

Making Cancer History®

### **Nobel Prize in Physiology or Medicine Media Event for Dr. Jim Allison**

#### **Dr. Patrick Hwu:**

Hello everyone. My name is Patrick Hwu and I am head of cancer medicine at MD Anderson. I would like to welcome everyone. Thank you so much for coming to this extraordinary day. It is a real privilege to introduce Jim Allison my good friend and colleague that I have known for many years also a fellow musician as this year's winner of the Nobel Prize in physiology or medicine.

As a melanoma and tumor immunologist myself, I have really seen firsthand the impact that Jim's research has had on patients. I have had many patients now in my clinic who are alive and well having had advanced melanoma because of the way that Jim took basic science findings to the clinic and has helped many people. Now, this research is now being applied not only in melanoma but to many other cancers as well. It's really revolutionized our cancer therapies today. So really, congratulations to [Jim]. [Applause]

Jim has been at MD Anderson now since 2012. He really came back to MD Anderson. He's from Texas. He grew up in Texas. He grew up in Alice, Texas. He used to tell me that as a kid, he would come from Alice to Houston in the summers to cool off. So we're really happy to have him at MD Anderson where he has continued to do cutting edge research and applying now his findings to many other kinds of cancers, understanding immune resistance and how they improve these therapies yet further.

Today, is such a momentous occasion for Jim and his family, and Sharma also herself is an outstanding clinical investigator, immunotherapist and son, Robert Allison, who's here, so congratulations to the whole family.

On behalf of the faculty and staff, our President, Peter Pisters from MD Anderson, we congratulate you on this much-deserved honor. We're very proud but also we're very happy for all of the patients that you helped, all of the patients that you help now and the patients in the future that will further be helped by your tremendous research. So again, congratulations, Dr. Allison. [Applause]

**Dr. Jim Allison:**

Thanks, Patrick, for those kind words. I want to start off by saying I'm still in a sort of state of shock. It is still sinking in, so I'll try to make some sense while I'm talking to everybody. It's really wonderful this morning to wake up to my son calling me at 5:30. He was the first to let me know that I won this prize. It's nice to have him and Sharma, my partner in life and in science. We work together now trying to improve immunotherapies. Also I want to thank a long, long line of students, post-doctoral fellows and colleagues at MD Anderson, at UC Berkeley and at Memorial Sloan-Kettering over the years that have helped bring this work to where it is, also the patients who, especially in the early trials, who delved in some risk of taking a drug which could potentially unleash their immune system to [another] cancer but also possibly to do harm, and frankly, that risk of infection was not all that serious and this could be managed. So, it's really turned out to help quite a number of patients.

I guess the reason I'm really thrilled about this is because I'm a basic scientist. I did not get into these studies to try to treat cancer, I got into them because I want to know how T cells work, and want to show that these set of molecules, CTLA-4, was the first cell-intrinsic negative regulators from immune response that immediately occur to me and some of the people in the lab. Maybe we can use this to unleash the immune system to attack cancer cells and so I'm lucky enough as a basic scientist

to see my work actually pick up, 20 years later actually, was really, really helping patients.

I want to say this modestly so I think that this award I was told about by the Nobel Committee when I was called this morning that this is the first prize they've ever given for cancer therapy. So, they've given some for cancer, the cause of cancer before, which is the first time for cancer therapy. I'd like to just give a shout-out to all the patients out there who are suffering from cancer to let them know that we are making progress. We can get durable responses in a fraction of patients with many, many different kinds of cancer. Of course, we still have a lot of work to do. There's some kinds of cancer – well, first of all, there's a fraction of patients who respond and melanoma is about 60%. We need to get that up as close to 100% as we can. The other cancers, is somewhat lower. We need to get all of those different patients that respond and also bring these therapies to some kinds of cancer that had not yet responded including glioblastoma, and pancreatic cancer, and the other things that you hear about it in the news all the time.

We're trying to do that at MD Anderson in the Immunotherapy Platform there that Padma Sharma and I run together. So we're trying to understand mechanisms of what goes on exactly in patients, both the way that works. I mean I understand the reasons for both so that we can do rational combinations in the future to bring the benefit to more patients so we still got a lot of hard work to do but the optimism comes – I think we know the basic rules now. We just got to work hard and learn the details and develop more personalized treatments for the majority of patients. So the good news is I think there's optimism that we can do that but it's going to take a while. So I guess I'll stop there and take any questions.

**Sharon Begley****(STAT News):**

Dr. Sharon Begley from STAT News. As you said when we started working on CTLA-4, it was with the idea of this might be useful for cancer someday. I wonder if you could just [unintelligible] your mindset at the time and what was it that got you up every morning, and going into the lab when it was just purely for understanding some basic thing in biologists?

**Dr. Jim Allison:**

Well, the dirty little secret I think for most scientists is, and what really motivates them, the significant thing mostly is the desire to know something that nobody else knows. Help with something [unintelligible], to be the first people to really figure out some kind of [unintelligible]. Ever since I was a kid, I really like to solve problems. I think that's what keeps scientists going. You set yourself on a path to – when I started working on T cells, nobody knew how [unintelligible] at all to know the structure of the molecule and recognize the things that they would attack and develop a – I didn't realize they actually make different molecules that were [unintelligible] and other modulators down the road. So it was really that that kept me going. Most of the time, the science was because of, well, you're frustrated mostly because there's no instant gratification of it. It's just the whole nature of science is trying to prove your hypotheses wrong. How do you do that and how do you do it, so you've got to be comfortable with a lot of things that you've got going.

I've had a lot of cancer in my family. My mother had passed away from lymphoma when I was 10 years old and she had radiation therapy. One of her brothers had lung cancer and had chemotherapy. I saw [unintelligible] so I got in immunology. I always had the hope, read them on the papers, take them in [unintelligible] that I was lucky to have as a mentor who, you know, in his 60's has been working hard. [Unintelligible] in adult models.

So I was obvious to the fact that I had to [unintelligible] work whenever I could. I would take a rest and go think about the problem and look at a better way to say, “What does this tell me that I could use to treat cancer?” It was one of those moments where you [unintelligible] sit on the floor with the brakes up against it to let you have all this - just disable the brakes to see if that will allow the immune system to attack cancer. So, I did a lot of experiments, and several years later, we did early clinical trials, and we have patients now – actually one patient from the Phase I trial, she’s been on [unintelligible] that got a single dose of CTLA-4, a patient with a [classic] melanoma who’s still around almost 19 years later. So these are very durable responses. Again, they’re a fraction of patients but that’s what we got to work on now. We know we can do it. We just got to learn how to do it better. I don’t know if you [unintelligible] this.

**Male 1:** Yes. I’m [Unintelligible] AFP, what was your reaction when you got the phone call? Tell us where you were.

**Dr. Jim Allison:** Well, I was in the hotel that the Cancer Research Institute, which I’ve been associated with for nine years, I was having a major meeting at Times Square with the – an international meeting with people who – immunological societies all over the world – well, Europe and the United States. So I was at that meeting and Pad Sharma gave an award there and gave a talk yesterday, and so I was in the room and my son called at 5:30, and then pretty soon, I started getting calls from other people. I’ve had a bunch of people came to our room – door, beating on the door at 6:00 in the morning [unintelligible]. We had a little party early this morning. It was really great with my friends, all of them working in this field one way or another. So [unintelligible].

**Male 1:** What was your emotional reaction to winning the Nobel Prize? I mean, when they - did you speak to the committee? Did they call you?

**Dr. Jim Allison:** You know, for some reason they had trouble and didn't get to reach me until after I knew about it from like my son and my friends, but they finally got me and we've talked about it. That was when the Committee had bring it up and said, "We'd never given one for cancer therapy." I guess it still hasn't completely dawned on me except that, as a basic scientist, to have my work really impact people is extraordinary. It's the best thing I could think about. It's anybody's dream to have that [unintelligible] to do work that is benefitting people. I'm still trying to figure that out. It's quite a shock to learn this at 5:30 in the morning. So I would say it's every scientist's dream to have, first of all, do fundamental work that's important, but then to have it translated to helping people is all and much more better recognized by the Nobel committee is, I think, try to bring attention to the issues of importance of basic science, and if there is hope, then that's [unintelligible].

**Male 1:** Thank you.

**Female 2:** Hi. My name is [Mabel]. I'm from [Delhi] Institute of Cancer. I'm calling from [unintelligible]. Congratulations on your [unintelligible]. I just wanted to ask you actually about Professor Honjo, who is [unintelligible]. How are you [Unintelligible] worked with him?

**Dr. Jim Allison:** Yes. I know Tasuku Honjo very well. We've worked together – well, not really work together, but known each other and discussed science, not on this, but on the other topics since the early '80s actually. So he made this discovery of this molecule, PD-1, which was the second checkpoint discovered and it about the time that – you know, we had a problem

understanding why CTLA-4 only worked in about 20% or so of patients. So, the number of possible explanations and of course, the most interesting one was it was not the only checkpoint if there's another one, and Honjo's work brought PD-1 to the fore. Now, we know those two together are extremely powerful. CTLA-4 has a response rate in melanoma by itself about 22%. If you add PD-1 blockade to it, it goes up to about 60%. So it just helped to show that this approach was good to broaden the impact, broaden the possibilities for helping patients.

**Female 2:** [Unintelligible] can you give us any comments or message to him?

**Dr. Jim Allison:** Sorry? I couldn't [unintelligible].

**Female 2:** Could you give us any message or comments to Professor Honjo?

**Dr. Jim Allison:** Yes. Just give him my best and say I look forward to seeing him in Stockholm. We shared the Tang Prize several years ago, so we go back a little bit.

**Malcolm Ritter**

**(Associated Press):** Malcolm Ritter from the Associated Press. Just to go back to your story of how you heard, it's not clear to me, you said there was – your phone rang at 5:30 but you didn't answer it, that there were other calls? I know...

**Dr. Jim Allison:** No, no, no. The phone rang at 5:30 and it was my son calling me, and we spoke just for a few seconds because there was a call from Sweden about, "Oh, well..." because he'd already told me that I won it, but it was a reporter from Sweden. So I talked with him briefly and then my friends all showed up and we started celebrating, and it was – while I waited, I still don't understand why the reporter had my number, but the Committee

didn't. But anyway, they finally found it and called me. I don't know what time it was.

**Female:** 7:30, it was.

**Dr. Jim Allison:** 7:00 or something like that.

**Malcolm Ritter**

**(Associated Press):** So you heard the news from your son?

**Dr. Jim Allison:** Yes.

**Malcolm Ritter**

**(Associated Press):** Okay. Thank you very much.

**Male 3**

**(Fuji TV):** [Unintelligible] from Fuji TV. You seem like a very modest person and not really wanting to take a lot of like first of all merit into the board or [unintelligible]. How do scientists – how does it feel to be able to share this award with a fellow scientist, let alone a friend like Dr. Honjo who you respect very much?

**Dr. Jim Allison:** It feels very nice. As I said, we did it [unintelligible] forward. It was just – I don't want to say one-off. It's not quite what I mean but it was a singular thing, and one of the worries was that it was going to be stuck at that 20-something percent. I know Honjo from the early days when we were both trying to figure out the T-cell antigen receptor structure, which we have done and we considered working together to [unintelligible] but that's where I first met him but he's done a lot of work on antibodies and other areas of immunology he's worked on, and very – made many, many really

important contributions to fundamental immunology, particularly at B cells or recently T cells as well. So, it was great to have [unintelligible] identify another one of these molecules and say they could have brought the [unintelligible] or the general theme of checkpoint blockade to cancer therapy.

**Male 3**

**(Fuji TV):** I have one more question about that, Doctor. [Unintelligible] you and Dr. Honjo like such great friends and both colleagues but also away from the workplace?

**Dr. Jim Allison:** Away from – sorry, what?

**Male 3**

**(Fuji TV):** Things that are unrelated to work like do you have any [crosstalk]?

**Female:** Are you friendly?

**Dr. Jim Allison:** Oh, yes. Yes, a little bit. I mean not all that much. Like I said, he's in Japan and I'm here, but we met at particularly scientific meetings, playing golf together. She plays golf. I don't play golf [unintelligible], but we got a cordial relationship. It's been many years and so [unintelligible].

**Male 4:** Are there are more questions in the room. Otherwise, I'll take some from the phone. Yes, [unintelligible].

**Male 5:** [Unintelligible]. Congratulations. I just want to ask why you [unintelligible] on immunotherapy, thinking about [unintelligible] why go to [unintelligible] blockers and not something that checkpoint [unintelligible]? Kind of explain your perspective on that [unintelligible].

**Dr. Jim Allison:** Well, I think, yes, I am using the immune system to treat cancer goes way, way high. The problem was it's sort of getting applied before we knew at the beginning how it worked. So, for example, with cancer vaccine, I think that the background [unintelligible] what we discovered with CTLA-4 is that after the first vaccination, [unintelligible] CTLA-4 was turned on by the antigen receptors [unintelligible] and really increasing the signal that seems to get worse. So every time you do it, you're turning the immune system off if you're doing the [unintelligible] and the modality was [unintelligible]. I think that the other thing is we just don't know after that, you still don't know the problem where to vaccinate, and get the therapeutic responses. Obviously, we could do a great job, we get to find folks for [unintelligible] in terms of really instantly mobilizing [unintelligible] cancer, we still have a lot to learn there. But, the basic I think it was a lot of the earlier therapies, you just started with [unintelligible] patient now, there's no details on the circuitry [unintelligible].

**Male 4:** One last question here from the back, just in the simplest way you could explain in the shortest time period, for average people, what does your and your colleagues' discovery mean for the future of people who may be suffering from cancer?

**Dr. Jim Allison:** I think that what we've learned - again, to put it very simple is that they are, built into the immune system, these inhibitory circuits that stop the immune system at a certain point so that it doesn't hurt the normal tissues and that also keeps it from attacking tumor cells as effectively as the T cells might. So we've got a way to [unintelligible] hit the brakes and let them take off. So, after many years of resistance, I think the flow of the cancer field has begun to accept immunotherapy now as the fourth pillar

along with radiation, surgery or chemotherapy, cancer therapy. What we have to look forward to is that unlike the other three, immunotherapy can be used in combination with the other three. I think that what we're looking forward to is combinations in the future, not just of multiple checkpoints, but of checkpoints with radiation, checkpoints with chemotherapy, and checkpoints with genetically-targeted small molecule drugs to really – I think that immunotherapy is going to be part - it's not going to replace all those others, but it could be part of the therapy that just all cancer patients is going to receive or will be receiving in five years or so. [Crosstalk] and there will be a [unintelligible] in a lot of patients.

**Male 4:** We're doing questions for the folks on the telephone.

**Operator:** At this time, if you would like to ask a question, please press the star and one (\*1) on your touchtone telephone. You may withdraw your question at any time by pressing the pound (#) key. Once again to ask a question, please press star and one on your touchtone telephone, and we will pause for a moment to allow questions to queue. [Pause] We do appreciate your patience and we will take our first question momentarily. [Pause] We will go ahead and take our first question from Ivan Couronne with AFP. Your line is now open.

**Ivan Couronne**

**(AFP):** Dr. Allison, can you talk about the other pillars precisely that you mentioned, how important do these conventional therapies remain, and what should patients think and tell the doctors about? Should all the funding go to these areas, to immunotherapy as opposed to the older therapies?

**Dr. Jim Allison:**

Yes, but first I think that there is still a place for the more conventional therapies. There are some cancers that we don't have the – so far the therapy hasn't worked yet; as I mentioned glioblastoma, pancreatic cancer. Those are big challenges, but the whole process of getting the immune system going after cancer starts with some tumor cell death, and that what really forms the large – anyway, without making it complicated, that causes inflammation that starts a whole cascade of immunologic events. So if you can kill cancers with radiation, and you can kill cancer cells with chemo, what we know now is that the traditional way of giving high doses of chemo or high doses of radiation, and try to kill that last cancer cell, every last cancer cell, is no longer the goal. It should not be the goal of those other therapies. You could moderate that use and just try to kill them out from your system – sorry, kill enough tumor cells to initiate the immune cascade, and they come in actually to resolve by activating the sustained T cells. I don't think all the funding, by any means, ought to go into that. I mean we know that with the small molecules, for example, those drugs have been developed with in-vitro assays and in xenografts – tested in xenografts. So human tumors growing in mice that don't have immune system. So most cases, we have no idea whatsoever in what those drugs do to the immune system. We need to know that if we're going to be in the [unintelligible] immunotherapies. Same for chemotherapy, we need to know how many chemotherapies can probably work. We even know the effects to the immune system though and if they are immunosuppressed, they have to come up with staging or dose scheduling that allow it to be used together, but I would say that what we need to do is to continue to fund patient research because that's where these ideas came from, not from trying to kill cancer but from trying to understand how the immune system works. If everything is translational and targeted on a given area, pretty soon there's going to be nothing to translate because there won't be any new ideas. So the big chunks come from the basic science

[unintelligible] so I think we got to keep that [unintelligible] say everybody's got to be trying to cure a disease. It does not work that way.

**Male 6:**

I apologize I did [unintelligible] to ask you, if you don't mind, [unintelligible] I just like to ask you a few words about how are you feeling by getting the Prize, and also what kind of change do your findings to give to the cancer treatment and perspective to the patients all around the world?

**Dr. Jim Allison:**

Yes. Well, I guess as far as I'm feeling, I'm still in kind of a state of shock actually, getting at this point and learning this, but the thing that gratifies me is I do consider myself [unintelligible] - I used to be, maybe having more than a basic science is that you just try learn about the immune system, [unintelligible] that came across something that we could explore with the help of a lot of really, really bright students. I think what this means to cancer patients is, I dare use the word "cure" which I know is a very dangerous thing to do. We have patients now that are 18 years out since their - they got one round of therapy and they're 18 years out, 14 years out, whatever. I think those patients can be considered cured and I think that that's the hope with these kind of therapies - one, because the immune system after all differs from conventional therapies in several ways. One is that once you got T cells, you've got them for the rest of your life and so they don't go away. If you give a chemotherapy drug, it's gone in hours so you really have to keep giving it until you kill every last tumor cell. You don't have to do that with your immune system cells, they'll be around and can keep coming after the tumor and changing as the tumor changes to recognize new [unintelligible] on the tumors as tumors are - the problem with cancer is the tumors are so heterogeneous because of genomic instability, and they're very hard to treat, but that makes them just easy targets for the immune system because the immune system loves

heterogeneity and the more antigens, the better. More mutations, the better. If we think of, again, what this offers, we're still got a long way to go. We're treating patients now and ideas to really running in detail how it works, maybe it's been a risk to more patients. It's a challenging thing but what we know now that we didn't know 10 years ago is it can be done at least with some patients, so we've got a grasp on it, we just need to work it.

**Male 6:** Do you already know how many patients already benefitted from this therapy?

**Dr. Jim Allison:** Not really but I think hundreds and thousands have been treated, so it's in thousands, I'm sure. I don't know. I've been trying to ask Bristol-Myers Squibb but I'd have to ask again. [Unintelligible] the market and they're going - nobody seems to know but it's a big number. Four years ago, for example, there were 5,000 patients at least who they had 10 years follow-up on, so the real number is somewhere [unintelligible], and with PD-1 and [unintelligible]. It used to be that this therapy was given to life stage patients who had no other options. Now, it's the first choice for melanoma, for example. Patients start on immunotherapy rather than chemo or even in genomically-targeted drugs. When the one patients get those are patients who fail immunotherapy now, and I think that's the way many, many cancers are headed.

**Male 4:** One more question from the phone?

**Operator:** We will take our next question from Tina Saey with Science News. Your line is now open.

**Tina Saey**

**(Science News):** Hi. I was wondering if you can tell us a little bit more about why certain cancers seem to respond to these checkpoint inhibitors better than others do.

**Dr. Jim Allison:** Yes. There are several reasons. One is there seems to be an association with the total mutational load, the mutational burden. Those that have a lot of mutations, those – we know now the [instance] of sort of the T cells, if it's cancer are preoccupied with targeting proteins that are made by the mutation that occur during the cancer process itself, not just the drivers, as they're called, that the cancer biologists have been referring, but it has the potential to recognize all the passengers as well. So melanoma, for example, can have 3,000 or so mutations per cell, so that's 3,000 potential targets. But you get down – it ranges, actually, to range from a few hundred to thousands, but if you get down to something like prostate cancer and maybe 30 expressed mutations. Now that doesn't mean that absolutely some response and we recently found in a study that we can see T cells are recognized or mutations out of even a small number of mutations, but that's part of it. The more mutations clearly, the more likely you ought to get one, or more that [unintelligible] can recognize well. Another one is that a lot of tumors are, what we call, "cold". They're immunological deserts. There's no T cells in them, so until you get the T cells in. We can't really do anything. We know now also the CTLA-4 will drive T cells in tumors, but they can also induce expression of more checkpoint inhibitors such as the ligand for PD-1, and so then you have to start thinking about giving some combinations [unintelligible], but there are some new ones coming along. Also in some tumors, it looks like they have active methods of suppressing multiple medicines, suppressing the immune system and protecting themselves from cancer. So there's no simple answer but some of these things, we can overcome. We know how

to overcome now. Other ones we don't know now and it's going to take a lot more research to understand how to do that.

**Tina Saey**

**(Science News):** Great. Thank you [Crosstalk].

**Male 4:** Okay. Thanks for everyone out. One more question, anyone? Okay. Thank you all for coming today, appreciate it.

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