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Developing New Therapies to Treat Glioblastoma

FOCUS ON FUTURE MEDICINE

Every New Year we look to the future and dream of what is possible. ReachMD Radio is proud to present our special - series Focus on Future Medicine.

You are listening to ReachMD XM160, the Channel for Medical Professionals. Glioblastoma multiforme is the most common and lethal form of brain cancer with most patient surviving just 14 months from the time of diagnosis. The Cancer Genome Atlas has recently reported results from its first comprehensive study focusing on this deadly disease. How might this new research help us develop new therapies? Welcome to the Clinician's Roundtable. I am Dr. Leslie Lundt and with me today is Dr. Stephen Baylin. Dr. Baylin is currently Professor of Oncology and Medicine, Chief of the Cancer Biology Division and Associate Director for research of this Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins. For the last 20 years Dr. Baylin had studies the role of epigenetic gene silencing in the initiation and progression of human cancer.

DR. LESLIE LUNDT:

Welcome to ReachMD, Dr. Baylin.

DR. STEPHEN BAYLIN:

Thank you, very nice to be here.

DR. LESLIE LUNDT:

Dr. Baylin along with Dr. Peter Laird of USC, you are the co-director of the epigenetic component of the Cancer Genome Atlas Study. Tell us a little bit about, how this work began?

DR. STEPHEN BAYLIN:

Well, the work in the Atlas project per se began multiple years ago when the Genome Institute at the NIH and the National Cancer Institute felt there was a need to study in depth genetic and epigenetic changes in some of the common forms of human cancer. The

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approach would use many, many samples of primary tumors from each of the tumor types chosen. Actually, they are aiming to try to get 500 samples per each tumor typed to be study.

DR. LESLIE LUNDT:

So, lets says, we talked in the intro about glioblastoma, tell us about that?

DR. STEPHEN BAYLIN:

So glioblastoma, which as you mentioned is the deadliest form of brain tumors and the most common was the initial cancer type chosen for study.

DR. LESLIE LUNDT:

Were you able to get 500 specimens.

DR. STEPHEN BAYLIN:

We are now approximately at 250 to 300 samples in the quest to go to 500, but that represents a lot of samples as of now been studied for comprehensive analysis.

DR. LESLIE LUNDT:

This project really involves a mind-boggling number of institutions and investigators. How would you manage all of these?

DR. STEPHEN BAYLIN:

Well, the central management comes from a very hardworking group of senior leaders and the folks working with them in each multiple component of the project that ranges from coordinating tissue acquisition, preparation of DNA and RNA for shipping out to the multiple analysis centers and a large effort to coordinate all the data in an informatics platform that can be cleared not only by the TCGA investigators but by the clinical research community as a public data base as well.

DR. LESLIE LUNDT:

Now thinking about the particular science, how does gene methylation make brain cancer cells more responsive to chemotherapy?

DR. STEPHEN B. BAYLIN:

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Well this is one of the new things about the Genome Atlas Project, though the human genome itself and multiple other ventures of this type usually include genetic changes, that is mutations and other changes in DNA that alter the ability of genes to function, and one type of epigenetic change, the one you mentioned which is called abnormal promoter DNA methylation, abnormal DNA methylation at the start site of genes can be associated with gene silencing and that can serve as an alternative to mutations for disruption of gene function, and so it was thought that a pilot project within this TCGA to sample that across the genome would be very valuable, and so it was included in this first effort.

DR. LESLIE LUNDT:

And how did the mismatch repair genes fit in.

DR. STEPHEN BAYLIN:

We have learnt something quite fascinating in the first phase of the project which received major attention in the first consortial paper that was published in nature several months ago, and that concerns gene that we knew got DNA hypermethylated and silenced the glioblastoma or GBM, but this gene from studies originally in our group at Hopkins, but validated in several large studies by other investigators at other institutions is involved with repair of DNA damage, and when the tumors lose this gene they becomes a susceptible to the DNA damage caused by one of the major treatment modalities for GBM which is temozolomide or alkylating agent usually in association with radiation, and so the methylation of this gene which we call O6MGMT predicts for sensitivity to the therapy and actually dose produce some increased survival and an increased disease-free interval in patients on temozolomide and/or temozolomide plus radiation therapy. Now, we knew that gene get silenced in DNA hypermethylated and GBM, but what we didn't t know until an analyses of all these tumors is first of all that in patient's who are treated, whose tumors had silencing of these gene, they are indeed, sensitive, more sensitive, but when they come back, they have a spectrum of mutations which results in an increased number of mutations which are due to the loss of this O6MGMT, so they do not repair across the genome if you will just as they are sensitive also to the DNA damage from the drug, and so what happens to these individuals in the tumor that some back, if they recur, they have many, many more mutations than patients who have not been treated, and those mutations are of the type predicted for the loss of O6MGMT. Now, it's a bit complicated, but here is where the mismatch repair genes play in. In a treatment of these tumors when they are damaged by the temozolomide, the tumor cells attempt to repair that damage to the mismatch repair enzymes which is a family of enzymes. But as long as they have that O6MGMT lost, its futile, they cant repair, and so what happens is when the cells go through this futile repair, they will die and that's the mechanism partly responsible for killing of the tumor cells by temozolomide. So what the tumors apparently do, they will select for a way around that, and the way to get around that is to mutate one or more of the mismatch repair of genes. Not only that they have to loss of O6MGMT to predict the type of mismatch repair mutations that will occur. So there is good news and there is bad news. The good news is that loss of this gene predicts for sensitivity to the leading agents that are used today. The bad news is that it may also predispose to loss of the mismatch repair enzymes and so you select for a tumor that will recur and that tumor in turn will have a number of increased mutations.

If you are just joining us, you are listening to Clinician's Roundtable on ReachMD XM160, the Channel for Medical Professionals. I am Dr. Leslie Lundt, your host and with me today is Dr. Stephen Baylin. We are discussing the Cancer Genome Atlas especially about the glioblastoma multiforme study.

DR. LESLIE LUNDT:

Dr. Baylin what is the implications of your work for future development of new treatment options?

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DR. STEPHEN B. BAYLIN:

Well, I think that's what is, is existing. The loss of O6MGMT will still be a very valuable test the DNA methylation of O6MGMT to predict for temozolomide sensitivity and will be used increasingly by clinicians we believe in the future to predict the sensitivity to the tumor. But now we have to think about if this paradigm, which uncovered in these for studies, is true, how would we go about designing perhaps ways to get around this to prevent either the recurrence or to treat the recurrences in the different way based on what we have learned. So the first thing it has to be done is to validate these studies by expanding their size and what TCGA will be doing now is try to get as many tumors of glioblastoma as they can from the patient's where they have both the tumor prior to therapy and the tumor after it recurred so that they can validate that these differences that we have seen in the first study are truly repeatable, and then if this is the case, we can think about multiple strategies for how we might treat this patient's early after they have responded to the first therapy to try to keep these tumors from recurring or have a longer disease-free interval, and what therapies we might anticipate as the way we would explore the recurrent tumors when they do arise based on this new knowledge or the types or tumors that are present.

DR. LESLIE P. LUNDT:

And how would you do that.

DR. STEPHEN B. BAYLIN:

Well, there are number of ways that we are thinking about, one could actually think about turning the gene back on in the early tumors that is trying to recur because if you are not going to use temozolomide again this might not hurt anything to turn the gene back on and that might reduce the numbers of mutations that would approve which might have something to do with driving recurrent tumors. This is the kind of thing that people are talking about. There are other strategies and therapeutic targets that have been learned about in the TCGA through many of the other gene changes, both genetic and epigenetic. They are suggesting networks and pathways that are fundamentally abnormal in these tumors that might have drug therapies directed at those pathways that could be brought into play in various strategies as well.

DR. LESLIE P. LUNDT:

Now, what if some of our listeners have glioblastoma patients that they would like to include in your work, how can they do that?

DR. STEPHEN B. BAYLIN:

Well, and I should mention that potential conflicts, although I am in no way part of the company, there is now a clinical test for the DNA hypermethylation of O6MGMT that is offered. So that the patient's tumor tissue can be analyzed for the presence or absence of the abnormal starts at DNA-methylation. That can be at the physician's discretion wowing into their predictions about the use of temozolomide, the sensitivities. So they can have that knowledge upfront on any patient who is operated on and where a small amount of tissue is available for DNA analysis.

DR. LESLIE P. LUNDT:

Okay, now is it possible to get our patients into the study?

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DR. STEPHEN B. BAYLIN:

There are multiple studies going on that are again further and further validating O6MGMT as a marker and many institutions do participate I think that the radiation oncology ECOG-type group has a large study going right now, I do not honestly know all the participating institutions or what the entry levels are, but there are certainly going to be trials where the people would be very interested in having patient's enrolled to look at outcomes.

DR. LESLIE P. LUNDT:

Is there is a place for listeners might be able to find out more about the Cancer Genome Atlas?

DR. STEPHEN B. BAYLIN:

If you go to the web and look up the Cancer Genome Atlas project, you will find multiple number, you will first of all find multiple ways that you can click in and learn more about the particulars of the project, number of people to call for information about this, so they have a website that can certainly be readily queried by any physicians.

DR. LESLIE P. LUNDT:

Right and just to be clear you are looking at cancers other than glioblastoma as well?

DR. STEPHEN B. BAYLIN:

Yes, the project was initially designed to do so and the acquisition of samples on ovarian cancer and non-small lung cancer predominantly the squamous cell type but probably also to include adenocarcinomas is now underway. This project has been approved by the advisory board at the NIH to be extended and other tumors such as breast, colon, kidney are almost assuredly going to be analyzed in this way as well.

DR. LESLIE P. LUNDT:

Good time to be a researcher?

DR. STEPHEN B. BAYLIN

Well, it’s a hopeful time and especially if one feels that the research is going to actually benefit patients in a reasonable amount of time and that is the greatest hope.

DR. LESLIE P. LUNDT:

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Well thank you for helping to teach us about it.

DR. STEPHEN B. BAYLIN:

Thank you for asking me to be on.

We have been speaking with Dr. Stephen Baylin of Johns Hopkins about the Cancer Genome Atlas project and the hopeful clinical implications of their work. I am Dr. Leslie Lundt. You are listening to ReachMD on XM160, the Channel for Medical Professionals. Please visit our website at ReachMD.com which features our entire library of shows through on-demand podcast. Thank you for listening.

Thank you for listening to ReachMD Radio on XM160, and this month's special series - Focus on Future Medicine.

You are listening to ReachMD, the Channel for Medical Professionals. Welcome to the CDC flu view update provided by the Influenza Division of the Centers for Disease Control and Prevention.

This week's featured speaker is Dr. Anthony Fiore, CDC liaison to the ACIP Influenza Vaccine Working Group.

CDC has just released information about flu activity during the May through September month of 2008 and this report has several interesting items of information about influenza activity, antiviral resistance, and the match between circulating influenza strains and those contained in this season's vaccine. First of all activity was low in the US during May through September of 2008. Almost all of the influenza A strains that were examined closely matched or exactly matched the vaccine strains for this season's vaccine and about 80% of the influenza B strains were similar. Looking at viral resistance about 11% of H1N1s were resistant during the US season, last season which represented about 2% of overall strains that were circulating. Over the summer months resistance continued to be observed among H1N1 strains at about 47% strains resistant to oseltamivir. All strains were sensitive to zanamivir. Also, there were no resistant strains identified among influenza B or influenza H3N2 strains. So it looks like that match is quite good with this season's influenza vaccine and getting vaccinated both for yourself and for your contacts is the best way to protect yourself from influenza. In addition, antiviral resistance continues to be observed in one of the influenza A subtypes. This will be monitored over the course of the season; however, the current treatment recommendations that is to use oseltamivir or zanamivir remain in place.

You have been listening to the CDC flu view update provided by the Influenza Division of the Centers for Disease Control and Prevention. For more details on this week show or to download the segment visit us at ReachMD.com and tour the CDCs flu view website at cdc.gov/flu.

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