MODERN APPROACH TO CANCER:
THE SEARCH FOR MORE EFFECTIVE, LESS TOXIC DRUGS:
USE OF INDIVIDUAL MOLECULAR PROFILES TO GUIDE TREATMENT:

The medical world is now consumed by pursuit of individualized approaches. In oncology, this has gone by the name of Personalized Medicine, Genomic Oncology or, simply, targeted therapy. This approach aims to replace conventional chemotherapy: well known as the evil, age-old, feared, and wicked man of cancer treatment.

Next to the disease itself, at times worse, is dread nausea, profound weakness, lassitude, trouble feeling limbs, and the general depletion wrought by chemotherapy. This burden of treatment draws life out of life. It was the dream, and it is increasingly the reality, to do away with general-action drugs which killed fast growing cells faster than normal cells. Obviously, many cancer cells are resting, or at least not in process of duplicating themselves; conversely, many health cells grow rapidly. Hair grows quickly, as do cells in the bone marrow, Cures were hard won, few and based upon admixture of combinations of drugs. As for major types of cancers like lung, pancreas, breast, ovary, colon, prostate, and so on, when found in late stage, we can do little to help.

The best outcomes rely on prevention or early detection. Once tumor is detected it can hopefully be removed by surgery or eliminated by local radiation. Most cancer, however, except skin cancer, is found when it is not well localized but spread into the region or advanced to distant sites of metastasis.

In periodic reviews here we will familiarize our patients, in plain language, about many of the concepts of molecular analysis, now used to increase our understanding of the cancer cell, and how each tumor, even of the same type, can vary widely. This is a key change in how we view cancer. Until recent times, looking at cancer, according to the site from which it arose

provided our best strategy. In fact, since we first dealt with treating cancer, its origin, was the primary guide to treatment. Therefore, breast cancer would be treated differently from lung cancer, and both these, differently from colon cancer, and so on.

The search for selective, personal treatment of individual tumors, is the central goal of research. Many strides have been made; exciting things are on their way. Here, I will provide a bird's eye view of the principles behind new, emerging, and modern approaches to both treatment and diagnosis. In this new view of cancer, different tumors are distinguished by the molecules they express, more than where they came from. For simplicity, I am going to refer to abnormal molecules as "broken" when they contribute to cancer. It must be clear, however, that I do not just mean that any old malfunction. An example is provided by a type of abdominal cancer which contains an abnormal protein on its surface. As it happens, this molecule, which plays a key role in this tumor, is the same molecule "broken" in a form of leukemia. Not surprisingly, these are each treated with the same drug which interferes with damaging activity and consequences of the broken protein, hopefully quelling its central cancer-causing role.

PROGRESS TOWARD PERSONALIZED MEDICINE: These are among the topics that we intend to approach regarding novel approaches to cancer.

- Early detection of cancer, monitoring treatment and surveillance for recurrence

- Calling upon internal soldiers—antibodies and cells:

    - Use of *antibodies* to eliminate cancer cells by self-destruction. Direct and indirect approaches.

    - Modification and use *of*

modified T cells to eliminate cancer

- Cutting the supply lines: attacking the pipeline that delivers oxygen, sugar and other needs.

- Use of DNA sequencing, in part or whole, to discover abnormalities, or mutations, which are treatable in targeted ways.

- The age of Big Data and Informatics to reveal common features of cancer and their role in initiation and progression of disease

The first topic is early detection of cancer. Most are familiar with colonoscopy, Pap smears and mammograms for their success in detection of colon, cervical, and breast cancer respectively. These techniques use traditional tools which can often find cancer at an early stage when it can be removed by surgery. Contrary to popular belief, most tumors take a long time to grow from when begin to when they are first detectable until they present a threat to life.
Consider a healthy individual over 50 who has no inborn risk of colon cancer. If the colonoscopy shows no early pre-cancerous growths, then a repeat scan is not recommended for another 5 years. Why? When Colon cancer arises, it goes through a typical process of growth. The growth is visible, and slow. For this reason, observing the colon, by colonoscopy at long intervals, is sufficient to detect early forms of the disease and remove it before it becomes dangerous. Similar concepts apply to cervical, breast, and skin cancer.

Normal cells or ones with unusual growth causing a polyp in the colon, precancerous changes on PAP, or small emerging mass in breast cancer, all exchange information with the blood that feeds them. Small vesicles of the surface molecules bud off and contain not only the surface components of the respective membranes but some innards from inside the cell, called the cytoplasm. The

cytoplasm within exosome vesicles includes pieces of protein, pieces of DNA or RNA. These small rafts are set forth from cells into the blood that streams by. It is worthwhile to note that the membranes and some internal molecules are aberrant in ways that contribute to cancerous activity. Sometimes these abnormalities may be viewed with straightforward metaphors, as if looking at a broken gas pedal or jammed brakes; sometimes differences are seen in associated fingerprints of other molecules which are expressed in greater or lesser number. Thus, faulty brakes which do not allow vehicle to stop, might show indirect evidence by measurements of the thickness of rubber on the tires or the number of moths on the windshield. The same would hold for a gas pedal, stuck to the metal. At the cellular level, molecular apparatus which increases proliferation and division of cells, would be expected to have changes in the number of normal particles that appear. Determination of a cancer fingerprint of circulating proteins or DNA or rna is difficult but possible.

Recently, several technological approaches have revealed telltale signs of cancer in circulating cells, within exosomes, and freely floating in plasma. One such approach was developed by a local team, including me. In the blood test, exosomes--as small as 1 billionth of a meter in diameter—are isolated from the blood and the pattern of normal proteins—some increased, others decreased, is compared between blood of cancer patients and blood of health patients. Consistent differences reveal “fingerprints” suggestive of tumor, even when it is not yet visible. This was the subject of a recently published paper attached and linked to the site.

In updates to come, we will approach the novel ways that the genes, proteins, DNA, and RNA are being used to identify and to treat early cancer. From a clinical viewpoint these are nearing readiness for suggested diagnosis, screening or monitoring known disease. Treatment, however, are not ready for prime time, but selection of treatments is already emerging.

Emerging, Novel molecular oncology: use of DNA sequencing or the pattern of proteins, DNA, or RNA alone or combined yield informative guidance for screening, diagnosis, treatment, prognosis prognosis and prediction of favorable therapy response.

More awaits on this curious journey of the emerging future of oncology.

Mark J. Adler, M.D.