# Workshop: Adjuvants and Adjuvanted Preventive and Therapeutic Vaccines for Infectious Disease Indications


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# Potential Needs for and Benefits of Adjuvants

- Enhance rapidity and/or “height”/intensity of response – for many Ags poor immunogenicity
- Enhance “breadth” of response- cross-protective and T cell mediated effects (protect against pathogen evolution)
- Enhance duration of response and/or ability to prime for later response (memory)
- Recent increased interest in adjuvants in part driven concerns re: H5N1, poor immunogen and insufficient manufacturing capacity, likelihood of strain drift
- Also potentially important for “vaccine resistant” or “host response deficient” global health challenges such as HIV, TB, malaria, influenza in elderly, as well as for oncology and other therapeutic vaccines

# Numerous Clinical Studies with Adjuvants Recent or Ongoing - Including:

- Mineral salts/gels
- Oil-in-water emulsions (MF59)
- Saponin-based (QS21)
- Microbial derivatives (MPL, CpG, LT)
- Endogenous human immunomodulators (cytokines)
- Virosomal/particle approaches
- ***and*** combinations of these = "Adjuvant Systems"

# Selected Mechanisms of Action

- Depends on adjuvant – often poorly understood/multiple
  - Stimulation/prolongation of Ag uptake through APC (alum)
  - Attraction of MNC, DC, PMN infiltrates, enhanced Ag processing and presentation (oil-in-water, MF 59)
  - Effects on cellular membranes (QS21)
  - TLR/other PRR agonists (MPL)
    - Release of pro-inflammatory cytokines
    - Enhance antibody & T cell responses
    - Likely also engage negative feedback pathways

*Note: Such mechanisms lead to immune/inflammatory responses that may be localized and/or systemic and antigen specific and/or non-specific*

*Also note: need for and responses to adjuvants may differ with different antigens, in different clinical settings (e.g. priming vs. recall) and in different populations*

# Adjuvant Benefits and Risks: FDA Perspectives

- **Enhanced immunity vs. inflammation, AEs, autoimmunity?**
- ***Safety expectations very high for preventive vaccines:***
  - ***healthy children***
  - ***global use***
  - ***large numbers***
  - ***confidence in immunization, public health, government, industry, and dependent public health outcomes, always at stake***

# Adjuvants: Potential Concerns/Risks

- Potentially antigen specific or non-specific potent immune and inflammatory stimulation
- Increased reactogenicity, local +/- systemic inflammation
  - Unclear which, if any, correlate with risk of rare SAEs
- Potential role in autoimmunity, short or long term?
  - Antigen specific (e.g. neural or cardiac antigens)
  - Auto-immune/inflamm disease, e.g. SLE, “idiopathic”
- Are there plausible risks to developing immune systems?
- *Reassuring observations to date:*
  - *Even strong TLR/PRR signaling likely similar to natural infection (caveat w/ recent UK CD28 agonist trial)*
  - *No strong evidence to date of major problems with compounds being most actively considered – <u>but limited numbers w/ controls, long term active follow-up, or in children</u>*

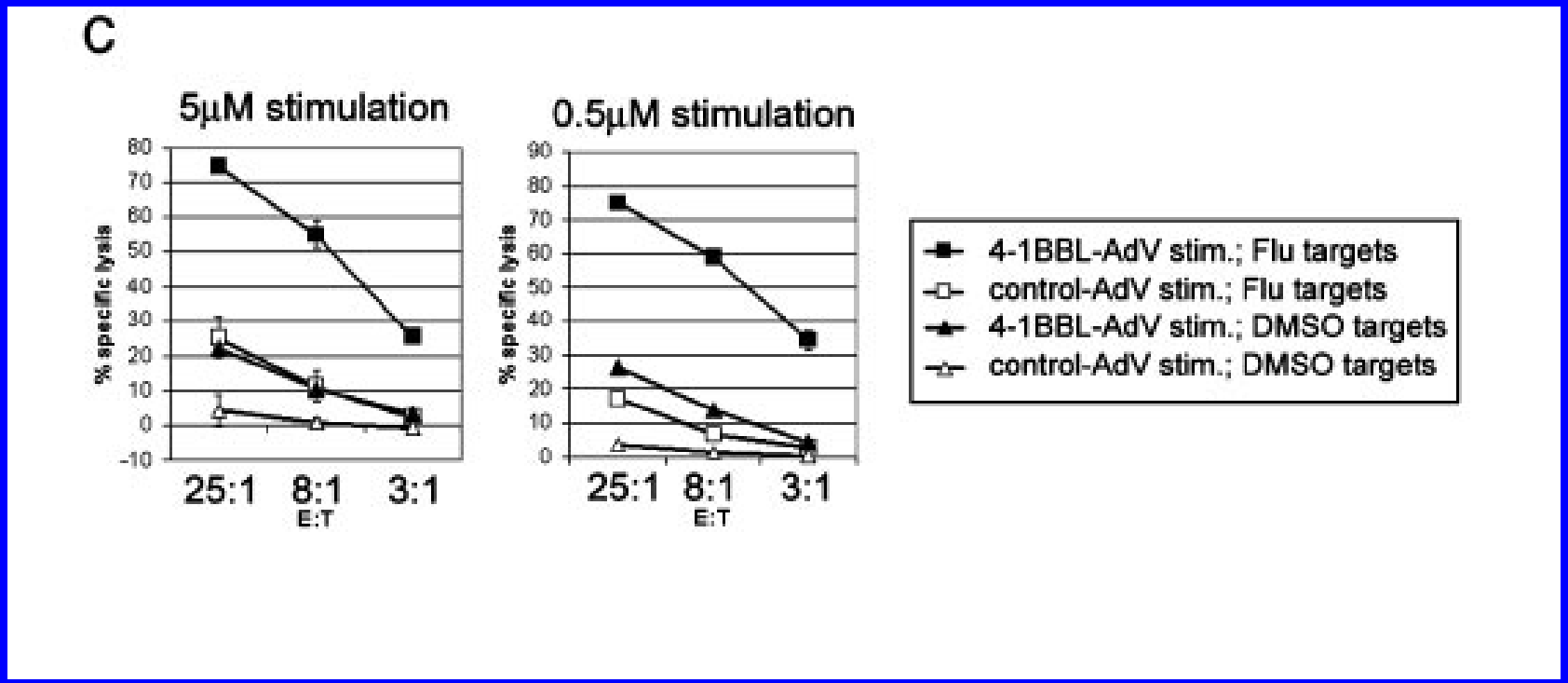
# Workshop Purpose

- To assess the current scientific knowledge base
- To facilitate the development of a research agenda to improve the safety & efficacy assessment of adjuvanted vaccines for the treatment and prevention of infectious disease
- To help formulate approaches to enhance nonclinical safety assessment of adjuvanted vaccines
- To receive an update on available clinical safety data from studies using adjuvanted vaccines

***We expect these discussions to help stimulate and inform growing interest and investigation of basic and clinical aspects of adjuvants, and help advance the successful development and evaluation of vaccines needed to address important global health challenges***

# Some Additional Scientific Issues

- May there be, in some cases, host (vs. pathogen) protective reasons for poor antigenicity (and a risk to overcoming them)? Or can we select/design better antigens?
- As we understand host protection, can we design adjuvants that work more specifically (? e.g. more distally or selectively) and cause less non-specific inflammation/cytokine release?
- Can new approaches to “vaccine toxicology” improve the predictive value of studies, both positive and negative? And further reduce possibly unneeded “classical” studies?
  - E.g. genomic response of MNCs/other cells, or cytokine production *in vitro*, *in vivo* or in animal models?
  - Better models, immune disease prone, neonatal?
    - *But many major differences in murine vs. human responses, and many strain specific differences (e.g. TLRs)*




*Bukczynski, J et al, Costimulatory ligand 4-1BBL (CD137L) as an efficient adjuvant for human antiviral - cytotoxic T cell responses. PNAS 2004 Feb 3;101(5):1291-6*

# Thanks!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# Novel Adjuvanted Vaccines- Examples

- **Malaria**
  - **AMA1-C1/Alhydrogel ± CPG 7909**
  - **RTS,S/AS02A;  RTS,S/AS01B**
  - **Pfs25/Montanide ISA 51**
- **HIV**
  - **Gp160MN/LAI  ± DC-Chol**
  - **Vacc-4x + GM-CSF**

# Novel Adjuvanted Vaccines- Examples

- Tuberculosis
  - Mtb72F/AS02A
  - HyVac4-IC31 (adjuvant: KLK peptide + ODN 1a)
- Influenza
  - FLUAD (adjuvant: MF59)
  - AS03-H5N1

# Novel Adjuvants in Approved Vaccines

## MPL containing adjuvants:

*AS04* – in hepatitis B vaccine (Fendrix*)

also in HPV vaccine (Cervarix*), and *investigational* genital herpes vaccine[1]

*AS01/AS02* – in *investigational* malaria vaccine(s)[2]

## MF59 adjuvant in influenza vaccine [3] (FLUAD *)

*approved in Europe


[1]Baldridge *et al.* (2004) Expert Opin. Biol. Ther. 4, 1129

[2]Mettens *et al.* (2008) Vaccine 26, 1072-1082

[3]Frey, S. *et al.* (2003) Vaccine 21, 4234