Cancer Vaccines Market Focused on Dendritic Cell Vaccine and Tumor Cell Vaccine

Project Report submitted in partial fulfillment of the requirement for the degree

of

Bachelor of Technology

In

Biotechnology

Under the Supervision of

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By

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CERTIFICATE FROM COMPANY

This is to certify that Ms. Shadali Singh, has successfully completed his internship from 1st February to 31st May 2016, in Roots Analysis, Mohali.

Gaurav Chaudhary
Director
Roots Analysis

CERTIFICATE

This is to certify that the work titled, "**Cancer Vaccines Market Focused on Dendritic Cell Vaccine and Tumor Cell Vaccine**" in partial fulfilment for the award of B.Tech Degree in Biotechnology of Jaypee University of Information Technology, Waknaghat has been carried out under my supervision. This work has not been submitted partially or wholly to any other University or Institute for the award of this or any other degree or diploma.

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(Ms.Shadali Singh)

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ABBREVIATIONS

TAA- Tumor Associated Antigens

ACT- Adoptive Cell Transfer

TIL- Tumor-Infiltrating Lymphocyte

CAR- Chimeric Antigen Receptor

CTL- Cytotoxic T-cells

USFDA- United States Food and Drug Administration

IND- Investigational New Drug

BLA- Biological License Application

NCI – National Cancer Institute

CBER- Center of Biological Evaluation and Research

DC- Dendritic Cell

CMO- Contract Manufacturing Organization

CRO- Contract Research Organization

NCCN- National Comprehensive Cancer Network

CSR- Corporate Social Responsibility

NGO- Non Governmental Organization

CEO- Chief Executive Officer

VP- Vice President

SEC- Securities and Exchange Commission

ADC- Antibody Drug Conjugate

3D- Three Dimension

QC- Quality Check

VC- Venture Capital

APC- Antigen Presenting Cell

CD4- Cluster of Differentiation 4

CD8- Cluster of Differentiation 8

NK- Natural Killer

IL-2- Interleukin 2

MHC- Major Histocompatibility Complex

HBV- Hepatitis B

HPV- Human Papillomavirus Infection

Ig- Immunoglobulin

DNA- Deoxyribonucleic acid

GM-CSF- Granulocyte Macrophage Colony Stimulating Factor

NCCN- National Comprehensive Cancer Network

NASDAQ- National Association of Securities Dealers Automated Quotation System

ViE- Variable Interest Equity

R&D- Research and Development

IDO- Indoleamine 2,3- Dioxygenase

TDO- Tryptophan 2,3- Dioxygenase

NSCLC- Non Small Cell Lung Cancer

EC- European Community

ASCO- American Society of Clinical Oncology

CTC- Common Terminology Criteria

OS- Overall Survival

JPO- Japan Patent Office

EPO- European Patent Office

IPO- Initial Public Offering

USD- United States Dollar

SUMMARY

Roots Analysis is a business research and a consulting company. It's a start-up established in the field of Biotechnology and Pharmaceuticals with an aim of providing an in-depth, exhaustive and dedicated research work in the field of biopharmaceuticals to its client.
During the internship period various different modules were taken over, making us acquainted with the Roots Analysis formats and working styles. During the period, I completed one report project on "**Cancer Vaccine Market Focused on DC cancer vaccine and tumor cell cancer vaccine**".

The report has been divided into 2 main sections, first involves a glimpse of the one month training sessions and the second section talks about the major project report.

The reports are a matter of copyright to the company and all the information cannot be disclosed. Thus, some information has been shared in this report.

1. COMPANY INTRODUCTION

Roots Analysis is a Business Research and Consulting Company. Founded by Mr. Gaurav Chaudhary in 2012. The firm is based in Chandigarh. Currently, it has employees around 22-25. It's a start-up established in the field of Biotechnology and Pharmaceuticals with an aim of providing an in-depth, exhaustive and dedicated research work in the field of biopharmaceuticals to its client.

The company is driven by Mr. Gaurav Chaudhary and with an expert team of business analysts. The teams under the guidance of Gaurav and Shivani perform exhaustive primary and secondary research on various emerging fields in the space of pharmaceutical/biotechnology industry. In addition to business research, the company handles various consultancy projects depending upon the requirements of the clients.

Apart from the work, Roots Analysis is actively involved in various CSR activities including NGO visits, fundraising events for NGO. The company operates 5 days in a weeks from 9am to 6pm. The timings are flexible that varies based on the workload and the work-plan of a particular analyst. The company handles projects in different segments of pharmaceutical and biotechnology which include medical devices, drugs and biologics and upcoming technologies, clinical trial tracker.

The work performed by the analysts of the company is based on two approaches;

- Primary Research
- Secondary Research

Primary Research, is basically a mode of getting information directly by interacting people of corporate world that includes company CEO, VPs, Directors, Diplomats, Experts, Investors related to specific industry for which the project is going on. However, the process gives us basic idea about the current market landscape of a particular company, technology or products. Moreover, it also gives an idea about futuristic outlook about the product. Apart from this, it also adds up credibility to our work.

Secondary Research, is a mode by which information related to products and technology is collected through secondary sources. It includes

1. SEC Finding

2. Annual Reports
3. Market Reports
4. Press Releases
5. Information at Company's website
6. Information available on internet

Based on these sources we collect all the needed information for a project and by making different assumption related to different constraints we try to predict or forecast the market of particular drug, technology or a device. The reports can be categorized into different segments, such as:

- Therapeutic Segments: Oncology, Diabetes Mellitus etc.
- Pharmaceuticals: Antibody Drug Conjugates (ADCs), Immune checkpoints inhibitors (ICIs), etc.
- Biopharmaceuticals: Polymer drug conjugates.
- Medical devices: Prefilled syringes, Auto-injectors etc.
- Emerging Technology: 3D Bio-printing etc.

2. WORK PROGRAMS

Since the training period was of 4 months (February 2016- May 2016). Therefore I was entitled to work on 1 major project on Cancer Vaccines- Dendritic Cell and Tumor Cell Vaccines during the course of training period.

1. 4 weeks: Training Sessions
2. 13 weeks: *Project Report- Cancer Vaccines Market Focused on Dendritic Cell Vaccine and Tumor Cell Vaccine*

The first month was designed in such a way that interns are able to learn all the aspects of different types of projects that Roots Analysis does. In this one month, training session were conducted once a week which covered different aspects of learning. Also, based on the learning, assignments were also allotted to the interns in order to evaluate them based on their learning through the training sessions.

After the first month, the project was allotted to me.

This project was allotted to me wherein my role was to capture the information available on secondary resource (as an analyst). However, through checks (QC) have been performed by the allotted team of 2 supervisors. The section of market forecast is still under progress and is worked upon by my supervisors. In this project, I was expected to collect the data, provide a structure to the report, and conduct some basic analysis and complete the first draft which was inclusive of the primary sections of the report.

The project involved an extensive study of the emerging market of DC and tumor cell cancer vaccines.

One of the key objective of this report is to understand the current and future state of these cancer vaccine classes. This is done by analyzing the following:

- DC cancer vaccines and tumor cell vaccine currently available in the market
- DC cancer vaccines and tumor cell vaccine currently in the pipeline
- Leading Companies working in this area
- CMO and CRO collaborations, funding instances
- Size of target consumer segments

The report prepared for the company will include:

- Preface

- Executive Summary
- Introduction
- Company Profiles and Drug Profiles
- Technology Profiles
- Partnerships
- VC Fundings
- Analysis/CMO CRO
- Market Forecast
- Market Overview
- Conclusion
- Appendix

3. TRAINING SESSION: 4 WEEKS

The basic objective for these session was to make us familiarize with the tasks, type of work that Roots Analysis is doing.

It is basically a 4-week training module designed in a way that all aspects of the project are covered during the training period. So that when the new projects are allotted to the interns, they are in already acquainted with the methods to progress further with the task allotted.

In this period, different things were explored including Blogs and Transcript writing, Market forecasting, Project allocation and Introduction to RA reports etc.

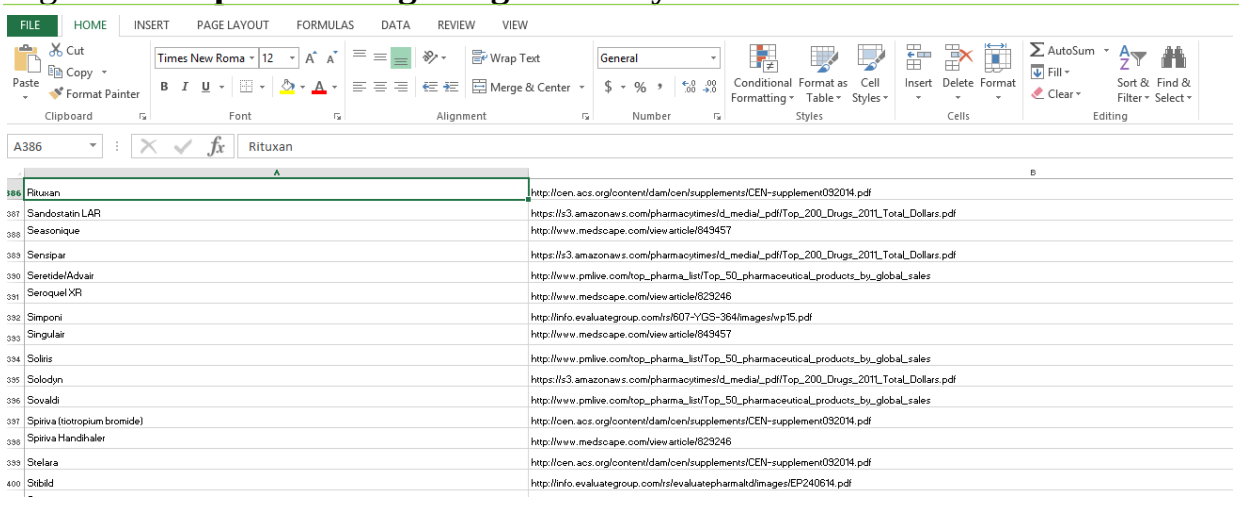
In the first week at RA, we had sessions on RA reports, sessions on basic grammar and on blogging. During this week we were not allotted with any evaluative assignment. However, we learnt about the formats and writing pattern that is followed by RA in their Business Reports.

Sub tasks of the major projects were allotted in the next three weeks. These included:

- List of drugs deliverable by auto-injectors for breast cancer, prostate cancer and Endometriosis. (A part of one of the consultancy projects)
- Interview contact list
- List of top 500 selling drugs, etc.

Figure 3.1, figure 3.2 and figure 3.3 are sample images of the database prepared. Due to confidentiality of the work the whole database cannot be shared.

Figure 3.1 **Top 500 Selling Drugs Globally**



	A	B
386	Rituxan	http://cen.acs.org/content/dam/cen/supplements/CEN-supplement092014.pdf
387	Sandostatin LAR	https://s3.amazonaws.com/pharmacytimes/d_media/_pdf/Top_200_Drugs_2011_Total_Dollars.pdf
388	Seasonique	http://www.medscape.com/viewarticle/849457
389	Sensipar	https://s3.amazonaws.com/pharmacytimes/d_media/_pdf/Top_200_Drugs_2011_Total_Dollars.pdf
390	Seretide/Advair	http://www.pmlive.com/top_pharma_list/Top_50_pharmaceutical_products_by_global_sales
391	Seroquel XR	http://www.medscape.com/viewarticle/829246
392	Simponi	http://info.evaluategroup.com/rs/607-YGS-364/images/wp15.pdf
393	Singulair	http://www.medscape.com/viewarticle/849457
394	Soliris	http://www.pmlive.com/top_pharma_list/Top_50_pharmaceutical_products_by_global_sales
395	Solodyn	https://s3.amazonaws.com/pharmacytimes/d_media/_pdf/Top_200_Drugs_2011_Total_Dollars.pdf
396	Sovaldi	http://www.pmlive.com/top_pharma_list/Top_50_pharmaceutical_products_by_global_sales
397	Spiriva (tiotropium bromide)	http://cen.acs.org/content/dam/cen/supplements/CEN-supplement092014.pdf
398	Spiriva Handihaler	http://www.medscape.com/viewarticle/829246
399	Stelara	http://cen.acs.org/content/dam/cen/supplements/CEN-supplement092014.pdf
400	Stribild	http://info.evaluategroup.com/rs/evaluatepharmaltd/images/EP240614.pdf

Source: Roots Analysis

Figure 3.2 **Auto-Injectors: Drugs for Prostate Cancer**

3	Histrelin acetate		Endo Pharmaceut	Prostate Cancer	Surgical Implant	50 mg	52 week	Phase 3	https://clinicalt
4	Bicalutamide		AstraZeneca	Prostate Cancer	Oral Administration	200 mg	Daily, 3 months	Phase 3	https://clinicalt
5	Ipilimumab	Antibody	Bristol-Myers Squ	Prostate Cancer	Intravenous	5 mg/ml	3 weeks (Induction Pha	Phase 3	https://clinicalt
6	Leuprorelin,flutamide		Takeda	**Prostatic Neoplasms**	Leuprorelin-Subcutaneou	11.25mg	Leuprorelin-Once in 3 m	Phase 3	https://clinicalt
7	Zoledronic		Novartis Pharmac	Prostate Cancer	Infusion	4 mg	Every 4 weeks	Phase 3	https://clinicalt
8	Docetaxel		**Dana-Farber Cancer Institute|Sanofi**	Prostate Cancer	?	Docetaxel-20 mg/m	Per week 7 weeks (along	Phase 3	https://clinicalt
9	Leuprorelin acetate	LHRH antagonist	Astellas Pharma Inc	Prostate Cancer	Intravenous	22.5 mg	2 doses in 6 months(In	Phase 3	https://clinicalt
10	Leuprolide Mesylate		**Foresee Pharmaceuticals Co., Ltd.| QPS-Qualitix**	Prostatic Neoplasms	Intravenous	50mg	1 dose in 6 months;	Phase 3	https://clinicalt
11	amg 162		Amgen	Bone Metastases in Men With : Hormone-Refractory Prostate Cancer, Advanced Breast Cancer, Advanced Cancer or Multiple Myeloma	Subcutaneous	120 mg	NA	Phase 3	https://clinicalt
12	Nadroparin		GlaxoSmithKline	Thrombosis, Venous	Subcutaneous	NA	46 weeks	Phase 3	https://clinicalt
13									

Sheet2 | pre menupausal breast cancer | prostate cancer

Source: Roots Analysis

Figure 3.3 **Auto-Injector: Drugs for Endometriosis**

ZOladex New - Microsoft Excel

FILE HOME INSERT PAGE LAYOUT FORMULAS DATA REVIEW VIEW

B30 | Therapeutic Modality

	Drug	Mode of Action	Company	Indication	Route of Administration	API Dosage	Dosage Frequency	Phase of Development	
2	Infliximab	Anti TNFa monc	Katholieke Univers	Endometriosis	Infusion	250mL	Once 0, 2 and 6th v	Phase 2	https://clinicaltrials.gov/ct2/show/NCT00
3	Triptorelin Acetate	Gonadotrophin Rel	Ipsen	Deep Infiltrating Enc	Intramuscular injection	3.75mg	Once every four week		https://ClinicalTrials.gov/show/NCT01942369
4	Tanezumab	mAb against nerve	Pfizer	Endometriosis	Intravenous	15 mg	Single dose	Phase 2	https://ClinicalTrials.gov/show/NCT00784693
5	ERB-041	Agonist of ERβ	Wyeth a subsidary o	Endometriosis	NA	75 mg and 150 mg	NA	Phase 2	https://ClinicalTrials.gov/show/NCT00110487
6	BGS649	Aromatase inhibitor	Novartis	Endometriosis	Oral Monotherapy	0.1 mg	3 doses at randomizat	Phase 2	https://clinicaltrials.gov/ct2/show/NCT01190475
7	Elagolix	GnRH receptor an	AbbVie	Endometriosis	Oral Administration	NA	1 dose in 6 months	Phase 3	https://ClinicalTrials.gov/show/NCT01620528
8	Lignocaine	Antiarrhythmia age	Isifer AB|Stockholm C	Endometriosis|Dysn	Intravenous injection for ana	NA	Three treatments give	Phase 2	https://ClinicalTrials.gov/show/NCT01329796
9	Zoladex	Adjuvant	AZ Jan Palfijn Gent|O	Infertility|Endometric	Subcutaneous	NA	3 months (after surgic	Phase 4	https://ClinicalTrials.gov/show/NCT01682642
10	Anastrazole Plus Luprol	Aromatase inhibitor	Centre for Endocrinol	Endometriosis	NA	Leuprolide acetate-11.25mg + anastrazole-	Once a day for 3 mont	Phase 4	https://ClinicalTrials.gov/show/NCT01769781
11	CCR1-Antagonist (BAY	CCR1-Antagonist	Bayer	Endometriosis	Oral Administration	600 mg	Thrice daily over 12 we	Phase 2	https://ClinicalTrials.gov/show/NCT00185341
12	Dienogest (Visanne, BA	Steroidal progestoge	Bayer	Endometriosis	Oral Administration	2 mg	once daily, 0-52 week	Phase 3	https://ClinicalTrials.gov/show/NCT01822080
13	ASP1707	Gonadotropin-rel	Astellas Pharma Europ	Endometriosis	Oral Administration	NA	NA	Phase 2	https://ClinicalTrials.gov/show/NCT01767090
14	Ulipristal	Selective progeste	Northwestern Universi	Endometriosis	NA	15mg	3 times a week for 3 m	Phase 4	https://ClinicalTrials.gov/show/NCT02213081
15	DR-2001a and DR-200	Cell surface protea	Duramed Research|T	Endometriosis	Administered vaginally	NA	Every month for 12 we	Phase 2	https://ClinicalTrials.gov/show/NCT00117481
16	Triptorelin acetate	Potent LHRH (GnR	Instituto de Investigac	Endometriosis|Infert	Subcutaneous injection	3,75 mg	Days 1, 28 and 56 afte	Phase 4	https://ClinicalTrials.gov/show/NCT01581359
17	Palmitoylethanolamide	N-acylethanolamir	University of Cagliari	Endometriosis|Chro	Sublingually and orally	600 mg and 400 mg	Twice for 10 days	NA	https://ClinicalTrials.gov/show/NCT02372903
18	Leuprolide	Gonadotropin Rele	University of Ioannina	Endometriosis|Infert	Injection route NA	3.75	once every 28 days, 3	NA	https://ClinicalTrials.gov/show/NCT01269125
19	MEdical Versus SUrgical Treatments of Rectal Endometriosis (confusion)								
20	Lidocaine	Class Ib type anti	Brigham and Women's	Endometriosis	Intravenous	8mg/kg	infused over 30 minute	NA	https://ClinicalTrials.gov/show/NCT01968694
21	Dynamized estrogen	Estrogen hormone'	University of Sao Paul	Endometriosis|Pelvi	NA	30 ml every 8 weeks	3 drops, 2 times a day	Phase 4	https://ClinicalTrials.gov/show/NCT02427386
22	Degarelix	GnRH antagonist	Centre for Endocrinol	Endometriosis	NA	80 mg	Once in three months	Phase 3	https://ClinicalTrials.gov/show/NCT01712763
23	Desogestrel	Progestin	Mahidol University	Endometriosis	Oral Administration	75 mcg	Once daily 6 months	NA	https://ClinicalTrials.gov/show/NCT01553480
24	Mifepristone	Progestational and	Mediterranea Medica	Endometriosis	Oral Administration	Variable (2.5mg, 5mg or 10mg)	6 months	Phase 2|Phase 3	https://ClinicalTrials.gov/show/NCT02271958
25	Oral Contraceptive	Steroids	Eunice Kennedy Shri	Endometriosis|Pelvi	Oral Administration	30ug-ethinyl estradiol & 0.15mg-levonorge	Once daily for 48 weel	Phase 3	https://ClinicalTrials.gov/show/NCT00229996
26	NBI-56418	GnRH agonist	Abbott	of ethinylestradiol (2	NA	Variable (75 mg & 150 mg)	Once daily for 12 week	Phase 2	https://ClinicalTrials.gov/show/NCT00109512
27	Raloxifene	Selective estroger	Eunice Kennedy Shri	Endometriosis|Pelvic Pain			Once daily for 6 month	Phase 2	https://ClinicalTrials.gov/show/NCT00001848

Source: Roots Analysis

4. CANCER VACCINES MARKET FOCUSED ON DC VACCINE AND TUMOUR CELL VACCINE

After reading about the cancer vaccines it was concluded that there are five major division of the vaccines based on their method of preparation (these has been talked about in the introduction part). Out of the five classes the scope of the report was narrowed down to two classes that are dendritic cell vaccines and tumor cell vaccines.

4.1. PIPELINE/DATABASE BUILDING

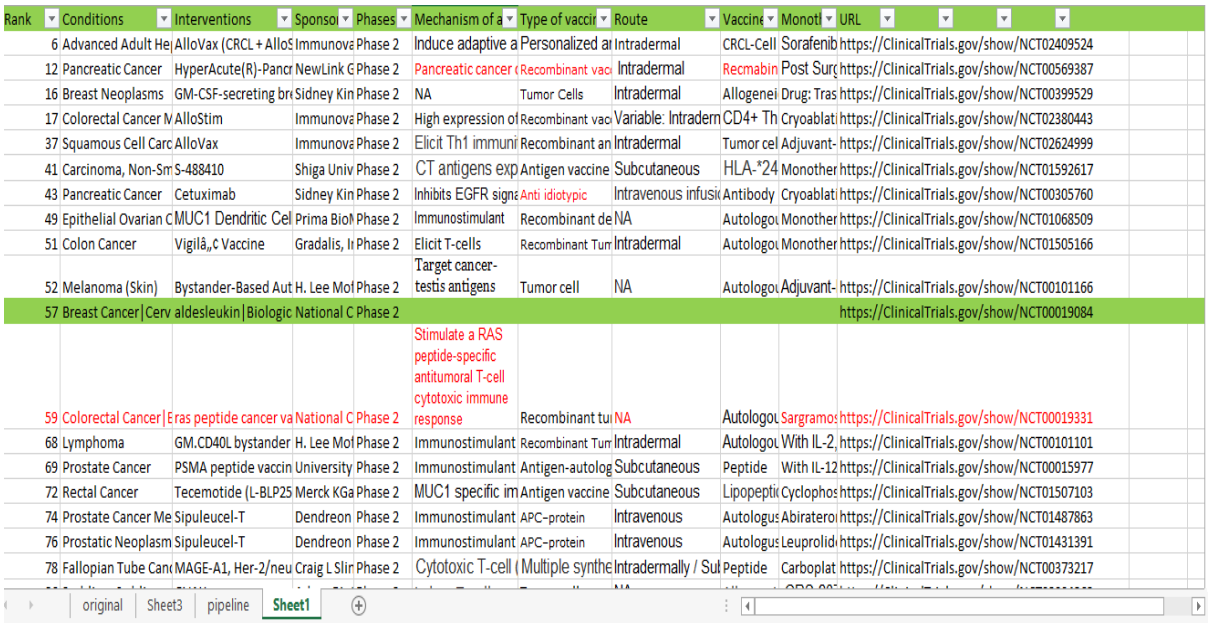
After the allotment of the project topics a database or pipeline was built for built. This is the work that has been performed in each and every research project. Because pipeline/database is an exhaustive collection which gives us an idea about the futuristic overlook of the project. By definition, Pipeline/ Database is actually a collection of all the devices/drugs or technology which are relevant to our project on which we are working on. For example; if we are working on a project related to ADC. Then the pipeline must contains all the antibody drug conjugates details that may be marketed/preclinical/Phase I/Phase II/Phase III.

The main source for these information includes

- Google Search
- Company's press release
- Various press release portals available world wide
- Company's pipeline
- Clinical trial website: clinicaltrials.gov.in
- Drug databases
- Annual Reports
- LinkedIn
- Press Releases

Therefore, after utilizing different source, an exhaustive secondary research for 2 weeks was performed and a database was prepared as shown in the figure below. Due to confidentiality of the work it is not possible to share whole database, but a sample view can be depicted from the picture as shown below.

Figure 4.1 **Pipeline: Cancer Vaccines**



Rank	Conditions	Interventions	Sponsor	Phases	Mechanism of a	Type of vaccir	Route	Vaccine	Monoth	URL
6	Advanced Adult He	AlloVax (CRCL + Allo	Immunova	Phase 2	Induce adaptive a	Personalized a	Intradermal	CRCL-Cell	Sorafenib	https://ClinicalTrials.gov/show/NCT02409524
12	Pancreatic Cancer	HyperAcute(R)-Panc	NewLink G	Phase 2	Pancreatic cancer	Recombinant vac	Intradermal	Recmabin	Post Surg	https://ClinicalTrials.gov/show/NCT00569387
16	Breast Neoplasms	GM-CSF-secreting br	Sidney Kin	Phase 2	NA	Tumor Cells	Intradermal	Allogenei	Drug: Tras	https://ClinicalTrials.gov/show/NCT00399529
17	Colorectal Cancer M	AlloStim	Immunova	Phase 2	High expression of	Recombinant vac	Variable: Intradern	CD4+ Th	Cryoablati	https://ClinicalTrials.gov/show/NCT02380443
37	Squamous Cell Carc	AlloVax	Immunova	Phase 2	Elicit Th1 immuni	Recombinant an	Intradermal	Tumor cel	Adjuvant-	https://ClinicalTrials.gov/show/NCT02624999
41	Carcinoma, Non-Sm	S-488410	Shiga Univ	Phase 2	CT antigens exp	Antigen vaccine	Subcutaneous	HLA-*24	Monother	https://ClinicalTrials.gov/show/NCT01592617
43	Pancreatic Cancer	Cetuximab	Sidney Kin	Phase 2	Inhibits EGFR signa	Anti idiotypic	Intravenous infusi	Antibody	Cryoablati	https://ClinicalTrials.gov/show/NCT00305760
49	Epithelial Ovarian C	MUC1 Dendritic Cel	Prima Bio	Phase 2	Immunostimulant	Recombinant de	NA	Autologou	Monother	https://ClinicalTrials.gov/show/NCT01068509
51	Colon Cancer	Vigilâ„¢ Vaccine	Gradalis, I	Phase 2	Elicit T-cells	Recombinant Tum	Intradermal	Autologou	Monother	https://ClinicalTrials.gov/show/NCT01505166
52	Melanoma (Skin)	Bystander-Based Aut	H. Lee Mof	Phase 2	Target cancer-testis antigens	Tumor cell	NA	Autologou	Adjuvant-	https://ClinicalTrials.gov/show/NCT00101166
57	Breast Cancer|Cerv	aldesleukin|Biologic	National C	Phase 2						https://ClinicalTrials.gov/show/NCT00019084
59	Colorectal Cancer|	Eras peptide cancer va	National C	Phase 2	Stimulate a RAS peptide-specific antitumoral T-cell cytotoxic immune response	Recombinant tu	NA	Autologou	Sargramos	https://ClinicalTrials.gov/show/NCT00019331
68	Lymphoma	GM.CD40L bystander	H. Lee Mof	Phase 2	Immunostimulant	Recombinant Tum	Intradermal	Autologou	With IL-2,	https://ClinicalTrials.gov/show/NCT00101101
69	Prostate Cancer	PSMA peptide vaccin	University	Phase 2	Immunostimulant	Antigen-autolog	Subcutaneous	Peptide	With IL-12	https://ClinicalTrials.gov/show/NCT00015977
72	Rectal Cancer	Tecemotide (L-BLP25	Merck KGa	Phase 2	MUC1 specific im	Antigen vaccine	Subcutaneous	Lipopepti	Cyclophos	https://ClinicalTrials.gov/show/NCT01507103
74	Prostate Cancer Me	Sipuleucel-T	Dendreon	Phase 2	Immunostimulant	APC-protein	Intravenous	Autologus	Abiratero	https://ClinicalTrials.gov/show/NCT01487863
76	Prostatic Neoplasm	Sipuleucel-T	Dendreon	Phase 2	Immunostimulant	APC-protein	Intravenous	Autologus	Leuprolid	https://ClinicalTrials.gov/show/NCT01431391
78	Fallopian Tube Can	MAGE-A1, Her-2/neu	Craig L Slin	Phase 2	Cytotoxic T-cell (	Multiple synthe	Intradermally / Sul	Peptide	Carboplat	https://ClinicalTrials.gov/show/NCT00373217

Source: Roots Analysis

A vast database of products under process were collected which lead to a hefty pipeline with 500 plus product candidates.

As mentioned earlier since cancer vaccines is a broad topic with large number of total products under development and the scope of the project was focused on Dendritic Cell Vaccines and Whole Cell vaccines. Which helped finalize a pipeline indicating a total of 8 molecules (Marketed + Phase III) that will influence the market within next 10 years. In the drug and company profile section, it was decided to profile these molecules.

4.2. INTRODUCTION

4.2.1. CANCER

A collection of related diseases; where the genetically modified cells divide numerously and spread into the other tissues. The human body comprises of trillion cells, cancer can originate from any of these cells in the body. In a healthy human cells grow and divide to form new cells as and when the body needs them. When cells grow old or become damaged, they die, and new cells take their place this process of programmed cell death that occurs in multicellular organisms is called apoptosis.

This orderly process is altered in cancer cells; new cells are generated when not needed and the cell apoptosis does not occur.

Three main types of genes that are affected by the genetic mutations of cancer cells include:

- ***Proto-oncogenes***: These are involved in division and normal growth of cells. However, alteration of these genes in a certain manner may transform them into oncogenes and allow growth and survival of abnormal cells.
- ***Tumor suppressor genes:*** Similar function as proto-oncogenes, these genes control cell growth and division. An alteration in these genes may lead to uncontrolled division of cells.
- ***DNA repair genes***: These genes manage the fixation of damaged DNA. The cells with mutation in these genes have a tendency to develop additional mutations in other genes. Together these mutations may cause the cells to become cancerous.

There are several types of cancers. Usually cancers are named according to the tissue, organ or type of cell they are associated with. For example, lung cancer, breast cancer, non-small cell lung cancer.[1]

Self-antigens as well as TAAs are both present on the surface of the cancer cells. Cancer cells can be marked as foreign or abnormal cells on the basis of TAAs present on its surface. The killer T cells attack on the cancer cells by recognizing these TAAs. The TAAs can be:

- Present in larger amounts on the surface of cancer cell in comparison to the normal cells.
- Self-antigens that are not present on the normal cells of a particular tissue but show their presence on the surface of abnormal/cancer cell for the same tissue for example specific embryonic tissue antigens expressed in an adult cancer. Antigens formed as a result of the gene mutations in cancer cells-neoantigens; the immune system has never encountered these antigens before.

[1]Source:http://www.cancer.gov/about-cancer/what-is-cancer#ui-id-3

4.2.2. EVOLUTION OF CANCER THERAPY

Cancer treatment has gone through a gradual development process. Surgery is the conventional form of cancer treatment. It is an efficient method to eliminate benign tumors that have not spread to different sites in the body. Surgery primarily is used to remove the entire tumor; however, it very rarely results in complete cure since tracing all the tumor sites is difficult.

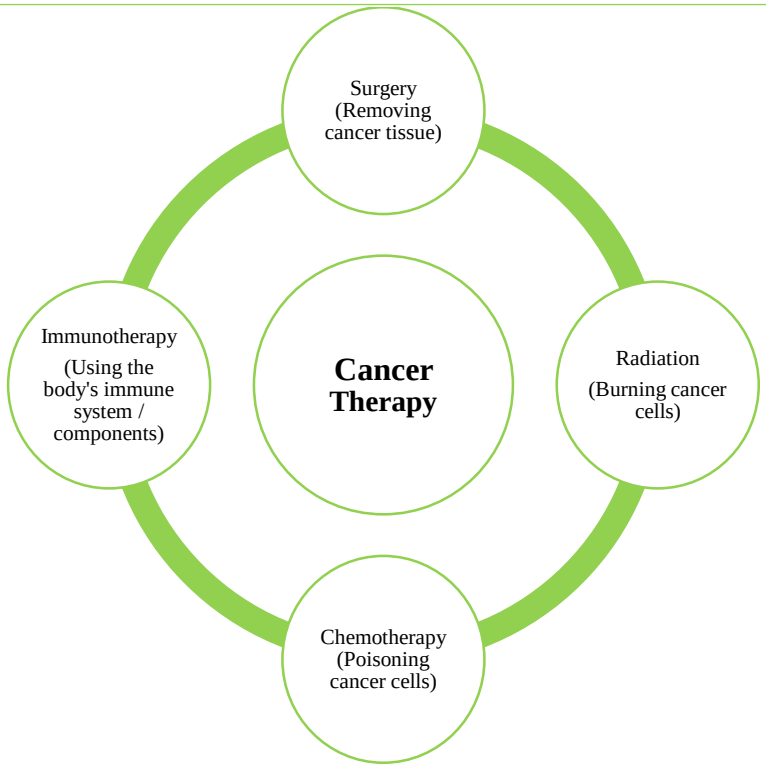
1896 saw the advent of radiation therapy when a German professor Wilhelm Conrad Roentgen delivered a lecture titled *Concerning a New Kind of Ray* (X-ray).[2] A few months later, methods were devised to use X-rays for elimination of cancer and soon radiation therapy came into being. Initially, radium was used with relatively low-voltage diagnostic machines. Over the years, several developments in radiation physics and computer technology took place making it possible to deliver radiations more precisely onto tumor sites. This type of treatment posed certain side effects to the patient as radiations hit the rapidly dividing normal cells in the area being treated.

The mustard gas was used as a chemical warfare agent during World War I by the US Army. The compound has potential hematopoiesis properties. Similar compound called nitrogen mustard were also found to work against lymphoma. Soon after, Sidney Farber[3] illustrated that aminopterin produced remissions in children with acute leukemia. With time, chemotherapy emerged as a potential alternative treatment for cancer-using chemical compounds as drugs to reduce tumors. However, chemotherapy too has several side effects since normal cells become victims to the treatment.[4]

Currently the focus is being shifted towards treatment by immunotherapy. This approach relies on the immune system and its components to fight the disease. Figure 4.2 depicts the four major treatment options for cancer.

[2]Source: Wilhelm C. Roentgen produced and detected the electromagnetic form of rays called Roentgen Rays (now called the X-Rays) and was awarded the Nobel Prize in Physics for the same
[3]Source: Sidney Farber, the American pediatric pathologist, is regarded as the Father of Modern Chemotherapy
[4]Source: http://www.cancer.org/cancer/cancerbasics/thehistoryofcancer/the-history-of-cancer-cancer-treatment-chemo

Figure 4.2 **Four Major Cancer Treatment Therapies**



Source: Roots Analysis

4.2.3. VACCINES

Back in 1790s, Edward Jenner laid the foundation of modern vaccinology. The tremendous medical potential in prophylactic vaccination was discovered by him. This lead to an ignition of campaigns nationwide subsiding the rate of life-threatening infectious diseases. Eradication of natural smallpox was the culminating point achieved in this field.[5]

A weakened or killed form of the disease causing agent, an associated toxin or a protein expressed on its surface that mimics the organism and stimulates the active acquired immunity for that particular disease is a vaccine. The agent is treated as a threat, destroyed and is recorded so that it can easily be recognized and destroyed by the immune system if these micro-organisms are encountered again.

When a body is presented with a vaccine,APCs recognize them as harmful molecules. The APCs will then digest the vaccine and display these antigens on its surface. B and T cells that specifically match with these antigens presented will come in contact with the APCs. The APCs activate these cells and signals for division of these cells is provided. The newly made B-cells produce antibodies, which are proteins that can move freely in the body binding to the

[5]Source: http://www.ncbi.nlm.nih.gov/pubmed/23734328

antigens that recognize the pathogens. Antibodies produced by B-cellsare the-essential immune effectors-induced by the vaccines. They have the capability of a specific toxin or pathogen binding. Cytotoxic CD8+ T lymphocytes (CTL) are one of the other potential effector that are stimulated by the vaccines. These function by killing the infected cells and hence limiting the spread of infectious agents. The growth factors and signals by CD4+ T helper lymphocytes support the generation and maintenance of these lymphocytes.

The immune response required to kill pathogens varies from pathogen to pathogen. Helper T-cells, conductors of body's immune response, play an important role. They release different protein signals that direct the suited cells to kill the pathogen. There is a deregulation of the immune response without these cells. The B and T cells are turned into memory cells that can last for a life time of an individual. Since these memory cells have encountered these pathogens before, they quickly recognize their specific pathogens. This leads to the mounting of a fast androbust response well before the pathogen finds its chance of replicating. Thus the disease cannot be caused. The goal of vaccines is to create long lived memory cells that protect the body from these specific pathogens for life[6].

4.2.4. CANCER VACCINES

The recent advancement in molecular and cellular immunology has helped develop a better understanding of the high rate and the complexity of interactions that occur between the tumor cells and the immune system. Two broad effects of these tumor-immune system interaction include either a strong anti-tumor response or TAA tolerance. This field is at its early stage of development.[7]

Since certain human tumors spontaneously undergo regression it is suggested that the immune system may have a guarding effect on the body from the cell's uncontrolled growth due to neoplastic alterations. Recognizing the tumor-associated antigen and directing cytotoxic responses to these antigens is the primary area of focus in immunology. There are variety of recognizable antigens ranging from three dimensional structures that can be identified by antibodies to short sequences of amino acids recognized by CTLs. In comparison to antibodies, used as single agents or in combination, T-cell mediated immune response has greater potential for tumor eradication.[8] Although antibodies effectively mediate regression of tumors in hematologic malignancies; however they show lower efficiency in case of solid tumors. As a

[6] Source:http://www.who.int/immunization/documents/Elsevier_Vaccine_immunology.pdf
[7]Source: http://theoncologist.alphamedpress.org/content/7/suppl_3/20.full
[8]Source: http://theoncologist.alphamedpress.org/content/7/suppl_3/20.full

result of this large amount of preclinical and clinical trials research aims at generating highly specific CTLs.

A major focus is towards generating cells with cytotoxic capabilities like the lymphokine-activated killer cells, natural killer (NK) cells and tumor-infiltrating lymphocytes. Immune manipulation has the potential to generate a major durable response which was depictured in the trials using interleukin-2 (IL-2).

CTL generation is a multifarious process which involves atleast two signals.

- First signal-recognition:

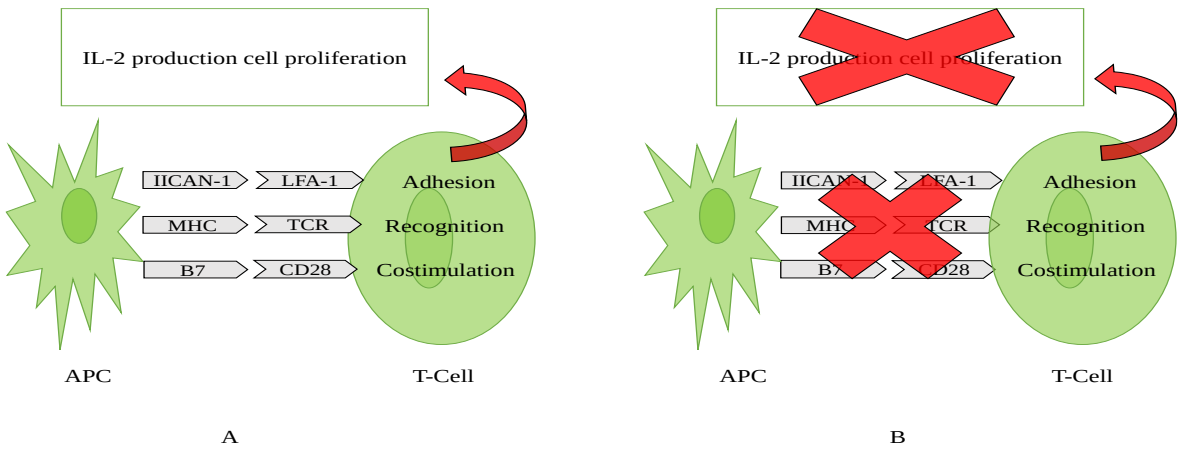
  Interaction of antigenic peptides with the T-cell receptors mediated by the major histocompatibility complex (MHC) of the antigen presenting cell.

- Second signal-co-stimulation:

  By the B7 family and adhesion molecules of the APCs. A state of anergy is reached if co-stimulation does not occur that is absenteeism of immune response towards the tumor antigen and no control over tumor growth.

Tolerance development and anergy are the primary weapons of the tumor antigens; making these the default responses of the immune system. Overcoming these barriers to stimulate appropriate recognition is the primary challenge in immunotherapy. The following figure 4.3 illustrates that APC-T-cell interaction and signals of recognition and costimulation are needed for T-cell activation by APC cells (A). Recognition signals provided without the costimulation leads to T-cell anergy (B).

Figure 4.3 **Dependence of APC T-cell Interaction on Recognition and Co-stimulatory Signals**

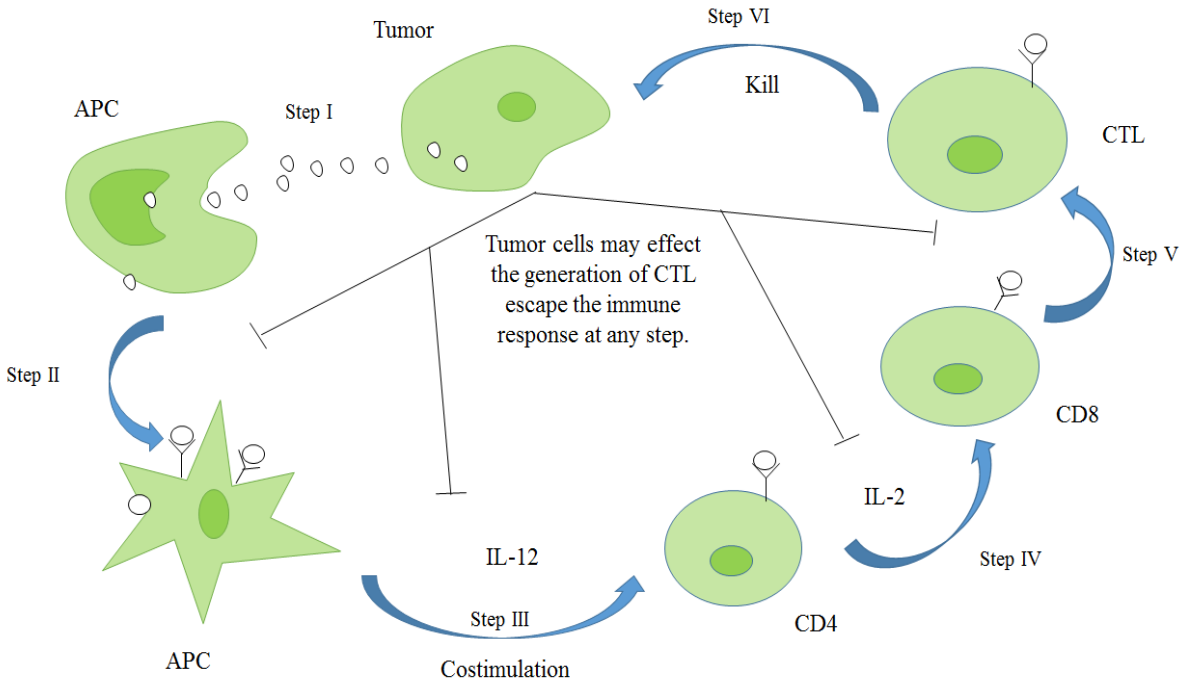


Source: Roots Analysis; http://theoncologist.alphamedpress.org/content/7/suppl_3/20/F1.expansion.html

4.2.5. BARRIERS OF CANCER VACCINE

The genetic manipulations makes the tumor cells less vulnerable to the programmed cell death. Only a small percentage of these cells go through apoptosis and a limited release of the residual apoptotic bodies that contain TAA. On interaction with the TAA, the APCs may mature if appropriate cytokine microenvironment is available; releasing the costimulatory signals as discussed earlier. An array of cytokines produced by the CD4 cells initiate the CTLs' clonal expansion. Figure 4.4 depicts the likely interaction between tumor cell and immune system.

Figure 4.4 **Interaction between Tumor cells and Immune System**

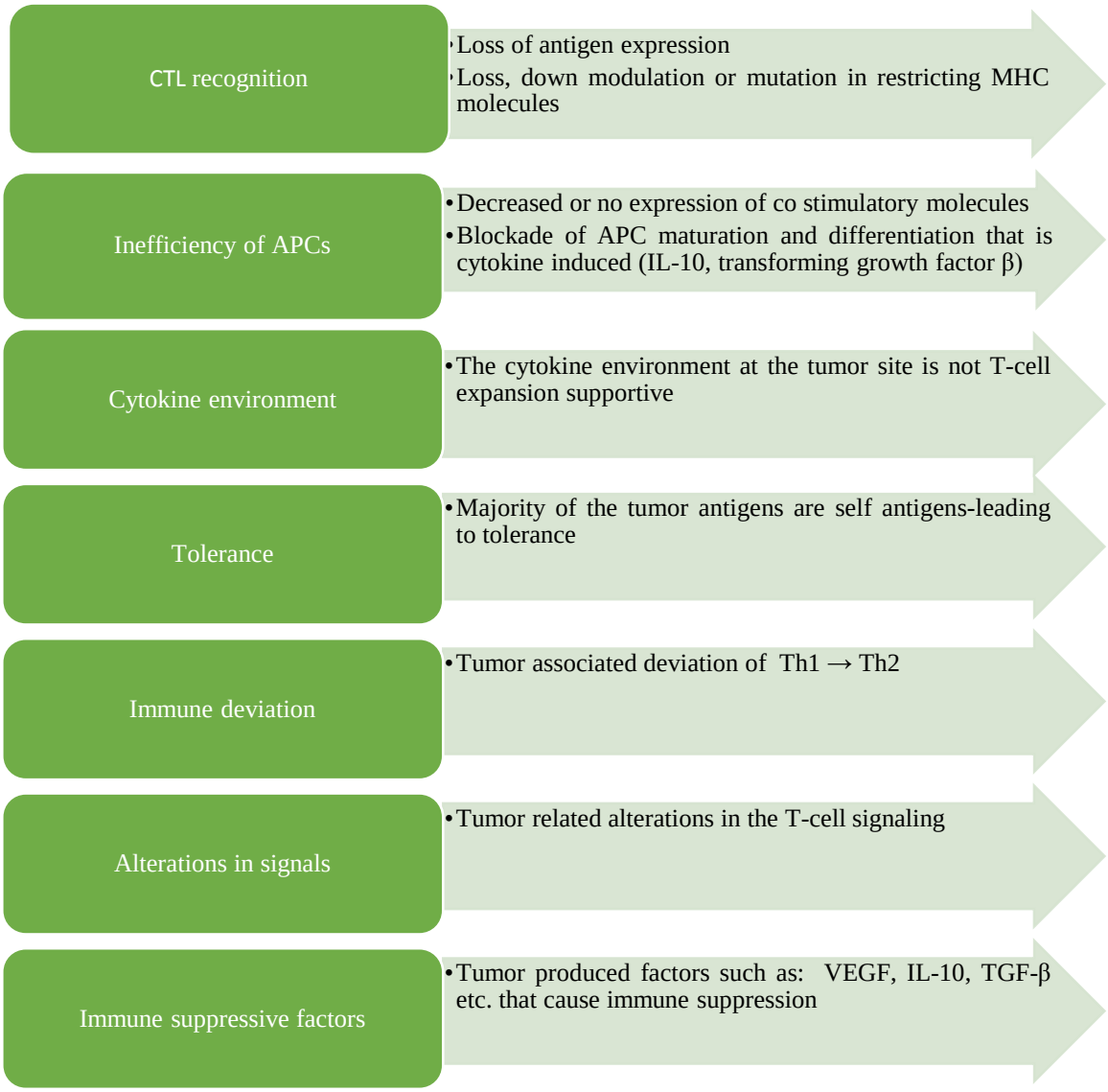


Source: http://theoncologist.alphamedpress.org/content/7/suppl_3/20/F2.expansion.html

Under the selective pressure certain mechanisms have been developed by the tumor cells to escape being targeted by the immune system. Tumor cells may escape the immune response by producing APC maturation interfering and recognition and costimulatory signal hindering factors.[9]

[9]Source:http://theoncologist.alphamedpress.org/content/7/suppl_3/20.full

Figure 4.5 **Potential Barriers to Cancer Vaccine**



Source: http://theoncologist.alphamedpress.org/content/7/suppl_3/20/T1.expansion.html

4.2.6. POTENTIAL TARGETS

A large number of clinical and preclinical trial are undergoing in the field of cancer vaccines for different types of tumors. Various strategies for vaccination are being designed and tested to overcome the barriers and come up with an optimal solution.

Table 4.1. mentions the antigens that are being targeted for various antigen types present on a range of tumor types.

Table 4.1 **Potential Antigen Targets for Cancer Vaccines**

Antigen Type	Antigen	Neoplasia
Tissue-specific Ag	Prostate-specific Ag	Prostate cancer
	Prostate-specific membrane Ag	Prostate cancer
	Tyrosinase	Melanoma
	Gp100	Melanoma
	α-fetoprotein	Liver cancer
Tumor-specific Ag	Immunoglobulin idiotype	B-cell NHL, myeloma
	TCR	T-cell NHL
	Bcr-abl fusion product	CML
	Mutant p53	Lung, colorectal, head and neck cancer, etc.
Cancer testis Ags	MAGE-1, MAGE-3	Melanoma, lung, and colorectal cancer
	NY-ESO-1	Melanoma and breast cancer
Overexpressed Ags	Her-2/*neu*	Breast, lung, and ovarian cancer
	Muc-1	Pancreatic, lung, breast, and colorectal cancer

Source: http://theoncologist.alphamedpress.org/content/7/suppl_3/20/T2.expansion.html

4.2.7. TYPES OF CANCER VACCINES

Cancer vaccines act as the modifiers of the biological response that spur the natural defense of the body's immune system against cancer. They aim at strengthening the immune system's ability of detecting and attacking cancer by stimulating a stronger basic bodily process.

Vaccines trick the body's immune system into thinking that an infection has occurred. Cancer vaccines can be protective in nature, such as the traditional vaccines for measles or polio-that intend to prevent the development of infection in the body. In addition, cancer vaccines can be used for the treatment of cancer.

4.2.7.1. CLASSIFICATION BASED ON ROLE OF CANCER VACCINE

Based on role of the cancer vaccine, these can be categorized into two broad types.

- Prophylactic (or preventive) vaccines
- Therapeutic (or treatment) vaccines

4.2.7.1.1. PROPHYLACTIC (PREVENTIVE) VACCINES

These vaccines fend off the development of cancer in a healthy person altogether. The preventive cancer vaccines act as immunostimulants. Antigens present on the infectious agents are present in the vaccine which are recognized as foreign by the immune system as a result they prevent the occurrence of the infection that might lead to cancer. Preventive cancer vaccines are focused on the cancer causing viruses- hepatitis B virus (HBV) which can cause

chronic hepatitis, cirrhosis, liver cancer and human papillomavirus (HPV) that cause a broad range of neoplastic diseases, from benign lesions to metastatic carcinomas.

Gardasil, Cervarix targeting the HPV, and Hepatitis B vaccine that targets HBV being the three preventive vaccines that have been approved by the U.S. Food and Drug Administration (FDA).

4.2.7.1.2. THERAPEUTIC (TREATMENT) VACCINES

The goal of this category of vaccine is to identify the already developed cancer cells and treat them by strengthening the body's immune response. The activation and direction of the cytotoxic T cells against the specific cancer cells, or generation of antibodies that recognize the cancer cell's surface molecules as targets is done by the introduction of one or more tumor cells associated antigen via the treatment cancer vaccine.

The development of treatment vaccines is more challenging than preventive vaccines as the factors like recognizing and generating target cell specific immunity and overcoming the different obstacles that cancer cells use to protect themselves and escape from the T cells act as a hindrance in their path. The first cancer treatment vaccine sipuleucel-T (Provenge®) was approved by the FDA in April 2010 for metastatic prostate cancer.[10]

These vaccine tend to:

- Stop the cancer cells from growing further
- Prevent recurrence of cancer
- In combination to remove any left-over cancer cells

4.2.7.2. CLASSIFICATION BASED ON SOURCE OF BIOLOGICAL MATERIAL

Therapeutic cancer vaccines can be classified on the basis of source of biological material as follows:

- Autologous
- Allogenic

4.2.7.2.1. AUTOLOGOUS CANCER VACCINES

The word autologous means *derived from oneself.* These are personalized vaccines that are made from an individual's own cells to generate the required immune response.

Cells from an individual are extracted (for instance tumor cells), a part of the cell or the whole cell is modified in a manner that its immuno-stimulation efficiency increases. Once these cells are modified, they are formulated into vaccines and administered into the individual. As a

[10]Source:http://www.cancer.gov/about-cancer/causes-prevention/vaccines-fact-sheet

result, the immune system recognizes and targets these autologous part to generate a stronger immune response. The memory T cells generated ensure that cancer does not reoccur. An example of autologous cancer vaccine that has been approved include Sipuleucel-T (Provenge®) for treatment of patients with resistant metastatic prostate cancer; with several such cancer vaccines in phase II and phase III of clinical development.

4.2.7.2.2. ALLOGENEIC CANCER VACCINES

As the word allo-"other" indicates, allogeneic cancer vaccines constitute of killed and modified tumor cells or tumor related antigens which are derived from one patient and are administered into another in order to generate a cytotoxic immune response.[11] The immunostimulatory material is non patient specific since it is derived from another member that belongs to the same species.

The ongoing preclinical trials suggest that allogeneic TAAs tend to have an increased level of immunogenicity for prostate cancer and melanoma, by providing additional danger signals. Cancer cell lines established to express a specific TAA for a particular tumor type are commonly used. This gives it the advantage of mass production, storage and modification prior to its usage which in turn accounts for a comparatively lower production cost, more availability and no patient related invasive procedures. Because of these reasons allogeneic cancer vaccines are considered to be a major modality for cancer vaccines.[12]

4.2.7.2.3. CLASSIFICATION BASED ON COMPOSITION

Cancer vaccines can vary in composition and mode of action. Currently the following classes of treatment vaccines are under investigation:

- Antigen vaccines
- Anti-idiotype vaccines
- DNA vaccines
- Dendritic cell vaccines
- Tumor cell vaccines

These sub-categories of cancer vaccines have been discussed in the following section. The focus of this report is dendritic cell vaccine and tumor cell vaccine. In addition, detailed information about each of these two type of cancer vaccines is available in subsequent chapters.

[11]Source:http://www.cancer.gov/publications/dictionaries/cancer-drug?cdrid=350082
[12]Source: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4181031/

4.2.7.2.4. ANTIGEN VACCINE

These vaccines constitute tumor antigens, the special proteins that are expressed by the tumor cells. Cancer cell attacking immune response is stimulated with the aim to kill those cells that bear these antigens.[13] It is desired that the target molecules are differently expressed on tumor cell and on normal cells; but as most of the antigens expressed by the tumor cells are a modification or mutated version of the self-proteins. Designing a vaccine that can overcome the tolerance is challenging; leading to chances of side effects such as autoimmunity.[14]

4.2.7.2.5. ANTI IDIOTYPIC VACCINES

A collection of idiotopes in an immunoglobulin (Ig) molecule are termed as idiotype. These are found in the hypervariable region of the Ig variable domain. Anti idiotypic vaccines comprise of three-dimensional immunogenic regions constituting antibodies. The idea behind this vaccine type is to trigger the body to produce antibodies against tumor cells. This happens as a result of the process where in the antibodies are seen as antigen by the other antibodies.[15]

Development of immune tolerance for the TAAs exists, as most of them are self-antigens and this raises a doubt and questions about the effectiveness of the vaccinations targeting these oncoproteins. But anti idiotypicmAbs come out as one of the most promising solution to this immune tolerance problem. Immunization against non-proteic antigens is also possible via this vaccination strategy. Efficient humoral and cell mediated immune response for a number of antigen mimicking anti-idiotypic antibodies is suggested according to ongoing clinical studies.[16] Identifying an anti-idiotypic antibody that stimulates both humoral and cell mediated immune response and functions as a true surrogate for a tumor associates antigen is the primary focus of this vaccine type.

4.2.7.2.6. DNA VACCINES

DNA vaccines approach involves injection of the antigen encoding DNA i.e., circularized TAA-encoding DNA constructs that are delivered either directly or via specific vectors, including certain liposomal preparations, viruses, bacterias and nanoparticles.[17] This delivery system gives access to various antigen-presenting pathways; direction of the expressions to specific intracellular sites, and fusion of additional genes or their co-delivery to achieve an enhanced responses. Vaccine designs are in their clinical trials showing positive results for

[13]Source: http://www.cancerresearchuk.org/about-cancer/utilities/glossary/antigen-vaccines2
[14]Source: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3019775/
[15]Source: http://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=44917
[16] Source: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3490135/
[17]Source: http://www.ncbi.nlm.nih.gov/pubmed/23734328

both fused microbial antigen and tumor antigens. Electroporation and such other physical methods are also being used to achieve increased expression.[18]

Simplicity, cost effectiveness, stability and safety are the key benefits that make this type of cancer vaccination attractive. The clinical trials suggest that these vaccines do not initiate any major unfavorable effects and are well tolerable. Various strategies with an objective to enhance the immunogenicity of DNA vaccines are being tested. These include triggering the immune response by fusing T cell activating molecules with the antigens, using xenogenes as a source of antigen, viral vector boosting after DNA vector priming and usage of immunomodulatory molecules.[19]

4.2.7.2.7. DENDRITIC CELL (DC) VACCINE

In the effort to generate an optimum technique for immunotherapy, dendritic cells- the most potent APC,have emerged to be essential targets owning to their property of orchestrating of both innate sand adaptive immunity. DC vaccination aims at reducing the tumor mass by eliciting an effector T cell response that is tumor specific and controlling relapse by inducing immunological memory T cells. DCs are provided with tumor specific antigens either by *ex vivo* culturing of patient derived DCs along with the tumor specific antigen or DCs are induced to take up the antigen *in vivo.*[20]

4.2.7.2.8. TUMOR CELL VACCINES

In thistype of vaccine, the tumor cancer cell is used and not just a targeted cell protein. These tumor cells are either killed or weakened to stop them from dividing and may be injected compounds like protein cytokines to generate a stronger immunostimulation. As mentioned earlier, cancer vaccines can be autologous or allogeneic; however, tumor cell vaccines can also be gene-modified vaccines.

Gene-Modified Vaccines

Patient's tumor cells are extracted and grown in the laboratory; to expand the scope of immune response these cells may be genetically modified expressing new proteins on the surface of these cells. Molecules such as granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-2 and other immune stimulatory and signaling molecules are expressed. A

[18]Source: http://www.ncbi.nlm.nih.gov/pubmed/15292504
[19] Source:http://www.ncbi.nlm.nih.gov/pubmed/25625927
[20]Source:http://www.nature.com/nrc/journal/v12/n4/full/nrc3258.html

stimulated immune system comes as an outcome of the molecule combination present on the genetically modified tumor cells.

Despite the high patient and tumor specificity there are certain draw-backs that are attached with this vaccine type. The cost and time consumption associated with creating an individualized vaccine; and the difficulty in isolating and growing a tumor cell in the laboratory considering the fact that there are certain cells that do not live outside the body for a long time.[21]

4.2.8. DISADVANTAGES OF CANCER VACCINES

Most of the cancer vaccines have been designed to specifically target a specific antigen on the cancer cell. Cancer vaccines are facing difficulties as:

4.2.8.1. ANTIGENS EXPRESSED ARE NOT ALWAYS SAME

Although they look similar not all the antigens expressed by a particular cancer type are same. There is a possibility of absence of the antigens against which the cancer vaccine is prepared. Targeted therapies show a response rate of 20 to 30 percent in general. It is a necessary to identify subgroups of patients and direct these targets towards each of these groups' individual cancer.

4.2.8.2. TUMOR CELL MUTATION

Most of these vaccines are used at the later stages of the disease treatment process, in most cases after the chemotherapy, or surgery or radiation therapy i.e. not before the standard therapies for cancer according to the NCCN guidelines. Such frontline therapies/ pre-treatments may induce mutation in the tumor cells, this might even cause changes in the vaccine targets. As a result of this the vaccine can become ineffective or less effective.

4.2.8.3. ADMINISTRATION TIME

As mentioned earlier, cancer vaccines are being tested as adjuvant therapy or a combination therapy with standard care such as chemotherapy. Which implies that the patient's own immune system is likely to be weaker due to the standard cancer therapies provided initially. Generation of an effective disease process can get too late in treating the cancer.

[21] Source: http://www.cancerquest.org/whole-cell-tumor-vaccines.html

It has now been recognized that an early administration of cancer vaccine as a treatment option is needed. This must happen before any negative impact of the radiation or chemotherapy or surgery is seen on the immune system.[22]

[22] Source: http://www.cel-sci.com/limitations_of_current_immunotherapies.html

4.3. COMPANY PROFILE AND DRUG PROFILE

With the help of the pipeline, the key players in the market were identified. These were divided on the basis of market share and profiled according to the understanding of their financial details, product portfolio, and recent funding and collaborations.

The information for these are generally captured from the company's annual report or by interviewing the potential clients. Under my training period, I profiled seven major companies in the DC and tumor cell vaccine pipeline.

In this report the company profiles are combined with the drug profiles. The drugs that have been profiled are either marketed or in phase III of clinical trials. Each drug profile consists of an overview of the product, history of development, the dosage form and regime, status of development of the product which provides an insight about the clinical trials that are ongoing, and the results of the trials that have been conducted.

A sample company profile of a company NewLink Genetics that has two products algenpantucel-L and tergenpumatucel-L has been added. A drug profile of algenpantucel-L has also been added. Seven such company and drug profiles were made for the report out of which one is being shared.

4.3.1. NEWLINK GENETICS

4.3.1.1. COMPANY OVERVIEW

NewLinkGenetics, a US based biopharmaceutical company, was founded in 1999. The company is headquartered at Ames, Iowa. It aims is to discover, develop and commercialize novel immuno-oncology products to improve the lives of the patients with cancer.[23] The products are designed such that cancer can be combat without significant incremental toxicity, as a monotherapy or in combination with other treatment regimes. As of December 2015, the company had employed 210 people.

In November 2011, the company went public and raised USD 43.4 million in its offerings.[24,25]In May 2013 NewLink Genetics was added to NASDAQ Biotechnology Index.[26] In addition, in April 2015, the company co-received Vaccine Industry Excellence (ViE) Awards at World Vaccine Congress 2015 along with Merck.[27]

4.3.1.2. FINANCIAL PERFORMANCE

The financial year of the company spans from January to December.As the company does not have any marketed, it is unable to generate revenue through sales of products. However, the company is able to generate revenue through grants, funding, licensing and collaborations. Figure 4.6 provides the revenue generated by NewLink Genetics in last five years including revenues generated in first quarter of 2016.

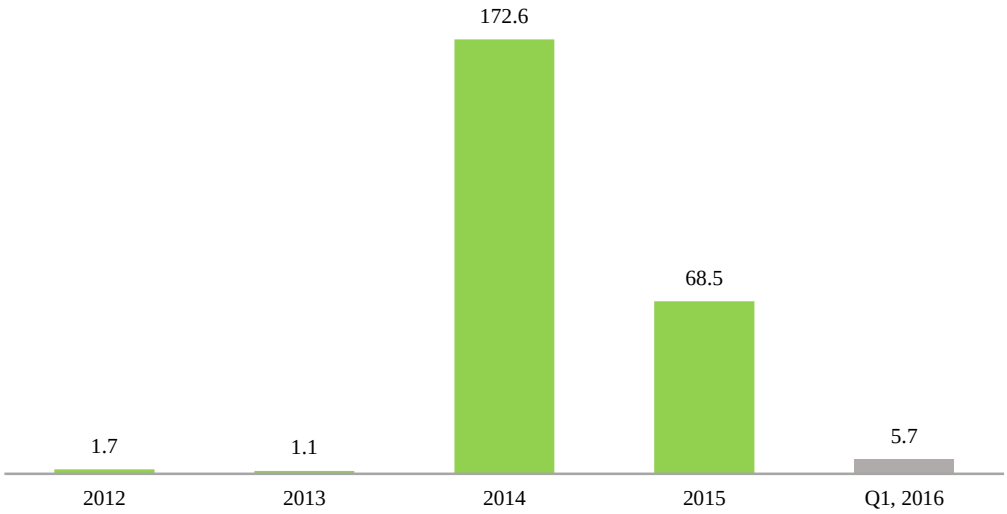
In March, 2012 NewLinksigned an agreement with Iowa Economic Development Authority (IEDA). Through the agreement, IEDA agreed to convertUSD 6 Million Forgivable Loan of NewLink to a Royalty Interest post evaluation and contribution of NewLink to the state. NewLinkagreed to pay IEDA a 0.5 percent capped royalty on future product sales.[28]

As of December 31, 2015, the company held cash, cash equivalents and certificates of deposits of amount totaling to USD 197.8 million.[29] The company claimed that this amount was sufficient to fund the on-going R&D activities. During the same time in 2014, the company held cash of USD 202.8 million. The decrease was due to increased expenses for R&D and pre-

[23] Source: http://www.newlinkgenetics.com/about-us/
[24] Source: http://investors.linkp.com/releasedetail.cfm?ReleaseID=633605
[25]Source: http://investors.linkp.com/releasedetail.cfm?ReleaseID=660301
[26] Source: http://investors.linkp.com/releasedetail.cfm?ReleaseID=765414
[27] Source: http://investors.linkp.com/releasedetail.cfm?ReleaseID=906369
[28] Source: http://investors.linkp.com/releasedetail.cfm?ReleaseID=659650
[29] Source: http://investors.linkp.com/releasedetail.cfm?ReleaseID=957708

commercialization development. The company had invested USD 71.4 million for its R&D activities.

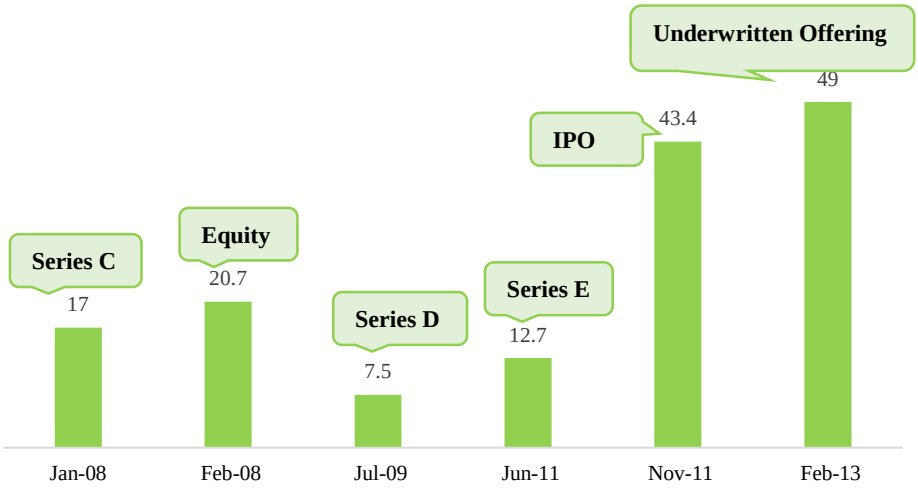
Figure 4.6**NewLink Genetics: Revenues (USD Million)**



Source: Annual Reports; Roots Analysis

As observed in the figure, the maximum revenue was generated in 2014. The increase was primarily attributable to the upfront payments of USD 150 millionfor IDO/TDO pathway from Genentech and USD 30 million for Ebola vaccine candidate from Merck alliances. Net of taxes, and amounts received under government contracts also contributed in the rise.[30] Figure 4.7 captures the VC funding instances of NewLink Genetics.

Figure 4.7 **NewLink Genetics: VC Funding Instances**



Source: Company Annual Reports; Crunchbase; Company Website; Roots Analysis

[30]Source: https://globenewswire.com/news-release/2015/02/26/710148/10122080/en/NewLink-Genetics-Corporation-Provides-Operational-Update-and-Reports-Fourth-Quarter-and-Year-End-2014-Financial-Results.html

4.3.1.3. TECHNOLOGY SNAPSHOT

The product candidates developed from the platform by the company target different cancers and provide multifaceted treatment options that will harness the power of the patient's own immune system. The company believes that these product candidates they have the potential of combining with and enhancing the current standard-of-care or other emerging immune-oncology therapies in order to achieve the best possible outcomes.[31]

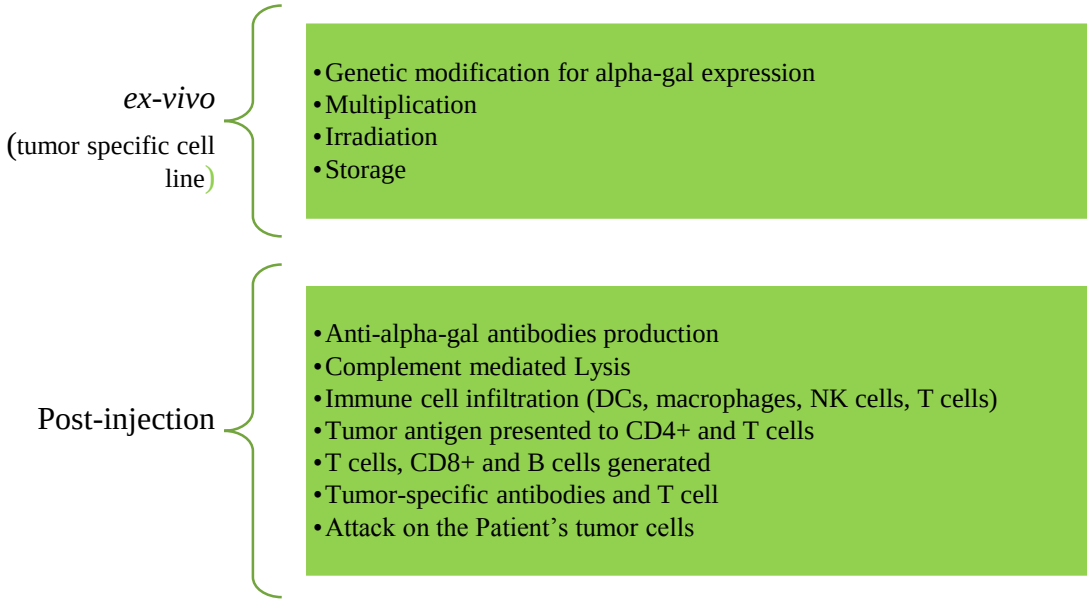
The company has two key platforms:

- HyperAcute[32] Cellular Immunotherapy
- IDO/TDO inhibitor

4.3.1.3.1. HYPERACUTE CELLULAR IMMUNOTHERAPY

As of December 2015, the company the exclusive commercial rights to HyperAcute Cellular Immunotherapy platform. The platform uses allogeneic, tumor specific human cell lines. These cells are modified to express a unique carbohydrate,alpha-gal. This technology takes the advantage of a pre-existing human immune response towards alpha-gal. With the help of a powerful chain reaction the body's natural defense is educated to identify cancer specific antigens and destroy the cancer cells. Figure 4.8 briefly describes the step involved.

Figure 4.8**HyperAcute Cellular Immunotherapy: Key Step**



Source: Company Website

[31] Source: http://www.newlinkgenetics.com/about-us/
[32]HyperAcute ® is a registered trademark of NewLink Genetics

Once tumor specific human cell lines are genetically altered to express alpha-gal, a master cell bank of select modified cells is established. This eliminates the need of extraction of any material from any patient. These immunotherapeutic cells are grown on large and later irradiated to stop the further growth of the cells. These cells are frozen until needed.[33]

Once these cells are injected into the skin, the anti-alpha-gal antibodies which are already present in every human, immediately target them. An immune response of rapid and powerful tissue destruction is initiated by the binding of the antibodies. This destruction is similar to the hyper acute rejection seen in organ transplants across species barriers.

The alpha-gal containing debris are taken up by the APCs of the immune system.The APCs process the debris which includes the tumor specific antigens that are a part of the immunotherapy cells. The same tumor specific antigens are present on the cancer cells of the patient. The patient's immune system is effectively educated to recognize and attack the tumor cells expressing these antigens since this process occurs in the powerful alpha-gal induced inflammatory environment. As a result, when the tumor cells are encountered elsewhere in the body, they are targeted by the immune system. Tumor destruction is then mediated by newly stimulated tumor specific antibody and T-cells which leads to suppression or elimination of tumor cells.[34]

There are multiple HyperAcute Immunotherapy programs in various stages of clinical development, including pancreatic cancer, lung cancer, melanoma, renal cell cancer and prostate cancer. Five product candidates are in the clinical trial, Algenpantucel-L being the lead candidate of the company in its phase III. The other products that use this technology are: Tergenpurnatucel-L, Dorgenmeltucel-L, HyperAcute Prostate, Hyperacute Renal.[35]

In September 2013, the company presented the data at the 2013 European Cancer Congress. The results of the lead candidates indicated that HyperAcute immunotherapy was capable to elicit anti-cancer immune response. Further, it demonstrated that greater expected response to salvage chemotherapy was observed following treatment with Algenpantucel-L in pancreatic cancer and Tergenpumatucel-L in NSCLC.[36]

[33] Source: Company website
[34] Source: http://www.newlinkgenetics.com/platforms/hyperacute-immunotherapies/
[35] Source: http://www.newlinkgenetics.com/pipeline/
[36] Source: http://investors.linkp.com/releasedetail.cfm?ReleaseID=793869

4.3.1.3.2. PATENT PORTFOLIO

The patent portfolio of NewLink Genetics includes ten patent families associated with HyperAcute technology. The company has licensed patent from Central Iowa Health System and Drexel University through licensing agreements in August 2001 and October 2004 respectively.[37]

Thefirst principal patent family comprises of patents and patent applications related to HyperAcute product candidates and HyperAcute technology. This patent family has been exclusively licensed from Central Iowa Health System. It includes two pending patent applications both in the United States and Europe covering isolated tumor antigens comprising alpha-Gal residues and 23 registered U.S. and foreign patents that are related with the HyperAcute technology.The patent covers broad pharmaceutical composition claims covering NewLink'sHyperAcute products for the treatment of cancer.

Table 4.2 provides a list of all the patents related to the HyperAcute Technology (the entire list has not been provided as per company's policies)

Table 4.2 **HyperAcute Technology: List of Patents**

Patent No.	Title	Publication Date
US 7,763,641	Broadspectrum heterocyclic substituted phenyl containing sulfonamide HIV protease inhibitors	6 October 2005
US 8,551,474	Antitumor vaccination using allogeneic tumor cells expressing alpha (1,3)-galactosyltransferase	14 April 2011
US 8,535,658		13 October 2011
EP 1549353 B1		31 March 2010
US 7,005,126	Method for tumor treatment using infusion of xenogeneic cells to induce hyperacute rejection and innocent bystander effect	NA

Source: Annual report; www.uspto.gov

Table 4.3 mentions the patents from the first patent family along with their expiry dates (the entire list has not been provided as per company's policies)

Table 4.3 **HyperAcute Technology: Patent Expiry**

Patent No.	Expiry Date
US 7,763,641	2024
US 8,551,474	
US 8,535,658	
EP 1549353 B1	

[37] Source: http://files.shareholder.com/downloads/AMDA-NRWRB/1892961307x0xS1126234-16-235/1126234/filing.pdf

Source: Annual Report

The second principle patent family for HyperAcute product candidate that is related to use of alpha-Gal in viral and cancer vaccines has almost expired. This patent family was licensed from Drexel University.The U.S. Patent No. 5,879,675, belonging to this family is expected to expire in March 2016.

4.3.1.3.3. MANUFACTURING FACILITIES

The vaccine related manufacturing facilities of NewLink are located at Ames and Ankeny in Iowa and Austin, Texas. The Ames manufacturing facilities is located at the Iowa State University Research Park. This facility comprises of both executive offices and manufacturing facility. In October 2010, the 14,000 square feet manufacturing portion of the facility became operational. In addition, the company continued to occupy a small pilot manufacturing in the same research park under the terms of a lease that expires in October, 2016.

In November, 2011, the company entered into a Memorandum of agreement for addendum to the lease, with Iowa State University Research Park Corporation, (ISURP). The Memorandum added additional space of 26,600 square feet to the facilities in Ames, Iowa. The lease is expected to expire in February 2017.

In February, 2014, the company signed a lease of 6,430 square feet for commercial facility and additional executive offices in Austin, Texas. The facility is expected to facilitate the commercialization efforts in addition to support the clinical operation activities. In February 2015, the company added additional 3,468 square feet to the facility. The lease is expected to be expired in September 2016.

In June 2014, the company signed an agreement with WuXi for commercial manufacturing of algenpantucel-L. The company has granted non-exclusive right for the production, when the drug is approved. Additionally, WuXi agreed to validate processes and equipment for the production.

In August 2014, NewLink leased 47,250 square feet space in Ankeny. The final production steps of its potential vaccine candidates, including irradiation and packaging of the products, and the distribution if approved are planned to be managed in Ankeny, Iowa.[38] The lease is expected to be expired in October 2017.

[38] Source: http://files.shareholder.com/downloads/AMDA-NRWRB/1892961307x0xS1126234-16-235/1126234/filing.pdf

4.3.1.4. DRUG PORTFOLIO

The immuno-oncology pipeline of the company includes HyperAcute® Cellular Immunotherapies and small molecule product candidates. Table 4.4 lists all the products of NewLink Genetics in the clinical pipeline.

Table 4.4**NewLink Genetics: Clinical Pipeline**

Product	Phase I	Phase II	Phase III
Algenpantucel-L	Pancreatic cancer (resected)		
	Pancreatic cancer (borderline resectable or locally advanced unresectable)		
Tergenpumatucel-L	NSCLC (advanced or metastatic)**		
Dorgenmeltucel-L	Melanoma**		
HyperAcute*Prostate	Prostate cancer		
HyperAcute*Renal	Renal cancer**		

** indicates the trial has enrolled patients

Source: www.newlinkgenetics.com

A brief description of each of the cancer vaccines being developed by the company under the key technology platform is given below:

Algenpantucel-L: HyperAcute Cellular Immunotherapy product candidates Algenpantucel-L is in its Phase 3 clinical trials for pancreatic cancer. The product consists of 2 modified pancreatic cancer cell lines-HAPa-1; HAPa-2, that have been modified to express alpha-gal.[39] The human pancreatic cancer cells that contain a mouse gene, marks the cancer cells as foreign to patient's immune systems. As a result of which the immune system therefore attacks these cancer cells just as they would attack any truly foreign tissue, destroying as much as it can.[40]

Tergenpumatucel-L: This HyperAcute Cellular Immunotherapy product candidates, being developed to fight non–small-cell lung cancer (NSCLC), is in its phase 2b of clinical development. It is an allogeneic, whole-cell immunotherapies.[41] As of now the product has yielded promising findings.[42]

Tergenpumatucel-L contains 3 NSCLC cell lines that have been modified to express alpha-gal carbohydrates on cell surface molecules.

[39] Source: http://www.newlinkgenetics.com/platforms/hyperacute-immunotherapies/pancreatic-cancer/
[40]Source: https://clinicaltrials.gov/ct2/show/NCT01836432
[41] Source: http://www.newlinkgenetics.com/platforms/hyperacute-immunotherapies/nsclc/
[42] Source: https://www.cancercommons.org/tag/tergenpumatucel-l-3/

Dorgenmeltucel-L: This HyperAcute Cellular Immunotherapy product candidates is being tested for patients with advanced melanoma and is at the completion of the Phase 2 study. Dorgenmeltucel-L consists of 3 melanoma cell lines that have been modified to express alpha-gal carbohydrates on the cell surface molecules.

HyperAcute® Prostate: This HyperAcute Cellular Immunotherapy product candidate is currently in its phase I of clinical trial and treats prostate cancer patients. Itis said toincrease the immune response against alphaGal epitopes, demonstrating the immunogenicity of the vaccine in prostate cancer patients.[43]

HyperAcute® Renal: HyperAcute® Cellular Immunotherapy product candidate is an allogeneic, whole-cell immunotherapies that educate the immune system to target and destroy a patient's own cancer cells. This product in its phase I is for patients with metastatic renal disease.[44]

[43]Source: http://files.shareholder.com/downloads/AMDA-NRWRB/0x0x621677/e5c770f0-2db5-47ff-a566-b0f4a886b8e9/NLNK_News_2012_12_13_General_Releases.pdf
[44] Source: http://www.newlinkgenetics.com/platforms/hyperacute-immunotherapies/renal-cancer/

4.3.2. ALGENPANTUCEL- L

4.3.2.1. PRODUCT OVERVIEW

As mentioned earlier, the lead product candidate of NewLink Genetics, Algenpantucel-L has been developed using the proprietary HyperAcuteCellular Immunotherapy technology platform. The vaccine candidate is administered intradermally. It is an allogeneic whole-cell immunotherapies that educates the immune system to target and destroy a patient's own cancer cells. HAPa-1 and HAPa-2 are the two modified pancreatic cancer cell lines that are modified to express the carbohydrate alpha(1,3)Gal.[45] Currently, the vaccine is under investigation for the treatment of pancreatic cancer in two phase III trials. The vaccine is being tested in combination with chemotherapy.

In October 2010, Algenpantucel-L received orphan drug designation and fast-track designation from the USFDA.[46] The orphan drug designation was granted for the treatment of pancreatic cancer whereas the fast-track designation was received for the adjuvant treatment of stage I/II resected pancreatic adenocarcinoma in combination with adjuvant gemcitabine chemotherapy. In November 2012 orphan drug designation was granted to algenpantucel-L by the EC.[47]

4.3.2.2. HISTORY OF DEVELOPMENT

In November 2005, the company initiated the phase I/II trial ofalgenpantucel-L for treatment of pancreatic cancer. The company decided to evaluate the product candidate in two phase II clinical trials. The first phase II clinical trial was initiated in December 2007. This trial evaluated patients with resected pancreatic cancer. The trial completed the patient enrollment in March 2010 and the study was completed in December 2014.[48] The second phase II trial was initiated in April 2015.

Further, the company has two on-going phase III clinical trials. In January 2010, the USFDA assigned a SPA on the trial design, clinical endpoints and statistical analyses plan for the phase III clinical trial, IMPRESS.[49]In October 2012, the company launched the phase III PILLAR trial.[50]In September 2013, the company announced the completion of patient enrollment in the phase III IMPRESS clinical study. The study enrolled a total of 722 subjects with surgically resected pancreatic resectable cancer.[51]

[45] Source: http://www.newlinkgenetics.com/platforms/hyperacute-immunotherapies/pancreatic-cancer/
[46] Source: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/OOPD_Results_2.cfm
[47] Source: http://investors.linkp.com/releasedetail.cfm?ReleaseID=721144
[48]Source: http://files.shareholder.com/downloads/AMDA-NRWRB/1892961307x0xS1126234-16-235/1126234/filing.pdf
[49] Source: http://investors.linkp.com/releasedetail.cfm?ReleaseID=912375
[50]Source: http://investors.linkp.com/releasedetail.cfm?ReleaseID=712478
[51]Source: http://investors.linkp.com/releasedetail.cfm?ReleaseID=791024

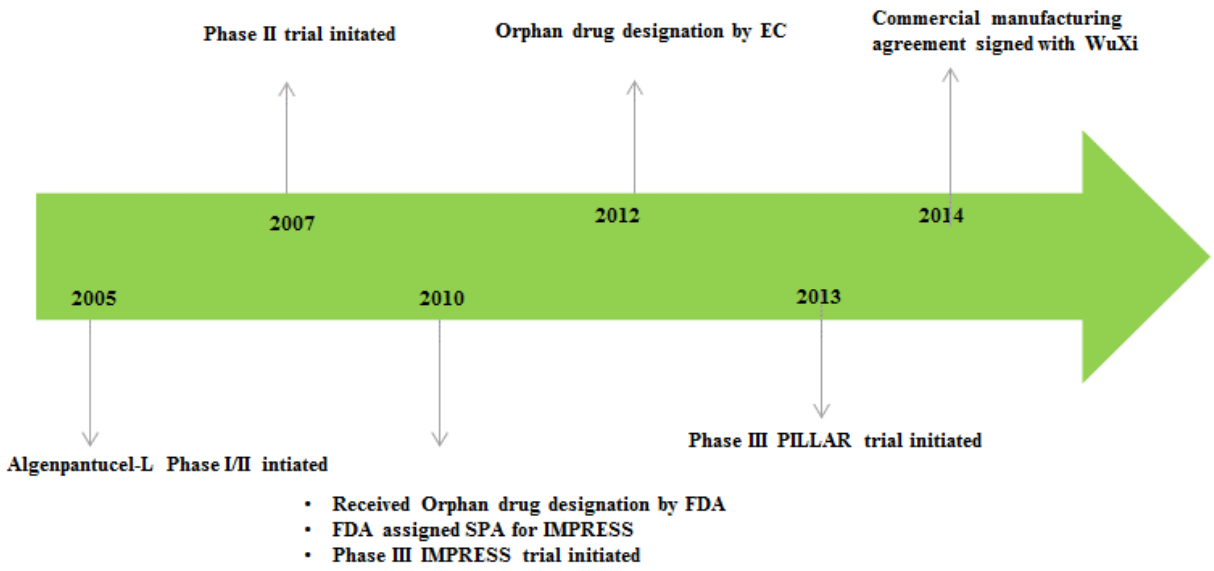
In May 2013, the company initiated the second phase III clinical trial, PILLAR. In December 2015, the company completed the enrollment of patients with borderline resectable or locally advanced unresectable pancreatic cancer in the clinical study.[52] The study enrolled 302 patients.

In March 2014, the first interim analysis of IMPRESS trial were completed and the review committee recommended study continuation without modification. In June 2014, the company presented the clinical data from IMPRESS trial in poster discussion session at ASCO 2014 Annual Meeting.[53] Later, in May 2015 the company announced continuation of the trial following of second interim analysis for IMPRESS phase III trial.[54,55]

In June 2014, the company signed an agreement with WuXi for commercial manufacturing of algenpantucel-L. The company has granted non-exclusive right for the production, when the drug is approved. Additionally, WuXi agreed to validate processes and equipment for the production.[56] The company is expected to report the primary results of the phase III IMPRESS clinical study in 2016.[57]

Figure 4.9 covers the major events in the historical timeline of algenpantucel-L.

Figure 4.9**Algenpantucel- L: Historical Timeline**



[52]Source: http://investors.linkp.com/releasedetail.cfm?ReleaseID=946998
[53] Source: http://investors.linkp.com/releasedetail.cfm?ReleaseID=851681
[54]Source: http://investors.linkp.com/releasedetail.cfm?ReleaseID=831235
[55]Source: http://investors.linkp.com/releasedetail.cfm?ReleaseID=912375
[56]Source: http://files.shareholder.com/downloads/AMDA-NRWRB/1892961307x0xS1126234-16-235/1126234/filing.pdf
[57]Source: http://files.shareholder.com/downloads/AMDA-NRWRB/1892961307x0xS1126234-16-235/1126234/filing.pdf

4.3.2.3. DOSAGE FORM AND REGIME

As mentioned earlier, the route of administration of the vaccine is intradermal. For surgically resected pancreatic cancer, a dosage regime of up to 18 immunizations is followed whereas in case of borderline resectable or locally advanced unresectable pancreatic cancer the injection is administered on 1, 8, 15, 29, 43 and 57days. Each injection of algenpantucel-L consists of 300 million immunotherapy cells.[58,59]

4.3.2.4. CURRENT STATUS OF DEVELOPMENT

Table 4.5 provides the details on the current status of development of algenpantucel-L either as a single therapy agent or in combination with other drugs. (Not all recorded the trials have not been shared as per company's policies)

Table 4.5**Algenpantucel-L: Current Status of Development[60]**

Indication	Type of therapy	Patient Segment	Phase of Development
Pancreatic Cancer	Combination with chemotherapy, chemoradiation	Naïve*	III (US)[61]
Pancreatic Cancer	Monotherapy	Naïve*	I/II (US)[62]

*Surgically Resected; ** Borderline Resectable; ***Borderline Resectable or Locally Advanced Unresectable;

Source: www.clinicaltrial.gov

4.3.2.5. CLINICAL TRIALS

As mentioned earlier, algenpantucel-L is being evaluated in twophase IIIclinical trials. The phase III trial IMPRESS (IMPRESS: Immunotherapy for Pancreatic Resectable cancer Survival Study) and PILLAR (PILLAR: Pancreatic Immunotherapy with algenpantucel-L for Locally Advanced non-Resectable).

Table 4.6 provides detailed information on clinical development plan for algenpantucel-L including information on the trial designs, location, start date/ end date for different trial phases ofalgenpantucel-L. (Not all recorded the trials have not been shared as per company's policies)

[58] Source: https://www.clinicaltrials.gov/ct2/show/study/NCT01072981?view=record
[59] Source: https://clinicaltrials.gov/ct2/show/study/NCT01836432
[60] The indications are organized in descending order by phase of development (highest to lowest)
[61] Source: https://www.clinicaltrials.gov/ct2/show/NCT01072981
[62] Source: https://clinicaltrials.gov/ct2/show/NCT00255827?term=Algenpantucel-L&rank=6&submit_fld_opt=

Table 4.6 **Algenpantucel-L: Clinical Trials**

Trial Title	Trial Phase	Trial ID	Trial Design	Location	Start Date/End Date
A Phase I/II Study of Algenpantucel-L (HyperAcute Pancreas) an Antitumor Vaccination Using Alpha(1,3)Galactosyltransferase Expressing Allogeneic Tumor Cells in Patients With Pancreatic Cancer	I/II	NCT00255827[63]	Non-Randomized, Safety/Efficacy, Study, Single Group Assignment, Open Label	US	Start date: November 2005 End date: September 2007
A Phase III Study of Chemotherapy and Chemoradiotherapy With or Without Algenpantucel-L (HyperAcute®-Pancreas) Immunotherapy in Subjects With Surgically Resected Pancreatic Cancer	III	NCT01072981[64]	Randomized, Safety/Efficacy Study, Parallel Assignment, Open Label,	US	Start date: April 2010 End date: NA

Note (Color Scheme: Trial status): Grey: Completed trials; Blue: Closed trials; Green: Open trials

Source: www.clinicaltrial.gov

Table 4.7 represents the primary and secondary endpoints evaluated in the clinical studies ofalgenpantucel-L.(Not all recorded the trials have not been shared as per company's policies)

Table 4.7 **Algenpantucel-L: Clinical Trial Endpoints**

Clinical Trial Endpoints	Phase III (IMPRESS) NCT01072981 (Pancreatic Cancer)	Phase III (PILLAR) NCT01836432 (Unresectable Pancreatic Cancer)	Phase II NCT00569387 (Pancreatic cancer)	Phase I/II NCT00255827 (Pancreatic cancer)
OS				
PFS				
DFS				
Emergent adverse events				

Note 1: OS: Overall survival; PSF: Progression free survival; DFS: Disease free survival; DLT: Dose-limiting toxicity; MTD: Maximum tolerant dose.

Note 2 (Color Scheme): Orange: Primary Endpoint; Blue: Secondary Endpoint; Gold: Other Endpoint

Note 3: Time Periods for the endpoints IMPRESS: 41-48 months; PILLAR: 13.5 months; phase II: 18 months; phase I/II: 6 months

Source: Roots Analysis

4.3.2.6. KEY CLINICAL TRIAL RESULTS

4.3.2.6.1. PHASE II TRIAL(RESECTED PANCREATIC CANCER)

In May 2012, the company presented the data from the trial (NCT00569387) at 2012 Digestive Disease Week. In addition, the results from the trial were presented at the 53rd Annual Meeting of the Society for Surgery of the Alimentary. Moreover, the company published the detailed

[63] Source: https://clinicaltrials.gov/ct2/show/NCT00255827?term=Algenpantucel-L&rank=6&submit_fld_opt=
[64] Source: https://www.clinicaltrials.gov/ct2/show/NCT01072981

results of the trial in the *Journal of Gastrointestinal Surgery.*[65] Later, in June 2012, NewLinkGenetics reported two and three year overall survival data from its phase II trial at the ASCO Annual Meeting 2012.[66]

In June 2013, the phase II (NCT00569387) study results were presented in oral presentation at the ASCO 2013 Annual Meeting with result stating a median overall survival that was more than double in patients with elevated levels of anti-mesothelin antibodies compared to those without elevated levels.[67]

In June 2014, the company presented the correlative data from phase II (NCT00569387) study at a poster presentation in Chicago during 50th ASCO Annual Meeting.[68],[69] The study evaluated algenpantucel-L along with gemcitabine and 5-FU-XRT for resected pancreatic cancer. The study enrolled 71 patients of which 67 patients were evaluable. The 69 patients were enrolled into two cohorts- low dose cohort (100 million cells; N=43) and high dose cohort (300 million cells; N=26). The dose was administered intradermally. The dosage was given in up to 14 vaccinations. Table 4.8 describes the results of the phase II trial (due to confidentiality of material the entire results have not been shared)

Table 4.8**Algenpantucel-L: Phase II Results**

Clinical Trial Endpoint	Result
1 year DFS	62 percent
Overall OS	86 percent
Patients with increased anti-CALR antibodies	48 percent
Median OS of patients with increased anti-CALR antibodies	35.8 months

Source: www.newlinkgenetics.com

Overall, algenpantucel-L was well tolerated and demonstrated favorable safety profile.[70] Additionally, the results of the study were compared with the RTOG-9704 trial in which patients received the same chemoradiation regimen.[71]

[65]Source: http://investors.linkp.com/releasedetail.cfm?ReleaseID=675694
[66] Source: http://investors.linkp.com/releasedetail.cfm?ReleaseID=679590
[67] Source: http://investors.linkp.com/releasedetail.cfm?ReleaseID=768574
[68] Source: http://investors.linkp.com/releasedetail.cfm?ReleaseID=851681
[69]Source: http://meetinglibrary.asco.org/content/129984-144
[70]Source:http://files.shareholder.com/downloads/AMDA-NRWRB/1892961307x0xS1126234-16-235/1126234/filing.pdf
[71] Source: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3539275/

4.4. TECHNOLOGY PROFILES

The report also focuses on the emerging technologies that are being developed by different players. Those technology have been profiled that have two or more DC or Tumor based cancer vaccine product in their clinical trial phases.

One of the eight short technology profiles of Immunicum has been added which has a DC vaccine based platform COMBIG.

4.4.1. IMMUNICUM

4.4.1.1. COMPANY OVERVIEW

Immunicum, a biopharmaceutical firm set up in 2002, is a spinoff from Sahlgrenska University Hospital, Sweden. It aims at improving the quality of life of cancer patients. The company Immunicum, purses to develop safe, sophisticated and efficient therapeutic cancer treatments with powerful and long lasting immune responses. The Company is Sweden based and has its offices in Göteborg.[72]COMBIG is the proprietary platform of Immunicum.

4.4.1.2. TECHNOLOGY SNAPSHOT

The company has developed three technology platforms for treatment of cancer through immunotherapy approaches. The three platforms are:

- COMBIG
- CD70
- Ad5PTDf35-adenovirus vector

A description of the COMBIG technology platform is provided in the following sections.

4.4.1.3. COMBIG

The COMBIG-DC platform uses pre-produced and freeze stored allogeneic DCs as an off-the-shelf immune enhancer. This cell-based immune enhancer is manufactured from healthy blood donors.It is not individually prepared for each specific patient.

The manufacturing process for COMBIG-DCs starts with isolation of monocytes from whole blood-derived buffy coats orleukapheresis. The isolated monocytes are then differentiated into immature DCs in vitro. Before they are washed and subsequently filled into cryotubes the DCs are activated during a restricted time period. Up to 70 doses are producedfrom one leukapheresis product. These are then stored in freezers.[73]

[72]Source: http://immunicum.se/wp-content/uploads/2015/11/Annual-Report-14-15.pdf
[73] Source: http://immunicum.se/technology/platforms/the-combig-platform/

Under the COMBIG platform there are two candidates: INTUVAX[74] and SUBCUVAX[75].

INTUVAX being the lead cancer immune primer. It utilizes each patient's own profile of tumor antigens. These antigens also include the whole set of unique and tumor-specific neoantigens that exist within the tumor. Central T-cell tolerance and autoimmune toxicity against healthy tissues does not form a concern for this product since the mutation-derived neoantigensare from within the tumor are fully tumor specific. Somatic mutations in tumors can generate neoepitopes that can elicit a strong immunologic response against mutant proteins.

Once the allogenic DCs are injected intratumorally an NK-cell mediated tumor cell death is induced by the NJ-cells that are recruited to the tumor. The recruited autologous DCs engulf the tumor antigen and migrate to the draining lymph nodes. The tumor antigen is presented to naïve T-cells which are converted into cytotoxic T-lymphocytes (CTLs). The CTLs the scan the body for cancer and attack tumor cells.[76]

4.4.1.4. PIPELINE

As mentioned earlier there are two candidates under COMBIG platform:

INTUVAX and SUBCUVAX.

INTUVAX uses allogenic dendritic cells as an adjuvant, which recruits patients own antigen presenting cells on injecting intratumourally eliciting an immune response. The vaccine is being tested forrenal cell carcinoma (phase II trial) and hepato cellular carcinoma (phase I trial) and gastrointestinal stromal tumors (phase I).

Whereas SUBCUVAX uses allogenic dendritic cells loaded with specific tumor antigens. This has not been designed for any specific indication yet; but the company has plans to, initiate a clinical phase I/II study in 2016, with the vector for oncolytic treatment of neuroendocrine tumors.[77]

4.4.1.5. PATENT PORTFOLIO

In 2015 JPO approved a patent for protection of the COMBIG-platform and EPO approved a patent that protects the production process of pooled INTUVAX cells.[78]

Immunicum's patent portfolio consists of a total of six patent families, covering the production process and the three platform technologies.[79]

[74] INTUVAX® is the registered trademark of Immunicum AB
[75] SUBCUVAX ® is the registered trademark of Immunicum AB
[76]Source: http://immunicum.se/technology/platforms/the-combig-platform/intuvax/
[77] Source: http://immunicum.se/wp-content/uploads/2015/11/Annual-Report-14-15.pdf
[78]Source: http://immunicum.se/about/history/
[79] Source: http://immunicum.se/technology/

Table 4.9 gives a description of the patents under the platform (due to confidentiality of material the entire results have not been shared)

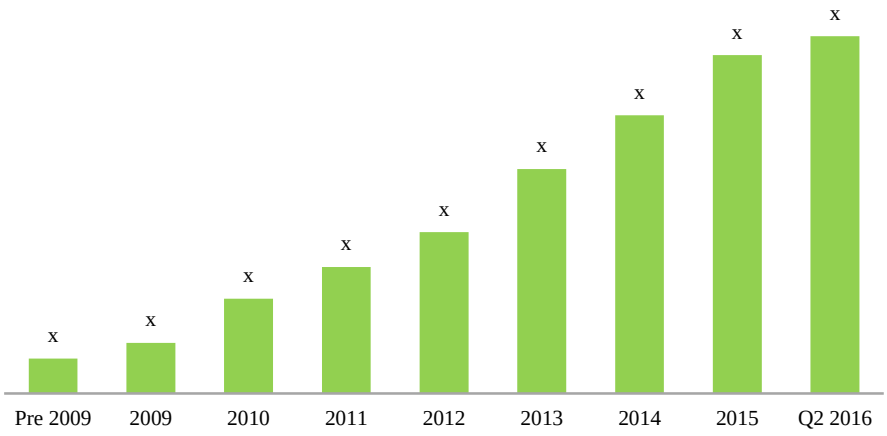
Table 4.9 COMBIG: Patents

Patent No.	Title	Publication Date
CN102782123	Improved composition for inhibiting tumor cell proliferation	14 November, 2012
EP2534242		19 December, 2012
WO2011098516		18 August, 2011

4.5. VC FUNDINGS AND PUBLICATION ANALYSIS

The funding instances of the companies in the pipeline were captured this gave a clearer picture of the companies that are leading the market in terms of funding instances generated and the total amount accumulated. Alongside publication analysis were done to pick out the current major focus area for research and get a better understanding of the type of research work type.

Following are some of the figures that depict the type of analysis drawn by the gathered data. The value of the charts cannot be reveled according to the companies' policies.

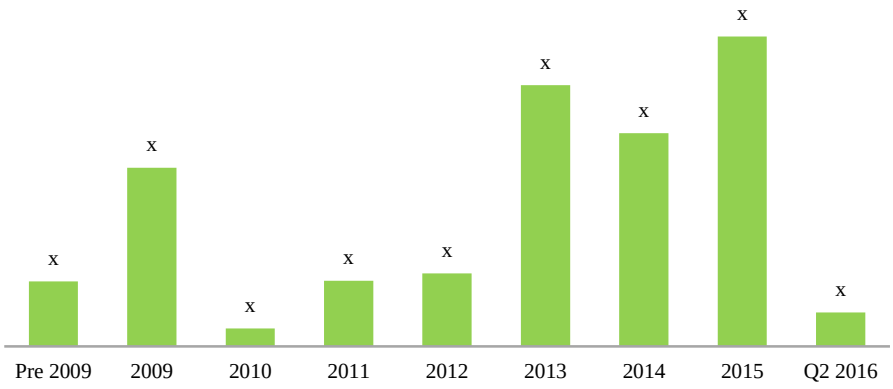


Note: 2016 data till May 2016
Source : Roots Analysis

Figure 4.10 Cumulative Funding Instances, Pre -2009-2016

As depicted by Figure 4.10, the number of funding instances is increasing at a healthy rate. There were x instances of funding identified in year 2014 and x instances in 2015.

Figure 4.11 depicts the total amount invested (in USD million) in a particular year. As evident from Figure 4.11, year xxxx saw the maximum investment over the last decade, in this area.



Source : Roots Analysis

Figure 4.10 Funding Instances: Total Amount Invested Annually (USD Million)

4.5.1. DISTRIBUTION OF THE FUNDING INSTANCES BY TYPE OF FUNDING

There are several ways in which financing can be done. For the purpose of this analysis, we have classified different types of investments into following major categories:

- **Grant**: It is the funding provided by various government agencies such as National Institute of Health, National Cancer Institute etc. Generally, the amount in form of grants is very less compared to other funding types.

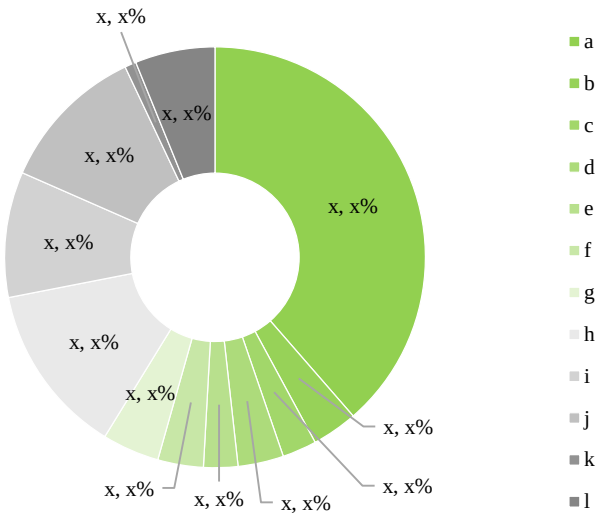
- **Debt**: In this type of funding, the company takes a loan from a bank or a group of investors and is required to pay back the money with the interest irrespective of whether the company is in profit or not.

- **Seed:** Seed funding is a type of an early investment which is required by a start-up to get started. The amount of invested is small and is required by any company to manage the early expenses in setting up the company. It is a highly risky investment. In general, the amount is smaller and, in our data set, we came across only two instances of seed funding. At the same time, the returns are considerably higher as the small investment generally translates into a high equity share.

- **Venture/Equity:** It is a type of investment done by an investor or a group of Venture Capital investors. In lieu of the money invested, the Venture Capitalists acquire a share in the stocks (equity) of the company; the percentage equity share depends upon the value of the company at the time of investment. Through this type of funding, the companies can secure a large amount of money. Venture Capitalists make investment in the company with a growth horizon that stretches from a few years to as long as ten years or more.

Within Venture investments, there are multiple rounds that are classified as **Series A, Series B, Series C, Series D, Series E** and so on, beginning with Series A after seed funding. As the start-up grows, additional capital is required which is achieved through subsequent funding rounds. VCs obtain profit when the company goes public and sells its shares on a stock exchange or when the company gets acquired by another company

Figure 4.12 shows the distribution of the number of funding instances under each category

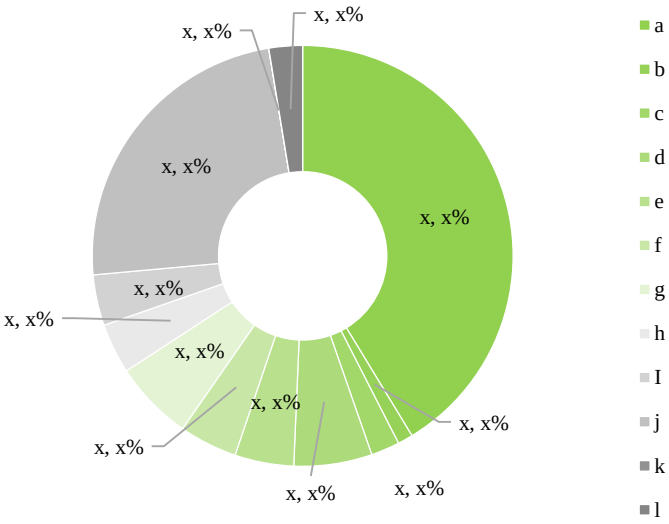


Source : Roots Analysis

Figure 4.12 Funding Instances: Distribution by Type, Pre -2009-2016

As observed, the maximum number of instances falls under the category of 'a' (x) followed by g(x) and j(x).

Figure 4.13 provides details on the total amount invested in each category



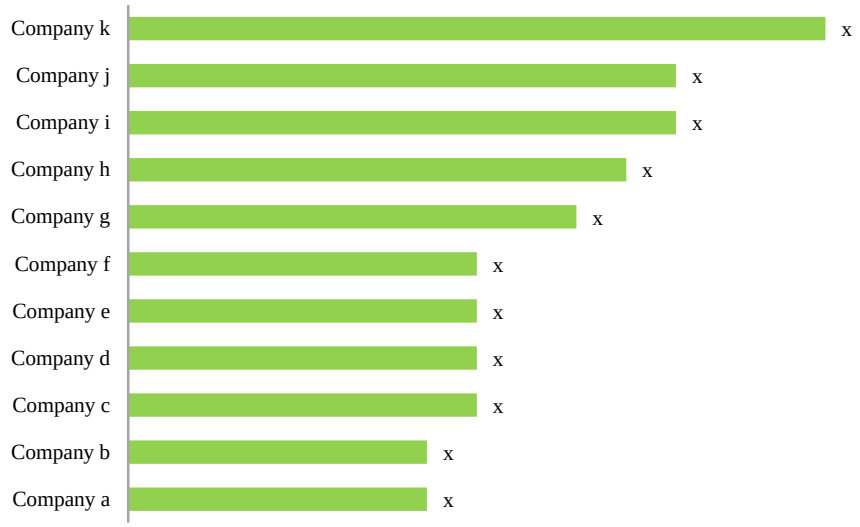
Source : Roots Analysis

Figure 4.13 Funding Instances: Distribution by Total Amount Invested (USD Million)

As highlighted in Figure4.13, the share of money invested in a particular type of investment is maximum in a (x %) followed by j(x %), e and f (x% each).

4.5.2. LEADING PLAYERS: DISTRIBUTION BY NUMBER OF FUNDING INSTANCES

Several companies such as x, x, x and x have raised capital several times in the last few years. This is evident from figure 4.14, which represents the number of funding rounds (both equity / debt).



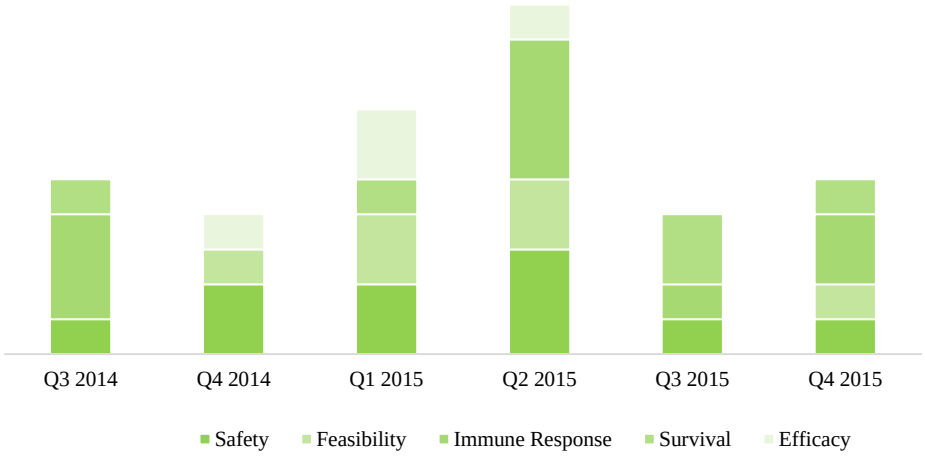
Source : Roots Analysis

Figure 4.14 Most Active Players: Distribution by Number of Funding Instances

As depicted in Figure x.x, Company k has received funding through x instances with total funding/investment amounting to USD x million. Compared to this, Company d received funding/investment in x instances with total investment amounting to USD x million (primarily as a result of USD x million venture funding of November 2009). Company k was followed by Company j andCompany i, which raised funds/investments in x rounds each receiving USD x million and USD x million respectively. However, Company h received total investment amounting to USD x million (primarily as a result of USD x million IPO equity in April 2015). Company g received funding/investment in x rounds with total investment amounting to USD x million.

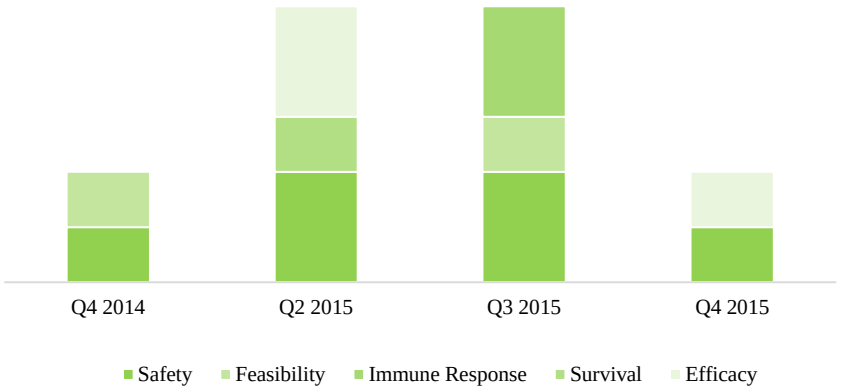
The next in line were companies that received funding/investment in x rounds Company f, Company e, Company c and Company d. Company f USD x and Company e USD x million respectively while Company c received USD x million. Company b-USD x million and Company a received USD x million in x funding rounds.

Figure 4.15 and figure 4.16 are samples of the publication analysis. Related publications were extracted for both vaccine types from a span of July 2014 to June 2016.



Note: Overall survival has been combined with survival for analysis purpose
Source : Roots Analysis

Figure 4.15 Publication Analysis: DC Cancer Vaccine (Distribution by Focus of Study)



Note: Overall survival has been combined with survival for analysis purpose
Source : Roots Analysis

Figure 4.16 Publication Analysis: Tumor Cell Cancer Vaccine (Distribution by Focus of Study)

Figure 4.15 and figure 4.16 represents the distribution of different publication on the basis of the study focus and date of publication. The focus areas have been highlighted with different colours based upon the study period.

4.6. FUTURE WORK

The report on Cancer vaccine- DC cells and tumor cell vaccines is currently under progress and the project is expected to release by the end of June.

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