Science Can't Wait: A Discovery Series | Part 3 | Featuring cancer researcher Daniel Hollern

00:00:00:06 - 00:00:43:16

Michelle Chamberlain

Welcome, everyone. Thank you so much for joining us today. My name is Michelle Chamberlain and I am the Vice President of Advancement at the Salk Institute. We welcome you to part three of our Science Can't Wait webinar series, brought to you in partnership with the Del Mar Foundation. Over the course of this three-part series, we've learned a lot about how sleep, diet, and exercise can impact our cognitive brain health, how many different genetic changes and plants can lead to plant resilience, and today, how the possibility of harnessing the immune system to battle breast cancer is possible.

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Michelle

We're grateful to the Del Mar Foundation for their incredible partnership and for their one for one match. Indeed, I'm excited to share that we're only $10,000 away from meeting the $50,000 match. So at the end of today's webinar, if you are as inspired by Salk science as I am, I hope you'll join us in this journey. Make a contribution, and a reminder that for those of you who are interested, donations of $1,000 or more qualify for our Discovery Society, our loyalty circle that provides access to special events, discussions with our scientists, and so much more.

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Michelle

Brief introduction to the Salk Institute. I think many of you are aware, but I want to emphasize that we are an independent nonprofit organization. We focus very much on scientific research and cancer, Alzheimer's, and so much more. We like to say that at Salk, this is where cures begin. In terms of the scientific research that we conduct at the Institute, it's often termed foundational or basic research.

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Michelle

So we're asking questions that are very early and we're publishing literally new knowledge to the world. So a great example of Salk research is a question asked in 1979 by Dr. Tony Hunter about whether or not a virus can change a healthy cell into a cancer cell, resulted in clinical trials that resulted in an FDA approved drug nearly 20 years later, and today is the host of a family of over 100 drugs.

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Michelle

We're all talking about artificial intelligence right now. Many of those questions started back in 1985, when Dr. Terry Sejnowski asked a question about whether the neural networks of the brain could be mimicked in a computer. And look at where we are today with ChatGPT and other tools. This is the long-term science that is pursued by the Salk Institute.

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Michelle

We do this in a very collaborative manner. We don't have departments here at the Salk. And in fact, you can have a plant scientist next to an immunologist next to a cancer biologist. And they're all sharing their findings not only with each other, but in their research pursuits. We believe that this interdisciplinary, collaborative approach is truly the secret to unlocking new knowledge and insights.

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Michelle

And it's something very unique to our institute. Questions that we're asking today are some really thoughtful, life changing questions that I think we can all take a step back and recognize how different health trajectories would be if we had answers to questions like what turns a healthy cell into a constantly replicating cancer cell? That's very relevant to today's topic.

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Michelle

But also, what if we could tell a plant to grow deeper roots and be more resilient, or select for certain traits? Think of what that could do for the climate and for the world's food supply. These are the foundational questions that are being asked today at Salk. And if they're not asked today, we won't have new therapies, treatments, medications, and other innovations tomorrow.

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Michelle

This is a very brief synopsis of what we cover here at Salk. It offers just a snapshot of much of our research that is happening today. This work is strengthened every day by the work that's happening in our labs. And that brings me, of course, to today's speaker, Dr. Daniel Hollern. Dr. Hollern is an assistant professor here at the Silk Institute.

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Michelle

His lab is focused on how we can harness the immune system to both identify and fight, especially breast cancer cells. You can see that Dr. Hollern has been recognized by many cancer funders, including the Susan G. Komen Cure and the W.M. Keck Foundation. We're so delighted that he's spending some time with us today, and I'd like to introduce him to everyone on the webinar.

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Michelle

Without further ado, Dan.

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Daniel Hollern

Thanks, Michelle. I really appreciate the introduction and the opportunity to share our exciting research with everyone today. Thank you for the members of the audience for taking interest in the science that's happening at the Salk, and also in my laboratory. So today, I'm exhilarated to share about a special immune cell that we can leverage in the fight against cancer.

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Daniel

So today we're going to learn about how B cells can be used as a superhero and really deliver more powerful immunotherapy strategies for cancer patients. So first let me tell you about how I got involved in cancer research. Like many of you, I was deeply impacted by cancer through the diagnosis of a family member, my grandfather, Grandpa Hollern.

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Daniel

So my grandfather was diagnosed with the stage four angiosarcoma, which is a highly lethal type of cancer that arises in the blood vessels. And what was really devastating about his diagnosis is when I learned that there were no effective treatments for his disease. And so this really felt unfair, and I really couldn't understand how this could be the case.

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Daniel

And so I turned to science for answers and switch my major into immuno oncology so I could go to work on the types of treatments that could help people like my grandfather. Now, one of the things that inspired my research during my grandfather's course of the disease was when they discovered cancer in his lymph nodes. So the lymph nodes are a really important tissue in our body.

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Daniel

For example, when we're when we fight infection, the infection is often recognized first in the lymph nodes. And that's where the immune response starts. And so when they identify cancer in his lymph nodes they of course you see cancer. You take it out. And the troubling thing that ended up happening when they took out his lymph nodes is he rapidly succumbed to his malignancy.

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Daniel

And so this really made me wonder could the cancer in his lymph nodes be priming the immune response that was actually protecting him against the advancement of his disease and keeping him healthy? So I started to wonder about the possibilities of immunotherapies for people like my grandfather. After all, we all have immune systems that could be taken advantage of with modern immunotherapies.

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Daniel

And this idea of using immunotherapy to treat cancer is not necessarily a new idea. In 2018, Dr. Jim Allison was recognized with a Nobel Prize for his work in developing immunotherapies that activate the T cell response against cancer. And in fact, of the two million people that have been diagnosed with cancer this year, a large percentage of them will receive an immunotherapy.

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Daniel

Now, the immunotherapy works for some patients, but the problem is, is that it doesn't work nearly well enough. Only 20 to 30% of the patients with advanced malignancies will respond to therapy and extend experience and extension of life. And also most patients aren't actually cured of their cancer. And so we have a lot of work to do and advancing immunotherapy.

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Daniel

But we've really only scratched the surface in what we can do because these treatments only target one type of immune cell called T cells. T cells are the cells that perform the killing of cancer cells. So we have things like killer T cells. So it makes a lot of sense to try to target these cells. However, they can't do the job alone.

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Daniel

They need help from other immune cells. And so the innovation, the innovative approach that my lab is taking to developing immunotherapy strategies is looking for ways that we can boost these T cells by leveraging other immune cells to fight cancer. And so through our research, what we've discovered are a very important type of immune cell called B cells that act as superheroes in the fight against cancer.

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Daniel

So let me tell you a little bit about the superpowers that B cells have. So one really cool thing about B cells is they can act as detectives that search our bodies for cancer cells and can identify cancer cells and alert the rest of the immune system that cancer is present in the body. So when they find cancer cells, they talk to these other immune cells and transmit information that, hey, we need to find these types of cancer cells, and then we need to destroy them.

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Daniel

And so they'll talk to mean cells like killer T cells and macrophages that work together in killing cancer cells. And so today we're going to talk about how B cells command T cells to destroy cancer cells. So I like to think of B cells as the commander of arm of the Army. And instruct the T cell tanks to start blasting holes in cancer cells.

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Daniel

Now B cells are also well recognized for their roles in secreting antibodies that protect all of our surfaces from infection. However, what we've discovered is that B cells can also release antibodies that act as heat seeking missiles for cancer cells. So B cells really have all these really unique powers that we can take advantage of to fight cancer. Now, you might be wondering, since our immune system already has B cells, why aren't they protecting us from cancer rising in the first place?

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Daniel

And the truth is, for most healthy people, this is what's actually happening in our bodies. It is thought that cancer cells arise in our bodies every day, but the immune system recognizes them and disposes them very readily. The problem is, is that some people, when their immune system becomes unhealthy, they're unable to remove those cancer cells. And so what we think about is how do we give cancer patients a boost in their B cell compartment so that they can have an immune system that is even better at fighting cancer?

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Daniel

And so we've been searching for such signals that can alert the B cells that there's the presence of cancer in the body, or, for example, tell the B cells when they find a cancer cell, you really need to destroy this cell. And so today we're going to talk about our discovery of how the CD40 signal can tell B cells to mount an immune response against cancer cells.

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Daniel

And so how do we activate the CD40 signal is by using the drug that we call CD40 agonist or CD40 AG. And we're going to learn about how does this drug work to mountain anti-tumor immune response. And so one of the ways that we started to learn how this drug works is by taking advantage of really unique technology that we have at the Salk Institute.

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Daniel

So what we're able to do is take a tumor apart cell by cell. So when we isolate individual cells, we'll be able to send them through a single cell sequencer. And what this tells us is each cell is instructions. So these instructions will tell the cell on what type of immune cell they're supposed to be, and also what types of function those cells are supposed to perform.

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Daniel

And so in this complicated chart on the right, what we've done is use this technology to look at every cell in the tumor microenvironment. And so we can really see what's going on as we move from a non-treated tumor to a tumor that's received our CD40 agonist drug. Just excuse me I'll get the laser pointer up. So what you can see with the delivery of this drug is we have a dramatic reduction in tumor cells, a huge expansion in T cells and also a three-fold increase in our B cell superheroes.

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Daniel

And so we wanted to determine if the efficacy of this drug was dependent on B cells. So here what we're looking at is the survival plot. And our lab models of aggressive triple negative breast cancer. So here on the y-axis you can see the probability of overall survival. And then you can see how long survival lasts over time.

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Daniel

And so in our two control groups in black and in magenta you can see that tumors rapidly progressed to lethality all by 50 days. However, what's really exciting is when we give this CD40 agonist drug that activates our B cell superheroes, we significantly extend overall survival. And we're already starting to cure a small percentage of tumors. Now, to show that B cells are

important for the efficacy of these drugs, we can inhibit the B cell response or remove our B cell superheroes.

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Daniel

And that's what you see here in green. And you can see without those B cells we no longer have those immense survival advantage. And it looks just like a non-treated tumor. So we know that B cells are really responsible for the efficacy of the drug. So now we wanted to learn how to be cells deliver this anti-tumor immune effect.

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Daniel

And so through computational analysis of our single cell sequencing data we had made the prediction that B cells were in command of those T cells tanks or the T cell killer cells that can kill cancer cells. And so the first thing I want to show you is our discovery that the B cells were directly interacting with these killer T cells.

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Daniel

And so what we did is we isolated B cells from the tumors. Either that when they were non-treated or received the CD40 agonist drug and then took advantage of this really cool live cell imaging technique so we could see what happens to the killer T cells when they're incubated with B cells from these two treatment groups. So on the left here you can see what happens in a non-treated tumor.

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Daniel

Our killer T cells are labeled in green and the B cells are unlabeled in gray. And so what I want you to appreciate is that the B cells do come into temporary contact with the T cells. But their interactions are very short lived. And you can see the T cells really aren't moving around very

much. However, in stark contrast, when we give the CD40 agonist treatment, you can see the B cells are much more active and they come into long lasting contacts with the T cells, and they even start to move around together.

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Daniel

You see this happening all throughout the image. And so what we think is that when the B cells come into contact with the T cells, they're helping activate those T cells and telling them, hey, we got cancer cells that we need to go find and destroy. And so the first thing that I wanted to look at in this investigation was whether or not the B cells and T cells were exchanging activation signals.

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Daniel

So what we're going to look at is some images of how these cells look in terms of activation when they're when they're in contact with one another. And so here I'm showing an analysis that we perform to look for the possibility that the B cells and T cells were exchanging activation signals. So in green here we've labeled the T cells with the fluorescent die.

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Daniel

And so in the merged image on the left your killer T cells are right here. And right here in gray is the position of our B cells. So in the image there right here. And then in in red we're labeling the activation of B cell and T cell receptors. So the B cell and T cell receptors are really an important activation pathway that show that the B cells and T cells have seen tumor antigen targets.

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Daniel

And so what you can see here is when these B cells and T cells are in contact with one another, they have this red punctuate staining symbolizing the activation of the B cell and T cell receptor

signaling pathways that control their activation. And so now having demonstrated that B cells are in interaction with killer T cells and are also responsible for their activation, we wondered how do these interactions with killer T cells look in the tumor and do they interact?

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Daniel

Do B cells also interact with other immune cells that help destroy the cancer cells? And so here we're looking at some immunofluorescence images that allow us to survey the extent of B cell interactions with other immune cells and how these B cell interactions are organized. So on the left we're looking at a non-treated tumor. And the first thing I want you to appreciate is where the tumor boundaries are.

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Daniel

So I'm running my cursor over the tumor boundaries. So above the cursor is where the proper tumor epithelium is. And then this whole area out here is the tumor margins where the immune cells can start to try to respond. So in green we've labeled B cells, in red we've labeled macrophages, in yellow we've labeled the killer T cells.

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Daniel

And so just to explain why we're labeling macrophages is the macrophages work together with the B cells and T cells. So when the killer T cell destroys the cancer cell we need a cleanup crew to go and chew those dead cancer cells up. And that's what the macrophages do. And when they chew up those dead cancer cells they help the B cells find the next target.

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Daniel

And so this really becomes a well energized army when they work together. And so on the right, what you can see with the CD40 agonist treatment is now that we have we have the B cells, the

macrophages and the killer T cells all organized together in an army that has invaded the tumor. So we like to think that they've they're moving through progressively through this tumor and causing the incineration of cancer cells.

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Daniel

And so the next thing we really wanted to demonstrate is the to see if this possibility is true. Are the B cells really in command of the ability of these T cells to kill cancer cells? And so what we first needed to check is do the B cells control the molecular expression of or the expression of molecules in these killer T cells that allow for the killer T cells to kill cancer cells.

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Daniel

And so the molecule that we focused on is perforin. And this is because perforin is the molecule that the killer T cells use to blast holes in cancer cells and cause those cancer cells to die. And so here you can see from our single cell sequencing analysis that without any treatment, the killer T cells really lack instructions to make perforin.

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Daniel

However, when we give the CD40 agonist treatment to cause that B cell superhero response, we can now see that perforin is being made in a large amount by those killer T cells. And again, if we give the CD 40 agonist treatment but we inhibit the B cell response, we no longer get the peripheral production in those killer T cells.

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Daniel

And so what this symbolizes is that the B cell response to the CD 40 agonist drug is equipping these killer T cells with molecules that they can use to destroy cancer cells. So now let's see what this looks like in live cell imaging. So here what I'm showing in this experiment is what

happens with killer T cells and their ability to kill cancer cells when they've been pre-incubated with either B cells that have not received the CD40 agonist drug, or when they've been pre with B cells that have received the CD40 agonist drug and were active in killing tumors or leading a response against tumors.

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Daniel

And so in these images what you're going to see are the killer T cells in green and the tumor cells in gray. And so first what you can see without any treatment is the killer T cells come into contact with cancer cells. But these cancer cells they're all maintaining their shape. They're all still viable. However when we give the killer T cells the B cells that have received the CD40 agonist drug, you can see that the killer T cells come into contact with the cancer cells.

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Daniel

And those cancer cells that have been in contact with those killer T cells are turning into blobs. So those cancer cells are all dead and no longer able to propagate a tumor. And so what does this look like in the context of the CD40 agonist drug. So again this is a very similar plot to the one I showed you earlier.

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Daniel

We're able to look at the probability of survival over time. So again, without any treatment or the placebo treatment, there's a rapid progression to lethality in our models of aggressive triple negative breast cancer with the CD4 agonist drug. You see this overall extension of overall survival and some cures. And if we remove this killer T cell response that's regulated by our B cell superheroes, we no longer have any response to the drug.

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Daniel

So together, what this research all shows is how important this this B cell response to the CD40 agonist drug is to mounting a killer T cell response. Now why this foundational research is really important is it has the potential to improve our therapy strategies that we're using today in the clinic. And so really, what I want to show you right here is the potential that we can use CD40 agonist treatments to significantly improve the standard immunotherapy that's given to cancer patients today.

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Daniel

So here again we're looking at survival in our lab models of aggressive triple negative breast cancer in black. You see the control group where this rapid progression and lethality in orange are the models that have been given the standard immunotherapy. This activates T cells by themselves and red here you can see when we give the CD40 agonist drug to activate our B cell superheroes.

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Daniel

And so you can see that this has even better efficacy and has those small percentage of cures. But when we activate the B cells and the T cells together, now combining the standard immunotherapy with the CD40 agonist treatment, we're able to radically improve the response rates and also the cure rates of these aggressive tumor models, which, by the way, are all resistant to chemotherapy.

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Daniel

And there's no chemotherapy involved in this in this therapeutic regimen that we're using right here. So what this means is that the by harnessing the full power of the immune system, we can dramatically improve the cure rates. And I think what this also symbolizes in the is the importance of doing the foundational research on how our immune systems work, so we can

start to identify new pathways that we can take advantage of to improve the immunotherapy of cancer.

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Daniel

And while we've shown that we can start to improve the standard of care by unlocking B cell superpowers, we believe that we can do an even better job. So that way, instead of curing 60% of tumors, that we can move that up much closer to 100% of tumors by just thinking about what other B cell superpowers can we unlock to enhance cure rates.

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Daniel

And so what I really want to emphasize is how important this type of research is. I often think about the perspective of family members of cancer patients and the cancer patients themselves, who die the day before these treatments become available. This really means that every second matters, that we really can't wait to, to do this type of foundational research that provides the opportunity to save lives ten, 20, and 50 years from now.

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Daniel

This is really why science can't wait. We have lives at stake and that we need to really go aggressively after developing the future treatments that can help these patients. And I really think that it's been an exciting and very gratifying experience and pursuing this research, in part because I have a very dedicated and mission driven team that works very hard, and they're also very brilliant.

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Daniel

And also, I really want to thank the support that we get at the Salk Institute from people that help fund our research, such as the developmental chair provided by the Rentschler family, the

California Breast Cancer Research Program, Metavivor, Susan G. Komen, Cure Bound, the W.M. Keck Foundation and the NCI, as well as the Salk Institute that is providing me with the Innovation Award.

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Daniel

And so I also want to thank all of you for attending and taking interest in how you can support the research that happens at the Salk Institute, so we can develop the new immunotherapy strategies that are going to help patients in the very near future. Thank you.

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Michelle

Thank you. Dan, that was excellent. As someone whose mother has had battled breast cancer twice, my aunt breast cancer twice, you know, I am now officially a huge fan of B cells and really appreciate how well I was able to follow your presentation on the research. For everyone who's still on the webinar, this is going to open our Q&A segment.

00:26:20:12 - 00:26:43:24

Michelle

If you scroll down to the bottom of your screen, there should be an option labeled Q&A that will open up a box for you to ask your questions. Dan, we already have quite a few questions that have come in. So one of the opening questions is how does the immune system normally recognize and fight cancer?

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Daniel

Yeah. So actually it's very similar to the ways that I'm I have showed today that we boosted with the CD40 agonist molecule. These are the things that are supposed to happen on a regular basis. It's just that over time, for some people, their immune system loses the ability to process the information that they need, that this is a cancer cell that we need to destroy.

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Daniel

And so what we're really doing is kind of giving those immune cells the information and waking them up so they can fight cancer again. So you would expect when cancer arises in a healthy patient, that the B cells are going to be alerting the killer T cells, hey, there's cancer here. We need to kill it. They also may secrete antibodies that are going to help remove those cancer cells.

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Daniel

And so these are some of the just sort of the B cell centric mechanisms that are taking place.

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Michelle

Thank you. And related to that you've spoken to it a bit, but maybe a little more detail about how tumors actively hide from the immune system. How does that take place?

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Daniel

Yeah. So when cancer cells arise in our bodies, they sometimes are able to produce molecules that give them quote unquote, immune privilege, meaning that they send messages to tell the immune system, hey, I'm a cell that's supposed to be here. You need to leave me alone. And there are treatments that are designed are being designed right now to intercept those, those mechanisms and disable them.

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Daniel

And I think also, one of the ways that we can work or where around it is by taking advantage of the B cells ability to make antibodies, because it's going to mark a target on those cancer cells

and say, hey, we absolutely need to destroy them. Ignore those messages. These are cells that we need to destroy, they're oncogenic.

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Michelle

All right. And are any of those ways that a tumor cell hides from the immune system are any of those unique to breast cancer, or are those elements that are present in most cancers.

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Daniel

Well, on many of the signals that breast cancer and the challenges that breast cancer presents, and using an immunotherapy or other treatment strategies to fight cancer is held in common by other aggressive, what we call solid tumor types, things like having that cancer of ovarian cancer. And so there is a lot of benefit from doing this foundational research and breast cancer, because there's also the opportunity to translate these findings to benefit patients with other cancer types.

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Michelle

Yeah, I think, Dan, sometimes that's a message that we're not strong enough in sharing, which is that foundational discoveries in one cancer are so often illuminating in other cancers. And although we know that the battle against cancer feels so long because there are so many individual types of cancer, every breakthrough and one reflects often a breakthrough in another. A next question that came in, what is the difference between B cells and dendritic cells?

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Daniel

Oh, that's a very good question. Very scientific. So I really appreciate that one. So dendritic cells and B cells do have some overlapping functions. So dendritic cells can also help the T cells

recognize cancer. Now what's unique about B cells is that unlike dendritic cells they can also secrete antibodies that help mark those cancer cells.

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Daniel

So a lot of times the dendritic cells are looking for a cancer cell that has been labeled with a B cell antibody to start pulling away their tumor targets and presenting them to T cells so that the T cells can fight. So they all work together, but they also have some overlapping functions.

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Michelle

All right. Excellent. This is another specific question. Are the CD40 agonist-based activation of B cells applicable for other forms of cancer.

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Daniel

Yeah. So right now the CD40 agonist drug is being evaluated in a couple of different cancer types. One is triple negative breast cancer. But it's also been involved in melanoma and pancreatic cancer. And so there's a lot of promise coming from the clinical work that's being done on this. But this therapy also is in need of a lot of optimization.

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Daniel

And so some of the research that we're focused on is how can we make these drugs that activate the B cell response work better, or what type of alternative therapies can we use to make sure that we have a very productive B cell response in the fight against cancer?

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Michelle

Excellent. All right. As we as we go through and aggregate the wealth of questions that have come in, one question that was just asked was an observation that so much of the funding for your research, Dan, has come from foundations and private sources and not necessarily from federal funding. So I want to give Dan just a moment to take a break and share that here at the Salk Institute,

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Michelle

we have always funded our science through a combination of federal funding and private philanthropy. But quite frankly, the research that Dan is, is describing here, the really high risk, high impact research that isn't guaranteed, an outcome that maybe isn't ripe for federal research. That's where private philanthropy always comes in and accelerates what we can do today. And so when you fast forward to 2026, where we find ourselves today, about 60% of our scientific funding is coming from private donors and foundations.

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Michelle

So all of you who have joined the Science can't wait effort, all of you who are taking advantage of the Del Mar Foundation's one for one match. You are part of this collective that is making research that otherwise would not be funded. And if research is not funded, it's not conducted. So you are truly making a difference. And we thank you.

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Michelle

Okay, Dan, hopefully I gave the team enough time to consolidate some of these questions. There's a couple of questions about the future. So in in your fields when you look to the next five to 10 years. What do you hope to see or what do you think success might look like? You know, if we were to advance ourselves to 2036.

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Daniel

Yeah, I think in our laboratories at the and both as I showed you, the military and other laboratories across the country, is that when we're doing preclinical research, we're able to discover ways that are actually curing tumors. And that's yet to been translated to the clinic. And so what I really hope for is now where we talk about a patient going in and receiving an immunotherapy and fully expecting to be cured.

00:33:57:04 - 00:34:32:10

Daniel

And I think that there's a lot of really exciting strategies that are being developed and that we want to develop in my laboratory, where we can engineer designer immune cells that are hard wired to recognize cancer cells and risk and be delivered to a patient such that basically, we're taking a patient that has a nonfunctional immune system and guaranteeing that they have a functional immune system, because we're giving them the actual cells that have been designed to recognize cancer and fight it.

00:34:32:10 - 00:34:49:01

Daniel

So these are things like advancing CAR-T therapies that people might have heard about. But we want to have B cell-based therapies that where B cell can be infused into a cancer patient and making sure that they get a curative anti-tumor immune response.

00:34:49:03 - 00:35:10:07

Michelle

That's incredible. It's just it's so inspiring to hear the basis of your science, Dan, about how the body and the immune system has what it needs to fight, but, you know, it's compromised in some instances, needs to be emboldened, signaled in others. But it's just it's a very inspirational message you talked in your response about B cells.

00:35:10:07 - 00:35:20:12

Michelle

One question that was just asked is what motivated you to focus on the B cell approach over the myriad of other approaches that you could have focused your research?

00:35:20:16 - 00:35:52:04

Daniel

So actually, to tell a little bit of a story, this actually started off with an objective, is to identify ways to make the anti-tumor immune response even stronger. So when I was a postdoc, I was basically doing a bunch of different immunotherapy strategies and manipulations and had started to investigate B cells. And what would happen if we started to manipulate B cells.

00:35:52:04 - 00:36:21:16

Daniel

And this is where I started to see, well, when we inactivate these cells, we lose the capacity of the immune system to recognize cancer altogether. Or alternatively, like I showed you today, if we start to activate these cells, we start to really improve tumor control. And so this really just got me fascinated and dedicated to this exciting line of research, because really very few people were even looking at this in the first place.

00:36:21:17 - 00:36:37:12

Daniel

And I thought, well, you know, with so much investment being given to T cells, I have an opportunity to fill a major gap in our research knowledge and also in our clinical capacity to improve immunotherapy.

00:36:37:14 - 00:36:52:19

Michelle

Excellent. And then along those lines of the B cells, a question was are there any barriers that you've seen in CD40 that if identified would better optimize B cell activation?

00:36:52:21 - 00:37:33:07

Daniel

Yeah. So as I mentioned these drugs are still in need of some optimization. So like many immunotherapies there some patients will experience toxicities some side effects like rash or other GI symptoms. And so there's there the research is looking for ways to minimize some of those side effects while maintaining the therapeutic advocacy against tumors. So that that's one of the obstacles that CD40 agonist faces is also like I showed you, we're able to cure some tumors, but not all of them.

00:37:33:09 - 00:38:06:06

Daniel

And so we still need to improve our immunotherapy strategy, whether it's using the CD40 agonists in combination with other immunotherapies like we showed with the standard immunotherapy. Or do we need to look outside of the CD40 for the agonist therapy and look for other ways to activate the best response? And we're really paying attention to that alternative line where we're going to try to look for other ways to harness this B-cell response, to develop new immunotherapies that are independent of the CD40 agonists.

00:38:06:08 - 00:38:24:05

Michelle

That makes sense. Dan, this next question requires a little bit of an opinion for you, but there's a question about whether or not you see this research changing the treatment of breast cancer. And specifically, can you imagine a future where there's no chemotherapy for breast cancer?

00:38:24:07 - 00:38:57:14

Daniel

Well I definitely believe that the message is getting out there that we need to be harnessing B cells in our immunotherapy approaches. And so I do believe that at some point as we get more and more drugs and strategies, published as a in the preclinical setting that these, these strategies work, that they're going to be adopted in the clinic and would start to see clinical trials so that these cells are being leveraged in the immunotherapy response.

00:38:57:16 - 00:39:21:20

Daniel

CD40 agonist is one of those drugs that's just started to be evaluated in clinical trials and triple negative breast cancer. And so we're going to find out how well that works. And some of the early data suggests that it is working much better than the standard immunotherapy. The second question, can you remind me again, I'm sorry.

00:39:21:22 - 00:39:25:21

Michelle

Do you envision a world where chemotherapy wouldn’t be used?

00:39:25:22 - 00:39:53:03

Daniel

Yeah, yeah. So I think that that there should be a world because what we've shown in our preclinical models that are resistant to chemotherapy, that if we can properly manipulate the immune system, we can cure those tumors. And so I think this question is motivated by, chemotherapy comes with a lot of side effects. And can we get around that by using the immune system.

00:39:53:06 - 00:40:21:02

Daniel

And our research shows that that's fully possible. So now what I think we need is the consistency of this research. And a really well-elucidated logic that, hey, chemotherapy is no longer needed. It can be detrimental, in fact, to these immunotherapy treatments. And so can we improve patient outcomes by withholding the chemotherapy and giving them the appropriate cocktail of immunotherapy drugs to eliminate their tumor?

00:40:21:08 - 00:40:43:14

Michelle

Excellent. And for our guests who ask that question, it's one that's close to my heart as well, knowing that, you know, sometimes the long term effects of chemotherapy are very, very hard for the individual and a family to support. And the more that we can look here at the Salk, of course, lifespan is important, but the Salk is very focused on health span.

00:40:43:15 - 00:41:17:01

Michelle

How can we live fuller, richer, more active lives where we're cognitively plugged in while we are here? And that might be more important than extending life. And so when you give an answer like that, Dan, I think it gives us a lot of optimism about living fuller, quality lives. So there was a question that was asked to me, which I appreciate about what do I wish that people would understand more about scientific discoveries and foundational research?

00:41:17:01 - 00:41:41:20

Michelle

And one element that I want to share is Dan's research right now. And what you're hearing right now, I would bet that you are going to start hearing more and more about harnessing the power and the command of B cells, more therapies, more opportunity that comes from that line of thinking. But you're not going to hear about that tomorrow.

00:41:41:20 - 00:42:07:01

Michelle

You're not going to walk into an oncologist office necessarily tomorrow. And so what you really have is the cutting edge of science. This is where, by Dan publishing all of his results, pharmaceutical companies, biotechs, other researchers are going to take his findings, his new insights, and they're going to build on those as Dan and his lab continue to do the same.

00:42:07:01 - 00:42:35:18

Michelle

And that is going to lead to clinical trials, as Dan has shared, he would really love to see. And those clinical trials are going to lead to drug targets and therapy targets. And before you know it, we will have something new in the marketplace. If we want new innovations tomorrow, we need to invest in discovery today. That is what I very much hope that people will understand about Salk research.

00:42:35:20 - 00:42:58:19

Michelle

All right, Dan, just a couple more questions. Thank you for being so patient. The Q&A has been very, very active. There's a question about your background in computational biology and recognizing everything that's happening in the world with AI and computation. One of our participants would like to know how computational biology accelerates discoveries in cancer research.

00:42:58:21 - 00:43:23:04

Daniel

In the past, to understand what was happening at a molecular level in cancer, we had to look at individual molecules one by one. And that can be really slow. But now as I showed you with things like single cell sequencing, we can look at all the molecules and we can look at all the cells.

00:43:23:04 - 00:43:52:21

Daniel

And so then the trick is can you use machine learning methods to pull out the meaningful information from that data. And we've become really successful at doing that. And so it takes out a lot of the mystery on what do you do next or what is happening because it just gives you the answer. You can see, okay, this cell is present in the tumor.

00:43:52:22 - 00:44:35:19

Daniel

It's been programed to do this. For example, a T cell that's been programed to kill by producing perforin like I just showed you today, and a B cell that's been equipped to either present antigen or tumor antigen targets to T cells to get them activated. We can also see B cells programed to secrete antibodies. And so I guess to summarize, is that this type of technology just allows us to really accelerate our understanding of what's happening in these very complex mechanisms and start to really fill in the gaps much, much faster.

00:44:35:21 - 00:44:53:04

Michelle

Excellent. So two final questions, Dan, and then I will conclude with some remarks. First question is with incoming gifts and private support, how would you be putting those additional funds to work in your lab?

00:44:53:10 - 00:45:17:07

Daniel

Oh, through a variety of ways. So one of the things is, is that we need these hard-working scientists that perform the experiments and also contribute their brilliant insights into the project. So it helps fund the staff that actually performs the research. It also helps us to perform these expensive experiments, like the single cell sequencing that we perform is not cheap.

00:45:17:08 - 00:45:52:18

Daniel

It is an expensive technology, but it has a major payoff because we can see everything that we need to see to understand these complex mechanisms. Also, testing new immunotherapy drugs is also really expensive process as well. And so with the funding that we would get, we'd be able to start to innovate even further. And these types of immunotherapy strategies and, very similar to the point that you made, is where when you're working at the cutting edge and you want to try something new, oftentimes there's not government funding available for that type of research.

00:45:52:18 - 00:46:12:05

Daniel

And so what this allows us to do is fill in that gap that we're missing in the support to do the types of innovations that we need to start to break through and make these transformational changes for cancer patients and deliver them a type of therapy that's not been really conceived of before.

00:46:12:07 - 00:46:37:12

Michelle

Excellent. And then final question before I wrap up, could you share with the audience what makes this type of research so compelling or so much easier for you, so much more interesting because it's happening at the Salk about your lab at the Salk. What are the advantages of doing this here, Dan, rather than another institute or university?

00:46:37:14 - 00:47:04:13

Daniel

Yeah. That's that is a great, great question. And I guess, like the best way to answer is first, like, I've been so happy at the Salk because it's really transformed my thinking about what is possible with our research. And that's because I have world class collaborators and access to brilliant people to work with, and we get excellent feedback.

00:47:04:13 - 00:47:23:01

Daniel

And we have these brainstorming sessions where, you know, what, if we do this? How would this might work? Would this make a major impact on the elimination of cancer cells? And so I have weekly meetings with my collaborators and colleagues at the Salk, where we just get together and we start brainstorming on how we can attack cancer cells.

00:47:23:05 - 00:47:49:22

Daniel

The other thing that I brought up today is the immense technological advances that we have. Salk has world class core facilities that provide us the technology that we need to do this high-powered research. And, you know, that's, for example, the single cell sequencing and the live cell imaging that I showed you today, some of these things we couldn't do at other institutes.

00:47:49:24 - 00:48:06:00

Daniel

And then lastly, the Salk has been a major supporter of our research and recognized, for example, the innovation that we're doing in my laboratory. And so it provided funding so we can start to work on the breakthroughs that we're trying to deliver to cancer patients.

00:48:06:02 - 00:48:42:16

Michelle

All right. Well, well thank you, Dan. And in conclusion, as we move to some of our final slides, I just want to thank Dan for his fascinating presentation that that very much helped me to understand the immune system's response to cancer. I hope all of our participants in the online world feel the same. I hope that you've learned something about cancer and about the science that happens here at the Salk, and that we're able to earn your investment in our worthy research, and that you take advantage of the Del Mar Foundation's one for $1 for dollar match that leverages your gift.

00:48:42:17 - 00:49:11:06

Michelle

We're so fortunate to have the San Diego community, as represented by the Del Mar Foundation, so invested in the scientific insights and advancements, and we want to take advantage again. We're only $10,000 away from hitting that $50,000 generous gift. So please consider helping us to meet that threshold. In closing, this is the end of our three-part series. Time flies when you're having fun.

00:49:11:11 - 00:49:41:09

Michelle

We very much hope that will be able to partner with the Del Mar Foundation and bring more extraordinary research into your offices and living rooms in the future. Till then, there are many ways to connect with the Institute, from the Joan Jacobs Science and Music sessions to scientific webinars on the Salk campus, and maybe in in our most immediate future Symphony at Salk, which is our incredible concert under the stars, which will be held on August 15th.

00:49:41:12 - 00:50:04:11

Michelle

Tickets are available now and going fast, so if you're interested, you can use the information on this slide and or reach out to any of us. A huge thanks! In conclusion, again to the Del Mar Foundation for their partnership, for their leadership. We hope that this is the beginning of many other community organizations partnering with the Salk following the Del Mar Foundation's leadership.

00:50:04:11 - 00:50:15:10

Michelle

We hope that you all enjoyed this series. The recording will be available next week on salk.edu and until we see you again, we wish you the best. Thank you.