

Adjuvants in preventative vaccines: focus on Autoimmunity

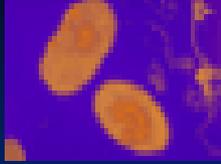
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Outline of Presentation

Adjuvants & Risk of Autoimmunity

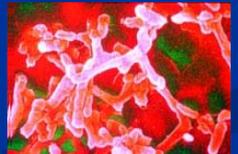


■ Part I: Background

- What are adjuvants & what role do they play in vaccines?

■ Part II: Autoimmunity

- Background: autoimmunity/autoimmunity disease
- What data is there regarding adjuvants & autoimmunity disease
- Can we predict autoimmunity in animal models
- What about the future



Vaccines

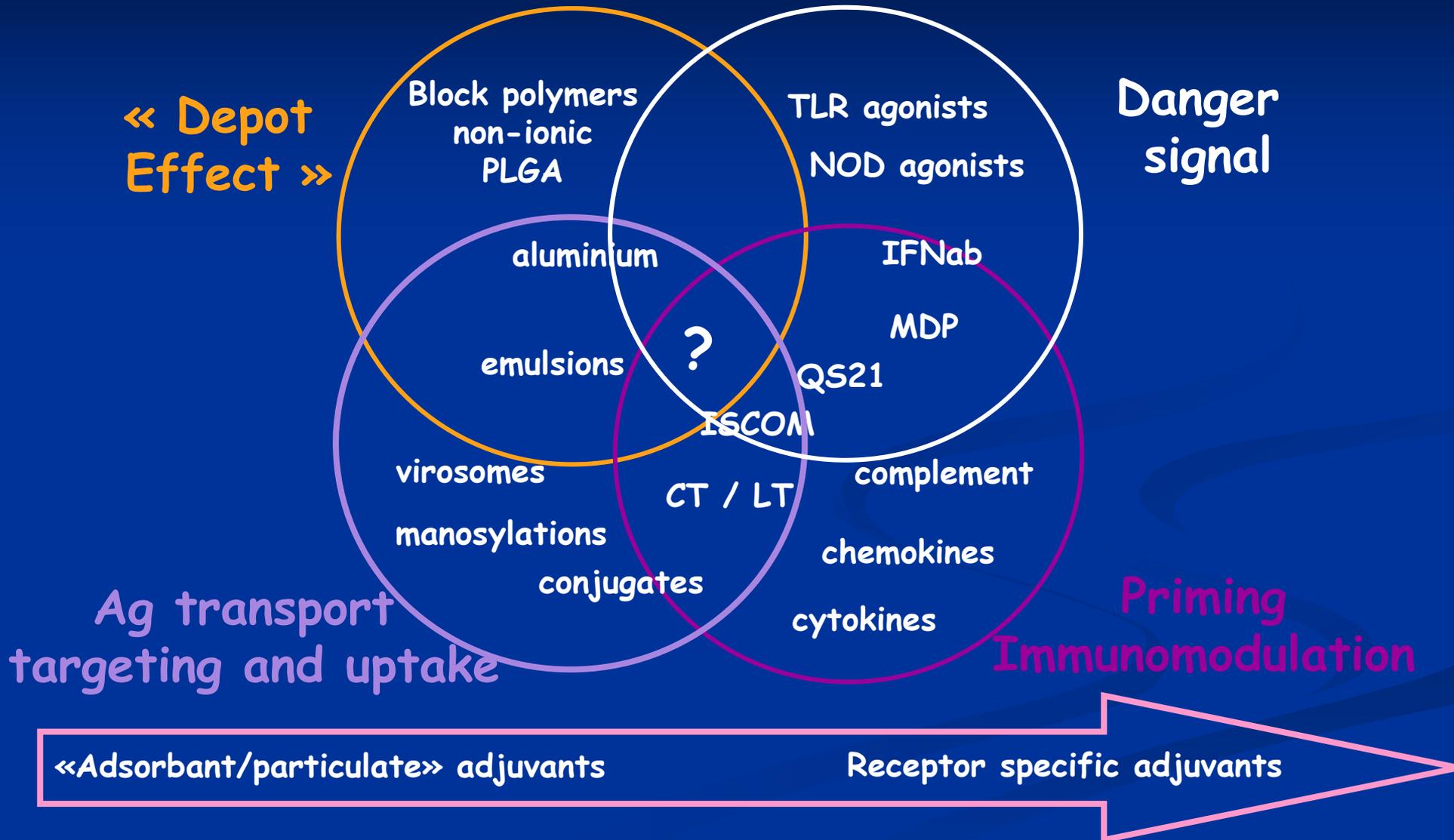
- **Vaccines play an important role in the prevention of disease**
 - Major socio-economic health benefit
- **Safety is key- for both prophylactic and therapeutic vaccines**
 - Prophylactic vaccines for infectious disease are given to healthy individuals

What role do adjuvants play ?

Adjuvare - to help

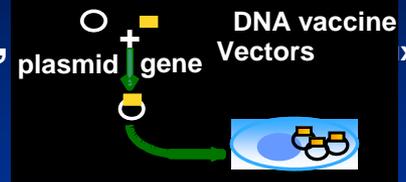
- **Aid an immune response; improve effectiveness of vaccines**
 - stimulate a specific immune response e.g. T cell mediated, Th₂, Th₁,
 - enhance stimulation in populations that have an inefficient immune response e.g elderly,
 - facilitate dose sparing- e.g pandemic situation
 - broaden cross-protection

Vaccine adjuvants: modes of action

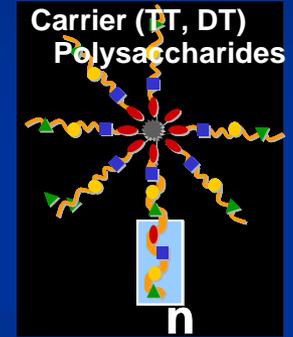


Vaccines are evolving: → need for adjuvants

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)



Adjuvant/formulation

Purity of Antigens

Rational — Design — Empirical

Vaccine immunogenicity

Adjuvant & Potential Risk of Autoimmunity?

Can an adjuvant induce autoimmune disease?

A subject of many debates & claims

What the papers say?

“Gulf war syndrome”



internet

Narcolepsy

Squalene: The Swine Flu Vaccine's
Dirty Little Secret Exposed



What does the data say?



Autoimmune Disease

- Autoimmune disease affects approx. 3%- 10% developed world population (*& rising*)

- **The etio-pathogenesis is complex**
 - a) genetics
 - b) environment
 - c) hormonal
 - d) immune

Autoimmune disease

(non exhaustive list)

Autoimmune disease: “A destructive reaction of the immune system against the bodies own constituents”

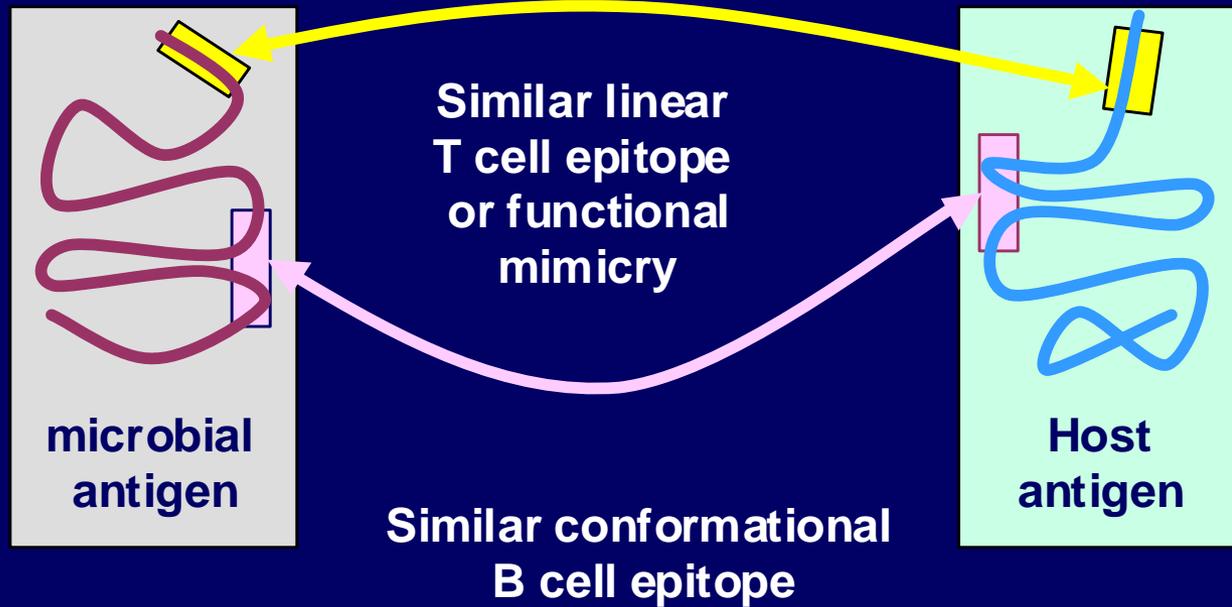
- **Systemic:** SLE, Sjögrens syndrome, scleroderma, Rheumatoid arthritis, dermatomyositis
- **Localised:**
 - Endocrine: diabetes Hashimotos thyroiditis, Addisons disease
 - Gastrointestinal: Coeliacs disease, pernicious anaemia
 - Dermatological: Vitiligo
 - Haematological: Autoimmune haemolytic anaemia
 - Neurological: Myasthenia gravis
- Note that women are twice as likely to be affected by autoimmune disorders than men

Evidence based causes?

- Multifactorial:
 - a) genetics; b) **environment**; c) hormonal; d) immune
- **Environmental**
 - Infection can trigger autoimmune disease
 - Antigen specific or non specific
 - **Antigen specific:** molecular mimicry
 - **Non antigen specific:** exacerbation of pre-existing autoimmune reaction by « **adjuvant** » effect

Molecular Mimicry

ANTIGENIC MIMICRY



Scheme by
PH. Lambert

Infection & autoimmune disease

INFECTION	AUTOIMMUNE DISEASE	SUGGESTED CROSS-REACTIONS / TRIGGERING MECHANISMS
<i>GrpA Strept.</i>	<i>Rheumatic Heart Disease</i>	<i>GAS Prot-M with valvular heart protein (Tcell mimicry)</i>
<i>Campylobacter jejuni</i>	<i>Guillain-Barré Syndrome</i>	<i>Campylobacter jejuni LPS oligosaccharides cross-reactivity with gangliosides (B cell mimicry)</i>
<i>Borrelia burgdorferi</i>	<i>Chronic Lyme arthritis</i>	<i>Borrelia Burgdorferi OspA cross-reactivity with human LFA-1 (Tcell mimicry)</i>
<i>VZV, EBV Rubella</i>	<i>Idiopathic Thrombocytopenia</i>	<i>Viral epitopes cross-reactivity with platelet glycoprotein IIb/IIIa (B cell mimicry)</i>
<i>Chlamydia trachomatis</i>	<i>Reactive arthritis</i>	<i>Chlamydia trachomatis epitopes cross-reactivity with natural ligand of disease-associated HLA-B27 subtypes (Tcell mimicry)</i>
<i>Rotavirus (AUS) / Enteroviruses (Finland)</i>	<i>Type I Diabetes</i>	<i>Epidemiological association (trigger effect?)</i>

Vaccines and Safety

- Vaccines are commonly & safely administered
 - humans & animals worldwide
- The reporting of an 'autoimmunity' event is rare
 - to establish a link of a rare event is difficult

Risk of Autoimmunity?

- Medical literature full of claims and counter claims
 - Convincing data from a few cases only eg
 - 1) swine flu (67-68) & Guillain Barré
 - 1/100 000 cases compared to 1/1000 000
 - 2) Measles mump & rubella & idiopathic thrombocytopenia
 - 1/30000 (children)

What About Adjuvants?

Marketed Adjuvanted Vaccines

- Oldest adjuvanted vaccines with alum
 - DTP (diphtheria-tetanus-pertussis vaccine); DTaP (diphtheria-tetanus-acellular pertussis vaccine) ; Some Hib (*Haemophilus influenzae* type b) conjugate vaccines; pneumococcal conjugate vaccine; Hep B & A vaccines ...etc
- Recent adjuvanted vaccines
 - **Squalene based adjuvants:**
 - MF59 (Focetria), AS03 (Pandemerix/ Arepanris)
 - **Others:** AS04 (AL(OH) +MPL; ceravix) ; AS04 in Fendrix



Squalene & Gulf War Syndrome



- Followed multiple vaccinations over short time period
 - vaccination protocol included anthrax adjuvanted vaccine (Al(OH) & squalene)- 6 doses
 - squalene = biochemical precursor to steroids.

- Symptoms: fatigue, rashes, headache, myalgias, autoimmune thyroid disease, increased allergies etc.....

- Hypothesis- anti-squalene antibodies

Squalene & GW syndrome

- Lippi *et al.*, 2010: “vaccination, squalene and anti-squalene antibodies- fact or fiction?”
 - Analysed approx. 10 key studies investigating gulf war syndrome
- Concluded: lack of evidence that the illness is related to an altered immune system
 - Squalene is poorly immunogenic
 - Low titres of antibodies to squalene are present in healthy individuals

Squalene Adjuvanted Vaccines

- MF59, AS03 (oil-in-water emulsion squalene based adjuvants)
 - Safety data
 - MF59 (Focetria) and AS03 (pandemrix)
 - safety data shows no severe adverse events associated with the vaccines. Some mild local reactogenicity observed (NIH meeting 2008)
 - MF59 shows no evidence that the presence of anti-squalene antibodies is increased (Lippi *et al.*, 2010)

Squalene Adjuvanted Vaccines

- WHO concurred fears of squalene in vaccine-inducing pathological anti-squalene antibodies are unfounded.
- Noted : experience of squalene-containing vaccines is in older age-groups. Recommended as squalene-containing vaccines are introduced in other age-groups, careful post-marketing follow up needed to detect any vaccine-related adverse events.

Narcolepsy and AS03

- In Finland during 2009-2010
 - 52/60 children and adolescents diagnosed with narcolepsy had received pandemrix (90%)
 - Narcolepsy with cataplexy: sleep disorder
 - prevalence of 0.05%
 - Strongly associated with HLA subtype DQB1*0602
 - Narcolepsy 9 times higher in vaccinated population of children in Finland, Sweden and Iceland, not associated with specific lots of vaccine
- FDA analysis— millions of doses given and no evidence of narcolepsy

Could adjuvants increase the risk of autoimmunity?

- Pathogenesis under scrutiny
- Shoenfeld *et al.*, 2011 states ‘although the independent role of each vaccine ingredient as well as host risk factors are yet to be defined there is accumulated data to suggest the possibility of an accelerated autoimmunity/inflammation following vaccination’
 - Raises questions on 4 syndromes: Gulf war, macrophage myofascitis, siliconosis and adjuvant disease
 - Notes the common denominator: clinical signs and symptoms; exposure to a component that provides an adjuvant effect

Animal data

- **Some animal data have suggested a link between vaccine/adjuvants and autoimmunity**
 - Complete Freund's adjuvants (mineral oil, Mycobacterium) induces allergic encephalitis in EAE models
 - Squalene (adjuvant component of AS03, AF03) can induce arthritis in rats and lupus in mice
- Not so evident:
 - NZB/NZW mice + mercuric chloride and Hepatitis B vaccine (intraperitoneal injection); NOD mice and DTaP-IPV or DTaP-IPV/Hib vaccine; NOD mice and *Haemophilus Influenza b* vaccine

Adjuvants and Risk of Autoimmunity?

risk



benefit

risk



benefit

Assessing autoimmunity disease

- Today:
 - non clinical safety studies can not adequately address a potential autoimmunity concern?
 - no validated model
 - lack of understanding in terms of cause and effect
 - predictivity of models tested to date is questionable
- Best available tool is clinical surveillance
 - ↪ Exaggerated level of precaution could stop development of useful vaccines for public-health

Future assessment It's not going to be easy?



Challenges

- **Autoimmunity disease is multifactorial**
 - a) genetics
 - b) environment
 - c) hormonal
 - d) immune
 - i) exaggerated pharmacology
 - ii) secondary effect, i.e. induction of a specific cytokine profile

Questions to be answered?

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



- **Current position : there are no validated models predictive of the risk of autoimmunity disease**
- **Do we need one? Is it possible to develop one?**

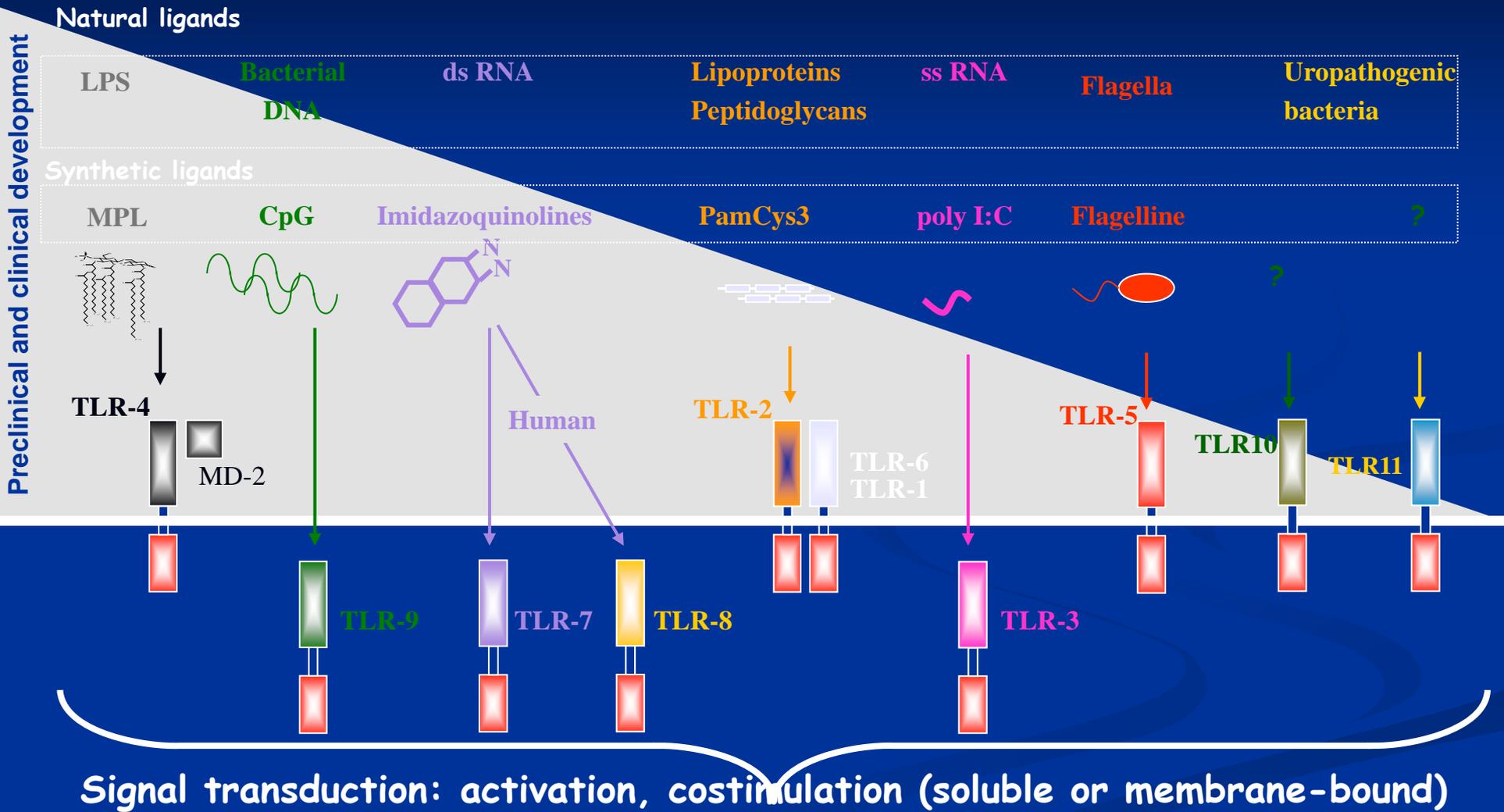
Non Clinical Challenges

- How do differences in species, strain, age, route of administration & dose affect our interpretation and understanding of potential immunotoxic effects?
- The occurrence of 'the event' appears low and is multifactorial with additional influences eg genetic
- Adjuvants are multiple in their mode of action
 - Eg Depot effect, danger signal, priming immodulators
- For further information: see Dietert et al.,: risk of autoimmune disease and challenges for immunotoxicity testing

Non Clinical Challenges

- Are some adjuvants more of a potential risk than others ?
- What about the Pattern Recognition Receptors (PPR's) & Toll Like Receptors (TLR's)?

TLR ligands mimicking supramolecular entities shared by families of pathogens



TLR & autoimmune disease links

- Type 1 diabetes & Multiple sclerosis – TLR 9; Lupus – TLRs 4 & 7 (9?); Experimental Autoimmune Encephalomyelitis – TLR 2; Autoimmune liver disease – TLR 3
- **What role do the TLR's play?**
 - Immune enhancement both intended and unintended effects?
 - including downstream biological effects, eg cytokine expression, influence on T cell
- **What is known about TLR expression, distribution and species specificity?**
- **Could stimulating the adaptive immune system & altering the T cell response increase the risk of autoimmunity?**
 - Understanding the regulation of homeostasis and immunity

Tackling the safety concerns

- **Need to reduce regulatory & public concerns**
- **Better scientific understanding**
- **In non clinical safety assessment- need to ensure the use of the most relevant models, to include the appropriate endpoints.**
 - Models need to be further understood and improved
 - Consideration of both innate immune cell receptors and adaptive immune responses, including cytokines
- **Future initiatives include**
 - HESI project (& IMI initiative)

HESI Initiative

- 2010: raised at HESI as an emerging issue
 - Not selected at this time
- Proposal from HESI to launch the project as a resource at initiation (RAI)
- Gathered 6 sponsors who will contribute a total of \$85,000

Risk Assessment of Autoimmunity associated with Adjuvants in Vaccines

Proposed Steering Team

Industrial Partners

Industry

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Sanofi-Pasteur

Lawrence Segal

GSKBio

Christopher Frantz

Medimmune

Deborah Novicki

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Martin Finkelstein

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Jan Willem van der Laan

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Marion Gruber

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Mineo Matsumoto

PMDA

Marc Pallardy

AFSAPSS

Günther Waxenecker

AGES

Academic Partners

University

Rodney Dietert

Cornell University

Mission

Can adjuvants induce autoimmunity as a result of an exaggerated effect, or is there an increased risk autoimmunity due to the genetic makeup of the vaccinees?

Objective

For the first phase of the project, the aim would be to identify the key issues based on literature and input from academic, industrial and governmental experts and provide a plan of action to move forward to help to solve.

For the second phase: a workshop would be organized to discuss in depth the knowledge, to write relevant working hypotheses, and recommendations for further research.

The potential impact of successfully addressing this issue is

Assessing the long-term safety of adjuvants

Reducing the public concern about the use of adjuvants in vaccines.



Any Questions ?