CLINICAL AND EXPERIMENTAL VACCINE RESEARCH

Towards Vaccine 3.0: new era opened in vaccine research and industry

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Joon Haeng Rhee
Department of Microbiology and Clinical Vaccine R&D Center, Chonnam National University Medical School, Gwangju, Korea

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Corresponding author: Joon Haeng Rhee, MD, PhD
Department of Microbiology and Clinical Vaccine R&D Center, Chonnam National University Medical School, 160 Baekseo-ro, Dong-gu, Gwangju 501-746, Korea
Tel: +82-61-379-8479, Fax: +82-61-379-8455
E-mail: jhrhee@chonnam.ac.kr

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Vaccination should be the most economical and sustainable way of combating with infectious diseases. Vaccines against diphtheria, tetanus, measles, mumps, rubella, polio, hepatitis, pneumococcus, and *Haemophilus influenzae* meningitis have lowered the incidence and mortality more than 97% [1]. The modern history of vaccination started from the landmark 1796 cowpox experiment of Edward Jenner. Jenner's vaccination concept was relayed to Louis Pasteur in the 19th century. Pasteur developed rabies vaccine in 1885, the first human vaccine manufactured in the laboratory. Ever since, scientists and physicians have focused on vaccination as the best defense against numerous bacterial and viral pathogens. The principles established by Louis Pasteur, that is, isolation, inactivation, and administration of disease causing microbes, have guided vaccine development throughout the 20th century. The overall vaccine research and developmental approach can be broadly categorized into three generations depending upon core technologies: 1) the "first generation" of vaccine development was essentially based on the basic principles of Pasteur, which consist of using inactivated pathogens in whole or live attenuated forms as vaccine (e.g., Bacillus Calmette Guerin [BCG], plague, pertussis, polio, rabies, and smallpox); 2) the "second generation" vaccines made up of purified microbial cell components (referred as subunit vaccines, e.g., polysaccharides, or protein antigens such as those used against tetanus, diphtheria, anthrax, pneumonia, influenza, hepatitis B, and lyme disease), which has more recently exploited recombinant DNA technology and polysaccharide chemistry; 3) the "third generation" vaccines utilizes the fruits of 'omics' researches and started with new antigen design based upon the 'reverse vaccinology' [2]. However, vaccine versions can be redefined from the perspective of industry and economy. I cautiously address that Vaccine 3.0 era just started and we need to prepare for the paradigm shift.

Vaccine 1.0

From the public health perspective, vaccination is regarded as the most economical way of preserving healthy lives of people. Vaccines are regarded as public commodity and stockpiled in governmental institutions. Almost every nation has basal vaccination programs against common infectious diseases as an important health policy. Vaccines have very unique position in the pharmaceutical industries. Vaccines had used to represent less than 2% of the global pharmaceutical market. Since vaccines are commodity, pricing should be very reasonable that national budgets could afford stockpiling and free vaccination to babies and citizens. In this regard, within pharmaceutical

industry, vaccines have long been regarded as a non-for-profit sector. As a result, until early 1990s, many pharmaceutical companies were leaving the field of vaccines. The Vaccine 1.0 era started from Jenner and lasted until mid 1990s. During this era, some technological innovation drove the vaccine industry, such as recombinant hepatitis B and attenuated varicella vaccines.

Vaccine 2.0

A turning point came during mid 1990s when the global vaccine market size was less than 5 billion dollars. The Vaccine 2.0 era was triggered by the success of premium conjugate vaccines targeting *H. influenza* type b (Hib) and pneumococcus. The tide was reversed and the vaccine industry became a very competitive area. From then, the vaccine market began to grow at double-digit rates and was expected to reach 15 billion dollars in 2010. However, the real vaccine market grew faster than expected and already passed 20 billion dollars in 2010. The total vaccine market sales in 2012 were estimated to be over 25 billion dollars (International Media Services [IMS] consulting group).

During late Vaccine 1.0 and early 2.0 periods, with the development of new bacterial and viral vaccines, recombinant vaccines, and of new technologies, and with the need of scale up production and the increase in the investment for large-scale clinical trials, many local producers disappeared and were acquired by bigger companies. Eventually the vaccine industry became increasingly concentrated with a small number of major players. Until the end of the Vaccine 2.0 era, five major companies (GSK, Sanofi Aventis, Merck, Pfizer/Wyeth, and Novartis/Chiron) had over 80% of the global market. The biggest pressure to vaccine industry was safety concern and huge amount of investment for larger scale clinical trials to prove safety of vaccines. As vaccines become more widely used, many events of vaccine calamities accumulated, which resulted in keen public arousal concerning vaccine safety. Because of the public allergy to vaccination side effects, anti-vaccination movements took power in developed countries [3]. With the aid of internet and other means of mass communication, the anti-vaccination sentiment disseminated very rapidly. Consequently, the approval agencies became more cautious in approving new vaccines. The more the approval agencies become cautious, the more increased the costs for developing new vaccines. Naturally, the vaccine field remains at best a "qualified" market that is strongly regulated and has high entry barrier and supply constraints. Though competition among the major market players has been very keen, they competed within a field that was protected by a high entry barrier. Local producers and newly sprung high-tech-based small biotech companies were not allowed to the high barrier-protected global vaccine market.

However, during the Vaccine 2.0 era, those major "monopsonistic" vaccine companies drastically changed the landscape of global vaccine industry. They globally expanded commercial vaccine markets over closed domestic and donor markets. Commercial markets are those markets, strongly regulated and intense competition exists and pricing is determined on the economical basis. Those big companies consequently become more capable of investing big money in the research and development of more profitable premium vaccines. The premium vaccine market is by far the largest part in monetary value the global vaccine market [4]. After many years of neglect, big pharmaceutical companies rediscovered vaccines as a major growth opportunity. To expand the profit potential and competitive edge of their products, they began to actively adopt new breakthrough technologies. Now vaccine industry is no more thought to be "none-for-profit." Among top 15 vaccines marketed in 2012, the number of commercial market vaccines exceeded non-commercial market vaccines (http://www.genengnews.com/insight-and-intelligence-and153/top-15-vaccines-of-2012/). Prevnar 13 and Gardasil were sold as much as 3.7 and 1.9 billion dollars, respectively.

Vaccine 2.0 market is moving toward addressing chronic diseases, curing more adults, and using multivalent combination vaccines. However, conventional ways of vaccine development governed the Vaccine 2.0 era seem to have almost reached to the limit. The global market landscape seems to be changing. Threats of emerging infections and bioterrorism changed public's attitude towards vaccine industry. Vaccine industry became an important component of national security in developed countries. However, it is obvious that five major multi-national vaccine companies' capacity is far behind the global needs of essential vaccines. Many countries started to encourage and subsidize domestic vaccine industry for their national security, which lead to explosive expansion of the field. In Korea, five pharmaceutical companies invested approximately 500 million dollars in constructing vaccine production facilities during last two or three years. In the United States, many young companies are moving forward to the global market with newly approved vaccines. Same trend is observed in China, Taiwan, and India. The door of barrier-

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protected vaccine industry seemed open ajar to the follower companies during later 2000s. The margins for newer vaccine technologies become widened. We arrived at another turning point in the vaccine history, booster expansion of vaccine industry. Probably, the Vaccine 3.0 era should have already started. Vaccine researchers should change gears to conform to the Vaccine 3.0 environment.

Vaccine 3.0

Vaccine research and development are experiencing a renaissance of interest from the global scientific community. This would be the potent driving force pushing the Vaccine 3.0 forward. There are four major reasons for this: 1) the lack of efficacious treatment for many devastating infections; 2) the emergence of multidrug resistant bacteria; 3) the need for improving the safety of the more traditional licensed vaccines; and finally, 4) the great promise for innovative vaccine design and research with convergence of omics sciences, such as genomics, proteomics, immunomics, and vaccinology [2]. The harbinger of Vaccine 3.0 should be the first approval of meningococcus type B vaccine developed by the reverse vaccinology techniques in 2011. This approach changed the direction of conventional vaccine development [2,5]. The use of reverse vaccinology triggered a cascade of changes that affected the entire vaccine development process, shifting the focus from the identification of a list of vaccine candidates to the definition of a set of high throughput screens to reduce the need for costly and labor intensive tests in animal models. Rino Rappuoli, the father of reverse vaccinology, addresses that a deep understanding of the epidemiology of vaccine candidates, and their regulation and role in host-pathogen interactions, must become an integral component of the screening workflow [5]. To cope with Vaccine 3.0 evolution, vaccinologist should develop new paradigm approaches for research and development. Following is the list of new approaches that seem to contribute to the Vaccine 3.0 paradigm.

Systems biological analysis of microbial pathogenesis

Reverse vaccinology approaches exposed some adverse concerns: they are genomic and antigenic variability among pathogens, needs for the in-depth study of population genomics and epidemiology of bacterial species, incomplete knowledge about *in vivo* gene expression regulation, needs for improvements in bioinformatics algorithms and functional genomic analyses, etc. Generally single subunit vaccines are less efficacious than whole cell vaccines. For the establishment of successful infection, multiple virulence factors interact with host factors. Multifactorial systems biologic approach will provide more holistic understanding over molecular pathogenesis and make the discovery of new pathogenic mechanisms possible. This will fill the gaps in current reverse vaccinology.

Conquering immunosenescence and development of vaccination strategies for the elderly population

In industrialized countries, the strongest demographic driving force for the growth of vaccine field. The growth of vaccination in developed countries is largely driven by the "senior citizen" segment of the population that is continuously expanding. Already, with vaccines directed at the prevention of influenza, pneumococcal infections, and zoster, in addition to the requirement of booster immunization, elderly vaccine has a huge growth potential [4]. However, the efficacy and effectiveness of vaccines exponentially decrease by aging. This becomes most apparent after a subject ages over 65-70 years, and results from complex changes in the immune system [6]. In developed countries, average life expectancy exceeds 80 years and most elderly people are vulnerable to infectious disease that will impose a huge burden to the community. As such, it is urgently required to develop new vaccine formulations and strategies that can overcome immunosenescence.

Search for safer and intelligent adjuvants

Both vaccine companies and approval authorities have been reluctant adopting new adjuvants to existing vaccines because of safety concerns. Immunopotentiating activities of vaccine adjuvants would increase the risk of reactogenicity. Until pathogen associated molecular pattern and pattern recognition receptor biology was elucidated, adjuvants were empirically incorporated to vaccines. Until couple of years ago, alum was the only vaccine adjuvant approved by Food and Drug Administration (FDA) and European Medicines Agency (EMEA). However, in the future, it is inevitable incorporating adjuvants in vaccines to enhance efficacy in elderly population and to save doses to immunize more people. Adjuvant can be used to induce desirable immune responses (humoral immunity or cell mediate immunity; Th1, or Th2, or Th17, or Treg) in the right immune compartment [7].

Multidisciplinary convergence of new technologies and new concepts

To achieve maximum safety and efficacy, new technologies

should be incorporated into existing vaccine formulations. For example, DNA vaccines, criticized to be ineffective in humans, are now under robust clinical trials in human subjects after new electroporation apparatuses were invented. New methods of administering vaccines are being actively developed, such as skin patches, aerosols via inhalation devices. Therapeutic vaccines will take larger share in the future vaccine market. Combinations of vaccines are becoming more common; mixing five to six or more components in a formulation. Vaccines against non-infectious disease will also contribute to the landscape of Vaccine 3.0. Anti-cancer immunotherapy and vaccines should be embraced by the vaccine industry. There are very active approaches to tackle metabolic syndromes with vaccine paradigm. These approaches cannot be successfully carried out by a single discipline. State-of-the-art disciplines of biology, immunology, medicine, chemistry, and engineering should very actively cooperate each other to make them successful. Vaccine community should be very open to diverse disciplines and new technologies and try to absorb them to nurture the Vaccine 3.0. In this regard, Korean Vaccine Society and its official journal Clin Exp Vaccine Res, to contribute to the Vaccine 3.0 evolution, should become the open platform where those diverse science disciplines and technologies could chemically interact.

References

1. Rappuoli R. From Pasteur to genomics: progress and challenges in infectious diseases. Nat Med 2004;10:1177-85.
2. Bagnoli F, Baudner B, Mishra RP, et al. Designing the next generation of vaccines for global public health. OMICS 2011;15:545-66.
3. Poland GA, Jacobson RM. The clinician's guide to the anti-vaccinationists' galaxy. Hum Immunol 2012;73:859-66.
4. Greco M. Development and supply of vaccines: an industry perspective. In: Levine MM, Kaper JB, Rappuoli R, Liu MA, Good MF, editors. New generation vaccines. 4th ed. New York: Marcel Dekker; 2004. p.75-87.
5. Donati C, Rappuoli R. Reverse vaccinology in the 21st century: improvements over the original design. Ann N Y Acad Sci 2013;1285:115-32.
6. Dorrington MG, Bowdish DM. Immunosenescence and novel vaccination strategies for the elderly. Front Immunol 2013;4:171.
7. Rhee JH, Lee SE, Kim SY. Mucosal vaccine adjuvants update. Clin Exp Vaccine Res 2012;1:50-63.

 http://dx.doi.org/10.7774/cevr.2014.3.1.1