Funding for Yale Cancer Answers is provided by Smilow Cancer Hospital.

Welcome to Yale Cancer Answers with your host Doctor Anees Chagpar.

Yale Cancer Answers features the latest information on cancer care by welcoming oncologists and specialists who are on the forefront of the battle to fight cancer. This week, it's a conversation about increasing an immune cells ability to target and kill cancer cells with Doctor Sidi Chen.

Doctor Chen is an associate professor of genetics at the Yale School of Medicine, where Doctor Chagpar is a professor of surgical oncology.

So Sidi maybe we can start off by you telling us a little bit more about yourself and what it is you do.

I'm a scientist by training and I got my PhD at the University of Chicago. I studied genetics and evolution and then I went to MIT studying cancer biology and that’s when I got motivated to find future cures for cancer and benefit the broader population.

So tell us a little bit more about your research and how you’re trying to cure cancer.

I believe currently we are in a new era of cancer medicine.
There are a number of new therapies on the horizon, including cancer immunotherapy, using immune checkpoints, and more recently on cell and gene therapy, and I think the future of medicine is the use of a variety of novel therapeutics for the patients, and these novel therapeutics would have to be better than what we have. Today, for example, they have to overcome the disease resistance relapse and have to have better safety profiles and have more balanced efficacy and toxicity ratio. And I can keep going, but I think for our patients we need better jobs. Absolutely, I couldn’t agree with you more tell us about your research and how you hope to do all of those things. I think no man can do it all. As a geneticist, I believe the true power of unbiased approach. All of us have the same genetic compositions. We all share the same genes in the genome. Of course there are variations.
But my approach has been let nature tell us what is the right? Approach. Which means we. Tend to go brawl in survey the entire genome or survey full set of genetic composition to see which genes. If you take it out or if you turn it on would help our own selves fight cancer cells better. And we do so by performing unbiased genetic screens such as CRISPR, knockout, CRISPR activation screen to find the therapeutic target that can overcome some of the problems. I mentioned previously, for example, resistance to cancer killing or tumor infiltration or metabolism, and by doing these screens we will be able to see through a big pile of haystacks to find the small set of needles that allow us to improve the property of immune cells such as T cells and thereby intense. Of Therapeutic FC and reduce the toxicity. Delve a little bit more into the details of that CD. Tell us a little bit more about how you go through this haystack and find these needles.
0:04:08.85 –> 0:04:10.47 what technologies you use.
0:04:10.47 –> 0:04:12.085 Not everybody might be aware
0:04:12.085 –> 0:04:13.7 of what exactly crisper is
0:04:13.763 –> 0:04:16.49 and how that works. Sure,
0:04:16.49 –> 0:04:18.87 let me slightly switch gears.
0:04:18.87 –> 0:04:21.792 CRISPR is not a technology from
0:04:21.792 –> 0:04:24.378 the gecko because it’s actually
0:04:24.378 –> 0:04:27.624 an immune system of the bacteria.
0:04:27.63 –> 0:04:30.99 But then, as the human beings
0:04:30.99 –> 0:04:35.95 harness those tools, those natural.
0:04:35.95 –> 0:04:39.597 Component for fun bacteria to become genetic
0:04:39.597 –> 0:04:43.648 tools the beauty of CRISPR is that it can be.
0:04:43.65 –> 0:04:46.946 Very easy to use and can be precisely
0:04:46.946 –> 0:04:49.179 targeted and can be scalable.
0:04:49.18 –> 0:04:52.98 So what we are doing is to use CRISPR to
0:04:53.078 –> 0:04:56.876 manipulate the genes for the expression.
0:04:56.88 –> 0:05:00.64 For example, we can take out a gene,
0:05:00.64 –> 0:05:05.63 or we can turn on a gene and we can do so.
0:05:05.63 –> 0:05:10.394 Thousands or 10s of thousands at a time.
0:05:10.394 –> 0:05:11.53 For example,
0:05:11.53 –> 0:05:14.946 if there are 20,000 genes in our genome,
0:05:14.95 –> 0:05:18.898 we can turn. One at a time,
0:05:18.9 –> 0:05:20.988 but we do it all together.
0:05:20.99 –> 0:05:25.73 And it’s like we enumerate each
0:05:25.73 –> 0:05:30.23 of the haystack and see by turning
0:05:30.23 –> 0:05:32.03 on each of the gene.
0:05:32.03 –> 0:05:34.326 Which genes would help our own cells
0:05:34.326 –> 0:05:35.31 kill cancer cell?
0:05:35.31 –> 0:05:35.76 Better?
0:05:35.76 –> 0:05:38.46 Because we’re doing so many at
0:05:38.46 –> 0:05:41.489 once and the chances we finding
those needles are much higher than.

Than using a traditional one at a time approach.

So you start turning on these genes to figure out which ones are going to help you in your fight against cancer and which ones are not. One would think however, that still that’s rather simplistic in terms of fighting cancers.

So how do you figure out which genes are particularly relevant for which particular cancers or which particular drugs, or is it the fact that you know certain genes are ubiquitous in terms of their effect in cancer?

Those are great questions. There are numerous ways to look to Rome and just take one of our recent study.

For example, we are taking triple negative breast cancer cells and we also take T cells as the cell from our own bodies immune cells to fight them. And then we turn on the genes in T cells using CRISPR and then we measure the ability of T cells to kill and there’s a becomes technical.

There’s an essay called Degranulation Assay which means we can see how fast these T cell degranulate meaning how fast they release the enzyme to kill.
cancer cells and by measuring the Generation, which means the T cell killing ability. Uh, one gene at a time, but in a massive pair of manner we can exhaust the entire genome for every gene. T cells and then we can. Identify which genes? When they’re activated, would enhance such an ability to kill cancer cells. And of course, this we. Initially perform in breast cancer cell killing, but then when we apply to other cancer types, we found this is also true because the gene is universal. And therefore the ability of T cells to cure cancer cells is controlled by the same gene, no matter it’s getting a breast cancer cell or killing leukemia myeloma cell. I mean, it certainly sounds incredibly interesting, but one of the things that might be curious is. You’re turning on these genes and kind of using CRISPR technology to activate these genes within a T cell, but in a human how would you activate that gene?
Or is there a way to turn on a particular genes in an in vivo system?

A cell therapy, by definition, is the usage of cells as therapeutics, and for many of you you might have heard of car keys or camera engine receptor T cells. That’s one form of cell therapy and what Carti or other form of self therapy does is that it takes the cells from a patient or from a healthy donor, and then you can perform genetic engineering in those cells. For example, putting cameras and antigen receptors on the surface. Enhance the expression or turn on the expression of a particular gene, and we can do it by demand by using genetic engineering or vector transgenes. So after we modify these genes in these T cells, the cells would become therapeutic candidate and those are the type of cells we can use to infuse back into. In our case, the animals to treat the cancer in those animal models. Of course, in the clinic, the proof of cell therapy, the cells were taken out from patient.
The genes have been modified and the cells have been reinfused into the patient to treat cancer. Then one would think that you would have some cells. The native cells that are in the patient’s that are not quote supercharged or or modified, and you’d have some cells that were the more therapeutic cells that had been reinfused. How do you get or is there a way to get patients to make their own cells? Have that supercharged ability so that when these cells die, there isn’t a continued need to have an infusion of these modified cells? Or is that something that isn’t done? A patient may not need the supercharged cells in the body for a very long period of time. And we to some degree we haven’t done the clinical study yet, but to some degree we believe it may be important to. Let the cells finish the job and then be done. Because we don’t want them to stick on forever. So I think some cells may be sufficient to kill the
cancer cells and we’re talking about the persistence issue, which is can be very long conversation, but.
The ideal situation would be we infuse those cells into the body.
The cells kill off the cancer and the cancer is gone, then the cells are gone too, and then the patient is back to normal.
So that would be ideal situation. But in the real clinic this is a much more complicated than that.
I mean, one of the things that we think about is recurrences or even patients who denovo are at an increased risk, and so when we think about the immune system.
Not only does the immune system help in terms of you know, clearing and having these supercharged cells would be useful in that context, but they may also be relevant in terms of preventing cancers from occurring.
At all, so in high risk individuals or in patients who are at high risk of recurrence, reducing the risk of recurrence.
O has this kind of therapy been thought about in those two contexts?
All you’re absolutely right.
In cancer treatment, there are many cases of relapse or
resistance and therefore multiple dosing is often required or beneficial, and it’s absolutely case by case in the clinic disease by disease indication by indication, and I think we are still early in the form of self therapy because currently self therapy infusion is only given once. And there have been clinical trials for multiple infusions, or.

Use as prophylaxis, but those much earlier studies the approved drugs were given as a single infusion for most of the time. OK, well, we’re going to take a short break for a medical minute. Please stay tuned to learn more about supercharged T cells fighting cancer with my guest doctor Sidi Chen. Funding for Yale Cancer Answers comes from Smilow Cancer Hospital hosting a smilow shares cancer Survivor Series June 8th and 15th. Register at Yale Cancer Center or email cancer. Answers at yale.edu.

Breast cancer is one of the most common cancers in women in Connecticut alone, approximately 3500 women will be diagnosed with breast cancer this year, but there is hope,
thanks to earlier detection, non invasive treatments and the development of novel therapies to fight breast cancer.

Women should schedule a baseline mammogram beginning at age 40 or earlier if they have risk factors associated with the disease.

With screening early detection and a healthy lifestyle, breast cancer can be defeated.

Clinical trials are currently underway at federally designated Comprehensive cancer centers such as Yale Cancer Center and Smilow Cancer Hospital to make innovative new treatments available to patients.

Digital breast tomosynthesis or 3D mammography is also transforming breast cancer screening by significantly reducing unnecessary procedures while picking up more cancers.

More information is available at yalecancercenter.org you’re listening to Connecticut Public Radio.

Welcome back to Yale Cancer Answers. This is doctor Anees Chagpar and I’m joined tonight by my guest doctor Sidi Chen.

We’re learning about his research into using T cells to fight cancer cells and right before the break
He was telling us about how you could use new technology to look for genes that may be particularly effective in terms of getting rid of cancer and then using CRISPR technology to activate these genes and potentially using it in cellular therapies in patients to treat cancers.

You had mentioned that your work right now is using largely animal models. Has this been tested in clinical trials or is that something that is coming down the Pike?

Thank you for the question, and my lab is Preclinical Research lab and of course my goal is to discover the therapeutic targets and pathways and how it works to build the portfolio or the platform.

We of course talking to different translational partners or potential partners to bring this further down into clinic. But this is a complicated process because cell therapy has complex manufacturing and complex regulatory path as well, so it’s not as easy as some of the traditional drugs.

Yeah, now you had mentioned that you had started your research.
Really looking at triple negative breast cancers.
So do you want to tell our audience a little bit about why you chose triple negative as a good cancer to look at to begin with?
Y asur Alice, you are a much better expert than me on breast cancer.
US we believed triple negative breast cancer is the type of breast cancer that there is no hormone targeted therapy which is very commonly used for the other types such as her two positive. So we believe we need to identify other novel therapeutic targets or therapeutic approaches to adjust the unmet need for this disease.
Yeah, I think that’s right, but I think so.
Certainly you know we we on this show talk a lot about targeted therapies and triple negative by definition don’t have a target as such.
They certainly are not responsive to endocrine therapy, being ER, PR negative.
One of the interesting things about triple negative breast cancer is that we’ve found that these are potentially more immunogenic in in the sense that...
they tend to have more tea infiltrating lymphocytes when you look at them, when people have looked at immunotherapies, they tend to respond to immunotherapy so.

You know, I wonder whether part of the rationale is to look at cancers that are particularly prime for immune regulation. Did that play into your thinking, and if so, will it affect which cancers you look at next in terms of the ability for these supercharged T cells to battle cancer? Ohh yes, of course, the breast cancer have different subtypes, and even between different patients or different level of immune infiltration or the tumor microenvironment is complex issues. There are tumors without. Any or there would be very little infiltrating T cells that you cancer fighting cell and on the other hand there are tumors that are filled with immune cells and in order for T cells to kill cancer cells, you need T cell to get there to the right place before they can do
their job and therefore we are also looking for a genetic component.

That controls the process of tumor infiltration.

Besides cancer killing, and in order to do so,

we are adopting a similar approach,

unbiased genetic screens and look for the genes when you either get rid of or when you turn on what helped the T cells get into the term micro environment,

and I think that property can be cancelled. Specific or can be more universal like what we have been doing now is use triple negative breast cancer as a starter model and then identify those genes to supercharge the T cells and then apply those findings into other disease indications such as other form of breast cancer or melanoma or pancreatic cancer or other cancer types.

So CD when you’ve started to look at these other cancers.

Have you found that there’s a difference in terms of the response of these? These supercharged T cells based on how immunogenic the cancer is in other words. If a cancer doesn’t have a lot of these infiltrating lymphocytes say like a luminal,
a breast cancer or a cancer that really doesn’t evade the immune system or isn’t as immunogenic, it is the effect different in those populations in those cancers in those patients than it is in cancers where there are a lot of tumor infiltrating lymphocytes or cancers that we know are highly immunogenic. Oh, thank you for the question and let me declare that I’m not the clinician, so therefore I cannot comment on the patient side, but however, based on the tumor models we use in animals. There are certainly differences in commonalities between different disease models. You find in cases where the genes regulating T cell cancer killing or cancer infiltration. Uh is specific for some type of cancer, but also there’s a set of genes that are common to multiple type of cancers. When we’re performing these T cell studies cell screening studies. And so. So have you looked at whether when you supercharged these T lymphocytes, whether there is a difference in terms of how effective they are coupled with other forms of therapy,
say immunotherapy or chemotherapy?

That’s a great question, and that’s exactly what we’re trying now, because as you know and.

Most of the late stage cancer cannot be cured by a single form of therapeutics, and that’s why having more options in more innovative therapeutics would allow us to have more choices for the patient to have multiple lines of therapy or have different combinations.

And we are studying different combinations in our lab, including immune checkpoint, antibodies and chemotherapy, and cell therapy with or without supercharged T cells and gene therapy.

Looking forward to see the signal of 1 + 1 greater than two or at least 1 + 1 greater than one. In terms of therapeutic efficacy and hopefully in terms of toxicity, 1 + 1 is smaller than one, or like at least not.

Bah, too much greater than two. So this is always a hot balance.

Have you gotten any initial results on that in terms of understanding what combines well with supercharge T cells versus what doesn’t?
Yeah, we’re still early in the game and our research is ongoing and with some initial observation is that if we combined it with.

The gene therapy, or a major base?

Imagine therapy because like one side of my study,

is to heat up the immune system in the tumor. Like we have an approach called

And we found self therapy and Meiji can be combined in order to.

Improve the therapeutic efficacy of one another.

This is natural because what major does is to heat up the immune system so the cells get in easier and recognize the cancer cell better and then the software app is to actually providing the T cells itself, supercharged them, and then let them do the job to kill cancer cells.

So I think naturally these work together. But of course there’s a long way to go.

How does gene therapy actually work in terms of the clinic? Just take us back a little bit.
that goes into your cells and kind of does its own little crisper in vivo help our audience to understand how that works? Yeah, sure, uh, gene therapy for cancer is still very early, and currently there’s very little. Approved shocks for gene therapy for cancer. Currently there are. A few examples, for example, are you can deliver the gene therapy product systemically, or you can deliver the gene therapy product directly into cancer and hopefully. Not just. Cheat the tumor you that you injected, but also create inflammatory response. That’s going to be systemic, meaning it has an effect on the distance side. This sounds challenging, but not impossible, because our own bodies connected immune system is connected. So what we’ve been doing and trying to use therapy to activate the immune system so that when it gets activated, it has the ability to chase down the cancer cells, not just from the tumor side, but also on the distant side.
For example, the metastasis.

So how exactly does gene therapy activate the immune system?

Because so many of us have heard about checkpoint inhibitors.

You told us a little bit about cellular therapy.

Tell us how gene therapy kind of revs up the immune system as well.

One of our earlier studies, we used CRISPR activation and again this is similar to what we do for supercharging T cells, but in this case we are promoting the expression of antigens because the cancer cells don’t want the expression of their own antigen on the surface. Therefore they downregulate what they could downregulate the expression of.

What we try to do is forced expression of those antigen to be hyperactivated or hyperexpressed and presented on the surface and therefore we’re like setting a light on those cancer cells and let the immune system see them better.

Doctor Sidi Chen is an associate professor of genetics at the Yale School of Medicine. If you have questions the address is canceranswers@yale.edu and past editions.
0:28:44.572 –> 0:28:47.084 of the program are available in audio
0:28:47.084 –> 0:28:49.065 and written form at Yale Cancer Center.org
0:28:49.07 –> 0:28:51.054 We hope you’ll join us next week
0:28:51.054 –> 0:28:53.31 to learn more about the fight against
cancer here on Connecticut Public radio.
0:28:53.31 –> 0:28:55.403 Funding for Yale Cancer Answers is
0:28:55.403 –> 0:29:00 provided by Smilow Cancer Hospital.