# INTIENT SUMMIT CELL & GENE THERAPY LUMINARY SPEAKER VIDEO

## VIDEO TRANSCRIPT

Going to transition now to our topic of advancing certain gene therapies. And we're going to get a perspective when we move to the panel from various stakeholders, including manufacturer, providers, and In a caregiver to a patient as well. So to start us off, I'd like to introduce Dr. college. So Dr. Shah is is the director of stem cell and translational immunotherapy at Brigham and Women's Hospital in Boston. Is also a principal faculty at Harvard Stem Cell Institute. And he's dedicated his work to the development of cell-based therapies for brain tumors. One of the biggest challenges in oncology. So Dr. Shah, we're delighted to have you with us. Thank you so much for being here and I'm going to pass it over to you to to start us off with your talk,

So thank you very much. Thank you. Pleasure to be here and thank you for the invitation. So I'll be brief, I think 10, 15 minutes. So give you a perspective from where we see cell and gene therapy is a particularly cell therapies moving into the, into the next phase and how how we can bring in the patients and their caregivers and everybody into, into the same way of thinking. And, and this is our wedge and where I think translating biological therapies into clinical care. It is starts with innovation, I think, but patient should be central to it. I think that is the key that, that now we're realizing or last decade that patient material coming from the patients, the biopsies, the AI data is critical to develop next level or next generation of innovative therapies. And probably I think before 2015 or 2014, I think patient wasn't very central to what was developing in the lab. And that has changed over time. I think that has to change, had to change if we're bringing newer, particularly cell-based therapies into the, into the patient settings.

And I think from an innovation perspective, we also probably will have to redefine what is innovation in the, in the healthcare settings because just in a waiting and patenting technology or, or, or a product is not enough. And if we have, if we look at the data from last decade again, many of these preclinical studies that were based on innovative findings and made their way into phase one, ultimately didn't end up into, into becoming standard of care or didn't even go to phase 3 trials. So I think the way we see innovation is, yes, you have innovation, but if you don't put orchestration around that innovation, and that includes preclinical models. That includes the choice of cell therapies. For example, I using patient's own cells. Are you using healthy donors and creating cells from those donors? And then the big bottleneck, how do we bring therapies from bench that are developed in the labs into, into clinical trials and ultimately patient care. And that is a bigger bottleneck where the industry and academia have to work together. And in our case, we've tried to create industry within the academia.

So that is the sort of a great evolution of startups that have, that come from academia. And take these therapies that are developed in the lab into the, into the next settings. So the orchestration around that innovation is critical. And just innovation doesn't really help the taking newer things, taking new innovative therapies into the clinics. And, and for, for, for innovation. I think we don't have to accept status quo.

And that's a big thing that, that very innovative therapies are when people do not accept what's going on currently. And usually people who noaa, and we know this from social change in the shadows that people who initiate or in a weight are, are orchestrators, are not necessarily the orchestrator. That means you have to team up with others to move things forward. So if you look at cell-based therapies in particular, many of you might not notice there are 22 buckets. The other logos, therapies and, and the allergenic, the orthologous, you know, basically use patient's own cells in. This is like more like T cells and NK cells and macrophages. Now you take them from the patient, modify them and put them back into the same patient. Now, the allergenic part is more off the shelf. That is would be more preferable because then you will have something ready for the patient off-the-shelf anytime. Where do you take it from the healthy individual and have something ready off the shelf? And both of them have advantages and disadvantages. But ideally, if we really had to readily take cell-based patient, you would like to have something off the shelf ready to go. And the timing is, is going to be critical. I'll give you an example of from one of our own studies how we have sort of gone more into the allergenic, an off-the-shelf approach.

And a few in my lab basically does a number of things. Looks at both allergenic therapies and other logos therapies. And we develop stem cells that release therapeutics that target not only the tumor, but also the tumor microenvironment. And so it's a mix of both allergenic, an orthologous, orthologous therapies. But the key is, for example, as I said earlier, I'll just give you an example in brain tumor patients. Now. Take an example. Now somebody who gets unfortunately brain tumors gets, gets a seizure or gets a headache and then I'm scheduled for an MRI immediately. And within 24 hours, you know that you have a brain tumor because it's a very clear signal in an MRI. Now at that point, There's two ways. You look at it. You will be scheduled for surgery immediately because it's not just the tumor is the pressure in the brain and that needs to be relieved.

And so, so surgery is, is one of the mainstays of treatment for GBM patients. For example, it's a highly malignant brain tumor, GBM where you get resection and then you get treated with chemo and radiation. So resection is, is an integral part of, of this. And if you look at the numbers, um, of the patients who have undergone resection, look at the tumor volumes, pre and post resection. Resection cavity is very so most of our work and that's what I said in the beginning, that the patient becomes critical because most of the therapies for brain tumor patients in preclinical studies in my studies are working, are focused on intact hymns. Now we know that we're not going to be treating an intact tumor in the brain tumor patient.

So we will have to develop innovative therapies that are targeting receptor tumor. So we've realized this almost a decade ago and most of our work has been focused on on developing therapies that go locally at the time of surgery in, in these, in these patients. And so we probably will have a clinical trial hopefully next year. We also, I don't want to go into the details. We also have developed this blood test where you can actually add the time of the MRI when you take the blood. Maybe once you get detected, you can take the blood from the patient. You can actually look at circulating tumor cells and you can identify receptors in these in these circulating tumor cells. And we have a cell bank. And actually the paper came out this morning.

If you are interested to read about this whole story. It just came out in Nature Communications this morning. We also have a cell bank for each receptor that will be actually targeting. So we can pick up the cells from the cell bank as targeting that specific receptor and keep them ready for the. When the patient gets surgery, we can encapsulate these cells in biocompatible gels, in place them in the tumor resection cavity. Gels are necessary because cannot place cells there because they get washed by the blood and cerebrospinal fluid that fills in the cavity.

So this is a newer technology that we have developed. But, but to come to the point that the central to developing this therapy and innovating something different was the patient. Because we understood that that patient would we can't we can't give out a logos therapies because imagine within the first five days and the patient gets diagnosed with GBM. To take their cells to modify those cells and put them in back into the patient within 56 days is literally impossible.

So we had to come something were to come up with something off the shelf. So I will end with a few slides. I think I still want to focus on the way to aspect. So these are the two papers. One, my first, last author paper where I was the corresponding author.

This is, I think 2010 or 11 where we looked at stem cell migration into the tumors and see, and later figured out how we can use these red cells to kill green cells. And a decade later, I think this is like 2019, our new study where we used cancer cells to kill cancer cells. So these are the two color-coded same cancer cell type, same cancer cells placed in the brain, and they love to track each other.

So we pioneered this technology where now we can actually take patient's own tumor cells and use them to treat and create their own cancer. And this is evolving technology where we have now CRISPR. The original tumor cells made them therapy resistant, engineered them to produce immune modulators and killing agents. And we've now compelling data is showing that we can actually cure tumors in mice. We can give them long-term immunity. So this is exciting. It was, the original paper was in science.

Scientists was in Science. Translational Medicine was highlighted quite a bit. We have a follow-up paper coming on the moon aspect of this in a few months. So the reason I wanted to bring, bring this slide in was to say that we had a vision that we might be using cancer cells to treat cancer. And, and we honestly, when we started it, we didn't know fully how to do it. And what happened in parallel was the technologies developed in parallel. And

I think when you're envisioning something down the road, you have to also bring into play that the technologies and other fields are also evolving. So can you factor them in that your wage and becomes a reality? And I think this is one classic example where we didn't, actually, when we started, we didn't know how we can actually use cancer cells to kill cancer cell then give long-term immunity. But with the advent of CRISPR new lentivirus vectors, this has, this has been now a possibility.

So I'll stop there and leave you with this. I think all of us I strongly believe, have the ability to make a difference. And sometimes we as scientists make it too complicated. So ideas and simple, you know, sort of suggestions from even high school students or people who are naive to signs are more than welcome. Thank you.