7 Profiling Vaccines for an Immunosenescent and Multimorbid Population

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Life expectancy is continuing to increase worldwide, and a recent report in *The Lancet* estimated that there is a 57% probability that life expectancy at birth among South Korean women in 2030 will be higher than 90 years and a 90% probability that it will be higher than 86.7 years [1]. Over the 3 million years of human evolution, and for 99.99% of the history of mankind, life expectancy was <30 years, but we have gained 55 years of life expectancy since 1700 and 35 years since 1900. So why has life expectancy increased so dramatically in recent years? In 1900, life expectancy in the United States was 47 years, compared to around 80 years now. This begs the question: What did people die of in 1900, and what do they die of today? At the beginning of the last century, infectious diseases were the cause of 57% of deaths. These diseases included diphtheria, tetanus, measles, smallpox, typhoid fever, pertussis and cholera. By 1998, the proportion of deaths due to infectious diseases had declined to <5%, and nowadays, non-communicable diseases such as ischemic heart disease, stroke, cancer, diabetes or Alzheimer's disease account for the majority of deaths. Evidently, life expectancy has been spectacularly increased by conquering infectious diseases through hygiene, clean water and vaccines. Vaccines have made an enormous contribution to controlling disease in infants and children, decreasing infant mortality and improving health among adults [2].

So one might wonder, what is next for vaccines? Have they reached the end of the road? The answer is a resounding no, as vaccines clearly still have a lot to contribute to society. The focus is now moving towards new target groups for vaccination, such as pregnant women or the elderly. These populations have not traditionally been the primary audience for vaccines, but are now garnering increasing attention as having the potential to yield considerable benefit from vaccination. Vaccines available for elderly include influenza (flu) and pneumococcal vaccines. Also, a

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vaccine for herpes zoster is also now available, although efficacy declines with age, and uptake remains low. Up to now, the industry never developed vaccines specifically for elderly, but rather, recycled childhood vaccines for use among the elderly. However, this paradigm is now changing, and specific plans to develop vaccines for the elderly are afoot, bringing together vaccinologists and immunologists to tailor the technology of vaccine to the elderly population.

Vaccination first started to be investigated by Jenner and Pasteur in the late 1700s and 1800s, respectively, using the basic empirical technique of growing a disease-causing pathogen, then inactivating by attenuating or killing it, and then injecting it into a subject. However, in the last 30 years, new advanced technologies have made it possible to produce vaccines that were previously impossible. Recombinant DNA, glycoconjugation and reverse vaccinology are part of an explosion of new technologies in immunology and synthetic biology, opening broad new horizons in vaccine technology. Innovations such as reverse vaccinology have revolutionized how vaccines are conceived over the last two decades. Indeed, genome sequencing has made it possible to discover novel vaccine antigens derived directly from genomic information [3]. The first vaccine to be derived by this process, namely, a vaccine against meningococcus B, is now available on the market and is administered systematically to all newborns in the United Kingdom since September 2015. Over the first 10 months of its use, two-dose vaccine effectiveness was reported to be 82.9% (95% CI 24.1–95.2) [4]. This new era of designing vaccines has been ushered in by technological progress in such areas as human immunology, structural biology and genomics, by opening new avenues of research into protective human immune response. The advent of high-throughput DNA sequencing has made it possible to map entire bacterial genomes, bringing to light a range of previously unknown vaccine antigens [5]. Genomics is used not only for antigen discovery but also for antigen expression, for conservation and for epidemiology [3]. In addition, computational advances have enabled rapid identification of potential vaccine antigens from among the wealth of genetic and immunological information that can be obtained in shorter times than ever before [6]. Reverse vaccinology has made it possible to target many pathogens that were difficult or impossible before, including superbugs, and may help to pave the way towards vaccines for the most problematic infectious diseases such as tuberculosis, malaria, HIV or hepatitis C.

Next-generation technologies in vaccine development include structural vaccinology or structure-based antigen design. A recent study of the prefusion structure of respiratory syncytial virus (RSV) fusion (F) glycoprotein identified antibodies that bind prefusion-specific antigenic sites, including one antibody, 5C4, that was found to be 50-fold more potent than the only available licensed monoclonal antibody to treat RSV, namely, palivizumab [7]. This study provided important evidence that antibodies against the site of vulnerability on the prefusion RSV F conformation can be induced. These studies provided the basis of the structure-based design of new stable and powerful immunogens that are now used for the development of an effective vaccine against RSV. Further next-generation technologies include synthetic biology, which uses viral vectors (e.g. CMV, adenovirus alphavirus), and synthetic nucleic acids such as RNA and DNA to deliver the genome into the cell and

teach the organism how to generate their own the vaccine subunits. Eventually, we may achieve the production of fully synthetic vaccines.

To enhance our understanding of the immune system, and how these new vaccines may elicit protection, systems biology is changing the paradigm in clinical trials. The conventional approach of taking large numbers of people and recording a limited number of variables for each can be replaced by systems biology, a new approach where few subjects can deliver large volumes of data. Large-scale screening for unknown components and connections within the immune system, notably using recent—omics technologies, in conjunction with powerful computational capacity to identify patterns and develop models of behaviour, will allow us to target specific functions or diseases with greater precision [8].

It is well established that immunity wanes with increasing age, as a result of the progressive deterioration of innate and adaptive immune responses [9]. In an approach termed "systems vaccinology," high-dimensionality studies of cellular and molecular responses to vaccines have been proposed to help formulate hypotheses regarding the mechanisms of immunosenescence and to identify potential biomarkers worthy of investigation. There is a growing body of evidence indicating that vaccine response is a function of the "bio-age" of a person's immune system. Fourati et al. recently reported that bio-age is determined by transcriptomic changes, with upregulation of several pro-inflammatory pathways in the elderly, likely to favour immunosenescence [10]. Conversely, participants with a younger bio-age showed more transcriptional modules involved in B-cell signalling and T-cell receptors. Finally, the bio-age score developed by Fourati et al. was able to distinguish between two groups of elderly patients (≥65), namely, "BioAge young" (aged 65–78) and "BioAge old" (aged 65–83), and both the bio-age score and the two groups of elderly identified by the bio-age signature were significantly associated in response to hepatitis B vaccine [10]. These findings show, for the first time, that it may be possible to identify, prior to vaccination, participants likely to be poor vaccine responders.

Adjuvant technology is a major component of vaccine development and, until recently, was a field with a relatively slow pace of development. Adjuvant substances added to vaccines for their synergistic, immune-enhancing effects have been in use for almost a century. Aluminium salts were the first adjuvant substances to be used in human vaccines and, indeed, remained the only adjuvant used in licensed vaccines for around 70 years [11]. Since the late 1990s, there has been an acceleration in new adjuvants. The oil-in-water emulsion MF59 was a key innovation and the first novel adjuvant to be released for many years. The MF59 adjuvanted trivalent inactivated vaccine (ATIV) was shown in a randomized trial to be efficacious against PCR-confirmed influenza in infants and young children, increasing vaccine efficacy from 43% to 86% [12]. ATIV also showed a satisfactory safety profile, with no difference in serious adverse events between groups [12]. A prospective, observational study evaluating the relative effectiveness of ATIV versus non-adjuvanted trivalent inactivated vaccine (TIV) in elderly (65 years and older) subjects in Lombardy, Italy, reported that the risk of hospitalization for influenza or pneumonia was 25% lower with ATIV [13]. AS01, a

liposome-based vaccine adjuvant system, has been shown to enhance specific immune responses to the antigen for selected candidate vaccines targeting malaria and herpes zoster [14]. A phase 3 study of the efficacy, safety and immunogenicity of candidate malaria vaccine RTS,S/AS01 reported that the vaccine provided protection against both clinical and severe malaria in African children [15]. Regarding herpes zoster, a subunit vaccine containing varicella–zoster virus glycoprotein E and the AS01B adjuvant system was found to significantly reduce the risk of herpes zoster in adults aged 50 years or older in a randomized trial, with vaccine efficacy between 96.6% and 97.9% for all age groups [16]. These developments open new avenues in vaccine development, particularly indicating the potential to develop new vaccines specifically for elderly populations, as opposed to simply recycling children's vaccines for use among adults.

In conclusion, recent developments in vaccine technology, combined with next-generation technologies such as structural vaccinology, systems biology and systems vaccinology, have enabled significant progress in our knowledge of immune response and how it can be stimulated. The future may bring vaccines for illnesses previously considered impossible to prevent and in populations with immunosenescence.

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