www.rndsystems.com/literature-request**
- **Novus Biologicals; please visit www.novusbio.com/mailing-list**

Cancer Research Products from Tocris

Category	Cat. No.	Product Name	Description	Unit Size
Cancer Metabolism				
ATP-citrate Lyase (ACLY)				
Other	4962	SB 204990	ATP-citrate lyase inhibitor; inhibits fatty acid synthesis	10 mg 50 mg
Carbonic Anhydrases (CA)				
Inhibitors	3620	Topiramate	CA II and CA IV inhibitor; also GluR5 antagonist	10 mg 50 mg
	4540	U 104	Potent CA IX and CA XII inhibitor	10 mg 50 mg
Carnitine Palmitoyltransferase (CPT)				
Inhibitors	4539	(*R*)-(+)-Etomoxir	CPT1 inhibitor; inhibits cardiolipin biosynthesis	10 mg 50 mg
Dihydrofolate Reductase				
Inhibitors	2039	CI 898	Potent dihydrofolate reductase inhibitor	10 mg
	1230	Methotrexate	Dihydrofolate reductase inhibitor	100 mg
Fatty Acid Synthase (FASN)				
Inhibitors	2489	C 75	Potent fatty acid synthase inhibitor; proapoptotic	10 mg 50 mg
	3540	Orlistat	Fatty acid synthase inhibitor; also pancreatic, gastric and carboxylester lipase inhibitor	10 mg 50 mg
GAPDH				
Inhibitors	2966	CGP 3466B	GAPDH inhibitor	10 mg 50 mg
Glucose Transporters (GLUT)				
Inhibitors	4484	STF 31	GLUT1 inhibitor	10 mg 50 mg
Glutamate Dehydrogenase (GDH)				
Inhibitors	4524	EGCG	GDH inhibitor	50 mg
Glutaminase				
Inhibitors	5460	968	Allosteric inhibitor of glutaminase	10 mg 50 mg
Glutathione				
Other	5479	CRID3 sodium salt	Glutathione *S*-transferase omega 1 inhibitor.	10 mg 50 mg
Hexokinases				
Activators	5133	GKA 50	Glucokinase activator	10 mg
Inhibitors	1646	Lonidamine	Mitochondrial hexokinase inhibitor	10 mg 50 mg
HMG-CoA Reductase (HMG-CoA)				
Inhibitors	3776	Atorvastatin	Potent HMG-CoA reductase inhibitor; inhibits cholesterol synthesis	10 mg 50 mg
	4942	Pitavastatin calcium	High affinity HMG-CoA reductase inhibitor; lowers cholesterol levels	10 mg 50 mg
Hypoxia Inducible Factor 1 (HIF-1) – for compounds please see page 55				
Lactate Dehydrogenase A (LDHA)				
Inhibitors	5189	GSK 2837808A	Potent and selective LDHA inhibitor	10 mg
Monoacylglycerol Lipase (MAGL)				
Inhibitors	5206	JJKK 048	Potent and selective MAGL inhibitor	10 mg
	4906	JW 642	Potent and selective MAGL inhibitor	10 mg 50 mg
	3836	JZL 184	Potent and selective MAGL inhibitor	10 mg 50 mg

Category	Cat. No.	Product Name	Description	Unit Size
	4715	JZL 195	Potent dual FAAH and MAGL inhibitor	10 mg 50 mg
	4872	KML 29	Highly potent and selective MAGL inhibitor	10 mg 50 mg
Monocarboxylate Transporters (MCTs)				
Inhibitors	4960	AR-C155858	MCT1 and MCT2 inhibitor; inhibits glycolysis and glutathione synthesis	1 mg
	5029	CHC	MCT inhibitor; decreases glycolysis	50 mg
	4186	UK 5099	MCT inhibitor; also inhibits pyruvate transport	10 mg 50 mg
MutT homolog-1 (MTH1)				
Inhibitor	5280	SCH 51344	Potent MTH1 inhibitor	10 mg 50 mg
NAMPT				
Inhibitors	4808	FK 866	Non-competitive and potent NAMPT inhibitor; induces apoptosis and autophagy	10 mg 50 mg
	4835	GPP 78	NAMPT inhibitor; also induces autophagy	10 mg 50 mg
	5207	STF 118804	NAMPT inhibitor	10 mg 50 mg
Na^+/H^+ Exchanger (NHE)				
Inhibitors	5358	Cariporide	Selective NHE1 inhibitor; cardioprotective and antitumor	10 mg 50 mg
	3378	EIPA	NHE inhibitor; also inhibits TRPP3 channels	10 mg 50 mg
	2727	Zoniporide	Selective NHE1 inhibitor; antitumor	10 mg 50 mg
Oxidative Phosphorylation (OXPHOS)				
Inhibitors	3616	Rotenone	Inhibits complex I of the mitochondrial electron transport chain	50 mg
PFKFB3				
Inhibitors	5121	3PO	PFKFB3 inhibitor; antiangiogenic	10 mg 50 mg
	5339	PFK 15	Selective PFKFB3 inhibitor	10 mg 50 mg
	5048	YZ9	PFKFB3 inhibitor; inhibits cell growth	10 mg 50 mg
Pyruvate Dehydrogenase (PDH)				
Inhibitors	5348	CPI 613	PDH and KGDH inhibitor	10 mg 50 mg
Pyruvate Dehydrogenase Kinase (PDK)				
Inhibitors	2755	DCA	Mitochondrial PDK inhibitor	100 mg
Pyruvate Kinase M2 (PKM2)				
Activators	4859	ML 202	PKM2 activator	10 mg
Ribonucleotide Reductase				
Inhibitors	3259	Gemcitabine hydrochloride	Ribonucleotide reductase inhibitor; inhibits DNA synthesis	10 mg 50 mg
Thymidylate Synthetase				
Inhibitors	4659	Floxuridine	Inhibitor of thymidylate synthetase; anticancer agent	50 mg
	3257	5-Fluorouracil	Thymidylate synthetase inhibitor	50 mg
	4460	Trifluorothymidine	Thymidylate synthetase inhibitor; induces DNA fragmentation	50 mg

Cancer Research Products – continued

Category	Cat. No.	Product Name	Description	Unit Size
Epigenetics in Cancer				
14-3-3 Proteins				
Inhibitors	2145	Difopein	High affinity inhibitor of 14.3.3 proteins; induces apoptosis	100 µg
Aurora Kinases – for compounds please see page 48				
Bromodomains (BRDs)				
Inhibitors	5266	BAZ2-ICR	Selective BAZ2 inhibitor	10 mg 50 mg
	5331	CPI 203	BET BRD inhibitor; arrests cell cycle at G_1 phase	10 mg
	5385	GSK 5959	Potent and selective BRPF1 inhibitor	10 mg 50 mg
	4650	I-BET 151	BET BRD inhibitor	10 mg 50 mg
	5289	OF 1	Selective BRPF1B and BRPF2 inhibitor	10 mg 50 mg
	4499	(+)-JQ1	Potent, selective BET BRD inhibitor; cell permeable	10 mg
	5173	MS 436	Potent and selective BRD4(1) inhibitor	10 mg 50 mg
DNA Methyltransferases (DNMTs)				
Inhibitors	3842	5-Azacytidine	DNMT1 inhibitor	50 mg
	2624	Decitabine	DNMT inhibitor	10 mg 50 mg
	4524	EGCG	DNMT1 inhibitor	50 mg
	5016	Fisetin	DNMT1 inhibitor	50 mg
	4359	Lomeguatrib	MGMT inhibitor	10 mg 50 mg
	3295	RG 108	Non-nucleoside DNMT inhibitor	10 mg 50 mg
	5155	SGI 1027	DNMT inhibitor	10 mg 50 mg
	2293	Zebularine	DNMT and cytidine deaminase inhibitor	10 mg
Other	4061	6-Thioguanine	Disrupts cytosine methylation; anticancer and immunosuppressive agent	50 mg
Histone Acetyltransferases (HATs)				
Inhibitors	4200	C 646	Selective p300/CBP inhibitor	10 mg 50 mg
	4827	Garcinol	PCAF/p300 inhibitor; anticancer	10 mg
	5045	L002	p300 inhibitor	10 mg 50 mg
	4903	NU 9056	Inhibitor of KAT5 (Tip60)	10 mg
Histone Deacetylases (HDACs)				
Inhibitors	2952	CI 994	Class I HDAC inhibitor; orally active	10 mg 50 mg
	3515	FK 228	Potent and selective class I HDAC inhibitor; antitumor	1 mg
	4077	MC 1568	Selective HDAC class II (IIa) inhibitor	10 mg 50 mg
	3747	NCH 51	HDAC inhibitor	10 mg 50 mg
	4643	PCI 34051	Potent and selective HDAC8 inhibitor	10 mg 50 mg
	4403	Pyroxamide	HDAC inhibitor	10 mg 50 mg

Category	Cat. No.	Product Name	Description	Unit Size
	4652	SAHA	Class I and II HDAC inhibitor	10 mg 50 mg
	2421	Scriptaid	HDAC inhibitor	10 mg 50 mg
	2682	Sodium 4-Phenylbutyrate	HDAC inhibitor	100 mg
	3850	Sodium butyrate	HDAC inhibitor	50 mg
	4270	TC-H 106	Class I HDAC inhibitor	10 mg 50 mg
	1406	Trichostatin A	Potent HDAC inhibitor	1 mg
	3402	Tubacin	HDAC6 inhibitor; inhibits α-tubulin deacetylation	1 mg
	2815	Valproic acid, sodium salt	HDAC inhibitor	100 mg
Histone Demethylases (KDMs)				
Inhibitors	4684	Daminozide	Selective KDM2/7 inhibitor	50 mg
	4593	GSK J1	Potent JMJD3/UTX inhibitor	10 mg 50 mg
	4688	GSK J2	Inactive isomer of GSK J1 (Cat. No. 4593)	10 mg 50 mg
	4594	GSK J4	Histone lysine demethylase inhibitor; cell permeable	10 mg 50 mg
	4689	GSK J5	Inactive isomer of GSK J4 (Cat. No. 4594); cell permeable	10 mg 50 mg
	4464	IOX 1	Histone demethylase inhibitor; cell permeable	10 mg 50 mg
	4972	JIB 04	Pan Jumonji histone demethylase inhibitor; active *in vivo*	10 mg 50 mg
	4977	RN 1	LSD1 inhibitor	10 mg 50 mg
	5089	TC-E 5002	Selective KDM2/7 inhibitor	10 mg 50 mg
Lysine Methyltransferases (KMTs)				
Inhibitors	5163	A 366	Potent and selective G9a/GLP inhibitor	10 mg 50 mg
	4504	Chaetocin	SUV39H1 inhibitor	1 mg
	4703	3-Deazaneplanocin A	Histone methyltransferase inhibitor	1 mg
	5567	EPZ 004777	Highly potent DOT1L inhibitor	10 mg
	4892	(*R*)-PFI 2	Potent and selective SETD7 inhibitor	10 mg
	5400	(*S*)-PFI 2	Negative control of (*R*)-PFI 2 (Cat. No. 4892)	10 mg
	4541	SGC 0946	Highly potent and selective DOT1L inhibitor; cell permeable	10 mg 50 mg
	3861	UNC 0224	Potent G9a inhibitor	10 mg 50 mg
	4343	UNC 0638	Selective G9a and GLP inhibitor	10 mg 50 mg
	5132	UNC 0642	Potent and selective G9a and GLP inhibitor	10 mg 50 mg
	4904	UNC 1999	Potent and selective EZH2/EZH1 inhibitor	10 mg 50 mg
	4905	UNC 2400	Negative control of UNC 1999 (Cat. No. 4904)	10 mg
Other	5307	MM 102	WDR5/MLL interaction inhibitor	10 mg
	5267	OICR 9429	High affinity and selective WDR5 antagonist	10 mg 50 mg
	5323	WDR5 0103	WDR5 antagonist	10 mg 50 mg

Cancer Research Products – continued

Category	Cat. No.	Product Name	Description	Unit Size
MBT Domains				
Inhibitors	4666	UNC 1215	Potent inhibitor of L3MBTL3 Kme reader domain; cell permeable	10 mg 50 mg
	4516	UNC 926	L3MBTL1 domain inhibitor	10 mg 50 mg
Poly (ADP-ribose) polymerase (PARP) – for compounds please see page 52				
Protein Arginine Methyltransferases (PRMTs)				
	5128	C 21	Selective PRMT1 arginine methyltransferase inhibitor	1 mg
	5099	TC-E 5003	Selective PRMT1 inhibitor	50 mg
Protein Ser/Thr Phosphatases – for compounds please see page 44				
Protein Tyrosine Phosphatases – for compounds please see page 44				
RNA/DNA Polymerase				
Inhibitors	1489	Mithramycin A	Inhibitor of DNA and RNA polymerase	1 mg
	1567	Thiolutin	Bacterial RNA polymerase inhibitor	1 mg
Other	3253	Triptolide	Inhibits RNAPII-mediated transcription; antitumor, anti-inflammatory and immunosuppressive	1 mg 10 mg

Receptor Signaling: Growth Factor Receptors

Anaplastic Lymphoma Kinase (ALK)				
Inhibitors	5310	ASP 3026	Potent ALK inhibitor	10 mg 50 mg
	4368	Crizotinib	Potent c-MET/ALK inhibitor	10 mg 50 mg
	5098	KRCA 0008	Potent Ack1 and ALK dual inhibitor; orally bioavailable	10 mg 50 mg
	5640	PF 06463922	High affinity and selective ALK and ROS1 inhibitor	10 mg 50 mg
EGFR				
Inhibitors	1276	AG 1478	Highly potent EGFR-kinase inhibitor	10 mg 50 mg
	0414	AG 490	EGFR-kinase inhibitor; also JAK2, JAK3 inhibitor	10 mg 50 mg
	1555	AG 825	Selective ErbB2 inhibitor	10 mg 50 mg
	2417	BIBU 1361	Selective inhibitor of EGFR-kinase	1 mg 10 mg
	2416	BIBX 1382	Highly selective EGFR-kinase inhibitor	1 mg 10 mg
	5022	BMS 599626	Potent, selective EGFR and ErbB2 inhibitor	10 mg
	3360	CGP 52411	EGFR inhibitor	10 mg 50 mg
	1110	Genistein	EGFR-kinase inhibitor; also estrogen and PPARγ ligand	10 mg 50 mg
	2239	GW 583340	Potent dual EGFR/ErbB2 inhibitor; orally active	10 mg 50 mg
	2646	HDS 029	Potent inhibitor of the ErbB receptor family	1 mg 10 mg
	3580	HKI 357	Dual irreversible inhibitor of ErbB2 and EGFR	10 mg 50 mg
	3000	Iressa	Selective EGFR inhibitor; orally active	10 mg 50 mg
	3352	JNJ 28871063	Potent ErbB receptor family inhibitor	10 mg 50 mg

Category	Cat. No.	Product Name	Description	Unit Size
	1037	PD 153035	EGFR-kinase inhibitor	10 mg 50 mg
	2615	PD 158780	Potent ErbB receptor family inhibitor	10 mg 50 mg
	4941	PKI 166	Potent EGFR-kinase inhibitor	10 mg
	3599	TAK 165	Potent and selective ErbB2 inhibitor	10 mg 50 mg
FGFR				
	4002	FIIN 1	Potent, irreversible FGFR inhibitor	10 mg 50 mg
	3724	PD 161570	Selective FGFR inhibitor	10 mg 50 mg
	3044	PD 173074	FGFR1 and FGFR3 inhibitor	10 mg 50 mg
	3300	SU 5402	Potent FGFR and VEGFR inhibitor	1 mg
FLT3				
Inhibitors	4033	5'-Fluoroindirubinoxime	FLT3 inhibitor; displays antiproliferative activity	10 mg 50 mg
	2591	TCS 359	Potent FLT3 inhibitor	10 mg 50 mg
Insulin and Insulin-like Receptors				
Activators	1819	Demethylasterriquinone B1	Selective IR activator	5 mg
	3435	Insulin (human) recombinant	Endogenous peptide agonist	10 mg
Inhibitors	4774	BMS 536924	Dual IR/IGF1R inhibitor	10 mg 50 mg
	5111	GSK 1838705	Potent IR and IGF1R inhibitor; also inhibits anaplastic lymphoma kinase (ALK)	10 mg 50 mg
	2956	Picropodophyllotoxin	Selective IGF1R inhibitor	10 mg
	2768	PQ 401	IGF1R inhibitor	10 mg 50 mg
Other	5154	HNGF6A	Humanin analog; increases insulin sensitivity	1 mg
PDGFR				
Inhibitors	1222	DMPQ dihydrochloride	Potent, selective inhibitor of PDGFRβ	10 mg 50 mg
	3304	SU 16f	Potent and selective PDGFRβ inhibitor	10 mg 50 mg
	3335	SU 6668	PDGFR, VEGFR and FGFR inhibitor	10 mg 50 mg
Sphingosine-1-phosphate Receptors				
Agonists	4543	CS 2100	Selective $S1P_1$ agonist	10 mg 50 mg
	4677	CYM 50260	Potent and selective $S1P_4$ agonist	10 mg 50 mg
	4678	CYM 50308	Potent and selective $S1P_4$ agonist	10 mg 50 mg
	3601	CYM 5442	Selective $S1P_1$ agonist	10 mg 50 mg
	4897	CYM 5541	Selective $S1P_3$ allosteric agonist	10 mg 50 mg
	4289	RP 001	Potent $S1P_1$ agonist	10 mg 50 mg
	2284	SEW 2871	Cell-permeable, selective $S1P_1$ agonist	10 mg 50 mg
	1370	Sphingosine-1-phosphate	Endogenous agonist at $S1P_{1-5}$	1 mg

Cancer Research Products – continued

Category	Cat. No.	Product Name	Description	Unit Size
	4747	TC-G 1006	Potent and selective $S1P_1$ agonist	10 mg 50 mg
	4363	TC-SP 14	Potent $S1P_1$ receptor agonist	10 mg 50 mg
Antagonists	4679	CYM 50358	Potent and selective $S1P_4$ antagonist	10 mg 50 mg
	2392	JTE 013	$S1P_2$ antagonist	10 mg
	4195	VPC 23019	$S1P_1$ and $S1P_3$ antagonist	10 mg
	3602	W146	Potent and selective $S1P_1$ antagonist	1 mg
TGF-β Receptors				
Inhibitors	2939	A 83-01	Selective inhibitor of TGF-βRI, ALK4 and ALK7	10 mg 50 mg
	3264	GW 788388	Selective inhibitor of TGF-βRI	10 mg 50 mg
	2718	LY 364947	Selective inhibitor of TGF-βRI	1 mg 10 mg
	3742	RepSox	Potent and selective inhibitor of TGF-βRI	10 mg 50 mg
	1614	SB 431542	Potent and selective inhibitor of TGF-βRI, ALK4 and ALK7	1 mg 10 mg
	3263	SB 505124	Selective inhibitor of TGF-βRI, ALK4 and ALK7	10 mg 50 mg
	3211	SB 525334	Selective inhibitor of TGF-βRI	10 mg 50 mg
	3269	SD 208	Potent ATP-competitive TGF-βRI inhibitor	10 mg 50 mg
Other	5068	ITD 1	Selective inhibitor of TGF-β signaling	10 mg 50 mg
VEGFR – for compounds please see page 56				

Intracellular Signaling

Abl Kinase				
Inhibitors	4274	AP 24534	Potent multi-kinase and pan-Bcr-Abl inhibitor	10 mg 50 mg
	4399	GNF 2	Selective allosteric inhibitor of Bcr-Abl tyrosine kinase activity	10 mg 50 mg
	4908	GNF 5	Selective allosteric inhibitor of Bcr-Abl; analog of GNF 2 (Cat. No. 4399)	10 mg 50 mg
	4965	PD 180970	$p210^{Bcr/Abl}$ kinase inhibitor; also inhibits c-Src and KIT	10 mg
	4730	PPY A	Potent inhibitor of Abl T315I mutant and wild-type Abl kinases	10 mg 50 mg
Akt (Protein Kinase B)				
Activators	4635	SC 79	Akt activator	10 mg 50 mg
Inhibitors	3897	API-1	Selective Akt/PKB inhibitor	10 mg
	2151	API-2	Selective inhibitor of Akt/PKB signaling; antitumor and antiviral	10 mg
	2558	10-DEBC	Selective Akt/PKB inhibitor	10 mg 50 mg
	2926	FPA 124	Akt/PKB inhibitor	10 mg 50 mg
	4144	GSK 690693	Akt inhibitor; antitumor	10 mg 50 mg
	4598	PHT 427	Dual Akt and PDK1 inhibitor; antitumor	10 mg 50 mg

Category	Cat. No.	Product Name	Description	Unit Size
AMPK				
Activators	3336	A 769662	Potent AMPK activator	10 mg 50 mg
	2840	AICAR	AMPK activator	50 mg
	2864	Metformin	Activator of LKB1/AMPK	100 mg
	4039	PT 1	AMPK activator	10 mg 50 mg
	5138	RSVA 405	AMPK activator	10 mg 50 mg
	5285	ZLN 024	Allosteric AMPK activator	10 mg 50 mg
Inhibitors	3093	Dorsomorphin	Potent and selective AMPK inhibitor	10 mg 50 mg
Broad Spectrum Protein Kinase Inhibitors				
Inhibitors	0542	H-7	Protein kinase inhibitor	10 mg 50 mg
	1683	K 252a	Protein kinase inhibitor	200 µg
	2002	Ro 31-8220	Protein kinase inhibitor	10 mg
	1285	Staurosporine	Non-selective protein kinase inhibitor	100 µg
Glycogen Synthase Kinase 3				
Inhibitors	4083	3F8	Potent and selective GSK-3β inhibitor	10 mg 50 mg
	3966	AR-A 014418	Selective GSK-3 inhibitor	10 mg 50 mg
	3194	BIO	Potent, selective GSK-3 inhibitor	10 mg 50 mg
	3874	BIO-acetoxime	Selective GSK-3α/β inhibitor	1 mg 10 mg
	4423	CHIR 99021 hydrochloride	Highly selective GSK-3 inhibitor	10 mg 50 mg
	4953	CHIR 99021	Hydrochloride salt of CHIR 99021 (Cat. No. 4423); selective GSK-3 inhibitor	10 mg 50 mg
	1616	SB 216763	Potent, selective GSK-3 inhibitor	1 mg 10 mg 50 mg
	1617	SB 415286	Potent, selective GSK-3 inhibitor	10 mg 50 mg
	4353	TC-G 24	Potent and selective GSK-3β inhibitor	10 mg 50 mg
	3869	TCS 2002	Potent GSK-3β inhibitor	10 mg 50 mg
	3835	TWS 119	GSK-3β inhibitor	10 mg
G-protein Signaling				
Inhibitors	5050	CASIN	Cdc42 GTPase inhibitor	10 mg 50 mg
Other	5233	CCG 1423	Rho/SRF pathway inhibitor	10 mg 50 mg
	2974	CCG 2046	Inhibitor of regulator of G-protein signaling 4 (RGS4)	10 mg 50 mg
	4028	CCG 63802	Inhibitor of regulator of G-protein signaling 4 (RGS4)	10 mg 50 mg
	3872	EHT 1864	Potent inhibitor of Rac family GTPases	10 mg 50 mg
	4266	ML 141	Selective inhibitor of Cdc42 Rho family GTPase	10 mg 50 mg

Cancer Research Products – continued

Category	Cat. No.	Product Name	Description	Unit Size
	2161	NSC 23766	Selective inhibitor of Rac1-GEF interaction; antioncogenic	10 mg 50 mg
	3324	QS 11	ARFGAP1 inhibitor; modulates Wnt/β-catenin signaling	10 mg 50 mg
	2221	Rac1 Inhibitor W56	Selective inhibitor of Rac1-GEF interaction	1 mg
	2849	SecinH3	Sec7-specific GEF inhibitor (cytohesins)	10 mg 50 mg
Heat Shock Proteins				
Inhibitors	1515	17-AAG	Selective Hsp90 inhibitor	1 mg
	2435	CCT 018159	Hsp90 inhibitor	10 mg 50 mg
	2610	17-DMAG	Water-soluble Hsp90 inhibitor	1 mg
	4701	EC 144	High affinity, potent and selective Hsp90 inhibitor	10 mg
	3387	Gedunin	Hsp90 inhibitor; exhibits anticancer and antimalarial activity	10 mg
	1368	Geldanamycin	Selective Hsp90 inhibitor	1 mg
	1589	Radicicol	Hsp90 inhibitor; antifungal antibiotic	1 mg
	3803	VER 155008	Hsp70 inhibitor	10 mg 50 mg
Other	4734	TRC 051384	Inducer of heat shock protein Hsp70	10 mg
Histone Deacetylases – for compounds please see page 35				
LIM kinases (LIMKs)				
	4745	LIMKi 3	Potent LIM kinase inhibitor; antitumor	10 mg
MAPK				
Activators	4753	AL 8697	Potent and selective p38α inhibitor	10 mg 50 mg
	1290	Anisomycin	JNK, SAPK and p38 activator	10 mg 50 mg
	3314	BI 78D3	Selective, competitive JNK inhibitor	10 mg 50 mg
	4924	CEP 1347	Inhibitor of JNK signaling	1 mg
	5095	DBM 1285	p38 inhibitor; anti-inflammatory	10 mg 50 mg
	3706	FR 180204	Selective ERK inhibitor	10 mg 50 mg
	4550	IQ 3	Selective JNK3 inhibitor	10 mg 50 mg
	1264	SB 202190	Potent, selective inhibitor of p38	10 mg 50 mg
	1202	SB 203580	Selective inhibitor of p38	1 mg 10 mg 50 mg
	1402	SB 203580 hydrochloride	Selective inhibitor of p38; water-soluble	10 mg
	1962	SB 239063	Potent, selective p38 inhibitor; orally active	10 mg
	5040	SB 706504	p38 inhibitor	10 mg 50 mg
	3528	SCIO 469	Selective p38 inhibitor	10 mg 50 mg
	1496	SP 600125	Selective JNK inhibitor	10 mg 50 mg
	5044	SR 3576	Highly potent and selective JNK3 inhibitor	10 mg 50 mg
	3607	SU 3327	Selective JNK inhibitor	10 mg 50 mg

Category	Cat. No.	Product Name	Description	Unit Size
	3222	TCS JNK 6o	Selective JNK inhibitor	10 mg 50 mg
	3916	VX 702	Orally active p38α and p38β inhibitor	10 mg
	3915	VX 745	Potent and selective p38α inhibitor	10 mg 50 mg
	4132	XMD 8-92	Selective ERK5/BMK1 inhibitor	10 mg 50 mg
MEK				
Inhibitors	1777	Arctigenin	Potent MEK1 inhibitor; also inhibits IκBα phosphorylation	10 mg 50 mg
	4842	BIX 02189	Selective MEK5 and ERK5 inhibitor	10 mg 50 mg
	4192	PD 0325901	Potent inhibitor of MEK1/2	10 mg 50 mg
	4237	PD 184352	Selective MEK inhibitor	10 mg 50 mg
	2605	PD 198306	Selective inhibitor of MEK1/2	10 mg
	1213	PD 98059	MEK inhibitor	1 mg 10 mg 50 mg
	1969	SL 327	Selective inhibitor of MEK1 and MEK2; brain penetrant	1 mg 10 mg 50 mg
	1868	U0124	Inactive analog of U0126 (Cat. No. 1144)	10 mg
	1144	U0126	Potent, selective inhibitor of MEK1 and MEK2	5 mg 25 mg
Mnk				
	2731	CGP 57380	Selective inhibitor of Mnk1	1 mg 10 mg 50 mg
	5183	ETP 45835	Mnk1 and Mnk2 inhibitor	10 mg 50 mg
Monopolar Spindle 1 Kinase				
Inhibitors	3994	AZ 3146	Potent and selective monopolar spindle 1 (Mps1) kinase inhibitor	10 mg 50 mg
	5142	Mps1-IN-1	Selective monopolar spindle 1 (Mps1) kinase inhibitor	10 mg
	4750	TC Mps1 12	Potent and selective monopolar spindle 1 (Mps1) kinase inhibitor; orally active	10 mg 50 mg
mTOR				
Inhibitors	3725	KU 0063794	Selective mTOR inhibitor	10 mg
	4820	PF 04691502	Potent and selective dual PI 3-K/mTOR inhibitor	10 mg 50 mg
	4823	PF 05212384	Potent and selective dual PI 3-K/mTOR inhibitor	10 mg
	4257	PP 242	Dual mTORC1/mTORC2 inhibitor	10 mg 50 mg
	1292	Rapamycin	mTOR inhibitor; immunosuppressant	1 mg
	5264	Temsirolimus	mTOR inhibitor; antitumor	10 mg
	4247	Torin 1	Potent and selective mTOR inhibitor	10 mg 50 mg
	4248	Torin 2	Potent and selective mTOR inhibitor	10 mg 50 mg
	4282	WYE 687 dihydrochloride	Potent and selective mTOR inhibitor	10 mg 50 mg
	4893	XL 388	Potent and selective mTOR inhibitor; antitumor	10 mg 50 mg

Cancer Research Products – continued

Category	Cat. No.	Product Name	Description	Unit Size
Other Kinases				
	5326	CHR 6494	Potent and selective haspin kinase inhibitor	10 mg
	3622	IPA 3	Group I p21-activated kinase (PAK) inhibitor	10 mg 50 mg
	3604	(5*Z*)-7-Oxozeaenol	Potent and selective TAK1 MAPKKK inhibitor	1 mg
PERK				
	5107	GSK 2606414	Potent and selective PERK inhibitor; orally bioavailable	10 mg 50 mg
PI 3-kinase				
Activators	1983	740 Y-P	Cell-permeable PI 3-kinase activator	1 mg
Inhibitors	5595	A66	Potent and selective PI 3-kinase p110α inhibitor	10 mg 50 mg
	3671	AS 252424	Selective inhibitor of PI 3-kinase γ	10 mg
	3578	AS 605240	Potent and selective PI 3-kinase γ inhibitor	10 mg 50 mg
	4839	AZD 6482	Potent and selective PI 3-Kβ inhibitor	10 mg 50 mg
	3606	BAG 956	Dual PI 3-kinase and PDK1 inhibitor	10 mg 50 mg
	4674	CZC 24832	Selective inhibitor of PI 3-kinase γ	10 mg 50 mg
	4026	GSK 1059615	Potent PI 3-kinase inhibitor	10 mg 50 mg
	4840	KU 0060648	Dual PI 3-K and DNA-PK inhibitor	10 mg 50 mg
	1130	LY 294002	Prototypical PI 3-kinase inhibitor; also inhibits other kinases	5 mg 25 mg
	2418	LY 303511	Negative control of LY 294002 (Cat. No. 1130)	5 mg
	3977	3-Methyladenine	Class III PI 3-kinase inhibitor; also inhibits autophagy	50 mg
	4820	PF 04691502	Potent and selective dual PI 3-K/mTOR inhibitor	10 mg 50 mg
	4823	PF 05212384	Potent and selective dual PI 3-K/mTOR inhibitor	10 mg
	2930	PI 103	Inhibitor of PI 3-kinase, mTOR and DNA-PK	1 mg 10 mg 50 mg
	2814	PI 828	PI 3-kinase inhibitor, more potent than LY 294002 (Cat. No. 1130)	1 mg 10 mg 50 mg
	3894	PP 121	PI 3-K inhibitor; also inhibits RTKs	10 mg 50 mg
	4264	TG 100713	PI 3-kinase inhibitor	10 mg 50 mg
	1232	Wortmannin	Potent, irreversible inhibitor of PI 3-kinase; also inhibitor of PLK1	1 mg 5 mg
Protein Kinase D				
Activators	4087	PS 48	PDK1 activator	10 mg 50 mg
Inhibitors	4644	CID 2011756	Pan PKD inhibitor; cell permeable	10 mg 50 mg
	3327	CID 755673	Selective PKD inhibitor	10 mg
	4975	CRT 0066101	Potent PKD inhibitor	10 mg
	3962	kb NB 142-70	Selective PKD inhibitor; analog of CID 755673 (Cat. No. 3327)	10 mg 50 mg

Category	Cat. No.	Product Name	Description	Unit Size
Protein Ser/Thr Phosphatases				
Inhibitors	4210	Ascomycin	Calcineurin phosphatase inhibitor; analog of FK 506 (Cat. No. 3631)	1 mg
	5140	GSK 2830371	Potent and selective allosteric inhibitor of Wip1 phosphatase	10 mg 50 mg
	1136	Okadaic acid	Protein phosphatase 1 and 2A inhibitor	25 µg
	2302	Sanguinarine	Inhibitor of protein phosphatase 2C (PP2C)	10 mg 50 mg
	2305	Tautomycetin	Selective PP1 inhibitor	50 µg
Protein Tyrosine Phosphatases				
Inhibitors	3979	Alexidine	Selective inhibitor of PTPMT1	50 mg
	2821	Sodium orthovanadate	Protein tyrosine phosphatase inhibitor	100 mg
Raf Kinase				
Inhibitors	4836	AZ 628	Potent Raf kinase inhibitor	10 mg 50 mg
	4453	GDC 0879	Potent B-Raf inhibitor	10 mg 50 mg
	3185	L-779,450	Potent Raf kinase inhibitor	10 mg 50 mg
	5036	ML 786	Potent Raf kinase inhibitor; orally bioavailable	10 mg
	2650	SB 590885	Potent B-Raf inhibitor	10 mg 50 mg
	1321	ZM 336372	Potent, selective c-Raf inhibitor	10 mg 50 mg
Rho-kinase (ROCK)				
Inhibitors	4927	AS 1892802	Potent ROCK inhibitor; orally bioavailable	10 mg 50 mg
	0541	Fasudil	Inhibitor of ROCK and nucleotide dependent kinase	10 mg 50 mg
	2485	Glycyl-H 1152	Selective ROCK inhibitor, more selective analog of H 1152 dihydrochloride (Cat. No. 2414)	1 mg
	4009	GSK 269962	Potent and selective ROCK inhibitor	10 mg 50 mg
	3726	GSK 429286	Selective ROCK inhibitor	1 mg 10 mg 50 mg
	2414	H 1152	Selective ROCK inhibitor	1 mg
	2415	HA 1100	Cell-permeable, selective ROCK inhibitor	10 mg
	5061	RKI 1447	Potent and selective ROCK inhibitor; antitumor	10 mg 50 mg
	4118	SB 772077B	Potent ROCK inhibitor; vasodilator	10 mg 50 mg
	3667	SR 3677	Potent, selective ROCK inhibitor	10 mg 50 mg
	1254	Y-27632	Selective p160ROCK inhibitor	1 mg 10 mg 50 mg
Ribosomal S6 Protein Kinases (RSKs)				
Inhibitors	4037	BRD 7389	p90 ribosomal S6 kinase inhibitor	10 mg 50 mg
	4032	PF 4708671	S6K1 inhibitor	10 mg 50 mg
	2250	SL 0101-1	Selective p90 ribosomal S6 kinase (RSK) inhibitor	1 mg

Cancer Research Products – continued

Category	Cat. No.	Product Name	Description	Unit Size
Sir2-like Family Deacetylases				
Inhibitors	3233	AGK 2	Selective SIRT2 inhibitor	10 mg 50 mg
	4754	AK 7	Selective SIRT2 inhibitor; brain penetrant	10 mg 50 mg
	2780	EX 527	Selective SIRT1 inhibitor	1 mg 10 mg 50 mg
	4127	Salermide	SIRT1 and SIRT2 inhibitor	10 mg 50 mg
	3521	Sirtinol	Selective sirtuin family deacetylase inhibitor	10 mg 50 mg
	1542	Splitomicin	Sir2p inhibitor	10 mg 50 mg
Sphingosine Kinase (SphK1)				
Inhibitors	2097	SKI II	Selective non-lipid inhibitor of sphingosine kinase	10 mg 50 mg
Src Family Kinases				
Activators	4582	MLR 1023	Selective allosteric activator of Lyn kinase	10 mg 50 mg
Inhibitors	3914	A 419259	Inhibitor of Src family kinases	10 mg
	3963	AZM 475271	Src tyrosine kinase inhibitor	10 mg 50 mg
	4361	Bosutinib	Dual Src-Abl inhibitor; antiproliferative	10 mg 50 mg
	2471	ER 27319	Selective Syk kinase inhibitor	10 mg 50 mg
	1629	Herbimycin A	Src family kinase inhibitor; also Hsp90 inhibitor	100 µg
	4660	KB SRC 4	Potent and selective c-Src inhibitor	10 mg 50 mg
	2877	MNS	Selective inhibitor of Src and Syk	50 mg
	3063	1-Naphthyl PP1	Src family kinase inhibitor; also inhibits c-Abl	10 mg 50 mg
	3785	PD 166285	Potent Src inhibitor; also inhibits FGFR1, PDGFRβ and Wee1	1 mg 10 mg
	1397	PP 1	Potent, selective Src family kinase inhibitor	10 mg
	1407	PP 2	Potent, selective Src family kinase inhibitor	10 mg
	1923	pp60 c-src (521-533) (phosphorylated)	Inhibits tyrosine kinase activity of pp60c-src and pp60v-src	1 mg
	3642	Src I1	Dual site Src kinase inhibitor	10 mg 50 mg
Other	4763	Pyridostatin	Stabilizes G-quadruplexes; targets the proto-oncogene Src	10 mg 50 mg
Transferases				
Inhibitors	2406	FTI 276	Farnesyltransferase (FTase) inhibitor; antitumor	1 mg
	2407	FTI 277	Prodrug form of FTI 276 (Cat. No. 2406)	1 mg
	2430	GGTI 298	Geranylgeranyltransferase I (GGTase I) inhibitor	1 mg
	4294	LB 42708	Selective farnesyltransferase (FTase) inhibitor	10 mg 50 mg
	3416	Tris DBA	*N*-myristoyltransferase-1 inhibitor; antiproliferative	10 mg 50 mg
Translocation, Exocytosis & Endocytosis				
Other	1231	Brefeldin A	Disrupts protein translocation to Golgi	5 mg
	2334	D15	Endocytosis blocker	1 mg

Category	Cat. No.	Product Name	Description	Unit Size
	4417	DBeQ	Selective and reversible p97 inhibitor	10 mg 50 mg
	3922	Eeyarestatin I	Potent inhibitor of ER–associated protein degradation and translocation	10 mg
	1850	Exo1	Inhibits Golgi-ER traffic; blocks exocytosis	10 mg 50 mg
	5172	FLI 06	Inhibitor of Notch signaling	10 mg 50 mg
	1987	Leptomycin B	Inhibits nuclear export of proteins; antitumor	5 µg
Trk Receptors				
Agonists	2837	BDNF (human)	Activates TrkB and p75 receptors	10 µg
	3826	7,8-Dihydroxyflavone	TrkB agonist	10 mg 50 mg
	4607	LM 22A4	Potent TrkB agonist	10 mg 50 mg
Inhibitors	2617	AG 879	TrkA inhibitor	10 mg
	2238	GW 441756	Potent, selective TrkA inhibitor	10 mg 50 mg
Other	2272	Ro 08-2750	Inhibits NGF binding to $p75^{NTR}$ and TrkA	1 mg 10 mg 50 mg
Wnt Signaling				
Inhibitors	4675	CCT 031374	Inhibits TCF-dependent transcription; lowers β-catenin levels	10 mg 50 mg
	2634	DAPT	γ-secretase inhibitor	10 mg 50 mg
	3532	endo-IWR 1	Axin stabilizer; promotes β-catenin phosphorylation	10 mg 50 mg
	3947	exo-IWR 1	Negative control for endo-IWR 1 (Cat. No. 3532)	10 mg 50 mg
	4344	FH 535	Inhibitor of Wnt/β-catenin signaling	10 mg 50 mg
	4505	ICG 001	Inhibits TCF/β-catenin-mediated transcription	10 mg 50 mg
	4299	iCRT 14	Inhibits β-catenin-responsive transcription (CRT)	10 mg 50 mg
	3533	IWP 2	PORCN inhibitor; inhibits Wnt processing and secretion	10 mg 50 mg
	4651	JW 67	Wnt pathway inhibitor; induces degradation of active β-catenin	10 mg 50 mg
	3534	PNU 74654	β-catenin binder; inhibits Wnt signaling	10 mg 50 mg

Nuclear Receptors

Androgen Receptors				
Agonists	3812	CI-4AS-1	Steroidal androgen receptor agonist	10 mg 50 mg
	2822	Testosterone	Endogenous androgen receptor agonist	50 mg
Antagonists	3389	Bicalutamide	Non-steroidal androgen receptor antagonist	10 mg 50 mg
	4094	Flutamide	Non-steroidal androgen receptor antagonist	50 mg
	1759	Nilutamide	Androgen receptor antagonist; orally active	100 mg

Cancer Research Products – continued

Category	Cat. No.	Product Name	Description	Unit Size
Modulators	3813	TFM-4AS-1	Selective androgen receptor modulator (SARM)	10 mg 50 mg
Other	4946	AIM 100	Suppresses Tyr267 androgen receptor phosphorylation; Ack1 inhibitor	10 mg 50 mg
	4626	Andrographolide	Inhibits NFκB; blocks androgen receptor (AR) expression	50 mg
	3572	GSK 650394	Inhibits androgen-stimulated growth of prostrate cancer cells	10 mg 50 mg
	4396	Piperlongumine	Induces apoptosis; depletes androgen receptors in prostate cancer cells	10 mg 50 mg
Aromatase				
Inhibitors	3388	Anastrozole	Potent aromatase (CYP19) inhibitor	10 mg 50 mg
	3759	Exemestane	Steroidal aromatase (CYP19) inhibitor	10 mg 50 mg
	4382	Letrozole	Potent, reversible non-steroidal aromatase inhibitor	10 mg 50 mg
	3278	YM 511	Potent aromatase (CYP19) inhibitor	10 mg 50 mg
Aryl Hydrocarbon Receptors				
Agonists	1803	ITE	Endogenous aryl hydrocarbon receptor agonist	10 mg
Antagonists	3858	CH 223191	Potent aryl hydrocarbon receptor (AhR) antagonist	10 mg 50 mg
	3859	6,2',4'-Trimethoxyflavone	Aryl hydrocarbon receptor antagonist	10 mg 50 mg
Modulators	4628	DiMNF	Selective aryl hydrocarbon receptor modulator (SAhRM)	10 mg 50 mg
Ligands	4393	L-Kynurenine	Tryptophan catabolite; endogenous aryl hydrocarbon receptor ligand	50 mg
Other	4995	Phortress	Prodrug of the antitumor agent 5F 203	10 mg 50 mg
Estrogen and Related Receptors				
Agonists	1417	Daidzein	Estrogen receptor agonist; induces cell cycle arrest	50 mg
	1494	DPN	Highly potent ERβ agonist	10 mg 50 mg
	4276	ERB 041	Potent ERβ agonist	10 mg 50 mg
	2823	α-Estradiol	Endogenous estrogen receptor agonist	50 mg
	2824	β-Estradiol	Endogenous ER agonist	100 mg
	3523	FERb 033	Potent and selective ERβ agonist	10 mg 50 mg
	1426	PPT	Subtype-selective ERα agonist	10 mg 50 mg
Antagonists	1047	ICI 182,780	Estrogen receptor antagonist	1 mg 10 mg 50 mg
	1991	MPP	Highly selective ERα antagonist	10 mg 50 mg
	2662	PHTPP	Selective ERβ antagonist	10 mg 50 mg
	3928	XCT 790	Selective ERRα antagonist/inverse agonist	10 mg 50 mg
	2183	ZK 164015	Potent estrogen receptor antagonist	10 mg 50 mg

Category	Cat. No.	Product Name	Description	Unit Size
Modulators	5263	Bazedoxifene	Potent and selective estrogen receptor modulator (SERM)	10 mg 50 mg
	3412	(*Z*)-4-Hydroxytamoxifen	Metabolite of tamoxifen (Cat. No. 0999)	10 mg 50 mg
	2280	Raloxifene	Selective estrogen receptor modulator (SERM)	50 mg
	0999	Tamoxifen	Estrogen receptor partial agonist/antagonist	100 mg
Other	3705	Endoxifen	Potent antiestrogen; ERα ligand	10 mg 50 mg
Estrogen (GPR30) Receptors				
Agonists	3577	G-1	Potent and selective GPR30 agonist	10 mg 50 mg
Antagonists	3678	G-15	High affinity and selective GPR30 antagonist	10 mg 50 mg

Cell Cycle and DNA Repair

ATM & ATR Kinase				
Inhibitors	5198	AZ 20	Potent and selective ATR kinase inhibitor; antitumor	10 mg 50 mg
	2639	CGK 733	ATR and ATM kinase inhibitor	10 mg 50 mg
	3544	KU 55933	Potent and selective ATM kinase inhibitor	10 mg
	4176	KU 60019	Potent ATM kinase inhibitor	10 mg 50 mg
	3190	Mirin	MRN-ATM pathway inhibitor	10 mg 50 mg
Aurora Kinases				
Activators	3084	Anacardic acid	Aurora kinase A activator; also inhibits histone acetyltransferase	10 mg 50 mg
Inhibitors	4291	CCT 137690	Potent pan-Aurora kinase inhibitor	10 mg 50 mg
	3988	Hesperadin	Potent Aurora kinase B inhibitor	10 mg 50 mg
	4821	PF 03814735	Aurora kinase A and B inhibitor	10 mg 50 mg
	4584	SNS 314	Potent pan-Aurora kinase inhibitor	10 mg 50 mg
	4066	TC-A 2317	Potent, selective Aurora kinase A inhibitor	10 mg 50 mg
	5286	TC-S 7010	Potent and selective Aurora kinase A inhibitor	10 mg 50 mg
	2458	ZM 447439	Aurora kinase B inhibitor	10 mg
Calpains				
Inhibitors	2950	Acetyl-Calpastatin (184-210) (human)	Selective calpain inhibitor	1 mg
	0448	Calpeptin	Calpain and cathepsin L inhibitor	10 mg 50 mg
	5208	E 64	Potent and irreversible cysteine protease inhibitor	10 mg 50 mg
	1146	MDL 28170	Potent, selective calpain and cathepsin B inhibitor	10 mg
	3358	MG 101	Calpain inhibitor; activates p53-dependent apoptosis	5 mg
	1748	MG 132	Proteasome and calpain inhibitor; inhibits NF-κB activation	5 mg
	1269	PD 150606	Cell permeable calpain inhibitor	10 mg 50 mg

Cancer Research Products – continued

Category	Cat. No.	Product Name	Description	Unit Size
Casein Kinase 1				
Inhibitors	2902	D 4476	Selective CK1 inhibitor; also inhibits TGF-βRI	10 mg 50 mg
	3610	(*R*)-DRF053	Dual CK1/cdk inhibitor	10 mg 50 mg
	4896	LH 846	Selective CK1δ inhibitor	10 mg 50 mg
	4281	PF 4800567	Selective CK1ε inhibitor	10 mg 50 mg
	3316	PF 670462	Potent and selective CK1ε and CK1δ inhibitor	10 mg 50 mg
Casein Kinase 2				
Inhibitors	2275	TBB	Selective cell-permeable CK2 inhibitor	10 mg 50 mg
	3675	TMCB	Dual-kinase inhibitor; inhibits CK2 and ERK8	10 mg 50 mg
	4432	TTP 22	High affinity, selective CK2 inhibitor	10 mg 50 mg
Cdc25 Phosphatase				
Inhibitors	1867	NSC 663284	Potent, selective Cdc25 phosphatase inhibitor	10 mg
	1547	NSC 95397	Selective Cdc25 dual specificity phosphatase inhibitor	10 mg 50 mg
Cell Cycle Inhibitors				
	4406	10058-F4	Inhibits c-Myc-Max dimerization	10 mg 50 mg
	5144	CFM 4	CARP-1 mimetic; proapoptotic	10 mg 50 mg
	1230	Methotrexate	Cytotoxic agent	100 mg
	3715	Narciclasine	Antiproliferative agent; slows cell cycle progression	1 mg
Checkpoint Kinases				
Inhibitors	5199	AZD 7762	Potent and selective ATP-competitive inhibitor of Chk1 and Chk2	10 mg 50 mg
	3034	NSC 109555	Selective Chk2 inhibitor	10 mg 50 mg
	2694	PD 407824	Selective inhibitor of Chk1 and Wee1	1 mg 10 mg
	4277	PF 477736	Selective Chk1 inhibitor	10 mg 50 mg
	2560	SB 218078	Inhibitor of Chk1	1 mg 10 mg
	3038	TCS 2312	Potent Chk1 inhibitor	1 mg
Chemotherapeutics – for compounds please see page 59				
Cyclin-dependent Kinases				
Inhibitors	2072	Aminopurvalanol A	Cdk inhibitor	10 mg 50 mg
	2457	Arcyriaflavin A	Potent cdk4/cyclin D1 and CaM Kinase II inhibitor; antiviral agent (anti-HCMV)	10 mg
	3968	AZD 5438	Potent cdk1, cdk2 and cdk9 inhibitor	10 mg 50 mg
	3094	Flavopiridol	Cdk inhibitor	10 mg 50 mg
	1398	Kenpaullone	Potent cdk inhibitor; also inhibits GSK-3	10 mg
	2152	NSC 625987	Cdk4 inhibitor	10 mg 50 mg

Category	Cat. No.	Product Name	Description	Unit Size
	3135	NU 2058	Cdk1 and cdk2 inhibitor	10 mg 50 mg
	3301	NU 6140	Cdk2 inhibitor	10 mg 50 mg
	4786	PD 0332991	Potent, selective cdk4/6 inhibitor; brain penetrant	10 mg 50 mg
	3140	PHA 767491	Dual cdk9/cdc7 inhibitor; also inhibits MK2	10 mg 50 mg
	1580	Purvalanol A	Cdk inhibitor	10 mg 50 mg
	1581	Purvalanol B	Cdk inhibitor	10 mg 50 mg
	4181	Ro 3306	Cdk1 inhibitor	10 mg 50 mg
	2609	Ryuvidine	Cdk4 inhibitor; also SETD8 inhibitor	10 mg 50 mg
	4875	Senexin A	Cdk8 inhibitor	10 mg
	4075	SNS 032	Potent cdk2, cdk7 and cdk9 inhibitor	10 mg 50 mg
	2907	SU 9516	Potent cdk2 inhibitor	10 mg 50 mg
DNA-dependent Protein Kinase (DNA-PK)				
Inhibitors	3271	Compound 401	Selective DNA-PK and mTOR inhibitor	10 mg 50 mg
	2088	DMNB	DNA-PK inhibitor	10 mg 50 mg
	2828	NU 7026	Selective DNA-PK inhibitor	10 mg 50 mg
	3712	NU 7441	Potent and selective DNA-PK inhibitor	10 mg 50 mg
DNA, RNA and Protein Synthesis				
Inhibitors	4215	4E1RCat	Protein translation inhibitor; blocks eIF4F subunit interaction	10 mg 50 mg
	3561	L189	DNA ligase I, III and IV inhibitor	10 mg 50 mg
	1489	Mithramycin A	Inhibitor of DNA and RNA polymerase	1 mg
	5340	NSC 617145	Werner syndrome helicase (WRN) helicase inhibitor	10 mg 50 mg
	4723	T2AA	PCNA inhibitor	10 mg 50 mg
Hsp70				
Inhibitors	3803	VER 155008	Hsp70 inhibitor	10 mg 50 mg
Hsp90				
Inhibitors	1515	17-AAG	Selective Hsp90 inhibitor	1 mg
IRE1				
Modulators	4865	APY 29	Inhibits IRE1α autophosphorylation; activates IRE1α endoribonuclease activity	10 mg 50 mg
Kinesin				
Inhibitors	5454	BRD 9876	ATP non-competitive kinesin Eg5 inhibitor	50 mg
	5261	Dimethylenastron	Inhibitor of mitotic motor kinesin Eg5	10 mg 50 mg
	3703	K 858	Selective ATP-uncompetitive mitotic kinesin Eg5 inhibitor	10 mg 50 mg

Cancer Research Products – continued

Category	Cat. No.	Product Name	Description	Unit Size
	1305	Monastrol	Selective inhibitor of mitotic kinesin Eg5	10 mg 50 mg
	5109	SB 743921	Potent kinesin spindle protein (KSP) inhibitor	10 mg 50 mg
	2191	*S*-Trityl-L-cysteine	Potent, selective inhibitor of mitotic kinesin Eg5	50 mg
Monopolar Spindle 1 Kinase – for compounds please see page 42				
MuT Homolog-1 (MTH1) – for compounds please see page 34				
p53				
Activators	2185	NSC 146109	Activates p53-dependent transcription; genotype-selective antitumor agent	10 mg 50 mg
	5065	NSC 319726	Reactivator of mutant p53	10 mg 50 mg
	2936	NSC 66811	MDM2 antagonist. Disrupts MDM2-p53 interaction	10 mg 50 mg
	3984	Nutlin-3	MDM2 antagonist; inhibits MDM2-p53 interaction	10 mg 50 mg
	2443	RITA	MDM2-p53 interaction inhibitor	1 mg 10 mg
	3929	SJ 172550	MDMX inhibitor; disrupts MDMX-p53 interaction	10 mg 50 mg
	3365	Tenovin-1	Protects against MDM2-mediated p53 degradation	10 mg 50 mg
	3356	WR 1065	p53 activator; also ROS scavenger	10 mg 50 mg
Inhibitors	3843	Cyclic Pifithrin-α	p53 inhibitor	10 mg 50 mg
	3503	HLI 373	Hdm2 inhibitor; activates p53-dependent transcription	10 mg 50 mg
	1267	Pifithrin-α	p53 inhibitor; also aryl hydrocarbon receptor agonist	10 mg 50 mg
	2653	Pifithrin-μ	Inhibitor of p53-mitochondrial binding	10 mg 50 mg
Other	3023	CP 31398	p53-stabilizing agent	10 mg 50 mg
	3362	MIRA-1	Restores mutant p53 activity; proapoptotic	10 mg 50 mg
	1862	PRIMA-1	Restores mutant p53 activity; induces apoptosis	10 mg 50 mg
	3710	PRIMA-1^{MET}	Restores mutant p53 activity	10 mg
	3214	RETRA	Antitumor agent; suppresses mutant p53-bearing cancer cells	10 mg 50 mg
	4240	SCH 529074	Restores mutant p53 activity	10 mg 50 mg
Pim Kinase – for compounds please see page 54				
Polo-like Kinase (PLK)				
Inhibitors	3116	Cyclapolin 9	Selective, ATP-competitive PLK1 inhibitor	10 mg 50 mg
	2977	GW 843682X	Selective inhibitor of PLK1 and PLK3	1 mg 10 mg 50 mg
	4292	SBE 13	Potent and selective PLK1 inhibitor	10 mg 50 mg
	5403	TAK 960	Potent and selective PLK1 inhibitor	10 mg 50 mg
	4459	TC-S 7005	Potent and selective PLK2 inhibitor	10 mg

Category	Cat. No.	Product Name	Description	Unit Size
Poly(ADP-ribose) Polymerase (PARP)				
Inhibitors	3734	BYK 204165	Selective PARP-1 inhibitor	10 mg 50 mg
	4140	EB 47	Potent PARP-1 inhibitor	10 mg 50 mg
	4514	JW 55	Tankyrase inhibitor; inhibits canonical Wnt signaling	10 mg 50 mg
	5084	MN 64	Potent and selective tankyrase inhibitor	10 mg 50 mg
	4106	Nicotinamide	PARP-1 inhibitor	50 mg
	1401	NU 1025	Potent PARP inhibitor	10 mg 50 mg
	3255	PJ 34	Potent PARP inhibitor	10 mg 50 mg
	5049	TC-E 5001	Potent Tankyrase inhibitor	10 mg 50 mg
	4855	WIKI4	Tankyrase inhibitor; inhibits Wnt signaling	10 mg 50 mg
	3748	XAV 939	Tankyrase inhibitor; inhibits Wnt signaling	10 mg 50 mg
Telomerase				
Inhibitors	2981	BIBR 1532	Selective telomerase inhibitor	10 mg 50 mg
	2483	Costunolide	Inhibitor of human telomerase activity	1 mg 10 mg
	4253	TMPyP4 tosylate	Inhibitor of human telomerase	50 mg

Cell Death and Drug Resistance

Apoptosis and Autophagy Inducers				
	5330	AEG 40730	IAP antagonist; induces apoptosis	10 mg 50 mg
	3681	Bendamustine	Cytostatic agent; exhibits DNA alkylating and purine analog properties	10 mg 50 mg
	2626	Carboplatin	DNA cross-linking antitumor agent	50 mg
	5144	CFM 4	CARP-1 mimetic; proapoptotic	10 mg 50 mg
	3868	CHM 1	Potent antitumor agent; inducer of apoptosis	10 mg 50 mg
	5292	Cladribine	Deoxyadenosine analog; pro-apoptotic	10 mg 50 mg
	2841	Curcumin	Antitumor, anti-inflammatory and antioxidant	50 mg
	4091	Cyclophosphamide	Alkylating agent; chemotherapeutic	50 mg
	2137	2,3-DCPE	Selectively induces cancer cell apoptosis	10 mg 50 mg
	3590	Gambogic acid	Apoptosis inducer; activates caspases and inhibits Bcl-2 family proteins	10 mg 50 mg
	3258	Mitomycin C	DNA cross-linking antitumor agent	10 mg
	4429	NQDI 1	Inhibitor of apoptosis signal-regulating kinase 1 (ASK1)	10 mg 50 mg
	2623	Oxaliplatin	DNA cross-linking antitumor agent	50 mg
	5359	Rifaximin	Apoptosis inducer; pregnane X receptor agonist and antibiotic	50 mg

Cancer Research Products – continued

Category	Cat. No.	Product Name	Description	Unit Size
	4297	SMER 28	Positive regulator of autophagy	10 mg 50 mg
	5197	Spautin 1	Selectively promotes apoptosis of cancer cells under starvation conditions	10 mg 50 mg
	2706	Temozolomide	DNA-methylating antitumor agent	10 mg 50 mg
Bcl-2 Family				
Activators	5314	SMBA 1	High affinity and selective activator of Bax	10 mg 50 mg
Inhibitors	1785	Bax inhibitor peptide V5	Inhibitor of Bax-mediated apoptosis	1 mg
	1541	HA14-1	Bcl-2 inhibitor; induces apoptosis	10 mg 50 mg
	5368	Maritoclax	Mcl-1 inhibitor; proapoptotic	10 mg 50 mg
	4762	MIM1	Mcl-1 inhibitor; proapoptotic	10 mg 50 mg
	4038	TW 37	Bcl-2 inhibitor; induces apoptosis	10 mg 50 mg
Other	3367	AT 101	Downregulates Bcl-2 and Mcl-1; pro-apoptotic	10 mg 50 mg
	2160	Bax channel blocker	Inhibits Bax-mediated mitochondrial cytochrome c release	10 mg 50 mg
	1964	Gossypol	Proapoptotic; downregulates Bcl-2 and Bcl-XL	50 mg
Caspases				
Activators	2251	Cisplatin	Potent pro-apoptotic anticancer agent; activates caspase-3	50 mg
Inhibitors	2172	AZ 10417808	Selective non-peptide caspase-3 inhibitor	10 mg 50 mg
	2166	Z-DEVD-FMK	Cell-permeable, irreversible caspase-3 inhibitor	1 mg
	2163	Z-VAD-FMK	Cell-permeable, irreversible caspase inhibitor	1 mg
Chemotherapeutics – for compounds please see page 59				
Cytokine and NFkB Signaling				
Inhibitors	3713	Cryptotanshinone	STAT3 inhibitor; also displays multiple other activities	10 mg 50 mg
	4288	ISO 1	Macrophage migration inhibitory factor (MIF) inhibitor	10 mg 50 mg
	4079	Niclosamide	STAT3 inhibitor; also inhibits mTORC1 signaling	50 mg
	1778	Ro 106-9920	Inhibitor of NF-κB activation	10 mg 50 mg
	4963	SC 144	gp130 inhibitor; blocks cytokine-triggered gp130 signaling	10 mg 50 mg
	3035	SD 1008	JAK2/STAT3 signaling pathway inhibitor	10 mg 50 mg
	5309	SP 100030	NF-κB and AP-1 dual inhibitor	10 mg 50 mg
	2476	SR 11302	Inhibitor of AP-1 transcription factor; antitumor agent	10 mg
	2816	Withaferin A	Inhibits NF-κB activation	1 mg
Deubiquitinating Enzymes				
Inhibitors	3998	LDN 57444	Ubiquitin C-terminal hydrolase-L1 (UCH-L1) inhibitor	10 mg 50 mg
	2647	NSC 632839	Inhibitor of ubiquitin isopeptidase activity	10 mg 50 mg
	4566	NSC 687852	Inhibitor of UCHL5 and USP14	10 mg 50 mg
	4485	P 22077	USP7 inhibitor	10 mg 50 mg

Category	Cat. No.	Product Name	Description	Unit Size
	4733	P005091	USP7 inhibitor	10 mg 50 mg
	5197	Spautin 1	USP10 and USP13 inhibitor; inhibits autophagy	10 mg 50 mg
	5179	TCID	Selective ubiquitin C-terminal hydrolase-L3 (UCH-L3) inhibitor	10 mg 50 mg
JAK Kinase – for compounds please see page 58				
Ligases				
Inhibitors	3561	L189	DNA ligase I, III and IV inhibitor	10 mg 50 mg
	5191	PTC 209	Bmi-1 inhibitor; antitumor	10 mg 50 mg
	2978	PYR 41	Ubiquitin-activating enzyme (E1) inhibitor	10 mg 50 mg
	4817	SKPin C1	Inhibits Skp2-mediated p27 degradation; induces cell cycle arrest	10 mg 50 mg
	4375	SMER 3	Selective inhibitor of E3 ubiquitin ligase	10 mg 50 mg
	5076	SZL P1-41	Selective Skp2 inhibitor; suppresses E3 ligase activity	10 mg 50 mg
Multidrug Transporters				
Inhibitors	4193	CP 100356	P-gp inhibitor	10 mg 50 mg
	3241	Ko 143	Potent and selective BCRP inhibitor	1 mg 10 mg
	4169	KS 176	Selective BCRP inhibitor	10 mg 50 mg
	4107	Probenecid	MRP inhibitor	50 mg
	4042	PSC 833	Inhibitor of P-gp-mediated MDR	1 mg
	3722	Reversan	Selective MRP1 and P-gp inhibitor	10 mg 50 mg
Other	5119	Calcein AM	Substrate for MDR	1 mg
Pim Kinase				
Inhibitors	3589	PIM-1 Inhibitor 2	Pim-1 kinase inhibitor	10 mg 50 mg
	4592	R8-T198wt	Pim-1 kinase inhibitor	1 mg
	2979	TCS PIM-1 1	Selective, ATP-competitive Pim-1 kinase inhibitor	10 mg 50 mg
	3714	TCS PIM-1 4a	Selective, ATP-competitive Pim kinase inhibitor	10 mg 50 mg
Proteasome				
Inhibitors	2564	AM 114	20S proteasome inhibitor	10 mg 50 mg
	4285	HBX 41108	Selective USP7 inhibitor	10 mg
	4088	IU1	USP14 inhibitor	10 mg 50 mg
	2267	Lactacystin	Cell-permeable, potent and selective proteasome inhibitor	200 µg
	4045	PSI	Proteasome inhibitor; also prevents activation of NF-κB	5 mg

Cancer Research Products – continued

Category	Cat. No.	Product Name	Description	Unit Size
Angiogenesis				
Antiangiogenics				
	4706	Borrelidin	Antiangiogenic; inhibits threonyl-tRNA synthetase	1 mg
	1768	Fumagillin	Methionine aminopeptidase-2 inhibitor; antiangiogenic	1 mg
	1807	2-Methoxyestradiol	Apoptotic and antiangiogenic agent	10 mg 50 mg
	4664	Obtustatin	Potent and selective $\alpha 1\beta 1$ inhibitor	100 µg
	4744	P11	Potent antagonist of $\alpha v\beta 3$-vitronectin interaction; antiangiogenic	1 mg
	4885	R 1530	Multi-RTK inhibitor; inhibits angiogenesis	10 mg 50 mg
	1495	Combretastatin A4	Antiangiogenic	10 mg 50 mg
	1461	Linomide	Immunomodulator with antiangiogenic properties	10 mg 50 mg
	2710	OGT 2115	Antiangiogenic; heparanase inhibitor	1 mg 10 mg
	1098	Tranilast	Antiallergic; inhibits inflammatory mediator release from mast cells	10 mg 50 mg
FGFR – for compounds please see page 38				
Hedgehog Signaling				
Activators	4366	SAG	Potent Smoothened receptor agonist; activates the Hedgehog signaling pathway	1 mg
Inhibitors	1639	AY 9944	Inhibitor of Hedgehog (Hh) signaling; inhibits Δ7-dehydrocholesterol reductase	10 mg
	1623	Cyclopamine	Inhibitor of Hedgehog (Hh) signaling	1 mg
	3889	GANT 58	GLI1 antagonist; inhibits Hedgehog (Hh) signaling	10 mg 50 mg
	3191	GANT 61	GLI antagonist; inhibits Hedgehog (Hh) signaling	10 mg 50 mg
	4917	M 25	Potent Smoothened (Smo) receptor antagonist	10 mg 50 mg
	5262	PF 5274857	Potent and selective Smoothened (Smo) receptor antagonist	10 mg 50 mg
	4886	RU-SKI 43	Hedgehog acyltransferase (Hhat) inhibitor; cell permeable	10 mg 50 mg
	1974	SANT-1	Inhibitor of hedgehog (Hh) signaling; antagonizes smoothened activity	10 mg 50 mg
	3617	SANT-2	Inhibitor of Hedgehog (Hh) signaling; antagonizes smoothened activity	10 mg 50 mg
	1638	U 18666A	Inhibitor of Hedgehog (Hh) signaling; also inhibits cholesterol synthesis	10 mg
Hypoxia Inducible Factor (HIF-1)				
Activators	4565	ML 228	HIF pathway activator	10 mg 50 mg
Inhibitors	4408	DMOG	Prolyl hydroxylase inhibitor	10 mg 50 mg
	4451	IOX 2	Potent, selective HIF-1α prolyl hydroxylase-2 (PHD2) inhibitor	10 mg 50 mg
	4324	KC7F2	HIF-1α inhibitor; down-regulates HIF-1α protein synthesis	10 mg 50 mg
	2954	PX 12	Thioredoxin-1 inhibitor	10 mg 50 mg

Category	Cat. No.	Product Name	Description	Unit Size
	5243	TC-S 7009	High affinity and selective HIF-2α inhibitor	10 mg 50 mg
Other	4705	Chetomin	Blocks interaction of HIF-1α, HIF-2α and STAT2 with CBP/p300	1 mg
Matrix Metalloproteases – for compounds please see page 58				
PDGFR – for compounds please see page 38				
VEGFR				
Inhibitors	4350	Axitinib	Potent VEGFR-1, -2 and -3 inhibitor	10 mg 50 mg
	4471	DMH4	Selective VEGFR-2 inhibitor	10 mg 50 mg
	3882	(*E*)-FeCP-oxindole	Selective VEGFR-2 inhibitor	10 mg
	3883	(*Z*)-FeCP-oxindole	Selective VEGFR-2 inhibitor	10 mg
	2542	Ki 8751	Potent, selective VEGFR-2 inhibitor	10 mg 50 mg
	1459	SU 4312	Potent inhibitor of VEGFR tyrosine kinase	10 mg
	3037	SU 5416	VEGFR inhibitor; also inhibits KIT, RET, MET and FLT3	10 mg 50 mg
	3768	Sunitinib	Potent VEGFR, PDGFRβ and KIT inhibitor	10 mg 50 mg
	3909	Toceranib	Potent VEGFR and PDGFR inhibitor	10 mg 50 mg
	5422	XL 184	Potent VEGFR inhibitor; also inhibits other RTKs	10 mg 50 mg
	2499	ZM 306416	VEGFR inhibitor	1 mg 10 mg
	2475	ZM 323881	Potent, selective inhibitor of VEGFR-2	1 mg 10 mg
Wnt Signaling – for compounds please see page 46				

Invasion & Metastasis

Autotaxin				
Inhibitors	4196	HA 130	Selective autotaxin inhibitor	10 mg 50 mg
	4078	PF 8380	Potent autotaxin inhibitor	10 mg 50 mg
	3404	S 32826	Potent autotaxin inhibitor	10 mg
Chemokine Receptors				
Agonists	4780	VUF 11207	Potent CXCR7 agonist	10 mg 50 mg
Antagonists	3299	AMD 3100	Highly selective CXCR4 antagonist	10 mg 50 mg
	4179	AMD 3465	Potent, selective CXCR4 antagonist	10 mg 50 mg
	4487	(±)-AMG 487	CXCR3 antagonist; inhibits cell migration and metastasis	10 mg 50 mg
	3581	C 021	Potent CCR4 antagonist	10 mg 50 mg
	5130	CTCE 9908	CXCR4 antagonist; antitumor	1 mg
	4528	(±)-NBI 74330	Potent and selective CXCR3 antagonist	10 mg
	2517	RS 504393	Highly selective CCR2 chemokine receptor antagonist	10 mg
	2725	SB 225002	Potent and selective CXCR2 antagonist	10 mg 50 mg

Cancer Research Products – continued

Category	Cat. No.	Product Name	Description	Unit Size
	2757	UCB 35625	Potent CCR1 and CCR3 antagonist	1 mg 10 mg
Dynamin				
Inhibitors	1774	Dynamin inhibitory peptide	Dynamin inhibitor	1 mg
	1775	Dynamin inhibitory peptide, myristoylated	Cell-permeable dynamin inhibitor	1 mg
	1776	Dynamin inhibitory peptide, myristoylated (control)	Control peptide version of dynamin inhibitory peptide, myristoylated (Cat. No. 1775)	1 mg
	2897	Dynasore	Non-competitive dynamin inhibitor	10 mg 50 mg
	4222	Dynole 34-2	Dynamin I inhibitor	10 mg 50 mg
	3982	Mdivi 1	Dynamin inhibitor; attenuates mitochondrial division and apoptosis	10 mg 50 mg
	4224	MitMAB	Dynamin inhibitor	10 mg 50 mg
Focal Adhesion Kinase				
Inhibitors	3414	FAK Inhibitor 14	Selective FAK inhibitor	10 mg 50 mg
	4278	PF 431396	Dual FAK/PYK2 inhibitor	10 mg
	3239	PF 573228	Potent and selective FAK inhibitor	10 mg 50 mg
	4498	Y 11	Potent and selective FAK inhibitor	10 mg 50 mg
G-Protein Signaling – for compounds please see page 40				
IκB Kinase				
Inhibitors	4547	ACHP	Selective IKKα and IKKβ inhibitor	10 mg
	4857	Amlexanox	Inhibitor of TBK1 and IKKε; antiallergic agent	10 mg 50 mg
	2539	IKK 16	Selective inhibitor of IKK	10 mg 50 mg
	2611	IMD 0354	Inhibitor of IKKβ	10 mg 50 mg
	4899	ML 120B	Novel IKK2-selective inhibitor	10 mg 50 mg
	4238	PF 184	Potent and selective IKKβ inhibitor	10 mg
	4569	PS 1145	Selective IKK inhibitor; orally active	10 mg 50 mg
	3318	SC 514	IKKβ inhibitor; attenuates NF-κB-induced gene expression	10 mg 50 mg
	2559	TPCA-1	Potent, selective inhibitor of IKKβ	10 mg
Integrin Receptors				
Inhibitors	4228	A 286982	Potent inhibitor of the LFA-1/ICAM-1 interaction	10 mg 50 mg
	3910	BIO 1211	Selective α4β1 (VLA-4) inhibitor	1 mg
	5051	BIO 5192	Highly potent and selective inhibitor of integrin α4β1	10 mg 50 mg
	4724	BTT 3033	Selective inhibitor of integrin α2β1	10 mg 50 mg
	3202	Echistatin, α1 isoform	αVβ3 and glycoprotein IIb/IIIa (integrin αIIbβ3) inhibitor	100 µg
	3498	RGDS peptide	Integrin binding sequence; inhibits integrin receptor function	10 mg
	3900	TCS 2314	α4β1 (VLA-4) antagonist	10 mg 50 mg

Category	Cat. No.	Product Name	Description	Unit Size
Modulators	4776	BIRT 377	Potent negative allosteric modulator of LFA-1	10 mg 50 mg
	4227	RWJ 50271	Inhibitor of LFA-1/ICAM mediated cell adhesion	10 mg 50 mg
JAK Kinase				
Inhibitors	4580	Atiprimod	JAK2 inhibitor	10 mg
	4556	CP 690550	Potent JAK inhibitor	10 mg 50 mg
	1571	Cucurbitacin I	Selective inhibitor of STAT3/JAK2 signaling	1 mg
	3395	Lestaurtinib	JAK2, FLT3 and TrkA inhibitor	1 mg
	4221	TCS 21311	Potent JAK3 inhibitor; also inhibits GSK-3β and PKC	10 mg 50 mg
	3115	WHI-P 154	JAK3 kinase inhibitor. Also inhibits EGFR	10 mg 50 mg
	1367	ZM 39923	Potent, selective JAK3 inhibitor	10 mg 50 mg
	1366	ZM 449829	Potent, selective JAK3 inhibitor	10 mg 50 mg
Liver Receptor Homolog 1 (LRH-1)				
Agonists	4378	DLPC	Selective LRH-1 agonist	50 mg
Other	4957	ML 179	Selective LRH1 inverse agonist	10 mg 50 mg
Matrix Metalloproteases				
Inhibitors	2961	Batimastat	Potent, broad spectrum MMP inhibitor	1 mg 10 mg
	2632	CL 82198	Selective inhibitor of MMP-13	10 mg 50 mg
	3780	CP 471474	Broad spectrum MMP inhibitor	10 mg 50 mg
	4090	Doxycycline hyclate	Broad-spectrum MMP inhibitor; tetracycline derivative	50 mg
	3995	GI 254023X	Selective ADAM10 metalloprotease inhibitor	1 mg
	2983	GM 6001	Broad spectrum MMP inhibitor	10 mg
	2631	Marimastat	Broad spectrum MMP inhibitor	1 mg 10 mg
	2916	Ro 32-3555	Potent, collagenase-selective MMP inhibitor	10 mg
	4187	UK 356618	Potent and selective MMP-3 inhibitor	10 mg
	2900	UK 370106	Highly selective MMP-3 and MMP-12 inhibitor	10 mg
	4188	UK 383367	Potent and selective BMP-1 (PCP) inhibitor	1 mg 10 mg
	2633	WAY 170523	Potent and selective inhibitor of MMP-13	1 mg 10 mg
MET				
Inhibitors	4368	Crizotinib	Potent c-MET/ALK inhibitor	10 mg 50 mg
	4239	PF 04217903	Highly selective c-Met inhibitor	10 mg 50 mg
	2693	PHA 665752	Potent and selective MET kinase inhibitor	10 mg 50 mg
	4101	SU 11274	Selective inhibitor of MET kinase activity	10 mg 50 mg
Microtubules				
	4138	ABT 751	Inhibitor of microtubule polymerization; antimitotic and antitumor	10 mg 50 mg
	1364	Colchicine	Inhibitor of tubulin	1 g

Cancer Research Products – continued

Category	Cat. No.	Product Name	Description	Unit Size
	1643	D-64131	Inhibitor of tubulin polymerization; antitumor *in vivo*	10 mg 50 mg
	3502	Epothilone B	Microtubule stabilization agent; promotes tubulin polymerization	100 µg
	2226	Flutax 1	Fluorescent taxol derivative	1 mg
	3728	Indibulin	Microtubule destabilizer	10 mg 50 mg
	5231	MPC 6827	Inhibitor of microtubule polymerization; antimitotic and antitumor	10 mg 50 mg
	1228	Nocodazole	Microtubule inhibitor	10 mg
	1697	Noscapine	Tubulin inhibitor; induces apoptosis	100 mg
	1097	Taxol	Promotes assembly and inhibits disassembly of microtubules	10 mg 50 mg
Pim Kinase – for compounds please see page 54				
Rho-kinase – for compounds please see page 44				
Urokinase				
Inhibitors	4372	BC 11	Selective urokinase (uPA) inhibitor	10 mg 50 mg
	0442	4-Chlorophenylguanidine	Urokinase inhibitor	100 mg
Wnt Signaling – for compounds please see page 46				

Chemotherapeutics

	4219	Banoxantrone	Prodrug topoisomerase II inhibitor	10 mg 50 mg
	3681	Bendamustine	Cytostatic agent; exhibits DNA alkylating and purine analog properties	10 mg 50 mg
	3389	Bicalutamide	Non-steroidal androgen receptor antagonist	10 mg 50 mg
	1100	Camptothecin	DNA topoisomerase inhibitor	25 mg
	4799	Capecitabine	Prodrug of 5-Fluorouracil (Cat. No. 3257); inhibits DNA synthesis	50 mg
	2626	Carboplatin	DNA cross-linking antitumor agent	50 mg
	4436	8-Chloroadenosine	Cytotoxic nucleoside analog; inhibits RNA synthesis	10 mg 50 mg
	2251	Cisplatin	Potent pro-apoptotic anticancer agent; activates caspase-3	50 mg
	2600	Clofarabine	Deoxycytidine kinase (dCK) substrate	10 mg 50 mg
	2688	CPT 11	DNA topoisomerase I inhibitor; antitumor	10 mg 50 mg
	4091	Cyclophosphamide	Alkylating agent; chemotherapeutic	50 mg
	4520	Cytarabine	Nucleoside analog; inhibits DNA replication	50 mg
	1467	Daunorubicin	RNA synthesis inhibitor	10 mg
	2624	Decitabine	DNA methyltransferase inhibitor	10 mg 50 mg
	3857	Dexrazoxane	Topoisomerase II inhibitor	10 mg 50 mg
	4502	DIM	Activates Chk2; induces G_2/M cell cycle arrest	50 mg
	4056	Docetaxel	Microtubule stabilizer	10 mg 50 mg
	2252	Doxorubicin	Antitumor antibiotic agent; inhibits DNA topoisomerase II	10 mg 50 mg
	3260	Epirubicin	Inhibits DNA synthesis and function; inhibits DNA topoisomerase II	10 mg

Cancer Research Products – continued

Category	Cat. No.	Product Name	Description	Unit Size
	1226	Etoposide	Topoisomerase II inhibitor	100 mg
	4659	Floxuridine	Inhibitor of thymidylate synthetase; anticancer agent	50 mg
	3495	Fludarabine	Purine analog; inhibits DNA synthesis	10 mg 50 mg
	3257	5-Fluorouracil	Inhibits RNA and DNA synthesis	50 mg
	4094	Flutamide	Non-steroidal androgen receptor antagonist	50 mg
	3259	Gemcitabine	DNA synthesis inhibitor	10 mg 50 mg
	3592	Goserelin	GnRH receptor agonist	10 mg
	2873	Leuprolide	GnRH receptor agonist	1 mg
	4619	Melphalan	DNA alkylating agent; cytotoxic and antineoplastic	50 mg
	4103	6-Mercaptopurine	Purine analog; inhibits DNA and RNA synthesis	50 mg
	1230	Methotrexate	Cytotoxic agent	100 mg
	3258	Mitomycin C	DNA cross-linking antitumor agent	10 mg
	4250	Mitoxantrone	Topoisomerase II inhibitor; immunosuppressive and antineoplastic agent	50 mg
	1759	Nilutamide	Androgen receptor antagonist; orally active	100 mg
	2623	Oxaliplatin	DNA cross-linking antitumor agent	50 mg
	2033	Pentostatin	Adenosine deaminase inhibitor	10 mg 50 mg
	2684	SN 38	DNA topoisomerase I inhibitor; antitumor	10 mg 50 mg
	1621	Streptozocin	DNA alkylator; antitumor and induces diabetes	100 mg 500 mg
	1097	Taxol	Promotes assembly and inhibits disassembly of microtubules	10 mg 50 mg
	2706	Temozolomide	DNA-methylating antitumor agent	10 mg 50 mg
	4061	6-Thioguanine	Anticancer and immunosuppressive agent	50 mg
	1256	Vinblastine	Disrupts microtubules	10 mg 50 mg
	1257	Vincristine	Disrupts microtubules	10 mg 50 mg
	3401	Vinorelbine	Selective mitotic microtubule antagonist	10 mg 50 mg
	4562	Topotecan	DNA topoisomerase I inhibitor; camptothecin (Cat. No. 1100) analog	10 mg 50 mg

Index

Cancer Research Target	For Products See Page
14-3-3 Proteins	35
Abl Kinase	39
Akt (Protein Kinase B)	39
AMPK	40
Anaplastic Lymphoma Kinase (ALK)	37
Androgen Receptors	46
Antiangiogenics	55
Apoptosis and Autophagy Inducers	52
Aromatase	47
Aryl Hydrocarbon Receptor	47
ATM and ATR Kinase	48
ATP-citrate Lyase (ACLY)	33
Aurora Kinases	48
Autotaxin	56
Bcl-2 Family	53
Broad Spectrum Protein Kinase Inhibitors	40
Bromodomains (BRDs)	35
Calpains	48
Carbonic Anhydrases (CA)	33
Carnitine Palmitoyltransferase (CPT)	33
Casein Kinase 1	49
Casein Kinase 2	49
Caspase	53
Cdc25 Phosphatase	49
Cell Cycle Inhibitors	49
Checkpoint Kinases	49
Chemokine Receptors	56
Chemotherapeutics	59
Cyclin-dependent Kinases	49
Cytokine and NFκB Signaling	53
Deubiquitinating Enzymes	53
Dihydrofolate Reductase	33
DNA Methyltransferases (DNMTs)	35
DNA-dependent Protein Kinase	50
DNA, RNA and Protein Synthesis	50
Dynamin	57
EGFR	37
Estrogen and Related Receptors	47
Estrogen (GPR30) Receptors	48
Fatty Acid Synthase (FASN)	33
FGFR	38
FLT3	38
Focal Adhesion Kinase	57
GAPDH	33
Glucose Transporters (GLUT)	33
Glutamate Dehydrogenase (GDH)	33
Glutaminase	33
Glutathione	33
Glycogen Synthase Kinase 3	40
G-protein Signaling	40
Heat Shock Proteins	41
Hedgehog Signaling	55
Hexokinases	33
Histone Acetyltransferases (HATs)	35
Histone Deacetylases (HDACs)	35
Histone Demethylases	36
HMG-CoA Reductase (HMG-CoA)	33
Hypoxia Inducible Factor 1 (HIF-1)	55
Insulin and Insulin-like Receptors	38
IκB Kinase	57
Integrin Receptors	57
IRE1	50
JAK Kinase	58
Kinesin	50
Lactate Dehydrogenase A (LDHA)	33
Ligases	54
LIM Kinase (LIMK)	41
Liver Receptor Homolog 1 (LRH-1)	58
Lysine Methyltransferases (KMTs)	36
MAPK	41
Matrix Metalloprotease	58
MBT Domains	37
MEK	42
MET Receptor	58
Microtubules	58
MnK	42
Monoacylglycerol Lipase (MAGL)	33
Monocarboxylate Transporters (MCTs)	34
Monopolar Spindle 1 Kinase	42
mTOR	42
Multidrug Transporters	54
MutT homolog-1 (MTH1)	34
NAMPT	34
Na^+/H^+ Exchanger (NHE)	34
Other Kinases	43
Oxidative Phosphorylation (OXPHOS)	34
p53	51
PDGFR	38
PERK	43
PFKFB3	34
PI 3-kinase	43
Pim Kinase	54
Polo-like Kinase	51
Poly (ADP-ribose) Polymerase (PARP)	52
Proteasome	54
Protein Arginine Methyltransferases	37
Protein Kinase D	43
Protein Ser/Thr Phosphatases	44
Protein Tyrosine Phosphatases	44
Pyruvate Dehydrogenase (PDH)	34
Pyruvate Dehydrogenase Kinase (PDK)	34
Pyruvate Kinase M2 (PKM2)	34
Raf Kinase	44
Rho-kinase (ROCK)	44
Ribonucleotide Reductase	34
Ribosomal S6 Protein Kinases (RSKs)	44
RNA/DNA Polymerase	37
Sir2-like Family Deacetylases	45
Sphingosine Kinase	45
Sphingosine-1-phosphate Receptors	38
Src Family Kinases	45
Telomerase	52
TGF-β Receptors	39
Thymidylate Synthetase	34
Transferases	45
Translocation, Exocytosis & Endocytosis	45
Trk Receptors	46
Urokinase	59
VEGFR	56
Wnt Signaling	46

Further Reading

Please refer to the list of recommended papers for more information.

Introduction

Hanahan and Weinberg (2000) The hallmarks of cancer. *Cell* **100** 57.

Hanahan and Weinberg (2011) Hallmarks of cancer: the next generation. *Cell* **144** 646.

Cancer Metabolism

Bustamante *et al* (1977) High aerobic glycolysis of rat hepatoma cells in culture: role of mitochondrial hexokinase. *Proc. Natl. Acad. Sci. USA* **74** 3735.

Butler *et al* (2013) Stalling the engine of resistance: targeting cancer metabolism to overcome therapeutic resistance. *Cancer Res.* **73** 2709.

Cairns *et al* (2011) Regulation of cancer cell metabolism. *Nat. Rev. Cancer* **11** 85.

Cairns and Mak (2013) Oncogenic isocitrate dehydrogenase mutations: mechanisms, models, and clinical opportunities. *Cancer Discov.* **3** 730.

Doherty *et al* (2014) Blocking lactate export by inhibiting the Myc target MCT1 disables glycolysis and glutathione synthesis. *Cancer Res.* **74** 908.

Feng *et al* (2012) Dysregulated lipid metabolism in cancer. *World J. Biol. Chem.* **3** 167.

Galluzzi *et al* (2013) Metabolic targets for cancer therapy. *Nat. Rev. Drug Discov.* **12** 829.

Imai *et al* (2009) Nicotinamide phosphoribosyltransferase (Nampt): a link between NAD biology, metabolism, and diseases. *Curr. Pharm. Des.* **15** 20.

Jiang *et al* (2014) Regulation of the pentose phosphate pathway in cancer. *Protein Cell* **5** 592.

Stincone *et al* (2014) The return of metabolism: biochemistry and physiology of the pentose phosphate pathway. *Biol. Rev. Camb. Philos. Soc.* **90** 927.

Todorova *et al* (2011) Tamoxifen and raloxifene suppress the proliferation of estrogen receptor-negative cells through inhibition of glutamine uptake. *Cancer Chemother. Pharmacol.* **67** 285.

Yang *et al* (2009) Glioblastoma cells require glutamate dehydrogenase to survive impairments of glucose metabolism or Akt signaling. *Cancer Res.* **69** 7986.

Epigenetics in cancer

Copeland *et al* (2009) Protein methyltransferases as a target class for drug discovery. *Nat. Rev. Drug Discov.* **8** 724.

Dawson and Kouzarides (2012) Cancer epigenetics: from mechanism to therapy. *Cell* **150** 12.

Drouin *et al* (2015) Structure enabled design of BAZ2-ICR, a chemical probe targeting the bromodomains of BAZ2A and BAZ2B. *J. Med. Chem.* **58** 2553.

Muller *et al* (2011) Bromodomains as therapeutic targets. *Expert Rev. Mol. Med.* **13** e29.

Rodríguez-Paredes and Esteller (2011) Cancer epigenetics reaches mainstream oncology. *Nat. Med.* **17** 330.

Suvà *et al* (2013) Epigenetic reprogramming in cancer. *Science* **339** 1567.

Virani *et al* (2012) Cancer epigenetics: a brief review. *ILAR J.* **253** 359.

Receptor Signaling

Ahmad *et al* (2012) Mechanisms of FGFR-mediated carcinogenesis. *Biochem. Biophys. Acta.* **1823** 850.

Anastas and Moon (2013) WNT signalling pathways as therapeutic targets in cancer. *Nature Reviews Cancer* **13** 11.

Chen and Sharon (2013) IGF-1R as an anti-cancer target—trials and tribulations. *Chin. J. Cancer* **32** 242.

Cox *et al* (2014) Drugging the undruggable RAS: Mission Possible? *Nature Reviews Drug Discov.* **13** 828.

Cuadrado and Nebrada (2010) Mechanisms and functions of p38 MAPK signaling. *Biochem. J.* **429** 403.

Derynck and Zhang (2003) Smad-dependent and Smad-independent pathways in TGF-β family signalling. *Nature* **425** 577.

Hilakivi-Clarke (2000). Estrogens, BRCA1, and breast cancer. *Cancer Res.* **60** 4993.

Lonergen (2011) Androgen receptor signaling in prostate cancer development and progression. *J. Carcinogenesis* **10** 20.

Further Reading – continued

Madhunapantula and Robertson (2008) Is B-Raf a good therapeutic target for melanoma and other malignancies. *Cancer Res.* **68** 5.

Opitz *et al* (2011) An endogenous tumor-promoting ligand of the human aryl hydrocarbon receptor. *Nature* **478** 197.

Polivka and Janku (2014) Molecular targets for cancer therapy in the PI 3-K/AKT/mTOR pathway. *Pharmacol. Ther.* **142** 164.

Rosenberg *et al* (2015) Targeting glutamatergic signaling and the PI 3-kinase pathway to halt melanoma progression. *Transl. Oncol.* **8** 1.

Santarpia *et al* (2012) Targeting the mitogen-activated protein kinase RAS-RAF signaling pathway in cancer therapy. *Expert Opin. Ther. Targets* **16** 103.

Selvam and Ogretmen (2013) Sphingosine kinase/sphingosine 1-phosphate signaling in cancer therapeutics and drug resistance. *Handb. Exp. Pharmacol.* **216** 3.

Talapatra and Thompson (2001) Growth factor signaling in cell survival: implications for cancer treatment. *J. Pharmacol. Exp. Ther.* **298** 873.

Tan *et al* (2015) Androgen receptor: structure, role in prostate cancer and drug discovery. *Acta. Pharmacol. Sin.* **36** 3.

Wei *et al* (2014) The activation of G protein-coupled receptor 30 (GPR30) inhibits proliferation of estrogen receptor-negative breast cancer cells *in vitro* and *in vivo*. *Cell Death Dis.* **5** e1428.

Witsch *at al* (2010) Roles for growth factors in cancer progression. *Physiology (Bethesda)* **25** 85.

Wu and Yu (2014) Insulin-like growth factor receptor-1 (IGF-IR) as a target for prostate cancer therapy. *Cancer Metastasis Rev.* **33** 607.

Yingling *et al* (2004) Development of TGF-β signaling inhibitors for cancer therapy. *Nat. Rev. Drug Discov.* **3** 1011.

Cell Cycle and DNA Damage Repair

Annunziata and O'Shaughnessy (2010) Poly (ADP-ribose) polymerase as a novel therapeutic target in cancer. *Clin. Cancer Res.* **16** 4517.

Barr *et al* (2004) Polo-like kinases and the orchestration of cell division. *Nat. Rev. Mol. Cell Biol.* **5** 429.

Dobbelstein and Sørensen (2015) Exploiting replicative stress to treat cancer. *Nat. Rev. Drug Discov.* **14** 405.

Fu *et al* (2012) Balancing repair and tolerance of DNA damage caused by alkylating agents. *Nat. Rev. Cancer* **12** 104.

Hochegger *et al* (2008) Cyclin-dependent kinases and cell-cycle transitions: does one fit all? *Nat. Rev. Mol. Cell Biol.* **9** 910.

Lapenna and Giordano (2009) Cell cycle kinases as therapeutic targets for cancer. *Nat. Rev. Drug Discov.* **8** 547.

Lord and Ashworth (2012) The DNA damage response and cancer therapy. *Nature* **481** 287.

Malumbres and Barbacid (2009) Cell cycle, CDKs and cancer: a changing paradigm. *Nat. Rev. Cancer.* **9** 153.

Rastogi and Mishra (2012) Therapeutic targeting of cancer cell cycle using proteasome inhibitors. *Cell Div.* **7** 26.

Williams and Stoeber (2012) The cell cycle and cancer. *Pathol.* **226** 352.

Angiogenesis

Greer *et al* (2012) The updated biology of hypoxia-inducible factor. *EMBO J.* **31** 2448.

Raza *et al* (2010) Pericytes and vessel maturation during tumor angiogenesis and metastasis. *Am. J. Hematol.* **85** 593.

Roca and Adams (2007) Regulation of vascular morphogenesis by Notch signaling. *Genes Dev.* **21** 2511.

Weis and Cheresh (2011) Tumor angiogenesis: molecular pathways and therapeutic targets. *Nat. Med.* **17** 1359.

Invasion and Metastasis

Jiang *et al* (2015) Tissue invasion and metastasis: Molecular, biological and clinical perspectives. *Semin Cancer Biol.* doi: 10.1016/j.semcancer.2015.03.008. [Epub ahead of print].

Karamouzis *et al* (2009) Targeting MET as a strategy to overcome crosstalk-related resistance to EGFR inhibitors. *Lancet Oncol.* **10** 709.

Panabières and Pantel (2014) Challenges in circulating tumor cell research. *Nat. Rev. Cancer* **14** 623.

Pantel and Speicher (2015) The biology of circulating tumor cells. *Oncogene* advance online publication doi: 10.1038.

Quail and Joyce (2013) Microenvironmental regulation of tumor progression and metastasis. *Nat. Med.* **19** 1423.

R&D SYSTEMS NOVUS BIOLOGICALS TOCRIS proteinsimple

bio-techne®

Global info@bio-techne.com bio-techne.com/find-us/distributors TEL +1 612 379 2956
North America TEL 800 343 7475 **Europe | Middle East | Africa** TEL +44 (0)1235 529449
China info.cn@bio-techne.com TEL +86 (21) 52380373

bio-techne.com

BR_CancerGuide_7165