



## Frans Claas (1951–2025): A Visionary in Transplantation Immunology

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**P**rofessor Frans Claas was a scientist whose groundbreaking work on HLA matching transformed organ allocation and immunological risk assessment. His contributions have been instrumental in improving transplant success rates and enhancing patient outcomes.

In 1973, Frans approached Jon van Rood at the Leiden University Medical Centre, the Netherlands, to take him on as a student. Immersed in a vibrant research environment with a strong translational focus, he developed a deep passion for immunogenetics.<sup>1</sup> After completing his studies, he joined the HLA antibody screening laboratory in 1976 as a supervisor, balancing patient care with expanding research responsibilities—an enduring drive that sustained him until his sudden death on February 2, 2025.

A dedicated scientist and respected mentor, Frans was approachable and constructive in critiquing both his own work and that of others. He was instrumental in helping to establish research at Erasmus MC, Rotterdam, in 1987, traveling by train weekly to share expertise on mixed lymphocyte reactions, alloimmune cellular infiltrates, and the importance of HLA matching. His warmth and generosity of knowledge left a lasting impression on me and all who worked with him.

In honor of Professor Claas's many achievements, we invited colleagues who worked closely with him to share

their recollections, highlighting his profound scientific contributions and remarkable character.

### How did working with Frans help to advance tolerance following organ transplantation?

**KATHRYN WOOD:** I was first introduced to Frans in the late 1980s when I visited Leiden at Jon van Rood's invitation. We had recently published data on the blood transfusion effect in organ transplantation, demonstrating that it was not necessary to expose the adult recipient immune system to all donor major and minor histocompatibility antigens to induce specific unresponsiveness to a fully incompatible transplant.<sup>2</sup> These results intrigued Jon and Frans, aligning well with their own work on tolerance to noninherited maternal antigens (NIMAs) and the mechanisms of "immune privilege" underlying maternal-fetal immunity.<sup>3,4</sup> Our discussion was intense and continued long into the evening over dinner. From that point onward, Frans and I became firm friends and collaborators, particularly through the European Commission-funded Riset (Reprogramming the Immune System for the Establishment of Tolerance). He proudly introduced me to his PhD students, including Dave Roelen and Sebastiaan Heidt, both of whom later trained in Oxford before returning to Leiden. Dave now directs the HLA Laboratory, while Sebastiaan leads international research on B cell memory in transplantation. Mentoring them was a great pleasure for both Frans and me.

### Frans' discovery of the role of early alloantigen exposure in the development of immune tolerance significantly influenced our understanding of transplant outcomes. How has this concept shaped our approach to achieving tolerance after transplantation?

**MEGAN SYKES:** Frans's article, published in *Science* was the first to suggest that tolerance to alloantigens can develop in human fetal life, recognized it as the human counterpart of the induced tolerance previously

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described in mice by Billingham, Brent, and Medawar.<sup>4</sup> Subsequent studies demonstrated that renal allografts from siblings sharing NIMA underwent less rejection than those sharing noninherited paternal antigens. Building on this finding, Frans and collaborators extended these observations to bone marrow transplantation from parental or HLA-haploidentical sibling donors, showing fewer complications when there was a NIMA mismatch rather than a noninherited paternal antigen mismatch. Frans speculated on, and wrote about, the potential mechanisms of the NIMA effect, emphasizing the importance of microchimerism between mother and fetus. He developed sensitive methodologies for separating microchimeric cells by flow cytometry, allowing further investigation of how this phenomenon shapes alloimmunity.

### Frans's breakthrough in enhancing transplant success for highly sensitized patients

**DAVE ROELEN:** Frans exemplified the collaborative spirit of the histocompatibility and immunogenetics field. He headed the HLA laboratory in Leiden, ensuring it became the National Reference Laboratory of the Netherlands. His pioneering work led to the introduction of a new concept for increasing the chance of transplantation for highly sensitized patients.<sup>5,6</sup> This culminated in the Eurotransplant Acceptable Mismatch Program (AM program), enabling over 2000 successful transplants to date for patients who would otherwise struggle to find a compatible donor. Frans later led the Eurotransplant Reference Laboratory with a focus on helping highly immunized patients via the AM program, as well as the organization of the EPT scheme of Eurotransplant. In 2008, Frans asked me to become head of the HLA laboratory so he could focus on research, including studies of differential immunogenicity of HLA mismatches, the definition of acceptable mismatches, immunological tolerance, heterologous immunity, and the immunology of pregnancy.

### In what ways did Professor Frans Claas revolutionize the field of HLA research?

**ANAT TAMBUR:** I was particularly drawn to Frans's work helping highly sensitized patients find their "needle in a haystack" donor. While he strongly supported comprehensive HLA matching, he recognized that many highly sensitized patients have only slim chances of finding a fully matched donor. His solution was to define "acceptable" or "permissible" mismatches. This sparked collaborations, notably with René Duquesnoy on the HLAMatchmaker software, designed to predict likely antibody reactivity.<sup>7</sup> From there, interest turned to understanding HLA/antibody interactions, particularly HLA epitopes driving differential immunogenicity. Frans and I often discussed how some epitopes provoke strong alloimmune responses while others do not. He had the unique ability to teach without making one feel patronized, instead ensuring you felt like a valued collaborator.

### How did Frans Claas influence your research on ABO-incompatible transplants?

**LORI WEST:** I first knew Frans through his pioneering HLA research and came to value him as a friend for his

convivial nature. Once my group began to explore the concept of "ABO-histocompatibility" in ABO-incompatible transplantation, Frans was keen to consider how emerging glycomics tools could advance our understanding of ABO-genotyping, glycan expression, and multiplexed assays to characterize ABO antibodies. He believed ABO-histocompatibility could fit logically within the established HLA-based framework of histocompatibility, and his advice was invaluable. Having navigated large consortia such as Eurotransplant, he recognized the regulatory and logistical hurdles of implementing changes in clinical practice but remained optimistic about the future of ABO-histocompatibility in improving patient outcomes. Frans was always generous in offering his insights—his voice and contributions are greatly missed.

### Frans's Leadership in the European Federation of Immunogenetics

**MARCO ANDREANI:** The news of Frans's passing brought great sadness to the European Federation of Immunogenetics (EFI) community. A respected scientist and friend, his story in histocompatibility and transplant immunogenetics leaves an indelible mark. Among his many achievements, he identified eplet mismatches affecting rejection despite otherwise acceptable compatibility.<sup>8</sup> Throughout his career, Frans's accomplishments were widely recognized. He served the EFI in numerous roles, including President (1998–2000), Chair of the Scientific Committee (1996–2005), and Editor of the EFI newsletter for many years. The EFI community will always treasure his contributions to science and admire his integrity, kindness, and generosity of spirit.

### Frans's dedication to Eurotransplant

**DIRK YSEBAERT AND DIRK VAN RAEMDONCK:** Frans strongly believed in international cooperation, not only in scientific research, but especially in achieving successful HLA matching for organ transplantation. He served on the Eurotransplant Board and ultimately stepped in as interim Medical Director during a challenging restructuring period (until September 2024). During regular Board meetings in Leiden and winter meetings in Austria, we came to know Frans as calm, kind, honest, and always ready to give sound counsel. We remain deeply grateful for his willingness to guide Eurotransplant through those difficult times and remember him for his warm personality and determination to find the best solutions for the benefit of patients.

### What are recollections of Frans Claas as a mentor?

**SEBASTIAAN HEIDT:** I met Frans in 2003 when I applied for a PhD position in the Leiden HLA laboratory. He fostered a relaxed, supportive atmosphere, and although my initial research on RhD immunization was struggled, he did not give up on me. He encouraged me to work as a postdoc in Kathryn Wood's laboratory in Oxford and, on my return, gave me growing responsibilities in Leiden—always keen to see his mentees flourish. After securing a permanent position, I joined the monthly "Shiraz" meetings, where research and opportunities were discussed over wine—although any bottle Frans disliked

went straight down the sink, as he believed wine should be enjoyed.

He hosted visiting scientists from all over the world, creating a laboratory that was both scientifically rigorous and fun. Frans's "yin and yang" approach meant working hard but enjoying life too—he was typically the first to start dancing at conference parties. His energy and approachability made him beloved worldwide, leaving tremendous legacy.

**Lloyd D'Orsogna:** I was fortunate to receive his mentorship during my PhD. I first met Frans in 2006 at the International HLA Summer School in Bangkok. His passion for histocompatibility was striking. One of the easiest decisions I ever made was leaving Australia to join his laboratory in the Netherlands. For years, it had been known that the alloreactive T-cell response to foreign HLA was far higher than the normal anti-microbial T cell response, but the mechanisms remained unknown. In Leiden, we demonstrated the extremely high frequency of peptide and allo-HLA specific cross-reactivity by virus-specific memory T cells, providing insight into a longstanding puzzle.<sup>9</sup>

### Frans was also a passionate educator. What made him such an effective teacher?

**MARLIES REINDERS:** Frans was an exceptional teacher and friend. We worked together in clinics, research, education, and management; he offered invaluable guidance for complex nephrology cases at Leiden University Medical Centre and led pioneering clinical trials, always emphasizing immunological training for young researchers. He was a master at making his subject compelling, and during conferences, his sessions drew such crowds that there were often long lines outside the presentation room. On a personal note, he offered invaluable mentorship and advice at every stage of my career.

### Honoring Frans: A legacy of expertise and friendship

**WILLEM WEIMAR:** Frans made a significant impact both nationally and internationally. At Erasmus MC, he played a crucial role in immunological research for kidney and heart transplantation, leading to numerous publications and presentations. We also collaborated in founding the Dutch Transplant Association and the Dutch Transplant Society in 1988. His unwavering dedication and expertise remain influential to this day.

**Maarten Naesens:** I first encountered Frans's work and lectures when I began my PhD in transplantation 2 decades ago. Whether through publications, Eurotransplant organizational efforts, or direct collaboration, his optimistic forward-thinking, and self-critical approach shapes much of the progress in HLA matching and immunogenetics. Crucially, he was able to translate these complex immunological insights into clinically accessible practice, benefiting patients and guiding colleagues less specialized in transplant immunology.

**Caner Süsal:** I shared countless unforgettable moments with Frans—servicing together on the Eurotransplant Executive Committee, teaching, debating in pro-con sessions, and traveling to conferences worldwide. His Eurotransplant AM program was critical in providing transplants for highly sensitized patients in Heidelberg, as it was in many other centers. He also helped advance transplant

immunology in Türkiye, training young scientists and supporting new tissue typing laboratories. Frans championed HLA matching, kidney paired donation, and strategies to reduce immunosuppression toxicity. His ever-present smile will and generous spirit will continue to inspire.

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