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Understanding Molecular Mechanisms of Cancers

### MOLECULAR MECHANISMS OF CANCER.

The complete genetic blueprint for 2 of the deadliest cancers, pancreatic cancer and brain cancer, was recently deciphered by a team at the Johns Hopkins Kimmel Cancer Center. Understanding the molecular mechanisms of these cancers can help us develop new therapeutic modalities. You are listening to ReachMD, The Channel for Medical Professionals. Welcome to The Clinicians Roundtable, I am Dr. Leslie Lundt and with me today is one of the investigators in this trial, Dr. Will Parsons. Dr. Parsons is a Fellow in Pediatric Oncology at the Johns Hopkins Kimmel Cancer Center. Dr. Parsons' long-term goal is to develop as an independent translational investigator in the molecular biology and treatment of brain tumors. He currently is undertaking a large scale genomic approach in collaboration with the Kinzler-Vogelstein labs to sequence more than 15,000 genes from several cases of both glioblastoma multiforme and medulloblastoma.

#### DR. LESLIE LUNDT:

Welcome to ReachMD Dr. Parsons.

#### DR. WILL PARSONS:

I appreciate you having me.

#### DR. LESLIE LUNDT:

Why study pancreatic and brain cancer Will?

#### DR. WILL PARSONS:

There are 2 reasons we did that, one was that they are both among relatively common cancers in the United States with pancreatic cancer occurring in roughly 40,000 new patients a year and brain cancer glioblastoma in about half of that and they also are ones that we have very limited treatment options.

#### DR. LESLIE LUNDT:

So, tell us what you have found so far.

#### DR. WILL PARSONS:

I am just going to go back a little bit if I may to explain the origin of why we are doing this study. Over the last 20 years or so, it has become clear that cancer is an essence of genetic disease. I am not meaning that it is something that's inherited from your parents, but it is a disease in which mutations in individual genes in a cell cause the cells to grow out of control and not die when they are supposed to and generally not be regulated in any way, and in the few cases, investigators have found specific genes causing that process and have been able to target them for therapies and for medicines and also in terms of diagnostics and has been remarkably successful in a few isolated instances. What's become clear though is that we really don't know the real framework and the vast majority of the genes and the genetic alterations that are causing these cancers. So, our goal here was to take a step back, start from the beginning and look at all the genes that are present in the human tumor cells and try and figure out what's going on.

**DR. LESLIE LUNDT:**

So what did you find?

**DR. WILL PARSONS:**

What we found was that the background and the landscape so to speak is much more complicated than we might have imagined. So, instead of having only 1 or 2 alterations in a single gene or it being in a very limited number of genes, we found the average tumor cell in pancreatic and brain cancer to have on the order of 60 different mutations or alterations occurring.

**DR. LESLIE LUNDT:**

In 1 cell.

**DR. WILL PARSONS:**

In 1 cell and part of the trick has been figuring out which of those are occurring just due to chance because in the replication of DNA in the cell there is always some background rate of errors that are occurring and some of them likely have nothing to do with the growth of the cell and try and differentiate those from ones that are really making a difference, and so, we have to derive all sorts of statistical kinds of tests for that and ways to look at it. In the end, all it comes down to is on the order of about 10 of them, 10 to 15 may be are actually playing a role in creating the cancer.

**DR. LESLIE LUNDT:**

Now in your paper, you mentioned pathways, tell us about that.

**DR. WILL PARSONS:**

Well one way to make this more simplified both in terms of making sense of it intellectually and also in terms of targeting these changes in terms of using them for diagnostics or therapeutics is to provide some order to it and in one way we can do that is by assigning these genes to different pathways, so for example, there might be a pathway that's involved in certain aspect of cell growth and there are number of different genes in that pathway, what we have found is that different tumors may have different mutations within different genes in that pathway. So, instead of all of them simply having something wrong with gene A, some proportion of them may have something wrong with gene A, some other proportion different tumor has something with gene B, and so on, so that the net effect is that the pathway is affected in nearly all the tumors, but that in any single individual tumor, there is some variety to it.

**DR. LESLIE LUNDT:**

What do we know Will about the difference between solid tumors and other problems like leukemia.

**DR. WILL PARSONS:**

We are still learning about that a little bit. Most of the studies that we have done so far have focussed on solid tumors and so the numbers in terms of numbers of mutations and things that I was talking about are most directly relevant to that. Other investigators have also been looking at leukemia or what we call from the more liquid tumors. There have been a couple of very interesting cases and leukemia is where a single alteration, in one case, a translocation between 2 different genes occurring in chronic myelogenous leukemia for example has been found in the vast majority of patients which is obviously a very nice finding because then it can be targeted with a single medicine or single group of medicines in most patients, so that's really been quite effective. We are still learning about some of the differences between the tumor types.

**If you are just joining us, you are listening to The Clinicians Roundtable on ReachMD, The Channel for Medical Professionals. I am Dr. Leslie Lundt, your host, and with me today is Dr. Will Parsons. We are discussing his research looking into the molecular mechanisms of cancer.**

**DR. LESLIE LUNDT:**

Will, it has been suggested that may be the development of new treatments is really not the way of the future for looking at cancer, should we may be focussing our energy on prevention and early detection instead of treatment necessarily?

**DR. WILL PARSONS:**

I think that's a great point and that's actually one of the things we are very interested in looking at. The important part to note about these studies we are doing is that we are just trying to find the background information such that we can design rationale purchase to all of these questions. So for example, by finding the different mutations that are commonly occurring in tumors, we can use it in number of ways.

1. You can obviously design medicines for those changes which is what you are first referring to.
2. You can use the changes for diagnosis and prognostication, for example, one of the mutations that we found in a decent minority of patients with glioblastomas was found to be associated with a much more benign relatively speaking clinical course. So instead of having a medium survival for about a year as most patients with that terrible tumor do, those patients had a survival of more like 4 years and might be susceptible to different treatment. Then the third leg of that is what you are getting at is something I think is really interesting in that once we have knowledge of these changes, our hope is that we will be able to use them for early diagnosis as well. For example, it is now possible to detect DNA and mutated DNA from tumors in blood even if it's not a leukemia or not a tumor that's normally in the blood. So, we could for example if we have common mutations or panel of mutations that are occurring in one of these tumors, to design a test from the blood to see if you see any these alterations and obviously that would be a way of hopefully diagnosing them earlier. So, both of these types of tumors, they are ones that create symptoms relatively late and at that point it is already a big problem.

**DR. LESLIE LUNDT:**

Then of course we have to think about ethical issues like insurance coverability, that's the word, if you have that certain panel of mutations that are likely to develop cancer, might you have a hard time getting insurance.

**DR. WILL PARSONS:**

I guess that's going to be one of the big ethical issues facing us in the century is how to handle this additional information about the patient. You know obviously, the basic principles are the same in terms of not sharing them in ways that the patients are not approving off and we have all the regulations that you know well about governing that, that clearly in these next years is going to be of infinite amount more genetic information available, so it is going to require us to be very careful about how we use them.

**DR. LESLIE LUNDT:**

So, what's next with your work?

**DR. WILL PARSONS:**

What's next is couple of different things. One is we are very interested in looking at other different tumor types and comparing them because some of the most valuable information we find is when we find things that are either common to multiple types of tumors, so for example, a gene might be mutated in brain cancers and also pancreatic cancers, but then it is also interesting to see what the differences are and for example as you are asking about the leukemias before what kind of differences in terms of number of mutations in terms of the types of genes that are mutated and what that might say about these things mechanistically. Looking at other kinds of tumors is one step. The other important part is followup on the findings that we have from these sources of studies, so these are only first step in terms of providing any improved therapies for patients for these kinds of cancers. First we find these genes, next we have to look at them and see, for example, what they are doing, how these mutations alter their function, try to figure out such ways in which we could target that in some ways in which we can use them for diagnostic. So, really the next step is following up on some of the interesting genes.

**DR. LESLIE LUNDT:**

Now, I assume that a lot of this work is done at multiple centers not just at Hopkins. How do you coordinate what must be a massive amount of information?

**DR. WILL PARSONS:**

It's absolutely true. It's a collaborative effort. Many of these "big science projects" that are being done these days by necessity require a bunch of different people, resources from different places, and talents from different groups. So, this project, for example, was done primarily here at Hopkins, but also with our collaborators at Duke University and a number of others. In part, that's because the samples are difficult to come by because it requires really carefully curated and analyzed samples such that we know that they are very pure tumor samples that does match normal DNA, for example, from the same patients and that we have associated clinical data, so we can make some sense of the results. So, it is something that requires a number of groups. Basically, the way we do it is frequent communication, a number of meetings, and having a very clear overall plan of which parts of the group are responsible for which parts of the project and then we adapt from there, a very effective way to do things, to rely on the talents of a number of different people.

**DR. LESLIE LUNDT:**

And in this most recent study how many patients roughly did you look at?

**DR. WILL PARSONS:**

Roughly we looked at on the order of 100 patients with each of the different types of tumors.

**DR. LESLIE LUNDT:**

So, you had mentioned that one of the next steps is to look at other tumors, what else besides glioblastoma and pancreatic CA are you interested in?

**DR. WILL PARSONS:**

We are interested in number of others actually and we are still trying to decide where to go next. In other studies we have already looked at breast and colon cancer on a slightly smaller scale than on this project. So, we are interested on those results as well.

**DR. LESLIE LUNDT:**

Now if people want to learn more about your work, where should they look?

**DR. WILL PARSONS:**

The simplest way to do it would be to in terms of looking on the Internet would be just to search for Johns Hopkins Sidney Kimmel Comprehensive Cancer Center and then search for any of these types of tumors that I am talking about.

**DR. LESLIE LUNDT:**

Fantastic. Will thank you so much for your time today.

**DR. WILL PARSONS:**

No problem. It is good talking to you.

**DR. LESLIE LUNDT:**

We have been speaking with Dr. Will Parsons from the Johns Hopkins Sidney Kimmel Cancer Center in Baltimore, Maryland. An interesting question perhaps the development of new therapeutics is not the way of the future for cancer treatment could provide for a thought. I am Dr. Leslie Lundt. You are listening to ReachMD, The Channel for Medical Professionals. For a complete program guide and downloadable pod casts, visit our website at [www.reachmd.com](http://www.reachmd.com). Thank you for listening.

**You are listening to ReachMD, The Channel for Medical Professionals. Here is a sample of the great shows airing this week. I am Lisa Deandre. Join me this week on The Clinicians Roundtable, when I will be speaking with Sue Kling Colson about the University of Michigan's Hospital Intensive Insulin Program.**

**This is Dr. Mark Nolan Hill. This week we will be speaking with Dr. John Dixon, Associate Professor of Medicine at Monash University Medical School in Melbourne, Australia. We will be talking about gastric banding surgery towards type 2 diabetes remission.**

**This is Susan Dolan, join me this week when my guest will be Amparo Gonzales, President of the American Association of Diabetes Educators discussing how diabetes educators are making a difference for patients and physicians.**

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