

Dissecting **CANCER**

How a clutch of scientists at different labs in the country are researching in different areas, from detection to methods of invasion of the deadly cells

**The Big C
will get Bigger**

Over **17 lakh**
new cases of cancer
expected by 2020 in India

Over **8.8 lakh**
people are expected to
succumb to cancer by 2020

Only **12.5%**
of patients come for
treatment in early stages
of the disease

Among females, breast cancer topped the list and among males mouth cancer

The northeast reported the highest number of cancer cases in both males and females



D Sundar,

DuPont young professor, dept of biochemical engineering & biotechnology, IIT-Delhi

Focus: **Mechanism by which ashwagandha can kill aggressive cancer cells**

Progress: **Research suggests that bioactives from ashwagandha powder can be candidates for new cancer drugs**

“Experiments have revealed that both alcoholic and water extracts from the ashwagandha possess considerable anticancer activity”

:: Vanita Srivastava

The molecular modelling lab of D Sundar in IIT-Delhi does not have fancy gadgets and apparatuses. His students work mostly on computer simulations, mapping the mechanism by which ashwagandha, an ayurvedic herb native to India, can be a potential candidate for treating cancer. The findings of his lab are “transported” to their collaborators in Japan where test tube experiments are done for further validation.

Sundar and his team have been, for the past decade, trying to decode the mechanism by which ashwagandha can kill aggressive cancer cells. Their findings were recently published in the journal *Cell Death and Disease* of the Nature Publishing Group. The study recommended that bioactives from ashwagandha can be candidates for further research and development of new drugs for cancer treatment.

“Experiments have revealed that both alcoholic and water extracts from the ashwagandha leaves possess considerable anti-cancer activity. We adopted bioinformatics approaches at IIT-Delhi to resolve the protein targets and their mechanism of action and are convinced that such an approach on other herbs has tremendous potential for drug discovery for cancer prevention and treatment,” said Sundar, a DuPont young professor in the department of biochemical engineering and biotechnology (DoBEB) at IIT-Delhi.

Welcome to the multi-disciplinary research platform where scientists from different labs in the country are unfolding the enigma behind cell proliferation and demystifying the science behind cancer formation. The experimental canvas of these scientists is vast – from fleshing out new

therapeutic targets to identifying potential candidates for cancer drugs to improved methods for early detection. All these experiments have a common goal: to find ways to defeat the deadly army of cells.

Immune Landscape

SV Chiplunkar, director of the Advanced Centre for Treatment, Research and Education in Cancer (ACTREC), the R&D epicenter of Tata Memorial Centre, maintains that cancer research is vital to understanding the basic biology of the disease. “We need to create a team of clinician scientists who are expected to play a vital role in translating research findings to clinical settings.” According to Chiplunkar, ACTREC, located in Kharghar on Mumbai’s outskirts, has achieved a seamless integration of basic and clinical research and has evolved as

a comprehensive cancer centre. On its 60-acre campus are the Cancer Research Institute (CRI), Clinical Research Centre (CRC) and Centre for Cancer Epidemiology (CCE) that provide a multidisciplinary approach to cancer research and patient care.

Chiplunkar’s lab mainly focuses on understanding immune dysfunctions in cancer patients and is working on developing immunotherapeutic treatment modalities. “We are investigating the ‘immune landscapes’ of oral cancer, breast cancer, cervical cancer, to understand which immune cell types infiltrate these tumours and how we can activate these cells to kill the cancer cells. We are also working on gall bladder and pancreatic cancers which have emerged as cancers associated with infection and inflammation,” she says.

Her team is researching on identifying



Sathes Raghavan

associate professor, IISc, Bengaluru

Focus: **Oncogenesis, or the process that causes a tumour to form**

Progress: **Designed anti-cancer therapies, including a drug that can stall DNA repair in cancer cells and improve the efficiency of radio and chemotherapy**

“Drugs and radiation kill cancerous cells, they also decimate normal tissues. This is why information on cancer cells and their differences from normal cells is crucial”

SV Chiplunkar, director,

Advanced Centre for Treatment, Research and Education in Cancer, Tata Memorial Centre, Mumbai

Focus: **Understanding immune dysfunctions in cancer patients**

Progress: **Have identified an immune cell type that contributes to tumour progression in patients with gall bladder cancer**

“There is an urgent need to create a pool of trained manpower both in basic and clinical cancer research”

Partha P Majumder

founder, National Institute of Biomedical Genomics, Kalyani, West Bengal

Focus: **Evidence of alternations in the DNA that cause diseases, including cancer**

Progress: **Identified that DNA alterations in about 10 genes result in oral cancer**

“We found that oral cancer is caused mainly by tumour suppressors. This is bad news. Drugs to act against oral cancer may be difficult to find”

SMahalingam

head, National Cancer Tissue Biobank, IIT-Madras

Focus: **Collection and preservation of human tissue**

Progress: **Collected samples from more than 1,200 patients, with 250-300 new additions annually**

“Biobanking of samples from Indian patients is mandatory for advancement of cancer therapeutics for our community”

“immune signatures” or biomarkers that will help in predicting the response to therapy. “We want to develop immune cell-based therapies for cancer patients. But we still do not have adequate infrastructure and regulatory policies developed to promote cancer research. We need to develop a strong network between research organisations engaged in cancer research and this has been initiated by the Tata Memorial Centre through National Cancer Grid (NCG),” adds Chiplunkar.

DNA and Cancer

The research terrain of Partha P Majumder, founder of National Institute of Biomedical Genomics (NIBMG) at Kalyani in West Bengal, is looking for evidence of alterations in the DNA (genomic alterations) that cause various human diseases, including cancer.

In 2008, the International Cancer Genome Consortium was formed to identify the DNA alterations that drive cells to become malignant as a result of exposure to various cancer-causing agents. India became a founding member of this voluntary consortium. The NIBMG and ACTREC carry out the Indian study on oral cancer as a part of this consortium, with Majumder leading the biological aspects of this study.

“Even though heritable basis can be found in only about 10% of cancer patients, at the cellular level, cancer is completely a disease of the genome. If you take a cell from a malignant tumour – a cancer tissue – the cell will invariably have DNA alterations that are not present in normal cells,” he says.

Inherited variations are present in every cell of an individual – cells of the cancer tissue and also normal cells. Such inherited variations are observed only in about 10% of cancer patients. In the remaining patients, the DNA alterations found in their cancer cells are acquired during the course of their life. These DNA alterations mostly happen because of exposure to environmental agents, such as toxic chemicals and use of tobacco.

There are two classes of genes that cause cancer. One is called the tumour suppressor gene. These express proteins that prevent tumours. Alterations in these genes abolish the production of these proteins and tumours form. The other class of genes are called oncogenes. These are usually dormant and do not express themselves, but when their DNA sequence is altered they express “rogue” proteins that cause cancer. It is easier to find drugs to act against “rogue” proteins produced by oncogenes, but it is difficult to “wake up” tumour suppressors that have “gone to sleep” because of DNA alterations.

“Unfortunately, we found that oral cancer is caused mainly by tumour suppressors. This is bad news as drugs to act against oral cancer may be difficult to find,” reckons Majumder.

Subrata Sinha, director, National Brain Research Centre (NBRC) in Manesar, Haryana, is researching around gliomas, tumours of the supporting cells of the brain. Gliomas can range from very highly malignant (median survival time less than 2 years) to those with less malignancy.

“Our aim is to identify specific molecular pathways in gliomas, which predispose towards therapeutic resistance and also find ways to tackle the same. We are studying surgically resected tissue or cell lines with the aim of identifying how some of these tumours that apparently look similar are different in molecular terms and would thus require different approaches for optimal treatment,” explains Sinha.

The NBRC team, which works in close collaboration with faculty from AIIMS, has come up with some interesting findings. Even within the seemingly most malignant gliomas, there is a difference in the oxygen available to the tumours. When oxygen levels fall, the cell tries to protect itself. This makes it become resistant to the drugs used to treat these tumours. Hence the survival rate of patients with tumour hypoxia is lower than those with tumours having more oxygenation. A gene signature of tumour hypoxia may be used to predict how patients will respond to treatment, and eventually suggest alternative drugs that affect hypoxia-induced chemotherapy resistance.

“We have identified a new cellular signalling pathway that drives the response to low oxygen and thus is able to push the tumour to a more resistant type. The role of this gene in hypoxia and inflammation, leading to cell invasion and migration into surrounding tissues, has been shown,” says Sinha.

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low oxygen and thus is able to push the tumour to a more resistant type. The role of this gene in hypoxia and inflammation, leading to cell invasion and migration into surrounding tissues, has been shown,” says Sinha.

New Anti-cancer Therapies

Sathes Raghavan is an associate professor researching on cancer at the Indian Institute of Science (IISc), Bengaluru. His laboratory is carrying out research in understanding oncogenesis (process causing the formation of tumour) and cancer treatment. His group has designed new anti-cancer therapies, including a drug that could stall DNA repair in cancer cells and improve the efficiency of radio and chemotherapy.

In 2013, his group discovered SCR7 (a chemical), the first biochemical inhibitor of NHEJ pathway, one of the key DNA repair processes in cells. Continued research on this drug in collaboration with Jinu George and Franklin John (Sacred Heart College, Kochi) has created a better form of SCR7, now called ESCR7. Tests on cancer cells in culture show that ESCR7 is five times as efficient in destroying cancer cells than its predecessor.

Recently a group of researchers, including those from Raghavan’s team, designed and synthesised a new potential drug. Called Disarib, it can kill cancer cells overproducing a protein called BCL2. This molecule, the researchers claim, works better than the current best BCL2 inhibitor in the market. Their finding was published in the journal *Biochemical Pharmacology*.

Though the initial findings of the studies seem promising, there is still a long way to go before we see Disarib on the shelves of a pharmacy, says Raghavan. A number of pre-clinical trials have to be done

before the drug even gets approved for clinical trials.

Biobank for Cancer

Established in 2015, the National Cancer Tissue Biobank (NCTB) at IIT-Madras is a unique, community-based venture in India. Jointly funded by the Department of Science and Technology, Government of India and IIT-Madras, this is a step towards reflecting on cancer incidence, diagnostics and treatment outcomes. “The collection and preservation of human tissue is vital for medical research. This type of biobanking of samples from Indian patients is mandatory for advancement of cancer therapeutics for our community,” says S Mahalingam, a professor in the department of biotechnology at IIT-Madras and in-charge of the biobank.

The NCTB collects tissue samples from patients suffering from different types of cancer. “At present, we have samples from more than 1,200 patients, with 250-350 new additions annually. Collected tissues are processed in 7 to 10 minutes to preserve the molecular and biological tumour profile as it is present in the human body,” explains Mahalingam.

Another cancer research team of IIT-Madras was in news recently for making a breakthrough in understanding how aspirin kills the cancer cell. Amal Kanti Bera, professor of biotechnology, and his team discovered that aspirin carries out a surgical strike on the mitochondria of cancer cells, destroying the unholy nexus between a mitochondrial protein called VDAC and an enzyme hexokinase. Dissociation of hexokinase from mitochondria limits the energy supply which is required for the survival of cancer cells. Aspirin also directly alters the structure of VDAC and increases the entry of calcium ions to mitochondria which triggers the release of toxic substances from it. Aspirin’s two-pronged attack on mitochondria forces the cancer cells to commit suicide.

As the excitement of their research being published in a prestigious journal wanes, Sundar and his team at IIT-Delhi brace themselves for yet another study on ashwagandha and its anti-cancer role. Endless studies and research finding knock on the lab doors of the scientists. What is important is that someday all these are translated into a remedial landscape for winning the battle against cancer. ■

Challenges

Regional cancer centres lack state-of-art facilities and trained manpower

Attracting talent for cancer study

Fund shortage

Early detection very difficult in rural areas

Maintaining data on follow up of cancer patients

Road Ahead

Multi-disciplinary collaboration between researchers and clinicians

Making the database of cancer patients more robust

Enhancing funds for cancer research

Improving the infrastructure and lab facilities

