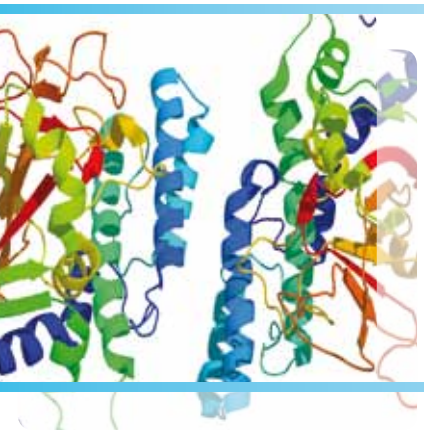


The PARP Family & ADP Ribosylation

Introduction

Poly(ADP-ribosyl)ation is a post-translational modification process which plays a critical role in diverse cellular functions such as DNA damage detection and repair, transcriptional regulation, intracellular trafficking, chromatin modification, mitotic apparatus formation, and cell death. The process is mediated by members of the family of poly(ADP-ribose) polymerases (PARPs), which transfer ADP-ribose units from nicotinamide dinucleotide (NAD) to certain residues in PARPs and onto target proteins. PARPs also mediate the polymerization of ADP-riboses via glycosidic bonds, creating long and branched ADP-ribose polymers, which are subsequently degraded by polyADPribose glycohydrolase (PARG). ADP-ribose polymers are thought to modify protein functions. In humans, the PARP family members are encoded by 17 different genes, while PARP-1 is the founding member [1-3].

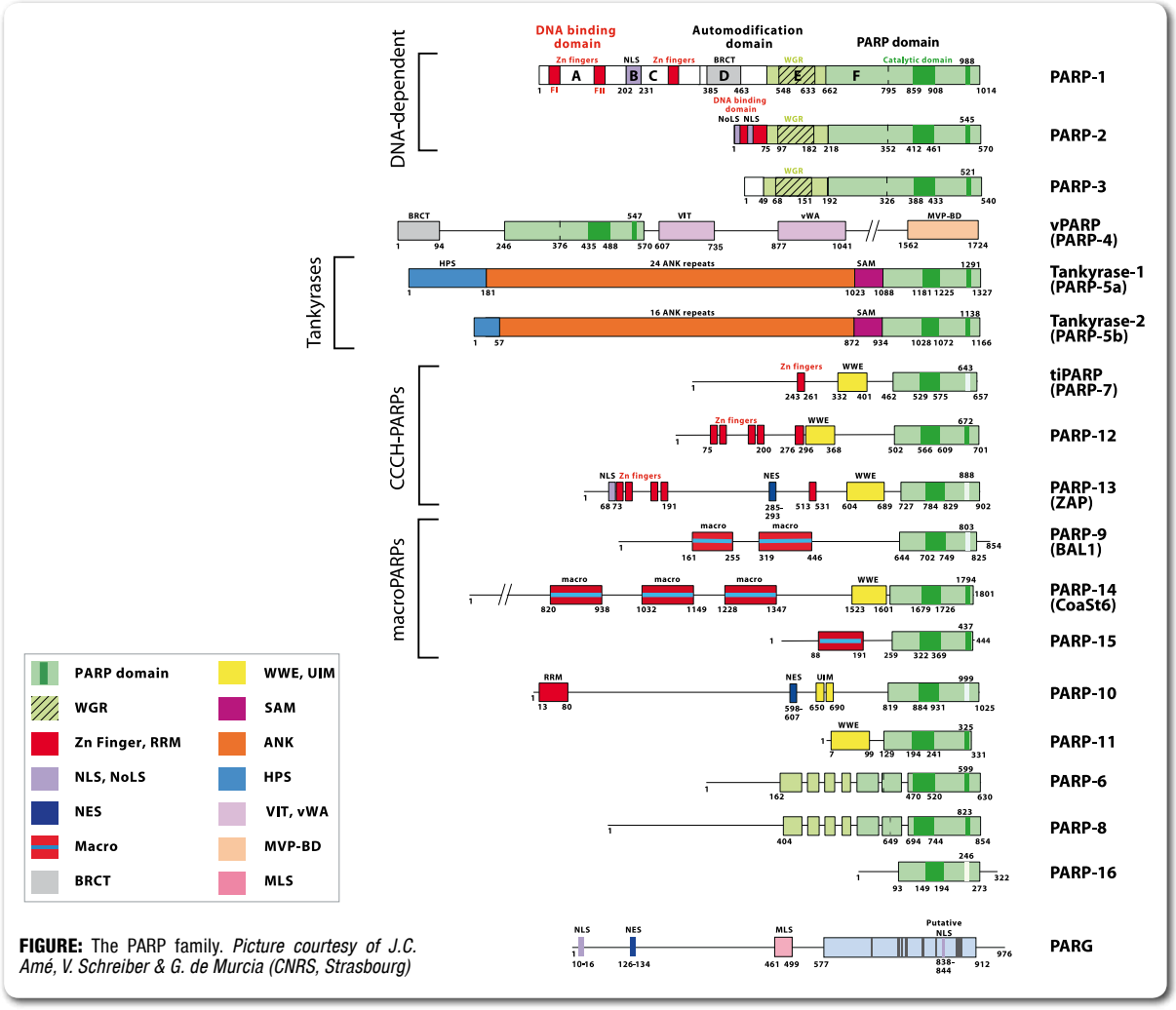


FIGURE: The PARP family. *Picture courtesy of J.C. Amé, V. Schreiber & G. de Murcia (CNRS, Strasbourg)*

The PARP Family

DNA Repair (Cell Survival)

PARP-1 has been implicated in multiple DNA repair pathways including single-strand break repair (SSBR), double strand break (DSB) repair and base excision repair (BER). The molecular mechanism of BER may involve a local chromatin relaxation mediated either by covalent modification of histones with poly(ADP-ribose) or by non-covalent interaction of histones with poly(ADP-ribose) that automodifies the enzyme. This might regulate the accessibility to other DNA repair proteins. In addition PARP-1 or poly(ADP-ribose) (PAR) may directly recruit repair proteins like XRCC1 (X-ray repair crosscomplementing 1) to the site of DNA damage [4-7]. PARP-2 is the only other known member of the PARP family to be activated by DNA strand breaks [8]. Although its DNA-binding domain is different from that of PARP-1, PARP-2 has been shown to interact with the SSBR/BER repair factors XRCC1, DNA polymerase β and DNA ligase III [9]. PARP-2 seems to be involved in later steps of the repair processes [10]. Beside its role in DNA repair, PARP-2 has been shown to be involved in diverse processes such as spermatogenesis, adipogenesis and T cell development [11]. BRCA1 and BRCA2 are tumor suppressor proteins important for DSB repair by homologous recombination. For a recent review see [12]. It has been demonstrated that BRCA1 or BRCA2 deficient cells have lost their ability to repair single-strand breaks by homologous recombination (HR) after PARP-1 depletion or inhibition, which can result in cell cycle arrest and apoptosis [13, 14]. This specific killing of tumor cells led to PARP inhibitors entering clinical trials and the screen for genes mediating such lethal sensitivity [15, 16]. Interestingly, it has been showed that antitumor chemotherapy with platinum analogs and PARP inhibitors can induce counter-mutation restoring HR capabilities of BRCA2 deficient cells [17, 18].

DNA-independent Activation

PARP-1 can also be activated by a DNA independent mode [19, 20]. This alternative mechanism is mediated by phosphorylated ERK2, showing that PARP-1 plays a role in the ERK signalling cascade mediating growth and differentiation. Activated PARP-1 increased ERK2-catalyzed Elk1 phosphorylation, histone acetylation, and the expression of the Elk1-targeted gene c-Fos [19].

Latest Insight

The Zn3 Domain has Dual Roles in Regulating the Function of PARP

PARP-1 has a modular structure and contains multiple independent domains that perform distinct functions. Recently, M.F. Langelier, et al. identified and mapped two different structural regions within the Zn3 domain: a novel zinc-ribbon fold essential for DNA-dependent PARP-1 activity and a homodimeric Zn3 structure contributing to the chromatin compaction activity of PARP-1.

LIT: The Zn3 domain of human poly(ADP-ribose) polymerase-1 (PARP-1) functions in both DNA-dependent poly(ADP-ribose) synthesis activity and chromatin compaction: M.F. Langelier, et al.; J. Biol. Chem. **285,** 18877 (2010)

Apoptosis / Necrosis (Cell Death)

Whereas activation of PARP-1 by mild genotoxic stimuli may facilitate DNA repair and cell survival, massive DNA damage may trigger hyperactivation of PARP-1 and cell death [21]. Excessive PARP-1 activity and PAR synthesis have been shown to induce cell death by causing NAD^+/ ATP depletion [22-23] as well as triggering the release and nuclear translocation of apoptosis inducing factor (AIF) [24, 25]. AIF induced cell death in response to the alkylating agent N-methyl- N'-nitro-N'-nitrosoguanidine (MNNG) requires calpains and Bax next to PARP-1 [26]. There seems to be a direct toxicity of PAR itself causing cellular death independent of energetic or transcriptional changes [27, 28]. PARP-1 activation is thought to be a key mediator of neuronal death during excitotoxicity, ischemia, and oxidative stress, as well as being of importance for other neuronal diseases [29-30].

PARP and Transcription

PARP-1 may regulate transcription by at least two different mechanisms. It can act as a modulator of the chromatin structure, but also functions as a component of enhancer/ promoter regulatory complexes. PARP-1 can interact with the enhancers and promoters of genes by a) direct sequence-specific binding to enhancers, b) recruitment via DNA binding transcription factors (e.g. NF-κB), and c) direct binding to DNA structures.

LITERATURE REFERENCES:

[1] Poly(ADP-ribose): novel functions for an old molecule: V. Schreiber, et al.; Nat. Rev. Mol. Cell Biol. **7,** 517 (2006) ▪ **[2]** cDNA sequence, protein structure, and chromosomal location of the human gene for poly(ADP-ribose) polymerase: B. W. Cherney, et al.; PNAS **84,** 8370 (1987) ▪ **[3]** Human nuclear NAD+ ADP-ribosyltransferase: localization of the gene on chromosome 1q41-q42 and expression of an active human enzyme in Escherichia coli: H. Herzog, et al.; PNAS **86,** 3514 (1989) ▪ **[4]** XRCC1 is specifically associated with poly(ADPribose) polymerase and negatively regulates its activity following DNA damage: M. Masson, et al.; Mol. Cell Biol. **18,** 3563 (1998) ▪ **[5]** Poly(ADP-ribose) binds to specific domains in DNA damage checkpoint proteins: J. M. Pleschke, et al.; J. Biol. Chem. **275,** 40974 (2000) ▪ **[6]** A requirement for PARP-1 for the assembly or stability of XRCC1 nuclear foci at sites of oxidative DNA damage: S. F. El-Khamisy, et al.; Nucleic Acids Res. **31,** 5526 (2003) ▪ **[7]** The role of poly(ADP-ribose) in the DNA damage signaling network: M. Malanga & F. R. Althaus; Biochem. Cell Biol. **83,** 354 (2005) ▪ **[8]** PARP-2, a novel mammalian DNA damage-dependent poly(ADP-ribose) polymerase: J. C. Ame, et al.; J. Biol. Chem. **274,** 17860 (1999) ▪ **[9]** Poly(ADP-ribose) polymerase-2 (PARP-2) is required for efficient base excision DNA repair in association with PARP-1 and XRCC1: V. Schreiber, et al.; J. Biol. Chem. **277,** 23028 (2002) ▪ **[10]** Feedback-regulated poly(ADP-ribosyl)ation by PARP-1 is required for rapid response to DNA damage in living cells: O. Mortusewicz, et al.; Nucleic Acids Res. **35,** 7665 (2007) ▪ **[11]** Toward specific functions of poly(ADP-ribose) polymerase-2: J. Yelamos, et al.; Trends Mol. Med. **14,** 169 (2008) ▪ **[12]** BRCA gene structure and function in tumor suppression: a repair-centric perspective: G. Murphy & M. E. Moynahan; Cancer J. **16,** 39 (2010) ▪ **[13]** Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase: H. E. Bryant, et al.; Nature **434,** 913 (2005) ▪ **[14]** Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy: H. Farmer, et al.; Nature **434,** 917 (2005) ▪ **[15]** Clinical poly(ADP-ribose) polymerase inhibitors for the treatment of cancer: C. Lewis & J. A. Low; Curr. Opin. Investig. Drugs **8,** 1051 (2007) ▪ **[16]** A synthetic lethal siRNA screen identifying genes mediating sensitivity to a PARP inhibitor: N. C. Turner, et al.; EMBO J. **27,** 1368 (2008) ▪ **[17]** Secondary mutations as a mechanism of cisplatin resistance in BRCA2-mutated cancers: W. Sakai, et al.; Nature **451,** 1116 (2008) ▪ **[18]** Resistance to therapy caused by intragenic deletion in BRCA2: S. L. Edwards, et al.; Nature **451,** 1111 (2008) ▪ **[19]** DNA-independent PARP-1 activation by phosphorylated ERK2 increases Elk1 activity: a link to histone acetylation: M. Cohen-Armon, et al.; Mol. Cell **25,** 297 (2007) ▪ **[20]** PARP-1 activation in the ERK signaling pathway: M. Cohen-Armon; TIPS **28,** 556 (2007) ▪ **[21]** Poly(ADP-ribose) makes a date with death: J. T. Heeres & P. J. Hergenrother; Curr. Opin. Chem. Biol. **11,** 644 (2007) ▪ **[22]** Poly(ADP-ribose) polymerase is a mediator of necrotic cell death by ATP depletion: H. C. Ha & S. H. Snyder; PNAS **96,** 13978 (1999) ▪ **[23]** Alkylating DNA damage stimulates a regulated form of necrotic cell death: W. X. Zong, et al.; Genes Dev. **18,** 1272 (2004) ▪ **[24]** Mediation of poly(ADP-ribose) polymerase-1-dependent cell death by apoptosis-inducing factor: S. W. Yu, et al.; Science **297,** 259 (2002) ▪ **[25]** Apoptosis-inducing factor mediates poly(ADP-ribose) (PAR) polymer-induced cell death: S. W. Yu, et al.; PNAS **103,** 18314 (2006) ▪ **[26]** Sequential activation of poly(ADP-ribose) polymerase 1, calpains, and Bax is essential in apoptosis-inducing factor-mediated programmed necrosis: R. S. Moubarak, et al.; Mol. Cell Biol. **27,** 4844 (2007) ▪ **[27]** Poly(ADP-ribose) (PAR) polymer is a death signal: S. A. Andrabi, et al.; PNAS **103,** 18308 (2006) ▪ **[28]** Neither energy collapse nor transcription underlie in vitro neurotoxicity of poly(ADP-ribose) polymerase hyper-activation: S. Fossati, et al.; Neurochem. Int. **50,** 203 (2007) ▪ **[29]** The role of poly(ADP-ribose) polymerase-1 in CNS disease: T. M. Kauppinen & R. A. Swanson; Neuroscience **145,** 1267 (2007) ▪ **[30]** Multiple roles for poly(ADP-ribose)polymerase-1 in neurological disease: T. M. Kauppinen; Neurochem. Int. **50,** 954 (2007)

PARP Proteins

Standard PARP Proteins

PARP-1 (human), (rec.) (high purity)

ALX-201-063-C020 20 µg

Produced in Sf9 cells. **PURITY:** ≥99% (SDS-PAGE)

LIT: Overproduction and large-scale purification of the human poly(ADP- ribose) polymerase using a baculovirus expression system: H. Giner, et al.; Gene **114,** 279 (1992) ▪ Poly(ADP-ribose) reactivates stalled DNA topoisomerase I and Induces DNA strand break resealing: M. Malanga & F.R. Althaus; J. Biol. Chem. **279,** 5244 (2004) ▪ Regulation of poly(ADP-ribose) polymerase-1 functions by leukocyte elastase inhibitor/LEI-derived DNase II during caspase-independent apoptosis: C. Leptrête, et al.; Int. J. Biochem. Cell Biol. **41,** 1046 (2009)

PARP-2 (mouse), (rec.) (high purity)

ALX-201-064-C020 20 µg

Produced in Sf9 cells (full length). **PURITY:** ≥98% (SDS-PAGE)

LIT: PARP-2, A novel mammalian DNA damage-dependent poly(ADP-ribose) polymerase: J.C. Ame, et al.; J. Biol. Chem. **274,** 17860 (1999) ▪ A bidirectional promoter connects the poly(ADP-ribose) polymerase 2 (PARP-2) gene to the gene for RNase P RNA. structure and expression of the mouse PARP-2 gene: J.C. Ame, et al.; J. Biol. Chem. **276,** 11092 (2001) ▪ Poly(ADP-ribose) reactivates stalled DNA topoisomerase I and Induces DNA strand break resealing: M. Malanga & F.R. Althaus; J. Biol. Chem. **279,** 5244 (2004)

PARP-3 (human), (rec.) (high purity)

ALX-201-170-C020 20 µg

Produced in Sf9 cells. **PURITY:** ≥97%

LIT: PARP-3 localizes preferentially to the daughter centriole and interferes with the G1/S cell cycle progression: A. Augustin, et al.; J. Cell Sci. **116,** 1551 (2003) ▪ Tankyrase-1 polymerization of poly(ADP-ribose) is required for spindle structure and function: P. Chang et al.; Nature Cell Biology **7,** 1133 (2005)

Minor Vault p193 Protein

Vault poly(ADP-ribose) polymerase (VPARP; PARP-4) was originally identified as a minor protein component of the vault ribonucleoprotein particle [1]. Vaults have been implicated in multidrug resistance of human tumors and are thought to be involved in macromolecular assembly and/or transport [2]. In addition to the association of VPARP with the cytoplasmic vault particle, subpopulations of VPARP localize to the nucleus and the mitotic spindle, indicating that VPARP may have other cellular functions. VPARP has been shown to associate with telomerase activity and interact with exogenously expressed telomerase-associated protein 1 (TEP1) in mammalian cells [3].

LITERATURE REFERENCES:

[1] The 193-kD vault protein, VPARP, is a novel poly(ADP-ribose) polymerase: V.A. Kickhoefer, et al.; J. Cell Biol. **146,** 917 (1999) ▪ **[2]** Cellular functions of vaults and their involvement in multidrug resistance: E. Steiner, et al.; Curr. Drug Targets **7,** 923 (2006) ▪ **[3]** Vault poly(ADP-ribose) polymerase is associated with mammalian telomerase and is dispensable for telomerase function and vault structure in vivo: Y. Liu, et al.; Mol. Cell. Biol. **24,** 5314 (2004)

Minor vault p193 protein (human), (rec.) (His-tag)

ALX-201-286-C010 10 µg

Produced in *E. coli*. Catalytic domain of human minor vault p193 protein (aa 220-574) is fused at the C-terminus to a His-tag.

LIT: In silico characterization of the family of PARP-like poly(ADP-ribosyl)transferases (pARTs): H. Otto, et al.; BMC Genomics **6,** 139 (2005)

PARP Family Proteins & Related Products

Product	Source	Prod. No.	Size
PARP-1 (human), (rec.) (high purity) (His-tag)	Produced in Sf21 cells	ALX-201-250-C010	10 µg
PARP-1 (catalytic domain) (human), (rec.) (His-tag)	Produced in Sf21 cells	ALX-201-232-C020	20 µg
PARP-1 (BRCT domain) (human), (rec.) (His-tag)	Produced in *E. coli*	ALX-201-255-C020	20 µg
[E^{988}K]PARP-1 (human), (rec.) (control)	Produced in Sf21 cells	ALX-201-254-C010	10 µg
PARP-1b (human), (rec.) (active) (His-tag)	Produced in Sf21 cells	ALX-201-253-C020	20 µg
PARP-2 (mouse), (rec.) (high purity) (His-tag)	Produced in Sf21 cells	ALX-201-251-C010	10 µg
PARP-3 (human), (rec.) (high purity) (His-tag)	Produced in Sf21 cells	ALX-201-252-C010	10 µg
Poly(ADP-ribose), standard	Automodified PARP-1	ALX-202-043-C001	1 µg
Poly(ADP-ribose), immunoblotting standard	Produced in *E. coli*	BML-SW100-0025	25 µg
PARP-1 (automodified) (bovine thymus), standard	Isolated from calf thymus	ALX-202-044-R100	100 µl
PARP-1 (bovine thymus), immunoblotting standard	Isolated from bovine thymus	BML-SW111-0100	100 µl
HL60 cell extract (non-induced)	Whole-cell extract	BML-SW101-0200	200 µl
HL60 cell extract (etoposide-induced)	Whole-cell extract	BML-SW102-0200	200 µl
PARG (bovine thymus)	Isolated from calf thymus	ALX-202-045-UC01	0.10 U

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

PARP Antibodies

Standard Antibodies

Poly(ADP-ribose) Antibodies

Poly(ADP-ribose), mAb (10H)

ALX-804-220-R100 100 µl

CLONE: 10H. **ISOTYPE:** Mouse IgG3. **IMMUNOGEN:** Purified poly(ADP-ribose). **SPECIFICITY:** Recognizes poly(ADP-ribose) synthesized by a broad range of PARPs (poly(ADP-ribose) polymerases) like human, mouse, rat or *Drosophila* PARP enzyme. **APPLICATION:** FC, IHC (PS), ICC, WB.

LIT: Monoclonal antibodies to poly(adenosine diphosphate ribose) recognize different structures: H. Kawamitsu, et al.; Biochemistry **23,** 3771 (1984) ▪ Poly(ADP-ribosyl)ation, genomic instability, and longevity: A. Bürkle; Ann. N Y Acad. Sci. **908,** 126 (2000) ▪ Detection of poly(ADP-ribose) by immunocytochemistry: a sensitive new method for the early identification of UVB- and H2O2-induced apoptosis in keratinocytes: H. Chang, et al.; Biol. Chem. **383,** 703 (2002) ▪ Flow-cytometric assessment of cellular poly(ADP-ribosyl) ation capacity in peripheral blood lymphocytes: A. Kunzmann, et al.; Immun. Ageing **3,** 8 (2006) ▪ Substrate-assisted catalysis by PARP10 limits its activity to mono-ADP-ribosylation: H. Kleine, et al.; Mol. Cell **32,** 57 (2008)

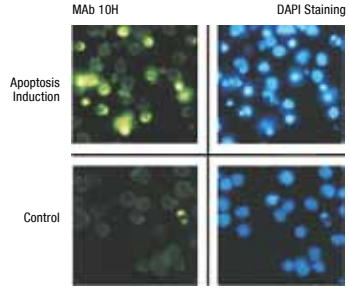


FIGURE: Detection of apoptotic cells by immunofluorescence.

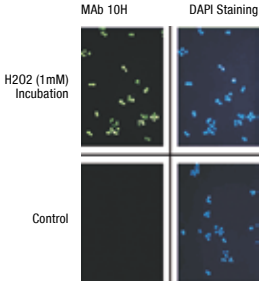


FIGURE: Detection of DNA damage.

Poly(ADP-ribose), pAb (96-10-04)

ALX-210-890-R100 100 µl

From rabbit. **IMMUNOGEN:** Poly(ADP-ribose) with methylated BSA. **SPECIFICITY:** Recognizes poly(ADP-ribose) of 6-100 bases in size, synthesized *in vitro* or *in vivo*. Shows some cross-reactivity with BSA. **APPLICATION:** ELISA, ICC, WB.

LIT: Failure to degrade poly(ADP-ribose) causes increased sensitivity to cytotoxicity and early embryonic lethality: D.W. Koh, et al.; PNAS **101,** 17699 (2004) ▪ MNNG-induced cell death is controlled by interactions between PARP-1, poly(ADP-ribose) glycohydrolase, and XRCC1: C. Keil, et al.; J. Biol. Chem. **281,** 34394 (2006) ▪ Ataxia telangiectasia mutated (ATM) signaling network is modulated by a novel poly(ADP-ribose)-dependent pathway in the early response to DNA-damaging agents: J.F. Haince, et al.; J. Biol. Chem. **282,** 16441 (2007) ▪ Substrate-assisted catalysis by PARP10 limits its activity to mono-ADP-ribosylation: H. Kleine, et al.; Mol. Cell **32,** 57 (2008) ▪ Regulation of poly(ADP-ribose) polymerase-1 functions by leukocyte elastase inhibitor/LEI-derived DNase II during caspase-independent apoptosis: C. Leptrête, et al.; Int. J. Biochem. Cell Biol. **41,** 1046 (2009)

PARP-1, mAb (C2-10)

BML-SA249-0100 100 µg

CLONE: C2-10. **ISOTYPE:** Mouse IgG1. **IMMUNOGEN:** Purified calf thymus PARP-1 (poly(ADP-ribose) polymerase-1). **SPECIFICITY:** Recognizes an epitope in the C-terminal part of the DNA binding domain of human, mouse, rat, hamster, bovine and primate PARP-1. Detects bands ~116kDa (intact PARP-1) and ~85kDa (apoptosis-induced cleavage fragment) by Western blot. Does not cross-react with chicken PARP-1. **APPLICATION:** ELISA, ICC, IP, WB.

LIT: Structural and functional analysis of poly(ADP ribose) polymerase: an immunological study: D. Lamarre, et al.; Biochim. Biophys. Acta **950,** 147 (1988) ▪ Specific proteolytic cleavage of poly(ADP-ribose) polymerase: an early marker of chemotherapy-induced apoptosis: S.H. Kaufmann, et al.; Cancer Res. **53,** 3976 (1993) ▪ Cleavage of poly(ADP-ribose) polymerase by a proteinase with properties like ICE: Y.A. Lazebnik, et al.; Nature **371,** 346 (1994) ▪ Nuclear poly(ADP-ribose) polymerase-1 rapidly triggers mitochondrial dysfunction: G. Cipriani, et al.; J. Biol. Chem. **280,** 17227 (2005) ▪ CCCTC-binding Factor Activates PARP-1 Affecting DNA Methylation Machinery: T. Guastafierro, et al.; J. Biol. Chem. **283,** 21873 (2008) ▪ Regulation of poly(ADP-ribose) polymerase-1 functions by leukocyte elastase inhibitor/LEI-derived DNase II during caspase-independent apoptosis: C. Leprête, et al.; Int. J. Biochem. Cell Biol. **41,** 1046 (2009)

PARP-2, mAb (4G8)

ALX-804-639-L001 1 ml

CLONE: 4G8. **ISOTYPE:** Mouse IgG1. **IMMUNOGEN:** Recombinant mouse PARP-2 (poly(ADP-ribose) polymerase-2). **SPECIFICITY:** Recognizes an epitope in domain E of human and mouse PARP-2. Detects a band of ~62kDa by Western blot. **APPLICATION:** ELISA, WB.

LIT: Anti-Poly-ADP-Ribose Polymerase-2 (PARP-2) Mouse MAb 4G8: Y. Monreal, et al.; Hybridoma **25,** 102 (2006) ▪ CCCTC-binding Factor Activates PARP-1 Affecting DNA Methylation Machinery: T. Guastafierro, et al.; J. Biol. Chem. **283,** 21873 (2008)

Minor vault p193 protein (human), mAb (p193-4)

ALX-801-023-C125 125 µg

ALX-801-023-C250 250 µg

CLONE: p193-4. **ISOTYPE:** Mouse IgG1. **IMMUNOGEN:** Minor vault p193 protein (VPARP; PARP-4). **SPECIFICITY:** Recognizes epitope aa 491-494 of human minor vault p193 protein. **APPLICATION:** IHC (FS), ICC, WB.

LIT: The Mr 193,000 vault protein is up-regulated in multidrug-resistant cancer cell lines: A.B. Schroeijers, et al.; Cancer Res. 60, 1104 (2000) * Multiple human vault RNAs. Expression and association with the vault complex: A. van Zon, et al.; J. Biol. Chem. **276,** 37715 (2001) ▪ Up-regulation of drug resistance-related vaults during dendritic cell development: A.B. Schroeijers, et al.; J. Immunol. **168,** 1572 (2002) ▪ The formation of vault-tubes: a dynamic interaction between vaults and vault PARP: A. Van Zon, et al.; J. Cell Sci. **116,** 4391 (2003)

Tankyrase-1, mAb (19A449)

ALX-804-234-C100 100 µg

CLONE: 19A449. **ISOTYPE:** Mouse IgG1κ. **IMMUNOGEN:** Recombinant human tankyrase-1 (PARP-5a). **SPECIFICITY:** Recognizes human and mouse tankyrase-1. Detects a band of ~110kDa by Western blot. **APPLICATION:** WB.

LIT: Tankyrase, a poly(ADP-ribose) polymerase at human telomeres: S. Smith, et al.; Science **282,** 1484 (1998) ▪ Mammalian telomeres end in a large duplex loop: J.D. Griffith, et al.; Cell **97,** 503 (1999) ▪ Cell cycle dependent localization of the telomeric PARP, tankyrase, to nuclear pore complexes and centrosomes: S. Smith & T. de Lange; J. Cell. Sci. **112,** 3649 (1999) ▪ Chromosomal mapping of the tankyrase gene in human and mouse: L. Zhu, et al.; Genomics **57,** 320 (1999) ▪ Tankyrase promotes telomere elongation in human cells: S. Smith & T. de Lange; Curr. Biol. **10,** 1299 (2000) ▪ DNA G-quadruplexes, telomere-specific proteins and telomere-associated enzymes as potential targets for new anticancer drugs: E. Raymond, et al.; Invest New Drugs **18,** 123 (2000) ▪ Tankyrase is a golgi-associated mitogen-activated protein kinase substrate that interacts with IRAP in GLUT4 vesicles: N.W. Chi & H.F. Lodish; J. Biol. Chem. **275,** 38437 (2000)

PARP-3

Human PARP-3 (hPARP-3) (540aa, with an approx. mass of 67kDa) is a core component of the centrosome and preferentially localized to the daughter centriole throughout the cell cycle. The N-terminal domain (54aa) of hPARP-3 is responsible for its centrosomal localization. An attractive hypothesis is that the presence of both PARP-1 and PARP-3 at the centrosome may link the DNA damage surveillance network to the mitotic fidelity checkpoint.

LITERATURE REFERENCES:

PARP-3 localizes preferentially to the daughter centriole and interferes with the G1/S cell cycle progression: A. Augustin, et al.; J. Cell Sci. **116,** 1551 (2003)

PARP-3, mAb (LA6B10)

ALX-804-466-R100 100 µl

CLONE: LA6B10. **ISOTYPE:** Mouse IgM. **IMMUNOGEN:** Synthetic peptide corresponding to N-terminal aa 8-22 ($M^{8}APKPKPWVQTEGPE^{22}$) of human PARP-3 (poly(ADP-ribose) polymerase-3). **SPECIFICITY:** Recognizes human and mouse PARP-3. **APPLICATION:** ICC.

LIT: PARP-3 localizes preferentially to the daughter centriole and interferes with the G1/S cell cycle progression: A. Augustin, et al.; J. Cell Sci. **116,** 1551 (2003) ▪ Tankyrase-1 polymerization of poly(ADP-ribose) is required for spindle structure and function: P. Chang, et al.; Nat. Cell Biol. **7,** 1133 (2005)

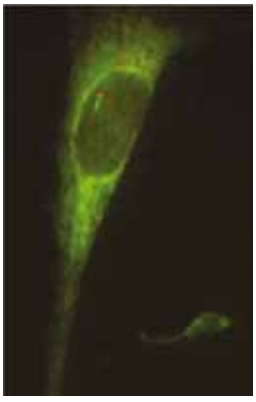


FIGURE: PARP-3 (red) preferentially localizes to the daughter centriole. The mother centriole (green) is immunostained with anti-acetylated α-tubulin in 3T3 cells. *Picture courtesy of C. Spenlehauer & G. de Murcia (CNRS, Strasbourg).*

Latest Insight

PARP-3 is a Mono-ADP-ribosylase that Activates PARP-1 in the Absence of DNA

PARP-3 is closely related to PARP-1 and PARP-2 with a high degree of similarity in the catalytic domain. Recently O. Loseva et al. have shown that PARP-3 is able to ADP-ribosylate itself as well as histone H1. In contrast to PARP-1 and PARP-2, PARP-3 is a mono-ADP ribosylase that activates PARP-1 in the absence of DNA. Their results indicate that this interaction is unrelated to DNA single-strand breaks.

LIT: PARP-3 is a mono-ADP-ribosylase that activates PARP-1 in the absence of DNA: O. Loseva, et al.; J. Biol. Chem. **285,** 8054 (2010)

PARP-3, pAb

ALX-210-541-R100 100 µl

From rabbit. **IMMUNOGEN:** Recombinant human PARP-3 (poly(ADP-ribose) polymerase-3). **SPECIFICITY:** Recognizes human, mouse and monkey PARP-3. **APPLICATION:** ICC, IP, WB.

LIT: PARP-3 localizes preferentially to the daughter centriole and interferes with the G1/S cell cycle progression: A. Augustin, et al.; J. Cell Sci. **116,** 1551 (2003)

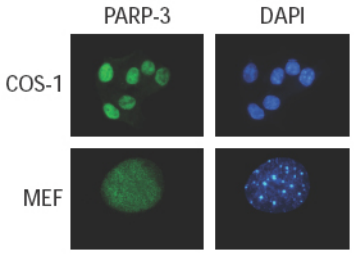


FIGURE: Immunodetection of PARP-3 in mouse embryonic fibroblasts fixed with 3.7% Formaldehyde, 0.1% Triton X-100 using PARP-3, pAb (dilution: 1:200).

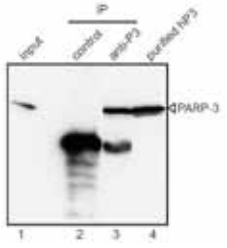


FIGURE: Immunoprecipitation. Cell lysates prepared from COS-1 cells were immunoprecipitated with PARP-3, pAb (lane 3) or with a control antibody (lane 2). Lane 1: input 1:15. Lane 4: purified recombinant human PARP-3.

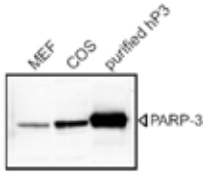


FIGURE: Western blot analysis of mouse embryonic fibroblasts (MEF), simian COS-1 cells (COS), purified recombinant human PARP-3 (Prod. No. ALX-201-170) using PARP-3, pAb.

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

PARP-10

M. Yu, et al. [1] identified and characterized a novel 150kDa protein, designated PARP-10. PARP-10 can associate with the oncoprotein c-Myc and possesses PARP activity, capable of poly (ADP-ribosyl)ating itself and core histones but neither Myc nor Max. PARP-10 shuttles between the nuclear and cytoplasmic compartments. This shuttling is controlled at least in part by a leucine-rich nuclear export sequence. Functionally PARP-10 inhibits transformation of primary cells (rat embryo fibroblasts) and might play a role in the control of cell proliferation. To regulate its target genes, c-Myc recruits several different cofactors. PARP-10 may function as an additional cofactor that is recruited by c-Myc [2]. H.Y. Chou, et al. [3] suggested that cell cycle-dependent phosphorylation of PARP-10 by CDK2 plays crucial functions in cell proliferation.

LITERATURE REFERENCES:

[1] PARP-10, a novel Myc-interacting protein with poly(ADP-ribose) polymerase activity, inhibits transformation: M. Yu, et al.; Oncogene **24,** 1982 (2005) ▪ **[2]** Overlap of the gene encoding the novel poly(ADP-ribose) polymerase Parp10 with the plectin 1 gene and common use of exon sequences: K. Lesniewicz, et al.; Genomics **86,** 38 (2005) ▪ **[3]** CDK-dependent activation of poly(ADP-ribose) polymerase member 10 (PARP10): H.Y. Chou, et al.; J. Biol. Chem. **281,** 15201 (2006)

PARP-10 (human), mAb (5H11)

ALX-804-626-L001 — 1 ml

CLONE: 5H11. **ISOTYPE:** Rat IgG1. **IMMUNOGEN:** Recombinant human PARP-10 (poly(ADP-ribose) polymerase-10) (aa 1-907). **SPECIFICITY:** Recognizes human PARP-10. **APPLICATION:** ICC, IP, WB.

LIT: PARP-10, a novel Myc-interacting protein with poly(ADP-ribose) polymerase activity, inhibits transformation: M. Yu, et al.; Oncogene **24,** 1982 (2005)

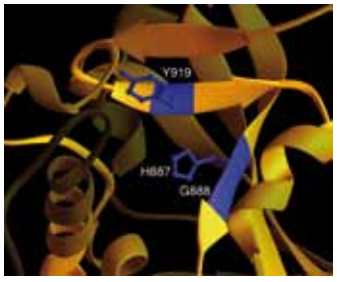


FIGURE: Catalytic domain of PARP-10. *Picture courtesy of B. Lüscher (University Aachen).*

XRCC1

Human XRCC1 (X-ray repair cross-complementing 1) is involved in base excision repair (BER) and single strand break repair (SSBR) and thought to act as a scaffolding protein for other repair factors. It has been shown to physically interact with several enzymes known to be involved in the repair of SSBs, including DNA ligase IIIα, DNA polymerase β, APE1, polynucleotide kinase/phosphatase, poly(ADPribose) polymerases 1 and 2 (PARP-1 and 2) and 8-oxoguanine DNA glycosylase (OGG1) [1-6].

LITERATURE REFERENCES:

[1] XRCC1 polypeptide interacts with DNA polymerase beta and possibly poly (ADP-ribose) polymerase, and DNA ligase III is a novel molecular ‚nick-sensor' in vitro: K. W. Caldecott, et al.; Nucleic Acids Res. **24,** 4387 (1996) ▪ **[2]** Reconstitution of DNA base excision-repair with purified human proteins: interaction between DNA polymerase beta and the XRCC1 protein: Y. Kubota, et al.; EMBO J. **15,** 6662 (1996) ▪ **[3]** Role of XRCC1 in the coordination and stimulation of oxidative DNA damage repair initiated by the DNA glycosylase hOGG1: S. Marsin, et al.; J. Biol. Chem. **278,** 44068 (2003) ▪ **[4]** XRCC1 stimulates human polynucleotide kinase activity at damaged DNA termini and accelerates DNA single-strand break repair: C. J. Whitehouse, et al.; Cell **104,** 107 (2001) ▪ **[5]** Poly(ADP-ribose) polymerase-2 (PARP-2) is required for efficient base excision DNA repair in association with PARP-1 and XRCC1: V. Schreiber, et al.; J. Biol. Chem. **277,** 23028 (2002) ▪ **[6]** Spatial and temporal cellular responses to single-strand breaks in human cells: S. Okano, et al.; Mol. Cell. Biol. **23,** 3974 (2003)

XRCC1 (human), pAb

ALX-210-304-R050 — 50 µl

From rabbit. **IMMUNOGEN:** Recombinant human XRCC1 (X-ray repair cross-complementing group 1). **SPECIFICITY:** Recognizes human XRCC1. **APPLICATION:** ELISA, ICC, IP, WB.

LIT: XRCC1 is specifically associated with poly(ADP-ribose) polymerase and negatively regulates its activity following DNA damage: M. Masson, et al.; Mol. Cell. Biol. **18,** 3563 (1998) ▪ Poly(ADP-ribose) polymerase-2 (PARP-2) is required for efficient base excision DNA repair in association with PARP-1 and XRCC1: V. Schreiber, et al.; J. Biol. Chem. **277,** 23028 (2002)

XRCC1 (human), pAb

ALX-210-539-R100 — 100 µl

From rabbit. **IMMUNOGEN:** Recombinant human XRCC1 (X-ray repair cross-complementing group 1) fused to a His-tag. **SPECIFICITY:** Recognizes human XRCC1. **APPLICATION:** ICC, IP, WB.

LIT: XRCC1 is specifically associated with poly(ADP-ribose) polymerase and negatively regulates its activity following DNA damage: M. Masson, et al.; Mol. Cell. Biol. **18,** 3563 (1998) ▪ XRCC1 is phosphorylated by DNA-dependent protein kinase in response to DNA damage: N. Levy, et al.; Nucl. Acids Res. **34,** 32 (2006) ▪ Radiation-induced mitotic catastrophe in PARG-deficient cells: JC. Amé, et al.; J. Cell Sci. **122,** 1990 (2009)

More PARP Family Antibodies & Related Products

Product	Host / Isotype	Specificity	Application	Prod. No.	Size
Poly(ADP-ribose), mAb (10H)	Mouse IgG3	Species independent	FC, ICC, IHC (PS), WB	ALX-804-220-R100	100 µl
Poly(ADP-ribose), mAb	Mouse IgG3	Species independent	ELISA, ICC, IP, WB	BML-SA216-0100	100 µl
Poly(ADP-ribose), pAb (96-10-04)	From rabbit	Species independent	ELISA, ICC, IP, WB	ALX-210-890-R100	100 µl
PARP-1, mAb (C-2-10) (affinity purified)	Mouse IgG1	Human, mouse, rat, hamster, monkey	ELISA, ICC, WB	BML-SA249-0100	100 µg
PARP-1, mAb (C-2-10)	Mouse IgG1	Human, mouse, rat, hamster, monkey	ELISA, IHC, WB	BML-SA250-0050	50 µl
PARP-1, mAb (F1-23)	Mouse IgG1	Human, bovine	ELISA, ICC, IP, ChIP, WB, FUNC	ALX-804-211-R050	50 µl
PARP-1, pAb	From rabbit	Human, mouse, bovine, chicken, monkey, *Xenopus*	ELISA, ICC, IHC (FS, PS), IP, WB	ALX-210-302-R100	100 µl
PARP-1, pAb	From rabbit	Human, mouse, rat, monkey, bovine	ICC, IP, WB, FUNC	ALX-210-221-R100	100 µl
PARP-1 (human), pAb	From goat	Human, mouse	WB	ALX-210-897-R100	100 µl
PARP-1 (human), pAb	From rabbit	Human	ICC, IHC, IP, WB	ALX-210-895-R100	100 µl
PARP-1 (mouse), pAb	From rabbit	Mouse	ICC, IHC, IP, WB	ALX-210-619-R100	100 µl
PARP-1 (BRCT domain), pAb	From rabbit	Human, mouse	IP, WB	ALX-210-540-R100	100 µl
PARP-1 (197-214), pAb	From rabbit	Human, bovine, chicken	ELISA, ICC, IP, WB	ALX-210-219-R100	100 µl
PARP-1 (215-228), pAb	From rabbit	Human, bovine, chicken	ELISA, ICC, WB	ALX-210-220-R100	100 µl
PARP-1 (509-524), pAb	From rabbit	Human, mouse, rat, bovine	ELISA, WB	BML-SA253-0025 BML-SA253-0100	25 µl 100 µl
PARP-2, mAb (4G8)	Mouse IgG1	Human, mouse	ELISA, WB	ALX-804-639-L001	1 ml
PARP-2 (mouse), pAb	From rabbit	Mouse	ICC, IHC, IP, WB	ALX-210-899-R100	100 µl
PARP-3, mAb (LA6B10)	Mouse IgM	Human, mouse	ICC	ALX-804-466-R100	100 µl
PARP-3, pAb	From rabbit	Human, mouse, monkey	ICC, IP, WB	ALX-210-541-R100	100 µl
Minor vault p193 protein (human), mAb (p193-4)	Mouse IgG1	Human	ICC, IHC (FS), WB	ALX-801-023-C125 ALX-801-023-C250	125 µg 250 µg
Minor vault p193 protein (human), mAb (p193-6)	Mouse IgG2b	Human	ICC, IHC (FS), WB	ALX-801-024-C125 ALX-801-024-C250	125 µg 250 µg
Minor vault p193 protein (human), mAb (p193-10)	Mouse IgG2a	Human	IHC (FS), WB	ALX-801-025-C125 ALX-801-025-C250	125 µg 250 µg
Tankyrase-1, mAb (19A449)	Mouse IgG1	Human, mouse	WB	ALX-804-234-C100	100 µg
PARP-10 (human), mAb (5H11)	Rat IgG1	Human	ICC, IP, WB	ALX-804-626-L001	1 ml

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

The Widest Panel of PARP Inhibitors

PARP Inhibitors

ABT-888

ALX-270-444-M001 1 mg
ALX-270-444-M005 5 mg

Potent inhibitor of PARP-1 and PARP-2 (potency ≤5nM *in vitro*). Enantiomeric purity ≥97% suitable for *in vivo* studies. Increases tumor growth delay resulting from radiation and DNA-damaging agents.

LIT: Inhibition of poly(ADP-ribose) polymerase enhances cell death and improves tumor growth delay in irradiated lung cancer models: J.M. Albert, et al.; Clin. Cancer Res. **13,** 3033 (2007) ▪ ABT-888, an orally active poly(ADP-ribose) polymerase inhibitor that potentiates DNA-damaging agents in preclinical tumor models: C.K. Donawho, et al.; Clin. Cancer Res. **13,** 2728 (2007)

5-AIQ . HCl

ALX-270-285-M001 1 mg
ALX-270-285-M005 5 mg

Water-soluble, potent inhibitor of poly(ADP-ribose) polymerase-1 (PARP-1).

LIT: Effects of 5-aminoisoquinolinone, a water-soluble, potent inhibitor of the activity of poly (ADP-ribose) polymerase on the organ injury and dysfunction caused by haemorrhagic shock: M.C. McDonald, et al.; Br. J. Pharmacol. **130,** 843 (2000)

3-Methyl-5-AIQ . HCl

ALX-270-450-M001 1 mg
ALX-270-450-M005 5 mg

Water-soluble, potent inhibitor of poly(ADP-ribose) polymerase-1 (PARP-1) (IC_{50}=0.23μM) *in vitro*. Exhibits outstanding therapeutic benefits in models of myocardial infarction, ischaemia-reperfusion of the liver and kidney, heart transplantation and acute lung inflammation.

LIT: Synthesis and PARP-1 inhibitory activity of 3-substituted analogues of the potent water-soluble PARP inihbitor 5-aminoisoquinolin-1-one (5-AIQ): E. C. Y. Woon, et al.; Bioorg. Med. Chem. (submitted), (2006)

3-Aminobenzamide

ALX-270-044-G001 1 g
ALX-270-044-G005 5 g

Inhibits endogenous PARP-1. Has minimal effect on bacterial toxin-mediated ADP-ribosylation. Inhibits stress-induced apoptosis.

LIT: Cell death protection by 3-aminobenzamide: impairment of cytoskeleton function in human NK cell-mediated killing: W. Malorni, et al.; BBRC **199,** 1250 (1994) ▪ 3-Aminobenzamide protects cells from UV-B-induced apoptosis by acting on cytoskeleton and substrate adhesion: W. Malorni, et al.; BBRC **207,** 715 (1995)

4-Amino-1,8-naphthalimide

BML-AP101-0020 20 mg
BML-AP101-0100 100 mg

Potent inhibitor of poly (ADP-ribose) polymerase-1 (PARP-1) (IC_{50}=0.18μM). Reduces ischemia-reperfusion injury in the heart and skeletal muscle.

LIT: 4-Amino-1,8-naphthalimide: a novel inhibitor of poly(ADP-ribose) polymerase and radiation sensitizer: A. Schlicker, et al.; Int. J. Radiat. Biol. **75,** 91 (1999)

Benzamide

ALX-270-174-G005 5 g

Inhibitor of poly(ADP-ribose) polymerase-1 (PARP-1). Neuroprotectant.

LIT: Nitric oxide activation of poly(ADP-ribose) synthetase in neurotoxicity: J. Zhang, et al.; Science **263,** 687 (1994) ▪ Substrate-assisted catalysis by PARP10 limits its activity to mono-ADP-ribosylation: H. Kleine, et al.; Mol. Cell **32,** 57 (2008)

3-(4-Chlorophenyl)quinoxaline-5-carboxamide

ALX-270-486-M005 5 mg

Potent quinoxaline-based PARP inhibitor with a 5-fold selectivity towards PARP-2 (IC_{50}=7nM) over PARP-1 (IC_{50}=33nM). Brain-permeant. Exhibits good pharmacokinetics.

LIT: Discovery of quinazolinone and quinoxaline derivatives as potent and selective poly(ADP-ribose) polymerase-1/2 inhibitors: A. Iwashita, et al.; FEBS Lett. **579,** 1389 (2005) ▪ Discovery of potent and selective PARP-1 and PARP-2 inhibitors: SBDD analysis via a combination of X-ray structural study and homology modeling: J. Ishida, et al.; Bioorg. Med. Chem. **14,** 1378 (2006)

DPQ

ALX-270-221-M001 1 mg
ALX-270-221-M005 5 mg

Very potent poly(ADP-ribose) polymerase-1 (PARP-1) inhibitor.

LIT: Dihydroisoquinolines: the design and synthesis of a new series of potent inhibitors of poly(ADP-ribose) polymerase: M.J. Suto, et al.; Anticancer Drug Des. **6,** 107 (1991) ▪ Poly(ADP-ribose) polymerase inhibitors attenuate necrotic but not apoptotic neuronal death in experimental models of cerebral ischemia: F. Moroni, et al.; Cell Death Differ. **8,** 921 (2001)

DR2313

ALX-270-452-M001 1 mg
ALX-270-452-M005 5 mg
ALX-270-452-M025 25 mg

Potent, water soluble competitive PARP inhibitor (IC_{50}=0.20μM and 0.24μM for PARP-1 and PARP-2 respectively).

LIT: A newly synthesized poly(ADP-ribose) polymerase inhibitor, DR2313 [2-methyl-3,5,7,8-tetrahydrothiopyrano[4,3-d]-pyrimidine-4-one]: pharmacological profiles, neuroprotective effects, and therapeutic time window in cerebral ischemia in rats: H. Nakajima, et al.; Pharmacol. Exp. Ther. **312,** 472 (2005)

EB-47 . dihydrochloride . dihydrate

ALX-270-383-M001 1 mg
ALX-270-383-M005 5 mg

Very potent and water soluble PARP-1 inhibitor (IC_{50}=45nM, 100% inhibition at 200nM). Shows cytoprotective effects against oxidative damage in cells and in in vivo models of reperfusion injury and inflammation.

LIT: The discovery and synthesis of novel adenosine substituted 2,3-dihydro-1H-isoindol-1-ones: potent inhibitors of poly(ADP-ribose) polymerase-1 (PARP-1): P.G. Jagtap, et al.; Bioorg. Med. Chem. Lett. **14,** 81 (2004) ▪ Substrate-assisted catalysis by PARP10 limits its activity to mono-ADP-ribosylation: H. Kleine, et al.; Mol. Cell **32,** 57 (2008)

4-Hydroxyquinazoline

ALX-270-279-G001 1 g

Potent inhibitor of poly(ADP-ribose) polymerase-1 (PARP-1) (IC_{50}=9.5μM).

LIT: Specific inhibitors of poly(ADP-ribose) synthetase and mono(ADP-ribosyl)transferase: M. Banasik, et al.; J. Biol. Chem. **267,** 1569 (1992) ▪ Regulation of kinase cascades and transcription factors by a poly(ADP-ribose) polymerase-1 inhibitor, 4-hydroxyquinazoline, in lipopolysaccharide-induced inflammation in mice: B. Veres, et al.; J. Pharmacol. Exp. Ther. **310,** 247 (2004)

5-Iodo-6-amino-1,2-benzopyrone

ALX-270-278-M001 1 mg
ALX-270-278-M005 5 mg

Inhibitor of poly(ADP-ribose) polymerase-1 (PARP-1).

LIT: Reversion of malignant phenotype by 5-iodo-6-amino-1,2-benzopyrone a non-covalently binding ligand of poly(ADP-ribose) polymerase: P.I. Bauer, et al.; Biochimie **77,** 374 (1995) ▪ Protective effects of 5-iodo-6-amino-1,2-benzopyrone, an inhibitor of poly(ADP-ribose) synthetase against peroxynitrite-induced glial damage and stroke development: M. Endres, et al.; Eur. J. Pharmacol. **351,** 377 (1998) ▪ Cancer cell selectivity of 5-iodo-6-aminobenzopyrone (INH2BP) and methyl-3,5-diiodo-4(4'-methoxyphenoxy) benzoate (DIME): E. Kirsten & E. Kun; Int. J. Mol. Med. **5,** 279 (2000) ▪ Inhibition of poly (ADP-ribose) synthetase by gene disruption or inhibition with 5-iodo-6-amino-1,2-benzopyrone protects mice from multiple-low-dose-streptozotocin-induced diabetes: J.G. Mabley, et al.; Br. J. Pharmacol. **133,** 909 (2001)

1,5-Isoquinolinediol

BML-AP102-0020 20 mg
BML-AP102-0100 100 mg

Potent inhibitor of inducible nitric oxide synthase (iNOS; NOS II) in mouse macrophages. Potent and selective PARP inhibitor. Inhibits nitric oxide (SIN-1) induced PARP activation in rat hepatocytes (at 20μM). Neuroprotectant.

LIT: Specific inhibitors of poly(ADP-ribose) synthetase and mono(ADP-ribosyl)transferase: M. Banasik, et al.; J. Biol. Chem. **267,** 1569 (1992) ▪ Nitric oxide activation of poly(ADP-ribose) synthetase in neurotoxicity: J. Zhang, et al.; Science **263,** 687 (1994) ▪ All trans retinoic acid induces apoptosis in acute promyelocytic NB4 cells when combined with isoquinolinediol, a poly(ADP-ribose) polymerase inhibitor: D.M. Berry, et al.; Leuk. Res. **24,** 307 (2000) ▪ Inhibition of NOS-2 induction in LPS-stimulated J774.2 cells by 1, 5-isoquinolinediol, an inhibitor of PARP: R. Olszanecki, et al.; J. Physiol. Pharmacol. **57,** 109 (2006) ▪

Minocycline . HCl

ALX-380-109-M050 50 mg

Semisynthetic. Tetracycline derivative with antimicrobial activity. Inhibitor of angiogenesis, apoptosis and poly(ADP-ribose) polymerase-1 (PARP-1). Anti-inflammatory and neuroprotective.

LIT: Minocycline exerts multiple inhibitory effects on vascular endothelial growth factor-induced smooth muscle cell migration: the role of ERK1/2, PI3K, and matrix metalloproteinases: J.S. Yao, et al.; Circ. Res. **95,** 364 (2004) ▪ Minocycline up-regulates BCL-2 levels in mitochondria and attenuates male germ cell apoptosis: M. Castanares, et al.; BBRC **337,** 663 (2005) ▪ Minocycline inhibits poly(ADP-ribose) polymerase-1 at nanomolar concentrations: C.C. Alano, et al.; PNAS **103**, 9685 (2006) ▪ Minocycline, a second-generation tetracycline, as a neuroprotective agent in an animal model of schizophrenia: Y. Levkovitz, et al.; Brain Res. **1154,** 154 (2007)

Nicotinamide

BML-KI283-0500 500 µ

Water-soluble amide of nicotinic acid. Component of the two most important coenzymes - NAD and NADP. Involved in numerous oxidation-reduction reactions in mammalian biological systems acting as an antioxidant. PARP-1 inhibitor.

LIT: Nicotinamide offers multiple protective mechanisms in stroke as a precursor for NAD^+, as a PARP inhibitor and by partial restoration of mitochondrial function: L. Kleidman, et al.; Pharmacology **69,** 150 (2003)

NU1025

ALX-270-370-M001 1 mg

ALX-270-370-M005 5 mg

ALX-270-370-M025 25 mg

A potent poly(ADP-ribose) polymerase 1 (PARP-1) inhibitor (IC_{50}=400nM) that potentiates the cytotoxicity of various DNA-active agents.

LIT: Potentiation of temozolomide and topotecan growth inhibition and cytotoxicity by novel poly(adenosine diphosphoribose) polymerase inhibitors in a panel of human tumor cell lines: C.A. Delaney, et al.; Clin. Cancer Res. **6,** 2860 (2000)

6(5*H*)-Phenanthridinone

ALX-270-251-M010 10 mg

Poly(ADP-ribose)polymerase (PARP) inhibitor. Displays immunosuppressive activity.

LIT: Immunosuppressive activities of 6(5H)-phenanthridinone, a new poly(ADP-ribose) polymerase inhibitor: D. Weltin, et al.; Int. J. Immunopharmacol. **17,** 265 (1995) ▪ Effect of 6(5H)-phenanthridinone, a poly (ADP-ribose)polymerase inhibitor, and ionizing radiation on the growth of cultured lymphoma cells: D. Weltin, et al.; Int. J. Radiat. Biol. **72,** 685 (1997)

PJ-34

ALX-270-289-M001 1 mg

ALX-270-289-M005 5 mg

ALX-270-289-M025 25 mg

Potent, water-soluble poly(ADP-ribose) polymerase (PARP) inhibitor (EC_{50}=20nM compared to EC_{50}=200µM of the prototypical PARP inhibitor 3-aminobenzamide (Prod. No. ALX-270-044)). Inhibits peroxynitrite (Prod. No. ALX-400-036)-induced cell necrosis (EC_{50}=20nM). Has significant, dose-dependent, anti-inflammatory effects.

LIT: Protective effects of PJ34, a novel, potent inhibitor of poly(ADP-ribose) polymerase (PARP) in in vitro and in vivo models of stroke: G.E. Abdelkarim, et al.; Int. J. Mol. Med. **7,** 255 (2001) ▪ Anti-inflammatory effects of a novel, potent inhibitor of poly (ADP-ribose) polymerase: J.G. Mabley, et al.; Inflamm. Res. **50,** 561 (2001) ▪ Systemic and hepatosplanchnic hemodynamic and metabolic effects of the PARP inhibitor PJ34 during hyperdynamic porcine endotoxemia: Z. Ivanyi, et al.; Shock **19,** 415 (2003)

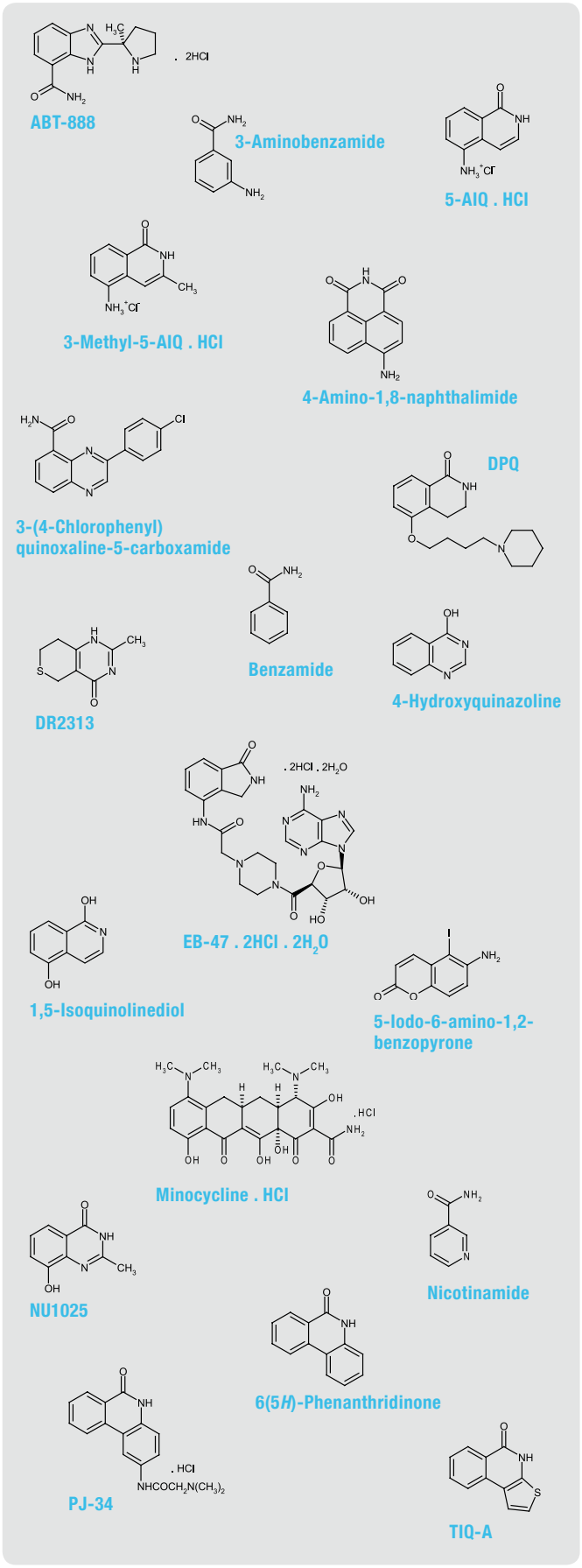
TIQ-A

ALX-270-365-M001 1 mg

ALX-270-365-M005 5 mg

Potent poly(ADP-ribose) polymerase-1 (PARP-1) inhibitor (IC_{50}=450nM). Neuroprotectant.

LIT: Novel isoquinolinone-derived inhibitors of poly(ADP-ribose) polymerase-1: pharmacological characterization and neuroprotective effects in an in vitro model of cerebral ischemia: A. Chiarugi, et al.; J. Pharmacol. Exp. Ther. **305,** 943 (2003) ▪Towards new neuroprotective agents: design and synthesis of 4H-thieno[2,3-c] isoquinolin-5-one derivatives as potent PARP-1 inhibitors: R. Pellicciari, et al.; Farmaco **58,** 851 (2003)



Latest Insight

PARP-2 Specific Inhibitors

PARP-1 and PARP-2 are poly(ADP-ribose)polymerases, which are involved in the maintenance of genomic integrity under conditions of genotoxic stimuli. The presence of two PARP enzymes that are both activated by DNA breaks raises questions about their individual roles under pathological conditions. New potent and selective PARP-2 inhibitors with 20 to 60-fold selectivity for PARP-2 over PARP-1 can be used for further characterization of PARP-2 in pathophysiological conditions.

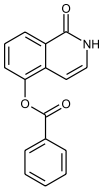
UPF1035

[5-Benzoyloxy-3,4-dihydroisoquinolin-1(2*H*)-one]

ALX-270-498-M001 1 mg

ALX-270-498-M005 5 mg

PARP-2 specific inhibitor with 60-fold selectivity for PARP-2 (IC_{50}=0.15 ± 0.04μM) over PARP-1 (IC_{50}=9.0 ± 0.7μM). Can be used for further characterization of PARP-2 in pathophysiological conditions.



LIT: On the way to selective PARP-2 inhibitors. Design, synthesis, and preliminary evaluation of a series of isoquinolinone derivatives: R. Pellicciari, et al.; ChemMedChem **3,** 914 (2008) ▪ Selective PARP-2 inhibitors increase apoptosis in hippocampal slices but protect cortical cells in models of post-ischaemic brain damage: F. Moroni, et al.; Br. J. Pharmacol. **157,** 854 (2009)

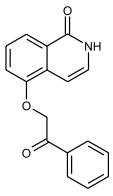
UPF1069

[5-(2-Oxo-2-phenylethoxy)-3,4-dihydroisoquinolin-1(2*H*)-one]

ALX-270-499-M001 1 mg

ALX-270-499-M005 5 mg

PARP-2 specific inhibitor with 26.7-fold selectivity for PARP-2 (IC_{50}=0.3 ± 0.08μM) over PARP-1 (IC_{50}=8.0 ± 0.9μM).



LIT: On the way to selective PARP-2 inhibitors. Design, synthesis, and preliminary evaluation of a series of isoquinolinone derivatives: R. Pellicciari, et al.; ChemMedChem **3,** 914 (2008) ▪ Selective PARP-2 inhibitors increase apoptosis in hippocampal slices but protect cortical cells in models of post-ischaemic brain damage: F. Moroni, et al.; Br. J. Pharmacol. **157,** 854 (2009)

PARG Inhibitors

ADP-HPD . NH_4 . $2H_2O$

ALX-480-094-C060 60 μg

Potent, noncompetitive, and specific inhibitor of poly(ADP-ribose) glycohydrolase (PARG) (IC_{50}=120nM) versus ADP-ribose (IC_{50}=120μM). Does not affect the activities of either PARP-1 or NAD:arginine mono(ADP-ribosyl)-transferase A even at 1mM concentration.

LIT: Specific inhibition of poly(ADP-ribose) glycohydrolase by adenosine diphosphate (hydroxymethyl) pyrrolidinediol: J.T. Slama, et al.; J. Med. Chem. **38,** 389 (1995) ▪ Mechanism of inhibition of poly(ADP-ribose) glycohydrolase by adenosine diphosphate (hydroxymethyl)pyrrolidinediol: J.T. Slama, et al.; J. Med. Chem. **38,** 4332 (1995) ▪ A cellular defense pathway regulating transcription through poly(ADP-ribosyl)ation in response to DNA damage: S. Vispe, et al.; PNAS 97, 9886 (2000)

Gallotannin

[Tannic acid]

ALX-270-418-G001 1 g

Inhibitor of poly(ADP-ribose) glycohydrolase (PARG). Cytoprotective in oxidatively stressed cells. Inhibitor of endothelial nitric oxide synthase (eNOS; NOS III). Induces cyclooxygenase-2 (COX-2) expression. Free radical scavenger.

LIT: The poly(ADP-ribose) glycohydrolase inhibitor gallotannin blocks oxidative astrocyte death: W. Ying, et al.; Neuroreport **11,** 1385 (2000) ▪ Inhibition of poly(ADP-ribose) glycohydrolase by gallotannin selectively up-regulates expression of proinflammatory genes: E. Rapizzi, et al.; Mol. Pharmacol. **66,** 890 (2004)

PARP Activator

Peroxynitrite . $C_4H_{12}N$

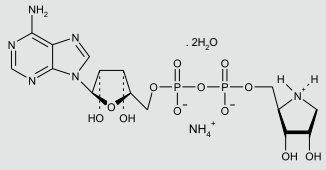
ALX-400-036-L001 1 ml

ALX-400-036-5001 5 x 1 ml

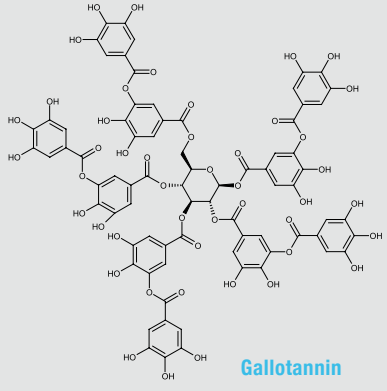
ALX-400-056-M020 **BULK** 20 mg

Oxidizing and nitrating agent. Produced from the reaction of nitrogen monoxide with tetramethylammonium superoxide according to the method of D.S. Bohle, et al. described in Meth. Enzymol. **269,** 302 (1996), and dissolved in 0.01M potassium hydroxide (KOH). This formulation of peroxynitrite has a low nitrite content (~1%), no hydrogen peroxide.

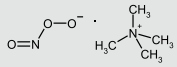
LIT: DNA damage induced by peroxynitrite: subsequent biological effects: C. Szabo & H. Ohshima; Nitric Oxide **1,** 373 (1997) ▪ Peroxynitrite: a biologically significant oxidant: M.P. Murphy, et al.; Gen. Pharmacol. **31,** 179 (1998) ▪ Peroxynitrite: an endogenous oxidizing and nitrating agent: C. Ducrocq, et al.; Cell. Mol. Life Sci. **55,** 1068 (1999) ▪ The chemistry of DNA damage from nitric oxide and peroxynitrite: S. Burney, et al.; Mutat. Res. **424,** 37 (1999) ▪ Peroxynitrite-induced cytotoxicity: mechanism and opportunities for intervention: L. Virag, et al.; Toxicol. Lett. **140-141,** 113 (2003) ▪ A new hammer in the redox toolbox: high-purity peroxynitrite for cell signaling and toxicology studies: S.R. Woodcock & B.A. Freeman; Chem. Res. Toxicol. **21,** 2227 (2008)



ADP-HPD . NH_4 . $2H_2O$



Gallotannin



Peroxynitrite . tetramethylammonium salt

ADP-Ribosylation

NAD-dependent ADP-ribosylation is a reversible post-translational modification involved in many cellular processes including DNA-repair, transcription, telomere function and apoptosis. Mono- and poly-ADP-ribosyltransferases (mARTs and pARTs/PARPs) catalyze the transfer of the ADP-ribose moiety from NAD^+ onto specific amino acid side chains in target proteins under the release of nicotinamide. This modification may lead to either activation or inactivation of the target protein. In contrast, protein-ADP-ribosylhydrolases (ARHs and PARGs) hydrolyze the α-glycosidic bond between ADPribose and the side chain, thereby restoring normal protein function (Figure) [1, 2].

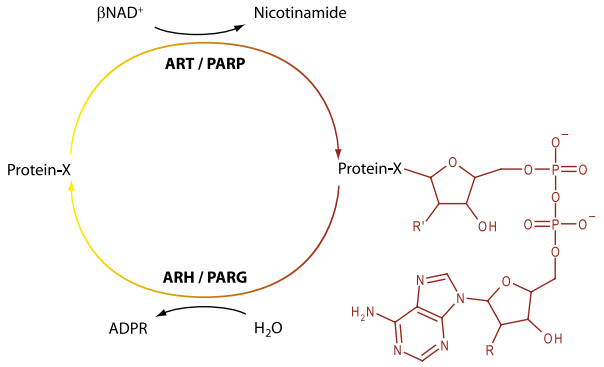


FIGURE: Posttranslational modification of proteins by reversible ADP-ribosylation. *Adapted from: The structure of human ADP-ribosylhydrolase 3 (ARH3) provides insights into the reversibility of protein ADP-ribosylation: C. Mueller-Dieckmann, et al.; PNAS **103,** 15026 (2006).*

Mono-ADP-ribosyltransferases (ARTs; mARTs)

Enzyme-modulated mono(ADP-ribosyl)ation was originally identified as the mechanism of action of several bacterial toxins [1]. The cholera, diphteria and pertussis toxins are mono-ADPribosyltransferases (ARTs; mARTs; EC 2.4.2.31), known to cause various pathologies after their translocation into mammalian host cells. These toxins interfere with protein synthesis, signal transduction, or cytoskeletal functions by ADPribosylating key target proteins. Mammalian ARTs constitute a family of structurally related proteins expressed on the cell surface or secreted in the extracellular compartment. Five paralogs (ART1-5) have been cloned. Only four of them are expressed in human due to a defective ART2 gene, and six in the mouse as the result of ART2 gene duplication (ART2.1, ART2.2) [3]. ARTs are expressed in different tissues and are involved in many physiological processes [4]. The ART substrate NAD gets released from damaged cells during inflammation. ADP-ribosylation activates P2X7, triggering calcium flux, exposure of phosphatidylserine, and formation of large membrane pores, ultimately resulting in apoptosis [5-7].

ADP-ribosylhydrolases (ARHs)

Three different ADP-ribosylhydrolases (ARH1-3) have been identified in human so far. ARH1 specifically hydrolyzes DP-ribosylarginine, whereas ARH3 degrades poly-ADP-ribose but does not cleave ADP-ribosyl-asparagine, -iphthamide, or -cysteine bonds. In addition, ARH3 catalyzes the production of ADP-ribose from O-acetyl-ADP-ribose. The exact function of ARH2 has not been determined so far [9, 10].

LITERATURE REFERENCES:

[1] ADP-ribosylation: K. Ueda & O. Hayaishi; Annu. Rev. Biochem. **54,** 73 (1985) ▪ **[2]** The structure of human ADP-ribosylhydrolase 3 (ARH3) provides insights into the reversibility of protein ADP-ribosylation: C. Mueller-Dieckmann, et al.; PNAS **103,** 15026 (2006) ▪ **[3]** The family of toxin-related ecto-ADP-ribosyltransferases in humans and the mouse: G. Glowacki, et al.; Protein Sci. **11,** 1657 (2002) ▪ **[4]** Use of genetic immunization to raise antibodies recognizing toxinrelated cell surface ADP-ribosyltransferases in native conformation: F. Koch-Nolte, et al.; Cell Immunol. **236,** 66 (2005) ▪ **[5]** NAD-induced T cell death: ADP-ribosylation of cell surface proteins by ART2 activates the cytolytic P2X7 purinoceptor: M. Seman, et al.; Immunity **19,** 571 (2003) ▪ **[6]** Triggering of T-cell apoptosis by toxin-related ecto-ADP-ribosyltransferase ART2: F. Scheuplein, et al.; Ann. N. Y. Acad. Sci. **1010,** 296 (2003) ▪ **[7]** P2X7 receptor-dependent and -independent T cell death is induced by nicotinamide adenine dinucleotide: H. Kawamura, et al.; J. Immunol. **174,** 1971 (2005) ▪ **[9]** Identification and characterization of a mammalian 39-kDa poly(ADP-ribose) glycohydrolase: S. Oka, et al.; J. Biol. Chem. **281,** 705 (2006) ▪ **[10]** The 39-kDa poly(ADP-ribose) glycohydrolase ARH3 hydrolyzes O-acetyl- ADP-ribose, a product of the Sir2 family of acetyl-histone deacetylases: T. Ono, et al.; PNAS **103,** 16687 (2006)

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

ARTs, ARHs and Related Proteins

ART2.1 (rat), (rec.) (His-tag)
ALX-201-287-C010 10 µg

Produced in *E. coli*. Rat ART2.1 is fused at the C-terminus to a His-tag.

ART2.2 (mouse), (rec.) (His-tag)
ALX-201-289-C010 10 µg

Produced in *E. coli*. Mouse ART2.2 is fused at the C-terminus to a His-tag.

ART2.2 (rat), (rec.) (His-tag)
ALX-201-288-C010 10 µg

Produced in *E. coli*. Rat ART2.2 is fused at the C-terminus to a His-tag.

Pertussis toxin *(Bordetella pertussis)*
BML-G100-0050 50 µg

From *Bordetella pertussis*.

SpvB *(Salmonella enterica)*, (rec.) (His-tag)
ALX-201-294-C010 10 µg

Produced in *E. coli*. *Salmonella enterica* SpvB is fused at the C-terminus to a His-tag.

ARH1 (human), (rec.) (His-tag)
ALX-201-290-C010 10 µg

Produced in *E. coli*. Human ARH1 is fused at the C-terminus to a His-tag.

ARH1 (mouse), (rec.) (His-tag)
ALX-201-291-C010 10 µg

Produced in *E. coli*. Mouse ARH1 is fused at the C-terminus to a His-tag.

ARH3 (human), (rec.) (His-tag)
ALX-201-292-C010 10 µg

Produced in *E. coli*. Human ARH3 is fused at the C-terminus to a His-tag.

ARH3 (mouse), (rec.) (His-tag)
ALX-201-293-C010 10 µg

Produced in *E. coli*. Mouse ARH3 is fused at the C-terminus to a His-tag.

FIGURE: Crystal structure of human ARH3.

ART Antibodies

Product	Host / Isotype	Specificity	Application	Prod. No.	Size
ART1 (human), mAb (GUGU1-A3)	Rat IgG2b	Human	FC, ICC	ALX-802-020-L001	1 ml
ART1 (human), pAb	From rabbit	Human	FC, ICC	ALX-215-037-R100	100 µl
ART1 (mouse), mAb (NOGU1-A111)	Rat IgG2a	Mouse	FC, ICC	ALX-802-028-L001	1 ml
ART1 (mouse), pAb	From rabbit	Mouse	FC, ICC	ALX-215-038-R100	100 µl
ART2.1 (mouse), mAb (GUGU2-B54)	Rat IgG2a	Mouse	FC, ICC	ALX-802-021-L001	1 ml
ART2.2 (mouse), mAb (NIKA-102)	Rat IgG2a	Mouse	FC, ICC	ALX-802-022-L001	1 ml
ART2.2 (mouse), pAb	From rabbit	Mouse	FC, ICC, FUNC (blocking)	ALX-215-039-R100	100 µl
ART2.2 (mouse), rAb (single domain, VHH) to (s+16a)	Llama IgG	Mouse	FUNC (blocking)	ALX-815-002-C100	100 µg
ART3 (human), mAb (GUGU3-A51)	Rat IgG2a	Human	FC, ICC	ALX-802-023-L001	1 ml
ART3 (mouse), mAb (GUGU3-A34)	Rat IgG2a	Mouse	FC, ICC	ALX-802-024-L001	1 ml
ART4 (human), mAb (NONI-B4)	Rat IgG2a	Human	FC, ICC	ALX-802-025-L001	1 ml
ART4 (human), pAb	From rabbit	Human	FC, ICC	ALX-215-042-R100	100 µl
ART4 (mouse), mAb (GUGU4-A53)	Rat IgG2a	Mouse	FC, ICC	ALX-802-026-L001	1 ml

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