[MUSIC PLAYING]

FADI LAKKIS: It's really nice to be here. I just wanted to start with a disclaimer. I'm neither a surgeon nor an immunologist. I'm actually a nephrologist. So I'm proud to be here in the Department of Medicine giving a lecture. I'm so proud to be giving it with my colleague, Warren, whom I've known now for many years. And we've grown to become scientific collaborators as well as good friends.

So with that, since we are in Pittsburgh, I'd like to start with the solid organ transplantation as the platform or the springboard to telling you a little bit about the immune system. And that then would lead into Warren's discussion of bone marrow transplantation and how to make it safer. So as many of you know, transplantation, thanks to Tom Stossel and other giants in the field, have become a great success story. More than 30,000 solid organ transplants are performed every year. Another 8,000 allergenic bone marrow transplantation are also done for multiple purposes, and they're very successful.

Some of them are lifesaving, like livers, lungs, and hearts, and bone marrows. Some are vastly life improving, such as kidney transplants, perhaps pancreas transplants. And more recently, that has propelled the transplant experts into doing the unthinkable, such as transplanting a uterus for someone with infertility, transplanting faces, or even limbs. So I think I'd say it's a wild frontier in some ways. But we owe it to the successes of transplanting the classical organs, such as the kidney, heart, and the liver, and more recently the lungs.

Now there are many reasons for success. And reasons for success often start with people who had the courage to try things that are different-- thank you-- things that are difficult, and require bravery. So that started with Alexis Carrel, a French surgeon who developed a very simple procedure to connect blood vessels to each other. And believe it or not, that was enough back then to win the Nobel Prize. But of course, that was well justified because that led to the explosion in surgical techniques, including the transplantation of solid organs.

Now without science, you cannot do much. And this echoes what Mark had said earlier. I think you are all fortunate here to be attending a series of lectures that Mark had envisioned that bring science to the clinic, because that's really what we're about at the end of the day. We want to improve the lives of our patients. But there's really no substitute to good science to do that.

So perhaps the first scientists that comes to mind, who started deciphering how organs are rejected was Peter McDowell in England, who was inspired in World War Ii by soldiers who came back from the front with severe burns, and was contemplating the idea of skin transplantation, which up till now is not successful in the allergenic setting. But he learned quite a bit on his way, again, earning a Nobel Prize.

And then, of course, the discovery of HLA, or the human leukocyte antigens, or the histocompatibility antigens. These are the proteins that mark our tissues as being different from each other, and they are the biggest barrier to transplant acceptance. But again, we also know that they're the ones that are responsible for activating the immune system. So that is a Nobel Prize without any questions asked.

And finally, you need a good immunosuppression. And there are many people who have contributed to the development of immunosuppression. But here I show the picture of Jean Borel, another French scientist, who working within the context of a pharmaceutical company discovered the calcium neuroinhibitors, cyclosporine, which then led to the development of [INAUDIBLE] here in Pittsburgh for the prevention of graft rejection.

So despite the fact that transplantation is a great success story, in reality, it really won the short-term battle. But we're losing the long term war. And what does that mean? The figure I'm showing you here applies to kidney transplantation, but the same graph can be drawn for other solid organs, and also for bone marrow transplantation, but for different reasons. So what I'm showing you here is that advances in science and in immunosuppression over the last 30 to 50 years has allowed us to reduce the rate of acute rejection dramatically.

So the acute rejection has come down dramatically. But over time, the chronic attrition or the slope of decline of graft survival has not really changed. So despite improvements from 1985 when cyclosporine was introduced to the present time that slope of losing grafts over time has not changed. So what are the reasons for this chronic allograft attrition, or the chronic attrition of transplanted organs? What can we do about it? So the reasons-- and again, I'm showing kidney as an example because of my background as a nephrologist. But the same reasons likely apply to all transplanted organs.

The first, surprisingly, because we've succeeded as transplanters, is the death of recipients with a functioning graft. And the reason they die is side effects of immunosuppression, primarily cardiovascular events, heart attacks, and strokes, infections, some of them fatal, of course, and malignancy. So remember, tumors, in a way, is a natural transplant. Tumors, due to the accumulation of mutations, acquire proteins that are non-self, that are foreign to us. And therefore, the immune system has to survey them and has to reject them when they are in their nascent phase.

But if your immune system is suppressed, you're at increased risk of malignancy, both denovo as well as recurrence of a prior malignancy. So all these are known side effects of immunosuppression. The second reason is chronic rejection, the slow form of rejection that causes graft loss over time. And it's common to all the solid organ transplants. It's characterized by narrowing of the blood vessels, and in the lung transplants, the narrowing of the bronchials, the airways.

And thirdly, is recurrent disease. Most of the autoimmune diseases that affect the liver, for example, or the kidney, do recurred after transplantation. So that is the reason why we're losing the long term war, or the war against the loss of organs. And this puts transplanters or transplant experts in a situation of a tug of war. We're trying to suppress rejection to improve survival of organs. But we end up increasing the side effects of medications. And then these lead to death of our patients, or in some cases, for example, the loss of the graft itself.

A shocking statistic, is that 30% to 50% of patients who have a liver transplant or have a heart transplant ended up requiring a kidney transplant later because they lost their kidney graft due to cyclosporine or [INAUDIBLE] pro-graft toxicity. So we're not there yet. We are still in a field that has had its early successes, but its long term failures are a wake up call.

So what do you do in a situation like this? And I think this is, I believe, what Mark is preaching, is that we go back to the fundamentals, we go back to science. There's really no substitute to understanding the pathophysiology of a disorder if you want to fix it, or if you want to improve it. So really, the fundamentals is our immune system. So we as humans have highly evolved immune systems that allow us to be such successful organisms to fight so many infections.

So, really, the immune system in a very reduced version is a way for us to detect something that is foreign. And often, it's a microbe that's a pathogen that is harmful to us, and to reject it, to eliminate it. Unfortunately, that same immune system also recognizes the transplanted organ. For example, the kidney shown here as foreign and rejects it. So what do we do currently as physicians and practitioners of the art of transplantation? Is to immunosuppress.

This is globally immunosuppression that weakens the immune system both against the good and the bad, the good being the transplanted organ that's saving someone's life, but by suppressing the immune defenses against pathogens were predisposing our patients to infection. And as I mentioned earlier, we're weakening their ability to survey tumors and fight tumors, as many of by now that the ability of the immune system to reject a tumor is unquestioned. So if someone is immunosuppressed, they will not be able to even reject a very, very early tumor, leading to an increased incidence in tumors.

So what we really want in the clinic is something you would refer to as tolerance. We want our immune systems to be fooled into thinking that the organ that we've transplanted itself and ignore it, or not reject it, while maintaining their ability to fight everything else that's potentially bad for us, such as infection. And in order to do that, again, it's really important or essential to understand the fundamentals of the immune response. So now I'm going to dig a little bit deeper, descend a little bit more, and tell you about the basic cells that are responsible for immunity in us as humans, but also applies to the experimental animals that we use in the lab, such as the mouse.

So at the center of all immune responses is the t-cell. I could be accused of being t-cell centric, but there's a reason for that. If you have a mouse, for example, that doesn't have t-cells, it will not reject a transplant. But the minute you put few t-cells into that mouse, and you can drop as little as 10 cells, and they will reject. If you take a human, and you deplete them of their t-cells using a very potent antibody, such as campath anti-CD52 They will not reject until their t-cells start coming back. So there's no question that t-cells are essential for the immune response that we're telling you about today.

And the reason they are so potent at immunity is that they have fantastic receptors known as t-cell receptors that can recognize foreign substances, or proteins, or antigens with very high molecular specificity. But they don't recognize them in vacuum as free floating proteins. They require the help of a specialized cell called the antigen presenting cells, the most famous of which is the dendritic cells shown here in green. And that can present these foreign proteins in little snippets or peptides that are bound to the HLA molecules.

These same molecules that define us as different, histocompatibility antigens, their real purpose in the immune system is to present these small peptides to the t-cells. But even that is not enough. The antigen-presenting cell has to provide other stimuli known as co-stimulatory signals to the t-cell, also provide cytokines, often referred to as signal two and three, respectively.

And in order for the antigen-presenting cell to acquire the ability to be such a good cell at activating a t-cell, it also senses information, integrates information from its environment. It could be non-self antigens, microbes, or even inflammation to become such a potent cell that activates the t-cell. And once the t-cell is activated, then it will migrate to the target organ in the case of transplantation that would be the graft. And there it forms additional interactions with antigen-presenting cells.

The t-cells expand further to increase in number, and that leads to rejection. So what can we do to deal with this monster of a system that is so well equipped that fighting infection and we don't want it to fight the transplant that we put in? So there are two approaches. And a different way of asking the question, how do we get there? How do we get from immunosuppression that weakens our immune systems to not specifically to either less immunosuppression or eventually the optimal, the ideal that we would like to achieve, which is tolerance?

And there are really two principle approaches. One is to through science and through investigation is to manipulate individual aspects of t-cell activation. And this is really what we've been doing for many years with good success, but limited in the long term. So you could manipulate the t-cell, you could deplete them, you could devise ways to silence them, you could manipulate the interaction between the antigen-presenting cell and the t-cell.

Maybe some of you know about belatacept, or CTLA4Ig, which blocks this co-stimulatory signal. Potentially in the lab, such as the paper that Mark mentioned, suggests that you could manipulate the management-presenting cell in the graph itself to limit rejection, or you could perhaps limit the migration of t-cells to the graft. These are all good, but they are incremental advances. Another way of thinking about it, which is not a new way, but this is something that we wish to or we hope to approach at QPMC, and [INAUDIBLE] in a more novel and safer way is to replace the immune system.

So think now that if you have a donor is going to give you a kidney, if you were to get a bone marrow from that donor, your immune system would be that of the donor. Therefore, the kidney, or the heart, or the liver that came from that donor is now self. It's not foreign to that immune system because both the immune system and the organ came from the same individual.

So that would be a perfect situation where you don't have to worry about rejection you don't have to worry about giving immunosuppression. But the problem is how do you do that safely? Until we can do that safely, we will not be able to, as Mark mentioned earlier, utilize bone marrow transplantation for applications that go beyond cancer and leukemias and apply them to something such as solid organ transplantation.