Patterns
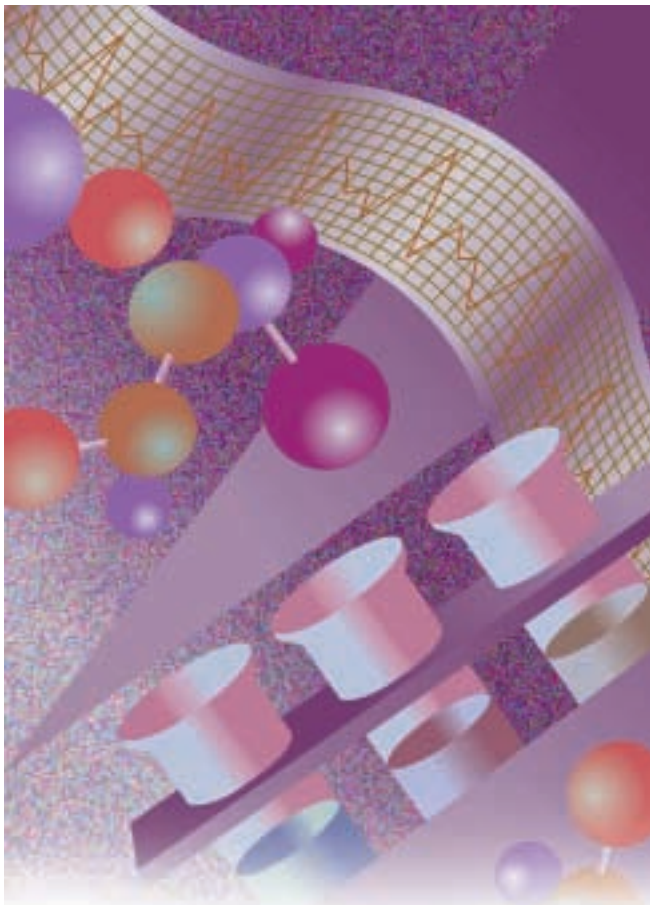# Patterns
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The Future of Cancer Research

by Daniel D. Von Hoff, M.D., F.A.C.P.

ACCC presented its annual Clinical Research Award to Daniel D. Von Hoff, M.D., F.A.C.P., at its 19th National Oncology Economics Conference held September 18-21, 2002, in Albuquerque, N. Mex. Dr. Von Hoff, director of the Arizona Cancer Center in Tucson, Ariz., was honored for his outstanding scientific accomplishments and dedication to cancer research, specifically in the field of gastrointestinal cancers. Further, ACCC recognized Dr. Von Hoff for being instrumental in laboratory and clinical trials that led to the Food and Drug Administration's approval of new antitumor agents. Dr. Von Hoff received the award at a luncheon held in his honor on Friday, September 20, where his presentation on the future of cancer research was met with a standing ovation.

To receive the latest and greatest phase I and II treatments, the approach for many comprehensive cancer centers has been for patients to come to them. The best model for conducting clinical trials, however, is one in which 1) all patients have access to all available therapies, 2) they never have to leave the care of the medical team that has been taking care of them, and 3) they are as close to home as possible. This model requires conducting the trials within a cancer center facility where community oncologists have at least one of their offices—and they are investigators on the phase I studies. Patients go on the trial and are cared for by their community oncologist, with the research nurses and data managers standing by.

A different, special model in phase I trials brought to the community cancer center requires an enormous infrastructure. Phase II trials require much less infrastructure because trials are all conducted in community oncologists' offices so patients can be treated as close to home as possible.

This special model works well: Therapeutics are developed more quickly and are available to more patients as soon as possible—without having to travel. This cooperative model accelerates the introduction of new agents, and I recommend it. With the number of active new agents coming along, we will need that new model as quickly as possible.

But does having access to phase I trials really make a difference?

In the old days, it really did not make much difference if community oncologists had access to phase I trials because the trials did not result in many approved drugs. From 1978 to 1983, 26 agents were taken into phase I trials, but just three (8 percent) were approved. What difference did it make to have access to phase I trials when the success rate was so low?

Now, however, the availability of phase I agents is more important than ever because more of them actually work. From 1984 to 1989, using special animal models, the number of agents taken into clinical trials that were approved by the Food and Drug Administration for clinical use climbed to 31 percent, or 8 out of 26. From 1990 to 1995, 46 percent (11 out of 24) were approved. Finally, from 1996 to 2001, about 66 percent of the drugs brought into phase I trials have been or will be approved. What a huge difference.

The future is the discovery of more and more targets through microarray and proteomics. The good news is we are going to have a chance for many new agents with new mechanisms of action. These agents are coming within the next nine months.

This year will bring us a tremendous number of new agents with new mechanisms of action that will need to be tested in phase I, II, and III clinical trials. The key to doing these as quickly as possible for our patients will be how we organize our teams. We need to use this first pattern: the special model in which phase I trials are conducted within a cancer center facility.

Although the future will bring a lot of targeting, I am worried about the precise targeting approach. Targeting will work for tumors in which one genetic abnormality is what gives the disease, such as CML (where Gleevec hits the target). Many people are worried about these supertargeted drugs because solid tumors have multiple

genetic abnormalities; these targeted approaches might be painstakingly slow and very incremental before we see advances.

Targeted approaches are nice, but what can we do to make progress more rapidly and in greater increments? It's not about the targets; it's about the patterns: patterns of gene expression (for prognosis), patterns of targets, and, perhaps the biggest advance, patterns of serum proteins, for early detection and for following patients.

Patterns of Gene Expression

The number one pattern being used today is the microarray of genetic expression.

The most important work this year in genetic expression measured by microarrays has been profiling for prognosis. Profiling was reported in *Nature*[1] by Steve Friend and his group, who found a gene expression pattern or profile, as they call it, that predicts clinical outcomes of breast cancer. There is a gene expression pattern, a profile that predicts a short interval to distant metastases. What is remarkable about this finding is that the gene expression pattern outperforms all currently used clinical parameters for predicting disease outcome. The only problem is no one has access to this yet.

Patterns of Targets to Hit

The next pattern is modular not molecular biology of targets, as Leland H. Hartwell and colleagues have shown.[2] Dr. Hartwell received the Nobel Prize for his studies in yeast. He makes the following points. The first principle is that we exist and cancer cells exist, too. Since the human race has existed this long, we couldn't possibly be vulnerable to a hit on just one target or protein (enzyme), because we would have died out. Therefore, hitting one target in cancer cells is so naïve that doing so probably won't cure the disease. To make a greater increment in our thinking, we need to change our thinking!

As an example, to attempt to kill a yeast cell, you can hit DHFR (a key enzyme, dihydrofolate reductase) with methotrexate, and there will be no cell death. The cell does just fine. Hit the yeast wall with nystatin and there is no yeast death. But hit both DHFR and the cell wall, and you have cell death. The "module" or "cassette" you have to hit is to hit *both* DHFR and the cell wall to have the effect of cell death. No one has any idea how these two together can kill the yeast cell.

The wiring of the cell is incredibly complex. This fact is depressing for all of us because it means that working out the modules that make human cancer cells vulnerable will probably take a very, very long time.

Although we need a much better understanding of the wiring of the cancer cell, there is a possible way around the problem. Without knowing the wiring, we can use the "CombinatoRx Approach" to empirically hit the module. Investigators at CombinatoRx are looking at hundreds of commonly used approved drugs. These are noncancer drugs, and each usually has multiple mechanisms of action.

What are they trying to do? They are looking for a pattern of different mechanisms of action that will kill the tumor cells. The researchers are empirically hoping that by using two drugs in different concentrations they will find by chance alone something that will inhibit the tumor cells (by hitting a pattern of targets).

We are ready to take the first promising combination of nontoxic agents into a phase I trial in two months. Here is the first foothold in taking two known agents and putting them together to kill tumor cells. Perhaps targeting a pattern of targets will make a real therapeutic difference.

Proteomic Patterns in Serum

The final pattern—use of proteomic patterns in serum—will be a spectacular piece of work that will have the biggest impact in our programs and practices and should be applied to multiple types of cancer. Petricoin and colleagues[3] have described the proteomic spectra in sera, which is generated by mass spectroscopy (surface-enhanced laser desorption and ionization, or SELDI-TOF, where TOF is time of flight.) You heat proteins on the slides until they fly off. Petricoin took a special training set of 50 women with stage I ovarian cancer and 50 unaffected women to identify a proteomic pattern that completely discriminated cancer from noncancer. Then they tried a blinded set of sera. They identified all 50 women with ovarian cancer and identified 63 of 66 nonmalignant as nonmalignant. The sensitivity was 100 percent, and specificity was 95 percent.

We are starting work to identify the pattern for the early diagnosis of pancreatic cancer using pancreatic cancer patient serum. The problem is if you tell people a year ahead of time that they have pancreatic cancer, what are you going to do?

The implications of this proteomic pattern work in the area of treatment and prevention are enormous. These proteomic patterns in sera could be a supersensitive marker for early diagnosis and a great way to determine whether patients are responding to a treatment. Wouldn't it be great if we could just take a serum sample for protein patterns? By the way, there are 15 different proteins in ovarian cancer, not one of them predictive by itself.

But how could we possibly prevent pancreatic cancer even if we had a profile for very early disease? Metformin reduces insulin resistance, decreases islet cell proliferation, and decreases pancreatic cancer in hamsters and in other animal models. Could this be indicative of a possible prevention strategy in which we take high-risk patients and put them on a prevention program to see if we can reverse the pattern?[4] Interestingly, we do not know where these proteins are coming from. Are they coming from the tumor cells or

ACCC president Edward L. Braud, M.D., (left) presents ACCC's annual award for outstanding achievement in clinical research to Daniel D. Van Hoff, M.D., director of the Arizona Cancer Center in Tucson, Ariz., and professor of medicine at the University of Arizona.

Table 1. 42 New Cancer Agents Currently in Development

Agent	Mechanism of Action	Sponsor
SAHA	Inhibition of histone deacetylase	Aton
PX-12	Inhibition of thioredoxin reductase	ProLx
2C4	Humanized Ab to HER 2/*neu*	Genentech
AG2037	GAR transformylase inhibitor	Pfizer
HMN214	Polo kinase inhibitor	Nippon Shinyaku
ILX651	Tubulin interactive agent	Ilex
NM-3	Oral VEGF inhibitor	Ilex
NB1011	Agent activated by TS	New Biotics
Troxacitabine	L-nucleoside targets mitochondria, DNA	Shire
SGN-15	cBR96 doxorubicin immunoconjugate	Seattle Genetics
TLK286	Activated by GST	Telik
Clofarabine	Nucleoside	Ilex
Tesmilifene	(Unknown mechanism of action)	YM Biosciences
G17DT	Gastrin analog vaccine	Aphton
GW 572016	Topo I receptor kinase inhibitor	Glaxco Smit Kline
CRX-26	Pattern agents	CombinatoRx
MGI114	DNA interactive (ERCC3 deficient)	MGI Pharma
CC5013	(Unknown mechanism of action)	Celgene
SCH 66334	Farnesyl transferase inhibitor	Schering
ET743	DNA interactive	Ortho
R115777	Farnesyl transferase inhibitor	Ortho
Psorospermine	Topo II inhibitor	Cyternex
IGN 241	Adeno-MDA-7 induces apoptotic death	Introgen
Ab EGFR	Antibody to EGFR	Abgenix
Aplidine	(Unknown mechanism of action)	PharmaMar
Kahalalide F	Lysosomal destabilization	PharmaMar
Remicade	Anti-TNF Ab	Centocor
IDEC 114	Anti-CD80 monoclonal antibody	IDEC
Liposomal vincristine	Tubulin interactive	INEX
NX211	Liposomal Topo I inhibitor	OSI
AB1007	Nanoparticle paclitaxol	ABI
RSR-13	Oxygen unloader (2-3 DPG)	Allos
Aeroplatin	Liposomal DACH platinum	Antigenics
C1033	EGFR antagonist	Pfizer
GW506U78	Guanine analog	Glaxco Smith Kline
G3139	Antisense to bcl 2	Genta
Oncophage	HSP vaccine	Antigenics
BAY 439006	Raf kinase inhibitor	Bayer
MK869	Oral neurokinin 1 antagonist	Merck
Apomine	FXR interactive	Ilex
LY293111 (MEPM)	Leukotriene antagonist	Lilly
LDP341	Proteosome inhibitor	Millenium

from the body's response to the pancreatic cancer?

In summary, the future is all about patterns:

■ Patterns of gene expression for prognosis
■ Patterns of targets to hit
■ Patterns of proteins (proteomics) to diagnose, follow the disease, and use in prevention.

There is no limit to what we can do if we make everything we have available to all of our patients. ❑

Daniel D. Von Hoff, M.D., F.A.C.P., is director of the Arizona Cancer Center in Tucson, Ariz., and professor of medicine at the University of Arizona.

References

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[2]Hartwell LH, Hopfield JJ, Leibler S, et al. From molecular to modular cell biology. *Nature.* Dec. 2, 1999;402(6761 suppl):C47-52.

[3]Petricoin EF, Ardekani AM, Hitt BA, et al. Use of proteomic patterns in serum to identify ovarian cancer. *Lancet.* Feb. 16, 2002;359(9306):572-577.

[4]Schneider MB, Matsuzaki H, Haorah J, et al. Prevention of pancreatic cancer induction in hamsters by metformin. *Gastroenterology.* April 2001;120(5):1263-1270.