Cutting The Brakes To Unleash The Immune System Against Cancer : A Recent, But Radical Remedy :

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Abstracts: Humans have known cancer since eons. However, treatment for cancer became available only in the beginning of the twentieth century. Initially, it consisted of surgery and radiotherapy, followed by chemo-therapeutic agents. Modern forms of chemotherapy became available after the mechanism of occurrence of cancer began to be known after the late 1970s. Herceptin (trastuzumab) targeted the Human Epidermal Growth Factor (Her) receptor, and thus ushered in a new era in the treatment of Her-2 positive, breast cancer, which is highly malignant. This was followed a decade later by Gleevec(Imanitinib) for the treatment of Chronic Myeloid Leukemia (CML).Gleevec inhibited the tyrosine kinase pathway. The recipients of the 2018 Nobel Prize in Physiology or Medicine discovered a novel form of pharmacotherapy, targeting cell mediated immune mechanisms, for the treatment of cancer. James Allison and TasukoHonjo, identified inhibitors of cell-mediated immune responses, namely CTLA4 and PD-1 respectively. Monoclonal antibodies targeting these, iminuzulab, pembrolizumab and nivolumab, called as immune checkpoint inhibitors, developed by them, helped treat metastatic cancers. These included malignant melanomas, prostate and breast cancers. These immune checkpoint inhibitors are thus, a radical remedy against mankind's modern scourge- cancer ![Parlikar S Natl J Integr Res Med, 2018; 9(6): 75-77]

Key Words: Cancer; Cell Mediated Immunity ;Monoclonal antibodies ; Immune Checkpoint Inhibitors

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Introduction:Siddhartha Mukherjee, the Pulitzer prize winning author and oncologist, graciously anointed cancer as the 'emperor ' of all maladies.Cancer's rise as man's Achilles heel has been phenomenal in the last two centuries. But cancer was known to the ancient Egyptians, Persians and Greeks. The Edwin Smith Surgical Papyrus, the first mention of the human brain, contains a description of a woman with breast cancer. Atossa, the queen of Persia, directed her slave Democles to sever her breasts to rid herself of breast cancer. The Greek physician Galen, postulated that black bile represented cancer. In the 19th century, tuberculosis, pneumonia, diarrhea and plague were the scourge of mankind. Cancer had not yet attained its now Draculean status. It was from the 1940s that it has been on the charge devouring men and women by the scores[1].

The quest for a cure for cancer was launched in right earnest by Sydney Farber, a pediatric pathologist at Boston's Children Hospital after the second World War.Before him radiotherapy and surgery were the cornerstones of the treatment of cancer[1].

Immunology was a nascent science in the beginning of the 20th century. The 1908 Nobel Prize to Mechnikov(for phagocytosis) and Ehlrich brought it into prominence. Paul Ehlrichthen outlined the role an immune response could play against cancer. Basic science research would then go on tounravel the mechanism of activation of T-lymphocytes in the late 70s. Subsequently, discovery of Toll-like receptors solved the puzzled of innate immunity(ChristianNuslein Volgaard, a Nobel laureate, had exclaimed with astonishment :*Das var Toll*- meaning that looks great- on seeing a giant fruitflyDrosophilia; hence the name 'Toll').

A glimpse into the role of T-cells in immunity: The human body has an innate ability to fight pathogens (bacteria, viruses, fungi etc.). This ability is called as **innate immunity.** During evolution, **adaptive immune responses** were added to this armament. Adaptive immune responses are divided into **cell-mediated immunity and humoralimmunity. T-lymphocytes**(which constitute 75% of the lymphocytes in humans) are the torchbearers of cell mediated immunity. They come in three types : helper T-cells, cytotoxic T-cells and suppressor T-cells.

These T-cells are the sentinels of the body. They patrol the length and breadth of the body on the lookout for an invader. Receptors located on the surface of these T-cells, called as **T-cell receptors**, bind to the antigen. There are about 10^{18} T-cell receptors, each specific for apotential antigen (Fig.1)

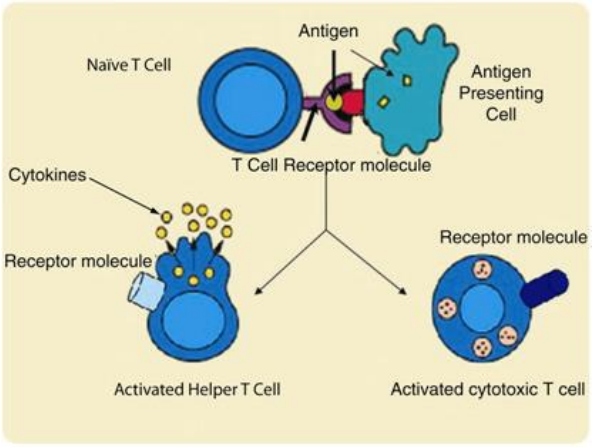
However, these T-cells (c.f.B-cells) lack functional autonomy. They are dependent on so called

antigen-presenting cells to recognize an antigen and engineer an immune response.

These antigen presenting cells bind to molecules called as **major histocompatibility complex(MHC)** in their endeavor to harness the cell mediated immune response. Cytotoxic T-cells bind **MHC II molecules** and express **CD_8receptors** (CD- cluster of differentiation), while helper T-cells bind **MHC I molecules** and express **CD_4 receptors.** The complex interaction between a T-cell and an antigen presenting cell (macrophage, dendritic cell and B cell) is called an **immunological synapse.**

Cytotoxic T-cells secrete **lymphokines,** which induce the apoptosis of virally infected cells. Helper T-cells garner the support of macrophages and B-cells in their quest to protect the body.**Regulatory T-cells** rein in the cytotoxic T-cells thereby checking autoimmunity against self[3].**[Fig.1]**

Fig 1: T-cell receptors, each specific for apotential antigen

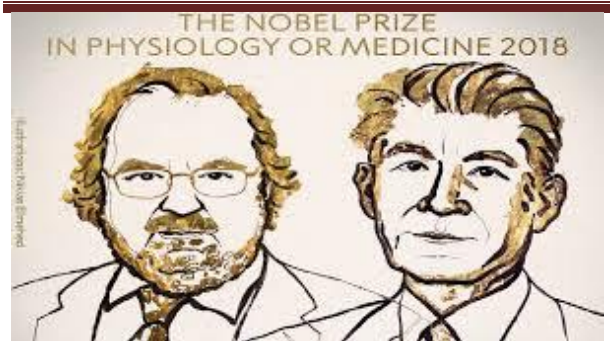


Research on the genesis of cancer, and the search for its Achilles heel : Fareed Zakaria, the host of the acclaimed CNN weekly, **Fareed Zakharia GPS(** Global Public Square), had once identified several 'moonshots' for the 21st century-discoveries vital for human longevity and progress. This word 'moonshot' was first used for research on cancer by Sydney Farber, and his socialite friend, Mary Lasker, to push for a cure for this monster after Neil Armstrong set foot on the moon in 1969. Their efforts culminated in The National Cancer Act signed by President Richard Nixon in 1971, committing millions of dollars into research and treatment of cancer.
James Watson, the discoverer of the DNA double helix, called this push 'premature', arguing, " Finding a cure for cancer at this stage, is like landing a man on the moon without knowing Newton's law of gravity[1] !.

Subsequent research: The grand old man, Peyton Rous (the oldest yet recipient of the Nobel Prize at the age of 87), had isolated the *Rous Sarcoma Virus,* which was implicated in cervical cancer. Bishop and Varmus discovered that a cancer cell arose from accumulated mutations within itself, thus finding oncogenes and proto-oncogenes. At John Hopkins, Bert Vogelstein unraveled these sequential changes in genes, and as a side-kick, discovered the p53 tumor suppressor gene (implicated in more than 50% of human cancers today). A scientist at MIT, Robert Weinberg, discovered a gene for cancer – **ras(a small G protein).**Just as turning on a switch turns on the fan, turning on ras unleashed sequential pathways downstream that resulted in unbridled growth of cells, the hallmark of cancer. Among the downstream pathways was kinase, an enzyme, which amplified the message from the messenger-ras. The success of Herceptin(Trastuzumab) in the treatment of metastatic breast cancer, and Gleevec (Imanitinib) in chronic myeloid leukaemia, were the fruits of these long endeavors. In science, progress is incremental. Then a moment arrives when an avalanche of discoveries pave the way for the dawn of a new era ! That era is now with us !We may have unearthed cancer's Achilles heel- the ras oncogene and the tyrosine kinase pathway. But as Bishop and Varmus proclaimed-cancer is a *distorted version* of our normal selves. It is a stealthy predator lurking in our bodies for decades. New weaponry is therefore needed when it strikes[1] !.

The contribution of the 2018 Nobel Laureates in Medicine [Fig.2] : Cell-mediated immune responses mediated by T-lymphocytes could be held in check to prevent an autoimmune response. A molecule called as **CTLA4,** discovered in the late 1980s,was found to possess this immunosuppressive effect. In 1994, James Allison, at the University of California, Berkeley, injected monoclonal antibodies against CTLA4 in transgenic mice which were inoculated with tumors. Lo behold ! The tumors vanished. Allison carried several studies in other forms of cancer such as prostrate, breast and melanomas. The

Fig 2 :Nobel Laureates in Medicine[2]



results were spectacular ! Allison's dogged perseverance culminated in the development of a drug,**ipilizumab** (initially codenamed MDX-010), by Bristol-Meyer's Squibb. Such monoclonal antibodies effective against tumor cells are called as **immune checkpoint inhibitors.**

TasukuHonjo's lab at Kyoto University in Japan identified a molecule similar to CTLA4. It was named as **PD-1** (*thought to protect against programmed cell death-apoptosis).* A ligand for PD-1 was subsequently discovered. It was called as **PD-L1.** Blockage of the PD-1/PD-L1 pathway by monoclonal antibodies was successful in treating unresectable metastatic cancers, such as malignant melanomas. Two such monoclonal antibodies directed against PD-1 ,**pembrolizumab** and **nivolumab**, were granted approval by the FDA in 2014 for the treatment of metastatic melanomas[2].

Leonardo de Vinci, the renaissance painter had famously asked, " Do you know that our soul is composed of harmony ?"The eminent English physiologist, Denis Noble, has called life 'a music' in his book ' The Music of Life : Biology Beyond Genes '.

"Every sickness
Is a musical problem,"
So said Novalis,
And every cure,
A musical solution."
-W H Auden[1]

The war against 'the emperor' of all maladies has reached a new frontier. Immune checkpoint inhibitors are the new cures against music gone awry !

References

1. Mukherjeee S. The Emperor of all Maladies : A Biography of Cancer.1st edition. Simon and Schuster ; 2011.
2. www.nobelprize.org/prizes/medicine/ 2018/ advanced information (Last accessed on 2nd October, 2018).
3. White GN. Immunology, Organ Interaction and Homeostasis.In : Rhoades R, Bell D (eds). Medical Physiology : Principles of Clinical Medicine.Philadelphia : Wolters Kluwer (Lippincott Williams and Wilkins) ; 3rd edition, 2009 : pg 192-3.

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