Futuristic Transformations in Industrial Cancer Research

Seven Glorious Years of Advancements (2011-18)

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Foreword

Cancer research and development has always maintained a steady pace for continued progress against the disease. Over the decade, the transformation observed in this field is quite significant that lays the ground for complete cure or eradication of cancer in future. We believe the advancements in the cancer research, development of progressive therapies, diagnostic technologies are the manifestation of the growing understanding of the disease mechanism.

Pharmaceutical and biotech companies including big players and the innovative startups are exhibiting tremendous potential to bring a paradigm shift in cancer cure. Diverse approaches of the companies in targeting the disease have shrunk the period of delivering therapy from bench to clinic. One such example is the two CAR-T cell-based gene therapies - Kymriah® and Yescarta® which received approval last year. CAR-T cell therapy research is a rapidly emerging form of cancer therapy which was believed to take almost not less than a decade to reach to patients a few years ago. The diagnostic technologies are also being made effortless and less painful for patients. These success stories have provided a boost to the investment in this field.

In this digest, we bring to you the advanced transformations made by the global cancer industry in this decade and the ongoing journey to make cancer cure ingenious. We will depict how the immunotherapy has made its mark to provide relief to patients from the harsh treatments like chemo and radiotherapy that were used over the decades. Then we will move over the futuristic approaches being incorporated by the companies to push the limitations of cancer treatment.

We hope this report will bring forth a clearer picture of the efforts being made globally to eradicate the disease from earth. It will help in mapping the future of cancer industry in coming times.

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Introduction

Undaunted efforts to bring effective and affordable cancer treatments with thinning adverse events have evolved the cancer industry over and over each year. Extensive research and development, rising interest of big biotech and pharma companies in cancer treatment and stronger determination of regulatory authorities to approve ground-breaking therapies for patients have sharply put the oncology field in line with the development of cancer treatment that society dreamt of a few decades before.

In the 20th century and early 21st century, cancer treatment was entirely dependent on the invasive surgical procedures, high doses of radiation (radiotherapy) or drugs (chemotherapy) to kill cancer cells and shrink tumors. The untargeted radio- or chemo-therapy or combination comes with lots of side effects, affecting the health and social life of patients.

While the patients were going through a tough time with then standard-of-care cancer treatment, researchers were figuring out the procedure to enhance the treatment efficacy and limit the side effects.

"In the late 19th century, William B. Coley, known as "Father of Immunotherapy" was trying to harness the innate power of the immune system to delete foreign invaders in the body in destroying cancer tumors."

The idea hugely went across the research community and came over with the advent of the gen-next cancer treatment- Immunotherapy- the treatment that empowers the immune system of the individual to detect and kill cancer cells in the body specifically.

The success of immuno-oncology (I-O) drugs in this decade has strengthened the idea that immune system can put a leash on the wild and uncontrollable tumors in the body. I-O drugs are the emerging class of treatment that have sharply directed the pool of investment and players towards it. Big players like Bristol-Myers Squibb (BMS), Merck and Roche, were the early birds to the market.

Rise of Immuno-oncology Treatment

Cancer treatment made a big leap with the first ever regulatory approval of the immunotherapy- Yervoy (ipilimumab) in 2011.

BMS's Yervoy received the Food and Drug Administration (FDA or USFDA) approval for the treatment of advanced melanoma- the deadliest form of skin cancer. It is a recombinant monoclonal antibody that targets CTLA-4 protein to activate the immune system for recognizing and killing cancer cells. It significantly improved the overall survival in inoperable and advanced melanoma patients.

Later in 2015, the approval of Yervoy was expanded to be used in patients at high risk of melanoma recurrence after surgery. Thus, it becomes an important drug to prevent the risk of cancer progression in patients. Yervoy is the manifestation of the significant change brought by the I-O drugs in the cancer treatment field. It had the worldwide sales of $1.24 billion in 2017, showing 18 percent sales growth than the previous year.

Yervoy is currently being developed with the other immune checkpoint inhibitors like Opdivo. Yervoy + Opdivo recently showed exciting clinical trial results in patients with kidney cancer and non-small cell lung cancer (NSCLC).

In 2014, the first PD-1 inhibitor- BMS's Opdivo (nivolumab) got approval for advanced melanoma treatment. Then, in over two years the drug obtained seven FDA approvals for seven types of tumors. Currently, it is in the market for the treatment of melanoma, advanced renal cell carcinoma- kidney cancer, squamous cell carcinoma of the head and neck, NSCLC, classical Hodgkin's lymphoma- a type of blood cancer, urothelial carcinoma- a type of bladder cancer, and hepatocellular carcinoma (HCC) - the most common type of liver cancer.

The drug has proved to be a "golden drug" for the company which increased the global revenue of BMS by $1349 million in 2017, signifying 7 percent growth than previous year. The drug also received approval in the European Union and Japan for cancer treatment. Yervoy or other cancer drugs as combination therapies indicates a stronger position of BMS in the cancer treatment market in future

The development of Opdivo with Yervoy or other therapies as combination therapies signifies a stronger position of BMS in the cancer treatment market in future.

[1] FDA New Drugs Approval Notification 2011, accessed at https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm381453.htm
[2] Novel Drug Approvals for 2014, accessed at http://wayback.archive-it.org/7993/20161022052129/http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm429247.htm
[3] Medgenera Market Insights, accessed at https://medgenera.com/bms-global-revenue-2017-bristol-myers-squibb-sales/

Cancer cells avoid the immune system attack in the body by placing a brake on the immune system by the PD-1/PD-L1 mechanism. Various anti-PD immunotherapies empowered immune system by pulling out those brakes and revolutionized the I-O field to precisely and vigorously defeat cancer cells.

Merck's PD-1 inhibitor, Keytruda (pembrolizumab) received first approval in 2014 for advanced and inoperable melanoma but later expanded its use for lung cancer, classical Hodgkin lymphoma and advanced head and neck squamous cell carcinoma. Keytruda is the first anti- PD-1 therapy that is approved for the first-line treatment of metastatic NSCLC. Last year, Merck's bestseller, Keytruda becomes the first therapy to treat cancer with genetic defects. FDA approved Keytruda for the treatment of adult and pediatric patients with advanced solid tumors that have been identified with biomarker referred to as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR).

MSI-H and dMMR tumors contain abnormalities that hamper the repair process of DNA inside the cell. Tumors containing these biomarkers are commonly found in colorectal, endometrial and gastrointestinal cancers. These biomarkers may also be found in the tumors developing in breast, prostate, bladder, thyroid gland and other places. About 5 percent of patients with advanced colorectal cancer contain MSI-H and dMMR tumors.

In 2016, Roche's Tecentriq (atezolizumab) got FDA-approval as the first PD-L1 inhibitor for the treatment of bladder cancer. Tecentriq is a monoclonal antibody designed to bind to protein PD-L1 which are usually expressed on tumor cells and tumor-infiltrating immune cells. Therefore, it allows the activation of T cells to identify and kill cancer cells. It also got approved for the treatment of NSCLC in patients with various genetic mutations. In 2017, EMD and Pfizer's PD-L1 inhibitor, Bavencio (avelumab) bagged the first FDA approval to treat Merkel-cell carcinoma- a rare skin cancer. AstraZeneca's anti-PD-L1 drug, Imfinzi (durvalumab) got approved to treat advanced bladder cancer based on tumor response rate and durability of response. It is the first immunotherapy which received FDA approval to treat NSCLC patients with inoperable mid-stage disease that has not spread widely around the body. The use of the drug at a stage where the lung cancer has only spread locally in patients has unlocked an opportunity to gear up the drug's annual sales to around $2 billion. The worldwide sales of the checkpoint inhibitors are expected to increase sharply in the next five years crossing $15 billion.

Immunomodulatory drugs like Rituxan (Roche) and Arzerra (Novartis) have also been approved to work in combination with chemotherapy for the treatment of blood cancers over the past few years. Loss of patent protection and stringent biosimilar competition pose serious challenge for these drugs to sustain their position in the market.

[1] New Drugs at FDA, accessed at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/default.htm

Table 1. FDA-approved immune checkpoint inhibitors (till 2017).

Trade Name	Drug	Company	Target	First Approval	Worldwide Sales in USD billions (2017)
Yervoy	Ipilimumab	BMS	CTLA-4	2011	$1.24
Opdivo	Nivolumab	BMS	PD-1	2014	$4.94
Keytruda	Pembrolizumab	Merck	PD-1	2014	$3.80
Tecentriq	Atezolizumab	Roche	PD-L1	2016	$0.52
Bavencio	Avelumab	EMD/Pfizer	PD-L1	2017	not generated
Imfinzi	Durmalumab	AstraZeneca	PD-L1	2017	$0.019

In 2017, Truxima™ (Celltrion, South Korea) which is biologically similar to the Rituxan (Roche, USA), became the first biosimilar monoclonal antibody approved for cancer indications globally.[1]

Truxima is a genetically engineered human monoclonal immunoglobulin G1 kappa antibody that is biosimilar to rituximab. It targets the CD20 protein which is expressed on the surface of B cells in many stages of cancer progression making it a good target for treatment.

Truxima received marketing approval in the European Union for treatment of patients with non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukemia (CLL), rheumatoid arthritis (RA), granulomatosis with polyangiitis and microscopic polyangiitis.

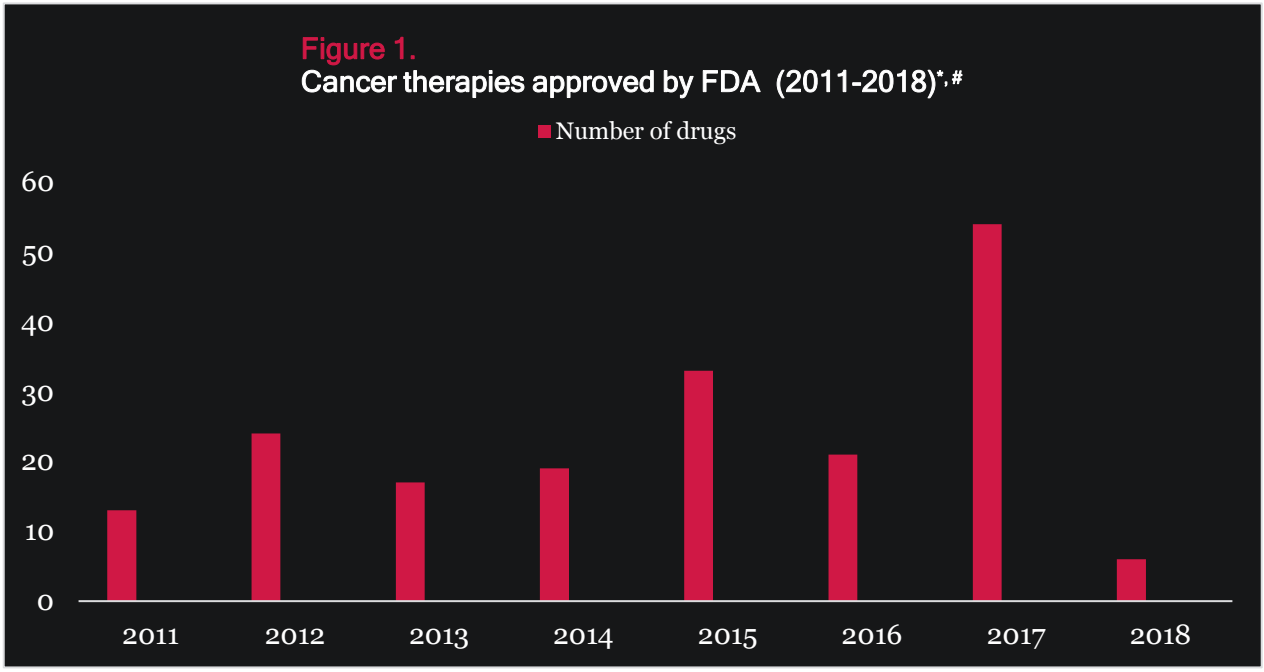
To minimize the loss of market share and to face biosimilar competition in future, Roche is improvising its next-generation cancer drug, Gazyva®. Anti-CD20 therapy, Gazyva along with chemotherapy showed significant improvement in the progression-free survival of previously untreated follicular lymphoma patients in a head-to-head study with the standard of care treatment, Rituxan®.

Currently, more than 1000 clinical trials are underway in the I-O field. Popular names like AstraZeneca, Incyte, Nektar Therapeutics, Tesaro, Pfizer, Novartis and Celgene are undergoing clinical studies to develop powerful combination therapies with top-selling checkpoint inhibitors. Startups like Rubius Therapeutics, LIft BioSciences are working on innovative ideas to get novel cancer medicines into the market. I-O drugs have performed exceedingly well, and this has drawn more attention on the ongoing development stage projects. The positive results of the pipeline projects will attract more investments in such companies.

Table 2. Significant ongoing combination clinical trials with checkpoint inhibitors.

Company	Candidate	Target	Combo / Indication	Phase
Incyte	Epacadostat	IDO1 Enzyme	Epacadostat+ Imfinzi®/NSCLC	Phase III will begin in 2018
Incyte	Epacadostat	IDO1 Enzyme	Epacadostat+ Keytruda®/Melanoma	Phase III
BMS	Relatimab	Lag 3 Enzyme	Relatimab+ Opdivo®/Colorectal Cancer	Phase II
BMS			Yervoy®+Opdivo® (Checkmate-238)/ Melanoma	Phase III
BMS			Yervoy®+Opdivo® (Checkmate-214)/ Renal cell carcinoma	Phase III
BMS	Urelumab	CD137	Urelumab+Opdivo®/ Solid tumor and B cell NHL	Phase I/II
Pfizer	Utomilumab	CD137	Utomilumab+Bavencio® (Javelin Medley)/Advanced cancer	Phase II
Roche	Emactuzumab	CSF-1R	Emactuzumab+Tecentriq® / Solid Cancers	Phase I
Roche	Cergutuzumab	carcinoembryonic antigen (CEA)	Cergutuzumab+Tecentriq® /solid cancer	Phase I
Nektar Therapeutics	NKTR-214	CD-122	NKTR-214+Opdivo® (Pivot-02)/Solid cancers	Phase I/II
Nektar Therapeutics			NKTR-214+Keytruda®+Tecentriq®(Propel)/Solid cancers	Phase I
Array BioPharma	ARRY-382	CSF-1R	ARRY-382+Keytruda®/Advanced solid tumor	Phase I/II
Checkmate Pharmaceuticals	CMP-001	TLR9 (CD289)	CMP-001+Keytruda®/ Melanoma	Phase I
Idera Pharmaceuticals	IMO-2125	TLR9 (CD289)	IMO-2125+Yervoy®+Keytruda® (Illuminate 204)/ Melanoma	Phase I/II

Global demographics indicate the need for innovative, life-saving cancer treatments with reduced drug resistance and adverse effects. The transformation from traditional chemotherapy to immunotherapy has stimulated the cancer treatment market. Healthcare professionals now opt for advanced therapeutics to increase treatment efficiency and reduce cancer recurrence after treatment. The number of approvals by regulatory authorities in oncology field has also spiked up in the past few years.



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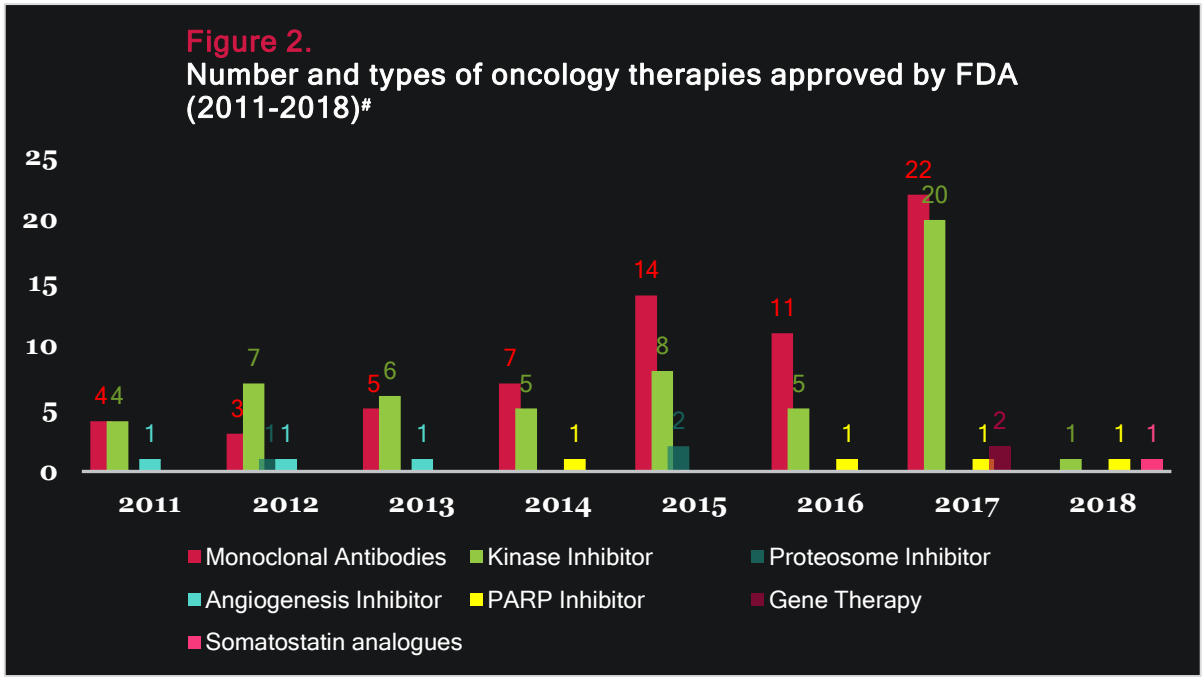
**new drug plus expanded label approvals*
\#till February 25, 2018

Apart from the blockbuster checkpoint inhibitors- Yervoy, Opdivo, Keytruda and Tecentriq, other monoclonal antibodies including Perjeta (pertuzumab), Xgeva (denosumab), Herceptin (trastuzumab) have shown encouraging outcomes in the treatment of various cancers, limiting the side effects of traditional chemotherapy.

Monoclonal antibodies- humanized, chimeric, and human gained popularity after the success of immune checkpoint inhibitors in improving the efficacy and reducing the side effects of cancer treatment. Targeted therapies attack and stop the activity of molecules in the body that plays an essential role in the growth and proliferation of the cancer cells. Kinase inhibitor, proteasome inhibitor, angiogenesis inhibitor and PARP inhibitors are some other important classes of targeted cancer medications that have been used either as monotherapy or in combination with standard chemotherapy to improve cancer treatment.



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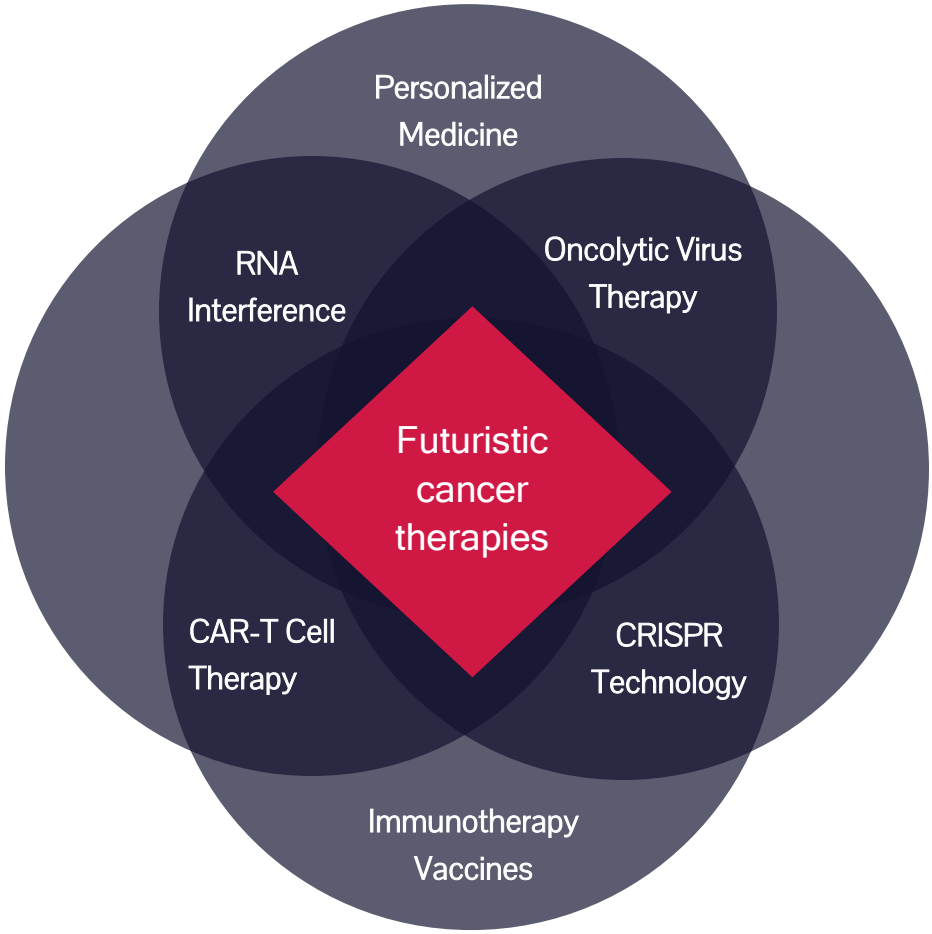
Immunomodulators that modulate patient's immune system to enhance their activity against cancer are being designed to improve immune response against tumors. Various classes of immunomodulators- interleukins, cytokines, chemokines and other are in development for cancer treatment.

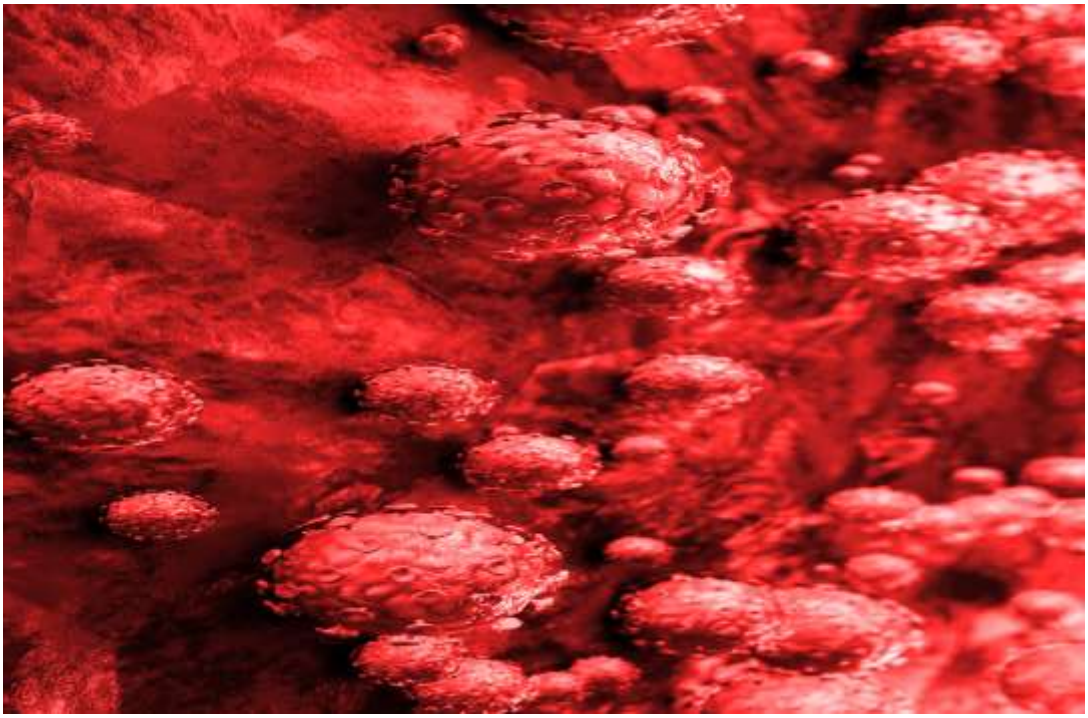
Immunotherapy holds largest cancer market revenue share globally in lung cancer followed by breast cancer, prostate cancer, and melanomas. Targeted immunotherapy has laid the foundation for development of precise, personalized treatment in the oncology field.

Futuristic Cancer Therapies

The transformations in global industrial cancer research is in line with futuristic cancer treatment.



Pushing Limits with Immunotherapy Vaccines and Oncolytic Virus Therapies



Human papillomavirus (HPV) is a DNA virus that gets easily transmitted through sex. It is the most common sexually transmitted infection which can cause genital warts leading to cervical, vulvar, and vaginal cancers in females, penile cancer in males and anal cancer, tonsils and tongue cancer in both. Cervical cancer is the second most common cause of cancer-related death globally, causing nearly 300,000 deaths every year. More than 80 percent of these deaths are reported in developing nations. These statistics have improved over the years due to the arrival of HPV vaccines in the market.

More than 100 types of HPV exist, but only 13 of them are found to be associated with cancer. Cervarix® (GlaxoSmithKline) and Gardasil® (Merck) are commercially available to prevent the diseases caused by HPV types 16 and 18. About 70 percent of cervical cancer associated with HPV is caused due to these two types of HPV.

Gardasil was approved in 2006 to prevent cervical cancer. Its improved version, Gardasil 9 (9vHPV) vaccine targets nine types of HPV. According to a study by Motiff Cancer Center, Gardasil 9 was shown to prevent approximately 90 percent of cervical cancer, 90 percent of HPV-related vulvar and vaginal cancer, 70 to 85 percent of high-grade cervical disease in females, and approximately 90 percent of HPV-related anal cancer and genital warts in males and females worldwide.[1]

[1] Joura et al. A 9-Valent HPV Vaccine against Infection and Intraepithelial Neoplasia in Women, N Engl J Med 2015; 372:711-723, DOI: 10.1056/NEJMoa1405044

Provenge (sipuleucel-T) the pioneering prostate cancer vaccine, was approved by the FDA in 2010.

Two pioneering next-generation immunotherapy companies, NantCell and NantKwest are developing novel anti-cancer Nant Cancer Vaccine. The strategy aims to combine low-dose radiation and chemotherapy with molecularly-informed, tumor-associated antigen vaccines and natural killer (NK) cells, to activate the patient's innate and acquired immune system for selective target and elimination of cancer cells.

NK cells are the body's first line of defense due to their innate ability to rapidly detect and destroy cells under stress, such as cancer or virally-infected cells. The Nant vaccine aims to improve and sustain the period of temporary recovery in cancer patients with reduced toxicity and higher efficacy than the current standard of care treatments.
In January 2016, the companies announced the Cancer Breakthroughs 2020 program to move to the next level of cancer care. It focuses on the development of efficient, personalized cancer treatments by utilizing the human body's innate immune system.

FDA has cleared the Nant Cancer Vaccine for clinical trials in pancreatic cancer patients. Further, the Nant Cancer Vaccine will further be tested in all types of cancer patients and at all stages of the disease.

Increasing incidence and prevalence of cancer has up roared the need for newer interventions. In the impetus search for novel techniques to treat cancer, various "healthy cell-friendly" viruses have been genetically engineered to develop into cancer-killing oncolytic viruses.

Oncolytic virus is a tumor-selective virus that selectively infects and kills cancer cells and also stimulates antitumor immune responses in the individual. These cancer-killing viruses are especially designed from naturally occurring viruses and are programmed to identify and kill cancer cells sparing healthy cells. The oncolytic viruses have successfully been developed into oncolytic immunotherapy agents.

The potential of oncolytic viruses as anti-cancer and oncolytic immunotherapy agents are well recognized as they act through multi-mechanism such as multimodal immunogenic cell death (ICD), autophagy and induction of adaptive antitumor immunity.

Amgen's Imlygic (talimogene laherparepvec or T-Vec) was FDA-approved in 2015 as oncolytic virus therapy for the treatment of melanoma. Imlygic is a genetically modified live oncolytic herpes virus therapy. Human adenovirus serotype 5 (AD5) was genetically modified into the oncolytic virus named Oncorine which was approved in China in 2005 for the treatment of head and neck squamous cell carcinoma (HNSCC).

Reolysin® or pelareorep, derived from wild type Reovirus (Oncolytics Biotech, Canada) is an oncolytic virus under development for the treatment of various cancers and cell proliferative disorders. It has received Orphan Drug Designation by FDA for the treatment of malignant glioma.

Australian biotech, Viralytics is developing its lead oncolytic candidate Cavatak™ which is a proprietary formulation of the common cold Coxsackievirus type A21. Korean biotech, SillaJen along with French partner Transgene and Chinese partner Lee's Pharma are developing the oncolytic virus, Pexa-Vec or pexastimogene-devacirepvec to target, infect and kill cancer cells. It is a modified Copenhagen strain vaccinia poxvirus that received Orphan Drug designation from the US FDA and the European Union to treat hepatocellular carcinoma and is currently in worldwide Phase III clinical trial.

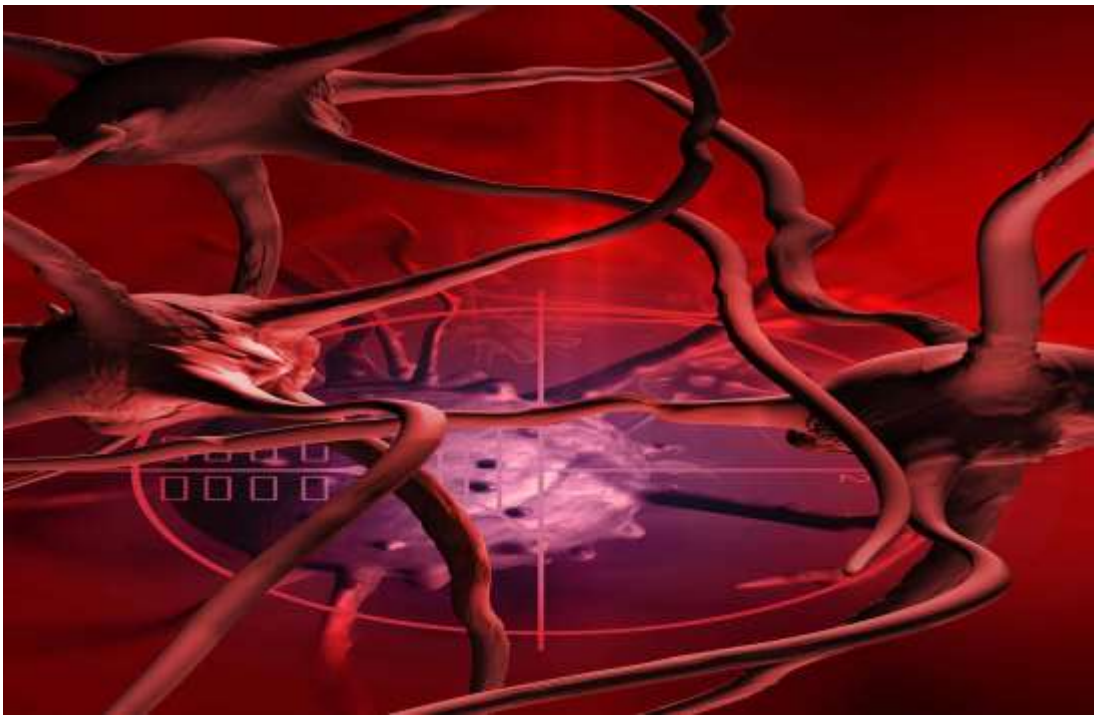
Celgene-backed Oncorus, DNAtrix, Genelux Corporation, Vyriad and Tilt Biotherapeutics have been well-funded for the development of novel oncolytic virus therapies. Pfizer has partnered with a startup, Western Oncolytics to develop novel, oncolytic vaccinia virus named, WO-12. Pfizer has also invested in a new oncolytic virus development company, Ignite. BMS has collaborated with a British firm, PsiOxus Therapeutics to develop oncolytic virus "NG-348" for treatment of solid tumors.

Oryx' viral therapy, ParvOryx is being tested along with other I-O drugs like Merck's Keytuda and BMS's Opdivo for development of cancer immunotherapies against various solid tumors.

PsiOxus' lead product unarmed oncolytic adenovirus therapeutic "enadenotucirev" is being tested in combination with BMS' Opdivo for the treatment of various late-stage tumors in cancer patients. Several other companies like Shanghai Sunway Biotech, Takara Bio, Otsuka Pharmaceutical, Jennerex, Transgene, Medigene, Cell Genesys, VCN Biosciences are also some of the key players in the oncolytic virus market.

Due to their high specificity and targeted oncolytic activity, research on oncolytic viruses has evolved and expanded over the years for treatment against various types of tumors with major mostly concentrated in North America, Central or North Europe followed by Australia, South Africa, China, Korea, Japan, and India. Oncolytic virus therapy is likely to be a promising novel treatment option for cancer.

Urge for Personalized Cancer Treatment



Cancer is a heterogeneous disease. All cells of the tumor may not be equally sensitive to a particular drug and gradually adapt according to the conditions in the body to survive and proliferate. Therefore, it is unlikely that a single treatment would guarantee elimination of all the different types of mutations-bearing cancerous cells. This often results in survival some cancerous cells and future recurrence of cancer resulting in requirement of stronger drug doses, which cause severe adverse effects.

Occurrence of tumor heterogeneity has forced scientists to explore and investigate the field of personalized cancer treatment. Genomics-guided diagnostic- liquid biopsy is evolving to collect precise information about an individual's cancer rather than treating them with a "suitable for all" drug. Liquid biopsy helps in the diagnosis and analysis of the tumor biomarkers in the body fluid samples of patients. It is useful in precise treatment selection, acquiring information about tumor response to therapy in real-time, mechanism of tumor progression and drug resistance mechanism to name a few. Liquid biopsy is a revolutionary minimally invasive technology and is expected to replace the traditional, painful tissue biopsy in future. Liquid biopsy market is forecasted to grow at a CAGR of 20.6 percent to reach over $3 billion in the next 10 years.[1]

Currently, the liquid biopsy kits and tests for cancer diagnosis capture the largest market share and are expected to contribute about 60 percent to liquid biopsy market by 2027.

[1] "Global Liquid Biopsy Market, Analysis and Forecast, 2017-2025, accessed at https://www.researchandmarkets.com/research/v427zv/global_liquid

Circulating tumor cells (CTCs) are the most dominating biomarker that is detected and analyzed for cancer diagnosis and monitoring. It captures a broad section of the liquid biopsy market.

Other types of biomarkers like circulating genetic materials- circulating tumor nucleic acids (ctDNA, ctRNA); exosomes; proteins are also being developed for disease diagnosis. Within a short period, a liquid biopsy can inform the physicians whether the patient is responding to the given therapy or not. So those who show the disappearance of mutation can stay in the treatment and the others can be switched to a different therapy, preventing any side effects of the fruitless treatment for a long time. The response of a tumor to ongoing therapy could be easily monitored in real-time during the treatment by liquid biopsy.

Apart from the cancer diagnosis, the liquid biopsy is also being developed for several other diseases like cardiovascular, infectious, immune disorders, genetic disorders by the analysis of different biomarkers.

In terms of region, North America has dominated in the use of the liquid biopsy for cancer diagnosis and treatment which has fueled the revenue growth for liquid biopsy in the region. Oncologists, as well as patients, are increasingly opting for the innovative diagnostic procedure for early-stage cancer detection and for reducing the risk of cancer recurrence. Europe holds the second lucrative market for liquid biopsy followed by Asian countries like India, China.

Entry of CAR-T Cell Therapy

2017 witnessed the FDA approval of two groundbreaking gene therapies based on CAR-T cell approach. CAR-T cell therapy involves the development of customized cancer treatment using patient's own cells. Typically, T-cells are collected from patients and genetically modified in culture to include a new gene encoding a specific protein- chimeric antigen receptor (CAR). After the modification, the cells are infused back into the patients to target the cancer cells. The CAR protein directs the T-cells to identify the tumor cells with a specific antigen on their surface and subsequently kill them.

Novartis' CAR-T cell immunotherapy, Kymriah (tisagenlecleucel-T) became the first FDA-approved treatment to treat pediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukemia (ALL) – a rare hard-to-treat pediatric blood cancer.

The approval expanded the horizon of cancer cure with a more personalized treatment option for patients. Hepatitis giant, Gilead Sciences entered into the futuristic CAR-T cell therapy space with the buyout of CAR-T therapy firm, Kite Pharma in $11.9 billion deal. The deal stroked well with the FDA approval of another CAR-T cell therapy, Yescarta (axicabtagene ciloleucel) developed by Kite Pharma. Yescarta is approved for the patients with relapsed/refractory aggressive B-cell non-Hodgkin lymphoma (NHL) who are ineligible for autologous stem cell transplant.

Both the approved therapies target CD19 antigen on the cancer cell surface. CD19 based therapy is expected to dominate the market in the next decade followed by the arrival of CD20 and CD22 antigen-based therapy for solid tumors.

In CAR-T cell therapies, patient's genetically engineered T-cells target the cancer cells in the body. This activity inside the body can cause an overactive immune response- cytokine release syndrome. This condition can cause mild but manageable flu-like symptoms in many patients, but in some of them, it can cause life-threatening complications like cardiac dysfunction and multiple organ failures.

Roche's Actemra® (tocilizumab) received approval by the US FDA to treat CAR-T cell therapy-induced cytokine syndrome.

Companies like Juno Clinic, Celgene, Cellectis, BlueBird Bio, Precision Biosciences, Baxalta, Ziopharm Oncology, Bellicum Pharmaceutical and Editas Medicine are also working on the development of CAR-T cell candidates.

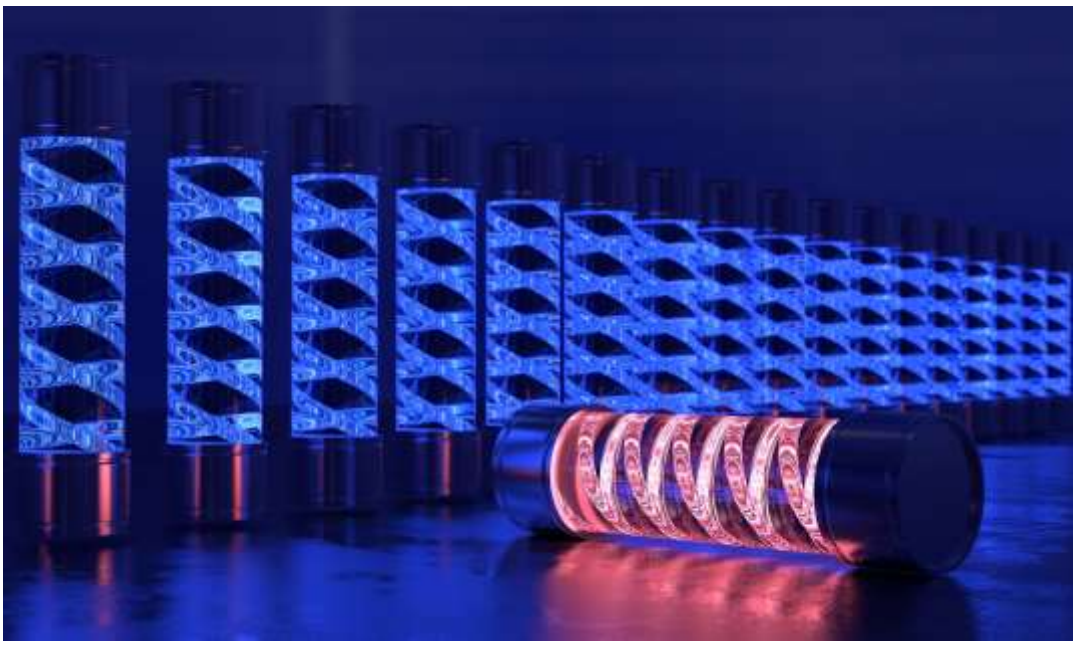
French firm Cellectis and Great Ormond Street Hospital, London treated a one-year-old girl, Layla with modified T-cells from a donor called UCART19 (Universal Chimeric Antigene Receptor T-cells) cells successfully. She was suffering from relapsed ALL and was in the last stages. Later another child diagnosed with an aggressive form of leukemia was also treated successfully with UCART19 therapy.

These miraculous cases of CAR-T therapy with high success rate have generated immense confidence among investors for CAR-T cell immunotherapy. However, large scale clinical studies with big data are required to be generated before boasting much about this new technology.

The increasing global demand for such genetically engineered treatment should push the global CAR-T cell therapy market to around $9 billion by 2030.

Every year millions of people worldwide, die of various types of blood cancers. CAR-T is believed to address the issue of low survival rate related to most blood cancers. It is forecast that North America will dominate the CAR-T cell therapy market followed by Europe in the next ten years or so.

Betting on RNAi-Based Cancer Therapy



After the American Scientists- Andrew Z. Fire and Craig C. Mello received Nobel Prize in Physiology and Medicine in 2006 for their path-breaking work on RNA interference (RNAi), RNAi has emerged as a hot tool to silence unwanted and faulty genes for treatment of cancer.

RNAi strands were demonstrated to selectively silence genes of interest. Billions of dollars have been invested in the therapeutic application of RNAi in humans. Several RNAi drugs are currently in clinical trials.

Companies like Quark Pharma, Silence Therapeutics, Alnylam Pharmaceuticals, Calando Pharmaceuticals, Silenseed are developing RNAi-based candidates for advanced cancer treatment. Various companies are also working on RNAi drugs for other conditions like glaucoma, viral infections, renal failure, choroidal neovascularization, diabetic retinopathy, diabetic macular edema and hypercholesterolemia. They include Arrowhead Research, Allergan, Tekmira Pharma and Craig C. Mello co-founded RXi Pharmaceuticals.

RXi Pharma acquired a 2015 founded startup MirImmune, in 2016. MirImmune has developed innovative RNAi compounds that can potentially target different checkpoints in cancer treatment. The company introduced anti PD-1 self-delivering RNAi compound into CAR-T cells. Mice with human ovarian cancer tumors when injected with the modified CAR-T cells, showed significantly reduced tumor growth. More similar studies in future would amalgamate powerful technologies to unlock new doors for effective cancer treatment. These techniques would combine the advantages of two promising immunotherapy approaches while reducing the typical side effects of combination drugs.

Despite some of the limitations of RNAi therapy, like its instability under physiological conditions, it comes with significant advantages. It promises a high level of safety as it does not interact with DNA, high efficacy, the principle of complementary base pairing gives an unrestricted choice of the target with specificity. The development of molecular biology, whole-genome sequencing and growing nucleotide sequence databases provide a strong foundation for RNAi based therapies.

Ending Cancer with CRISPR Technology- Is it the Future of Cancer Treatment?

Inspired by the defense mechanism of the bacteria, CRISPR-Cas9 technology has brought revolutionary change in genome engineering and is believed to steer the direction of healthcare in a new path altogether. Genetically-guided diagnostics and treatment have created a buzz in the medical space for high precision and reduction of the risk of adverse effects. Controlled gene editing by CRISPR technology has the unproven potential of reviving extinct species to curing impossible diseases.

The term CRISPR has been actively around for the last five years. CRISPR stands for 'Clustered Regularly Interspaced Short Palindromic Repeats' and was first discovered and reported in single-celled microorganisms of the archaeal group by a Spanish scientist, Francisco Mojica in 1993. Later, its function was elaborately studied and found to be a bacterial defense mechanism against invading viruses.

The research study by Jennifer Doudna at University of California, Berkeley, and Emmanuelle Charpentier at University of Umea, in 2012 proposed the possibility of altering CRISPR-Cas complex to use it as a biotechnology tool to reprogram or replace faulty or missing genome for therapeutic purposes. Since then the technological breakthrough is being widely studied to edit genes for treatment of cancers, genetic diseases, and blindness and has been vaunted as a "Nobel Prize-winning" technology.

CRISPR-Cas9 system allows the researchers to precisely modify or correct the mutations present in the human genome in order to treat various diseases. The modified versions of Cas9 can activate a gene expression instead of turning it off. This will help researchers to study gene's function.

Novartis and Regeneron-backed gene-editing startup Intellia Therapeutics founded by Jennifer Doudna in 2014, entered an IPO in 2016 and raised $108 million. In the same year, Editas Medicine had raised $94.4 million, and CRISPR Therapeutics raised $56 million in IPO. CRISPR Therapeutics was founded in 2014 by Emmanuelle Charpentier along with Jennifer Doudna and Rodger Novak. Several other companies are developing the CRISPR-based technology to treat diseases including blindness, Huntington's disease, Duchenne muscular dystrophy and some forms of cancer.

The success of PD-1 inhibitors in cancer treatment is significant. It gave a strong foothold to immunotherapy in cancer treatment market. In 2016, researchers from the University of Sichuan, China pioneered CRISPR trial in humans, playing around the PD-1 expression of cells. Genetically modified cells edited by CRISPR-Cas9 technique were delivered to a patient suffering from advanced NSCLC. The gene therapy switched off the gene encoding the PD-1 protein which is known to help cancer cells escape immune system attack by the PD-1/PD-L1 mechanism. If the technique is proven better in efficacy than the anti-PD monoclonal antibodies, it will send a big wave of transformation to the current scenario of cancer treatment. However, this technique is relatively unexplored, and it is too early to guess which treatment is better. Nevertheless, CRISPR is looked upon as the technology of future.

Scientists at the University of Rochester used CRISPR-Cas9 technique to target a protein named Tudor-SN that plays an essential role in the initiation of cell division. By removing Tudor-SN from human cells, scientists successfully reduced the growth of kidney and cervical cells.

Human trials of the CRISPR-Cas9 technique are expected to start this year in the US. Doctors at the University of Pennsylvania will modify human immune cells by CRISPR to fight different types of cancer- multiple myeloma, sarcoma, and melanoma. CRISPR Therapeutics is also expected to begin human clinical trial in Europe to treat a genetic defect in patients with beta- thalassemia, an inherited blood disorder this year. This technology has the power to reverse many untreatable, rare and inherited diseases and conditions. Although, concerns regarding the potential abuse and life-risking side effects like unintended mutations are doing rounds, broader insight into the technique to improve the target and cut process and strict framework for the implementation of CRISPR-Cas9 technology in human research could make this technology an unparalleled technique of treatment in future.

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The diverse techniques are being implemented in the cancer research and development to combat the disease downright. The companies are putting immense faith in the newer technologies and developing them with all energy to channelize them towards cancer cure. Hope to see more impactful and groundbreaking cancer therapies in future.

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