

Curing Cancer: Running on Vapor

Remedy: More Brainpower, Less Hype

George L. Gabor Miklos, Ph.D., and Phillip J. Baird, M.D., Ph.D.,

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 tran-

scriptomic 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



See Curing Cancer on page 8

Company Index

Abbott48	Celgene20	Genentech20	Midwest BioResearch32	Roche Applied Sciences1
Accium BioSciences34	Cell Therapeutics20	Genzyme20	Millenium Pharmaceuticals20	Rubicon Genomics46
Adolor64	Cellumen14	Geron48	Millipore25,56,71	Sciele Pharma64
Affitech48	Centocor14,42	Gilead Sciences20	Molecular Devices68	Senetek62
Affymetrix20	Cephalon20	GlaxoSmithKline16,28,45,64	Mologen16	Serologics25
Agilent Technologies26	Cesco Bioengineering74	Glycosan BioSystems71	MultiCell Technologies48	Shanghai Genomics14
Alexion Pharmaceuticals20	CH2M48	GoldenHelix38	Myriad Genetics20	Sigma-Aldrich25
Allergan20	Chem-Explorer16	GSK16,28	NanoViricides68	Sonus Pharmaceuticals61
AlphaVax64	ChemGenex62	GTC Biotherapeutics27,48	Nastech Pharmaceutical69	SPEC Chemicals38
Alteon68	Chem-Partner16	Guangzhou Baiyunshan18	NeuroSearch75	SpecruMedix26
Ambit Biosciences62	Chemtek Analytica1	Guava Technologies74	New Zealand Scientific1	Starvax16
Amgen6,13,20,52,58	China Huayuan Group18	Human Genome Sciences20	Nexus Biosystems27	Stem Cell Therapeutics62
Amylin Pharmaceuticals20	China Huayuan Life18	Hutchison MediPharma18	NicOx75	SupWare1
Analox Instruments1	Ciphergen Biosystems42	IBM22	NNE51	Synamatix46
Analytical Bio-Chemistry Laboratories34	Cipla58	ICX Technologies44	Northern Apex-RFID56	SynCo Bio Partners48,50
Apoxis14	Cogenics26	Idenix Pharmaceuticals65	Novagali Pharma75	Syngenta26
Applied Biosystems73	Coley Pharmaceutical62,69	illumina42,46	Novartis6,25	System Biosciences72
Applikon Biotechnology1	CoMentis62	ImClone Systems62	NovaScreen14	Tack Smart Filter Technology56
Apredica72	Coming72	Immtech Pharmaceuticals67	Novosom68	Tagsys RFID56
Array BioPharma69	Covance14,34	Immunomedics20	NuGEN Technologies71	TargeGen16
Ashfield Healthcare14	Crimson Pharmaceutical16	InCROM14	Octamer16	Tech Group56
Aspectrics26	Dasgip54	Inhibitex14	Oncolytics Biotech62	The Harbin Pharmaceutical Group Holding18
Astellas Pharma75	Deadline Solutions26	Integra Biosciences26	OncoStem Pharma58	Thermo Fisher Scientific25,26
AstraZeneca16,27,28,69	DelSite Biotechnologies69	Integrated DNA Technologies46	Ono Pharmaceutical28	Threshold Pharmaceuticals62
Avesthagen58	deltaDot42	Integrated Medicines1	Open Biosystems74	TopoTarget14
Baiyunshan Hutchison TCM18	diaDexus45	Invitrogen25	Opexa Therapeutics67	Transgene68
Basilea Pharmaceutica16	DiaMedica65	Isis Pharmaceuticals68	Organon14	Transgenomic26,42
Bayer50	Dionex73	Kalypsys75	OSI Pharmaceuticals42	U.S. Genomics45
Beckman Coulter73	DxS1	Kendle14	P2D26	Valeant Pharmaceuticals65
Beijing Pharmaceutical18	DynoChem26	Kiadis Pharma58	Performance Fluid Dynamics26	VasTox28
Biocon58	Eksigent1	Labcyte40	Pfizer28	VaxGen14
Bioengineering1	Eli Lilly16	Lexicon Genetics20	Pharmaplan51	Velocity1127
BioFocus28	Emerald Biosystems42	Lonza25	PharmaSeq46	Venturepharm16
Biogen Idec20	Entelos36	Lundbeck Pharmaceuticals48	Pharmaxis65	Vertex Pharmaceuticals20
Bio-Rad73	Enzo Biochem20	MacroChem75	Phenomenex1	Viking Pump71
Biotage72	EpiCept75	MatriCal72	Phylionix Pharmaceuticals42	Viragen61
BioTek Instruments74	Eppendorf73	MaxThera31	ProBioGen48	Vybrion26
BioTrove42	Eurand65	Maxygen20	Progenics Pharmaceuticals20	Waters71
Blue Stream Laboratories26	Fasteris42	MDS Pharma Services14	Protein Design Labs20	Wave Biotech LLC50,53
Bridge Pharmaceuticals16	FermaVir14	MedImmune20	Protex Therapeutics58	Wave Europe Ltd.53
Bristol-Myers Squibb62	Finesse Solutions26	Meditrina Pharmaceuticals75	QNA74	WuXi Pharmatech16
Bruker BioSpin73	Fluxion Biosciences74	Merck & Co.28,69	Quintiles14,34	Wyeth1,29,44,50
Caliper Discovery38,68	FMP54	Merck Serono61	Ranbaxy16,58	Xanthus Pharmaceuticals28
Alliances & Services38,68	Fuji Film Life Sciences72	Merck Serono61	Regeneron Pharmaceuticals20	Xceleron34
Callisto Pharmaceuticals29	Galapagos28	Micronix71	Renovis28	Xechem48
Cambridge Laboratories14	GE Healthcare53		Repligen69	
Carrington Laboratories69			Rigel Pharmaceuticals20,62	
			Roche16,58,68,72	

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Mary Ann Liebert, Inc. publishers

Curing Cancer

Continued from page 6

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 ini-

tial 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 let's 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

See Curing Cancer on page 10

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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

Curing Cancer

Continued from page 8

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 heterozygous 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**

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