The nascent rise of the therapeutic vaccines market

The therapeutic vaccines market is rapidly developing, growing from $290m in 2011 to a potential $11bn by 2018. ***Aiswariya Chidambaram*** *from* ***Frost & Sullivan*** *outlines the key focuses the therapeutics industry is eyeing up.*

Therapeutic vaccines market – The key milestone

Therapeutic vaccines have marked the advent of a new wave of highly specific and efficacious therapeutic agents that treat a disease or condition by stimulating the body's own immune response. The US Food and Drug Administration's [FDA's] approval of the world's first therapeutic vaccine, Provenge from Dendreon for advanced prostate cancer in men in 2010, has revolutionized the vaccines industry from prophylactic immunization to the treatment of several dreadful diseases. This has not only paved the way for a new generation of biological therapies, but has also reinforced the confidence of pharmaceutical/biotechnology companies, government bodies, investors and the public. The market for therapeutic vaccines, valued at $290 million in 2011, is expected to grow at a compound annual growth rate [CAGR] of 68 percent, over the next seven years to reach nearly $11 billion by 2018. However, there is still a certain degree of uncertainty associated with the exact approach towards therapeutic vaccines in terms of R&D investments, formulating strategies, establishment of regulatory pathways and reimbursement issues.

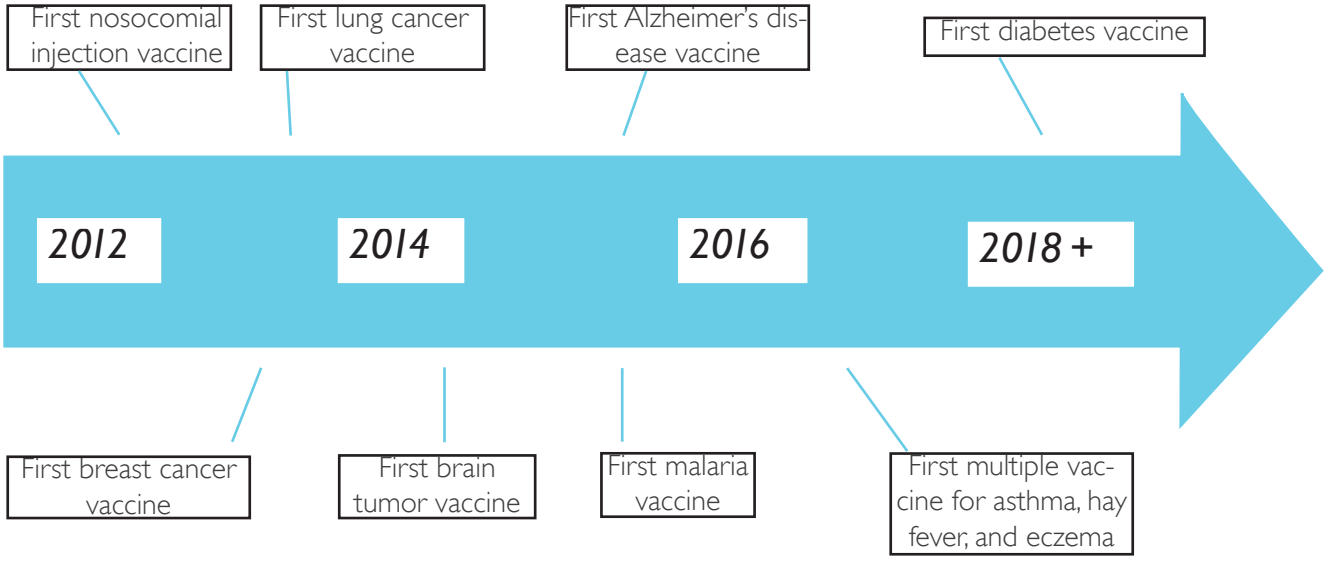

Fig1. Therapeutic Vaccines Market: Expected Timeline of Events (US), 2012-2018
Source: Frost & Sullivan analysis

Therapeutic vaccines technology – The four pillars

The four components that play a crucial role in the design of therapeutic vaccines are as follows:

a) Antigens

Antigens are the active, purified protein components of the vaccine that elicit a specific immune response within the host. In case of antigen-based tumor vaccines, the purified tumor proteins are not directly injected into the body, rather injected to stimulate the individual's antigen presenting cells [APCs] to take up the antigen and present it to the 'T' cells to trigger an immune response. Emerging technologies in antigenic components include:

- DNA/RNA
- Peptide-based
- Carbohydrate-based
- Heat-shock protein
- Recombinant vector [viral and bacterial]

The disease scope of antigenic components is no longer restricted to oncology or infectious diseases. It extends to chronic and metabolic diseases as well.

b) Adjuvants

Developing new classes of adjuvants enables the enhancement of antigen immunogenicity, significantly reducing the amount of antigen required. Alum is the most commonly used one. Oil-in-water emulsions and combination formulations are being investigated as next-generation adjuvants. Virosomes and immunological molecules such as toll like receptors [TLRs] and other inflammatory molecules are being increasingly explored by companies, owing to their well-proven safety and efficacy benefits.

c) Production systems

Many pharmaceutical/biotechnology companies focus on quick and cost-effective production of vaccines by investing in flexible production platforms that can be used across product segments. Recombinant protein technologies are promising new platforms, but are limited by low capacity and high cost. Novel approaches such as host cell lines, vector technologies, media platforms, production process technologies and infrastructures are increasingly being explored. Micro bioreactors have also come into visibility due to their potential in accelerating vaccine production.

d) Delivery systems

Vaccine manufacturers are increasingly focused on exploring innovative delivery devices as an opportunity to improve therapeutic efficacy, enhance ease of use for patients and healthcare providers, and reduce cost of administration. In therapeutic vaccines, particularly, the delivery method is developed in parallel as the vaccine is targeted. Non-invasive delivery techniques such as oral/nasal sprays, transdermal patches, vaccine implants and jet injectors are becoming more popular. Vaccine developers are also increasingly looking at developing in-house delivery technologies.

Key technology trends

Antigenic components [Core Vaccines]

DNA vaccines contain genes encoding the protein-antigen, which transcribes in the host cell to induce an immune response. DNA vaccines are the preferred choice of therapeutic vaccines for most biotechnology companies. These vaccines find extensive application in the R&D of vaccines for HIV, cancer and tropical infectious diseases.

Whole cell vaccines are dendritic cells and tumor cells that can be used as the antigenic compounds in therapeutic cancer vaccines to elicit a specific immune response and target cancerous cells.

Recombinant vaccines are recombinant technologies that employ the use of plasmid vectors to improve the specificity of antigenic components and reduce side effects considerably. Recombinant vector vaccines for both bacterial and viral infections such as HIV, rabies and measles are being investigated.

Carbohydrate conjugate vaccines contain pieces of purified surface capsules [polysaccharides] of disease-causing organisms attached to proteins of known immunogenicity. Carbohydrate-based vaccines for cancers targeting specific glycoproteins on target cells [e.g. mucins] are being investigated for therapeutic use.

Delivery systems

Novel delivery technologies are increasingly preferred to ensure pain-free administration, improved therapeutic efficacy, minimal intervention of trained professionals, and enhanced target-site specificity [cancer, neurology]. Non-invasive formulations such as oral vaccines, nasal sprays, lozenges, transdermal patches and so on improve patient compliance while intradermic microinjections administered directly into the dermal layer of skin rich in immune cells ensure rapid onset of action.

Additionally, use of nano particles in vaccine delivery offers improved safety and efficacy of injected vaccines with fewer antigens, sparing the need of an additional adjuvant. An example of this includes Particle Replication In Non-Wetting Templates [PRINT] technology, which was developed by Liquida Technologies.

Electroporation and other delivery methods [for HIV, oncology] find utility in nucleic acid-based vaccines to ensure proper uptake.

Finally, depot-based vaccine delivery systems are being developed by companies such as Immunovaccine and others, which have a promising future, especially for a cancer vaccine.

Adjuvants [carrier systems]

Adjuvant technologies are considered one of the most important growth drivers of the therapeutic vaccines market and are increasingly becoming a major area of focus for pharmaceutical companies. Next-generation adjuvant technologies play a crucial role in helping researchers overcome barriers associated with the development of effective vaccines against infectious diseases such as malaria, HIV and tuberculosis. Widely tested Antigenics' adjuvant, Q-21 is being assessed for nearly 20 indications, four of which have advanced to phase III clinical trials.

Adjuvants also play a crucial role in differentiating one product from another, thereby significantly impacting a company's market share. In the United States, the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health [NIH], has launched a new initiative to support the development of new candidate vaccine adjuvants.

Production systems

The appropriate choice of production systems is crucial for vaccine manufacturers, not only for cost-effective production, but also to meet global demand during times of emergency situations, such as pandemic outbreaks, epidemics and bio-terrorism. Production systems are also designed to produce properly glycosylated proteins that match those for the required antigenic potential.

Expression systems ranging from yeast to insect cell lines to mammalian cell lines have all been used for developing effective vaccines [mainly viral-based] for appropriate glycosylation patterns. Different antigenic targets work well with particular production systems– natural or synthetic organisms are preferred as vectors for the expression of immunogenic proteins for HIV, malaria and various cancers, virus-like particles for vaccines to treat rheumatoid arthritis, allergies and cancer, DNA vaccines express selected proteins, evoking immune responses for asthma, AIDS and cancer.

Plants [tobacco, ragweed, etc.] are exposed to bacteria or insects carrying the encoded gene, harvested and crushed, forming the basis of vaccines. Several companies such as Medicago, iBio, Fraunhofer, Novax, and Sembiosys, to name a few, are actively involved in the R&D of plant-based edible vaccines.

Key therapeutic areas – current trends and product developments

HIV/AIDS

The developments of HIV vaccines that induce specific immune responses pose a challenge to vaccine developers owing to the high antigenic variability. Researchers are actively working on designing such vaccines. Of the 42 HIV vaccine candidates in various stages of clinical development, eight of them are being investigated in phase I or phase II clinical trials. Hardly any vaccine candidates

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have progressed beyond phase 2b clinical phase. The core research areas include evaluation of basic aspects of pathogenesis, designing of safe and effective vectors, and broadly applicable vaccines for HIV treatment. Both prophylactic and therapeutic HIV vaccines are being investigated.

The major types of HIV vaccines constituting the phase I and phase II stages of clinical pipeline include Adenovirus vaccines, Poxvirus vaccines, protein and DNA vaccines. Geovax Hanke/Oxford employs conventional delivery mechanisms for the testing of DNA vaccines while innovative delivery systems are used by Inovio, Profectus and the Vaccine Research Center [VRC].

On successful commercialization, HIV vaccines are expected to command premium pricing, providing huge business prospects for pharmaceutical companies in the long-term future.

The key companies involved in the R&D of HIV vaccines are GSK, Sanofi-Pastuer, Virxsys, Inovio Pharmaceuticals, Novartis Vaccines, GeoVax, Celldex Therapeutics, Profectus Biosciences Inc., Swiss Vaccine Research Institute, IAVI (International AIDS Vaccine Initiative), and Bavarian Nordic.

Oncology

Cancer vaccines are the most researched among therapeutic vaccines, constituting more than half of the clinical pipeline of therapeutic vaccines. Many targeted drug delivery approaches such as DNA/RNA, miRNA vaccines, new combination vaccines, and adjuvants are being researched actively by many companies since they are very crucial for cancer vaccines. Recent FDA approval of the first therapeutic vaccine, Provenge, is a big boost for companies working on similar platforms and the cancer vaccine industry on the whole.

Cancer vaccines are being developed for multiple cancers as well as for specific types. Melanoma and human papillomavirus [HPV] are the most advanced in terms of R&D, constituting 39.1 percent and 10.7 percent of the total cancer vaccines research, respectively. Other cancer vaccines in late stages of development include breast cancer, cervical cancer, colorectal cancer and non-small cell lung cancer.

The therapeutic vaccines industry is likely to undergo a large number of licensing activities in the future. Merck and GSK are examples of two companies that have a robust pipeline of therapeutic vaccines by the acquisition/licensing of several promising candidates from smaller biotech firms.

The key companies involved in the R&D of cancer vaccines are Merck, GSK, Bellicum Pharmaceuticals, Geron, Northwest Biotherapeutics, Agenus, Dendreon, GlobeImmune, Inovio Pharmaeuticals, Transgene, Immatics, CureVac, Oncothyreon, Bavariian Nordic, CellDex, and Dendritic Nanotechnologies. Inc.

Fig. 2
Therapeutic Vaccines Market: Percent of Therapeutic Vaccine Candidates in Various Stages of Clinical Pipeline, by Disease Segment [Global], 2011
Note: All figures are rounded. The base year is 2011. Source: Frost & Sullivan analysis

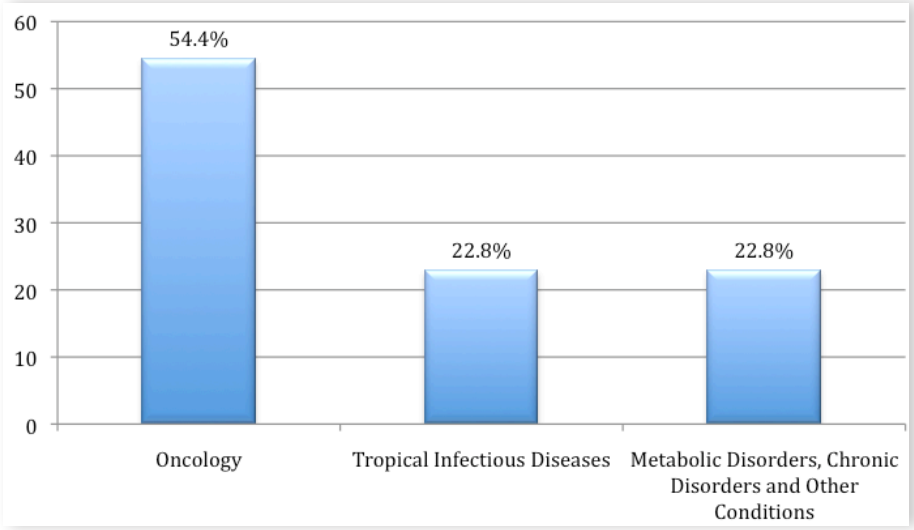
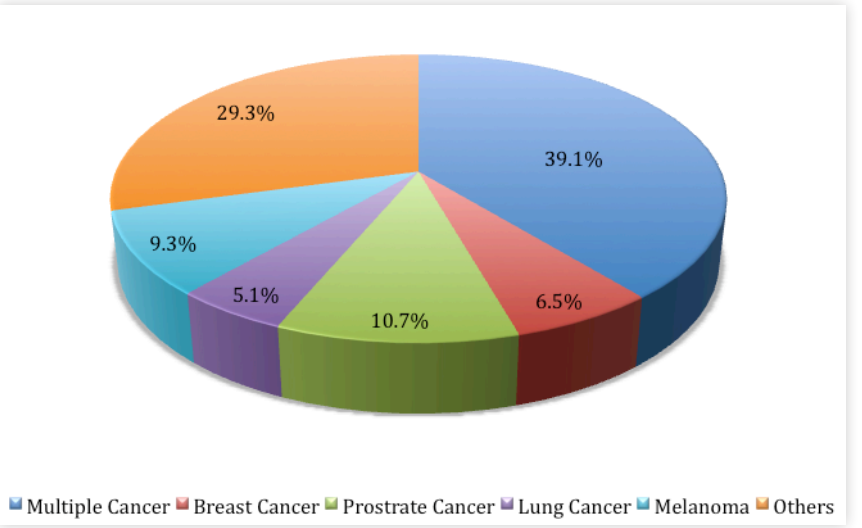


Fig. 3
Oncology Vaccines Market: Percent of Therapeutic Vaccine Candidates in Various Stages of Clinical Pipeline [Global], 2011

Note: All figures are rounded. The base year is 2011. Source: Frost & Sullivan analysis

Note: Others include cervical cancer, colorectal cancer, ovarian cancer and so on



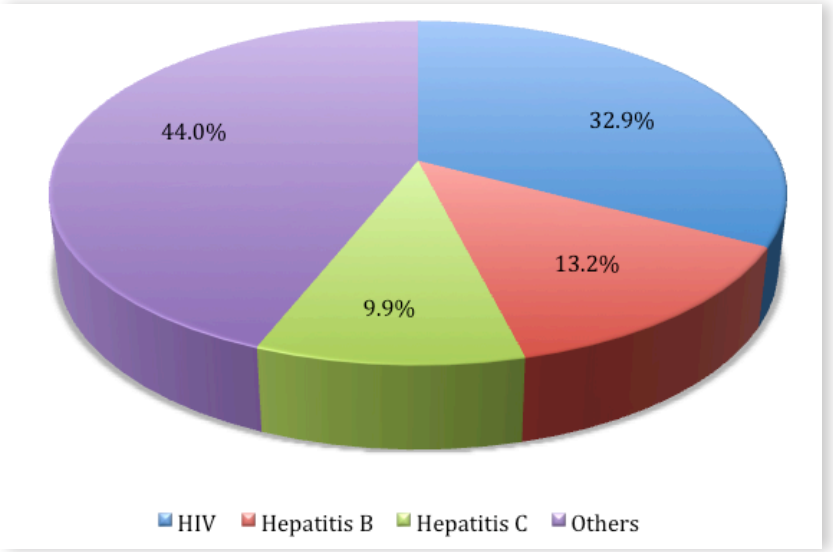


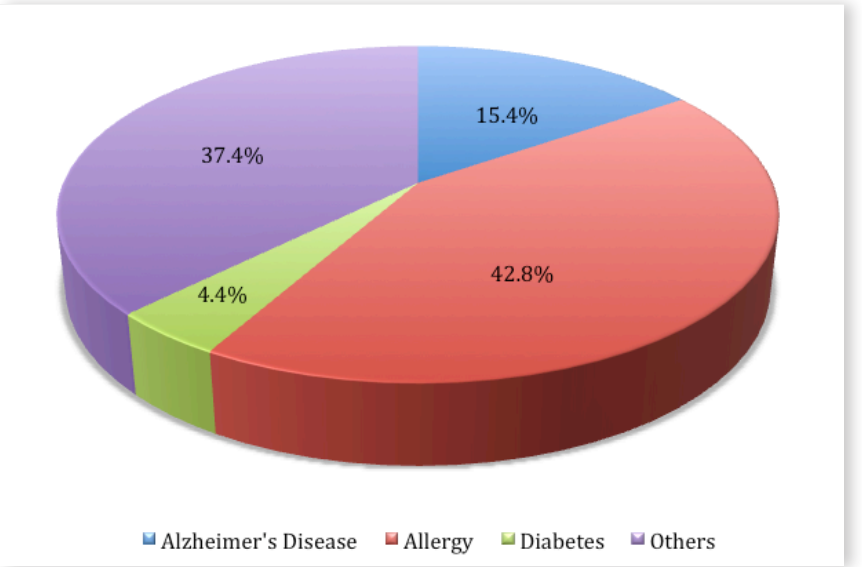
Fig 4
Tropical Infectious Diseases Market: Percent of Therapeutic Vaccine Candidates in Various Stages of Clinical Pipeline [Global], 2011
Note: Others include malaria, chikunguniya, dengue fever and so on.

Note: All figures are rounded. The base year is 2011. Source: Frost & Sullivan analysis.

Fig 5
Metabolic Disorders, Chronic Disorders and Other Conditions Vaccines Market: Per cent of Therapeutic Vaccine Candidates in Various Stages of Clinical Pipeline (Global), 2011

Note: Others include obesity, Parkinson's disease, dyslipidaemia and so on.

Note: All figures are rounded. The base year is 2011. Source: Frost & Sullivan analysis.



Metabolic diseases

Given the increasing target population, huge economic burden and changing lifestyle patterns, there is huge demand for developing both preventive and therapeutic vaccines for chronic disorders like diabetes, obesity and dyslipidaemia. The failure of obesity vaccines in the past reflects the present lean in R&D activities in this space.

Diabetes remains one of the key metabolic disorders of focus for vaccine researchers, with three to four vaccine candidates having entered the phase III clinical trials. Diamyd Medical is one of the noteworthy companies, with its lead vaccine candidate, Diamyd [GAD-based vaccine] in phase III stage of clinical development.

The R&D interest in other key segments such as obesity and dyslipidaemia could gain momentum with increasing support from federal funding agencies, academic institutions and non-profit organizations.

The key companies involved in the R&D of vaccines for metabolic diseases include Braasch Biotech, AndromedA Biotech, Diamyd Medical, and Cytos Biotechnology.

"there is still a certain degree of uncertainty associated with the exact approach towards therapeutic vaccines..."

Tropical infectious disease

High degree of antigenic variability, absence of preventive vaccines for parasitic diseases, and the unavailability of immunological correlates pose challenges with regard to the development of vaccines for tropical infectious diseases. For example, malaria remains the most actively researched disease area among other tropical infectious diseases with close to 60 vaccine candidates in the clinical pipeline.

Vaccines being developed for malaria target the following stages of infection:

- ☐ Pre-erythrocytic stage: This prevents the initiation of infection.
- ☐ Blood-Stage: These prevent the release of pathogens into the blood and reduce clinical disease.
- ☐ Sexual Transmission Blocking: This is aimed at preventing the spread of parasites.

Combination vaccines target multiple stages and can be more effective than single strategies.

Mosquirix [RTS, S] from GSK is currently being investigated in phase III clinical trials for malaria and is expected to hit the market in the next few years. GSK also entered into an agreement with Crucell [Johnson & Johnson] for the development of a more effective malaria vaccine, anticipated to be launched post 2015.

Other tropical infections such as hookworm infection, dengue and chikunguniya are relatively less researched, with a few vaccine candidates in the pipeline. Sanofi Pateur's lead vaccine candidate for dengue fever is currently in phase III clinical trials while Inviragen has vaccines for chikungunya and dengue in its pipeline.

The key companies involved in the R&D of vaccines for tropical infectious diseases include GSK, Sanofi-Pasteur, Bharat Biotech, Inviragen, Malaria Vaccine Initiative (MVI), Bio Ventures for Global Health [BVGH], Themis Bioscience, and International Vaccine Institute [IVI].

Neurology

R&D of vaccines for neurology is still an emerging field with hardly any products in the late stages of clinical development. Alzheimer's disease and Parkinson's disease are the two major areas of focus, with about six to seven vaccine candidates in pipeline. UneMed [tech transfer center of the University of Nebraska Medical Center] currently has a vaccine candidate for Parkinson's disease in pre-clinical trials while Affiris' vaccine candidate is in phase I. The key companies involved in the Alzheimer's space include Cytos, Affiris, Intellect Neurosciences and United Biomedical Inc. RECALL-VAX from Intellect Neurosciences is currently in phase II.

The key companies involved in the R&D of vaccines for neurological disorders include Unemed, AFFiRiS, Cytos Biotechnology, Intellect Neurosciences, and UBI.

Regulatory approval process–FDA concerns

Despite the 2010 approval of the first therapeutic cancer vaccine, Provenge (sipuleucel-T) for advanced prostate cancer in men, which validates the concept of immunotherapy as a novel treatment option that induces the immune system to invade cancer cells and generate a potential response, controversies regarding vaccine clinical trials and safety still prevails. Based on the differences between the conventional oncology therapies and the next-generation therapies, the FDA cautions companies to test cancer vaccines in patients with no evidence or minimal burden of the disease. Furthermore, appropriate selection of patient groups, study design, dose requirements and improved survival rates are crucial factors that need to be accounted for while considering the safety and efficacy of therapeutic vaccines. Nevertheless, immunotherapy is still in an infancy stage and companies are continuously striving to investigate the potential of therapeutic vaccines and combination therapies across various disease areas.

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Aiswariya Chidambaram is a Research Analyst with Frost & Sullivan's Healthcare practice. She has developed syndicated and customized market research on key therapeutic and service areas for both the European and global pharma and biotech markets. Her area of industry expertise covers diverse therapeutic segments and product portfolios, which includes diabetology, cardiovascular diseases, general medicine and women's healthcare. Aiswariya has also authored articles for reputed journals, magazines and newsletters in Europe. Additionally, she has awarded healthcare companies for demonstrating excellence in specific market/product segments and technologies. Aiswariya holds a Bachelor's in Technology, with a specialization in Biotechnology, from Anna University.

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