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Live vectors: are safe but effective vaccines possible?

Many human vaccines in use today are based on killed and attenuated viruses or bacteria, and were developed more than 30 years ago on an empirical basis with little or no knowledge of the protective antigens or the mechanism of protective immunity. Many of these vaccines cause side effects and, although the benefits clearly outweigh the risks, safety concerns (whether real or perceived) have undermined public confidence in certain vaccines [1] and have motivated the development of new vaccines based on the subunit approach (Table 1). This involves identification of protective antigen(s), definition of the protective mechanisms, and incorporation of the antigen(s) into an appropriate delivery system or adjuvant to enhance the immune response. This approach has been successful in generating new vaccines against hepatitis B virus, whooping cough and meningitis [2,3]. However, recombinant protein and polysaccharide-conjugated vaccines, as well as the traditional toxoided (chemically treated bacterial toxin) vaccines, are often poorly immunogenic and need to be presented to the immune system in a non-soluble form. Aluminium salts have traditionally been used as the adjuvant to non-specifically enhance immune responses to the antigen. However, more potent adjuvants (including those that work by mucosal routes) such as mutated bacterial toxins, non-replicating delivery systems and live viral and bacterial vectors, are now being explored for recombinant vaccine delivery [4].

The comprehensive review by Polo and Dubensky [5] highlights the tremendous potential of the virus-based vectors and also gives us some idea about their limitations. Although vaccines based on live vectors have been tested in animal models and in clinical trials, they are still some way off being licensed for routine use in humans, and several obstacles relating to immunogenicity and safety need to be addressed. Vaccines based on whole organisms are successful in eliciting potent adaptive immune responses, but live or inactivated viruses or bacteria also activate cells of the innate immune system and are generally pro-inflammatory.

Most, if not all, prophylactic vaccines work by generating functionally relevant antibodies, including those with virus-neutralizing or -opsonizing activity. Antibody production by B cells is dependent on help from T cells: Th1 cells for intracellular viruses and bacteria, and Th2 cells for extracellular and toxin-producing bacteria. Activation of T cells

Table 1. Relative merits of different types of vaccines[a]

	Attenuated	Inactivated	Live vectors	Nucleic acid	Subunit[b]
Immunogenicity[c]					
Total antibodies	++	+++	+	+/–	++
Functional antibodies	+++	++	++	+	+
Th1 cells	+++	+++	+++	+++	+
Cytotoxic T lymphocytes	+++	–	+++	+++	–
Effect of existing immunity	+	–	++	–	–
Risks	+++	+++	++	+/–	+/–
Ease of production	+++	+++	++	+++	+
Stability	+	++	+	+++	+++

[a]Merits are scored on an arbitrary scale denoting general attributes of vaccines in a particular category relative to other categories; not all vaccines in a single category will have identical properties.
[b]Attributes for protein vaccine with alum, which will vary with other adjuvants.
[c]Ability to stimulate different arms of the immune response *in vivo*.

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requires signals generated from interaction of the T-cell receptor with the processed antigenic peptide on the major histocompatibility complex (MHC) molecule, and also co-stimulatory signals and regulatory cytokines [e.g. interleukin 12 (IL-12)] from the antigen-presenting cells (APCs). This APC response can be induced by pathogen molecules (e.g. lipopolysaccharide, bacterial DNA and viral RNA) interacting with pattern-recognition receptors, including toll-like receptors on macrophages and dendritic cells. However, activation of innate cells with a range of pathogen molecules from a virus or bacteria can also induce pro-inflammatory cytokines, such as IL-1β, that lead to local and systemic reactogenicity, fever and neurological effects [6]. Therefore, the aim is to present the foreign antigen in a vector, adjuvant or inert vaccine delivery system, that will activate the innate, and hence the adaptive, immune response in a way that will not induce excessive inflammation. Some of the viral vectors under development have good safety profiles in clinical trials, but immune responses to the inserted heterologous antigens have not always been that spectacular.

Other problems, such as the limit imposed on repeated use because of immunity to the vector, can, in theory, be overcome by switching vectors for the booster doses. However, such problems still put vectors at a disadvantage over naked DNA or the purified recombinant vaccines. By contrast, major advantages of the live virus vector over the purified recombinant approach are that the antigen is replicating and that it is presented to the immune system in its native conformation. Because the antigen is synthesized in the host, it will be properly folded and glycosylated, and can gain entry to the endogenous route of antigen processing in the APCs, thus allowing induction of functionally important antibodies and class I-restricted T cells, respectively. The big question is whether it will be possible to generate persistent immunity to the heterologous antigen in humans using live vectors, without the potential problems associated with actively replicating viruses, especially in immunocompromised individuals. The answers should come from understanding the immunology of the problem and using molecular biology to design the solution.

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Want novel drugs in a hurry? You had better do the math!

The recent article in *Drug Discovery Today* entitled 'Prioritizing the proteome: identifying pharmaceutically relevant targets' by Swindells and Overington [1] focuses our attention on a new dynamic that promises to reshape the drug discovery process. In essence, the article highlights the increasing importance of complex and computationally demanding data-mining processes that are needed to extract information and knowledge from ever-larger and more-diverse data sets.

Consider, for example, that a typical protein structure takes 3–10 megabytes of storage. Multiply this by the 100,000 or more proteins thought to comprise the human proteome. Add to this the hundreds of thousands of corresponding protein structures from the pharmacological model species (dog, rat, mouse and primates), or to the hundreds of thousands, potentially millions, of protein structures from the various genomic model species, as well as the entire spectrum of infectious disease agents. This just begins to define the challenge, as well as the opportunity, posed by the massive influx of data from a growing arsenal of modern drug discovery tools [2]. Gene-expression array data, large-scale proteomics analyses, high-throughput small-molecule screening (each molecule potentially characterized by hundreds of descriptors), broad-spectrum clinical laboratory data or adverse drug reaction data generated through multi-test panels for thousands of clinical trial subjects or patients – each of these tools or data sources contains a wealth of information that today remains largely invisible or inaccessible.

The data sets generated by these new tools are often large in magnitude, sparse, noisy and multi-dimensional. In addition, they often afford only a well-buried, weak signal. Extracting information and knowledge from such data poses large computational and information-storage challenges. IBM's rapidly growing and highly successful commercial commitment to life science applications appears to be well thought out (not unexpectedly), and confirms the recognition of this important growing need. The complementary and

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