

## HspC Vaccines - A Scientific Primer

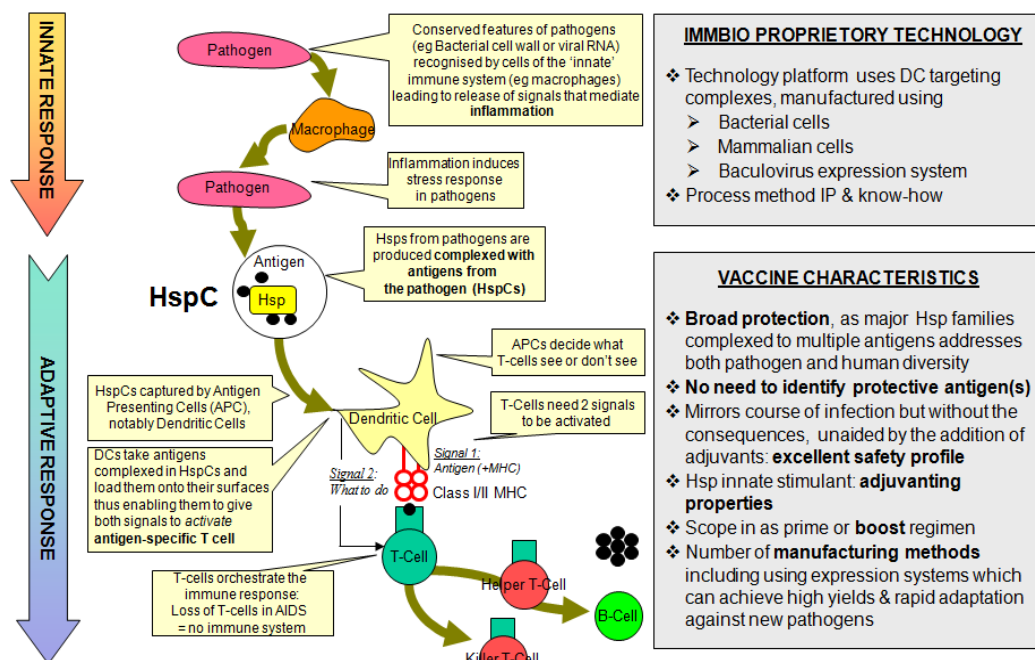
Hsps are molecular chaperones that bind polypeptide chains, prevent aggregation, and support protein folding (Hartl and Hayer-Hartl 2002). Expression of many Hsps is increased with stress (eg heat, anoxia, glucose starvation) and can comprise up to 15% of total cell protein. Members of these protein families are present in all species and are named on the basis of the approximate molecular weight of their members (eg 70 kDa Hsp70). Most Hsps have at least two functional domains: (i) a polypeptide binding domain, and (ii) an ATPase domain that controls binding and release of polypeptide substrates (Hartl and Hayer-Hartl 2002; Bolhassani and Rafati 2008).

In addition, 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).

Hsps are capable of delivering peptides to antigen-presenting cells (APCs) leading to MHC presentation for priming of adaptive immunity (Castellino *et al.* 2000). The amplification of Hsps by inflammatory stimuli such as fever results in a concomitant amplification of pathogen-specific antigens carried in Hsp complexes (HspCs). As pathogen-specific HspCs are naturally recognized by the immune system, the uptake of HspCs by APCs enables them to efficiently capture pathogen-specific antigens and thus mount specific immune responses against the infectious agent with the generation of both CD4 and CD8 T cell responses (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).

HspCs from pathogen-derived lysates can similarly be used as infectious disease vaccines and early work on the HspC platform technology using ImmBio's TB vaccine, enriched for BCG HspCs, showed protective efficacy against TB in the mouse aerosol challenge model (Colaco *et al.* 2004).



## HspC References

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