EDITORIAL

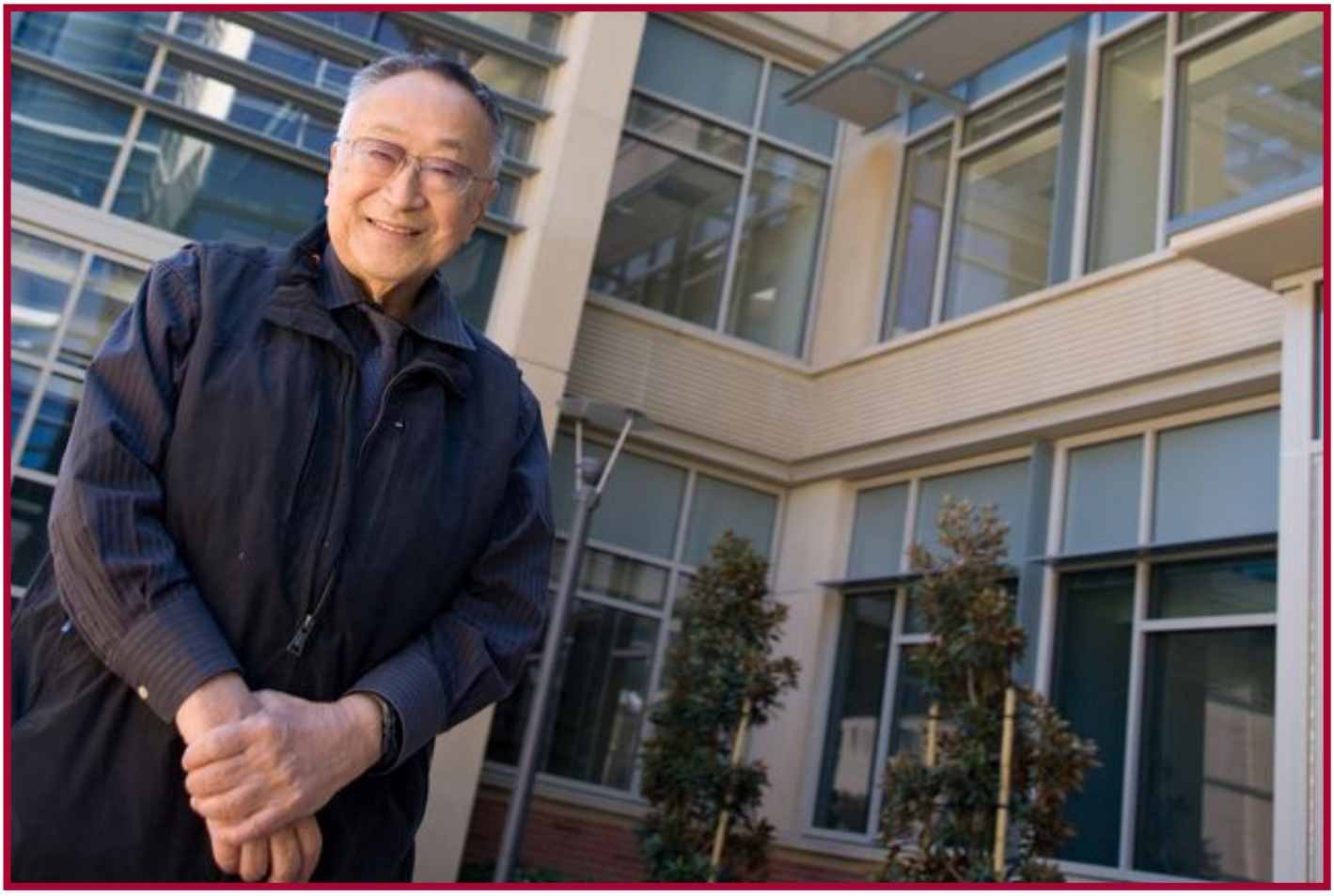
The Humoral Theory of Transplantation: A Story Less Told

Anat R. Tambur, *DMD, PhD, D(ABHI),*
Feinberg School of Medicine,
Northwestern University,
Chicago, Illinois

It has been almost two years since Paul I. Terasaki passed away. I had the honor and privilege to represent ASHI at his memorial, but I was asked to be mindful that the audience was mostly not of the medical field and certainly uninformed regarding HLA testing. The task appeared daunting. How does one explain the significance of Terasaki's inventions and contributions to our field in everyday language to a lay crowd? I found myself searching for analogies from daily life.

I remembered entering the field in the late 1980s, poring over hundreds of Terasaki's plates to pursue my doctoral thesis. The ease of testing an individual's serum against multiple analytes (60 or 72) was taken for granted. The appreciation of the ingenuity of devising these plates came only several years later as I was reading memoirs on how the HLA system was discovered and how cumbersome the original testing options were. It was very clear to me that without the Terasaki plates, progress in the field would have been much slower and testing for HLA antigens or antibodies would not have been a mainstay at numerous laboratories around the world. I thought of this invention as revolutionary.

In my talk at his memorial, I equated this development to the revolutionary effects of transforming room-sized computers into the small desktop or even laptop computers that are now so instrumental in our daily lives. Both advancements made a daunting and laborious task into one that is accessible to all and performed with ease, advancing science in the process. Dr. Terasaki's technical and scientific contributions would have



been great had he stopped at inventing the Terasaki plates, but he led or contributed significantly to multiple scientific and technical revolutions in our field. Most notable today is the formulation of the single antigen bead assay that has transformed our understanding of transplant immunology.

Dr. Terasaki's technical and scientific contributions would have been great had he stopped at inventing the Terasaki plates, but he led or contributed significantly to multiple scientific and technical revolutions in our field. Most notable today is the formulation of the single antigen bead assay that has transformed our understanding of transplant immunology.

Many obituaries were written praising Dr. Terasaki for his achievements and his influence on our field. My point in this essay, however, is to share a lesser-known story, as I believe that this story conveys a lesson of utmost importance that we could all stand to learn. It was only at the memorial that I heard this story for the first time. I assume that many of you have not heard about it, either.

Together with the pioneers of histocompatibility, Paul Terasaki contributed multiple publications documenting the role of HLA matching in kidney transplant outcomes. (Many of these publications can be viewed at piterasaki.org/publications.html, put together by one of Dr. Terasaki's sons, Mark.) It was a time of rapid data explosion, changes to how transplant histocompatibility was perceived and quick growth in the number of HLA laboratories (many were, at the time, called tissue typing laboratories). HLA matching became a buzzword. NIH and other agencies designated funds to scientists who proposed to study the phenomenon and help improve transplant outcome. One of the people to be awarded such a grant was Paul Terasaki. Importantly, HLA matching was already used for the first iteration of the organ allocation algorithm.

To collect additional data, Paul Terasaki collaborated with Tom Starzl, then at the Transplant Center in Denver. They set out to compare the outcome of kidney transplants from perfectly HLA-matched, live, blood relatives with that of live, HLA-mismatched, non-related donors. As Terasaki and Starzl analyzed more and more results, an alarming theme came to light. While HLA matching was important, many of the patients transplanted from unrelated, less-HLA-matched donors were doing extremely well (even years post-transplantation). Alas, that was definitely not the result that was expected to come out of this study.

Now comes the most important ethical question. What does one do when the results do not fit the hypothesis? What does one do when NIH funding was received to conduct this specific study and a contract was signed to perform typing for transplantation? Unfortunately, the driving force in science is "publish or perish:" Produce data that supports your original hypothesis, and you'll have a chance to get additional funding. In that environment, many people would fit the data to their hypothesis or, if they could not, avoid reporting the negative result rather than accepting and reporting that their original hypothesis was likely wrong. Regrettably, this is a common practice.

The greatness of Dr. Terasaki is that he chose to stay true to his core values and report the data as is. One can read in his own memoirs, as well as those of others, about how he stood on the podium and delivered his findings despite the very unhappy, perhaps even hostile, audience. In fact, he paid dearly, incurring the wrath of the professional community and government bureaucrats. The details are quite shameful to our scientific community. Suffice it to say that Dr. Terasaki lost his contract with the government, but even more appalling, his NIH funding was not renewed **and** was effectively taken away soon after he reported his findings, before the funding period was scheduled to end. This is an unheard-of response.

Dr. Terasaki's crime was to report the facts as they were, no matter what, and his punishment was disproportionate and unparalleled. Despite this, Dr. Terasaki continued to support our field, plowing unwaveringly toward understanding the humoral theory of organ transplantation.

In retrospect, we can now appreciate that Dr. Terasaki's findings were accurate. It was his belief in these results that sent him in search of other explanations. Those original observations led him to develop the crossmatch assay, a gold standard for clinical practice since 1969. This was a turning point in our field that allowed many more patients to receive a compatible organ and extend their lives. Additional advancements to our field, based on this original observation and critical thinking, are documented in the many publications that Dr. Terasaki and others, including many among us, have contributed.

The moral of this story: Don't let public opinion sway your thinking process. Work hard to obtain accurate data, and take the time to figure out its significance, even if it does not conform to current dogmas (or fashions). You may be confronted with less-supportive audiences or funding agencies, but who knows: You may have a chance to find something real and useful, and maybe one day everyone will appreciate your contribution, like we appreciate Dr. Terasaki.