



highlight

Nod-like Receptors (NLRs)

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International Edition

Introduction

The innate immune system comprises several classes of pattern recognition receptors, including Toll-like receptors (TLRs), NOD-like receptors (NLRs), and RIG-I-like receptors (RLRs). TLRs recognize microbes on the cell surface and in endosomes, whereas NLRs (also known as Nod-LRRs, NACHT-LRRs, and CATERPILLERS) and RLRs detect microbial components in the cytosol. NLRs are characterized by three distinct domains. They contain a Nod (also known as NACHT) domain and a LRR domain for ligand recognition. The N-terminal effector domain can be a caspase-recruitment domain (CARD), a pyrin domain (PYD), or a baculoviral inhibitory repeat (BIR)-like domain, all are known to be involved in the regulation of apoptotic and inflammatory signalling.

Nod1 and Nod2

Nod1 and Nod2 are intracellular PRM (pattern-recognition molecules) of the NLR (Nod-like receptor) family. Both proteins are implicated in the detection of bacterial peptidoglycan (PGN). Nod1 senses meso-diaminopimelic acid (DAP)-containing peptidoglycan found in the cell wall of Gram-negative bacteria,

while Nod2 seems to be a general sensor which is activated by muramyl dipeptide (MDP), the minimal motif common to all PGNs of Gram-negative as well as Gram-positive bacteria. Upon activation, Nod1 and Nod2 initiate a pro-inflammatory response through recruitment of the receptor-interacting protein 2 (RIP-2; RICK, CARDIAK) and subsequent activation of the NF- κ B and MAPK pathways (see Figure). Mutations in Nod2 have been reported to confer susceptibility to several chronic inflammatory disorders, including Crohn's disease.

Selected Review Articles

Signalling pathways and molecular interactions of NOD1 and NOD2: W. Strober, et al.; Nat. Rev. Immunol. 6, 9 (2006) • Nod-like proteins in immunity, inflammation and disease: J.H. Fritz, et al.; Nat. Immunol. 7, 1250 (2006)

- Intracellular NOD-like receptors in host defense and disease: T.D. Kaneganti, et al.; Immunity 27, 549 (2007) • Nod1 and Nod2 in innate immunity and human inflammatory disorders: L. Le Bourhis, et al.; Biochem. Soc. Trans. 35, 1479 (2007) • Mammalian NLR proteins; discriminating foe from friend: M. Kaparakis, et al.; Immunol. Cell Biol. 85, 495 (2007) • Intracellular NOD-like receptors in innate immunity, infection and disease: L. Franchi, et al.; Cell. Microbiol. 10, 1 (2008) • NLRs at the intersection of cell death and immunity: J.P. Ting, et al.; Nat. Rev. Immunol. 8, 372 (2008)

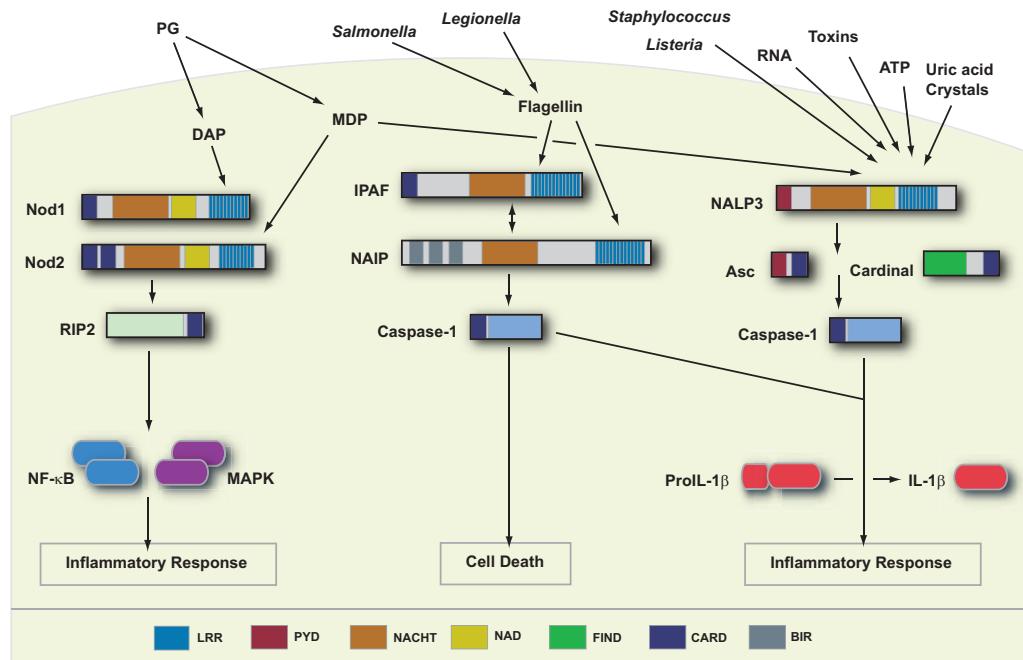


FIGURE: Activation of cytosolic NLRs by bacterial compounds and "danger"-signals.

NALPs, NAIP, IPAF & Inflammasomes

Inflammasomes are cytoplasmic multiprotein complexes that mediate the maturation of the proinflammatory cytokines IL-1 β , IL-18 and possibly IL-33 by controlling the activation of the inflammatory caspases-1 and -5. Several inflammasomes have been described and they are defined by the NLR protein that they contain: the NALP1 inflammasome, the NALP3 inflammasome and the IPAF inflammasome. Upon sensing of their respective ligands, NALP1 and NALP3 recruit the adaptor protein Asc (apoptosis-associated speck-like protein containing a CARD) through homophilic PYD-PYD interactions. Asc contains an N-terminal PYD and a C-terminal CARD that allows the recruitment of inflammatory caspases, especially caspase-1, to the platform through CARD-CARD interactions. The oligomerization of NALPs is believed to bring inflammatory caspases into close proximity, leading to their activation within the inflammasome. In contrast to the NALPs, IPAF does not recruit an adaptor molecule but directly activates caspase-1 via its CARD domain (see Figure). The assembly of the different inflammasomes leads to a common outcome, namely the activation of caspase-1. Caspase-1 is required for the processing and subsequent release of active proinflammatory cytokines such as IL-18 and IL-1 β , which is a major mediator of inflammation. IL-33, a cytokine that is involved in generating a TH2-cell response, is also cleaved by caspase-1. In addition, inflammasome activation can lead to host cell death in certain cell types, which might be important in restricting the intracellular replication of invasive bacterial pathogens.

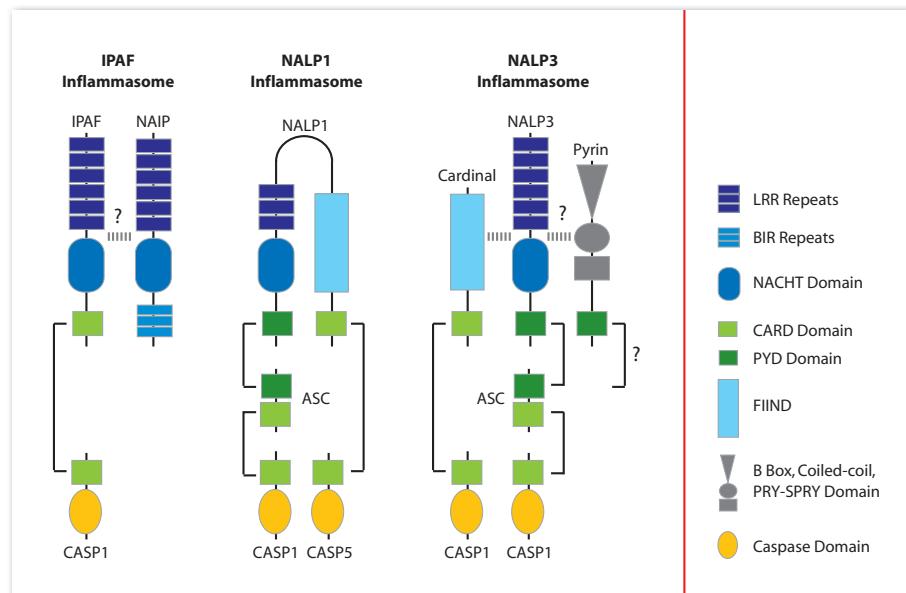


FIGURE: Schematic models of proposed caspase-1-activating inflammasomes. The ligand-sensing motifs (LRR repeats), initiate the formation of oligomers. PYD-PYD and CARD-CARD homotypic interactions are crucial for the recruitment and activation of either the adaptor Asc or the inflammatory caspases. IPAF and NAIP may be part of the same complex, similarly CARDINAL and Pyrin may be involved in the formation or regulation of NALP-based inflammasomes. Adapted from *Inflammatory caspases and inflammasomes: master switches of inflammation*: F. Martinon & J. Tschopp; *Cell Death Differ.* 14, 10 (2007).

Selected Review Articles

Inflammasome adaptors and sensors: intracellular regulators of infection and inflammation: S. Mariathasan & D.M. Monack; *Nat. Rev. Immunol.* 7, 31 (2007) • Inflammatory caspases and inflammasomes: master switches of inflammation: F. Martinon & J. Tschopp; *Cell Death Differ.* 14, 10 (2007) • NALP inflammasomes: a central

role in innate immunity: F. Martinon, et al.; *Semin. Immunopathol.* 29, 213 (2007) • The inflammasome: a danger sensing complex triggering innate immunity: V. Petrilli, et al.; *Curr. Opin. Immunol.* 19, 615 (2007) • COPs and POPs: modulators of inflammasome activity: C. Stehlík & A. Dorfleutner; *J. Immunol.* 179, 7993 (2007)

Nod1 [CARD4] & Nod2 [CARD15]

PAb to Nod1 (human) (AL184)

ALX-210-918-C050 50 µg

From rabbit. **IMMUNOGEN:** Synthetic peptide corresponding to aa 2-31 (E²EQGHSEMELIPSESH-PHIQLLSNRELLV³¹) of human Nod1 (CARD4). **SPECIFICITY:** Recognizes human Nod1. **APPLICATION:** WB.

MAb to Nod2 (human) (2D9)

ALX-803-307-1 1 Vial

CLONE: 2D9. **ISOTYPE:** Mouse IgG1. **IMMUNOGEN:** Recombinant human Nod2 (CARD15) (aa 28-301). **SPECIFICITY:** Recognizes human Nod2. **APPLICATION:** IHC, IP, WB.

PAb to Nod2 (human)

ALX-210-373-1 1 Vial

From rabbit. **IMMUNOGEN:** Recombinant human Nod2 (CARD15) (aa 28-301). **SPECIFICITY:** Recognizes human Nod2. Does not cross-react with SHAM. **APPLICATION:** IP, WB.

PAb to Nod2 (human) (CT)

PSC-2513-C100 100 µg

From rabbit. **IMMUNOGEN:** Synthetic peptide corresponding to 14 aa at the C-terminus of human Nod2 (CARD15). **SPECIFICITY:** Recognizes human Nod2. Does not cross-react with Nod1 (CARD4). **APPLICATION:** WB. **BP:** PSC-2513P.

PAb to Nod2 (human) (NT)

PSC-2511-C100 100 µg

From rabbit. **IMMUNOGEN:** Synthetic peptide corresponding to 16 aa at the N-terminus of human Nod2 (CARD15). **SPECIFICITY:** Recognizes human Nod2. Does not cross-react with Nod1 (CARD4). **APPLICATION:** WB. **BP:** PSC-2511P.

RIP2

MAb to RIP2 (human) (Nick-1)

ALX-804-139-C100 100 µg

CLONE: Nick-1. **ISOTYPE:** Rat IgG2a. **IMMUNOGEN:** Recombinant human RIP2 (receptor-interacting protein 2) (aa 1-322). **SPECIFICITY:** Recognizes human RIP2. **APPLICATION:** WB.

LIT: Participation of Rip2 in Lipopolysaccharide signaling is independent of its kinase activity: C. Lu et al.; *J. Biol. Chem.* 280, 16278 (2005) • PIDD mediates NF- κ B activation in response to DNA damage: Janssens, et al.; *Cell* 123, 1079 (2005)

Positive Control (Cell Lysate) for Antibodies to RIP2 (human)

ALX-840-604-R100 100 µl

Whole cell lysate of HEK 293T cells transfected with an expression plasmid for human RIP2 (receptor-interacting protein 2) (aa 1-541).

PAb to RIP2 (human) (CT)

PSC-2183-C100 100 µg

From rabbit. **IMMUNOGEN:** Synthetic peptide corresponding to aa 508-522 of C-terminal human RIP2 (receptor-interacting protein 2). **SPECIFICITY:** Recognizes human RIP2. Detects a band of ~60kDa by Western blot. **APPLICATION:** WB. **BP:** PSC-2183P.

PAb to RIP2 (NT)

PSC-2075-C100 100 µg

From rabbit. **IMMUNOGEN:** Synthetic peptide corresponding to aa 11-30 of N-terminal human RIP2 (receptor-interacting protein 2). **SPECIFICITY:** Recognizes human, mouse and rat RIP2. Detects a band of ~60kDa by Western blot. **APPLICATION:** WB. **BP:** PSC-2075P.

Antibodies to NALPs

MAb to NALP1 (human) (Nalpy1-4)

ALX-804-803-C100 100 µg

CLONE: Nalpy1-4. **ISOTYPE:** Mouse IgG1. **IMMUNOGEN:** Recombinant human NALP1 (NACHT-, LRR- and PYD-containing protein 1) (pyrin domain). **SPECIFICITY:** Recognizes the pyrin domain (PYD) of human NALP1. **APPLICATION:** IHC (FS, PS), ICC, IP, WB.

LIT: Inflammasome components NALP 1 and 3 show distinct but separate expression profiles in human tissues suggesting a site-specific role in the inflammatory response: J.A. Kummer, et al.; *J. Histochem. Cytochem.* **55**, 443 (2007)

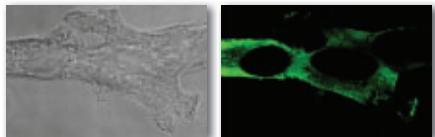


FIGURE: Detection of NALP1 in 293T cells transfected with a human NALP1 expression plasmid. *Left:* Phase contrast. *Right:* Staining with MAb to NALP1 (Nalpy1-4).

PAb to NALP1 (human) (AL176)

ALX-210-904-R100 100 µl

From rabbit. **IMMUNOGEN:** Synthetic peptide corresponding to aa 2-25 ($A^2GGAWGRACYLEFLKK-ELKEFQ^{25}$) of N-terminal human NALP1 (NACHT-, LRR- and PYD-containing protein 1). **SPECIFICITY:** Recognizes human NALP1. **APPLICATION:** WB.

LIT: The inflammasome: a molecular platform triggering activation of inflammatory caspases and processing of proll-beta: F. Martinon; *Mol. Cell.* **10**, 417 (2002)

PAb to NALP1 (human) (CT) (Bur 242)

ALX-210-017-R050 50 µl

From rabbit. **IMMUNOGEN:** Synthetic peptide corresponding to aa 1058-1077 ($C^{1058}VPS-PASQGDLHTKPLGTDD^{1077}$) of C-terminal human NALP1 (NACHT-, LRR- and PYD-containing protein 1). **SPECIFICITY:** Recognizes human NALP1. **APPLICATION:** IHC (PS), IP, WB.

LIT: A novel enhancer of the Apaf1 apoptosome involved in cytochrome c-dependent caspase activation and apoptosis: Z.L. Chu, et al.; *J. Biol. Chem.* **276**, 9239 (2001)

PAb to NALP1 (human) (NT) (Bur 241)

ALX-210-018-R050 50 µl

From rabbit. **IMMUNOGEN:** Synthetic peptide corresponding to aa 161-180 ($P^{161}SSPDHESP-SQESPNAPST^{180}$) of N-terminal human NALP1 (NACHT-, LRR- and PYD-containing protein 1). **SPECIFICITY:** Recognizes human NALP1. **APPLICATION:** IHC (PS), IP, WB.

LIT: A novel enhancer of the Apaf1 apoptosome involved in cytochrome c-dependent caspase activation and apoptosis: Z.L. Chu, et al.; *J. Biol. Chem.* **276**, 9239 (2001)

Positive Control (Cell Lysate) for Antibodies to NALP1 (human)

ALX-840-603-R100 100 µl

Whole cell lysate of HEK 293T cells transfected with an expression plasmid for human NALP1 (NACHT-, LRR- and PYD-containing protein 1) (aa 1-1429).

PAb to NALP2 (CT)

PSC-3027-C100 100 µg

From rabbit. **IMMUNOGEN:** Synthetic peptide corresponding to 12 aa near the C-terminal of human NALP2 (NACHT-, LRR- and PYD-containing protein 2). **SPECIFICITY:** Recognizes human, mouse and rat NALP2. **APPLICATION:** WB, BP: PSC-3027P.

MAb to NALP3 (human) (Nalpy3-a)

ALX-804-818-C100 100 µg

CLONE: Nalpy3-a. **ISOTYPE:** Mouse IgG1. **IMMUNOGEN:** Recombinant human NALP3 (NACHT-, LRR- and PYD-containing protein 3) (pyrin domain). **SPECIFICITY:** Recognizes human NALP3. Detects endogenous protein by ICC and WB. **APPLICATION:** ICC, WB.

LIT: NALP3 forms an IL-1beta-processing inflammasome with increased activity in Muckle-Wells autoinflammatory disorder: L. Agostini, et al.; *Immunity* **20**, 319 (2004)

MAb to NALP3 (human) (Nalpy3-b)

ALX-804-819-C100 100 µg

CLONE: Nalpy3-b. **ISOTYPE:** Mouse IgG1. **IMMUNOGEN:** Recombinant human NALP3 (NACHT-, LRR- and PYD-containing protein 3) (pyrin domain). **SPECIFICITY:** Recognizes human NALP3. Detects endogenous protein by IP and WB. **APPLICATION:** IHC (FS), IP, WB.

LIT: NALP3 forms an IL-1beta-processing inflammasome with increased activity in Muckle-Wells autoinflammatory disorder: L. Agostini, et al.; *Immunity* **20**, 319 (2004) • Inflammasome components NALP 1 and 3 show distinct but separate expression profiles in human tissues suggesting a site-specific role in the inflammatory response: J.A. Kummer, et al.; *J. Histochem. Cytochem.* **55**, 443 (2007)

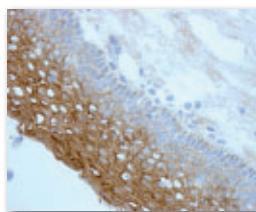


FIGURE: Staining of endogenous NALP3 in epithelial layer of human tonsil (frozen section) using MAb to NALP3 (Nalpy3-b) (Prod. No. ALX-804-819).

PAb to NALP12 (human) (AL236)

ALX-210-958-C100 100 µg

From rabbit. **IMMUNOGEN:** Synthetic peptide corresponding to aa near the N-terminus of human NALP12. **SPECIFICITY:** Recognizes human NALP12. **APPLICATION:** IP, WB.

Asc

PAb to Asc (AL177)

ALX-210-905-R100 100 µl

From rabbit. **IMMUNOGEN:** Synthetic peptide corresponding to aa 2-27 ($G^2RARDAIL-DALENLTAEELKKFKLKL^{27}$) of N-terminal human Asc (apoptosis-associated speck-like protein containing CARD; Pycard). **SPECIFICITY:** Recognizes human and mouse Asc. **APPLICATION:** ICC, IP, WB.

LIT: The inflammasome: a molecular platform triggering activation of inflammatory caspases and processing of proll-beta: F. Martinon, et al.; *Mol. Cell.* **10**, 417 (2002) • NALP3 forms an IL-1beta-processing inflammasome with increased activity in Muckle-Wells autoinflammatory disorder: L. Agostini, et al.; *Immunity* **20**, 319 (2004) • P2X7 Receptor Differentially Couples to Distinct Release Pathways for IL-1{beta} in Mouse Macrophage: P. Pelegrein, et al.; *J. Immunol.* **180**, 7147 (2008)

Positive Control (Cell Lysate) for Antibodies to Asc (human)

ALX-840-602-R100 100 µl

Whole cell lysate of HEK 293T cells transfected with an expression plasmid for human Asc (apoptosis-associated speck-like protein containing CARD; Pycard) (aa 1-195).

CARD8 [Cardinal]

PAb to CARD8 (human) (CT)

PSC-3187-C100 100 µg

From rabbit. **IMMUNOGEN:** Synthetic peptide corresponding to aa near the C-terminus of human CARD8 (caspase recruitment domain-containing protein 8). **SPECIFICITY:** Recognizes human CARD8. **APPLICATION:** WB, BP: PSC-3187P.

IPAF [CARD12]

MAb to IPAF (human) (Luna-1)

ALX-804-848-C100 100 µg

CLONE: Luna-1. **ISOTYPE:** Mouse IgG2b. **IMMUNOGEN:** Recombinant human IPAF (ice protease-activating factor) (aa 9-494). **SPECIFICITY:** Recognizes human IPAF. **APPLICATION:** WB.

PAb to IPAF (human)

PSC-3107-C100 100 µg

From rabbit. **IMMUNOGEN:** Synthetic peptide corresponding to aa near the C-terminus of human IPAF (ice protease-activating factor). **SPECIFICITY:** Recognizes human IPAF. **APPLICATION:** IHC, WB, BP: PSC-3107P.

NAIP

PAb to NAIP (human) (CT)

PSC-3315-C100 100 µg

From rabbit. **IMMUNOGEN:** Synthetic peptide corresponding to 13 aa at the C-terminus of human NAIP (neuronal apoptosis inhibitory protein). **SPECIFICITY:** Recognizes human NAIP. **APPLICATION:** WB, BP: PSC-3315P.

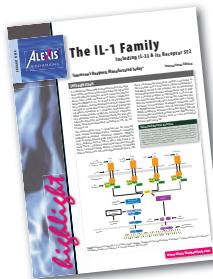
Pyrin

PAb to Pyrin (human) (AL196)

ALX-210-946-C100 100 µg

From rabbit. **IMMUNOGEN:** Synthetic peptide corresponding to aa 2-29 ($A^2KTPSDHLLSTLEELVPYD-FEKFKFKLQ^{29}$) of human pyrin (MEFV; mediterranean fever protein). **SPECIFICITY:** Recognizes human pyrin. **APPLICATION:** IP, WB.

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Nod-like Receptor Ligands

Nigericin . Na

[Antibiotic K 178]

ALX-380-050-M005	5 mg
ALX-380-050-M025	25 mg

Isolated from *Streptomyces hygroscopicus*.

R-848

[4-Amino-2-(ethoxymethyl)-a,a-dimethyl-1H-imidazo[4,5-c]quinoline-1-ethanol; S 28463; Resiquimod]

ALX-420-038-M005	5 mg
ALX-420-038-M025	25 mg

Selective ligand for Toll-like receptor 7 (TLR7) in mouse and for TLR7 and TLR8 in human. Potent antitumor and antiviral compound. Stimulates antibody secretion, cytokine production, protection from apoptosis and CD80 upregulation.

LIT: The immune response modifier resiquimod mimics CD40-induced B cell activation: G.A. Bishop, et al.; Cell. Immunol. 208, 9 (2001) ▪ Small anti-viral compounds activate immune cells via the TLR7 MyD88-dependent signaling pathway: H. Hemmi, et al.; Nat. Immunol. 3, 196 (2002) ▪ Human TLR9 or TLR8 independently confer responsiveness to the antiviral compound R-848: M. Jurk, et al.; Nat. Immunol. 3, 499 (2002) ▪ Resiquimod: a new immune response modifier with potential as a vaccine adjuvant for Th1 immune responses: J.J. Wu, et al.; Antivir. Res. 64, 79 (2004) ▪ Direct stimulation of human T cells via TLR5 and TLR7/8: flagellin and R-848 up-regulate proliferation and IFN-gamma production by memory CD4+ T cells: G. Caron, et al.; J. Immunol. 175, 1551 (2005) ▪ TLR agonists as vaccine adjuvants: comparison of CpG ODN and Resiquimod (R-848): R.D. Weeratna, et al.; Vaccine 23, 5263 (2005) ▪ Treatment of intravaginal HSV-2 infection in mice: a comparison of CpG oligodeoxynucleotides and resiquimod (R-848): M.J. McCluskie, et al.; Antivir. Res. 69, 77 (2006)

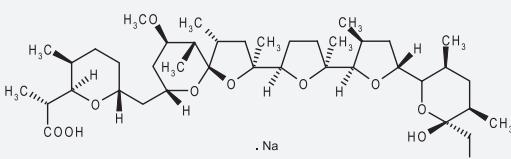
Imiquimod

[R-837]

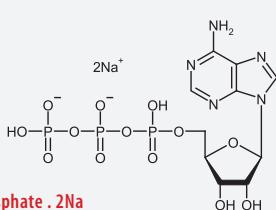
ALX-420-039-M100	100 mg
ALX-420-039-M250	250 mg

Topical immune response modifier that inhibits angiogenesis. Up-regulates IL-18 and down-regulates MMP-9 through recognition of TLR7 and subsequent activation of MyD88-dependent pathway.

LIT: Imiquimod applied topically: a novel immune response modifier and new class of drug: R.L. Miller, et al.; Int. J. Immunopharmacol. 21, 1 (1999) ▪ Small anti-viral compounds activate immune cells via the TLR7 MyD88-dependent signaling pathway: H. Hemmi, et al.; Nat. Immunol. 3, 196 (2002) ▪ In vivo and in situ modulation of the expression of genes involved in metastasis and angiogenesis in a patient treated with topical imiquimod for melanoma skin metastases: C. Hesling, et al.; Br. J. Dermatol. 150, 761 (2004) ▪ Imiquimod as an antiangiogenic agent: V.W. Li, et al.; J. Drugs Dermatol. 4, 708 (2005) ▪ Imiquimod is a strong inhibitor of tumor cell-induced angiogenesis: S. Majewski, et al.; Int. J. Dermatol. 44, 14 (2005)



Nigericin . Na



Adenosine 5'-triphosphate . 2Na

Ac-muramyl-Ala-D-Glu-amide

[MDP-LD; N-Acetyl muramyl-L-alanyl-D-isoglutamine]

ALX-151-035-M001	1 mg
ALX-151-035-M005	5 mg

Synthetic. Specific ligand for NALP3. For inactive control compound see MDP-DD (Prod. No. ALX-151-036).

Adenosine 5'-triphosphate . 2Na

[ATP . 2Na]

ALX-480-021-G001	1 g
ALX-480-021-G005	5 g

Specially crystallized and tested on biological activity.

LIT: Gout-associated uric acid crystals activate the NALP3 inflammasome: F. Martinon, et al.; Nature 440, 237 (2006)

Flagellin (high purity)

ALX-522-058-C010

10 µg

Isolated from *Salmonella typhimurium* strain 14028.

SPECIFICITY: Binds to human and mouse TLR5. BIOLOGICAL ACTIVITY: Activation of TLR5 in human epithelial cell assays based on NF-κB luciferase fusions.

LIT: Flagellin stimulation of intestinal epithelial cells triggers CCL20-mediated migration of dendritic cells: F. Sierra, et al.; PNAS 98, 13722 (2001) ▪ Pathophysiological role of Toll-like receptor 5 engagement by bacterial flagellin in colonic inflammation: S.H. Rhee, et al.; PNAS 102, 13610 (2005)

New NALP3 Inflammasome Activator

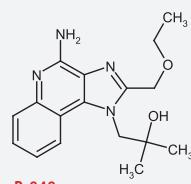
Monosodium urate (crystals)

[MSU Crystals; Uric Acid Crystals]

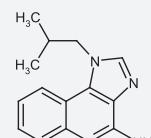
ALX-400-047-M002	2 mg
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Specially crystallized and tested on biological activity.

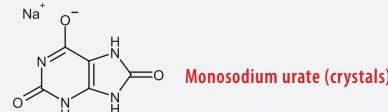
LIT: Gout-associated uric acid crystals activate the NALP3 inflammasome: F. Martinon, et al.; Nature 440, 237 (2006)



R-848



Imiquimod



Monosodium urate (crystals)

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