Modern Drug Discovery and Development in the Area of Cancer: Indian Context

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10.1 What Is Cancer?

Cancer is a perturbation of intricate balance between "cell division" and "cell death." Normal cells divide up to certain extent or limit which is called "Hayflick" limit and then die to maintain normal body homeostasis. Cancer cells do not obey "Hayflick" limit and proliferate uncontrollably to form a tumor. In a simplistic description, cancer is a deregulated cell division due to changes in the genetic material of a cell. According to WHO, cancer is a commonly used name for a large group of diseases with similar characteristic features. Some other commonly used terms to describe cancer include malignant tumors and neoplasms. The most important characteristic feature of cancer is rapid multiplication of cancerous cells and spreading to different parts of the body is known as metastasis. Metastatic cancer is a leading cause of death among the cancer patients across the world (WHO 2018). Some other major

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characteristic features of cancer cells include the capability to acquire autonomous growth signals, evasion of growth inhibitory signals, angiogenesis, and unlimited replication.

Cancer Key Facts Worldwide

- According to WHO, cancer is the second leading cause of death due to diseases in the world.
- In 2018, an estimated 9.6 million have died from cancer.
- One sixth of deaths worldwide are due to different types of cancer.
- Lung and breast cancers are most common type of cancer by incidence.
- Lung and colorectal cancer are leading causes of death.
- Tobacco, alcohol, higher BMI, low consumption of fruit and vegetables, and sedentary life style are the leading causes of mortality in cancer patients worldwide.

Source: WHO (2018)

Cancer Statistics of India

- From 1990 to 2016, death due to cancer is doubled from 0.38 to 0.81 million deaths.
- About 1.15 million estimated incidence of new cancer in 2018 and is expected to be doubled by year 2040.
- About 2.25 million people are living with cancer disease.
- Breast and oral cancers are predominant types.

Source: Cancerindia.Org (2020)

10.1.1 Whether Cancer Is a Disease of Humans?

Cancer disease is not limited to human beings. Incidence of cancer is reported in many of the animal species as well as plants. It is reported that in over 140 species of eudicots plants, *Agrobacterium tumefaciens* causes a disease named as "Crown gall," which is characterized by the uncontrolled division of cells around the infection, forming a tumor (Helen and Stafford 2000). Unlike cancer in humans, metastasis does not occur in plants as the plant cells are anchored in place by the cell walls.

In the animal kingdom, cancer is a much more widespread disease. Death due to cancer has been reported in wild animals, marine animals as well as domestic animals. The mortality rate due to cancer in many of the animal species is similar to that of human beings. Recent news coverage by National media regarding cancer death in animals is that of an eleven-year-old Royal Bengal Tiger named Yash, which was suffering from a rare form of cancer and died at Sanjay Gandhi National Park (SGNP) in Mumbai on 28 May 2019. A point of scientific interest in this news

coverage is "rare form of cancer." It indicates the incidence of different types of cancer in animals similar to humans.

Peto's Paradox
Cancer is basically a consequence of mutation in the somatic cells. By virtue of cause of cancer, it should have been the fact that more the number of somatic cells, higher the chances of cancer. Statistically, it was not found true. This is called as "Peto's paradox," after the scientist Richard Peto, who noticed that cancer prevalence is not correlated with body size. For example, blue whales have thousand times more somatic cells than human; however, cancer incidence is much lower in blue whales compared to humans. Similarly, elephants have trillions more cells than us and live long time, yet they have lower cancer rates.

Wide variety of cancer types, their causes and characteristic features have thrown a mammoth challenge to the researchers to find out the effective cure for cancer. Though many of the cancer types, particularly in early stages, are being cured through variety of therapeutics available, the later stage of cancer is a huge challenge for researchers. Many of the researchers are focusing their research on prophylactics—a medication used to prevent the occurrence of disease. Providentially, Indian system of traditional medicine, Ayurveda, has given new hopes to discover prophylactics.

10.1.2 How Old Is Cancer?

The fossil remains of duck-billed dinosaurs, which lived 7 million years ago, is the oldest evidence of cancer incidence shown by Rothschild BM of the North-eastern Ohio Universities College of Medicine (Rothschild et al. 2003) while evidence of cancer incidence in human beings has been witnessed throughout recorded history. Fossils, mummies in Egypt, and manuscripts of ancient history are valuable evidence of cancer incidence during ancient history. The "Edwin Smith Papyrus," an ancient Egyptian medical text on "Trauma surgery" which dates back to about 3000 BC is the available oldest description of cancer disease. In this textbook, there is a mention about cauterization to remove eight cases of tumors using a tool called fire drill. The textbook describes that there is no treatment for this disease (The American Cancer Society Medical and Editorial Content Team 2014).

However, in a study published in "Nature Reviews Cancer" in 2010 by researchers from University of Manchester (David and Zimmerman 2010), it has been debated that cancer is a modern, man-made disease caused by external factors such as pollution and diet. They have cited the fact that evidence of cancer in fossils

and early humans is very limited. Many types of cancer commonly identified in adult human are not seen in non-human primates. It is evidently true that modern world is having higher exposure for carcinogens.

In the literature, Hippocrates (460–370 BC), an ancient Greek physician, used the term "Karkinos" (Greek word for crab) to describe cancer. Around 47 AD, the Grecko-Roman philosopher Celsus translated the Greek word karkinos to the Latin word for crab: Cancer. Interestingly, the term "Oncology"—a branch of medicine that deals with the cancer, is also derived from ancient Greek. Aelius Galenus (130–200 AD), another famous Greek physician used the term Oncos (swelling) to describe cancer.

The invention of compound microscope in 1590 and its subsequent use for scientific investigations facilitated major breakthroughs in the area of cancer. Using microscope, pathologists described specific cancers, documented the incidences and types of cancer. Today, many advancements have been made in research in the area of cancer. More than 100 types of cancers have been reported worldwide so far. Researchers have succeeded in developing treatments for some of the cancer types already including radiation, chemo-, immuno-, hormone, and targeted therapy. However, still we are far away from finding cure to many types of cancer which are affecting human beings irrespective of their class or lifestyle, including celebrities, world leaders to poor people.

10.2 Cancer Types and Incidence

International Classification of Diseases for Oncology has grouped cancer into six major categories based on histology (National Cancer Institute n.d.).

Carcinoma is a malignant neoplasm of epithelial origin. It accounts for 80–90% of all cancer cases. Two major subtypes of carcinoma are: (1) adenocarcinoma and (2) squamous cell carcinoma. Examples include skin, breast, lung, prostate cancer, etc.

Sarcoma is a rare type of cancer which originates from connective tissues like bone, cartilage, and muscle. Examples includes osteosarcoma, glioma, chondrosarcoma, etc.

Myeloma is a cancer of plasma cells, a type of white blood cells of blood.

Leukemia also called as blood cancer refers to the cancers of the bone marrow, which leads to overproduction of abnormal blood cells.

Lymphoma are solid cancers and usually originates from the glands or nodes of the lymphatic system.

Mixed Type of cancer may have two or more components of cancer. Example, adenosquamous carcinoma, carcinosarcoma, etc.

Another type of classification of cancer is based on the site of cancer and is more popular. Examples include breast, oral, lung, cervical, stomach, colon, and prostate cancer.

10.3 Cancer in India

There are no reports available regarding incidence of cancer in ancient Indian civilizations. However, there is a mention of cancer like disease, particularly Granthi (small in size) or Arbuda (large in size) and remedies for the same in ancient manuscripts of Ayurveda. According to available reports, cancer cases in India are recorded from seventeenth century onwards. During later part of the nineteenth century, doctors of Indian Medical Services started publishing cancer case series (Smith and Mallath 2019). The efforts at policy level was seen in 1946, in which a national committee recommended setting up of facilities to diagnose and manage cancer burden in Indian states. Soon after independence, in 1950, the Cancer Research Institute was established by Prof. VR Khanolkar as a dedicated center to understand intricacies of disease to evolve treatment regime. Currently, CRI is part of the Advanced Centre for Treatment, Research and Education in Cancer (ACTREC), which is mandated to function as a national center for treatment, research, and education in cancer. Indian Cancer Society, established in 1951 by Dr. DJ Jussawalla and Naval Tata, is a first non-government, non-profit organization in India with a mission to create awareness about cancer, facilitate early detection, and providing support for treatment of cancer for poor cancer patients. Subsequently, Dr. Jussawalla established the first Population Based Cancer Registry (PBCR) in Mumbai in 1963 with financial support from Indian Cancer Society. India's National Cancer Registry Program started in 1982 and over the years, several population based cancer registries were added. At present, a total of 31 population based cancer registries and 29 hospital based cancer registries are functional across India. These cancer registries are playing imperative role in controlling the impact of cancer on the community by providing a framework for assessment.

It is pertinent to mention that the Lady Tata Memorial Trust, established by Sir Dorabji Tata in 1932 in memory of his wife, Lady Meherbai, who died of leukemia, started financial support for R&D in the area of cancer. Subsequently, considering the incidences of cancer and its impact on Indian population, CSIR, DAE, ICMR, and DBT started support for the cancer research in India. According to bibliometric reports, number of publications in the area of cancer in 1990 was about 300. By 2010, the number was almost 1500 publications per year (Sullivan et al. 2014).

10.3.1 Role of Council of Scientific & Industrial Research, India

Council of Scientific & Industrial Research, India was formally established in 1942 for development of natural resources and industries in India by setting up of research laboratories to assist the nation building. The health of the increasing population was then a major area of concern. Life expectancy was very low. The Central Drug Research Institute (CDRI) at Lucknow was the first laboratory of CSIR established in 1951 exclusively for drug research. In due course of time, other research laboratories to advance the biomedical research were established in India. National Chemical Laboratory, Pune, and Indian Institute of Chemical Technology were

focusing on development of indigenous process technologies for lifesaving drugs to support Indian pharma industries. CSIR-CDRI, apart from new drugs, also significantly contributed to the development of indigenous process technologies for more than 80 drugs. During the last more than 75 years of CSIR's existence, a large number of newer laboratories were added to its fold. With advancement in biomedical sciences, newer aspects of drug research were initiated. Due to intermixing of various disciplines many of the laboratories, not directly working in healthcare sector, also made valuable contributions to this area. Among the CSIR Institutes, Central Drug Research Institute, Lucknow; Indian Institute of Chemical Biology, Kolkata; Centre for Cellular & Molecular Biology, Hyderabad; Indian Institute of Integrative Medicine, Jammu; and Indian Genomics and Integrative Biology are currently pursuing fundamental as well as translational research programs in the area of cancer.

10.3.2 Role of Other Government Organizations

Several institutes established by Department of Biotechnology, Department of Science & Technology, Indian Council for Medical Research also significantly contributing to the cancer research in Indian context. Contributions from the research teams at Indian Institute of Science, Bengaluru and Jawaharlal Nehru Centre for Advanced Scientific Research, Bengaluru in advancing knowledge frontiers in the area of cancer is noteworthy. ICMR played a major role in setting up cancer therapy regimen across India. They set up indigenous treatment protocols for adjuvant and neo-adjuvant therapy in Indian patients. ACTREC and AIIMS also developed their indigenous therapy protocol by modifying international guidelines which is very useful in Indian context.

Significant contributions of Indian Research Organizations in Cancer research are discussed in the subsequent sections of this of chapter.

10.3.3 Predominant Cancer Types in India

Available reports indicate that incidence of most of the types of cancers that affect world population is prevalent in Indian population as well. During last two and a half decades, the cancer burden has actually doubled from 0.38 million in 1991 to 0.81 million deaths in 2016. About 2.25 million people in India are living with cancer. Predominant types of cancer in 1990 and 2016 are given in Table 10.1. Various studies indicated that use of tobacco products is the single most preventable cause of cancer.

Among the cancer types, breast cancer is predominant in Indian women in terms of morbidity and mortality, followed by cervical, ovarian, and uterine cancer. Interestingly, in urban women population, breast cancer is leading whereas, in rural women population, cervical cancer is the leading cause of morbidity and mortality. Death due to cervical cancer is almost one women per 8 min in India

Table 10.1 Top ten cancer types in India in 1990 and 2016 based on incidence rate

	1990	2016
1	Cervical cancer	Breast cancer
2	Stomach cancer	Lip and oral cavity cancer
3	Lip and oral cavity cancer	Cervical cancer
4	Breast cancer	Stomach cancer
5	Pharynx cancer other than nasopharynx	Lung cancer
6	Lung cancer	Pharynx cancer other than nasopharynx
7	Colon and rectum cancer	Colon and rectum cancer
8	Esophageal cancer	Esophageal cancer
9	Leukemia	Leukemia
10	Larynx cancer	Prostate cancer

Source: The burden of cancers and their variations across the states of India: the Global Burden of Disease Study 1990–2016 (India State-Level Disease Burden Initiative Cancer Collaborations 2018)

(NCDIR 2012–2014). Currently, the estimated rate of incidence of breast cancer is 25.8 per one lakh women, which is expected to become 35 per one lakh women by 2026 if adequate measures are not taken. Mortality rate among the breast cancer patients is nearly 50% (Fig. 10.1).

Among the Indian men, the predominant cancer types include oral cancer followed by lung, esophagus, and stomach. Analysis of incidence of cancer in different states of India provided very interesting information regarding lifestyle and predominant cancer types. Figure 10.2 gives a pictorial representation of cancer incidence and risk factors in different states of India. Though different geographical regions of India have different predominant types of cancer, consumption of tobacco and pollution are reported to be major factors causing cancer in the Indian population in several regions.

According to 3-year report of population based cancer registries 2012–2014 published by National Centre for Disease Informatics and Research, ICMR, Aizawl district in Mizoram reported highest cancer incidence among males. In females, the Papumpare district in Arunachal Pradesh reported highest incidence of cancer (NCDIR 2012–2014).

According to the aforesaid report, lung cancer, mouth cancer, esophagus cancer, and stomach cancer are predominant types in males across the Population Based Cancer Registries (PBCRs) in India. Lung cancer is predominant type in Delhi, Mumbai, Chennai, Kolkata, Bangalore, Thiruvananthapuram, etc. Oral cancer is the leading type of cancer in Bhopal, Ahmedabad Urban, Nagpur, Pune, Barshi, etc. The PBCRs in the state of Meghalaya, Assam, and Patiala reported highest incidence of cancer in esophagus while breast cancer is predominant type of cancer in 19 registry areas and Cervix uteri is the leading site in six registry areas among females.

Data from various PBCRs and HBCRs indicate that cancer incidence is highest in North-East region of Indian subcontinent. Major factors attributed for high incidence include lack of awareness, socioeconomic conditions, and difficulty of access to the facilities.

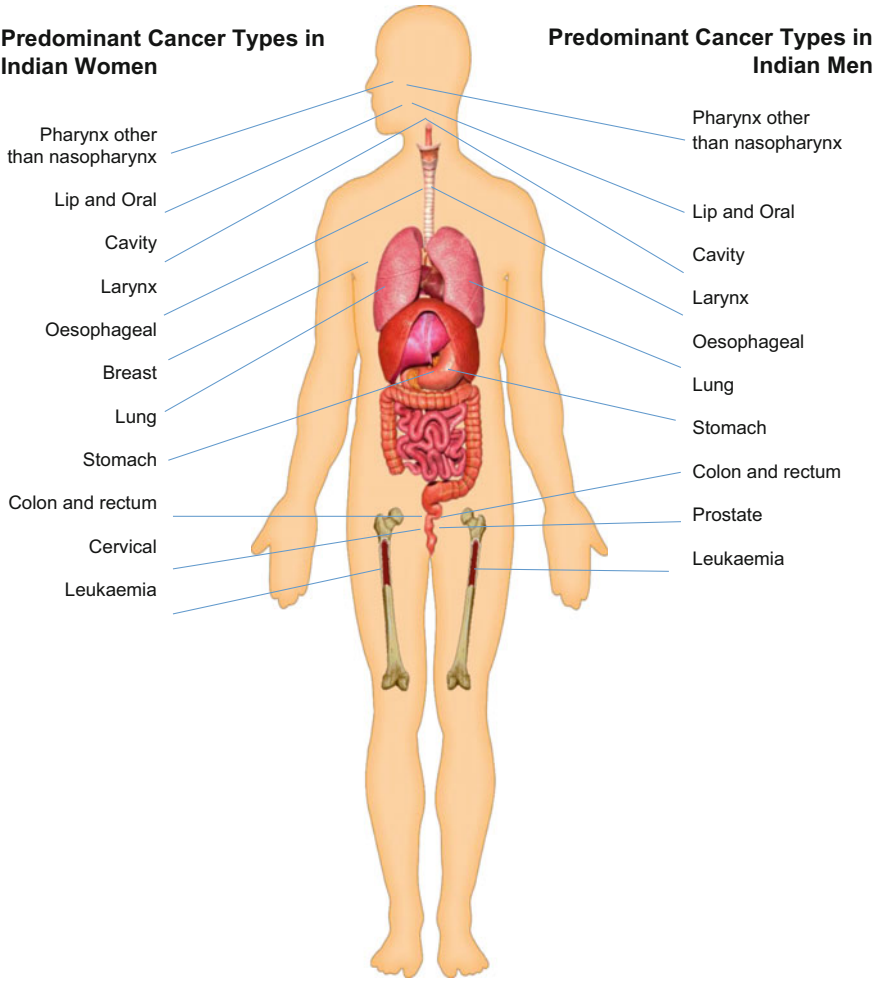


Fig. 10.1 Different types of cancer predominant in Indian population

10.4 Cancer Therapy

Advancement of Science & Technology led to development of multiple strategies and several therapeutics to treat cancer. Type of treatment to be given to a cancer patient is being decided based on the cancer types and other associated factors. Some of the popular treatment methods and therapies are briefly described below:

Surgery is a procedure to remove cancer from patient body. Ways include cryosurgery, precise surgery through laser beams, hyperthermia, etc.

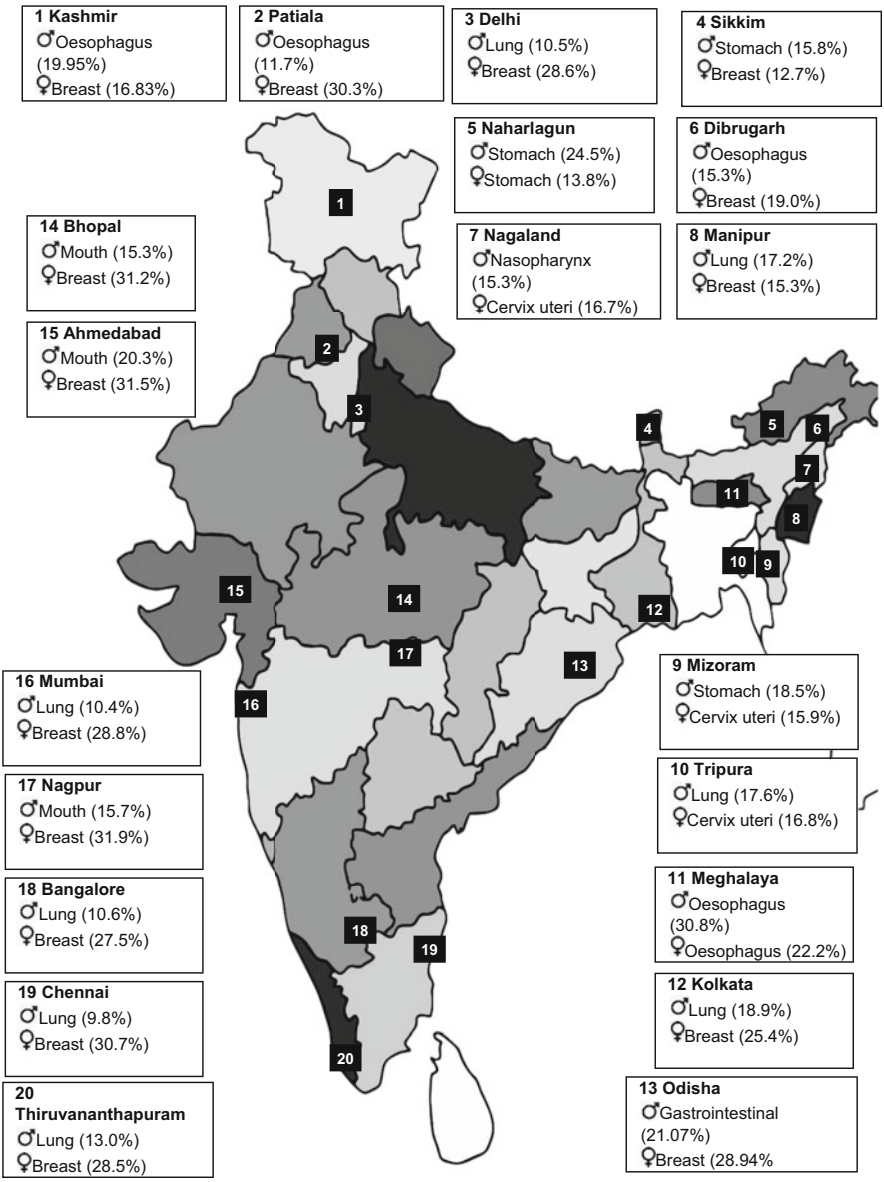


Fig. 10.2 Leading sites of cancer in male and female as reported in population based cancer registry across India. Leading site based on the proportion relative to all sites of cancer incidence. Percentage value in parenthesis indicates the relative proportions of cancer incidence at leading site relative to all sites of cancer

Radiation therapy uses high dose of radiation (X-rays, gamma rays, and charged particles, etc.) to kill cancer cells and shrink tumor. Radiation kills cancer cells by damaging their genetic structure or functional proteins. In systemic radiation therapy, substances like radioactive iodine used, which traverse through blood to kill cancer cells. Disadvantage of radiation therapy is that the radiation can also damage normal cells, which may lead to further complications (Oncology Nurse Advisor 2014).

Chemotherapy uses drugs to kill cancer cells. Unlike surgery and radiation therapy, chemotherapy acts throughout the body and kill cancer cells that have metastasized. Three main goals of chemotherapy in cancer treatment include cure, control, and palliation. Chemotherapy drugs are often divided into groups based on their mechanism of action. Drugs which damage DNA of cancer cells are called as alkylating agents. This type of drugs used in treatment of many types of cancer including leukemia, lymphoma, myeloma, sarcoma, etc. Some popular alkylating agents are cyclophosphamide, melphalan, carboplatin, cisplatin, etc. Chemo drug that interferes with normal metabolism of cells is called antimetabolites. Examples include 5-fluorouracil, 6-mercaptopurine, cytarabine, etc. Anthracycline chemotherapy acts on the enzymes inside cancer cells. Some of the drugs of this group include actinomycin-D, bleomycin, doxorubicin, etc. Mitotic inhibitors stop cell division. Mitotic inhibitors include docetaxel, paclitaxel, etc. Topoisomerase inhibitors are irinotecan, teniposide, etc.

Immunotherapy also called as biologic therapy improves immune system to fight cancer. Monoclonal antibodies, oncolytic virus therapy, T-cell therapy, and vaccines are some of the types of immunotherapy being used worldwide. Immunotherapeutic agents act in many ways. Antibodies are used to flag cancer for subsequent killing of them by immune system. Immune checkpoint inhibitors like nivolumab, ipilimumab, and atezolizumab help the immune system respond more strongly to a tumor. Adoptive cell transfer attempts to boost the natural ability of T cells to fight cancer. USFDA has approved first oncolytic virus therapy in 2015 to treat melanoma. Genetically modified version of herpes simplex virus are injected directly into areas of melanoma, which enters cancer cells, multiplies and kills cancer cells. Release of antigens in this process triggers the immune system of host to target all the cancer cells which have same antigens (Cancer.Net 2020a).

Hormone therapy uses inhibitors of hormone and slows or stops the growth of breast and prostate cancers, which are dependent of hormones for growth. For example, estrogen causes growth of breast cancer in some women. Clinicians use medicine like tamoxifen to block the effect of estrogen on the growth of cancer cells in breast tissue. Aromatase inhibitors like anastrozole and letrozole are used to prevent estrogen production in postmenopausal women to prevent the recurrence of breast cancer. Fulvestrant binds with the estrogen receptor and eliminates it rather than just blocking it. Similarly, variety of medicines are used to control testosterone, which causes growth of prostate cancer in men (University of Rochester Medical Centre n.d.) (Table 10.2).

Table 10.2 Top 20 blockbuster cancer drugs 2017

	Drug name	Manufacturer	Condition or diseases treated	Generic name
1	Revlimid	Celgene	Multiple myeloma	Lenalidomide
2	Avastin	Roche	Breast, colorectal, lung, kidney, ovarian cancers	Bevacizumab
3	Herceptin	Roche	HER2+ breast cancer	Trastuzumab
4	Rituxan	Roche	Non-Hodgkin's lymphoma, chronic lymphocytic leukemia	Rituximab
5	Opdivo	Bristol-Myers Squibb; Ono Pharmaceutical	Metastatic melanoma, colon cancer, lung cancer, renal cell carcinoma, head and neck cancer, Hodgkin lymphoma, and liver cancer	Nivolumab
6	Gleevec	Novartis	Chronic myeloid leukemia, gastrointestinal stromal tumors	Imatinib
7	Imbruvica	Johnson & Johnson/ Pharmacyclics	Mantel cell lymphoma, chronic lymphocytic leukemia	Ibrutinib
8	Velcade	Johnson & Johnson/ Takeda	Multiple myeloma, mantle cell lymphoma	Bortezomib
9	Zytiga	Johnson & Johnson	Prostate cancer	Abiraterone acetate
10	Xtandi	Astellas Pharma/Pfizer	Prostate cancer	Enzalutamide
11	Alimta	Eli Lilly	Non-small cell lung cancer	Pemetrexed
12	Gardasil	Merck & Co.	Cervical cancer	Human papillomavirus quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant
13	Ibrance	Pfizer	Breast cancer	Palbociclib
14	Perjeta	Roche	HER2-positive breast cancer	Pertuzumab
15	Tasigna	Novartis	Chronic myeloid leukemia	Nilotinib
16	Xgeva	Amgen	Bone metastases	Denosumab
17	Afinitor	Novartis	Breast cancer	Everolimus
18	Jakafi	Incyte/ Novartis	Polycythemia vera; myelofibrosis	Ruxolitinib
19	Tarceva	Roche	Non-small cell lung, pancreatic cancers	Erlotinib
20	Keytruda	Merck & Co.	Advanced melanoma; non-small cell lung cancer; head and neck squamous cell cancer	Pembrolizumab

Source: The balance. Top 20 Blockbuster Cancer Drugs. Available from URL: https://www.thebalance.com/top-cancer-drugs-2663234

Targeted therapy deploys targeted delivery techniques for delivery of specific drugs to target the specific genes, proteins, or the tissue that contributes to growth and survival of cancer. Differential biochemical/physiological features of cancer cells compared to normal cell are targeted. For example, targeted drugs can work to block or turn off chemical signals that control growth and division of cancer cells. They may stop angiogenesis to kill cancer cells or may carry specific toxins to kill cancer cells, but nor normal cells. Clinicians are using several types of agents in targeted therapy including monoclonal antibodies and small molecule drugs depending upon the need with due diligence. Diligence is important considering the fact that all cancers do not have same targets.

For example, about 20–25% cases of breast cancers are marked with high concentration of Human Epidermal Growth Factor Receptor 2 (HER2). HER2 has been indicated for its role in the growth of cancer cells. Trastuzumab, a monoclonal antibody, is used to treat non-metastatic HER2-positive breast cancer. Pertuzumab, a recombinant humanized monoclonal antibody is used to treat stage II and III breast cancer in combination with trastuzumab and chemotherapy.

Epidermal Growth Factor Receptor (EGFR) content is high in colorectal cancers, which play important role in growth of colorectal cancer. Panitumumab, a fully human monoclonal antibody, is used in targeted therapy for colorectal cancer. Similarly, angiogenesis in colorectal cancer is also targeted using antibodies as well as small molecule drugs. EGFR is also targeted in treatment for lung cancer.

For treating melanoma, BRAF gene is targeted on case to case basis. Dabrafenib and vemurafenib are FDA approved targeted therapies for stage III and IV melanoma (Cancer.Net 2020b).

The advancement of knowledge frontiers has opened up new methodologies for targeted therapy for cancer. Recently, a team of researchers led by Dr. Prabhat Mishra has developed a platform technology of nanocarriers for personalized oncotherapy. In this platform technology, they have used inverse hexagonal nano liquid crystalline particles to host anticancer drug formononetin, an optical beacon tetraphenylethene, and a tumor targeting ligand anisamide to ensemble drug targeting, imaging, and non-invasive therapeutic properties. In vitro and in vivo studies confirmed the enhanced efficacy of targeted. In the coming years, it is anticipated that targeted therapy will be a major type of cancer therapy (Urandur et al. 2018) (Fig. 10.3).

10.4.1 Drug Resistance in Cancer

Resistance to chemotherapy and targeted therapies at molecular level has posed a greater challenge to researchers and clinicians in finding a cure to cancer. Drug resistance has rendered the arsenal of anticancer drugs to remain on shelves. In-depth studies on cancer drug resistance mechanism have revealed complexity of resistance process in cancer cells. Individual's genetic differences, multi-drug resistance, epigenetic factors, altered drug metabolism, and gene amplification are some of

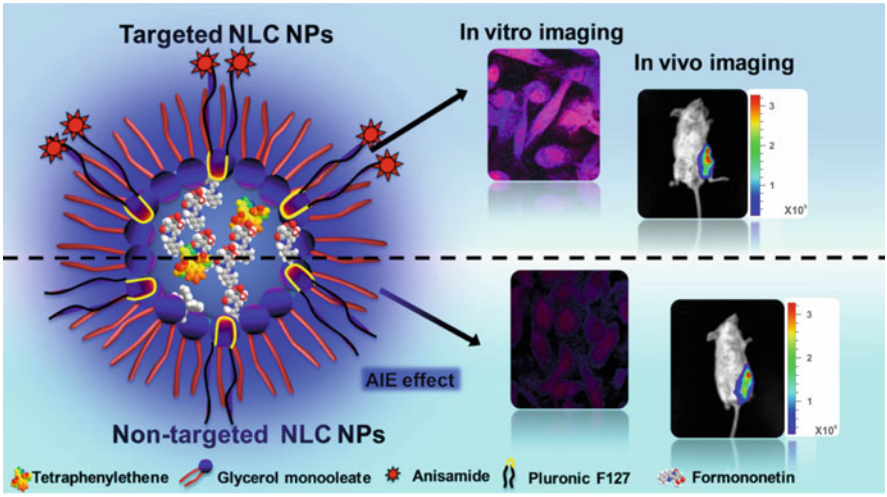


Fig. 10.3 Anisamide anchored lyotropic nano liquid crystalline particles with aggregation-induced-emission effect—a smart optical beacon for tumor imaging and therapy

the major reasons of drug resistance. Drug resistance to tyrosine kinase inhibitors is one of the very well-studied drug resistance mechanism in cancer. Tyrosine kinases play important role at cellular level, including cell cycle control. Several drugs have been discovered targeting tyrosine kinase inhibitors for treatment of various cancers and were found successful in treating cancer. Imatinib, gefitinib, erlotinib, sorafenib, sunitinib, and dasatinib are some of the widely used TK inhibitors, which have same mechanism of action—competitive ATP inhibition at the catalytic binding site. Studies have revealed that cancer cells have acquired resistance post-treatment with above TK inhibitors. Studies also revealed that apart from mutation, alternative splicing, alternative signaling pathways, and epigenetic factors contributed to the resistance to TK in patients. Following the drug resistance cases, researchers and clinicians are now focusing on alternative approaches for cancer treatment using the available drugs with a minimum scope for resistance and also alternate drug targets.

Similar to drug resistance, cancer cells have also exhibited resistance to radiation therapy. Several recent breakthrough discoveries have advanced the knowledge frontiers in cancer cell resistance to radiation therapy. Recently, a team of researchers from JNCASR, led by Prof Tapas K. Kundu has shown that downregulation of Positive Co-factor (PC4) leads to enhanced autophagy. The enhanced level of autophagy allows cancer cells to withstand the stress caused by radiation and cells become resistant to radiation (Sikder et al. 2019). This finding will have implications on radiation therapy of cancer.

10.5 Cancer Therapeutics: Indian Context

10.5.1 Generics

Advances in research and development across the globe had augmented the cancer therapy options. However, access to anticancer drugs, due to high cost has remained as a burning issue. The generic substitutions of commonly used chemotherapy drugs played significant role in the affordability and accessibility. Generic medicines are basically those drugs which have lost IP protection, and are being produced by manufacturers other than the firm or agency which innovated the drug. By definition, generic drug is same as original drug in dosage, safety, strength, route of administration, quality, and performance.

Historically important and fortunate development towards affordability of drugs in India was the passage of Indian Patent act of 1970, which recognized only process patents and not product patents for pharmaceuticals. This act was criticized by many western observers on ethical grounds but this legislation was the need of the hour for the Nation. The architect of the patent law of 1970, S. Vedaraman, the then Director of the Indian Patent Office defended the act by stating "We are not against patents. We are prepared to pay decent license fees. But we in India cannot afford monopolies." This act provided impetus to the Indian pharmaceutical industries. In the subsequent decades, driven by the abundant skilled human and material resource, low costs, and enhanced demand (domestic and international), the Indian pharmaceuticals sector witnessed a tremendous growth.

10.5.2 Contribution of Indian Pharmaceutical Sector

Indian pharmaceutical industry is playing instrumental role in world pharma sector owing to its outstanding competency and capabilities, particularly, reverse engineering and manufacture of generic medicines at significantly lower costs. Indian industries export drugs to more than 200 countries, which comprises of 20% of generic drugs. In 2018, the Indian pharmaceutical sector was valued at US$ 36.7 billion. Market share of generic drugs estimated to be around 71%. Affordability and accessibility of drugs worldwide is attributed to the low cost supply of quality drugs from India. As per the available reports, global healthcare programs like "Global Fund to Fight AIDS, Tuberculosis and Malaria" and UNICEF rely on generics manufactured in India. India is popularly known as Pharmacy of world.

Among the Indian pharma companies, CIPLA has played important role in bringing down the cost of cancer therapy in India. In 2012, Cipla cut prices of key cancer drugs by nearly 75%. Price of the kidney cancer drug sorafenib was reduced to Rs. 6840 for a month's supply, down from 28,000. Lung cancer drug gestinib was reduced to Rs. 4250 down from 10,000. Price of temozolomide, used to treat brain tumor, reduced to Rs. 5000 from Rs. 20,000. According to Dr. Y. K. Hamied, former Chairman and Managing Director, "Cipla had brought down the cost of treatment of AIDS and malaria worldwide. Continuing its contribution towards affordable and

accessible treatment for patients, they have included cancer, not only in India but globally. It was one of the bold step taken by Indian pharma, which was followed by other pharma companies in due course of time." The price cut triggered price war among the pharmaceutical companies and many other firms followed the footsteps of Cipla and reduced the cost of cancer drugs in India subsequently.

10.5.3 Contribution of Council of Scientific & Industrial Research, India

CSIR labs like CDRI, IICT, NCL, IIIM, IGIB, IICB, and CCMB have played significant role in two major aspects—development of process technology for manufacture of generics and development of scientific and technical workforce to cater to the needs of pharma companies. CSIR-CDRI developed process technology for cyclophosphamide and transferred to Sarabhai Research Centre, Baroda in 1978. Cyclophosphamide is used as chemotherapy to treat lymphoma, multiple myeloma, leukemia, ovarian cancer, and breast cancer. In 1985, CSIR-CDRI developed indigenous technology for tamoxifen citrate (anti-breast cancer) and licensed to Cipla, Mumbai. Similarly, CSIR-IICT was involved in development of cheaper alternative chemical routes for several lifesaving anticancer drugs such as etoposide, vinblastine, vincristine, and mitoxantrone, which were licensed to industries for commercial production.

A noteworthy contribution from CSIR-IICT, Hyderabad has been development of technology for Bayer's Nexavar (Sorafenib)—a lifesaving anticancer drug, priced at Rs. 280,000 for a month's dosage. IICT licensed the technology to the Indian

company NATCO which is selling the same anticancer drug sorafenib tosylate at Rs. 8800 per month's dosage at a whopping 97% cost reduction. This anticancer drug is the first example of "compulsory license" in India even when the patent on product was valid to mandate a generic drug maker to produce an inexpensive medicine in public interest.

10.5.4 Biosimilars

Indian pharmaceutical companies have grown up as the global market leaders in biosimilars which is also true in case of cancer therapeutics. Notably, Herceptin (trastuzumab), used in certain breast and stomach cancer patients was the first biologic to be approved by FDA, was also the first similar biologics manufactured by an Indian company, which received USFDA approval to market in the United States. Indian guidelines for approval of biologics is even stringent than generics. Recently, Mylan and Biocon launched a bevacizumab biosimilar in India which treats several types of cancers.

At the moment, there are more than 100 Indian biopharmaceutical companies busy in manufacturing and marketing of biosimilars in India which is called as "similar biologics" by Indian regulatory agencies. Biosimilar market in India was approximately US$ 300 million in 2015. Indian sales are close to US$ 250 million and has CAGR of about 14%.

10.5.5 Anticancer Drugs from Traditional System of Medicine

Traditional Indian system of medicine has always been a source of healthcare need for Indian population from time immemorial. It has also inspired modern drug discovery for several diseases. According to Ayurveda, cancer is inflammatory or non-inflammatory swelling called as Granthi (small in size) or Arbuda (large in size). Researchers have provided scientific data to prove the anticancer potential of many of the herbs used in Ayurveda, e.g., Allium sativum, *Curcuma longa*, *Annona atemoya*, *Phyllanthus niruri*, *Piper longum*, *Withania somnifera*, *Emblica officinalis*, *Andrographis paniculata*, *Ocimum sanctum*, *Tinospora cordifolia*, *Semecarpus anacardium*, *Ziziphus mauritiana*, *Podophyllum hexandrum*, etc.

Paclitaxel (Taxol) isolated from *Taxus brevifolia* is used in cancer treatment clinically. It acts as mitotic inhibitor. Vincristine and vinblastine isolated from *Catharanthus roseus* are also in clinical use for cancer treatment. They act as microtubule inhibitors and arrest cell cycle. The anticancer properties of several plants is still under investigation and some have shown promising results. Curcumin isolated from Curcuma longa is shown to inhibit cell proliferation in wide variety of cell limes. It has also shown to reduce VGEF and bFGF mediated angiogenesis. Withaferin A isolated from *Withania somnifera* is shown to induce apoptosis in variety of cancer cells. Triterpenic acids isolated from *Boswellia serrata* are shown to inhibit topoisomerase I and II. It is found to be effective against brain tumor.

Literature discloses strong evidence from traditional medicinal plants based cancer medicines with relatively few side effects.

10.5.6 Contribution of CSIR Institute

Another success story of CSIR in the area of cancer is development of herbal medicine by CSIR-IICB, Kolkata. The invention relates to the use of extract from leaves of *Murraya koenigii* and *Tribulus terrestris* for the treatment of benign prostate hyperplasia. This herbal formulation for prostate diseases has been licensed to M/s East India Pharmaceuticals Works (L), Kolkata. Product is in market with Brand Name: Prostalyn.

10.5.7 Advances in Comprehensive Cancer Care in India

Though cancer therapy regimen advanced lot in terms of targeted therapy applications, in major Indian hospitals, classical therapy belongs to surgery, radiation, and chemotherapy. Hormone therapy is mostly used in endocrine cancers. Many times, the treatment also include combination of two or more therapy from the above, the common ones are radiation therapy, chemotherapy, and surgery. The treatment course depends upon the diagnosis of the condition and its current stage. Cyber Knife Surgery, a non-invasive, pain free robotic radiation therapy is the latest in cancer treatment in India claiming no side effects as such.

Other advanced therapies like stem cell transplant therapy and immunotherapy are still very costly and mostly unaffordable to common Indian patients. At present, three immunotherapy drugs are available in India—Pembrolizumab (Keytruda®), Nivolumab (Opdivo®, Opdyta®), and Atezolizumab (Tecentriq®)—which are

approved by DCGI (Drug Controller General of India) for stage-IV lung cancer patients. Recently, another ICI or checkpoint inhibitor—Durvalumab (Imfinzi®)—showed efficacy in stage 3 inoperable lung cancer. The drug will be launched in India soon. When immunotherapy suits for a patient, it works really well. But there are lot of cases, it does not even work and ends up with its side effects. Therefore, we have to be always cautious in applying to each case if we can manage its affordability issues.

Recently, AIIMS took an initiative and established 182 bed specialized cancer hospital (Dr. BR Ambedkar Institute Rotary Hospital) where they are planning to start advanced cancer care clinical trials for immunotherapy and biosimilars and other mAbs.

10.6 Modern Drug Discovery and Development in the Area of Cancer in India

In general, the modern drug discovery and development efforts in India can be traced back to pre-independent India. The first new drug discovered and developed in India is Urea stibamine (carbostibamide) by UN Brahmachari, Campbell Medical College, Kolkata for the treatment of Leishmaniasis in 1922. Soon after Independence of India, setting up of premier research institutes, particularly CSIR-CDRI, Lucknow; CSIR-NCL, Pune; CSIR-IIIM, Jammu, and CSIR-IICT, Hyderabad, under the umbrella of Council of Scientific & Industrial Research, ushered a new era for drug discovery for diseases of national priorities. These laboratories successfully discovered and developed several new drugs. Out of the 20 new drugs discovered and developed in independent India, 13 are from CSIR.

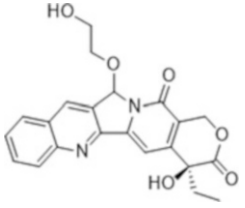
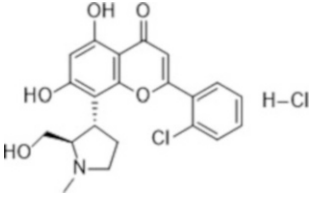
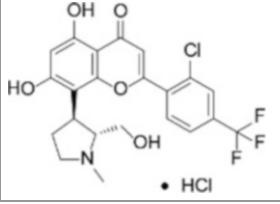
Though there are no success story of new cancer drug discovery and development in India, it is worth to mention the efforts of Indian Pharma in finding cure to different types of cancer. Table 10.3 enlists the efforts of Indian companies and organizations towards discovery and development of cancer drugs.

In 2002, CSIR-CDRI collaborated with Dabur Research Foundation in an ambitious program on discovery and development of novel anticancer agents. The program was extended further for lead optimization and drug candidate selection up to 2009. However, the efforts didn't yield the desired level. Couple of leads identified under this program was dropped during preclinical development stage.

Among the Pharma companies, Dr. Reddy's Laboratories, Hyderabad, an Indian multinational Pharmaceutical company had been the first Indian company to launch drug discovery research in India. It launched drug discovery program in 1994, followed by Ranbaxy, Torrent Pharmaceuticals Ltd., Wockhardt Ltd., Piramal Enterprises Ltd., Dabur Research Foundation, etc.

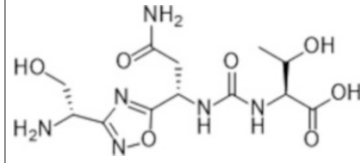
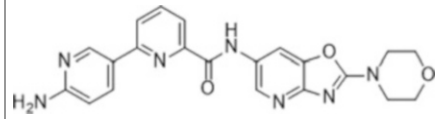
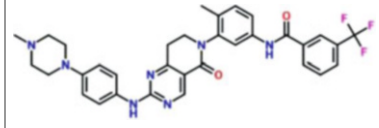
Dr. Reddy's laboratory developed topoisomerase inhibitor DRF-1042 up to Phase I clinical trial. Further development abandoned as licensee "Clintech" could not raise funds for Phase II clinical trial. Piramal Life Sciences is developing P276 and P1446 targeting cyclin-dependent kinases. P276 is in Phase II clinical trials in the USA, whereas P1446 is in Phase I clinical trial in Canada and India.

Table 10.3 Status of modern drug discovery and development efforts by Indian pharmaceutical companies

Name of the firm	Candidate drug	IUPAC name	Structure	Drug target	Latest stage of development as per available reports
Dr. Reddy's Laboratories	DRF 1042	(19*S*)-19-ethyl-19-hydroxy-12-(2-hydroxyethoxy)-17-oxa-3,13-diazapentacyclo [11.8.0.0^{2,11}.0^{4,9}.0^{15,20}] henicosa-1 (21),2,4,6,8,10,15(20)-heptaene-14,18-dione		Topoisomerase-I	Abandoned after partner Clintech couldn't raise funds for Phase II
	DRF 1644	Unknown	Unknown	Topoisomerase-I	Phase I clinical trial
Piramal Life Sciences	P276	2-(2-chlorophenyl)-5,7-dihydroxy-8-[(2*S*,3*R*)-2-(hydroxymethyl)-1-methylpyrrolidin-3-yl] chromen-4-one		Cyclin-dependent kinase	Received IND status from USFDA for mantle cell lymphoma and currently in Phase II clinical trials in the USA
	P1446	4H-1-Benzopyran-4-one, 2-[2-chloro-4-(trifluoromethyl)phenyl]-5,7-dihydroxy-8-[(2R,3S)-2-(hydroxymethyl)-1-methyl-3-pyrrolidinyl]-, hydrochloride (1:1)		Cyclin-dependent kinases	Phase I in Canada and India. Does not have IND status from USFDA

(continued)

Table 10.3 (continued)

Name of the firm	Candidate drug	IUPAC name	Structure	Drug target	Latest stage of development as per available reports
Aurigene Discovery Technologies	CA-170 (AUPM-170)	(((S)-3-amino-1-(3-((S)-1-amino-2-hydroxyethyl)-1,2,4-oxadiazol-5-yl)-3-oxopropyl)carbamoyl)-L-allothreonine		Programmed cell death protein-1 and V-domain Ig suppressor of T-cell activation	Licensed to Curis (2015); Under Phase I clinical trial in patients with advanced tumors and lymphomas
	CA-4948 (AU-4948)	6-(6-aminopyridin-3-yl)-*N*-(2-morpholin-4-yl-1,3-benzothiazol-6-yl)pyridine-2-carboxamide		IRAK4 kinase	Licensed to Curis (2015); Phase 1 clinical trial in patients with non-Hodgkin's lymphoma
	Debio-1142	*N*-[4-methyl-3-[2-[4-(4-methylpiperazin-1-yl)anilino]-5-oxo-7,8-dihydropyrido[4,3-d]pyrimidin-6-yl]phenyl]-3-(trifluoromethyl)benzamide		Jak2 tyrosine kinase and Src tyrosine kinase	Licensed to Debiopharm (2011), preclinical studies carried out in 2013. No further updates since then
	AUNP-012	CAS Number 1353563-85-5		Immune checkpoint modulator	Licensed to Pierre Fabre (2014)—preclinical stop 2015

Jubilant	CK-103 (TG-1601)	Unknown	Unknown	BRD4 protein and Bromodomain and extra-terminal domain protein	Licensed to Checkpoint Therapeutics; Phase I clinical trial to be initiated
Curadev	RG70099 (CRD1152)	Unknown	Unknown	Indolamine 2,3-dioxygenase and Trp 2,3-dioxygenase	Licensed to Roche (2015), preclinical—ongoing

Source: Websites of the concerned pharmaceutical companies and information available in public domain including Clinical Trial Registries

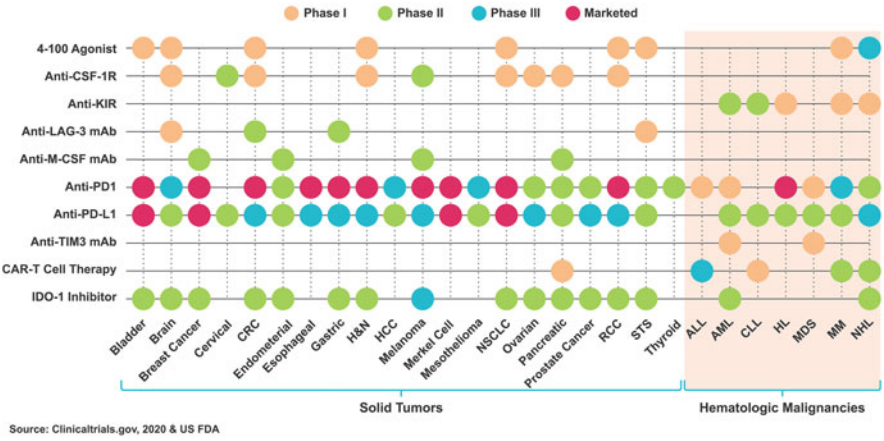
Aurigene Discovery Technologies has discovered multiple anticancer candidate drugs. It has licensed AUPM-170 (CA-170) and AU-4948 (CA-4948) to Curis in 2015. CA-170 is being developed as dual PD-L1/Vista inhibitor and is under Phase I clinical trial in patients with advanced tumors and lymphomas. CA-4948 is being developed as inhibitor of IRAK4 kinase and is currently under Phase 1 clinical trial in patients with non-Hodgkin's lymphoma. Two more leads discovered by Aurigene, Debio-1142 (Jak2 tyrosine kinase inhibitor; Src tyrosine kinase inhibitor) and AUNP-012 (immune checkpoint modulator) have reached preclinical stage.

Another lead compound CK-103 (TG-1601) discovered by Jubilant Biosys as BET (bromodomain and extra-terminal) inhibitor has been licensed to Checkpoint Therapeutics; Phase I Clinical Trial to be initiated. RG70099 (CRD1152) discovered by Curadev as Dual IDO1/TDO inhibitor has been licensed to Roche (2015). As per the latest reports available, preclinical studies are ongoing.

Few more leads discovered by Indian pharma companies and government organizations are currently under preclinical developmental studies. Few of them are potential reach to clinical trial stage shortly.

10.7 Novel target for Cancer therapy

Targeted therapy revolutionized the cancer treatment by minimizing the side effects in patients over conventional chemotherapeutics. However, there are still unmet medical needs in cancer, especially for patients with advanced metastatic disease where drug resistance plays a pivotal role for disease recurrence. Currently, monoclonal antibodies (MAbs) against different modern day drug targets are of better choice than their small molecule inhibitors as off-target effects or toxicity of small molecule inhibitors are way too high than MAbs. Immune Checkpoint Inhibitors (ICI) like PD1, PDL1, and CTLA4 are in the hit list of current novel targets and are the major stakeholder of coming 5 years of cancer therapy.



Here are some basics of immune checkpoint blockade therapy. The fundamental function of immune system is to discriminate between self and foreign molecule.

This led immune system to attack the harmful foreign substances and rescue its own healthy cells. To perform this, immune system uses the checkpoint mechanism (molecules on certain immune cells like T cells that need to be activated or inactivated to start an immune response). Under normal conditions, the checkpoint proteins like PD-1 (Programmed Death-1 and its ligand PDL-1) and CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) are expressed in T-cell surface. They perform a critical role in downregulating the immune response against the self cells and promoting the self-tolerance by suppressing T-cell inflammatory activity. However, the evolution in cancer leads to the overexpression of these checkpoints proteins in the surface of cancer cells which help them to rescue from the attack of immune system. Recently in the field of immunotherapy, the Nobel prize in medicine was awarded to James P. Allison and Tasuku Honjo for their immense contribution in immune checkpoint blockade therapy against PDL-1 and CTLA-4 immune proteins, respectively. There are several checkpoints inhibitors which are approved by FDA and some drugs are in clinical trials in all forms of cancer per se. The diagram below indicates the predominance of anti-PD1/PDL1 in overall cancer therapy trends for last 2 years.

From January to June 2019, FDA released 23 approvals for different oncology indications and closer look of the list clearly emphasizes two facts; one is how important is proper drug combinations and another is the recent surge in ICI based immunotherapy combinations with targeted small molecule drugs.

Considering the disease heterogeneity even in a single type of cancer, modern day cancer therapy is like a personalized medicine. Examples are many, such as melanoma with and without B-Raf mutations are having different treatment regimen, lung cancer treatment depends on EGFR mutation status. In this context, discovery of new drugs targeting novel proteins are of paramount importance. Here are some examples of clinically validated novel cancer drug targets:

PI3K-mTOR pathway inhibitor: Phosphatidylinositol-3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) signaling cascade is one of the most major intracellular pathways that are being known as a master regulator for different types of cancer. Herculean efforts have been made to the development of drugs targeting PI3K-mTOR signaling pathways, some of them are currently being pursued in active clinical trials, and it is becoming increasingly evident that PI3K-mTOR inhibitors are shown to be promising agents as anticancer therapeutics. PI3K inhibitors are categorized into dual PI3K-mTOR inhibitors, pan-PI3K inhibitors and isoform-specific inhibitors, on the other hand, mTOR inhibitor like rapamycin are either being used as combination therapy or in the active clinical trial against solid tumors in combination with some chemotherapeutic drugs.

Smac Mimetics as Cancer Therapeutics: One of the hallmarks of cancer is to bypass the programmed cell death. The well-known IAP (inhibitor of apoptosis) proteins are overexpressed in numerous cancer types, thus making them promising target for cancer therapeutics. There are several Smac mimetics small molecule inhibitors that mimic Smac, an endogenous antagonist of IAP

proteins. In recent years, the Smac mimetics inhibitors show favorable response in preclinical trials. The potential of these mimetics are to directly trigger cancer cell death by alone and more importantly, synergistic response with the conventional therapeutics, radiotherapy, and immunotherapy. Presently, numerous Smac mimetics are under evaluation in early clinical trials as monotherapy and in combination for several cancers (i.e., GDC-0917/CUDC-427, LCL161, AT-406/Debio1143, HGS1029, and TL32711/birinapant) (Fulda 2015).

Hedgehog pathway Inhibitor: The hedgehog (Hh) pathway plays a critical role in cancer development and around 25% of all cancers have aberrant Hh pathway activation. Vismodegib (Erivedge) is the first hedgehog pathway inhibitor approved by FDA in 2012. It is used in some situations to treat people with metastatic basal cell skin carcinoma.

Proteasome Inhibitor: Proteasome helps to break down proteins into smaller parts that the cell doesn't need. Drug that blocks proteasomes from working are called proteasome inhibitors. They result in a load of unwanted proteins in the cell, which forces cancer cells to die. Bortezomib (Velcade) is the first FDA approved proteasome inhibitor drug used to treat myeloma and melanoma. Currently, multiple clinical trials are ongoing using proteasome inhibitor as a combination with other drugs or MAbs.

Epigenetic regulation in Cancer manifestation:

Chromosomal abnormalities like aneuploidy and translocations are regarded as hallmarks of malignancy. The abnormal expression of the non-histone proteins, which are also involved in the maintenance of the chromatin structure, might result in these chromosomal abnormalities as well as alteration in gene regulation during oncogenesis. Recent advances in the field of epigenetics suggest that oncogenic development could be closely associated with the altered epigenetic state of the genome. Such epigenetic changes involve aberrant DNA methylation, the alteration of chromatin components in DNA packaging (Ellis et al. 2009; Sharma et al. 2009), altered posttranslational modifications of histones, and also anomalous expression of noncoding RNAs like miRNAs. Chromatin alterations and DNA methylation cumulatively alter the epigenetic regulation of gene transcription in all the stages of tumor progression. Histone acetyltransferases and deacetylases are known to aberrantly express in cancers, resulting in anomalous acetylation of histones as well as non-histone proteins. Thus both expression as well as the posttranslational modifications of non-histone proteins might play determining roles in the onset of cancer and its progression. Microarray analysis from various tumor tissues has revealed the importance of miRNAs in the prediction, diagnosis, and prognosis of tumor formation. **Oncogenic miRNAs (oncomiRs)** are usually overexpressed in cancers while tumor suppressive miRNAs are downregulated quite similar to their mRNA counterparts. When these oncomiRs or tumor suppressor miRNAs are repressed or stimulated, respectively, the oncogenic properties of a tumor cell is significantly reduced. Certain cancers become addicted to these oncomiR to such an extent that suppression of the oncomiR results in complete reduction of the tumor (Reddy 2015; Block et al. 2017).

Apart from the DNA methylation status, the most studied histone modification studied in the context of Cancer is histone methylation. From studies of various cancer genomes and epigenomes through the high throughput sequencing and mass spectrometric analysis, we find recurrent translocation and mutations in a variety of lysine methyltransferases. Various studies have established the dichotomous role of EZH2 in human cancer cells. EZH2 was found to be overexpressed in prostrate and breast cancer which resulted in poor prognosis (Margueron and Reinberg 2011). On the contrary, recent studies have revealed coding mutations in the EZH2 gene in various lymphoid and myeloid neoplasms establishing it as a tumor suppressive gene. However, EZH2 inhibition for cancer treatment holds a great promise and also disrupts the quiescence phase of cancer stem cells. There are several EZH2 inhibitors like EPZ6438, CPI-1205, GSK126, CPI-0610, etc. that have been under consideration, gaining potential success in hematologic malignancies along with solid tumors.

Perspective in the Indian Context: In India, the number of cancer patients is dramatically increasing. The reason could be due to the gradual increase in life expectancy and also rapidly changing life style of Indian population. Although over the period large number of cancer clinics (most of these are private hospital/clinics) have emerged in different parts of the country, the fundamental drugs have hardly changed for the middle class and lower middle class Indian (in terms of annual income). Most of the drugs used are broad based cytotoxic agents, such as doxorubicin, cisplatin, and 5FU. The cancer specific or target specific drugs are not reachable for the common Indian, due to the cost of these drugs. So need of the hour would be to produce less toxic targeted drugs in cheaper rate. Although the world is moving towards the combination of targeted chemotherapy and immunotherapy, for most of the Indian, it is impossible to pay for these treatments. India need to invest more effort to generate immunotherapeutics and antineoplastic biologicals indigenously. The traditional Indian medicine, in combination with cheaper chemotherapeutics, is experimentally shown to be more effective and less toxic. We need to explore this possibility with mega consortium.

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References

Block TM, Rawat S, Brosgart CL, Francisco S (2017) HHS Public Access 76:69–81

Cancer.Net (2020a) Understanding immunotherapy. https://www.cancer.net/navigating-cancer-care/how-cancer-treated/immunotherapy-and-vaccines/understanding-immunotherapy

Cancer.Net (2020b) Understanding targeted therapy. https://www.cancer.net/navigating-cancer-care/how-cancer-treated/personalized-and-targeted-therapies/understanding-targeted-therapy

David AR, Zimmerman MR (2010) Cancer: an old disease, a new disease or something in between? Nat Rev Cancer 10(10):728–733. https://doi.org/10.1038/nrc2914

Ellis L, Atadja PW, Johnstone RW (2009) Epigenetics in cancer: targeting chromatin modifications. Mol Cancer Ther 8:1409–1420

Fulda S (2015) Promises and challenges of smac mimetics as cancer therapeutics. Clin Cancer Res 21(22): 5030–5036

Helen A, Stafford (2000) Crown Gall disease and Agrobacterium Tumefaciens: a study of the history, present knowledge, missing information, and impact on molecular genetics. Bot Rev 66 (1):99–118

India State-Level Disease Burden Initiative Cancer Collaborators (2018) The burden of cancers and their variations across the states of India: the global burden of disease study 1990–2016. Lancet Oncol 19:1289–1306. https://doi.org/10.1016/S1470-2045(18)30447-9

Margueron R, Reinberg D (2011) The Polycomb complex PRC2 and its mark in life. Nature 469 (7330):343–349. https://doi.org/10.1038/nature09784

National Cancer Institute (n.d.) SEER training modules, Cancer registration & surveillance modules: cancer classification. https://training.seer.cancer.gov/disease/categories/classification.html

NCDIR (2012–2014) Three-year report of population based cancer registries, Bangalore: National Cancer Registry Programme, National Centre for Disease Informatics & Research, Indian Council of Medical Research. http://ncdirindia.org/All_Reports/PBCR_REPORT_2012_2014/ALL_CONTENT/PDF_Printed_Version/Chapter2_Printed.pdf

Oncology Nurse Advisor (2014) Radiation therapy for cancer (fact sheet). https://www.oncologynurseadvisor.com/home/for-patients/fact-sheets/radiation-therapy-for-cancer-fact-sheet/

Reddy KB (2015) MicroRNA (miRNA) in cancer. Cancer Cell Int 15:4–9

Rothschild BM, Tanke DH, Helbling M et al (2003) Epidemiologic study of tumors in dinosaurs. Naturwissenschaften 90:495. https://doi.org/10.1007/s00114-003-0473-9

Sharma S, Kelly TK, Jones PA (2009) Epigenetics in cancer. Carcinogenesis 31:27–36

Sikder S, Kumari S, Mustafi P, Ramdas N, Padhi S, Saha A, Bhaduri U, Banerjee B, Manjithaya R, Kundu TK (2019) Non-histone human chromatin protein PC4 is critical for genomic integrity and negatively regulates autophagy. FEBS J 286:4422. https://doi.org/10.1111/febs.14952

Smith RD, Mallath MK (2019) History of the growing burden of cancer in India: from antiquity to the 21st century. J Glob Oncol 5:1–15. https://doi.org/10.1200/JGO.19.00048

Sullivan R, Badwe RA, Rath GK, Pramesh CS, Shanta V, Digumarti R, D'Cruz A, Sharma SC, Viswanath L, Shet A, Vijayakumar M, Lewison G, Chandy M, Kulkarni P, Bardia MR, Kumar S, Sarin R, Sebastian P, Dhillon PK, Rajaraman P, Trimble EL, Aggarwal A, Vijaykumar DK, Purushotham AD (2014) Cancer research in India: national priorities, global results. Lancet Oncol 15(6):e213–e222

The American Cancer Society Medical and Editorial Content Team (2014) Early history of cancer; Defining cancer. https://www.cancer.org/cancer/cancer-basics/history-of-cancer/what-is-cancer.html

The Balance (2018) Top 20 blockbuster cancer drugs. https://www.thebalance.com/top-cancer-drugs-2663234

University of Rochester Medical Centre (n.d.) Health encyclopedia; Hormone therapy for cancer treatment. https://www.urmc.rochester.edu/encyclopedia/content.aspx?contenttypeid=85&contentid=p07236

Urandur S, Banala VT, Shukla RP, Mittapelly N, Pandey G, Kalleti N, Mitra K, Rath SK, Trivedi R, Ramarao P, Mishra PR (2018) Anisamide anchored lyotropic nano liquid crystalline particles with AIE effect - a smart optical beacon for tumor imaging and therapy. ACS Appl Mater Interfaces 10:12960. https://doi.org/10.1021/acsami.7b19109

WHO (2018) Cancer, Key facts. https://www.who.int/news-room/fact-sheets/detail/cancer

Cancerindia. Org (2020) Cancer statistics. http://cancerindia.org.in/cancer-statistics

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