Tuberculosis: the U-shaped curve of concern

-Gill Higgins-

Fears of a revival of tuberculosis, even in economically developed countries, have been fed by the increase in susceptibility to this disease associated with HIV. In addition, resistance to first-line antituberculosis drugs is growing. The upshot of this is a clear need for the development of improved tools for tuberculosis control. The feasibility of an improved prophylactic immunisation approach was discussed at the annual conference of the Australasian Society for Immunology, held in Auckland, New Zealand, in December.

Infection with *Mycobacterium tuberculosis* continues to cause more deaths worldwide than any other single micro-organism.

At one time, certain developed countries were looking towards complete elimination of the disease, but in the last couple of years, a U-turn has taken place, with tuberculosis once again becoming a major public health concern *[see boxed text]*.

Tuberculosis incidence

The situation in developing countries remains grim. The present midpoint estimate runs at 7 million cases of tuberculosis/year, with 2.5 million tuberculosis-related deaths. This accounts for 6.7% of annual total mortality in these countries.

In the USA, the number of cases in 1988 stood at 22 500. This represented about 9 cases in every 100 000 people. The aim was to reduce this to 3/100 000 by the year 2000. However, the opposite has occurred. In 1990, 25 700 cases were recorded. The numbers may seem small compared with the incidence in developing countries, but the significance is great, as growing concerns in the USA could lead to increased funding for research.

The ideal method of overcoming this situation would be to have an effective prophylactic vaccine, noted Dr D B Young from Hammersmith Hospital in London, UK. Already in use is the bacille Calmette Guérin (BCG) vaccine, an attenuated strain of bovine tuberculosis. This is one of the most widely used vaccines in the world, but also one of the most controversial.

The reason for this is its questionable efficacy in clinical trials, as shown in Table I. It is obvious from these data that more consistent protection is required. Probably BCG induces immune mechanisms which prevent dissemination but fail to eliminate *M. tuberculosis*. Accordingly, BCG is sufficiently effective in preventing childhood tuberculosis, while its efficiency in adults is inadequate. This is the major drawback of BCG since tuberculosis is primarily a disease of the elderly.

Genetic manipulation has potential

One possible approach to improving upon the BCG vaccine is to use further attenuated variants of *M. tuberculosis* as potential vaccine candidates. Techniques for the genetic manipulation of mycobacteria offers the prospect for rational attenuation of *M. tuberculosis*, although practical problems of working with such slow-growing bacteria continue to hinder progress in this direction[1].

Efficacy of BCG vaccine in various trials

Patient population	No. in trial	Efficacy
UK schoolchildren	40 000	78%
US schoolchildren	7000	74%
Puerto Rican schoolchildren	80 000	33%
US adults	35 000	14%
South Indian adults	132 000	0%

A possibility also exists to clone genes for specific antigens, thus leading to more potent vaccines. This is provided that specific protective antigens can be recognised.

The protective antigen

Current thinking on specific immunity to intracellular bacteria is that CD4 T-cell-derived interferon-γ, which activates antimycobacterial activity in macrophages, is of major importance. Therefore, the ideal vaccine would be composed of one, or a few, defined antigens recognised by CD4 T-cells.

However, not all CD4 cells are the same. They can be differentiated into functional subsets on the basis of the pattern of cytokines which they release. Those that release interferon-γ are known as Th1 cells. The value of this knowledge is clearly demonstrated by studies of susceptibility to *Leishmania major* in mice. If Th1 CD4 cells are primed the animal is resistant. If Th2 CD4 cells are primed, the disease is fatal.

The challenge, then, is to identify the protective antigens, as opposed to the pathogenic antigens.

To date, according to Dr Young, 7 recombinant proteins have been identified using various monoclonal antibodies, but none possess particularly strong protective properties.

It is possible that the relevant T-cell antigens may not be recognised by antibodies. Therefore, other methods of identification are needed. An alternative that is currently in use is 2-dimensional gel electrophoresis of lysates of *M. tuberculosis* followed by direct testing with viable T lymphocytes[2]. In this way, the T-cell responses of patients with tuberculosis can be compared with those of

ISSN 0156-2703/92/1912-003/$1.00

controls (healthy BCG vaccinees exposed to *M. tuberculosis*).

Transport needed

If a suitable subunit vaccine was developed, it would still require an appropriate carrier system in order to take effect. Either the microbial protein antigen could be incorporated into novel adjuvants or cloned into replicating recombinant carrier systems[3]. The latter include vaccinia virus, deletion mutants of *Salmonella*, and BCG itself. More recently, several strategies have been devised which allow artificial introduction of proteins into the cytoplasmic class I pathway under experimental conditions. Such achievements are expected to have a direct impact on the design of vaccine carriers[4].

Which way forward?

In conclusion, it appears that the development of a new vaccine for tuberculosis is technically feasible, but it remains a long-term goal that is contingent upon advances in the understanding of cellular immune responses. Also, opinion is still divided over the approach that will result in the most efficient product.

It may consist of one or more protective antigens reconstituted in an appropriate delivery system. Alternatively, the multiple lymphocytes and complex interactions involved in the immune response may mean that a simple antigen preparation will be inadequate. Thus, it may be better to concentrate on generating attenuated mutant strains of pathogenic mycobacteria which retain most of their immunogenicity but are unable to cause clinical disease.

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1. Young DB, et al. Tuberculosis: Prospects for Vaccine development. Australasian Society for Immunology Inc (Programme and abstracts): 70, Dec 1992 **2.** Kaufman SHE, et al. Tuberculosis & Leprosy: Attempts to Identify T-cell Antigens of Potential Value for Vaccine Design. Scandinavian Journal of Immunology 36, (Suppl. 11): 85-90, 1992 **3.** Kaufman SHE. Vaccines against tuberculosis: The Impact of Modern Biotechnology. Scandinavian Journal of Infectious Diseases (Suppl. 76): 54-59, 1990 **4.** Kaufman SHE and Young DB. Vaccination against Tuberculosis and Leprosy. Immunobiology 184: 208-229, 1992.

ISSN 0156-2703/92/1912-004/$1.00