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Strategies to Overcome Cancer Drug Resistance

**Cancer cells almost always defeat drug therapies. Will we ever prevent or overcome drug resistance? I am your host, Dr. Bruce Bloom, and joining us to discuss modeling cancer therapy on an HIV combination therapy model is Dr. Jeffrey Settleman, Director of Center for Molecular Therapeutics and Professor Of Medicine at both Massachusetts General Hospital Cancer Center and Harvard Medical School in Boston.**

#### DR. BRUCE BLOOM:

Dr. Settleman, welcome to ReachMD.

#### DR. JEFFREY SETTLEMAN:

Good to be here.

#### DR. BRUCE BLOOM:

So what are the major challenges currently associated with cancer medicine?

#### DR. JEFFREY SETTLEMAN:

Well, right now, we have got a number of really exciting drugs coming through the various pipelines of development in industry and one of our key challenges going forward is to match the right patients with the right drugs. As we learn more and more about the genomic differences between tumors and they vary greatly from one patient to another. We are starting to appreciate how those differences play a key role in determining whether a patient will respond to a particular treatment or not, so if we can figure this out ahead of time and match the right patient with the right drug, we have a much better chance of clinical benefit from treatment.

#### DR. BRUCE BLOOM:

Do the genomics of cancer vary either within a patient?

**DR. JEFFREY SETTLEMAN:**

They can, in fact a patient can have multiple tumors or a primary tumor with metastasis and those can reveal differences in their underlying genetics, which creates an additional challenge to effectively treating the whole cancer, and its something that has become increasingly apparent as we have developed better methodologies for digging deep into the genomic information of cancer specimens.

**DR. BRUCE BLOOM:**

So one of the reasons that cancer wins is the cancer cells become resistant to the drugs that we provide for the patient. What causes this drug resistance?

**DR. JEFFREY SETTLEMAN:**

Well, when we talk about drug resistance, which is one of the most important limitations to successful cancer therapy, we really have to think about 2 kinds of resistance mechanisms - one that we call de novo resistance where patients demonstrate essentially a lack of response to the initial treatment and a second kind, which we call acquired resistance where patients that initially respond to treatment, then develop resistance. If the second form that we have been most interested in studying, although its becoming clear that there are some molecular similarities involved in the 2 different mechanisms, but in terms of acquired drug resistance, the kind that develops during treatment, we know that to a large degree, we can explain these mechanisms of acquired resistance by the emergence of specific mutations in genes that for one reason or another will prevent the ability of the drug to do its thing for an extended period of time. These mutations can arise either spontaneously or they can be induced by some of the treatments that are commonly used in cancer therapy such as traditional chemotherapy and radiation therapy, these are all treatments that cause DNA damage, cause mutations, and thereby stimulate cells to acquire mechanisms of resistance related to genetics. Now there are also nongenetic mechanisms of resistance that seem to be emerging recently and these reflect essentially an intrinsic property of tumor cells or a subset of tumor cells, some people think these are the cancer stem cells that might be intrinsically resistant to drug treatment and so when we think about acquired resistance, we have to think about the properties of this small subpopulation of cells that might grow out during treatment.

**DR. BRUCE BLOOM:**

When we talk about cancer cells creating resistance, do they actively do this, in other words; do we think of them as sort of smart cells that are trying to overcome this or is this just a random process that happens because they are so many cells in the body, some of them are likely to be resistant.

**DR. JEFFREY SETTLEMAN:**

Ya as far as anyone can tell, we think this is really not a purposeful activity of the cancer cell, but rather its an accident of the kind of genetic variation that we all experience and one of the great forces of nature of course being natural selection accounted for and large part by the spontaneous changes in our genome that can contribute to diversity and in the case of a cancer cell, it can lead to drug resistance. So it seems to be just an accident of nature and given the large numbers of tumor cells involved in a typical cancer, there are

certainly more than enough opportunity for cells to find what seem like clever ways around the problem of an effective drug.

**Dr. BLOOM, DDS:**

So what remains to be learned about drug resistance and how are we going to learn that?

**DR. JEFFREY SETTLEMAN:**

Well, its clear that we have to figure out whether mutations explain some, most, or all of drug resistance, there is an emerging notion that epigenetics or non-mutational mechanisms that relate to the genome, might be playing a role and to learn more about these things, I think its going to be important to dig deeper into the genomic analysis of a large number of clinical specimens, some of that is challenged by the fact that there are fewer and fewer autopsies being performed on cancer patients since we do not have access to material that has tumors essentially that have grown through drug and have experienced resistant mechanisms that we can study. One of the approaches we can use to learn about how cancer cells could overcome effective drugs is to model this in vitro and this is something we are very interested in, that is we take cell lines to arrive from tumors, from human tumors, we grow them in culture, we find drugs that are very effective against these cells, and then we simply keep these cells growing in the presence of drug until most of the cells are killed off, but a few remaining cells, resistant cells, eventually emerge and then by studying those resistant cells, we can learn something about mechanisms that seem to be relevant to humans.

**DR. BRUCE BLOOM:**

And when you do that in vitro testing, if you give massive amount of drugs right at the beginning do all the cancer cells die?

**DR. JEFFREY SETTLEMAN:**

So the issue regarding using large amounts of a drug upfront, the problem there being that there is a lot of toxicity associated with cancer drugs. Even the rationally targeted drugs that's everyone is excited about these days like Gleevec and Tarceva, these are drugs that are somewhat selective, but they are not completely selective for their target and so once we start increasing the dose while we might be getting more effective suppression of the target that we are hitting, we are also probably going to start hitting other targets and that's where toxicity comes in. So we have to be very careful about how much drug we use upfront.

**DR. BRUCE BLOOM:**

So how is drug resistance currently managed?

**DR. JEFFREY SETTLEMAN:**

Well, as we are learning more about the mechanisms underlying resistance, we are starting to be able to develop rational approaches to overcoming that resistance. Currently the approach is to just move on to the next available drug treatment when one fails. When resistance develops, we often just look for the next possible experimental therapy and that approach is generally unsuccessful or yields some short-term successes, but I think as we begin to understand some of these mechanisms and develop rational strategies to overcome them, we will be doing a better job with managing resistance.

**DR. BRUCE BLOOM:**

Now, in HIV, we use drug cocktails that seem to have provided a solution to overcoming drug resistance, would a similar approach apply in cancer?

**DR. JEFFREY SETTLEMAN:**

Almost certainly; its clear that cancer cells can find their way around the problem of attack by a single agent even an effective one and they do it pretty quickly, so by coming at the cancer cell from multiple angles, we think we have a much better chance of either preventing resistance, overcoming resistance, or simply providing less escape routes for a cancer cell that just wants to grow and divide.

**DR. BRUCE BLOOM:**

And what kind of combinations are used suggesting or you are looking at in the lab?

**DR. JEFFREY SETTLEMAN:**

Well, right now there's a lot of interest in simply taking 2 effective drugs that work in a particular cancer as single agents and putting them together, there is not a lot of rationale signs driving those kinds of decisions, but in some respects were limited by what we have available, which is still a relatively small number of drugs, but there are other combinations that are looking hopeful, that are based on somewhat more rational approaches, for example, there is a great interest now in combining drugs that target the tumor and the blood supply to the tumor or the vascular supply, the angiogenesis inhibitors and so by combining a drug that targets the tumor cell itself as well as the drug that locks its supply of blood, this might be an effective therapeutic strategy, so those kinds of combinations are certainly being examined.

**DR. BRUCE BLOOM:**

And how would we make sure that in these kinds of drug combinations that one drug wasn't reducing the efficacy of the other drug and how did they do that in the HIV treatment? How did they build those models?

**DR. JEFFREY SETTLEMAN:**

Well, in HIV treatment, I am less familiar with the development of the cocktail approach there and I think cancer problem faces different challenges in the sense that HIV drugs target the HIV genome, which is very different from our genome and one of the differences in how we approach cancer is that we are attacking proteins in the cancer cell, which are derived from our own genome and the difficulty there is that those same genes or may be slightly altered versions are present in our normal tissues and so when we develop drugs that target the cancer cell, we have to worry about toxicity. With the HIV therapy, when we are targeting the viral genome, which looks significantly different from our own genome; there is less of an issue of toxicity there, so we can start piling drugs on top of each other in the HIV setting where as we couldn't do the same thing necessarily with cancer because we would start to quickly accumulate toxicities.

**DR. BRUCE BLOOM:**

So right now, we employ drug regimens that give patients the maximum tolerated dose in attempt to kill the most cells without killing the patient. If we were to move towards a combination model, do you see us employing much lower doses that might work synergistically and actually reduce side effects?

**DR. JEFFREY SETTLEMAN:**

It is possible that we can use lower doses with some of these more rationally targeted agents, what we are starting to appreciate is that in patients where a drug works very effectively, we can sometimes back off on a dose and still see a strong clinical response. The reasons for that are not entirely clear, but it may just reflect a therapeutic window that results from a cancer cell being that much more sick or \_\_\_\_\_ in its growth properties than the normal tissue; in other words its more vulnerable to attack by these agents despite its ability to grow quickly, so its possible that in some cases, we might be able to back off from the MTD and use lower doses and then that of course might enable us to start combining more drugs, which will almost certainly get away forward.

**DR. BRUCE BLOOM:**

Is there a difference in the way we would approach preventing acquired resistance in the first place versus overcoming acquired resistance when it occurs?

**DR. JEFFREY SETTLEMAN:**

Ya, I think the idea of preventing resistance is an important one that's probably not getting too much attention these days, but the reason why we think its particularly important is because what we are starting to realize is that multiple different resistance mechanisms can arise even within the same patient; they could arise at different tumor sites or in primary tumor and metastasis, and so what that means is that if we are thinking about developing agents that can overcome resistance, we may have to use multiple agents in the same patient because there may be multiple distinct mechanisms of acquired resistance present. So the idea of preventing resistance obviously would overcome that problem by blocking cells from developing resistance before it arises and to do that we need to understand more about what the pathway to resistance looks like and whether there might be an intermediate cell state that gives rise to resistance and we are beginning to think that that in fact may be the case.

**DR. BRUCE BLOOM:**

I would like to thank our guest, Dr. Jeffrey Settleman, Director of the Center for Molecular Therapeutics and Professor of Medicine at both the Massachusetts General Hospital Cancer Center and the Harvard Medical School in Boston for joining us to discuss overcoming drug resistance in cancer based on a combination therapy model.

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