2109 Gala Scientists Panel Transcript

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Panel:
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Affiliate Member, Hariri Institute for Computing and CS&E
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Michael: David, tell us how long you have been researching the environmental causes of breast cancer and other cancers?

Dr. Sherr:

When I was younger I was told the people generally die of "old age". Turns out, old age is not exactly a diagnosis. As I got older I saw that more and more people were being diagnosed with and dying from cancer. I also saw the devastating effect that a cancer diagnosis has on, not just the cancer patient, but also the patient's family and friends. That's when I started paying attention to cancer statistics. In the United States, over 600,000 Americans die each year from cancer. That is over one person dying every minute of every day. 40,000 of those deaths are from breast cancer. If you get 8 hours of sleep tonight, almost 600 people will have died due to cancer in that time. People are dying. Something has to be done. Those certainly were compelling numbers, but it wasn't until I read articles suggesting that most of those cancers could be prevented that I decided to spend the rest of my career working to prevent cancer. That was around 1996.

Michael: You formed the Find The Cause Consortium in 2014. Tell us why you picked the other 3 labs and how has it benefited the progress of the research?

Dr. Sherr:
Over the last 10 years, our understanding of cancer has changed so fast, and the technologies have advanced so quickly, that the only way to get the job done is through team science. So when FTC asked me how to make the most progress in the shortest amount of time I suggested a team approach, something similar to NIH program projects (but hopefully more likely to get funded). My expertise is in immunology and cancer biology. But I can't fight through data sets of literally millions of data points to find needles in haystacks. That's what Stefano can do with computational biology, sometimes in the space of minutes. I know how breast cancers behave, but I don't know enough about how normal breast cells are supposed to behave, so I asked Charlotte to join. Her expertise is in the area of breast cell development and progression to malignancies. I'm pretty good at understanding how environmental chemicals suppress the immune

system, but I need Gail to show me all the intricate details of the insane signaling pathways that cancers exploit to survive and spread. Forming a consortium of "the best athletes" was the obvious mechanism to attack a complex problem like breast cancer.

Michael: Stefano, much of the research that the rest of the consortium does begins with your work. As we heard in the video, you mine these large amounts of data and look for patterns to determine whether a chemical should be further studied. Tell us how you do that.

Dr. Monti:

Yes, with the help of Find The Cause, we are developing fast, accurate, and inexpensive methods to determine the long-term carcinogenicity of chemicals, that is, whether exposure to a given chemical(s) increases your cancer risk.

For context, there are more than 80K chemicals in commercial use, and only ~1,500 (less than 2%) have been thoroughly tested for carcinogenicity. This number doesn't account for the fact that we are not exposed to single chemicals but to combinations of them, with potential synergistic effects, and those combinations need to be tested as well. So how do we do it?

The best method to determine if a chemical is a human carcinogen would be to test it in humans, probably not the most ethical approach. An acceptable alternative solution is to use animal models. In fact, the current gold-standard for carcinogenicity testing is the 2-year rat bioassay, which involves testing a chemical on more than 800 animals over the course of two years and see whether they develop tumors in any organ. Based on this approach, *testing a single chemical may cost up to $4M*. Most of those 1,500 chemicals tested used that method, among others.

So, we take a different approach. We use human cell lines and computational modeling. We expose the cells to the chemicals, and we extract chemical-specific fingerprints (or signatures) that uniquely describe the cell response to each chemical. Then, based on the fingerprints of chemicals already known (to be carcinogens or non-), we train a computer to distinguish between the two groups.

Think of it as a crystal ball. You come to us with a new, unknown chemical, and through this crystal ball, we'll be able to tell you, to predict, whether exposure to that chemical will increase your cancer risk. How accurate is our crystal ball? Well, it's pretty accurate, between 75 and 85% (that is between 7 and 8 out of 10 predictions are correct), but we need to considerably increase its accuracy (pushing it to 90/95%).

We are now at a point where the chemical screening method we developed and published needs to be optimized. And we know how to do it, based on what we learned from our study.

Michael: Gail, you mention in the video that you are working on a method of detecting when a person has been exposed to a carcinogen. Tell us more about that.

Dr. Sonenshein:
Yes, the critical question is how do you know when a person has been exposed to a carcinogen? To address this question, we are developing a sensitive, rapid assay to test for carcinogen exposure using readily accessible samples from individuals.

Our test is based on evidence generated by our lab that shows when cells are exposed to carcinogens, they modify the nature of the factors they normally release into the blood. This can either mean turning on a new factor, shutting off a pre-existing one or changing the level of expression. We are currently working to identify changes that can indicate a heightened risk of developing cancer.

This test will allow us to assess:

1. Carcinogen exposure in real-time,
2. Detect people at risk when hopefully the process can be intercepted and
3. Prevent further exposure

Michael: Charlotte, you specialize in researching breast development and at what points in that development cells are more at risk to exposure to environmental toxins. That research has led you to the work you are currently focused on in the area of immunology. Tell us about the connection between breast cancer and the immune system.

Dr. Kuperwasser:

The connection between the immune system and cancer has become front and center due to the success of immunotherapies as a powerful treatment for cancer that activate the immune system to kill tumor cells. However, the role the immune system plays in the formation of cancer is just as important and is a critical area to also target for the prevention of cancer.

In order for a cancer to form in the first place, two things must happen: first normal cells must sustain enough mutations that over time this enables them to grow uncontrollably and break free from the constraints of normal cell behavior. Second, cancer cells must evade the immune system. That is because our immune system is actually continually identifying and killing off cells (abnormal, precancerous and cancerous cells) that have acquired genetic mutations. In fact, this process is such a critical checkpoint that all cancers including metastatic ones have developed ways to turn off this surveillance by the immune system. This immune surveillance is a powerful way to prevents cancer.

Therefore, if we want to prevent cancer, and it's unlikely we will be able to prevent the mutations that environmental chemicals induce in normal cells to cause them to be cancerous, then we can find a way to make sure we can keep the immune system active and responsive so that it continually kills off cancer cells and prevent tumors from forming in the first place.

Michael: David, your work focuses in large part on receptors in our cells and how environmental toxins can trigger cancer growth. How does that work?

Dr. Sherr:

Our initial studies were directed towards figuring out how cells know that there are environmental chemicals around. It turns out that cells have receptors that evolved perform several critical functions but, as bad luck would have lit, also recognize and respond to environmental. You could think of is like a doorbell on a house. When you need to know that there's someone outside, the visitor rings the doorbell once. That's what happens when this receptor is activated by environmental chemicals. Unfortunately, the receptor seems to get stuck in the on position so like a bell ringing incessantly it makes the occupants crazy. We know that this happens early on after exposure to some environmental chemicals; later on, this doorbell drives cancers to metastasize and to suppress the one system capable of killing the cancer, the immune system.

Michael: How do you turn the AHR receptor off?

Dr. Sherr:

We have developed inhibitors of the receptor that bind to it like environmental chemicals do but the inhibitors fail to activate the receptor. This way the environmental chemicals are displaced and unable to ring the doorbell. It's like unplugging the doorbell.

Michael: So, is this a therapeutic drug?

Dr. Sherr:

We are now developing these drugs as secondary prevention agents. That is, we believe we can tell when the doorbell is ringing even before overt cancers arise. This would be the precancer time at which we would treat people with the inhibitors, shutting off the doorbell and preventing cancer from ever happening.

Michael: Charlotte, it is my understanding that when you get a grant, you are obligated to keep your research focused within the parameters of the grant. Can you explain how the funding that you get from Find The Cause differs?

Dr. Kuperwasser:

I like to think of the funding from Find The Cause much like the financing during the Age of Exploration when small groups were supported to search for extensive overseas discoveries. During this time, explorers were tasked and financed to take high risks in order for the high rewards. However, current biomedical funding does not occur in this same way- rather we are required to already have conducted experiments and have minimized all risk. It's like asking the explorers to have the routes already mapped out and their paths already well charted. If this were the case, no new lands would have ever been discovered. Such is the case with something as daunting as understanding the environmental causes of cancer. Without Find The Cause funding, the discoveries we are trying to make just would not be possible.

Michael: Stefano, what is your ultimate goal?

Dr. Monti:

Our ultimate goal is to rid your kitchen cabinet, and your bathroom cabinet, and your pantry, and your children's playground, basically, your living environment, of nasty substances that are harmful to your health. This is the ultimate goal of what is called primary prevention.

We also have a complementary goal, that I think can take advantage of the methods we are developing. We live in the real world, a world that has already been heavily contaminated, a world where it is hard to regulate chemicals, even when they're known to cause harm. So, it would be great to be able to identify subjects at risk, that is, individuals who have been exposed to more chemicals than others (who have a higher "exposure burden"), and/or whose genetic profile makes them more vulnerable to those exposures. The tools we are developing, based on the derivation of chemical fingerprints, could help us detect those same fingerprints in human blood, for example, and thus identify individuals that need to be screened more often (think of mammography, or bronchial brushing, or liquid biopsy), or "preemptively" treated (e.g., with the type of immune therapies Dave is working on). This is the goal of secondary prevention, or interception.

So, our approach has the potential of advancing both primary and secondary prevention.

Michael: Gail, you mention in the video that the funding from FTC is the seed that you believe is going to grow a big tree. Can you explain that?

Dr. Sonenshein:

The current funding levels at the National Institute of Health, or NIH and other government agencies is very low, which means that they are now only funding studies that are safe – basically almost completed. This is especially true for studies on environmental chemicals where funding opportunities are even lower. Because the current funding situation, it takes about 3-4 years to accumulate the data necessary to be competitive for a NIH grant.

The only way we can get that preliminary data -- is through seed money, such as the funds provided by Find The Cause, to all of the scientists on this stage. And I would like to reiterate how very grateful we all are to Find The Cause for this funding.

Michael: David, speaking of seed money, you have an exciting announcement to make. There are many commercial real estate professionals in this room and they would love to learn your trick of leveraging investor money on 15-1 ratio.

Dr. Sherr:

Because the Find The Cause funds allow us to do high risk research, we were able to generate enough preliminary data to support three grant applications, two of them going to the NIH. All three of those will be funded which means the influx of about $1.8 million into our laboratory over the next five years. But again, what we do with that money is strictly proscribed by the grants. To take risks and make leaps in progress, we actually need more discretionary funds, the kind of funding provided by Find The Cause.