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Advanced Vaccine Research

Methods for the Decade of Vaccines

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Preface

Only clean water has contributed to improving global health more than vaccines (Andre *et al.*, 2008). Vaccines have completely, or nearly, eradicated some of the most deadly viral and bacterial infections (e.g. smallpox, poliomyelitis, diphtheria, tetanus, pertussis, measles, mumps and rubella) (Rappuoli *et al.*, 2011). On top of direct effects, by preventing infections in vaccinated subjects, vaccines also have a number of indirect benefits for the individual and society (Andre *et al.*, 2008). Indeed, vaccines can generate herd immunity, which plays a key role in protecting individuals at higher risk of infection including the immunocompromised, elderly and cancer patients, those in which the use of the vaccines is contraindicated, and those with limited or no access to resources to buy them. Vaccination has also been shown to reduce the incidence of certain cancers (Chang, 2003; Harper *et al.*, 2006). Indeed, some infective agents are associated with cancer, such as HBV with liver cancer and HPV with cervical cancer. Furthermore, vaccines are a key component in the fight against antibiotic resistance both directly and indirectly. By targeting bacterial pathogens, vaccines directly reduce the need for the use of antibiotics. Antiviral vaccines, such as the ones against influenza, can also have an indirect effect on reducing the emergence of antibiotic resistant strains by decreasing complications associated with super-infections, which routinely require antibiotic use.

Most of the vaccines currently available for human use were developed on the basis of Louis Pasteur's principle of inactivating or killing the infectious agent and then using it to induce protective immunity into the host (Rappuoli *et al.*, 2011). However, scientists have recently realized that for several pathogens (e.g. serogroup B *Neisseria meningitidis* (MenB), HIV, malaria), conventional vaccinology methods are not sufficient or adequate.

After the publication of the first bacterial genome in 1995 (Fleishmann *et al.*, 1995), it became clear that availability of the genomic sequence of pathogens was an invaluable source of information for vaccine research. In fact, only five years later, a new antigen identification approach, named reverse vaccinology, was applied to MenB (Pizza *et al.*, 2000). The approach was termed reverse vaccinology because antigens were selected prior to experimental testing (Rappuoli, 2000). Later, with the explosion of the omics era, vaccine discovery could benefit from techniques that generate data complementary to reverse vaccinology. With the advent of high-throughput sequencing technologies, the availability of multiple genomes of the same species allowed comparative genomics studies to be performed, critical to determine the level of conservation of vaccine candidates (He *et al.*, 2010).

However, none of the genomic approaches can provide all the information required for vaccine design and characterization. Techniques based on immunomics, such as the so-called antigenomics, can identify candidates expected to be immunogenic in humans (Meinke *et al.*, 2005; Rinaudo *et al.*, 2009; Vytvytska *et al.*, 2002). Approaches based on transcriptomics or proteomics are able to identify candidates expressed by pathogens under different growth conditions. Studies done to date using the different approaches have generally shown a significant degree of overlap and have

identified subsets of the surface and secreted antigens predicted by reverse vaccinology (Bagnoli *et al.*, 2011; Bensi *et al.*, 2012; Doro *et al.*, 2009; Etz *et al.*, 2002; Grifantini *et al.*, 2002; Rodriguez-Ortega *et al.*, 2006; Stranger-Jones *et al.*, 2006). However, each approach supplies different information that altogether can be used to select the best candidates.

Despite the recent progress made by omics science and high-throughput technologies we should not assume that vaccine research can be performed without the tight support of basic research. Indeed, it is still highly dependent on experimental studies and empirical observations. It is of critical importance to determine the role played by antigens in virulence, and interactions with the host, as well as their function and biochemical properties such as the structure. Structural biology represents a powerful means to identify protective epitopes, especially in highly variable antigens. Available vaccines are against pathogens whose antigens are relatively stable. Microbes that have rapid and extensive antigenic variability, remain a major challenge for vaccine researchers (Rappuoli and Aderem, 2011). Structural studies on the antigens can be performed to understand the degree of surface exposure of the epitopes and to design peptides optimized to generate neutralizing antibodies (Dormitzer *et al.*, 2008).

Another important aspect that requires a basic research approach is the discovery of mechanisms of protection. Pathogens against which successful vaccines have been developed, have known protective mechanisms and in all cases humoral response appears to be the driving mechanism (Moriel *et al.*, 2010). On the contrary, when protective mechanisms and correlate of protection are not clear (e.g. *Staphylococcus aureus*, malaria, HIV, *Candida albicans*, tuberculosis), successful vaccines could not be developed (Bagnoli *et al.*, 2012; Dubensky *et al.*, 2012; He *et al.*, 2010). Therefore, basic immunology studies to shed light on their mechanisms of protection are needed to support vaccine development against these pathogens. Accumulating literature indicate that innate and cell mediated immunity are important against several pathogens, such as *Mycobacterium tuberculosis* (Doherty and Andersen, 2005; Hoft, 2008), *Candida albicans* and *S. aureus*.

In this regard, adjuvant formulations stimulating T-cell-mediated immunity are certainly another important area of investigation for next generation vaccines. Traditionally, adjuvants have been used to increase antibody-mediated responses. However, the important role of adjuvants in stimulating T-cell responses is also becoming clear. Recently, the role of Toll-like receptors as adjuvant targets is emerging as a promising area of investigation.

Usually, prior to clinical trials, most of the information available on protective efficacy of candidate vaccines is obtained in animal models and in *in vitro* studies. However, this approach has several limitations in predicting human immune response to vaccines. This is particularly true for those pathogens mentioned earlier for which correlate of protection in humans are unknown. Indeed, several failures in phase III clinical trials on HIV, malaria, and *S. aureus* have been recorded (Proctor, 2012; Shinefield *et al.*, 2002; Spellberg and Daum, 2010, 2012). The possibility to use different high-throughput technologies (e.g. next generation sequencing) to monitor the host response to vaccination and disease as well as to interrogate T- and B-cell repertoires in a large collection of individuals will allow the discovery of signatures of protection in humans. By integrating as many biological measurements as possible, systems biology will provide a powerful tool to analyse and interpret host responses to vaccines in clinical trials.

The aim of this book is therefore to illustrate the impressive technological advance that is increasing the quality standards of vaccines and is paving the way to develop vaccines against diseases for which efficacious medical treatments are still lacking. The examples that we have used comprise very different diseases; we include not only infectious diseases, but also cancer. We believe that these will be the vaccines of the future, the 'vaccines for 2020'.

References

Andre, F.E., Booy, R., Bock, H.L., Clemens, J., Datta, S.K., John, T.J., Lee, B.W., Lolekha, S., Peltola, H., Ruff, T.A., *et al.* (2008). Vaccination greatly reduces disease,

disability, death and inequity worldwide. Bull. World Health Organ. *86*, 140–146.

Bagnoli, F., Baudner, B., Mishra, R.P., Bartolini, E., Fiaschi, L., Mariotti, P., Nardi-Dei, V., Boucher, P., and Rappuoli, R. (2011). Designing the next generation of vaccines for global public health. OMICS *15*, 545–566.

Bagnoli, F., Bertholet, S., and Grandi, G. (2012). Inferring reasons for the failure of *Staphylococcus aureus* vaccines in clinical trials. Front. Cell. Infect. Microbiol. *2*, 16.

Bensi, G., Mora, M., Tuscano, G., Biagini, M., Chiarot, E., Bombaci, M., Capo, S., Falugi, F., Manetti, A.G., Donato, P., *et al.* (2012). Multi high-throughput approach for highly selective identification of vaccine candidates: the group a streptococcus case. Mol. Cell. Proteomics *11*, M111.015693.

Chang, M.H. (2003). Decreasing incidence of hepatocellular carcinoma among children following universal hepatitis B immunization. Liver Int. *23*, 309–314.

Doherty, T.M., and Andersen, P. (2005). Vaccines for tuberculosis: novel concepts and recent progress. Clin. Microbiol. Rev. *18*, 687–702.

Dormitzer, P.R., Ulmer, J.B., and Rappuoli, R. (2008). Structure-based antigen design: a strategy for next generation vaccines. Trends Biotechnol. *26*, 659–667.

Doro, F., Liberatori, S., Rodriguez-Ortega, M.J., Rinaudo, C.D., Rosini, R., Mora, M., Scarselli, M., Altindis, E., D'Aurizio, R., Stella, M., *et al.* (2009). Surfome analysis as a fast track to vaccine discovery: identification of a novel protective antigen for Group B Streptococcus hypervirulent strain COH1. Mol. Cell. Proteomics *8*, 1728–1737.

Dubensky, T.W. Jr., Skoble, J., Lauer, P., and Brockstedt, D.G. (2012). Killed but metabolically active vaccines. Curr. Opin. Biotechnol. *23*, 917–923.

Etz, H., Minh, D.B., Henics, T., Dryla, A., Winkler, B., Triska, C., Boyd, A.P., Sollner, J., Schmidt, W., von Ahsen, U., *et al.* (2002). Identification of *in vivo* expressed vaccine candidate antigens from *Staphylococcus aureus*. Proc. Natl. Acad. Sci. U.S.A. *99*, 6573–6578.

Fleishmann, J.A., Mor, V., and Laliberte, L.L. (1995). Longitudinal patterns of medical service use and costs among people with AIDS. Health Serv. Res. *30*, 403–424.

Grifantini, R., Bartolini, E., Muzzi, A., Draghi, M., Frigimelica, E., Berger, J., Ratti, G., Petracca, R., Galli, G., Agnusdei, M., *et al.* (2002). Previously unrecognized vaccine candidates against group B meningococcus identified by DNA microarrays. Nat. Biotechnol. *20*, 914–921.

Harper, D.M., Franco, E.L., Wheeler, C.M., Moscicki, A.B., Romanowski, B., Roteli-Martins, C.M., Jenkins, D., Schuind, A., Costa Clemens, S.A., and Dubin, G. (2006). Sustained efficacy up to 4.5 years of a bivalent L1 virus-like particle vaccine against human papillomavirus types 16 and 18: follow-up from a randomised control trial. Lancet *367*, 1247–1255.

He, Y., Rappuoli, R., De Groot, A.S., and Chen, R.T. (2010). Emerging vaccine informatics. J. Biomed. Biotechnol. *2010*, 218590.

Hoft, D.F. (2008). Tuberculosis vaccine development: goals, immunological design, and evaluation. Lancet *372*, 164–175.

Meinke, A., Henics, T., Hanner, M., Minh, D.B., and Nagy, E. (2005). Antigenome technology: a novel approach for the selection of bacterial vaccine candidate antigens. Vaccine *23*, 2035–2041.

Moriel, D.G., Bertoldi, I., Spagnuolo, A., Marchi, S., Rosini, R., Nesta, B., Pastorello, I., Corea, V.A., Torricelli, G., Cartocci, E., *et al.* (2010). Identification of protective and broadly conserved vaccine antigens from the genome of extraintestinal pathogenic *Escherichia coli*. Proc. Natl. Acad. Sci. U.S.A. *107*, 9072–9077.

Pizza, M., Scarlato, V., Masignani, V., Giuliani, M.M., Arico, B., Comanducci, M., Jennings, G.T., Baldi, L., Bartolini, E., Capecchi, B., *et al.* (2000). Identification of vaccine candidates against serogroup B meningococcus by whole-genome sequencing. Science *287*, 1816–1820.

Proctor, R.A. (2012). Is there a future for a *Staphylococcus aureus* vaccine? Vaccine *30*, 2921–2927.

Rappuoli, R. (2000). Reverse vaccinology. Curr. Opin. Microbiol. *3*, 445–450.

Rappuoli, R., and Aderem, A. (2011). A 2020 vision for vaccines against HIV, tuberculosis and malaria. Nature *473*, 463–469.

Rappuoli, R., Mandl, C.W., Black, S., and De Gregorio, E. (2011). Vaccines for the twenty-first century society. Nat. Rev. Immunol. *11*, 865–872.

Rinaudo, C.D., Telford, J.L., Rappuoli, R., and Seib, K.L. (2009). Vaccinology in the genome era. J. Clin. Invest. *119*, 2515–2525.

Rodriguez-Ortega, M.J., Norais, N., Bensi, G., Liberatori, S., Capo, S., Mora, M., Scarselli, M., Doro, F., Ferrari, G., Garaguso, I., *et al.* (2006). Characterization and identification of vaccine candidate proteins through analysis of the group A Streptococcus surface proteome. Nat. Biotechnol. *24*, 191–197.

Shinefield, H., Black, S., Fattom, A., Horwith, G., Rasgon, S., Ordonez, J., Yeoh, H., Law, D., Robbins, J.B., Schneerson, R., *et al.* (2002). Use of a *Staphylococcus aureus* conjugate vaccine in patients receiving hemodialysis. New Engl. J. Med. *346*, 491–496.

Spellberg, B., and Daum, R. (2010). A new view on development of a *Staphylococcus aureus* vaccine: insights from mice and men. Human Vaccin. *6*, 857–859.

Spellberg, B., and Daum, R. (2012). Development of a vaccine against *Staphylococcus aureus*. Semin. Immunopathol. *34*, 335–348.

Stranger-Jones, Y.K., Bae, T., and Schneewind, O. (2006). Vaccine assembly from surface proteins of *Staphylococcus aureus*. Proc. Natl. Acad. Sci. U.S.A. *103*, 16942–16947.

Vytvytska, O., Nagy, E., Bluggel, M., Meyer, H.E., Kurzbauer, R., Huber, L.A., and Klade, C.S. (2002). Identification of vaccine candidate antigens of *Staphylococcus aureus* by serological proteome analysis. Proteomics *2*, 580–590.

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