BIOGRAPHICAL MEMOIRS

# Alberto C. C. Frasch

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Elected to the NAS, 2006

*A Biographical Memoir by Oscar Campetella, Roberto Docampo, and Wanderley de Souza*

Figure 1 Alberto C. Frasch. *Photo courtesy of the Universidad Nacional de San Martín.*

**Alberto Carlos Clemente Frasch's** seminal discoveries on key *Trypanosoma cruzi* antigens greatly deepened our understanding of the pathogenesis of Chagas disease, a condition that affects millions in Latin America. His pioneering research led to the development of critical diagnostic tools and played a foundational role in advancing the molecular biology of the pathogen, particularly in Argentina, where he was instrumental in shaping the field. Carlos leaves behind an enduring legacy of leadership, vision, and unwavering dedication. His relentless pursuit of excellence, tireless commitment to scientific progress, and generous mentorship of students navigating the challenges of academia and innovation were hallmarks of his life and career. He will be remembered not only as a brilliant scientist but also as a compassionate mentor and a cherished friend.

## Early Life and Education

Alberto Carlos Clemente Frasch was born on January 26, 1949, in Buenos Aires, Argentina, into a family where dentistry was part of daily life. He was the eldest son of Emilio Frasch, a professor of dentistry at the University of Buenos Aires, and Norma Borghello, a talented artist. His younger brother, Eduardo, also became a dentist. As a child and teenager, Carlos practiced judo and developed a passion for philately. Over time, he built a remarkable stamp collection, one he would later sell to help purchase an apartment with his wife after they married. His upbringing was shaped by his father's home-based dental practice and his mother's creative world of paintings and ceramic sculptures, works that Carlos deeply admired and kept with him throughout his life, both in his home and in his heart.

He began his studies at the dental school at the University of Buenos Aires where he earned his degree in 1971. He was awarded a gold medal for achieving the highest academic qualifications in his class at the end of the course. He then transferred to medical school and completed the first three years, dedicated to basic medical sciences. Following this period Frasch collaborated with María E. Itoiz at the dentistry school and Rómulo L. Cabrini at the National Atomic Energy Commission in Buenos Aires. Together, they conducted

micro spectrophotometric studies on epithelial cells to localize enzymes and assess the effects of radiation. This research resulted in eight published journal articles and would earn Frasch a Ph.D. in Dentistry in 1977. As he advanced through his academic journey, Carlos realized that neither dentistry nor medicine was his true calling and found himself increasingly drawn to science and research. His turning point came through a conversation with a biochemistry professor at the medical school, where Carlos was working as a teaching assistant. The professor asked if he truly wanted to be a good scientist. When Carlos replied yes, the professor challenged him: why not leave medicine behind and devote himself fully to scientific discovery?

## Shifting Career Paths

His growing interest in biochemistry led him to pursue postdoctoral research under the guidance of Andrés O. M. Stoppani, director of the Department of Chemical Biology at the University of Buenos Aires's Medical School. Stoppani, a former disciple of Bernardo Houssay—who won the 1947 Nobel Prize in Physiology or Medicine for his research on the pituitary gland's role in blood sugar regulation—led one of Argentina's most prestigious biochemistry research groups. Additionally, Stoppani had supervised the Ph.D. thesis of Cesar Milstein, who later won the 1984 Nobel Prize in Physiology or Medicine for his discovery of monoclonal antibodies. Frasch joined Juan José Cazzulo's laboratory, which was focused on studying *Trypanosoma cruzi* within Stoppani's department. There, he began research on trypanosomes—a subject he would continue to explore for more than forty years. His initial studies characterized the enzymatic activity of various ATPases, including the solubilized F1 segment of the *T. cruzi* ATP synthase. These findings demonstrated similarities to mammalian mitochondrial ATP synthases, revealing the evolutionary conservation of this enzyme in early diverging eukaryotes.

In 1977, Carlos married Graciela Colombo, the woman who would become his lifelong partner. They met through mutual acquaintances from dental school after both had graduated. Together, they built a family and raised two children, Federico and Carolina. Despite his deep dedication to science, Carlos was always present at home. He never missed a school event and took part in the day-to-day life of his family with enthusiasm and care. Carlos encouraged his children to choose their own paths, always supporting them with quiet strength, tailored guidance, and unconditional love. In 2018, he became a proud grandfather with the birth of his grandson, Valentino—a role he embraced with the same warmth and dedication that defined his entire life.

By early 1978, Cazzulo had the opportunity to visit several laboratories in Europe and the United States that specialized in trypanosome research. Aware of this, Frasch asked him to identify a suitable lab where he could further his postdoctoral training. Cazzulo was particularly impressed by the work of Piet Borst at the University of Amsterdam, who had recently discovered the glycosomes in African trypanosomes. Despite initial doubts, Borst was impressed by Frasch's strong training and research potential and successfully secured a position for him at the university. This decision proved fruitful, and within just a year and a half Frasch published eight journal articles between 1980 and 1982 on key findings related to antigenic variation and mitochondrial DNA in trypanosomatids.

At the time, Borst was investigating antigenic variation—a survival mechanism in African trypanosomes by which they change their surface coat to evade host antibodies. Working alongside George A. M. Cross from the University of Cambridge in the United Kingdom, Borst and his team sought to uncover the molecular mechanism behind this process. Cross had identified previously that the coat was composed of a single protein called variant surface glycoprotein (VSG). Frasch played a crucial role in this research, helping to provide the first evidence that VSG gene activation involves the production of an expression-linked copy of the gene. This groundbreaking period in Amsterdam was pivotal for Frasch's scientific career, establishing him as an expert in molecular biology and laying the foundation for the development of this field in Argentina.

## Return to Argentina

Frasch returned to Argentina to work in Stoppani's department, where he supervised graduate students and continued research on *T. cruzi* mitochondrial DNA (minicircles) and the effects of trypanocidal drugs. In 1984, he moved to the Campomar Foundation in Buenos Aires, Argentina's most prestigious research institution at the time; it was led by Luis F. Leloir, who had won the 1970 Nobel Prize in Chemistry for his work on the discovery of sugar nucleotides and their role in the synthesis of polysaccharides. There, Frasch established an independent research group focused on the molecular biology of *T. cruzi* and made several significant breakthroughs. In 1995, Frasch relocated to the National University of San Martin (UNSAM), where he partnered with Rodolfo Ugalde and Juan J. Cazzulo to establish the Institute of Biotechnological Research and the Licenciatura en Biotecnología. The institute was literally designed and built under his supervision, enabling UNSAM to lead in the field of genetics, molecular biology, and biotechnology. He served as its director until his retirement.

Carlos's seminal discoveries on the repetitive structure of the main parasite antigens led to improvements in the diagnosis of Chagas disease and provided a rationale for further applications on vaccine development. Of particular relevance

was the molecular definition of the mucins: heavily glycosylated proteins that cover the parasite surface and serve as shield against the immune system. This advance, together with the cloning and expression of the *trans*-sialidase (an enzyme that sialylates mucins allowing the parasite interaction with the host cell), uncovered central events in the pathogenesis of Chagas disease. Carlos's expert scientific vision led him to suggest that at least one of those repetitive antigens probably was shed into the milieu. The analysis led to the definition of the shed acute phase antigen (SAPA), an antigenic repetitive extension that allows the *trans*-sialidase to remain in the bloodstream, where it induces several modifications in the immune system. It also led to improvements in the early diagnosis of congenital Chagas disease. Frasch's involvement in Chagas disease research led him to form excellent relationships with Brazilian colleagues through participation in the annual meetings on basic research in Chagas diseases held in Caxambu in the Minas Gerais state. One result was a 1989 publication coauthored by two of the authors of this memoir. Electron microscopy immunocytochemistry allowed the localization of some high molecular weight proteins in specific regions of the parasite. For instance, in 1989 researchers in Álvaro Souto-Padron's laboratory observed intense labeling of the trypomastigote surface and the flagellar pocket with antibodies recognizing the SAPA antigen. Frasch was invited several times by Brazilian agencies to analyze scientific projects to be funded.

Frasch's efforts to understand the organization of the *T. cruzi* genome led him to participate in its sequencing project, providing important insights into the parasite's genetic composition. This work resulted in the publication of the first draft of the *T. cruzi* genome, which was featured on the cover of *Science* in 2005. During these years, Carlos focused on post-transcriptional gene regulation, emphasizing RNA-binding proteins and the role of 3' untranslated regions in controlling gene expression. He identified key RNA-binding proteins, such as TcUBP-1, which influence mRNA stability and translation throughout the parasite's life cycle. By examining RNA-protein interactions and their role in gene expression, he offered new insights into the regulatory pathways of *T. cruzi* biology. His publications up to 2018 advanced understanding of RNA regulons and gene regulatory networks in trypanosome molecular biology.

In his later years as a researcher, Frasch's interest expanded to the neural bases of depression and the effect of stress on the nervous system. More specifically, he focused on alternatives for diagnosing mental disorders based on molecular biology tools. Early in 2000, he and his team explored differences in brain gene expression between control and chronically stressed animals. These initial studies led to the identification of a putative candidate, the neuronal protein M6a. Subsequent studies showed that M6a is a stress-sensitive protein and depicted M6a cellular functions in neurons. Later, he reported the presence of M6a in blood and in human saliva, and this positioned M6a as an interesting candidate for diagnosis. Over twenty years, his research traveled from studies in animal brains to seminal studies aimed at identifying stressed and depressed humans from a saliva sample. His work was pioneering in molecular studies in brain gene expression and in the study of extracellular vesicles in body fluids as a source of biomarkers for mental diseases. Carlos's neuroscience adventure was guided by his knowledge of molecular biology, his innovative spirit, and above all, his background in another area of biology, which gave a different perspective to his research. His neuroscience research led to the publication of twenty-one articles and one review authored by himself and nearly a dozen by his disciples. Worth mentioning, most researchers that worked on the neuroscience research line led by Carlos were women. Carlos was very respectful of their decisions, especially those related to motherhood. Currently, three of those women lead research groups at the institute he founded.

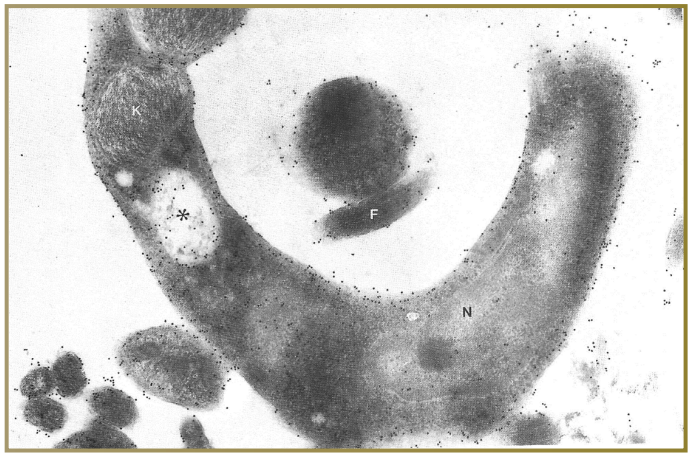


Figure 2 Transmission electron microscopy of a thin section of an infective trypomastigote stage of *Trypanosoma cruzi* incubated in the presence of antibodies that recognize the SAPA protein that is revealed using gold nanoparticles conjugated to secondary antibodies. The gold particles are seen on the parasite surface and in the flagellar pocket (asterisk). After Souto Padron et al. *Eur. J. Cell Biol*. 50:272-278 (1989).

## Awards and Honors

Frasch received many awards and honors throughout his career, including a Guggenheim Foundation fellowship (2001), the Konex Award (2003) from Argentina's Konex Foundation, and the Bernardo Houssay Award (2015). He was an adviser to the World Health Organization (1983–2010) and was named a Foreign Associate of the U.S. National Academy of Sciences (2006) and International Research Scholar of the Howard Hughes Medical Institute (1997–2011).

## Final Thoughts

Carlos led by example: always close, always listening, always inspiring. Regardless of how busy he was, his door was always open. He believed in others, often more than they believed in themselves. He was a doer and a dreamer, a mentor and a leader who lit the way for others with quiet determination and deep care.

Carlos remains a model of perseverance, kindness, and leadership—a tireless scientist, an inspiring mentor, and above all, a profoundly generous soul. Carlos passed away on December 29, 2023, in Buenos Aires, surrounded by his wife and children.

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