Vaccination Immunology: Prevention and beyond
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The Dutch Society for Immunology has been organising an annual educational course in Immunology since 1974. These courses are intended for a broad public varying from master students, PhD-students and technicians (BSc) to academic group leaders. Each course aims to demonstrate both the basics, the state-of-the-art knowledge, as well as the clinical aspects of an important theme in immunology. The course in 2008 was entitled “Vaccination Immunology: Prevention and beyond”. In the last two decades, the appearance of novel infectious diseases (e.g. aids, SARS) and the benefit and cost-effectiveness of vaccination reinforced the long-standing notion that prevention of infectious disease must be key in national health programmes. In addition, novel immunological insights and new technical developments changed traditional vaccination approaches. Finally, the growth of revenues of vaccines made vaccine development an attractive target for the pharmaceutical industry. Together, these changes led to a revival of vaccination research. The Lunteren NVVI course of 2008 gathered leading and renowned scientists to discuss new emerging immunological concepts and the latest progress in the field of vaccination.

Vaccination is one of the best-known practical applications of our knowledge of basic principles in immunology. Long before the mechanisms underlying immunological memory were unravelled, it was recognised that individuals that had survived exposure to a pathogen could become resistant to reinfec-tion. Since the demonstration by Edward Jenner in the 18th century that human inoculation of cow pox virus generates protective immunity against the human disease variant, vaccination has become standard health care practice.

A number of key topics and current challenges in vaccine research were discussed during the meeting:

1. Optimising vaccine efficacy against infectious diseases

1.1. Vaccine composition and vaccine delivery systems

Traditionally, most vaccines against infectious diseases consist of live attenuated or inactivated pathogens that induce strong immunity. Immune activation is generated upon recognition of danger signals in the form of pathogen-associated molecular patterns (PAMPs) that are expressed by the micro-organism through pathogen recognition receptors (PRRs) on antigen presenting cells and other cell types. Whole cell vaccines induce strong immunity, but may also give side-effects. Both Louis Boon and Jan Wilschut pointed out that side-effects are especially unwanted in prophylactic vaccines as they involve vaccination of healthy individuals against a disease that may never strike [1,2]. The occurrence of side-effects and the subsequent call of health authorities for well-defined and purified vaccines gave rise to major efforts in the development of single subunit vaccines. Purified subunit vaccines lack danger signals, which in turn resulted in the need for adding immune stimulating substances, i.e. adjuvants, to the vaccine. Consequently, the study of adjuvants has become a field of science in itself. Kingston Mills explained that the understanding of the mechanisms of protective immunity against a pathogen has become almost a prerequisite for modern vaccine design [3]. Good examples of diseases where the lack of complete immunological insight still hamper vaccine development were presented by Jean Pieters for Mycobacterium tuberculosis and by Rob Sauerwein for malaria [4,5]. In the case of malaria however, Sauerwein indicated that encouraging progress has been achieved with whole parasite vaccines. In addition, one subunit vaccine (GSK) shows promising efficacy in a clinical trial.

To date, the pros and cons of whole cell vaccines or subunit vaccines remain a matter of debate for almost all infectious targets. The recognition that whole cell vaccines may induce side-effects and that efficacy of subunit vaccines may be limited by the available...
adjuvants has led to the search for alternative vaccine formulations that closely mimic a specific pathogen without being pathogenic themselves. Jan Wilschut gave insight in the promise of virosomes as vaccine modalities [2].

Next to various vaccine compositions, the vaccine delivery systems are being reinvestigated. Claire Boog discussed the promising results of new delivery systems, like bioneedles and non-invasive delivery systems in the form of adhesive patches [6].

1.2. Vaccine efficacy and correlates of protection

There was clear consensus among the speakers that a major hurdle in vaccine development is formed by the parameters by which vaccine efficacy can be measured. Clinical endpoints may be difficult to measure objectively, as Bram Palache pointed out for influenza vaccines [7]. In addition, Chris Meijer demonstrated that for some vaccination programs clinical endpoints will take too long to measure; the efficacy of vaccines to prevent cervical cancer induced by human papilloma virus can only be measured after 15–20 years [8]. Therefore, there is a high need for alternative or intermediate endpoints in the form of correlates of protection (COPs). COPs are immunological parameters that can be measured after natural infection or vaccination which have predictive value for protection against reinfection. Although the search for optimal COPs is intense, they are often still poorly defined. Regularly, COPs defined in in vitro studies and in animals cannot be translated to the in vivo situation in humans. Clearly, the identification of optimal COPs is one of the main challenges for the future of vaccine research against infectious diseases.

1.3. Vaccines and current practice

Next to efficacy, practical hurdles in vaccine applications form drawbacks for vaccine development. Besides the cost of vaccine preparation, especially the speed of vaccine manufacturing was debated. Louis Boon pointed out that optimised manufacturing platforms may increase the speed of vaccine preparation, which will reduce the required amount of antigens per vaccine was put forward by most speakers as a possibility to combat limiting vaccine quantities.

Finally, although much research is devoted to develop new vaccines, many current vaccines already show good efficacy. Jan Wilschut pointed out that the search for new influenza vaccines is fueled by the current vaccine efficacies that are approximately 60% in the elderly, but exhibit relatively poor immunogenicity in immunologically naïve persons, such as young children [2]. For the same reason, the current vaccines are unlikely to protect in pandemic outbreaks due to lack of pre-exposure to new emerging virus. Bram Palache debated the intriguing paradox between the research efforts for new influenza vaccines and the observed underuse of current influenza vaccines [7]. Indeed, the WHO recommended that priority for influenza control should be given to increase the use of available influenza vaccines.

2. Vaccine development for non-infectious diseases

2.1. Vaccines to redirect the immune response

Vaccines were originally defined as ‘an inoculum or combination thereof for active immunization’. To date, the principle of vaccination has spread to other fields of immunology. The renewed appreciation of immune suppressive cell types, like regulatory T cells (Tregs), have led to vaccination strategies specifically aiming to counteract or exploit immune suppression to either boost or suppress immune activation. Vaccine approaches are nowadays being developed and applied with the aim to prevent or treat cancer, allergy, autoimmune diseases, addiction (nicotine, cocaine) and neurological disorders, like Alzheimer. Many vaccination approaches against non-infectious diseases aim for therapeutic vaccines to combat already established diseases. In most of these cases the principle of vaccination or immunotherapy is to redirect the immune response. If we take this into account, the definition of a vaccine should be broadened to ‘a substance or combination of substances that is administered to human/animals to induce or alter an active immune response’.

The current research on the specific redirection of the immune response by vaccination explores three main strategies. Kingston Mills elaborated on the use of different PAMPs as adjuvants to induce polarisation of specific Th subsets. Many PAMPs induce Th1 polarisation, but agonists of the TLR2 (toll-like receptor 2) stimulate Th2 responses [3]. In addition, PAMPs can also promote the induction of Tregs. Apart from the use of specific adjuvants, differences in T cell polarisation may be achieved by the route of vaccine administration. Whereas intradermal vaccination promotes Th1 responses, oral vaccination is well known for its ‘tolerising’ properties, which in fact is polarisation away from Th1 and towards induction of mucosal humoral immunity. Sublingual vaccination shows promising results. Finally, in the last decade, more knowledge about different types of antigen presenting cells and different effector functions of T and B cell subsets paved the way for specific cell-targeting strategies in vaccination. José Villadangos showed that different DC subtypes have different efficacies of inducing a protective immune response. The targeting of specific DC subtypes in vivo or the generation of various DC subtypes in vitro might therefore allow the design of more effective immunotherapies tailored to specific outcomes.

2.2. Vaccines to dampen undesired immune reactions

Immunotherapy has been used successfully for the treatment of IgE-mediated allergy for almost 100 years. Verena Niederberger showed that immunotherapy may effectuate a state of allergen-specific nonresponsiveness [9]. There are several potentially underlying immunological mechanisms that all involve deviation of the allergen-specific immune response. Allergen-specific immunotherapy leads to a shift in Th polarization from the Th2-dominated allergen-specific, detrimental immune response toward an innocuous Th1 response. Alternatively, allergen-specific immunotherapy may induce Tregs that dampen the allergic immune response and create tolerance. Finally, IgGs may be induced that antagonize the effect of IgE through competition with the IgE for epitope binding. David Wraith showed the promise of peptide vaccines to induce Treg in animal models as a means to treat autoimmune diseases [10]. Both speakers emphasized that with these vaccination approaches caution is needed to prevent immune activation and to thus create opposite effects (sensitization or anaphylaxis) as aimed for.

2.3. Combining immunoactivatory vaccines with therapies that attenuate immunosuppression

Kingston Mills pointed out that the realization that Tregs can limit immune responses has led to attempts to improve efficacy of immunoactivatory vaccines by Treg depletion [3]. This is of particular interest for therapeutic vaccines against chronic infections and cancer, as in these cases chronic suppression is prevalent. Indeed, this was underlined by Gosse Adema, who gave insight into the use of DC vaccination against cancer [11]. He advocated that DC vaccination in cancer should be administered in an adjuvant setting when a low tumor burden is present to circumvent the extensive
networks of immune suppression in established tumors. Alternatively, Gosse Adema suggested the use of combinational therapies in which DC vaccination therapy is combined with Treg depletion or CTLA-4 blockade to suppress immunological negative feedback mechanisms.

3. Challenges for the future of vaccine research

The meeting showed that, although the basic concepts of vaccination may not have changed since Jenners’ discovery, the rationales behind vaccine compositions have been challenged and are being rechallenged. A better understanding of the immunological mechanisms underlying protective immunity against pathogens remains especially needed for the development of vaccines against pathogens that evade or adapt to the immune system. In addition, more fundamental knowledge is needed to identify reliable immunological parameters that can be used as alternative markers for vaccine efficacy against infectious diseases.

Vaccination as an approach to redirect undesired immune responses is a challenging concept and the success of immunotherapy in allergy is encouraging for the whole field of vaccination against non-infectious diseases. In spite of the wealth of information that has surfaced on the regulation of polarization of the immune response, much of the immunological networks that control polarization in specific environments within the body still remain to be unraveled. In vivo success of targeting Tregs to specifically disengage or activate the suppressive arms of the immune system to either boost or suppress immune activation still needs to be demonstrated.

The intensification of vaccination research is understandable in the light of the high mortality and morbidity of infectious diseases, the threats of pandemic outbreaks by new emerging pathogens and the still suboptimal treatment modalities for cancer, allergy and autoimmunity. The further unraveling of the basic mechanisms that confer protective immunity or control immune direction is a need to advance vaccination research and a major challenge for todays’ scientists.

References


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