



Dr. Barbara Hempstead, O. Wayne Isom Professor of Medicine and Co-Division Chief, Division of Hematology and Medical Oncology at Weill Medical College of Cornell University and New York–Presbyterian Hospital — 3-1-07

Dr. David Lemberg: Welcome to SCIENCE AND SOCIETY — our world, our well being, our future.

Our next guest is Dr. Barbara Hempstead, O. Wayne Isom Professor of Medicine and Co-Division Chief, Division of Hematology and Medical Oncology at Weill Medical College of Cornell University and New York–Presbyterian Hospital. Weill Cornell Medical College is a principal academic affiliate of New York–Presbyterian Hospital and offers an innovative curriculum that integrates the teaching of basic and clinical sciences, problem-based learning, office-based preceptorships and primary care. Physicians and scientists of Weill Cornell Medical College are engaged in cutting edge research in such areas as stem cells, genetics and gene therapy, cardiovascular medicine, AIDS, obesity and cancer.

The primary focus of Dr. Hempstead’s basic research is the role of growth factors, called neurotrophins, and their receptors in human physiology and pathology. She has authored more than 70 scientific articles, with two papers published in *Science* and one in *Nature* in the last four years. Five of Dr. Hempstead’s articles are rated must read or higher in the Faculty of 1000 rankings. She has been editor of the *Journal of Investigational Medicine* and is a member of the Editorial Board of the *Journal of Biological Chemistry*. Welcome, Dr. Barbara Hempstead.

Dr. Barbara Hempstead: Thank you.

Lemberg: Barbara, thank you so much. We are honored to have you as a guest on SCIENCE AND SOCIETY today. Thanks for making the time.

Hempstead: Sure.

Lemberg: Let’s begin with the overall topic of molecularly targeted cancer therapy. Can you give us some background and tell us about current findings?

Hempstead: I believe one nice way to start with this topic is to just think about how cancer has been treated over the course of probably the last 40 years. Most clinicians who treat cancer really design therapy, based on see what would work type of approach. And, therefore, we started with radiotherapy in the 1950s, single-agent chemotherapy in the 1960s, made really substantive leaps

forward with combination chemotherapy in the latter part of the last century. And only now are really entering the phase of molecularly targeted therapy. Let me just spend a moment or two talking to you really what that means.

Over the course of really the last 30 years, we've had a variable explosion of science that really is directed at how cancer develops, how it progresses, how it metastasizes. And really molecularly targeted therapy utilizes those insights to design new types of treatments that look at why cancer cells go awry. So, some of the major scientific observations were firstly, that chromosomes in cancer have a lot of instability. Many times, they're gene duplications, rearrangements, or even growth losses of chromosomes.

About 30 years ago, we also found that some of these genes were very important genes, called oncogenes that were dysregulated and, in fact, really groundbreaking work showed that if you just simply expressed those genes in a cell, you could make it a cancer cell. Additional work really from the 1980s showed that in addition to these types of gene dysregulation, that there were other normal growth factors that were present on the surface of cells that allowed them to proliferate in a nearly uncontrolled fashion and that these growth factors and their receptors were also mechanisms that cancer cells use to essentially gain immortality.

Over the course of about the last 10 years, we've had incredible strides in structural biology and we now understand how these growth factors and their receptors interact, how these receptors get dysregulated. And this has allowed us to come up with strategies for impairing this entire process. So, it's really been the understanding how these receptors and other things that are dysregulated, obviously, in a cancer cell can now become really druggable targets. And thus, this better type of understanding of how cancer cells have all these different genetic mutations really allows us to come up with targeted therapy that really targets the critical events that cancer cells use.

Lemberg: Barbara, thank you very much. I'd like to make sure I'm understanding, so we're talking about variously chromosomal instability and then the existence of oncogenes and then, growth factors and receptors on cell surfaces that can be druggable targets.

Hempstead: That's correct.

Lemberg: So, cancer really is a highly complex and deep system that doesn't represent one disease, for example, but possibly a wide variety.

Hempstead: Well, I think when we look at cancer under the microscope, we tend to see cells that are very dysregulated and immature. But, in fact, if one looks at a chromosomal level or at a genetic level, we see really far more complex changes that have gone on in the cell. There are surprisingly few cancers, in which there's only one inciting genetic abnormality. Most cancers, particularly cancers of solid tumors, such as breast cancer, colon cancer, etc., have many, many genetic mutations by the time they're recognized by patients or clinicians. And I think this is obviously one of the challenges. The cell has adopted many, many changes that allow it to become invasive and metastatic.

Lemberg: So, is there even any hope of effective therapy if a solid tumor contains so many different mutations?

Hempstead: I think we can learn a lot from some of the easier cancers to study. And indeed, a significant amount of work has shown that targeted therapy does work in cancers, such as leukemias. I think really the poster child for targeted therapy is CML, which is chronic myelogenous leukemia, and this is a disease that is characterized at a molecular level by just regulation of a tyrosine kinase.

Now because of this dysregulation, one was able to identify small molecule inhibitors of this kinase and, in so doing, impair the activity of this kinase. And thus, reduce the burden of cancer cells in the chronic phase of this disease. This drug is called Gleevec — it's been extremely effective in the majority of patients with CML in controlling this disease, reducing the number of tumor cells dramatically.

Unfortunately, what happens in a proportion of the patients is they become resistant to Gleevec over time and the mechanisms by which they become resistant are, in and of themselves, very exciting, as well, because the tumor learns to mutate around the Gleevec molecule and acquire additional mutations that render it insensitive to Gleevec or simply, amplifies this abnormal tyrosine kinase. And thus, the next challenge is to come up with sort of super Gleevec drugs or other molecularly targeted therapy that allow the inciting kinase mutations to be controlled.

Lemberg: So, cancer therapy, really, is like an arms race.

Hempstead: It is, and at some level, you have to respect the cancer cell tremendously because in order for it to evade the normal mechanisms of restriction imposed by, say, the immune system, the ability to acquire a blood supply so that it can grow, the ability to become highly motile so that it can leave its original area, pass through the bloodstream or the lymphatics and sort of set of shop in another locale, it really is a pretty impressive cell. And I think that clearly targeting any one of these different attributes will have some benefit. Clearly, what is in front of cancer biologists right now is trying to figure out what are the appropriate cocktails of drugs that one needs to use to impair this whole process of tumor genesis.

Lemberg: Right, the most efficacious approach.

Hempstead: Right, right. And in some diseases, such as solid tumors, I think we've seen significant benefits from molecularly targeted therapy. But, they haven't been home runs, and the next phase, I think, of molecularly targeted approaches is to identify what are the genetic signatures of cells and how many molecularly targeted therapies need to be used in combination, sequentially, or at the same time, that will stop a cancer in its tracks.

Lemberg: Barbara, thank you. And this makes me think that the entire field now is multidisciplinary.

Hempstead: It certainly is. I think we're now understanding at a much more sophisticated level, the role of the tumor vasculature. This was an area that we always were able to see under the

microscope, but really didn't know what some of the molecules might be that regulated the growth of the blood vessels within the tumor. I think we now understand that some of these are, rather, blood vessels that are co-opted from local blood vessels, and others really arise from hematopoietic progenitor cells that hone to the tumor and allow the tumor vasculature to grow.

Lemberg: Why do hematopoietic progenitors hone to cancer cells?

Hempstead: Well, maybe this is one of the attributes of a cancer cell that makes it an effective cancer cell. So, by up-regulation of growth factors, such as VEGF, vascular endothelial growth factors, it allows these new blood vessels to proliferate in the area of the tumor. Clearly you need not only little tiny capillaries but also major arteries, capillary beds and a venule bed, as well to allow blood to pass effectively into a tumor and allow it to grow at a maximum rate. So, you know, I think there's a tremendous amount to be learned by asking how the tumor cell became as effective as it has become.

Lemberg: So interesting and, of course, so deadly.

Hempstead: Right, right.

Lemberg: Barbara, could we talk about some of the new technologies that you alluded to, new technologies that came to use to identify new cancer targets?

Hempstead: Well, I think one of the areas that is particularly important is the use of gene chips. And these are large arrays of genes. And as many as 30,000 on a single chip. And we can extract nucleic acid RNA from a tumor. And I think it's important to realize in this case that not only are you probing the genes expressed in the tumor, but also in the host tissue, the stroma around the tumor. These are the fibroblasts, the connective tissue, the immune cells and the tumor vasculature, all in one fell swoop.

And then, we can probe the expression and profile the genes that are either up-regulated or suppressed in a cancer. Now, this is an unbelievable amount of data if one thinks about it. You get information on 30,000 genes. And one of the real tricks here is to try and ferret out which are the important genes, which are the ones that will yield molecularly targeted therapy and those that are simply the noise in the system. So, a variety of other approaches have also been used to look at how genes are disregulated in cancer progression.

One of these types of approaches is called the loss of heterozygosity or loss of gene expression. Tumor cells can actually suppress or silence genes, not only by mutation or by large deletion of DNA, but they can epigenetically silence portions of the chromosomes. And if these genes are genes that normally suppress cell growth, obviously, this can have deleterious consequences. So, looking at not only the genetic instability, but also how genes are silenced effectively by cancer cells is also critically important. Some of this work was actually done initially by individuals here at Cornell, Francis Barany, in particular.

There's also a tremendous amount of interest in things called micro-RNAs. These are small RNAs that are sort of master switches that can turn on and turn off whole clusters of genes at the

level of RNA translation. Micro-RNAs, which only consist of probably several hundred rather than tens of thousands of genes, are also being used to see how they are disregulated in cancer progression. So, hopefully, these types of approaches will give us sort of a fingerprint of a tumor. And provide us with new targets that can be druggable.

Lemberg: And I'm thinking it would be very interesting to compare profiles within the same tumor.

Hempstead: Absolutely. So, one of the challenges here has been to try and identify what's happening to the cancer cell, itself. And what's happening in the host response to the cancer because you can have cancers that look very much the same even at a genetic basis and yet, patients will have very different responses to chemotherapy or other targeted drugs. And obviously, one would predict that these are due to innate differences in the host.

Lemberg: Barbara, are you suggesting that host responses really are idiosyncratic, or are there general responses across cohorts?

Hempstead: I think we don't know the real answer to that question. Clearly, we are genetically very, very heterogeneous and clearly, there are major differences in immune response from one individual to another. There are also different ways in which we metabolize drugs. And any of those one could anticipate would be very important in the host response to a tumor, and also the susceptibility to really effective therapy, chemotherapy, radiotherapy or molecularly targeted therapy.

Lemberg: Well could we take a leap of faith and talk about the possibility of personalized medicine?

Hempstead: I think this is where it really gets exciting. You know, once we can identify what some of these genetic profiles are, then we can really move in a very dramatic manner to try to determine whether a patient's tumor puts them at a good risk or at poor risk for progression of disease, response to therapy or whatever. And I think this is really the area where large clinical trials are so important.

I think there are many examples of where this is beginning to be used. Clearly in the breast cancer arena, several recent papers have shown that there are gene chips that can interrogate as few as 70 or 100 genes. And perhaps even better than our eyes can, looking at cells under the microscope, and our clinical acumen will allow us to predict whether breast cancer places a patient in a very good prognosis or a poorer prognosis.

I think that although these are limited studies right now, which use patients from one or only several institutions, hopefully, these will be replicated as one looks across multiple ethnicities of patients, different stages of disease, and will allow us to be able to really predict tumors that will not need any treatment at all, say perhaps surgery or radiation therapy, versus those tumors that would benefit from conventional chemotherapy or conventional molecularly targeted therapy like Herceptin. And those patients for which we really don't have the answer right now. And

those patients would probably best be placed on investigative trials with new agents to try and come up with better therapy.

So, I think this country has utilized clinical trials very effectively in pediatric oncology. Most children with leukemia are placed initially on clinical trials. I think in the adult population, we haven't been so successful. And many patients are a little bit afraid of going on a clinical trial. But I think present-day clinical trials, where we can access tumors with these sophisticated mechanisms of gene chip analysis, will provide us with the types of data we need to help develop this whole array of personalized therapy.

Many times, the information we really need can only be assessed in a longitudinal manner. We need to know what's happening with the tumor before therapy if it's initiated during therapy, and also at relapse, so we have a much better handle on how tumor cells succeed in the face of the best therapy that we can give them.

Lemberg: Barbara, thank you very much. I'm wondering if you could speak to the possibilities of early detection and then, also a little bit about patient counseling.

Hempstead: I think early detection is an extremely interesting area that really has been understudied. One area at Weill Cornell where this is happening is really in early lung cancer detection. The use of high-speed CT scans to look at patients who are previous smokers and at high risk, is very exciting in that we can detect very small tumors. And we're using fine-needle aspirates of tumors, as well as local adjacent tumors to start to profile the initial inciting events in lung cancer pathogenesis.

Other areas where an ounce of prevention is a pound of cure, so to speak, is really in human papillomavirus and the development of a vaccine for this. Work is also going on at Weill Cornell on prevention, utilizing retinoic acid and other things along those lines. And having tools, genetic tools, gene chip tools, etc. will allow us to identify the critical mechanisms required for the progression of a relatively benign proliferation of cells to allow them to acquire the attributes of an invasive and metastatic cancer.

Lemberg: Barbara, thank you for a wonderful conversation today.

Hempstead: Well, thank you, it's been a pleasure.

Lemberg: Thank you. Our guest is Dr. Barbara Hempstead, O. Wayne Isom Professor of Medicine, Department of Medicine and Co-Division Chief, Division of Hematology and Medical Oncology at Weill Medical College, Cornell University and New York Presbyterian Hospital. Thanks for being with us on SCIENCE AND SOCIETY.