PET Lipid A Vaccine Adjuvant and Related Technologies

Adjuvants Play an Important Role in Modern Vaccines

Why Use Adjuvants?

- Modern subunit vaccines utilize highly purified protein/peptide antigens
- Such antigens by themselves are not able to stimulate an effective immune response
- Effective adjuvants can be antigen dose / frequency sparing
- Effective adjuvants can prime & boost *the right* type of immune responses

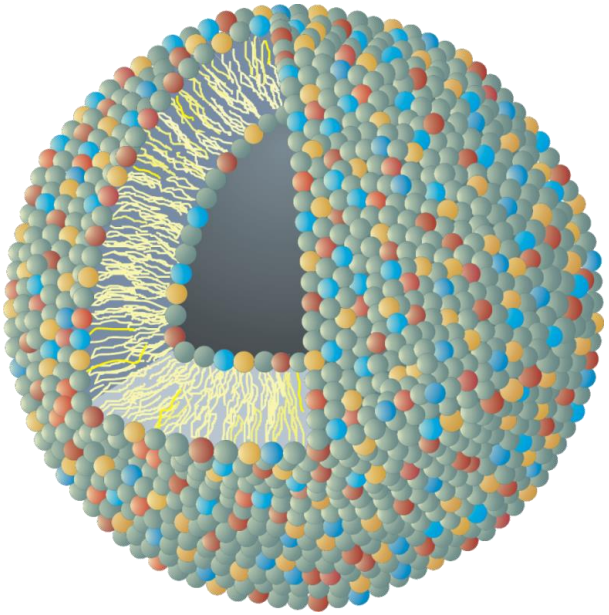
Why TLR4 Agonists?

- TLR4 agonists represent the next generation of adjuvants
- Successfully approved by FDA (MPL® adjuvant in Cervarix™)
- Proven biology and MOA
- Ability to shape desired immune response (cellular, humoral)

PET Lipid A is the only fully syntheticTLR4 agonist available for adjuvant use with composition of matter patent protection

Oncothyreon Vaccine Platform

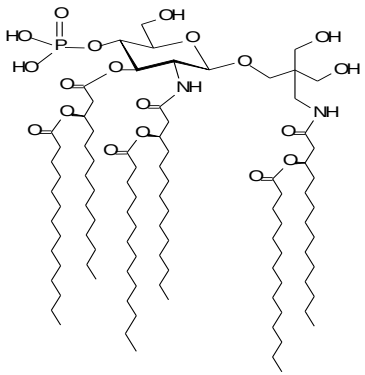
- **PET Lipid A adjuvant**
  - Phase 1 safety data
  - Fully synthetic product
  - >10-fold greater potency relative to MPL® [1]
  - Composition of matter patent & manufacturing IP
- **Liposomal microparticle formulation**
  - Liposomes composed of cholesterol and two phospholipids: DPPC and DMPG
  - Simple to manufacture, scalable
  - Accommodates sterile filtration
- **Di-lipidated peptide antigen**
  - Proprietary peptide antigen formulation for liposomal delivery
  - Increases humoral immunity to peptide



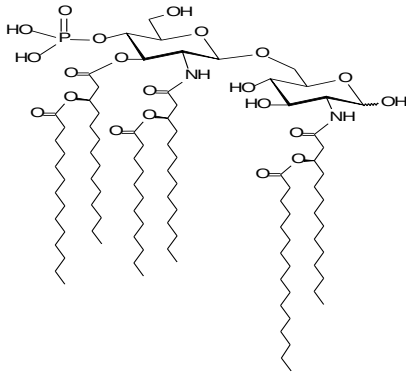
[1] MPL = monophosphoryl lipid A

PET Lipid A Adjuvant

- **Properties of PET Lipid A**
  - **Like MPL, PET Lipid A is a "detoxified" form of LPS**
  - **Interacts with TLR4 to active antigen presenting cells**
- **Comparison to MPL®**
  - **MPL® which is a natural product derived from *Salmonella minnesota* LPS; PET Lipid A is fully synthetic, eliminating lot to lot variability and allowing better quality control**
  - **PET Lipid A is >10-fold more potent than MPL in pro-inflammatory cytokine assays using human PBMCs**
  - **MPL® is owned exclusively by GSK and not available for license**



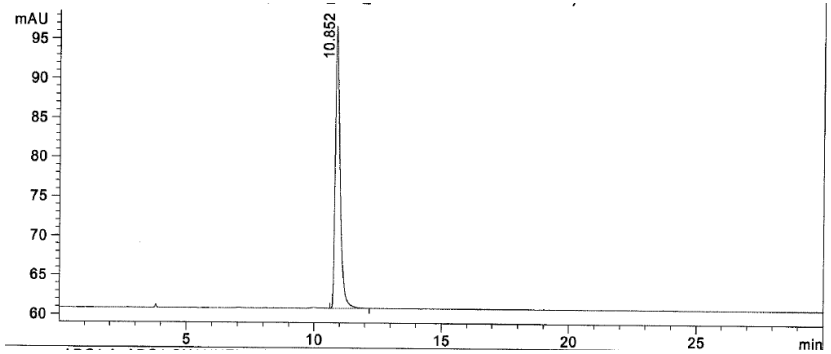
PET-A – Lipid A pentaerythritol-6-chain-C_{14}-mono-phosphate



MPL – 6acyl-Monophosphoryl Lipid A (4, 5 acyl forms are also present) in mixture

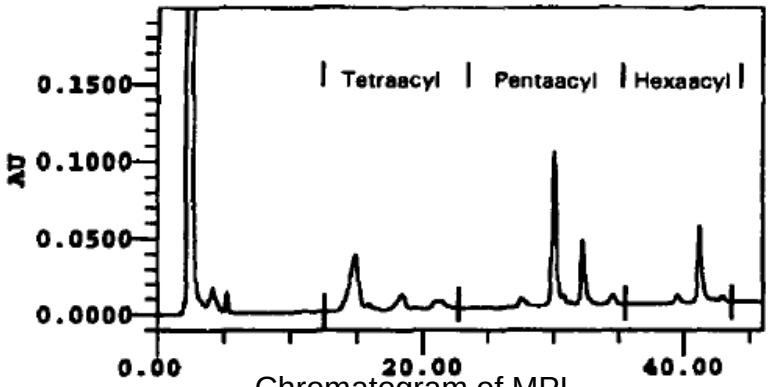
Fully Synthetic PET Lipid A Advantages vs MPL®

- **PET Lipid A**
  - **Fully synthetic**
    - **Single, potent hexa-acyl C14 form**
    - **BSE/TSE free**
  - **Manufactured under cGMP**
    - **High chiral and chemical purity**
    - **Lot-to-lot consistency**



Chromatogram of PET Lipid A

- **MPL®**
  - **Variable mixture of acyl congeners derived from bacterial (*Salmonella minnesota*) fermentation, isolation, hydrolysis, and purification**

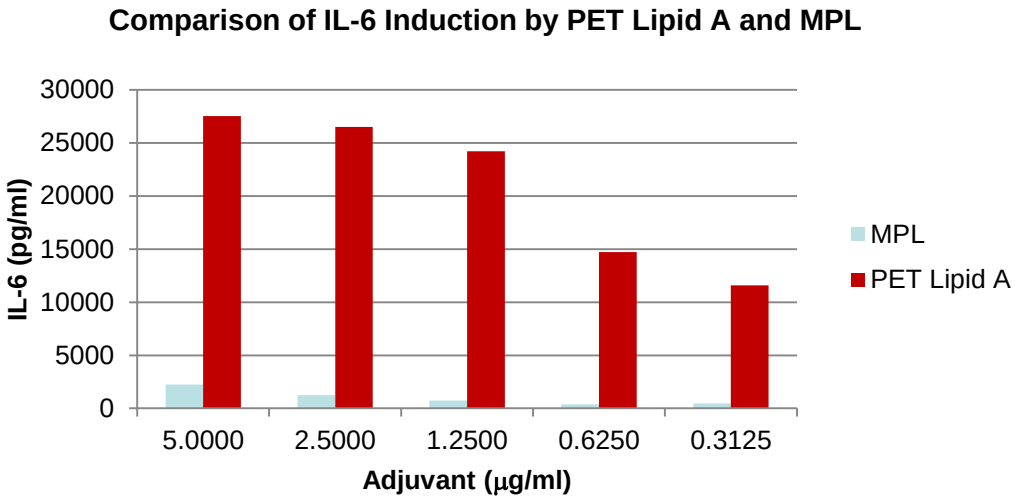


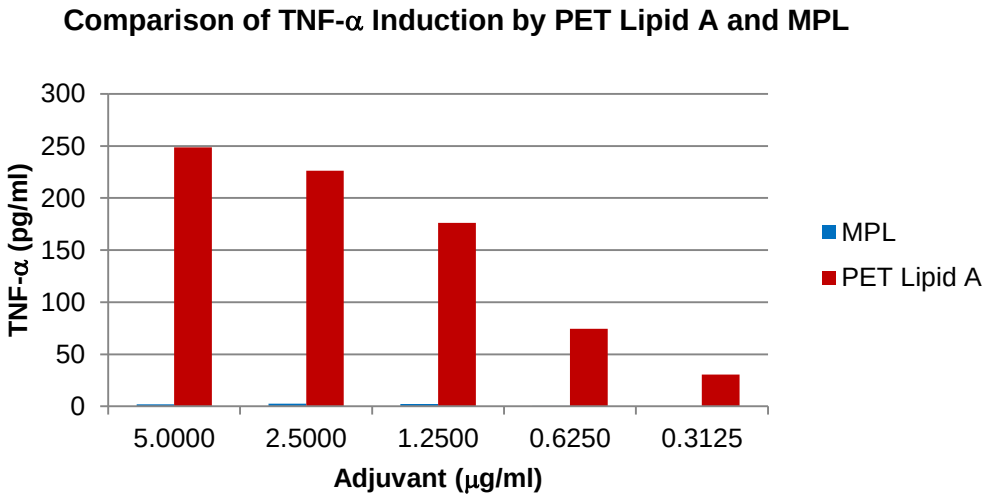
Chromatogram of MPL
(Journal of Chrom A, Ribi ImmunoChem 1997)

"Underacylated lipid A structures, containing four or five fatty acids, induce markedly less host defense responses and can inhibit, in a dose-dependent manner, the strong endotoxic response triggered by hexa-acylated LPS."

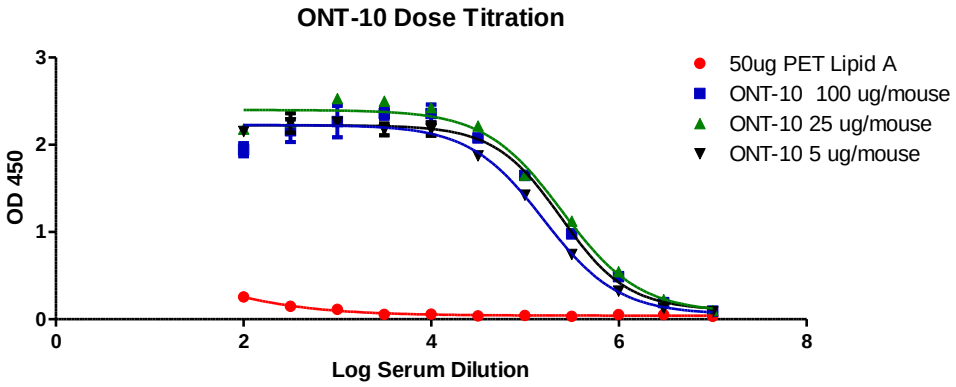
Teghanemt A. et al., 2005. Molecular basis of reduced potency of underacylated endotoxins. J Immunol. 175(7):4669-76.

PET Lipid A is More Potent than MPL in Human PBMC Cytokine Assays

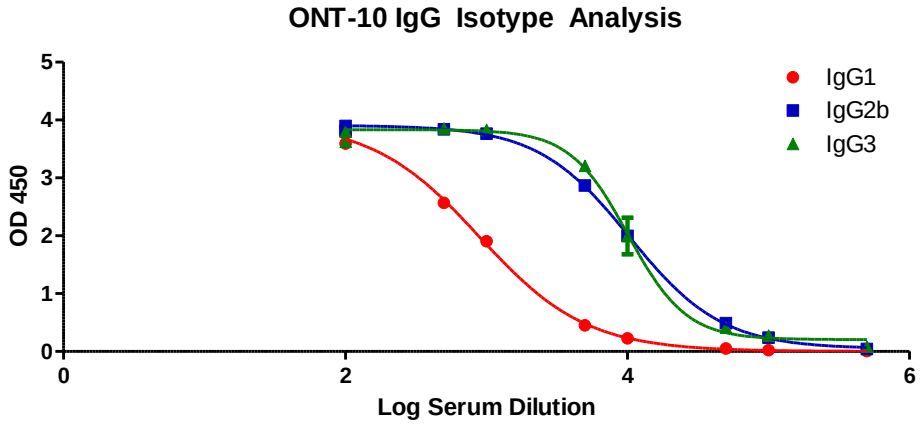




PET Lipid A Induces a Robust Humoral Response in Mice



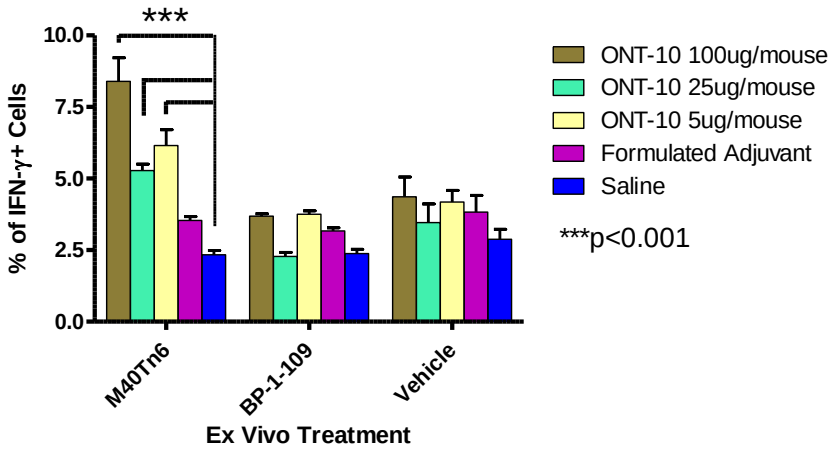
- **Potent induction of high titer IgG response**
  - **Antibody titer endpoints >1:500,000**



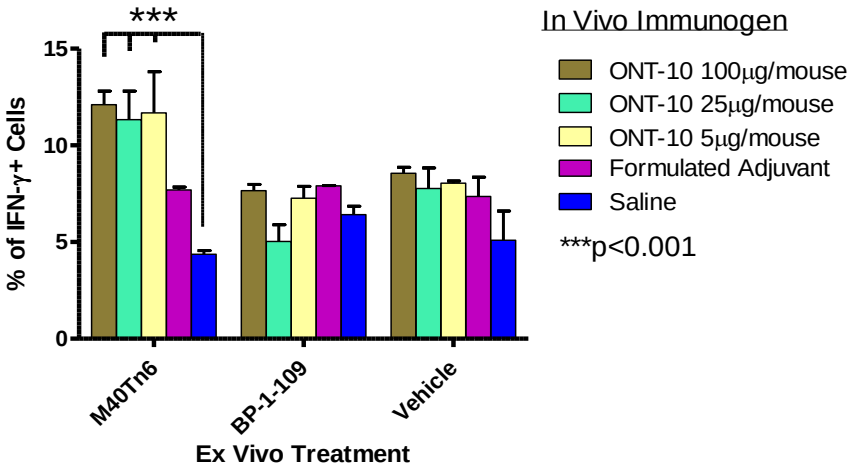
- **Isotype analysis consistent with Th1 response**
  - **IgG2b, IgG3>IgG1**

PET Lipid A Induces a CD4+ and CD8+ T-cell Response

Intracellular IFNγ Quantification in CD4+/CD8- Splenocytes of Immunized C57BL6J Female Mice



Intracellular IFNγ Quantification in CD4-/CD8+ Splenocytes of Immunized C57BL6J Female Mice



PET Lipid A's Properties Favor its Use as a Vaccine Adjuvant

- **Fully synthetic hexa-acyl structure provides for:**
  - **More than 10-fold more potent induction of inflammatory cytokines compared with MPL®**
  - **Straightforward manufacturing, characterization**
- **Supports robust cellular (CD4, CD8) and humoral (Th1 Ab) response**
  - **Superior profile compared to historical data with MPL® formulations**
- **Favorable safety profile**
  - **Demonstrated safety profile in ONT-10 Phase 1 clinical trial**

PET Lipid A Manufacturing is Proprietary and Scalable

- **Manufacturing is exclusively owned & controlled by Oncothyreon**
  - **Manufacturing IP**
  - **Utilize contract manufacturing organizations for production**
- **Current cGMP process is 5-step synthesis**
  - **Successful cGMP campaign Excellent chemical purity and stability**
  - **Qualified analytical methods**
- **Process scale-up activities underway to support future clinical development of pipeline products***

* ONT-10 is Oncothyreon's MUC1 – based therapeutic cancer vaccine combined with PET Lipid A in Phase 1 clinical trials. This product is not available for license.

PET Lipid A Has Comprehensive Intellectual Property Protection

- **US issued patents on composition, methods**
  - **US 7,820,627**
  - **US 8,097,593**
- **Foreign issued patents on composition, methods**
  - **EP 1 549 322**
  - **AU 2003228966**
  - **CA 2,485,253**
  - **JP 2004-50238**
- **Additional patents/applications around liposome formulation, di-lipidation, and others**

Additional Information

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