Salad Bar Vaccines

Infectious diseases continue to be major scourges world wide. Microbes of one variety or another lead to some 13 million deaths each year. Acute respiratory infections exact the heaviest toll on the young; thus, in 1992, 2.8 million children succumbed to them. Likewise, diarrheal disease led to the demise of 2.2 million individuals, whereas malaria killed another million. Vaccines offer the best hope for reducing these shocking numbers. In fact, immunization may be the best medicine. In terms of cost-effectiveness, even antibiotics cannot match the benefits of vaccines. The UNICEF estimates suggest that immunization against measles, tetanus, and tuberculosis, for example, costs between $2 and $15 per "discounted year of healthy life" gained, which is a statistical measure of the value of a vaccine. In contrast, other interventions may cost as much as $25 to $1,000 for the same benefits. More important, vaccines are extremely safe. Despite the few serious reactions that have been reported from the current generation of the pertussis vaccine, those risks are miniscule compared to contracting the disease itself. For good reason, then, vaccines are perceived to be "better than the cure." In fact, in infectious diseases, the conceptual focus has begun to concentrate on vaccinations instead of finding treatments.

A consensus now seems to prevail among the players in the vaccine business that still larger gains against microbes could be achieved with the application of new technologies that are very much in the offing. In the past, vaccine development was considered as much of an art as a science. Recent advances, however, have introduced novel approaches, a few of which are already proving themselves. Immunologically, the knowledge being garnered would lodge the art of vaccination firmly on a rational basis rather than on an empirical one. This should stand the vaccinologists in good stead given the worrisome fact that the multidrug-resistant strains of a number of pathogens are sprouting continuously.

Until recently, the repertoire of vaccines comprised mainly live vaccines, crippled or truncated vaccines, and "wannabe" vaccines based on protein or peptide fragments of a pathogen, such as the influenza virus. However, the field is entering a new phase as scientists begin to apply molecular genetic techniques in an attempt to neutralize various pathogens. As a result, considerable efforts are afoot to make vaccines from DNA instead of the usual procedures utilizing viral particles or their proteins. Optimistic projections call for "all-in-one" immunizations (i.e., "DNA vaccines") that in the future would have the potential to elicit immunity against multiple diseases.

Molecular biological techniques are helping researchers not only to improve the existing vaccines, but to devise innovative strategies to combat infections. It would not be a hyperbole to suggest that, in fact, a paradigm shift might be taking place in vaccinology. The central issue in existing vaccines – again, say, in those against the influenza virus – is the variability of the virus. A vaccine based on one strain might not work against a different one of the same virus, and new strains do evolve when least expected. Most changeable of all is the "spiky" coat of the virus. This antigenic drift, which results from spontaneous mutations in the coat protein, allows the infectious particles to sneak past the immune surveillance despite presumed immunity. However, the viral core proteins, or nucleo-proteins, vary less from strain-to-strain, and, hence, are more stable.

The premise of "DNA vaccination" rests on this stability. A DNA vaccine consisting of a gene for a target nucleoprotein can protect against various strains of a virus, and could be considered, in a limited sense, generic. In essence, this approach is quite simple: Recombinant DNA with the sequences of interest in saline solution is injected into the muscle of an experimental animal. Muscle cells "soak up:" the DNA and start expressing the nucleo-protein that is required for the cell to stimulate immune response. Potentially, this strategy has the advantage of eventually evoking a two-pronged attack both by the antibodies and immune response on the infecting pathogen. Such a dual assault on the invading pathogen establishes the efficacy of a vaccine.

Despite its conceptual appeal and apparent simplicity, this approach would be limited by the mode of administration, for it is fraught with some serious unresolved issues.

To circumvent such difficulties, another strategy portends to have considerable impact in the foreseeable future. Genetically altered plants – including potatoes, bananas, alfalfa sprouts, and other foods – could provide plentiful and cost-effective sources of "edible" vaccines and other therapeutic agents for an array of human diseases.

The viability of this strategy was recently documented in studies in which mice were fed transgenic potatoes that were genetically engineered to produce antibodies against a strain of *E. coli* that causes diarrheal conditions such as cholera. Ingestion of the recombinant potatoes orally in the form of food stimulated the rodent immune response, and requisite antibodies could be detected in experimental animals. Another strategy uses engineered transgenic tobacco plants to produce secretory immunoglobulin that is the immune system's first line of defense against microbes that embed the lining of the mouth, stomach, gastrointestinal tract, and other mucosal surfaces. The tobacco plant was created by crossing its four independent, genetically modified varieties, each of which contained a gene encoding one of the antibody's four polypeptides. The intriguing finding is that the transgenic tobacco plants are able to assemble antibodies in a physiologically active form in a single cell, whereas two different cell types are required in mammals under *in vivo* conditions to produce a functional antibody. These approaches to produce antibodies in larger quantities fling the door open to a wide range of vaccines.

Previously, such secretory antibodies could only be produced in but minute quantities in mammalian cells in culture – a painstaking and time-, cost-, and labor-intensive route. The fact that plants are the most efficient "factories" to produce large amount of proteins would set the stage for production of vaccines in high volumes at relatively low cost. Attempts are, thus, underway to prevent tooth decay using plant-derived antibodies. Compared with tobacco, however, alfalfa and other edible plants would be more palatable and more readily acceptable to potential users. In fact, researchers are formulating a dental paste from transgenic alfalfa.

The potatoes that produced antibodies in mice were cloned to produce a protein subunit from a variant of *E. coli*. The targeted antibodies were detectable in the rodent bloodstream and in secretions in their guts. Because rodents do not get the human form of the diarrheal disease, it remains to be seen whether such antibodies can provide protective immunity in humans as well. It is anticipated that in the longterm, technology will be refined to the extent that genetic information from various pathogens could be successfully inserted in bananas, peaches, pears, and other fruit for oral administration to elicit specific immunity against a variety of microbes. Thus, it is envisioned that in not too distant a future there may well be a "salad bar" of other plants readily available to protect humans against many infectious diseases.

Suggested Readings:

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