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# PATENT LANDSCAPING EXEMPLAR REPORT: EBOLA VACCINES

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# 1 INTRODUCTION

Patent documents provide a wealth of commercially relevant information and patent landscaping aims to provide an overview of a particular technology area. Patent information can be largely disordered and with high volume of data across many territories, it can be overwhelming to find and extract meaningful and relevant information. Patent landscaping provides a visual and informative way to gauge the extent of activity of patenting in a particular technology area.

At IP Pragmatics, we use patent landscaping tools to help us to analyse the patent situation across a particular technology field. Our clients have used landscaping for a wide variety of reasons:


Patent landscaping analysis can be used to inform a number of activities; for example landscaping can be performed prior to filing a patent application to be aware what patents have been filed and the type of claims which are being granted. This can feed into the tactical preparation and filing of related patents, as well as informing general IP strategy.

A typical patent landscaping report can be used to understand:

- What are the overall trends in patenting in this field over time, territory, application area?
- Which are the major companies and universities patenting in this chemical class?
- How does their patenting strategy compare with that of their major competitors?
- Which application areas may the technology be used for?
- Which fields are being exploited by which companies?
- Where does the company's portfolio currently sit in the landscape?
- Where are there potential in-licensing opportunities to strengthen the patent protection of the client?
- Where are there out-licensing opportunities to generate additional revenue for the company?

The analysis can also give an initial indication of patentability for early-stage technologies and analyse the freedom to operate in a particular technology sector.

## 2 EXECUTIVE SUMMARY

The purpose of this report is to give an example of commercially valuable information which can be gained through patent landscapes. This exemplar project examines the patenting environment protecting Ebola vaccines as of searches conducted in September 2016.

Ebola is a viral infectious disease which has gained increasing research and development attention in light on the epidemic outbreak of the disease in West Africa in 2014. A number of vaccines are in development for immunity to Ebola virus and possibly for providing post-exposure protection. The pipeline consists of a number of different platform delivery technologies.

This report aims to understand the broad patent landscape for patent application filings relating to Ebola virus vaccines. The first section of the report looks at the patent publishing trends in the sector over time, the top International Patent Classification (IPC) codes, the number of patents by top assignees, highly cited patents, top inventors, countries in which patent applications have been filed and countries from which patents have claimed priority.

In addition a patent landscape map has been analysed in terms of generation of a contour map based on the use of different technical terms in the set of related patents, and plots these patents on the map. Peaks on the map pertain to frequently used terms and indicate the matter of patents in close proximity. The maps enable a clear understanding of where patents and their assignees are positioned in relation to each other and the technical area they are covering.

Sub-searches of the broad patent landscape were conducted to drill deeper down into the trends around different vaccine delivery platforms for Ebola virus, notably:

- Adenovirus vectors
- Vesicular Stomatitis Virus (VSV) vectors
- Virus-Like Particles (VLP)

Each sub-search was analysed in terms of top publishing trends per year, the number of patents by top assignees, countries in which patent applications have been filed and their position on the landscape map.

The final section of the report looks at the patents for the vaccines which are in the later stages of development, these companies and vaccines are:

- Merck - VSV-EBOV (V-920)
- GlaxoSmithKline - ChAd3-ZEBOV
- Johnson & Johnson - Ad26-EBOV & MVA-EBOV

## 3 EBOLA BACKGROUD AND MARKET

Vaccines are essential to reduce the burden of a wide variety of diseases and can be also used preventatively. The global vaccine market was valued at $34.1 billion in 2015. The market is poised to reach approximately $45.2 billion by 2021, growing at a compound annual growth rate (CAGR) of 6.3% from 2016 to 2021.[1] Growth is attributed to a number of factors including new products to meet unmet needs, improving economic conditions of developing countries and increased investment by major pharmaceutical companies. In addition, continuous improvements in vaccine design, delivery technologies and manufacturing will also help in market growth.

One such example of unmet need for vaccine development is for the Ebola virus. The virus has been the focus of intense research activity in the past few years in response to the outbreak in Western Africa in 2014. The virus first occurred in 1976 and since then five different subtypes of the Ebola virus have been identified across Africa.[2] The US Centre for Disease Control and Prevention (CDC) has reported has reported that the total number of cases was 28,616 in the hardest hit countries of Guinea, Sierra Leone and Liberia, which resulted in 11,310 deaths.[3]

Whilst the outbreak in West Africa was declared officially "over" by the WHO in March 2016, vaccine development is still key to prevent further outbreaks. At the time of writing, no vaccine has been approved by the US Food and Drug Administration (FDA) for protection against the Ebola vaccine virus in humans. There are, however, a number of vaccines which are currently in the pipeline. The pipeline is not limited to one platform technology with examples of DNA vaccines, virus-like particles (VLP) and viral vectors being developed. Within the viral vectors segment there are also different approaches being utilised including live replicating vesicular stomatitis virus (rVSV), adenovirus and vaccinia virus.

The vaccines which are in the latest stages of development are Ad26.ZEBOV (Johnson & Johnson / Bavarian Nordic), ChAd3-EBO-Z (GSK / NIAID) and rVSV-ZEBOV (Merck / NewLink / Public Health Agency of Canada).

The following table outlines vaccines for Ebola virus which are in development:

[1] BCC Research - Global Markets for Vaccine Technologies, January 2017.

[2] Haaris A. Shiwani, Rebabonye B. Pharithi, Barkat Khan, Christian Binoun-A Egom, Peter Kruzliak, Vincent Maher, Emmanuel Eroume-A Egom, An update on the 2014 Ebola outbreak in Western Africa, Asian Pacific Journal of Tropical Medicine, Volume 10, Issue 1, January 2017, Pages 6-10

[3] Centres for Disease Control and prevention. 2014 Ebola outbreak in West Africa - case count. [Online] Available from: www.cdc.gov/vhf/ebola/outbreaks/2014-west-africa/case-counts.html [Last Accessed - 23 March 2017]

| Product | Company | Clinical Trial Phase |
|---|---|---|
| **ChAd3-ZEBOV (Chimp adenovirus 3 vectored glycoprotein)** | GlaxoSmithKline and US National Institute of Allergy and Infectious Diseases (NIAID) | Phase I - Completed<br>Phase II – Underway<br>Phase III – Underway |
| **VSV-EBOV (rVSV vectored glycoprotein) V-920** | Merck Vaccines USA (Licensed from NewLink Genetics Corp; Public Health Agency of Canada) | Phase I – Completed<br>Phase II – Underway<br>Phase III – Underway<br>Also, in use for flare ups in North Africa |
| **Ad26-EBOV & MVA-EBOV** | Johnson & Johnson and Bavarian Nordic | Phase I - Completed<br>Phase II – Completed<br>Phase III – Underway |
| **An unnamed recombinant protein Ebola vaccine candidate** | Novavax | Phase I – Underway |
| **GamEvac/GamEvac Combi (HPIV-3 vectored glycoprotein)** | Russian Federal Ministry of Health | Phase I – Underway |
| **An unnamed oral adenovirus platform vaccine** | Vaxart | Under development |
| **An unnamed vesicular stomatitis virus candidate (VesiculoVax Prophylactic Vaccine)** | Profectus Biosciences | Phase I – Underway |
| **An unnamed alternative recombinant protein** | Protein Sciences | Under development |
| **An unnamed DNA vaccine** | Inovia | Under development |
| **An unnamed recombinant rabies vaccine ((Ebola [Zaire] + rabies) (bivalent) vaccine)** | Exxell BIO Inc (licensed from Thomas Jefferson University & US National Institute of Allergy and Infectious Diseases (NIAID) | Preclinical development stage |
| **Human adenovirus 5 vectored 2014 glycoprotein insert** | Beijing Institute of Biotechnology (BIT) & Tianjin CanSino Biotechnology Inc | Phase I – Completed<br>Phase II - Underway |
| **Ebola ΔVP30 H2O2 treated (Whole virus vaccine)** | University of Wisconsin | Under development |
| **Nasal Vaccine** | University of Texas Austin ( Developed in collaboration with the Public Health Agency of Canada | Preclinical development stage |
| **INO-4212 (polyvalent DNA vaccine)** | Inovio Pharmaceuticals Inc (exclusive worldwide license agreement with the University of Pennsylvania) | Phase I – Underway |
| **DPX-Ebola** | Immunovaccine Inc | Preclinical development stage |
| **Recombinant Vector EbolaVaccine** | Etubics Corp | Preclinical development stage |

| Product | Company | Clinical Trial Phase |
|---|---|---|
| **GOVXE-301 / GOVXE-302 / GOVXE-303** | GeoVax Labs Inc | Preclinical development stage |
| **Ebola vaccine** | Soligenix Inc (collaboration agreement with University of Hawaii at Manoa (UH Manoa) and Hawaii Biotech, Inc. (HBI)) | Preclinical development stage |
| **Ebola vaccine based on Ac-DEX (Acetalated Dextran) nanoparticle platform technology** | Peptineo | Preclinical development stage |
| | BioComo Inc. | Candidate development |
| **mRNA-based ebola vaccine** | Massachusetts Institute of Technology | Preclinical development stage |
| **PIKA adjuvant-based ebola vaccine & FiloGP-Fc Subunit Vaccine** | US Army Medical Research Institute of Infectious Diseases (In collaboration with Yisheng Biopharma) | Preclinical development stage |

Table: Vaccines currently under development for Ebola. Complied based on information from the World Health Organisation (WHO)[4] and GlobalData.

[4] http://www.who.int/medicines/emp_ebola_q_as/en/

## 4 METHODOLOGY

IP Pragmatics has access to a range of proprietary and subscription patent databases and landscape analytical tools. For search and patent landscape analysis IP Pragmatics' subscribe to Derwent Innovation (formally Thomson Innovation).

A search strategy is typically constructed following a review of the technology area with the client and our comprehensive searches of public domain records (e.g. publications) and patent records to identify relevant patent publications for Ebola virus vaccines. A series of key words are used to search patent databases to allow for the broadest and yet most relevant patent set, this ensure all potentially relevant patents are captured.

The following document collections were searched:

Full Text: US Granted; US Applications; European Granted; European Applications; WIPO Applications; Australian Innovation; Australian Granted; Australian Applications; British Granted; British Applications; Canadian Granted; Canadian Applications; French Granted; French Applications; German Utility Models; German Granted; German Applications

Bibliographic: Japanese Applications; Korean Granted/Examined; Korean Applications; Other Authorities (covered by INPADOC); plus enhanced Derwent World Patent Index (DWPI) data fields

Sub-searches are then conducted, further utilising key words to identified a smaller number of patents which are more closely related to a particular are, in this case vaccine delivery technologies of adenoviral vectors, virus like particles and vesicular stomatitis virus.

For the mapping, we use Thomson Innovation's proprietary ThemeScape™ mapping tool. ThemeScape™ uses term frequency and other algorithms to cluster documents based on shared language. The text from one record is compared with the text from all other patent records within the search collection. The outcome of this analysis is a visualisation of the patent space with each patent (dot) represented once in the map, with patents in close proximity sharing more phraseology than those located apart. The patents are grouped into map "contours" to show areas of high and low patenting activity organised into common themes. The illustration shows these contour lines, with the "mountain peaks" representing a concentration of patents. Each peak is labelled with the key terminology concepts contained in the patents within the cluster.

**It should be noted that this analysis is not intended as a legally binding opinion on freedom to operate or patentability. Instead it aims to provide an overview patent landscape analysis through identifying the complexity of the patent landscape in order to identify competing approaches and third party patents that may need to be considered.**

## 5 PATENT SEARCH PARAMETERS: EBOLA VACCINES - BROAD LIST

The following broad string was drafted utilising key search terms to identify the overall landscape for innovation across vaccines for Ebola using IP Pragmatics' subscription landscape tool, Thomson Innovation.

The following document collections were searched:

Full Text: US Granted; US Applications; European Granted; European Applications; WIPO Applications; Australian Innovation; Australian Granted; Australian Applications; British Granted; British Applications; Canadian Granted; Canadian Applications; French Granted; French Applications; German Utility Models; German Granted; German Applications

Bibliographic: Japanese Applications; Korean Granted/Examined; Korean Applications; Other Authorities (covered by INPADOC); plus enhanced Derwent World Patent Index (DWPI) data fields

The following search string was used to search the above collections:

CTB=(((Ebola ADJ Virus) OR (Ebola ADJ (hemorrhagic OR haemorrhagic) ADJ fever) OR ebolaviruses OR Ebola) AND vaccine) AND DP>=(19940101);

CTB means that the key words were searched within the title, abstract and claims of the above patent databases. DP means publication date of the application from 01/01/1994 to the date the search was conducted on 19/08/2016.

This search generated a list of **568 INPADOC families** (2356 individual cases).

# 6 PATENT SEARCH ANALYSIS: EBOLA VACCINES FILING TRENDS

## 6.1.1 TOP INTERNATIONAL PATENT CONVENTION (IPC) CODES

### TOP IPC – GENERAL

The International Patent Classification (IPC) provides a hierarchical system of language independent symbols for the classification of patents and utility models according to the different areas of technology to which they pertain. The IPC divides technology into eight sections with approximately 70,000 subdivisions. The appropriate IPC symbols are indicated on each patent document, of which more than 1,000,000 were issued each year in the last 10 years.

In order to verify the relevance of the patents listed, and to look in more detail at the areas of technical focus shown in the landscape map, an analysis of top 10 current IPC codes from the broad list was performed (see table below). As mentioned above, IPC codes are a mechanism of categorising the patents by detailed subject matter and have been used in part to frame the BROAD list via the initial searches, so there will be some bias towards the top-level codes used in the search in these results.

Each patent is typically classified according to one or a few IPCs as they may cover one or a number of technology fields. The top 10 IPC listing highlights and explains those IPC codes that have most frequently occurred within the patent families listed:

| Ranking | Top 10 IPC | Definition |
|---|---|---|
| **#1** | A61K003900 | **A61K** – Human Necessities /Medical or Veterinary Science; Hygiene / Preparations for Medical, Dental, or Toilet Purposes<br>**39/00** – Medicinal preparations containing antigens or antibodies |
| **#2** | A61K003912 | **A61K** – As above<br>**39/12** – Medicinal preparations containing antigens or antibodies / Viral antigens |
| **#3** | A61P003112 | **A61P** – Human Necessities / Medical or Veterinary Science; Hygiene / Specific Therapeutic Activity of Chemical Compounds or Medicinal Preparations<br>**31/12** – Antiinfectives, i.e. antibiotics, antiseptics, chemotherapeutics / Antivirals |
| **#4** | A61P003500 | **A61P** – As above<br>**35/00 –** Antineoplastic agents |
| **#5** | A61K003939 | **A61K** – As above<br>**39/39 –** Medicinal preparations containing antigens or antibodies / characterised by the immunostimulating additives, e.g. chemical adjuvants |
| **#6** | A61K0039395 | **A61K** – As above<br>**39/395 -** Medicinal preparations containing antigens or antibodies / Antibodies (agglutinins A61K 38/36); Immunoglobulins; Immune serum, e.g. antilymphocytic serum |
| **#7** | A61K004800 | **A61K** – As above<br>**48/00 -** Medicinal preparations containing genetic material which is inserted into cells of the living body to treat genetic diseases; Gene therapy |

| Ranking | Top 10 IPC | Definition |
|---|---|---|
| **#8** | C12N000700 | **C12N –** Chemistry; Metallurgy / Biochemistry; Beer; Spirits; Wine; Vinegar; Microbiology; Enzymology; Mutation Or Genetic Engineering / Micro-Organisms Or Enzymes; Compositions Thereof ; Propagating, Preserving, Or Maintaining Micro-Organisms; Mutation Or Genetic Engineering; Culture Media<br>**7/00 –** Viruses, e.g. bacteriophages; Compositions thereof; Preparation or purification thereof |
| **#9** | A61P003704 | **A61P** – As above<br>**37/04 –** Drugs for immunological or allergic disorders / Immunomodulators - Immunostimulants |
| **#10** | A61K003921 | **A61K** – As above<br>**39/21 –** Medicinal preparations containing antigens or antibodies / Viral antigens / Retroviridae, e.g. equine infectious anemia virus |

**Table 1.** List of international patent classification codes relating to Ebola vaccines.

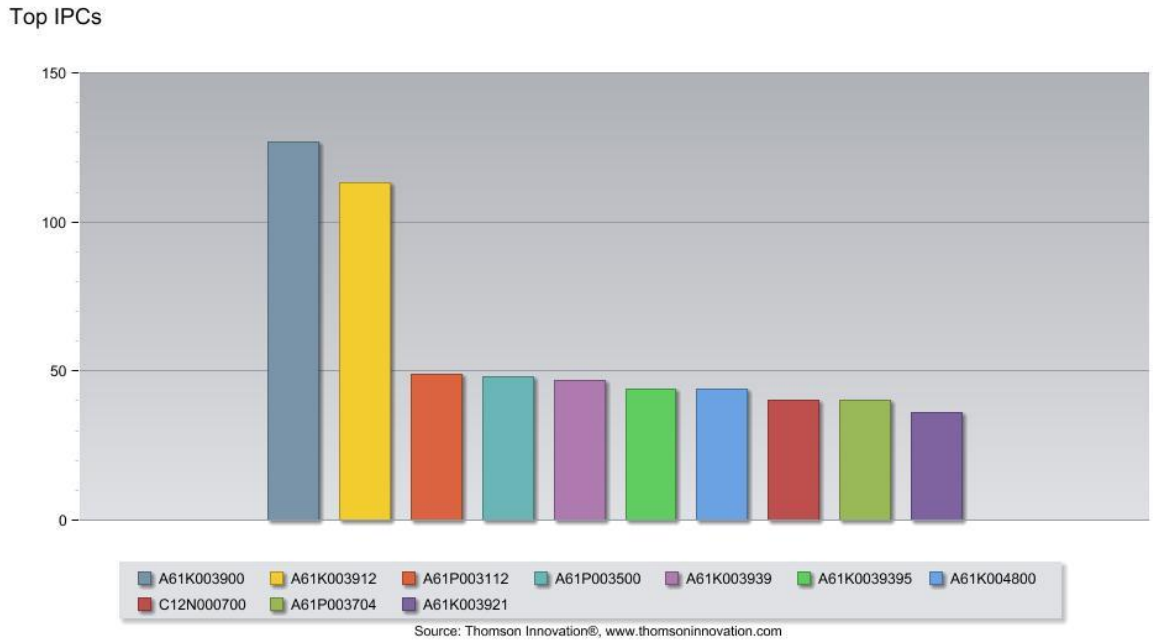



**Figure 1.** Top IPCs across the broad Ebola vaccine patent landscape.

Most of the top 10 IPCs relate to medical preparations which contain antigens and antibodies, as is the basis of most vaccines. The top 2 IPCs with over 100 families each cover antigen and antibodies for medicinal purposes, both generally and specifically for viral antigens. Other sub-categories which relate to antibodies and antigens include immunostimulating additives such as chemical adjuvants, immunoglobulins, immune serum and antigen/antibody introduction through gene therapy approaches. Other IPCs relate to alternative vaccine strategies including Antivirals which are able to induce a mimicked immune response, such as using mRNA or DNA and attenuation of live viruses. Although the category relation to reteroviridae antigens doesnot appear to be directly relevant, it appears to cover vaccine strategies for both Ebola and retroviruses.

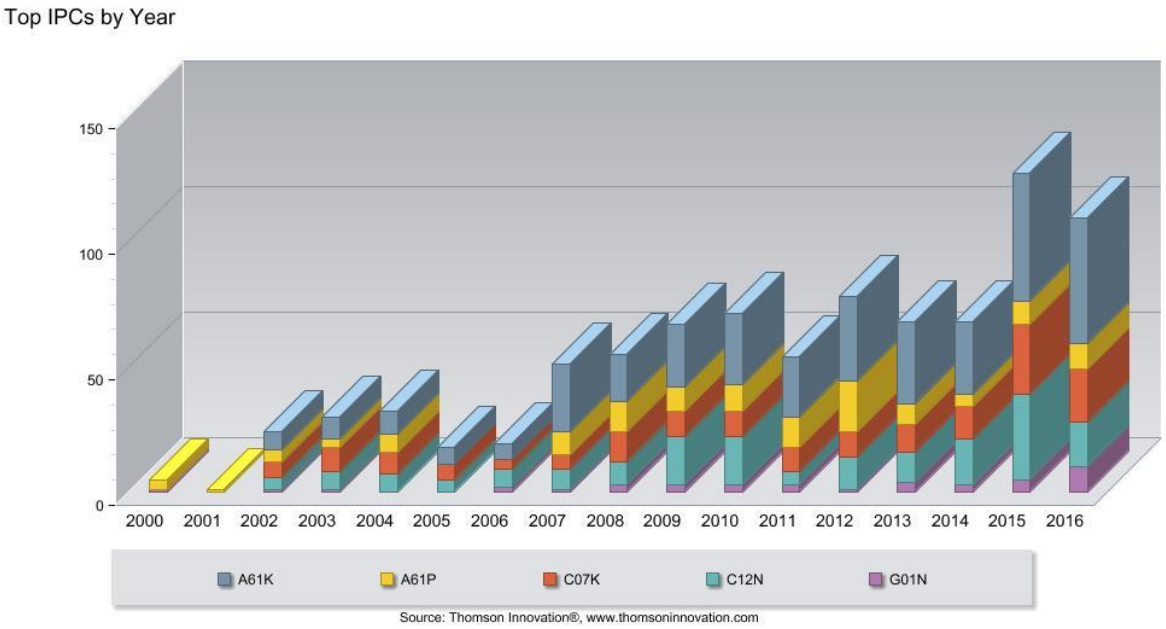
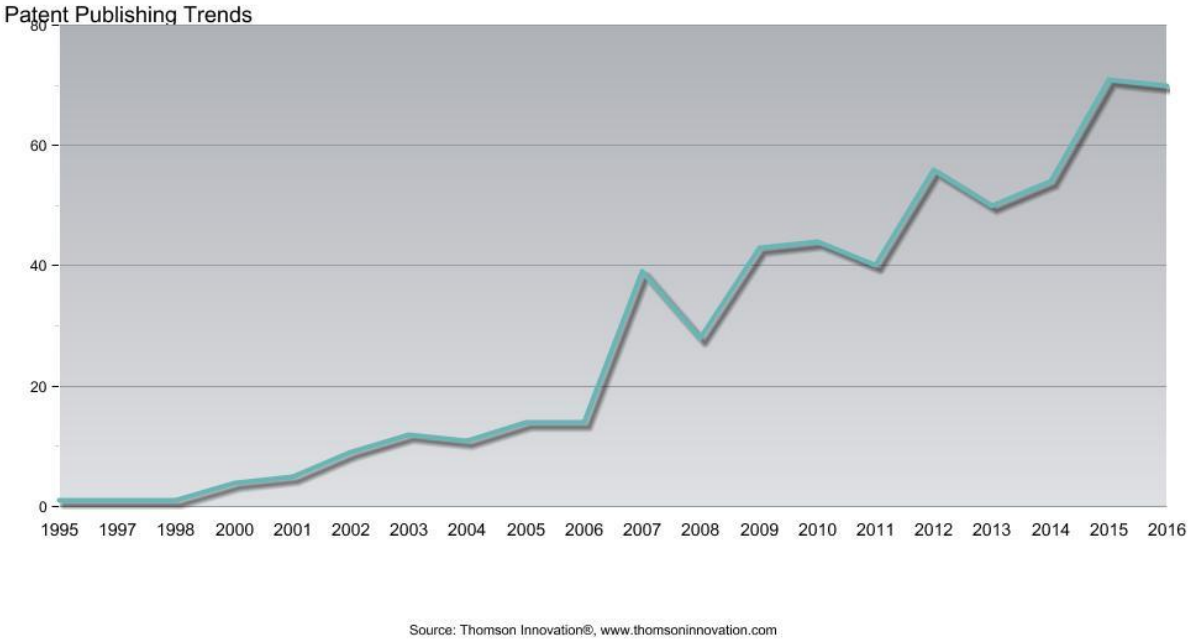



**Figure 2.** Top 5 IPCs by year across the broad Ebola vaccine patent landscape.

### 6.1.2 PUBLISHING TRENDS

#### BY YEAR

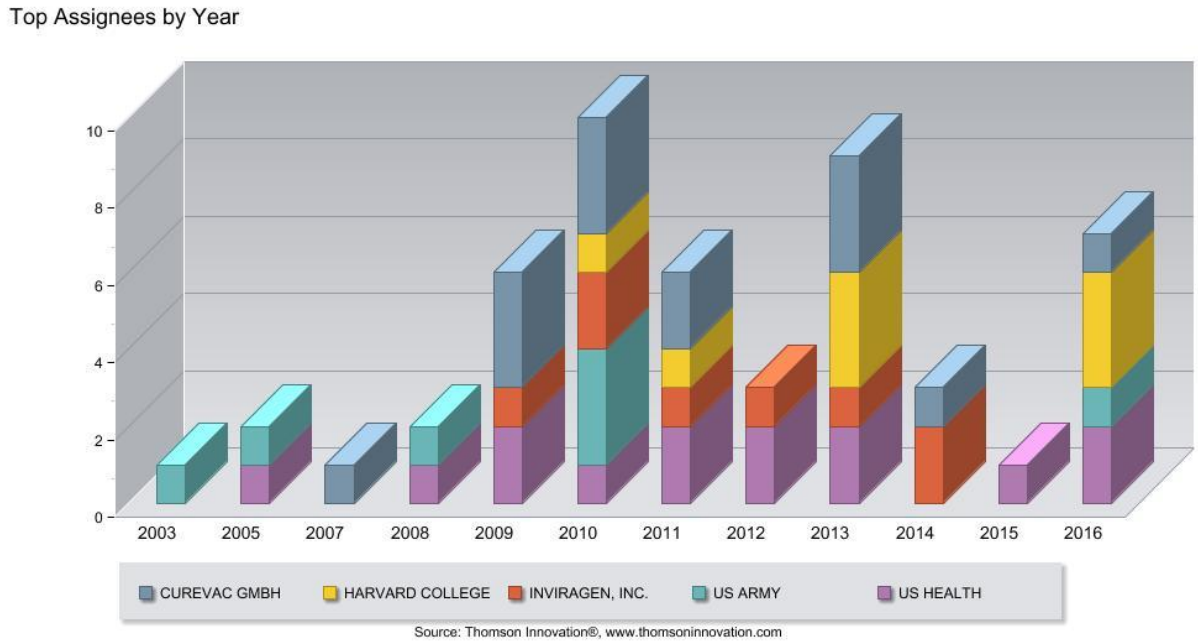



There has been a steady increase in the number of patent application publications in this space over the last 20 years. The application numbers have shown a sharp increase particularly since 2006 which coincides with various interests in vaccine development for Ebola over the last 10 years. The current number of annual filings is relatively low with around 75 filings and generally is increasing year-on-year, likely reflecting the increased interest of finding vaccine for Ebola during the epidemic over the last few years. Since there is an 18 month delay between submission of a patent application

and publication, it can be expected that the next few years to see an increase in filings due increased levels of research spurred by the epidemic is West Africa.

## BY ASSIGNEE

| Assignee/Applicant | Document Count | Percentage |
|---|---|---|
| **US Health** | 15 | 12.00% |
| **Curevac Gmbh** | 14 | 11.20% |
| **Inviragen, Inc.** | 8 | 6.40% |
| **Harvard College** | 8 | 6.40% |
| **US Army** | 7 | 5.60% |
| **Crucell Holland Bv** | 7 | 5.60% |
| **Univ Pennsylvania** | 6 | 4.80% |
| **Univ Emory** | 6 | 4.80% |
| **Georgetown University** | 5 | 4.00% |
| **Crucell Holland B.V.** | 5 | 4.00% |
| **Bavarian Nordic AS** | 5 | 4.00% |
| **Immunovaccine Technologies Inc** | 5 | 4.00% |
| **Copenhagen University** | 5 | 4.00% |
| **Genphar, Inc.** | 5 | 4.00% |




The top assignee for Ebola vaccines is the US Department of Health. They hold patents claiming optimised vaccines for Ebola covering a number of different approaches such as filovirus, adenovirus with modified antigens and glycoproteins and isolated human Ebola nucleotides.

Various different departments of the US Government such as the Health Department and the US Army are assignees with high numbers of filings in the Ebola vaccines space. From the vaccine development pipeline table (see above) it can be seen that US government departments are

collaborating and in some cases leading on the development of a number of different Ebola vaccine projects.

CureVac also has a high number of filings in this area. The company is a German biopharmaceutical company which is developing therapies based on messenger RNA. The company website currently does not expressly list that it is working on an Ebola vaccine but lists many undisclosed projects. However it was announced in 2015 that the company was collaborating with the Bill & Melinda Gates Foundation through an investment of $52 million to develop mRNA-based vaccines for a wide range of diseases, again not specifically mentioning Ebola.

Inviragen was an independent research and development vaccine company, but since has been acquired by Takeda in 2013. The patents filed by Inviragen relate to a live attenuated virus compositions which can be applied to a wide number for viruses, one of the examples given in the application is Ebola.

Harvard College's applications cover a wide range of vaccine approaches including nanocarriers for vaccines, new vaccine comprising a bisphosphonate and a carrier, new isolated polypeptide for mediating an immune response and attenuated RNA viruses.

Crucell Holland is a biotechnology company specializing in vaccines and biopharmaceutical technologies, which is a subsidiary of Johnson & Johnson (J&J). Their applications in this search relate to novel replication-defective recombinant adenovirus having adenovirus serotypes for the production of vaccines for Ebola and malaria and nucleic acid encoding modified filovirus glycoprotein, which can also be used as a vaccine. J&J in collaboration with Bavarian Nordica are working in the development of vaccines Ad26-EBOV & MVA-EBOV which are in phase II.

The University of Pennsylvania's filing in this search concerns antigens to particular strains of the Ebola virus, a passive immunization regimen, adenovirus and adeno-associated virus delivery systems and a novel chimeric Ebola envelope protein. The university have licensed their technology to Inovio Pharmaceuticals Inc which is developing a vaccine which is in phase I trials.

Emory University, based in the US, has a handful of filings relating to Ebola vaccines, their applications include a new virus-like particle and adjuvant polypeptide. Likewise, the US organisation Georgetown University has a few patents in this search. Their filings protect their ligand-targeted cationic liposome complexes approach to vaccination.

Immunovaccine Technologies Inc's filings relate to a vaccine composition comprising an antigen; liposomes; a polyI:C polynucleotide; and a carrier and another application concerning a new lipid derivative.

Copenhagen University's application claim a novel nucleic acid construct for use as a vaccine. GenPhar, is closed biopharmaceutical company which used to offers a range of vaccine to the US Army against a number of diseases including Ebola. Their applications relate to recombinant adenoviruses and replication-incompetent recombinant virus for Ebola and a wide range of other infectious diseases.

### 6.1.3 ASSIGNEES FOR HIGHLY CITED PATENTS

The following table identifies the top patents which are cited in other patent applications. This citation rate is an indication of the number of times a patent is cited by another which may anticipate or is similar to the claimed invention or that generally reveals the current state-of-the-art of the technology. An indication of the so called 'forward citations' gives an indication as to the patent's value or significance. Therefore, a patent which is highly cited by another entity may indicate that this patent is likely to be fundamental or important.

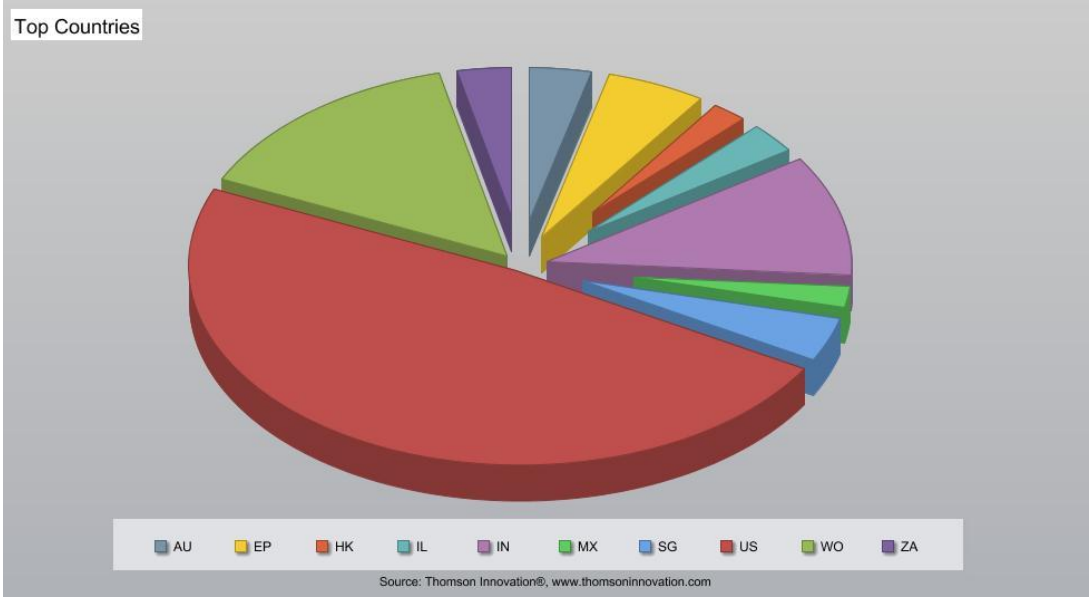
| Assignees/Applicant (first) | Patents | Cited by | Avg Citation |
|---|---|---|---|
| **US Army** | 7 | 166 | 23.71 |
| **Curevac GMBH** | 13 | 260 | 20 |
| **University Pennsylvania** | 6 | 17 | 2.83 |
| **University Emory** | 5 | 12 | 2.4 |
| **CRUCELL HOLLAND BV** | 5 | 11 | 2.2 |

### 6.1.4 TOP INVENTORS

The top inventor across the broad landscape is Gary Nabel who is a named inventor on patents assigned to University of Michigan and a number of US government departments including US Health and US Government Health and Human Services. Likewise, Nancy Sullivan is the named inventor on many of the US government patent applications as well as Crucell Holland B.V. and University of Rochester. Other inventors on US government patents include Zhi-Yong Yang, Maria Grazia Pau and Sina Bavari. Ingmar Hoerr and Jochen Probst are the named inventors on almost all patent application from Curevac. Dan Stinchcomb, O'Neil Wiggan and Jorge Osori is the inventor of patents assigned to Takeda and Inviragen, Inviragen is now part of Takeda.

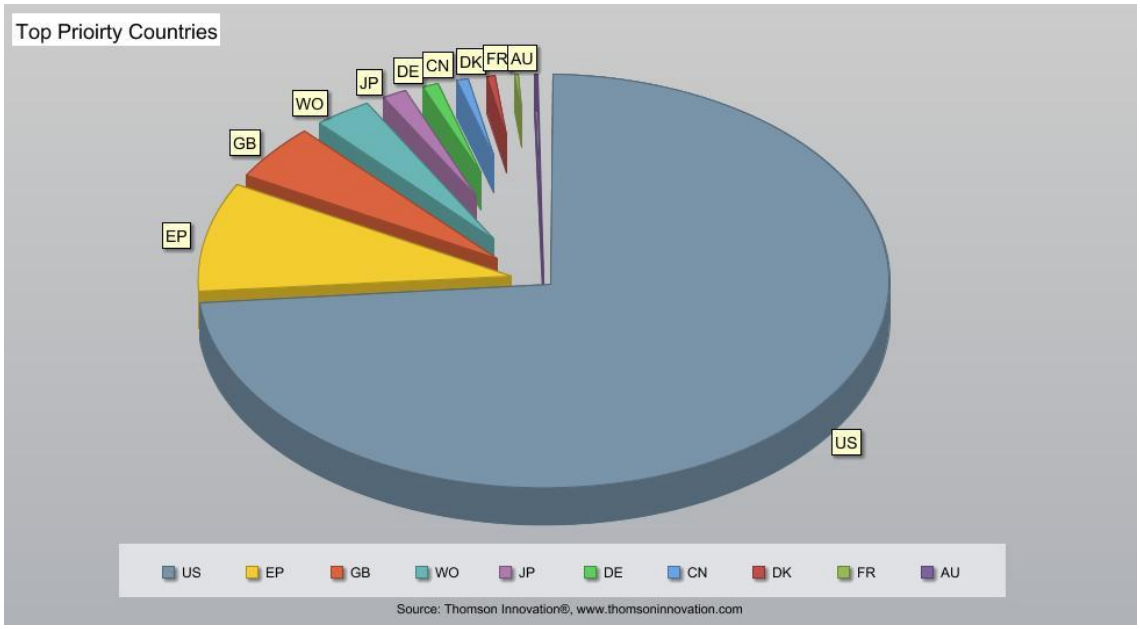
| Inventor | Document Count | Percentage |
|---|---|---|
| **Nabel, Gary J.** | 12 | 13.48% |
| **Hoerr, Ingmar** | 11 | 12.36% |
| **Stinchcomb, Dan T.** | 10 | 11.24% |
| **Osorio, Jorge E.** | 10 | 11.24% |
| **Wiggan, O'Neil** | 10 | 11.24% |
| **Probst, Jochen** | 9 | 10.11% |
| **Sullivan, Nancy** | 7 | 7.87% |
| **YANG, ZHI-YONG** | 7 | 7.87% |
| **Pau, Maria Grazia** | 7 | 7.87% |
| **Bavari, Sina** | 6 | 6.74% |

### 6.1.5 FILING COUNTRY TRENDS




The top filing countries indicates all the countries or jurisdictions where patent applications have been filed. A large proportion of applications have been filed in the US, India, European patent office and worldwide applications under the Patent Convention Treaty (PCT) system. This reflects the global interest in Ebola vaccine development. Other countries such as Australia, Hong Kong, Israel, Mexico, Singapore and South Africa are also prominent.

### 6.1.6 PRIORITY COUNTRY TRENDS




The top priority countries can be analysed to see where the patent applications are initially filed and claiming their priority from. This can be a good indication of the countries where the majority of research and innovation in a particular technology field if taking place since organisations generally file patent applications first in local territories where their research bases are located. Likewise for

universities the priority country will usually tend to be the country in which they are based. In this case nearly three quarters of applications are initially filed in the US indicating the US as a centre for Ebola vaccine research and development, both from US universities, US government departments and companies which are based or have their head research and development facilities. Europe and Great Britain also represents a small but significant number of locations for initial filings from both companies and universities.

## 7 THEMESCAPE MAP: EBOLA VACCINES

Thomson Innovation can be used to generate sophisticated patent landscapes to visualise the relationship between patents in a common field based on key words within the claims and/or abstracts/text of individual patents within the searched field. This can be used to locate competing or similar patents to the patents of interest. As with a geographic landscape the contour lines and intensity of peaks on the patent landscape represent areas of high patent activity with closely related concepts.

The set of INPADOC patent families identified in the broad search was mapped using Thomson Innovation's proprietary ThemeScape™ mapping tool. ThemeScape uses term frequency and other algorithms to cluster documents based on shared language – in this case the English Title from the patents together with the DWPI-enhanced Titles and Abstracts were mapped. It uses several algorithms to perform terminology-based clustering. The text from each record is compared with the text from all other patent records within the search collection. The map uses vectors to give each patent record a proximity score to all of its peers. The outcome of this analysis is a visualisation of the patent space with each patent (dot) represented once in the map, with patents in close proximity sharing more phraseology than those located apart. Each peak is labelled with the key terminology concepts contained in the patents within the cluster.

We used the Themescape tool on the Ebola virus vaccine patent set, mapping one representative patent from each of the INPADOC families. The resulting map is shown below, with some broad subject areas highlighted. This allows us to identify some broad areas of interest in the field, represented by the highest "peaks" on the map.

The map has been overlaid with the key areas in which the patents fall on the map. Broadly sectors on the landscape include virus like particle, multiprotein compositions which resemble viruses which can be used as a vaccine delivery system. The amino acid positioning covers patents which tend to involve genetic manipulation of viral vectors to make them for suitable as a delivery platform. The cell culture section relates to patent application for methods of vaccine production. The segment entitled viruses indicates that may application claim not just Ebola but expand the scope of the claims to a wider range of viruses to which their vaccine technology could protect against. The antigen & immune system and cytotoxicity segments of the map are somewhat linked in that they cover aspects of the immune repose and how can be utilised to induce immunity against diseases.

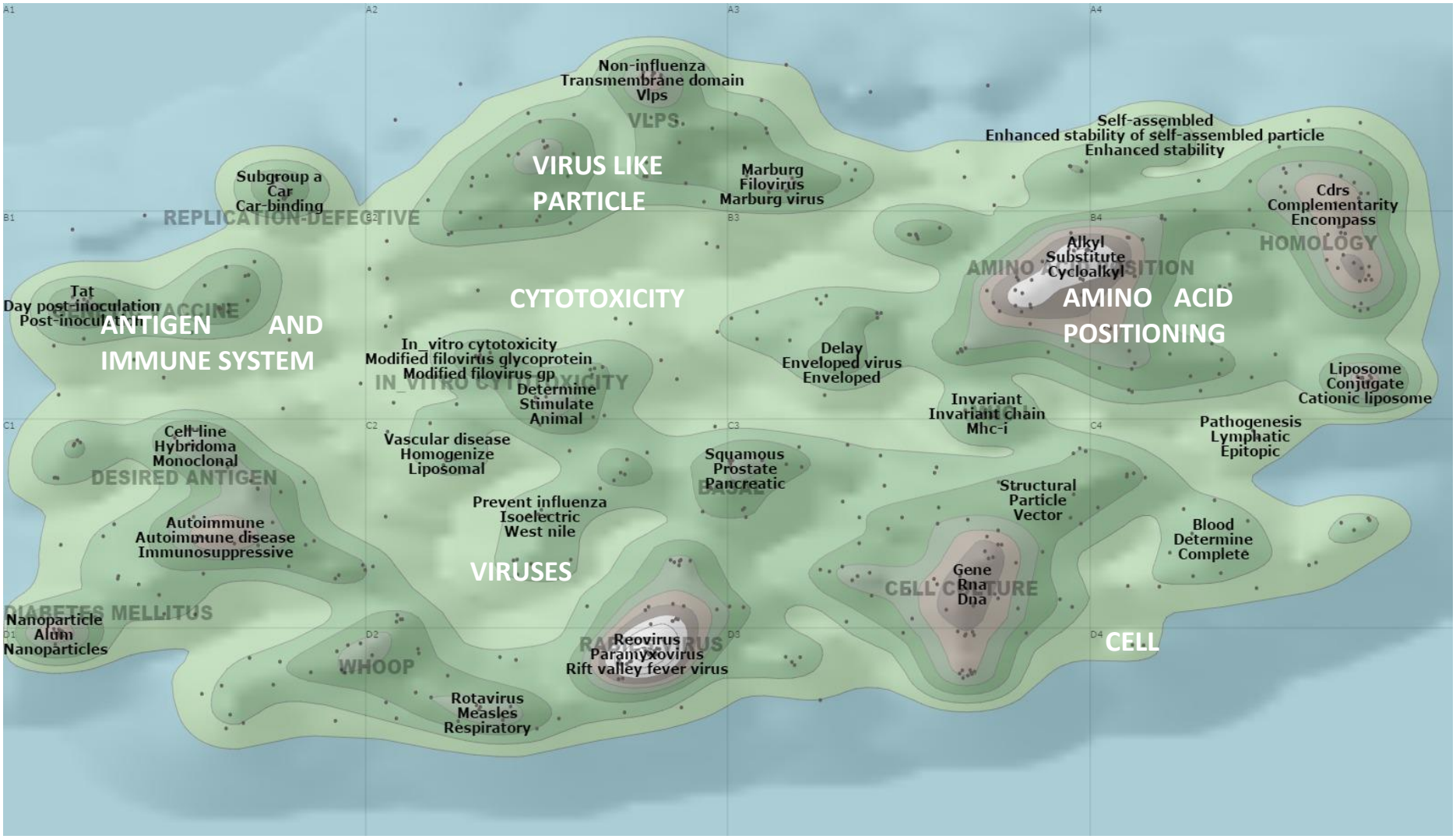



Fig 3**. Themescape for Ebola Vaccines patent landscape**. Each dot indicates the location of an INPADOC patent family on the map. The map has been overlaid with the key areas in which the patents fall on the map.

# 8 EBOLA VACCINE: SUBSEARCHES

There are a number of different vaccine approaches which have been utilised in the development of Ebola vaccines. This section will look at the key filing organisations in the areas of 3 key vaccine platforms being used for Ebola virus vaccines:

1. Adenovirus vectors
2. Vesicular Stomatitis Virus (VSV) vectors
3. Virus-Like Particles (VLP)

Both Adenovirus and VSV are viral vector platforms which are engineered to deliver antigens. These platforms are popular as they induce a cellular immune response. Adenovirus is a non-enveloped double stranded DNA virus, which has been isolated from a number of mammalian species. Adenoviruses in use for Ebola vaccine development include human recombinant and chimpanzee. VSV is an enveloped, single-stranded RNA virus of the *Rhabdoviridae* family that infects cattle. The virus causes a zoonotic disease in humans but pre-existing immunity in humans is limited enabling its use as a vaccine vector.[5] One advantage of recombinant VSV over other viral vector vaccines for Ebola is the use for post exposure protection.

VLP is a protein-based approach where multiprotein structures are generated that mimic the organization and conformation of authentic native viruses but lack the viral genome, potentially yielding safer and cheaper vaccine candidates. VLP vaccines are currently commercialised worldwide for hepatitis B virus and human papilloma virus.[5]

Other vaccine types which are in development for Ebola virus include DNA vaccines and vaccinia viral vector vaccines. These will not be covered in this report.

The search strings used can be found in Appendix 1.

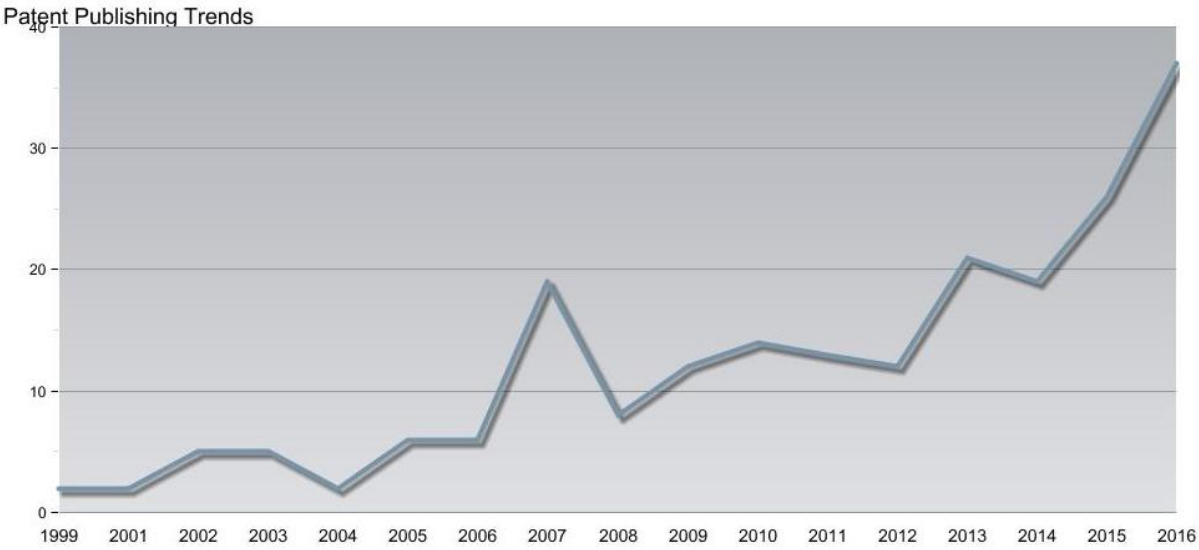
## 8.1 ADENOVIRUS

The use of adenoviral vectors as a delivery strategy for vaccine is a popular one, both generally and within the field of Ebola vaccine development. A sub-search revealed 208 patent families relating to the use of adenovirus in Ebola vaccines. This relatively high number of filings indicates that adenoviral victors are particular popular. Looking at the top assignees there are a number of companies which appears to be using this approach.

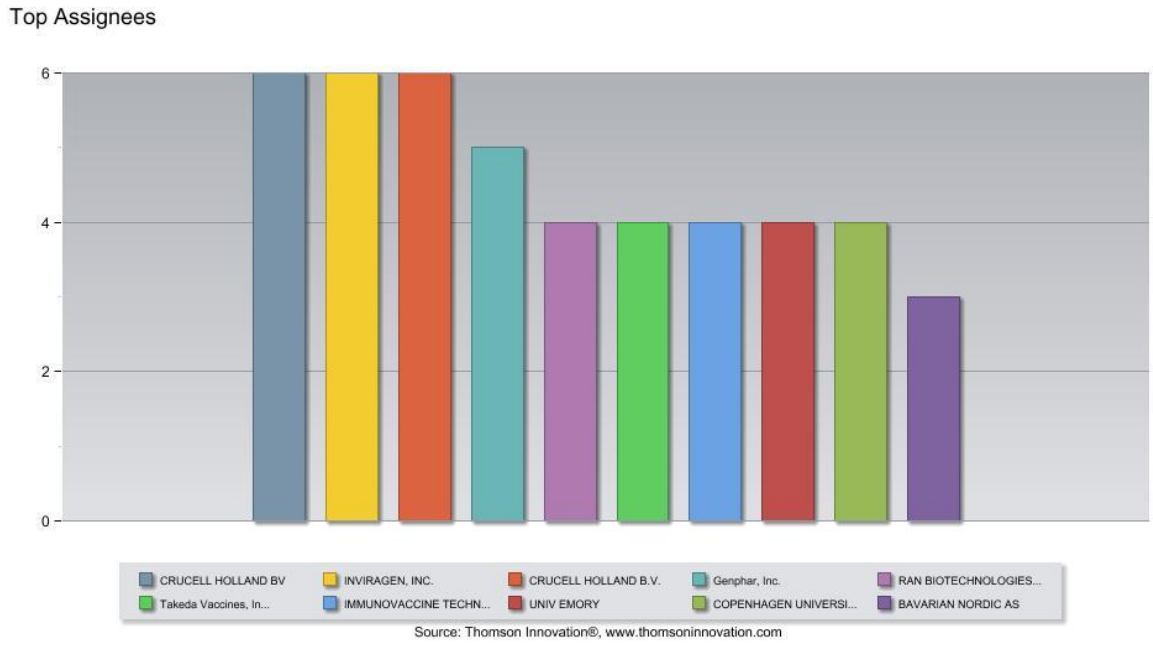
### 8.1.1 PUBLISHING TRENDS BY YEAR

Filings for adenovirus and adenoviral vectors relating to Ebola virus have been steadying increased over the last 20 years, with 37 INPADOC families filed in 2016.

[5] Sridhar S. Clinical development of Ebola vaccines. Therapeutic Advances in Vaccines. 2015;3(5-6):125-138. doi:10.1177/2051013615611017.




### 8.1.2 TOP ASSIGNEES




The top assignee for the sub-search for Ebola vaccines and adenovirus is Crucell, with a total of 12 INPADOC families. As stated above, Crucell is a subsidiary of Johnson & Johnson and is working on the development of the adenovirus-based Ad26-EBOV vaccine. The patent applications they hold relate to a modified filovirus glycoprotein (GP) for vaccine production which reduces cytotoxicity (WO2006037038A1), recombinant replication-defective adenoviruses (WO2006040330A2 / WO2007104792A2), method of inducing an immune response against a filovirus antigen in a subject using Adenovirus serotype 26 and serotype 35 filovirus vaccines (WO2012082918A1) and methods recombinant adenoviral vectors in vaccination regimens (WO2004037294A2).

Crucell are also a co-assignee with Bavarian Nordic on the WO2016036955A1 patent which expands on the original vaccine platform where the vaccine combination comprises (i) a first composition comprising an adenovirus vector comprising a nucleic acid encoding an antigenic protein of a first

filovirus subtype, together with a carrier; and (ii) a second composition comprising a modified vaccinia Ankara (MVA) vector comprising a nucleic acid encoding antigenic proteins of at least two filovirus subtypes, together with a carrier, where one of the compositions is a priming composition and the other composition is a boosting composition. One of the adenovirus vector claimed is AD26.

Inviragen Inc is the assignee with the second highest number of INPADOC patent families in this sub-search. Inviragen was an independent vaccine development company, which has since been acquired by Takeda in 2013. Their patent relates to live attenuated virus composition which is claimed to be used in the vaccination against various disease included Ebola and adenoviruses. This patent does not cover adenoviral vectors per se for the preparation of vaccinations (WO2009014774A1). Takeda are also listed as assignees on a few of these patents.

Genphar was a biopharmaceutical company which used to develop vaccines; the company is now closed down. The patent applications covered replication incompetent recombinant adenovirus for a wide range of diseases including Ebola virus.

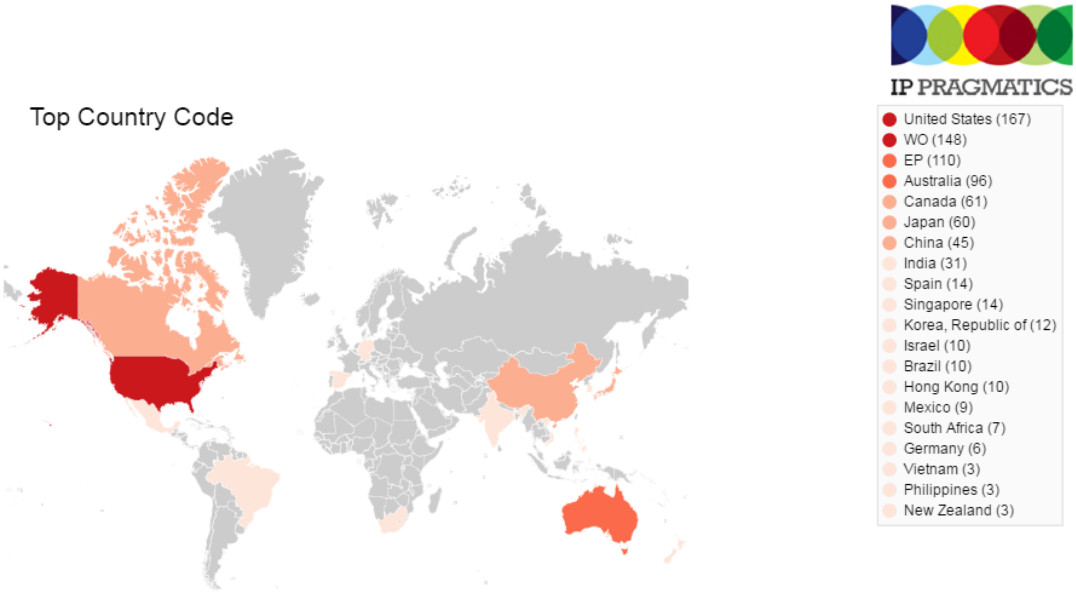
RAN Biotechnologies provides chemicals specially optimized for microfluidic and biotechnological applications, including capturing, purifying and rapidly detecting microbes and proteins. Their patents relate to the detection of biologicals including adenovirus and Ebola virus. This patent doesn not cover adenoviral vectors for the preparation of vaccinations.

Immunovaccine is a Canadian company which develops cancer immunotherapies and infectious disease vaccines using their own proprietary vaccine platform. The main patent hit in this search, WO2009146523A1, claims a composition useful for inducing antibody response or cell-mediated immune response to antigen in subject, comprising an antigen, liposomes, a polyI:C polynucleotide, and a carrier comprising a continuous phase of a hydrophobic substance. This patent does not cover adenoviral vectors for the preparation of vaccinations but preparations against a number of diseases including Ebola virus and adenovirus.

There are 2 universities in the top 10 assignees. One of which is the US Emory University who has a number of patent filings in this space including vasoactive intestinal peptide antagonist for treating or preventing viral infections, use of flagellin for treating viral infection, an adjuvant polypeptide and new virus-like particles for immunisation. The other university is Copenhagen University, Denmark whose filings relate to an adenoviral vector system for immunisation against a number of diseases including Ebola virus.

### 8.1.3 JURISDICTIONAL COVERAGE

The map below outlines the location of all the filed applications relating to adenoviral Ebola vaccines. There are a high number of filings in the US as well as through regional filings systems including the World Intellectual Property Office PCT system and the European Patent Office (both of which are not demonstrated on the map below.




### 8.1.4 POSITION ON LANDSCAPE

The patents identified through the adenovirus searches were mapped onto the full patent landscape from the broader search conducted in Sections 6 & 7 of this report (see figure below). The red dots representing the adenovirus identified patent families are distributed across all themed segments of the landscape; including many within the amino acids positioning, which covers applications claiming genetic engineering of adenovirus vectors through amino acid mutation.

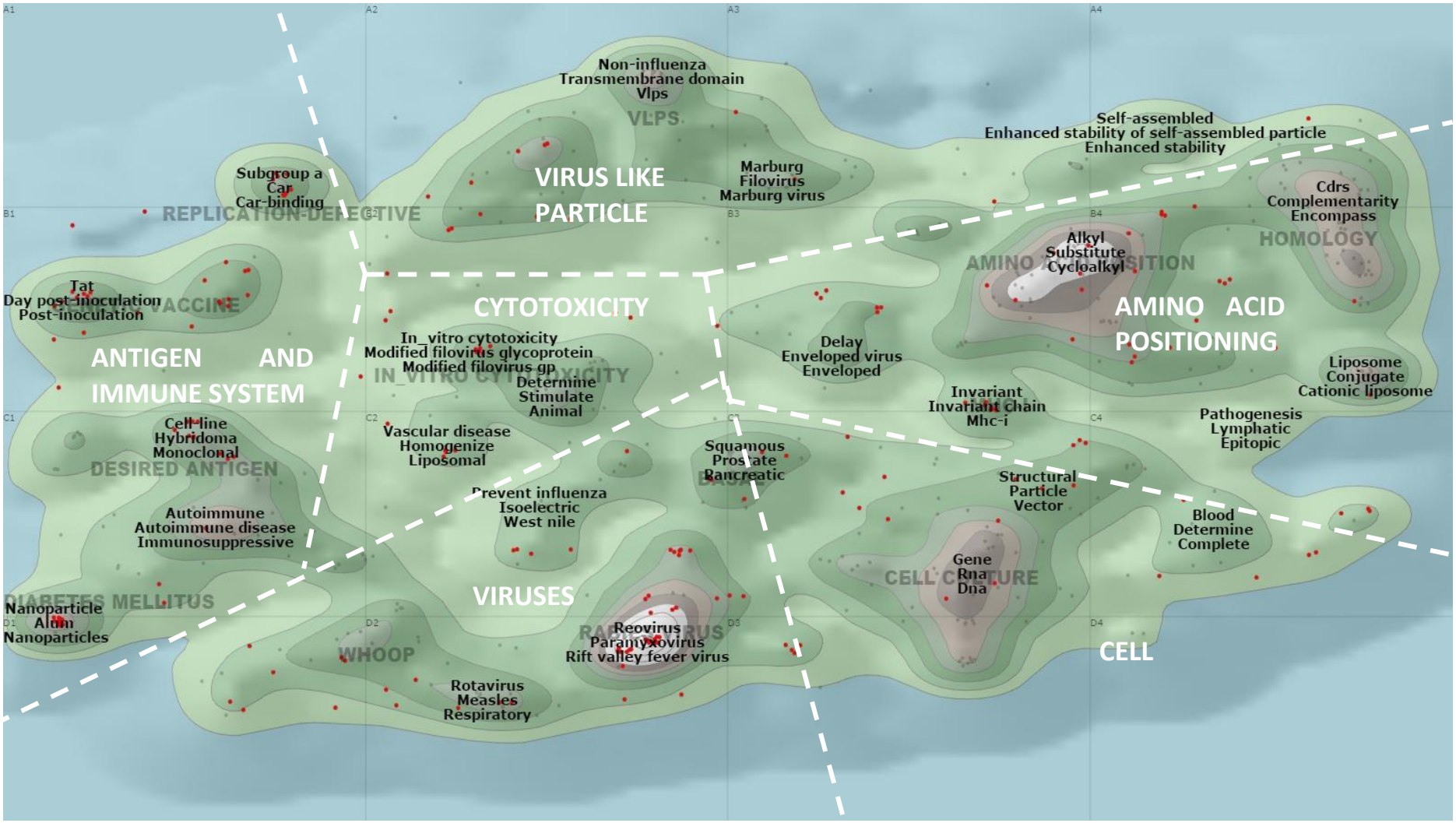


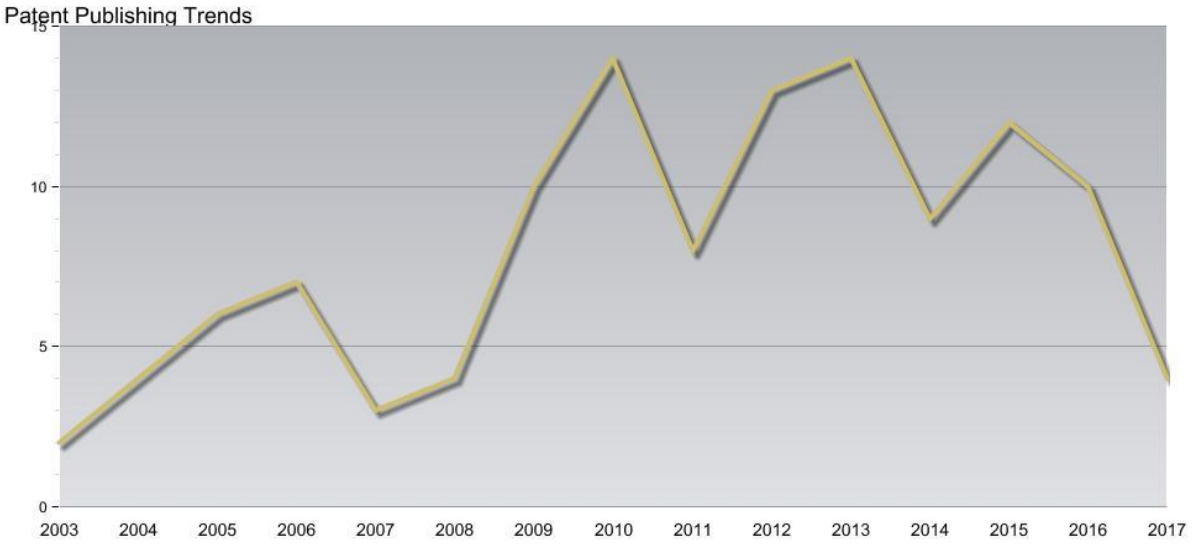

Fig 4**. Themescape for Ebola Vaccines patent landscape with Adenovirus sub-search**. Each grey dot indicates the location of an INPADOC patent family on the map and the red dots indicates the IPADOC patent families which are hits for the Adenovirus sub-search.

## 8.2 VIRUS LIKE PARTICLE

Virus like particles (VLPs) are a more recent technology development than recombinant viral vectors. VLPs are a multiprotein structure, which resemble the organisation and conformation of native viruses. There are not as many filing in this area compared to adenovirus and VSV, likely reflecting the fact that the use of VLPs is a newer approach. The search only revealed 38 patent families (157 individual cases).

### 8.2.1 PUBLISHING TRENDS BY YEAR

Filing rates for VLP Ebola vaccine have been low, with no consistent change in filing rates over the last 15 years.

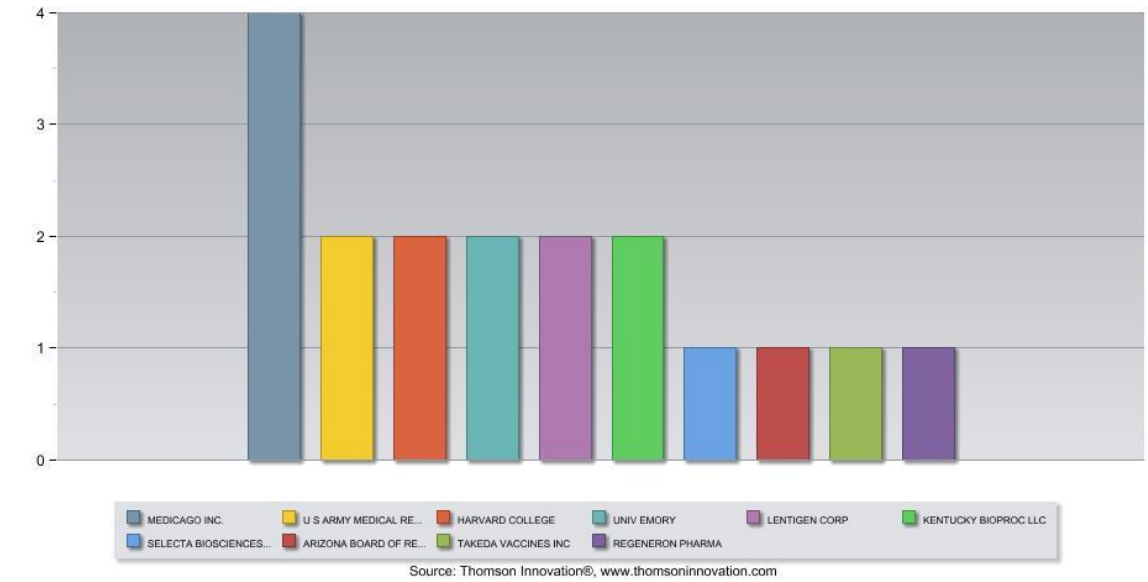



Source: Thomson Innovation®, www.thomsoninnovation.com

### 8.2.2 TOP ASSIGNEES

There are only 6 assignees which have more than 1 patent family in this sub-search.

Top Assignees




Source: Thomson Innovation®, www.thomsoninnovation.com

Medicago's patents broadly claim the method of producing virus like particles used in composition for preventing and/or treating viral infections, by introducing nucleic acid comprising active regulatory region into plant, and incubating plant under favourable conditions. One of the viruses which the method can be used with to create an immune response as a vaccine is Ebola. The company is a clinical-stage biotechnology company which develops vaccines using VLPs and using a transient expression system in tobacco plants. Its website states that the company has just engaged with the Canadian government to develop Ebola monoclonal antibodies.

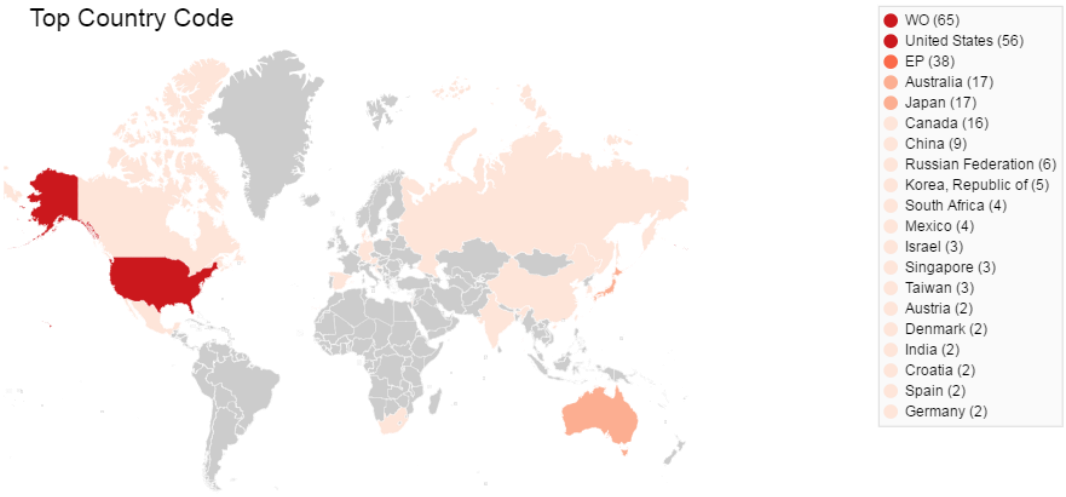
US Army Medical Research Institute of Infectious Diseases Department of the Army also has interest in the use of VLP for vaccine development. Its patent applications relate to a new filovirus virus-like particle for diagnosing, preventing and/or treating Ebola and Marburg virus (WO2006046963A2) and nano-VLP composition for Ebola immunisation (WO2016022916A2).

Lentigen is a biotechnology company which develops lentiviral gene delivery and expression technology. Their patent hits in this search claims a vaccination regime which comprises vaccinating a mammal comprising administering a non-integrating, replication-incompetent retroviral vector (NIV) to the mammal and administering a virus-like particle (VLP) to the mammal (WO2012103510A2).

There are also a number of academic institutes which feature in the top 6 assignees; these include University of Emory and Harvard College. University of Emory's patents relate to a new virus-like particle (VLP) which can be used for Ebola virus vaccination (WO2004042001A2). Harvard's patents claim a new vaccine, comprising a bisphosphonate and a carrier (WO2012054807A2) and the method of delivering compound to cytosol of immune cell comprises passing cell suspension comprising immune cell through microfluidic device and contacting suspension with compound (WO2016070136A1).

### 8.2.3 JURISDICTIONAL COVERAGE

The map below outlines the location of all the filed applications relating to VLP Ebola vaccines. The highest number of filings have been through the World Intellectual Property Office PCT system (which is not demonstrated on the map). In addition there are a high number of filings in European Patent Office (not demonstrated on the map) and the United States.




### 8.2.4 POSITION ON THE LANDSCAPE

The majority of VLP patent families identified in this sub-search appear within the top centre of the patent landscape map of the broader search conducted in Sections 6 & 7 of this report (see figure below). Unsurprisingly, the majority of these patent fall within the VLP segment on the landscape.

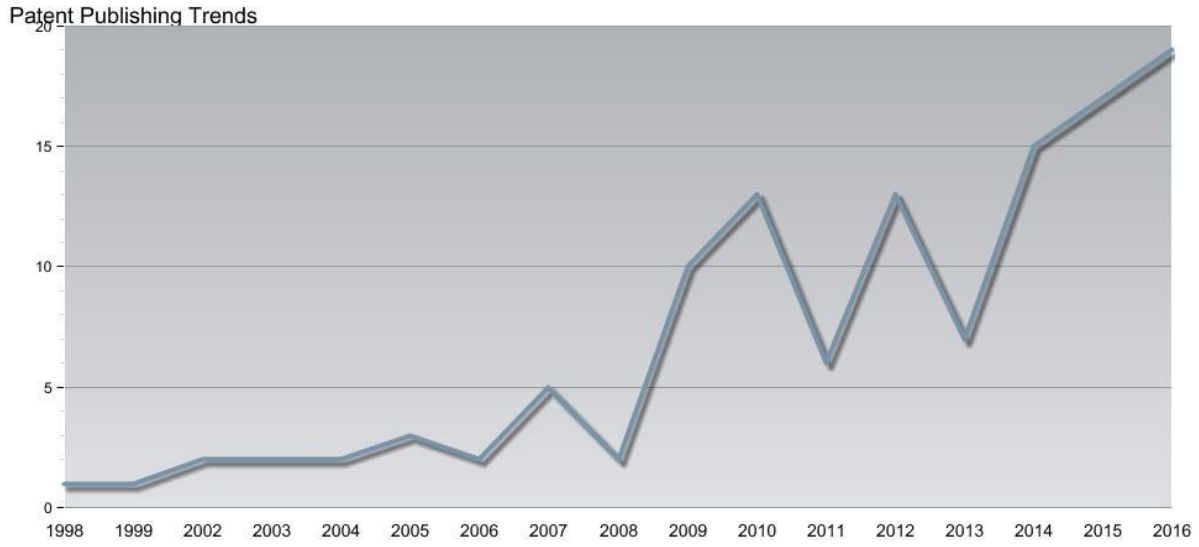

Fig 5**. Themescape for Ebola Vaccines patent landscape with Virus-Like Particle (VLP) sub-search**. Each grey dot indicates the location of an INPADOC patent family on the map and the red dots indicates the IPADOC patent families which are hits for the VLP sub-search.

## 8.3 VESICULAR STOMATITIS VIRUS (VSV)

VSV is an alternative viral vector which can be used as an Ebola virus vaccine delivery platform. From the patent numbers it suggests that VSV is not as popular as adenovirus, as there are a lower number of patent families identified. This sub-search generated a list of 118 INPADOC families (506 individual cases).

### 8.3.1 PUBLISHING TRENDS BY YEAR

Over the past 20 years filing rates relating to the use of VSV vaccines for Ebola have shown a general increase, with peaks and trough variations year-on-year. The numbers are relatively low with less than 20 patent families filed in 2016.




Source: Thomson Innovation®, www.thomsoninnovation.com

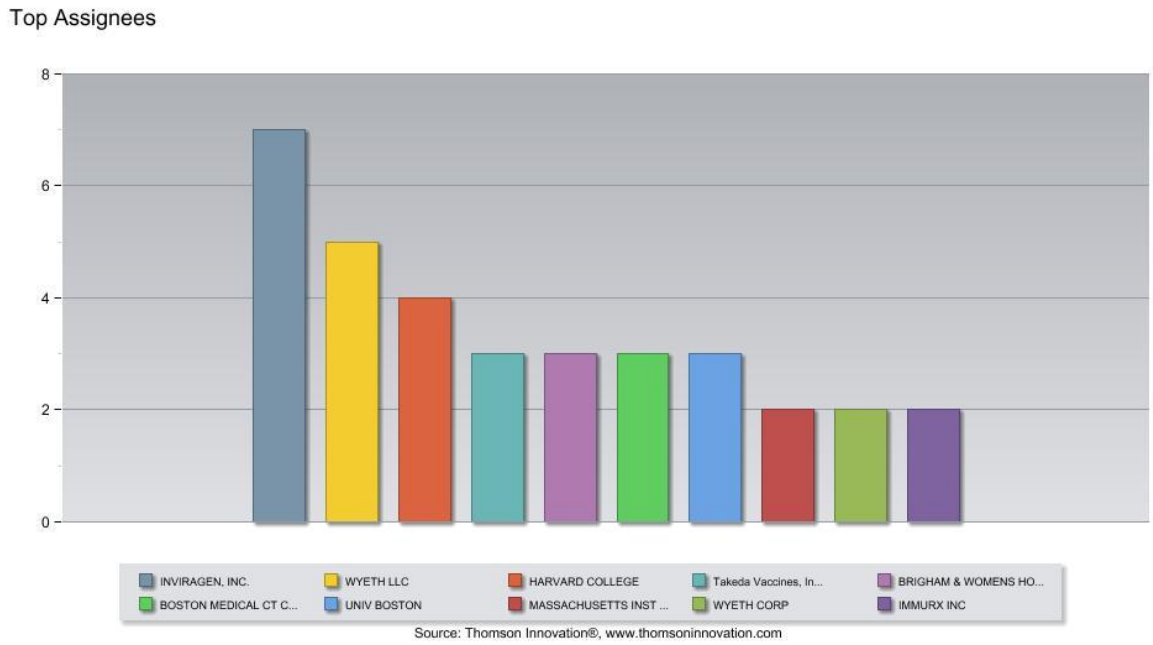
### 8.3.2 TOP ASSIGNEES

Inviragen Inc is the assignee with the highest number of INPADOC patent families. Inviragen was an independent vaccine development company, which has since been acquired by Takeda in 2013. The patents filed relate to live attenuated virus composition which is claimed to be used in the vaccination against various disease including Ebola and VSV infections. This patent does not cover VSV vectors for the preparation of vaccinations (WO2009014774A1). Takeda are also listed as assignees on a few of these patents.

The assignee with the second highest number of patent families assigned to them is Wyeth. Wyeth was a pharmaceutical company purchased by Pfizer in 2009. Its patent families concern an isolated, genetically modified VSV for use as an immunogenic composition against a number of diseases including Ebola virus (WO2009082664A2).

ImmuRx is developing adjuvant platforms for the treatment of cancer and infectious disease. Their patent applications covers a new adjuvant combination comprises CD40 agonist, natural killer T cell

(NKT) activator, and desired antigen; useful for synergistically enhancing T cell immunity and treating cancer, inflammatory, autoimmune, and infectious diseases (WO2008133983A1).

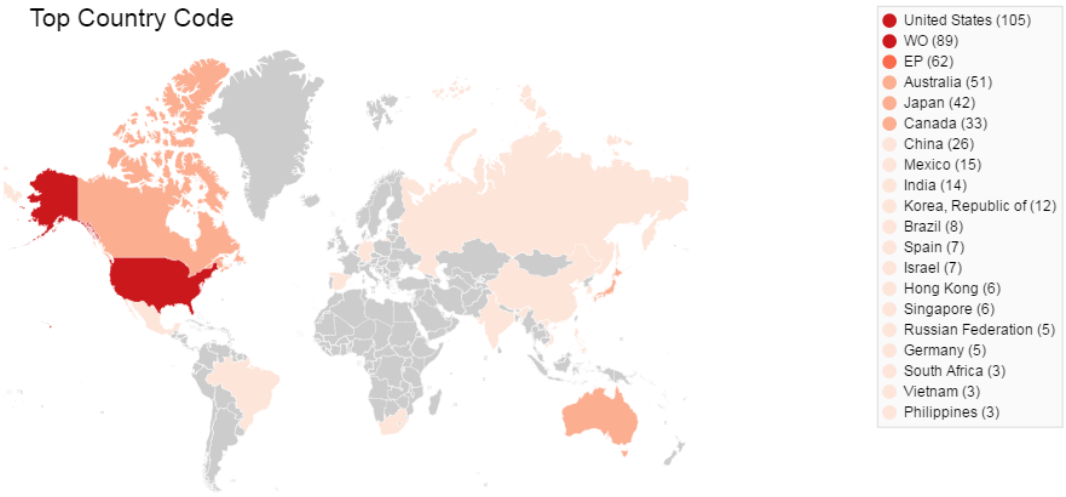



There are a number of universities and research institutes in the top 10 assignee list. One of those is Harvard College whose filings cover attenuated vaccines for non-segmented negative sense RNA viruses (WO2007044483A2) and nanocarrier for vaccinating subject having e.g. cancer comprises immunomodulatory agent that stimulates immune response in T and B cells (WO2009051837A2). Also Brigham and Women's Hospital is part of Harvard and they have filed applications covering treating infection by an enveloped virus in subject, such as Ebola virus, Marburg virus, Nipah, hepatitis-C virus, Arenavirus, poxvirus or herpesvirus, involves administering to subject a papain-like cysteine protease inhibitor (WO2006091610A2) and the co-assignee on some of the Harvard applications identified above.

University of Boston and Boston Medical Centre are co-assignees on applications which covers new recombinant viral vector, comprising all or a portion of a gene from three or more different viruses, useful for inhibiting or treating infection, by three or more different viruses in a subject such as Ebola virus (WO2009120306A1). As well as being co-assignees on a composition to treat Ebola virus infection by expressing gene(s) from the Ivory Coast ebolavirus (ICEBOV) species in a recombinant viral vector (WO2009116983A2) and a pre- or post-exposure treatment for filovirus or arenavirus infection using a recombinant viral vector that encodes a gene selected from a number of different viruses including Ebola (WO2009116982A2).

### 8.3.3 JURISDICTIONAL COVERAGE

The map below outlines the location of all the filed applications relating to VSV Ebola vaccines. There are a high number of filings in the US as well as through regional filings systems including the World Intellectual Property Office PCT system and the European Patent Office (both of which are not demonstrated on this map). There is also a high rate of filing in Australia, Japan and Canada.




### 8.3.4 POSITION ON LANDSCAPE

The patents identified through the VSV searches were mapped onto the full patent landscape from the broader search conducted in Sections 6 & 7 of this report (see figure below). The red dots representing the VSV identified patent families are distributed across all themed segments of the landscape.

The small dense cluster on the lower left-hand side of the map, which is circled in red, relates to a series of patents for vaccine nanotechnology self-assembling nanocarriers that have been claimed in relation to a wide number of diseases including Ebola virus. The larger cluster in the centre of the landscape maps indicated that many VSV patent applications also make claims to wider diseases such as rabies, Rift Valley fever virus and West Nile virus. The cluster in the cell culture segment of the map are for patents which claims VSV which have been genetically modified through addition and/or removal of genes and amino acid mutation , with the aim of making VSV a more suitable vector for vaccination delivery.


Fig 6**. Themescape for Ebola Vaccines patent landscape with VSV sub-search**. Each grey dot indicates the location of an INPADOC patent family on the map and the red dots indicates the IPADOC patent families which are hits for the VSV sub-search.

## 8.4 COMPARATIVE TRENDS

### 8.4.1 COMPARATIVE LANDSCAPE

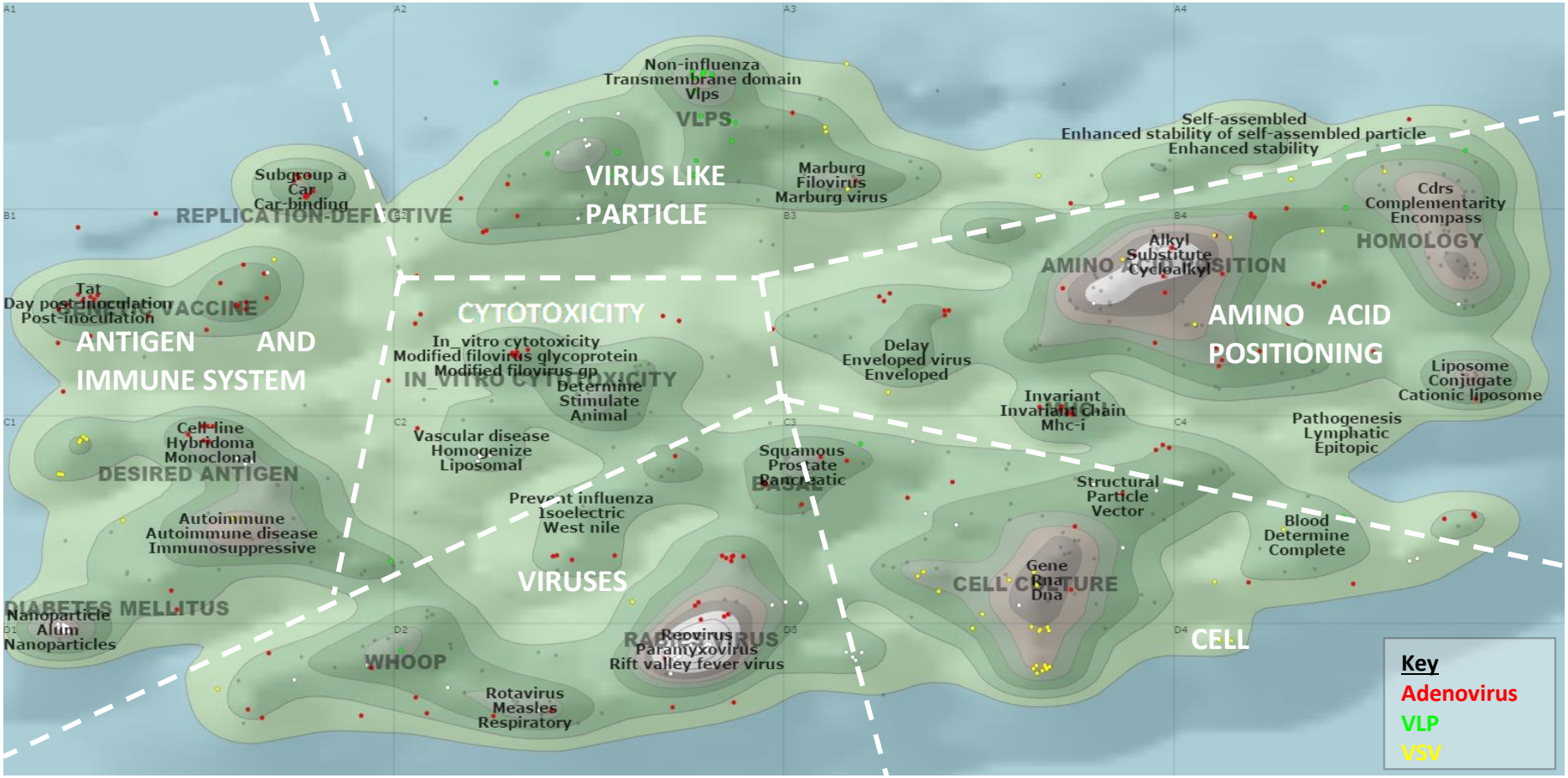
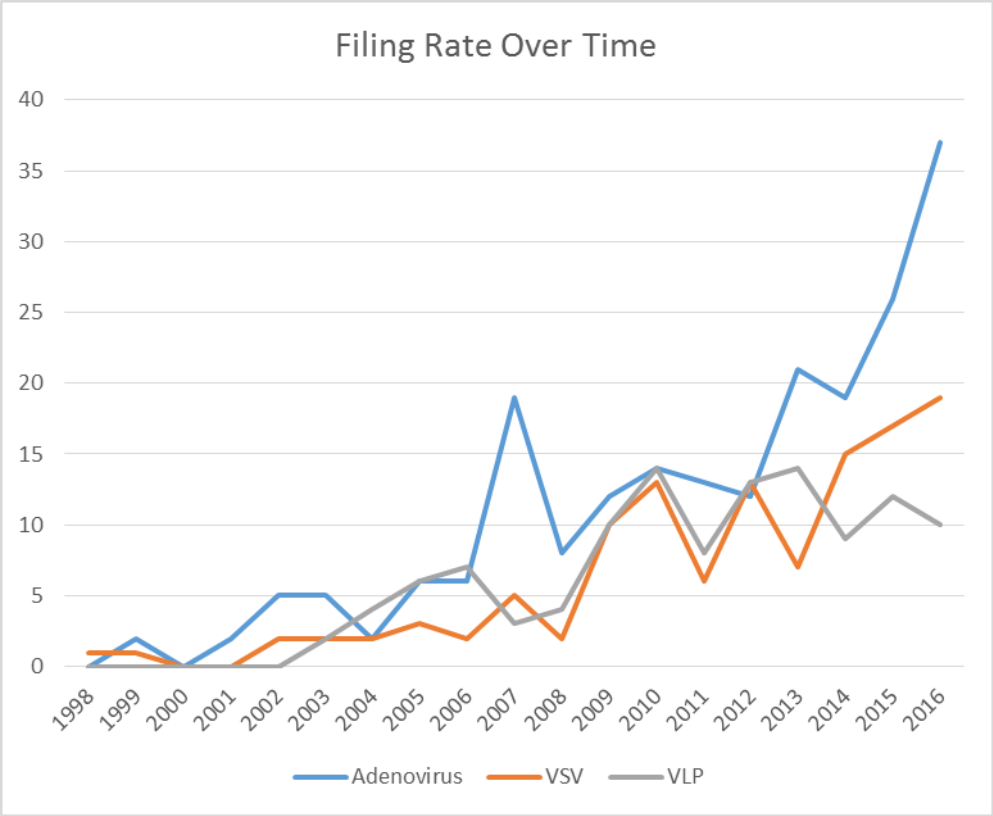



Fig 7**. Themescape for Ebola Vaccines patent landscape with adenovirus, VSV and VLP sub-search**. Each grey dot indicates the location of an INPADOC patent family on the map and the coloured dots indicates the IPADOC patent families which are hits for the sub-searches in accordance with the key. White dots indicate patents which are the result of more than 1 sub-search.

The landscape map above highlights the locations of all patent families for searches with keywords relating to adenovirus (red), VLP (green) and VSV (yellow). White dots indicate patent families which are the result of more than 1 sub-search.

### 8.4.2 COMPARATIVE FILING TRENDS

The graph below compares the relative filing rate of adenovirus, VSV and VLP INPADOC patent family filings. Adenovirus shows higher rates of filing across the time period, this is most likely due to the fact that recombinant adenoviral vectors are a more established vaccine delivery platform. Conversely, VLP is a more recent technology for vaccine delivery and has no filings in the beginning of this study period and has shown an increase in the past few years.



# 9 KEY PATENTS OF RELEVANT COMPANIES

There are 3 vaccines which are the furthest developed for the Ebola virus these are:

- Merck - VSV-EBOV (V-920)
- GlaxoSmithKline - ChAd3-ZEBOV
- Johnson & Johnson - Ad26-EBOV & MVA-EBOV

The following section of the report outlines the key patents which underpin these companies' developments, some of which have been in-licensed or filed by one of their subsidiary companies.

## 9.1 MERCK

Whilst Merck is now in charge of the development of the VSV-EBOV vaccine, the original work was done at the National Microbiology Laboratory in Winnipeg, Canada with a patent being filed by the Public Health Agency of Canada. A license to the patent was granted to NewLink Genetics in 2010, who in turn sub-licensed its rights to the patent to Merck in order to increase the speed with which the vaccine could be produced and entered into clinical trials. It has been reported that Newlink paid $200,000 for the licence for the Ebola vaccine from the Public Health Agency of Canada with no ongoing royalties.[6]

In December 2016 it was announced that the latest major trial had favourable results and received Breakthrough Therapy Designation from the United States Food and Drug Administration and PRIME status from the European Medicines Agency, enabling faster regulatory review of the vaccine once it is submitted.[7] In January 2016, the Gavi global alliance for vaccines and immunization group signed a $5 million advance purchase commitment to buy the VSV-ZEBOV vaccine.[8] NewLink Genetics has signed a deal in 2014 to Merck for $30 million (U.S.) in an upfront payment, to be followed by a milestone payment of $20 million (U.S.) for sales outside of Africa.[9]

The details of the main patent family which claims the vaccine are as follows:

**Title: Recombinant vesicular stomatitis virus vaccines for viral hemorrhagic fevers**

**Abstract/DWPI**: A recombinant vesicular stomatitis virus (VSV) particle (I) comprising a nucleic acid molecule encoding a foreign glycoprotein inserted into the viral genome, is new.

**Assignee/Applicant:** CANADA MIN HEALTH; CANADA MIN IND COMMUNICATIONS RES CENT; FELDMAN H; FELDMANN H; JONES S; STROEHER U

**Priority date**: 26th July 2002

**Family legal status:**

[6] http://www.canada.com/health/Canadian+developed+Ebola+vaccine+licensed+Merck/10409011/story.html
[7] http://www.who.int/mediacentre/news/releases/2016/ebola-vaccine-results/en/
[8] http://www.reuters.com/article/us-health-ebola-vaccine-idUSKCN0UY0OT
[9] http://www.reuters.com/article/us-health-ebola-merck-idUSKCN0J814A20141124

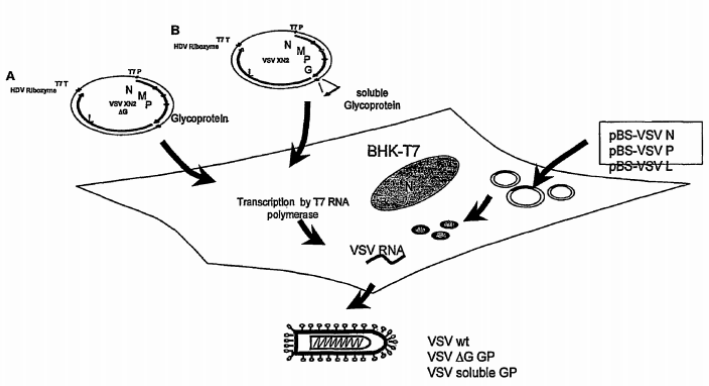
| Publication Number | Publication Date | Title | Status |
|---|---|---|---|
| **WO2004011488A2** | 05/02/2004 | Recombinant Vesicular Stomatitis Virus Vaccines For Viral Hemorrhagic Fevers | Entered into regional and national phase |
| **US20060193872A1** | 31/08/2006 | Recombinant vesicular stomatitis virus vaccines for viral hemorrhagic fevers | Granted as US8012489B2 |
| **US8012489B2** | 06/09/2011 | Recombinant vesicular stomatitis virus vaccines for viral hemorrhagic fevers | Granted – Active |
| **AT455124T** | 15/01/2010 | Rekombinante Vesicular Stomatitis Viren Als Impstoff Gegen Virale Haemorrhagische Fieber | Granted – Lapsed |
| **AU2003250680A1** | 16/02/2004 | Recombinant Vesicular Stomatitis Virus Vaccines For Viral Hemorrhagic Fevers | Application lapsed |
| **CA2493142A1** | 05/02/2004 | Recombinant Vesicular Stomatitis Virus Vaccines For Viral Hemorrhagic Fevers | Granted as CA2493142C |
| **CA2493142C** | 12/11/2013 | Recombinant Vesicular Stomatitis Virus Vaccines For Viral Hemorrhagic Fevers | Granted – Active |
| **DE60330966D1** | 04/03/2010 | Rekombinante Vesicular Stomatitis Viren Als Impstoff Gegen Virale Haemorrhagische Fieber | Granted – Active |
| **EP1527087A2** | 04/05/2005 | Recombinant Vesicular Stomatitis Virus Vaccines For Viral Hemorrhagic Fevers | Granted as EP1527087B1/B2 |
| **EP1527087B1** | 13/01/2010 | Recombinant Vesicular Stomatitis Virus Vaccines For Viral Hemorrhagic Fevers | Granted – amended during opposition proceedings |
| **EP1527087B2** | 17/07/2013 | Recombinant Vesicular Stomatitis Virus Vaccines For Viral Hemorrhagic Fevers | Granted – Result of opposition proceedings Active in CH, DE, ES, FR, GB, IT |
| **ES2338416T3** | 07/05/2010 | Vacunas De Virus Recombinantes De La Estomatitis Vesicular Contra Las Fiebres Hemorragicas. | Granted – amended during opposition proceedings |
| **ES2338416T5** | 20/11/2013 | Vacunas recombinantes del virus de la estomatitis vesicular contra la fiebre hemorrágica vírica | Granted – Active |

**Claims granted (US):**

1. A vaccine comprising:

a live, replication-competent recombinant vesicular stomatitis virus (VSV) particle comprising a nucleic acid molecule encoding a viral hemorrhagic fever (VHF)

Figure 1



glycoprotein selected from the group consisting of a glycoprotein from Lassa virus; a glycoprotein from Marburg virus; and a glycoprotein from Ebola virus, inserted into the viral genome wherein the foreign glycoprotein has replaced the native VSV glycoprotein and only the VHF glycoprotein is expressed on the surface of the recombinant VSV particle, wherein said recombinant VSV particle is infectious.

2. The vaccine according to claim 1 wherein the first gene of the recombinant VSV codes for the VHF glycoprotein.

3. A method of vaccinating an individual comprising:

administering to an individual a live, replication competent recombinant vesicular stomatitis virus (VSV) particle comprising a nucleic acid molecule encoding a viral hemorrhagic fever (VHF) glycoprotein selected from the group consisting of a glycoprotein from Lassa virus; a glycoprotein from Marburg virus; and a glycoprotein from Ebola virus, inserted into the viral genome wherein the foreign glycoprotein has replaced the native VSV glycoprotein and only the VHF glycoprotein is expressed on the surface of the recombinant VSV particle, wherein said recombinant VSV particle is infectious and simulates infection by said VHF virus but does not cause disease or symptoms associated with said VHF.

4. The method according to claim 3 wherein the first gene of the recombinant VSV codes for the VHF glycoprotein.

5. The method according to claim 3 wherein the particle is administered orally.

6. The method according to claim 3 wherein the particle is administered intranasally.

## 9.2 JOHNSON & JOHNSON

Johnson and Johnson, through their subsidiary Crucell, is developing two Ebola vaccines on different delivery platforms. It is developing Ad26-EBOV using a recombinant adenovirus vector and MVA-EBOV using an alternative genetically engineered viral vector, a modified vaccinia Ankara (MVA).

The Ad26-EBOV vaccine regimen, which was discovered in a collaborative research program with the National Institutes of Health (NIH), uses a prime-boost combination of two components that are based on AdVac® technology from Crucell Holland B.V., one of the Janssen Pharmaceutical Companies, and the MVA-BN® technology from Bavarian Nordic, a biotechnology company based in Denmark.[10] According to a press release from Bavarian Nordic at the time of the deal in 2014, the terms of the deal include that Bavarian Nordic will receive an upfront payment of US$ 25 million and is entitled to up to US$ 20 million in development and regulatory milestones, in addition to royalties for commercial sales outside Africa. Additionally, through a private placement, Johnson & Johnson Development Corporation will invest DKK 251 million (approximately US$ 43 million) to subscribe for new shares of Bavarian Nordic.[11]

The core patents for the 2 vaccines are as follows:

[10] https://www.jnj.com/media-center/press-releases/johnson-johnson-announces-formation-of-ebola-vaccine-development-consortia-gains-funding-from-innovative-medicines-initiative

[11] http://www.bavarian-nordic.com/media/media/news.aspx?news=4241

**Title: Adenovirus serotype 26 and serotype 35 filovirus vaccines**

**Abstract/DWPI**: The present invention provides recombinant adenovirus vectors (serotype 26 and serotype 35) encoding filovirus antigens. Method of inducing a protective immune response against a filovirus antigen in a subject, involves administering recombinant adenovirus vector comprising a nucleic acid encoding a filovirus antigenic protein, where the adenovirus vector comprises an adenovirus 26 capsid protein or an adenovirus 35 capsid protein. Preferred Protein: The filovirus antigenic protein is glycoprotein and is from an Ebola virus, preferably Marburg virus.

**Assignee/Applicant:** Crucell Holland B.V. The Government of the United States of America as represented by the Secretary of the Department of Health and Human Services

**Priority date**: 14/12/2010

**Family legal status:**

| Publication Number | Publication Date | Title | Status |
|---|---|---|---|
| **WO2012082918A1** | 21/06/2012 | Adenovirus serotype 26 and serotype 35 filovirus vaccines | Entered national and regional phase |
| **AU2011343798A1** | 11/07/2013 | Adenovirus serotype 26 and serotype 35 filovirus vaccines | Granted as AU2011343798B2 |
| **AU2011343798B2** | 14/07/2016 | Adenovirus serotype 26 and serotype 35 filovirus vaccines | Granted – active |
| **CA2821289A1** | 21/06/2012 | Adenovirus serotype 26 and serotype 35 filovirus vaccines | Filed, awaiting examination |
| **EP2655604A1** | 30/10/2013 | Adenovirus serotype 26 and serotype 35 filovirus vaccines | Under examination |
| **CN103370411A** | 23/10/2013 | Adenovirus serotype 26 and serotype 35 filovirus vaccines | Granted as CN103370411B |
| **CN103370411B** | 04/05/2016 | Adenovirus serotype 26 and serotype 35 filovirus vaccines | Granted – active |
| **US20140017278A1** | 16/01/2014 | Adenovirus Serotype 26 and Serotype 35 Filovirus Vaccines | Under examination |
| **KR2014019304A** | 14/02/2014 | Adenovirus Serotype 26 and Serotype 35 Filovirus Vaccines | Under examination |
| **US20140017278A1** | 16/01/2014 | Adenovirus Serotype 26 and Serotype 35 Filovirus Vaccines | Under examination |
| **EA201390866A1** | 30/05/2014 | Adenovirus Serotype 26 and Serotype 35 Filovirus Vaccines | - |
| **JP2014503206A1** | 13/02/2014 | Adenovirus Serotype 26 and Serotype 35 Filovirus Vaccines | Granted as JP6054876B2 |
| **JP6054876B2** | 27/12/2016 | Adenovirus Serotype 26 and Serotype 35 Filovirus Vaccines | Granted – active |

**Claims (Granted - AU2011343798B2):**

1. A method of inducing an immune response against a filovirus antigen in a subject, the method comprising administering to the subject, as a priming vaccination, an immunologically effective amount of a recombinant adenovirus 26 vector comprising a nucleic acid encoding a filovirus

antigenic protein, followed by a boosting vaccination which includes the administration of a recombinant adenovirus 35 vector comprising a nucleic acid encoding a filovirus antigenic protein.

2. The method of claim 1, wherein the adenovirus vector is administered intramuscularly.

3. The method of claim 1 or claim 2, wherein the filovirus antigenic protein is a glycoprotein.

4. The method of claim 1 or claim 2, wherein the filovirus antigenic protein is from an Ebola virus.

5. The method of claim 4, wherein the Ebola virus is of species Zaire.

6. The method of claim 5, wherein the filovirus antigenic protein is encoded by a polynucleotide sequence as shown in SEQ ID NO: 1.

7. The method of claim 4, wherein the Ebola virus is of species Sudan/Gulu.

8. The method of claim 7, wherein the filovirus antigenic protein is encoded by a polynucleotide sequence as shown in SEQ ID NO: 2.

9. The method of claim 7, wherein the filovirus antigenic protein is encoded by a polynucleotide sequence as shown in SEQ ID NO: 3.

10. The method of any one of claims 1-3, wherein the filovirus antigenic protein is from Marburg virus.

11. The method of claim 10, wherein the filovirus antigenic protein is encoded by a polynucleotide sequence as shown in SEQ ID NO: 4.

12. Use of an immunologically effective amount of a recombinant adenovirus 26 vector comprising a nucleic acid encoding a filovirus antigenic protein in the manufacture of a medicament for inducing an immune response against a filovirus antigen in a subject as a priming vaccination, wherein the medicament is formulated for administration with a boosting vaccination comprising a recombinant adenovirus 35 vector comprising a nucleic acid encoding a filovirus antigenic protein.

13. Use of a recombinant adenovirus 35 vector comprising a nucleic acid encoding a filovirus antigenic protein in the manufacture of a medicament for inducing an immune response against a filovirus antigen in a subject as a boosting vaccination, wherein the medicament is formulated for administration with an immunologically effective amount of a recombinant adenovirus 26 vector comprising a nucleic acid encoding a filovirus antigenic protein as a priming vaccination.

**Title: Methods and Compositions For Inducing Protective Immunity Against Filovirus Infection**

**Abstract/DWPI**: The present invention provides compositions, vaccines and methods for inducing protective immunity against filovirus infection, particularly protective immunity against infection of one or more subtypes of Ebola viruses and Marburg virus. Vaccine combination comprises (i) a first composition comprising an adenovirus vector comprising a nucleic acid encoding an antigenic protein of a first filovirus subtype, together with a carrier; and (ii) a second composition comprising a modified vaccinia Ankara (MVA) vector comprising a nucleic acid encoding antigenic proteins of at least two filovirus subtypes, together with a carrier, where one of the compositions is a priming composition and the other composition is a boosting composition.

**Assignee/Applicant:** BAVARIAN NORDIC A/S, DK CRUCELL HOLLAND B.V., NL THE UNITED STATES OF AMERICA as represented by THE SECRETARY DEPARTMENT OF HEALTH AND HUMAN SERVICES, US

**Priority date**: 3rd September 2014

**Family legal status:**

| Publication Number | Publication Date | Title | Status |
|---|---|---|---|
| **WO2016036955A1** | 03/09/2014 | Methods And Compositions For Inducing Protective Immunity Against Filovirus Infection | Awaiting entry into national and regional phase – BR and EP have been designated |

**Claims (Pending – WO2016036955A1):**

1. A vaccine combination comprising

(i) a first composition comprising an immunologically effective amount of an adenovirus vector comprising a nucleic acid encoding an antigenic protein of a first filovirus subtype, together with a pharmaceutically acceptable carrier; and

(ii) a second composition comprising an immunologically effective amount of an MVA vector comprising a nucleic acid encoding antigenic proteins of at least two filovirus subtypes, together with a pharmaceutically acceptable carrier; wherein one of the compositions is a priming composition and the other composition is a boosting composition.

2. A vaccine combination according to claim 1, wherein the first composition (i) further comprises an adenovirus vector comprising a nucleic acid encoding an antigenic protein of a second filovirus subtype.

3. A vaccine combination according to claim 2, wherein the first composition (i) further comprises an adenovirus vector comprising a nucleic acid encoding an antigenic protein of a third filovirus subtype.

4. A vaccine combination according to claim 1, wherein the adenovirus vector in the first composition (i) comprises a nucleic acid encoding an antigenic protein with SEQ ID NO:l .

5. A vaccine combination according to claim 4, wherein composition (i) further comprises an adenovirus comprising a nucleic acid encoding an antigenic protein with SEQ ID NO:2.

6. A vaccine combination according to claim 5, wherein composition (i) further comprises an adenovirus comprising a nucleic acid encoding an antigenic protein with SEQ ID NO:3.

7. A vaccine combination according to anyone of claims 1-6, wherein the MVA vector in composition (ii) comprises a nucleic acid encoding antigenic proteins of at least four filovirus subtypes.

8. A vaccine combination according to any one of claims 1-7, wherein the MVA vector in composition (ii) comprises a nucleic acid encoding antigenic proteins from four different filovirus subtypes having SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 4, and SEQ ID NO: 5.

9. A vaccine combination according to any one of claims 1-8, wherein the adenovirus vectors are rAd26 or rAd35 vectors.

10. A vaccine combination according to any one of claims 1-9 for use in generating a protective immune response against at least one filovirus subtype, wherein the first composition is used for priming said immune response and the second composition is used for boosting said immune response.

11. A vaccine combination according to any one of claims 1-9 for use in generating a protective immune response against at least one filovirus subtype, wherein the second composition is used for priming said immune response and the first composition is used for boosting said immune response.

12. A method of inducing an immune response against a filovirus in a subject, the method comprising:

a. administering to the subject a first composition comprising an immunologically effective amount of an adenovirus vector comprising a nucleic acid encoding an antigenic protein of a first filovirus subtype;

and b. administering to the subject a second composition comprising an immunologically effective amount of an MVA vector comprising a nucleic acid encoding antigenic proteins of at least two strains of filovirus, wherein steps (a) and (b) are conducted in either order.

13. A method according to claim 12 wherein the first composition further comprises an adenovirus vector comprising a nucleic acid encoding an antigenic protein of a second filovirus subtype.

14. A method according to claim 13, wherein the first composition further comprises an adenovirus vector comprising a nucleic acid encoding an antigenic protein of a third filovirus subtype.

15. A method according to claim 12, wherein the adenovirus vector in the first composition comprises a nucleic acid encoding an antigenic protein with SEQ ID NO: l .

16. A method according to claim 15, wherein the first composition further comprises an adenovirus comprising a nucleic acid encoding an antigenic protein with SEQ ID NO:2.

17. A method according to claim 16, wherein the first composition further comprises an adenovirus comprising a nucleic acid encoding an antigenic protein with SEQ ID NO:3.

18. A method according to anyone of claims 12-17, wherein the MVA vector in the second composition comprises a nucleic acid encoding antigenic proteins of at least four filovirus subtypes.

19. A method according to anyone of claims 12-18, wherein the MVA vector in the second composition comprises a nucleic acid encoding antigenic proteins from four different filovirus subtypes having SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 4, and SEQ ID NO: 5.

20. A method according to anyone of claims 12-19, wherein the adenovirus vectors are rAd26 or rAd35 vectors.

21. A method according to anyone of claims 12-20, wherein step (b) is conducted 1-12 weeks after step (a).

22. A kit comprising:

(i) a first composition comprising an immunologically effective amount of an adenovirus vector comprising a nucleic acid encoding an antigenic protein of a first filovirus subtype, together with a pharmaceutically acceptable carrier; and

(ii) a second composition comprising an immunologically effective amount of an MVA vector comprising a nucleic acid encoding antigenic proteins of at least two filovirus subtypes, together with a pharmaceutically acceptable carrier; wherein one of the compositions is a priming composition and the other composition is a boosting composition.

23. A kit according to claim 22, wherein the first composition (i) further comprises an adenovirus vector comprising a nucleic acid encoding an antigenic protein of a second filovirus subtype.

24. A kit according to claim 23, wherein the first composition (i) further comprises an adenovirus vector comprising a nucleic acid encoding an antigenic protein of a third filovirus subtype.

25. A kit according to claim 22, wherein the adenovirus vector in the first composition (i) comprises a nucleic acid encoding an antigenic protein with SEQ ID NO: l .

26. A kit according to claim 25, wherein composition (i) further comprises an adenovirus comprising a nucleic acid encoding an antigenic protein with SEQ ID NO:2.

27. A kit according to claim 26, wherein composition (i) further comprises an adenovirus comprising a nucleic acid encoding an antigenic protein with SEQ ID NO:3.

28. A kit according to anyone of claims 22-27, wherein the MVA vector in composition (ii) comprises a nucleic acid encoding antigenic proteins of at least four filovirus subtypes.

29. A kit according to anyone of claims 22-28, wherein the MVA vector in composition (ii) comprises a nucleic acid encoding antigenic proteins from four different filovirus subtypes having SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 4, and SEQ ID NO: 5.

30. A kit according to anyone of claims 22-29, wherein the adenovirus vectors are rAd26 or rAd35 vectors.

31. A kit according to anyone of claims 22-30, for use in generating a protective immune response against at least one filovirus subtype, wherein the first composition is used for priming said immune response and the second composition is used for boosting said immune response.

32. A kit according to anyone of claims 22-30, for use in generating a protective immune response against at least one filovirus subtype, wherein the second composition is used for priming said immune response and the first composition is used for boosting said immune response.

33. A vaccine combination according to any one of claims 1-9 or a kit according to any one of claims 22-32 for use in the preparation of a pharmaceutical composition or medicament, wherein the first composition is used for priming said immune response and the second composition is used for boosting said immune response.

34. A vaccine combination according to any one of claims 1-9 or a kit according to any one of claims 22-32 for use in the preparation of a pharmaceutical composition or medicament, wherein the second composition is used for priming said immune response and the first composition is used for boosting said immune response.

## 9.3 GSK / NIAID

The ChAd3-ZEBOV vaccine is being co-developed by NIH's National Institute of Allergy and Infectious Diseases (NIAID) and GlaxoSmithKline (GSK).; The candidate NIAID/GSK Ebola vaccine was developed collaboratively by scientists at the NIAID Vaccine Research Center (VRC) and at Okairos, a biotechnology company acquired by GSK. It contains segments of Ebola virus genetic material from two virus species, Sudan and Zaire. The Ebola virus genetic material is delivered by a carrier virus (chimpanzee-derived adenovirus 3 or cAd 3) that causes a common cold in chimpanzees but causes no illness in humans.[12]

The following is the core patent which covers their vaccine:

**Title: Chimpanzee Adenoviral Vector-Based Filovirus Vaccines**

**Abstract/DWPI**: This invention provides vaccines for inducing an immune response and protection against filovirus infection for use as a preventative vaccine in humans. In particular, the invention provides chimpanzee adenoviral vectors expressing filovirus proteins from different strains of Ebolavirus (EBOV) or Marburg virus (MARV).

**Assignee/Applicant:** Glaxosmithkline Biologicals SA ; US Dept Health & Human Services ; US Dept Health & Human Services ; Ammendola V ; Asiedu C ; Cheng C ; Colloca S ; Cortese R ; Nabel G J ; Nicosia A ; Okairos Ag ; Sullivan N J

**Priority date**: 16th April 2010

[12] https://www.niaid.nih.gov/news-events/niaidgsk-experimental-ebola-vaccine-appears-safe-prompts-immune-response

**Family legal status:**

| Publication Number | Publication Date | Title | Status |
|---|---|---|---|
| **WO2011130627A2** | 20/10/2011 | Chimpanzee Adenoviral Vector-Based Filovirus Vaccines | Entered national and regional phase |
| **US20130101618A1** | 25/04/2013 | Chimpanzee Adenoviral Vector-Based Filovirus Vaccines | Granted as US9526777B2 |
| **US9526777B2** | 27/12/2016 | Methods for the induction of Ebola virus-specific immune responses comprising administering a replication-defective chimpanzee adenovirus vector expressing the Ebola virus glycoprotein | Granted – Active |
| **US20170044571A1** | 16/02/2017 | Chimpanzee Adenoviral Vector-Based Filovirus Vaccines | Under Examination |
| **EP2560680A2** | 27/02/2013 | Chimpanzee Adenoviral Vector-Based Filovirus Vaccines | Under examination |

**Claims (Granted – US9526777B2):**

1. A method of inducing a protective immune response against an Ebola virus infection in a subject, the method comprising intramuscularly administering to the subject 1010 to 1012 viral particles of a recombinant chimpanzee adenovirus type 3 (ChAd3) vector comprising a nucleic acid encoding an Ebola virus glycoprotein, followed by administering to the subject a prophylactically effective amount of a modified vaccinia virus Ankara (MVA) vector comprising a nucleic acid encoding the Ebola virus glycoprotein.

2. The method of claim 1, wherein the Ebola virus is of species Zaire.

3. The method of claim 2, wherein the Ebola virus glycoprotein is encoded by a polynucleotide sequence as shown in SEQ ID NO:10 (Z GP wild-type).

4. The method of claim 1, wherein the Ebola virus is of species Sudan/Gulu.

5. The method of claim 4, wherein the Ebola virus glycoprotein is encoded by a polynucleotide sequence as shown in SEQ ID NO: 11 or 13 (S/G GP codon-optimized or wild-type).

# 10 APPENDIX 1 – PATENT SEARCH STRINGS

| Search string | INPADOC | Individual Cases |
|---|---|---|
| CTB=((Ebola ADJ Virus) OR (Ebola ADJ hemorrhagic ADJ fever) OR ebolaviruses OR Ebola) AND vaccine | 571 | 2356 |
| CTB=(((Ebola ADJ Virus) OR (Ebola ADJ hemorrhagic ADJ fever) OR ebolaviruses OR Ebola) AND vaccine) AND CTB=(adenovir*) AND DP>=(19940101) AND DP<=(20160819); | 205 | 818 |
| CTB=(((Ebola ADJ Virus) OR (Ebola ADJ hemorrhagic ADJ fever) OR ebolaviruses OR Ebola) AND vaccine) AND CTB=(VSV OR (vesicular ADJ stomatitis ADJ virus )) AND DP>=(19940101) AND DP<=(20160819); | 118 | 506 |
| CTB=(((Ebola ADJ Virus) OR (Ebola ADJ hemorrhagic ADJ fever) OR ebolaviruses OR Ebola) AND vaccine) AND CTB=( VLP OR (virus ADJ like ADJ particle)) AND DP>=(19940101) AND DP<=(20160819); | 38 | 157 |