Cancer Therapy Innovation
A Delphi Panel Overview

Executive Summary

Since the declaration of a war against cancer in the early 1970s, and our increasing understanding of functions in normal and in cancer cells, a number of potential targets and technology platforms have been postulated. Only a few of those platforms are beginning to be included in the armamentarium of cancer therapies. Concepts of the use of monoclonal antibodies, and angiogenesis as a target in cancer, are decades old. Although logical in their approach to cancer, these and other technology platforms required advances in understanding of cell functions, cascades, protein interactions, antigen production and presentation before any of these treatments could be attempted.

The advent of hormone therapy (estrogen antagonists) for breast cancer marked a major shift in the approach to cancer. A subset of patients could be identified who were known to be susceptible to this agent (until resistance appeared), and the first customization of therapy was achieved. True, this new therapy was originally made second or third line after traditional chemotherapy, but eventually, antiestrogen therapy achieved first-line status. Another significant step was the acceptance and, later, demand of the patient to be involved in decisions regarding their own therapy.

The announcement of the successful identification of most of the human genome significantly raised the expectations of some researchers and clinicians, as well as the general public, that the 'cure' for cancer was at hand. While some major progress may be expected as a result of the Human Genome Project, no one in the field is talking about 'cures'; in fact there are a number of questions as to what the real contribution of the project results will be.

The research community has accepted tumor regression as the logical endpoint in clinical research. Published articles still measure the outcomes of therapy in terms of complete and partial responses. Furthermore, even the 'complete' responses are followed for a limited period of time, often as little as four weeks. If a week after that the tumor begins to progress, and the patient dies, according to the clinical criteria that patient had a complete response. The evidence is becoming overwhelming that cancer is a series of clones with differing characteristics, and it is unlikely that any single agent can eliminate all the clones.

Introduction

There is a common belief among cancer researchers that there are several basic genetic transformations common to most cancers, which, depending upon the site involved, will manifest secondary genetic alterations characteristic of the particular tumor. Identification of the basic transformations has thus far eluded researchers. While we have identified several genetic markers in groups of cancers, their roles in the development of cancer remain a mystery. This is not to suggest that great progress has not been made. Recently, the absence of a gene located on chromosome 21 (map 2) has been associated with increasing tumor aggressiveness. In fact, patients with extra copies of this gene, (e.g. patients with Down's syndrome), rarely develop cancer. The assigning of functions to genes identified by the Human Genome Project will no doubt provide more direct targets for cancer therapy. Since cancer is a clonal disease, different cell lines arising from individual cells, the individual's polymorphic patterns influence his or her response to therapy as well.

Clones surviving one type of therapy tend to spread, as a result of their competitive advantage over less successful clones, making the cancer refractory to the original therapy. In the case of estrogen receptor positive breast cancer, there is the bitter adage which states that all women become resistant to Tamoxifen, just before they die. Furthermore, metastases, which are successful clones, may ultimately bear little resemblance to the original tumor, making therapy difficult at best. It is for this, among other reasons, that a multidrug approach to cancer is considered to be the best approach. Even customized therapies, which use the patient's own cells to provide tumor antigens, are based on the assumption that what is retrieved from the patient is the predominant clone, not necessarily the only clone.

The shift in the types of drugs being investigated and the narrowing focus of cancer drug targets have raised a group of issues that will need resolution if new cancer therapies are to reach the patient in need.

Current Approaches

Since the declaration of a war against cancer in the early 1970s, and our increasing understanding of functions in normal and in cancer cells, a number of potential targets and technology platforms have been postulated. Only a few of those platforms

are beginning to be included in the armamentarium of cancer therapies. Concepts of the use of monoclonal antibodies, and angiogenesis as a target in cancer, are decades old. Although logical in their approach to cancer, these and other technology platforms required advances in understanding of cell functions, cascades, protein interactions, antigen production and presentation before any of these treatments could be attempted. In addition, production issues, questions of selectivity, sensitivity, bioavailability, toxicity, administration routes, tissue targeting and others, had to be addressed before it was possible to bring any new type of drug to the clinic.

The presence of new technology as therapy generally presents new regulatory issues as well. Up until the last few years, the major technology platforms included post-surgery radiation or chemotherapy. Chemotheraputic agents have tended to be highly toxic, presenting the patient with a quality of life that fell far short of the ideal, in order to see the tumor regress for some limited period of time, in a small percentage of patients. In order to have more efficacious treatments, and treat larger percentages of patients, combination chemotherapy became the norm. The toxic effects of the combinations were often so severe as to make the patient unable to continue therapy.

The advent of hormone therapy (estrogen antagonists) for breast cancer marked a major shift in the approach to cancer. A subset of patients could be identified who were known to be susceptible to this agent (until resistance appeared), and the first customization of therapy was achieved. True, this new therapy was originally made second or third line after traditional chemotherapy, but eventually, antiestrogen therapy achieved first-line status. Another significant step was the acceptance and, later, demand of the patient to be involved in decisions regarding their own therapy. It was recognition by patients that therapy could be less systemically toxic, and that quality of life was an issue of merit, that led to patient fund raising, and lobbying for more and better treatments for breast cancer. This activism is often credited with the push that led to the development, testing, and ultimate approval of Herceptin [**Genentech (South San Francisco, CA)**], the first breast cancer monoclonal antibody therapy. While it is true that only 25-30% of women over-express Her-2, and therefore are likely to respond to Herceptin, the door was opened forever to patients influencing the directions of research and of their own treatment. Herceptin was not the first monoclonal antibody approved for a cancer. In 1997, Rituxan [Genentech, **IDEC (San Diego, CA)**] was approved for non-Hodgkin's lymphoma. Since these two monoclonals were approved, a significant number of monoclonal antibodies have gone into development for a wide variety of cancers.

The Role of Genomics in Cancer Drug Development

The announcement of the successful identification of most of the human genome significantly raised the expectations of some researchers and clinicians, as well as the general public, that the 'cure' for cancer was at hand. While some major progress may be expected as a result of the Human Genome Project, no one in the field is talking about 'cures'; in fact there are a number of questions as to what the real contribution of the project results will be. What can the results of the project provide to research? Can it be the identification of new targets or pathways, the understanding of the differences between normal cells and cancer cells, the recognition of which patients can respond to particular therapies, the means to customize drugs, a means to predict when a patient in remission is about to come out of remission? Will it provide new tools for diagnosis and prognosis? How long will it take before we will see the products of the Genome Project used in cancer therapy?

Cancer Vaccines: Dream or Reality – Elite Cancer Treatment or Global Cancer Preventive

For years, some scientists have proposed that the best treatment and hope for cancer prevention would be in the area of vaccines. Until recently, cancer vaccines were not within reach of the clinical community. Now, vaccines are a reality. How do they work? Are they a practical, economically viable therapy for a large number of cancer patients? For what types of cancer will vaccines be used? What problems will there be in getting approval for vaccines? Will vaccines be individually based, or can there be generic antigens that can be more universally applied? Why are the current antigens inadequate? What can be done to amplify antigens? How are vaccines to be delivered?

Endpoints In Cancer Clinical Research

Ever since the 1970s and the so-called 'war on cancer,' the research community has accepted tumor regression as the logical endpoint in clinical research. Published articles still measure the outcomes of therapy in terms of complete and partial responses. Furthermore, even the 'complete' responses are followed for a limited period of time, often as little as four weeks. If a week after that the tumor begins to progress, and the patient dies,

according to the clinical criteria that patient had a complete response. The evidence is becoming overwhelming that cancer is a series of clones with differing characteristics, and it is unlikely that any single agent is eliminating all the clones. It is becoming more apparent that cancer must be considered a chronic disease, for which the absence of progression and patient survival are more realistic goals. It is interesting to note that the FDA only relatively recently came to accept the concept of tumor regression as an acceptable endpoint. What will it take to get acceptance for non-progression survival? How will clinical trials have to change to prove efficacy under a new endpoint? Will this mean that clinical trials with non-progression survival can only be performed by the largest and wealthiest companies because of the longer time necessary to prove the endpoint? What regulatory issues will arise if new endpoints are established? What other issues will be created by changes in clinical endpoints?

Cancer Therapy – 10 Years From Now

At this time, chemotherapy is still the predominant form of cancer treatment (after surgery). The search for more targeted therapies has taken precedence over making incremental improvements in old therapies. Despite this move toward more targeted therapy, it is well established that monoclonal antibodies are not the ultimate anticancer drug. They are large, they do not necessarily penetrate beyond the periphery of a tumor, they may cause antigenicity problems, depending on how they were produced, and may fail based on patient characteristics. What monoclonal antibodies have done, very well, is identify targets. It is now clear that small molecules may be used to get to the same target without the attendant problems of monoclonal antibodies. Right now in clinical trials a number of new targets and technologies are being tested. These include angiogenesis antagonists, apoptosis agonists, cell cycle modulators, signal transduction modulators, and a number of kinase inhibitors. Most of these are not new; most have taken a long time to come into clinical trials. Finally, there is intensive ongoing research in vaccines.

Will the genome yield new drugs, or rather better targets for new drugs? Specifically, how will understanding the human genome affect drug discovery and development in cancer? While it is becoming ever more evident that there is no magic bullet in cancer treatment, and the word 'cure' is a non-sequitor, the dream of prevention persists. With a number of vaccine technologies in development, is cancer prevention a reality? Will cancer vaccines overcome the problems found in other types of cancer therapies? If we accept the premise that 'cure' is unlikely, and that cancer may have to be treated as a controllable chronic disease, what changes must we make in clinical trials and in regulatory requirements to accommodate the new paradigm of cancer therapy?

We asked experts at the cutting edge of the new technologies to offer their opinions on the issues presented by the new technologies, and to project what the changing cancer therapy field would look like in 10 years.

Results of Delphi Panel Interviews

Role of Genomics in Cancer Drug Development

What will be the major impact of the Human Genome Project on cancer therapy in the near term?

From a young researcher in the Genomics Department at a noted cancer research institute in New York City:

> *What we can do, and what the Genome Project is telling, is that there are pathways that are active in the disease that we can block. They're not the pathogenic reason for cancer, so if you block them, you're going to slow its growth, and the tumor will recur and then another pathway will be dominant and hopefully, you'll be able to block that too. So it's identifying the pathways and getting things to block the pathways that will be the future.*

A leading genomics investigator at a famous New England research institute added:

> *…there are at least two levels …where these genomics will be very valuable. One is a genetic characterization of the patient's cancer. Which pathways have been damaged, which ones have not been touched, and which ones are activated as compensatory pathways for either good or bad consequences? … based on that, the selection of one form of therapy or one agent over another will be much more rational and therefore more effective…. Then there is a second level, which is not about the disease itself, the cancer itself, but is about general features of the organism…how that would affect the efficacy of a drug. Clearly, drugs are to a large extent metabolized in the liver, eliminated through the kidney very often, and through the bile as well. There are differences therefore in the biodistribution, metabolism, availability of a drug that can be very different from one individual to another. We already have known this for many years. Hopefully, it will become easier and quicker to validate. And, it will permit better adjustment of the therapy. So with those two levels, the genomics can really have a big impact.*

How do you leverage the new information into useful drug therapy?

…genomics can accelerate the discovery of new targets, meaning just by virtue of being able to look at all these different genes that are either expressed normally or abnormally and in various situations… let's say that using these genomics techniques and taking these genomewide surveys, you're able to identify 10 or 12 new proteins that seem to be critical in the growth of colon cancer cells. What happens is that normally that work might have taken a decade or two, now it takes less than a year. And so the front end has been accelerated, but still what needs to be done is, on the back end, one needs to take each of those individual proteins and use sort of very classical techniques in order to find compounds that interfere with those proteins or enhance the reaction of those proteins that lead to a good therapeutic effect. There are large-scale efforts at doing that, but I'd say that the discovery of the information, the technology we have now to discover new genes is more advanced than the technology we have to discover new drugs.

What needs to be done to bring drug discovery up to the level of gene discovery?

…there are wonderful things happening in fields like combinatorial chemistry, which allows one to discover new compounds by the legion; and so the marriage of the two, the marriage of genomics and combinatorial chemistry for example, and high-throughput screening is going to be very fruitful. But I think right now a lot of those things are still on the drawing board. They're getting off the drawing board. If you talk to people in the know, experiments are going on right now, but …I think it's going to be a year or two before we see the first things falling out of that. Then, after you discover a target and you develop some type of drug that you think interferes with the protein or DNA or whatever, then it's a whole different ball of wax to actually come up with a therapeutically useful drug in the clinic.

What is the impact of the Human Genome Project on the future direction of prostate cancer therapy?

A medical director of prostate cancer research at a famous East Coast prostate cancer lab stated:

I think the Genome Project is going to help identify those targets and whether it's again vaccines or other kinds of therapies. I think as soon as we can really utilize the information from the Genome Project…that's one of the things that isn't out there yet. We still haven't figured out the best way of utilizing all that information or understanding it, but as soon as we can, then I think that's going to really drive a lot of this targeted therapy. And I think a lot of us do have prevention in our minds and that's definitely my goal in life…if I could help to push the field toward prevention, I would be extremely excited because putting myself or family members in that situation, I definitely want to know that there are ways of preventing these diseases.

A research director at a West Coast cancer institute told:

We're the first group actually using the Human Genome in prostate and it just blows you away. The power is staggering… in terms of identifying targets, risk prognostication, pathways that are active in the disease. I mean, what we've learned in the past 4 months has been staggering. The therapy is based on the Genome in the next year, for clinical trials. In terms of regulatory issues, gene therapy is going to have no role. I mean, most of these drugs are going to be small molecules or antibodies…it's just that identifying the targets is what this Genome Project will do.

The chief of medicine at a major Western cancer center said about the impact of the Project on choosing targets:

I would think there would be, yes. It's just hard to imagine it wouldn't as they understand more and more what the key molecules are in the malignant process. Whether it's p53 and some of the others, whether it needs to be a genetic manipulation is less clear to me than knowing the importance of the target and the proteins. For example, p53 may be just using the p53 protein in terms of therapeutic agents. But I think it definitely will…it's an example of helping to identify new, good targets other than what mice thought looked like good targets.

A researcher at a New England university research institute expressed his thoughts on the impact of the Genome Project:

I think it will impact cancer therapy in two broad ways: one is, I think it's going to accelerate and improve our ability to discover new targets for therapy. That's going to be the thing that makes an impact the quickest. That's a very long process and one of the things that…people will be able to do this, particularly to identify new targets, but in the beginning, genomics research and genomic techniques will not allow [us] to get to a drug faster. The second thing that it will do, and this will take more time, is ultimately it will allow people to develop drugs more quickly because we'll know a lot more about

the science, but genomics can also be used to assess response of different cells in cancers to the particular therapies. So that will help aid in increasing the speed at which new therapeutics are developed.

How close are we to seeing a drug for cancer, say in the next 5 to 10 years, that is derived from genomic research?

The CEO of a biotech company remarked:

*Well, if you're **Human Genome Sciences (Rockville, MD)**, you would say within the next 5 years absolutely, from HGS. If you were **Millennium (Cambridge, MA)**, you would say absolutely in the next 5 to 10 years. As HGS from their approach, they have…I'm sure it's on their web site, but somewhere in the range of three to five targets that they're taking forward, that are in the clinic, that they would argue are genomically derived. Millennium has one target in their Bayer collaboration that Bayer has accepted as a small-molecule target, which is in development. So, they would argue that's from a genomics approach. And then operations such as ours are heading to the clinic in the next 1 to 2 years, which means actually out there in the 5- to 10-year time frame. But these companies that are focusing on using highly parallel approaches to discovery are definitely doing that. They're making discoveries and pushing them forward, so the time is now…it's happening. So it's not just a promise. Certainly it's not the promise of genomics, it's a reality. That was the design and aim [of the Human Genome Project], to accelerate the discovery process, to take away from the one gene, one molecule approach. As these genomic approaches have converged and integrated multiple independent but complementary technologies, it really has achieved the goal of casting a broad net and being able to focus on what's really important in managing disease.*

A leading cancer research investigator suggested:

I think that …[the ability to identify new targets]… is realizable in the foreseeable future… which is also better because it doesn't carry with it so much in the way of ethical considerations…in the sense that, if you're diagnosed with cancer and you can use genomics and functional genomics, and proteomics to determine what are the particular targets of your cancer that will make it more susceptible to particular drugs, I don't think there's much in the way of ethical decision making about doing such things.

A well-known researcher said:

I'd be surprised if we're using it in anything other than experimental protocol settings for at least 10 years. It's just going to take that long to prove that it works, validate that it's better than what we have. And to get the technology out there to enough places where they can do it. I mean, 10 years I think would be an optimistic estimate.

What ethical issues may be raised by the Human Genome Project in cancer therapy?

An East Coast university hospital department head said:

The… issue of using genomics research to determine whether someone has an innate sensitivity or risk for cancer carries with it a lot of ethical issues that need to be addressed before any of that moves forward. For example, the implications of screening someone in their 20s for susceptibility to cancers that may not develop for 30 to 40 years, is huge because it depends on where that information is to go. Would that affect someone's ability to get health insurance, for example. Would it change someone's ability to get a job if their prospective employers had access to the information? And this would be particularly important in diseases where we don't have very good therapies or if there are not preventative protocols in place that have been shown to be effective. So I think that that's a lot more problematic in terms of ethic issues and I wouldn't want to see it proceed forward until all of those things are addressed. I mean, we have a similar problem right now in people looking for BRCA1, BRCA2, and all those issues. It causes quite a bit of concern among patients and families and physicians, and then the whole issue of…if your sister is diagnosed with breast cancer, do you need to be tested? I mean, there are a lot of issues there… we're a long ways away from solving those issues as a society.

Cancer Vaccines: Dream or Reality – Elite Cancer Treatment or Global Cancer Preventive

Would you be kind enough to start out by giving a brief description of what a cancer vaccine does?

A pioneering cancer vaccine researcher from a Midwest cancer center stated:

…The whole immunization procedure, using preventive materials for viruses, became known as vaccination. And it was extended to cancer because people were being immunized, but up till now, people who have the cancer are the ones who have gotten the treatment, so it's not a preventive. Now, there are situations where it does prevent the disease from coming back, so instead of just treating obvious tumor masses and making them shrink, that's where we started out…we've moved further and

further forward…or backwards, depending on how you look at it, in the disease, closer to the beginning of the disease…. There are trials that have been done in patients who have no apparent disease…they have had melanoma, at least that's where it's been used mostly, and they're using it now also in breast cancer…where they have disease that is not apparent, where it's either gone away after other therapy or it hasn't reappeared after surgery. And then the vaccine is given, and the time to reoccurrence of disease is measured. And vaccines have been effective in those circumstances too.

Can there be a preventive cancer vaccine?

The cancer vaccine researcher continued:

…in a sense a preventive use of it…prevent it from coming back…prevention of recurrence. Now, we do want, and this takes it full circle…we do want to use it as a preventive eventually. I've always talked about it, even from the beginning, even when I was forced to use it in people with advanced disease. I've talked about it as a preventive measure, to prevent the cancer from occurring in the first place. And I think we're closer to that than we have been in any time in the past because we now know a lot more about the materials, the chemical materials, that can immunize people with these various cancers. So we don't have to use tumor-derived materials anymore, which is always the big stumbling block. You can't really, ethically, even though I don't think it would cause any problems, but it always gives people pause to think that they might use cancer-derived materials in people who don't have a cancer. So that's always been the psychological stumbling block and I would imagine that the FDA would probably not pass it actually, I don't know. But it would be much easier if we could say, this chemical, which has nothing to do with a cancer cell except that it happens to be on a cancer cell, but was chemically made, synthesized…this chemical could be used to prevent the cancer.

Are you talking about a specific antigen?

Yes, a specific antigen. So I mean, things like…there are known proteins now and protein fragments, peptides that are immunogenic. They are not perfected…they really are not as immunostimulatory as whole-cell vaccines are, so the task really is now to define materials that work as well as the whole cell. There are people at high risk of getting a disease and that's been known. If you take a specific incidence…let's say, in breast cancer. In women who have a very strong family history, mother, sisters, all have breast cancer…we know that their chance of getting breast cancer is exceedingly high, much higher than usual…those people would be a candidate. And there are women who don't have a strong family history but already have had a history of atypia in a biopsy.

Or maybe have the presence of BRCA1 or one of the immunomodulators?

The SA1 gene, they could even have had carcinoma in situ, which is not quite a cancer, you know. These are all people who would be candidates for it.

How far down the road would you say that a true vaccine of this type would be readily available?

Oh, it's actually very close. I would say very close. The stumbling block is really not the availability of antigen, but the availability of good enough antigen, strong enough ones. But there are so many people in this field now that I very confidently say that it's within 5 to 6 years. Because there are so many people who are now involved in this kind of research and it's moving so rapidly, that I would imagine that it's going to be no more than that, before we have at least the beginning of trials with it. I'm not sure it would be available widespread in public, but there will be clinical trials with materials that are strong enough, so they have a hope of being prevented. There are trials right now, for example, with Theratope, which is a kind of breast cancer vaccine. It's not a very strong material; it generates only antibodies, but there is some evidence that it prevents the progression of disease in advanced breast cancer. It's now being used to try to prevent reoccurrence of disease after you get rid of the disease with chemotherapy...when you reduce it to microscopic disease. That's the beginning of it. There are some vaccines being tested, but I think we have to get stronger materials.

…but if these things become cheap, it could be a public health [program]. But I think if it's a chemical and the price can come down, then everyone can get it. Any woman can get it. And I think something like that will eventually become widespread. I can't see that it's going to be a big issue in a few years.

Have we arrived at the point where we know what kinds of antigens to use in a vaccine?

The inventor of a cancer vaccine theorized:

There's a short list of about seven to eight different things and none of them is very strong as an antigen. And even with telomerase, this universal antigen, that's not a very

strong antigen either, it's just universal. Well, there are several candidates now for universal antigens that are stronger than telomerase and stronger than the other ones I think - one we just described is called MG-50. And ones that I'm trying to get at with my colleague where we purposely look for things that are stronger than the natural ones. You can actually screen libraries of peptides – 9-amino acid or 10-amino acid peptides. And you can find out ones that are stronger than the natural. What you screen them with is T-cells…T-cells that are immunized by the natural materials. And then you screen for the stronger antigens with the T-cells. Now, that gives a hope anyway, of getting stronger antigens and discovering them. The other way is looking for brand-new antigens by this new genomic technique – microarrays. So I think there are a number of different strategies that can be applied to look for better antigens than nature gives . So all of these things are happening at the same time. We know how to immunize T-cells and test for whether something is an antigen. We know several different ways of screening genes and proteins and other things…to look for new materials, new antigens, or stronger antigens that mimic the natural antigens, things like that. So these are all happening at once. I think that's going to lead to chemically defined vaccines that really work.

Would there be a necessity, then, for those women, if we're talking about breast cancer, who have some polymorphism, to apply pharmacogenomics and have a virtually customized vaccine?

A cancer vaccine pioneer stated:

Oh yes. That's true, that could possibly happen. My strategy has always been to get something that's universally applicable, something you take off a shelf and give to anyone. That's my approach. Now, the other approach is exactly what you're saying…get customized materials. You see exactly what antigens people have in their body and you make them something that's stronger than what they have or boost the reactivity to what they have. There are a lot of ways of doing it. But that's more of a boutique approach. It depends. Both can work, it's just that my own preference has been for public health.

Why haven't the customized vaccines been successful so far?

From the researcher spearheading antigen amplification techniques:

If you use a patient's own materials, then you have two strikes against you. One is, if the material does resemble self and it very closely resembles a self of a person that you're immunizing. I mean, if you gave it to someone else, it might be a little more different and might have more of a chance of being not self. At least, you're taking these materials from whole cells and you end up as they did with lysates or something like that…then you would at least have some foreign substances in there, the different HLA antigens. There's a chance that the body could perceive those as being different from self. And I think you do need that. You do need some perception that what the body is receiving is different from self, that you make a response to it. So the dendritic cells may be the vehicle that we use eventually, but the materials that are being put in them so far are not very immunogenic. The peptides aren't; individual peptides certainly aren't. They're finally getting to cocktails of peptides, which may be a little bit better, but the peptides themselves are not very good. I mean, MUC-1 is not too terrifically strong. Even the melanoma peptides are OK, but they're not generating much of a response, so I think something more has to be done than just using what nature gives, so we have to go on a search for new antigens that are better than the ones that are found. They actually may be found in tumors, but they may turn out to be stronger than the ones we've already discovered. And I think we do have to have a purposeful search for those that are stronger.

Most people are not familiar with dendritic cells. If you wouldn't mind just giving a basic definition of what this therapy is going to be like, what it would involve?

From the East Coast researcher investigating advanced customized vaccines delivered by dendritic cells:

This is a customized form of cell therapy where the procedure is to isolate or generate so-called dendritic cells from every patient, load them with tumor antigen, and then infuse them back into patients with the expectation that that would potentiate antitumor-specific immune response and will lead to the eradication or containment of the tumor in the patient. The antigens would come directly from the tumor cells of the patient. There are two strategies: one of them is that you isolate antigen from the tumor cells of every patient and that strategy is based on the assumption that the important and powerful antigens are unique to each patient. And the second strategy, which is technologically simple but maybe less effective, is to use tumor antigen that had been characterized and shared among many cancer patients, so you can generate them in the lab and treat many patients with it. But they're all antigens that are present in tumor cells and the notion is that you induce an immune response against those antigens, and the immune response will now recognize all the tumor cells expressing or presenting those antigens.

If the patient's tumor has its own unique antigens, why doesn't the immune system recognize that it's not 'self'?

A leading vaccine investigator explained:

> *… the basic underlying fact for that explanation stems from the recognition that tumor cells are inherently genetically unstable, and what it means is, while the tumor is growing and progressing, it undergoes changes, many of them random, because of breakdown of regulation of the faithfulness of the genome and so forth. That generates changes in the normal constituents of the tumor, the proteins. And that generates a new antigen, because that will be seen as foreign by the immune system.*

In contrast, an expert in genomics research told us:

> *Cancer cell antigens are very similar to normal cell antigens, if they weren't, they'd be recognized as 'not self.' So the difficulty is that the cancer cell antigen is not different enough to trigger an immune response. So the antigens being tested in vaccines, tend to be weak antigens at best. A number of labs are working to modify or amplify these antigens, and in some cases synthetic antigens may be used to elicit an immune response.*

How can you optimize the vaccination?

A leading expert in dendritic cell research said:

> *…the importance of a vaccination is the combination of the potency of the antigen and the effectiveness of the vaccination and one can offset the other. Can you imagine a situation that the antigen is less than most powerful, but you offset its weakness by improving the vaccination and vice versa …one of the methods incidentally is by using dendritic cells. That's only one of the methods. The notion behind using dendritic cells is that they provide a more powerful vehicle to activate the immune system, and that's actually the big interest in that particular strategy; that's why it's so popular. The dendritic cells have been designed by nature to present antigens to the immune system in a proper and optimal fashion. That is, the immune system does not react necessarily to the presence of a foreign antigen or virus. But it reacts to the foreign antigen only if that antigen is transferred from the virus or from the tumor cell to the dendritic cell. Actually we call it the professional antigen-presenting cell.*

A cancer vaccine researcher at an East Coast university cancer center said:

> *That goes back to a lot of animal work that we and others have done…in our case, we were trying to insert proteins called cytokines that are normally expressed by immune cells in the body in response to infection and they're the proteins that provide the cross talk between immune cells and get the whole activation cascade going to recognize something new that's invaded. Well, we figured, if that works for infection, then why not try this in cancer. So we took cancer cells and we inserted genes for one whole panel of these proteins because at the time, about 10 years ago, we didn't know which ones would be most important. And in our mouse modeling of this, one came out on top and that was granulocyte-macrophage colony-stimulating factor. The acronym is GMCSF. So, about the same time we identified this protein…several people … had found that this was an important protein for growing in culture dishes, what we think now is the most potent professional antigen-presenting cell, the pivotal cell in the body, the pivotal immune cell in the body that is responsible for initially recognizing this danger, this new change or invader, and then causing the cascade of events that will result in a sufficient immune response to get rid of it.*

Does this mean that the customized dendritic cell approach to vaccination is the best approach?

From a leader in the field of pancreas and breast cancer vaccine therapy:

> *…we don't do that. We don't do that because we're not sure what in pancreas or breast cancer is most important for the dendritic cells to take up and utilize as a signal to the rest of the immune system. So, what we do is, we put GMCSF in the original tumor cell so we're starting one stage earlier. And then we're using the tumor cell irradiated, making GMCSF, putting it under the skin, intradermal injections, and then we let the tumor cell, through GMCSF, attract the dendritic cells and let them pick out what's important. So, we're kind of a step earlier. So that other method is a good one if, in fact, you know what it is you're trying to target. But we're being unbiased about this and saying, we're not as smart as the dendritic cell, let the dendritic cell do the work.*

What would be the cost of dendritic cell therapy?

A pioneer researcher in dendritic cell therapy postulated:

> *If the dendritic cell approach would prove to be the most or only efficacious intervention in cancer, which is a big 'if', then it will carry with itself the complexity and cost due to the fact that it's a customized therapy. And the complexity stems from two things: one, it's customized, you have to do it for every patient, and it's somewhat complex because it involves dealing with the cells of the patient outside the*

body and then putting them back. So that runs on the realm of the term 'cellular' therapy. It's kind of like genetic therapy. That adds complexity because you need a certain set of facilities to do that, you need trained personnel, and it adds costs. And there is no question it's a limitation from the point of view of accessibility to the patient population largely other than in developed countries that can afford that. So, let me just put it a little bit in context. First of all, the cost that is of a concern to many people…the expected cost of such a treatment would be comparable but actually much less than the cost that we're now accustomed to use for chemotherapy because the cost of the treatment that is now predicted would be comparable to a chemo treatment, except that it will probably not be accompanied by adverse effect toxicities which double and triple the real cost of chemotherapy.

So at this point, it will never be…if we have to go this route…the equivalent of taking pills or injection that you can distribute all over the world, and it will not cost pennies…once perfected, it will probably cost in the range of hundreds to a few thousands of dollars today. If that treatment will be effective in the next 2 to 3 years, the third generation of treatment will cost in the range of tens of thousands of dollars, which are associated with chemo after all…but tens of thousands of dollars is very expensive in many areas of this world. So that's the downside of that.

Is it possible to take something like dendritic therapy earlier in the course of a disease? Would it be possible then to take the therapy to the point where, even if there is no overt disease, that it might be used as almost a preventive measure?

A leading researcher in vaccine therapy remarked:

It absolutely is and that would happen after the technology has proven itself on the cancer patients themselves and taken into the so-called prophylactic area. That's a viable possibility. My bias is toward something that is going to be more generalizable and in fact, our approach currently is more generalizable than it was 10 years ago, where we had to take each tumor cell from each individual patient. Now, we actually, based on the hypothesis that these dendritic cells can come in and pick out the proteins, they don't need to be compatible with the tumor cells, so they don't need to be of the same patient with the tumor cell. So we've been actually using lines of the same type of cancer because we know that the antigen is going to be similar for the same type of cancer. So ours is already something that's in the freezer for any patient with pancreas cancer, as long as they fit the type of criteria, stage of disease that we're looking for, etc. So right now, I don't have to say to each patient, it depends on whether I can make a vaccine out of your tumor or not. The goal long term is to figure out what it is, what proteins are specifically in those tumor cells that the immune system sees…if we can figure that out…then the potential is to be able to provide it even more widespread and more easily as a recombinant vaccine. Ideally, if some of these proteins are early changes, …I think we have a vaccine we can test in you and then see if it works and pray that that's going to be one way of trying to combat at least cancers that are genetic …genetically linked…

But getting a vaccine into essentially a public health setting is probably not unrealistic. I mean, we do it in other disease states and the infrastructure is basically there… you're going to have to apply it to oncology.

From the vice president of research at an East Coast consulting and venture capital company:

It doesn't bother me that there are small foci of vaccine development. That's true of any drug and in an early stage of development, you're going to go to thought leaders and clinical experts that are going to be able not only to help you design and conduct your trials, but will have the patients available for those trials. That's going to be centers of excellence around the country and it's going to be fairly focal. That will expand, of course, as drug development expands, because you get into situations where you just need more patients and you need more exposure and you need to cover and quite frankly we always looked at covering not only thought leaders but geography to make sure that we were recruiting optimally. But getting a vaccine into essentially a public health setting is probably not unrealistic. I mean, we do it in other disease states and the infrastructure is basically there…you're going to have to apply it to oncology. But I really don't see anything on the horizon that's going to allow to vaccinate the general population against some form of cancer. I think it's still going to be for the most part… you're going to deal with high-risk individuals in any particular type of disease…. Now, are you talking about autologous vaccines where you'd have to take them into the lab, grow up the cells, and then go back? Because I really think that's a significant limitation….The whole idea of having to have a central lab where you can go and

grow these things up and ship them back, that's really a very negative aspect of the thing as far as my evaluation goes. I hadn't been terribly enthused about that. It's not going to happen in the next 5 years, but what we'll do is we'll address, …right now the situation probably most of these vaccines will go to is minimal residual disease and keep pushing that to the point of not just active vaccines but passive vaccines. And that is the hook. There are many large pharma efforts that are investing their time and resources into these strategies that will pay off 10 years from now if not 20….

A West Coast medical director of prostate cancer researcher summed it up by saying:

I wish vaccines would work, but there is no data at all that there is any benefit. The trials to date have yet to show anything and I don't see much in the pipeline that has that much benefit. I'm unfortunately not very excited about it. The reason is that tumors downregulate their class 1 and class 2 antigens, so no matter what you do, you're not going to get a good immune response against tumors.

The Need for New Endpoints

There seems to be a split in the medical community in terms of measuring endpoints in clinical trials, from the older system that looks at tumor regression to the view of cancer being considered more of a controllable chronic disease where non-progression survival seems to be an endpoint. What do you view as appropriate and realistic endpoints in clinical trials? ODAC (Oncologic Drugs Advisory Committee) **recently made some comment about not accepting non-progression survival as an endpoint, they're still looking at tumor regression as the acceptable endpoint.**

*No, I think you have to take it on a case-by-case and disease-specific basis. It's very hard to generalize. And I think what you're going to see more is, they're kind of having these consensus trials. Now, take an area like prostate cancer. Well, the new trend in prostate cancer is getting all the data together to show to the FDA that PSA (prostate-specific antigen) is a valid endpoint and that data is being gathered now, the statistical analysis is being done from the RTOG (*Radiation Therapy Oncology Group*) data and I think that will be very beneficial. And then during novel clinical trial designs, to show that there is benefit to a drug, even if it is not just disease regression. I don't think ODAC is going to be short sighted…I think you have to take it on a case-by-case basis. And if the mechanism clearly shows that it puts cells in a G1 arrest, you're not going to expect marked tumor regression in that patient. But it may be normally clinically beneficial to the patient …quality of life is always a funny term. It's certainly hard to quantify. Yes, something that lends to a patient's life and makes it better I think is going to be an important endpoint in clinical trials in the future. I think you know now, that when I talk to a patient, it's very different from a year ago. Now, what I say is, I want to give you the least invasive therapy possible, the least aggressive therapy, because the magic bullets are close. ZD-1839 just finished phase III clinical trials. It's a hell of a drug. These things are there, so it's different. I would have said something different a year ago, like, let's be aggressive and try to get that tumor under control. It's now, let's give you as least as possible because the magic bullets…I can smell 'em.*

A clinician and researcher weighed in with:

You know, I think it's that you can't be afraid of the disease. Historically, with prostate cancer, there have been very few drugs developed. Six years ago, the NCI (National Cancer Institute) budget for all of prostate cancer was probably less than $20 million. And part of the reason is in breast cancer, I give Taxol, the lesion shrinks 4 cm to 2 cm; therefore I had a PR [partial response]. But you can't do that in prostate cancer, so I think a little bit has to be to think creatively and now that we have drugs that attack the molecular mechanism, we have to be able to use these surrogates to validate the drug working in patients. So in prostate cancer, take it seriously and treat it as a chronic disease. Don't jump the gun. The key is, you need an arsenal for the long term to fight a disease…you don't want to use all that arsenal at once. Spread it out as long as you can because the hope is that what's here today will last you a few years and then something magic in the pipeline will come 2 years later.

The director of research at a biotech company reported his experience:

So one of the key things I think for companies is to strategically say: in what tumor type can I expeditiously get this study done and probably get an approval, but then also somehow have the resources to begin the battle upstream to broaden the market. I think that's the real challenge with it. And it would probably take a lot of discussion with the FDA to convince them…here's an agent we want to do broadly. I think right now they'd say you have to do it in multiple diseases. Maybe they can be re-educated about this, but once they become entrenched in something, it takes quite a while to get them back out of it. The FDA, after years not embracing that [tumor regression], finally embraced it and has become fairly

tightly wedded to it. I think response…what they like about response is the idea that you're somehow measuring something…what I don't like about it is the reliability to be able to measure what you're trying to measure. And there are all sorts of problems with that…

…I think the best endpoint in studies is really progression-free survival rather than tumor response, and I think that overall survival is not a good one because we have too many different treatments now that may be the explanation for what happens or interfere with an impact, whereas, if you start with patients at a point of time and say, here's where your tumor is, here's what you're measuring to call tumor progression…you can measure regression at the same time, but understand that there are all sorts of confounding factors that limit our ability to accurately interpret that and that it probably is easier to measure disease progression than regression, and then you define that as your endpoint, and use that as a curve for a population. I think response still has its uses…as much as I've not liked responses, you have to admit, when you go back into studies, it does give you at least some way to relatively validate that you're having an active fact.

Several researchers and clinicians commented similarly to the scientific officer of a biotech company:

I love the study where gemcitabine got approved in pancreatic cancer in at least one of the trials that I saw, where there were essentially no responses in either arm in the particular study I'm thinking of, but there was a 13% progression-free survival rate a few months later in the 5-FU arm, but a 34% progression-free survival rate with gemcitabine. So actually in terms of controlling disease for a period of time, it looked like it was about three times as effective.

Last year, I think it was, the ODAC actually convened a meeting of your traditional chemo doctors and they very vociferously reaffirmed disease regression and overall survival and attacked progression-free survival, but I think the logic of it is so solid…how can you hold to an overall survival when you're going to do treatment to A, B, C, and D afterwards…so, this doesn't make sense. And response in and of itself, the FDA I don't think responds itself. There are some situations they will accept it, but they still want to see a durability of the response anyway. I think that over time, that will be eroded down, but I was really surprised at how ODAC came out and specifically said, now, we still don't like this idea of progression-free survival. Now, having said that, most of the studies that people send to the FDA…there certainly are an increasing number of studies where the major endpoint is the progression-free survival or event-free survival and I think that increasingly is the best test.

Now, you take something like follicular lymphoma, with a variable history…there, something like response rate and just saying, here's something that's active and we need another agent that's active and that's basically the argument that got Rituxan approved. So I think you still have all those endpoints to deal with and at least progression-free is a shorter one than overall survival. But there are some situations I think where you really do need survival or potentially some other intermediate endpoint and the problem is how you validate how that intermediate endpoint relates to the major endpoints of progression-free or overall survival. That's where things I think are still in a muddle.

From a leader in cancer vaccine research:

…think that everyone just about will agree with the statement that all we want is to feel good and to be healthy and to be able to go about doing our things. I couldn't care less and I don't think anyone could care if they are full of tumors as long as that tumor doesn't impact on your quality of life. The issue is … how you evaluate the effectiveness of the treatment and what's called clinical endpoint. There is a debate on that so that's a tough issue and it's a hotly debated issue: how you measure effectiveness of a new treatment. People used to measure effectiveness of a new treatment by asking the question, have I caused a regression of a tumor, or looking literally at the size and there are increasing incidents. Now, from the point of view of a patient, I wouldn't care about the size of the tumor… what we care about is, what is our quality of life and how long will we live? So if the tumor regresses quickly but it doesn't impact on our quality of life and we will die at the same rate as an untreated patient who has a big tumor, I couldn't care less if that treatment has reduced the tumor or not. So in many instances, there doesn't seem to be a correlation between impacting on the size of a measurable tumor and the quality of life or the survival of the patient. And that's simply reflecting the fact that what impacts on the survival of a patient is not the size of the tumor that you measure but some other hidden metastases that we don't see, where the treatment does not impact.

A West Coast cancer center research director stated:

I mean, survival is still the gold standard. And particularly disease-free survival and you know, you get into a situation again where you're talking generalities and if I were looking at something where we have a lot of

success like, for instance…I suppose in breast cancer…we're making some pretty good strides. There's some difficulty there with saying, well, stable disease for ten years is going to be OK. On the other hand, I think we would think it a significant milestone if we could find a drug that would produce stable disease in lung cancer. We're not even close there and it's still the major problem. I mean, self-created mostly by lifestyle and smoking but we're having a major impact on cancer-related mortality outside of that area. But certainly that's a major unmet medical need.

From an East Coast clinician utilizing vaccine therapy:

Well, originally I treated over a period of about 6 weeks and during that time or just after that time, I evaluate. So after about 8 weeks I was able to look at those patients to see whether they had gotten a response. Now eventually what I did was to say, if they got a shrinkage of disease or if the disease was at least stable, I would continue on with monthly injection…. Indefinitely, as long as the disease did not grow. Now, if the disease grew, then I'd stop because I had lost. If the disease stayed the same size or shrank, then I knew I was winning, so I continued. Now, what usually happens was, I get shrinkage. In some cases, I got no growth and the no growth lasted for years and both of those I think were equally useful to the patient, because if there is no growth of disease that wasn't huge to begin with, and the patient stayed alive, then they're happy. They're alive and they have no symptoms. At first I wasn't willing to accept that, because that wasn't shrinkage and shrinkage is what is demanded by chemotherapy criteria. But the best bottom line is survival, and if you get no change in the tumor, and the patient is alive 10 years later, that's a response. By the same token if you get 100% shrinkage that lasts 4 weeks, that's not a response. See? They call that a complete remission in chemotherapy. It goes away and stays away for 4 weeks. That's it! Four weeks! Now, if it comes back on the fifth and the patient died on the sixth week, then that's on paper a complete remission…response rate is raised by that percentage made by that patient. That's ridiculous. It's clearly ridiculous and what the patient wants is to live, and if a patient's disease does not change one iota over several years, that patient has responded. And of course, I prefer if the disease shrinks and goes away and everyone accepts that as a response…

…I think that the patients eventually can be cured. I hope I haven't spoken out of turn, but this one patient is coming to see me next week, but he's not the only one. I have had several people where I used a different vaccine that a company was making and we ran out of vaccine after a few years. I treated this patient and she went on for seven years and we had to stop treatment because the company decided they weren't going to pursue this vaccine. She was one of the few people who had a great response and it wasn't financially to their interest. So we ran out of vaccine and she's been fine since then. Now, that's been about five to six years more.

A leading researcher in prostate cancer expressed her opinion as follows:

I'm part of that bias, that I think we do have to rethink. I think cancer is not one disease and is lots of different diseases, and patients complicate it more because every patient responds differently. So I think that if our goals are cure and we give up on those patients who show some response, we can keep going longer with a good quality of life, and that's key, a good quality of life. I think that's important because I think AIDS is the best example. AIDS used to be a deadly disease…you'd get the diagnosis and you were dead within 2 years. It's a chronic disease...we have several good therapies for it, with people living good lives with it. It's not perfect, but people are living and they're living functioning lives. So, if we could do that with some of these cancers, like pancreas cancer where 30,000 get it a year and 30,000 die of it a year…I'll tell you…my patients would be happy to hear I've made it a chronic disease …it's interesting, because pancreas cancer is probably one of the only cancers for which the only approved drug is approved, not based on prolongation of life, but on improvement in quality of life. The only hope that I can give my patients is that, look, you take this experimental therapy or that experimental therapy that gives you a few more months…it's the next chance or the next new therapy that may be available.

I think it's important to understand that we don't know a lot yet about whether these new approaches are going to have a role in treatment and I don't think people should be misguided and think that they are the next answer to cancer. I think, if anything, they are going to fall into the group of prolonging life a while, helping to make it a chronic disease. Controlling…I think that's a good word…controlling the disease. But I think that patients should be encouraged to enroll in studies because, so far at least, it's turning out to be a relatively safe therapy without many of the toxicities that we typically think of for cancer-oriented therapies. So the more we can learn about them, the faster we can make them better. So I try to encourage people to be willing to consider them. Now, to be honest with you, it hasn't been hard in the cancers I deal

with because there aren't a lot of options, but I do hope that people realize the best we can do is to do it in association with studies where we can really learn as much as we can.

From the CEO of a cancer venture capital company:

This is an enormous, enormous issue confronting the whole field. I think that I would encourage you, in doing your analysis, to talk to the FDA …and the ODAC reviewers. It's very frustrating in these companies in that clearly, there is a huge medical need as more and more of the developed world gets into the age bracket where cancer is an issue. There is an awareness that there are new and more selective modalities being developed, so clearly the issue of surrogate markers is making a huge impact in how we think about the time frames and the commercialization. We would not, for example, invest in a company trying to go after, as their only business model, a first-line therapy for breast cancer, because that will require 10-year survival studies. On the other hand, someone who has a treatment for very rare blood cell cancer…[such as] Cell Therapeutics, just got arsenic trioxide approved for an extremely rare indication which is the acute promyelocytic leukemia, which affects a handful of people in the US. But that was the right way to get approval from the FDA, because the APL patients who had relapsed after prior therapy had failed have basically no options. So they could do pivotal trials on a fairly small number of patients and basically show a high rate of complete remission in patients for which there were no options. So the intermediate point between taking very narrow, very difficult-to-treat indications, which is where most biotech companies go today, and the 10-year survival studies, would be to have believable surrogate markers such as the tumor markers, or a biochemical marker. I mean, the frustrating thing has been that PSA, for example, is now so broadly used that there are on the order of 15 million per year who get the PSA test. Since it became broadly available, it is the gold standard at the urology office for getting an indication of whether a patient is at risk for prostate cancer. But the FDA has shown in their guidance that they do not believe that PSA is an adequate surrogate marker for prostate cancer. So lowering PSA (statistically significant numbers) in a prostate cancer trial would not be sufficient for product approval.

From a researcher at a university-based cancer center in New England:

Well, I think ultimately the goal is cure, in every sense. That's not always achievable yet, unfortunately. So that's why the secondary endpoint of disease stabilization and quality of life has become an important surrogate for that. Now, I'm not sure that I agree with the statement that it's not accepted because, in fact, there are many drugs…in fact, most of the drugs we use for adult cancer treatment… that are approved for the use of stabilization of disease or partial lengthening of life, of disease-free interval, in patients with metastatic cancers. There are many many drugs that come to mind in terms of breast cancer, lung cancer, pretty much any solid tumor. There are many drugs that are clearly not curative in lymphoma and leukemia, but are proven for those purposes. And then there are even drugs that were approved for quality of life and the drug that comes to mind is gemcitabine in pancreatic cancer, which was proven not necessarily to have a survival advantage, but to have a quality-of-life advantage over other therapies. I think there is already a movement afoot to accept these things. I think that patients accept them as something that will allow them to live longer. I think they all hope that they will be cured by it and that if they're not cured by it, that it allows them to live long enough so that if a cure comes up in the time that they gain by having these drugs, that the drugs helped get them there. So I think that that's moving forward. I think that we shouldn't fool ourselves and say that that is equivalent to a cure, because it clearly isn't.

Cancer Therapy 10 Years from Now

From an East Coast genomics researcher:

I think 5 to 10 years from now, I really believe that what we're going to be doing is, and I'm talking both on a research and a clinical level, I really believe we're going to be telling people…when people are diagnosed with cancer, they're going to be given a diagnosis which is very specific to their particular type of cancer as opposed to a generic term. And what I mean by that is, we know that cancer is a disease of genes sometime during life. In the process, what happens is that certain normal physiological pathways that allow for cell growth, division, survival and so forth, are usurped and they're corrupted. That's what leads to malignancy. So, we know that there are aberrant pathways that are operational in all types of cancers, we just don't know exactly what those pathways are. As we identify them in a systematic way using genomics and gene expression profiling and so forth, what we're going to be able to do is now say, instead of Ms Smith, you have breast cancer…we're going to say, Ms Smith, you have cancer, which involves disregulation of pathways A, B, C, and Q, and because of that, what we're going to do is, we have a drug that targets pathway A and we're going to give it to you. So sort of rational therapy based on genetic phenotyping of tumors as opposed to just sort of empiric therapy based on histopathological classification of tumors.

From an expert in prostate cancer:

I think that even the non-vaccine people…I think everyone is thinking about targeted responses and I think even for chemotherapy or other biologic type therapies, such as you hear about antiangiogenesis and apoptosis therapies…these are all going to be targeted…we need to know what it is that's different in the cancer cell that can be specifically targeted and therefore, hopefully, we will really decrease the chances of causing significant side effects. In addition, I think that many people are moving toward this concept of trying to make cancer a chronic illness, so I think we will change our measurements and more things will get approved based on that. I think there's been a precedent and I think that will continue.

I don't think there are going to be these single magic bullets that take care of every disease; I think that in part because of the regulatory paradigm right now and as much as anything, we're just going to keep improving individual tumor types in different ways.

From a West Coast cancer center:

Well, I'd like to see systemic therapy change by going more and more to these targeted molecules and at a faster rate than what is happening. The major obstacle to that is the reimbursement system in the country, specifically HCFA (Health Care Financing Administration), and then following their lead, the insurance industry and then behind that, the whole economy of medical oncology and hematology that's built around the administration of those chemotherapies. And I think the physicians…I think Rituxan is a good example. I mean, physicians who have used it are very pleased with it, the only thing that limits their use of it is really the reimbursement issues. I think the same thing would be true of Herceptin. I think the biggest difficulty Herceptin has…I mean, I don't think it works as well as Rituxin…I think it's an effective agent in the right patient…it makes the oncologist have to think about who he gives it to and who he doesn't give it to, but also because breast cancer is a much more common disease, that carriers are more up in arms about trying to block its use, than they have been with Rituxan. I think that is going to happen. I don't think it's going to happen as fast as it should have, but I think that as long as the capitalization is there for the biotech companies to get the trials done to show the effects, I think there will be other agents that are going to be coming out that are examples of targeted therapy. I think the practicing doctor is going to embrace targeted therapies. He's going to become convinced that, yes, these really do work, and whether they're on an immunologic basis or they were on a ligand receptor basis or tyrosine kinase…there are just all of these issues that these products work, they have different toxicity profiles, and that they're really easier to give the patients and I think, increasingly, they'll be as efficacious or more efficacious than chemotherapy. What I think won't move as fast as it should is having these move up to be first-line approaches. That's just the way the system is built right now, and we have a lot of semi-effective chemotherapy agents that, because of our experience with them, are going to retard how quickly the new move into wide use.

I feel more optimistic about it, probably more so right now than 10 years ago, because I think the pace of drug approval has increased but I think the rate of approval of these reagents should still be faster than it's going to be. So, I think we really are making improvements. I don't think there are going to be these single magic bullets that take care of every disease; I think that in part because of the regulatory paradigm right now and as much as anything, we're just going to keep improving individual tumor types in different ways. There's going to be these nontumor-specific agents that can be used in others that are going to be greatly impeded because of the reimbursement situation and the regulatory system…that part I'm very grieved by.

I think the key is that targeted therapies are going to be increasingly accepted and is definitely a good way to go in oncology and it makes great sense. The biggest obstacle to that in terms of the application and success is the reimbursement system. As long as HCFA is primarily dictating that, it's going to be difficult. Now, having said that, I think some of the companies, once you're successful, maybe people like that because it makes competition harder to follow along. I think maybe some of the industry has gone along with it just for that reason. It's thought as being a benefit. I think the real risk is, you can have a great product and if you don't have the wherewithal to do…you have to make good, strategic decisions about where you use it and it isn't necessarily just the size of the initial marketplace. They have to look at their strategies. It used to be the most important thing was just to get your drug approved. Now, you have to have a secondary strategy that, if you get it approved, how do you make sure it's going to be used more widely than that indication if you ever want to really grow the market substantially?

According to a leader in vaccine therapy:

Well, no one's crystal ball is perfect here, but I think that the themes which we believe in, which we're investing in, are that there will be safer and more selective

treatments and that is, not only large molecules such as antibodies or related molecules or even antibodies linked to toxins or other selected destruction moieties, but also small molecules that more selectively target the tumor types and I think that the days of the broadly acting cytotoxics that blow away every dividing cell in the body, those will still be used in tertiary care centers in places where there are no other options for particular treatments. But increasingly patients in cancer, even more than other diseases except for AIDS, are having a say in what kind of treatment they get. I think one of the reasons, for example, that Herceptin has been so successful is not because it's a particularly effective drug because it's not, it's a very tiny percentage of women's breast cancer that actually responds, but compared to the other modalities, it's a much safer and more selective treatment. I think that is the paradigm you'll see over the next 5 and 10 years – increasing numbers of biological agents like antibodies which are selectively targeting disease, new paradigms, I think angiogenesis, apoptosis, and other cell cycle-related, and then immune approaches or more selective small molecules, that can, in a more tailored sense, either through diagnostic or prognostic staging of disease, be targeting a particular cancer in a way where the patient has a higher likelihood of getting treated and less of the side-effect profile. I think increasingly, if you think about the developed world that is at risk of cancer, they will demand. They will not just ask for, they will demand from their clinicians, 'What options do I have doc, that will give me the best quality of life?' I think that will be the only thing slowing down... the regulatory authorities need to get comfortable with quality-of-life adjuncts or ways of measurement and get comfortable with the new modalities. One of the areas we're going to probably invest in is pain therapeutics. How do you improve quality of life by improving the treatment for cancer and other related pain? The largest selling cancer drug is not even a drug that treats cancer, it's Neupogen to treat increased white blood cell count as an adjunct to chemo. I think that this whole trend from acute to chronic treatment, the trend toward safer, more selective drugs, and using genomic and other tools to get more selective biochemical and genetic markers will happen; it's just hard for me or anyone else to predict, will it happen in 5 years? Some of it will. And in 10 years, absolutely.

The CEO of a venture capital company stated:

I mean, we're voting with our feet. I mean, the reason we set up an oncology-focused venture fund is, we think that it's almost unparalleled in history that you have a major, major disease category, and cancer is number 2 to heart attack in terms of mortality and increasing at a faster rate, because of the demographics. It has been so poorly treated for so many years and there has been such an incredible amount of great research, which is starting to culminate in commercial value. The only analogy that I can think of is cardiovascular disease in the mid-70s, when the identification of ACE inhibitors and beta blockers for hypertension and understanding the cholesterol biosynthetic pathway by Brown and Goldstein led to the whole statin classes. The history here is instructive in terms of the future of cancer in that people thought that after ***Merck (Whitehouse Station, NJ)*** *came out with Mevacor in 1987, that would mean that the game was over for everyone else trying to get into cardiovascular. The reality is, the statins are turning out to be perhaps the most successful class of drugs in the history of pharmaceuticals. I think that the same will happen over time in the oncology area. All of us are going to be of an age where we're at risk…if you live long enough, your cells will divide out of control, so the hope and excitement is to have new and more selective and safer modalities for disease or disease risk. That will absolutely happen. The only thing which we're not smart enough to guess, which is why we have to make multiple bets, is who will have the winning hand and how rapidly it will play out.*

From a New England research institute:

Well, in part that's philosophy in the sense of, where does the drug company want to invest its money? I think that you can make the argument that certainly if you come up with a drug that is a cure for a high percentage of patients, that that is something worth putting research time, money, and development into…from a drug company's point of view. On the other hand, there are plenty of drugs that even cause regression but don't cause long-term cure of patients' disease. A good example is Taxol, which is an amazingly successful drug in terms of financial gain for the company that makes it, but it doesn't cure that many people, if any. My sense is that drug companies are going to go with what works and if it works in a significant number of patients in a big enough disease, even if it isn't a curative therapy, it's a good step. The other thing is that we're only beginning to see the drugs that are more specifically targeted come out now. I think Herceptin being one, STI-571 (Gleevec) being another. These are the drugs that have been in development for 10 to 15 years. In the pipeline, is, I would hope, a number of other drugs that are going to make it, that

makes it seem that this is going to work better and better in the future.

I mean, you don't treat ovarian cancer with the same drugs you treat lung cancer or the same drugs you treat colon cancer with, so you already select in each of those cases a set of drugs that you think is more likely to work and has been shown to work better in those diseases. So yes, this is targeting in a more specific way, a particular population of patients. Ultimately I think that's where we're going to go with cancer care…we're going to find patients, we're going to figure out what the molecular alterations are in their cancer, and base our trials, and then ultimately our therapies, around the particular types of mutations and the drugs we have that fight those mutations.

I would say that what we're trying to do is really to do two things at once. One is something that's going to happen sooner and the other is a goal that we hope will come along eventually. The first goal is to understand how a cancer cell becomes a cancer cell and understanding what are the mutations that cooperate together to make a cancer cell. And we've made the first step in that direction, but it's a very crude step and what we need to do for here and what we are doing, is to try to make cells that ever increasingly mimic or model real human cancers. And to do that in as many different types of human cancers as possible. The ultimate goal in this part of the project is to make a cell line that is identical to a particular cancer in a particular stage, to make a Stage II breast cancer, to make a 3A lung cancer. The other part of this, then, is we're hoping that what we learn from this may allow [us] to stage cancer in a different way that will be more meaningful than the anatomic ways that we stage cancer now. Now, the ultimate goal here and one that will take some time, is that by creating such models, and validating that they are indeed similar or good mimics of human cancers, is that they will be useful for identifying targets for drug therapy and then, if possible, testing against those targets to gain efficacious compounds.

Delphi Summary

The more closely targeted therapies, the less toxic drugs, and use of drugs of high specificity and selectivity have led to an understanding that in reality, cancers must be considered and treated as chronic diseases, diseases that in most cases can be controlled, rather than cured. This understanding has in turn led to a further shift in the types of therapies being investigated. Combined with patients' activism, and demands for quality-of-life considerations, the trend has shifted from the highly toxic chemotherapeutic agents of the recent past, to therapeutics which target very specific functions within the tumor.

Current Therapeutic Regimens

- Conventional chemotherapy, while still of use in patients with no other options, is becoming less desirable as first-line therapy because of its toxic effects, and negative effects on quality of life.
- Monoclonal antibodies are increasingly being used in susceptible cancers as a result of their ability to be selective against specific antigens. However, they are large and often cannot penetrate deeply within a tumor. Not enough specific antigens have been identified to provide therapy for most cancers. Antigenicity reactions are possible, as are risk of secondary malignancies.
- Hormone therapy and hormone receptor antagonists have had some success in patients who are susceptible to them. Inevitably, patients become resistant to these therapies. These therapies also tend to have side-effect profiles, which can negate their effectiveness.

Future Treatments

- Small molecules may take the place of monoclonal antibodies, eliminating the antigenicity problems, providing better targeting, deeper tumor penetration.
- Vaccines may initially used as customized therapy, utilizing the patients' own antigens, which have been amplified or modified to produce an immune response upon being reintroduced into the patient.
- It is anticipated that the Human Genome Project will provide better targets, which can overcome the issues associated with the clonal nature of cancer.
- Multiple or combination therapies will likely be the treatment of choice. It is unlikely that any single agent or antigen will suffice as total therapy for any cancer.

Cancer Vaccines

- Initially, antigens are derived from the patient's tumor, making the therapy highly selective and with high specificity.
- Generic antigens to cancer types are under investigation to make the preparation of the vaccine easier, and make a relatively few antigens effective for a large population.
- In theory, vaccines and 'booster shots' may be universally used as part of a public health cancer prevention campaign. ■