Strategy to optimize the immune response to poverty related disease vaccines with adjuvants

Challenges:

A major challenge for the development of effective vaccines for poverty related diseases (PRD) is the lack of funding/resources meaning that developers do not have the luxury of screening a large number of candidates, and any failure in clinical trials due to formulation or adjuvant can close a project down even if the antigen is potentially a good candidate. In addition, PRD vaccines are typically developed in infrastructures where there is not a large portfolio of other vaccines under development so investment in novel adjuvants or other immune enhancement technologies is limited, so access to such technologies is preferable from other sources. To minimize the risk of failure during vaccine development, the following considerations must be taken into account when deciding on the use of adjuvants to ensure cost effectiveness.

- Minimise risk of failure
  - Use adjuvants where safety/toxicity issues are least likely to occur
  - Where supply is assured or feasible
- Rational selection (broad screening and clinical evaluation too expensive)
- Minimise cost of development
  - Extemporaneous (point of use formulation) preferred over pre-formulated

Strategy:

1) Optimization of antigen

- Soluble monomeric proteins are bad candidates to start with (require very potent adjuvants & therefore risky)
- Evaluation multimeric formulations if possible:
  i. Conjugate to carrier protein (any)
  ii. Conjugate to virosomes
  iii. Conjugate to a virus (e.g. alpha virus)
  iv. Express as fusion protein in self-assembling system (but NOT human virus origin i.e. not HBsAg, HBc, etc.)
- Select one of the above and test both monomeric and multimeric forms.

2) Selection of adjuvant and formulation

- Follow the flowchart on the following page for selection of adjuvant
- Then pre-clinical down selection:
  - Immunogenicity in mice by same route as intended in man
    - Down select on limiting dilutions
  - Demonstrate comparable behaviour of adjuvant on human PBMC and on mouse PBMC
    - If behaviours are not the same then discard
    - If behaviours are the same, down select on limiting dilutions
(1) Do not use an adjuvant

Not scientifically feasible (immune response not sufficient)

(2) Use an adjuvant which is already in an approved vaccine i.e. alum, MF59, ASO3, MPL

No Access

(3) Use a generic form of (1) (i.e. same receptor or mode of action) i.e. o-i-w emulsion, GLA

No Access/ Doesn’t exit

None are scientifically appropriate

(4) Use an adjuvant that is in mid-late clinical development (>1 clinical trial with safety data)

No Access/ Doesn’t exit

None are scientifically appropriate

(4.1) Use an adjuvant that is in early clinical development (=1 clinical trial with safety data)

No Access/ Doesn’t exit

None are scientifically appropriate

(5) Use an adjuvant that has been used in pre-clinical trials

Formulation optimisation

Extemporaneous

Available under GMP conditions or easy to manufacture under GMP

Available clinical data with other antigens

if more than 1 prioritise based on clinical data, equivalence & cost/supply

Prioritise based on # of clinical trials & reject all with adverse events.

Then prioritise on immune bias reported in clinic, safety in age group & GMP-supply & cost

Ok, if no adverse events reported, & preclinical data shows appropriateness

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Preclinical Strategy A

Preclinical Strategy A

Preclinical Strategy A

Preclinical Strategy B

Preclinical Strategy B

Preclinical Strategy B

Low risk

High risk