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## Novel synthetic inhibitors of the TLR4 Pathway

Lead compounds in the development of new  
anti-endotoxic agents selectively targeting CD14

- Act as Lipid A antagonists
- Potent inhibition. Recommended starting concentrations *in vitro*: 1-25  $\mu$ M, *in vivo* experiments (rat, mouse): 10-20 mg/Kg
- Efficient in rodent models of inflammatory diseases, endotoxin mediated septic shock and neuropathic pain
- Good toxicity profile
- Inactive control compounds available

IAXO compounds are Glycolipids and Benzylammonium Lipids designed to act as Lipid A antagonists. They have been shown to potently modulate the CD14 and Toll-like Receptor 4 (TLR4) pathway *in vitro* and *in vivo* and are efficient in rodent models of inflammatory diseases, neuropathic pain and LPS (endotoxin) induced septic shock.

The novel family of synthetic IAXO compounds [see References] not only can inhibit LPS-stimulated TLR4 activation by competitively occupying CD14 and thereby reducing the delivery of activating endotoxin to MD-2-TLR4 but may also shed light on the features of CD14-dependent and TLR4-independent signalling pathways. The functional properties described so far suggest that molecules IAXO-101, IAXO-102 and IAXO-103 can be considered lead compounds in the development of new anti-endotoxic agents selectively targeting CD14. IAXO compounds act as Lipid A antagonists with an inhibiting potency *in vitro* in the range of 5  $\mu$ M. IAXO compounds are efficient in rodent models of inflammatory diseases, endotoxin-mediated septic shock and neuropathic pain (10-20 mg/kg) with a good toxicity profile.

LPS binds first to lipopolysaccharide binding protein in serum and is then transferred to CD14. CD14 is a 55-kDa glycoprotein expressed on the surface of myelomonocytic cells as a GPI-

anchored receptor or secreted in a soluble form. The LPS binding site of CD14 is located at the N-terminal region of the protein in a large hydrophobic pocket that accommodates the phosphorylated lipid A moiety. Additionally, since also the carbohydrate portion of LPS contributes to the binding to CD14 its irregular and flexible structure provides CD14 with the ability to bind different forms of LPS with a comparable high affinity and probably explains its ligand promiscuity. CD14 is thought to be involved in the recognition of a number of other ligands, acting as a co-receptor for TLR1, TLR2, TLR6, TLR4, and TLR3. CD14 indeed functions as an LPS sensing receptor whose role is to enhance the sensitivity of innate immune cells to LPS by binding to picomolar signalling concentrations of LPS and facilitating its recognition by TLR4:MD-2.

CD14 has been shown to be largely dispensable for the response to high concentrations of LPS, which occur almost normally in CD14-deficient macrophages. This notable observation suggests that an excess of LPS can be also sensed by means of a CD14-independent pathway, which possibly implies either direct LPS recognition by TLR4:MD-2 or the participation of different LPS binding proteins.

<b>IAXO-101</b> [Methyl 6-deoxy-6-N-dimethyl-N-cyclopentylammonium-2, 3-di-O-tetradecyl- $\alpha$ -D-glucopyranoside iodide] (Synonyms: Cpd. 2 [1, 3], FP1 [2], Cpd. 1 [4])	INAX-001-M001	1 mg	€ 275
<b>IAXO-102</b> [Methyl 6-Deoxy-6-amino-2,3-di-O-tetradecyl- $\alpha$ -D-glucopyranoside] (Synonyms: Cpd. 5 [1], Cpd. 2 [4])	INAX-002-M001	1 mg	€ 275
<b>IAXO-103</b> [N-(3,4-Bis-tetradecyloxy-benzyl)-N-cyclopentyl-N,N-dimethylammonium iodide] (Synonyms: Cpd. 7 [1], Cpd. 3 [4])	INAX-003-M001	1 mg	€ 275
<b>IAXO-201</b> (Inactive Control Compound for IAXO-102) (Synonyms: Cpd. 4 [1], Cpd. 10 [3])	INAX-004-M001	1 mg	€ 275
<b>IAXO-202</b> (Inactive Control Compound for IAXO-101 & IAXO-103) (Synonyms: Cpd. 3 [1])	INAX-005-M001	1 mg	€ 275

- [1] Glycolipids and benzylammonium lipids as novel antiseptics agents: synthesis and biological characterization. Piazza M, et al. J Med Chem. 52:1209 (2009)
- [2] Glial TLR4 receptor as new target to treat neuropathic pain: efficacy of a new receptor antagonist in a model of peripheral nerve injury in mice. Bettoni I, et al. Glia. 56:1312 (2008)
- [3] Inhibition of lipid a stimulated activation of human dendritic cells and macrophages by amino and hydroxylamino monosaccharides. Peri F, et al. Angew Chem.46:3308 (2007)
- [4] Evidence of a specific interaction between new synthetic antiseptics agents and CD14. Piazza M, et al. Biochemistry. 48:12337 (2009)