MSP1.42 Vaccine Adjuvant Development

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Merozoite Surface Protein-1 C-terminal 42 kDa fragment (MSP1.42)

- Preclinical studies with Baculovirus MSP1.42 and Complete Freund's Adjuvant
  - Highly immunogenic in rabbits and *Aotus* monkeys
    - Chang et al., 1992
  - Protection of *Aotus* monkeys against *P. falciparum* challenge
    - Chang et al., 1996
    - Stowers et al., 2001
  - Antibody titers to MSP1.42 significantly associated with protection from clinical malaria and severe parasitemia in Papua New Guinean children
    - Al-Yaman et al., 1996

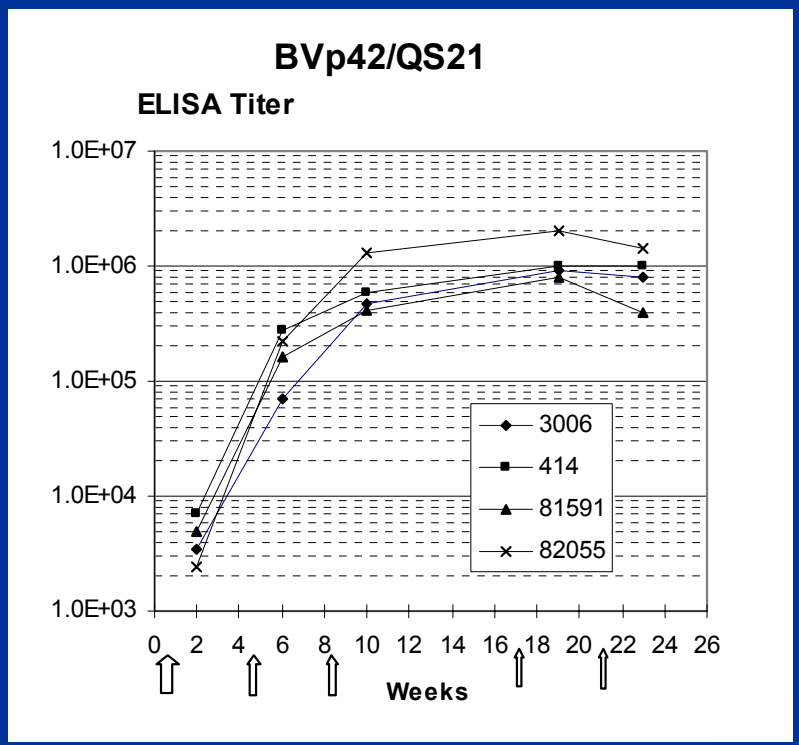
Various Adjuvant Formulations Evaluated with MSP1.42 in *Aotus* Model

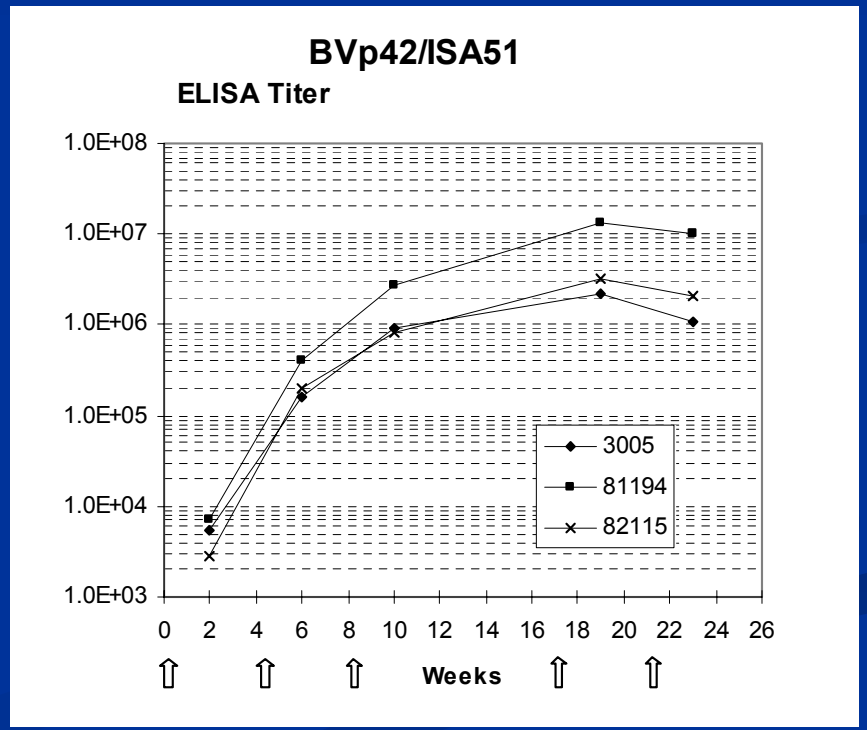
- MF-59
  - oil-in-water emulsion containing squalene, polysorbate 80, & sorbitan trioleate
- MTP-PE
  - synthetic muramyl dipeptide derivative
- **QS21**
  - **purified saponin from soapbark tree *Quillaja saponaria***
- **Montanide ISA51**
  - **water-in-oil emulsion similar to Incomplete Freund's Adjuvant**
    - **manufactured from highly purified raw materials**

Pre-clinical *Aotus* immunogenicity: MSP1.42/QS21 & MSP1.42/ISA-51

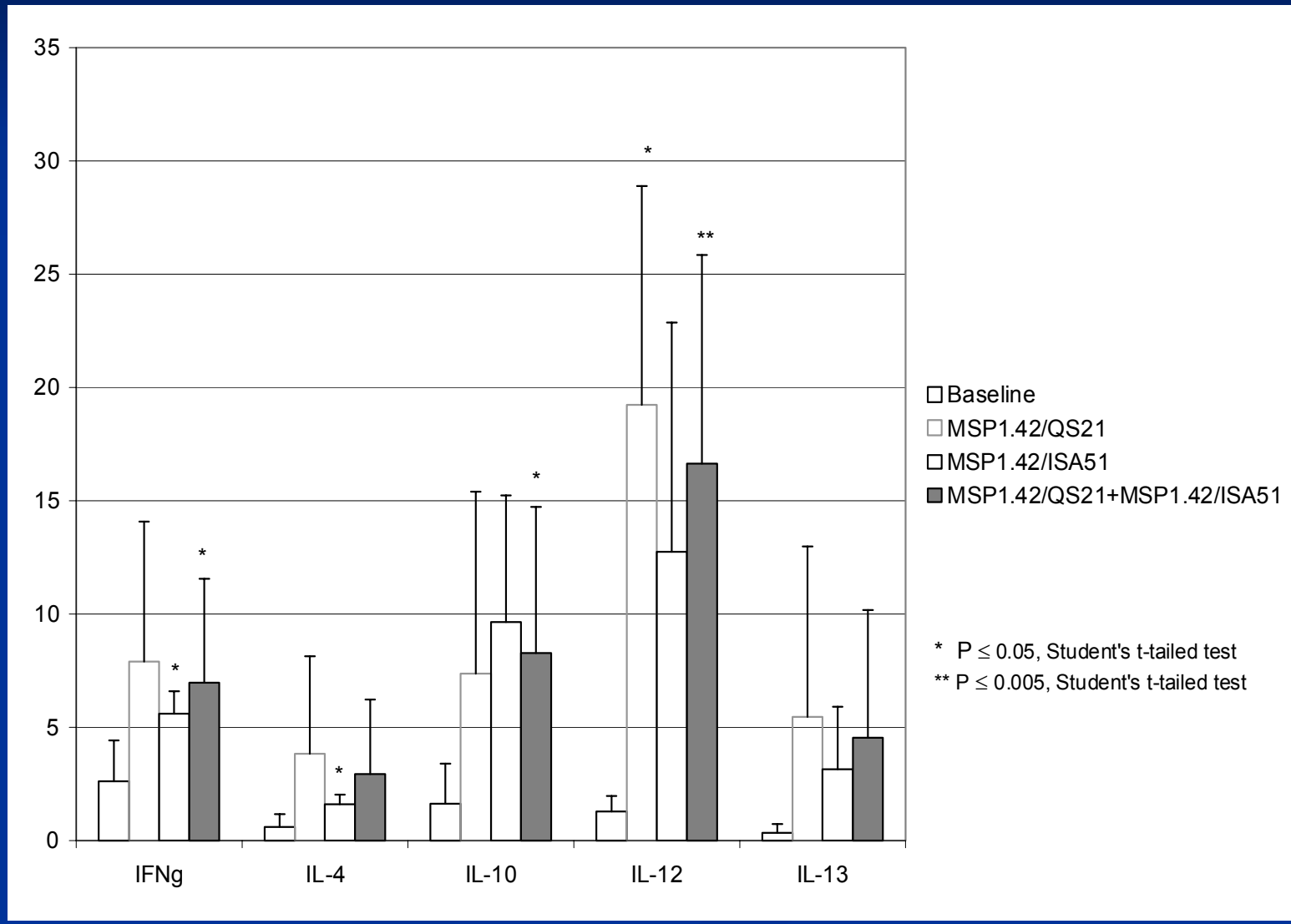
100 ug MSP1.42/0.5 ml + 50 ug QS-21/0.5 ml or 0.5 ml ISA-51

3.5 X 10^5 parasites

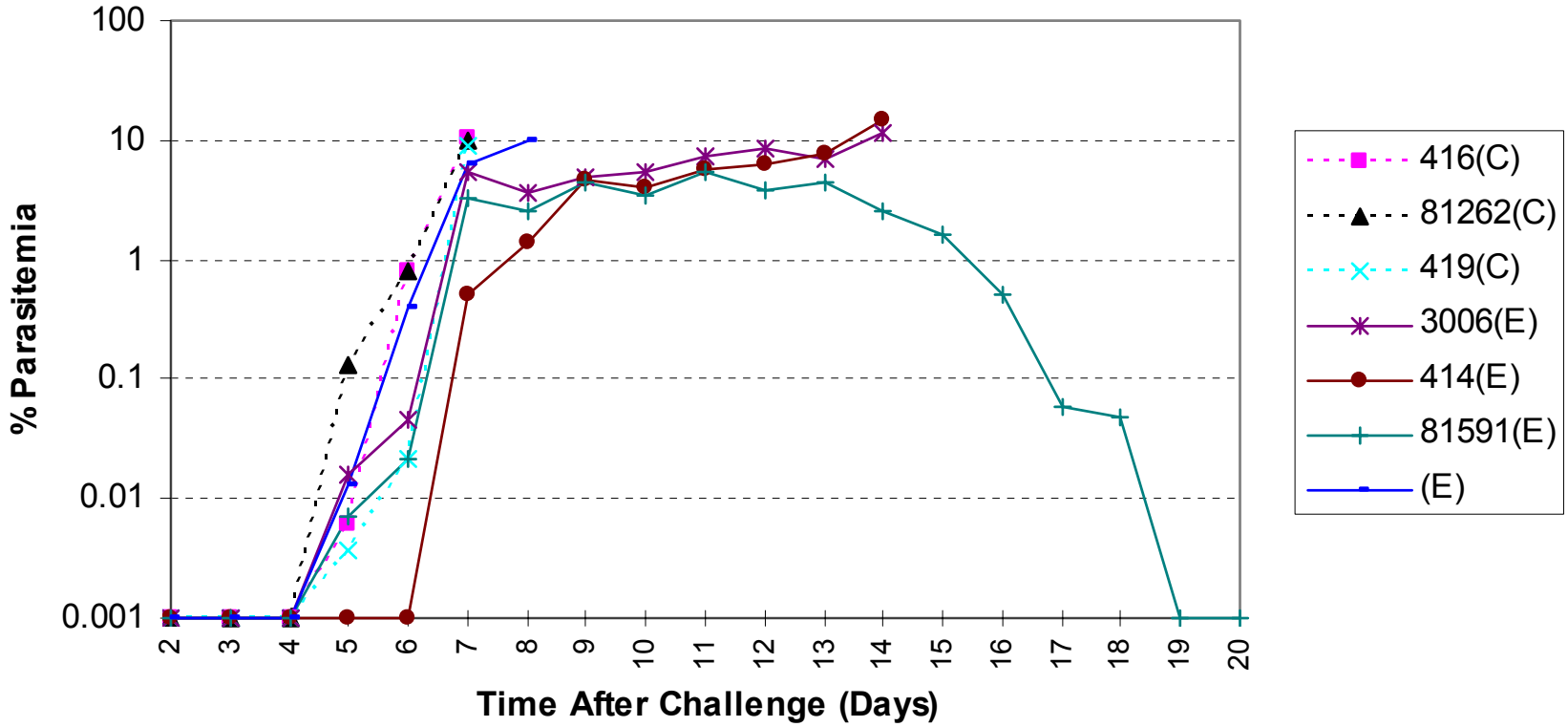




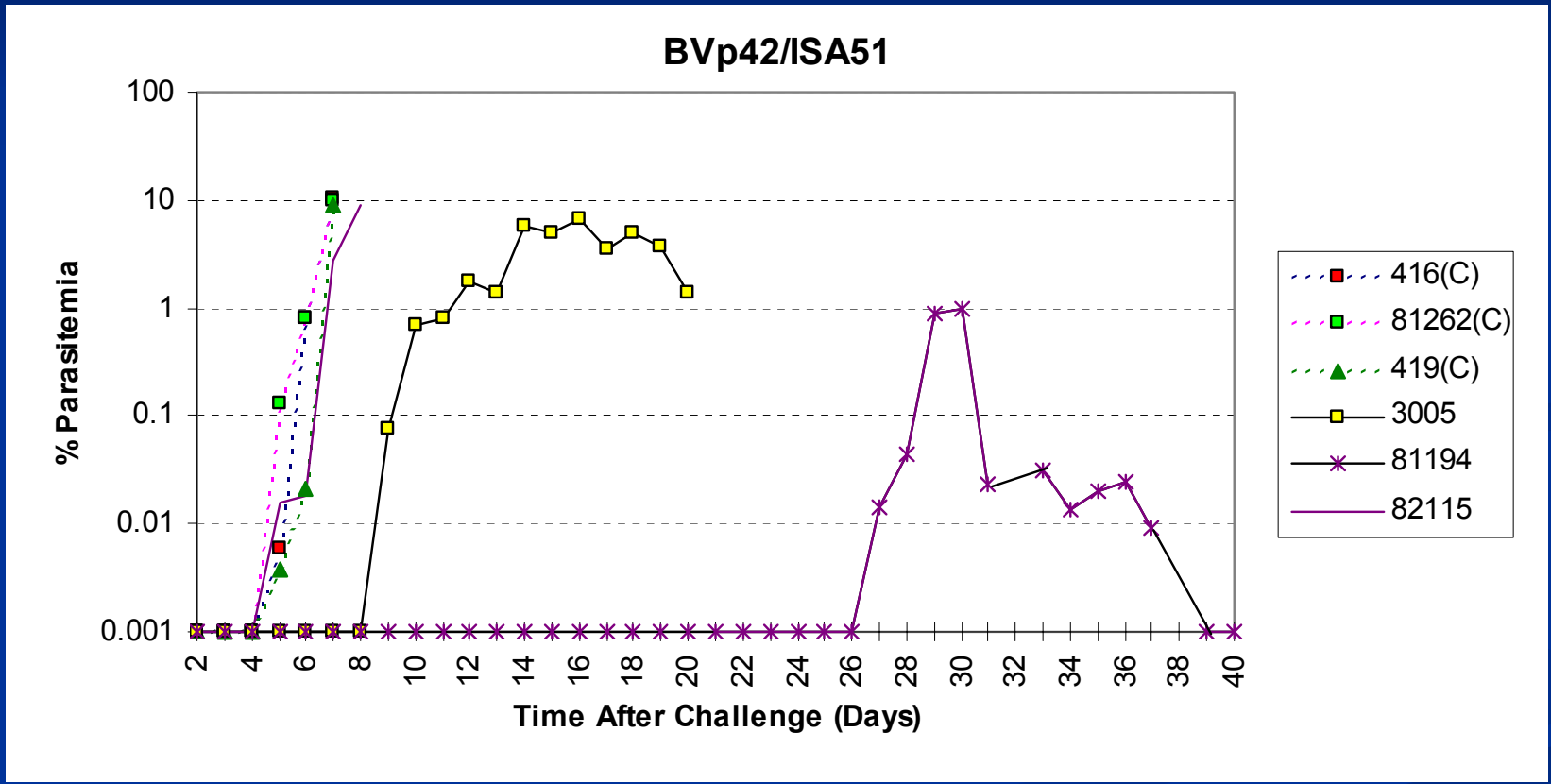
Intracellular cytokine profiles: MSP1.42/QS21 & MSP1.42/ISA-51



Pre-clinical immunogenicity/efficacy: MSP1.42/QS21 formulation



Pre-clinical immunogenicity/efficacy: MSP1.42/ISA-51 formulation



MSP1.42 Adjuvants: Safety & Tolerogenicity in Primates

- MSP1.42 formulated with QS-21 or ISA51 well-tolerated in non-human primates (*Aotus*)
  - No systemic effects noted
  - Minimal local effects at site of injection and draining lymph nodes
  - No anemia observed in non-human primates vaccinated with MSP1.42 in QS-21 or ISA51

Conclusions

- Both QS-21 and ISA-51 induce potent antibody and cell-mediated immune responses to MSP1.42 in *Aotus lemurinus griseimembra*
  - Cytokine responses correspond to mixed Th1/Th2 responses for both formulations
- Both QS-21 and ISA-51 induce partial protective immunity to *P. falciparum* blood stage challenge
  - Management of parasitemia for extended time periods in comparison to normal controls
  - Spontaneous clearance of parasitemia (self-cure) in some animals
- MSP1.42 formulated with either QS-21 or ISA-51 were well tolerated in non-human primate model

Stimulon™ QS-21 - Clinical Experience

- QS-21 administered to > 3100 subjects.
- Over 80 clinical trials (Phase I / II) completed with various vaccines. Various Phase I / II trials ongoing. Two Phase III trials ongoing.
- 3 QS-21 doses evaluated (25, 50, & 100 μg).
- Administration by either subcutaneous or intramuscular routes.
- Enhanced antibody and cell-mediated immune responses to melanoma, HIV, and malaria antigens.
  - Cell mediated responses: CTL, mixed Th1/Th2 cytokine responses
  - Antigen dose-sparing effect

QS-21 Clinical Trials – Infectious or Neurodegenerative Diseases

- **HIV**
  - gp120 (MN)
  - gp120 (W61D)
  - Nef,gag,env lipopeptides
- ***S. pneumoniae***
  - 23-valent polysaccharide vaccine
  - Heptavalent conjugate
- **Malaria**
  - **RTS,S**
  - **(T1B4)MAP**
  - **SPF66**
- **Influenza**
  - split virion
- **Hepatitis B Therapeutic**
- **Human Papilloma Virus (Genital Warts)**
- **Herpes Simplex**
- **Alzheimer's Disease**

ISA-51 - Clinical Experience

- ISA-51 administered to > 1000 subjects.
- Numerous, repeated doses administered
  - Well-tolerated with transient local and mild systemic reactions
- Administration by subcutaneous route
- Production of high antibody titers, T helper responses, CTL responses to ganglioside, melanoma, HPV, & HIV antigens

ISA-51 Clinical Trials
Cancer and Infectious Diseases

- Breast cancer
  - NeuGcGM3/VSSP ganglioside vaccine (Phase I)
- Cervical cancer
  - HPV E7 peptide vaccine (Phase I/II)
- Melanoma
  - Gp100(280)peptide + tetanus toxoid peptide vaccine (Phase I)
- HIV
  - Envelope synthetic peptide vaccine (Phase I)

Future Directions

- Production and formulation of cGMP MSP1.42 for human clinical & field trials
  - Evaluation of potency, stability, immunogenicity, toxicity
- Testing of cGMP MSP1.42 preparation with both adjuvants in *Aotus* model with respective adjuvant controls
  - Immunogenicity – antibody & cell-mediated
  - Efficacy - blood stage *P. falciparum* challenge
  - Local toxicity – histopathology at injection site
  - Systemic toxicity – blood & urine biochemistry
- Optimization of MSP1.42/adjuvant formulations to minimize local adverse side effects & maximize immunogenicity

Collaborators & Sponsors

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