Past and future of vaccination and immunology – Part 2: Immunology now and what to expect in future

To assess what the future holds in immunology and vaccination, one should know more than antibodies fight antigens

Evolution enabled mankind to survive and don't perish readily when attacked by microorganisms or toxins. Our organism is capable of recognizing and eliminating harmful elements. Yet, death due to infectious diseases remains the scourge of man. Vaccines are a powerful tool to prevent the spread of germs. The previous entry to this blog mentioned the role Jenner and Pasteur played at the end of the 18th and the 19th century in the down of vaccines. In many countries, like in the United States, vaccines against 14 diseases are available. Vaccines became a powerful means of public health and avoided around 6 million deaths worldwide annually (1, 2).

Infectious diseases affected the course of history (3). The plaque is one of them. The pandemic of SARS-Cov-2 might have such an impact on history as well (4). To soften the blow the recent pandemic has on every aspect of life worldwide, vaccines became available within an unusually short time.

The dream of immunologists and public health

Why was it possible to develop vaccines aimed at SARS-CoV-2 in such an extraordinarily short time? Techniques applied diverted from what was in use before, is one reason, and enhanced methodology to manufacture the products rapidly (5). The precedent of widespread use of preparations, based on procedures quite recently invented in immunology and genetic, encouraged scientists now to envisage even more daring projects. An example is a suggestion to develop one vaccine to work against several coronaviruses with one application (6). Because of the impact such a vaccine would have on the population's health, those interested in public health ought to be eager to follow up on developments in vaccination and immunology, at least superficially.

An outlook of how immunologists predict the advancement of their science (7) should help to understand what we have to expect. In future, public health should be involved in the logistic aspects of vaccination and the stimulation of societies for the cooperation into vaccination. Before immunologists and those in the field of virology entirely take over in working against infectious diseases, those in public health should understand at least the basics of what the colleagues in the laboratories are up to. A good entry point to do this, one might briefly resort to the history of immunology.

Progresses in immunology

One of the most outstanding achievements was eradicating smallpox in the seventieth of the last century (8). Only the elderly might remember being vaccinated against smallpox, and some even can still show the scare which remained. This achievement has to be accounted for the development of immunology, genetics, microbiology, and related fields in science such as virology.

However, the general public was grossly unaware of the accomplishments. At best, it is known that there are antibodies fighting antigens. Most probably, no prominent headline in the newspapers in 1960 announced to the general readership that the Nobel prize for Physiology or Medicine that year was awarded to the Australian scientist Sir F. Macfarlane Burnet. The award was given to Burnet for his contribution in virology, related to the fundamental paradigm of the "clonal selection theory" (9). The theory helped explain the diversity of antibodies as a response to antigens (10, 11).

Elementary discoveries in immunology, genetics, and biology were obtained in animal models and greatly evaded public recognition, although quite a number of Nobel awards were granted to scientists working on immunology. Important mechanisms were detected in yeast and animal models, included mice, squid, sea urchins, and nematodes (7). Those not directly involved in this type of research, important publications mentioning the animal model used, hardly raised the interest of those seeping through the overwhelming numbers of scientific publications. In addition, interest focused on non-communicable diseases for the previous decades. The SARS-CoV-2 pandemic now suddenly turned attention to infections and vaccines.

Basic of the immunological system

First, it might be helpful to reflect, what happens, when a microorganism or toxin tries to invade the organism. As a first attempt, the **innate system** attacks with phagocytes and dissolves the invaders. The **adaptive or acquired immunity**, as a follow-up response, uses lymphocytes and antibodies to fight against the intruders. Cells of the innate system, which phagocytes microorganisms, are neutrophils, macrophages, dendritic cells, eosinophils, mast cells, and natural killer cells. Acute-phase proteins, cytokines, and the complement system dissolve the microorganism. The acquired immunity acts through T- and B lymphocytes, dendritic cells, antigen-presenting cells (APC), and antibodies (12) *.

Mus musculus and homo sapiens

Significant breakthroughs in research were achieved utilizing mice models. However, the immune system of *Mus musculus* and Homo sapiens differ considerably. Both species are 60 to 80 million years apart in evolution, differ in 3.1 billion base pairs and 30.000 protein-coding genes. There are distinct differences for several factors in the innate- and adaptive immune system (13). Some new approaches in the development of therapies and vaccines in animal mice models worked well. Outstanding examples are the therapy of rheumatoid arthritis with biologic response modifiers and the immunotherapy for metastatic melanoma (14, 15).

However, phase 1 trials in humans can go seriously wrong, even after successful testing in an animal model before injecting volunteers. Working on a monoclonal antibody that directly stimulates T cells, six male volunteers fell seriously sick after an i.v. dose of the anticipated therapeutic medication. Four of them almost died but finally could be saved (16). The incident became well known as theralizumab episode and underlines the quest for 'new approaches to studying immune responses in humans (7).
How to study immunological reactions in humans?

Advanced methods exist now to study human immunological reactions in blood and lymph nodes, observing plasma cytokines and specific cell populations, as well as use tissue

imaging. Fine needle aspirate samples can be obtained from lymph nodes. Findings then can be linked to the "omic" technologies, such as reactions related to the function of genes, mRNA, and epigenetic modifications. Focus presently is laid on the expectation that 'chances are '…that 'in the next 10 to 50 years, we may have another outbreak like SARS-CoV-2' (6). We should be prepared for such a case.

System vaccinology and the chimeric spike

The idea of creating a vaccine against multiple forms of a virus genera was pursued already. One example is vaccines to protect against human papillomavirus causing cervical cancer. Thus, research into developing one vaccine against multiple sets of viruses is not an unusual undertaking. Yet, the cellular and molecular network driving the immune response to vaccination must be studied thoroughly (7). Here 'systems biology' can help. For system biology, those scientists in microbiology, immunology, and virology come together and, combined with computational approaches and 'omics' technologies, generate the new field of 'system vaccinology' (17). An example, how 'system vaccinology' might work is the research dealing with the spike protein of the coronaviruses.

Targets are coronaviruses of the Beta group. SARS-CoV and SARS-CoV-2 belong to a subgroup called Sarbecoviruses. Members of this group are supposed to jump from animals to humans easily. To the Beta group, also the MERS-CoV belongs, known to infect man-handling camels. The spike protein, the structure of how coronaviruses enter the cell, might be known to the general public by now. Immunologists distinguish between the head and the stem of the protein. The virus infects the cell through the receptor-binding domain (RBD). At the human cell, it meets the angiotensin-converting enzyme 2 (ACE2), which was mentioned in a previous entry to this blog. The idea now is to attach RBD nanoparticles of several viruses to the vaccines. This stimulates immunity against not only one but additional beta coronaviruses, which are supposed to threaten us in the future. Vaccines, which are made in this way, contain mRNA in the form of a '**chimeric spike'**.

Cryo-electron microscopy (cryo-EM)

How can scientists be sure that their research expectations are fulfilled or not? They have a fascinating technology on hand to visualize antigen-antibody reactions. The technique is called cryo-electron microscopy (cryo-EM) and allows a view of the structure of cells, viruses, and proteins at the molecular level (18). For instance, copies of the SARS-CoV-2 spike protein are mixed with neutralizing antibodies obtained from patients suffering from the virus within the laboratory. The mixture is then deep-frozen with liquid nitrogen. The crystals gained are placed in a large structure, being a four-million-dollar expensive microscope. Within the machine, the samples are bombarded with electrons to expose the atomic resolution of the spike-antibody complexes. The images provided by the device are screened by computer software at more than 1000 different angles. This process might last some days. In the end, those being familiar with the technique will detect imagines of spikes attached with antibodies (6).

Mosaic vaccine

Another attempt tries to stimulate immunity against the stem of the spike protein, where a viral enzyme fuses with the human cell. It is thought that this region doesn't differ much between the specific members of the coronavirus family. Therefore, such a vaccine, targeting

the stem, might protect against different virus genera. Small proteins (eight multimers) taken from RNA sequences of the stem of the spike protein from several sarbecoviruses are combined with nanoparticles taken from bacterial proteins. The result is a '**mosaic vaccine**', inoculated in mice, challenged with sarbecoviruses. It was found that mice antibodies neutralized the viruses targeted with the 'mosaic vaccine' and against viruses not used to make the vaccine (19).

Creating vaccines stimulating B- and T cells

Most vaccines presently administered are not thought to work against more than one type of virus. At best, one hopes that the vaccine also works against a mutation of the pathogen. Vaccines against the flu mutate rapidly. Vaccines designed to work against the virus causing the flu last year don't work the following year. Nevertheless, the advice is that a general defense against the flu viruses is achieved over a lifetime over time. A similar approach targets the B cells in the case of the coronavirus family. The B cell identifies Y-shaped proteins on the surface of antigens. Y-shaped proteins are immunoglobulins, while secreted from B cells, immunoglobulins work as antibodies. B cells are known to react strongly when each arm of the Y-shaped antibody attaches to different epitopes of different viruses. Omics technologies now available allow designing mRNA vaccines making use of the beneficial property of the B cells.

By surveying the role of B cells, naturally, T cells are also in the focus of vaccine developers. Vaccines stimulating T cells were of interest some time ago. T cells destroy damaged or infected cells. The development of vaccines to inhibit metastasis in cancer stimulating T cells ($CD8^+$) could be advantageous (20). Combining the B cell approach with the capacity of the T cells might work against HIV, for which, up to now, no vaccine could be developed (21).

Conclusion

Up to now, no 'pan-coronavirus' vaccine was licensed for a human trial. That was true for mRNA vaccines only a couple of months ago, before they were registered to be used for humans. Long-time effects remained unexplored. History will show whether the worldwide usage of the vaccines was safe and that the SARS-CoV-2 epidemic justified exposing millions and millions of people to what presently still is claimed a temporary allowance of the remedies. To vaccinate people only temporarily is not possible. One gets the shot or not, and that's it. Jenner and Humboldt must have had the courage to proceed with their vaccination trials. Those in charge of suggesting vaccination with mRNA vaccines follow the example of Jenner and Humboldt. What can be done with the omics technology and machinery on hand is fascinating. The techniques already proved their value for curative medicine and disease prevention in animals. History has shown that any advancement in technology cannot be stopped to be applied. Sometimes improvements are not necessarily helpful for mankind. At least the progress made, as outlined here, has the potential to be of great value.

*Details of the role of cells and factors in immunity and function see table 1 of reference 12 through Google search.

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