the most studied animals at NIMH. I’ll remind you that our mission is to transform the understanding and treatment of mental illnesses through basic and clinical research, paving the way for prevention, recovery, and cure.

I also strongly feel that there are many ethical goods that come out of the use of animals in research. When we understand the biology of systems in any organism we understand general principles that apply to humans because all life has a common origin. This knowledge helps us understand devastating physical and behavioral disorders in humans because we have more insight into the underlying biology of the disorder. And these insights lead to treatments, cures, and prevention that can be applied to humans and other animals. We are developing deep insights into the nature of human beings and I think this is incredibly important. And I believe that the more dominant human beings become on this planet we will desperately need this information if we are to keep the balance of life here.

Finally, a word on animal welfare. I think the NIMH, partially because it really understands the nature of suffering and how it can develop, has always paid a lot of attention to animal welfare. I believe we and this community pay more attention than almost any other segment of human-animal interaction (the only exception to that, I think, is what goes on in veterinarians’ offices). But if you think about almost every other use or interaction of humans with animals, animals come out worse, in many cases much worse. To pay attention to animal welfare through the Animal Welfare Act has been an incredible benefit both to animals used in research and ultimately I think to us, by helping us to understand the illnesses that this Institute studies.

References


Animal Models in Immunology and Transplant Medicine

Linda Cendales

I am going to talk about how the Emory Transplant Center (ETC) established a comprehensive program for transplantation and how the use of animal research for our advances is crucial. I’m also going to share with you a little bit of my academic interest, vascularized composite allotransplantation, which basically is the allotransplantation of any vascularized peripheral tissue (such as skin, bone, nerve) as a functional unit for tissues that cannot be reconstructed in any other way. An example of it is a hand.

The risk-benefit ratio in transplantation is the risk that the patients take when they choose a life-saving or quality-of-life transplant versus the risks of taking immunosuppression with all the [associated] complications (including infection, malignancy, and death).

I’ll share with you our approach to transplantation at the ETC. Figure 1 shows what is often called the Larsen Circle of Life, with discovery at the lab, our translational research in nonhuman primates at the Yerkes National Primate Research Center, and our clinical applications. Examples of the projects that we have in the lab are antigen presentation, memory, and protective immunity. Examples of our translational studies in nonhuman primates include protocols on memory, xenotransplantation, and novel immunosuppression. Some of our novel clinical trials include studies in hand, islet, and kidney transplants, and pediatric transplantation.

Briefly, the alloimmune response has [several] signals. Signal 1 is where cyclosporine, for example, works. Signal 2 is where I am going to focus more in this talk.

When we transplant an organ, we bring with it antigen-presenting cells (APCs), which activate the recipient’s T cells. Studies have shown that blockage of this stimulation reduces rejection. Studies in mice inducing diabetes and transplanting islets in the renal capsule [showed that] block-
ing the B7 family with CTLA4-IG reduces rejection and produces long-term survival of islets in diabetic mice. The investigators did a control and the mice rejected (Lenschow et al. 1992). Then Parker and colleagues (1995) showed that it was possible to prolong rejection-free diabetic mice after islet transplantation by using anti-CD154 (Parker et al. 1995). The next step was by Larsen (Larsen et al. 1996): he blocked both signals CTLA4-Ig and CD154 in the APC and the T cell and showed longer rejection-free survival. In subsequent studies by Allan Kirk (Kirk et al. 1997) in a nonhuman primate model of kidney transplantation, all the controls without immunosuppression rejected within the first week. When he gave CTL4-IG alone, the monkeys were rejection-free for longer, but did reject within the first 30 days. Administration of anti-CD40, which is [another] component of the costimulation of the blockade alone, further deferred rejection in the monkeys. They had rejection by 3 months, but reversed it and prolonged the kidney transplants free of rejection.

The next step was to give both together. Again there was prolongation of kidney transplant with costimulation blockade. Next was the rationale of translating—making a medication that would include this concept that has been studied in animals for 10 years but making it more potent. In this study, Larsen and his group (2005) at the ETC developed a more potent medication called Belatacept, which is based on costimulation to block the CTLA4-Ig. Through animal experimentation they were able to identify the amino acids necessary to change to improve efficacy. This medication has been translated to the clinic and is currently in phase III studies in clinical trials (Vincenti et al. 2005). Among the benefits of this medication, it’s more specific to the immune response so instead of, for example, cyclosporine, which depletes the immune system in a more general way, costimulation blockade and Belatacept block only a signal in the alloimmune response, making it more specific. Another benefit is that it’s given once monthly versus a number of medications that transplant patients need to take daily.

Based on these advances in immunosuppression as well as in transplantation and microsurgery, we have been able to move forward to include patients for both quality-of-life and life-saving transplants. This is where vascularized composite allotransplantation has emerged as a partner in the field of transplantation. But like any emerging field, we have faced challenges. One of the challenges was, initially, the absence of clinically relevant animal models in which we could not understand the specificities of this transplant but also apply novel immunosuppression before its translation to the clinic.

We wanted to establish a nonhuman primate model because, in the era of biologic immunosuppression, the most relevant clinical model is in nonhuman primates to evaluate novel approaches. Taking into consideration, as we all do, the well-being of our animals and their social development,
we designed a transplant that includes every single tissue present in any composite allograft—bone, nerve, tendon, vessels, and skin. The transplant involves taking a piece of a forearm from one animal to another.

One of the benefits is that, even in the case of graft loss, the animals do not lose any function. In fact, as soon as they recover from the anesthesia, they go back to the cage and have full use of the upper extremity. Another benefit is that we can biopsy the tissues serially without graft loss and the animal does not experience any dysfunction either in the upper extremity or in the hand.

We started with our first group, which was without immunosuppression. As in humans, all the monkeys rejected within the first week. Then we applied immunosuppression similar to that for kidney transplantation. When we started decreasing the immunosuppression to evaluate rejection of these transplants, what we saw was comparable to what we were seeing in human hand transplants: with a decrease of immunosuppression, a rash in the skin develops. This is a benefit compared to other organ transplants as we can visualize the transplant. The rejection is well demarcated or circumscribed to the transplant. Similar to humans, the transplants in the nonhuman primates show comparable hair growth and similar magnitude and distribution of the T cell infiltrate in rejection.

Something novel that we have established is a nonhuman primate model to study the gene expression of markers that have been increased at the time of rejection in other transplants. We are comparing it with the histology to understand better the mechanisms of rejection.

In summary, so far, in terms of vascularized composite allografts we have been able to establish a nonhuman primate model for the study of this particular transplant, which is responsive to immunosuppression. We have moved forward with novel immunosuppression applications for clinical translation.

But we continue with our challenges and certainly the burden of immunosuppression is an important one. We have moved forward with novel approaches and are evaluating co-stimulation blockade based on Belatacept, the medication developed at Emory. Briefly, monkeys that received a transplant without immunosuppression rejected within the first week as we saw in the prior slide. An animal treated with Belatacept is rejection free at this time.

Our first clinical application for vascularized composite allograft is hand transplantation for the reconstruction of below-the-elbow amputations. We are actively recruiting patients. Our program is in collaboration with the Atlanta Veterans Affairs (VA), which is the only VA hand transplant program in the United States. Our VCA Emory-VA Program is based on a multidisciplinary approach: we have the Emory Transplant Center, plastic surgery, neuroscience, a crucial component of our program is the Division of Animal Research and the Yerkes National Primate Research Center, and all the veterinary services. We have immunology, pathology, mental health, hospital services, infectious diseases, pharmacy, prosthetics, the Georgia Tech School of Applied Physiology, Life Link (our organ procurement organization), public health, VA Research and Development, oral and maxillofacial surgery, radiology, public relations, the Mason House (where we host our transplant patients), the Simulation Lab, Pastoral Care and Bioethics, as well as the Atlanta Clinical and Translational Science Institute—all working together to move the field forward in a systematic way and offer our patients outcomes that are the same as or better than those we have seen so far.

I want to share a couple of patient stories to show the clinical translation of the research that we do from the bench to the bedside and the importance of its application. First is the story of a patient who has been approved to move forward with a bilateral hand transplant because she wants to take care of her kids and she would like to go to the bathroom independently. Our next patient approved for our program is a veteran who lost the lower extremity and the right upper extremity in the Iraq conflict. I will share with you our current outcomes.

I was involved in the first two hand transplants in the United States and I’ll describe the second patient that we did in the United States. His transplanted hand was matched for skin pigmentation, gender, blood type, and size. He has discoloration in his transplanted hand, which is similar to what we saw in our nonhuman primates—very well demarcated and circumscribed to the allograft. A 1-minute video showing the outcome was taken when I was still taking care of him in Louisville. Every single activity shown in the video he could not do with his body-powered prosthesis. He is a construction worker and was able to return to full work by month four.

All these patients have been shown to acquire or regain sensation. It’s not normal [sensation], but it allows them to feel surfaces and differentiate between rough and smooth surfaces and between hot and cold, so it’s a functional protective sensation. They recover sensation to the fingertips within the first 6 months, which is more rapid than we see in replantation.

Some of the advances so far: We started with the lack of an animal model in which to carry out our experiments to be able to translate our findings to the clinic. We established a nonhuman primate model that is responsive to immunosuppression. We started with a burden of immunosuppression. We have been able to minimize regimens. We have also established a comprehensive program from the bench to the bedside in our field of transplantation.

Reviewing the Larsen Circle of Life, we incorporated this new partner in transplantation, vascularized composite allo-transplantation, into our ETC approach to transplantation, including hand and other potential clinical applications for the reconstruction of tissues that cannot be reconstructed with autologous tissue. We integrate our discoveries in the lab, our observations through our translational research in nonhuman primates, and our clinical applications for the improvement of human health. The questions generated in the clinical cycle back to the lab and our animal models to complete the circle of life.
was asked to speak about infectious diseases and animal models in the context of how we can, now and in the future, deal with emerging infectious diseases. I think it’s important to point out that whereas we share a lot of our pathophysiology with animals in terms of diseases that humans get, we also share infectious diseases with animals. I think this makes infectious diseases unique in terms of both what we do for humans and applications for animals, in terms of economic impacts, agricultural use of animals, and companion animals.

First, a bit of historical context. We have a tendency in this country to make premature declarations of victory over a lot of things, and over 40 years ago we thought we had licked infectious diseases. There was quite a bit of hubris at the success we had with treatments being developed in terms of antibiotics. And there was a lot of hope that infectious diseases would be gradually phased out and discarded over time. But the reality, unfortunately, was that [that thinking] was very much premature.

An article in Nature (Jones et al. 2008) identified at least 335 infectious diseases that emerged between 1940 and 2004. What’s interesting to look at from that article are the global trends, which you can see in the four charts of Figure 1 that depict globally where this is occurring. Panels A and B list zoonotic diseases, from wildlife and nonwildlife, respectively. It is important to keep in mind that infectious diseases are travelling back and forth between humans and animals and that animal reservoirs represent a major source of infectious disease [for humans].

At the National Institute of Allergy and Infectious Diseases (NIAID), we have a dual mandate, which is slightly different from most other [NIH] institutes. We have the typical mandate of other institutes, which is to maintain and grow a basic and applied research portfolio in [our] mission, primarily microbiology and immunology. But importantly, we are the one institute that can, without doing anything specific, find ourselves facing brand new diseases that we must rapidly respond to and try to bring to bear as many resources as possible to bring these new diseases under control.

[I’ll offer] some highlights. In 2001, anthrax was less than a bang and more a whimper, but this belies the fact that pieces of paper and the postal system turned out to be a tremendous delivery device to cause not only in some cases death but also widespread panic and fear. In 2003, 2 years later, SARS (sudden acute respiratory syndrome) gave us an example of a disease that was wholly unexpected to arise. There was very little in the research base that anticipated something with the attributes of SARS. [The experience reflects] the ill-defined and unanticipated interplay between culinary preferences and animal handling in certain parts of the world that allowed the disease to emerge. We dodged a bullet on SARS, I would have to say. The mortality rate for the disease is 10%, which doesn’t sound terribly frightening except that, to put that in context, the 1918 influenza pandemic, which was responsible for 50 million deaths around the globe, had a fatality rate of only 3%, so 10% mortality is quite high. We were lucky with SARS because it turns out to be a disease that is not contagious until after you’ve become symptomatic. So if you can isolate everyone who’s been exposed and let the disease run its course, you can stop transmission in its tracks. With flu, on the other hand, you’re