Association of Autoimmunity with Adjuvants in Vaccines

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Outline of presentation

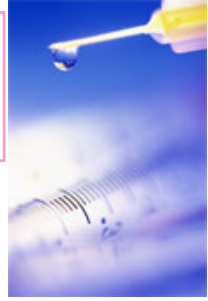
- **Vaccines and adjuvants – background**
  - what are adjuvants?
  - why do we need them?
- **Safety concerns regarding adjuvants in vaccines?**
  - Autoimmunity
    - Causes of autoimmunity
    - Predictive models
    - Pattern recognition receptors (PPR's)
  - Proposal for HESI

Vaccines

- **Vaccines play an important role in the prevention of disease**
  - Major socio-economic health benefit

- **Safety is key- for both prophylactic and therapeutic vaccines**
  - Prophylactic vaccines for infectious disease are given to healthy individuals

Vaccines are evolving: → new requirements

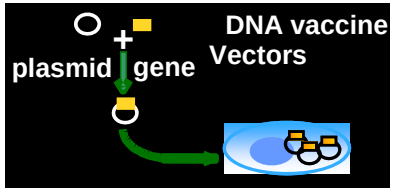


Adjuvant/formulation

Purity of Antigens

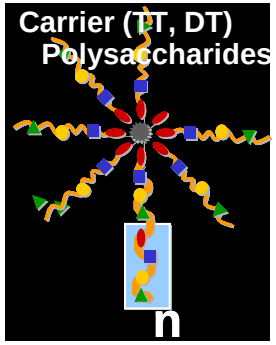
Rational ▪ Design ▪ Empirical ▪

Peptides, recombinant proteins,
DNA (Synthetic vaccines)

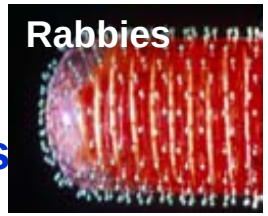


Modified viral or
bacterial vectors encoding antigens

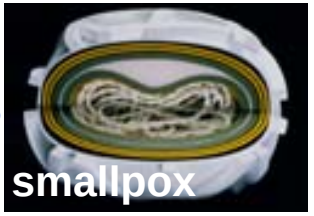
Bacterial polysaccharides
(Plain or conjugated)



Purified proteins (virus or bacteria)
(sub-unit vaccines)



Inactivated vaccines
(Killed germs)



Live attenuated vaccines
(Live germs)

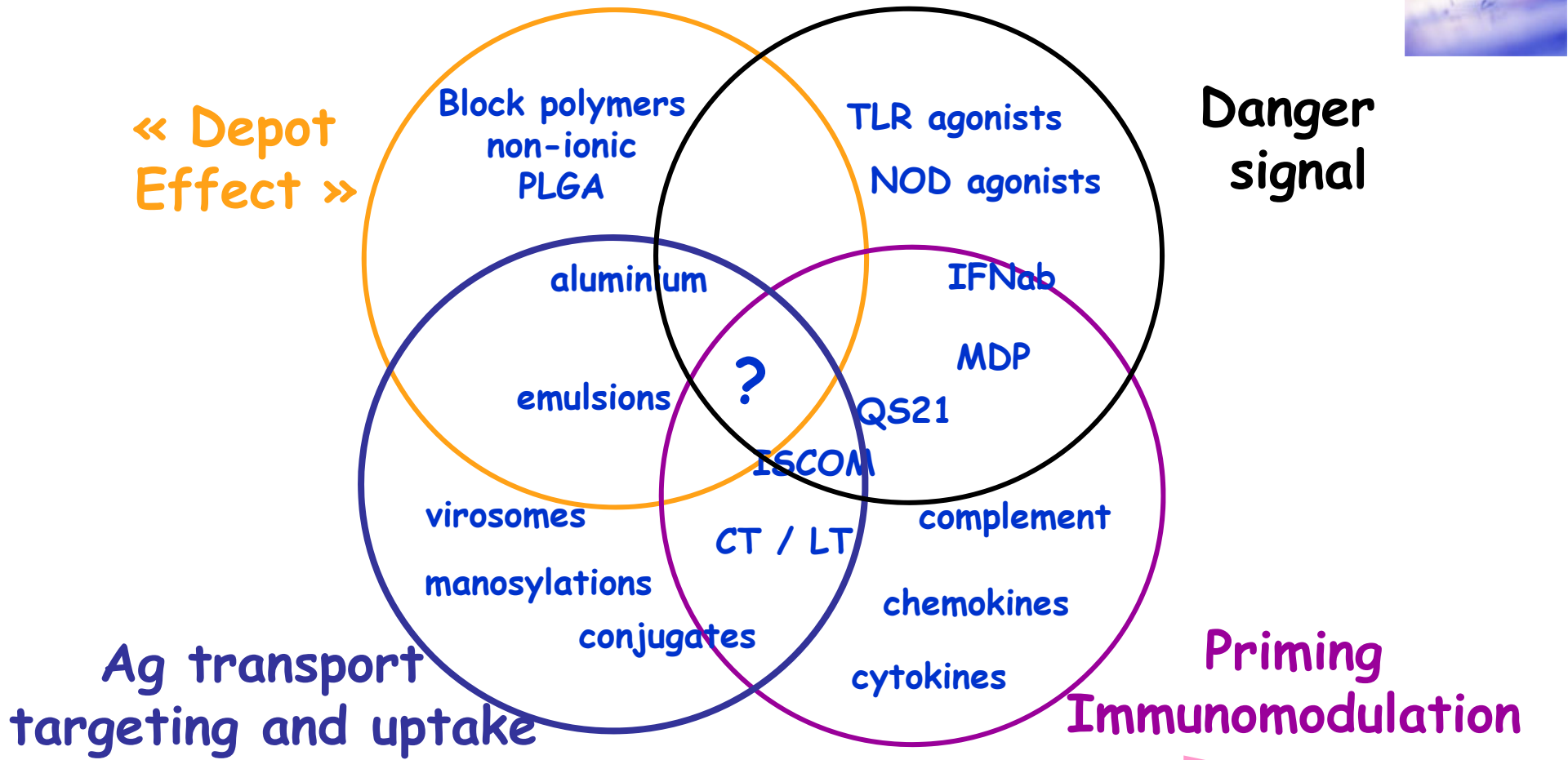
Vaccine immunogenicity

Why use an adjuvant?

Adjuvare - to help

- **Aid an immune response to improve effectiveness of vaccines**
  - stimulate a specific immune response e.g. T cell mediated, Th_2, Th_1,
  - enhance stimulation in populations that have an inefficient immune response e.g elderly,
  - facilitate dose sparing- e.g pandemic situation
  - broaden cross-protection

Vaccine adjuvants: modes of action



«Adsorbant/particulate» adjuvants → Receptor specific adjuvants

Classifying adjuvants

Categorizing adjuvants according to mechanism of action:

1. DC activators
2. Pathogen Recognition Receptor ligands (PRR agonists incl. TLR-, NLR-and RLR-agonists)
3. Ligands of co-stimulatory molecules
4. Cytokines & chemokines
5. Blockers of "immuno-inhibitors"
6. T reg inhibitors
7. Particulate delivery systems

- They can also be classified in the literature under other headings, such as oil-based adjuvants, toll like receptor dependent adjuvants etc.

Safety First

- Vaccines/Adjuvants are under high public and regulatory scrutiny
- FDA/regulatory authorities hesitant to license adjuvanted vaccines
- Particular concern relates to the risk of developing autoimmunity

Autoimmunity

- **Complex and multi-factorial**
  - Occurs in up to 3-5% general population
- **Possible triggers**
  - Genetic
  - Environmental
    - Exposure to micro-organisms
      - Eg molecular mimicry
    - External influence may increase susceptibility
  - Can be T and/or B cell mediated

Could adjuvants increase the risk of autoimmunity?

- **Some animal data have suggested a link between vaccine/adjuvants and autoimmunity**
  - Complete Freund's adjuvants (mineral oil, Mycobacterium) induces Experimental Allergic Encephalitis
  - Squalene (adjuvant component of AS03, AF03) can induce arthritis in rats and lupus in mice

Questions to be answered?

- **What is the relevance of these models and are they predictive for man**

  - **Current position : there are no validated animal models predictive of the risk of autoimmunity in humans**
  - **However, can we neglect these signals?**

Questions to be answered?

- **Is the potential induction of autoimmunity related to**:
  - a) genetics
  - b) exaggerated pharmacology
  - c) a secondary effect, i.e. induction of a specific cytokine profile

- **How do differences in species, strain, route of administration & dose affect our interpretation and understanding of potential immunotoxic effects**

Adjuvants that stimulate PPR's

- **Adjuvants targeted to affect the innate immune system may also target the adaptive immune system**
  - Eg **Stimulating the PPR's via the Toll like receptors**
  - Could stimulating the adaptive immune system & altering the T cell response increase the risk of autoimmunity?
    - Understanding the regulation of homeostasis and immunity of different T cell subtypes could be critical in developing an efficient safe adjuvant

TLR ligands mimicking supramolecular entities shared by families of pathogens

Natural ligands

LPS | Bacterial DNA | ds RNA | Lipoproteins Peptidoglycans | ss RNA | Flagella | Uropathogenic bacteria

Synthetic ligands

MPL | CpG | Imidazoquinolines | PamCys3 | poly I:C | Flagelline | ?

Preclinical and clinical development

TLR-4 MD-2 TLR-9 Human TLR-7 TLR-8 TLR-2 TLR-6 TLR-1 TLR-3 TLR-5 TLR10 TLR11 ?

Signal transduction: activation, costimulation (soluble or membrane-bound)

Questions to be answered

- **What is the role of the TLR's in immune enhancement both intended and unintended effects**
  - **including downstream biological effects, eg cytokine expression, influence on T cell**
- **TLR expression, distribution and species specificity**

Questions to be answered

- **Are we including the relevant organs/endpoints in our toxicology studies?**
  - Immune organs-
    - for example: lacrimal glands- target of autoimmune disease sjogrens syndrome- are these part of the routine evaluation
  - Cell mediated responses? Treg cells?

Combining adjuvants and differences in potency

- **Adjuvants can be a mix of components**

Adjuvants	AF03	MF59	AS03
Manufacturer	sanofi pasteur	Novartis	GSK
Squalene	12.5 mg/dose	9.8 mg/dose	10.7 mg/dose
Surfactants	Sorbitan mono-, di-, trioleate (1.9 mg/dose)	Sorbitan triolate (1.2 mg/dose)	
	Macrogol cetostearyl ether (2.4 mg/dose)	Polysorbate 80 (1.2 mg/dose)	Polysorbate 80 (4.9 mg/dose)
	Total ~4.5 mg/dose	Total ~2.4 mg/dose	Total ~4.9 mg/dose
Others	Mannitol, PBS solution	WFI, Na-citrate buffer	WFI, Na-citrate buffer α-tocopherol (11.86 mg/dose)
Emulsion size	<100 nm	~160nm	150-165 nm

Combining adjuvants and differences in potency

- **Do we know whether there a difference between adjuvants e.g. is it the dose of squalene thats important or is chemical composition?**

Tackling the safety issues

- **Reduce regulatory & public concerns**
- **Better scientific understanding and use of the most relevant models, to include the most appropriate endpoints.**