Curing Cancer: Running on Vapor

Remedy: More Brainpower, Less Hype

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It's easy to tell when an area has run out of ideas. The hype becomes extreme, and technology substitutes for brainpower. The cancer research area has reached this sorry state. The tiniest increase in the survival time of drug-treated cancer patients or median time to progression is touted as a cure, and wildly unrealistic claims about personalized cancer medicine emanate from the highest governmental and academic sources. In contrast, Andy Grove, the former Chairman and CEO of Intel, who has tried to shake this dysfunctional cancer mindset. "In cancer, everybody plays his individual part to perfection, everybody does what's right by his own life, and the total just doesn't work."

How have we reached this low point where a generation of young scientists, biotechnologists, and the massive resources of big pharma are basically running on vapor? The answers are not hard to find. First, understanding some basic clinical facts is a good place to start. Second, clinically irrelevant research avenues need to be jettisoned—pronto. Resources and intellectual horsepower need to flow into areas that have clinical impact.

Broadly speaking, cancers come in two forms, solid tumors, which make up 90% of cancers, and liquid tumors, such as leukemias. Most cancer patients do not die from the primary tumor; 90% die as a result of metastasis, which causes organs to shut down over a number of years.

The rogue cells that leave home are genomically different than those that remain, a finding based on clinical data from single-cell analyses of breast cancer patients by Riethmuller and Klein. Furthermore, primary tumors are highly heterogeneous. Samples taken from different regions of the same tumor have cancer cells that differ enormously at the genomic and transcriptomic levels. In addition, treating any cancer with drugs unavoidably selects for those cells that are, or can become, drug-resistant. Thus when drug treatment is stopped, the cancer returns in a more dangerous drug-resistant form.

A recent, in-depth analysis by members of Amgen and Novartis on why cancer drug discovery is so difficult shows that there have only been incremental improvements in treatment outcomes. Oncology is close to having the worst record for investigational drugs in clinical development, with a success rate three times lower than cardiology. Meanwhile, the price tag for front-line cancer therapy has become astronomical.

The clinical reality for metastatic colorectal cancer is that the FDA-approved combination regimen of IFL (irinotecan, bolus fluorouracil, and leucovorin) plus Avastin increases median overall survival by 4.7 months. This small increase comes with a host of side effects, which impinge upon quality of life, as well as placing a burden on the patient and the healthcare system.

While this small increase is hailed by the FDA as being impressive, the clinical reality is that there is no cure for metastatic colorectal cancer. The much-vaunted blockbuster drug Avastin is simply an antibody supplement incorporated into an already complex chemotherapeutic drug regimen that may slow down the cancer process depending on the genetic constitution of that individual. The cost of drugs for metastatic colorectal cancer alone would exceed $1.5 billion per year if all the patients in the U.S. received treatment.

The clinical reality for metastatic breast cancer is similar. The latest treatment with Herceptin followed by lapatinib and capecitabine only increased the median time to progression from 4.4 to 8.4 months. Furthermore, 70% of patients

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do not respond to Herceptin, and resistance develops in virtually all patients.

Of these two big killers, both remain incurable, and this sobering fact contrasts with the glowing reports on Avastin and Herceptin emanating from the financial and tabloid media.

The much touted success of Gleevec for the rare liquid cancer Chronic Myelogenous Leukemia (CML) is not generalizable to solid tumors; resistance to Gleevec in CML develops rapidly, as does resistance to nearly every tested cancer drug. Many of the initial responders to Gleevec in blast crisis relapse within months, and the growing consensus is that Gleevec is an exception, rather than a new paradigm.

The Gleevec case should be seen in its proper clinical perspective, namely a treatment that largely involves single cells amenable to attack because of their presence in the circulation. Metastatic tumors, which cause 90% of all deaths, by contrast have hundreds to thousands of surgically inaccessible growths dispersed throughout an organ; they cannot be attacked out in the open as is the case with tumor cells in the circulation. There is little point in singing the praises of Gleevec and pretending that it is a proof of principle for solid tumors.

So what are the responses of government agencies and academic institutions to this clinical reality? They are simplistic: well, yes, progress is slow, it's a complex problem, but we are moving in the right direction. If billions of dollars are poured into DNA sequencing of primary tumors, then we hope to find the critical mutations that cause cancer and then make drugs to them, so that each patient can have a unique treatment. And lets not forget, the Human Genome project was such an outstanding success that we can simply do the same thing for cancer by hyping a Cancer Genome Project. The public will love it, the scientists will love it, and the taxpayer will assuredly fund it.

It's not hard to spot the fatal flaws. First, a primary tumor is so heterogeneous that each cell within it is likely to have a unique genomic signature at the level of mutations, as well as at the level of gross genomic

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LETTER TO THE EDITOR

Why would your *GEN* magazine print an article that disparages the safety of this country's food supply? The arguments for labeling of cloned animal product, made by Ms. Spector, make no more sense than segregating and labeling the milk or meat from a pair of identical twin dairy cows. The animals are identical genetically. Their produce is identical. Which of the twin's products should the consumer fear?

Before accepting any future articles from Ms. Spector's antiagricultural technology group, it would be prudent to ask her for scientific proof of her biases. You will find that there is no test, either toxicological, residue, or component, that can differentiate her natural food from conventionally raised food. All Ms. Spector has to sell is fear and slander. For her marketing effort, she should pay *GEN* for the advertising space and replace the title with "AntiBiotechnology Group Preys on Public's Fears".

Elden Lamprecht, DVM, Ph.D.,
Oakdale, MN

Rebecca Spector replies

Elden Lamprecht's assertion that animal clones are no different than natural-born twins is not fully supported by the facts. Studies repeatedly show that clones are not perfect copies; further, many cloning scientists believe that all clones are inherently abnormal animals. As a review in the *New England Journal of Medicine* stated, "it may be exceedingly difficult, if not impossible, to generate healthy cloned animals…."(Rudolf Jaenisch, 2004; "Human Cloning—The Science and Ethics of Nuclear Transplantation")

Despite Dr. Lamprecht's cry of "slander," we did not suggest that consumers should fear anything. Our piece explains what the majority of consumers are thinking and feeling and explores why they may be so doing. This is important if the biotech industry means to make its products more attractive to consumers and the food companies that cater to them.

Genetic Engineering and Biotechnology News offered the Center for Food Safety the opportunity to address its readers in a spirit of dialogue, which we appreciate and find a very constructive approach. We hope that other readers found something of value to consider in the piece that may lead to a broader consideration of the issue of labeling food from cloned animals.

Rebecca Spector,
Center for Food Safety

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imbalances and methylation signatures. Second, the cells that will be dangerous to the health of the patient and will depart to other organs make up only a minute fraction of the tumor. They are also genomically different to the cells in the primary tumor.

Bioinformatic and statistical methods aimed at sorting the innocent bystander mutations from the causative ones completely miss the main clinical point: which of the millions of mutations, methylation changes, and genomic imbalances are in the cells that leave the primary tumor? This cannot be ascertained bioinformatically; it involves isolating the cells that depart.

In addition, which of the genomic alterations that are in the departing cells will be instrumental in the processes of extravasation, lodgement in an organ, and then in subsequent metastatic growth? Most of the cells that leave home don't survive the journey in the blood or lymph systems, and many cancerous cells that eventually do lodge in a distant organ simply remain dormant.

The clinical issue is straightforward. If a solid tumor is detected before any of its cells have disseminated and the tumor is resected, then the patient is cured. Hence, the key is early detection. Instead of misguided megasequencing projects and bioinformatic deconvolutions that are manifestly tangential to the main issues of dissemination and metastasis, it would seem more prudent to invest in the development of diagnostic technologies for detecting cancer growths, as well as the properties of cells that are destined to metastasize.

For those of us who actually participated in the original Human Genome Project, or who have spent most of our lives examining the pathologies of various cancers, the latest moon shot of the NCI is a disgrace to clear thinking. Lavishing taxpayers money onto DNA sequencing of primary tumors in a vain attempt to hit paydirt is a clear sign of both desperation and a lack of the most basic scientific rigor.

What is still not understood by vociferous supporters of The Cancer Genome Project is that the original Human Genome Project dealt with a homogeneous population of normal diploid cells. This is different from the primary tumors, which are heterozgeneous and have a genomic signature unique to every patient.

Nobel Laureate Sydney Brenner, Ph.D., once mused whether we have reached a decadent phase where scientists no longer think anymore and cannot see what the problems are. In the executive suites of the cancer megaproject it certainly seems so. When the front-line treatment for solid tumors is still chemotherapy and radiation, and the best that blockbuster drugs can achieve is to prolong the inevitable by either a few months or not at all, then it's surely time to stop the delusion. Personalized cancer cures are not "just around the corner," and carte blanche DNA sequencing will produce just that—carte blanche. Unpalatable, yes; realistic, yes.

We believe that scarce resources can be used most prudently in areas of clinical reality, not in research areas that are clinically irrelevant and represent the misguided dreams of a few. Is the future of cancer medicine one in which doctors become financial advisors, telling their patients whether they can or cannot afford expensive treatments of dubious survival value? Surely not. The future is far brighter. The solution is to get back to using old fashioned human brainpower to develop noninvasive screening technologies for detecting the earliest possible cancerous growths. GEN