Beyond CAR-T: Re-engineering Cells into Life-saving Therapies

Our cells have the innate ability to protect us. The idea of using cells as medicine emerged with bone marrow transplants, and then CAR-T therapy for blood cancers. Now, scientists are beginning to engineer much more complex living therapeutics by tapping into the capabilities of living cells to treat a growing list of diseases.

The power of cellular therapy is being explored to halt and reverse disease, restore damaged organs, and, ultimately, cure many life-threatening conditions. Important advances in the understanding of disease biology and major innovations in gene editing, protein engineering and cell culture technology have created a highly fertile scientific environment in which cell therapy research is flourishing.

We are talking to Dr. Lawrence Fong, Efim Guzik Distinguished Professor in Cancer Biology and Cancer Immunotherapy Program lead at UCSF about treatments and disease area focus, advantages of harnessing the power of cellular therapy, challenges faced, new initiatives and global awareness of these programs.

Full Transcript:

Priya Menon: Hello and welcome to CureTalks. This is Priya Menon your host. Today, on CureTalks, we are discussing cellular therapy. We have with us Cancer Immunotherapist Dr. Lawrence Fong from the UCSF Helen Diller family Comprehensive Cancer Center. Dr. Fong has over two decades of experience, working with preclinical and clinical studies of FDA-approved immunotherapies. Joining Dr. Fong on the panel today are Patient Advocates, Heidi Floyd and Cynthia Chmielewski. Welcome to CureTalks everyone. Using cell therapy to halt and reverse disease, restore damaged organs and ultimately cure, many life-threatening conditions is now a realistic goal for our scientists. Dr. Fong, can you briefly in layman's language explain what cell therapy is?

Dr. Lawrence Fong: Well, cell therapy is a treatment approach where we actually give cells either from the same patient or from another individual to really try to address a certain type of disease. We've actually been using cell therapies for over 50, 60 years in the form of bone marrow transplantation. And so, in that example, what we do was will either take bone marrow from the same patient or from somebody else and give it to that patient to restore their ability to actually make blood cells typically following chemotherapy and radiation therapy, that's given for their treatment. But one of the things that we found with the bone marrow transplants was that in addition to allowing the patient to make their own blood cells, these transplants also transferred, immune cells and those immune cells within the graft what's given to the patient, actually helps to kill the cancer cells within the patients. And so building upon that one of the areas of excitement in cancer therapies now, is really to hone in, on those immune cells that are capable of killing the cancer cells and that's where many groups, including our own or working on ways to engineer a patient's own immune cells, or again immune cells from another host and give them back to an individual with cancer. And we now have FDA approved treatments for b-cell malignancies to leukemias and lymphomas as well as for multiple myeloma and there's a lot of activity trying to broaden that out to other cancers at the present time. And these are in the form of these CAR-T cells or Chimeric Antigen Receptor-T cells, that's a way of engineering those immune cells to actually recognize the cancer.

Priya Menon: Dr. Fong, other than cancer, are we using cell therapy in other diseases as well?

Dr. Lawrence Fong: Absolutely. I think this is an area where there's a lot of interest in actually using cells again from donors to help treat disease and there are examples where for instance, with islet cell transplants were taking those pancreatic islet cells to help people with diabetes. And there also is interest in terms of, on the regenerative medicine efforts to think about ways that we can give cell therapies that might actually help a patient heal or restore areas that might have been impacted by disease. But this is an emerging area that is continuing to evolve and develop.

Priya Menon: I know I'm going to ask you a question which I keep getting like see it being discussed in forums and people are very confused about it. When you say stem cell therapy, right, what does that intend, is that part of cell therapy? How are stem cells, if they are, how are stem cells used in cell therapy?

Dr. Lawrence Fong: When we think about stem cell therapy, we often will think about situations where we give a cell that can give rise to other cells and repopulate and continue to maintain a person hopefully for the rest of their lives. And the best example of that is these bone marrow transplants or what we also call peripheral stem cell therapies where we can actually harvest circulating stem cells from a patient, or from a donor and then give those back to a patient. And those stem cells are actually what's able to repopulate in this case, a patient's immune system. We're looking at stem cell therapies and other context not just focusing on bone marrow replenishing blood production but looking at other tissues because as we've learned in the laboratory, that there are stem cells for many different types of tissues and this is an active area of research in terms of trying to see what stem cells we could think about giving to a patient that might restore a tissue, that might be impacted by disease.

Priya Menon: Dr. Fong, what is the Living Therapeutics Initiative that UCSF is having and what are some of the disease areas that are being explored under this?

Dr. Lawrence Fong: Yeah so, the UCSF over the last two to three years we've initiated a program that's called The Living Therapeutics Initiative that's focused on developing and Manufacturing cell therapies. And the thinking here is that rather than giving a treatment that is inert and goes into a patient and basically is cleared out of the system, we're giving cells that are living and persisting within the patient that will help treat a disease. And so, the example that I gave with regards to CAR-T cells is one example, but there are actually other immune based treatments to target cancer that are also being studied including using T cell receptors and other targeting domains that we can use to potentially treat cancer. But it is really expanded beyond cancer. You can think about situations where engineering immune cells rather than trying to kill cancer cells, actually trying to quiet autoimmune disease or other types of diseases where the immune system is actually overactive. You could also think about situations where individuals might have genetic errors that prevent them from producing certain molecules or proteins and by actually engineering the cells you can actually have those cells now make the protein in an individual and, probably the best examples of those are the efforts, focused on hemophilia and thalassemia. And then there are also is interest in terms of using these cells to help with other diseases including heart disease and so I think it's really broadened how we can think about medicine and one of the hopes is with these living therapies, you give the treatment and you might give it once or twice but then once the cells are on board, the patient might be potentially cured or might enter into a long remission and not require continued treatment as they might with many of these different diseases.

Priya Menon: Dr. Fong, I believe toxicity is one of the challenges that are faced by cell therapies, could you talk us through some of the tools that could be used to manage and improve these?

Dr. Lawrence Fong: Yeah, absolutely. As you might imagine as we give something living into a person that might elicit a response either from those cells that we have put into the person or from a person's body actually adapting to those immune cells. And this has certainly been the case with CAR-T cells where we are giving patients these engineered T-cells that are hard wired to recognise proteins on those cancer cells and when they see that they become very activated, which is what we want them to do and they expand within a

person, often times ten thousand or a 100 thousand-fold. And whenever you have that type of an activation the immune system basically sends out messages to the body, it's very similar to when a person might have an over-whelming infection like even Covid infection, where we have a lot of these immune and inflammatory mediators, proteins that send out danger signals throughout the body. And so, as a result people who get these treatments can develop, these potentially life-threatening side effects that include high fevers, dropping of the blood pressure, difficulty breathing and as these treatments have been developed, we actually have been understanding how these are actually triggered and what some of those proteins that mediate the signals are.and in doing so we can actually use treatments that actually target those proteins. And so one of the examples is IL-6, we know with CAR-T treatments we can develop what's called cytokine release syndrome or CRS. And one of the cytokines that really goes up is IL-6. And so, there's actually antibodies that we can give to block those cytokines in IL-6 six in particular and in doing so that basically is an effective way to actually treat this toxicity. As we get more experience with more treatments, we're hoping that our understanding of what triggers these side effects will continue when build upon the success with these anti IL-6 antibodies and have other drugs that we can use to help prevent the side effects that come on. But that said, what we do now is when someone gets these treatments, we typically bring them into the hospital so that we can observe them for a period of time. And if they develop any of these side effects, we can give them treatments to quiet down the immune response. One of the hopes is with technologies we could try to shift some of that treatment from the hospital out of the hospital and this is where there's a lot of research that's going on including using wearables so that we might be able to detect some of these side effects. Even while a person is at home and be able to bring them back, this is all actually being developed, so it's not standard now but you could Envision a year or two years from now, this might become much more common approach to really make this an easier treatment for everyone.

Priya Menon: Thank you Dr. Fong, I like to bring in the panel for their questions now. Heidi you can start with yours.

Heidi Floyd: Thank you. Am I unmuted?

Priya Menon: Yes.

Heidi Floyd: Okay. Very good. Thank you, Dr. Fong for what you're doing, it's very exciting. And I personally have many friends who have been helped by this type of research and very excited about the future. Half a century, I believe if I'm not mistaken, the cells of Henrietta Lacks really sparked, a kind of a revolution in cancer research, her cells in particular among other types of research not just cancer, of course, and that was kind of a continuation of years of distrust between underserved populations and the research community as we all know. Before we kind of dive into more details, can you please just briefly explain to us, to everyone how the industry has changed to become a lot more inclusive and transparent for the rest of our community?

Dr. Lawrence Fong: Absolutely, I think one of the travesties in the case with Henrietta Lacks was really not consent or information that was actually provided to Ms Lacks and our approach to clinical research, as well as delivering a all these different treatments now require informed consent, where people actually understand what it is we're doing, what the potential risks are and often times with some of these treatments, we may not know what those risks are, but we convey that in and of itself to individual. And then to understand whether or not the cells or the genes that might be identified, within an individual could be used in the future. And so, I think one of these keys is now a uniform and universal use of informed consent where everybody has a right to know exactly what is going to happen, but also what the risks are. And they also have the opportunity not to participate or not to receive a treatment and so that has been a big change from what happened that time.

Heidi Floyd: Very good. Thank you very much. That's something that's frequently discussed in our community. So, I wanted to make sure that I kind of address that right from the get-go. There are scores of us not just Cindy and myself, there are scores of patient advocates out there globally who like everyone else were just fascinated by the incandescent promises of everything that you just discussed, the cells therapies,

the wearables everything going forward, particularly the work is being done by the LTI. Is there any mechanism for patients to be directly involved with this initiative to help in a capacity not just like clinical trials but also clinical trials are there advocacy panels, any way that we could work with this or other learning institutions to help expedite any future cures?

Dr. Lawrence Fong: Absolutely. I think for these new treatments, it really takes a village in order to get these types of treatments off the ground and this is something that UCSF is not actually able to do on its own. It really requires a partnership with patients, with advocates, with the community in order to really get this type of in approach off the ground. As you might imagine these treatments are very complicated and take a lot of resource actually to develop and not just develop in the laboratory but to actually translate them into the clinic where we can actually give something actually to a person. And this is a really time-consuming and costly endeavour. And this is where resources are actually needed to support this. And in many ways with our existing funding mechanisms, like from the National Institutes of Health and other avenues, a lot of the times this type of research is actually not supported. And so, this is where advocacy to help support this type of work and also the need to raise funds to actually develop these treatments is critically important. And, at UCSF we've been fortunate to be able to start this initiative, really driven by the community interest and philanthropy and resources that were raised if we didn't have that, there actually would be no initiative. We think about it on a chalkboard, but it wouldn't exist. And so that's a clear example, where wasn't for community support this whole initiative would not have started.

Heidi Floyd: Okay, thank you. Well, that's great. Dr. Fong, can you please explain for those of us listening who may not be familiar with all the complex terms and ideas used in detailed research? Explain how this research if it does not pose any, poses zero ethical issues compared to previous research that we may have been reading about that might have caused concern, if you could just kind of clarify that for us, I'd be grateful.

Dr. Lawrence Fong: What, I think part of what we're doing with this treatment is really to improve how we target cancer in our case. And so, one of the challenges is that when we study new treatments they may or may not work unfortunately, and so critical to all of this is making sure that everyone who is involved and most importantly the patient understands that that is indeed the case. And so long as we're all understanding that these treatments some of them are now FDA approved, as I mentioned, but a lot of the treatments that were developing are actually not FDA-approved, people understand that that is the case, and that this treatment shouldn't be considered something that the patient might benefit from. Now, that said all of these treatments that are now FDA approved, the only way that we got them to be FDA-approved was we brought patients on these trials, they were informed of the potential risks and it's only through these studies that we are able to do that. And so, it's critically important that patients, understand the risk. But again, the goal of all of this is actually to have better treatments in our case for cancer.

Heidi Floyd: Thank you so much for your time and your answer the questions.

Dr. Lawrence Fong: Okay.

Priya Menon: Thank you, Heidi, Cindy you can go with yours.

Cynthia Chmielewski: Sure. Thank you so much Dr. Fong. This is such an exciting topic and I'm such a science nerd that this fascinates me so much and being a myeloma patient many of my friends have benefited from the CAR-T cell therapy. I mean patients who are completely out of options, just gave them a whole new lease on life. So, talking about these cellular therapies, I know many of them have to be manufactured. That means, I guess, the cells are taken out of your bodies or a donor's bodies and cells taken to maybe a place, like your lab, to some happy manufactured to then go after your cancer. The FDA approves the final treatment but is there any regulation about manufacturing process to make sure it's safe, to make sure that my cells get back to me, to make sure my cells aren't mixed with somebody else's cells. I mean, it just seems kind of scary as a patient that I give you some cells and six weeks later, I get them back, but I don't know where they go, and if they're safely being manufactured or if they're even mine.

Dr. Lawrence Fong: Yeah, no. That's a critical question, a critical issue and to address that, absolutely yes, there are many checks and balances in place in terms of making sure that a person gets the right cells. And so, if these are what we call autologous products, in other words cells from the same person, those basically have identifiers that basically track with the product all the way through including when they're infused back into an individual. And often times when the cells are produced the processing in and of itself, actually get separated so that these are processed either in this machine, or in this room or somewhere where it's segregated from another cell product for another individual. And so that type of identification and tracking is actually critically important through the whole process. And one of the technical terms we use for that is chain of custody. There has to be a chain where we actually know where the cells were and that these are the right cells. I think to your other point, the FDA requires specific criteria, what we call release criteria to determine whether or not we can administer cells to a patient. And these are processes where we need to make sure that the cells are not infected, that the cells actually are doing what we think that they're doing that they're doing and that we've actually mitigated risk for the person who's actually receiving this cell. And so often times, there will be a very thick manual that basically defines all of the processes that are there but also what those release criteria are where the cells need to meet that threshold before they can actually be administered to an individual. And so, this is an area that is fairly heavily regulated, and it is an evolving field as you might imagine as our cell therapies develop and evolve and become more sophisticated, those types of criteria will also evolve. But, at the present time, just to lay your concerns there are quite a few checks and balances in place to avoid any of these problems that that you're worried about. In the real world there's always going to be potential for mistakes, but the goal is to really minimize that.

Cynthia Chmielewski: Thank you. I'm a little bit more relieved that there's some regulation going on there and not everyone can just manufacture their own T-cell product. So that makes me feel a little bit better and I was reading on your site about that AI program that was able to identify like those antigens in the kidney cancer and then make a CAR-T, that was exciting. But my concern is because I'm a myeloma patient, the myeloma CAR-Ts have not lasted as long in the body persist to as in the other types of cancers. And one of the things that they are talking about is this thing called T-cell exhaustion that are T cells are used and too exhausted to do the job or to persist. Now we don't know if that's for sure but that's one of the things I'm hearing about and I'm imagining that's not going to only be with myeloma patients that other people's T cells may be beat up over time and maybe not be the great ones to make the product. So, should patients who are diagnosed with cancer like harvest their T cells ahead of time, like we harvest being a myeloma patient, I harvest my stem cells right away, so I can have that stem cell transplant. Should I be harvesting T cells? Or is there a way to revitalize T-cells to make them stronger? Or should we be looking at other immune cells that might not wear out as much? Maybe like natural killer cells, or other types of immune cells can? So, can you talk a little bit about that T-cell exhaustion?

Dr. Lawrence Fong: Yeah, well when we think about T-cell exhaustion one of the ways to think about it is these T cells in our body, we rely on them to actually fight infection like with covid or the flu or other types of viruses. In our case, we're actually relying on them to target the cancer. And what happens is that these immune cells are great at addressing an infection. Something that comes on, you clear the infection, it goes away and then the immune system sort of quiets down after that. And one of the ways that it can quiet down is through these T cells becoming exhausted. They did their thing, they kill the infected cells and now, they basically stopped their function. In the setting of cancer, the problem is that the cancer cells may continue to persist despite this burst of the T-cells basically targeting the cancer cells and as a result while they're killing the cancer cells, they may not be able to kill every last cancer cell and as a result they basically become rendered non-functional or what we call exhausted. At this point in time, we don't know if we were to harvest your T cells early in a course of multiple myeloma versus late. How much that would affect the product. We think that that would actually improve the CAR-T cells that we get out of that. But those studies are actually now being done where we're now giving CAR-T rather than waiting for treatment refractory multiple myeloma. We are giving it to folks earlier and earlier in the disease and so I think those studies we will learn whether or not getting the T-cells and banking them be advantageous, but we don't know the answer to that. I think for your other question is can we actually make the CAR-T cells resistant to exhaustion? This is something that we and many groups and many companies actually are working on if we can actually engineer these T cells not just to recognize the cancer but actually to resist exhaustion, we could potentially

get around that. And so, this is something that is really a big push throughout the field to develop. And as you mentioned, people are thinking about other cell types like NK cells or Gamma Delta T-cells or other cells that might resist exhaustion. But this is something that unfortunately is inherent with a lot of cancers, with some cancers we get that big expansion, and it clears the cancer and that happens with diseases like leukemias and some lymphomas, but with others, like multiple myeloma, it's just the harder disease to clear. And as a result, we have to figure out ways to actually make these CAR-T cells perform even better.

Cynthia Chmielewski: Okay, that kind of makes sense to me now. So, keep on working on that. The other thing I guess, I'm a little bit interested in are these gene-editing technologies, like TALEN and CRISPR. I guess when you're giving someone else's cells to you, the allogeneic products, sometimes that risk of graft-versus-host disease exist but it will be really nice to have an off the shelf product. Because right now, we're waiting way too long for these products. People are being put on waiting lists and sometimes they just can't. So an off-the-shelf, Allo product will be fine. So, how is this Gene editing helping this graft-versus-host disease?

Dr. Lawrence Fong: Yeah. So, what happens, whenever we think about transplants or giving cells from another individual into a patient, what happens is that our bodies actually can recognize cells as being foreign and will reject them just like they recognize how cells could be infected by viruses. If something is not right, the immune system is primed to basically kill those cells. And so, as a result, the cells that you give to a patient, if they're derived from somebody else, not only can mediate graft-versus-host which means the cells basically targeting tissues in the person, the recipient of those cells. But there's also a potential for hosts versus graft. So, a person's, the patient's immune system basically rejecting the cells that are being given to that individual. And so, for these off-the-shelf treatments we have to actually engineer these cells so that they actually don't express some of these proteins that the immune system uses to recognize these differences between individuals and so that's where the CRISPR and TALEN technologies come in, where you can edit these out in an effort to have these cells escape immune recognition. And this is something that we're still continuing to learn and understand which genes we actually need to edit and which we don't need to edit. And the hope is if we understand that fully that we can have full off-the-shelf treatments. I think right now this is still very much investigational experimental therapies but to your point, having something off the shelf that we can give somebody is very different than in autologous product where we actually have to wait in some cases months for that treatment and that might come on top of having waited months to get a slot to actually get the treatment. And so, I think this is one of the critical areas that again many groups including our own are working on, because it would be a huge advance.

Cynthia Chmielewski: Yes, thank you so much. This is such an exciting field. I just love it, I guess the tech science geek but yeah, thank you.

Dr. Lawrence Fong: You are welcome.

Priya Menon: Thank you, Cindy. One last question Dr. Fong before we can wrap up for today. I know you work extensively on CAR-T cells, so can you tell us what is the latest exciting thing that's happening with CAR-T?

Dr. Lawrence Fong: Well. I think a lot of the excitement that's going on now is that we have a lot of developments that are going on in the laboratory where we're developing new circuits to reprogram these CAR-T cells and as we touched upon briefly thinking about more and more targets that we could go after, that might broaden these treatments across many different cancers. I think the other component is now that we have these CAR-T cells in the clinic, we can actually learn why they're working and why they're not working in an individual. And so, this is whereas an example with multiple myeloma, some patients can have durable responses but unfortunately, a lot of people unfortunately have their myeloma come back following these CAR-T cells. We're not batting a thousand at this point. And so, there's actually a lot of room for improvement. And I think by us seeing this clinically and then being able to take samples from our patients who are being treated, we can actually understand what is exactly going on. Is it indeed, T-cell exhaustion, or is it something else that's going on, that basically is making these treatments in some patients not as

durable as we'd like them to be. And so, I think that is another really exciting development. Before we were administering these to people, we had to focus on in the laboratory like how these cells worked and whatever models we could develop in that context. But now, what I argue for is actually the clinic has also become part of the laboratory and at places like, UCSF we actually have the infrastructure to really try to learn as much as we can from everybody that we treat. And I think, for me that also is incredibly exciting and should enable better treatments down the road.

Priya Menon: Thank you. Thank you, Dr. Fong for sharing all that information. Indeed, it's a very interesting field and we are really following what's happening and what new treatments come out. So, thank you very much. Heidi and Cindy thank you for all your questions and putting this topic today. Thank you very much and we also thank UCSF Helen Diller Family Comprehensive Cancer Center. This talk will be available on curetalks.com. Everyone, have a good day. Thank you.

Thank you.