CANCER CURES AND BLOCKBUSTER DRUGS:
WHO CAN HANDLE THE TRUTH?

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Statement

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THE FRONT LINES OF CANCER
The patients
The costs of anticancer drugs
Patient time and incentives
Pharmaceutical sales
The media
Governmental institutions

DO NOT LISTEN TO WHAT THEY SAY -- GO SEE.
Patients rarely die from a primary tumor
Facts and figures from the American Cancer Society
Facts and figures from the National Cancer Institute
Different cancers respond differently to chemotherapy and radiation
Blockbuster drugs

THE CHICAGO DRUG SHOW
The 2007 progress report

THE CANCER CELLS THAT LEAVE HOME HAVE EXTRA DNA CAPABILITIES
Normal cells
Cancer cells
The danger lies in the diversity within a cancer cell population
The cancer cells that leave home have increased informational diversity
Most cells in a primary tumor never leave

DRUG RESISTANCE AND THE RETURN OF CANCER
Normal cells are inflexible in a crisis
Cancer cells have additional flexibility in a crisis
How different is drug resistance in each person?
Handling the truth

NEW FRONTIER OR YET ANOTHER UNFULFILLED PROMISE?
Personalized treatment for the individual patient
DNA profiling
Single letter mutations
Drug combinations
The reality of massively disrupted DNA contents

THE EARLIEST STAGES OF CANCER
Once four DNA copies are attained, all hell breaks loose
The mutationists
The BRCA1 and BRCA2 breast cancer genes

CANCERGATE
Finding all the mutations in all cancers
The fatal flaw
Cancer genes
The Delusionists and the Spin Doctors
The clinical deliverables: patients are still waiting…and waiting…and waiting

THE HOPE

FAILURE IS NOT A CRIME. FAILURE TO LEARN FROM FAILURE IS.

REFERENCES
In the movie *A Few Good Men*, there is a heated exchange between the military characters portrayed by Tom Cruise and Jack Nicholson, an exchange which is relevant to the War on Cancer.

Jessep: You want answers?
Kaffee: I want the truth!
Jessep: You can’t handle the truth!

The distinction between answers and truth is perfectly illustrated in the cancer arena where competing interests form a volatile mix. The patients want cures, the media want stories, the researchers want grants, politicians want votes, the doctors want to save lives and the pharmaceutical companies want to sell drugs.

The War on Cancer has become a global industry where fact and fiction have become indistinguishable and where the truth often goes missing. Some truths are airbrushed out, leaving doctors to deal with the fears and financial predicament of their patients. What do the front lines in cancer treatment and management really look like?

To better appreciate them, we attempt to provide the latest facts. The medical ones can be checked at the National Cancer Institute, (http://seer.cancer.gov), the American Cancer Society, (www.cancer.org), the Armed Forces Institute of Pathology, (www.afip.org) and in the referenced scientific articles. The business figures are from *The Wall Street Journal*, *BusinessWeek*, *Forbes*, *CNNMoney* and pharmaceutical companies.

THE FRONT LINES OF CANCER

The patients

Dina Rabinovitch, author of *Take off your party dress; when life’s too busy for breast cancer*, reveals the day to day traumas of a breast cancer patient with an advanced form of the disease. The cancer has spread to other organs and her third different drug treatment is underway. It began with chemotherapy and intravenous doses of the blockbuster drug Herceptin and when the cancer returned, Omnitarg was prescribed. Now the regimen is; five pills per day of the latest miracle drug Tykerb, plus eight daily tablets of the chemotherapeutic agent Xeloda every two weeks out of three, plus two morphine tablets and a diclofenac every morning and evening.

She states bluntly; My cancer keeps recurring. Nobody can tell me why. I did the genetic screening and I don’t, apparently, carry the faulty genes. So angry and increasingly so cynical about these doctors in whom I have to put complete trust.

The costs of anticancer drugs

In 2007, the costs per patient for major anticancer drugs were summarized in the *Journal of the National Cancer Institute*. If used for a full year, the two blockbusters, Herceptin for breast cancer and Avastin for lung cancer, would cost $36,000 and $106,000, respectively. For colorectal cancer, Erbitux and Vectibix would cost $120,000 and $96,000, respectively, while for breast cancer Tykerb would amount to $35,000. Cancer drugs represent 40% of all Medicare drug expenditures.

These skyrocketing costs place doctors in the position of having to advise their patients about whether the clinical benefits are worth the financial burden. Nearly a third of them report discomfort in telling patients about costs and another 20% do not consider it to be their role. Many physicians say they are not health policy persons and just want to do the best job for the patient.

Physicians are trained to save lives and have little time to evaluate the effectiveness of a blockbuster drug or genetic test. Furthermore, cancer genetics has moved so rapidly that most doctors do not have the specialist molecular and statistical knowledge to make informed decisions about molecular tests, the clinical claims of which are usually overstated and often have little validity.
Patient time and incentives

The director of the American Society of Clinical Oncology, Dr Peter Eisenberg states that the system does not value a doctor’s time with patients. The system also provides incentives to prescribe drugs with the highest profit margins and many doctors follow the money, after all, oncology is a business. Dr Richard Deyo of the University of Washington points out that: there are plenty of patients for whom there’s little hope, who are terminally ill, whom chemotherapy is not going to help, who get chemotherapy. What choice do oncologists have? By ending treatment the doctor would be acknowledging that hope is gone. Treatments therefore go ahead.

Pharmaceutical sales

In 2006, the breast anticancer drug Herceptin and the colorectal anticancer drug Avastin generated $2.6 and $1.7 billion in sales, while Erbitux generated $1.1 billion in the colorectal market. Worldwide, anticancer drug sales are expected to rise nearly 20% per year through 2010 to reach between $60 and $70 billion. All large pharmaceutical companies strive to produce new anticancer drugs. GlaxoSmithKline, for example, predicts it will launch five new anticancer drugs in the next three years.

The media

The public’s desperation for cancer cures distorts its perceptions of breakthroughs and miracle drugs. With headlines such as Breakthrough liver cancer treatment found and the spectacular but completely incorrect, US scientists have cracked the entire genetic code of breast and colon cancers, offering new treatment hope, it is a wonder that oncology wards are not completely deserted. Unfortunately they are working at full capacity. Breakthroughs have become totally devalued and are accepted uncritically by the public, charitable organizations, politicians and the media.

The fascination with cancer cures is illustrated by the media’s attention to celebrities. In the 1970s it was Betty Ford and Happy Rockefeller with breast cancer. In the 1990s, it was General Norman Schwarzkopf and Time magazine Man of the Year Andy Grove, both with prostate cancer. Currently it’s Elizabeth Edwards whose breast cancer has spread to the bone marrow and White House Press Secretary Tony Snow, whose colorectal cancer has spread to the liver. Snow’s message is that a lot of conditions are now curable or people are racing toward cures. Celebrities serve as pillars of hope, but their comprehension of cancer cures conflicts with clinical reality. Cancers that have spread are quite unlike diabetes and heart conditions where people live for decades by taking fairly harmless drugs.

Governmental institutions

Far away from the frontlines of the War on Cancer, the directors of various institutions vigorously defend the progress in curing cancer. No matter how implausible, almost anything is said to attract more funding. The previous director of the National Cancer Institute, Andrew von Eschenbach, outlined an extraordinary goal; eliminating death and suffering from cancer by 2015. This statement was so misleading that senior scientists were aghast at such overt distortions of scientific reality. It is also a very dangerous statement as it provides false hope to patients. Some cancer sufferers, believing it to be true that death and suffering from cancer will be eliminated by 2015, could delay seeking treatment in the hope that a pill will soon be available to cure their cancer.

When it’s all said and done, where are all the promised cancer cures since Richard Nixon signed the National Cancer Act into law on the 23rd of December 1971?

In terms of the fiery exchange that began this essay, do we wish to face the truth, or not? The choice is an intensely personal one. If readers prefer not to know the facts, they should read no further.
Patients rarely die from a primary tumor

Problems arise when a cancer spreads (metastasizes) to another part of the body and destroys a vital organ\textsuperscript{20-23}. In breast cancer, it is not the lump that is the killer, it is the cells that leave that lump and spread to the brain and bones, for example, eventually replacing a vital organ with tumor tissue. Ninety percent of the deaths from cancer are due to the spread of these maverick cells that develop the capacity to leave home and embark on a journey throughout the body. If a primary tumor is diagnosed before any of its cells have left and the tumor is surgically removed, the patient is completely cured. This is the \textit{only} cure that exists; removal of a primary tumor before any of its cells have moved to other parts of the body.

Facts and figures from the American Cancer Society

An estimated 560,000 US citizens will die from cancer in 2007 (www.cancer.org). The five largest categories of deaths will be; lung cancer, (160,000), colorectal (53,000), breast (41,000), pancreas (33,000) and prostate (27,000). Most cancers will occur in individuals 55 years or older. Deaths from childhood cancers, between the ages of 0 and 14, are relatively rare, estimated to be 1,500.

Facts and figures from the National Cancer Institute

The latest figures from the NCI’s publicly accessible databases reveal the relative 5 year survival of patients with various metastatic cancers over the 30 year period, 1973 to 2004 (http://seer.cancer.gov/csr).

- survival with metastatic breast cancer improved from 19 to 23 percent.
- survival with metastatic colorectal cancer improved from 6 to 9 percent.
- survival with metastatic prostate cancer improved from 28 to 34 percent.
- survival with metastatic lung cancer improved from 1 to 2 percent.

The improvements in survival are less than 0.2 percent per year, a miniscule change. Dr Jane Weeks, an oncologist at the Dana-Farber Cancer Center provides clinical candour; \textit{A surprisingly high proportion of patients with metastatic solid tumors don't realize that there is no chance for cure. I’ve wondered how many patients in exactly that situation have been shocked to learn otherwise from the coverage about Elizabeth Edwards}\textsuperscript{17}.

The truth is that all metastatic cancers are incurable despite the enormous sums of money poured into research and drug development, as well as the large amounts of chemotherapy, radiation and new drugs that have been poured into patients\textsuperscript{24,25}.

Some patients do respond to blockbuster drugs. Increased survival times, however, are of the order of months, not years. Side effects are common and the quality of life is dreadful. Approximately ten percent of breast cancer patients who receive Herceptin, for example, develop cardiac toxicity, while another thirty percent develop metastases to the brain\textsuperscript{26}.

Different cancers respond differently to chemotherapy and radiation

There are hundreds of different types of cancer that have been carefully classified by pathologists (www.afip.org). Each differs in its aggressiveness to spread and its resistance to drugs.

A common misconception is that if one type of cancer can be cured, so can all others. The case of Lance Armstrong, who was cured of testicular cancer, is believed to be generalizable to other cancers. However, cancer is a variety of types. Thus testicular cancer encompasses seminoma, embryonal carcinoma, teratoma and choriocarcinoma. Seminomas are generally slow growing, whereas non-seminomas tend to spread more quickly. Grade 1 seminomas are sensitive to both chemotherapy and radiation therapy and if detected early enough and treated, over ninety percent of patients are alive after 5 years and hence are considered to be cured\textsuperscript{27}. 
In contrast, other cancers, such as colorectal cancer, pancreatic cancer and melanomas of the skin are intrinsically resistant to radiation and chemotherapy. Less than five percent of patients with pancreatic cancer are alive after five years.

**Blockbuster drugs**

The effectiveness of anticancer drugs is measured in two major ways. The most accurate is Median Overall Survival, the time by which half the patients have died from disease. The other is Progression-Free Survival, which essentially measures how long after drug treatment the cancer begins to grow again. This is a subjective measurement since it involves estimating tumor size by scans. Given these two methods, how do the various drugs perform?

**THE CHICAGO DRUG SHOW**

The annual meeting of the American Society for Clinical Oncology is the premier forum in which upcoming cancer treatments are presented. It is the cancer equivalent of the Detroit Auto show. New drugs are exhibited by all the pharmaceutical firms and media and stock market analysts report on the upcoming drug pipeline. This year's meeting was attended by 30,000 oncologists, researchers and drug and biotechnology company representatives. What progress emerged on cancer cures?

**The 2007 progress report**

**Nexavar.** Onyx Pharmaceuticals and Bayer HealthCare Pharmaceuticals reported on a new use for their drug Nexavar. In combination with chemotherapy, Nexavar boosted median overall survival of liver cancer patients by 2.8 months. This improvement was described in *Forbes* as a *breakthrough liver cancer treatment* and by Dr Llovet of the Mount Sinai School of Medicine in New York city as; *a new reference standard for systemic therapy of liver cancer patients after thirty years of research and more than 100 randomized controlled trials performed*. Surely after thirty years, innumerable clinical trials, billions of dollars invested and an increased median survival time of 2.8 months, the use of the word breakthrough is absurd.

**Axitinib.** Pfizer reported that their drug Axitinib plus chemotherapy for advanced pancreatic cancer boosted median overall survival by 1.3 months compared to chemotherapy alone. When used for metastatic breast cancer, Axitinib plus chemotherapy boosted progression-free survival by 1.2 months compared to chemotherapy alone. However, along with this extra 5 weeks of life, there were common adverse events such as nausea, fatigue, proteinuria, stomatitis/mucositis, hypertension, diarrhea and neutropenia. Further risks are documented in Pfizers Annual Report Forms, 10-K, 10-Q and 8-K.

**Erbitux.** ImClone Systems and Bristol-Myers Squibb provided data on Erbitux for head and neck cancer, the results being highlighted in *BusinessWeek*. Erbitux plus a chemotherapeutic regimen boosted median overall survival for head and neck cancer patients by 2.7 months compared to chemotherapy alone.

**Avastin.** The *Wall Street Journal* reported on data released by Genentech on the drug Avastin. Avastin plus interferon boosted progression-free survival for kidney cancer by 4.8 months compared to interferon alone. In addition, Avastin plus a chemotherapeutic regimen for advanced forms of lung cancer boosted median progression-free survival by 6 weeks compared to chemotherapy alone.

**Herceptin.** The *New York Times* reported on concerns with the allocation of patients to receive Herceptin, which is held to be the paragon of personalized medicine in breast cancer.

Women with breast cancer are classified into two groups on the basis of molecular tests involving a gene called HER2. The groups are termed HER2-positive and HER2-negative. Only HER2-positive patients usually receive Herceptin, as the drug is thought to have little benefit for the HER2-negative group. However, it was reported that some women experienced a benefit irrespective of their HER2 status, indicating that Herceptin may be being incorrectly targeted to these two groups.
These findings left some doctors incredulous and confused as to what treatments to now apply to their breast cancer patients. *Here we are, 10 years into it and we don’t know how to test for it*, said Dr Marc Citron an oncologist from Lake Success, New York 29.

The main message to emerge from this prestigious forum is that specific drugs in combination with chemotherapeutic regimens do extend median survival for a period varying from weeks to months. However, these figures apply to a population of patients, not to an individual. One patient may survive for years, whereas another is gone after a few weeks. Currently there is no accurate way by which a doctor can predict an outcome for a particular patient.

**THE CANCER CELLS THAT LEAVE HOME HAVE EXTRA DNA CAPABILITIES**

The cells that leave the primary tumor have different DNA characteristics to those that remain. It is their altered properties that enable these emigrants to leave in the first place and for their descendants to infiltrate and destroy vital organs 20,21,22,30,31.

**Normal cells**

All normal cells have two copies of their DNA, one set from the mother and one set from the father. There are thus two DNA code books (instructions-for-cell-survival) in every normal cell. If one book is damaged, there is always a good copy from which to make repairs in an emergency. Normal cells carefully follow the instructions encoded in their DNA and execute them in a particular order and at specified times. Normal cells are tightly constrained by their two-book genetic operating manuals.

**Cancer cells**

By contrast, cancer cells that have left the primary tumor and are in transit or have arrived at their final destinations, have massively disrupted DNA contents. Their instructions-for-cell-survival books have been copied and they have more than two of them, but with profound differences. Enormous errors have occurred during the copying process so their books now contain some extra chapters, sentences and paragraphs, while some other chapters, paragraphs and sentences have been completely deleted. Furthermore, differing amounts of text have been shifted from one place to another and at the most basic level, single letters have been changed. These single letter changes are commonly referred to as mutations 6,32.

The extent of these massive alterations in DNA is aptly described by Dr Garth Anderson, of the Roswell Park Cancer Institute in Buffalo, NY; *in most adult solid tumors the genome is shot to hell by the time the tumor is found* and *a mutation will not be in every cell in the tumor* 33.

**The danger lies in the diversity within a cancer cell population**

The mistake-prone process of DNA copying, cutting and pasting that goes on in cancer cells produces remarkable outcomes. **Cancer cells no longer have to obey instructions.** They have been liberated from the rigidity of conventional two-book genetic operating manuals. The ongoing process of massive alterations in DNA provides a cancer cell population with novel instructions on how to cope with various emergencies. Thus when chemotherapeutic drugs are encountered, some cancer cells in the population have different ways of dealing with drugs. No matter what defenses the body may deploy, some cancer cells in a population always have a new combination of instructions ready to face a crisis.

**The cancer cells that leave home have increased informational diversity**

The cancer cells that leave a primary tumor are often first found in the nearest lymph node draining the tumor and later in more distant places such as the bone marrow. A comparison of the DNA contents of individual cancer cells from the lymph nodes and bone marrow of the same patient to those of individual cells in the primary tumor reveals that cancer cells at these different locations have accumulated their own specific changes in their DNA contents 22.
The cancer cells that leave the primary tumor represent a diverse population upon which selection will act. Some cancer cells are destroyed by the immune system, others reach the lymph nodes and progress no further, whereas still others reach an organ but are held in check by the local resident cell population and cannot proliferate. Finally, some cancer cells survive all these hazards, grow at their new sites and ultimately destroy a vital organ. In a nutshell, this is metastatic cancer.

Most cells in a primary tumor never leave

Only a small number of the cells in a primary tumor ever develop the DNA alterations to emigrate \(^{21,34,35}\). If all cells had the capacity to leave, no primary tumor would be left \(^{21}\). When the cells of a primary tumor are tested both clinically and experimentally for their ability to form a new tumor, only approximately 1 in 50,000 cells has the capacity to do so \(^{34-38}\). Only cells that have sufficiently altered genetic operating systems or stem cell-like properties \(^{39-41}\) break free of the local constraints and depart. Normal cells always remain in their local neighborhood.

**DRUG RESISTANCE AND THE RETURN OF CANCER**

**Normal cells are inflexible in a crisis**

When normal cells are subjected to chemotherapeutic drugs, the cells have a limited capacity to either inactivate the drug or to expel it using various pumps that are found at the cell surface \(^{42,43}\). Some cells respond better than others, since they have more efficient versions of these pumps and/or more efficient drug inactivating systems. As the level of the drug increases, however, the inactivation and pump systems are overwhelmed and normal cells die from drug toxicity. They lack operational flexibility, even in times of crisis, because they can only implement the fixed instructions in their two-book operating manuals.

**Cancer cells have additional flexibility in a crisis**

By contrast, when cancer cells encounter a chemotherapeutic drug, the diversity within the cell population is so great that some cells always have a novel combination of instructions courtesy of their massively disrupted DNA contents. Some cells survive and grow back even in the face of different drug combinations. Thus the return of cancer is understandable when viewed from the perspective of cancer cell populations, the members of which have diverse and flexible operating systems. These attributes have yet to be recognized by most cancer researchers who are generally unfamiliar with classical manipulations of large chunks of DNA and the consequences of the additive effects of genes that are slightly sensitive to abnormal dosage \(^{44}\).

The flexibility inherent within a massively disrupted DNA cell population was clearly demonstrated by the experimental removal of the main drug pumps from cells \(^{45-48}\). With their frontline multidrug defences completely missing, such cells were nevertheless rapidly able to become drug resistant because of their massively disrupted DNA contents.

**How different is drug resistance in each person?**

Every human being (except for identical twins) is unique at the DNA level. Hence each cancer cell population follows a unique trajectory as the cells leave the primary tumor. Each woman with breast cancer will not only differ in terms of drug resistance, but also in her intrinsic ability to control the growth of any particular cancer. For example, breast cancers in African-American women are more aggressive and less responsive to treatment than breast tumors in Caucasian women \(^{49}\). Some women will have cancers that return quickly, others more slowly. The majority of women who respond to Herceptin will develop drug resistance within a year \(^{50}\), but others take longer. Some cancers will even remain dormant for years.

**Handling the truth**

The earlier statements of Dina Rabinovitch, *My cancer keeps recurring. Nobody can tell me why*, are now less mysterious when viewed in the context of the differences in flexibility between normal and cancer cells.
Most cancers rapidly become drug resistant because each population of cancer cells is different in terms of its massively altered DNA contents. Each cancer reacts to drugs in its own way leading to the selection of those cells with novel genetic operating systems that resist drug effects. It is the ability of any cancer population to continuously adapt that makes it so dangerous.

NEW FRONTIER OR YET ANOTHER UNFULFILLED PROMISE?

Personalized treatment for the individual patient

Examining a person’s DNA profile has been popularized by forensic medicine and is now being applied to cancer patients. Dr Victor Velculescu of John Hopkins University explains personalized cancer treatment 51.

A cancer patient comes into a clinic and has her tumor analyzed. Then she is treated based on a spectrum of her mutations with a cocktail of drugs. It doesn't mean a new drug for each person, just a different combination of drugs.

The above seems like a dream come true and is being heavily promoted as the new frontier in cancer, with billions of taxpayers dollars due to be spent in this new area 52-55. Pharmaceutical companies have recognized the potential of increased sales and are designing new drugs to target cancer-based gene products in order to obtain the biggest slice of this upcoming $60-$70 billion market.

DNA profiling

Current DNA profiling technology of single letter DNA mutations is straightforward, but how relevant is a drug combination prescribed on the basis of profiling a primary tumor to shutting down metastatic growths?

Single letter mutations

When fully sampled, a primary breast tumor will harbor millions of mutations 6,32,56. In addition, each breast and colorectal patient analyzed to date 6 has been found to have a unique combination of mutations 15. This huge number of mutations, plus the unique combination of them in an individual, poses enormous challenges in demonstrating the clinical relevance of mutations. Clinical relevance cannot be sufficiently emphasized.

Since only about 1 in 50,000 of the cells in a primary tumor has the potential to become metastatic 34-38, which of the millions of mutations are in the dangerous cells that leave? It is not possible to determine this without first isolating these maverick cells from the bulk of the solid tumor. Since this is not done, DNA profiling reflects the sum total of all the mutations in the primary tumor. Any clinically relevant mutations remain diluted by millions of clinically irrelevant mutations. A DNA profile from a primary tumor consists almost entirely of noise.

Drug combinations

Future personalized drug combinations will require clinical trials and separate FDA approval. There are currently only five FDA-approved combination regimens for one of the most intensely trialled major cancers, colorectal cancer 57, but the number of possibilities for new drug targets generated by the millions of mutations in a primary tumor is astronomical. The mere thought of developing new drugs each specific to one of the millions of potential new targets, given the current ten year time frame for the development and testing of each new drug, is delusory.

Drug combinations can be dangerous. As Dr Steven Hirschfeld of the FDA points out; These are all myths having to do with anticancer drugs…that they’re very targeted, when in fact all these drugs have multiple targets. That they’re nontoxic, when in fact the latest ones have their own set of side effects. And that they’re cures, when they are not 58. There are no anticancer drugs that are specific for a single target; all bind to several 59,60.

The data show that each cancer cell population is unique, each anticancer drug is nonspecific and each patient differs with respect to drug resistance. Personalized cancer medicine in its currently practiced form of determining the extensive DNA profile of a primary tumor via single letter changes and then prescribing drug
combinations is simply another promotional exercise. The glib statement that, *it doesn’t mean a new drug for each person, just a different combination of drugs*, is completely out of touch with the reality of clinical, pharmaceutical and FDA implementations.

The reality of massively disrupted DNA contents

Current personalized cancer medicine focuses on single letter mutations rather than the massively disrupted DNA component of cancer. Half a century of genetics, however, shows that the effects of massive changes involving many genes dwarf the effects of single letter mutations. Analyses of additions and deletions of DNA in experimentally manipulable organisms reveal that varying the dosage of large chunks of DNA has far more important biological effects on the flexibility of genetic operating systems than the small scale mutational changes that can be induced in normal cells.

So how have we reached this preoccupation with personalized DNA profiling of mutations when our answer lies not in the bulk of the tumor, but in the tiny population of maverick cells with their massively disrupted DNA contents? The answers lie in the fashions that dictate cancer research.

THE EARLIEST STAGES OF CANCER

To understand how cancer begins, it is useful to examine readily accessible tissues for the earliest stages. One such place is the cervix where billions of PAP smears and other gynecological examinations have been conducted. Here the first microscopically recognizable changes reveal that some cells have four copies of their DNA instead of two. Why is this finding so important?

Once four DNA copies are attained, all hell breaks loose

The *two-copy to four-copy* event is rare but can occur spontaneously in any normal cell population. Two normal cells may fuse, or a normal cell may replicate its DNA but then not divide. Such events can also be caused by viral infection.

Once attained, a four-copy DNA state is 1000-fold more unstable than a two copy state. These cells with their doubled-up DNA begin to jettison the excess DNA or to silence their genes by mutation or chemical modifications. Systems fail, errors increase enormously and deletions, additions, rearrangements and mutations devastate the DNA.

Thus every-day cell biological processes, once started, wreak havoc. A population of cells is generated with massively disrupted DNA contents leading to modifications in metabolism and further accumulation of changes including single letter mutations. The flexibility of this population far exceeds anything that can be achieved by mutations alone in a two-copy DNA system. It is this flexibility which drives the spread of cancer and subsequent drug resistance.

The mutationists

The *theory* of the mutational basis of cancer in humans is predicated on the progressive accumulation of mutations in “cancer” genes in two-copy DNA systems. This interpretation received a boost when three specific genes were experimentally introduced into a cell line and those human cells formed tumors when transplanted into mice. Mutations then became the drivers of cancer and the massively altered DNA contents of the metastatic cells in patients, which are crucial to drug resistance, were quietly ignored.

The results from this artificial three gene system, however, turned to dust. Reexamination of the original cells not only revealed them to have massively altered DNA contents, but other investigators could not repeat these findings using exactly the same three genes.

These inconvenient truths, however, were ignored and investigators began a frenzied search for mutated “cancer” genes in every tumor source. Having found mutations, however, few investigators attempted to determine their clinical significance. It is axiomatic that if a mutation in a gene causes cancer, then reintroducing a good copy
of that gene into a cancerous cell should restore the cell to normalcy. When this simple test was conducted, however, the cells did not revert to normalcy. The basic premise of causality failed the most elementary test.

Worse follows. Recent population-based data on two famous breast “cancer” genes calls into question the clinical significance of the extensively studied mutations in these genes, for which many women are tested.

The BRCA1 and BRCA2 breast cancer genes

Most women are aware of these two genes and dread that they may carry mutations within them. After decades of detailed examination of mutations in these genes, however, definitive clinical data now reveal that breast cancer specific rates of death among women who are carriers of BRCA1 or BRCA2 mutations, are no different to those of women without these mutations. Clinical data have thus rendered irrelevant a decade or more of mutation-based research data.

Despite all the clinical and experimental data to the contrary, leading cancer figures regard the mutational basis of cancer as some sort of Final Truth which is not to be questioned; only the details need to be filled out. Cancer researchers ferociously defend any genes on which they work as being absolutely crucial to some aspect of cancer, no matter how tenuous, distant or vaguely relevant, the clinical connection may be. This is hardly surprising; finding “cancer” genes is now a prerequisite for fundraising and for Big Science enterprises.

CANCERGATE

Finding all the mutations in all cancers

The director of the National Institutes of Health, Elias Zerhouni, approved major funding for a pilot project to find all the mutations in certain cancers. As reported in the New York Times in 2005, this search would be expanded into a $12 billion megaproject if it were to show signs of success. In June of 2007, however, it was revealed that fifty percent of the particular brain samples to be used for this study are unusable. This is due to the discovery of large amounts of dead (necrotic) tissue in the samples. Any competent pathologist would have pointed out this problem before the start of the project, since large amounts of necrotic tissue are a well-known hallmark of this particular brain cancer, termed glioblastoma multiforme. For the megaproject proponents to somehow stumble upon this basic realization, after more than two years, is nothing short of a scandal. In scrambling to limit the fallout from this deficiency in planning, the NCI is now allocating more funds to determine the best practices to use in tissue sample preservation.

The fatal flaw

There is an even bigger problem with the mutational basis of the megaproject. Most of the hundreds of so called “cancer” genes that have already been prioritized to date have been designated as such on the basis of statistical attributes, not on their clinical significance. Reanalysis of these much-touted data on newly found “cancer” genes has now shown that; few if any of these genes are in fact significant. There is no proper statistical basis for their elevation to “cancer” gene status.

Cancer genes

The public is lead to believe by prominent cancer researchers and the media that every important “cancer” gene is in the process of being tracked down by applications of new sophisticated technologies. The promise is that once all “cancer” genes have been cataloged, it will be clear where the drug targets will be found. However, the criterion being used for a “cancer” gene is simply that it carries a mutation in some tumors. Thus a particular gene which was found to be mutated in only 1 out of 61 lung cancer patients is still considered to be a “cancer” gene. Another gene, mutated in 74 out of 199 colorectal cancers, 1 out of 24 lung cancers, none out of 11 pancreatic cancers and none out of 12 brain cancers, is nevertheless classified as a “cancer” gene. The “cancer” gene proponents seem unable to comprehend that such weak correlations are not indicative of causation.
More recently, analysis of over 500 genes considered to be potentially critical in causing cancer, were tested for the presence of mutations in each of them in over 200 different tumors.

Nearly 40% of the histologically documented tumor samples from patients had no mutations whatsoever in these supposedly important “cancer” genes.

The party line on such data is straightforward. As long as a particular gene is mutated in some cancers, it is considered to be a “cancer” gene, even though the data fail to satisfy even the minimum scientific standards for causality. When the standards have fallen this low, then we are no longer in the realm of world class research but in the realm of voodoo genes and scientific spin. It is nothing short of a disgrace.

The Delusionists and the Spin Doctors

There is now an overwhelming amount of clinical and drug resistance data pointing to the ill-conceived nature of the mutational megaproject and for the lack of a causative role of hundreds of “cancer” genes. The spin doctors are nevertheless busy, arguing that if you turn over every rock, there is a lot more to be found. Indeed there is. However, the reality is that most of what is found has no clinical relevance whatsoever. What we are witnessing is third rate science. It is indicative of stale and unimaginative leadership.

The mutational Delusionists doggedly continue to examine the minutiae of the wounded (the millions of mutations in primary tumors), hoping to learn what is going wrong. They fail to face the one important issue in the War on Cancer, are mutations the main enemy? As the clinical data on BRCA1 and BRCA2 have revealed so clearly, mutations are not the main drivers of cancer. The focus needs to be on clinically relevant entities that bear on the survival of the patient, namely the massively altered DNA contents in metastatic cells that play a pivotal role in drug resistance and survival.

The clinical deliverables: patients are still waiting…and waiting…and waiting

The above findings expose the contrasts among the absolute necessity for careful examination of tumor tissues, the statistical pitfalls inherent in data analyses and the importance of generating data that relate to the survival of the patient. Unless First Class standards are soon reinstated, there will be no clinical deliverables. As pointed out recently in Newsweek by Sharon Begley, This is no way to cure cancer.

The realism is that there is currently no magic bullet that targets a specific solid cancer for reasons that should now be apparent. It is massive DNA alterations that drive cancer. Thus if drugs are currently still the only immediate source of therapies, then they need to be applied in innovative ways to metastatic growths.

It is paradoxical that American medical technology is outstanding, that American doctors are better paid than anywhere else in the world and yet vacuous cancer enterprises of marginal clinical value are so strongly supported by American institutions.

The National Cancer Institute has an annual $5 billion budget and a unique track record. It has consistently delivered one product year after year; unfulfilled promises of cancer cures (they’re still just around the corner). Are patients and doctors still unable to see that the current approach, namely; more money, more technology and more stratospheric hype, is not leading to cures?

THE HOPE

Cervical cancer demonstrates the generic way ahead, with its exemplary diagnosis and treatment involving regular PAP smears and liquid based cytology. Of the projected 560,000 cancer deaths in the US in 2007, only about 4000 will be due to cervical cancer. In parts of Asia, however, cervical cancer is the biggest killer of women because diagnosis is either not performed or left too late.

Increased investment is needed in imaging and screening technologies for early detection such as nanotechnologies that are able to detect whether cancer cells have left the primary tumor and accumulated in
lymph nodes. It is time for early diagnosis and prevention to take precedence over research aimed at shutting down cancers after they have spread. Cancer agencies, well meaning charitable organizations and foundations need to stop being automatic teller machines for basic science.

One immediate preventative measure is staring everyone in the face. More people in the US will die from lung cancer in 2007 (approximately 160,000), than all the deaths from colorectal, breast, pancreas and prostate cancer combined. Tobacco usage is also a risk factor for the development of many other cancers. Stop its usage and the incidence of lung and other cancers will be greatly reduced.

FAILURE IS NOT A CRIME. FAILURE TO LEARN FROM FAILURE IS.
Walter Wriston, former chairman of CitiCorp

It is time to heed Walter Wriston’s warning. The failure of various institutions to learn from failure is a tragedy for cancer patients. If the current mindset is not replaced, the next 30 years will be a carbon copy of the last. The losers will be members of our families, our neighbors and our friends.

This is the third article in a series. All three will be available on line at www.securegenetics.com

The first is;

The second is;
Miklos, G.L.G. & Baird, P.J. Curing Cancer; Running on Vapor, Genetic Engineering and biotechnology News, (GEN), 2007, May 1, 27, (9), 6-10.

REFERENCES
100. Leaf, C. *Fortune* 149, 76-97 (2004).

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