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Vector-based genetically modified vaccines: Exploiting Jenner's legacy

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ABSTRACT

The global vaccine market is diverse while facing a plethora of novel developments. Genetic modification (GM) techniques facilitate the design of 'smarter' vaccines. For many of the major infectious diseases of humans, like AIDS and malaria, but also for most human neoplastic disorders, still no vaccines are available. It may be speculated that novel GM technologies will significantly contribute to their development. While a promising number of studies is conducted on GM vaccines and GM vaccine technologies, the contribution of GM technology to newly introduced vaccines on the market is disappointingly limited.

In this study, the field of vector-based GM vaccines is explored. Data on currently available, actually applied, and newly developed vectors is retrieved from various sources, synthesised and analysed, in order to provide an overview on the use of vector-based technology in the field of GM vaccine development. While still there are only two vector-based vaccines on the human vaccine market, there is ample activity in the fields of patenting, preclinical research, and different stages of clinical research. Results of this study revealed that vector-based vaccines comprise a significant part of all GM vaccines in the pipeline. This study further highlights that poxviruses and adenoviruses are among the most prominent vectors in GM vaccine development.

After the approval of the first vectored human vaccine, based on a flavivirus vector, vaccine vector technology, especially based on poxviruses and adenoviruses, holds great promise for future vaccine development. It may lead to cheaper methods for the production of safe vaccines against diseases for which no or less perfect vaccines exist today, thus catering for an unmet medical need. After the introduction of Jenner's vaccinia virus as the first vaccine more than two centuries ago, which eventually led to the recent eradication of smallpox, this and other viruses may now be the basis for constructing vectors that may help us control other major scourges of mankind.

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1. Introduction

Ever since the discovery by Edward Jenner, more than two centuries ago, that vaccinia virus could be used to protect people from variola, vaccines have been of utmost importance in fighting infectious diseases [1], as they are the most cost effective tools for the prevention of infectious diseases. To date several types of vaccines are available, including live-attenuated, inactivated, subunit or split, toxoid, conjugate, DNA, and recombinant vectored vaccines [2]. While conventional vaccines, like live-attenuated or inactivated wild-type, have successfully protected vaccinees from various infectious diseases over the years, they are not available for most infectious diseases and for those who cannot afford them. Conventional vaccine production methods, which predominantly use viruses and bacteria or their products, produced with classical production methods, are labour intensive, expensive, and time consuming, while some of the desired antigens cannot be produced in this way [3]. Furthermore, highly virulent pathogens can only be produced under expensive special safety conditions, while attenuated agents may have a tendency of reverting to their pathogenic form and can usually only be used in fully competent individuals [4].

To overcome the challenges of traditional vaccine production, the development and use of novel generations of vaccines, like those based on GM technologies, are being considered more and more frequently. The advent of these novel technologies may also be expected to create opportunities for the development of vaccines targeting new indications and/or application fields. Since there are many major indications for which no or only unsatisfactory vaccines are available, like AIDS, malaria, and tuberculosis, the exploitation of novel technologies, like the use of vector-based vac-

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cine candidates or vector-based production of protective antigens, may eventually allow us to fill the gap of this unmet medical need. To date several vaccines for humans, based on GM technologies have been licensed (for review see e.g. [5–8]) and a lot of candidates are in the pipeline.

An interesting approach for vaccine development based on GM technology is the use of vectors, which carry selected genes encoding antigens that induce protective immunity. They can either be used as vaccines proper, or for the production of antigens that are incorporated in vaccines. The present paper only deals with vectors that are actually used as vaccines and not just for the production of immunogens. Vectors can be classified in three different categories: viral, bacterial, and plasmid [9]. Vectors can either be fully replicative or only cause abortive infection, still allowing the expression of the desired immunogens. They can be administered either parenterally or via mucosal membranes [10]. A major advantage of vector-based GM technology, is that the immunogens of interest are *de novo* synthesized, thus not only allowing for the induction of antibody and T helper cell mediated immunity, but also for the induction of protective cytotoxic T cell responses, mimicking a natural immune response against the immunogen. This balanced immune response opens pathways that were previously inaccessible with traditional vaccine technology using 'non-live' immunogens. Especially the induction of CD8+ CTL responses may be of particular interest for vaccines against certain virus infections and cancers [11]. Our previous study provides additional insights regarding the strengths, weaknesses, opportunities, and threats of such technology [12].

In the present study, the potential of vector-based vaccines is evaluated. Data obtained from literature, granted patents, and different stage clinical trials are synthesised and analysed in the light of data from currently registered vaccines providing an overview of the potential of currently used and newly generated vectors in the field of vaccine development. The data suggest that vector-based vaccines may offer a cost-effective alternative for the production of safe vaccines against diseases for which no or less perfect vaccines exist today, thus catering for a huge unmet medical need.

2. Methodology

The methods applied in this study have been split in four different stages: evaluation of literature, patents, clinical trials, and registered GM and non-GM vaccines. Each stage was individually examined in detail and the complete data set was compiled. These stages were decided upon in order to provide a complete overview of the genetically modified (GM) vector-based vaccine pipeline and market.

2.1. Literature research

To map the early research stage of emerging vectors, a literature search was performed on available candidate vector vaccine studies. Data was collected on various types of GM vectors and their properties, as mentioned in both research publications and reviews. The search was conducted using a combination of Embase, Medline, Web-of-science, Pubmed, Cochrane, and Google Scholar. Medical Subject Headings (MeSH) and Boolean Operators were utilised in order to develop a basis for the syntax. The search was restricted to publications/translations in English. This syntax and the search results were analysed by an independent biomedical information specialist from Erasmus Medical Centre medical library. Additional information on the search terms for different search engines can be found in the supporting information (S1).

A total of 1756 hits were obtained [13]. 511 duplicates were removed, resulting in 1245 publications. Restrictions for further analysis included articles not describing vaccines or vaccine technologies, and articles not describing novel vaccine technologies. Publications were restricted to those published in the period 2009–2014. The total set contained 87 review articles on GM vaccines.

In order to retrieve more papers on vector-based GM vaccine candidates, an additional search was performed on Pubmed including relevant search terms "*vaccine*", "*vector*" and "*GM*". Reviews were retrieved adding the search term "*review*" to the previously mentioned terms or by searching for reviews only. Papers dating from the period 1998 to 2014 were collected and 18 new results were added to the previous 87 (Table 1).

A total of 38 publications, specifically on the topic of vector-based vaccines, were selected from this pool and analysed in detail. The clinical studies and reviews evaluated are shown in Table 2, and the results of this literature study can be found in Table 6.

2.2. Search for patents

Patents have multiple technology classifications based on their claims, and since they are classified in technological classes, patents related to GM vaccines were collected into a database. Patent data concerning GM vaccines was retrieved from Espacenet, which provides access to over 90 million patent documents worldwide [14]. Search terms used were "*Medicinal preparations containing antigens or antibodies*", "*Medicinal preparations containing genetic material which is inserted into cells of the living body to treat genetic diseases; Gene therapy*" and "*Mutation or genetic engineering; DNA or RNA concerning genetic engineering, vectors, e.g. plasmids, or their isolation, preparation or purification; Use of hosts therefore*", in combination with search words vaccin* (Boolean operator), and genetic* OR modif*, respectively. The results were deduplicated based on the priority numbers. The syntax and search results were analysed by a patent specialist from the Netherlands Enterprise Agency (RVO) [15], a governmental institution in the department of Economic Affairs. A total number of 40.308 unique patents were found and an original database was created, including all classes and subclasses.

As patent information in the patent database is condensed into Cooperative Patent Classification (CPC) codes, the previous search was repeated, combining the previous search with CPC codes for vectors and search term vaccine*. A total of 96 unique CPC codes were used, resulting in 32.738 vector-based vaccine patent documents. As CPC codes describe the classification in each technical area on various levels, the definitions of the CPC codes used were retrieved from Espacenet, and a comprehensive table was created including the CPC codes, their definitions, and the number patents containing this specific code. All search terms can be found in Table 3. The results are illustrated in Fig. 1 and a complete overview of these CPC codes and their description can be found in the supporting information (S2). It should be noted that the

Table 1
Results of literature search.

Database	Hits	Hits after deduplication
Embase.com	945	940
Medline (OvidSP)	364	97
Web-of-science	323	123
PubMed publisher	8	4
Cochrane DARE	7	2
Google scholar	100	79
Total initial search	1756	1245
Total set after applying restrictions		87
Additional vector search results		18
Final set used for detailed analysis		38

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