Houston Philosophical Society
Minutes of 623rd Meeting, March 20th, 2008

CALL TO ORDER: 8:12 P.M.

President Newell Boyd called to order the 622nd meeting of the Society in its 87th year. After the introduction of guests, Dr. Boyd introduced the speaker, Dr. John Mendelsohn, President of M.D. Anderson Cancer Center and professor of cancer medicine and faculty member, University of Texas Graduate School of Biomedical Sciences. Dr. Mendelsohn is a magna cum laude graduate of Harvard College and a cum laude graduate of Harvard Medical School. He is at the forefront in understanding how growth factors regulate the proliferation of cancer cells by activating receptors on the surface of the cells and is a pioneer in anti-receptor therapy and anti-tyrosine kinase therapy as new forms of cancer treatment. Dr. Mendelsohn spoke on "Targeting Abhorrent Behavior of Cells and People."

Dr. Mendelsohn traced the New Age of Molecular and Genetic Medicine from its beginnings in the Atomic Age and the Age of Genetics. The Atomic Age began with the discovery of electrons by Thompson in 1897, the nucleus in 1911 by Rutherford, the atom in 1913 by Bohr, the proton by Rutherford in 1918, and the neutron by Chadwick in 1932, and continued through to the splitting of the atom in 1939 and the development of the atomic bomb in 1945. This age was paralleled by the Age of Genetics (1), the period of discovery, of the population sciences and biology, beginning with the discovery of the operations of heredity by Mendel between 1866 and 1900, of natural selection by Darwin in 1871, of inherited diseases by Garrod in 1908, and of genes by Morgan in 1926. It culminated in the discovery by Avery in 1944that genes are DNA and the discovery of the structure of DNA by Watson and Crick in 1953 and the publication of their article, A Structure for Deoxyribose Nucleic Acid," in NATURE April 23, 1995, which showed a diagram of the double helix along which genes are paired, T with A and C with G, and laconically concluded, "It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material."

The discovery of the structure of DNA in 1953 ushered in the Age of Genetics (2): the Age of Molecular Genetics. Milestones were marked by the breaking of the DNA Code, the synthesis of DNA, DNA segment construction and insertion, DNA sequencing, DNA mutations, and finally, the completion of the Human Genome

Project in 2003, which mapped the human genome, the set of 25,000 paired genes in each of the million million cells in our bodies, all coming from one sperm and one egg that formed a single cell, your primordial stem cell.

The Age of Genetics has been followed by the New Age of Molecular and Genetic Medicine. The DNA in genes codes for RNA, which codes for proteins, and different parts of our bodies express different sets of genes, such as IQ, eye color, or muscle mass. All of these cells, however, express a common set of genes which control cell proliferation and survival. The body regenerates everything but brain cells, and even the failure of the brain to regenerate is disputed. Proteins carry out a variety of cell activities: structure/ architecture; energy production; activity and movement; enzymes that synthesize and destroy; reception and production of internal signals and external communications; regulatory controls; programmed cell death; and defense.

The first premise in targeting cancer is that cancer is caused by mutations or malfunctions of key genes controlling cell proliferation, and genes that protect the integrity of DNA. Thus cancer can be targeted by curtailing the inappropriate expression of oncogenes, blocking the function of proteins coded for by oncogenes, replacing genes or their proteins coded for by defective suppressor genes, and protecting DNA integrity. Chronic myelocytic leukemia (CML) is an example of a new paradigm of cancer treatment based on this premise. Basic research between 1960 and 1985 showed that in CML a chromosome rearrangement creates an abnormal gene, bcr-abl, which produces a specific abnormal protein that promotes cell proliferation. Drug development between 1987 and 1997 involved screening for an inhibitor specific for this enzyme. Between 1998 and 2000, clinical trials demonstrated the efficacy of Gleevec in CML. In May 2001, based on a registration trial led by M.D. Anderson, the FDA approved Gleevec. The success of this approach is shown by the fact that in 1999 the average lifespan of a person with CML was three years. Now, in 2008, 95% of CML patients are alive five years later. Many common cancers, however, are caused by more than one gene, so that 4, 5, or 6 may need to be controlled.

The second targeting premise is that cancer is characterized by a failure of biochemical signaling pathways that regulate all cellular activities. Approaches based on this premise target cancer by inhibiting signals that activate cell proliferation, enhancing signals that stimulate specialized functioning of cells (differentiation), and blocking signals that promote cell survival and activating signals that promote cell death. Dr. Mendelsohn's drug, Erbitux, inhibits reception

so that signals for proliferation will not be activated. Subsequently, others have developed drugs that are chemicals that act inside the cell to prevent proliferation. Today, drugs are working on both the outside and the inside of cells to block signals.

The third targeting premise is that cancer is influenced by the biologic and molecular environment in the patient. This premise has led to the development of anti-angiogenesis drugs, which cut off the blood supply to the cancer; anti-metastasis drugs and agents; the manipulation of chemicals in the blood and in specific organs called cytokines, which can regulate cancer cells; and an immunological attack on cancer. An example is the treatment of pancreatic cancer xenografts with gemcitabine and C225, which blocks a receptor. Cancer stimulates new blood vessel cells and keeps them alive. This drug targets gene products and normal cells around the tumor. Also, the first human leukemia vaccine was developed at M.D. Anderson to immunize the body against its own cancer. In leukemia, proteins that normally stay inside the cell are expressed on the surface where they can be targeted to build an immune response by stimulating good cells to divide and stimulating T-cells to develop an immune response to leukemia. As a result of immunization, 23% of patients went into complete remission and nearly half were alive 3 years later. Before this, the life span was only months.

The fourth targeting premise is that new knowledge and technologies enable "personalized" early detection and treatment of cancer. Detection focuses on proteins in the blood (e.g., PSA), abnormal genes in cells (e.g., the BRCA 1 gene), imaging (e.g., PET scan), and endoscopy Treatment focuses on creating new drugs that target specific cancer-causing genes and their products, inhibitory RNA molecules, and industrially produced antibodies, e.g., Herceptin. New therapies include a multi-tracer approach to selection and monitoring of therapy. We hope, for example, to be able to track the effect of chemotherapy by targeting glucose to determine whether the brain is still taking in a lot of sugar after chemotherapy, reducing the time for knowing whether the chemotherapy worked from 2-3 months to 2-3 days. Gene expression therapy can identify patients with a complete response to chemotherapy. Formerly, we took out breast cancer and, if more abnormalities were found, we used chemotherapy. Now we are experimenting with doing chemotherapy first. In 6 of 24 patients, the chemotherapy destroyed the tumor and in the other 18 it shrank it. The question was whether we could identify the 6 in advance of therapy. Computer sorting of the genes showed that the 6 had a group of 12-15 genes with high expression. It is possible to take a biopsy and look at the level of expression to determine whether the cancer will be receptive a

certain chemotherapy in a certain person. We are now trying to target chemotherapy to the person.

Targeting premise five is that the greatest impact on cancer deaths can be achieved by identifying genetic, environmental and lifestyle factors that increase the risk of cancer, and prescribing behavioral modifications and therapeutic interventions that can prevent cancer or reverse precancerous lesions. Factors affecting cancer deaths include smoking and weight control, inherited genetic risks, modification of the environment, chemoprevention, and survivorship. One third of all cancer would stop if no one smoked. If a person does not smoke before turning twenty, he probably will not smoke. Also, fat produces cancer growth factors. We can screen for inherited genetic risks and modify the environment. Having checkups is important. Only 75% of women get mammographies, and 50% get colonoscopies. Vitamin deficiency affects cancer, but it is believed Americans get enough vitamins in their diets. Lung cells are shed in a week. Cancer is produced when they are not shed. It is believed we can trick cells with embryonic stem cells. Study is needed to determine whether we can use these cells to replace damaged organs. This research overlaps cancer research because abnormally functioning stem cells probably cause cancer. The same personalized approach could probably be taken to other diseases, although cancer is the most complex.

In 1936 the 5-year survival rate for cancer was 33%. Today in 2008 it is 63%. The mission of the M.D. Anderson Cancer Center is to eliminate cancer in Texas, the nation, and the world through outstanding integrated programs in patient care, research, education and prevention. Its vision is to be the premier cancer center in the world based on the excellence of its people, its research-driven patient care, and its science.