frontiers | Research Topics

Transplantation pillars

Edited by
Reza Abdi, Stuart Knechtle and Jerzy Kupiec-Weglinski

Published in
Frontiers in Transplantation

ISSN 1664-8714
ISBN 978-2-8325-6142-3
DOI 10.3389/978-2-8325-6142-3

About Frontiers

Frontiers is more than just an open access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers journal series

The Frontiers journal series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the *Frontiers journal series* operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews. Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the *Frontiers journals series*: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area.

Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers editorial office: frontiersin.org/about/contact

Transplantation pillars

Topic editors
Reza Abdi — Brigham and Women's Hospital, Harvard Medical School, United States
Stuart Knechtle — Duke University, United States
Jerzy Kupiec-Weglinski — University of California, Los Angeles, United States

Citation
Abdi, R., Knechtle, S., Kupiec-Weglinski, J., eds. (2025). *Transplantation pillars*. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-8325-6142-3

Table of contents

04 Hilliard Seigler, M.D. and the origins of kidney transplantation and immunology at Duke
Stuart J. Knechtle and Justin Barr

09 Paul Russell: the transcendentalist surgeon of America
Reza Abdi

13 Robert S. Schwartz, MD, a transformative figure in immunosuppression that revolutionized transplantation
Xian C. Li

16 Robert H. Rubin and infectious disease in transplantation
Jay A. Fishman

19 A Mentee's perspective on Dr. Anthony Monaco: the quiet giant of transplantation
Satish N. Nadig

21 R. Randal Bollinger, M.D., Ph.D., Master Surgeon
Stuart J. Knechtle and Allan D. Kirk

25 Walter Brendel and the dawn of transplantation research in Germany
Walter G. Land

31 Paul I. Terasaki, Ph.D: a pioneer in transplant medicine and a dedicated philanthropist
Jon Kobashigawa

35 Terry B. Strom: not just a pillar but a foundation
Manikkam Suthanthiran

39 Ronald W. Busuttil, M.D., Ph.D.— TTS 2024 Medawar Prize Laureate
Jerzy W. Kupiec-Weglinski

frontiers | Frontiers in Transplantation

TYPE Perspective
PUBLISHED 22 May 2023
DOI 10.3389/frtra.2023.1196455

OPEN ACCESS

EDITED BY
Ernesto Molmenti,
Northwell Health, United States

REVIEWED BY
Austin Schenk,
Ohio State University, United States
Derek Orlando Pipolo,
Trauma and Emergency Hospital Dr. Federico Abete, Argentina

*CORRESPONDENCE
Stuart J. Knechtle
stuart.knechtle@duke.edu

RECEIVED 29 March 2023
ACCEPTED 21 April 2023
PUBLISHED 22 May 2023

CITATION
Knechtle SJ and Barr J (2023) Hilliard Seigler, M.D. and the origins of kidney transplantation and immunology at Duke.
Front. Transplant. 2:1196455.
doi: 10.3389/frtra.2023.1196455

Hilliard Seigler, M.D. and the origins of kidney transplantation and immunology at Duke

Stuart J. Knechtle[1]* and Justin Barr[2]

[1]Duke Transplant Center, Department of Surgery, Duke University School of Medicine, Durham, NC, United States, [2]Ajmera Transplant Center, University of Toronto, Toronto, ON, Canada

The contributions of Dr. Hilliard Seigler to the founding of the Duke kidney transplantation program were considerable in both surgery and immunology. Some of these highlights are summarized based upon interviews with Dr. Seigler by the authors.

KEYWORDS
kidney, transplantation, immunology, HLA, MHC typing, histocompatibility

In 1962, Duke School of Medicine Dean Barnes Woodhall and Surgery Chairman Clarence Gardner recruited Dr. D. Bernard Amos as Professor of Experimental Surgery and Immunology with the intent of beginning organ transplantation at Duke on a scientific basis. Dr. Del Stickel was assigned the surgical task of developing kidney transplantation. In 1965, Dr. Hilliard Seigler completed his surgical residency at the University of North Carolina, Chapel Hill and contacted Dr. Amos to arrange a fellowship in immunogenetics as a means of pursuing a scientific platform for organ transplantation. Using Dr. Amos' background in tissue typing and serologic matching, the team decided it would be best to start with living donor kidney transplantation. Although some individuals were opposed to living donor transplantation on ethical grounds, the Duke team advocated that living donations based on tissue matching would be most successful and discussed living kidney donations with an *ad hoc* ethics committee at Duke, a precursor of the current system of institutional review board. While there were different opinions in the ethics committee, the final decision supported the notion of living donor kidney transplants with donor–recipient pairs matched according to objective immunologic testing methods.

Dr. Seigler was part of the group that trialed punch skin grafts as a screening tool for compatibility, placing skin grafts from prospective donors onto recipients and measuring responses (Figure 1). In addition, the investigators placed multiple skin grafts on each other in order to serve as controls and to validate methodologies. The serologic testing of recipients relied on approximately 30 panels of human lymphocytes to screen alloantibodies and became a particular focus of the group. They quickly learned that in order to make sense out of the genetics of a major histocompatibility complex (MHC), antigens that inbred patient populations would be needed as a starting point, as well as sharing such immunogenetic information across transplant groups. This prompted Dr. Amos to host the first international histocompatibility workshop at Duke in 1964 with the aim of sharing and standardizing assay methods and reagents. These workshops continued biannually until 1970. With respect to inbred patient populations, Seigler explained,

FIGURE 1
Dr. Hilliard Seigler on right performing skin grafts in laboratory.

> We got the most helpful information at Duke from two groups, even though we had looked at the Bantu tribe in Africa and an Indian tribe in Guatemala. We got the most information from tiny little towns in the mountains of North Carolina, which had been relatively closed for generations. They were little areas where there wasn't a lot of travel to or from, and the families were quite large. We had 6, 8, or 10 children in the families, and we got incredible genetic information out of those.

> Another group that we worked with was the Amish, and we worked with them in Lancaster, Pennsylvania. They had incredible Bibles that would have five to seven generations that were documented, so we got a lot of information in terms of understanding the genetics of these antigens that we were looking at. That was what eventually became known as the major histocompatibility complex in man or HLA.

The name HLA for the human MHC was assigned at the first histocompatibility workshop in Durham in 1963. Paul Terasaki proposed that the locus be named LA for Los Angeles (his location), while others felt that this was too specific to Dr. Terasaki. Bernard Amos, borrowing from the mouse MHC nomenclature (H2), proposed that merging H with LA would blend the letters and be a satisfactory compromise as "HLA." Amos' motion was accepted. Although subsequently others have claimed that HLA stands for human leukocyte antigen, the above story is the actual history of the name.

The ethical controversy about proceeding with clinical kidney transplantation at Duke weighed on the first pioneers of transplantation at Duke, including Del Stickel, who performed the first transplant in 1965. He and Seigler proceeded despite the negative feelings of some members of the ethics committee. A professor in the law school alleged that "Del Stickel and I were immoral and non-ethical, because we were taking normal organs out of normal people and putting them in somebody else."

The transplant program started only with living donors. In fact, the first 7 years of kidney transplants consisted exclusively of living donor kidney transplants based on thorough immunogenetic testing. Bernard Amos, recruited to Duke as an internationally recognized mouse immunogeneticist, also developed a reliable and consistent serologic screening method in humans to detect preformed antibodies, aiming to avoid early antibody-mediated rejection. Amos attracted multiple surgeons, such as Seigler, and other clinicians and scientists interested in learning transplant immunology. Seigler completed an NIH-supported fellowship in immunogenetics with Amos, identifying tissue antigens and determining what role they did or did not play in the human immune response, specifically organ rejection. His second goal was to work toward the elusive goal of transplant tolerance.

Based on the extensive typing of donors and recipients, including placing donor candidate skin grafts pre-kidney transplant on recipient candidates, the results of the living donor program led by Del Stickel, Bernard Amos, Hilliard Seigler, and Everett Anderson (urologist) proved to be excellent, relying initially on low-dose azathioprine (50 mg/day) without steroids as immunosuppression (1) in HLA-identical donor–recipient pairs. The 50-year follow-up on those early results was recently reported by Seigler et al. and compared to national outcomes, exceeding them by a wide margin (2) and supporting the validity and impact of pretransplant immunologic optimization of donor–recipient pairing. Seigler also investigated the relative influence of haplotype mismatches using skin grafting and mixed lymphocyte reactions (3).

In addition, Seigler played an instrumental role in the establishment of the Southeast Organ Procurement Foundation (SEOPF), the precursor of the United Network for Organ Sharing (UNOS). As Seigler tells the story, it involved Dr. David Hume of Medical College of Virginia:

> Dave Hume had been at Medical College of Virginia, and he'd come down from Harvard. Bernard Amos and myself and Del Stickel drove up to Richmond and we talked to Hume because Hume was just turning out transplants but was having a lot of rejection. When you have a lot of rejection you get a big pool of patients that have rejected, and they're very difficult to do a second, or third, transplant.

> He was very sensitive to the fact of, "Look, I'm a force, but I need a way to get these difficult patients off of my list so we can go forward, and you guys down there at Duke are all about this typing business—maybe we ought to get together." We established what we called "The Southeastern Organ Procurement Foundation" or SEOPF. We recruited other people, we got the University of Virginia involved, and the University of North Carolina was involved. We had as a great donor source the pathologist at Grady Hospital in Atlanta because they had a lot of potential donors, and so we got together as a group for organ sharing. SEOPF eventually became UNOS. That started here (Duke) also just like the histocompatibility did.

Another significant research activity of Seigler during those years was to collaborate with Dr. Paul Ebert, a cardiac surgeon at Duke at the time, in performing canine heart transplants and considering non-human primate heart transplants. Seigler and colleagues compared the immunogenetics of chimpanzees and humans, finding considerable similarities between the tissue antigens of chimpanzees and humans. Chimp and human cells were often totally cross-reactive with respect to eliciting identical immune responses in mixed lymphocyte reactions. At that time, chimpanzees were being considered as potential organ donors to humans, prompting the MHC typing of animals at Yerkes Primate Center in Atlanta as well as the colony at Rijwik in Holland. That work also extended into typing gorillas and orangutans for comparisons to humans. Dr. Keith Reemtsma, a transplant cardiothoracic surgeon in Louisiana, had actually performed approximately nine chimpanzee to human kidney transplants, several with a long survival of many months. Reemstma and Seigler communicated about this work because of the relevance of immune typing to the xenotransplant model. As Seigler explains, "He (Dr. Keith Reemtsma) sent me slides from a lady that he had transplanted chimp to human. This was a biopsy about 9 months out. The slides looked like it was an HLA identical transplant." Eventually, however, a cellular immune response and severe [digoxin] toxicity occurred, so no long-term results developed because the patient succumbed to a cardiac arrest.

Seigler and his Duke colleague Paul Ebert had started canine heart transplants in the laboratory, and after achieving technical success they wanted to expand in 1967 into human heart transplants or xenotransplants, considering non-human primate donors based on the immunologic typing experience (4–7). However, this intention was not realized, although Seigler's background with non-human primate typing did prompt a clinical experiment of cross-circulation of a chimpanzee with a child in hepatorenal failure (8, 9).

Dr. Seigler's career pathway, while continuing involvement with transplantation, shifted to surgical oncology due to the clinical needs of the Duke Department of Surgery. He developed the melanoma clinic at Duke and led major innovations in clinical oncology research. He quickly became the most efficient surgeon in the Duke operating room, beginning his cases at 7 a.m. in a system where scheduled first starts began at 7:30 a.m. He was known for wheeling patients in and out of the operating room or even mopping the floor himself, charming assistants and staff with wit and enthusiasm. His mentoring in transplant immunology influenced the careers of Drs. Wayne Flye, Thalachallour Mohanakumar, Randy Bollinger, and Allan Kirk, and continues to impact scores of medical students, residents, and faculty, including the present authors (**Figure 2**). Through establishing the critical importance of HLA matching for successful kidney transplantation, cofounding the precursor to UNOS, making seminal discoveries in the potential of cross-species organ sharing, and pioneering canine cardiac transplant, his contributions continue to influence the field. His influence is well summarized in the words of the Chair of Surgery at Duke during Dr. Seigler's early career:

> Many times I have reflected upon your numerous and significant contributions to the Department. You were very wise in obtaining fundamental training in immunology with Bernard Amos and have pursued the field brilliantly ever since. Your trainees in the laboratory have represented the Surgical Program extremely well and will be a great tribute to you in the future. In addition, you have been most successful in obtaining NIH and VA research support, which has meant much to our productivity and national image. Be assured that these are both recognized and greatly appreciated.

> With my special thanks again to a wonderful friend and colleague and with very best wishes to you. David C. Sabiston, Jr., M.D.

FIGURE 2
Dr. Hilliard Seigler, center, at a transplant meeting; Dr. Clyde Barker behind him.

Data availability statement

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

Author contributions

This is an original work by the authors and has not been submitted elsewhere for consideration. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Seigler HF, Gunnells JC Jr, Robinson RR, Ward FE, Amos DB, Rowlands DT, et al. Renal transplantation between HL-A identical donor–recipient pairs. Functional and morphological evaluation. *J Clin Invest.* (1972) 51(12):3200–15. doi: 10.1172/JCI107147

2. Shaw BI, Villani V, Kesseli SJ, Nobuhara C, Samoylova ML, Moris D, et al. A historical cohort in kidney transplantation: 55-year follow-up of 72 HLA-identical, donor–recipient pairs. *J Clin Med.* (2021) 10(23):5505. doi: 10.3390/jcm10235505

3. Seigler HF, Ward FE, Amos DB, Phaup M, Stickel DL. The immunogenicity of human HLA haplotypes as measured by skin graft survival times and mixed leukocyte reactions. *J Exp Med.* (1971) 133:411–23. doi: 10.1084/jem.133.3.411

4. Ward FE, Seigler HF, Metzgar RS, Reid DM. Cross-reactivity of primate alloantigens: absorption of anti-HLA reactivity from human alloantisera by chimpanzee lymphocytes. *Tissue Antigens*. (1973) 3:389–401. doi: 10.1111/j.1399-0039.1973.tb00509.x

5. Gilbertsen RB, Metzgar RS, Seigler HF. Immunological studies on T and B lymphocytes in chimpanzees: effect of thymectomy and irradiation. *Transplant Proc*. (1974) 4:183–8.

6. Ward FE, Seigler ED, Guthrie CE. Chimpanzee families. H.F., Metzgar, R.S., Reid, D.M., Hill. Histocompatibility testing. *Transplant Proc*. (1974) 4:129–34.

7. Seigler HF, Ward FE, Metzgar RS, Phaup MD, Adams BJ. Mixed lymphocyte culture responses in chimpanzee families. *Transplant Proc*. (1974) 4:135–9.

8. Patterson JH, MacDonell RC Jr, Zwiren GT, Seigler HF, Metzgar RS, Keeling M. Cross-circulation between humans in hepatic coma and chimpanzees. In: Bourne GH, editor. *Non-human primates and medical research*. New York/London: Academic Press (1973). p. 257–68.

9. MacDonell RC Jr, Patterson JH, Zwiren GT, Seigler HF, Metzgar RS, Caplan DB, et al. Cross-circulation between children in hepatic coma and chimpanzees–clinical, biochemical and coagulation observations. *J Pediatr*. (1973) 82:591–7. doi: 10.1016/S0022-3476(73)80583-9

frontiers | Frontiers in Transplantation

TYPE Perspective
PUBLISHED 06 June 2023
DOI 10.3389/frtra.2023.1191149

OPEN ACCESS

EDITED BY
Paolo Cravedi,
Icahn School of Medicine at Mount Sinai, United States

REVIEWED BY
Alessandro Alessandrini,
Harvard Medical School, United States
Jordi Ochando,
Icahn School of Medicine at Mount Sinai, United States

*CORRESPONDENCE
Reza Abdi
rabdi@rics.bwh.harvard.edu

RECEIVED 21 March 2023
ACCEPTED 05 May 2023
PUBLISHED 06 June 2023

CITATION
Abdi R (2023) Paul Russell: the transcendentalist surgeon of America.
Front. Transplant. 2:1191149.
doi: 10.3389/frtra.2023.1191149

Paul Russell: the transcendentalist surgeon of America

Reza Abdi*

Transplantation Research Center, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States

I first met Dr. Russell in the Fall of 2000 at the Massachusetts General Hospital (MGH). I entered the Russell-Round-Room which was packed with surgeons and physicians of MGH, among whom there was no shortage of self-esteem. I came across a handsome man, full of vigor and competence, standing still for nearly two hours in the corner of the room near the blackboard. He was remarkably attentive to the questions, for which he had very concise responses. He was soft-spoken with an inviting smile, and had a welcoming, modest air about him. Despite his remarkable academic achievements, he was strikingly unassuming and serene – features likely ingrained in his very nature.

KEYWORDS

Russell, surgeon, transplant, thinker, research

I first met Dr. Russell in the Fall of 2000 at the Massachusetts General Hospital (MGH). I entered the Russell-Round-Room which was packed with surgeons and physicians of MGH, among whom there was no shortage of self-esteem. I came across a handsome man, full of vigor and competence, standing still for nearly two hours in the corner of the room near the blackboard. He was remarkably attentive to the questions, for which he had very concise responses. He was soft-spoken with an inviting smile, and had a welcoming, modest air about him. Despite his remarkable academic achievements, he was strikingly unassuming and serene—features likely ingrained in his very nature.

Growing up in Iran, where one is infused with the mystical poetry of Rumi and Hafiz, I was struck by the mystic aura of a "thinker" around him. In addition to being an outstanding physician-scientist, his success in mentoring outstanding scientists and building superb programs, all very different features, were indeed indebted to his "thinker" quality which formed the foundation for a superb research environment for all comers with talent. He reminded me of the famous transcendentalist writers of Concord (MA)—Ralph Waldo Emerson and Henry David Thoreau—who were drawn to the mysticism of the East and Hafiz's poetry. Thoreau and Emerson were also, despite being at the pinnacle of their writing careers, better known for their unassailable mysticism with a wider perspective about life. Their simplicity and ingenuity were as remarkable as their intellectual greatness.

Recently, I was privileged to interview Dr. Russell. It was an inspiring and uplifting experience. He was residing at the same place as his old friend, Francis Moore, another giant of American surgical research and a key person leading the efforts to the first successful kidney transplantation in 1954. Moore had passed away long ago. It was Moore who called Dr. Russell one Sunday morning in the mid- 1960s to "say that he had heard on the radio of a patient recently admitted to the MGH who might prove to be a perfect donor of a liver for one of his patients." A phone call led to the formation of the Boston Interhospital Organ Bank and later, the broader based New England Organ Bank and the establishment of one of the earliest systems of organ sharing for transplantation.

FIGURE 1
Allene, Paul, and Peter and Jean Medawar.

FIGURE 2
Exterior shot of the museum (Top) and Dr. Russell inside the museum with Sarah Alger, Director of the museum (Bottom). Photo credit for all: MGH Photography Lab.

During our interview over Zoom, at age 97 recovering from COVID, he looked straight into the camera for two hours, gracefully poised but solid, sharply focused with his undivided attention. His memory was impeccable, and his responses were again short and to the point, all likely reflecting his lifelong characteristics. More than 20 years had passed since the first time I met him, and his soul was unaltered. He remained that larger-than-life man with vigor, sharp intellect, and above all, kindness.

Dr. Russell was born in 1925 and raised in Chicago, Illinois. It is probably unknown to many Bostonians that, some of their finest surgeons had come from the Mid-west. His father was a self-made man who became a very famous football player in 1913, played quarterback and earned All-Big Ten honors. Dr. Russell's mother, on the other hand, was an avant-garde artist who had a major role in the formation of modern dance in America. Dr. Russell was trained in the labs of two Nobel Laureates– Charles Huggins and Peter Medawar. Medawar was an unknown zoologist who was conducting experiments which were not of interest to many immunologists at that time. Medawar was then 39 years old. Medawar's reply to Dr. Russell's request for a research fellowship position was cheerfully negative that "This is an undergraduate teaching department of zoology". Medawar's reply which described the types of ongoing projects in his lab, made it even more attractive to Dr. Russell. He used all sorts of means and eventually ended up joining Dr. Medawar's lab (Figure 1).

Most of Dr. Russell's surgery training was at MGH, where he became the Chair of the Department of Surgery and served in that role for nearly a decade. They began kidney transplantation on April 24, 1963 at MGH. His contributions to the field of clinical transplantation are enormous. Notably, he pioneered the concepts of brain death and organ donation. Dr. Russell formed one of the earliest classical academic research labs in the U.S. around preclinical and clinical models of transplantation (1–21). He recruited a scientist, Dr. Henry Winn, who was trained in the lab of the Nobel Laureate George Snell. Dr. Winn was amongst the very first immune-geneticists in pre-clinical organ transplantation research. Dr. Russell's lab attracted numerous key figures early on, not all mentioned here, including Anthony Monaco, Benedict Cosimi, David Sachs, Robert Colvin, Hugh Auchincloss, Megan Sykes and Frank Delmonico. In recognizing 200 years of evolution and innovation in medicine, MGH erected a museum named the Paul S. Russell, MD Museum of Medical History and Innovation (Figure 2).

During our interview, we went over many chapters of his life, over many of his magnificent research accomplishments, but the only time he stopped looking into the camera and gazed upward with his face shining more brightly than usual, was when I asked him about his wife. His answer this time was again brief. He described decades of living with Allene in only a few words, that "she was a wonderful woman" (Figure 3). His response and luminescent expression reminded me of a poem by the Persian Sufi Poet, Rumi: "that if you love someone with your heart and soul, there is no such thing as separation." If I were to describe Dr. Russell with one word. I would say Optimism. He truly

FIGURE 3
Paul and his wife Allene.

embodies optimism in its fullest sense and inspires others to embrace it as well.

Dr. Russell has seen it all: the unmatched efforts of Abraham Flexner who single-handedly built what then became the foundation of American Medical Research, with the financial support of Rockefeller, at the beginning of the 20th century; the peak of academic research and rise of some of the finest physician-scientists of our time. He has also been witnessing the widespread commercialization of medicine and a tsunami of cultural changes which, one way or other, are impacting American medical leadership and research. While it has been said that the generation of physician-scientists is at the verge of "extinction", Dr. Russell remains a rarer breed still, a "physician-thinker" that we may never see again (22–24).

Data availability statement

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

Author contributions

The author confirms being the sole contributor of this work and has approved it for publication.

Conflict of interest

The reviewer AA declared a shared affiliation with the author to the handling editor at the time of review.

The author RA declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Benson EM, Colvin RB, Russell PS. Induction of IA antigens in murine renal transplants. *J Immunol.* (1985) 134(1):7–9. doi: 10.4049/jimmunol.134.1.7

2. Billingham RE, Russell PS. Studies on wound healing, with special reference to the phenomenon of contracture in experimental wounds in rabbits' skin. *Ann Surg.* (1956) 144(6):961–81. doi: 10.1097/00000658-195612000-00005

3. Cosimi AB, Burton RC, Colvin RB, Goldstein G, Delmonico FL, LaQuaglia MP, et al. Treatment of acute renal allograft rejection with OKT3 monoclonal antibody. *Transplantation.* (1981) 32(6):535–9. doi: 10.1097/00007890-198112000-00018

4. Cosimi AB, Colvin RB, Burton RC, Rubin RH, Goldstein G, Kung PC, et al. Use of monoclonal antibodies to T-cell subsets for immunologic monitoring and treatment in recipients of renal allografts. *N Engl J Med.* (1981) 305(6):308–14. doi: 10.1056/NEJM198108063050603

5. Jeannet M, Pinn VW, Flax MH, Winn HJ, Russell PS. Humoral antibodies in renal allotransplantation in man. *N Engl J Med.* (1970) 282(3):111–7. doi: 10.1056/NEJM197001152820301

6. Johnson GJ, Russell PS. Reaction of human lymphocytes in culture to components of the medium. *Nature.* (1965) 208(5008):343–5. doi: 10.1038/208343a0

7. Medawar PB, Russell PS. Adrenal homografts in mice, with special reference to immunological adrenalectomy. *Immunology.* (1958) 1(1):1–12. PMID: 13513137; PMCID: PMC1423877

8. Monaco AP, Abbott WM, Othersen HB, Simmons RL, Wood ML, Flax MH, et al. Antiserum to lymphocytes: prolonged survival of canine renal allografts. *Science.* (1966) 153(3741):1264–7. doi: 10.1126/science.153.3741.1264

9. Monaco AP, Wood ML, Russell PS. Adult thymectomy: effect on recovery from immunologic depression in mice. *Science.* (1965) 149(3682):432–5. doi: 10.1126/science.149.3682.432

10. Russell PS. The weight-gain assay for runt disease in mice. *Ann N Y Acad Sci.* (1960) 87:445–51. doi: 10.1111/j.1749-6632.1960.tb23211.x

11. Russell PS, Chase CM, Colvin RB, Plate JM. Induced immune destruction of long-surviving, H-2 incompatible kidney transplants in mice. *J Exp Med.* (1978) 147(5):1469–86. doi: 10.1084/jem.147.5.1469

12. Russell PS, Chase CM, Colvin RB, Plate JM. Kidney transplants in mice. An analysis of the immune status of mice bearing long-term, H-2 incompatible transplants. *J Exp Med.* (1978) 147(5):1449–68. doi: 10.1084/jem.147.5.1449

13. Russell PS, Chase CM, Madsen JC, Hirohashi T, Cornell LD, Sproule TJ, et al. Coronary artery disease from isolated non-H2-determined incompatibilities in transplanted mouse hearts. *Transplantation.* (2011) 91(8):847–52. doi: 10.1097/TP.0b013e3182122f82

14. Russell PS, Chase CM, Sykes M, Ito H, Shaffer J, Colvin RB. Tolerance, mixed chimerism, and chronic transplant arteriopathy. *J Immunol.* (2001) 167(10):5731–40. doi: 10.4049/jimmunol.167.10.5731

15. Russell PS, Chase CM, Winn HJ, Colvin RB. Coronary atherosclerosis in transplanted mouse hearts. I. Time course and immunogenetic and immunopathological considerations. *Am J Pathol*. (1994) 144(2):260–74. PMID: 7906094; PMCID: PMC1887157

16. Russell PS, Monaco AP. The biology of tissue transplantation. *N Engl J Med*. (1964) 271:776–83. CONCL. doi: 10.1056/NEJM196410082711507

17. Sachs DH, Winn HJ, Russell PS. The immunologic response to xenografts. Recognition of mouse H-2 histocompatibility antigens by the rat. *J Immunol*. (1971) 107(2):481–92. doi: 10.4049/jimmunol.107.2.481

18. Shield CF, Cosimi AB, Tolkoff-Rubin N, Rubin RH, Herrin J, Russell PS. Use of antithymocyte globulin for reversal of acute allograft rejection. *Transplantation*. (1979) 28(6):461–4. doi: 10.1097/00007890-197912000-00005

19. Simmons RL, Russell PS. The immunologic problem of pregnancy. *Am J Obstet Gynecol*. (1963) 85:583–93. doi: 10.1016/0002-9378(63)90305-3

20. Skoskiewicz M, Chase C, Winn HJ, Russell PS. Kidney transplants between mice of graded immunogenetic diversity. *Transplant Proc*. (1973) 5(1):721–5. doi: 10.1084/jem.147.5.1449

21. Corry RJ, Winn HJ, Russell PS. Primarily vascularized allografts of hearts in mice. The role of H-2D, H-2 K, and non-H-2 antigens in rejection. *Transplantation*. (1973) 16 (4):343–50. doi: 10.1097/00007890-197310000-00010

22. Jain MK, Cheung VG, Utz PJ, Kobilka BK, Yamada T, Lefkowitz R. Saving the endangered physician-scientist - A plan for accelerating medical breakthroughs. *N Engl J Med*. (2019) 381(5):399–402. doi: 10.1056/NEJMp1904482

23. Milewicz DM, Lorenz RG, Dermody TS. National Association of MD-PhD Programs Executive Committee. Rescuing the physician-scientist workforce: the time for action is now. *J Clin Invest*. (2015) 125(10):3742–7. doi: 10.1172/JCI84170

24. Lawton JS. Commentary: Opposing forces will lead to surgeon scientist extinction. *J Thorac Cardiovasc Surg*. (2020) 159(5):1921–2

frontiers | Frontiers in Transplantation

TYPE Perspective
PUBLISHED 25 August 2023
DOI 10.3389/frtra.2023.1258950

OPEN ACCESS

EDITED BY
Stuart Knechtle,
Duke University, United States

REVIEWED BY
William Kitchens,
Emory University, United States

*CORRESPONDENCE
Xian C. Li
✉ xcli@houstonmethodist.org

RECEIVED 14 July 2023
ACCEPTED 16 August 2023
PUBLISHED 25 August 2023

CITATION
Li XC (2023) Robert S. Schwartz, MD, a transformative figure in immunosuppression that revolutionized transplantation.
Front. Transplant. 2:1258950.
doi: 10.3389/frtra.2023.1258950

Robert S. Schwartz, MD, a transformative figure in immunosuppression that revolutionized transplantation

Xian C. Li*

Immunobiology and Transplant Science Center and Department of Surgery, Houston Methodist Hospital, Houston, TX, United States

While the transplant community celebrated more than a million transplant patients in the United States, we are reminded that our journey to such a celebratory success is the results of remarkable breakthroughs and brilliant innovators. Among those, immunosuppression drugs are undoubtedly a cornerstone of transplant success, an area where Dr. Robert Schwartz is undeniably a transformative figure and a pioneer. His seminal studies on 6-mercaptopurine in 1959 gave birth to an entirely new specialty of immunosuppression that dramatically accelerated the advancement of clinical organ transplantation.

KEYWORDS
transplantation, immunosuppression, graft rejection, immune tolerance, graft survival

In 2022, the transplant community celebrated a milestone, i.e., over a million patients transplanted in the United States (1). In hindsight, our journey to such a celebratory success has been extraordinary, a journey that is marked with remarkable breakthroughs and brilliant innovators. Among those, immunosuppression drugs are undoubtedly a cornerstone of transplant success, an area where Dr. Schwartz is undeniably a transformative figure and a pioneer (**Figure 1**). His seminal studies on 6-mercaptopurine (an analogue of Azathioprine) in 1959 gave birth to an entirely new specialty of immunosuppression, and at a time when graft rejection was universal, his discoveries dramatically accelerated the advancement of clinical organ transplantation (2). As a physician-scientist, Dr. Schwartz had an amazing repertoire of accomplishments: a long-time professor of medicine at Tufts University, chief of hematology at Tufts for nearly 30 years, deputy editor of New England Journal of Medicine for 15 years, recipient of the Peter Medawar prize, Thomas Starzl award, and Stratton award, just to list a few.

My first encounter with Dr. Schwartz was, by all count, ordinary. In 2000, the international transplant congress (TTS2000) was held in Rome, Italy, where Dr. Schwartz was honored with the Peter Medawar prize, the highest award in the transplant community. I was a freshly minted assistant professor at Harvard with a strong interest in transplant tolerance (3), and like other junior members in the community, I descended to Rome with tremendous hope and excitements. I caught a glimpse of Dr. Schwartz during the award ceremony, but his name was simply ingrained in my mind because of immerse admiration. Interestingly, the opportunity that got me to know him personally was nothing short of extraordinary. In the summer of 2001, we sent our 7-year-old daughter Stephanie to a summer camp in Wellesley, Massachusetts, where she quickly befriended another camper, a lovely girl called Annie McDonald Schwartz. Annie was overjoyed and believed that Stephanie was also adopted from China (both were the only Asians in the camp). Annie demanded that her parents Adam and Michele meet us and arrange

FIGURE 1
Dr. Robert Schwartz (right), a renowned hematologist and an innovator in transplant immunosuppression. Pictured here with Dr. Stefan Tullius (left) in 2015. (with permission from Dr. Tullius at Brigham and Women's Hospital).

playdates, and because of that, both families also became close friends. We then commuted frequently between Newton (where we lived) and Wellesley (where they lived) visiting each other, and little did I know that Adam is the elder son of Dr. Schwartz. At that time, Adam taught creative writing class at Wellesley College and Michele was a professional photographer for the Boston Globe newspaper.

Adam introduced me to his father over a family party one Saturday afternoon in his house at Wellesley. Adam thoughtfully ordered thin crust pizza from Figs Beacon Hill, an upscale restaurant in Boston, saying that thin crust is his father's favorite. That was the occasion that we met and had our first conversion that felt nothing like thin crust. Similar to many conversations that followed, that first one still feels so fresh, enlightening, and profound. I acted like many other junior faculties, and when face to face with a giant in the field, my first goal was to extract as many insights as possible over how to establish a successful career and how to do impactful research. That was also the time that I got a closer peek at his unparalleled style and personality.

It was a pure joy to listen to Dr. Schwartz telling stories and explaining complex concepts in captivating words. When his wife Ruth (in a real estate business) asked why there are T cells and B cells, but no A cells, in immunology, he explained vividly the Thymus and Bursa of Fabricius in chicken, structures where those cells are derived, emphasizing that it took a brilliant English educator Ivan Roitt to coin the words T cells and B cells. I remember the moment that all kids stopped playing and joined the audience, and all cheered with blissful smiles. He had a unique way of commanding words, and his voice certainly had an attention-grabbing tune. I learned later that Dr. Schwartz was repeatedly recognized as the best in his teaching from medical students at Tufts University Medical School, winning 13 annual outstanding teaching awards. He served as deputy editor for the New England Journal of Medicine for almost 15 years, a leading medical journal in the world, attesting to his incredible knowledge and language skills. I read again and again his 1959 Nature paper describing how 6-mercaptopurine as an immunosuppressant that rendered the mature immune system unresponsive to protein antigens (4), the style, accuracy, and precision in the paper are truly exemplary even to this day.

Despite his stature, Dr. Schwartz was remarkably humble and approachable, a trait that is also possessed by many other trailblazers in the field. He often attributed his discovery as simply having been "lucky". He proclaimed that he is a hematologist, not a transplantor, and less concerned about organ rejection. He insisted that his recognition in the transplant world was just "something nice" to see. Based on his recollection (5), his chief, Dr. Dameshek, assigned him the task of finding new therapies other than total body irradiation to prevent bone marrow allograft rejection. He turned to chemicals known to have activities in lymphoblastic leukemia and wrote to multiple companies requesting materials for his experiments. It turned out that only one company replied and sent him a chemical compound called 6-mercaptopurine. He later learned that 6-mercaptopurine works the best in rabbits, an animal model that he used at that time for all his studies. That was perhaps the reason why he factored "luck" into his landmark findings. The truth of the matter is that all his studies are down to details, well designed, well thought of and accurately presented, leaving practically nothing to "alternative explanations". He initially found that 6-mercaptopurine rendered a mature immune system "tolerant" to protein antigens and also markedly extended skin graft survival in rabbits (4, 6). Those observations in fact set off an intense chain of reactions that eventually made chemical immunosuppression a clinical reality in relatively a short period of time. An analogue of 6-mercaptopurine Azathioprine was designed thereafter, tested in dogs by Sir Roy Calne and others, and quickly entered the clinic. Some kidney transplant patients, though a small percentage, survived for years when treated with Azathioprine, an outcome never seen before (Figure 2) (7). The enthusiasm generated led to the development of other more powerful immunosuppressive drugs in the 1970s and 1980s that clearly transformed clinical transplantation. The introduction of

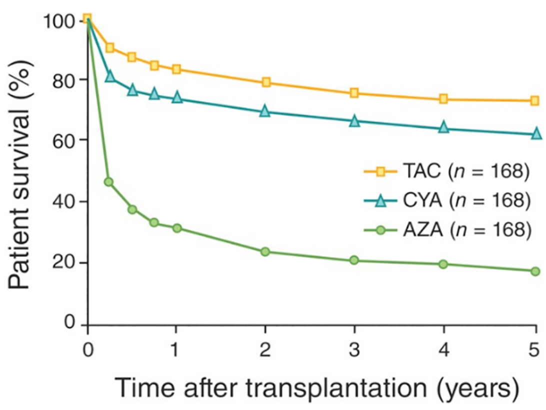


FIGURE 2
Kidney transplant survival in the clinic in the era of chemical immunosuppression. AZA, azathioprine; CYA, cyclosporine A; TAC, tacrolimus or FK506 (6).

cyclosporine A and later FK506 resulted in an explosion in the volume as well as the type of organs transplanted (8). Dr. Joseph Murray remarked in his 1990 Nobel laureate that "real breakthrough (in transplantation) came with the introduction of immunosuppression drugs by Schwartz and Dameshek in 1959".

Dr. Schwartz embodied an era in which the United States' biomedical enterprise produced brilliant physician-scientists, an era that we may not see again. When I asked for career advice in our first conversation, he unexpectedly encouraged me to seriously think about going back to the clinic, he correctly predicted the corporatization of medicine and the constrains of fundamental discovery research for future generations. Now more than 20 years later, I am still in awe of his insights. Indeed, we are facing mounting challenges now not only in discovery research, but also the dwindling pool of physician-scientists, who are often bogged down by limited resources, time, and bureaucratic burdens (9).

After his retirement, Dr. Schwartz enjoyed photography, a hobby that he developed from his profession as a hematologist. He often said that "pictures of blood as seeing through microscope are nothing short of astonishing, with different shapes, sizes, and colors". Thus, it's a natural transition for him in seeing beauty through the lens of a camera. His love of photography also became a shared family affair with his daughter in law Michele, who is a professional photographer. Dr. Schwartz joked that he first met Michele when she was assigned by the Boston Globe to photograph him in the editorial office of New England Journal of Medicine, which is located in the Countway library at Harvard Medical School. Michele also gracefully shared her expertise and equipment with me including high-end camera lenses, and some of them are still with me to this day.

Dr. Schwartz passed away in August 2017 at the age of 89, he will always be remembered as a transformative figure in immunosuppression, a cornerstone of transplant success that we all celebrate today (10).

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Author contributions

XL: Writing – original draft, Writing – review–&–editing.

Funding

The author declares that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

References

1. Pullen LC. A complex puzzle realized: US achieves one million organ transplant. *Am J Transplant*. (2023) 23:1–2. doi: 10.1016/j.ajt.2022.12.003

2. Starzl TE. History of clinical transplantation. *World J Surg*. (2000) 24:759–82. doi: 10.1007/s002680010124

3. Li XC, Wells AD, Strom TB, Turka LA. The role of T cell apoptosis in transplantation tolerance. *Curr Opin Immunol*. (2000) 12:522–7. doi: 10.1016/S0952-7915(00)00133-3

4. Schwartz R, Dameshek W. Drug-induced immunological tolerance. *Nature*. (1959) 183:1682–3. doi: 10.1038/1831682a0

5. Schwartz R. MD: the Dawn of immunosuppression. *Transplantation*. (2015) 99 (11):2239–40. doi: 10.1097/TP.0000000000000987

6. Schwartz R, Dameshek W, Donovan J. The effects of 6-mercaptopurine on homograft reactions. *J Clin Invest*. (1960) 39:952–8. doi: 10.1172/JCI104116

7. Starzl TE. The long reach of liver transplantation. *Nat Med*. (2012) 18:1489–92. doi: 10.1038/nm.2927

8. Halloran PF, Kreepala C, Eincke G, Loupy A, Sellares J. Chapter 10, therapeutic approaches to organ transplantation. In: Li XC, Jevnikar AM, editors. *Transpl. Immunol*. Hoboken, NJ: Wiley and Sons (2016). 184–216p.

9. Williams CS, Iness AN, Baron RM, Ajijola OA, Hu PJ, Vyas JM, et al. Training physician-scientists: view from program directors and aspiring young investigators. *JCI Insights*. (2018) 3(23):e125651. doi: 10.1172/jci.insight.125651

10. Starzl TE, Zinkernagel RM. Transplantation tolerance from a historical perspective. *Nat Rev Immunol*. (2001) 1(3):233–9. doi: 10.1038/35105088

frontiers | Frontiers in Transplantation

TYPE Perspective
PUBLISHED 21 November 2023
DOI 10.3389/frtra.2023.1315397

OPEN ACCESS

EDITED BY
Reza Abdi,
Harvard Medical School, United States

REVIEWED BY
Alfred Tector,
University of Miami, United States

*CORRESPONDENCE
Jay A. Fishman
fishman.jay@mgh.harvard.edu

RECEIVED 10 October 2023
ACCEPTED 02 November 2023
PUBLISHED 21 November 2023

CITATION
Fishman JA (2023) Robert H. Rubin and infectious disease in transplantation. Front. Transplant. 2:1315397. doi: 10.3389/frtra.2023.1315397

Robert H. Rubin and infectious disease in transplantation

Jay A. Fishman*

Transplant Infectious Disease and Compromised Host Program and Transplant Center, Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States

Robert H. Rubin, M.D. was among the first physician-scientists to focus attention on the infectious diseases associated with immune suppression. A superb bedside clinician and teacher, he developed many of the concepts central to the care and improved survival of organ transplant and stem cell transplant recipients. These concepts have provided the basis of clinical investigation and basic research for multiple generations of infectious disease specialists, immunologists, and transplant surgeons.

KEYWORDS
Robert Rubin, infectious diseases, transplantation, physician-scientist, immune suppression

No one who practices organ transplantation is untouched by the contributions of Robert H. Rubin as a visionary in the practice and teaching of science and medicine. Dr. Rubin was a graduate of Williams College and Harvard Medical School. After medical residency at the Peter Bent Brigham Hospital, he was a medical intelligence officer at the Center for Disease Control. He completed his infectious disease training at the Massachusetts General Hospital (MGH) and Tufts Medical Center. Dr. Rubin was Chief of Transplant Infectious Disease at the MGH for over twenty years before becoming Clinical Director of Infectious Disease at the Brigham and Women's Hospital (Figure 1). Early in his time at MGH, he co-directed the Medical Intensive Care Unit with his wife, Dr. Nina Tolkoff-Rubin (who he described as the "best doctor" he ever met). He also was among the first faculty in the joint Harvard Medical School (HMS)-Massachusetts Institute of Technology (MIT) Division of Health Sciences and Technology (HST) program, and he would ultimately become the Gordon and Marjorie Osborne Professor of Health Sciences and Technology in the Harvard-Massachusetts Institute of Technology Division of Health Sciences and Technology. In 1995 he was the first internist appointed as Microbiologist in the Department of Surgery at MGH in recognition of his role in the developing organ transplant program. He became a Professor of Medicine at Harvard Medical School in 1999.

Dr. Rubin's studies at the interface of technology, bedside clinical care and research drug development and business provided a platform for development of innovative and interdisciplinary programs in science and technology, in clinical investigation at Harvard and MIT, but also at the Sloan School of Business and at the Harvard School of Public Health. He developed (with Professor Christopher Walsh) an elective course in clinical pharmacology and therapeutics for which he received multiple teaching awards. The Clinical Investigator Training Program, with Dr. Alan Moses, was a program in clinical research which trained dozens of young physician-scientists and provided a Master of Medical Science degree in Clinical Investigation. The didactic materials for this program became the basis for training programs in clinical investigation in Israel and Latin America. In each venue, he developed a new group of young minds who could work across traditional boundaries—much as he did himself- and speed the advancement of medical knowledge to the bedside. His pioneering studies of radiological imaging of

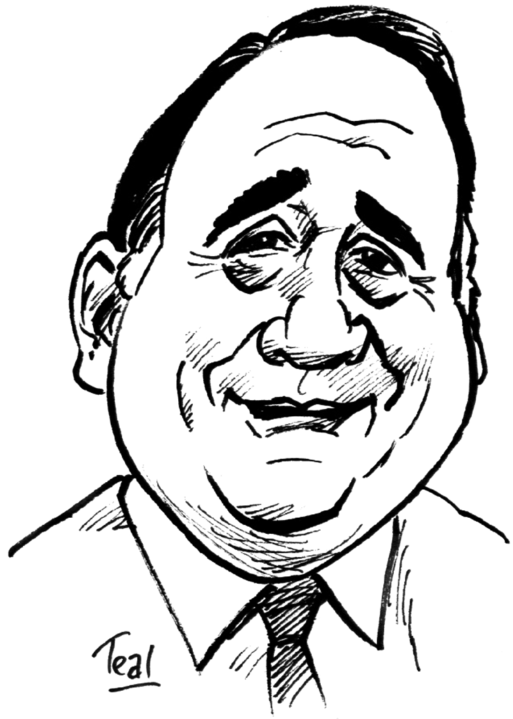


FIGURE 1
Robert H. Rubin as drawn for the President's Address, Jay A. Fishman, M.D., American Society of Transplantation, Seattle, WA, 2005.

infectious disease and inflammatory processes (the Rubin scans") quickly became part of clinical care. Bob wrote over 400 original reports, reviews, chapters, and textbooks. Some of his early papers are classics of diagnosis and new approaches to thinking about mechanisms of disease and therapy.

The skills and concepts developed at the bedside lead him to initiate and chair committees on Transplant Infectious Disease for the Transplantation Society, the Immunocompromised Host Society, the American Society of Transplant Physicians and in a series of International Conferences on Transplantation Infectious Disease. His approaches were captured in a book, co-edited with Dr. Lowell Young, Clinical Approach to Infection in the Compromised Host and as Editor-in-Chief of *Transplant Infectious Disease*, an official journal of the Transplantation Society.

Bob was best known for his skills as a teacher and clinician. Twice each day, Transplant Infectious Disease physicians would round with the abdominal transplant teams—adjusting immunosuppression, organizing diagnostic procedures, selecting antibiotics, and arguing about patient management with expert transplant surgeons, nephrologists, hepatologists as well as bench immunologists and pathologists. Discussions were often "intense". At the bedside, he was an instinctual clinician for the sickest and most complex patients. He focused attention on the "net state of immunodeficiency", a conceptual framework for all the host factors that contribute to infectious risk—as well as the epidemiological exposures that defined the specific organisms causing infection in each community—known as "the sentinel chicken" (as opposed to the canary of coal mines). His "equation" of the "semi-quantitative relationship" between immunosuppression and infectious exposures is taken as gospel—any intervention that reduces risk (vaccines, prophylaxis) allows greater degrees of immunosuppression and lowers the risk for graft rejection. Conversely, infection became a measure of the technical skill of the surgical team and the intensity of immunosuppression.

His rigor as a bedside clinician and teacher led to the development of most of the diagnostic paradigms for infection and the evolution of most current prophylactic and therapeutic regimens for infection in transplantation. Bob's creative juices were stimulated by unexplained fevers and syndromes in these immunosuppressed patients. At first, his contributions were diagnostic and epidemiologic—discovering outbreaks of Legionnaires disease and *Pseudomonas* transmitted by ventilation ducts wafting bacteria over transplant recipients. Then, he "discovered" cytomegalovirus—CMV—and began to characterize the syndrome that has tormented transplanters since the beginning of the field (1–4). His efforts led, in part, to the clinical development of fluconazole and ganciclovir. These observations resulted in his characterization of the "net state of immunodeficiency" and the "timeline of post-transplant infections" that have guided the development of prophylactic regimens (e.g., for urinary tract infection, Pneumocystis and CMV) and diagnosis (infections at the "wrong time" indicating unusual epidemiologic hazard or excessive immunosuppression) (5–8). These are now considered among the gospels of transplantation. He also used a broad understanding of science and medicine to make predictions about the mechanisms of multiple important clinical syndromes—CMV and other viral infections—and the modulation of immunosuppression as a part of the "therapeutic prescription" required for the successful eradication of infections in these susceptible hosts. His intuitive understanding of the multiple effects of viruses—opportunistic infections, graft rejection, malignancy—are only now being elucidated at the molecular level. His legacy is immense.

He was an amazing teacher to 1,000's of students. He was a sponge for new knowledge. He set impossibly high standards. All with the goal of training a generation of inquisitive clinician-scientists and accelerating the speed and relevance of the advancement of medical knowledge. He had the ability to synthesize and explain complex concepts. What did he teach? This was where some of Bob's unique skills emerged. Bob was never constrained by the usual intellectual barriers. He was never impressed by the memorization of lists of diseases and therapies. He always wanted to know how to do everything better—for family and friends and for our patients. Bob had a clear vision of the level of performance needed to optimize the clinical care of complex patients. We participated in some of the earliest organ transplants in HIV-infected individuals—in the pre-HARRT era—with predictably poor outcomes. He routinely supported talented female and minority trainees before this was even entertained elsewhere. We went to the OR to observe and ended up holding retractors and suction—at a time when transplant programs were understaffed. He obtained new antimicrobials for patients with viral and fungal infections—and developed regimens for prophylaxis and therapy that remain standards today. Bob was fond of quoting Dr. Louis Weinstein—one of his teachers—as saying "There are only three things we don't know about antimicrobial therapy: which drug to use, how much and for how long".

Bob began to pose questions based on his experience as a clinician and epidemiologist. How do we use organs from infected donors? Which other latent infections became activated in the transplant recipient? Why was graft and patient survival less good in patients infected with CMV ("indirect effects")? And what was the role of other viruses in transplant outcomes? The questions he posed have guided the evolution of research into host-pathogen relationships, clinical pharmacology, and host defense mechanisms. His teaching has, without question, saved many lives among our most susceptible patients. Robert Rubin cared deeply about several things—family and friends, his patients, and new ideas. His extraordinary efforts were among the first aimed at the advancement of the translational science and clinical knowledge within our field. We are all better for having experienced his passion and skill. By force of personality, Bob was destined to be a leader.

Perhaps a vignette captures some of the essence of Robert Rubin as a mentor.

It's Tuesday. Life seems under control as an ID Fellow. My beeper goes off. Bob is away. He calls from the plane: "You're covering. Everyone is fine. Oh, and I need you to give a talk for me". As in most clinical spheres, things didn't always go smoothly—but he defended my efforts strenuously. He left me a box of slides on his way out the door—in a few days, I am supposed to give a talk for Bob Rubin—on another continent. I'd been in this situation many times before. The talk was always on a topic on which Bob was a world's expert, and for which I would only generously be considered an amateur—to an audience which is expecting Bob. So, off I would go to great and far-away places like Venice, Rio, London, Sydney, Vancouver. There was no point of discussion. Bob deferred to no one except Nina and their daughter, Melissa. Once you joined the Rubin clan you were "all in". Thus, Bob (and Nina and Melissa) decided that my family (not me) needed a Golden retriever—I refused as I was "too busy"—so he bought us our first dog anyway—not for me, but for my family—as I "had no judgement worth noting in this area". As usual, he was right. Bob was always right.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Author contributions

JF: Writing – original draft.

Funding

The author declares that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The handling editor RA declared a shared parent affiliation with the author JF at the time of review.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Cheeseman SH, Stewart JA, Winkle S, Cosimi AB, Tolkoff-Rubin NE, Russell PS, et al. Cytomegalovirus excretion 2–14 years after renal transplantation. *Transplant Proc.* (1979) 11:71–4. PMID: 222020

2. Cheeseman SH, Rubin RH, Steward JA, Tolkoff-Rubin NE, Cosimi AB, Cantell K, et al. Controlled clinical trial of prophylactic human-leukocyte interferon in renal transplantation: effects on cytomegalovirus and herpes simplex virus infections. *N Engl J Med.* (1979) 300:1345–9. doi: 10.1056/NEJM197906143002401

3. Ramsey PG, Rubin RH, Tolkoff-Rubin NE, Cosimi AB, Russell PS, Greene R. The renal transplant patient with fever and pulmonary infiltrates: etiology, clinical manifestations, and management. *Medicine (Baltimore).* (1980) 59:206–22. doi: 10.1097/00005792-198005000-00003

4. Rubin RH, Cosimi AB, Hirsch MS, Herrin JT, Russell PS, Tolkoff-Rubin NE. Effects of antithymocyte globulin on cytomegalovirus infection in renal transplant recipients. *Transplantation.* (1981) 31:143–5. doi: 10.1097/00007890-198102000-00016

5. Rubin RH. The compromised host as sentinel chicken. *N Engl J Med.* (1987) 317:1151–3. doi: 10.1056/NEJM198710293171809

6. Schooley RT, Hirsch MS, Colvin RB, Cosimi AB, Tolkoff-Rubin NE, McCluskey RT, et al. Association of herpesvirus infections with T-lymphocyte subset alterations, glomerulopathy, and opportunistic infections following renal transplantation. *N Engl J Med.* (1983) 308:307–13. doi: 10.1056/NEJM198302103080603

7. Fishman JA, Rubin RH. Infection in the organ transplant patient. *N Engl J Med.* (1998) 338:1741–51. doi: 10.1056/NEJM199806113382407

8. Fishman JA. Infections in solid organ transplantation. *N Engl J Med.* (2007) 357:2601–14. doi: 10.1056/NEJMra064928

frontiers | Frontiers in Transplantation

TYPE Perspective
PUBLISHED 27 February 2024
DOI 10.3389/frtra.2024.1375316

Check for updates

OPEN ACCESS

EDITED BY
Stuart Knechtle,
Duke University, United States

REVIEWED BY
Paolo De Simone,
University of Pisa, Italy

*CORRESPONDENCE
Satish N. Nadig
✉ satish.nadig@nm.org

RECEIVED 23 January 2024
ACCEPTED 13 February 2024
PUBLISHED 27 February 2024

CITATION
Nadig SN (2024) A Mentee's perspective on Dr. Anthony Monaco: the quiet giant of transplantation.
Front. Transplant. 3:1375316.
doi: 10.3389/frtra.2024.1375316

A Mentee's perspective on Dr. Anthony Monaco: the quiet giant of transplantation

Satish N. Nadig[1,2,3]*

[1]Feinberg School of Medicine, Northwestern University, Chicago, IL, United States, [2]Department of Surgery, Northwestern Medicine, Chicago, IL, United States, [3]Comprehensive Transplant Center, Northwestern Memorial Hospital, Chicago, IL, United States

A mentee's perspective of an academic journey on a path paved by a pioneering transplant surgeon-scientist.

KEYWORDS
anti-thymocyte globulin, mentorship, leadership, transplant, immunology

On July 22, 2021, at 4:40 pm Eastern Standard Time, I received a touching and heartfelt email from Dr. Anthony Monaco. In this email, there was one line that epitomized his entire being.

> "I am sure that you know that the best gift and reward a teacher and mentor can receive is the distinction achieved by their students".

Anthony Monaco MD, FACS, was the founding director of the Harvard transplant service at Boston City Hospital that evolved into the Division of Transplant Surgery at Beth Israel Deaconess Medical Center, which bears his name today. Before this major feat, saw a man fiercely dedicated to his craft and the generally unaccepted idea of transferring tissues from one person to another. He and his contemporaries spent the greater part of the 1960s–2000s racing to find ways to evade the human immune system. Radical ideas of taking animal serum inoculated with that of humans and purifying the antibodies from this reaction to deplete effector T cells, set the foundation for the very immunosuppressant medications that we consider the "gold standard" today (1). His groundbreaking work started an entire field of medicine that, one could argue, is one of the most miraculous advancements in medicine of the last century. He rose the ranks to Division Chief and President of every important transplant society, including the American Society of Transplant Surgeons and The Transplantation Society. Yet, to me (and a score of others), these accomplishments are not what actually defines Tony. It is, in fact, the legions of mentees that he fostered along the way to make sure the field of Transplantation … his field, was kept in good stead and would progress beyond even his imagination. Although this tribute could delineate all of the tangible professional accomplishments that Tony achieved in his lifetime, of which there are many, I would rather take a moment and underscore the man and the mentor that Tony was.

It was the summer of 2003 and I had just matched to the Beth Israel Deaconess Medical Center as the first student from the Medical University of South Carolina to match in a surgical residency at a Harvard hospital. Insecurities abound. One of my very first rotations was on the very busy and demanding transplant service (a field I already knew I had an interest in.) It was during this first week that I met Dr. Monaco.

With an intimate esophageal phonated "hello", I realized that I was in the presence of greatness. He would round with only the junior most member of the team, which was thankfully me at that time, and on rounds, he would ask all about my life and interests. He learned early on of my passion for the basic sciences and that I had not completed a PhD in medical school that I had initially set out to do- a source of regret and a lost opportunity for me. He asked about my family, my hobbies, and my ambitions. In the words of Walt Whitman … he was "curious, not judgmental". My first case with him was a cervical lymph node excision for a patient with post-transplant lymphoproliferative disorder. He donned a patriotic U.S.A. surgical cap and had me do the subcuticular stitch after the excision. Classical music was in the background and I was in rhythm … until the last stitch which I promptly and accidentally cut through the knot and the wound unraveled. I was sure this would stain my future surgical career. He on the other hand, responded with the grace that I would later realize was his signature. He comforted me and said "it is not what happens to us it is how we respond … call for a new stitch and start over".

Over the course of my early days with Tony, he worked tirelessly to make sure I was set up for a future in the field. He reached out to Sir Peter Morris and Professor Kathryn Wood on my behalf to introduce the idea of pursuing a Doctor of Philosophy at Oxford University and sat with me for months editing, line by line, various grants so that I may secure funding for this opportunity. I would sit in his office as he would take calls from Drs. Joseph Murray and Thomas Starzl. He would finish his conversation, hang up the phone, and re-direct his undivided attention to an intern from Irmo, South Carolina interested in a career in transplantation. After 4 failed grant attempts, the 5th hit from the American Society of Transplantation and this transplant surgeon was born from the nurturing support of Dr. Anthony Monaco.

Yet, as I learned from so many since … my story was not unique. He seemed to be a mentor to so many and each received the same undivided attention. Leaders in the field including, but not limited to, Mark Hardy (his first fellow), A. Benedict Cosimi, Manikkam Suthanthiran, Martha Pavlakis, Douglas Hanto, Elizabeth Pomfret, James Pomposelli, and Xian Li were touched by Dr. Monaco. The loss of a larynx did not quiet his presence. His soft, gentle prodding and ability to make you believe you could be better than what you imagine was unparalleled. Yes, he reached the greatest heights in his career, but what's more is that he served as the platform from which a whole generation of leaders lifted off.

Sixteen years after I first met Tony, he remained present in my life as he did for the entirety of his mentee clan. Finally, it was *his* email that encouraged the leap in my own career to take on a programmatic leadership role. His salient and persuasive point hinged on the fact that it was our duty to try and reach as many people as possible for the betterment of *our* field.

Dr. Anthony Monaco will, no doubt, be remembered for his work on anti-lymphocyte globulin and the development of many transplant programs along with the litany of discoveries and breakthroughs which we enjoy as mainstream today. Yet his legacy will carry on for one reason alone … the score of people that he inspired to go on and serve as role models for future generations.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Author contributions

SN: Writing – original draft, Writing – review & editing.

Funding

The author declares that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Reference

1. Monaco AP, Campion JP, Kapnick SJ. Antilymphocyte globulins. Clinical use of antilymphocyte globulin. *Transplant Proc.* (1977) 9(1):1007–18. PMID: 325727

frontiers | Frontiers in Transplantation

TYPE Opinion
PUBLISHED 27 August 2024
DOI 10.3389/frtra.2024.1469916

OPEN ACCESS

EDITED BY
Matthew Cooper,
Medical College of Wisconsin, United States

REVIEWED BY
Alfred Tector,
University of Miami, United States

*CORRESPONDENCE
Stuart J. Knechtle
✉ stuart.knechtle@duke.edu

RECEIVED 24 July 2024
ACCEPTED 06 August 2024
PUBLISHED 27 August 2024

CITATION
Knechtle SJ and Kirk AD (2024) R. Randal Bollinger, M.D., Ph.D., Master Surgeon.
Front. Transplant. 3:1469916.
doi: 10.3389/frtra.2024.1469916

R. Randal Bollinger, M.D., Ph.D., Master Surgeon

Stuart J. Knechtle* and Allan D. Kirk

School of Medicine, Duke University, Durham, United States

KEYWORDS

transplant, surgeon, research, teacher, mentor, immunology

Introduction

R. Randal Bollinger began life in Dearborn, Michigan, on 3 October 1944. He graduated in 1966 cum laude from Tulane University, New Orleans, where he majored in biology. During college, he studied biology for a year with Professor Karl Grell in Tubingen, Baden-Württemburg, Germany. He also immersed himself in New Orleans culture, participating as a tuba player in Mardi Gras parades. His affinity for New Orleans and for biological sciences led him to enroll at Tulane University School of Medicine, where he came under the influence of Dr. John MacDonald, a pioneer in kidney transplant surgery. MacDonald and Bollinger published several papers together on the relationship between gut bacterial flora and immune responses in transplantation models (1). At Tulane, Bollinger was elected to the Alpha Omega Alpha honor society and earned a Master of Science in biochemistry. Dr. MacDonald encouraged Bollinger to pursue further scientific training, and Bollinger sought to come to Duke to study immunology with Dr. D. Bernard Amos.

Bernard Amos had been recruited to Duke by the medical school dean Barnes Woodall and surgery department chairman Clarence Gardner because of Amos's immunogenetics background. He had been asked to develop an organ transplant program scientifically based on the then burgeoning immunogenetic principles of histocompatibility, to guide donor–recipient selection. At Duke, Bollinger pursued a Ph.D. in immunology with Amos and Dr. David Scott on the tolerogenic benefits of donor antigens conjugated to recipient spleen cells (2, 3). In addition to his doctoral work at Duke, he was accepted in 1970 into the general surgical residency program of Dr. David C. Sabiston, Jr., in which Bollinger continued to excel. His surgical residency was interrupted by 2 years of service with the United States Airforce. In 1980, Dr. Sabiston asked him to join the Duke surgery faculty, and he was appointed chief of transplantation in 1983.

As chief of transplantation at Duke, Dr. Bollinger grew the deceased donor kidney transplant program, as the early years of the program under Drs. Stickel and Seigler had focused on living donor transplants. He also adopted new immunosuppressive agents as they became available in the 1980s, including participating in the clinical trial of OKT3 (anti-CD3T cell-directed monoclonal antibody) and early use of cyclosporine, the first clinically available calcineurin inhibitor. He directed the programmatic development that led to the first liver transplant in North Carolina in 1986, which he personally performed (both the donor and recipient procedures) with the assistance of his colleagues William Meyers and Richard McCann. See Figure 1: Drs. Bollinger and McCann performing experimental liver transplantation. He supported the development of pancreas transplantation by training Dr. Ben Vernon in his lab and recruiting him to the faculty after his fellowship at the University of Wisconsin. Vernon performed the first pancreas transplant at Duke in 1989. In addition to routinely performing

FIGURE 1
Dr. Randy Bollinger and Dr. Richard McCann performing an experimental liver transplant.

demanding organ transplants, Bollinger developed an interest in surgery for inflammatory bowel disease, performing continent ileostomies, or Koch pouches, in combination with total colectomy. He was rapidly promoted to professor of surgery and immunology.

As an administrative leader, in addition to serving as chief of transplantation, Dr. Bollinger served as general surgery division chief, opened a multidisciplinary transplant clinic, and established a Transplant Clinical Business Unit. In 1997, he obtained his MBA from the Fuqua School of Business. His impact was felt in the southeast region as a leader among the North Carolina organ procurement organizations and nationally as a councilor of the American Society of Transplant Surgeons, president of the South-Eastern Organ Procurement Foundation (SEOPF, the nation's first organ procurement body), and president of the United Network of Organ Sharing (UNOS), which evolved from the SEOPF.

His research interests focused on transplant immunology, including immune tolerance, transplantation in sensitized recipients, and xenotransplantation. He received continuous National Institutes of Health funding for over two decades, including a program project in xenotransplantation, and contributed 131 manuscripts to the scientific literature. Major accomplishments included extending pig-to-baboon cardiac xenograft survival using soluble complement factor infusion, transgenic pig hearts expressing human CD59 and decay accelerating factor (DAF) or membrane cofactor protein (MCP) complement regulatory proteins, and the use of *ex vivo* perfusion of porcine livers as a bridge to liver transplantation. He also conducted seminal studies with Stuart Knechtle and Ed Halperin in the use of total lymphoid irradiation as a means of inducing graft acceptance (4).

"Randy," as he insisted on being called even by his residents, became a beloved mentor, renowned for his patience and good humor in the operating room. His integrity and character were as much revered as his surgical and scientific abilities. His sense of humor was not far beneath his surface, exemplified by his performing a "rain dance" around the operating room table following reperfusion of a transplanted kidney. His dance included musical incantations for rain (urine production) to the percussion accompaniment of a Richardson retractor banging on a sterile stainless-steel bowl. Even if this act failed to elicit urine, it was guaranteed to produce laughter among the operating room team.

Randy won virtually every teaching award offered at Duke, including the David C. Sabiston, Jr. Teaching Award (1987), given to the top teacher in the department of surgery, the Golden Apple Award (1984 and 1989), given to the top teacher of medical students in any department, and the Distinguished Teacher Award (1989), given to the top teacher in the institution. If the impact of surgical educators is best measured by their trainees, then Randy Bollinger had a profound impact on the field of transplantation. His mentees that went on to careers in transplant surgery include Richard McCann, Ben Vernon, Stuart Knechtle, Allan Kirk, Bradley Collins, John Magee, Doug Farmer, Robert Harland, Rolf Barth, and Shu Lin. These were attracted to the field of transplantation by Randy's infectious enthusiasm, teaching skills, dedication to his patients,

FIGURE 2
Randy Bollinger and Duke Surgery Department Chair Allan Kirk at the dedication of the Duke Organ Transplantation ward.

and consistent example of excellence. His lab jump-started the academic careers of many of these, including our own (4, 5), by creating an environment of inquiry, experimentation, opportunity, and collaboration. Randy was known to carry a small camera in his pocket, to use it frequently—long before the convenience of smart phones—and to document high points for his trainees or patients. Figure 2: Dr. Randy Bollinger (center) with Dr. Stuart Knechtle (left) and Dr. Allan Kirk (Surgery Department Chair, right) at dedication of the new Abdominal Transplant Unit, Duke Hospital). For his many contributions to his surgery department, he was recognized as a master surgeon, honored for embodying the ideals of an academic surgeon-clinician, teacher, and scientist. Forever dedicated to education, on his retirement from practice, he endowed a scholarship to support medical students interested in surgical research. The Bollinger Award has sponsored tuition for over 20 medical students, many of whom have gone on to pursue academic surgical practice.

An example of Dr. Bollinger's commitment to patient care was shown on the occasion of his 25th wedding anniversary. Although he had driven to a resort in Asheville, North Carolina, with his wife Monica to celebrate, there was a liver donor available that night, out of state. The Learjet that left Raleigh-Durham airport with a small team stopped in Asheville to pick up Randy who had driven to the airport with Monica who kissed him goodbye (with tears of love and regret). Not until years later did they find time to return to the same resort to actually celebrate. Monica was surely as flexible, patient, and forgiving as Randy was to his residents and students.

Author contributions

SK: Writing – original draft, Writing – review & editing. AK: Writing – review & editing.

Funding

The authors declare no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The authors declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

References

1. Mc Donald JC, Zimmerman G, Bollinger RR, Pierce WA. Immune competence of germ-free rats. I. Increased responsiveness to transplantation and other antigens. *Proc Soc Exp Biol Med*. (1971) 136(3):987–93. doi: 10.3181/00379727-136-35412

2. Bollinger RR, Scott DW. Creation and properties of histocompatibility antigen-cell conjugates. I. Preparation and immunological properties of rat histocompatibility antigens. *Transplantation*. (1980) 29(6):444–8. doi: 10.1097/00007890-198006000-00003

3. Bollinger RR, Scott DW. Creation and properties of histocompatibility antigen-cell conjugates. II. Antibody tolerance after treatment with donor histocompatibility antigen chemically coupled to recipient spleen cells. *Transplantation*. (1980) 29(6):449–53. doi: 10.1097/00007890-198006000-00004

4. Knechtle SJ, Halperin EC, Saad T, Bollinger RR. Prolonged heart xenograft survival using combined total lymphoid irradiation and cyclosporine. *J Heart Transplant*. (1986) 5(3):254–61.

5. Kirk AD, Bollinger RR, Finn OJ. Rapid, comprehensive analysis of human cytokine mRNA and its application to the study of acute renal allograft rejection. *Hum Immunol*. (1995) 43(2):113–28. doi: 10.1016/0198-8859(94)00158-m

frontiers | Frontiers in Transplantation

TYPE Perspective
PUBLISHED 17 September 2024
DOI 10.3389/frtra.2024.1461399

OPEN ACCESS

EDITED BY
Stuart Knechtle,
Duke University, United States

REVIEWED BY
Carlos Marroquin,
University of Vermont, United States

*CORRESPONDENCE
Walter G. Land
land.w.damps@gmail.com

RECEIVED 08 July 2024
ACCEPTED 30 August 2024
PUBLISHED 17 September 2024

CITATION
Land WG (2024) Walter Brendel and the dawn of transplantation research in Germany.
Front. Transplant. 3:1461399.
doi: 10.3389/frtra.2024.1461399

Walter Brendel and the dawn of transplantation research in Germany

Walter G. Land[1,2]*

[1]German Academy for Transplantation Medicine, Munich, Germany, [2]Laboratoire d'excellence (LabEx) TRANSPLANTEX, Faculté de Médecine, Université de Strasbourg, Strasbourg, France

Walter Brendel was a physiologist who headed the Institut of Experimental Surgery at the University of Munich (LMU) from 1961 until 1989. His legendary career began with the development of an anti-human lymphocyte globulin (ALG) at his Institute during the late 1960s. The initial successful treatment of a small number of patients culminated in the co-treatment of the first successfully heart-transplanted patient in Capetown, South Africa (successful reversal with ALG of an acute allograft rejection). Walter Brendel was a pioneering personality whose work has laid a wide platform for the promotion of interdisciplinarily conducted innovative research programs in various domains of translational science and medicine. Among the many innovative achievements, the most notable are: discovery of involvement of the alternative pathway of complement activation in hyperacute xenograft rejection; induction of immunological tolerance to horse IgG as a means to prevent anaphylactic reactions during ALG therapy; development and clinical implementation of the extracorporeal shock wave lithotripsy for extracorporeal destruction of renal and ureteral calculi. The legacy of Brendel continues with the foundation of the *Walter-Brendel Kolleg für Transplantationsmedizin* (i.e., the German Transplant School for Transplantation Medicine), which has been held annually since 1994.

KEYWORDS

antilymphoyte globulin, heart transplantation, xenograft rejection, extracorporeal shock wave lithotripsy, injury hypothesis, immunological tolerance to horse gammaglobulin

Walter Brendel (*6 November 1922 in Karlsruhe; †29 August 1989 in Munich) was the son of Elisabeth Brendel, born Sigwart, and Wilhelm Brendel, the director of a trading company. He studied medicine in Heidelberg, where he gained his doctorate in 1948. He then worked from 1950 as a resident and later as a senior resident in Physiology at the W.-G. Kerckhoff Institute of the Max Planck Society in Bad Nauheim, Germany. There he researched the circulation and regulation of body temperature until 1961. In 1959 he habilitated (to a "Privatdozent") at the University in Giessen and began teaching there. From 1961, he headed the Institute of Experimental Surgery at the Surgical Clinic of the Ludwig-Maximilians-Universität (LMU) in Munich, the foundation of which had been initiated by Rudolf Zenker. In 1965 he became an associate professor and in 1969 a full professor of experimental surgery—the first such chair in Germany. From 1969, he headed his Institute for Surgical Research, which had its own building in the Munich University Clinic ("Klinikum Großhadern") from 1979. Brendel headed the Institute until the beginning of 1989.

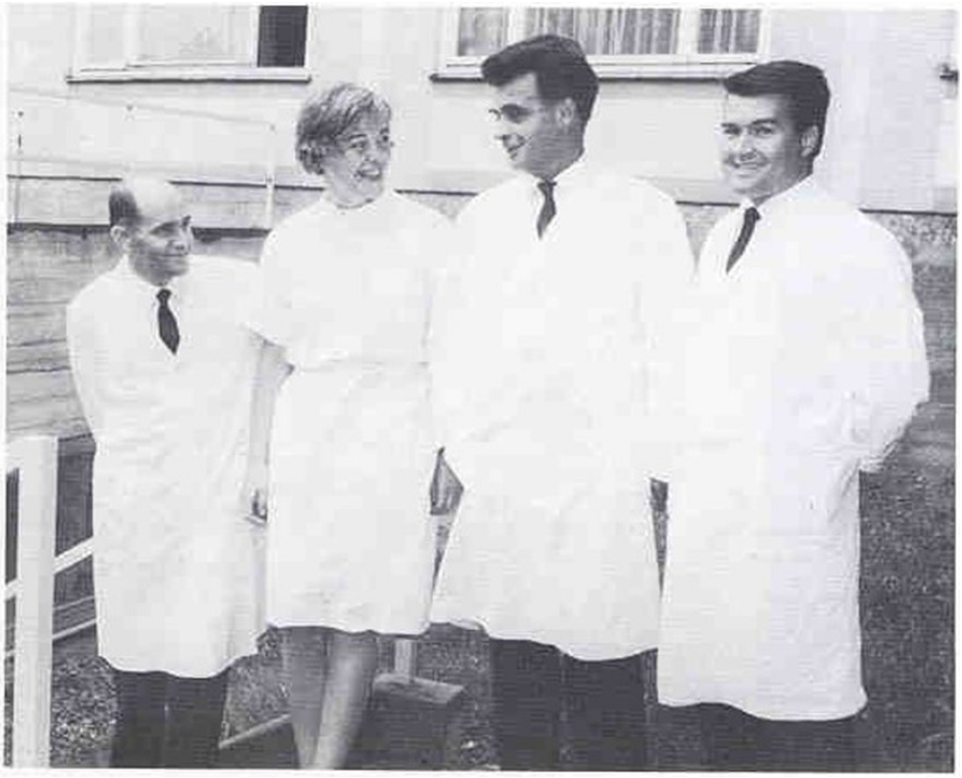


FIGURE 1
The Munich "ALG-Team" of the Institute of Experimental Surgery at the University in Munich (LMU), in 1967 (from left to right): Dr. Rudolf Pichlmayr, MTA Christa Schülgen, Prof. Walter Brendel, Dr. Walter Land.

Brendel's legendary career began at the Institute for Experimental Surgery with his decision to develop a horse (initially) anti-dog lymphocyte serum/(subsequently) anti-human lymphocyte globulin, a research program that was conducted by a group led by Rudolf Pichlmayr (1). In 1967, after Pichlmayr moved to the Hannover Medical School in Germany, I joined the group to continue the research program on this promising new immunosuppressant (2). (In fact, I was lucky enough to get a position as a research assistant at Brendel's institute, which wasn't that easy: In addition to the usual documents, Brendel—as was typical for him—asked for two requirements: playing an instrument and practizing sport,—I made it with guitar, soccer, and skiing).

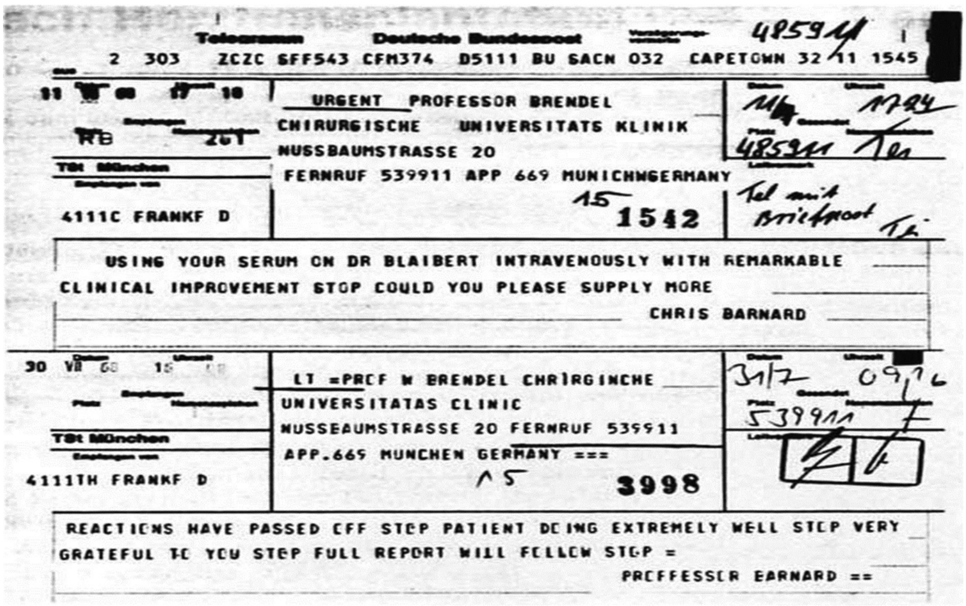
The story of the anti-human lymphocyte globulin production then proceeded rapidly: Drawing on extensive experimental studies on a horse anti-dog lymphocye serum administered to kidney transplanted dogs (3) and in close cooperation between the Brendel Institute and the Behringwerke, Marburg, Germany, a horse anti-human lymphocyte globulin (ALG) was produced for clinical use (Figure 1).

In initial therapy trials on a small series of patients with various autoimmune diseases, ALG was administered intravenously in doses between 1,5 ml and 3, 5 ml daily and found to be effective and safe, notably without causing any anaphylactic adverse effects (4). However, the first transplant patient to receive the Munich ALG was Philip Blaiberg, the first successful heart transplant recipient, operated upon by Christiaan Barnard and his team in Cape Town, South Africa (Figure 2). In June 1968, 6 months post-transplant, the patient experienced a life-threatening acute steroid-resistant rejection episode. Facing the imminent death of his patient, Barnard—recalling Brendel's visit to Capetown in December 1967 at the occasion of the first heart transplant when he told him about the first series of ALG-treated patients with autoimmune disease—decided to administer the Munich ALG as a last resort. Barnard's request for support was swiftly addressed: we promptly dispatched several ampoules of ALG as a "life-and-death shipment" via airmail.

Treatment of the patient was initiated immediately, with our guidance provided through daily phone calls. Under daily intravenous administration of 5 ml ALG (plus 2.5 ml twice a week), the acute rejection episode could be completely reversed within three weeks (Figure 3) (5, 6). On Brendel's advice [intuitively estimated, not based on hard experimental nor solid clinical data (!)], ALG was applied intravenously in high doses (7). Undoubtedly, with the successful treatment of an acute cardiac allograft rejection episode in 1968, Brendel and his Institute entered the international stage of experimental and clinical organ transplantation. Later on, the "Munich ALG" was also applied to the first successfully heart-transplanted patient in Germany (8)—this time in the form of an immunosuppressive induction therapy.

Walter Brendel was a pioneering personality whose work at the interface of technology, physiology, and immunology extended far

FIGURE 2
Walter Brendel (right) and Christiaan Barnard on the occasion of the award ceremony for "Jugend forscht", Frankfurt, Germany, 1969.



Telegramm Deutsche Bundespost
2 303 ZCZC SFF543 CFM374 D5111 BU SACN 032 CAPETOWN 32 11 1545

URGENT PROFESSOR BRENDEL
CHIRURGISCHE UNIVERSITATS KLINIK
NUSSBAUMSTRASSE 20
FERNRUF 539911 APP 669 MUNICHWGERMANY
1542
4111C FRANKF D

USING YOUR SERUM ON DR BLAIBERT INTRAVENOUSLY WITH REMARKABLE
CLINICAL IMPROVEMENT STOP COULD YOU PLEASE SUPPLY MORE
CHRIS BARNARD

LT =PRCF W BRENDEL CHRIRGINCHE
UNIVERSITATAS CLINIC
NUSSBAUMSTRASSE 20 FERNRUF 539911
APP.665 MUNCHEN GERMANY ===
3998
4111TH FRANKF D

REACTICNS HAVE PASSED CFF STCP PATIENT DCING EXTREMELY WELL STCP VERY
GRATEFUL TC YCU STCP FULL REPORT WILL FCLLCW STCP =
PRCFFESSCR BARNARD ==

FIGURE 3
Two telegrams from Barnard to Brendel after the successful treatment of the patient Blaiberg with the "Munich ALG": partial text: … "using your serum on Dr. Blaiberg intravenously with remarkable clinical improvement—could you please supply more" … "reactions have passed off—patient doing extremely well—very grateful to you—report will follow" ….

beyond the production of ALG. Freely referencing Alexander von Humboldt, his motto was: "Everything in biology is interconnected". Accordingly, his work has laid a wide platform for the promotion of interdisciplinarily conducted innovative research programs in various domains of translational science and medicine. His credo was to push boundaries always in search of new horizons, combined with a certain "experimental courage" in the entire field of experimental medicine!

Accordingly, Brendel's ingenuity did not necessarily consist of designing and carrying out elegant experiments, but rather in his ability to spark the creativity of his colleagues to think outside the box and to conceptualize, invent, and devise unusual approaches to tackle a particular scientific challenge. For example, he didn't want an experiment to be carried out that had already been tackled in a similar form elsewhere: His motto was: Innovation first!

To achieve this goal, Brendel sometimes applied unconventional "tactics". For example, in 1968 at the Second Congress of The Transplantation Society (TTS) in New York, xenotransplantation moved to center stage. Brendel asked me to look for a model experimental set-up that would elucidate the mechanism of hyperacute xenograft rejection. When he realized that I wasn't making any progress, he ordered me to go for a 3-day walk in the forest! After three days, I gained his approval with the idea of setting up an isolated *in vitro* xenohemoperfusion system in which rat kidneys are perfused with dog blood components with constant pressure (9, 10). In these studies, besides others, we were able to show for the first time that the alternative pathway of complement activation plays a dominant role in hyperacute xenograft rejection in widely divergent species combinations. In more detail: In this system, rejection criterion was defined as cessation of xenograft perfusion flow rate with constant perfusion pressure and histologic findings of aggregation of thrombocytes and endothelial lesions. Notably, this *in vitro* experimental set-up allowed for the perfusion of rat kidneys with variously modified dog blood. Evidence for an alternative pathway of complement activation was provided by a series of perfusion experiments using this modification set-up: These experiments showed, among other findings, that hyperacute xenograft rejection did occur when rat kidneys were perfused with complement-containing dog blood that had been depleted of both preformed xenohemoagglutinating antibodies and preformed xenocomplement-fixing antibodies through adsorption (10).

A similar scenario led to the successful induction of immunological tolerance to horse gammaglobulin. Brendel's daily insistence on finding ways to reduce the anaphylactic side effects in ALG-treated patients to horse globulin led to successful attempts to induce immunological tolerance to this xenogenic protein fraction in dogs and humans. By applying Dresser's principle (11), we were able to induce a state of immunological tolerance (as documented by the antigen elimination assay) via intravenous injection of small amounts of highly purified (ultracentrifuged) horse IgG (12, 13).

One of Brendel's main concerns has always been to achieve and maintain a high scientific standard in the research activities tackled at his institute. To this end, he launched two remarkable scenarios, one in the Austrian Alps, the other within the Institute.

1. External event: Since the late 1960s, he organized annual workshops in the winter mountains (which became known as the famous "ski-immunology" Meetings), where he brought his staff together with invited prominent heroes from the fields of immunology, tissue typing, and organ transplantation, who gave "State-of-the-Art" lectures on their recent work. (Notable and renowned attendees of these meetings included prominent leaders, amongst them Sir Peter Medawar, Leslie Brent, Ian Mitchison, Jon van Rood, Ruggero Ceppellini, Roy Calne, Peter Morris, Georges Mathé, Nick Tilney, Tony Monaco, Fritz Bach, David Sachs, and Kathryn Wood). The meetings were characterized by lively discussions, which usually continued into the evening over food and wine, often ending only at midnight.
2. Inside the institute, he encouraged the staff members working on different topics to share their knowledge, experience, concepts, and experimental designs. In fact, Brendel's Institute was known for an outstanding interdisciplinary team spirit that prevailed at this Institute during this time. In order to promote and maintain this interdisciplinary teamwork, Brendel organized social events in which every member of the Institute had to participate, including:

   - the obligate daily coffee break after lunch in a small coffee room where all colleagues sat closely together to discuss the political and academic issues of the day. (Participation in these coffee breaks was a "must" for everybody);
   - an annual dinner in a fish restaurant on the day after carnival (Bavarian "Fasching");
   - an annual skiing day in the Alps near Munich in winter (Brendel mastered all the slopes with ease, those who didn't dare to tackle a more difficult piste were looked at somewhat "wryly" and with pityingly).

An example of excellent interdisciplinary teamwork involved colleagues working in the field of Hemorrhagic Shock and Resuscitation Regimens, who shared their ideas, knowledge, study designs, and experiments with their colleagues from the field of Transplant Immunology—and vice versa!

The result of this tight-knit interdisciplinary discussion paid off 20 years later when the leader of the shock and resuscitation team, Konrad Messmer, now Director of the Division of Experimental Surgery at the University in Heidelberg asked me—now Head of the Division of Transplant Surgery at the LMU in Munich, Klinikum Grosshadern—to conduct a clinical trial in kidney transplant recipients using the oxygen free radical scavenger superoxide-dismutase ("SOD") to reduce postischemic allograft reperfusion injury) (14). The clinical trial was successfully implemented and the results obtained (reduced postischemic reperfusion injury → reduction of rejection episodes) formed the basis for the development of the *Injury Hypothesis* (15), which, together with Polly Matzinger's *danger hypothesis* (16), is now regarded as a paradigmatic part of modern immunology.

Of note, the research topics in Brendel's Institute of Experimental Surgery were not restricted to fields of organ transplantation but also included other disciplines such as research on the above-mentioned shock/microcirculation (17) and pathophysiology of traumatic brain edema (headed by Alexander Baethmann) (18).

Amongst these envisaged topics, another highlight of innovative research at Brendel's Institute is the experimental and clinical implementation of the extracorporeal shock wave lithotripsy [ESWL]), a device for extracorporeal destruction of renal and ureteral calculi using shock waves, which was developed in collaboration with Dornier GMBH (19, 20). Originally developed in Munich, this treatment method subsequently spread worldwide and served as a successful conservative therapy for kidney stone disease.

Many of the young researchers at Brendel's Institute went on to have later on stellar careers and leading positions in their disciplines; in the field of organ transplantation in particular Rudolf Pichlmayr and Ulrich Hopt in Germany and Hans-Werner Sollinger in Madison, WI, USA. Additionally, many of today's activities in Germany in the field of experimental/translational medicine, particularly in the area of organ transplantation, can be traced back to the work of Walter Brendel, one of which is based on the aforementioned outstanding interdisciplinary team spirit that prevailed at Brendel's institute.

Indeed, it is this original idea of organ transplantation as a multi-/interdisciplinary speciality that paved the way for the founding of the *Walter-Brendel Kolleg für Transplantationsmedizin* (i.e., the German Transplant School for Transplantation Medicine), which has been held annually since 1994 (21). Accordingly, inspired by Brendel, the idea of unifying the various areas of organ transplantation in a future common new discipline called "*Transplantation Medicine*" was already put forward in the 1980s in an article in which I discussed a subspecialization of colleagues in life (leading) positions who provide special transplantation-related care of the patient (22).

In Germany,—fostered by the continuous activities of the German Academy for Transplantation Medicine over the years (23)—the early visionary proposal culminated recently in its realization in 2023 with the enactment of *The German Transplant Certification* (24). Certified educational programs are offered by the German Transplantation Academy in the form of a 5-day course within the *Walter-Brendel Kolleg für Transplantationsmedizin*, the so-called "*Walter-Brendel Curriculum*" (21), in collaboration with the German Transplantation Society: The legacy of Walter Brendel continues!

Author contributions

WL: Writing – original draft, Writing – review & editing.

Acknowledgment

I am grateful to Prof. Dr. Alexander Baethmann for providing original material on Walter Brendel.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Pichlmayr R, Brendel W, Beck G, Schmittdiel E, Pichlmayr I, Thierfelder S, et al. Gewinnung von heterologen immunseren gegen menschliche lymphocyten. *Klin Wochenschr*. (1968) 46(5):249–58. doi: 10.1007/BF01770881

2. Land W, Brendel W, Pichlmayr R, Wagner E, Beck G, Schmittdiel E, et al. Gewinnung eines antihumanlymphocytenserums durch immunisierung eines pferdes mit leukämischen lymphocyten unter gleichzeitiger verabreichung eines antihumanerythrocytenserums vom pferd. *Klin Wochenschr*. (1970) 48(12):757–9. doi: 10.1007/BF01497135

3. Pichlmayr R, Brendel W, Zenker R. Production and effect of heterologous anti-canine lymphocyte serum. *Transplantation*. (1968) 6(1):144. doi: 10.1097/00007890-196801000-00032

4. Trepel F, Pichlmayr R, Kimura J, Brendel W, Begemann H. Therapieversuche mit antilymphocytenserum bei autoaggressionskrankheiten des menschen. *Klin Wochenschr*. (1968) 46(16):856–64. doi: 10.1007/BF01746244

5. Brendel W, Land W. Surprising results of intravenous therapy using antilymphocyte serum in organ transplantations. *Dtsch Med Wochenschr*. (1968) 93 (48):2309–13. doi: 10.1055/s-0028-1110931

6. Land WG. 50 Years ago: first successful treatment of acute allograft rejection after a human heart transplantation. *Dtsch Med Wochenschr*. (2018) 143(25):1864–5. doi: 10.1055/a-0573-5623

7. Brendel W. Intravenous use of high dosage of ALG. *Laval Med*. (1970) 41 (2):255–9. Available online at: https://pubmed.ncbi.nlm.nih.gov/4929502/

8. Sebening F, Klinner W, Meisner H, Schmidt-Habelmann P, Struck E, Spelsberg F, et al. Bericht über die transplantation eines menschlichen herzens. *DMW – Dtsch Med Wochenschr*. (1969) 94(17):883–9. doi: 10.1055/s-0028-1111134

9. Land W, Brendel WSchilling A, Aldenhoff J, Lamerz R, Pielsticker K, Mendler N BW. *In vitro* studies on the mechanism of hyperacute xenograft rejection. *Transplant Proc*. (1971) 3:888–90. Available online at: https://pubmed.ncbi.nlm.nih.gov/4937986/

10. Schilling A, Land W, Pratschke E, Pielsticker K, Brendel W. Dominant role of complement in the hyperacute xenograft rejection reaction. *Surg Gynecol Obstet*. (1976) 142(1):29–32. Available online at: https://pubmed.ncbi.nlm.nih.gov/1105839/

11. Dresser DW. Specific inhibition of antibody production. II. Paralysis induced in adult mice by small quantities of protein antigen. *Immunology*. (1962) 5:378–88. Available online at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1424098/

12. Land W, Seifert J, Fateh-Moghadam A, Hopf U, Brendel W. Immunological tolerance induced in adult dogs by small amounts of horse IgG. *Transplantation*. (1969) 8(5):748–50. doi: 10.1097/00007890-196911000-00037

13. Brendel W, Land W, Hopf U, Seifert J. Induction of tolerance in man to horse-IgG. *Lancet*. (1969) 294(7630):1141–2. doi: 10.1016/S0140-6736(69)90744-2

14. Land W, Schneeberger H, Schleibner S, Illner WD, Abendroth D, Rutili G, et al. The beneficial effect of human recombinant superoxide dismutase on acute and chronic rejection events in recipients of cadaveric renal transplants. *Transplantation*. (1994) 57(2):211–7. doi: 10.1097/00007890-199401001-00010

15. Land WG, Messmer K. The danger theory in view of the injury hypothesis: 20 years later. *Front Immunol*. (2012) 3:349. Available online at: http://journal.frontiersin.org/article/10.3389/fimmu.2012.00349/abstract

16. Matzinger P. The evolution of the danger theory. *Expert Rev Clin Immunol*. (2012) 8(4):311–7. doi: 10.1586/eci.12.21

17. Messmer K, Brendel W. [Pathophysiologic aspects of the hypovolemic, cardiogenic, and bacteriotoxic shock]. *Med Welt*. (1971) 22:1159–64. Available online at: https://pubmed.ncbi.nlm.nih.gov/4935726/

18. Baethmann A, Brendel W, Koczorek KR, Enzenbach R. Pathophysiologie des traumatischen hirnödems: befunde und hypothesen. *Dtsch Med Wochenschr*. (1970) 95(18):1020–4. doi: 10.1055/s-0028-1108583

19. Chaussy C, Brendel W, Schmiedt E. Extracorporeally induced destruction of kidney stones by shock waves. *Lancet*. (1980) 316:1265–8. doi: 10.1016/S0140-6736(80)92335-1

20. Chaussy C, Schmiedt E, Jocham B, Brendel W, Forssmann B, Walther V. First clinical experience with extracorporeally induced destruction of kidney stones by shock waves. *J Urol*. (1982) 127:417–20. doi: 10.1016/S0022-5347%2817%2953841-0

21. Walter-Brendel-Kolleg für Transplantationsmedizin. Available online at: https://www.walter-brendel-kolleg.de/ (Accessed September 10, 2024).

22. Land W. Is there room for "transplantation medicine" as a medical discipline in its own right? *Transpl Int*. (1988) 1:43–6. doi: 10.1007/BF00337848

23. German Academy for Transsplantation Medicine. Available online at: https://www.akademie-fuer-transplantationsmedizin.de/ (Accessed September 10, 2024).

24. Nashan B, Settmacher U, Koch M. The German transplant certification. *Hepatobiliary Surg Nutr*. (2024) 13(2):382–6. doi: 10.21037/hbsn-24-36

frontiers | Frontiers in Transplantation

TYPE Perspective
PUBLISHED 06 November 2024
DOI 10.3389/frtra.2024.1500493

OPEN ACCESS

EDITED BY
Jerzy Kupiec-Weglinski,
University of California, Los Angeles,
United States

REVIEWED BY
David W. Gjertson,
University of California, Los Angeles,
United States

*CORRESPONDENCE
Jon Kobashigawa
jon.kobashigawa@cshs.org

RECEIVED 23 September 2024
ACCEPTED 23 October 2024
PUBLISHED 06 November 2024

CITATION
Kobashigawa J (2024) Paul I. Terasaki, Ph.D: a pioneer in transplant medicine and a dedicated philanthropist.
Front. Transplant. 3:1500493.
doi: 10.3389/frtra.2024.1500493

Paul I. Terasaki, Ph.D: a pioneer in transplant medicine and a dedicated philanthropist

Jon Kobashigawa*

Department of Cardiology, Cedars-Sinai Smidt Heart Institute, Los Angeles, CA, United States

In the last five decades, remarkable surgical and medical advances ensued within the field of organ transplantation. These strides were marked by significant breakthroughs in transplant immunology, with Dr. Paul I. Terasaki standing as a true pillar of the field. This article highlights major milestones in Dr. Terasaki's life, his groundbreaking accomplishments in the field of transplant medicine, and his enduring philanthropic contributions to numerous medical and community organizations.

KEYWORDS
transplantation, histocompatibility, micro-cytotoxicity, philanthropy, humoral immunity

In the last five decades, remarkable surgical and medical advances ensued within the field of organ transplantation, supported by the revolutionary achievements of pioneers who helped turn what most considered "experimental" in the 1950s and 1960s into the gold-standard treatment option for patients with end-organ diseases (1). These strides were marked by significant breakthroughs in transplant immunology, with Dr. Paul I. Terasaki standing as a true pillar of the field (2). Dr. Terasaki pushed the boundaries of transplant immunology and histocompatibility science with his transformative contributions to our understanding of tissue typing and humoral rejection (3). In addition, Dr. Terasaki demonstrated an unwavering commitment to humanity through his philanthropic efforts. This commentary highlights major milestones in Dr. Terasaki's life, his groundbreaking accomplishments in the field of transplant medicine, and his enduring philanthropic contributions to numerous medical and community organizations.

Paul I. Terasaki, PhD, was born into a humble family in Los Angeles, California, on September 10th, 1929 (3). In 1942, during World War II, his family was forced to relocate to an internment camp in Arizona, where he lived in one modest room shared with his parents, his two brothers, and his aunt. Dr. Terasaki described their living conditions as poor, and the education he received during those three years of confinement as suboptimal (3). After World War II, his family hesitated to return to California and decided to move to Chicago, where Dr. Terasaki finished high school and then was enrolled as a pre-medicine student at the University of Illinois.

In 1948, feeling it was safe to return to Los Angeles, the Terasakis moved back, and Paul was transferred to the University of California Los Angeles (UCLA) to complete his degree in Zoology. He went on to earn three degrees at UCLA: a bachelor's degree in preventive medicine and public health, as well as a master's and a Ph.D in zoology (4). In 1954, he married Hisako Sumioka, a young artist, and the couple had four children (5).

After graduating, he joined the Department of Surgery at UCLA, where his research initially focused on chicken skin grafts. He developed an interest in transplant tolerance and eventually was awarded a postdoctoral fellowship to work in London for a year under future Nobel Prize laureate Peter Medawar. This experience shaped the rest of his career (3). Dr. Terasaki recalls that at that time, the debate about cellular vs. humoral contribution to graft rejection was ongoing, but he leaned mostly towards B-cells and focused on antibody involvement (3, 6).

Returning to UCLA as an "assistant research zoologist," Dr.Terasaki worked tirelessly for the next five years, putting in 18-hour days (7, 8). In 1964, he made a major breakthrough by introducing the micro-cytotoxicity test. The test required only 1 microliter—one lambda—of serum to identify human leukocyte antigens (HLA) (Figure 1) (9). The "micro-test" was adopted as a standard in the United States in 1968, and two years later, in 1970, it was adopted as an international standard for genetically matching transplant candidates and recipients. In addition, the test was instrumental in resolving cases of disputed paternity and linking HLA to various diseases (10–12). At that time, Dr. Terasaki linked the presence of preformed antibodies against donor HLA antigens and hyperacute graft rejection (13). This finding set the ground for the need to test for these antibodies and to perform lymphocyte cross-match in patients awaiting transplantation.

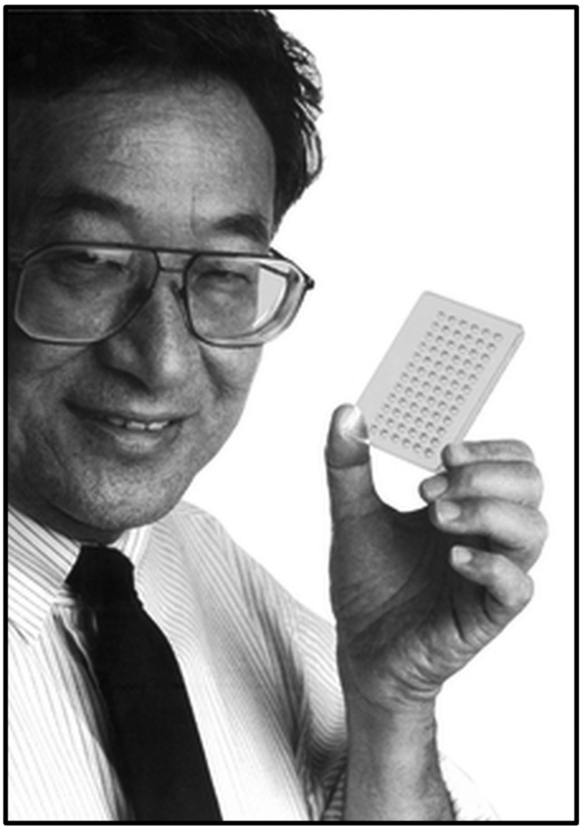


FIGURE 1
Dr.Paul I. Terasaki holding the Terasaki Plate. Source: https://terasaki.org.

In 1969, Dr. Terasaki became a professor of surgery at UCLA, and he founded the UCLA Tissue Typing Laboratory that year (14). In the 1970s and 80s, the Terasaki lab conducted most of the world's HLA-typing and donor-recipient matching (6). His team developed kits that allowed samples from across the globe to be shipped to Los Angeles with enough numbers of cells for cross-matching (6).

Dr. Terasaki was instrumental in establishing the UCLA kidney registry at UCLA in 1970, which eventually developed into an International Kidney Registry encompassing 52 transplant centers worldwide (15). Dr. Terasaki played a pivotal role in setting the first United Network for Organ Sharing (UNOS) kidney allocation system criteria, and the UCLA kidney transplant he championed served as a precursor for the national transplant database (16).

Additionally, in 1970, he developed, along with Geoffrey Collins, a simple cold storage method to keep donor kidneys viable for longer periods, making it possible to transport organs over long distances (11, 15, 17). In 1984, he founded One Lambda, Inc., a transplant diagnostic company with eight of his former students, to provide diagnostic tools for transplant centers to better match and monitor their patients pre/post-transplant (18).

In 1995, Dr.Terasaki reported that transplants between spouses who were unrelated and poorly HLA-matched had favorable outcomes (19). This led to a significant increase in transplants between spouses, friends, distant relatives, and even complete strangers, expanding the pool of available donors (15). In the late 1990s, One Lambda began to introduce a solid-phase system for identifying HLA antibodies using purified HLA and later recombinant techniques to identify HLA antibodies accurately and laid the groundwork for the creation of the "calculated" percent-reactive antibody, which provides a uniform estimate of how incompatible a transplant candidate is with potential donors (15). It also enabled laboratories to perform a virtual crossmatch, which streamlined organ allocation, significantly increasing the number of transplants among sensitized patients. One Lambda, Inc. was acquired by Thermo Fisher Scientific in 2012 and continues to play a central role in advancing tissue typing (20).

Following Dr.Terasaki's retirement from UCLA in 1999, he founded the Terasaki Foundation, a dedicated research center to study cancer immunotherapy and the role of humoral immunity in organ transplantation (14). Dr. Teraskai's recent contributions to the field transplant have demonstrated that HLA antibodies play a major role in late graft failure, reshaping the transplant community's understanding of chronic graft failure (21).

Dr.Terasaki held numerous leadership positions within the transplant community, including serving as president of the International Transplantation Society and the American Society of Histocompatibility and Immunogenetics, the OPTN/UNOS Board of Directors, and the Histocompatibility and Scientific Advisory Committees (6, 16). Throughout his career, he published over 900 scientific papers, authored more than 20 books, and mentored over 100 postdoctoral scholars (4, 6).

In addition to his groundbreaking scientific achievements, Dr.Terasaki is well-known for his philanthropic endeavors.

Throughout his life, he donated $58 million to UCLA to support the Terasaki Life Sciences Building, the UCLA International Institute (later renamed the Paul I. and Hisako Terasaki Center for Japanese Studies), and endowed faculty chairs in that discipline and in U.S.–Japanese relations (4). The Terasakis also established the Nibei Foundation to facilitate fellowship opportunities and partnerships between Japanese and Japanese-American professors and doctors (4).

Paul and his wife, Hisako, were committed to preserving Japanese history in the US. Paul served on many committees, including the Japanese American National Museum in Los Angeles, the Memorial to Japanese American Patriotism in World War II in Washington D.C., and the US-Japan Council, and gave generously to these organizations. After the tsunami, he sponsored 20 Los Angeles college students to volunteer in Japan; the goal was to have the students understand the Tohoku disaster and learn about Japanese history and culture (22). Among many organizations supported by Paul & Hisako Terasaki (Table 1), notable contributions were made to Japanese American Citizens League, Keiro Senior Healthcare, Los Angeles Jewish Symphony, Los Angeles County Museum of Art, Little Tokyo Service Center-(Budukon), Manzanar Committee Smithsonian Institution, The Transplantation Society, the United States-Japan Bridging Foundation, UCLA-The Nikkei Student Union, University of Tokyo, Venice Japanese Community Center, and West LA United Methodist Church. Dr Terasaki also donated an endowed chair in the Department of Surgery at UCLA.

TABLE 1 List of organizations supported by Paul & Hisako Terasaki contributions.

American Association for the Study of Liver Diseases	Lupus Foundation Of Northern California
American Liver Association	Manzanar Committee
American Society for Histocompatibility and Immunogenetics	Mayo Clinic
Asia America Symphony Association	Media Bridges
Cedars Sinai Medical Center	Medical and Health Sciences Foundation
Centenary Sanctuary Fd	Nanka Fukuoka Kenjinkai
Beckman Research Institute—City of Hope	National Inventors Hall of Fame®
Claremont School of Theology	National Japanese American Memorial
DENSHO	Nikkei for Civil Rights and Redress
Foundation FOR Cardiology & Transplant Research	Pacific Lodge Boys Home
Friends of the Smithsonian	Physicians for Social Responsibility
Go For Broke—National Education Center	Pittsburgh Foundation
Grateful Crane Ensemble	Pittsburgh University Medical Center
Harbor-UCLA Hematology	Poston Community Alliance
Higashi Honganji Buddhist Temple	Senior Foundation Charitable Corporation
Japanese American Living Legacy	Smithsonian Institution
Japanese American Cultural & Community Center	The Transplantation Society
Japanese American Citizens League	Toberman Neighborhood Center
Japanese American Memorial to Patriotism During World War II	Tomo No Kai
Japanese American National Museum	Transplant Recipients International Organization
Japanese American Artist Foundation	A Tribute To Issei Pioneers
Japan America Media Association	TRIO
Japan Community Health Care Organization	UCLA-Asian Pacific Alumni
Japanese Language Foundation	Ucla—Japan Tour
JWCH Institute	UCLA Foundation
Kaiser Permanente	UCLA-The Nikkei Student Union
Keiro Senior HealthCare	University Kidney Research Organization
Kizuna	UT Southwestern Medical Center
The Los Angeles Biomedical Research Institute	University Of Tokyo
Los Angeles Jewish Symphony	United States-Japan Bridging Foundation
Los Angeles Philharmonic Association	U.S.-Japan Council
Los Angeles County Museum of Art	Venice Japanese Community Center
Little Tokyo Service Center-(Budukon)	West LA United Methodist Church

Ordered Alphabetically.

In recognition of his achievements, he received numerous prestigious awards, including the Medawar Prize in 1996—the world's highest honor for contributions to the field of transplantation—and the UCLA Medal in 2012, the university's highest distinction (20). In 2013, the American Society of Transplantation honored him as an Innovator in Transplantation (15). For his dedication to preserving the history of Japanese Americans, Terasaki was also awarded the U.S.-Japan Council Lifetime Achievement Award in 2014 (22).

Despite his inauspicious childhood, Dr. Terasaki went on to achieve enormous success as a pioneer in transplant medicine, a mentor to countless health professionals, and a dedicated benefactor to numerous academic, social service, and community organizations. Dr. Terasaki passed away on January 25, 2016, at the age of 86. His legacy will continue to inspire generations to come, and he will be remembered with deep respect and admiration for his groundbreaking contributions and the lives he touched.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Author contributions

JK: Writing – original draft.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Pilch NA, Bowman LJ, Taber DJ. Immunosuppression trends in solid organ transplantation: the future of individualization, monitoring, and management. *Pharmacotherapy*. (2021) 41:119–31. doi: 10.1002/phar.2481

2. Terasaki PI. A brief history of HLA. *Immunol Res*. (2007) 38:139–48. doi: 10.1007/s12026-007-0020-4

3. Terasaki PI. Courage and character, leaders and legends: an interview with Paul I. Terasaki, PhD. Interview by Linda Ohler. *Prog Transplant*. (2012) 22:4–5. doi: 10.7182/pit2012275

4. Paul Terasaki, 86, transplant medicine pioneer, philanthropist, UCLA faculty member and alumnus | UCLA. Available online at: https://newsroom.ucla.edu/releases/paul-terasaki-86-transplant-medicine-pioneer-philanthropist-ucla-faculty-member-and-alumnus (accessed September 10, 2024).

5. Niiya B. Paul Terasaki | Densho Encyclopedia. (2023) Available online at: https://encyclopedia.densho.org/Paul_Terasaki/#cite_note-ftnt_ref4-4 (accessed September 7, 2024).

6. Gale RP, Opelz G. Paul I Terasaki (10 September, 1929–25 January, 2016). *Bone Marrow Transplant*. (2016) 51:621–2. doi: 10.1038/bmt.2016.70

7. Watts G. Paul Ichiro Terasaki. *Lancet*. (2016) 387:1156. doi: 10.1016/S0140-6736(16)30010-1

8. Terasaki Institute—Our Legacy. Available online at: https://terasaki.org/institute/about-us/legacy.html (accessed September 7, 2024).

9. Terasaki PI, McClelland JD. Microdroplet assay of human serum cytotoxins. *Nature*. (1964) 204:998–1000. doi: 10.1038/204998b0

10. Schlosstein L, Terasaki PI, Bluestone R, Pearson CM. High association of an HL-A antigen, W27, with ankylosing spondylitis. *N Engl J Med*. (1973) 288:704–6. doi: 10.1056/NEJM197304052881403

11. Cecka JM. Interview with Dr Paul Terasaki. *Am J Transplant*. (2003) 3:1047–51. doi: 10.1034/j.1600-6143.2003.00194.x

12. Terasaki PI. Resolution by HLA testing of 1000 paternity cases not excluded by ABO testing. *J Fam L*. (1977) 16:543.

13. Terasaki PI, Marchioro TL, Starzl TE. Sero-typing of human lymphocyte antigens: preliminary trials on long-term kidney homograft survivors. (1965)

14. Dr. Paul I. Terasaki. Available online at: https://international.ucla.edu/japan/article/180854 (accessed September 10, 2024).

15. Cecka JM, Gjertson DW, Reed EF. Paul I. Terasaki, PhD, 1929–2016. *Am J Transplant*. (2016) 16:1365–6. doi: 10.1111/ajt.13747

16. In Memoriam: Paul Terasaki, Ph.D.—UNOS. Available online at: https://unos.org/news/in-memoriam-paul-terasaki-ph-d/ (accessed September 10, 2024).

17. Collins GM, Bravo-Shugarman M, Terasaki PI. Kidney preservation for transportation: initial perfusion and 30 h' ice storage. *Lancet*. (1969) 294:1219–22. doi: 10.1016/S0140-6736(69)90753-3

18. Paul Terasaki Obituary (1929–2016). Los Angeles, CA—Los Angeles Times. Available online at: https://www.legacy.com/us/obituaries/latimes/name/paul-terasaki-obituary?id=16378170 (accessed September 10, 2024).

19. Terasaki PI, Cecka JM, Gjertson DW, Takemoto S. High survival rates of kidney transplants from spousal and living unrelated donors. *N Engl J Med*. (1995) 333:333–6. doi: 10.1056/NEJM199508103330601

20. The Lifesaving Work of Paul Terasaki | National Inventors Hall of Fame®. Available online at: https://www.invent.org/blog/inventors/paul-terasaki-tissue-typing (accessed September 10, 2024).

21. Kaneku H, O'leary JG, Banuelos N, Jennings LW, Susskind BM, Klintmalm GB, et al. *de novo* donor-specific HLA antibodies decrease patient and graft survival in liver transplant recipients. *Am J Transplant*. (2013) 13:1541–8. doi: 10.1111/ajt.12212

22. 2014 USJC Annual Conference—U.S.-Japan Council. Available online at: https://www.usjapancouncil.org/2014-usjc-annual-conference/ (accessed September 10, 2024).

frontiers | Frontiers in Transplantation

TYPE Perspective
PUBLISHED 02 December 2024
DOI 10.3389/frtra.2024.1519975

Check for updates

OPEN ACCESS

EDITED BY
Jerzy Kupiec-Weglinski,
University of California, Los Angeles,
United States

REVIEWED BY
Xian C. Li,
Houston Methodist Hospital, United States
Reza Abdi,
Brigham and Women's Hospital and Harvard Medical School, United States

*CORRESPONDENCE
Manikkam Suthanthiran
msuthan@med.cornell.edu

RECEIVED 30 October 2024
ACCEPTED 01 November 2024
PUBLISHED 02 December 2024

CITATION
Suthanthiran M (2024) Terry B. Strom: not just a pillar but a foundation.
Front. Transplant. 3:1519975.
doi: 10.3389/frtra.2024.1519975

Terry B. Strom: not just a pillar but a foundation

Manikkam Suthanthiran*

Weill Cornell Medical Center, NewYork-Presbyterian, New York, NY, United States

KEYWORDS

transplantation—kidney, immunobiology, pillar, IL-15, lymphocyte-mediated cytotoxicity

Introduction

I was delighted when the much-admired Jerzy Kupiec-Weglinski, the erudite editor of Frontiers in Transplantation, invited me to contribute a Pillar article on Terry Barton Strom, MD, the much accomplished and quintessential transplantation immunobiologist of our time (Figure 1).

English being a foreign language for me, I first looked up the meaning of "Pillar" before writing this piece, and I came to the inevitable conclusion that Terry Strom transcended the definition of a pillar and his inspiring and innovative contributions to the transplantation field merited the "Foundation" label as well!

I have also come to realize that there are six degrees of (academic) separation. In the first degree, one is invited to present one's own primary data at a bona fide scientific meeting; in the second, you are asked to summarize your research work in a symposium; in the third degree, one is invited to chair a session on a relevant topic at a meeting but not allowed to speak; in the fourth, one is invited to chair a session at a meeting on a subject one has very little expertise but the invitation was rendered because the invitee occupies an influential position like an Editorship of a Journal or serves on a funding agency; in the fifth degree, one finagles an invitation to participate at an industry-sponsored meeting held at an exotic patch with travel and accommodation far superior to academic societies; in the sixth degree, one's invited to write an obit piece or a pillar article! Of course, writing this article about my inspirational mentor and dear friend, Terry Strom was a labor of love.

An enshrined principle in every religion is that one must leave the world a better place than one found it. Terry Strom most certainly not only enriched the field of immunobiology and transplantation but also stimulated each of us to be better individuals in the highly competitive academic medicine enterprise.

A series of fortunate developments garnered my admission to the Peter Bent Brigham Hospital, Boston, MA in 1975. There was no pampering "orientation" to my fellowship, and I started my transplant service rotation bright and early on July 1, 1975. I had a second lucky break—Terry Strom was my transplant attending! On the first evening of my fellowship, I called Terry to seek his permission to return to Detroit Children's Hospital to attend to my 9-year-old nephew who had just been re-admitted for a post-operative complication following total correction of Tetralogy of Fallot. I was deeply concerned about making this request on my very first day of fellowship. I have not forgotten his most humanistic response that still brings tears to my eyes: "Please go and come back only when you feel comfortable."

Luck plays a major role in all our lives. I was most fortunate that Terry Strom was not only my brilliant and nurturing mentor but also my most cherished friend. In the laboratory headed by the gentleman-scholar, Charles Bernard Carpenter, Terry Strom

FIGURE 1
Terry B. Storm, MD. I could have chosen a more formal picture, but I thought this one captures Terry's boyish exuberance and his approach to life: taking the work seriously by not taking himself seriously.

provided the spark and served as a stellar role model for taking the science seriously but not himself. His clarity of thought, the complementary eloquence, and the grace with which he treated others were inspirational for me and much admired by one and all. Indeed, at any national or international meeting, if one saw an admiring crowd of scientists in the hallways, Terry Strom was likely to be at the center of the crowd.

My professional career was clearly ignited and sustained by Terry Strom, and he was the "invisible hand" behind my career progression. One of the greatest joys of an investigative career is to collaborate with individuals of high intellect, and it was an unmitigated pleasure to collaborate with Terry who had the rare combination of scientific rigor and generosity of spirit.

Academic career in brief

Terry Strom's career in transplantation started with his renal fellowship under the legendary John P. Merrill, the Chief of the Cardio-Renal Division at the Peter Bent Brigham Hospital, Boston, MA. Charles (Bernie) Carpenter was the head of the Immunology Laboratory and Terry was the dynamic force in Bernie's laboratory, home to many future practitioners of transplantation immunology. I met Terry in Bernie's lab when he was as a young Assistant Professor of Medicine at the Harvard Medical School. Twenty-two years later, 1991, was a banner year for Bernie's disciples when they garnered all the awards at the annual meeting of the American Society of Transplantation where the awards were presented by luminaries like Suren Sehgal and Jean F Borel (Figure 2). Terry's ascendency on the academic ladder was inevitable and he rose through the ranks to full professorship. In the ledger with loss and gain columns, a significant loss to Brigham and a substantive gain to Beth Israel Hospital was Terry's move to Beth Israel Deaconess Medical Center to become the head of the Department of Immunology with a logistically broadened scope of transplantation and autoimmunity. Terry's magnetic personality attracted an international cadre of talented individuals who have emerged from his inspiring mentorship as leaders of the transplantation immunology field.

Some of his significant scientific contributions

Terry Strom was an exceptional scientist who defied pigeonholing as a basic, or translational, or an applied researcher. The quantitative aspect of his research productivity was only rivalled by its qualitative features. His original discoveries included the identification of cholinergic agents augmenting lymphocyte-mediated cytotoxicity (1) (LMC), a prototypic model for the effector mechanism contributing to allograft rejection; elucidation of the critical contributions of microtubular assembly to the effector activity in LMC (2); and the discovery of the counter-regulatory role of cyclic nucleotides on LMC (3). Terry and his talented colleagues demonstrated that the hormone insulin, known almost exclusively for its glycemic homeostatic role, enhances cytotoxic activity in the LMC assay (4); that insulin receptors are displayed on alloimmune *T* cells (5); and that the expression of these insulin receptors signal activation status of the two major types on immune cellular elements, the *T* cells and the B cells (6).

The IL-2 receptor alpha (CD25) is essential for the high affinity interaction of the IL-2 receptor complex with its ligand IL-2, and *T* cell clonal expansion. Terry Strom's incisive experiments demonstrating that anti-CD25 monoclonal antibodies prolong the survival of mouse cardiac allografts in fully H-2 mismatched donor-recipient combinations paved the way for the clinical of monoclonal antibodies directed at the CD25 antigen in the clinic for the prevention of allograft rejection (7).

Living up to the Albert Einstein's adage "a man should look for what is, and not for what he thinks should be", the Strom laboratory unhesitatingly reported the surprising finding that IL-2 knock out mice reject allogeneic islet allografts as vigorously as the wild type mice (8)—a courageous publication in the face of the then prevailing paradigm that IL-2 is essential for allograft rejection. This novel observation also helped also to widen the idea that the salutatory effects of calcineurin inhibitors transcend their ability to block IL-2 transcription. Equally audacious was the publication from the team of Strom Nicholas Tilney that allograft rejection is not only associated with cytotoxic effectors but also with the emergence of suppressor cells (9)—christened as T regulatory cells in the current vernacular.

The IL-2 receptor complex consists of the alpha chain (CD25), beta chain, and common gamma chain. IL-15 has its unique alpha chain but utilizes the same beta chain and gamma chain used by

FIGURE 2
American society of transplantation awardees -circa 1997. L. W. Miller (Pesident, American Society of Transplantation), S.N. Sehgal (Rapamycin pioneer), T.B. Storm, L. A. Turka, C.B. Carpenter, M.H. Sayegh, M. Suthanthiran, J-F. Borel (Cyclosporine pioneer).

IL-2 for transmembrane signaling of *T* cells. The Strom lab not only introduced IL-15 to the transplant community (10), but successfully deciphered the distinct roles of IL-2 and IL-15 in the destiny of *T* cells (11).

The transformative PCR assay that garnered the Nobel Prize for Kary B. Mullis was brilliantly adopted by the Strom laboratory to profile preclinical (12) and clinical samples (13) and decipher informative intragraft profiles that have endured over time. It was pure joy for my own laboratory to collaborate with Strom's laboratory in broadening the versatile PCR assay to enable absolute quantification of transcripts (14) and advancing urine as a robust surrogate biospecimen for the invasive kidney allograft biopsy (15). Altogether, the Strom laboratory has had a transformative impact on our understanding of allograft rejection and tolerance.

Peer recognition

Terry Strom's discoveries and paradigm shifting research contributions have been duly recognized by honorific societies. He was elected member of the American Society for Clinical Investigation and the Association of American Physicians. He was the first Past President of the American Society of Transplantation and served as the President of the Clinical Immunology Society. The American Society of Nephrology bestowed its highest honor, the Homer Smith Award, and the University of Pittsburgh recognized Terry with the Starzl Prize in Surgery and Immunology. Terry Strom received every senior award from the American Society of Transplantation: The Established Investigator Award, the Distinguished Achievement award, and the AST Mentoring Award.

Concluding remarks

The renowned Irish Poet William Butler Yeats closed his memorable 1937 poem "The Municipality Gallery Revisited" closed his memorable piece with this line: "Think where man's glory most begins and ends, And say my glory was I had such friends". In my case, it was the long and enduring friendship with Terry Strom. An added bonus was his multitalented wife, Dr. Margot Strom.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Author contributions

MS: Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Acknowledgment

An exceptional exponent of immunology, Terry Strom published hundreds of original articles in the transplantation immunology and the autoimmunity arenas. It is an unenviable task to choose from the cornucopia of original findings from the Strom laboratory. My apologies for the inadvertent omission of some of the classics and the failure to name the brilliant scientists who traversed through the Strom laboratory since in my experience only those whose names are left out remember!

Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Strom TB, Deisseroth A, Morganroth J, Carpen- ter CB, Merrill JP. Alteration of the cytotoxic action of sensitized lymphocytes by cholinergic agents and activators of adenylate cyclase. *Proc Natl Acad Sci U S A*. (1972) 69(10):2995–9. doi: 10.1073/pnas.69.10.2995

2. Strom TB, Garovoy MR, Carpenter DB, Merrill JP. Microtubule function in immune and nonimmune lymphocyte-mediated cytotoxicity. *Science*. (1973) 181 (4095):171–3. doi: 10.1126/science.181.4095.171

3. Strom TB, Carpenter CB, Garovoy MR, Austen KF, Merrill JP, Kaliner M. The modulating influence of cyclic nucleotides upon lym- phocyte-mediated cytotoxicity. *J Exp Med*. (1973) 138(2):381–93. doi: 10.1084/jem.138.2.381

4. Strom TB, Bear RA, Carpenter CB. Insulin- induced augmentation of lymphocyte-mediated cytotoxicity. *Science*. (1975) 187(4182):1206–8. doi: 10.1126/science.163492

5. Helderman JH, Strom TB. Emergence of insulin receptors upon alloimmune T cells in the rat. *J Clin Invest*. (1977) 59(2):338–44. doi: 10.1172/JCI108646

6. Helderman JH, Strom TB. Specific insulin bind- ing site on T and B lymphocytes as a marker of cell activation. *Nature*. (1978) 274(5666):62–3. doi: 10.1038/274062a0

7. Kirkman RL, Barrett LV, Gaulton GN, Kelley VE, Ythier A, Strom TB. Administration of an anti-interleukin 2 receptor monoclonal antibody prolongs cardiac allograft survival in mice. *J Exp Med*. (1985) 162(1):358–62. doi: 10.1084/jem.162.1.358

8. Steiger J, Nickerson PW, Steurer W, Moscovitch-Lopatin M, Strom TB. IL-2 knockout recipient mice reject islet cell allografts. *J Immunol*. (1995) 155(1):489–98. doi: 10.4049/jimmunol.155.1.489

9. Schneider TM, Kupiec-Weglinski JW, Towpik E, Padberg W, Araneda D, Diamantstein T, et al. Development of suppressor lymphocytes during acute rejection of rat cardiac allografts and preservation of suppression by anti-IL-2-receptor monoclonal antibody. *Transplantation*. (1986) 42(2):191–6. doi: 10.1097/00007890-198608000-00017

10. Pavlakis M, Strehlau J, Lipman M, Shapiro M, Maslinski W, Strom TB. Intragraft IL-15 transcripts are increased in human renal allograft rejection. *Transplantation*. (1996) 62(4):543–5. doi: 10.1097/00007890-199608270-00020

11. Li XC, Roy-Chaudhury P, Hancock WW, Manfro R, Zand MS, Li Y, et al. IL-2 and IL-4 double knockout mice reject islet allografts: a role for novel T cell growth factors in allograft rejection. *J Immunol*. (1998) 161(2):890–6. doi: 10.4049/jimmunol.161.2.890

12. O'Connell PJ, Pacheco-Silva A, Nickerson PW, Muggia RA, Bastos M, Kelley VR, et al. Unmodified pancreatic islet allograft rejection results in the preferential expression of certain T cell activation transcripts. *J Immunol*. (1993) 150 (3):1093–104. doi: 10.4049/jimmunol.150.3.1093

13. Lipman ML, Stevens AC, Bleackley RC, Helderman JH, McCune TR, Harmon WE, et al. The strong correlation of cytotoxic T lymphocyte-specific serine protease gene transcripts with renal allograft rejection. *Transplantation*. (1992) 53(1):73–9. doi: 10.1097/00007890-199201000-00014

14. Li B, Sehajpal PK, Khanna A, Vlassara H, Cerami A, Stenzel KH, et al. Differential regulation of transforming growth factor beta and interleukin 2 genes in human T cells: demonstration by usage of novel competitor DNA constructs in the quantitative polymerase chain reaction. *J Exp Med*. (1991) 174(5):1259–62. doi: 10.1084/jem.174.5.1259

15. Li B, Hartono C, Ding R, Sharma VK, Ramaswamy R, Qian B, et al. Noninvasive diagnosis of renal-allograft rejection by measurement of messenger RNA for perforin and granzyme B in urine. *N Engl J Med*. (2001) 344(13):947–54. doi: 10.1056/NEJM200103293441301

TYPE Perspective
PUBLISHED 22 January 2025
DOI 10.3389/frtra.2024.1530925

OPEN ACCESS

EDITED BY
Alan Langnas,
University of Nebraska Medical Center,
United States

REVIEWED BY
Paolo De Simone,
University of Pisa, Italy

*CORRESPONDENCE
Jerzy W. Kupiec-Weglinski
✉ jkupiec@mednet.ucla.edu

RECEIVED 19 November 2024
ACCEPTED 12 December 2024
PUBLISHED 22 January 2025

CITATION
Kupiec-Weglinski JW (2025) Ronald W. Busuttil, M.D., Ph.D.— TTS 2024 Medawar Prize Laureate.
Front. Transplant. 3:1530925.
doi: 10.3389/frtra.2024.1530925

Ronald W. Busuttil, M.D., Ph.D.— TTS 2024 Medawar Prize Laureate

Jerzy W. Kupiec-Weglinski*

The Dumont-UCLA Transplantation Center, Department of Surgery, Division of Liver and Pancreas Transplantation, David Geffen School of Medicine at UCLA, Los Angeles, CA, United States

The Transplantation Society (TTS) has been presenting the Medawar Prize at its biennial Congresses since 1990 in recognition of Sir Peter Medawar's seminal contributions to organ transplantation. This prestigious award acknowledges individuals for their outstanding accomplishments in experimental and clinical transplantation. On September 25, 2024, I was honored to introduce Ronald W. Busuttil, M.D., Ph.D., as the 2024 Medawar Prize Laureate during the 30th TTS Congress in Istanbul, Turkey. This article highlights the remarkable achievements and critical milestones in Dr. Busuttil's over 40-year career in organ transplantation, which have profoundly advanced scientific knowledge and clinical practice, embodying the true spirit of this accolade.

KEYWORDS

Ronald Busuttil, Medawar Prize, liver transplantation, surgical scholar, ischemia-reperfusion injury

Dr. Ronald W. Busuttil (Figure 1), known as "Dr. B" or "Ronnie" among friends, is currently a Distinguished Professor and Executive Chairman Emeritus at the University of California Los Angeles (UCLA) in the Department of Surgery and the founding Chief of the Division of Liver and Pancreas Transplantation at Ronald Reagan Medical Center, Los Angeles, California, USA.

The desire to pursue a medical career began in his teenage years, inspired by paternal great-grandfather, who was the private dentist to the king of Egypt. The Busuttil family, with Maltese and Italian roots, resided in Egypt until the Arab-Israeli War in 1948, prompting their relocation to the United States when Ronnie was only four, ultimately settling in Tampa, Florida. He graduated *magna cum laude* from Loyola University in New Orleans and later earned his M.D. and Ph.D. in pharmacology at Tulane University, under the tutelage of future Nobel Laureate, Lou Ignarro. Years later, Dr. Ignarro commended his former student as an exceptionally skilled surgical operator, highlighting his precision during cardiac ischemia experiments on dogs, which were conducted "without a single drop of blood on the floor."

Dr. Busuttil has dedicated his entire career to UCLA, where he first trained as a vascular surgeon, became faculty, and founded the Liver Transplant Program in 1984, one of the first in the country. For over 36 years, he has served as its Director and Chief Surgeon, making diverse and significant contributions to the field. His outstanding surgical expertise, demonstrated through over 7,200 liver transplants, including more than 1,000 children, at UCLA, UC Irvine, and Cedar Sinai, has critically advanced the care and management of transplant patients globally. The program ranks among the largest in the world, covering a comprehensive range of transplantation and hepato-biliary surgery for adults and children. One of the hallmark areas of Dr. B's

FIGURE 1
Dr. Ronald W. Busuttil, TTS 2024 Medawar Prize Recipient (Credit: Reed Hutchinson).

clinical innovation addresses the crucial problem in our field, i.e., the donor organ shortage. His pioneering efforts have facilitated the life-saving expansion of the organ pool by refining donor-recipient matching criteria (1), transplantation for malignancies (2), implementing technical modifications of extended criteria donor allografts (1), deceased split donor livers (3), and living donations (4). An exceptional clinician and educator at the bedside, he was instrumental in formulating key concepts that enhanced the care and survival of liver transplant patients.

Dr. Busuttil recalls the day he performed his first liver transplant at UCLA. It was February 1, 1984, when he received a call about a donor liver while at his accountant's office. With a limited timeframe to retrieve and successfully transplant the organ, he and two colleagues embarked on a 17-mile journey to St. Joseph Medical Center in Burbank. Before heading to the hospital, they quickly stopped at a 7/11 convenience store to buy a cooler and four bags of ice, as donor organs were transported in an Igloo cooler back then. Dr. Busuttil describes the first human liver transplant he performed as both "intimidating" and "encouraging," referring to it as the "case of 17" due to the 17-h duration from the donor operation to the transplant's completion, the 17 units of blood required—"which was very, very good," he says—and the fact that the patient was discharged in 17 days. Dr. Busuttil notes that the patient going home 17 days post-transplant in 1984 was particularly uplifting. This began what would become one of the country's largest and most esteemed transplant centers. Over 7,200 liver transplants would not go without remarkable individual stories. A notable one involves a 1-year-old child diagnosed with a giant hepatic hemangioendothelioma, who underwent a liver transplant on August 8, 1984, his fifth clinical case. Today, she is over 40 years old, happily married and doing well.

Throughout his career, Dr. Busuttil has aimed to reflect a dedication to being a compassionate and considerate physician and surgeon, a commitment to his patients and trainees, and an unwavering focus on saving lives. He emphasizes that liver transplantation embodies this commitment, in addition to vision, self-direction, and the integrity to navigate complex cases. In 2000, Dr. Busuttil remarked, "Burnout does not exist in my vocabulary, I thrive on what I do. Most of these people are at death's door. They are the sickest of the sick. Six months after surgery, you literally cannot recognize them."

Despite a rigorous clinical workload, Dr. Busuttil has embodied the essence of a surgical scholar, with scientific work encompassing all aspects of liver transplantation, including hepatic physiology, immunology, preservation, technical procedures, and ethical considerations. His laboratory research focuses on organ ischemia-reperfusion injury (IRI), which compromises clinical outcomes and exacerbates the shortage of available donor organs for life-saving surgeries. In the 1970s, he initiated translational studies that defined signaling pathways for pharmacological intervention using steroids to mitigate donor organ IRI. In 1975, he published the results of a randomized, double-blind study in dogs, which documented that pretreatment with methylprednisolone improved heart recovery following ischemia. The study suggested that lysosomal membrane stability and the regulation of cyclic GMP levels might play a crucial role in the mechanism of cardiac ischemic damage (5). Years later, he conducted a randomized single-center double-blind phase 2 clinical trial that revealed how treatment with recombinant P-selectin glycoprotein ligand IgG (rPSGL-Ig) could prevent injury in marginal livers, thereby expanding the organ donor pool (6). This was the first clinical trial to demonstrate a positive impact of an adhesion molecule antagonist on liver IRI in transplant patients.

Dr. Busuttil has been funded by NIH since 1981, with extramural grants exceeding $50M. Throughout his 50-year tenure as a surgical scholar, he has published over 950 peer-reviewed papers, including more than 60 in the *Annals of Surgery* alone, accumulating over 53,000 citations, and achieving an impressive h-index of 114. Additionally, he has written over 90 book chapters and is currently the co-editor of the preeminent textbook, *Transplantation of the Liver*, which is now in its fourth edition.

Dr. Busuttil has served as the President of the International Liver Transplantation Society (ILTS) and the American Society of Transplant Surgeons (ASTS). His numerous accolades reflect contributions to the field, including the ASTS Francis D. Moore Excellence in Mentorship Award, the ASTS Pioneer Award, the Thomas E. Starzl Prize in Surgery and Immunology, the American Surgical Association Medallion for Scientific Achievement, the TTS Award for Education and Training, the ILTS Distinguished Service Award, and the Society of University Surgeons Lifetime Achievement Award, among others. Under Dr. Busuttil's leadership, the ASTS established its Foundation to provide research funding for young transplant surgeon-scientists. The inaugural Ronald & JoAnn Surgeon Scientist Scholarship was presented at the 2024 American Transplant Congress, while honoring Dr. Busuttil's profound impact on generations of transplant surgeons.

Dr. B. has consistently made time for personal interactions with medical students, residents, and fellows, engaging in clinical rounds, one-on-one meetings, and hosting a monthly Journal Club at his home for three decades. His unwavering commitment to education and mentorship has shaped many future leaders in transplantation. Indeed, the UCLA transplant surgery fellowship is internationally acclaimed as one of the premier programs, having trained over 380 transplant surgeons from the United States and other countries. Notably, at least 25 alumni now lead their own transplant programs across the U.S., Asia, and Europe. Some former trainees conveyed to my residence in July 2022 to celebrate Dr. B's retirement (Figure 2). Yes, he achieved remarkable success in his career, but even more significant is his profound impact in nurturing a new generation of leaders in transplantation.

Less known is Ronnie's life beyond the operating room. He is passionate about tennis and running, having completed the NYC marathon twice. His love for cars, likely a trait passed down from his father, a car dealer in Tampa, has led him to attend many renowned races, such as the Monte Carlo Grand Prix and the Indianapolis 500, as well as to compete in the Mille Miglia, a 1,000-mile road race in Italy, three times. Furthermore, I can confirm that the rumors about Dr. B's impressive collection of Italian sports cars sharing his residence address in Bel Air, California, are indeed true. Ronnie often credits his career success to the steadfast support of his wife of over 50 years, JoAnn, along with their two daughters, Amber, and Ashley, and four grandsons, the eldest of whom was aptly named… Oliver.

On a personal note, I am fortunate to have been recruited by Dr. Busuttil from Harvard nearly 30 years ago. His guidance has shaped my life, and I am grateful to call him a friend. Moving from the Brigham and Women's Hospital, the cradle of modern organ transplantation, and leaving Boston for La-La-Land was difficult, but it has proven rewarding. With over four decades of experience in transplant research, I am convinced that fostering mutual understanding and crosstalk between clinical and basic

FIGURE 2
Dr. Busuttil's retirement party (Beverly Hills, CA; July 30, 2022). From left to right: Avi Shaked, John Colonna, Steve Colquhoun, Curtis Holt, Kim Olthoff, David Imagawa, Milan Kinkhabwala, Jim Markmann, Mark Ghobrial, Sherfield Dawson, Ron Busuttil, Pauline Chen, JoAnn Busuttil, Nick Nissen, Sunil Geevarghese, Angeles Baquerizo, Ian Carmody, Jerzy Kupiec-Weglinski, John Duffy, Johnny Hong, Fauzia Butt, Fady Kaldas, Ali Zarrinpar, Keri Lunsford, Daniel O'Brien, Julian Horwitz.

research is crucial for the success of our scientific endeavors. Dr. Busuttil's vision and support have been instrumental in our achievements at the Dumont-UCLA Liver Transplant Laboratory. The continuing NIH funding and publication record in top-tier scientific journals, which extend beyond the transplant field, underscores the broad relevance of our research findings for both the scientific community and clinicians. My initial encounter with Dr. Busuttil at the TTS Congress in Barcelona in 1996 culminated in his well-deserved induction into the pantheon of Medawar Awardees at TTS 2024.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any identifiable images or data included in this article.

Author contributions

JK: Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Cameron AM, Ghobrial RM, Yersiz H, Farmer DG, Lipshutz GS, Gordon SA, et al. Optimal utilization of donor grafts with extended criteria. *Ann Surg*. (2006) 243:748–53. doi: 10.1097/01.sla.0000219669.84192.b3

2. Duffy JP, Vardanian A, Benjamin E, Watson M, Farmer DG, Ghobrial RM, et al. Liver transplantation criteria for hepatocellular carcinoma should be expanded. *Ann Surg*. (2007) 246:502–9. doi: 10.1097/SLA.0b013e318148c704

3. Yersiz H, Renz JF, Farmer DG, Hisatake GM, McDiarmid SV, Busuttil RW. One hundred in situ split-liver transplantations. *Ann Surg*. (2003) 238:496–505. doi: 10.1097/01.sla.0000089852.29654.72

4. Zarrinpar A, Busuttil RW. Liver transplantation: past, present and future. *Nat Rev Gastroenterol Hepatol*. (2013) 10:434–40. doi: 10.1038/nrgastro.2013.88

5. Busuttil RW, George WJ, Hewitt RL. Protective effect of methylprednisolone on the heart during ischemic arrest. *J Thorac Cardiovasc Surg*. (1975) 70:955–65. doi: 10.1016/S0022-5223(19)39644-8

6. Busuttil RW, Lipshutz GS, Kupiec-Weglinski JW, Ponthieux S, Gjertson DW, Cheadle C, et al. RPSGL-Ig for improvement of early liver allograft function: a double-blind, placebo-controlled, single-center phase II study. *Am J Transplant*. (2011) 11:786–97. doi: 10.1111/j.1600-6143.2011.03441.x

Frontiers in
Transplantation

Explores innovation in organ, tissue, and cell transplantation

A multidisciplinary journal which communicates bench-to-bedside progress and breakthroughs in the ever-evolving transplant field, to improve clinical practice and save lives.

Discover the latest Research Topics

See more →

Frontiers

Avenue du Tribunal-Fédéral 34
1005 Lausanne, Switzerland
frontiersin.org

Contact us

+41 (0)21 510 17 00
frontiersin.org/about/contact