Journal of the Minnesota Academy of Science

Volume 53 | Number 1 Article 7

1987

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Recommended Citation

Haase, A. T. (1987). Biotechnology in the Conquest of Infectious Diseases. *Journal of the Minnesota Academy of Science, Vol. 53 No.1*, 26-27.
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Biotechnology in the Conquest of Infectious Diseases

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I would like to discuss the enormous potential of biotechnology and molecular biology to benefit human medicine in the future, focusing on the applications of this technology to prevent and/or treat infectious disease.

I will first elaborate on the application of molecular biology to prevent viral disease. To provide a common basis for understanding, some basic concepts of virology are needed. Viruses are composed of a protein coat or capsid structure that surrounds a piece of deoxyribonucleic acid or DNA. The nucleic acid encodes all the information necessary to produce progeny virus in an infected cell. As obligate parasites, viruses enter a cell, reproduce their genetic material, subvert the cell to protein subcomponents that comprise the capsid, direct assembly of the newly synthesized DNA and proteins into progeny viral particles, and exit from the host cell. Viruses perform all of these functions not infrequently at the expense of the host cell and often show an amazing lack of gratitude for the efforts made on the part of the host cell. In the end, viruses may destroy the host cell, maim it in some fashion, or transform it (resulting in the formation of a cancerous cell). Such effects at the cellular level cumulatively have an adverse effect on the health and well-being of the host animal.

Vaccines have long been used to prevent these unfortunate consequences of viral infections. Not long ago, entire hospitals were devoted to the care of patients with poliomyelitis, housed in row after row of iron lung machines. With the advent of the polio vaccine, these hospitals have thankfully ceased to exist. Vaccination involves using a preparation of virus that has been rendered inactive or noninfectious but is still capable of stimulating a protective immune response. Although traditional methods for producing viral vaccines have proven successful in ridding mankind of such scourges as polio and smallpox, developing vaccines for some other viruses has proven difficult. The techniques for manipulating DNA and proteins that are embodied in biotechnology permit the development of more effective vaccines. One such example is the production of subunit vaccines, which are composed of only the immunogenic protein components of the virus and are, therefore, noninfectious to the host.

One of the first and most notable subunit vaccines developed via biotechnology is against hepatitis B. Hepatitis B virus is an enormous contributor to human morbidity, even some mortality, on a worldwide scale. As you may know, hepatitis B virus infects the liver, which results in dysfunction that is readily seen as jaundiced skin. But the virus is also associated with hepatic cancer. Thus, prevention of this disease will have an enormous impact on two different serious diseases. Some time ago, a native or natural subunit vaccine was developed by purifying noninfectious viral particles from the blood of infected patients. Unfortunately, these particles were difficult and expensive to purify in quantity. They were also not particularly efficacious. More recently, virologists and molecular biologists have used recombinant DNA technology to cheaply produce in yeast cells a safe and effective hepatitis B vaccine. Restriction enzymes and nucleases were used to insert, or clone, pieces of the hepatitis B DNA (viral genes) that code for certain coat proteins into plasmids or other types of DNA vector systems that then transfer the viral DNA into yeast. The yeast are then manipulated during fermentation to express or produce hepatitis B viral coat proteins in massive quantities. These proteins self-associate to form aggregate complexes that are easily and cheaply purified. The degree of progress made with this particular vaccine is evident. It has been tested and licensed by the FDA and may be in use this year.

This technology holds even greater promise for the production of subunit vaccines for viruses where conventional approaches would simply not be safe. This is the case with the AIDS virus. In a disease that invariably is fatal, one can not consider using vaccines that are not assured to be 100% safe. Yet recombinant DNA technology permits molecular biologists to clone and produce that portion of the virus that can elicit protective antibodies devoid of any infectious viral component. In fact, the cowpox virus, which was the very first vaccine used by Jenner to immunize humans against smallpox virus, is now being used as an expression vehicle for immunologically important coat proteins of the AIDS virus. The elegant feature of this combined vaccine is that as the vaccinated host is producing antibodies against the smallpox group of viruses, they are also producing antibodies against the AIDS agents as well. This is a very important advance because the cowpox or vaccinia virus can accommodate a large amount of additional foreign genetic material. Therefore, a polyvalent vaccine that protects against a number of different viral agents, or strains thereof, can be produced.

Probably the most advanced approach to vaccination is the production of immunogenic "designer," or engineered, proteins. Using engineered peptides and polypeptides may well be better than using the natural forms produced through

conventional or recombinant DNA methods. This approach is a result of revolutionary new technologies such as x-ray crystallographic analysis of protein structure, computerized modeling and simulation of molecular thermodynamics, computational chemistry, etc. These technologies now allow us to better understand the biochemical and physical features of the viral coat proteins essential to immunity so that better immunogens can be designed. Such analyses have resulted in improved peptide vaccines for polio virus. Various investigators have used molecular modeling techniques to study regions on the poliovirus that are most prominently exposed and would probably be recognized by the immune system. In conjunction with monoclonal antibody technology, virologists have identified specific segments of the coat proteins comprising the poliovirus virion that are responsible for inducing immunity. With this information, peptides corresponding to these segments have been synthesized *in vitro* that have protected vaccinated animals from poliovirus infection.

I now want to turn from prevention of disease to the diagnosis of viral diseases. Hybridoma technology has truly accelerated the development of viral diagnostic systems in recent years. Hybridomas are immortalized immune cells, which produce relatively pure antibodies (to viruses and other pathogenic agents) in large quantities. These monoclonal antibodies are much more valuable than antibodies extracted from the serum of immunized animals because of their innate specificity and strict homogeneity. Labelled monoclonal antibodies can be used to specifically "tag" biological substances such as membrane proteins that are only present on the surface of cancerous or infected cells. This facilitates the rapid diagnosis of a given pathological condition. For example, an infection with Herpes simplex virus, type 1 (the cold sore virus) can be rapidly diagnosed in a few hours by staining infected cells with a fluorescently labeled monoclonal antibody against a specific viral coat protein. Some bacterial infections can now be diagnosed in much the same way thereby allowing the physician to treat his/her patient with the most efficacious antibiotic or other drug.

The other disease diagnosis area that has undergone a recent revolution because of biotechnology is the area of genetic disorders. Recombinant DNA technology permits the clinician to definitively identify and confirm that a patient is carrying a defective gene based on the sequence of his or her DNA. Gene diagnosis at the molecular level is extraordinarily sensitive and is quickly becoming easier to perform in the common clinical laboratory.

These new diagnostic techniques are particularly important developments for AIDS diagnosis. AIDS is a very frustrating disease for clinicians and patients because antibodies against the AIDS viral coat proteins may not be detectable for some time. Consequently, current serological tests, which rely on the presence of anti-AIDS antibodies in the blood may not accurately diagnose a potential AIDS victim until much later in life. The end result is that the potential exists to transmit the disease via transfusions from blood donors who were unaware that they were infected with the AIDS virus. So, in the future, we look to technologies such as gene synthesis and recombinant DNA to be very beneficial in terms of early, accurate detection of pathological conditions.

I will conclude with some brief comments about products for disease therapy using these new techniques. The advantages of recombinant products are their unlimited availability, inexpensive manufacturing cost, high degree of purity, and their possibly greater intrinsic activity. I turn again to the field of virology for illustrations. When a virus infects a host cell, virus-specific genetic information, usually in the form of double-stranded ribonucleic acid (RNA), will be produced in the cell. This special form of RNA will evoke the production of minute quantities of interferon. Interferon travels to adjacent, uninfected cells and induces an anti-viral state that protects those adjacent cells from viral infection. Molecular biologists are taking advantage of this protective feature of cells and have isolated and cloned into bacteria, via recombinant DNA technology, the gene encoding interferon. Through bacterial fermentation, large quantities of interferon can be produced. Testing of this agent can then be undertaken in an attempt to commercialize it as a new pharmacological product for preventing virus infections. Other gene products such as clotting factors, blood proteins, clot-dissolvers like tissue plasminogen activator (TPA), lymphokines like tumor necrosis factor, and many other beneficial substances have been or will be produced through biotechnology. The ready availability of such agents for the diagnosis and prevention or treatment of disease surely heralds the onset of a new age in human medicine.