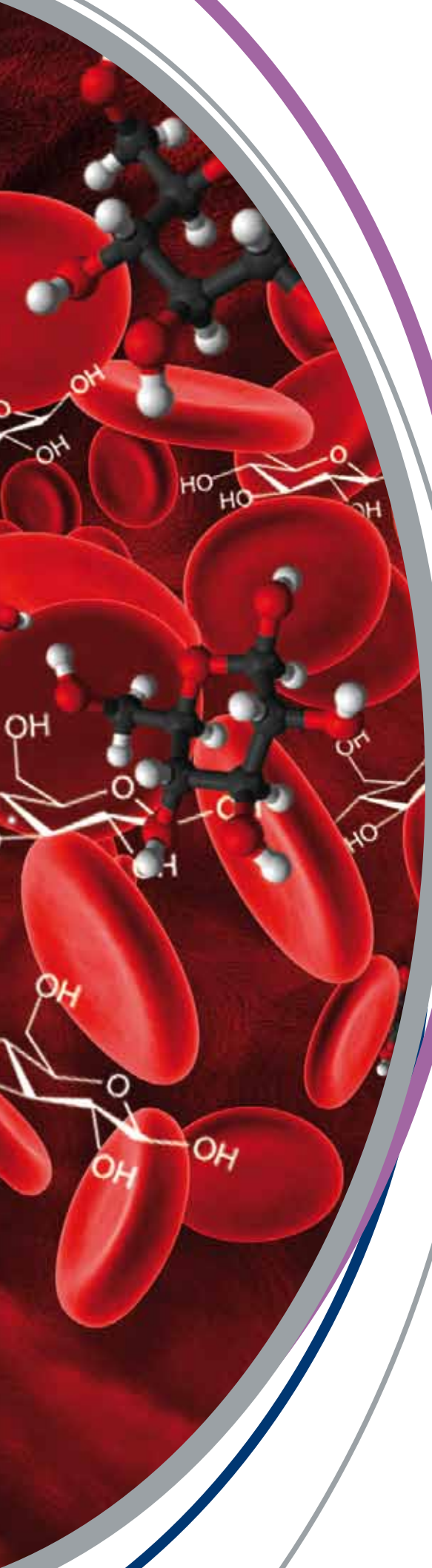

Diabetes

Insulin Signaling

PTPases

PI 3-K / Akt Pathway

GSK-3

Nutrient Sensing (mTOR / AMPK)

PPARs

GLP-1, DPPIV & Neprilysin

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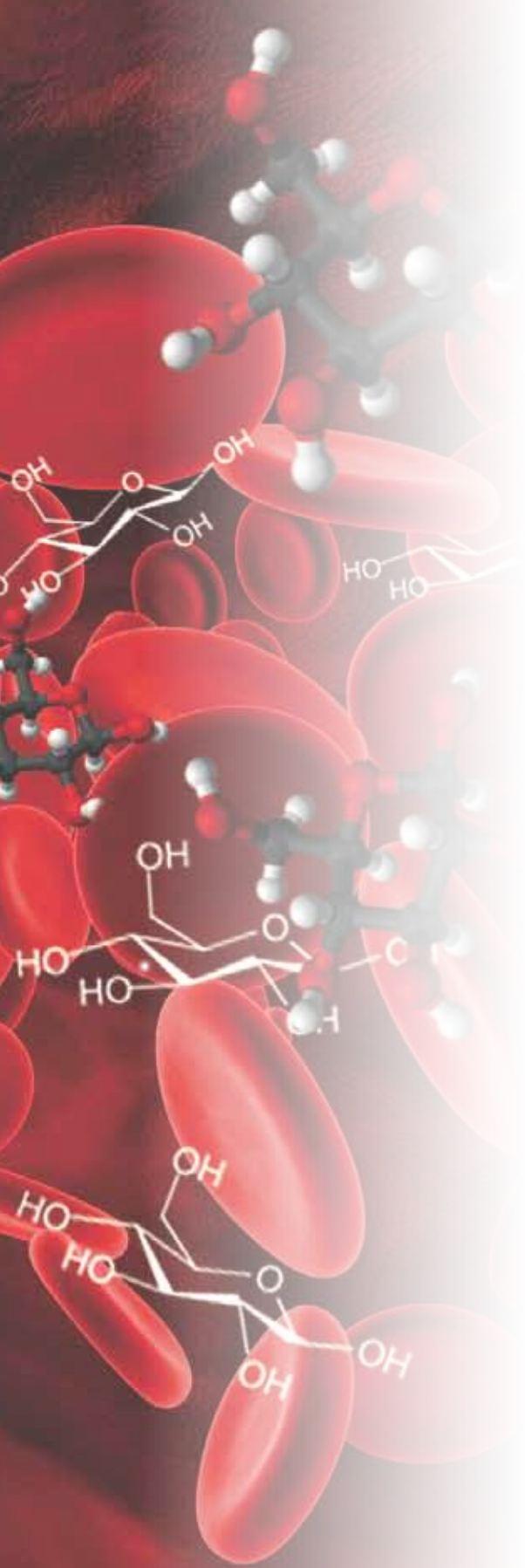

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International Edition 06/2010

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Purified (PF) = Purified (Preservative free); FC = Flow Cytometry; ICC = Immunocytochemistry; IP = Immunoprecipitation; IHC = Immunohistochemistry (FS = Frozen Sections, PS = Paraffin Sections); WB = Western blot; BP = Blocking Peptide

Introduction

Insulin and Diabetes

Diabetes is a chronic metabolic disorder affecting ~5% of the population in industrialized nations. The disease can be divided into two major types referred to as type 1 and type 2. Type 1 diabetes results from autoimmune destruction of pancreatic β-cells. This leads to a complete dependence on exogenous insulin to regulate blood glucose levels. The presence of auto-islet antibodies (glutamic acid decarboxylase (GAD), insulin and insulinoma antigen-3) is the best current marker to distinguish between diabetes type 1 and type 2.

The more prevalent form, type 2 diabetes, accounts for more than 90% of patients. Type 2 diabetes is characterized by the abnormal metabolism of glucose and fat. Several studies have established that type 2 diabetes is caused by a combination of insulin resistance in skeletal muscle, liver and adipose tissue and impaired insulin secretion from the pancreatic β-cells. Pancreatic β-cell dysfunction is a key element in the pathogenesis of type 2 diabetes. The reasons for β-cell failure are not completely understood. Several theories exist to explain the decrease in insulin secretion. These include a reduction of β-cell mass and impaired β-cell function through either β-cell exhaustion, desensitization to glucose stimulation, deposition of islet amyloid or lipotoxicity. With time, progressive β-cell failure leads to insulin deficiency and hyperglycemia. Hyperglycemia is the hallmark of type 2 diabetes and contributes to the pathogenesis of diabetes by impairing both insulin action and insulin secretion. Further progression of diabetes leads to the development of diabetic complications which include various micro-vascular (retinopathy, nephropathy and neuropathy) and macrovascular (cardiovascular and cerebrovascular) disorders.

A model for the development of type 2 diabetes was proposed by J.M. Fernandez-Real & J.C. Pickup (Figure 1). In this model several environmental risk factors such as diet, obesity, exercise, stress and age are thought to reduce insulin release and action in individuals with a susceptibility to the disease.

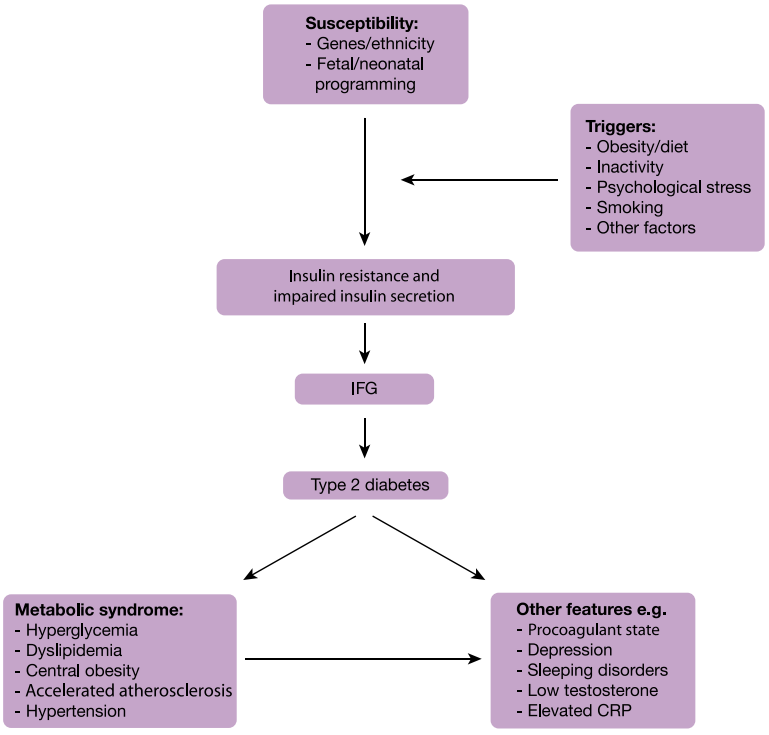

FIGURE 1: A model for the development of type 2 diabetes. Diabetes and the metabolic syndrome develop when environmental trigger factors, such as obesity, cause insulin resistance and impaired insulin secretion in genetically or otherwise susceptible people. Abbreviation: IGT/IFG, impaired glucose tolerance/impaired fasting glucose. Adapted from: Innate immunity, insulin resistance and type 2 diabetes: J.M. Fernandez-Real & J.C. Pickup; Trends Endocrinol. Metab. **19,** 10 (2008).

In addition it was suggested that a disorder of the innate immune system is responsible for the pathophysiology of type 2 diabetes, insulin resistance and several other chronic diseases such as atherosclerosis. In the proposed model (Figure 2), type 2 diabetes is associated with a general activation of the innate immune system, in which there is a chronic, cytokine-mediated state of low grade inflammation. This would explain most pathophysiologies of type 2 diabetes, including insulin resistance and impaired β-cell function, and many of the associated clinical conditions such as atherosclerosis and dyslipidemia.

LITERATURE REFERENCES:

The twentieth century struggle to decipher insulin Signaling: P. Cohen; Nat. Rev. Mol. Cell Biol. **7,** 867 (2006) (Review) ▪ Role of insulin, adipocyte hormones, and nutrient-sensing pathways in regulating fuel metabolism and energy homeostasis: a nutritional perspective of diabetes, obesity, and cancer: S. Marshall; Sci. STKE **2006,** re7 (2006) (Review) ▪ Abnormalities in insulin secretion in type 2 diabetes mellitus: P.J. Guillausseau, et al.; Diabetes Metab. **34 Suppl 2,** S43 (2008) (Review) ▪ Beta-cell failure in type 2 diabetes mellitus: C. Lencioni, et al.; Curr. Diab. Rep. **8,** 179 (2008) (Review) ▪ Genes and type 2 diabetes mellitus: L. Groop & V. Lyssenko; Curr. Diab. Rep. **8,** 192 (2008) (Review) ▪ Innate immunity, insulin resistance and type 2 diabetes: J.M. Fernandez-Real & J.C. Pickup; Trends Endocrinol. Metab. **19,** 10 (2008) ▪ Islet inflammation in type 2 diabetes: from metabolic stress to therapy: M.Y. Donath, et al.; Diabetes Care **31 Suppl. 2,** S161 (2008) ▪ Inflammatory mechanisms in the regulation of insulin resistance: H. Tilg & A.R. Moschen; Mol. Med. **14**, 222 (2008)

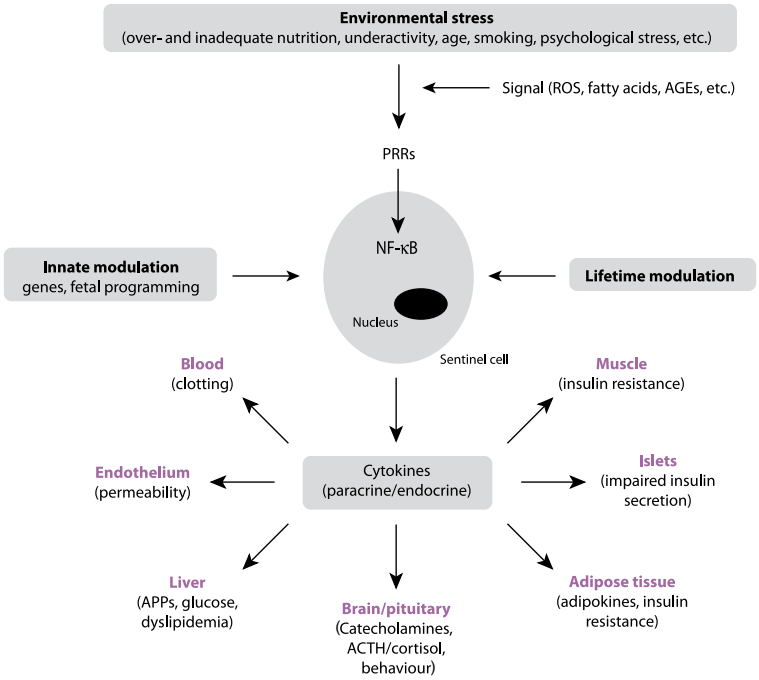

FIGURE 2: Innate immunity and type 2 diabetes. Sentinel cells, such as macrophages, hepatocytes, endothelium and adipocytes, detect environmental threats to the host through pattern-recognition receptors (PRRs). This activates the inflammatory NF-κB pathway, releasing cytokines that act on many cells in the body to produce the clinical and biochemical features of the metabolic syndrome and type 2 diabetes (in parentheses). Abbreviations: ACTH, adrenocorticotrophic hormone; AGE, advanced glycosylation end product; APP, acute-phase protein; ROS, reactive oxygen species. Adapted from: Innate immunity, insulin resistance and type 2 diabetes: J.M. Fernandez-Real & J.C. Pickup; Trends Endocrinol. Metab. **19,** 10 (2008).

Latest Insight

Recent findings indicate that TLRs (Toll-like receptors) - especially TLR4, a sensor for endogenous lipids and free fatty acids - mediate the link between the metabolic and immune systems. Studies on TLR4 deficient mice have shown that these animals become obese, apparently due to overeating, demonstrating once more the important role of TLR4.

LITERATURE REFERENCES:

Toll-like receptors in endocrine disease and diabetes: W. Kanczkowski, et al.; Neuroimmunomodulation **15,** 54 (2008)

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Insulin Signaling

The anabolic hormone insulin is released by the β-cells of the pancreas islets in response to elevated levels of nutrients in the blood. It serves as the key regulator of plasma glucose by maintaining a balance between the intestinal absorption, liver production and cellular uptake of glucose and its metabolism by peripheral tissues. Insulin triggers the uptake of glucose, fatty acids and amino acids into adipose tissue, muscle and the liver and promotes the storage of these nutrients in the form of glycogen, lipids and proteins. At times of starvation, insulin levels are low and this directs insulin-sensitive cells to mobilize stored fuels.

At a cellular level, insulin/insulin-like growth factor (IGF)-signaling regulates multiple processes, including carbohydrate and lipid metabolism, gene transcription, DNA synthesis, apoptosis, and cell proliferation. Insulin and insulin-like growth factors (IGF-1 and IGF-2) bind to members of the insulin receptor tyrosine kinase family, including insulin receptors (IRs) and the IGF-1 receptor (IGF1R). The heterotetrameric insulin receptor consists of 2 extracellular β subunits that bind insulin and 2 transmembrane α subunits with tyrosine kinase activity. Upon ligand binding, the activated insulin receptor phosphorylates tyrosine residues on intracellular substrates such as the insulin receptor substrates (IRS1-4), IRS5/DOK4, IRS/DOK5, Gab-1 and Shc isoforms. This leads to the activation of downstream signaling molecules including the mitogen-activated protein kinase (MAPK) cascade, other serine/threonine kinases (Akt, GSK-3, mTOR, PKC) and phosphoinositide 3-kinase (PI 3-K).

LITERATURE REFERENCE:

Insulin signaling and the regulation of glucose transport: L. Chang, et al.; Mol. Med. **10,** 65 (2004) ▪ Insulin signaling: P. Bevan; J. Cell Sci. **114,** 1429 (2001)

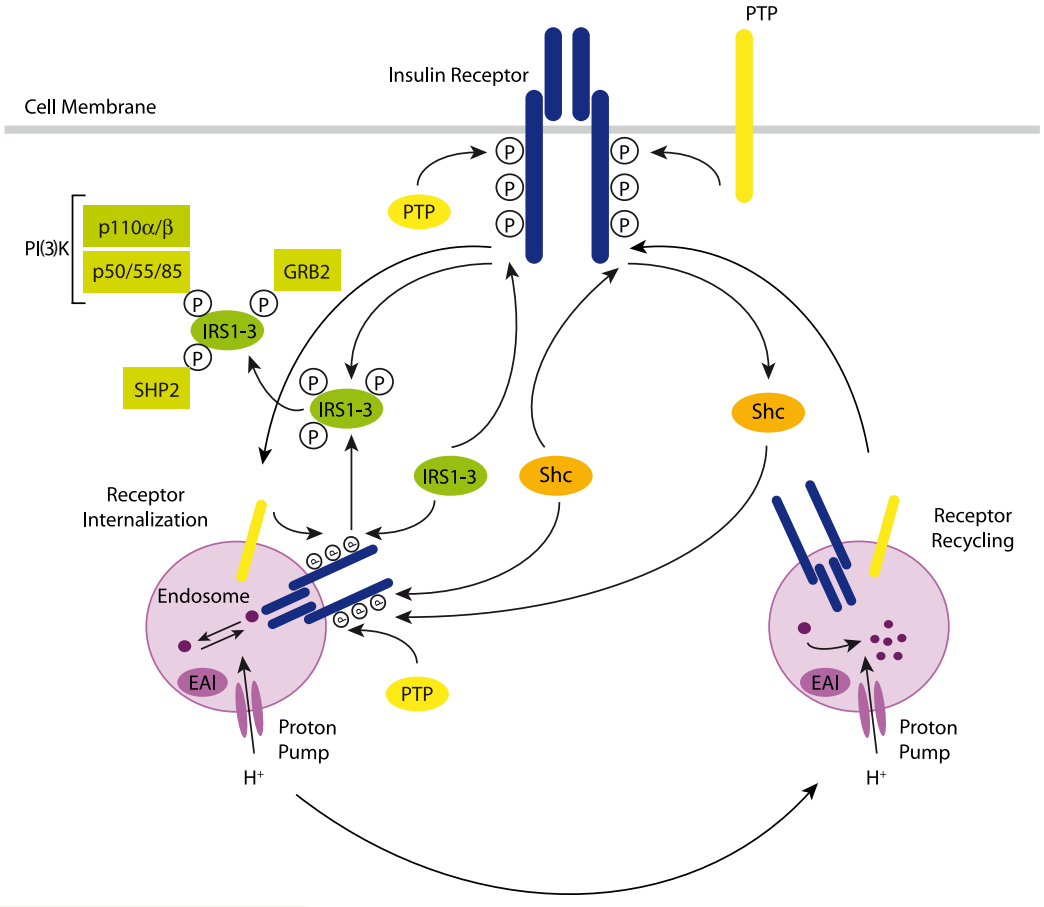


FIGURE 3: Simplified illustration of the insulin signaling pathway. Adapted from: Insulin signaling: P. Bevan; J. Cell Sci. **114,** 1429 (2001).

Insulin

Insulin, mAb (SPM139)
ADI-905-433-1 1 ml

CLONE: SPM139. **ISOTYPE:** Mouse IgG1. **IMMUNOGEN:** Swine insulin. **SPECIFICITY:** Recognizes human, rat, bovine, rabbit and pig Insulin. **APPLICATION:** IHC.

C-Peptide (human), mAb (91/1F9)
ALX-803-049-C100 100 µg

CLONE: 91/1F9. **ISOTYPE:** Mouse IgG2b. **IMMUNOGEN:** Human proinsulin. **SPECIFICITY:** Recognizes human C-peptide. Cross-reacts with human proinsulin. **APPLICATION:** IHC (FS), IP, WB.

Insulin Receptor (IR) Peptides

Insulin receptor (1142-1153)
[H-Thr-Arg-Asp-Ile-Tyr-Glu-Thr-Asp-Tyr-Tyr-Arg-Lys-OH]

BML-P314-0500 0.5 mg

This sequence, is derived from the insulin receptor β-subunit cytoplasmic domain, inclusive of regulatory autophosphorylation sites $Tyr^{1146/1150/1151}$. It has been used as an insulin receptor tyrosine kinase substrate and the phosphorylated peptide as a protein tyrosine phosphatase substrate.

[$pTyr^{1146}$]Insulin receptor (1142-1153)
[H-Thr-Arg-Asp-Ile-pTyr-Glu-Thr-Asp-Tyr-Tyr-Arg-Lys-OH]

BML-P315-0500 0.5 mg

This phosphopeptide sequence, corresponds to the insulin receptor regulatory region. Can be used as a tyrosine phosphatase substrate.

[$pTyr^{1146/1150}$]Insulin receptor (1142-1153)
[H-Thr-Arg-Asp-Ile-pTyr-Glu-Thr-Asp-pTyr-Tyr-Arg-Lys-OH]

BML-P321-0500 0.5 mg

This sequence, is derived from the insulin receptor β-subunit cytoplasmic domain, inclusive of regulatory autophosphorylation sites $Tyr^{1146/1150/1151}$. The unphosphorylated version of this peptide (Prod. Nr. BML-P314) has been used as an insulin receptor kinase substrate. The phosphorylated peptide has been used as a protein tyrosine phosphatase substrate.

[$pTyr^{1146/1150/1151}$]Insulin receptor (1142-1153)
[H-Thr-Arg-Asp-Ile-pTyr-Glu-Thr-Asp-pTyr-pTyr-Arg-Lys-OH]

BML-P318-0500 0.5 mg

This phosphopeptide can be used as a substrate for protein tyrosine phosphatases.

[$pTyr^{1150}$]Insulin receptor (1142-1153)
[H-Thr-Arg-Asp-Ile-Tyr-Glu-Thr-Asp-pTyr-Tyr-Arg-Lys-OH]

BML-P316-0500 0.5 mg

This phosphopeptide corresponds to the insulin receptor regulatory region. Can be used as a tyrosine phosphatase substrate.

[$pTyr^{1151}$]Insulin receptor (1142-1153)
[H-Thr-Arg-Asp-Ile-Tyr-Glu-Thr-Asp-Tyr-pTyr-Arg-Lys-OH]

BML-P317-0500 0.5 mg

This phosphopeptide corresponds to the insulin receptor regulatory region. Can be used as a tyrosine phosphatase substrate.

Insulin receptor phosphopeptide, sampler pack
BML-P319-0001 1 Kit

Contains 0.5 mg each of the insulin receptor peptides (BML-P314, BML-P315, BML-P316, BML-P317, BML-P318 and BML-P321).

Insulin Receptor (IR) Antibodies

Product	Specificity	Application	Prod. No.	Size
[$pTyr^{1150}$/Tyr^{1151}]Insulin receptor, mAb (10C3)	Human	ELISA, WB	ADI-905-645-100	100 µg
[$pTyr^{1158/1162/1163}$]Insulin receptor and [$pTyr^{1131/1135/1136}$]IGF-1 receptor, pAb	Human	WB	BML-SA392-0020 BML-SA392-0100	20 µl 100 µl
[$pTyr^{1158}$]Insulin receptor and [$pTyr^{1131}$]IGF-1 Receptor (human), pAb	Human	WB	BML-SA390-0020 BML-SA390-0100	20 µl 100 µl
[$pTyr^{1322}$]Insulin receptor, mAb (21G12)	Human, mouse and dog	ELISA, WB	ADI-905-646-100	100 µg
[$pTyr^{972}$]Insulin receptor, pAb	Human, mouse and (rat)	WB	ADI-CSA-720-E	100 µl
Insulin receptor β subunit, mAb (CT-3)	Human, mouse, rat and monkey	IHC, WB	BML-SA432-0100	100 µg
Insulin receptor β subunit, mAb (C18C4)	Human	WB	ADI-905-683-100	100 µg
Insulin receptor, mAb (9H4)	Human, mouse, rat and dog	ELISA, IHC, WB	ADI-905-647-100	100 µg

Insulin Receptor Substrates (IRS) Peptide and Antibodies

IRS-1 (Tyr^{608}) peptide

[H-Lys-Lys-His-Thr-Asp-Asp-Gly-Tyr-Met-Pro-Met-Ser-Pro-Gly-Val-Ala-OH]

BML-P320-0001 1 mg

This sequence, is derived from (insulin receptor substrate-1) (IRS-1) inclusive of Tyr-608 (mouse) -612 (human). It contains the insulin receptor tyrosine kinase substrate motif YMXM (Tyr-Met-X-Met). This peptide has been used as a substrate for purified insulin receptor (K_m=90 µM) and other tyrosine kinases in phosphocellulose binding assays. The tyrosine phosphorylated version of this peptide binds to phosphatidylinositol 3-kinase (PI 3-K) SH2 domain and activates the enzyme.

[pTyr^{612}]IRS-1, pAb

ADI-CSA-725-E 100 µl

From rabbit. **IMMUNOGEN:** Synthetic phospho-peptide derived from the sequence of human IRS-1 (sequence identical with mouse, rat and chicken). **SPECIFICITY:** Recognizes human, (mouse, rat and chicken) IRS-1. **APPLICATION:** WB.

[pTyr^{1229}]IRS-1 (human), pAb

BML-SA393-0020 20 µl

BML-SA393-0100 100 µl

From rabbit. **IMMUNOGEN:** Synthetic peptide corresponding to a portion of human IRS-1 (insulin receptor substrate-1) phosphorylated at Tyr^{1229}. **SPECIFICITY:** Recognizes human IRS-1 phosphorylated at Tyr^{1229}. **APPLICATION:** WB. **BP:** BML-SP393.

[pTyr^{941}]IRS-1 (human), pAb

BML-SA394-0020 20 µl

BML-SA394-0100 100 µl

From rabbit. **IMMUNOGEN:** Synthetic peptide corresponding to a portion of human IRS-1 (insulin receptor substrate-1) phosphorylated at Tyr^{941}. **SPECIFICITY:** Recognizes human IRS-1 phosphorylated at Tyr^{941}. Tyrosine 941 of IRS-1 is in a phosphatidylinositol 3-kinase (PI 3-K) binding site motif. **APPLICATION:** WB. **BP:** BML-SP394.

[pTyr^{896}]IRS-1 (human), pAb

BML-SA396-0020 20 µl

BML-SA396-0100 100 µl

From rabbit. **IMMUNOGEN:** Synthetic peptide corresponding to a portion of human IRS-1 (insulin receptor substrate-1) phosphorylated at Tyr^{896}. **SPECIFICITY:** Recognizes human IRS-1 phosphorylated at Tyr^{896}. Tyrosine 896 of IRS-1 is a Grb-2 SH2 domain binding site. **APPLICATION:** WB. **BP:** BML-SP396.

Insulin Receptor (IR) Inhibitors

Hydroxy-2-naphthalenylmethylphosphonic acid

[HNMPA]

BML-EI247-0005 5 mg

BML-EI247-0025 25 mg

Membrane impermeable inhibitor of insulin receptor tyrosine kinase activity (IC_{50}=100µM). Was shown to inhibit both tyrosine and serine autophosphorylation by the human insulin receptor.

HNMPA-(AM)$_3$

BML-EI248-0005 5 mg

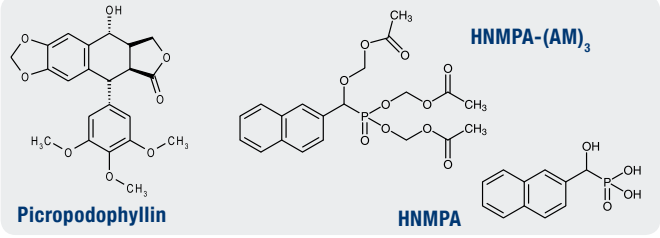
BML-EI248-0025 25 mg

Cell permeable analog of HNMPA. Inhibits insulin receptor tyrosine kinase activity (IC_{50}=100µM) and insulin-stimulated glucose oxidation in isolated rat adipocytes (IC_{50}=10µM). Has no effect on PKA (at concs. up to 1mM) or PKC (at concs. up to 420µM).

Picropodophyllin

BML-EI372-0001 1 mg

Potent and selective inhibitor of insulin-like growth factor 1 receptor (IGF-1R, IC_{50}=6nM). Efficiently blocks IGF-1R activity, reduces pAKT and pERK1/2, induces apoptosis in IGF-1R-positive tumor cells and causes complete tumor regression in xenografted and allografted mice. Picropodophyllin downregulates IGF-1R by interfering with the action of β-arrestin 1/MDM2.



Insulin Receptor (IR) Kinase

Insulin receptor kinase β subunit (human), (rec.) (GST-tag)

BML-SE195-0020 20 µg

Produced in insect cells. The 46kDa cytoplasmic domain of the β-subunit of the human insulin receptor (βIRK) (aa 941-1343) is fused to a GST-tag. **APPLICATION:** Enzyme kinetics and inhibition studies and for phosphorylation of target substrates.

Insulin receptor kinase β subunit (human) (rec.) (His-tag)

BML-SE516-0020 20 µg

Produced in insect cells. The cytoplasmic (kinase) domain of human insulin receptor is fused to a His-tag.

Shc

Shc, pAb
ALX-210-535-R100 100 µl

From rabbit. **IMMUNOGEN:** Recombinant human Shc portion (aa 1180-1620). **SPECIFICITY:** Recognizes human, mouse and hamster p46shc, p52shc and p66shc isoforms of phosphorylated and unphosphorylated Shc. **APPLICATION:** ELISA, IP, WB.

Shc, mAb (11F6)
ADI-905-665-100 100 µg

CLONE: 11F6. **ISOTYPE:** Mouse IgG1.**IMMUNOGEN:** Synthetic peptide derived from sequence near the carboxy-terminus of Shc, conjugated to hemocyanin. **SPECIFICITY:** Recognizes human and mouse Shc. **APPLICATION:** ICC, IHC, WB.

[pSer^{36}]Shc, mAb (6E10)
ALX-804-358-C100 100 µg

CLONE: 6E10. **ISOTYPE:** Mouse IgG1. **IMMUNOGEN:** Synthetic peptide corresponding to aa 33-39 (E^{33}LPpSPSA^{39}) of shc phosphorylated at Ser^{36}. **SPECIFICITY:** Recognizes human, mouse and dog shc phosphorylated at Ser^{36}. Does not cross-react with non-phosphorylated shc. **APPLICATION:** WB.

[pTyr^{317}]Shc, mAb (15E11)
ALX-804-359-C100 100 µg

CLONE: 15E11. **ISOTYPE:** Mouse IgG1. **IMMUNOGEN:** Synthetic peptide corresponding to a portion of Shc phosphorylated at Tyr^{317}. **SPECIFICITY:** Recognizes human, mouseand dog Shc phosphorylated at Tyr^{317}. **APPLICATION:** IHC, WB.

[pTyr$^{239/240}$]Shc, mAb (1E3)
ALX-804-357-C100 100 µg

CLONE: 1E3. **ISOTYPE:** Mouse IgG1. **IMMUNOGEN:** Synthetic peptide corresponding to aa 236-243 (D^{236}HQpYpYNDF^{243}) of shc phosphorylated at Tyr^{239} and Tyr^{240}. **SPECIFICITY:** Recognizes human, mouse and dog p46shc, p52shc and p66shc when phosphorylated at Tyr$^{239/240}$. Does not cross-react with non-phosphorylated shc. **APPLICATION:** IHC, WB.

Insulin-like Growth Factor

Insulin-like growth factor (IGF)-1 is a powerful mitogenic peptide synthesized predominantly by the liver. It circulates in the plasma and is one of the main mediators of the actions of growth hormone (GH). Postnatal, IGF-1 promotes cell proliferation, differentiation and survival. However, IGF-1 has also effects on insulin sensitivity and several studies suggest that IGF-1 levels may be altered in insulin resistance states and type 2 diabetes.

LITERATURE REFERENCE:

The role of IGF-I and its binding proteins in the development of type 2 diabetes and cardiovascular disease: V.A. Ezzat, et al.; Diabetes Obes. Metab. **10,** 198 (2008) (Review)

IGF-1 (human), (rec.)
ADI-908-059-020 20 µg

Recombinant human IGF-1 protein expressed in *E. coli*.

[pTyr^{1316}]IGF-1 receptor, mAb (2B9)
ADI-905-643-100 100 µg

CLONE: 2B9. **ISOTYPE:** Mouse IgG1. **IMMUNOGEN:** Synthetic phospho-peptide derived from the sequence of human IGF-1 receptor, conjugated to hemocyanin. **SPECIFICITY:** Recognizes human IGF-1 receptor. **APPLICATION:** ELISA, WB.

IGF-1 receptor kinase β (human), (rec.) (GST-tag)
BML-SE232-0020 20 µg

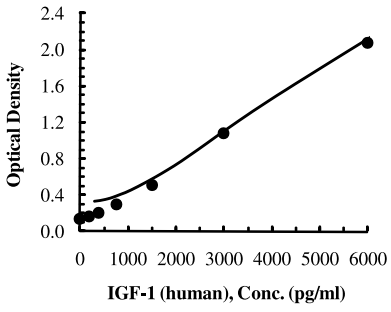
Produced in baculovirus. The 46kDa cytoplasmic domain of the β-subunit of human IGF-1 receptor kinase (IGF-1RK) (aa 929-1337) is fused to GST. **APPLICATION:** Kinetic studies, inhibitor screening, and phosphorylation of target substrates.

IGF-1 receptor, mAb (7G11)
ADI-905-644-100 100 µg

CLONE: 7G11. **ISOTYPE:** Mouse IgG1. **IMMUNOGEN:** Synthetic peptide derived from the sequence near the carboxy-terminus of human IGF-1 receptor, conjugated to hemocyanin . **SPECIFICITY:** Recognizes human IGF-1 receptor. **APPLICATION:** WB.

IGF-1 (human), EIA kit
ADI-900-150 96 wells

For the quantitative determination of human IGF-1 in plasma and serum. **SENSITIVITY:** 48.5 pg/ml (range 187 - 6,000 pg/ml).



HIGHLIGHT

Purified (PF) = Purified (Preservative free); FC = Flow Cytometry; ICC = Immunocytochemistry; IP = Immunoprecipitation; IHC = Immunohistochemistry (FS = Frozen Sections, PS = Paraffin Sections); WB = Western blot; BP = Blocking Peptide

Protein Tyrosine Phosphatases [PTPases]

Protein tyrosine phosphatases (PTPases) are important in cellular signal transduction and metabolism. The PTPase family can be divided into two categories: Intracellular (non-receptor type) PTPases (e.g. PTP1B); and transmembrane (receptor type) PTPases (e.g. LAR). Several PTPases have been described to catalyze the dephosphorylation of the insulin receptor. These include PTPα, LAR, CD45, PTPε, SHP2, TC-PTP and PTP1B. However, the implication of these PTPases in the regulation of insulin signaling is still controversial. The most convincing data supports a critical role for PTP1B in insulin action, which makes PTP1B an attractive candidate for the drug design for type 2 diabetes and obesity.

LITERATURE REFERENCES:

Protein tyrosine phosphatases: the quest for negative regulators of insulin action: E. Asante-Appiah & B.P. Kennedy; Am. J. Physiol. Endocrinol. Metab. **284,** E663 (2003) (Review) ▪ Involvement of the small protein tyrosine phosphatases TC-PTP and PTP1B in signal transduction and diseases: from diabetes, obesity to cell cycle, and cancer: N. Dube & M.L. Tremblay; Biochim. Biophys. Acta **1754,** 108 (2005) ▪ Protein tyrosine phosphatases: structure-function relationships: L. Tabernero, et al.; FEBS J. **275,** 867 (2008) (Review)

PTP1B

PTP1B (human), (rec.)

BML-SE332-0050 50 µg

Produced in *E. coli*. Human PTP1B (protein tyrosine phosphatase 1B) (aa 1-322). **APPLICATION:** Useful for the study of tyrosine phosphatase kinetics, substrate specificity and for screening inhibitors.

[pTyr^{992}]EGF receptor (988-998)

[EGFR (988-998); H-Asp-Ala-Asp-Glu-pTyr-Leu-Ile-Pro-Gln-Gln-Gly-OH)]

BML-P323-0001 1 mg

This sequence, DADEpYLIPQQG, is from an autophosphorylation site (Tyr^{992}) of epidermal growth factor receptor (EGFR). An excellent substrate for mammalian PTP1B with K_m=3.9 µM) and *Yersinia* PTPase. May be used in non-radioactive phosphatase assays incorporating the BIOMOL GREEN™ reagent (Prod. Nr. BML-AK111).

PTP1B drug discovery kit

BML-AK822-0001 1 Kit

The PTP1B Tyrosine Phosphatase Drug Discovery Kit is a colorimetric, non-radioactive assay designed to measure the phosphatase activity of purified PTP1B. This 96 well assay is useful for screening inhibitors and modulators of PTP1B activity. The kit includes human, recombinant PTP1B (residues 1-322; MW=37.4 kDa), expressed in *E. coli*. The detection of free-phosphate released is based on the classic Malachite green assay and offers the advantages of convenient, 1-step detection and excellent sensitivity, without radioactivity.

LAR

LAR (human), (rec.)

BML-SE113-0200 200 U

Produced in *E. coli*. Soluble catalytic LAR-D1 domain (350 aa).

LAR Tyrosine Phosphatase Assay Kit for Drug Discovery

BML-AK815-0001 1 Kit

The LAR tyrosine phosphatase assay kit is a colorimetric, non-radioactive assay designed in a 96 well microplate format. It may be used to screen inhibitors and modulators of LAR phosphatase activity, and perform other experiments on LAR enzyme kinetics. The kit includes purified human LAR cytoplasmic domain (residues 1275-1613; MW=37 kDa), expressed in an *E. coli* expression system. The assay entails LAR dephosphorylation of a synthetic 12-mer peptide based on the regulatory autophosphorylation region of the IR β subunit cytoplasmic domain (residues 1142-1153) and phosphorylated at LAR's preferred dephosphorylation site Tyr-1146. The phosphate released is quantified with the BIOMOL GREEN™ reagent. A tyrosine phosphatase inhibitor, RWJ-60475 is included as a control "hit" for inhibitor screening.

HIGHLIGHT

TC-PTP

T cell protein tyrosine phosphatase (human), (rec.)

BML-SE114-0200 200 U

Produced in *E. coli*. T cell phosphatase with a C-terminal 11 kDa deletion (TCΔC11) (aa 1-317).

PTP-IA2 [Protein Tyrosine Phosphatase IA2]

PTP-IA2 (catalytic domain) (human), (rec.) (GST-tag)

BML-SE278-0020 20 µg

Produced in *E. coli*. The catalytic domain of human PTP-IA2 (protein tyrosine phosphatase IA2) (aa 693-970) is fused at the N-terminus to a GST-tag. **APPLICATION:** Study of enzyme kinetics and regulation, dephosphorylation of target substrates, and inhibitor screening.

PTP-IA2 (intracellular domain) (618-628), mAb (98/4H6)

ALX-803-056-C100 100 µg

CLONE: 98/4H6. **ISOTYPE:** Mouse IgG1. **IMMUNOGEN:** Recombinant human IA-2ic (protein tyrosine phosphatase IA2 (intracellular domain)). **SPECIFICITY:** Recognizes an epitope (aa 618-628) of human, mouse and rat IA-2ic. **APPLICATION:** IHC (FS), IP, WB.

PTP-IA2 (intracellular domain) (605-772), mAb (97/4D9)

ALX-803-057-C100 100 µg

CLONE: 97/4D9. **ISOTYPE:** Mouse IgG1. **IMMUNOGEN:** Recombinant human IA-2ic (protein tyrosine phosphatase IA2 (intracellular domain)). **SPECIFICITY:** Recognizes an epitope (aa 605-772) of human, mouse and rat IA2ic. **APPLICATION:** IHC (FS), IP, WB.

PTP-IA2 (intracellular domain) (771-979), mAb (103/2C4)

ALX-803-058-C100 100 µg

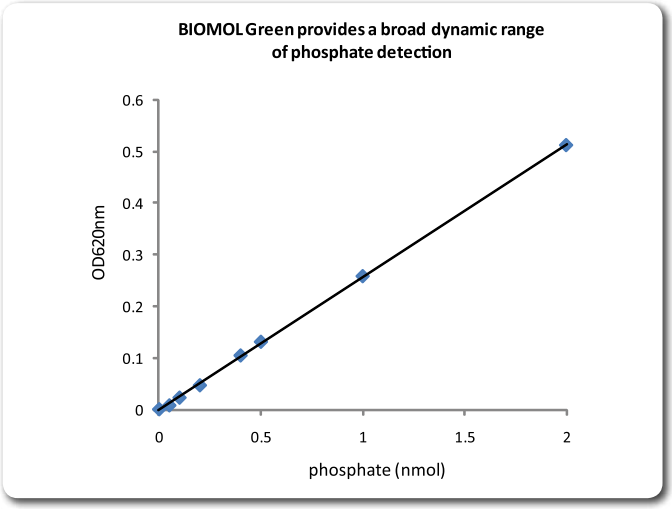
CLONE: 103/2C4. **ISOTYPE:** Mouse IgG1. **IMMUNOGEN:** Recombinant human IA-2ic (protein tyrosine phosphatase IA2 (intracellular domain)). **SPECIFICITY:** Recognizes an epitope (aa 771-979) of human, mouse and rat IA2ic. **APPLICATION:** IHC (FS), IP, WB.

Related Products

BIOMOL Green™ Reagent

BML-AK111-0250 250 ml

BIOMOL GREEN™ provides a simple and convenient method for colorimetric phosphate quantitation (abs. 600-680 nm). Unlike other molybdate/malachite green-based assays, BIOMOL GREEN™ doesn't require multiple solutions or reagents prepared fresh on the day of the assay. BIOMOL GREEN™ is extremely stable (>6 mos. at 4°C) and is simply mixed, at room temperature, with any enzymatic reaction that has released free phosphate. Reported applications include assays for phospholipid phosphatases, tyrosyl-tRNA synthetase (coupled with pyrophosphatase) and a viral RNA triphosphatase. BIOMOL GREEN™ has perhaps been most widely applied to protein phosphatase assays. Typically, a protein phosphatase (e.g. PTP1B (Prod. No. BML-SE332) or LAR (Prod. No. BML-SE113)) is simply incubated with an appropriate phosphopeptide (e.g. IR5,9,10 (Prod. No. BML-P318)). Addition of BIOMOL GREEN™ stops the reaction and begins color development, which is read 20-30 min later. BIOMOL GREEN™ may be used in cuvette or microplate-based assays and is ideal for high-throughput applications. Each kit comes with a standardized phosphate solution for assay calibration.



PI 3-Kinase [PI 3-K] Pathway

The PI 3-K (phosphatidylinositol 3-kinase) pathway plays a pivotal role in the metabolic and mitogenic action of insulin. PI 3-K is a heterodimeric enzyme consisting of a p85 regulatory subunit as well as a p110 catalytic subunit. It gets activated by several hormones including growth factors and insulin. Upon activation, PI 3-K catalyzes the phosphorylation of phosphoinositols (e.g. the formation of PIP3 from PIP2), which subsequently leads to the recruitment of Akt (PKB; protein kinase B) to the cell membrane. Activated Akt regulates the activity of many downstream proteins involved in multiple aspects of cellular physiology (see Figure 4). Among others, Akt phosphorylates and regulates components of the glucose transporter 4 (GLUT4) complex, protein kinase C (PKC) isoforms and GSK-3, all of which are critical for insulin-mediated metabolic effects.

LITERATURE REFERENCES:
Phosphoinositide 3-kinase in disease: timing, location, and scaffolding: M.P. Wymann & R. Marone; Curr. Opin. Cell Biol. **17,** 141 (2005) (Review) ▪ Targeting phosphoinositide 3-kinase: moving towards therapy: R. Marone, et al.; Biochim. Biophys. Acta **1784,** 159 (2008) (Review)

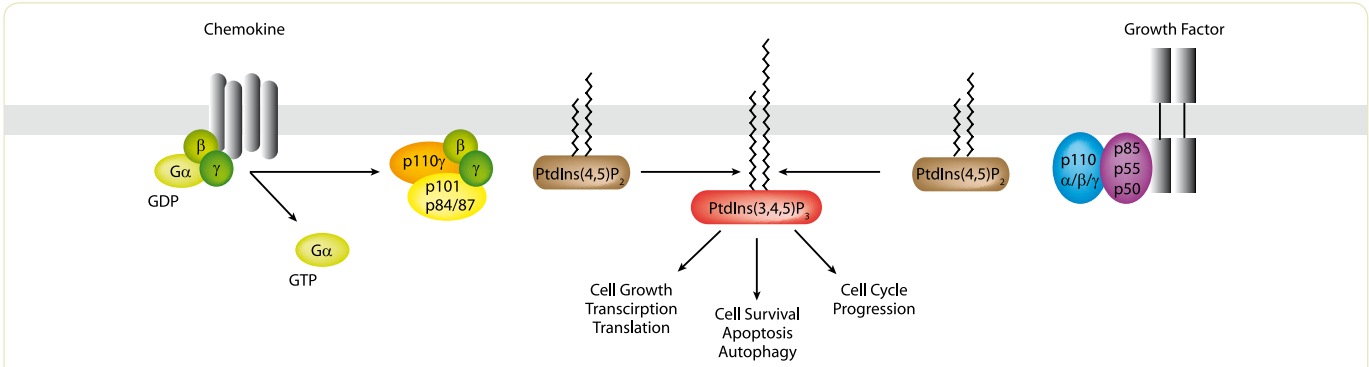


FIGURE 4: Simplified activation scheme of class I PI 3-Ks. Heterodimeric PI 3-Kα, PI 3-Kβ, and PI 3-Kδ complexes are activated downstream of growth factors, cytokine receptors and their substrates, whereas PI 3-Kγ activation is triggered downstream of G protein-coupled receptors (GPCRs). *Adapted from: Targeting phosphoinositide 3-kinase: moving towards therapy: R. Marone, et al.; Biochim. Biophys. Acta* ***1784,*** *159 (2008).*

PI 3-Kinase Proteins

PI 3-kinase p110α/p85α (human), (rec.)

BML-SE436-0020 20 µg

Produced in insect cells. Complex of human full length p110α and p85α subunits of PI 3-kinase. **APPLICATION:** Kinetic and functional studies, phosphorylation of target substrates, drug screening.

PI 3-kinase p110α/p85 (bovine), (rec.)

ALX-201-119-C005 5 µg

Produced in Sf9 cells. Untagged bovine PI 3-K p110α/p85 dimer.

PI 3-kinase p110γ (human), (rec.)

ALX-201-055-C010 10 µg

Produced in Sf9 cells. Full length human PI 3-kinase p110γ fused at the N-terminus to a His-tag.

LIT: Cloning and characterization of a G protein-activated human phosphoinositide-3 kinase: B. Stoyanov, et al.; Science **269,** 690 (1995) ▪ Lipid kinase and protein kinase activities of G-protein-coupled phosphoinositide 3-kinase gamma: structure-activity analysis and interactions with wortmannin: S. Stoyanova, et al.; Biochem. J. **324,** 489 (1997) ▪ Linkage of G protein-coupled receptors to the MAPK signaling pathway through PI 3-kinase gamma: M. Lopez-Ilasaca, et al.; Science **275,** 394 (1997) ▪ Gbetagamma stimulates phosphoinositide 3-kinase-gamma by direct interaction with two domains of the catalytic p110 subuni: D. Leopoldt, et al.; J. Biol. Chem. **273,** 7024 (1998)

PI 3-Kinase Antibodies

PI 3-kinase, mAb (AB6)

ADI-KAM-PI200-E 100 µg

CLONE: AB6. **ISOTYPE:** Mouse IgG1. **IMMUNOGEN:** Recombinant human p85α protein. **SPECIFICITY:** Recognizes human, mouse and rat PI 3-kinase. **APPLICATION:** ICC, IP, WB.

PI 3-kinase p110δ (human), pAb

ALX-210-747-C200 200 µg

From rabbit. **IMMUNOGEN:** Synthetic peptide corresponding to aa 1026-1044 (S^{1026}WKTKVNWLAHNVSKDNRQ^{1044}) of the C-terminal domain of human PI 3-kinase p110δ. **SPECIFICITY:** Recognizes human PI 3-kinase p110δ. Detects a band of ~110kDa by Western blot. **APPLICATION:** IHC (PS), ICC, WB. **BP:** ALX-165-034.

PI 3-Kinase Activators

PI 3-kinase SH3 domain binding peptide

[H-Arg-Lys-Leu-Pro-Pro-Arg-Pro-Arg-Arg-OH]

BML-P311-0001 1 mg

IRS-1 (Tyr^{608}) peptide

[H-Lys-Lys-His-Thr-Asp-Asp-Gly-Tyr-Met-Pro-Met-Ser-Pro-Gly-Val-Ala-OH]

BML-P320-0001 1 mg

PI 3-kinase Inhibitors

N-Acetyl-Asp-Tyr(2-malonyl)-Val-Pro-Met-Leu-NH_2
ALX-151-026-M001 1 mg

N-Acetyl-Asp-Tyr(PO_3H_2)-Val-Pro-Met-Leu-NH_2
ALX-151-027-M001 1 mg

(±)-Naringenin
ALX-385-010-G001 1 g

AS-252424
ALX-270-465-M001 1 mg
ALX-270-465-M005 5 mg
ALX-270-465-M025 25 mg

AS-604850
ALX-270-461-M001 1 mg
ALX-270-461-M005 5 mg
ALX-270-461-M025 25 mg

AS-605240
ALX-270-462-M001 1 mg
ALX-270-462-M005 5 mg
ALX-270-462-M025 25 mg

Compound 15e
ALX-270-455-M001 1 mg
ALX-270-455-M005 5 mg

Luteolin
ALX-385-007-M010 10 mg
ALX-385-007-M050 50 mg

LY 294002
BML-ST420-0005 5 mg
BML-ST420-0025 25 mg

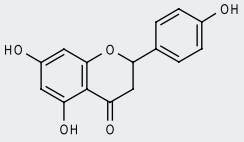
LY-303,511
ALX-270-410-M001 1 mg
ALX-270-410-M005 5 mg

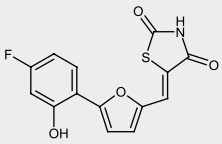
PI-103
ALX-270-460-M001 1 mg
ALX-270-460-M005 5 mg
ALX-270-460-M025 25 mg

PI 3K-SH2-OMT
BML-ST425-0500 0.5 mg

TGX-221
ALX-270-464-C100 100 µg
ALX-270-464-M001 1 mg

Wortmannin
BML-ST415-0001 1 mg
BML-ST415-0005 5 mg
BML-ST415-0020 20 mg


(±)-Naringenin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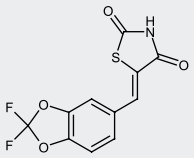
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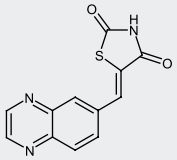
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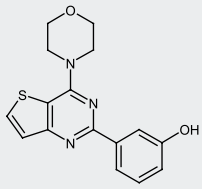
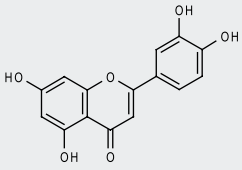
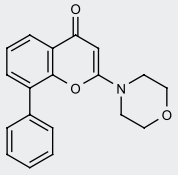
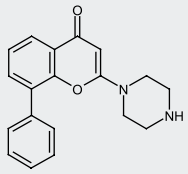

Compound 15e


Luteolin


LY 294002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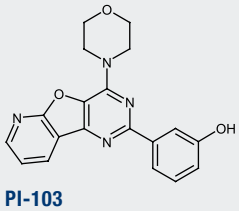
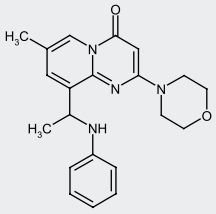
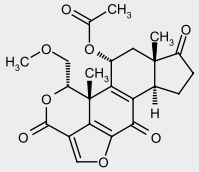

PI-103


TGX-221


Wortmannin

Purified (PF) = Purified (Preservative free); FC = Flow Cytometry; ICC = Immunocytochemistry; IP = Immunoprecipitation; IHC = Immunohistochemistry (FS = Frozen Sections, PS = Paraffin Sections); WB = Western blot; BP = Blocking Peptide

Akt [PKB; Protein Kinase B]

Phosphorylation Site of the Akt Isoforms

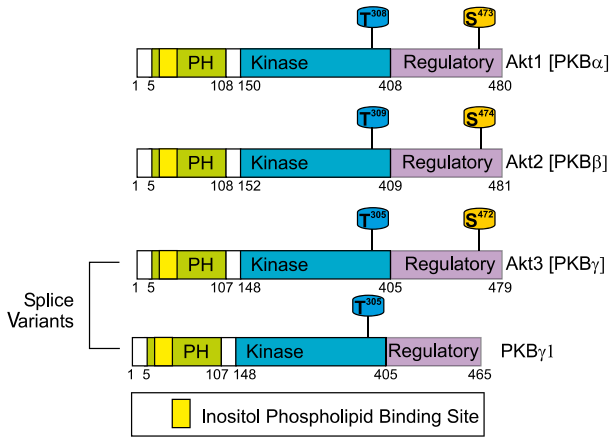


FIGURE 5: Akt Isoforms.

Akt1 shares 81% and 83% amino acid identity with Akt2 and Akt3, respectively. Although the three isoforms show broad tissue distribution, Akt1 is the most ubiquitously expressed. Akt2 is expressed at lower levels than Akt1 except in insulin-responsive tissues where it predominates. In particular, Akt2 is more abundant and more highly activated than Akt1 in adipocytes. Akt3 is expressed in testes and brain. The C-terminal sequence of the three isoforms are shown below. Note that the phosphorylation site differs slightly between the three isoforms.Thus the phosphorylation site Ser^{473} of Akt1 corresponds to Ser^{474} in Akt2 and Ser^{472} in Akt3 respectively.

Akt1: V^{461}DSERRPHFPQFS^{473}YSASSTA^{480}
Swiss-Prot-Link: P31749
Akt2: L^{461}LELDQRTHFPQFS^{474}YSASIRE^{481}
Swiss-Prot-Link: P31751
Akt3: D^{461}NERRPHFPQFS^{472}YSASGRE^{479}
Swiss-Prot-Link: Q9Y243

Akt Proteins

Akt1 (human) (rec.) (GST-tag)

BML-SE416-0005 5 µg
BML-SE416-0020 20 µg

Produced in insect cells. Full length active enzyme. **APPLICATION:** Kinetic and functional studies, phosphorylation of target substrates, drug screening.

Akt2 (human), (rec.)

ADI-PPK-411-Z 5 µg

Active recombinant human full length Akt2 protein expressed by baculovirus in Sf9 insect cells.

Akt2 (human), (rec.) (GST-tag)

BML-SE247-0020 20 µg

Produced in a baculovirus expression system. The ΔPH domain of human Akt2 (PKBβ; protein kinase B β) (aa 119-481) is fused at the N-terminus to a GST-tag. **APPLICATION:** Useful for kinetic, substrate, inhibitor studies and drug screening.

[T^{308}E, S^{473}D]Akt2 (human) (rec.) (GST-tag)

BML-SE248-0020 20 µg

Produced in insect cells. ΔPH domain of human Akt2 (PKBβ; protein kinase B β) (aa 119-481) fused to a GST-tag. Constitutively active due to S^{473}D and T^{308}E mutations. **APPLICATION:** Useful for kinetic, substrate and inhibitor studies. 5x more active than BML-SE247.

Akt3 (human), (rec.) (GST-tag)

BML-SE369-0005 5 µg
BML-SE369-0020 20 µg

Produced in insect cells. Full length active enzyme. **APPLICATION:** Kinetic and functional studies, phosphorylation of target substrates, drug screening.

Akt Substrates

Akt substrate

[H-Arg-Pro-Arg-Ala-Ala-Thr-Phe-OH]

BML-P129-0001 1 mg

Derived from variations on the GSK-3 phosphorylation site, it conforms to the Akt/PKB consensus motif, Arg-Xaa-Arg-Xaa-Xaa-(Ser/Thr). Unlike other Akt-PKB peptide substrates, it is not phosphorylated by p70 S6 kinase or MAPKAP kinase-1.

PAK4 & Akt substrate

[H-Cys-Lys-Arg-Pro-Arg-Ala-Ala-Ser-Phe-Ala-Glu-OH]

BML-P194-0001 1 mg

Suitable substrate for PAK4, Akt, and PAK7.

Crosstide

[H-Gly-Arg-Pro-Arg-Thr-Ser-Ser-Phe-Ala-Glu-Gly-OH]

BML-P149-0001 1 mg

This peptide sequence corresponds to the sequence of GSK-3 surrounding the serine phosphorylated by MAP kinase activated protein kinase (MAPKAP kinase-1) and p70 S6 kinase. Acts as a substrate for Akt (PKB), K_m=4µM. Useful in phosphocellulose kinase assays.

Crosstide (biotinylated)

[Biotin-Gly-Arg-Pro-Arg-Thr-Ser-Ser-Phe-Ala-Glu-Gly-OH]

BML-P191-0001 1 mg

This peptide sequence corresponds to the sequence of GSK-3 surrounding the serine phosphorylated by MAP kinase activated protein kinase (MAPKAP kinase-1) and p70 S6 kinase. Acts as a substrate for Akt (PKB), K_m=4µM. The N-terminal biotin allows this peptide to be used in kinase assays with streptavidin-bound membranes.

Akt Antibodies

Product	Specificity	Application	Prod. No.	Size
Akt, mAb (5C10)	Human, mouse, rat, dog	WB	ALX-804-553-C100	100 µg
Akt, mAb (19G7)	Human, mouse, rat, dog, hamster	ELISA, IP, WB	ALX-803-303-C100	100 µg
Akt, pAb	Human, mouse, rat, *drosophila*	WB	ALX-210-226-C200	200 µg
Akt, pAb	Human, mouse and rat	WB	ADI-KAP-PK004-D ADI-KAP-PK004-F	50 µg 200 µg
Akt (mouse), pAb	Mouse	ELISA, IP, WB	ALX-210-534-R100	100 µl
Akt (dephosphorylated), mAb (11A11)	Human, mouse, rat, dog	IHC, WB	ALX-804-400-C100	100 µg
[pSer^{473}]Akt, mAb (11E6)	Human, mouse, rat, dog	FC, IHC, WB	ALX-804-401-C100	100 µg
[pSer^{473}]Akt, pAb	Mouse, (human, rat, bovine and chicken)	WB	ADI-905-773-100	100 µg
[pThr^{308}]Akt, pAb	Human and mouse	WB	ADI-KAP-PK007-E	100 µl
Akt1, mAb (5G12)	Human, rat, dog	IHC, WB	ALX-804-633-C100	100 µg
Akt1/2, pAb	Human, mouse and rat	WB	ADI-905-755-100	100 µg
Akt2, pAb	Human, mouse, rat, bovine, chicken, dog, guinea pig, hamster, monkey, pig, rabbit, sheep and *Xenopus*	ELISA, WB	ADI-KAP-PK008-E	100 µg
Akt2 (human), mAb (8B7)	Human	IHC, WB	ALX-804-634-C100	100 µg
Akt3 (human), mAb (66C1247.1)	Human	WB	ALX-804-379-C100	100 µg
Akt3, mAb (9B2)	Human and mouse	WB	ADI-905-821-100	100 µl

Akt Assay Kits

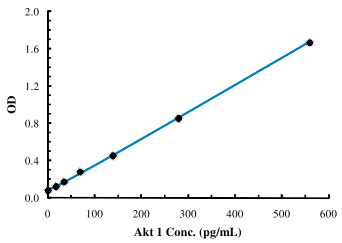
NEW

[pSer^{473}]Akt1/2 EIA kit

ADI-900-162 — 96 wells

For the quantitative determination of [pSer^{473}]Akt1/2 in cell lysates of human, mouse, and rat origin.

SENSITIVITY: 5.5 pg/ml (range 17.5 - 560 pg/ml).



Akt Kinase activity kit

ADI-EKS-400A — 96 wells

For the measurement of Akt in partially purified, purified, or crude enzyme preparations from any species. This is a non-radioactive Akt kinase activity assay, providing a safe, rapid and reliable method for the screening of inhibitors or activators of Akt and for quantitating the activity of Akt in purified or partially purified enzyme preparations. The Akt Kinase activity kit is based on a solid phase enzyme immunoassay (EIA) that utilizes a specific synthetic peptide as a substrate for Akt and a polyclonal antibody that recognizes the phosphorylated form of the substrate. The assay is designed for the analysis of Akt (1, 2, 3) activity in the solution phase.

HIGHLIGHT

Purified (PF) = Purified (Preservative free); FC = Flow Cytometry; ICC = Immunocytochemistry; IP = Immunoprecipitation; IHC = Immunohistochemistry (FS = Frozen Sections, PS = Paraffin Sections); WB = Western blot; BP = Blocking Peptide

Akt Inhibitors

BML-257

BML-EI336-0010	10 mg
BML-EI336-0050	50 mg

Deguelin

ALX-350-118-M005	5 mg
ALX-350-118-M025	25 mg

(-)-Epigallocatechin gallate

ALX-270-263-M010	10 mg
ALX-270-263-M050	50 mg

ML-9

BML-EI153-0010	10 mg
BML-EI153-0050	50 mg

PKC-412

BML-EI370-0001	1 mg
BML-EI370-0005	5 mg

SH-5

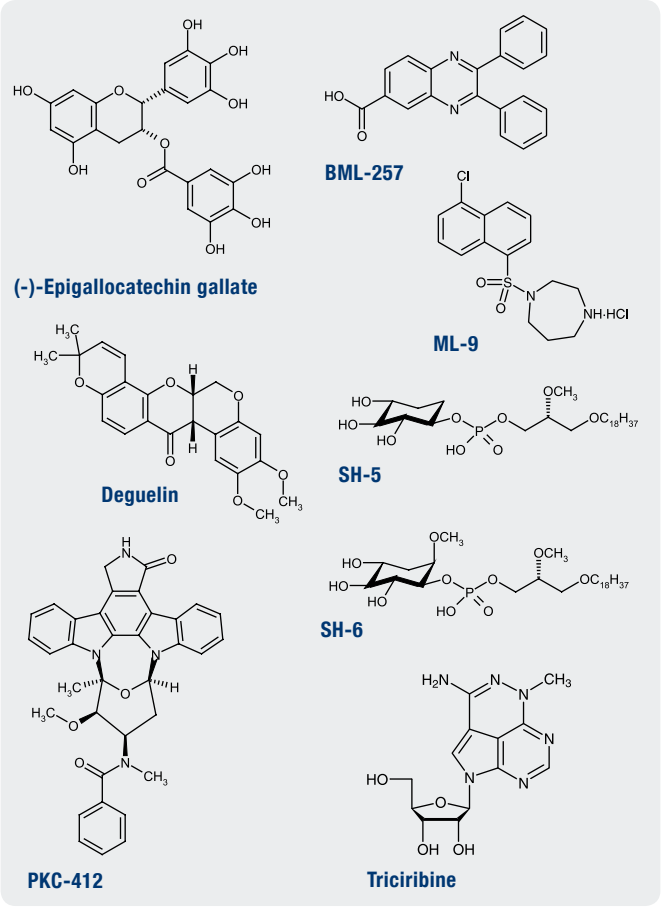
ALX-270-349-MC05	0.5 mg
ALX-270-349-M001	1 mg

SH-6

ALX-270-350-MC05	0.5 mg
ALX-270-350-M001	1 mg

Triciribine

BML-EI332-0001	1 mg
BML-EI332-0005	5 mg



PDK

PDK1, pAb

ADI-KAP-PK112-D	50 µg
ADI-KAP-PK112-F	200 µg

From rabbit. **IMMUNOGEN:** Synthetic peptide derived from the sequence of human PDK1. **SPECIFICITY:** Recognizes human, mouse, rat, dog, monkey, pig and rabbit PDK1 (Pyruvate dehydrogenase kinase). **APPLICATION:** IHC, WB.

PDK1 (human), (rec.) (His-tag)

BML-SE351-0005	5 µg
BML-SE351-0020	20 µg

Produced in insect cells. Active, full length PDK1. **APPLICATION:** Kinetic and functional studies, phosphorylation of target substrates, drug screening.

PDKtide

BML-P250-0100	100 µg

This peptide, KTFCGTPEYLAPEVRREPRILSEEEQEMFRDFDYIADWC, is derived from AKT1 and PKN2/PRK2. It is a substrate for PDK1, CDK9/Cyclin T1 and JAK2.

PDKtide (biotinylated)

BML-P251-0100	100 µg

This peptide, Biotin-Ahx-KTFCGTPEYLAPEVRREPRILSEEEQEMFRDFDYIADWC, is derived from AKT1 and PKN2/PRK2. It is a substrate for PDK1, CDK9/Cyclin T1 and JAK2.The biotin allows peptide to be used in kinase assays with streptavidin-bound membranes.

SGK

SGK1 (human), (rec.) (GST-tag)

BML-SE398-0005 5 µg

BML-SE398-0020 20 µg

Produced in insect cells. **APPLICATION:** Kinetic and functional studies, phosphorylation of target substrates, drug screening.

SGK-1 (truncated NT 60 aa) (human), (rec.)

ADI-PPK-459-Z 5 µg

Active recombinant human SGK-1 containing an N-terminal GST tag, (truncated NT 60 a.a.).

SGK-1 (CT), pAb

ADI-KAP-PK015-C 25 µg

ADI-KAP-PK015-E 100 µg

From rabbit. **IMMUNOGEN:** Synthetic peptide derived from sequence near the C-terminus of human SGK-1 or OVA. **SPECIFICITY:** Recognizes human and monkey SGK-1. **APPLICATION:** IHC, WB.

SGK-1 (NT), pAb

ADI-KAP-PK016-C 25 µg

ADI-KAP-PK016-E 100 µg

From rabbit. **IMMUNOGEN:** Synthetic peptide derived from sequence near the N-terminus of human SGK-1 or OVA. **SPECIFICITY:** Recognizes human SGK-1. **APPLICATION:** WB.

SGK2 (human), (rec.) (GST-tag)

BML-SE350-0005 5 µg

BML-SE350-0020 20 µg

Produced in insect cells. Active, full length serum- and glucocorticoid-induced kinase 2 is fused at the N-terminus to a GST-tag. **APPLICATION:** Kinetic and functional studies, phosphorylation of target substrates, drug screening.

SGK3 (human), (rec.) (GST-tag)

BML-SE415-0005 5 µg

BML-SE415-0020 20 µg

Produced in insect cells. Full length active enzyme. **APPLICATION:** Kinetic and functional studies, phosphorylation of target substrates, drug screening.

SGKtide, (substrate)

ADI-SPK-110-J 1 mg

Synthetic SGKtide substrate peptide.

Akt Activator

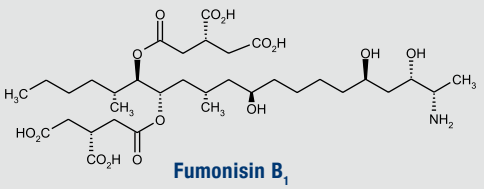
Fumonisin B_1

BML-SL220-0001 1 mg

BML-SL220-0005 5 mg

A fungal metabolite produced by *Fusarium moniliforme*. Mycotoxin. Activates Akt (protein kinase B; PKB), which leads to increased survival, inhibition of GSK-3β activity and post-translational stabilization of cyclin D1. Inhibits sphinganine N-acyl-transferase(ceramide synthase)(IC_{50}=0.1µM). Inhibits de novo sphingolipid biosynthesis (IC_{50}=0.7µM for sphingomyelin labeling by [^{3}H]sphinganine, cultured cerebellar neurons). Inhibits growth of axons in cultured hippocampal neurons by blocking glycosphingolipid synthesis. Induces DNA damage in the liver and cancer. Induces apoptosis.

LIT: A potential mechanism for fumonisin B(1)-mediated hepatocarcinogenesis: cyclin D1 stabilization associated with activation of Akt and inhibition of GSK-3beta activity: D. Ramljak, et al.; Carcinogenesis **21,** 1537 (2000) ▪ **For a comprehensive bibliography please visit our website.**



Fumonisin B_1

PTEN

PTEN (human), (rec.) (His-tag)

BML-SE402-0010 10 µg

Produced in *E. coli*. Full-length human PTEN (aa 1-403) fused to a N-terminal His tag.

PTEN, mAb (11G8.1)

ALX-804-451-C100 100 µg

CLONE: 11G8.1. **ISOTYPE:** Mouse IgG. **IMMUNOGEN:** Recombinant human PTEN. **SPECIFICITY:** Recognizes human and mouse PTEN (epitope aa 152-200). Detects a band of ~60 kDa by Western blot. **APPLICATION:** IP, WB.

PTEN, mAb (6H2.1)

ALX-804-254-C100 100 µg

CLONE: 6H2.1. **ISOTYPE:** Mouse IgG. **IMMUNOGEN:** Recombinant human PTEN. **SPECIFICITY:** Recognizes human, mouse and rat PTEN (epitope aa 304-403). Detects a band of ~60kDa by Western blot. **APPLICATION:** ELISA, IHC, ICC, IP, WB.

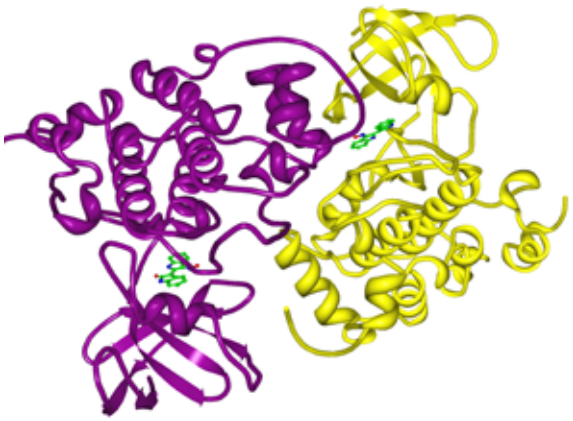
Ship2

Ship2 (catalytic domain) (human), (rec.)

BML-SE539-0010 10 µg

Produced in *E. coli*. Recombinant catalytic domain of SHIP2 (Inppl1) fused to a His tag.

GSK-3 [Glycogen Synthase Kinase-3]



CRYSTAL STRUCTURE: Crystal structure of human GSK3-β complexed with Indirubin-3'-monoxime (Prod. No. ALX-270-271).

Glycogen synthase kinase-3 (GSK-3) is a multifunctional cytoplasmic serine/threonine kinase. This enzyme has several unique features compared to other kinases: i) GSK-3 is generally active ii) upon extracellular stimulation, GSK-3 gets inactivated through phosphorylation and iii) GSK-3 acts as a negative regulator in most pathways (except in NF-κB signaling).

GSK-3 is a key regulator of glycogen and protein synthesis and thus plays an important role in insulin signal transduction and metabolic regulation. Increased GSK-3 activity has been linked to pathology in diseases such as Alzheimer's disease and type 2 diabetes. Several GSK-3 inhibitors, such as the aloisines, the paullones and the maleimides, have been developed as therapeutic agents.

LITERATURE REFERENCES:

GSK-3: tricks of the trade for a multi-tasking kinase: B.W. Doble & J.R. Woodgett; J. Cell Sci **116,** 1175 (2003) (Review) ▪ 9-cyano-1-azapaullone (cazpaullone), a glycogen synthase kinase-3 (GSK-3) inhibitor activating pancreatic beta cell protection and replication: H. Stukenbrock, et al.; J. Med. Chem. **51,** 2196 (2008) ▪ Glycogen synthase kinase-3 (GSK-3) inhibitors reach the clinic: M. Medina & A. Castro; Curr. Opin. Drug Discov. Devel. **11,** 533 (2008) ▪ Targeting glycogen synthase kinase-3 (GSK-3) in the treatment of Type 2 diabetes: K. MacAulay & J.R. Woodgett; Expert Opin. Ther. Targets **12,** 1265 (2008)

GSK-3 Protein

GSK-3β (human), (rec.) (GST-tag)

BML-SE355-0005 5 µg

BML-SE355-0020 20 µg

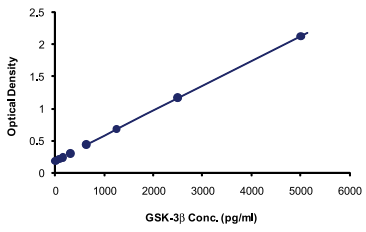
Produced in insect cells. Full length human GSK-3β is fused at the N-terminus to a GST-tag. **APPLICATION:** Kinetic and functional studies, phosphorylation of target substrates, drug screening.

GSK-3 ELISA Kits NEW

GSK-3β EIA kit

ADI-900-144 96 wells

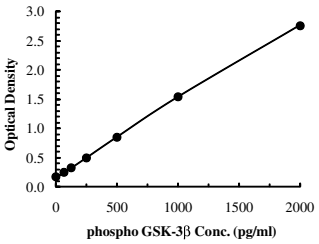
For the quantitative determination of GSK-3β in cell lysates of human and rat origin. **SENSITIVITY:** 74.4 pg/ml (range 78.1 - 5,000 pg/ml).



[pSer⁹]GSK-3β EIA kit

ADI-900-123A 96 wells

For the quantitative determination of [pSer⁹]GSK-3β in cell lysates of human, mouse, and rat origin. **SENSITIVITY:** 9.0 pg/ml (range 62.5 - 2,000 pg/ml).



HIGHLIGHT

GSK-3 Antibodies

[pSer^{21}]GSK-3α, mAb (9B8)

ADI-905-759-100 100 µg

CLONE: 9B8. **ISOTYPE:** Mouse IgG1. **IMMUNOGEN:** Synthetic phospho-peptide derived from the sequence of GSK-3β, conjugated to KLH. **SPECIFICITY:** Recognizes human, mouse, rat and dog GSK-3α. **APPLICATION:** ELISA, WB.

GSK-3α/β, mAb (1H8)

ADI-KAM-ST002-D 50 µg

ADI-KAM-ST002-F 200 µg

CLONE: 1H8. **ISOTYPE:** Mouse IgG2b. **IMMUNOGEN:** Recombinant *Xenopus* GSK-3β protein. **SPECIFICITY:** Recognizes human, mouse, rat, bovine, dog, hamster, monkey, pig, rabbit and sheep GSK-3α/β. **APPLICATION:** WB.

GSK-3α/β, mAb (1HB)

BML-SA364-0100 100 µl

CLONE: 1HB. **ISOTYPE:** Mouse IgG2a. **IMMUNOGEN:** Recombinant *Xenopus laevis* glycogen synthase kinase-3 (GSK-3). **SPECIFICITY:** Recognizes human, mouse, rat and *X. laevis* GSK-3α and β. **APPLICATION:** ELISA, IP, WB.

[pTyr^{216}/Tyr^{279}]GSK-3α/β, mAb (6D3)

ADI-905-762-100 100 µg

CLONE: 6D3. **ISOTYPE:** Mouse IgG1. **IMMUNOGEN:** Synthetic phospho-peptide derived from the sequence of GSK, conjugated to hemocyanin. **SPECIFICITY:** Recognizes human and mouse GSK-3α/β. **APPLICATION:** WB.

[pTyr^{216}/Tyr^{279}]GSK-3α/β, pAb

ADI-KAP-ST012-E 100 µl

From rabbit. **IMMUNOGEN:** Human GSK-3α/β synthetic peptide containing phosphorylated tyrosine 216/279. **SPECIFICITY:** Recognizes human and mouse GSK-3α/β. **APPLICATION:** ELISA, WB.

GSK-3β, mAb (11B9)

ALX-804-548-C100 100 µg

CLONE: 11B9. **ISOTYPE:** Mouse IgG1. **IMMUNOGEN:** Synthetic peptide corresponding to the activation loop of GSK-3β (glycogen synthase kinase-3β). **SPECIFICITY:** Recognizes the activation loop of human, mouse, rat and dog GSK-3β. **APPLICATION:** WB.

GSK-3β, pAb

ADI-905-679-100 100 µg

From rabbit. **IMMUNOGEN:** Synthetic peptide derived from sequence near the C-terminus of human GSK-3β. **SPECIFICITY:** Recognizes human, mouse, rat and bovine GSK-3 β. **APPLICATION:** IHC, WB.

GSK-3β, pAb

ADI-KAP-ST002-C 25 µg

ADI-KAP-ST002-E 100 µg

From rabbit. **IMMUNOGEN:** Synthetic peptide derived from the sequence of rat GSK-3β; sequence identical to human. **SPECIFICITY:** Recognizes human, mouse, rat and bovine GSK-3β. **APPLICATION:** IHC, WB.

[pSer^{9}]GSK-3β, mAb (2D3)

ALX-804-374-C100 100 µg

CLONE: 2D3. **ISOTYPE:** Mouse IgG1. **IMMUNOGEN:** Synthetic peptide corresponding to a portion of phosphorylated GSK-3β (glycogen synthase kinase-3β). **SPECIFICITY:** Recognizes human, mouse and dog GSK-3β phosphorylated at Ser^{9}. Does not cross-react with non-phosphorylated GSK-3β, GSK-3α or phosphorylated GSK-3α. **APPLICATION:** WB.

[pSer^{9}]GSK-3β, mAb (3A8)

ADI-905-761-100 100 µg

CLONE: 3A8. **ISOTYPE:** Mouse IgG1. **IMMUNOGEN:** Synthetic phospho-peptide derived from the sequence of GSK-3β, conjugated to KLH. **SPECIFICITY:** Recognizes human, mouse, rat and dog GSK-3β. **APPLICATION:** ELISA, WB.

[pSer^{9}]GSK-3β, pAb

ADI-KAP-ST011-E 100 µg

From rabbit. **IMMUNOGEN:** Synthetic phospho-peptide derived from the sequence of human GSK-3β. **SPECIFICITY:** Recognizes human, mouse, rat and *Xenopus* GSK-3β. **APPLICATION:** ELISA, WB.

GSK-3 Inhibitors

Aloisine
[RP106]

ALX-270-386-M001 1 mg

Potent, cell permeable, selective ATP-competitive inhibitor of CDK1/cyclin B (IC_{50}=700nM), CDK5/p25 (IC_{50}=1.5μM), and GSK-3 (IC_{50}=920nM).

Aloisine A
[RP107]

ALX-270-385-M001 1 mg

Cell permeable, potent, selective, reversible and ATP-competitive inhibitor of CDK1/cyclin B (IC_{50}=150nM), CDK2/cyclin A (IC_{50}=120nM), CDK2/cyclin E (IC_{50}=400nM), CDK5/p25 (IC_{50}=200nM), CDK5/p35 (IC_{50}=160nM) and GSK-3α (IC_{50}=500nM). Also inhibits GSK-3β (IC_{50}=650nM) and c-Jun N-terminal kinase (JNK) (IC_{50}~3-10μM).

Alsterpaullone
ALX-270-275-M001 1 mg

ALX-270-275-M005 5 mg

Potent inhibitor of CDK1/cyclin B (IC_{50}=35nM). Potent and selective inhibitor of CDK2/cyclin A, CDK2/cyclin E (IC_{50}=200nM), CDK5/p25 (IC_{50}=40nM), CDK5/p35 (IC_{50}=40nM) and GSK-3β.

3-Amino-1*H*-pyrazolo[3,4-b]quinoxaline
ALX-270-387-M001 1 mg

ALX-270-387-M005 5 mg

Selective inhibitor of GSK-3β (IC_{50}=1μM).

AR-A014418
ALX-270-468-M001 1 mg

Synthetic. Cell permeable, specific and potent inhibitor of GSK-3 (IC_{50}=104nM). Inhibition is competitive with respect to ATP (K_i=38nM).

1-Azakenpaullone
ALX-270-430-M001 1 mg

ALX-270-430-M005 5 mg

Potent and ATP-competitive inhibitor of GSK-3β (IC_{50}=18nM).

6BIO
ALX-430-156-M001 1 mg

Potent, reversible and ATP-competitive inhibitor of GSK-3α/β.

10Z-Hymenialdisine
ALX-350-289-C500 500 μg

ALX-350-289-M001 1 mg

Isolated from sponge *Axinella carteri*. Inhibitor of DNA damage checkpoint at G2 phase (IC_{50}=6μM), cyclin-dependent kinases CDK1/cyclin B (IC_{50}=22nM), CDK2/cyclin A (IC_{50}=70nM), CDK2/cyclin E (IC_{50}=40nM), CDK4/cyclin D1 (IC_{50}=600nM), CDK5/p25 (IC_{50}=28nM), GSK-3β (IC_{50}=10nM), and casein kinase 1 (CK1) (IC_{50}=35nM).

Indirubin
ALX-270-361-M001 1 mg

ALX-270-361-M005 5 mg

Synthetic. Inhibitor of cyclin-dependent kinases (CDK1/cyclin B (IC_{50}=10μM), CDK2/cyclin A (IC_{50}=2.2μM), CDK2/cyclin E (IC_{50}=7.5μM), CDK4/cyclin D1 (IC_{50}=12μM), CDK5/p35 (IC_{50}=5.5μM)) and of GSK-3β (IC_{50}=600nM).

Indirubin-3'-monoxime
BML-CC207-0001 1 mg

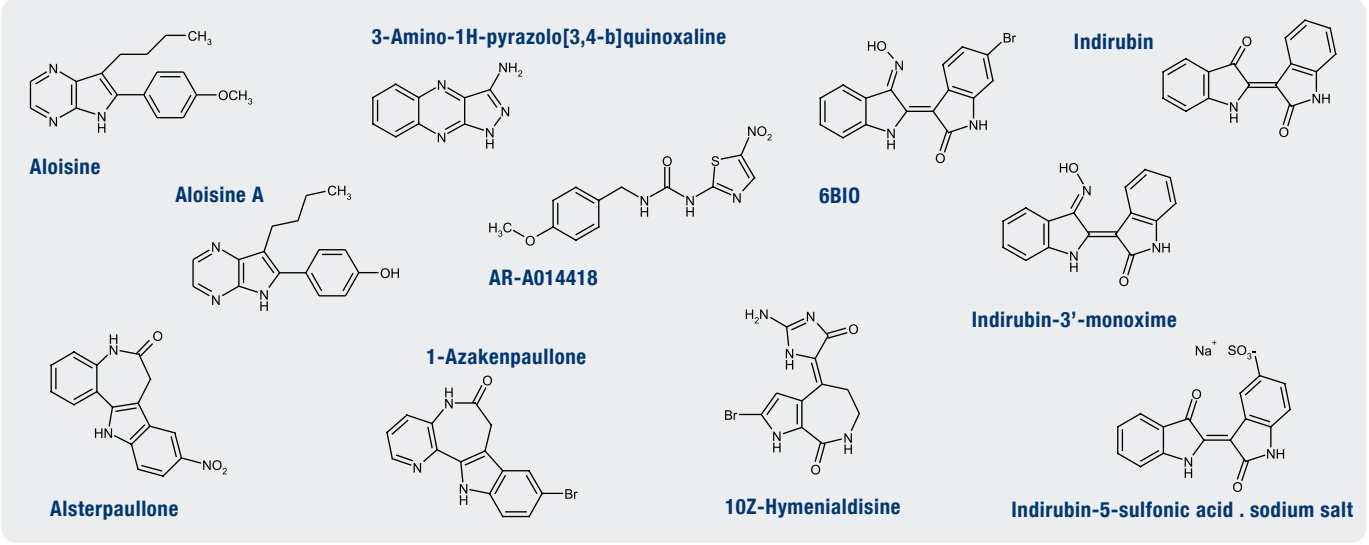
BML-CC207-0005 5 mg

A potent inhibitor of glycogen synthase kinase-3β (IC_{50}=22 nM). Also inhibits CDK1 ($p34^{cdc2}$; IC_{50}=180 nM) and CDK5 (IC_{50}=100 nM). It reversibly arrests asynchronous HBL-100 cells at G2. Induces apoptosis in the mammary carcinoma cell line MCF-7 (10 μM).

Indirubin-5-sulfonic acid . sodium salt
ALX-270-296-M001 1 mg

ALX-270-296-M005 5 mg

Inhibitor of cyclin-dependent kinases (CDKs), with selectivity for CDK1/cyclin B (IC_{50}=55nM), CDK2/cyclin A (IC_{50}=35nM), CDK2/cyclin E (IC_{50}=150nM), CDK4/cyclin D1 (IC_{50}=300nM), CDK5/p35 (IC_{50}=65nM) and GSK-3β (IC_{50}=280nM).



5-Iodo-indirubin-3'-monoxime

ALX-270-424-M001 1 mg

Potent inhibitor of GSK-3β (IC_{50}=9nM).

Kenpaullone

BML-EI310-0001 1 mg

BML-EI310-0005 5 mg

Potent inhibitor of CDK1/cyclin B (IC_{50}=400nM). Also inhibits CDK2/cyclin A (IC_{50}=680nM), CDK5 (IC_{50}=850nM) and with much less effect other kinases. More recently, kenpaullone has been found to be a useful GSK-3β inhibitor (IC_{50}=23nM).

Manzamine A

ALX-350-294-M001 1 mg

Isolated from *Xestospongia sp.* GSK-3 Inhibitor.

SB-216763

BML-EI312-0001 1 mg

BML-EI312-0005 5 mg

Potent and selective inhibitor of GSK-3β (IC_{50}=34nM). Stimulates glycogen synthesis in human liver cells and mimics other actions of insulin.

SB-415286

BML-EI311-0001 1 mg

BML-EI311-0005 5 mg

Potent and selective inhibitor of GSK-3β (IC_{50}=78nM). Stimulates glycogen synthesis in human liver cells and mimics other actions of insulin.

Staurosporine

ALX-380-014-C100 100 µg

ALX-380-014-C250 250 µg

ALX-380-014-M001 1 mg

ALX-380-014-M005 5 mg

Isolated from *Streptomyces staurosporeus*. Potent cell permeable inhibitor of a variety of protein kinases, e.g. GSK-3β (IC_{50}=15nM).

Staurosporine

BML-EI156-0100 100 µg

BML-EI156-1000 1 mg

TDZD-8

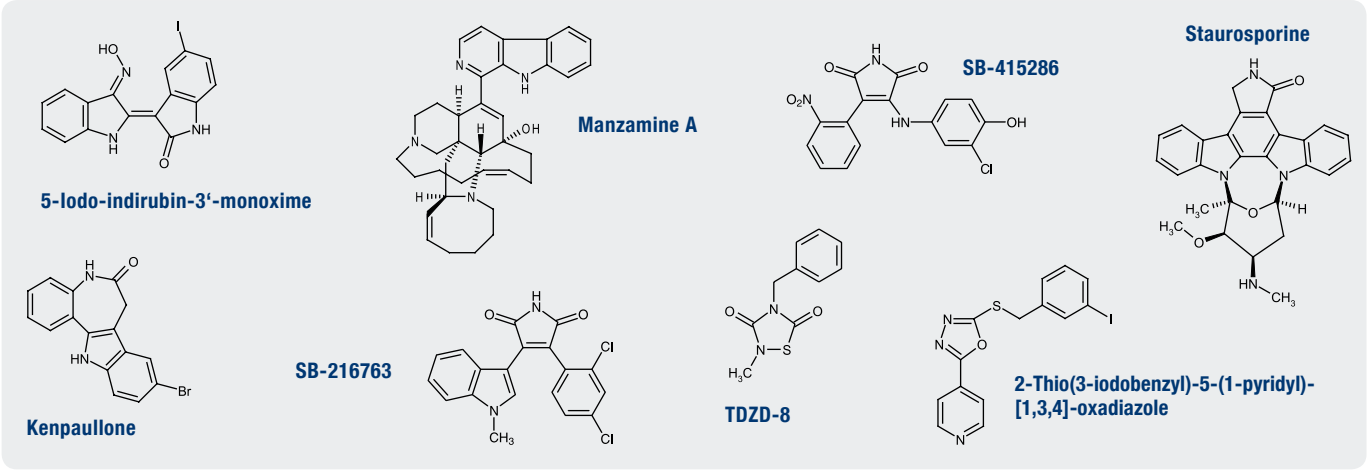
ALX-270-354-M005 5 mg

Highly selective, non-ATP competitive inhibitor of GSK-3β (IC_{50}=2µM). Binds to the active site of GSK-3β. Does not significantly affect the activities of Cdk 1/cyclin B, CK-II, PKA, and PKC (IC_{50}>100µM).

2-Thio(3-iodobenzyl)-5-(1-pyridyl)-[1,3,4]-oxadiazole

ALX-270-358-M005 5 mg

Potent inhibitor of GSK-3β (IC_{50}=390nM).



GSK-3 Substrates

GSK-3 substrate

[H-Arg-Arg-Arg-Ala-Ala-Glu-Glu-Leu-Asp-Ser-Arg-Ala-Gly-pSer-Pro-Gln-Leu-OH]

BML-P151-0001 1 mg

Corresponds to the sequence of the ε subunit of eIF2B surrounding serine 540, a target of GSK-3 (glycogen synthase kinase-3) phosphorylation, with the addition of a phosphoserine in the 4 position. This phosphoserine allows for more efficient phosphorylation of the second serine in the peptide (K_m=49µM for GSK-3β, 83µM for GSK-3α). Useful in phosphocellulose GSK-3α and -β assays.

GSK-3 substrate II

[H-Tyr-Arg-Arg-Ala-Ala-Val-Pro-Pro-Ser-Pro-Ser-Leu-Ser-Pro-Ala-Ser-Ser-Pro-His-Gl n-pSer-Glu-Asp-Glu-Glu-OH]

BML-P193-0001 1 mg

This peptide was derived from glycogen kinase I.

Nutrients & Nutrient Sensing

Nutrients (e.g. glucose, amino acids and fatty acids) can serve as important signaling molecules in complex pathways. Three major nutrient signaling pathways have been identified so far: the hexosamine signaling pathway, the mTOR signaling pathway and the AMPK pathway. These pathways regulate different aspects of energy metabolism and influence various cellular processes such as cell growth, proliferation and survival.

The hexosamine signaling pathway converts fructose-6-phosphate into uridine diphosphate N-acetyl glucosamine (UDP-GlcNAc). UDP-GlcNAc is a substrate for the addition (via an O-linkage) of a single N-acetylglucosamine to serine or threonine residues of nuclear and cytoplasmic proteins (O-glycosylation). O-glycosylation is a highly dynamic posttranslational modification that plays a role in key biological processes such as gene expression, cell growth, cell differentiation and fuel metabolism. Several studies have described a link between O-glycosylation and the induction of insulin resistance and type 2 diabetes. In addition, the hexosamine biosynthesis pathway regulates the secretion of both adiponectin and leptin from adipose tissue.

LITERATURE REFERENCE:
The hexosamine signaling pathway: deciphering the "O-GlcNAc code": D.C. Love & J.A. Hanover; Sci. STKE **2005,** re13

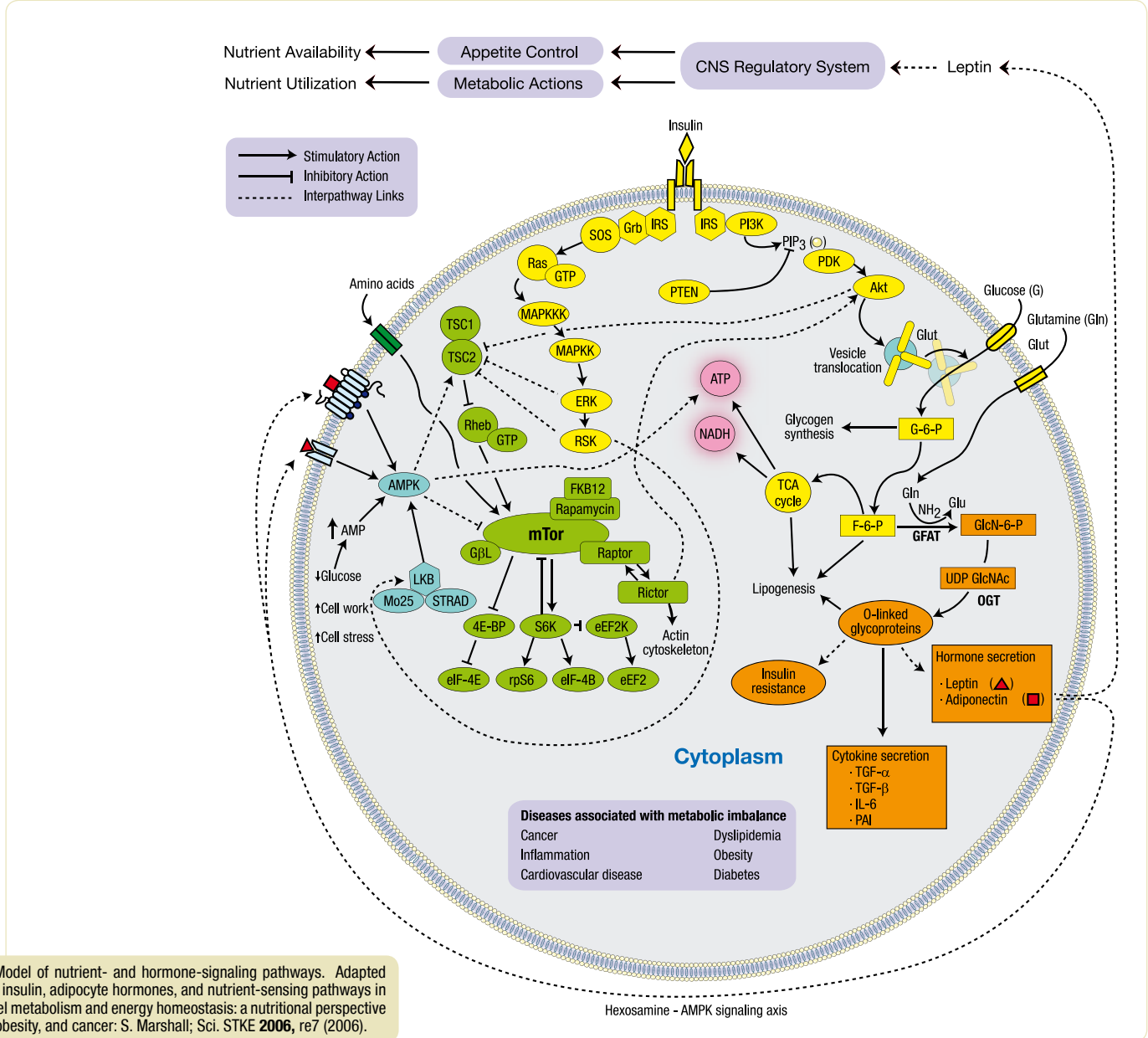


FIGURE 6: Model of nutrient- and hormone-signaling pathways. Adapted from: Role of insulin, adipocyte hormones, and nutrient-sensing pathways in regulating fuel metabolism and energy homeostasis: a nutritional perspective of diabetes, obesity, and cancer: S. Marshall; Sci. STKE **2006,** re7 (2006).

The mTOR Pathway

The mTOR (mammalian target of rapamycin) signaling pathway monitors intracellular amino acid availability and cellular energy status and links this information with external signals from cell surface receptors (such as the insulin receptor). This sensory input is then biochemically integrated and elicits a coordinated response that controls fundamental biological processes such as cell growth, cell proliferation and survival.

LITERATURE REFERENCE:
Expanding mTOR signaling: Q. Yang & K.L. Guan; Cell Res. **17,** 666 (2007)

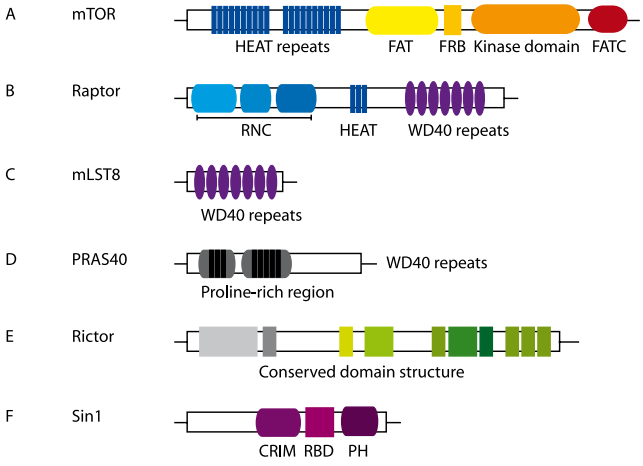


FIGURE 7: Schematic of mTOR complex components. Abbreviations: HEAT: a protein-protein interaction structure of two tandem anti-parallel ahelices found in huntingtin, elongation factor 3, PR65/A and TOR; FAT: α domain structure shared by FRAP, ATM and TRRAP; FRB: FKBP12/rapamycin binding domain; FATC: FAT C-terminus; RNC: Raptor N-terminal conserved domain; WD40: about 40 amino acids with conserved W and D forming four anti-parallel beta strands; CRIM: conserved region in the middle; RBD: Ras binding domain. Adapted from: Expanding mTOR signaling: Q. Yang & K.L. Guan; Cell Res. **17,** 666 (2007).

mTOR (human FRB Domain), pAb

ALX-215-065-1 — 1 Vial

From rabbit. **IMMUNOGEN:** Recombinant human mTOR (FKBP12-rapamycin-binding (FRB) domain). **SPECIFICITY:** Recognizes the FRB domain of fusion proteins expressed in *Saccharomyces cerevisiae*. Not tested, but expected to recognize endogenous human FRB domain. **APPLICATION:** ICC, WB.

LIT: The anchor-away technique: rapid, conditional establishment of yeast mutant phenotypes: H. Haruki, et al.; Mol. Cell **31,** 925 (2008)

mTOR, pAb

ALX-210-065-C050 — 50 µg

From rabbit. **IMMUNOGEN:** Human mTOR (mammalian target of rapamycin) (aa 1223-1290). **SPECIFICITY:** Recognizes human and rat mTOR. **APPLICATION:** IP, WB.

LIT: Identification of TOR signaling complexes: more TORC for the cell growth engine: R.T. Abraham; Cell **111,** 9 (2002)

mTOR, pAb

ADI-905-687-100 — 100 µg

From rabbit. **IMMUNOGEN:** Synthetic peptide derived from the sequence of human mTOR. **SPECIFICITY:** Recognizes human and mouse mTOR. **APPLICATION:** WB.

Raptor, mAb (10E10)

ADI-905-765-100 — 100 µg

CLONE: 10E10. **ISOTYPE:** Mouse IgG1. **IMMUNOGEN:** Synthetic peptide derived from sequence of raptor, conjugated to hemocyanin. **SPECIFICITY:** Recognizes human, mouse, rat and dog raptor. **APPLICATION:** WB.

Rictor, mAb (1G11)

ADI-905-766-100 — 100 µg

CLONE: 1G11. **ISOTYPE:** Mouse IgG1. **IMMUNOGEN:** Synthetic phospho-peptide derived from the sequence of rictor, conjugated to hemocyanin. **SPECIFICITY:** Recognizes human, mouse and rat rictor. **APPLICATION:** WB.

TSC1, pAb

ADI-905-713-100 — 100 µg

From rabbit. **IMMUNOGEN:** Synthetic peptide derived from the sequence of human TSC1. **SPECIFICITY:** Recognizes human, mouse and rat TSC1. **APPLICATION:** ICC, WB.

PRAS40 (human) (rec.)

BML-SE308-0025 — 25 µg

Produced in *E. coli*. Human PRAS40 (proline-rich Akt substrate 40) (aa 2-256).

[pThr^{246}]PRAS40 (human), pAb

BML-SA360-0020 — 20 µl
BML-SA360-0100 — 100 µl

From rabbit. **IMMUNOGEN:** Synthetic peptide corresponding to a portion of human PRAS40 (proline-rich Akt substrate 40) phosphorylated at Thr^{246}. **SPECIFICITY:** Recognizes PRAS40 phosphorylated at Thr^{246}. **APPLICATION:** WB.

Related Products

Rapamycin

BML-A275-0001 — 1 mg
BML-A275-0005 — 5 mg

Macrocyclic-triene antibiotic possessing potent immunosuppressant activity. It forms a complex with FKBP12 that binds to an effector, thus inhibiting IL-2 and other growth promoting lymphokines. The effectors were recently identified as FRAP (FKBP12 rapamycin-associated protein) and RAFT1 (rapamycin and KFBP12 target). Rapamycin/FKBP complex does not inhibit FRAP PI 4-kinase activity, but does inhibit FRAP autophosphorylation. Rapamycin induces inhibition of p70^{s6k}, p33^{cdk2} and p34^{cdc2}. Selectively blocks signaling leading to the activation of p70/85 S6 kinase. Enhances apoptosis. Activator of autophagy both *in vitro* and *in vivo*.

FKBP12, pAb

ALX-210-142-R100 — 100 µl

From rabbit. **IMMUNOGEN:** Synthetic peptide corresponding to aa 1-13 (G^{1}VQVETISPGDGR^{13}) of human FKBP12 (FK506 binding protein 12kDa). **SPECIFICITY:** Recognizes human, mouse and rat FKBP12. **APPLICATION:** IHC (FS, PS), IP, WB. **BP:** ALX-156-002.

LIT: The effects of FK506 on retinal ganglion cells after optic nerve crush: E.E. Freeman and C.L. Grosskreutz; IOVS **41,** 1111 (2000) ▪ Immunophilin expression in the HIV-infected brain: C.L. Achim, et al.; J. Neuroimmunol. **157,** 126 (2004)

p70 S6K (substrate)

ADI-SPK-109-J 1 mg

Synthetic p70S6K/Rsk substrate peptide for use in kinase assays.

p70 S6K (human), (rec.)

BML-SE345-0005 5 µg

BML-SE345-0020 20 µg

Produced in insect cells. Full length active p70 S6 K (ribosomal protein S6 kinase (70kDa)).

[pThr^{389}]p70 S6K (human), pAb

ALX-210-068-C050 50 µg

From rabbit. **IMMUNOGEN:** Synthetic peptide corresponding to aa 383-395 (CV^{383}QFLGFpTYVAPSV^{395}) of C-terminal human p70 S6K (ribosomal protein S6 kinase (70kDa)) phosphorylated at Thr^{389}. **SPECIFICITY:** Recognizes human p70 S6K phosphorylated at Thr^{389}. **APPLICATION:** WB.

p70 S6K, pAb

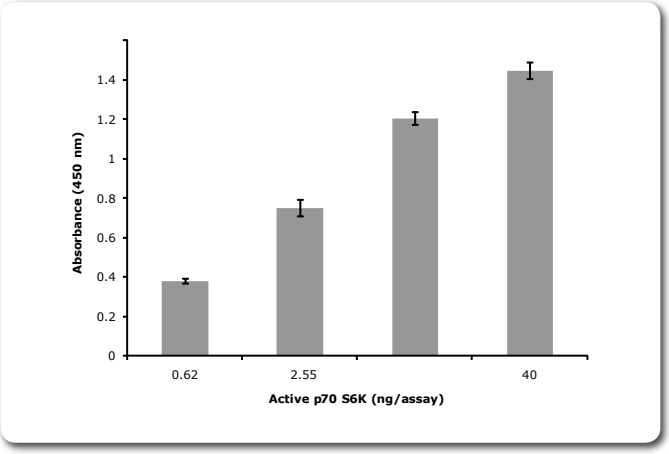
ADI-KAP-CC035-E 100 µg

From rabbit. **IMMUNOGEN:** Synthetic peptide derived from sequence near the C-terminus of human p70 S6K. **SPECIFICITY:** Recognizes human, mouse, rat and bovine p70 S6K. **APPLICATION:** ELISA, IP, WB.

p70 S6K activity kit

ADI-EKS-470 96 wells

For the measurement of p70 S6K activity in partially purified, purified, or crude enzyme preparations from any species.



The AMPK Pathway

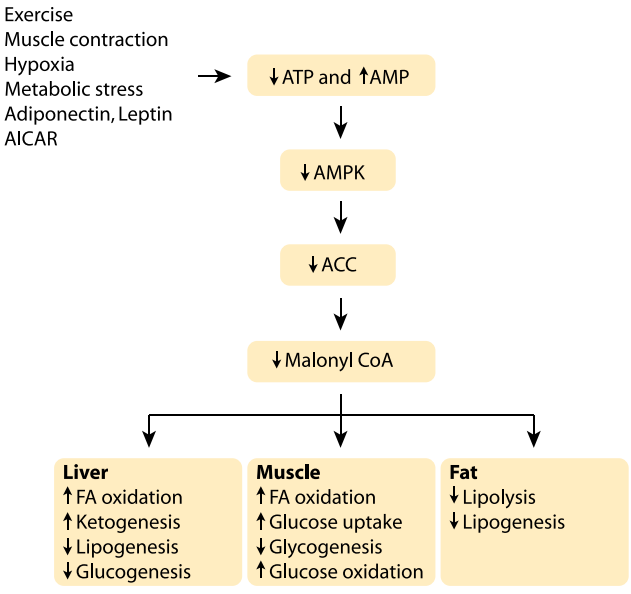


FIGURE 8: Metabolic effects of adenosine monophosphate activated protein kinase (AMPK). Abbrevations: AICAR = 5-aminoimidazole-4-carboxamide-ribofuranoside; ACC = Acetyl CoA carboxylase. Adapted from: Treating insulin resistance: future prospects: C.J. Bailey; Diab. Vasc. Dis. Res. **4,** 20 (2007).

The serine-threonine kinase AMPK (AMP-activated protein kinase) is activated in response to low cellular energy and responds by suppressing cell growth and biosynthetic processes. One mechanism of how AMPK senses cellular energy levels involves the allosteric activation of the kinase activity of AMPK. Low cellular energy is characterized by reduced ATP and elevated AMP levels. In this case AMP directly activates AMPK and triggers a signal transduction cascade that regulates the activity of various downstream targets including transcription factors, enzymes and other regulatory proteins. A prominent downstream target of AMPK is mTOR. The phosphorylation of mTOR plays an important role in restoring ATP levels by inhibiting energy-consuming processes such as cell growth and protein synthesis.

In addition to allosteric activation, the activity of AMPK can also be regulated through phosphorylation. The serine-threonine kinase LKB1 as well as the hormones adiponectin and leptin can influence the phosphorylation state of AMPK.

AMPK is a key regulator of glucose and lipid metabolism. In the liver, activation of AMPK results in enhanced fatty acid oxidation and decreased production of glucose, cholesterol, and triglycerides. Pharmacological activation of AMPK in vivo improves blood glucose homeostasis, cholesterol concentrations and blood pressure in insulin-resistant rodents. This makes AMPK an attractive pharmacological target for the treatment of type 2 diabetes.

LITERATURE REFERENCES:

The role of AMP kinase in diabetes: P. Misra & R. Chakrabarti; Indian J. Med. Res. **125,** 389 (2007) ▪ AMP-activated protein kinase: Role in metabolism and therapeutic implications: G. Schimmack, et al.; Diabetes Obes. Metab. **8,** 591 (2006)

AMPK Proteins

AMPK (human), (rec.) (His-tag)

BML-SE491-0005 5 µg

BML-SE491-0020 20 µg

Produced in insect cells. Full length active AMPK composed of subunits α1, β1 and γ1. **APPLICATION:** Kinetic and functional studies, drug screening.

AMPK Substrates

SAMS peptide

[H-His-Met-Arg-Ser-Ala-Met-Ser-Gly-Leu-His-Leu-Val-Lys-Arg-Arg-OH]

BML-P231-0001 1 mg

This peptide is derived from rat acetyl-CoA carboxylase and is known to be a good substrate for AMPK.

SAMS peptide (biotinylated)

[Biotin-His-Met-Arg-Ser-Ala-Met-Ser-Gly-Leu-His-Leu-Val-Lys-Arg-Arg-OH]

BML-P232-0001 1 mg

This peptide contains a biotin group at its N- terminus. It is derived from rat acetyl-CoA carboxylase and is known to be a good substrate for AMPK. The biotin allows peptide to be used in kinase assays with streptavidin-bound membranes.

SAMS peptide (phosphorylated) (biotinylated)

[Biotin-His-Met-Arg-Ser-Ala-Met-pSer-Gly-Leu-His-Leu-Val-Lys-Arg-Arg-OH]

BML-P233-0001 1 mg

This peptide contains a biotin group at its N- terminus and a phospho-serine. It is derived from rat acetyl-CoA carboxylase. It may be used as a control peptide for unphosphorylated SAMS Peptide (BML-P231 and BML-P232). The biotin allows peptide to be used in kinase assays with streptavidin-bound membranes.

AMARA peptide substrate

[H-Ala-Met-Ala-Arg-Ala-Ala-Ser-Ala-Ala-Ala-Leu-Ala-Arg-Arg-Arg-OH]

BML-P270-0001 1 mg

This peptide is a substrate for AMPK and SIK kinases.

AMPK Inhibitor

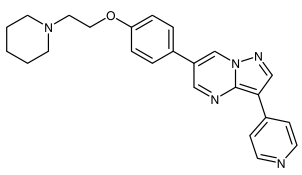
BML-275

[Compound C; Dorsomorphin]

BML-EI369-0005 5 mg

BML-EI369-0025 25 mg

Cell permeable pyrrazolopyrimidine derivative that inhibits AMP kinase (K_i=109nM in the absence of AMP) in an ATP-competitive manner. It displays no significant inhibition of ZAPK, SYK, PKCT, PKA and JAK3. Decreases food intake in mice and inhibits the effects of AICAR and metformin. It has recently been shown to inhibit BMP type I receptors ALK2, ALK3 and ALK6.



AMPK Activator

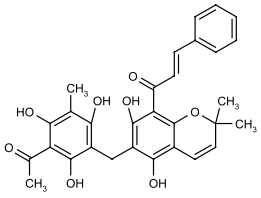
Rottlerin

[Mallotoxin]

ALX-350-075-M010 10 mg

ALX-350-075-M025 25 mg

Isolated from *Mallotus philippinensis*. Mitochondrial uncoupler that depolarizes the mitochondrial membrane potential, reduces cellular ATP levels, activates 5'-AMP-activated protein kinase (AMPK) and affects mitochondrial production of reactive oxygen species (ROS). Potent activator of multiple Ca^{2+}-sensitive K^+ channels. **LIT:** The mouse ear edema: a quantitatively evaluable assay for tumor promoting compounds and for inhibitors of tumor promotion: M. Gschwendt, et al.; Cancer Lett. **25,** 177 (1984) ▪ Rottlerin, a novel protein kinase inhibitor: M. Gschwendt, et al.; BBRC **199,** 93 (1994)



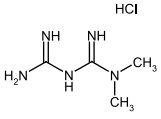
Metformin

ALX-270-432-G001 1 g

ALX-270-432-G005 5 g

Antidiabetic agent. Reduces the cardiovascular complications of diabetes. Does not induce hypoglycemia.

LIT: Effects of metformin and thiazolidinediones on suppression of hepatic glucose production and stimulation of glucose uptake in type 2 diabetes: a systematic review: A. Natali and E. Ferrannini; Diabetologia **49,** 434 (2006) ▪ **For a comprehensive bibliography please visit our website.**



Latest Insight

AMPK is strongly stimulated by exercise and plays a central role in sensing energy status. A recent study found that treatment of sedentary mice with AICAR mimicked many of the positive effects of exercise. Four weeks of AICAR treatment induced metabolic genes, decreased fat mass, increased oxygen consumption and enhanced running endurance by 44%. This study not only helps to characterize the molecular pathways that lead to the beneficial effects of exercise, but also suggests that exercise mimetic drugs may have therapeutic potential in treating muscle diseases like wasting and frailty or more broadly for treatment of obesity or heart disease where exercise has positive benefits.

LIT: AMPK and PPARdelta agonists are exercise mimetics: V.A. Narkar et al.; Cell **134,** 405 (2008)

AICAR

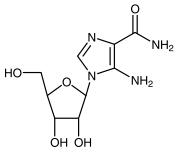
[5-Aminoimidazole-4-carboxamide 1-ß-D-ribofuranoside]

BML-EI330-0050 50 mg

BML-EI330-0250 250 mg

Activates AMP Kinase in whole cells. Mimics the effects of insulin on the expression of two gluconeogenic genes PEPCK and glucose-6-phosphatase. Inhibits PPARα coactivation and adipocyte differentiation. Substrate for the AICAR transformylase activity of ATIC.

Lit: 5-aminoimidazole-4-carboxamide ribonucleoside. A specific method for activating AMP-activated protein kinase in intact cells?: J.M. Corton et al.; Eur. J. Biochem. **229,** 558 (1995)



PPARs [Peroxisome Proliferator-activated Receptor]

The PPAR (Peroxisome proliferator-activated receptor) family members play important roles in glucose and lipid metabolism and atherosclerosis. PPARs are ligand-activated transcription factors belonging to the superfamily of nuclear receptors. Both endogenous and pharmacologic ligands exist for PPARs. Upon binding, the ligands can heterodimerize with the retinoid X receptor, bind to the PPAR response element of its target gene and either activate or repress gene expression. Three forms of PPARs have been identified α, γ and β/δ. The three subtypes exist in different tissues in varying quantities with different effects (see Table below).

PPARγ is highly expressed in adipose tissue and is involved in fatty acid uptake, glucose homeostasis and insulin resistance. It is the primary target of the thiazolidinediones (TZDs). The TZDs constitute a class of oral anti-diabetic agents that exert insulin-sensitizing effects in adipose tissue, skeletal muscle, and liver. In addition, TZDs also have beneficial effects on other components of the metabolic syndrome. They may influence cardiovascular risk and decrease inflammatory responses in insulin resistance. Within adipocytes, TZDs suppress the synthesis of IL-6, TNF-α, PAI-1, MCP-1 and angiotensinogen. Thus, TZDs have been used in patients with type 2 diabetes and pre-diabetic insulin resistance.

LITERATURE REFERENCES:

Peroxisome proliferator-activated receptor (PPAR) in metabolic syndrome and type 2 diabetes mellitus: M.A. Jay & J. Ren; Curr. Diabetes Rev. **3,** 33 (2007) (Review) ▪ Inflammation in diabetes mellitus: role of peroxisome proliferator-activated receptor-alpha and peroxisome proliferator-activated receptor-gamma agonists: P. Libby & J. Plutzky; Am. J. Cardiol. **99,** 27B (2007) (Review) ▪ Effects of peroxisome proliferator-activated receptors on lipoprotein metabolism and glucose control in type 2 diabetes mellitus: R.S. Rosenson; Am. J. Cardiol. **99,** 96B (2007) (Review) ▪ Fat and beyond: the diverse biology of PPARgamma: P. Tontonoz & B.M. Spiegelman; Annu. Rev. Biochem. **77,** 289 (2008) (Review)

Subtype	Distribution	Physiological involvement
PPARα	Liver, kidneys, heart, gut, skeletal muscle, adipose tissue	Lipid catabolism and oxidation, gluconeogenesis
PPARβ/δ	Ubiquitous	Adipocyte differentiation (minor), function incompletely understood
PPARγ	Adipose tissue, large intestine, hemato-poietic cells, kidney, liver, intestinal mu-cosa	Glucose and fatty acid uptake, gluconeogenesis, lipogenesis, glycogenesis, adi-pocytes differentiation, macrophage maturation, modulation of inflammation

TABLE: Distribution and actions of the PPARs. Adapted from: PPARα: therapeutic role in diabetes-related cardiovascular disease: A.Y. Cheng & L.A. Leiter; Diabetes Obes. Metab. **10,** 691 (2008).

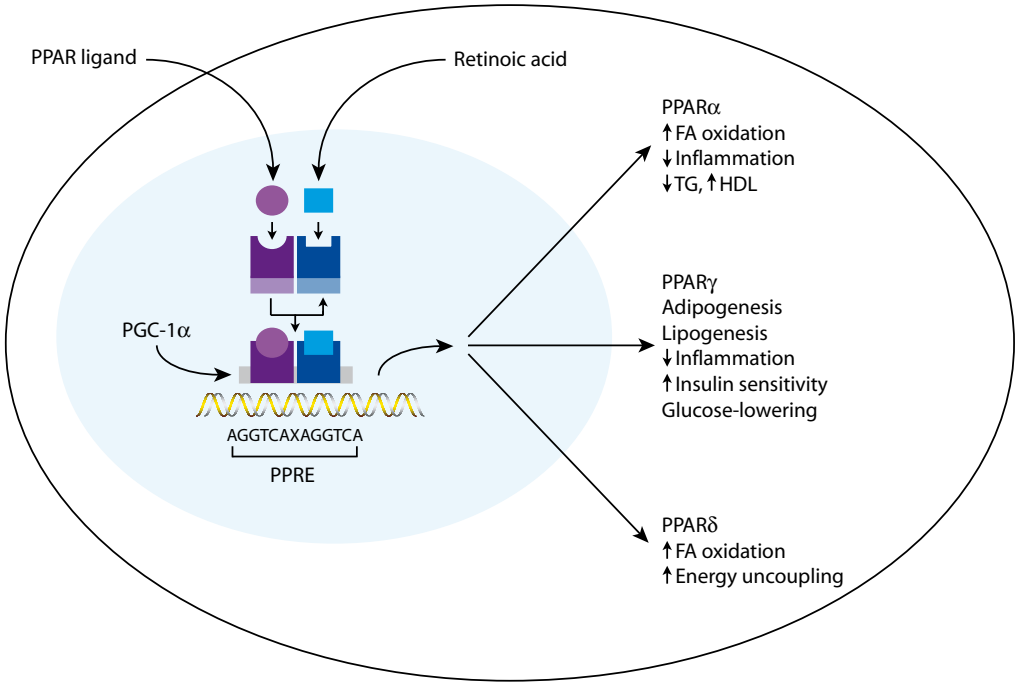


FIGURE 9: Actions of peroxisome proliferator-activated receptor (PPAR) ligands. Abbreviations: PGC-1α = PPAR coactivator PGC-1α; FA = fatty acid; TG = triglyceride; HDL = high-density lipoprotein; PPRE = PPAR response element. Adapted from: Treating insulin resistance: future prospects: C.J. Bailey; Diab. Vasc. Dis. Res. **4,** 20 (2007).

PPAR Antibodies

PPAR, pAb

ALX-210-117-R100 100 µl

From rabbit. **IMMUNOGEN:** Synthetic peptide corresponding to aa 484-498 (I^{484}KKTETDMSLHPLLQ^{498}) of the C-terminal domain of rat PPARγ2 (peroxisome proliferator activated receptor γ2). This sequence is completely conserved in human, mouse, rat, bovine, chicken and pig PPARγ1, PPARα and NUC1. **SPECIFICITY:** Recognizes mouse and rat PPARγ2. Detects a band of ~55 kDa by Western blot. Cross-reacts with recombinant rat PPARα in Western blot and recombinant mouse PPARγ1 in immunoprecipitation. **APPLICATION:** IP, WB.

LIT: mPPAR gamma 2: tissue-specific regulator of an adipocyte enhancer: P. Tontonoz, et al.; Genes Dev. **8,** 1224 (1994) ▪ Differential expression of peroxisome proliferator-activated receptors (PPARs): tissue distribution of PPAR-alpha, -beta, and -gamma in the adult rat: O. Braissant, et al.; Endocrinology **137,** 354 (1996)

PPARα, mAb (3B6/PPAR)

ALX-804-255-C100 100 µg

CLONE: 3B6/PPAR. **ISOTYPE:** Mouse IgG2b. **IMMUNOGEN:** Purified recombinant PPARα (peroxisome proliferator activated receptor α). **SPECIFICITY:** Recognizes human, mouse and rat PPARα. Detects a band of ~52 kDa by Western blot. **APPLICATION:** IP, WB.

LIT: Evidence that PPARalpha is complexed with the 90 kDa heat shock protein and the hepatitis virus B X-associated protein 2: W.K. Sumanasekera, et al.; J. Biol. Chem. **278,** 4467 (2003) ▪ PPARalpha activators inhibit vascular endothelial growth factor receptor-2 expression by repressing Sp-1-dependent DNA binding and transactivation: M. Meissner, et al.; Circ. Res. **94,** 324 (2004)

PPARα (mouse), pAb

ALX-210-190/1-R100 100 µl

From rabbit. **IMMUNOGEN:** Synthetic peptide corresponding to aa 1-18 (M^{1}VDTESPICPLSPLEADD^{18}) of mouse PPARα (peroxisome proliferator activated receptor α). A single aa substitution (I8 to L8) exists between the mouse and human protein. **SPECIFICITY:** Recognizes mouse PPARα. Detects a band of ~52kDa by Western blot. Does not cross-react with PPARδ or PPARγ. **APPLICATION:** ICC, IP, WB. **BP:** ALX-165-029.

[pSer^{12}]PPARα (mouse), pAb

ALX-210-361-C100 100 µg

From rabbit. **IMMUNOGEN:** Synthetic peptide corresponding to aa 8-19 (^{18}CPLpSPLEADDL^{19}) of mouse PPARα (peroxisome proliferator activated receptor α) phosphorylated at Ser^{12}. **SPECIFICITY:** Recognizes mouse PPARα phosphorylated at Ser^{12}. Detects a band of ~52 kDa by Western blot. **APPLICATION:** WB. **BP:** ALX-165-055.

LIT: MCF-7 and T47D human breast cancer cells contain a functional peroxisomal response: M.W. Kilgore, et al.; Mol. Cell Endocrinol. **129,** 229 (1997) ▪ Diverse signaling pathways modulate nuclear receptor recruitment of N-CoR and SMRT complexes: R.M. Lavinsky, et al.; PNAS **95,** 2920 (1998)

[pSer^{21}]PPARα (mouse), pAb

ALX-210-362-C100 100 µg

From rabbit. **IMMUNOGEN:** Synthetic peptide corresponding to aa 14-25 (L^{14}EADDLEpSPLSE^{25}) of mouse PPARα (peroxisome proliferator activated receptor α) phosphorylated at Ser^{21}. **SPECIFICITY:** Recognizes mouse PPARα phosphorylated at Ser^{21}. Detects a band of ~52kDa by Western blot. **APPLICATION:** WB. **BP:** ALX-165-056.

LIT: See Prod. No. ALX-210-361.

PPARγ2 (mouse), pAb

ALX-210-192-R100 100 µl

From rabbit. **IMMUNOGEN:** Synthetic peptide corresponding to aa 1-16 (M^{1}GETLGDSPIDPESDS^{16}) of human PPARγ2 (peroxisome proliferator activated receptor γ2). **SPECIFICITY:** Recognizes mouse PPARγ2. Detects a band of ~56kDa by Western blot. Does not cross-react with PPARα or PPARδ. **APPLICATION:** ICC, WB. **BP:** ALX-165-031.

LIT: Diverse signaling pathways modulate nuclear receptor recruitment of N-CoR and SMRT complexes: R.M. Lavinsky, et al.; PNAS **95,** 2920 (1998) ▪ Delayed activation of PPARgamma by LPS and IFN-gamma attenuates the oxidative burst in macrophages: A.A. Von Knethen & B. Brune; FASEB J. **15,** 535 (2001) ▪ Activation of peroxisome proliferator-activated receptor gamma by nitric oxide in monocytes/macrophages down-regulates p47phox and attenuates the respiratory burst: A. Von Knethen & B. Brune; J. Immunol. **169,** 2619 (2002) ▪ A human peripheral blood monocyte-derived subset acts as pluripotent stem cells: Y. Zhao, et al.; PNAS **100,** 2426 (2003)

PPARδ, pAb

ALX-210-191/1-R100 100 µl

From rabbit. **IMMUNOGEN:** Synthetic peptide corresponding to aa 1-14 (M^{1}EQPQEETPEAREE^{14}) of mouse PPARδ (peroxisome proliferator activated receptor δ). This sequence is ~86% conserved in human PPARδ. **SPECIFICITY:** Recognizes mouse and rat PPARδ . Detects a band of ~49kDa by Western blot. Does not cross-react with PPARα or PPARγ. **APPLICATION:** IHC (FS), ICC, WB. **BP:** ALX-165-030.

PPAR Modulators

BADGE

ALX-270-353-G025 25 g

Antagonist of PPARγ. Binds to PPARγ with an apparent Kd of 100µM.

Bezafibrate

BML-GR211-0001 1 g

BML-GR211-0005 5 g

Synthetic PPAR agonist. Induces fatty acid peroxisomal β-oxidation in rat white adipose tissue. Displays anti-inflammatory, anti-atherosclerosis and anti-obesity activity.

Carnosic acid

ALX-270-264-M010 10 mg

ALX-270-264-M050 50 mg

Isolated from *Rosmarinus officinalis*. Inhibits lipid peroxidation induced by NADH or NADPH oxidation. PPARγ activator.

Ciglitazone

BML-GR205-0005 5 mg

BML-GR205-0025 25 mg

Synthetic. Selective PPARγ agonist (EC_{50}=3µM).

Ciprofibrate

ALX-270-475-M025 25 mg

ALX-270-475-M100 100 mg

ALX-270-475-M250 250 mg

Hypolipidemic compound. PPARα agonist.

Clofibrate

ALX-270-256-M500 500 mg

ALX-270-256-G001 1 g

Activates PPARα and induces cytochrome P450 4A1 and 4A3.

5,8,11,14-Eicosatetraynoic acid

BML-ET004-0020 20 mg

BML-ET004-0100 100 mg

Inhibits arachidonic acid uptake. Inhibits cyclooxygenase (ID_{50}=8 µM) and all lipoxygenases (ID_{50}=10, 0.3, and 0.2 µM for 5-, 12- and 15-LO respectively) in whole cells. Inhibits PLA_2 and cytochrome P-450. Modulates Ca^{2+} entry into cells. Stimulates luteinizing hormone release from cultured pituitary cells. PPAR agonist.

Fenofibrate

ALX-270-481-G005 5 g

Hypolipidemic compound. PPARα agonist (EC_{50}=18µM for mouse and EC_{50}=30µM for human PPARα). Also binds to PPARγ, but with at least 10-fold less affinity and is inactive at PPARδ (up to EC_{50}=100µM).

GW1929

ALX-420-029-M001 1 mg

ALX-420-029-M005 5 mg

Potent (<10nM) and subtype-selective (>1'0000-fold) PPARγ agonist which does not contain a thiazolidinedione moiety. The glucose-lowering effect of GW1929 in rats is 100-fold more potent than that of troglitazone (Prod. No. ALX-270-355).

GW501516

ALX-420-032-M001 1 mg

ALX-420-032-M005 5 mg

Specific agonist for PPARδ (EC_{50}=1.1nM) with a 1'000-fold selectivity over the other human subtypes.

GW-9662

BML-GR234-0010 10 mg

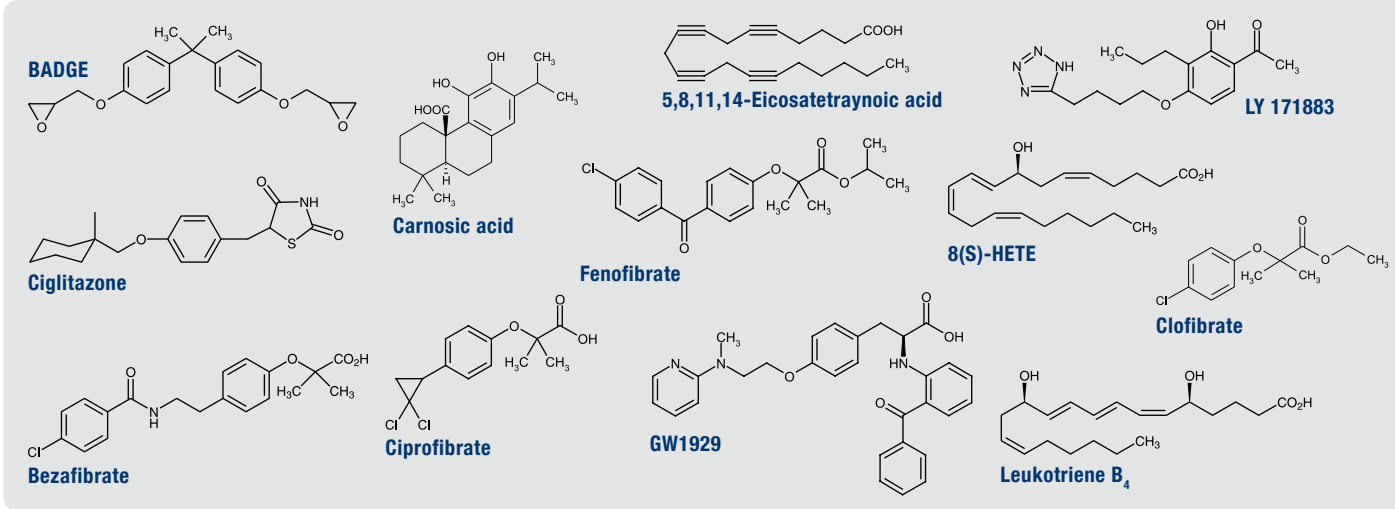
BML-GR234-0050 50 mg

Blocks the PPARγ-induced differentiation of monocytes to osteoclasts by >90% at a dose of 0.1µM. Much more potent antagonist than BADGE (Prod. No. ALX-270-353).

8(S)-HETE

BML-H008-0050 50 µg

Activator of PPARα.



Leukotriene B_4

BML-LB004-0050 50 µg

Activator of PPARα. Stimulates a number of leukocyte functions, including aggregation, stimulation of ion fluxes, enhancement of lysosomal enzyme release, superoxide anion production, chemotaxis and chemokinesis.

LY 171883

BML-RA101-0010 10 mg

BML-RA101-0050 50 mg

Competitive leukotriene D_4 (LTD_4) antagonist. Has also been shown to bind to the γ-isofom of the peroxisome proliferator activated receptor (PPARγ).

MK-886

BML-EI266-0005 5 mg

BML-EI266-0025 25 mg

Inhibitor of PPARα activation. Inhibits 5-lipoxygenase activating protein (FLAP) and leukotriene biosynthesis (IC_{50}=102nM).

Naproxen

ALX-270-102-G005 5 g

PPAR agonist. Widely used non-steroidal anti-inflammatory drug.

N-Oleylethanolamide

BML-SL231-0010 10 mg

BML-SL231-0050 50 mg

Activates TRPV1. Does not activate cannabinoid receptors (CB) but is a PPARα agonist (EC_{50}=120nM) *in vitro* and *in vivo*; induces satiety through activation of PPARα. Inhibits ceramidase.

Pioglitazone

ALX-270-367-M001 1 mg

ALX-270-367-M005 5 mg

Pioglitazone selectively activates PPARγ. It is about one tenth as potent as rosiglitazone (EC_{50}~500nM for human and mouse PPARγ).

15-Deoxy-$\Delta^{12,14}$-prostaglandin J_2

BML-PG050-0001 1 mg

BML-PG050-0005 5 mg

Suggested natural ligand for PPARγ.

Pseudolaric acid B

ALX-350-108-MC01 0.1 mg

ALX-350-108-M001 1 mg

Isolated from *Pseudolarix kaempferi*. Activates PPARα and the phospholipase C (PLC) signaling pathway. Stimulates peroxisomal fatty acyl-CoA oxidase activity.

Rosiglitazone

ALX-350-125-M025 25 mg

ALX-350-125-M100 100 mg

Potent insulin sensitizing agent. PPARγ agonist. Hepatoxic. Antidiabetic.

T0070907

BML-GR212-0010 10 mg

BML-GR212-0050 50 mg

Potent and selective PPARγ antagonist. Blocks PPARγ function in both cell-based reporter gene and adipocyte differentiation assays.

Tetradecylthioacetic acid

BML-GR236-0010 10 mg

BML-GR236-0050 50 mg

Tetradecylthioacetic acid (TTA) is a novel thio-fatty acid which cannot undergo β-oxidation. Activates rodent PPARs with rank order PPARα > PPARδ > PPARγ.

Troglitazone

BML-GR210-0005 5 mg

BML-GR210-0025 25 mg

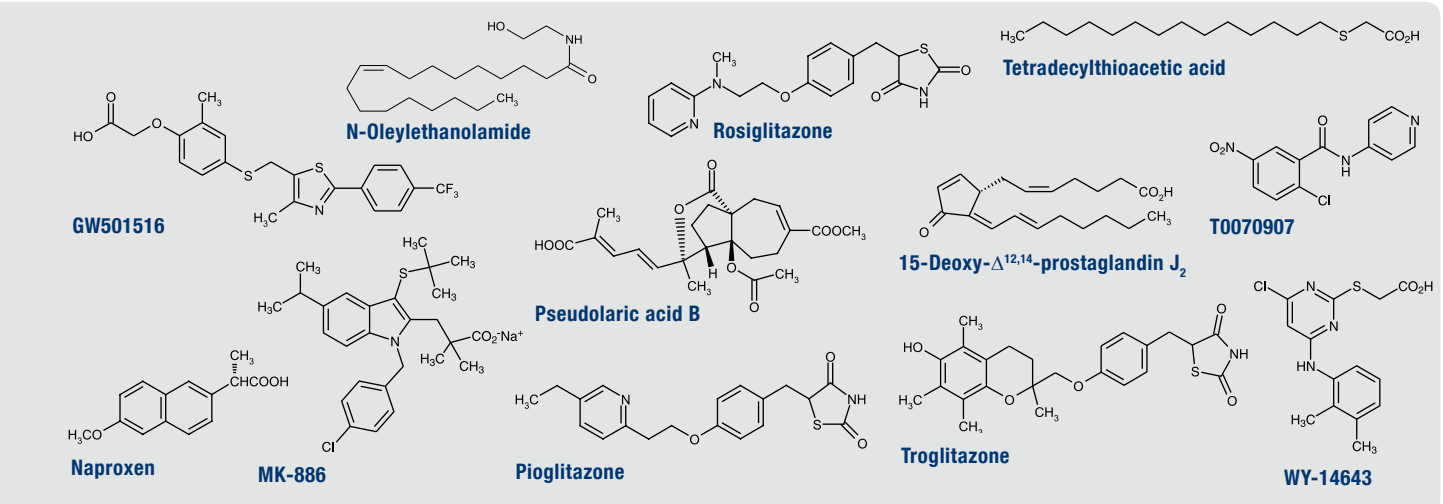
Synthetic. Potent and selective PPARγ ligand. Binds to the PPARγ ligand-binding domain and recruits ligand-specific transcriptional coactivators at 1µM. In skeletal muscle and adipocyte cell cultures, the EC_{50} of troglitazone is about 10µM.

WY-14643

BML-GR200-0050 50 mg

BML-GR200-0250 250 mg

Widely used activator of PPARs.



Purified (PF) = Purified (Preservative free); FC = Flow Cytometry; ICC = Immunocytochemistry; IP = Immunoprecipitation; IHC = Immunohistochemistry (FS = Frozen Sections, PS = Paraffin Sections); WB = Western blot; BP = Blocking Peptide

Proteolytic Regulation of GLP-1 by DPPIV and Neprilysin

Glucagon like peptide-1 (GLP-1), along with glucose-dependent insulinotropic polypeptide (GIP), are incretin peptide hormones, which are released upon ingestion of food. Proglucagon is secreted and processed by proprotein convertases PC1/3 and PC2 into glucagon, GLP-1, GLP-2, and other bioactive peptides, depending on tissue type. GLP-1 (7-36) amide stimulates insulin and somatostatin secretion, and inhibits secretion of glucagon, ultimately resulting in satiety [1]. It is cleaved by dipeptidyl peptidase 4 (DPPIV) and neprilysin (NEP) into GLP-1 (9-36) amide, a form, that reverses the glucoregulatory actions of GLP-1 (7-36) amide [1-3]. Thus incretin mimetics, DPPIV/NEP inhibitors, and GLP-1 (9-36) amide peptides are of interest for treatment of diabetes and obesity [4]. Several DPPIV inhibitors are in use in the clinic.

LITERATURE REFERENCES:
[1] Biology of incretins: GLP-1 and GIP: L.L. Baggio & D.J. Drucker; Gastroenterology **132,** 2131 (2007) ▪ **[2]** GLP-1 (9-36) amide, cleavage product of GLP-1 (7-36) amide, is a glucoregulatory peptide: D. Elahi, et al.; Obesity **16,** 1501 (2008) ▪ **[3]** Characterisation of the processing by human neutral endopeptidase 24.11 of GLP-1(7-36) amide and comparison of the substrate specificity of the enzyme for other glucagon-like peptides: K. Hupe-Sodmann, et al.; Regul. Pept. **58,** 149 (1995) ▪ **[4]** Structural studies of a bifunctional inhibitor of neprilysin and DPP-IV: C. Oefner, et al.; Acta Crystallogr. D Biol. Crystallogr. **D63,** 975 (2007)

Glucagon

Glucagon

BML-GP1432-0100 100 µg

Human prepro-glucagon [51-81]. Blocking and immunizing peptide for the glucagon polyclonal antibody (BML-GA1181). **APPLICATIONS:** Standard for radioimmunoassay, coating peptide in enzyme immunoassays, complementary peptide for immunohistochemistry.

Glucagon, pAb

BML-GA1181-0025 25 µl

BML-GA1181-0100 100 µl

From rabbit. **IMMUNOGEN:** Natural pig pancreatic glucagons. **SPECIFICITY:** Recognizes mammalian glucagon. **APPLICATION:** IHC

Glucagon like Peptides [GLPs]

GLP-1, pAb

BML-GA1176-0025 25 µl

BML-GA1176-0100 100 µl

From rabbit. **IMMUNOGEN:** Synthetic peptide corresponding to aa 1-19 of human GLP-1. **SPECIFICITY:** Recognizes mammalian GLP1. **APPLICATION:** IHC. **BP:** BML-GP1436

GLP-1 (7-36) amide, pAb

BML-GA1178-0250 1 Vial

From rabbit. **IMMUNOGEN:** Synthetic peptide corresponding to aa 7-36 of human GLP-1. **SPECIFICITY:** Recognizes human, rat and other mammalian species GLP-1. **APPLICATION:** RIA. **BP:** BML-GP1438

GLP-2, pAb

BML-GA1179-0025 25 µl

BML-GA1179-0100 100 µl

From rabbit. **IMMUNOGEN:** Synthetic peptide corresponding to aa 1-33 of human GLP-2. **SPECIFICITY:** Recognizes mammalian GLP-2. **APPLICATION:** IHC. **BP:** BML-GP1439

DPPIV Proteins

DPPIV (human), (rec.)

BML-SE434-0025 25 mU

Active recombinant human DPPIV (aa 29-766).This represents a naturally-occurring cleaved (soluble) form of DPPIV. **BIOLOGICAL ACTIVITY:** Study of enzyme kinetics, cleave target substrates, and screen for inhibitors.

DPPIV (human), (rec.)

ALX-201-128-1 1 Vial

Produced in Sf9 cells.

DPPIV Kits

DPPIV assay kit for biological samples

BML-AK498-0001 1 Kit

The DPPIV assay kit for biological samples is a complete assay system designed to measure DPPIV activity in biological fluids such as plasma, serum, urine, and saliva. Uses for the kit include correlation of DPPIV activity with disease states or determination of the efficacy of DPPIV inhibitors administered *in vivo*. **QUANTITY:** 96 assays

DPPIV drug discovery kit

BML-AK499-0001 1 Kit

The DPPIV drug discovery kit is a complete assay system designed to screen inhibitors of DPPIV (DPP4; CD26). Using a convenient microplate format, DPPIV activity is monitored either colorimetrically, or fluorimetrically using substrates provided in the kit.

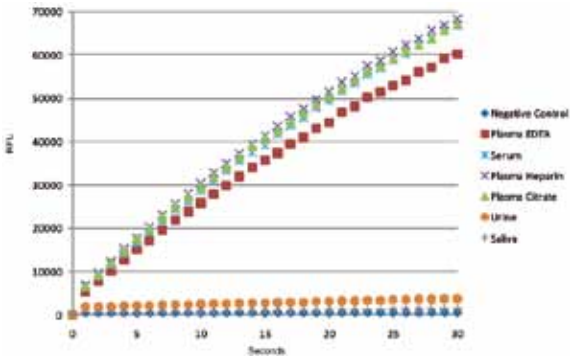


FIGURE: DPPIV activity in biological samples

HIGHLIGHT

DPP Substrates

GP-pNA

[H-Gly-Pro-p-nitroanilide]

BML-P188-0025 25 mg

Chromogenic substrate for dipeptidyl peptidase IV (DPIV, DPPIV, CD26), DPP7/II, DPP8, DPP9, FAP, PCP/PRCP, POP/PREP, and likely other prolyl peptidases. Can be used *in vitro* for inhibitor screening, on cultured cells, and in biological fluids. Hydrolysis of this substrate can be monitored at 405-410nm.

GP-AMC

[H-Gly-Pro-7-amino-4-methylcoumarin]

BML-P189-0005 5 mg

Fluorogenic substrate for dipeptidyl peptidase IV (DPIV, DPPIV, CD26) (k_{cat}/K_m=2.6 x $105^{s-1}M^{-1}$), DPPII/VII, DPP8 and DPP9, FAP (fibroblast activation protein), and likely POP/PREP, but not glutamate carboxypeptidase II. Can be used *in vitro*, for inhibitor screening, and in biological fluids. Ex = 380nm, Em=460nm.

VP-AMC

BML-P448-0005 5 mg

Fluorogenic substrate likely cleaved by dipeptidyl peptidase IV (DPIV, DPPIV, CD26), DPP8, FAP (fibroblast activation protein), and other prolyl peptidases. Can be used *in vitro*, for inhibitor screening, and in biological fluids. Ex = 380 nm, Em = 460 nm.

DP-AMC

BML-P449-0005 5 mg

Fluorogenic substrate cleaved by dipeptidyl peptidase IV (DPIV, DPPIV, CD26) (K_m=28µM, k_{cat}/K_m=3.7 x 103M-1s-1), DPPII/VII (K_m=1.12mM, k_{cat}/K_m=40.0 $M^{-1}s^{-1}$), and likely DPP8 and other prolyl peptidases. Can be used *in vitro*, for inhibitor screening, and in biological fluids. Ex = 380 nm, Em = 460 nm.

WP-AMC

BML-P450-0005 5 mg

Fluorogenic substrate likely cleaved by dipeptidyl peptidase IV (DPIV, DPPIV, CD26), DPP8, and other prolyl peptidases. Can be used *in vitro*, for inhibitor screening, and in biological fluids. Ex = 380 nm, Em = 460 nm.

DPPIV [CD26] Antibody

DPPIV (human), pAb

BML-SA451-0100 100 µg

From rabbit. **IMMUNOGEN:** Synthetic peptide corresponding to a portion of human DPPIV. **SPECIFICITY:** Recognizes human DPPIV. **APPLICATION:** WB.

DPPIV Inhibitors

Diprotin A

[H-Ile-Pro-Ile-OH]

ALX-260-036-M005 5 mg

ALX-260-036-M025 25 mg

Synthetic. Inhibitor of dipeptidyl aminopeptidase IV.

LIT: Diprotins A and B, inhibitors of dipeptidyl aminopeptidase IV, produced by bacteria: H. Umezawa, et al.; J. Antibiot. **37**, 422 (1984) ▪ Purification and some properties of a membrane-bound dipeptidyl peptidase IV of guinea pig casein-induced intraperitoneal leukocytes: M. Kudo, et al.; J. Biochem. **97,** 1211 (1985) ▪ Murine thymocytes possess specific cell surface-associated exoaminopeptidase activities: preferential expression by immature CD4- CD8- subpopulation: B. Bauvois; Eur. J. Immunol. **20,** 459 (1990)

Diprotin B

[H-Val-Pro-Leu-OH]

ALX-260-013-M005 5 mg

ALX-260-013-M025 25 mg

Synthetic. Inhibitor of dipeptidyl aminopeptidase IV.

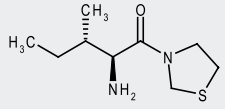
LIT: Diprotins A and B, inhibitors of dipeptidyl aminopeptidase IV, produced by bacteria: H. Umezawa, et al.; J. Antibiot. **37,** 422 (1984)

P32/98

BML-PI142-0010 10 mg

BML-PI142-0050 50 mg

P32/98 (Ile-thiazolidide) is a specific, competitive transition-state substrate analog inhibitor of dipeptidyl peptidase IV (DPIV, DPPIV, CD26), with a Ki of 130nM. Useful in diabetes research. Has been used *in vivo* and in tissue culture.



P32/48

Related Products

FAP (human), (rec.)

BML-SE409-0010 10 µg

Active recombinant human FAP (aa 29-760), representing a naturally-occurring cleaved (soluble) form. **BIOLOGICAL ACTIVITY:** Study of enzyme kinetics, cleave target substrates, and screen for inhibitors.

POP/PREP (human), (rec.)

BML-SE545-0010 10 µg

Active recombinant human POP/PREP/PEP with an N-terminal purification tag. **BIOLOGICAL ACTIVITY:** Study of enzyme kinetics, cleave target substrates, and screen for inhibitors.

Neprilysin

Neprilysin (human), (rec.) (His-tag)

BML-SE532-0010 10 µg

Produced in Sf9 cells.

Neprilysin (rat kidney), (purified)

BML-SE512-0010 10 µg

Isolated from rat kidney.

Mca-RPPGFSAFK(Dnp)

BML-P227-0001 1 mg

Fluorogenic substrate for ECE-1 and ECE-2, ACE1 and ACE2, neprilysin, MMP-2 and MMP-9, thimet oligopeptidase, as well as cathepsin A, cathepsin X/Z, BACE, and insulinase, but not MMP-1. Mca fluorescence is quenched by the Dnp group until cleavage separates them. Ex.: 328nm, Em.: 393nm, although the following Ex/Em have also been used: 320-340/400-420. This substrate is useful for inhibitor screening and kinetic analysis.

LIT: Phosphinic tripeptides as dual angiotensin-converting enzyme C-domain and endothelin-converting enzyme-1 inhibitors: N. Jullien, et al.; J. Med. Chem. **53,** 208 (2010)

Neprilysin (human), cAb (E19-P)

ALX-810-204-R100 100 µl

ALX-810-204-R500 500 µl

ALX-810-204-L001 1 ml

CLONE: E19-P. **ISOTYPE:** Rabbit IgG. **IMMUNOGEN:** Synthetic peptide corresponding to a C-terminal sequence of human neprilysin (CD10; CALLA). **SPECIFICITY:** Recognizes human neprilysin. **APPLICATION:** IHC (FS, PS).

Neprilysin (human), cAb (E19-P) (Ready-to-Use)

ALX-810-404-L007 7 ml

ALX-810-404-L015 15 ml

CLONE: E19-P. **ISOTYPE:** Rabbit IgG. **IMMUNOGEN:** Synthetic peptide corresponding to a C-terminal sequence of human neprilysin. **SPECIFICITY:** Recognizes human neprilysin. **APPLICATION:** IHC (PS).

Antidiabetic Agents

Antidiabetic Agents

Genipin

ALX-350-383-M025 25 mg

ALX-350-383-M100 100 mg

Isolated from *Gardenia jasminoides Ellis.* Cell permeable inhibitor of uncoupling protein 2 (UCP2). Increases glucose-stimulated insulin secretion, mitochondrial membrane potential and ATP levels in pancreatic island cells. Induces apoptosis. Protein cross-linking agent. Anti-inflammatory and anti-angiogenic.

LIT: Genipin-induced apoptosis in hepatoma cells is mediated by reactive oxygen species/c-Jun NH2-terminal kinase-dependent activation of mitochondrial pathway: B.C. Kim, et al.; Biochem. Pharmacol. **70,** 1398 (2005) ▪ Genipin inhibits UCP2-mediated proton leak and acutely reverses obesity- and high glucose-induced beta cell dysfunction in isolated pancreatic islets: C.Y Zhang, et al.; Cell Metab. **3,** 417 (2006) ▪ Glucose sensing by POMC neurons regulates glucose homeostasis and is impaired in obesity: L.E. Parton, et al.; Nature **449,** 228 (2007)

Glyburide

[Glibenclamide]

BML-KC120-0001 1 g

BML-KC120-0005 5 g

An antidiabetic sulfonylurea which selectively blocks ATP-sensitive K^+ channels. It blocks vascular smooth muscle relaxation produced by K_{ATP} channel openers. High affinity binding sites are widely distributed and have been identified in the cardiovascular system, the CNS and in pancreatic β-cells. It displays a large potency difference in pancreatic tissue (IC_{50} in the nM range) versus vascular tissue (IC_{50} in the µM range).

Glipizide

ALX-550-271-M100 100 mg

ALX-550-271-G001 1 g

ALX-550-271-G005 5 g

Antidiabetic agent. ATP-dependent K^+ channel blocker. Blocks K^+ channels in pancreatic β cells leading to an increase in calcium and insulin.

LIT: RP 49356 and cromakalim relax airway smooth muscle in vitro by opening a sulphonylurea-sensitive K^+ channel: a comparison with nifedipine: D. Raeburn & T.J. Brown; J. Pharmacol. Exp. Ther. **256,** 480 (1991) ▪ Quantitative autoradiography of the binding sites for [125I] iodoglyburide, a novel high-affinity ligand for ATP-sensitive potassium channels in rat brain: D.R. Gehlert, et al.; J. Pharmacol. Exp. Ther. **257,** 901 (1991)

Metformin

ALX-270-432-G001 1 g

ALX-270-432-G005 5 g

Antidiabetic agent. Reduces the cardiovascular complications of diabetes. Does not induce hypoglycemia.

LIT: Effects of metformin and thiazolidinediones on suppression of hepatic glucose production and stimulation of glucose uptake in type 2 diabetes: a systematic review: A. Natali and E. Ferrannini; Diabetologia **49,** 434 (2006) ▪ **For a comprehensive bibliography please visit our website.**

Pterostilbene

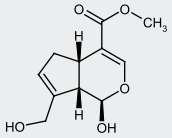
ALX-385-034-M025 25 mg

ALX-385-034-M100 100 mg

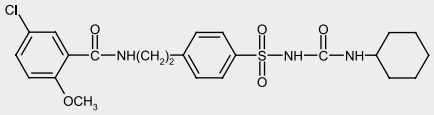
ALX-385-034-M500 500 mg

Synthetic. Cell permeable natural methoxylated analog of resveratrol (Prod. No. ALX-270-125). Antioxidant, antiproliferative, anti-inflammatory, anti-hyperglycemic and anti-diabetic agent. Induces apoptosis. Inhibits activator protein 1 (AP-1) and NF-κB activation. Moderately inhibits COX-1 and COX-2 (IC_{50}=19.8µM and 83.9µM).

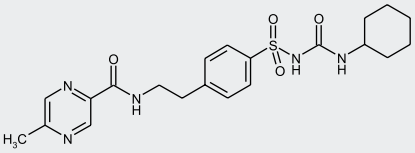
LIT: Pterostilbene, a new agonist for the peroxisome proliferator-activated receptor alpha-isoform, lowers plasma lipoproteins and cholesterol in hypercholesterolemic hamsters: A.M. Rimando, et al.; J. Agric. Food Chem. **53,** 3403 (2005) ▪ Effect of pterostilbene on hepatic key enzymes of glucose metabolism in streptozotocin- and nicotinamide-induced diabetic rats: L. Pari & M.A. Satheesh; Life Sci. **79,** 641 (2006) ▪ **For a comprehensive bibliography please visit our website.**



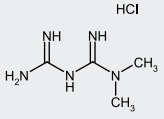
Genipin



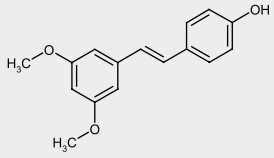
Glyburide



Glipizide



Metformin



Pterostilbene

HDACs

There is clear evidence of HDAC involvement in diabetes pathogenesis, and its pre-disposing factors, obesity and inflammation [1]. Development of adult type 2 diabetes in a rat model of intrauterine growth retardation is associated with HDAC1-induced epigenetic changes and these could be reversed by HDAC inhibition [2]. Due to its repression of GLUT4 expression in skeletal muscle, HDAC5 is implicated in regulation of blood glucose [3-5]. HDAC inhibitors have been found to prevent cytokine-induced toxicity in pancreatic ß-cells [6] and to increase the pool of ß-cells during development [7].

LITERATURE REFERENCES:

[1] Role of histone and transcription factor acetylation in diabetes pathogenesis: S.G. Gray & P. De Meyts; Diabetes Metab. Res. Rev. **21,** 416 (2005) ▪ **[2]** Development of type 2 diabetes following intrauterine growth retardation in rats is associated with progressive epigenetic silencing of Pdx1: J.H. Park, et al.; J. Clin. Invest. **118,** 2316 (2008) ▪ **[3]** Restoration of insulin-sensitive glucose transporter (GLUT4) gene expression in muscle cells by the transcriptional coactivator PGC-1: L.F. Michael, et al.; PNAS **98,** 3820 (2001) ▪ **[4]** Regulation of peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC-1 alpha) and mitochondrial function by MEF2 and HDAC5: M.P. Czubryt, et al.; PNAS **100,** 1711 (2003) ▪ **[5]** AMP-activated protein kinase regulates GLUT4 transcription by phosphorylating histone deacetylase 5: S.L. McGee, et al.; Diabetes **57,** 860 (2008) ▪ **[6]** Inhibition of histone deacetylases prevents cytokine-induced toxicity in beta cells: L. Larsen, et al. Diabetologia **50,** 779 (2007) ▪ **[7]** Histone deacetylase inhibitors modify pancreatic cell fate determination and amplify endocrine progenitors: C. Haumaitre, et al.; Mol. Cell Biol. **28,** 6373 (2008)

HDAC Antibodies

Product	Specificity	Application	Prod. No.	Size
HDAC1, mAb (10E2)	Human and mouse	IHC, ICC, IP, WB	ALX-804-599-C200	200 µg
HDAC1, pAb	Human, rat and mouse	IHC, IP, WB	BML-SA401-0100	100 µg
HDAC2, pAb	Human, rat and mouse	IHC, IP, WB	BML-SA402-0100	100 µg
HDAC3, pAb	Human, canine, hamster and rat	IP, WB	BML-SA403-0100	100 µg
HDAC4, pAb	Human	WB	BML-SA404-0100	100 µg
HDAC4 (NT), pAb	Human and mouse	WB	ALX-210-339-C100	100 µg
HDAC5, pAb	Human and mouse	IP, WB	ALX-210-340-C100	100 µg
HDAC6, pAb	Human and mouse	IP, WB	ALX-210-341-C100	100 µg

HDAC Inhibitors

Trichostatin A

BML-GR309-0001 1 mg

BML-GR309-0005 5 mg

Trichostatin A (TSA) is a potent and reversible inhibitor of histone deacetylases. In HeLa cells, TSA blocked cell cycle progression at G1 and induced a 12-fold increase in intracellular levels of gelsolin. In cells latently infected with HIV-1, TSA induced the transcriptional activation of the HIV-1 promoter, which resulted in a marked increase in virus production. In NIH 3T3 cells, TSA induced reversion of oncogenic ras-transformed cells to a normal morphology. In Jurkat cells, TSA inhibited IL-2 gene expression (IC_{50}=73nM) and displayed immunosuppressive activity in a mouse model. Induces increased acetylation of GATA4, a cardiac-specific transcription factor and increases cardiac muscle cell differentiation. Trichostatin A is a useful tool for induction of hyperacetylation of cellular histones and for further elucidation of their role in gene expression.

LIT: Histone deacetylase: a regulator of transcription: A.P. Wolffe; Science **272,** 371 (1996) ▪ Trichostatin A induces morphological changes and gelsolin expression by inhibiting histone deacetylase in human carcinoma cell lines: Y. Hoshikawa, et al.; Exp. Cell Res. **214,** 189 (1994) ▪ Trichostatin A inhibits both ras-induced neurite outgrowth of PC12 cells and morphological transformation of NIH3T3 cells: M. Futamura, et al.; Oncogene **10,** 1119 (1995) ▪ Selective inhibition of IL-2 gene expression by trichostatin A, a potent inhibitor of mammalian histone deacetylase: I. Takahashi, et al.; J. Antibiot. (Tokyo) **49,** 453 (1996)

Suberoyl bis-hydroxamic acid

BML-GR323-0100 100 mg

BML-GR323-0500 500 mg

Induces cellular differentiation. Inhibits histone deacetylases.

LIT: Cytodifferentiating agents affect the replication of herpes simplex virus type 1 in the absence of functional VP16: C.M. Preston & McFarlane, M.; Virology **249,** 418 (1998)

Depudecin

BML-EI319-0100 100 µg

Depudecin is a fungal metabolite that reverts ras- and src-transformed NIH3T3 cells to a flat phenotype (1µg/ml). It is a potent HDAC inhibitor (IC_{50}=4.7µM for HDAC1) and displays anti-angiogenic activity.

LIT: Depudecin, a microbial metabolite containing two epoxide groups, exhibits anti-angiogenic activity in vivo: T. Oikawa et al.; Biol. Pharm. Bull. **18,** 1305 (1995) ▪ Depudecin induces morphological reversion of transformed fibroblasts via the inhibition of histone deacetylase: H.J. Kwon et al.; PNAS **95,** 3356 (1998) ▪ Synthesis and cellular characterization of the detransformation agent, (-)-depudecin: J. Shimada et al.; Chem. Biol. **2,** 517 (1995) ▪ Depudecin: a novel compound inducing the flat phenotype of NIH3T3 cells doubly transformed by ras- and src-oncogene, produced by Alternaria brassicicola: M. Matsumoto et al.; J Antibiot. (Tokyo) **45,** 879 (1992)

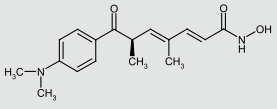
Sodium butyrate

[Butyric acid . sodium salt]

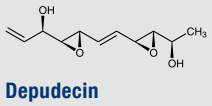
ALX-270-301-G001 1 g

Short-chain fatty acid shown to be an inhibitor of histone deacetylases (HDACs). Induces apoptosis.

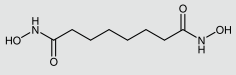
LIT: Sodium butyrate inhibits histone deacetylation in cultured cells: E.P. Candido, et al.; Cell **14,** 105 (1978) ▪ Reduction of telomerase activity in human liver cancer cells by a histone deacetylase inhibitor: M. Nakamura, et al.; J. Cell Physiol. **187,** 392 (2001) ▪ Effects of retinoic acid and sodium butyrate on gene expression, histone acetylation and inhibition of proliferation of melanoma cells: K. Demary, et al.; Cancer Lett. **163,** 103 (2001) ▪ **For a comprehensive bibliography please visit our website.**



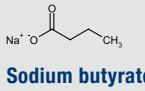
Trichostatin A



Depudecin



Suberoyl bis-hydroxamic acid



Sodium butyrate

Activity Assay Kits

The *Fluor de Lys*® (Fluorescent deacetylation of lysine) Assay System was developed for simple, nonradioactive measurement of deacetylase activity. Deacetylation of a *Fluor de Lys*® substrate by a source of deacetylase activity, including purified enzyme or enzyme complex, cell lysate or whole cells, sensitizes the substrate so that, in a second step, treatment with the appropriate *Fluor de Lys*® Developer produces a fluorophore (see Figure 10). The assay is compatible with class I, IIb & IV HDACs and sirtuins and a variety of substrates are available based on acetylated sites found in p53 and histones. The new *Fluor de Lys*®-Green substrate (incorporated into BML-AK530) offers a higher sensitivity and an excitation and emission (485/530nm) that avoids quenching and fluorescent interference from compounds absorbing in the near UV and blue range. *Fluor de Lys*® Substrate is cell-permeable and allows cell-based determination of HDAC activity (Prod. No. BML-AK503). The *Fluor de Lys*® system is the basis of several activity assays/ drug discovery kits for HDACs (Prod. No.s BML-AK500, BML-AK511, BML-AK516, BML-AK518, BML-AK530 & BML-AK531) and sirtuins (BML-AK555, BML-AK556 and BML-AK557) that allows straightforward screening for new modulators of deacetylase activity.

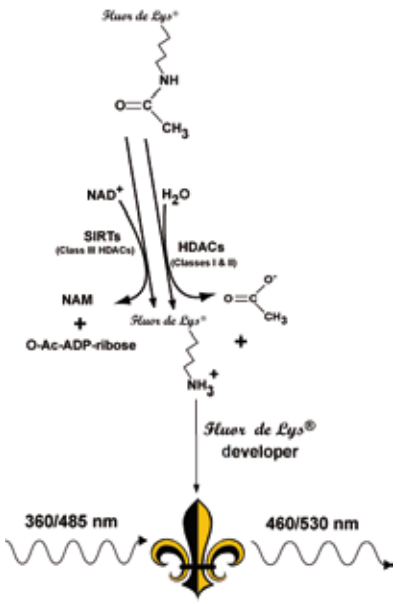


FIGURE 10: Mechanism of the *Fluor De Lys*® HDAC assay. Deacetylation of the substrate sensitises it to the developer, which then generates a fluorophore (symbol). The fluorophore is excited with 360 nm light and the emitted light (460 nm) is detected on a fluorometric plate reader.

Selected citations using the *Fluor de Lys*® activity assays:

X. Zhou et al.; PNAS **98,** 10572 (2001) ▪ K.J. Bitterman et al.; J. Biol. Chem. **277,** 45099 (2002) ▪B. Heltweg and Jung, M.; Anal. Biochem. **302,** 175 (2002) ▪ K. Ito et al.; PNAS **99,** 8921 (2002) ▪ S. Milutinovic et al.; J. Biol. Chem. **277,** 20974 (2002) ▪ R.M. Anderson et al.; Science **302,** 2124 (2003) ▪ K.T. Howitz et al.; Nature **425,** 191 (2003) ▪ G.V. Kapustin et al.; Org. Lett. **5,** 3053 (2003) ▪ D.K. Kim et al.; J. Med. Chem. **46,** 5745 (2003) ▪ C.G. Kleer et al.; PNAS **100,** 11606 (2003) ▪ K. Zhao et al.; Nat. Struct. Biol. **10,** 864 (2003) ▪ T. Suzuki et al.; Bioorg. Med. Chem. Lett. **13,** 4321 (2003) ▪ B.G. Cosio et al.; Am. J. Respir. Crit Care Med. **170,** 141 (2004) ▪ C.M. Gallo et al.; Mol. Cell Biol. **24,** 1301 (2004) ▪ N. Gurvich et al.; Cancer Res. **64,** 1079 (2004) ▪ L.H. Wang et al.; Nat. Med. **10,** 40 (2004) ▪ J.G. Wood et al.; Nature **430,** 686 (2004) ▪ F. Yeung et al.; EMBO J. **23,** 2369 (2004) ▪ J.L. Avalos et al.; Mol. Cell **17,** 855 (2005) ▪ K. Ito et al.; N. Engl. J. Med. **352,** 1967 (2005) ▪ A. Mai et al.; J. Med. Chem. **48,** 7789 (2005) ▪ E. Michishita et al.; Mol. Biol. Cell **16,** 4623 (2005) ▪ A.D. Napper et al.; J. Med. Chem. **48,** 8045 (2005) ▪ T. Suzuki et al.; J. Med. Chem. **48,** 1019 (2005) ▪ P. Aksoy et al.; BBRC **349,** 353 (2006) ▪ V.C. de ▪ Boer et al.; Mech. Ageing Dev. **127,** 618 (2006) ▪ S.L. Gantt et al.; Biochemistry **45,** 6170 (2006) ▪ W. Gu et al.; Bioorg. Med. Chem. **14,** 3320 (2006) ▪ D. ▪ Herman et al.; Nat. Chem. Biol. **2,** 551 (2006) ▪ X. Li et al.; Cancer Res. **66,** 9323 (2006) ▪ V.M. Nayagam et al.; J. Biomol. Screen. **11,** 959 (2006) ▪ J.M. Solomon et al.; Mol. Cell Biol. **26,** 28 (2006) ▪ P.H. Kiviranta et al.; Bioorg. Med. Chem. Lett. **17,** 2448 (2007) ▪ T.F. Outeiro et al.; Science **317,** 516 (2007) ▪ S. Lain et al.; Cancer Cell **13,** 454 (2008) ▪ B. Jung-Hynes et al.; J. Biol. Chem. **284,** 3823 (2009)

Product	Prod. No.	Size
Fluor-de-Lys® HDAC fluorometric activity assay kit	BML-AK500-0001	1 Kit
Color-de-Lys™ HDAC colorimetric activity assay kit	BML-AK501-0001	1 Kit
Fluor-de-Lys® HDAC1 fluorometric drug discovery assay kit	BML-AK511-0001	1 Kit
Fluor-de-Lys® HDAC8 fluorometric drug discovery kit	BML-AK518-0001	1 Kit
Fluor-de-Lys® HDAC fluorometric cellular activity assay kit	BML-AK503-0001	1 Kit
Fluor-de-Lys® HDAC3/NCOR1 fluorometric drug discovery kit	BML-AK531-0001	1 Kit
Fluor-de-Lys®-Green HDAC2 fluorometric drug discovery assay kit	BML-AK512-0001	1 Kit
Fluor-de-Lys®-Green HDAC fluorometric activity assay kit	BML-AK530-0001	1 Kit
Fluor-de-Lys® HDAC6 fluorometric drug discovery kit	BML-AK516-0001	1 Kit

Purified (PF) = Purified (Preservative free); FC = Flow Cytometry; ICC = Immunocytochemistry; IP = Immunoprecipitation; IHC = Immunohistochemistry (FS = Frozen Sections, PS = Paraffin Sections); WB = Western blot; BP = Blocking Peptide

Sirtuins [SIRTs]

Sirtuins perform multiple regulatory functions in gene expression and metabolism via their action on histones, transcription factors, structural proteins and enzymes [1]. An enzyme family consisting mostly of NAD^+-dependent lysine deacetylases (class III HDACs) [2], the sirtuins also include some ADP-ribosyl transferases [3]. All sirtuins use one important metabolic cofactor, NAD^+, as a cosubstrate and the acetylation/deacetylation cycle occurs at the expense of another, acetyl-CoA. It has therefore been suggested that sirtuins sense the cell's energetic state, for example via NAD^+ and/or nicotinamide concentrations [4, 5] or the NAD^+:NADH ratio [6], and that their activity is regulated accordingly. Several of the seven members of the human sirtuin family (SIRT1-SIRT7) [2] are known to be profoundly involved in the regulation of insulin signaling [3, 7-9] and energy metabolism [10-18] and are therefore considered promising therapeutic targets for diabetes and obesity [19]. In rodent studies, SIRT1 activators such as resveratrol [20] and SRT1720 [21] have been shown to improve insulin sensitivity [17, 21-23], lower plasma glucose [17, 21-23], increase mitochondrial function [17, 21-23] and muscle aerobic capacity [17, 23] and to protect against diet-induced obesity and/or its associated pathologies [17, 22, 23].

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Sirtuin Kits

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The SIRT1 fluorescent activity assay is based on the unique ***Fluor de Lys***®-SIRT1 substrate/developer II combination. The ***Fluor de Lys***®-SIRT1 substrate is a peptide comprising amino acids 379-382 of human p53 (Arg-His-Lys-Lys(Ac)). The assay's fluorescence signal is generated in proportion to the amount of deacetylation of the lysine corresponding to Lys^{382}, a known *in vivo* target of SIRT1 activity. ***Fluor de Lys***®-SIRT1 was the substrate deacetylated most efficiently by SIRT1 from among a panel of substrates patterned on p53, histone H3 and histone H4 acetylation.

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Fluor-de-Lys® SIRT3 fluorometric drug discovery assay kit

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The SIRT3 fluorimetric assay system is based on the ***Fluor de Lys***® substrate/developer II combination. The ***Fluor de Lys***®-SIRT2 substrate is unique peptide based on amino acids 317-320 of p53 (Gln-Pro-Lys-Lys(Ac)), a site of regulatory acetylation by PCAF acetyltransferase (Lys^{320}). It was selected as the best substrate for SIRT3 from a panel of substrates patterned on p53, histone H3, and histone H4.

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Product	Specificity	Application	Prod. No.	Size
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SIRT2 (human), pAb	Human	WB	BML-SA444-0100	100 µl
SIRT3, pAb	Human, rat and bovine	WB	BML-SA463-0100	100 µl
SIRT5, pAb	Human, mouse, rat and bovine	WB	BML-SA464-0100	100 µl

Sirtuin Activators

Butein

ALX-350-246-M010 10 mg

Plant polyphenol. Activator of human deacetylase SIRT1. Specific tyrosine kinase inhibitor. Potently inhibits the tyrosine kinase activity of the EGF receptor and p60c-src. Potent antioxidant and anti-inflammatory agent. Inhibits glutathione reductase and rat liver glutathione S-transferase. Inhibits aromatase, showing chemopreventive properties. Directly inhibits IKK.

Lit: Butein, a specific protein tyrosine kinase inhibitor: E.-B. Yang, et al.; BBRC **245,** 435 (1998) ▪ Flavonoids inhibit cell growth and induce apoptosis in B16 melanoma 4A5 cells: K. Iwashita, et al.; Biosci. Biotechnol. Biochem. **64,** 1813 (2000) ▪ Small molecule activators of sirtuins extend Saccharomyces cerevisiae lifespan: K.T. Howitz, et al.; Nature **425,** 191 (2003) ▪ The plant polyphenol butein inhibits testosterone-induced proliferation in breast cancer cells expressing aromatase: Y. Wang, et al.; Life Sci. **77,** 39 (2005) ▪ Butein, a tetrahydroxychalcone, inhibits nuclear factor (NF)-kappaB and NF-kappaB-regulated gene expression through direct inhibition of IkappaBalpha kinase beta on cysteine 179 residue: M.K. Pandey, et al.; J. Biol. Chem. **282,** 17340 (2007) ▪ **For a comprehensive bibliography please visit our website.**

Piceatannol

ALX-270-202-M001 1 mg

ALX-270-202-M005 5 mg

ALX-270-202-M010 10 mg

ALX-270-202-M050 50 mg

Synthetic. Activator of human deacetylase SIRT1. Originally isolated from *Euphorbia lagascae*. Selective protein tyrosine kinase Syk inhibitor.

Lit: Piceatannol, a stilbene phytochemical, inhibits mitochondrial F0F1-ATPase activity by targeting the F1 complex: J. Zheng & V.D. Ramirez; BBRC **261,** 499 (1999) ▪ Microarray analysis of piceatannol-induced changes in gene expression in human gastric cancer cells: D. Jeoung, et al.; Biotechnology Lett. **24,** 463 (2002) ▪ Small molecule activators of sirtuins extend Saccharomyces cerevisiae lifespan: K.T. Howitz, et al.; Nature **425,** 191 (2003) ▪ **For a comprehensive bibliography please visit our website.**

Quercetin . dihydrate

ALX-385-001-G005 5 g

ALX-385-001-G025 25 g

Isolated from *Sophora japonica L.* Activator of human deacetylase SIRT1. Antioxidant flavonoid. Inhibitor of mitochondrial ATPase, cAMP- and cGMP-phosphodiesterases. Inhibitor of protein tyrosine kinases and protein kinase C (PKC). Induces apoptosis. Blocks cells at the G_0/G_1 interface. Reversible inhibitor of fatty acid synthase (FAS). Inhibits the production of the inflammatory mediators nitric oxide (NO), TNF-α and IL-12 in activated macrophages

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Resveratrol

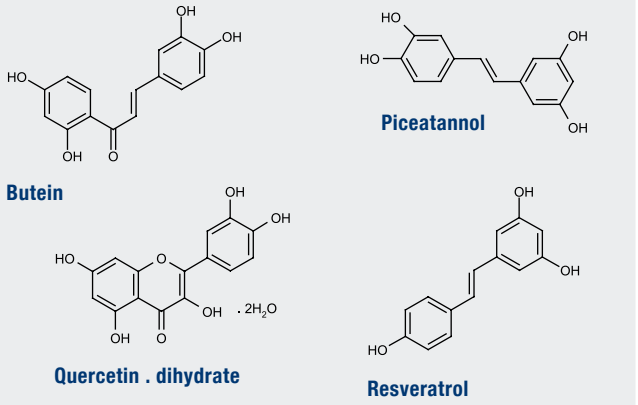
[*trans*-3,4',5-Trihydroxystilbene]

BML-FR104-0100 100 mg

BML-FR104-0500 500 mg

Phenolic antioxidant found in grapes and wine. Potent activator of human deacetylase SIRT1 (maximum effect at 100-200µM). Improves insulin sensitivity in rodent models. Increases longevity in yeast. Displays antiproliferative effect on human breast epithelial cells. Displays a variety of pharmacological activities including: estrogen receptor agonist activity, inhibition of ribonucleotide reductase and DNA synthesis, inhibition of eicosanoid synthesis, cell cycle arrest at S/G2 phase and induction of apoptosis. Inhibits PKD in vitro (IC_{50}=200µM) and *in vivo* (IC_{50}=800µM), but not PKC isoforms. Protects against 4-hydroxynonenal (4-HNE) induced oxidative stress and apoptosis. Shows cancer chemopreventive activity. Specific inhibitor of cyclooxygenase-1 (COX-1). Inhibits the hydroperoxidase activity of COX-1.

LIT: Cancer chemopreventive activity of resveratrol, a natural product derived from grapes: M. Jang, et al.; Science **275,** 218 (1997) ▪ Small molecule activators of sirtuins extend Saccharomyces cerevisiae lifespan: K.T. Howitz, et al.; Nature **425,** 191 (2003) ▪ Resveratrol improves mitochondrial function and protects against metabolic disease by activating SIRT1 and PGC-1alpha: M. Lagouge, et al.; Cell **127,** 1109 (2006) ▪ Small molecule activators of SIRT1 as therapeutics for the treatment of type 2 diabetes: J.C. Milne, et al.; Nature **450,** 712 (2007) ▪ Resveratrol improves health and survivalof mice on a high-calorie diet: J.A. Baur, et al.; Nature **444,** 337 (2006) ▪ Specific SIRT1 activation mimics low energy levels and protects against diet-induced metabolic disorders by enhancingfat oxidation: J.N. Feige, et al.; Cell Metab. **8,** 347 (2008) ▪ Resveratrol interferes with AKT activity and triggers apoptosis in human uterine cancer cells: E. Sexton, et al.; Mol. Cancer **5,** 45 (2006) ▪ Resveratrol and its analogs: Defense against cancer, coronary disease and neurodegenerative maladies or just a fad?: P. Saiko, et al.; Mutat. Res. **658,** 68 (2008) ▪ **For a comprehensive bibliography please visit our website.**



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Tel. 1-800-942-0430 / (610) 941-0430
Fax (610) 941-9252
info-usa@enzolifesciences.com

Switzerland & Rest of Europe

ENZO LIFE SCIENCES AG
Industriestrasse 17, Postfach
CH-4415 Lausen / Switzerland
Tel. + 41/0 61 926 89 89
Fax + 41/0 61 926 89 79
info-ch@enzolifesciences.com

Benelux

ENZO LIFE SCIENCES BVBA
Melkerijweg 3
BE-2240 Zandhoven / Belgium
Tel. +32/0 3 466 04 20
Fax +32/0 3 466 04 29
info-be@enzolifesciences.com

France

ENZO LIFE SCIENCES FRANCE
c/o Covalab s.a.s
13, avenue Albert Einstein,
69100 Villeurbanne / France
Tel. +33/0 472 440 655
Fax +33/0 437 484 239
info-fr@enzolifesciences.com

Germany

ENZO LIFE SCIENCES GmbH
Marie-Curie-Strasse 8
DE-79539 Lörrach / Germany
Tel. +49/0 7621 5500 526
Fax +49/0 7621 5500 527
info-de@enzolifesciences.com

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ENZO LIFE SCIENCES (UK) LTD.
Palatine House
Matford Court
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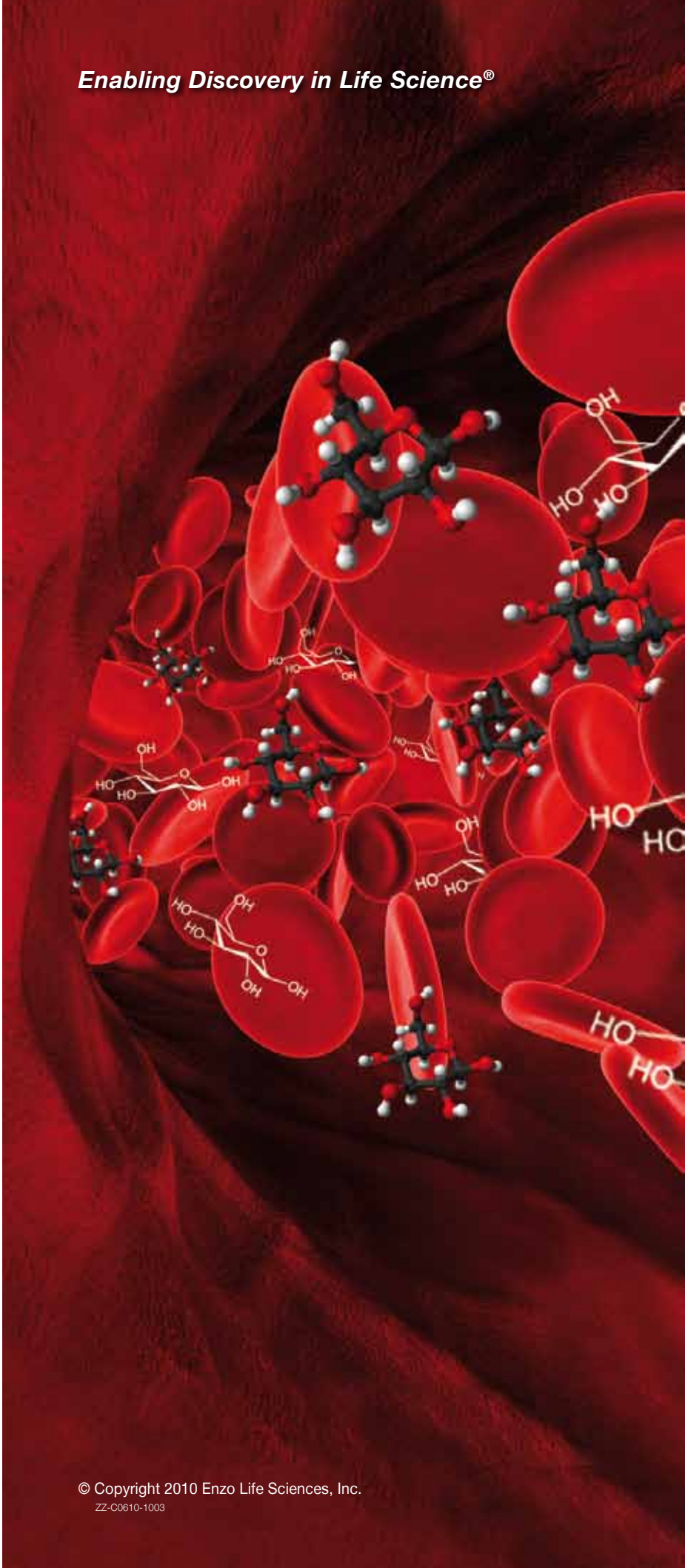

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