In memoriam Frans H.J. Claas

Frans Claas, a towering figure in histocompatibility and immunogenetics, passed away on Sunday, February 2, 2025, at the age of 73. He died unexpectedly during a vacation in South Africa where he was with his wife, Ilse, and close friends, Ronald and Diënne Bontrop.

Born on October 6, 1951, in Eindhoven, the Netherlands, Frans came from a deeply Catholic family. Early in life, he considered becoming a pope, but other career paths were also on his mind, including biology, or professional football (he almost made it to professional football club MVV Maastricht as a goalkeeper). He started secondary school in 1964 in Eindhoven and after completing his Gymnasium education in 1970, he finally chose to study biology at Leiden University. When charged with a practical research project in 1973, he did not like the available fundamental biochemical research projects. Instead, he approached Jon van Rood at the Academic Medical Center in Leiden and successfully applied as a student assistant in his laboratory. Here, he started working on the topic of transplantation tolerance in mouse models. After earning his biology degree in 1976, Frans remained in the laboratory of van Rood and began his PhD studies, which he completed in 1985 with a thesis titled 'The Interaction of Drugs and γ-Type Endorphins with Polymorphic Cell Membrane Antigens'. He took over supervision of the Leiden HLA laboratory, first working mainly on diagnostics before gradually increasing his scientific work. Frans made sure there was a good atmosphere in the laboratory by organizing football and table tennis competitions, 'Sinterklaas' celebrations and cabaret shows. Under his supervision the Leiden laboratory became the National Reference Center for Histocompatibility Testing. At the same time, Frans became Director of the Eurotransplant Reference Laboratory, which further strengthened his position as an authority in histocompatibility and immunogenetics. In 1996, he was appointed full Professor of Immunogenetics of Transplantation at Leiden University, with his inaugural lecture entitled 'The subtle differences between mine and thine'.

Over the years Frans has been very active in the European arena of immunogenetics and histocompatibility through the European Federation for Immunogenetics (EFI). His first official role in EFI was in 1991 when, together with Marius Giphart, Ieke Schreuder and Jon van Rood, he organized the 5th EFI annual conference, the first outside of Strasbourg. He was Chairman of the EFI Scientific Committee from 1996 to 2005, the committee responsible for the scientific program of the annual conferences and for the selection of recipients the

prestigious Julia Bodmer and Ceppellini awards. He was one of the initiators of the International Summer School. During his time as HLA laboratory director at the LUMC he also oversaw the EFI office, which is situated close to the Leiden hospital. Furthermore, he was the Editor-in-Chief of the EFI Newsletter for more than 20 years, which has been pivotal for the communication between EFI members. His most esteemed contribution to EFI was by serving as President from 1998 to 2000.

Frans was an extraordinary scientist who always prioritized scientific progress and patient welfare over personal recognition. With over 600 peer-reviewed papers to his name, Frans' scientific legacy is vast. His achievements earned him several prestigious awards, including the 2006 ASHI Distinguished Scientist Award, the 2015 EFI Ceppellini Award, the 2015 ASHI Rose Payne Distinguished Scientist Award, and the 2017 van Loghem Award of the Dutch Society for Immunology. In recognition of his impact on society, he was knighted by the King of the Netherlands as a Knight of the Order of the Netherlands Lion in 2017 upon his retirement.

During his career Frans has been active in several areas of research,[1] from which a few highlights will be described here. One of his groundbreaking contributions which transformed kidney allocation in Eurotransplant came in 1988 when he introduced a novel approach to improve the chance of transplantation for highly sensitized patients awaiting a kidney transplant.[2] By extensive antibody screening using complement-dependent cytotoxicity (CDC) assays, he identified 'acceptable mismatches' that could predict a negative crossmatch. This pioneering work led to the introduction of the successful Eurotransplant Acceptable Mismatch Program,[3] which has enabled over 2,000 highly sensitized patients to undergo transplants to date. By working together with Rene Duquesnoy, who had just developed HLAMatchmaker,[4] Frans quickly realized the potential of epitope analysis for highly sensitized patients. Already in 2004 he adapted the concept of what is now called "molecular matching," for highly sensitized

patients, by introducing the idea of defining additional acceptable antigens through triplet (later known as eplet) sharing.[5] Frans worked tirelessly to increase the impact of the acceptable mismatch approach, and showed through the European Union funded Eurostam consortium that highly sensitized patients (who often have an HLA type that is uncommon in the local donor population) could benefit from organ exchange beyond the borders of the current allocation organizations.[6,7] His dream was to create a European-wide Acceptable Mismatch program for the most difficult to transplant patients.

Frans was a pioneer in the research on HLA epitopes and molecular mismatch. His team discovered early on that increased HLA triplet mismatches were linked to a higher risk of *de novo* donor-specific antibody (dnDSA) formation, while antigen mismatched but triplet-matched transplants did not trigger dnDSA.[8] Under his supervision, the user-friendly HLA-EMMA software was developed for amino acid mismatch analysis.[9] His team also explored the role of molecular mismatch in the setting of hematopoietic stem cell transplantation (HSCT). Recently, HLA-EMMA was used to define permissible mismatches in 9/10 unrelated donor pediatric stem cell transplants.[10] Several years earlier he showed that HLAMatchmaker analysis was not informative for T cell reactivity in HSCT, since there was no correlation with the cytotoxic T cell precursor (CTLp) frequency.[11] Paradoxically, more amino acid mismatches at the alpha-helices and beta-sheet resulted in a lower CTLp frequency, a finding explained by the need for some level of similarity between mismatched HLA and self-HLA for direct allo-recognition.[12] Closely related to these findings were his studies on heterologous immunity, where cross-reactivity of virus-specific T cells with allogeneic HLA helps to explain the relatively high frequency of T cells exhibiting direct alloreactivity.[13,14]

Frans' work extends beyond transplantation, as he made significant strides in understanding immunological tolerance during pregnancy.[15] Actually, this was already a subject of interest during his early work with Jon van Rood when studying non-inherited maternal HLA antigens.[16] Later in life he explored the T cell signature and monocyte fingerprint in the human placenta, investigating their correlation with pregnancy outcomes.[17-21] Also in this research line, immunogenetics was of interest, as his team showed that some degree of HLA matching, similar to the natural situation, is beneficial for a successful pregnancy after oocyte donation.[22,23] In his research, Frans boldly tackled controversial topics, which is exemplified by a paper that revealed a correlation between oral sex and a lower incidence of the pregnancy complication preeclampsia.[24] They proposed that soluble HLA in seminal fluid might play a role in inducing immunological tolerance.[25]

Besides science, Frans was also a committed manager who always kept the bigger picture in mind. He was co-founder of the Dutch Transplant Society in 1988, and co-founder of the Dutch Transplant Foundation in 1997. He was a long-time member of the board of Dutch Transplant Foundation, the Europdonor board, as well as the board of Eurotransplant. He served as member of the supervisory board of Matchis, and was member of the supervisory board and scientific advisory board of the Dutch Biomedical Primate Research Center. Between 2023 and 2024 Frans took on the role of interim medical director of Eurotransplant.

Beyond his scientific and managerial accomplishments, Frans will be remembered by his colleagues for his kindness and generosity. He took a personal interest in everyone he met, regardless of their background, and was deeply committed to mentoring scientists worldwide. The Leiden laboratory, under his leadership, hosted colleagues from all corners of the globe. His collaborative spirit was felt far and wide, and his exceptional social skills made him a cherished mentor and friend. The vast number of emails, text messages and phone calls form colleagues all over the world after Frans' passing are exemplary for his global impact. Many had found a true friend in him and enjoyed his presence, also outside of the lecture hall or conference room. This is partly because Frans also had a passion for life outside the laboratory — he loved dancing, enjoyed good food, and liked to talk with friends while enjoying a good Belgian beer or Italian red wine (preferentially from Puglia). As an avid runner, he completed numerous marathons, including the Bordeaux Médoc Marathon, which combined his love of running with his appreciation for fine wine.

Frans will be missed, but his spirit will live on in the generation of scientists who he has inspired to advance the field for the better of the patient. We could not have had a better mentor.

Sebastiaan Heidt

This in memoriam will also be published in the HLA journal.

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