Vaccine development in the discovery space: Understanding the key players in the immune response to a pathogen helps inform vaccine design

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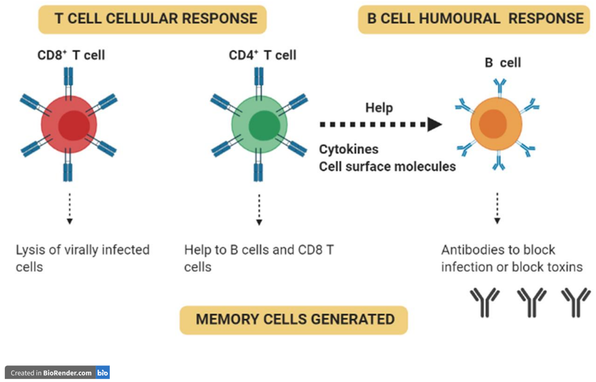
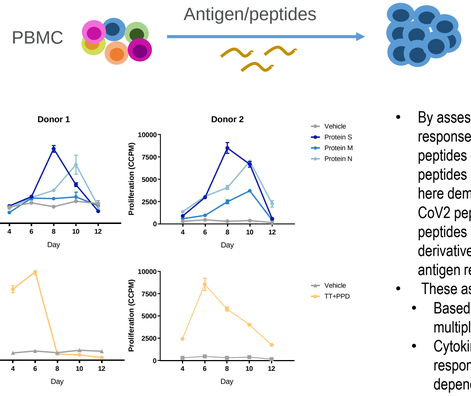
1 Abstract



As a first step of vaccine design the immunogenicity or ability of a novel vaccine to invoke an immune response needs to be assessed. The assays used will be determined by the type of vaccine and whether it is designed to elicit both a B cell and T cell response. *In vitro* assays using cells from healthy human donors can provide information on whether the antigen used can drive T cell activation and how T cells are polarized, which may in turn influence the B cell response. *In vivo* assays assess the systemic immune response and allow for B cell and T cell responses to be measured and infectious challenge studies to be performed.

2 Immunogenicity- human T cell responses



- By assessing the proliferation and cytokine responses of T cells from healthy human donors to peptides or proteins, the immunogenicity of these peptides can be evaluated. The example shown here demonstrates T cell proliferation to SARS-CoV2 peptide (S, M, N) pools or to positive control peptides (Tetanus Toxoid and purified protein derivative (*M. tuberculosis* tuberculin) – in an antigen recall response.
- These assays can help guide antigen selection:
  - Based on the magnitude of response across multiple donors.
  - Cytokines elicited can indicate if a Th1 or Th2 response is generated which can be critical, dependent on the pathogen a vaccine is targeted against.
  - CD4 and CD8 T cell subsets can be evaluated.

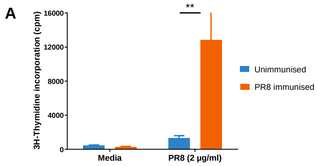
3 Immunogenicity – *in vivo* T cell responses

Prime: Antigen +/- Adjuvant

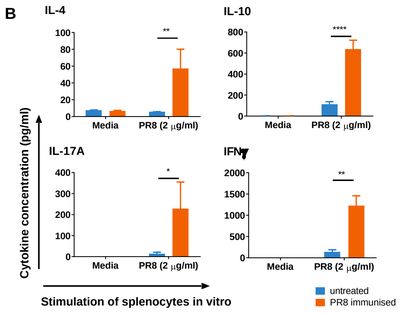
Boost: Antigen +/- Adjuvant

Necropsy

- Example: Proliferation of splenocytes to Influenza peptide (A) and cytokine production (B) following *in vivo* immunization with inactivated Influenza A PR8/34 shows that a T cell response was mounted *in vivo*, and can be detected *in vitro*.

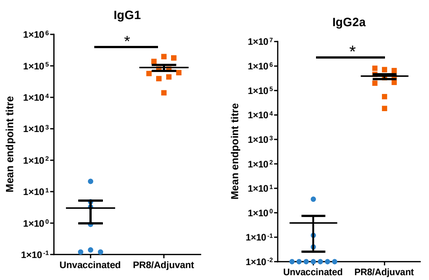


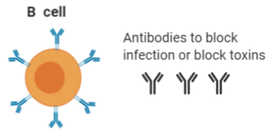
- The ability of a vaccine to drive T cell responses can be tested by assessing cytokine production and T cell proliferation following re-stimulation of splenocytes *in vitro* with the relevant antigen.
- Route of administration, dose and adjuvant used can be assessed in terms of how this affects the quality, magnitude and polarization of the cellular and humoral response.



4 Immunogenicity – *in vivo* B cell responses

Total IgG or IgG subclass responses to immunisation indicate whether a high affinity IgG B cell response has been mounted to a novel vaccine.





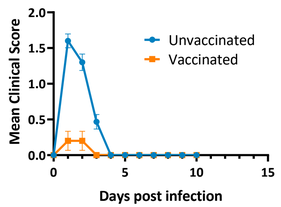
- Mice were immunized with inactivated Influenza PR8/34/Adjuvant
- To assess if high affinity IgG responses had been mounted, mouse anti-Influenza IgG1 and IgG2a were measured in serum taken from in-life and terminal bleeds (d42).
- For BSL3 pathogens the ability of a vaccine to induce neutralizing antibodies can be assessed by the ability to block pseudo virus entry into permissive cell types.

5 Protection/Challenge Models

Prime: Antigen +/- Adjuvant | **Boost: Antigen +/- Adjuvant** | **Infection** | **Necropsy**

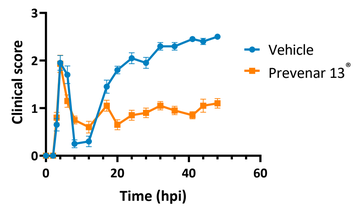
A full model of infection will enable survival and replication of the pathogen and presentation with clinical signs similar to in man, for some pathogens finding a suitable model is challenging and may mean that viral or bacterial load is the only readout available to assess vaccine efficacy

Influenza H3N2



- Clinical observations in mice challenged intranasally with H3N2 following vaccination with inactivated influenza + adjuvant. A significant decrease in clinical scores was observed in the vaccinated group (****P<0.001, multiple t-test).

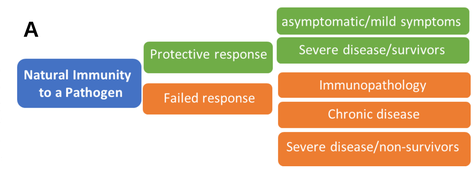
S. pneumoniae

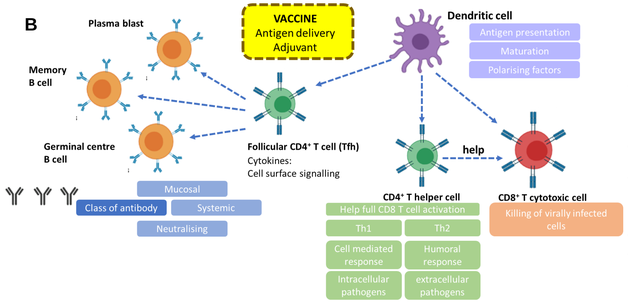


- Clinical observations in mice challenged intranasally following vaccination with Prevenar 13®. A significant decrease in clinical scores was observed in the vaccinated group (****P<0.0001, multiple t-test).

6 Conclusions

By understanding what natural immunity to a pathogen looks like this gives us the tools to design an effective vaccine; the immune response in patients which have mounted a protective response and those that fail to do so or develop immuno-pathology will often differ in terms of polarisation, magnitude and balance of humoral versus cellular immunity; by understanding disease at this level this informs the kind of response a vaccine should be aiming to achieve (A).





While the focus of many vaccines are to produce neutralizing antibodies, unless this provides sterilizing immunity, a CD4 and CD8 T cell response will also be required to generate full protection and this should be considered for effective vaccine design and when considering readouts in immunogenicity studies. (summarized in B)

Advances in the understanding of T and B cell biology led to the discovery of the CD4 Tfh (T follicular helper) subset, which is critical in providing help to B cells within lymph nodes or spleen; helping Germinal Centre formation, where affinity maturation occurs, and also in formation of plasma blasts and long term memory B cells.

Therefore, if the aim of a vaccine is to produce neutralizing antibodies and a long lasting memory B cell population, a vaccine must also drive an appropriate CD4 T cell response. While T cell responses can be easily assessed in PBMC, human B cell/Tfh interactions are more challenging, but the use of tonsil organoid cultures or slices may complement human PBMC assays and in vivo immunogenicity models in driving early vaccine development.