

Approaches

There are two broad approaches to infectious disease management, beyond hygiene measures:

❖ **Treatment by drug therapy**

In some cases, infection can be treated by therapeutic agents. Drug therapy is usually initiated once symptoms are evident, hence the subject is already suffering the consequences of infection. At this stage of infection, therapy does little to halt the onward transmission of the disease, with significant transmission occurring prior to symptoms, hence before containment measures. As pathogens continually evolve, there is a concern that resistance will continually emerge, eroding or negating product efficacy. Whilst a number of antibiotics are available, the number of anti-viral agents is more limited, reflecting the technical complexity of intervening in the viral cycle, where use of host cells is needed for replication. Often, anti-viral agents only reduce the period or the peak burden of infection. In chronic viral infections, clearance of latent infection has proved difficult and hence in time, viral escape and replication may re-start, sometimes with severe consequences.

❖ **Prevention by vaccination (Prophylaxis)**

Protection is achieved by creating immunological "memory". Though this clearly cannot prevent subsequent contact with the pathogen, if this occurs, the body is able to mount a sufficiently rapid and specific response to contain and eliminate the pathogen. The key is to generate memory safely, without incurring the full infection.

The major unmet needs are in circumstances where neither acceptable therapeutic agents nor vaccination are available, especially where the consequences of infection are severe.

The 18th century landmark work by Edward Jenner concluded that vaccination by cowpox safely confers a degree of protection against lethal smallpox. Milk maids, coming into contact with cowpox, were found to not succumb to smallpox. This is due to some close similarities between the two viruses, generating cross protection but with the important difference that whereas smallpox is a dangerous pathogen infecting humans, cowpox is not. As another example, BCG - a mycobacterium infecting cows - can have sufficient homology to TB, which infects humans, to provide safe protection. However, BCG's efficacy is variable, varying geographically and waning over time. Unfortunately, after a BCG prime vaccine, use of a second dose is ineffective in boosting protection.

There are only limited cases where a safe live vaccine is protective against another, dangerous pathogen, so various technologies have been developed to achieve the same objective. In essence, these seek to modify the pathogen so that it is no longer disease-causing, while still inducing immunity, such as:

- ❖ Vaccination with killed pathogen - hence no risk from a live pathogen initiating infection.
- ❖ Attenuation of the pathogen - altering its virulence, to render it harmless.
- ❖ Subdivision of the pathogen - hence vaccinating with only a part (or parts) of the pathogen.
- ❖ Identification of a specific pathogen's protein which elicits an immune response (defined as an antigen). DNA vaccines are a variant of the approach, aiming to generate the protein of interest in situ.

However, each of these methods has major drawbacks:

- Highly attenuated vaccines lose some breadth of protection, if the degree of modification is too great, due to low homology. Insufficient attenuation runs the risk of reversion.
- Killed or subunit vaccines alone induce only weak protective immune responses, hence require the addition of an adjuvant. The dendritic cell (DC), the key antigen presenting cell (APC) has no natural mechanism to take up naked DNA, proteins or part of pathogens, as these are not normal elements of the immune system. The mode of action of many adjuvants is unknown and difficult to predict, often being specific to a particular vaccine. Technical and regulatory complexity has thus far limited the number of adjuvants in commercial use.

Alternatives such as conjugation, incorporation of antigen to a safe viral vector or construction of Virus Like Particles are at various stages of development and in some cases, on the market.

Frequently, pathogens mutate over time, so there are a changing number of variants in circulation. Many of the newer vaccines are based on single or limited number of antigens, as opposed to killed, live or attenuated vaccines, where a number of proteins in the vaccine contribute to generating broad, cross-strain protection. Multivalent products, to increase the breadth protection to some degree, often have high cost of goods, being multiple products added together. Many of the major unmet needs for anti-infective vaccines are in countries where high vaccine prices limits their affordability.

The Vaccine Market

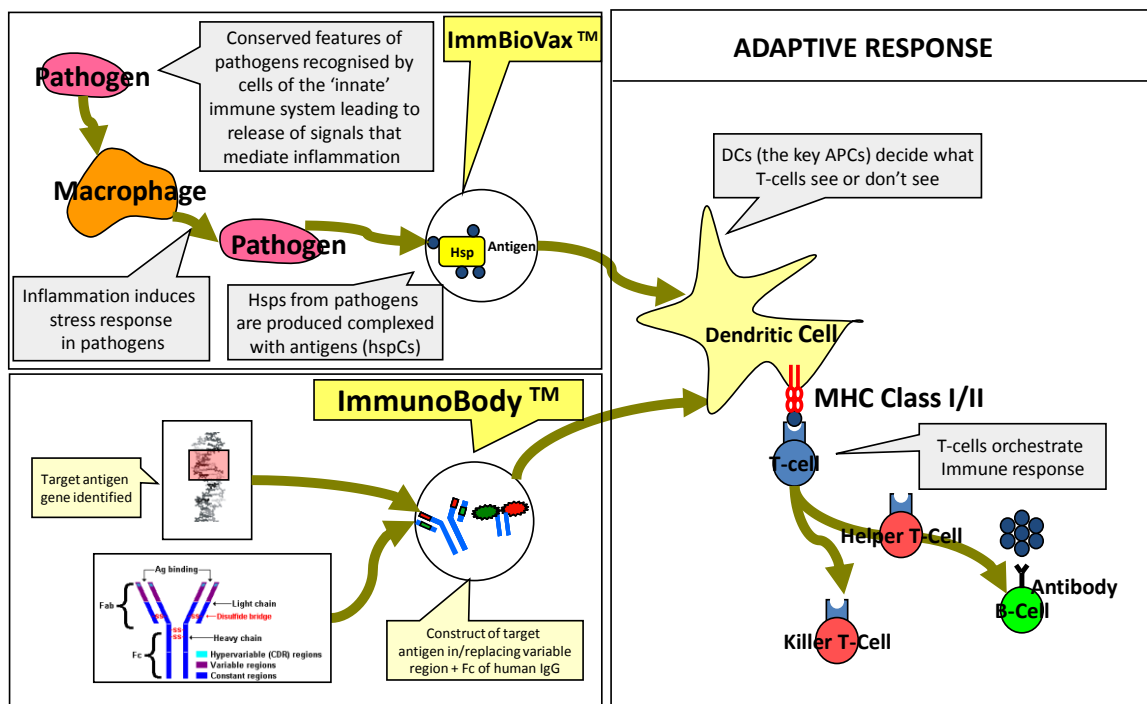
The vaccine market is worth over \$17 billion pa, having grown in recent years by between 5-10% pa. It is forecast to continue to grow solidly, driven by volume and new products. Although many of the newer products have been launched at price levels higher than prior prevailing levels, these still generate a significant net positive health economic impact to purchasers. Patent life, though relevant, is not critical in determining price, as biological products and processes require substantial know-how and cost of goods is a significant proportion of the selling price. Sales and marketing costs are much lower than for therapeutics, due to the differences in nature of the markets. Vaccines are currently available against 25 pathogens. However, if available, vaccines could be cost-effective against around a further 40 pathogens.

ImmBio's Approach: Maximising the Use of Normal Immunological Processes

Recent advances in immunology have provided insights into the working of this complex system. The immune system has two parts – an initial "innate" stage, which responds non-specifically to foreign bodies and then an "adaptive" response, which is specifically against that particular foreign body, notably by generating T-cells and antibodies. Dendritic cells (DCs) are central to the system and recent work highlights their role in recognising different classes of pathogens, so that the subsequent immune pathway and processing responses are appropriate. ImmBio's approach has been to generate vaccines which use normal immune pathways to the fullest extent, safely generating broad protective adaptive immunity. Consequently the products do not need the addition of adjuvants or other targeting mechanisms. Hsps generate an innate response and hence can be viewed as having adjuvant properties in their own right.

- ❖ **ImmBioVax™** vaccines, comprise pathogen-derived hspCs that mimics the way the immune system moves from the innate response to a specific response, using a range of hsps, coupled to a broad range of the pathogen's proteins.
- ❖ **ImmunoBodies™** mimics the follow-up mechanism of locking in memory via a fusion protein comprising of antibody (to correctly target and bind to dendritic cells) and antigen (specific to pathogen).

Both B and CTL cell responses are generated, anticipated to particular benefit infants and elderly, as the immune system capability alters with age. Successful protection requires a broad-based immunological response.



Addressing Pathogen Variability

A key challenge is to cope with both variations between people's immune systems and those of the pathogen (ie strain variation), which often increases over time, due to mutation. Both ImmBio's technologies address this requirement for protective "breadth":

- **ImmBioVax™** address the polygenic and polymorphic nature of MHC molecules and pathogen variability by appropriately loading a range of pathogen's peptides and proteins into dendritic cells. This in turn requires the vaccine to contain a range of the Hsp families, as each is associated with different proteins and peptide in their prime role as chaperones.
- **ImmunoBodies™**, again by using normal loading pathways, presents all the peptides of an antigen. In pathogen strain variation, there will typically be only some differences between the antigen's epitopes and hence the majority will be conserved between strains. Since multi-epitope recognition is generated by ImmunoBodies, the vaccine provides broad (cross-strain) protection.

Vaccine Economics

Given the high cost and long duration to develop each new vaccine, new platforms which are able to address many hitherto difficult pathogens are highly attractive. ImmBio has already demonstrated that for each platform, after the initial process design for the lead programmes, subsequent new targets benefit from accelerated timelines.

For vaccines on the market, beyond the essential requirement for safety, efficacy has to be assessed against the likelihood of infection, its impact and relevant costs to the healthcare system. Especially for universal take-up of a vaccine, there has to be a net positive health economic benefit and hence acceptable underlying cost of goods. Both ImmunoBodies™ and ImmBioVax™ manufacturing processes can produce high volumes of vaccine, at the dose level targeted, very cost effectively.