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"Biomedical Research A Pursuit Without Boundaries"
Nobel Prizes in Physiology and Medicine and Chemistry 2012

..... "I like to think of Medicine in our day as an ever broadening and deepening river, fed by limpid streams of pure sciences. At its borders the river has eddies and currents, expressive of certain doubts and errors that fringe all progress; but it makes continuous advances on the way to the ocean of its destiny".

- **C.A.Herter (1865-1910), U.S.Physician,**
  Scientist, Neurologist,
  Pathological Chemist
  Founder of Journal and Biological Chemistry 1905,
  In his address at the opening of the medical college at
  Colombia University, 1909.

BACKGROUND:

It has happened before several times. In over a century of Nobel prize awards, the distinction in physiology and Medicine mainly and in chemistry to some extent, have been conferred on scientists who are physicians and also on chemists, biologists / molecular biologists or cell biologists, geneticists etc., in their basic or primary interest and pursuit. In other words, **"Physiology and Medicine"** has the unique distinction of deserving of Nobel prizes by outstanding non-physicians more frequently, than any other discipline. Also noteworthy is the fact that prizes in chemistry have been conferred upon physicians, microbiologists and biological chemists. In fact, the prizes have revealed a phenomenon that medicine has no boundaries among chemical, biological, physical disciplines and has been enriched by discoveries on the chemical basis of life processes. In fact, the great biochemist of the last century Arthur Kornberg himself, a physician scientist and the discoverer of DNA synthesizing enzymes never missed an opportunity to confirm his conviction that chemistry is the language of life (read medical sciences). All this to say that science in general, and medicine and medical sciences in particular have no boundaries. For progress in medical education, research and applications in health care this is a vital ideology. Nobel prizes in 2012 for physiology and medicine and for chemistry provide yet another striking evidence, to such an inherent characteristic of medical/biomedical science and its progress.

NOBEL PRIZE IN PHYSIOLOGY AND MEDICINE 2012

The Nobel award in physiology and medicine for 2012 was conferred on Dr.John Gurdon and Dr.Shinya Yamanaka for the pathbreaking discoveries in cell biology made by them nearly fifty years apart from one another. The far reaching implications of their separate yet complementary work leading to regenerative medicine, opens up vistas in applications from designing "medical kits of cells" designed to replace damaged or diseased tissues to cloning humans, the latter raising serious ethical issues. Without the Gurdon-Yamanaka contributions some of these complex tasks would have remained in the science fiction domain.

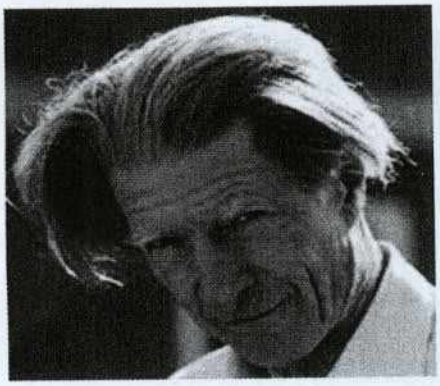

Fig. 1: Dr. John Gurdon

Fig. 2: Dr. Shinya Yamanaka

Dr.Gurdon's work opened the door for the creation of stem cells. In the late 50's and 60's, at the University of Oxford he conducted studies in which the nucleus of a specialized cell from a frog of the species Xenopus laevis-first, from a late embryonic cell and later adult intestinal or skin cells was transferred into an egg from which the nucleus had been removed. This gave rise to a normal frog that could produce offspring. An adult cell was pluripotent and, under certain conditions it could develop into all cell types, including eggs and sperm. This was proven for the first time, with the new insight that the nucleus of such a cell had the blue print for the most complex architechure in nature "the life form". This maneuver was designated Somatic Cell Nucleus Transfer (SCNT). Gurdon was a healthy maverick and conducted this daring experiment, despite skepticis all around.

Central to his discovery was the fact that the more than 200 different cell types, skin, bone, neurons, liver, immune cells etc, in fact, numbering over 50 trillion all carried a nucleus containing an identical genetic blue print. It is like all the workers in our University including faculty, students, and trustees and soon have embedded copies of job descriptions of everyone, under their skin without telling them which is theirs. Once they develop into a specialized entity (differentiation) they cannot turn back. Gurdon, ever a daring enquirer, with a healthy reverence for the empirical, designed these studies to create a pluripotent stem cell, and made history, which had to wait 50 more years; a Japanese baby boy born the same year when Gurdon published his work in 1962, 50 years later as a physician-scientist, discovered yet another facet of this biological phenomena to share the Nobel prize, in 2012 for physiology and medicine.

Gurdon's work infact rewrote cellular development and differentiation, and led to cloning more complex organisms than Dolly, the cloned sheep in 1997; mice, cows, pigs, wolves, wild cats are some of the assortment of life forms which came out of the SCNT hat by the magic (?) of one of the most startling discoveries, which took fifty years and another breakthrough in the same field, with a difference, to earn the ultimate recognition of the Nobel. For obvious ethical, religious and sociological sensitivities. Man is still not cloned, though therapeutic cloning using SCNT in the human is permissible.

Yamanaka's work almost forty years subsequent to Gurdon's breakthrough on Somatic Cell Nuclear Transfer, marked another step (leap?) forward in transforming adult mouse cells into pluripotent stem cells, without nuclear transfer. Four genes involved with the embryonic state in their

expressed form were inserted into the adult cell and an **"induced Pluripotent stem cell"** (iPSC) was born which could be directed to give rise to any tissue in the body. These four genes are Oct/soX2, Klf4, and C-Myc, which together programme the crucial events in cellular function. The selection and discovery that these four genes together could reprograme adult cells to pluripotent embryonic like state out of the 24 genes selected with key roles in mouse embryonic cells in a most ingenious experimental feat. These iPS cells could give rise to a large variety of tissue types when incorporated into mice. Use of a developmental gene Nanog expressed in such an experiment generated chimeric mice. These mice had tissues made up of a mixture of cells derived from their own embryonic stem cells and cells derived from iPS cells. These were also transmitted to the next generation.

Generation of human iPS cells from human fibroblasts was also accomplished by Yamanaka subsequently, using the same techniques used for mice cells. Thus a new field of biomedical research was born. Future holds great promise. Nerve cells lines from Parkinson's disease patients in order to study the processes that trigger degeneration, evaluation of toxicity of drugs without the need to do human or animal studies are a few of the promises of regenerative medicine. Cloning of the human is fraught with some very basic ethical and far-reaching complexities, though it is within reach. This ought not to distract mankind in the light of the enormous benefits these developments can bring in medicine in this century and also in our understanding of the marvels of nature's ways in life processes, as long as we strictly adhere to ethical guidelines.

NOBEL PRIZE IN CHEMISTRY 2012

The Nobel prize in chemistry 2012 was awarded to Dr. Brian K. Kobilka and Dr. Robert J. Lefkowitz for studies on Gprotein coupled receptors, which form a remarkable modular system that facilitates transmission of a large variety of signals over the cell membrane, between cells and over long distances in the body. The molecular mechanisms of how these receptors function in detail is understood today largely because of the studies and contributions of Kobilka and Lefkowitz.

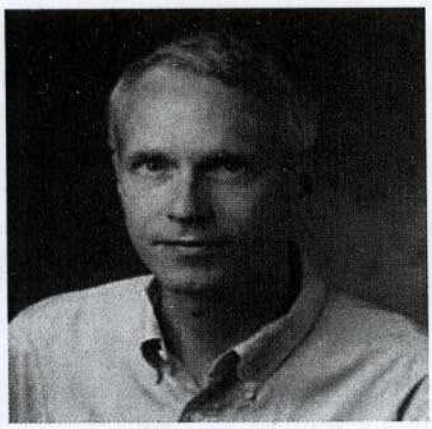

Fig. 2: Dr. Brian Kobilka

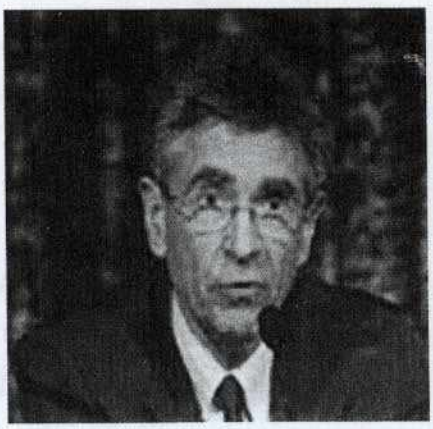

Fig. 3: Dr. Robert Lefkowitz

All cells in the human body are surrounded by a plasma membrane, a phospholipid bilayer, to help maintain a specific mix of biochemically active set of ingredients, preventing unwanted passage into the cell of substances from outside. For functional activity the biochemical machinery needs instructions from outside. Changes in hormone levels and sensing and response to odor molecules, to give examples, elicit electrical signals that transfer information to the brain. Constant communication among cells and the environment need a molecular frame work. Brain, in order for vision, smell, taste and etc. to be received respond, needs a mechanism of molecular signaling and a response machinery. Gprotein-Coupled Receptors (GPCR) are the molecular framework for such a signaling network. They are also called 7TM receptors as their polypeptide chain passes through the plasma membrane seven times. In fact these molecular sensors and their functionality are such a vital part of life in its their sensory, and functionally vital communication network and its operation, Man's ability to match it by inventing systems network communication, may gain some advantage by understanding these phenomena, though it is a long way to simulate it. Structural biological work on Gprotein receptors for engaging the fine delineation of the mechanisms of signaling and communication that takes place in life processes are now understood thanks to the decades long contributions of these physician-scientists poignantly, chosen for Nobels for **'Chemistry'** in 2012.

SIGNIFICANCE

It is noteworthy that the Nobel prize for physiology and medicine 2012 is shared by a cell biologist and a physician scientist Gurdon, the cell biologist five decades ago, even as a student, prepared the ground work for the breakthrough which occurred 40-50 years later in the stem cell area. Yamanaka, an M.D. from the University of Kobe in Japan, took a shot at being an orthopedic surgeon, switched to get a Ph.D from University of Osaka and dived deep in to cell and molecular biology and did pioneering work in what will turn out to be hopefully a revolution in medicine. It is amusing, according to his own admission, he would not have found orthopedic surgery a well suited pursuit!

The Nobel prize for chemistry 2012 was shared by two scientists who are both physicians qualified with M.D. in internal medicine from the most prestigious of medical schools; Kobilka, an M.D from Yale University works at Stanford University school of medicine and Lefkowitzan M.D in internal medicine at Duke university school of medicine. New Biology which is an integration of structural, molecular and cell biology is the broad field in which the chemical understanding of life processes such as GPCR functions were pursued by both Kobilka and Lefkowitz.

There is a lesson for us in India from these exciting events and rewards. Medicine as a pursuit in its service to fellowmen has no equal in value. Medicine as a pursuit of pure knowledge of life processes has no match in challenges to man's imagination or ingenuity, nor does it have boundaries; chemistry, physics and mathematics all pure sciences find their phenomenal challenges in solving problems in biological systems, more so in relevance to human biology i.e. medicine. The sooner we adopt such an approach to medical education and research, we will find the newer generation of our

medical scientists engaging in intellectual voyages on the ocean of biological phenomena to discovery. Medically relevant and significantly original research from our medical institutions on par with the best will be a outcome of this new paradigm. Can we afford to fail the newer generation of students who will be physicians of the future this great opportunity?

Suggested reading:

1. For 2012 Nobel Prizes, browse
   www.nobelprize.org/Medicine/2012
   www.nobelprize.org/chemistry/2012
   (also find Nobel lectures 2012, for)
   Physiology and Medicine; Chemistry
   All four recipients, under their names

2. Genetic chemistry and future of Medicine
   Arthur Kornberg, San Diego Univ.Press 1, August 1988 51 pages

3. Blueprint for Discovery
   The Quest for 21st Century Cures, Univ. of Rochester School of Medicine, 1999

4. Basic Research, the Life Line of Medicine
   Arthur Kornberg, 1997
   www.Nobelprize.org/medicine/1959/kornberg

5. Of Serendipity and Science
   www.rockfeller.edu/Pubinfo/paskeur/kornberg/essay.html

6. Future is invented, not predicted
   (www.caut.ca), Arthur Kornberg

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