In eukaryotes, the several meters long genomic DNA needs to be packed into chromosomes with a diameter of only several hundred micrometers. This is achieved through an elaborated scheme of packaging that starts with the formation of nucleosomes from DNA winding around an octamer core of histones H2A/H2B/H3/H4, followed by linking the core with H1 and packing into chromatin, and leading finally through undefined hierarchy steps to the packed chromosome.

Once thought of as static, non-participating structural elements, it is now clear that histones are integral and dynamic components of the machinery responsible for regulating gene expression. The core histones contain a central histone fold domain, which is flanked by N- and C-terminal tails. These tails, which protrude from the surface of the chromatin polymer and are protease sensitive, comprise 25-30% of the mass of individual histones, thus providing an exposed surface for potential interactions with other proteins. Histone tails are the targets of several modifications including acetylation, methylation, ubiquitination, ADP-ribosylation and phosphorylation. These modifications play a central role in regulating chromatin structure and function.

Historically, histones have been divided into five classes: the linker histones H1 and the core histones H2A, H2B, H3 and H4. The H1 class is subdivided into 8 subtypes H1.0-H1.5, H1T and H1X. More variants have been described. Of special interest are three H2A variants: H2AX, which is phosphorylated at Ser139 (four residues from the C-terminus) in response to the introduction of DNA double-strand breaks, H2AZ, which appears to alter nucleosome stability, and macroH2A, which appears to be enriched on the inactive mammalian X chromosome (see Fig. 1).

Also, recent data suggest that histones may be able to distinguish between healthy and malignant cells, since many tumor cells expose abnormal surface structures. This is consistent with the finding that histone H1 is non-toxic for normal cells, whereas it is able to distinguish between healthy and malignant cells, since many tumor cells expose abnormal surface structures. This is consistent with the finding that histone H1 is non-toxic for normal cells, whereas it is able to distinguish between healthy and malignant cells.

Histone modifications are involved in various biological processes, including gene expression, DNA repair, and chromatin remodeling. For example, histone acetylation and methylation are associated with gene activation and repression, respectively. Histone phosphorylation and ADP-ribosylation are involved in DNA repair and other cellular processes.

Furthermore, histone modifications play a central role in regulating chromatin structure and function. These modifications include acetylation, methylation, ubiquitination, ADP-ribosylation, and phosphorylation. These modifications are dynamically regulated in response to various cellular signals and can alter the accessibility of chromatin to transcription factors and other regulatory proteins.

Histones are also targets of various post-translational modifications, such as acetylation, methylation, and ubiquitination. These modifications are involved in regulating gene expression and chromatin structure. For example, histone acetylation is associated with gene activation, while histone methylation is associated with gene repression.

Finally, histone modification patterns are often linked to specific developmental stages, cell types, and functions. For example, histone modifications are involved in the regulation of cell differentiation, gene expression in response to environmental signals, and the response to various stress conditions.

These mechanisms are critical for understanding the complex relationship between gene expression and chromatin structure, and for developing new therapeutic strategies to target histone modifications in disease.
Gene Regulation - Histone Deacetylases [HDACs]

Histone deacylases (HDACs) and histone acetyltransferases (HATs) are enzymes that influence transcription by selectively deacetylating or acetyllating the ε-amino groups of lysine residues located in the N-terminal region of core histone proteins. Chromatin acetylation correlates with transcriptional activity (euchromatin), whereas deacetylation correlates with gene silencing. HDACs are also involved in the reversible acetylation of non-histone proteins (e.g. p53, tubulin and various transcription factors). Altered HDAC and/or HAT activities are present in many types of cancers. Mammalian HDACs have been classified into three classes. Class I (HDACs 1, 2, 3 & 8) are homologs of yeast RPD3 and localize to the nucleus. Class II (HDACs 4, 5, 6, 7, 9, 10 & 11) are homologs of yeast Hda1 and are found in both the nucleus and cytoplasm. HDAC11 has properties of both class I and class II HDACs. Class III (Sir71 - Sir77) are homologs of yeast Sir2 and form a structurally distinct class of NAD-dependent enzymes found in both the nucleus and cytoplasm.

Conserved from yeast to human, HDAC classes I and II are inhibited by trichostatin A (Prod. No. 380-068) and appear to use a divalent zinc-binding motif. The metal-coordinated active site activates an H2O molecule for direct targeting and hydrolysis of the acetyl group to form acetic acid. Acetylation of lysines in histones neutralizes the positive electric charge between the negatively charged DNA backbone and tips the balance towards relaxing the chromatin, while deacetylation would shift the balance back to condensing the chromatin and silencing gene expression. In a similar way PARP-1 adds to histones hundreds of negatively charged ADP-ribose units, which repel histones away from the negatively charged DNA backbone and thus induces chromatin relaxation to facilitate access of DNA repair enzymes and gene expression.

Unlike HDAC classes I and II, Sir2-like proteins catalyze a unique reaction, that like PARP-1, requires the coenzyme NAD+. In this reaction, nicotinamide is liberated from NAD+ and the acetyl group of the substrate is transferred to cleaved NAD+, generating the novel metabolite O-acetyl-ADP ribose. Due to the NAD+ dependency, Sir2 might be the link between metabolic activity and genome stability and, finally, aging.

Inhibitors of HDAC classes I and II serve as potent anti-cancer agents. A proposed mechanism for the anti-tumor effects of HDAC inhibitors is that the accumulation of acetylated histones leads to activation (and repression) of the transcription of a selected number of genes whose expression causes inhibition of tumor cell growth and induction of apoptosis.

Selected Latest Review Articles:

Latest Product Additions

HDAC Class I & II Inhibitors

**NEW** MS-275

[N-(2-Aminophenyl)-4-[N-(pyridine-3-ylmethoxy-carbonyl)aminomethyl]benzamide] 1mg

Preferentially inhibits HDAC1 (IC50 = 300mM) versus HDAC3 (IC50 = 8µM) and has no inhibitory activity towards HDAC8 (IC50 = 100µM).

**NEW** Oxamflatin

[(2E)-5-[3-(Phenylsulfonyl)aminophenyl]pent-2-en-4-ynoic acid] 1mg

Potent inhibitor of mammalian HDAC (IC50~15.7nM).

**NEW** ITSA1

[N-(1H-Benzotriazol-1-yl)-2,4-dichlorobenzamide] 1mg

Cell-permeant benzotriazole amide that counteracts and complements histone and tubulin deacetylase (HDAC and TDA1) inhibitors in elucidating mechanisms of inhibition and the role of acetylation in various cellular responses such as transcription, differentiation, cell cycle progression, and apoptosis. Does not modify histone-acetyltransferases (HATs) or the levels of HDACs.

Latest Insight on Sir2 Activators

**NEW** Splitomicin

[N-(2-Hydroxy-6-pentadecylbenzoic acid; 6-Pentadecylsalicylic acid] 5mg

Cell-permeable salicylic acid analog that acts as a potent, non-competitive inhibitor of p300 and PCAF (p300/CBP-associated factor) histone acetyltransferase (HAT) activities (IC50>8.5 µM and ~5µM, respectively).

**NEW** CTPB

[(4-Chloro-3-fluoromethylphenyl)-2-ethoxy-6-pentadecylbenzamide] 5mg

Potent activator of p300 HAT, but not of PCAF (p300/CBP-associated factor) HAT activities.

Product Overview HDAC, HAT & Related Products

Enzymes & Substrates
- Histone Deacetylase (rat) 200-052-L002 2ml
- Histone Deacetylase Substrate (Fluorometric) 260-137-M001 1mg
- Histone Deacetylase Colorimetric Assay Kit 850-294-KI01 1 Kit
- Histone Deacetylase Fluorometric Assay Kit 850-230-KI01 1 Kit

For Prices visit our Online Catalog at www.alexis-e-bio.com, contact your Local Distributor, or call +41 61 926 89 89
**Gene Regulation - Histone Deacetylases [HDACs]**

**HDAC Class I & II Inhibitors & Related Products**
- Apicidin 350-005-M001 1mg
- HC toxin 630-102-M001 1mg
- ITS1 270-362-M005 5mg
- M344 270-297-M001 1mg 270-297-M005 5mg
- MC 1293 270-344-M005 5mg
- MS-275 270-378-M001 1mg 270-378-M005 5mg
- Nullscript 270-302-M001 1mg 270-302-M005 5mg
- Oxamflatin 270-379-M001 1mg
- SAHA [Suberoylanilide hydroxamic acid] 270-288-M001 1mg 270-288-M005 5mg
- Not available for sale in the United States of America.
- SBHA [Suberyl-bishydroxamic acid] 270-366-M010 10mg
- Not available for sale in the United States of America.
- Scriptaid 270-298-M001 1mg 270-298-M005 5mg
- Sodium butyrate 270-301-G001 1g
- Sodium 4-phenylbutyrate 270-303-M100 100mg
- Trichostatin A 380-068-M001 1mg 380-068-M005 5mg
- Valproic acid, sodium salt 550-304-G005 5g

**HDAC Class III [Sir2] Inhibitors**
- Sirolin 270-308-M001 1mg 270-308-M005 5mg
- Splitomicin 270-380-M001 1mg 270-380-M005 5mg

**HDAC Class III [Sir2] Activators**
- Butein 350-246-M010 10mg
- Piceatannol 270-202-M010 10mg 270-202-M030 50mg
- Quercetin, dihydrate 350-001-G005 5g
- Resveratrol 270-125-M005 50mg

**HAT Inhibitor & Activator**
- Ancillary acid
- CTPB 420-003-M005 5mg

**Antibodies to HDAC Class I & II**
- anti-Histone Deacetylase 1 PAb, from rabbit 210-256-C100 100µg
  - Reactivity: BP: 158-006
- anti-Histone Deacetylase 2 PAb, from rabbit 210-257-C100 100µg
  - Reactivity: BP: 158-007
- anti-Histone Deacetylase 3 PAb, from rabbit 210-258-C100 100µg
  - Reactivity: BP: 158-008
- anti-Histone Deacetylase 4 (human) (CT) PAb, from rabbit 210-338-C100 100µg
  - Reactivity: BP: 158-009
- anti-Histone Deacetylase 4 (NT) PAb, from rabbit 210-338-C100 100µg
  - Reactivity: BP: 158-010

**Antibodies to Coactivators/Co-repressors & DNA Methytransferases**

**Gene Regulation - PARP-1 & its Homologs**

Picture courtesy of J.-C. Amé & G. de Murcia (CNRS, Strasbourg).

More Resources at www.alexis-e.biz

- Detailed product description and data sheets for all products
- Extensive general and product specific literature references.
- Bethyl Laboratories, Inc. Antibodies to DNA Repair Enzymes and Transcription Factors.

**Latest insight:** A variety of HDAC 1 & 2 inhibitors have been found to upregulate Sir-2-4 & -7 and downregulate Sirt-1, -5 & -6. For details see: Differential regulation of the Sir2 histone deacetylase gene family by inhibitors of class I and II histone deacetylases: S. Kyrklund et al.; Cell Mol. Life Sci. 60, 1999 (2003)

**Antibody Reactivity:**
- = Human
- = Mouse
- = Others

**Application:**
- = ELISA
- = Flow Cytometry
- = Immunocytochemistry
- = Immunohistochemistry
- = Immunoprecipitation
- = Western Blot
- = Other Application

**BP:**
= Product Number of corresponding Blocking Peptide
Gene Regulation - PARP-1 & its Homologs

Poly(ADP-ribosyl)ation plays an important role in a rich variety of physiological phenomena like: 1) DNA-base excision repair and genotoxic stress resistance, 2) signalling of DNA damage, 3) regulation of genomic stability in cells under genotoxic stress, 4) transcriptional regulation, 5) stimulation of nuclear proteosomal function, and 6) ageing and longevity, and in pathophysiological phenomena like: 1) diabetes mellitus, 2) ischaemia-reperfusion damage in brain, heart, kidney and bowel, 3) septic and haemorrhagic shock, and 4) acute and chronic inflammatory disorders.

PARP-1 plays a pivotal role in the cell’s decision to survive or die. In response to DNA damage PARP-1 binds on DNA strand breaks, becomes activated and inhibits transcription. This results in a cell cycle arrest to allow DNA repair. In neuronal cells in response to massive DNA damage, PARP-1 activation signals apoptosis-inducing factor (AIF) release from the mitochondria which translocates to the nucleus resulting in a caspase-independent pathway of apoptosis. However, overactivation of PARP-1 leads to depletion of NAD⁺ and hence also to depletion of overall ATP, resulting in energy deprivation, often followed by necrosis.

Modulation of NAD⁺ levels by PARP-1 has a linkage to the Sir2 histone deacetylase, which depends on high NAD⁺ and low nicotinamide levels for deacetylation. For details see chapter “Histone Deacetylases”.

PARP-1 also emerges as component of enhancer/promoter regulatory complexes critical for gene regulation. PARP-1 has been shown to modify and form stable complexes with transcription factors Oct-1, B-MYB, TEF-1, AP-1, p53 and NF-kB. It has been demonstrated to inhibit transcription initiation by poly(ADP-ribosyl)ating TATA-box-binding proteins thus preventing the formation of the initiation complex.

A recent article reports PARP-1 to act as a positive coactivator of E2F-1-mediated transcription during re-entry of quiescent cells into S phase (C.M. Simbulan-Rosenthal, et al.; Oncogene 22, 8460 (2003)). In contrast to other PARP-1 interactions, PARP-1 does not poly(ADP-ribosyl)ate E2F-1 but binds to it independently of its DNA and catalytic domains.

Selected Latest Review Articles:


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**Gene Regulation - PARP-1 & its Homologs**

**PARP-1 Inhibitors**

- **NEW** EB-47, HCl, 2H2O
  - [1-Pyrenezasoxacetate-4-(1H-purin-9-yl)-1-dloxy-p-D-riboturanor]-N-2,3-dihydro-1H-isoindol-4-yl-1-one, dihydrochloride, dihydrate
  - Very potent and water soluble PARP-1 inhibitor (IC50 = 45 nM, 100% inhibition at 200 nM).

- **NEW** NU1025
  - 8-Hydroxy-2-methylquinazoline-4-one
  - Potent PARP-1 inhibitor (IC50 = 400 nM).

- **NEW** TIO-A
  - Thiou[2,3-c]quinolin-5-one
  - Potential PARP-1 inhibitor (IC50 = 450 nM). Neuro-protectant.

**Product Overview PARP-1 & its Homologs and Related Products**

**Enzymes & Standards**

- **PARP-1 (human) (rec.)** (high purity)
  - 201-063-C120
  - 270-365-M005 1mg
  - 270-365-M005 5mg

- **PARP-1 (bovine) (-90%)**
  - 202-042-C101
  - 270-370-M005 1mg
  - 270-370-M005 5mg

- **PARP-1 (bovine) (automodified) Standard**
  - 202-044-R100
  - 270-370-M005 10µL
  - 270-370-M005 50µL

- **PARP-2 (mouse) (rec.)** (high purity)
  - 201-064-C120
  - 270-370-M005 1mg
  - 270-370-M005 5mg

- **PARP-3 (human) (rec.)** (high purity)
  - 201-175-C120
  - 270-370-M005 1mg
  - 270-370-M005 5mg

**Poly(ADP-ribose) Glycohydrolase [PARG] Inhibitor**

- **ADP-HPD**. ammonium salt, dihydrate
  - 400-049-C100
  - Potent PARP-1 inhibitor (IC50 = 270-365-M005 5mg)
  - 270-365-M005 10mg

**Antibodies**

- **anti-PARP-1**
  - MAb (19H4), mouse IgG2a, 804-211-R100 100µL
  - MAb (p193-6), mouse IgG2b, 804-220-R100 100µL
  - MAb (bovine), mouse IgG1, 210-304-R100 100µL

- **anti-PARP-2**
  - MAb (6A12), mouse IgG1, 804-214-R050 50µL
  - MAb (LA6B10), mouse IgG3, 804-220-R100 100µL

- **anti-PARP-3**
  - MAb (C2-10), mouse IgG1, 804-211-R100 100µL
  - MAb (LA6B10), mouse IgG3, 804-220-R100 100µL

- **anti-PARP-4**
  - MAb (p193-4), mouse IgG2a, 804-214-R050 50µL
  - MAb (p193-10), mouse IgG2b, 804-220-R100 100µL

**Enzymes & Standards**

- **PARG** [Poly(ADP-ribose) glycohydrolase] (bovine)
  - 202-046-C010
  - 202-046-C010 10µg

- **EB-47**
  - 270-278-G001 1g
  - 270-278-G001 5g

- **DTQ-6**
  - 270-279-G001 1g
  - 270-279-G001 5g

**Activators**

- **Peroxynitrite**. tetramethylammonium
  - 480-039-M025
  - 480-039-M025 25mg

- **Nicotinamide**
  - 480-008-C100
  - 480-008-C100 10g

**Inhibitors**

- **5-Iodo-6-amino-1,2-benzopyrone** [INH2BP]
  - 270-370-M005
  - 270-370-M005 5mg

- **6(5H)-Phenanthridine**
  - 270-251-M010
  - 270-251-M010 10mg

- **PJ-34**
  - 270-289-M001
  - 270-289-M001 1mg

**More Resources at [www.alexis-e-biz](http://www.alexis-e-biz)**

- Detailed product description and data sheets for all products.
- Extensive product literature references.
- LKT Laboratories, Inc. DNA Alkylating Reagents.
- Bethyl Laboratories, Inc. Antibodies to DNA Repair Enzymes and Transcription Factors.
- JENA Jena Bioscience Recombinant Transcription Factors.
- ProSci, Inc. Polyclonal Antibodies to AIF.
Gene Regulation - Ubiquitination & Sumoylation

Regulation of protein functions can be activated by posttranslational protein modifications. One of the most studied modifications has been conjugation to ubiquitin, a highly conserved protein of 76 aa residues, which mainly targets substrate proteins for degradation by the 26S proteasome to peptides. This reaction involves the formation of an isopeptide bond between the C-terminal glycine residue of ubiquitin and the ε-amino group of a lysine residue of an acceptor protein. Ubiquitination requires ATP and three different enzymes, an ubiquitin activating enzyme (E1), an ubiquitin conjugating enzyme (E2) and an ubiquitin ligase (E3).

Among the many targets of ubiquitin-mediated proteolysis are many short-lived proteins involved in cell cycling, such as Myc and the androgen receptor, and transcriptional activators which do not require DNA binding for their degradation, such as p53, c-Jun and Hif-1α (for a review see [2]). However under certain circumstances ubiquitination of transcription factors, independent of proteolysis, is also required for the activation function of some transcription factors. Furthermore ubiquitin can form conjugates with histones and is part of the histone-code. The histone-code hypothesis proposes that posttranslational modifications in histone tails are ‘read’ by other histones and/or proteins, and are translated into silencing or activation of gene transcription. For example phosphorylation of Ser10 of histone H3 antagonizes methylation of Lys9, but serves as a synergist for the acetylation of Lys4 and/or Lys14. Another example is the methylation of histone H3 at Lys4 and Lys79, which requires the ubiquitination of histone H2B at Lys123 (for reviews see [3-5]).

Ubiquitination leads to substrate ubiquitination by forming isopeptide bonds between the C-terminus of ubiquitin and the ε-amino group of lysine residues on the target proteins. The ubiquitin molecule contains two lysine residues which have been used to classify the different ubiquitin conjugates: mono-ubiquitin, di-ubiquitin, poly-ubiquitin and ubiquitin chains. The length and the number of ubiquitin molecules on a target protein are used as a signal that a protein is targeted for degradation by the proteasome. In general, poly-ubiquitination is stronger than mono-ubiquitination and preferentially targets proteins which are involved in cell cycle regulation, such as proteolysis are many short-lived proteins involved in cell cycling, such as Myc and the androgen receptor. The ubiquitin conjugating enzyme (E2) and an ubiquitin activating enzyme (E1), and an ubiquitin activating enzyme (E1). The activated SUMO-1 acts as a repressor also by targeting histones and so expands the histone code [11].

Two ubiquitin-like molecules are the methylation of histone H2B at Lys4 and ubiquitin conjugating enzyme (E2), and an ubiquitin activating enzyme (E1). The activated SUMO-1 acts as a repressor also by targeting histones and so expands the histone code [11].

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- Extended description of the ubiquitin and proteasome degradation pathway.
- Broad panel of related products.

Antibodies

DUB-3 is a cytokine ( interleukin-4 & -6) inducible deubiquitinating enzyme that blocks cell proliferation and can initiate apoptosis when constitutively expressed.

NEW Pab to DUB-3 (human) (Antrin-3)
9701-610-0100 100µg


NEW DeNEDDylating Enzyme

NEDD8 is a highly conserved cysteine protease that deNEDDylates cullins. NEDD8 appears to be specific for NEDD8 as neither ubiquitin nor SUMO C-terminal extensions are utilized as substrates.

NEW NEDD8 (human) (rec.)
201-171-C050 50µg
Produced in E. coli. Liit. NEDD8, a highly conserved cysteine protease that deNEDDylates cullins. NEDD8 appears to be specific for NEDD8 as neither ubiquitin nor SUMO C-terminal extensions are utilized as substrates.

NEW Pab to UBE1 (human) (Antrin-3)
210-391-R100 100µl

NEW APBP1/Uba3 (human) (rec.) (GST)
280-913-C025 25µg

NEW NEDD8 Activating Enzyme E1 (human) (rec.)
280-912-C050 50µg
Produced in E. coli. NEDD8 activating enzyme APPBP1/Uba3 heterodimer catalyzes the activation of the C-terminal carboxyl group of NEDD8 by forming a high-energy thioester bond in an ATP-dependent manner. The activated NEDD8 is then transferred to a lysine of the target protein by UbeH12 without the requirement of an E1 ligase.

NEW APPBP1/Uba3 (human) (rec.) (GST)
280-913-C025 25µg
[APBP1/Uba3 (human) (rec.) (GST)] of N-terminal human APBP1. NEDD8 Activating Enzyme E1 (human) (rec.)

NEW NEDD8 Activating Enzyme E1 (human) (rec.)
280-912-C050 50µg
Produced in E. coli. NEDD8 Activating Enzyme E1 (human) (rec.)

NEW NEDD8 Activating Enzyme E1 (human) (rec.)
280-912-C050 50µg
Produced in E. coli. NEDD8 Activating Enzyme E1 (human) (rec.)

NEW Pab to UBE1 (human)
210-391-R100 100µl

NEW NEDD8 (human) (rec.)
280-912-C050 50µg
Produced in E. coli. NEDD8 Activating Enzyme E1 (human) (rec.)

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NEW NEDD8 Activating Enzyme E1 (human) (rec.)
280-912-C050 50µg
Produced in E. coli. NEDD8 Activating Enzyme E1 (human) (rec.)

NEW NEDD8 Activating Enzyme E1 (human) (rec.)
280-912-C050 50µg
Produced in E. coli. NEDD8 Activating Enzyme E1 (human) (rec.)
**Gene Regulation - Ubiquitination & Sumoylation**

### Product Overview NEDD8, SUMO & Ubiquitin

#### NEDD8 and Related Products

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<td>BST-E-312-C500</td>
<td>APPR-B (ub8) [NEDD8 Activating Enzyme E1] (human) (rec.)</td>
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#### SUMO and Related Products

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<td>BST-U-818-M01</td>
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#### Ubiquitins

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<td>Ubiquitin (bovine) (Fluorescein)</td>
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#### Ubiquitin Mutants

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<th>Quantity</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>BST-U-530-M002</td>
<td>Ubiquitin (human) (Mutant, K6 only)</td>
<td>2 µg</td>
<td></td>
</tr>
<tr>
<td>BST-U-530-M001</td>
<td>Ubiquitin (human) (Mutant, K6 only)</td>
<td>1 mg</td>
<td></td>
</tr>
</tbody>
</table>

#### Ubiquitin Activating Enzymes

<table>
<thead>
<tr>
<th>Product Code</th>
<th>Description</th>
<th>Quantity</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>BST-E-311-C025</td>
<td>Ubiquitin Activating Enzyme Subunit [SAE1/SAE2] (human) (rec.)</td>
<td>10 µg</td>
<td></td>
</tr>
<tr>
<td>BST-U-820-C500</td>
<td>Ubiquitin Activating Enzyme Subunit [SAE1] (human)</td>
<td>50 µg</td>
<td></td>
</tr>
<tr>
<td>BST-U-820-R500</td>
<td>Ubiquitin Activating Enzyme Subunit [SAE1] (human)</td>
<td>500 µg</td>
<td></td>
</tr>
</tbody>
</table>

#### Ubiquitin Conjugating Enzymes (mammalian) Set

<table>
<thead>
<tr>
<th>Product Code</th>
<th>Description</th>
<th>Quantity</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>BST-U-830-C100</td>
<td>Ubiquitin Conjugating Enzymes (mammalian) Set</td>
<td>1 Set</td>
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</tbody>
</table>
Gene Regulation - Ubiquitination & Sumoylation

Suppressors of Cytokine Signalling [SOCS]

Cytokines regulate the survival, proliferation, differentiation and function of immune cells as well as cells from most other organ systems by binding to receptors at the cell surface to activate complex signal transduction pathways including the Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway.

JAKs phosphorylate tyrosine residues in the cytoplasmic domain of the receptor, creating recognition sites for signalling proteins with Src homology 2 (SH2) or other phosphotyrosine binding domains. Members of the signal transducers and activators of transcription (STAT) family are latent transcription factors with SH2 domains that are phosphorylated by JAKs upon binding to the receptor, enabling them to dimerize and enter the nucleus where they regulate gene transcription. Rhampt cytokine signal transduction can have disastrous biological consequences, and for this reason, signalling pathways are tightly controlled at multiple points. SH2-containing phosphatase (SHP) proteins are constitutively expressed and can attenuate cytokine signal transduction by dephosphorylating signalling intermediates such as JAK and its receptor. Members of the protein tyrosine phosphatase (PTP) family are also constitutively expressed and sumoylate STATs to inhibit transcriptional activation. To date, the only known inducible inhibitors of cytokine signalling are the suppressor of cytokine signalling (SOCS) proteins.

SOCS proteins can recognize cytokine receptors or the associated JAKs and attenuate signal transduction both by direct interference with signalling and by targeting the receptor complex for ubiquitin-mediated proteasomal degradation.

SOCS have emerged as key physiological regulators of cytokine responses including T cell activation and differentiation, inflammation signalling including induction by TLR signalling and insulin/ leptin signalling.

There are eight CIS and SOCS family proteins (CIS-1, SOCS1, SOCS2, SOCS3, SOCS4, SOCS5, SOCS6 and SOCS7), each of which has a central SH2 domain, an N-terminal domain of variable length and sequence, and a C-terminal 40-amino-acid module called the SOCS box. The N-terminus of the SOCS box motif contains an ~10 residue binding motif termed the “BC box” that binds the elongin B-elongin C heterodimer. The BC box binds to elongin C, which in turn associates with cullin2 or cullin3 and Rbx1 to form a multiprotein complex capable of acting as an E3 ubiquitin-ligase. Together with a ubiquitin-activating enzyme (E1) and a ubiquitin-conjugating enzyme (E2), the E3 ubiquitin ligase acts to tag proximal proteins with polyubiquitin chains, leading to their degradation by the proteasome.

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Latest Product Additions

Antibodies to SOCS Proteins


More Resources at www.alexis-e-biz