Advancing Regulatory Science for MCMs
Case study: ISCOMATRIX® Adjuvant

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IOM Workshop
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Agenda

• Problems faced in adjuvant development
• ISCOMATRIX® adjuvant as a case study for tools that can be used
  • Animal models
  • In vitro biomarkers
  • Gene profiling
  • Integrated databases
• Proposed solutions
Problems faced in adjuvant development

- Adjuvants are platform technologies
  - Adjuvant not registered
- Need to understand the science
- Different risk:benefit profile for MCMs
- “Perceived” threats
  - How to test?
- Lack of pre clinical biomarkers for safety
- Adjuvant development largely industry based
  - Lack of transparency
- How to turn science and understanding into licensed products
ISCOMATRIX® adjuvant technology

- Proprietary adjuvant for use in vaccines
- Complex of ISCOPREP® saponin, cholesterol and phospholipid
- Reformulated in 2000
- Partnered with Merck and Pfizer
Use of tools to evaluate ISCOMATRIX® adjuvant: a case study

• Mode of action – what?
  • Immunogenicity in animal models/humans
  • Integrated safety database non clinical/clinical

• Mechanism of action – how?
  • Animal models – eg knock out mice
  • Human DC’s
  • Cytokine profiles – in vitro and in vivo
  • Gene profiling
Use of animal models to evaluate immunogenicity

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TLR3 = Poly I:C
TLR4 = MPL
TLR9 = CpG ODN
IMX = ISCOMATRIX
W/O = ISA-51

Combos of 2 or 3 better than 1 or 4
Responses can be broad or more specific
Cannot necessarily extrapolate from one antigen to another
Animal models also provide information on kinetics and potential mechanisms.

Wilson et al., 2011, submitted
**In vitro** studies in human DCs inform both immunogenicity & antigen processing/presentation

*Schnurr et al., 2009, JI. 182: 1253-1259.*

*Schnurr et al., 2005, Blood. 105: 2465-2472.*

In vitro biomarkers can be used to detect potential safety signals (MM6 cell line)

- IL1β pg/ml
  - ISCOMATRIX® adjuvant
  - ISCPREP® saponin

- IL8 pg/ml
  - ISCOMATRIX® adjuvant
  - ISCPREP® saponin

- TNFa pg/ml
  - ISCOMATRIX® adjuvant
  - ISCPREP® saponin

- IL6 pg/ml
  - ISCOMATRIX® adjuvant
  - ISCPREP® saponin

Cut off (determined from LPS)

Hana Golding and Martina Zaitseva (CBER) 2010
Gene profiling in NHP can aid in understanding of tolerability of vaccines.
Use gene profiling to develop candidate classifier for tolerability of vaccines

I-Ming Wang (Merck) MVAF 2010
Use of candidate classifier to evaluate novel adjuvanted vaccines

Novel vaccine/adjuvant combinations

(Module 3-1)
Integrated databases enable risk assessment and risk identification related to the adjuvant

- Non clinical studies
  - Database for GLP tox studies ISCOMATRIX® adjuvant alone from all studies
  - Major findings from vaccine studies
- Clinical studies
  - Database of all safety information where ISCOMATRIX® adjuvant is used
    - Detect and analyse safety signals
    - Meta analysis/Subgroup analysis
    - MEDRA queries
Solutions for advancing regulatory science for adjuvants for use in MCMs

- Share and evaluate knowledge
  - Establish adjuvant advisory group
    - FDA, industry and academics
- Develop series of workshops
  - Safety biomarkers
  - “Perceived” threats – scientific rationale
  - Adjuvant combinations
  - Others
Solutions for advancing regulatory science for adjuvants for use in MCMs

- Enhanced broad based collaborations
  - FDA, industry and other academics
  - Establish seminar series at FDA
  - More resources at FDA to enable more informal scientific discussions
- Licensure of adjuvant for broad use in MCMs for emergency use
  - Master File to adjuvant pre Licensure dossier
  - Minimal human data
  - Animal models
  - Use scientific rationale and new tools to support