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Vaxvec: The first web-based recombinant vaccine vector database and its data analysis

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Abstract

A recombinant vector vaccine uses an attenuated virus, bacterium, or parasite as the carrier to express a heterologous antigen(s). Many recombinant vaccine vectors and related vaccines have been developed and extensively investigated. To compare and better understand recombinant vectors and vaccines, we have generated Vaxvec (<http://www.violinet.org/vaxvec>), the first web-based database that stores various recombinant vaccine vectors and those experimentally verified vaccines that use these vectors. Vaxvec has now included 59 vaccine vectors that have been used in 196 recombinant vector vaccines against 66 pathogens and cancers. These vectors are classified to 41 viral vectors, 15 bacterial vectors, 1 parasitic vector, and 1 fungal vector. The most commonly used viral vaccine vectors are double-stranded DNA viruses, including herpesviruses, adenoviruses, and poxviruses. For example, Vaxvec includes 63 poxvirus-based recombinant vaccines for over 20 pathogens and cancers. Vaxvec collects 30 recombinant vector influenza

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Conflict of Interest

The authors declare no conflict of interest.

vaccines that use 17 recombinant vectors and were experimentally tested in 7 animal models. In addition, over 60 protective antigens used in recombinant vector vaccines are annotated and analyzed. User-friendly web-interfaces are available for querying various data in Vaxvec. To support data exchange, the information of vaccine vectors, vaccines, and related information is stored in the Vaccine Ontology (VO). Vaxvec is a timely and vital source of vaccine vector database and facilitates efficient vaccine vector research and development.

Keywords

vaccine; recombinant vector vaccine; recombinant vaccine vector; database; Vaxvec; bioinformatics

1. Introduction

A recombinant vector vaccine is a vaccine that uses a live attenuated microbe, such as a bacterium, virus or parasite, as the vaccine vector to express a heterologous antigen(s). The first experimentally verified recombinant vector vaccine is a Vaccinia virus recombinant that expresses hepatitis B surface protein (HBsAg), which was shown to induce immunity sufficient to protect against the host chimpanzees against virulent hepatitis B viral infection [1, 2]. Since the report of the first successful recombinant vector vaccines, numerous recombinant vector vaccines and related vaccine vectors have been reported in the areas of veterinary and human vaccine research and development. Recombinant vector vaccines have been developed to treat various infectious diseases and cancers [3]. Currently, more than 10 viral vector veterinary vaccines have been licensed for commercial use [4, 5]. For example, viral vector vaccines using fowl poxvirus and herpesvirus of turkey as vectors and expressing infectious laryngotracheitis virus antigens are commercially available for poultry usage in the USA [5]. Three live bacterial vaccines have been available commercially in the world: *Salmonella enterica* serovar Typhi Ty21a, *Vibrio cholerae* CVD 103-HgR, and *Mycobacterium bovis* strain Bacillus Calmette–Guérin (BCG) [6]. The BCG strain has been used as a human vaccine against tuberculosis. However, with the possible exception of BCG, there is still no licensed recombinant vector vaccine or recombinant vaccine vector for human use [4].

Different types of recombinant vaccine vectors and their associated vaccines exist, and they may function with different mechanisms. Usually, vaccine vectors are bacterial or virus vectors. However, parasitic and fungal vaccine vectors also exist. Recombinant vector vaccines closely mimic a natural infection and therefore are able to stimulate robust and long-term immune responses in vivo. However, biased immune responses may be stimulated by different vectors. For example, the modified vaccinia virus Ankara (MVA) and the modified Copenhagen strain NYVAC are both poxvirus vectors. However, MVA triggers more CD8⁺ T cells while NYVAC favors preferentially specific CD4⁺ T cells [7]. The safety profiles of different vectors also differ. With the vast amounts of data related to recombinant vector vaccines published, a comparative and systematic study is required for better understanding the mechanisms of recombinant vaccine vectors and vaccines using these vectors.

VIOLIN (<http://www.violinet.org>) is the first web-based comprehensive vaccine database and analysis system that has included over 3,250 vaccines for over 200 infectious diseases and many non-infectious diseases (*e.g.*, cancers and arthritis) [8, 9]. Each of the curated vaccines has been reported to induce significant protection against a disease in at least a laboratory animal model. Many of the vaccines in VIOLIN are verified recombinant vector vaccines. However, the general VIOLIN database does not include specific information about individual recombinant vaccine vectors and how these vectors are used in different vaccines.

To address the many needs related to the recombinant vector vaccines, we have developed Vaxvec (<http://www.violinet.org/vaxvec>), a web-based vaccine vector and vaccine database and analysis program. As a relatively independent program under the umbrella of the VIOLIN system, Vaxvec includes the information for a large set of vaccine vectors, vaccines using these vectors, and protective antigens used in these recombinant vector vaccines. The analysis of these data enhances our understanding on these topics.

2. Methods

2.1. Vaxvec system and database design

Developed with classical three-tier architecture, Vaxvec was built on two HP ProLiant DL380 G6 servers running the Redhat Enterprise Linux operating system. A Vaxvec query is submitted from the Vaxvec web user interface (presentation tier). The query is then processed using PHP/SQL (middle tier, application server) against a MySQL relational database (data tier, database server). Query results are displayed in an accessible web browser. The two HP servers regularly back up each other's data.

Figure 1 illustrates the workflow of the Vaxvec/VIOLIN database design and implementation. For each recombinant vaccine vector, the database contains the following information: the vector name, Vaccine Ontology ID, preparation, vector function, advantage, disadvantage, storage, safety, stability, and reference. The information for each recombinant vector vaccine includes the general vaccine information, including name, antigen name, vaccine vector, vaccine status (*i.e.* licensed, clinical trial, or research), host animal model, vaccination route, protection protocol, and efficacy. The information of a gene encoding a protective antigen that was inserted into the vaccine vector was added to the database by an internal script to retrieve the information from NCBI using the NCBI Gene, Protein, or Nucleotide ID. The antigen was also labeled as a "protective antigen" and linked to a corresponding recombinant vector vaccine. For each record, comprehensive citation information is included. The citation information was automatically retrieved from PubMed [10] through an internal script using the PubMed ID (*i.e.*, PMID). All vaccine vectors and vaccines are assigned with Vaccine Ontology (VO) IDs.

2.2. Semi-automatic annotation of vaccine information

To efficiently annotate, store, and review vaccine vectors and related vaccines, a semiautomatic Vaxvec annotation system was developed based on an in-house web-based literature mining and curation system called Limix [9, 11, 12]. This system includes two

programs: vaccine and protective antigen data curation program, and a vaccine vector data curation program. Using a user-friendly web interface, a data curator can search peer-reviewed articles, type and edit text, and submit the annotated text to the backend database. Only after the annotated text is reviewed and approved by a domain expert, the annotated data can be available online for public searching and viewing. All annotation records in the Vaxvec annotation system are stored in the database and can be traced for checking. The two features mentioned in the above section, *i.e.*, automatically retrieving gene or reference information using an NCBI Gene ID (or other NCBI IDs) or a PubMed PMID ID, are also integrated in the web-based data curation system.

2.3. Generation of the taxonomy tree of recombinant vaccine vectors

To classify different microbes used as vaccine vectors, a taxonomy tree of these microbes were generated. To generate such a tree, the taxonomy IDs of different microbe organisms acting as recombinant vectors were first extracted. The OntoFox tool [13] was used to extract the hierarchy of these organisms based on the NCBITaxon ontology [14]. The OntoFox option of “Include Computed Intermediates” was applied to include only the closest ancestors of more than one low level taxonomy terms. The Protégé OWL editor [15] was used to display the results.

2.4. Analysis of vaccine vectors and corresponding recombinant vector vaccines

All vaccine vectors and recombinant vector vaccines were analyzed using the frontend database search or backend database queries using MySQL scripts. The direct database queries using MySQL scripts were sometimes performed for prompt categorization and comparison of the data stored in the database.

2.5. Analysis of protective antigens utilized in recombinant vector vaccines

For each protective antigen used in recombinant vector vaccine development, the Vaxign software program was used for analysis of subcellular localization and adhesin probability [16, 17]. All protective antigens used in recombinant vector vaccines were analyzed using the Clusters of Orthologous Groups (COG) for antigen clustering analysis. A Vaxvec BLAST search program was developed for sequence similarity search. This program is accompanied with our customized BLAST library that contains the protective antigens used in the development of recombinant vector vaccines.

2.6. Vaxvec data query and result display online

The Vaxvec web interface includes three types of query: (1) query for vaccine vectors, (2) query for recombinant vector vaccines, and (3) query for protective antigens used in the recombinant vector vaccines. The three types of queries can communicate with each other. A vaccine vector page includes links to all vaccines that use the vector. A web page of a recombinant vector vaccine also includes the link to the vaccine vector page and the information of used protective antigen(s).

2.7. Vaxvec data exchange, transfer, and download

The Vaccine Ontology (VO) is a community-based biomedical ontology in the area of vaccines and vaccination [18–20]. In this study, VO is used for ontologically storing the itemized information of vaccine vectors, recombinant vector vaccines, and corresponding protective antigens.

3. Results

3.1. Vaxvec system design and statistics

The Vaxvec system is designed to focus on three aspects: recombinant vaccine vectors, recombinant vector vaccines, and protective antigens used in recombinant vector vaccines. The recombinant vaccine vectors annotated in Vaxvec have been used in at least one recombinant vector vaccine. Many recombinant vector vaccine candidates are not associated with positively reported vaccine efficacy. We have restricted our inclusion of recombinant vector vaccines to those that have been experimentally verified to be effective in at least one laboratory animal model [8]. Although the information about failed vaccines and vectors may be informative, such information is often difficult to interpret and analyze. Our restriction on experimentally verified vaccines and vectors allows us to focus our time on identifying enriched features useful for future vaccine development. The genes expressed in recombinant vector vaccines encode protective antigens. The annotation and analysis of these protective antigens provide a basis of possible rational vaccine design and enhance our understanding of protective vaccine immunity.

As of April 2, 2015, Vaxvec has included 59 recombinant vaccine vectors (Table 1). These vectors have been used by 196 recombinant vector vaccines (Table 2). In total 67 protective antigens have been found to be used in development of these recombinant vector vaccines. Frequently, one antigen was used in different recombinant vector vaccine, and more than one antigen might be used for a single recombinant vector vaccine. These vaccines are developed against cancer and the infections of 63 pathogens (Table 2). Below we provide more specific description and analysis on these records in Vaxvec.

3.2. Analysis of Vaxvec vaccine vectors

To classify the relations among different recombinant vaccine vectors, a taxonomy tree of these vectors were generated (Figure 2). The resulting tree shows that the reported recombinant vectors cover various types of microbe organisms including bacteria, viruses, parasites, and fungi.

Recombinant viral vectors have been intensively studied [21]. Vaxvec includes 41 recombinant viral vectors. The most commonly used viral vectors include dsDNA vaccines, including adenoviruses, herpes viruses, and poxviruses. Adenoviruses are able to infect a broad range of hosts, grow in high titers in cell culture, and induce high levels of transgene production without risking potential integration of viral genes into the host genome [22]. Therefore, adenoviruses are safe to use and inexpensive to manufacture. Inherently adenovirus vectors can stimulate multi-faceted innate immune responses through Toll-like receptor (TLR)-dependent and TLR-independent pathways [22]. Via an adjuvant-like effect,

the adenovirus vectors promote the generation of humoral and cell-mediated immune responses against vaccine antigens. Herpesviruses are important mammalian pathogens that cause acute and chronic infections and can persist in the hosts for life. Example herpes virus vaccine vectors are human simplex virus-1 (HSV-1) [23] and cytomegalovirus (CMV) [24, 25].

The Vaxvec database includes 63 poxvirus vector vaccines (Table 3). Poxviruses are double-stranded DNA viruses. The poxvirus genome is very large and allows the insertion of more than 10 kb of foreign DNA without reducing viral infectivity and other essential functions [26]. Unlike other DNA viruses, poxviruses possess their own transcriptional machinery, enabling sufficient cytoplasmic self-replication. This feature is advantageous since it prevents potential gene mutation during the integration of viral genome into the host genomic DNA. Furthermore, the poxvirus vectors offer high level expression of foreign genes and thus result in robust cellular immunity to the gene products [22]. The three most commonly used poxvirus vector vaccines include the attenuated modified vaccinia virus Ankara (MVA), ALVAC [27], and NYVAC [28]. Different fowlpox virus vaccine vectors have also been well studied [28].

Many other types of viruses, including retroviruses and ssRNA viruses, have also been used as recombinant vaccine vectors (Figure 2).

Vaxvec also collects 15 bacterial vaccine vectors, for example, *Mycobacterium bovis* vaccine strain BCG, *Salmonella enterica* strain SL3261 and *Brucella abortus* RB51 vaccine vectors (Table 1). The human tuberculosis BCG strain has been used as a vector for development of 8 vaccines against the infections of different pathogens including HIV [29], *M. tuberculosis* [30], *Plasmodium* spp. [31], *Streptococcus pneumoniae* [32], and *Toxoplasma gondii* [33]. *Brucella abortus* strain RB51 is a licensed live and attenuated cattle vaccine strain [34]. RB51 is able to stimulate strong CD4+ and CD8+ T-cell mediated immune responses [35]. Recombinant RB51 strains have been developed to overexpress *Brucella* antigens for enhancing its *Brucella* vaccine efficacy [36] or protective against heterogeneous *Neospora caninum* infections [37, 38].

The other types of vaccine vectors included in the Vaxvec database include one protozoan *Leishmania tarentolae* vaccine vector and one fungal *Saccharomyces cerevisiae* vaccine vector. The nonpathogenic lizard protozoan parasite *L. tarentolae* has been used as a vector for three vaccines against *L. infantum* infection [39], *L. major* infection [40], and HIV-1 infection [41]. The safe and stable *S. cerevisiae* yeast vaccine vector has been used to develop two oral vaccines against porcine pleuropneumonia [42, 43].

3.3. Analysis of recombinant vector vaccines in Vaxvec

As of April 2, 2015, Vaxvec includes 196 recombinant vaccines (Table 2). These include 135 vaccines for 40 viruses, 18 vaccines for parasitic pathogens, 22 for 11 Gram-negative bacteria, 11 for Gram-positive bacteria, and 9 cancer vaccines.

As a demonstration, 30 different recombinant vector influenza vaccines are listed in Table 4. The major influenza virus serotypes are H5N1 and H1N1. These 30 vaccines use 17

different recombinant vectors and have been tested in 7 different animal models (Table 4). These results demonstrate the diversity and intensity of recombinant vector influenza vaccine research.

3.4. Analysis of protective antigens used in generation of recombinant vector vaccines

In total 67 protective antigens have been found to be used in the recombinant vector vaccines in Vaxvec (Note: more protective antigens are being annotated). A customized BLAST sequence similarity search is also available on the Vaxvec website for users to search antigens that share sequence similarity with an input DNA or protein sequence.

Based on a Vaxign data analysis [16, 17], 13 (19%) out of the 67 antigens are likely adhesins (Table 5). Adhesins are critical for pathogens to invade host cells. An antibody that neutralizes an adhesin function would block the invasion of a pathogen. Therefore, adhesins are typically considered as good vaccine antigen candidates [44]. Our analysis found that these adhesin antigens have been used in development of different recombinant vector vaccines using various vaccine vectors (Table 5). A previous study found that approximately 40% of protective antigens in Gram-negative bacteria and 54% of protective antigens in Gram-positive bacteria are adhesins or likely adhesins [45]. Therefore, the percentage of adhesins used in recombinant vector vaccines appears to be much less than that the percentage of protective antigens in bacteria. The implication of such a phenomenon deserves further investigation.

3.5. Vaxvec data query and display

The Vaxvec provides user-friendly web interfaces for users to query and analyze the data stored in the Vaxvec database. Specifically, Vaxvec include three query programs that query three different types of data: recombinant vectors, recombinant vector vaccines, and protective antigens used in recombinant vector vaccines. The results of these three Vaxvec query programs are interlinked as shown in the query example Figure 3. This query example starts with a query of the keyword term “BCG” (Figure 3A). The BCG vaccine vector has been used in nine vaccines (Figure 3B), including a malaria vaccine rBCGMSP1-15 [31] (Figure 3C). This malaria vaccine uses a *Plasmodium yoelii* protein merozoite surface protein 1 precursor (MSP1). The detailed information about the protein is available in another web page (Figure 3D). Therefore, this example demonstrates how the three key query features are interlinked. A user can also start by querying a specific recombinant vector vaccine or a protective antigen directly.

3.6. Vaxvec data sharing

The Vaccine Ontology (VO) is a community-based ontology that logically represents the terms of vaccines, vaccine components (including recombinant vaccine vectors), vaccination, vaccine-induced immune responses, and the relations among these terms [19, 20]. All the recombinant vectors, recombinant vector vaccines, and protective antigens used in these recombinant vector vaccines, and the relations among these terms, have been ontologically represented in VO. Figure 4 provides a demonstration of how VO represents a recombinant vaccine vector ‘canarypox vaccine vector’ (VO_0001043). Developed using the human- and computer-interpretable Web Ontology Language (OWL) format [46], these

VO represented data can be retrieved and processed easily using software programs and applied for different usages.

4. Discussion

To the best of our knowledge, Vaxvec is the first web-based, publically available database and analysis system that targets the curation and analysis of recombinant vaccine vectors, recombinant vector vaccines that use these vectors, and related protective antigens. The data contained in the Vaxvec database are all manually curated. Analysis of Vaxvec data uncovers important statistics and many enriched patterns from these experimentally verified recombinant vaccine vectors, recombinant vector vaccines, and protective antigens.

While we have tried our efforts to annotate as many recombinant vectors and associated vaccines as possible, it is most likely that we have missed many vectors and vaccines reported in the literature. However, our studies have already provided valuable insights about the important topic of recombinant vectors and recombinant vector vaccines. We intend to frequently update our database in the future. In addition to the manual curation method, we will also investigate how computational methods, such as ontology-based literature mining and meta-analysis [19, 47, 48], would improve the database annotations and updates.

The Vaxvec resource may be used for different applications. For example, the records of recombinant vectors and experimentally verified vaccines that use these vectors provide us a basis for designing our future recombinant vector vaccines. The enriched patterns of protective antigens used in these recombinant vector vaccines may also facilitate rational design of protective antigens to be used in recombinant vector vaccine development. In addition, the records stored in Vaxvec may be used to further our systematic understanding of the fundamental mechanisms of recombinant vaccine vectors and recombinant vector vaccines. Current Vaxvec research includes the information of host immune responses and vaccine efficacy against virulent pathogen challenge. However, we have not focused in this paper on the analysis of differential host immune responses for different vectors and vaccines, such as vaccine-induced antibody titers. We will later focus our efforts on the host-side responses to vectors and vaccine administrations. In the era of booming vaccine research, Vaxvec provides a timely repository and platform for advanced research and development of recombinant vaccine vectors and recombinant vector vaccines.

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Figure 1. Vaxvec/VIOLIN workflow and system design

Experimentally verified data of recombinant vaccine vectors, recombinant vector vaccines, protective antigens, is manually annotated from peer-reviewed PubMed publications and stored into the Vaxvec and VIOLIN databases. Vaccine Ontology (VO) IDs assigned for vaccines, vectors, and antigens were used for data sharing and data integration in Vaxvec. An internal program was generated to extract comprehensive citation information using a PubMed ID (PMID) of a referenced paper. The NCBI IDs for the genes, proteins, or nucleotides of protective antigens are identified and used by an internal script to retrieve detailed information about individual protective antigens. DNA and protein sequences were used for COG and Vaxign analyses. Customized BLAST analysis was also generated.

Search:
Keywords: BCG in Any Field
Select: Any or No Pathogen
Search

Index	Vaccine vector name	No. of vaccines using this vector
1	<u>Bacillus Calmette-Guerin vaccine vector</u>	8

(A)

Bacillus Calmette-Guerin vaccine vector

Vaxvec ID	12
Vaccine Vector Name	<i>Bacillus Calmette-Guerin vaccine vector</i>
Alternative Names	BCG, rBCG
Vector VO ID	VO_0001023
Function	BCG is commonly used as a vaccine against tuberculosis, but is also often used as a bacterial vector for HIV
Advantage	Relatively inexpensive to produce, easy to administer, induces strong cellular immune response; antiparasitic may be used against allergic diseases. (Kumar <i>et al.</i> , 1000)
Disadvantage	Induction of persistent tuberculin positivity in vaccinated individuals; necrotic reactions in those in
Storage	Stored by freeze-drying, but stabilization methods need improvement. (Ghoshgiri <i>et al.</i> , 1999)
Safety	Live, attenuated
Related Vaccine(s)	- Recombinant vector vaccine 1. BCG-DHMT (<i>Mycobacterium tuberculosis</i>) 2. rBCG-Sbz2b (<i>Escherichia coli</i>) (<i>Escherichia coli</i>) 3. rBCG-Ag85A/Ag85B (<i>Mycobacterium tuberculosis</i>) 4. rBCG-SINgag (Simian Immunodeficiency Virus) 5. rBCG-SINgag and rBCG-SINgag Prime-boost SHIV vaccine (Human Immunodeficiency Virus) <u>6. rBCGMSP1-15 (<i>Plasmodium</i> spp.)</u> 7. rBCG/pMVAH1-rp-gp (<i>Toxoplasma gondii</i>) 8. C. www.vaxvec.org & BCG3 (<i>Bacillus Calmette-Guerin</i>)

(B)

Vaccine Information

- Vaccine Name: rBCGMSP1-15
- Target Pathogen: *Plasmodium* spp.
- Target Disease: Malaria
- Type: Recombinant vector vaccine
- Status: Research
- Host Species for Licensed Use: Mouse
- Antigen: MSP1-15 as a fusion protein with the α antigen of *Mycobacterium tuberculosis*
- MSP1 from *P. yoelii* str. 17XNL gene engineering:
  - Type: Recombinant vector construction
  - Description: A 2.4-kbp fragment containing an α -k-MSP1-15 (Matsumoto *et al.*, 1998).
  - Detailed Gene Information: [Click Here](#)
- Vector: BCG vaccine vector
  - Vector name: BCG vaccine vector
  - VO vector ID: VO_0001023
- Immunization Route: Intravenous injection (i.v.)

(C)

Host Response

Mouse Response

- Host Strain: C57BL/6, C3H/He, A/J
- Host gender: Female
- Vaccination Protocol: C3H/He mice were immunized intravenously with PBS-T80 or PBS-T80 only. 30 days later, the same amount of each vaccine was injected intravenously.
- Vaccine Immune Response Type: VO_0003057
- Challenge Protocol: Mice were challenged with 10^4 *P. yoelii* 17XNL.
- Efficacy: 3 out of 7 mice immunized with GST-MSP1-15 in RAS and PBS-T80 showed no parasitemia. Data showed the three adjuvants examined are effective for vaccination.

References

Matsumoto *et al.*, 1998: Matsumoto S, Yukitake H, Kanbara H, Yamakura T. Malaria parasite infection depending on MSP1-stimulated interferon gamma production in mice.

(D)

Gene Name MSP1 from *P. yoelii* str. 17XNL

Sequence Strain (Species/Organism)	<i>Plasmodium yoelii</i> yoelii str. 17XNL
VO ID	VO_0011212
NCBI Gene ID	3791597
NCBI Protein GI	82596427
Locus Tag	PY05748
Genbank Accession	AABL01001865
Protein Accession	XP_726257
Taxonomy ID	352914
Gene Starting Position	990
Gene Ending Position	6308
Gene Strand (Orientation)	-
Protein pl	5.05
Protein Weight	188296.05
Protein Length	1772

>ref|NW_863564.3|:990-6308
TTTAAATATATTAATACAATTAAT
ACAGAAATACACCTTCATATATGAT
TCCGATCTTCCGATTTTGACACT
TATATTTTTCAGACATGATTAACCT
ATTATCATCTCTAAACATCCAGCAT
ACACCTAATAATCCATCAATCCAT
CTAAACCATGATTATTAGTTGTTT
AAATCCGCAAGTTTTCCTCAATT
TTTCATTTTATAATTAATCAATCT
TTTCATATATCTTTAAGATCTCA
AGTTTCAGCTCTATGGTAGCAATT
TTGTTAAAGATTATTCCTGCAAT

Figure 3. Example of Vaxvec queries for vaccine vector, vaccine, and protective antigen information

(A) The vaccine vector name “BCG” is queried in Vaxvec. (B) Resulting vaccines in Vaxvec. (C) Detailed information for one recombinant vector vaccine rBCGMSP1-15. (D) The information for the gene (MSP1) used in the vaccine generation.

Figure 4. VO representation of ‘canarypox vaccine vector’

This is an example demonstration of how VO represents a recombinant vaccine vector. The figure was generated as a screenshot from the Ontobee [49] website (http://purl.obolibrary.org/obo/VO_0001043).

Table 1

Selected vaccine vectors and their associated vaccines in Vaxvec

vector name	NCBI Taxonomy ID	VO ID	Vaxvec ID	No. of Vaccines
Viral vaccine vectors (in total 41), selected:				
ALVAC vv	-	VO_0001128	77	17
Fowlpox virus vv	-	VO_0001040	21	14
NYVAC vv	10249	VO_0001093	37	9
Baculovirus vv	10469	VO_0001084	19	7
complex adenovirus vv	-	VO_0001086	36	7
ORF virus vv	10258	VO_0001108	68	6
herpesvirus of turkey vv	37108	VO_0001067	43	6
Vesicular stomatitis virus vv	11276	VO_0001025	11	5
Newcastle disease virus vv	11176	VO_0001060	44	4
vaccinia virus Tian Tan (MVT) vv	10253	VO_0001109	69	4
Vaccinia vv	10245	VO_0000600	32	4
Raccoon poxvirus vv	10256	VO_0001048	67	4
Bacterial vaccine vectors (in total 15), selected:				
BCG vv	33892	VO_0001023	12	8
<i>Salmonella typhimurium</i> SL3261 vv	-	VO_0001031	17	6
<i>Vibrio cholerae</i> vv	666	VO_0001044	46	4
<i>Brucella abortus</i> RB51 vv	1198700	VO_0000020	13	3
Fungal vaccine vectors (in total 1):				
<i>Saccharomyces cerevisiae</i> vv	4932	VO_0001122	76	2
Parasitic vaccine vectors (in total 1):				
<i>Leishmania tarentolae</i> vv	5689	VO_0001028	29	3

Note: *: vv represents “vaccine vector”. The complete list of recombinant vaccine vectors is available here: http://www.violinet.org/vaxvec/stat.php?order_by=num_vaccine&order=DESC.

Table 2

Recombinant vector vaccines annotated in Vaxvec

Pathogen or disease	No. of pathogen species or diseases	No. of recombinant vector vaccines
Viruses	40 (total)	136 (total)
Virus examples:		
Influenza virus	1	34
HIV	1	12
Ebola virus	1	10
Bacteria	17 (total)	33 (total)
Bacteria examples:		
<i>M. tuberculosis</i>	1	4
<i>A. pleuropneumoniae</i>	1	4
<i>B. pertussis</i>	1	3
Parasites	8 (total)	18 (total)
Parasite examples:		
<i>Plasmodium</i> spp.	1	7
<i>Leishmania major</i>	1	2
Cancer	1	8
Total	66	196 (total)

Table 3

Poxvirus vector vaccines collected in Vaxvec

#	Pathogen	Vaccine name	Antigen	Animal (efficacy)	Refs (PMID)
ALVAC vaccine vector					
1	African horse sickness virus	ALVAC-AHSV	VP2 and VP5	horses (++)	19490959
2	Bluetongue virus	ALVAC-BTV-VP2/VP5	VP2 and VP5	sheep (++)	17059856
	Cancer	ALVAC-P53	p53	mice (+)	8643480
3	Canine distemper virus	ALVAC-CDV-H/F	H and F	ferrets (+)	10864646
4	Equine influenza virus	ALVAC-EIV	HA	horses (+)	16621023
5	Feline leukemia virus	ALVAC-FL-env/gag	env and gag	cats (++)	8383248
6	HIV	ALVAC-HIV-2	env, gag and pol	monkey (+)	11413371
7	Influenza virus (H5N1)	ALVAC-ALH5	HA	pigs (+)	19428840
8	JEV	ALVAC-JEV	prM, E, and NS1	rhesus monkeys (++)	10466959
9	Measles virus	ALVAC-MV-HA/F	HA and F glycoproteins	dogs (+)	1736535
10	Nipah virus	ALVAC-NiV-G	NiV glycoprotein	pigs (++)	16873250
11	Nipah virus	ALVAC-NiV-F	NiV fusion protein	pigs (+)	16873250
12					
13	West Nile virus	ALVAC-WNV-prM/E	prM and E	dogs & cats (+)	15893618
14	West Nile virus	ALVAC-WNV-prM/E	prM and E	horses (++)	17687109
15	Rabbit hemorrhagic disease virus	ALVAC-RHDV (vCP309)	capsid protein	rabbits (++)	9041672
16	Rabies virus	ALVAC-RV	glycoprotein G	cats (++)	23059358
Capripoxvirus vaccine vector					
17	Bluetongue virus	rCPV-BTV-Cpox	VP2, VP7, NS1 & NS3	goats (+)	17669563
18	Peste des petits ruminants	rCPV-PPR	glycoproteins H or F	sheep (++)	24837763
19	Peste des petits ruminants	rCPV-PPRVH	H and F	goats & sheep (++)	20471441
Fowlpox virus vaccine vector					
20	Classical swine fever virus	rFPV-CSFV-E0	E0	mice and piglets (+)	18320824
21	Hemorrhagic enteritis virus	rFPV-HEV	hexon of HEV	turkeys (++)	10396636

#	Pathogen	Vaccine name	Antigen	Animal (efficacy)	Refs (PMID)
22	IBDV	FP-IBDV-VP2	VP2	chickens (+)	23644721
23	IBDV	rFPV-IBDV-VP2	VP2	chickens (+)	10753704
24	IBDV	rFPV-IBDV-VP 2,4,3	VP 2, VP4 and VP3	chickens (+)	8394069
25	Infectious laryngotracheitis virus	FPV-LT vaccine	gD and gI	chickens (+)	22845318
26	Infectious laryngotracheitis virus	rFPV-ILTV	gD and gI	chickens (+)	21313847
27	Influenza virus (H5N1)	vFP89-H5	HA	ducks (++)	23845804
28	Influenza virus (H5N1)	rFPV-AI-H5A-IL6	HA	cherry valley ducks (+)	22902682
29	Influenza virus (H5N8)	vFP89-HA	HA	chickens (++)	20521642
30	Influenza virus (H5N1)	rFPV-H5AI-L2	HA	chickens (++)	20077933
31	Influenza virus (H5N1)	Trova-AI-H5	HA	pigs (+)	19428840
32	Newcastle disease virus	rFPV-NDV-H/F	HA and NA	chickens (++)	2167557
33	<i>Plasmodium berghei</i>	rFP9-Malaria-CSP	CSP	mice (+)	17908809
34	Canine distemper virus	rFP-RPV-H/F	H and F	ferrets (+)	9185963
Modified Vaccinia Ankara (MVA) virus vaccine vector					
35	African horse sickness virus	rMVA-AHS-VP2	VP2	mice (++)	21298069
36	CCHFV	rMVA-CCHF	Gn and Gc	mice (++)	24621656
MVTT vaccine vector					
37	Cancer	rMVTT-HPV16-E6/E7	mutated HPV16 E6 and E7	mice (+)	12665900
38	CCHFV	rMVA-CCHF	envelope glycoprotein	mice (+)	24621656
39	Chikungunya virus	MVA-CHIKV	C, E3, E2, 6K, and E1	mice (++)	24403588
40	HIV	rMVTT-SIV-gpe	Gag, Pol, and Env	rhesus monkeys (+)	23487457
41	HIV	rMVA-SIV-CD40L	Env	rhesus macaques (+)	24920805
42	Influenza virus (H5N1)	rMVTT-HA-QH(H5N1)	HA	mice (++)	24358269
43	<i>Plasmodium vivax</i>	MVA-PvTRAP	TRAP	mice (+)	24379295
44	Rift Valley fever virus	rMVA-GnGc	Gn and Gc	lambs (+)	24933081
NYVAC					
45	Canine distemper virus	NYVAC-CDV-H/F	H and F	ferrets (+)	10864646
46	HIV-2	NYVAC-HIV-2	env and gag-pol	rhesus macaques (+)	11101054

#	Pathogen	Vaccine name	Antigen	Animal (efficacy)	Refs (PMID)
47	Equine herpesvirus-1	NYVAC-EHV-1-vP1014	gene 64	ponies (+)	16269205
48	HIV	NYVAC-SIV	gag, pol, and env	macaques (+)	9557706
49	JEV	NYVAC-JEV	prM, E, and NS1	rhesus monkeys (++)	10466959
50	JEV	NYVAC-JEV-prM/E/NS1	prM, E, and NS1	pigs (+)	1326813
51	<i>Plasmodium berghei</i>	NYVAC-CSP	CSP	mice (+)	8613376
52	<i>Plasmodium falciparum</i>	NYVAC-Pf7	7 <i>P. falciparum</i> genes	humans (+)	9607847
53	Pseudorabies virus	NYVAC-PRV-gII/ gp50	gII and gp50	pigs (+)	8904669
Other vaccinia virus vaccine vector					
54	Rinderpest virus	v2RVFV	H and F	cattle (++)	11752138
55	Influenza virus	dVV-HA5(H5N1)	HA	mice (++)	19279103
Raccoon poxvirus vaccine vector					
56	Influenza virus(H5N1)	RCN-HA (H5N1)	HA	mice (++)	22921740
57	Rabies	RCN-rabies-G	glycoprotein G	cats (+)	15203914
58	<i>Yersinia pestis</i>	RCN- F1-V	F1 and V	dogs (+)	20158332
59	<i>Yersinia pestis</i>	RCN-IRES-tPA-YpF1	F1 protein	mice (+)	12559803
Swinepox virus vector					
60	Influenza virus (H1N1)	rSPV-HA1	HA	pigs (++)	22391400
61	Influenza virus H1N1/H3N2	rSPV/H3-2A-H1	HA of H1N1 & H3N2	pigs (++)	23135159
62	Porcine circovirus 2	rSPV-PCV2-CAP	ORF2	pigs (+)	22884664
63	<i>Streptococcus suis</i>	rSPV-MRP	truncated MRP	mice (+)	22515033

Abbreviations: +: partial protection; ++: Complete protection. JEV: Japanese encephalitis virus, IBDV: Infectious bursal disease virus, CCHFV: Crimean-Congo Haemorrhagic Fever virus

Table 4

Recombinant vector influenza vaccines annotated in Vaxvec

#	Strain	Vaccine names	Vector names	Animal (Efficacy)	References (PMID ID)
1	H1N1	AchERV-sH1N1-HA	Baculovirus vv	pigs & mice (++)	24260476
2	H5N1/H7N2/ H9N2	BV-H5/H7/H9	Baculovirus vv	ferrets (+)	23618102
3	H1N1	BPZE1-FHA (H1N1)	<i>B. pertussis</i> BPZE vv	mice (+)	21624415
4	H3N2	rPIV5-H3 (H3N2)	Bovine parainfluenza virus vv	mice (+)	17254623
5	H3N8	ALV/AC-EIV (H3N8)	Canarypox vv	ponies (+)	16621023
6	H5N1	ALV/AC-AI-H5	Canarypox vv	pigs (+)	19428840
7	H5N1	rDEV-re6 (H5)	Duck enteritis virus vv	broilers (+)	23267833
8	H5N1	rDEV-us78HA	Duck enteritis virus vv	ducks (++)	21865383
9	H5N1	vFP89-H5	Fowlpox virus vv	ducks (++)	23845804
10	H5N1	rFPV-AL-H5A-IL6	Fowlpox virus vv	ducks (+)	22902682
11	H5N8	vFP89-HA (H5N1)	Fowlpox virus vv	chickens (++)	20521642
12	H5N1	vPF221	Fowlpox virus vv	chickens (++)	20521642
13	H5N1	rFPV-H5A1-L2	Fowlpox virus vv	chickens (++)	20077933
14	H5N1	Trovac-AI-H5	Fowlpox virus vv	pigs (+)	19428840
15	H5N1	rHVT-H5	herpesvirus of turkey vv	chickens (+)	23402113
16	H5N1	rHVT-H5 (H5N1)	herpesvirus of turkey vv	chickens (+)	23402112
17	H5N1	rMVT-HA-QH	MVTT vv	mice (++)	24358269
18	H5N1	MVTT-HA-QH	MVTT vv	mice (++)	24358269
19	H6N2	rNDV-H6	Newcastle disease virus vv	chickens & turkeys (+)	21793434
20	H5N1	rNDV-H5	Newcastle disease virus vv	chickens (+)	24320551
21	H5N1	rNDV-H5 (H5N1)	Newcastle disease virus vv	ducks (++)	23402116
22	H5N1	rORFV-D1701-V- HA5n (H5N1)	ORF virus (parapoxvirus) vv	mice (+)	24376753
23	H5N1	PAV3-HA (H5N1)	Porcine adenovirus 3 vv *	mice (+)	21179494
24	H1N1	Pv-HA (H1N1)	Pseudorabies virus vv	pigs (+)	24431235
25	H5N1	RCN-HA (H5N1)	Raccoon poxvirus vv	mice (++)	22921740
26	H7N7	RSV-H7	Rous sarcoma virus vv	chickens (++)	2839718
27	H1N1	rSPV-HA1 (H1N1)	Swinepox virus vv	pigs (++)	22391400
28	H1N1/H3N2	rSPV/H3-2A-H1	Swinepox virus vv	pigs (+)	23135159

#	Strain	Vaccine names	Vector names	Animal (Efficacy)	References (PMID ID)
29	H1N1	rVEE-HA (H1N1)	VEE vv	mice (++)	8648713
30	H5N1	VSV* G-H5 (H5N1)	Vesicular stomatitis virus vv	chickens (++)	24874923

Abbreviations: *: vv represents “vaccine vector”. +: partial protection. ++: Complete protection

Table 5

Vaccine antigens in Vaxvec with predicted adhesin or adhesin characteristics

#	Antigen	Pathogen	Vaxge n ID	RefSeq / GenBank	Location	Vaccine name	Vector
1	S1	Infectious bronchitis virus	1673	AAV52771.1	Extracel.	Ac-CMV-S1	baculovirus vv
2	gp70	Feline leukemia virus FeLV	1411	AAB30310.1	Unknown	ALVAC-FL-env/gag	ALVAC vv
3	E	Japanese encephalitis virus	554	AAK31640.1	Unknown	NYVAC-JEV-prM/E/ NS1	NYVAC vv
4	VP60	Rabbit hemorrhagic disease virus	1669	CAA80883.1	Extracel.	rORFV-RHDV-VP60	ORF virus vv
5	E	West Nile virus	590	ABH06950.1	Unknown	ALVAC-WNV-PrM/E	ALVAC vv
6	PspA	<i>Streptococcus pneumoniae</i>	620	YP_815641.1	OM	pspA-rBCG	BCG vv
7	Ag85B	<i>M. tuberculosis</i>	118	NP_216402.1	Periplasm	LT-BCG-Ag85B /Rv3425	Lentivirus vv
8	GP	Zaire ebolavirus	452	NP_066246.1	Extracel.	AdC7-ZGP	chimpanzee adenovirus vv
9	Ag85A	<i>M. tuberculosis</i>	154	NP_218321.1	Periplasm	rBCG-Ag85A/ Ag85B	BCG vv
10	VP7	Murine rotavirus	676	AAA50493.1	Unknown	HSV1[VP7/6/2]	HSV-1 vv
11	VP2	Infectious bursal disease virus	1636	AAP84370.1	Unknown	rFPV-IBDV-VP2	fowlpox vv
12	P97	<i>Mycoplasma hyopneumoniae</i>	1062	YP_115696.1	OM	rAd-P97c	porcine adenovirus 3 vv
13	VP60	Rabbit hemorrhagic disease virus	1669	CAA80883.1	Periplasm	RB51-SRS2	RB51 vv

Note: All antigens have a predicted adhesin probability > 0.51. Extracel.: Extracellular.