Vaccine design: emerging concepts and renewed optimism

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Arguably, vaccination represents the single most effective medical intervention ever developed. Yet, vaccines have failed to provide any or adequate protection against some of the most significant global diseases. The pathogens responsible for these vaccine-recalcitrant diseases have properties that allow them to evade immune surveillance and misdirect or eliminate the immune response. However, genomic and systems biology tools, novel adjuvants and delivery systems, and refined molecular insight into protective immunity have started to redefine the landscape, and results from recent efficacy trials of HIV and malaria vaccines have instilled hope that another golden age of vaccines may be on the horizon.

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Introduction

Traditionally, vaccines have been prepared by isolating an infectious agent, attenuating or inactivating it, and presenting it to the human immune system. This approach has proven extremely efficient against pathogens with relatively low antigen variability such as smallpox, polio, measles, mumps and rubella. However, pathogens with complex immune evasion strategies and the ability to evolve rapidly call for novel and more sophisticated strategies, which have begun to yield new and highly efficacious vaccines (Table 1).

Since the time of Jenner, Koch, and Pasteur, we have attained a detailed molecular understanding of how pathogens interact with the human immune system, permitting molecular identification of particular antigens involved in effective pathogen recognition by our immune system. These antigens can be produced, modified, combined and presented in novel ways to achieve more focused and controlled immune responses. These

innovative means of antigen presentation include liposomes [1], virus-derived vectors [2] or even self-amplifying RNA encapsulated in liposomes [3]. Epitope level control over the immune response is now being achieved by grafting epitopes onto protein scaffolds [4]. By sequentially administering diverse immunogens, scientists are currently formulating strategies to elicit certain lineages of protective and potently neutralizing antibodies against HIV [5••]. Whole genome sequencing is being used to predict antigens of larger pathogens such as bacteria and protozoa, and to maximize coverage of diverse isolates by enabling vaccination with composite, or mosaic antigens. Systematic approaches to predict protective immune responses from transcription and expression profiles of cohorts of genes involved in early immune responses are also being used to guide and accelerate vaccine development.
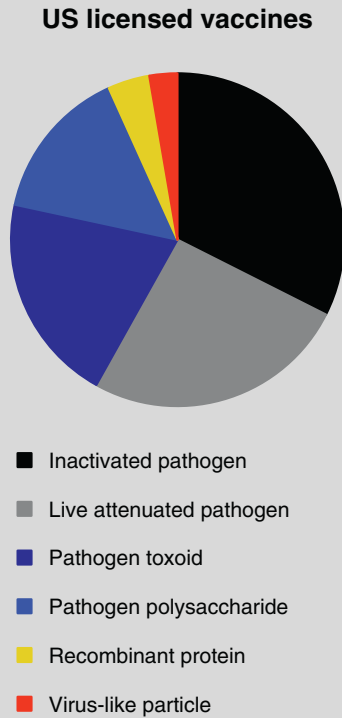
Collectively, these novel approaches leverage high throughput sequencing and bioinformatics to identify promising antigens, molecular adjuvants to target specific innate cellular receptors and drive desired inflammatory responses, advanced DNA, RNA, and protein delivery systems, and are beginning to exploit detailed molecular insights gained from studying protective immune responses generated in the context of natural infection, and a greater understanding of naïve immune repertoires. This review will discuss the state of the art approaches and technologies being explored to facilitate vaccine development (Table 2).

Reverse vaccinology, systems biology and personalized medicine

The development of next-generation sequencing and proteomic techniques has enabled researchers to mine entire microbial genomes, transcriptomes and proteomes to identify novel candidate immunogens. This reverse vaccinology approach has enjoyed considerable success in the past decade, beginning with *Neisseria meningitides*, and continuing with *Streptococcus pneumonia*, pathogenic *Escherichia coli*, and antibiotic resistant *Staphylococcus aureus* [6,7•]. These and other pathogenic, multidrug resistant microbial strains pose a major public health threat. The emergence of antibiotic resistance and the slowing development of novel antibiotics may combine to expand the market for vaccines, which is likely to increase the impact of efficient approaches. As described in Figure 1, the reverse vaccinology strategy utilizes genome informatics as opposed to traditional biochemical and genetic tools to identify antigen targets with promising characteristics such as surface expression, secretion, and/or high conservation, which can then be empirically tested and

Table 1

US licensed vaccines

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- ■ Inactivated pathogen
- ■ Live attenuated pathogen
- ■ Pathogen toxoid
- ■ Pathogen polysaccharide
- ■ Recombinant protein
- ■ Virus-like particle

Class	Target	Example	Licensed	Efficacy
Inactivated pathogen	Hepatitis A	Havrix™	1995	94%
	Influenza	Fluarix™	2005	62%[3]
	JEV [1]	Ixiaro™	2009	91%
	Plague virus	Plague Vaccine™	n.a.	n.a.
	Poliovirus	IPOL™	1990	99%
	Rabies virus	RabAvert™	1997	100%
Live attenuated pathogen	Tuberculosis	BCG Live™	1990	50%
	Influenza	FluMist™	2003	87%
	Measles/Mumps/ Rubella	M-M-R II™	1971	100%
	Rotavirus	RotaRix™	2006	87%
	Smallpox	ACAM2000™	2007	95%
	Typhoid	Vivotif Berna™	1989	50-80%
	Varicella	Varivax™	1995	85-90%
	Yellow fever	YF-VAX™	1978	95%
Toxoid	Diphtheria, Tetanus, Pertussis	Tripedia™	2001	95%
Pathogen polysaccharide	*Haemophilus B*	Hiberix™	2009	97%
	Meningococcus	Menveo™	2010	85-100%
	Pneumococcus	Prevnar™	2000	97%
Recombinant protein	Hepatitis B	Comvax™	1996	95%
	Influenza	Flublok™	2013	45%[3]
VLP	HPV [2]	Gardasil™	2006	89%

(1) Japan. encephalitis virus (2) Human papillomavirus (3) Including unmatched strains

References:
(1) FDA; Complete List of Vaccines Licensed for Immunization and Distribution in the US
(2) http://www.immunizationinfo.org/vaccines/

Table 2

Advantages (+) and disadvantages (−) of different vaccine development methods

Traditional vaccinology
- (+) No knowledge of pathogen genome or proteome required
- (+) Offers effective protection against many pathogens
- (+) Well established production and inactivation paths
- (−) Approach has not succeeded for several major, immune evasive pathogens
- (−) Limited to pathogens that can be cultured
- (−) Use of live, attenuated pathogens raise safety concerns
- (−) Inactivation may disrupt critical conformational epitopes

Reverse vaccinology
- (+) Offers rapid and systematic discovery of novel vaccine candidates
- (+) Provides for identification of conserved epitopes that ensure broad protection
- (+) Enables the design of non-natural vaccines with enhanced properties
- (−) Ability to identify macromolecules other than proteins is limited
- (−) Requires knowledge of pathogen genomes and proteomes
- (−) Approach may perform best for microbial or other complex pathogens

Structural vaccinology
- (+) Offers a path forward for pathogens where traditional methods have failed
- (+) Enables the identification and targeting of critical epitopes
- (+) Enables the design of non-natural vaccines with enhanced properties
- (−) Requires structure and sequence information about critical epitopes
- (−) It may be possible to elicit binding but not neutralizing antibodies, or strong T-cell responses to peptides that are poorly presented during natural infection