

# The impact of genomics on vaccine design

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After 200 years of practice, vaccinology has gained new perspectives for preventing infectious diseases. Sequencing of complete bacterial genomes led to the development of new large-scale technologies, such as bioinformatics, proteomics and DNA microarrays. By examining genetic content, as well as transcription and expression profiles, a more detailed understanding of bacterial pathogenesis can be reached. Moreover, the whole-genome perspective is expected to provide an instrumental contribution to vaccine development, particularly to target those pathogens for which the traditional approaches have failed so far. In this review, we describe how genomic approaches can be used to identify novel vaccine candidates or create safer live-attenuated vaccines.

Over the years, immunization has experienced several milestones, from the early attempts of 'variolation' to modern, genetically engineered vaccines. Since its introduction more than 200 years ago, vaccination has prevented illness and death for millions of individuals every year. However, despite the success of vaccinology, infectious diseases are still the leading cause of death worldwide. All vaccines available are based on killed or live-attenuated microorganisms, on toxins detoxified by chemical treatment, on purified antigens and on polysaccharide conjugated to proteins (Figure 1). The knowledge of the pathogenesis of microorganisms, the identification of the main virulence factors and the characterization of the immune response after infection has been fundamental for the design of second-generation vaccines based mainly on highly purified antigenic components [1].

Recently, there have been two major innovations in vaccine design. The first was the advent of modern molecular biology techniques. These techniques gave rise to two efficacious recombinant vaccines: the hepatitis B vaccine, which is based on a highly purified envelope protein [2] and that against *Bordetella pertussis*, based on three highly purified proteins [3]. The latter also pioneered the use of structure-function studies to produce a genetically detoxified toxin that maintained an unaltered antigenic conformation [4].

Until recently, vaccine design was based on conventional approaches using biochemical, microbiological and

serological methods to identify single antigen components that can be produced either in pure form from the pathogen cultivated in laboratory conditions or by using recombinant DNA technology. The antigens are then tested for their ability to induce an immune response. This approach can take years or decades, and in many cases fails to identify protective antigens that are relevant *in vivo* during infection. The approach needs the pathogen to be grown *in vitro* and therefore is not applicable to noncultivable organisms.

The second revolution in vaccine design is more recent and is a result of the use of genomic technology. Sequencing of the first bacterial genome *Haemophilus influenzae* marked the beginning of a 'genomic era', changing the landscape of modern biology and leading to a new approach in vaccine design. So far, ~172 complete genomes of pathogens and nonpathogens are available and more than 400 other microorganisms are being sequenced [Genomes OnLine database (GOLD) at <http://wit.integratedgenomics.com/GOLD/>]. It is now possible to determine the complete genome sequence of a pathogen in a short period of time (months) at low cost. Genomic information can then be used to screen the inclusive set of proteins potentially encoded by a microorganism, in search of potential vaccine candidates – an approach known as reverse vaccinology [5].

Moreover, it is now possible to compare the sequences of related bacteria and pathogens against commensals of the same or related species, and even bacteria with different or similar pathogenic profiles, identifying putatively disease-related genes (comparative genomics).

Functional genomics approaches are complementary to *in silico* antigen discovery. These include the large-scale analysis of gene transcription by DNA microarrays, the identification of the whole set of proteins encoded by an organism (proteomics) by two-dimensional gel electrophoresis and mass spectrometry, as well as the comparative genome-proteome technologies.

## Reverse vaccinology

The first example in which genomic technology was used for the identification of potential vaccine candidates is the vaccine against *Neisseria meningitidis* serogroup B [6], the major cause of sepsis and meningitis in children and young adults. For several decades, studies using conventional approaches to vaccine research failed to provide an effective and universal vaccine against meningococci B

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## **Table of Contents Pracis De Ganomique**

1. Understanding the eBook Pracis De Ganomique
  - The Rise of Digital Reading Pracis De Ganomique
  - Advantages of eBooks Over Traditional Books
2. Identifying Pracis De Ganomique
  - Exploring Different Genres
  - Considering Fiction vs. Non-Fiction
  - Determining Your Reading Goals
3. Choosing the Right eBook Platform
  - Popular eBook Platforms
  - Features to Look for in an Pracis De Ganomique
  - User-Friendly Interface
4. Exploring eBook Recommendations from Pracis De Ganomique
  - Personalized Recommendations
  - Pracis De Ganomique User Reviews and Ratings
  - Pracis De Ganomique and Bestseller Lists
5. Accessing Pracis De Ganomique Free and Paid eBooks
  - Pracis De Ganomique Public Domain eBooks
  - Pracis De Ganomique eBook Subscription Services
  - Pracis De Ganomique Budget-Friendly Options

6. Navigating Pracis De Ganomique eBook Formats
  - ePub, PDF, MOBI, and More
  - Pracis De Ganomique Compatibility with Devices
  - Pracis De Ganomique Enhanced eBook Features
7. Enhancing Your Reading Experience
  - Adjustable Fonts and Text Sizes of Pracis De Ganomique
  - Highlighting and Note-Taking Pracis De Ganomique
  - Interactive Elements Pracis De Ganomique
8. Staying Engaged with Pracis De Ganomique
  - Joining Online Reading Communities
  - Participating in Virtual Book Clubs
  - Following Authors and Publishers Pracis De Ganomique
9. Balancing eBooks and Physical Books Pracis De Ganomique
  - Benefits of a Digital Library
  - Creating a Diverse Reading Collection Pracis De Ganomique
10. Overcoming Reading Challenges
  - Dealing with Digital Eye Strain
  - Minimizing Distractions
  - Managing Screen Time
11. Cultivating a Reading Routine Pracis De Ganomique
  - Setting Reading Goals Pracis De Ganomique
  - Carving Out Dedicated Reading Time
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  - Distinguishing Credible Sources
13. Promoting Lifelong Learning
  - Utilizing eBooks for Skill Development
  - Exploring Educational eBooks
14. Embracing eBook Trends
  - Integration of Multimedia Elements

- Interactive and Gamified eBooks

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