Silvia Pierangeli was one of the most respected, prolific and well-liked investigators in the field of antiphospholipid antibody (aPL)/antiphospholipid syndrome (APS) research. In the course of a 25-year academic career, she combined passion for her work, talent, prodigious energy, an ability to pursue several tasks at once, a winning personality, an abiding spirit of generosity, and a strong association with colleagues across the globe.

Born in Buenos Aires, Argentina, to Dr. Hector and Mrs. Suzanna Pierangeli, who were themselves of scientific background and owned and operated a diagnostic laboratory in Buenos Aires, Silvia was educated at Buenos Aires National University where she received a PhD degree in Biochemistry. After working in her parents’ laboratory for a few years, she went on to start one of her own. In 1986, she was awarded a Fulbright Scholarship and moved from Argentina with her husband and two young children to the University of Louisville in Louisville, Kentucky, where she received her second PhD degree in Microbiology and Immunology.

Dr. Pierangeli joined me (E.N.H.) as a postdoctoral fellow in 1987 to start what we named the Antiphospholipid Standardization Laboratory. As that name suggests, our major interest at the time was in popularizing and advocating a standard method for performance of the anticardiolipin antibody (aCL) test and investigation of the specificity of aCL antibodies and the lupus anticoagulant, with particular interest in the differential specificity of aCL antibodies produced in APS versus infectious diseases. By the mid-1990s, interest expanded to the mouse model of thrombosis and exploration of the pathogenesis of aPLs in APS using this in vivo model. By the first decade of the 21st century, Dr. Pierangeli’s interests grew exponentially in using in vivo and in vitro strategies to probe cellular and intracellular effects of aPLs as well as studies of biological agents that might ameliorate the clinical complications of APS. Her contributions fall into four major categories (1) standardization of aCL and anti-β2-glycoprotein I (anti-β2GPI) tests; (2) using mouse models of thrombosis and fetal loss to study the pathogenic effects of aPLs and mechanisms by which these antibodies might be induced; (3) investigation of agents that ameliorate the effects of these antibodies so offering possible treatment options; and (4) development of a unique assay that distinguishes aPL in APS versus those produced in other disorders.

Dr. Pierangeli’s work on standardization of the aCL and more recently, the anti-β2GPI test extended over 25 years. Recognizing the significant variability in performance of the tests and test results, she embarked on a tireless effort to promote standard test performance through multiple publications, workshops, membership in International Committees interested in standardization efforts, and making herself available to provide advice to countless laboratories and groups worldwide. Her efforts culminated in the assembly of experts 2 years ago to reach consensus on performance of the aCL and anti-β2GPI assays, which was published recently.1 In addition, she was made chairman of the Clinical and Laboratory Standards Institute (CLSI) Document Development Committee on Antiphospholipid Antibodies, which is engaged in formalizing standard methods for the aCL and anti-β2GPI enzyme-linked immunosorbent assays (ELISA).

Focusing on the anti-β2GPI test, Dr. Pierangeli assembled another group of experts to prepare reference calibrators for the assay (using an approach similar to that used in 1986 to prepare aCL calibrators) and to develop units of measurement for levels of anti-β2GPI antibodies, which are expected to be adopted universally. Of special note for this journal were several contributions in specially aPL/APS themed issues in both 2012 and 2008.2–6

Dr. Pierangeli’s second area of work involved mouse models of thrombosis and fetal loss. The model entails the use of anesthetized mice whose femoral veins can be isolated and a thrombus induced by a standardized pinch injury, the vein is transilluminated and thrombus image projected on to a screen enabling the dynamics of thrombus formation and

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Silvia Pierangeli, PhD (1955–2013)

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disappearance to be quantified. Dr. Pierangeli and colleagues embarked on numerous studies using this model in an effort to probe thrombosis pathogenesis in APS.\textsuperscript{7} Some earlier findings were that mice passively infused with human immunoglobulin G (IgG), immunoglobulin M, or immunoglobulin A aPLs were subject to enhanced thrombus size and duration.\textsuperscript{8} Likewise aPL antibodies induced in mice by immunization with β2GPI, human IgG aPL or viral peptides (homologous with select β2GPI regions) resulted also in enhanced thrombus size.\textsuperscript{9–11} Probing the mechanism of aPL-induced thrombosis, she along with her colleagues demonstrated in vivo activation of endothelial cells by aPL, and utilizing knockout mice, they showed that expression of endothelial cell markers intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion protein 1 (V-CAM 1) were required for thrombosis.\textsuperscript{12,13} More recently, she along with her colleagues showed the importance of tissue factor (TF).\textsuperscript{14} ApoER2\textsuperscript{15} (a splice variant of apolipoprotein endothelial receptor 2), annexin A1\textsuperscript{16} C5aR\textsuperscript{17} (complement 5a receptor), and C6\textsuperscript{18} (suggesting the membrane attack complex) in the pathophysiology of thrombosis in APS. These in vivo studies were accompanied by other in vitro work examining the intracellular molecular mechanism of aPL-induced endothelial and platelet activation.

Dr. Pierangeli also investigated how aPL antibodies might be induced in mice. In addition to earlier studies showing that human anti- β2GPI, human IgG aPL, and viral-derived peptides could induce aPL, she examined the role of major histocompatibility complex II (MHC II), different MHC II and Toll-like receptors in aPL formation. In addition, using TLR knockouts, Pierangeli and colleagues demonstrated the essential role of TLR7 and TLR 9.\textsuperscript{19,20} APL-induced thrombosis led to the discovery that TLR7 and TLR 9 are essential for aPL pathogenic properties.

Turning her attention to agents that would ameliorate the clinical complications of APS, Pierangeli demonstrated that hydroxychloroquine and fluvastatin decreased the thrombogenic effects of aPL in mice. In addition, she examined the ameliorative effects of the peptides—TIF,\textsuperscript{21} Domain L\textsuperscript{22} anti-NFκb specific inhibitor,\textsuperscript{23} anti-C5MoAb,\textsuperscript{24} C5aR antagonist peptides,\textsuperscript{25} and coversin (REV 576),\textsuperscript{26} a novel C5 inhibitor. Her interest in these agents to “treat” aPL-induced thrombosis led to her becoming a major participant in the APS-ACTION group led by Dr. Doruk Erkan, which has gathered clinical and laboratory investigators from across the world to conduct clinical trials on patients with APS.

On the basis of a demonstration that aCL antibodies in patients with APS and infectious disease have different binding properties, Dr. Pierangeli and colleagues developed and marketed the APhL ELISA test, which appears to be as sensitive as the aCL test for APS but more specific. For several years up to the time of her demise, she advocated replacement of the aCL test by this assay.

Dr. Pierangeli published more than 200 peer-review articles, reviews, chapters, and editorials. The crowning moment of her professional career was in 2010 when she organized the highly successful 13th International Congress on Antiphospholipid Antibodies, Galveston, Texas. This event attracted hundreds of participants from around the world and resulted in several significant publications, including a comprehensive collection of articles from the conference in a book entitled Antiphospholipid Syndrome: Insights and Highlights from the 13th International Congress on Antiphospholipid Antibodies, coedited with Dr. Doruk Erkan.\textsuperscript{27}

While her investigative work was exceptional, people will remember her just as well for her winning personality. She was gregarious, caring, generous, and unafraid of challenges that might have presented. She mentored dozens of fellows, residents, and students; she was a member of several committees (including NIH Study Sections) and on many editorial boards of peer-review journals. She was a wonderful mother to her daughters Cecilia and Eugenia and shared many treasured moments with her husband, Álvaro Schlehe. Her goodwill and tremendous contributions to her field will undoubtedly inspire generations of young investigators to emulate her life.

\textbf{References}

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