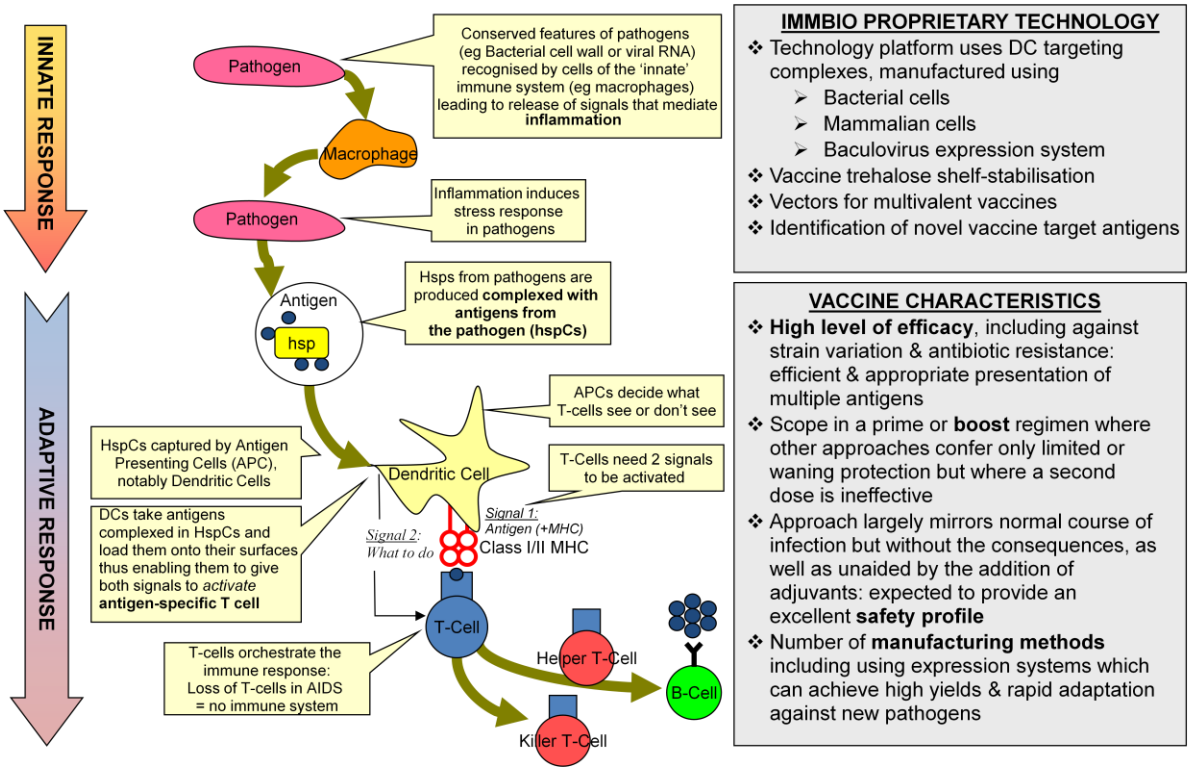
ImmBioVax Vaccines - A Scientific Primer

ImmBioVax vaccines are pathogen-derived multi-subunit vaccines isolated from cell substrates stressed to mimic the inflammatory response to infection. The vaccines are enriched in heat shock proteins complexes (hspCs) that directly target Dendritic cells (DCs) and facilitate both their capture of chaperoned antigen and maturation.

Hsps are molecular chaperones that bind polypeptide chains, prevent aggregation, and support protein folding (Hartl and Hayer-Hartl 2002). Their expression is increased with stress (eg heat, anoxia, glucose starvation, inflammation) and can comprise up to 15% of total cell protein. In addition to their cellular role as chaperones, hsps have now been shown to have important immunological functions acting as the link between the innate and acquired immune responses to pathogens (Colaco 1998; Bolhassani and Rafati 2008; Murshid *et al*. 2008; Dhodapkar *et al*. 2008; Oglesbee *et al*. 2002).
Hsps can induce a number of innate immune responses, activate dendritic cells (DCs), upregulate surface expression of MHC class II and stimulate secretion of pro-inflammatory cytokines (eg IL6, IL12). Hsps can also stimulate the production of chemokines (eg RANTES) which attract other immunological cells (Lehner *et al*. 2004; Wang *et al*. 2002).
As chaperones, hsps *in situ* are found complexed to cellular proteins and these hsp-antigen complexes (hspCs) are capable of delivering peptides to DCs leading to MHC presentation for priming of adaptive immunity (Castellino *et al.* 2000, Singh-Jasua *et al.* 2000). Hence, pathogen-derived hspCs are naturally recognized by the immune system and their uptake by DCs enables them to efficiently capture pathogen-specific antigens and mount both specific CD4 and CD8 T cell responses against the infectious agent (Tobian *et al*. 2004a, 2004b).

HspCs and chaperone-rich cell lysates have been extensively studied as potent multivalent anticancer vaccines (Srivastava 2002, 2006; Murshid *et al* 2008). The use of specific antibodies to deplete these lysates of intact proteins or HspCs has unequivocally demonstrated that the protein fragments chaperoned by Hsp and not intact proteins were both necessary and sufficient for the efficient cross-presentation of antigens and the specific priming of CD8+ T cell responses (Binder and Srivastava 2005). Moreover, when compared to antigenic peptides, unfractionated lysates or purified Hsps, these HspC preparations demonstrated superior ability to activate DCs and were able to induce potent, long lasting and tumour-specific T-cell-mediated immunity (Zeng *et al*. 2006; Srivastava 2006; Murshid *et al* 2008).
Similarly, hspCs from pathogen-derived lysates can be used as effective infectious disease vaccines and early work on the development of hspC™ technology at ImmBio, showed that candidate TB vaccines, enriched for BCG hspCs, gave protection against TB in the mouse aerosol challenge model (Colaco *et al.* 2004) which is the basis of the ImmBioVax™ vaccine platform.



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