

CHALLENGES AND ACHIEVEMENTS IN INFECTIOUS AND AUTOIMMUNE DISEASES

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Pasteur coined the expression “vaccine” from “vacca”, to honor Jenner, who pioneered vaccination against smallpox by making use of cowpox. These days the notion of therapeutic vaccines has been extended to cancer, autoimmune diseases and recently a vaccine approach has been envisaged even for Alzheimer disease. With recent advances in isolating and defining tumor-specific antigens and their genes, there is little doubt that specific tumor vaccines will become a significant factor in the armamentarium against cancer. The central hypothesis behind active vaccination for cancer treatment is that tumor cells express unique antigens that are capable of inducing a specific response. A proposed vaccine would have to deliver this antigen to the immune system, which would recognize it as foreign and destroy any cell bearing this antigen. Many of the tumor associated antigens in humans, however, are non mutated self proteins. Overcoming the tolerance of the immune system toward them is crucial for their utilization as anti-tumor vaccines, and this could be achieved by employing tumor-specific peptides.

Cancer

There is a vast literature concerning this subject (1) and only a few examples can be given as illustration. Most efforts in the field of tumor vaccination have been in the area of melanoma, above all, around the family of MAGE genes and the proteins or peptides derived from them (2, 3), as well as around MART antigens (4). In human studies, 39 tumor-bearing patients with metastatic melanoma were treated with three subcutaneous injections of the MAGE-3 A1 peptide at monthly intervals. Of the 25

patients who received the complete treatment, 7 displayed significant tumor regressions. Three regressions were complete and two of them led to a disease-free state which persisted for more than two years (Thierry Boon and his colleagues in Bruxelles).

Humanized monoclonal antibody against the ErbB2-HER2 receptor, under the trade name Herceptin, is now being used successfully – in conjunction with chemotherapeutic drugs – against breast cancer in those individuals who exhibit a high density of the receptor on their cancerous cells. We have been studying for the last 10 years, together with Professor Yossi Yarden, monoclonal antibodies of similar specificity (5). Most of them inhibit tumor growth in nude mice, but some accelerated tumor growth. Among the inhibitory anti-ErbB2 antibodies, some acted after internalization, whereas others prevented the heterodimerization of ErbB2 with other members of the ErbB family.

Specificity

Specificity is one of the most important considerations in the development of vaccines against infectious diseases, and consequently, small structural antigenic variations may lead to drastic changes in the efficacy of a vaccine. It is of interest that in the case of the first vaccine ever developed, against smallpox, the vaccine consisted of the heterologous cowpox virus, Vaccinia, that was not identical to the disease-causing pathogen. Yet it was capable of inducing very effective protection against infection and eventually led to complete global eradication of this dreadful disease. However, in the case of most viruses, even small antigenic changes resulting from genetic variation, lead to change of specificity and interfere completely with the protective capacity of the vaccine. Thus, in the case of influenza for example, a new vaccine is required almost annually to fend off the newly emerging strains.

I would like now to extend this concept of specificity to cancer and to autoimmune diseases (6). I mentioned before the MAGE genes and the studies of Boon. Similarly, Steven Rosenberg had success with MART genes, also in melanoma.

Autoimmune diseases

Whenever it is possible to identify the putative cause of the disease, it should be possible to find a close molecular analog which will combat the disease. In one case of an autoimmune disease, that of multiple sclerosis,

we have succeeded in developing a drug/vaccine which has by now been approved by the FDA in the United States, as well as seventeen other countries (6, 7).

This drug – or vaccine – as I prefer to call it – is a polymer composed of four kinds of amino acids, and prepared so as to resemble and cross-react immunologically with the main troublemaker of the myelin sheath of the brain, the myelin basic protein (MBP). This myelin basic protein can provoke an experimental disease – allergic encephalomyelitis, and our substance, denoted by us Copolymer 1, or Cop 1 – can suppress the onset of the disease, and in rhesus monkeys and baboons, we showed that it can heal the actual disease. As this is an experimental model disease for multiple sclerosis, we moved to clinical trials. The phase 2 clinical trial was most successful. This was followed by several more big trials, before the FDA approved the drug/vaccine for daily injections for the exacerbating-remitting type of multiple sclerosis. We have proved recently that it can be given efficiently by oral route (8), and a trial involving 1800 participants is going on now in 18 countries. Copolymer 1 does not seem to have any effect on any other autoimmune disease.

Copolymer 1 is a potent inducer of Th2 regulatory cells in both mice and humans. Highly reactive Cop 1 specific T-cell lines were established from both brains and spinal cords of Cop 1 treated mice. In contrast, no reactivity to the control antigen lysozyme could be obtained in lymphocytes isolated from the central nervous system (CNS) of mice injected with lysozyme. Adoptively transferred labeled Cop 1 specific suppressor cells were found in brain sections seven and ten days after their injection to the periphery, whereas lysozyme specific cells were absent in the CNS (9). Cop 1 induced Th2 cells cross the blood-brain barrier and accumulate in the CNS, where they can be stimulated in situ by MBP and thereby exert therapeutic effects in the diseased organ.

In the same spirit we have approached another autoimmune neurological disease: myasthenia gravis, in which the disease is caused by an immunological attack on the acetylcholine receptor of our nerve cells. We are already successful in preparing a specific drug/vaccine against myasthenia gravis by limited amino acid substitution in two myasthenogenic peptides from the α -subunit of acetylcholine receptor. The analogs formed can heal the experimental myasthenia gravis in mice and rats provoked by injecting the complete acetylcholine receptor of the Torpedo electrical fish (10), and we hope to start clinical trials next year. In principle, in every autoimmune disease in which you can put your finger on

a potential candidate causing the disease, it should be possible to produce a close chemical relative that will suppress the disease.

Alzheimer's disease

From recent reports it appears that even immunization against Alzheimer's disease becomes a cogent possibility (11-13). One hallmark of Alzheimer's is amyloid plaque, a protein deposit that builds up in brains of those with the disease. In mice genetically engineered to develop an Alzheimer's-like condition, immunization with b-amyloid (Ab), the protein fragment that forms the plaque, reversed or prevented plaque formation and neural damage. The finding raised the possibility that immunization with Ab may eventually be used as a treatment, or prophylactically, for Alzheimer's disease. Indeed, a phase I clinical trial has begun with 24 patients. Trials in mice of a possible vaccine for Alzheimer's disease have shown that it reduces the behavioural defects and the brain damage seen in the disease, and it actually prevents memory loss. As promising as these results are, a human vaccine remains a long way off.

Infectious diseases

Coming back to infectious diseases, WHO recently reported that almost two million people die from tuberculosis every year, malaria kills over 1 million people per year, mostly in Africa, and newly-released figures show that AIDS killed an estimated 3 million people in 2000. Coming back to tuberculosis, it is estimated that between 2000 and 2020, nearly one billion people will be newly infected, 200 million people will get sick, and 35 million will die from tuberculosis, so we are badly in need of a successful vaccine.

Concluding remarks

We understand well many immunological phenomena at the cellular and molecular level, but the increase in our knowledge also extends the definable 'unknown'. Today we wish to understand not only the role of antibodies and immune cells, the signals triggering them and the various soluble macromolecules which immunocytes spill out, but also the pathways the signals provoke, the nature of the movement of the cells and the extent to which this knowledge may help us to develop newer and better drugs and vaccines, and as the next generation struggles with these problems, they too

will learn that the more the sphere of knowledge grows, the larger becomes the surface of contact with the unknown.

For all these approaches to diseases, we must work together, as one world, globally. Globalization describes trends dramatically and relentlessly, increasing connections and communications among people, regardless of nationality and geography. But globalization without integration leads to a Babel Tower. So to improve health, and I mean first of all the developing world – we need both globalization and integration of our efforts. And this must be done with great speed, as standing still is the fastest way of moving backwards in a world that is changing at an ever more rapid pace.

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