Dr. Sonia Skarlatos—Leader, Colleague, and Friend: From Vascular Biology to Gene Therapy and the Cardiovascular Cell Therapy Research Network

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Nothing is so strong as gentleness, nothing so gentle as real strength.
—St. Francis De Sales

Prologue

IT IS INDEED A DAUNTING TASK to write a memorial essay, to be able to relate to others the essence of a life with great impact. I write in remembrance of Sonia Skarlatos, PhD, who died after a short and valiant fight with cancer, following a life lived as a unique leader in a long and ongoing fight against cardiovascular disease.

I write both as a member of the Cardiovascular Cell Therapy Research network, which Sonia pioneered, and also as an individual scientist who has shared with Sonia a parallel evolution of professional interests. Perhaps the best light I can shine on her professional and personal excellence is through my own stories about Sonia and our interactions over the past 20 years. I hope and believe that these anecdotes will evoke special memories and will resonate with many scientists and colleagues of Dr. Skarlatos. I am sure that each will have their own memory of her distinctive warmth and thoughtfulness. She artfully mixed these traits with her deep scientific understanding and profound desire to help advance our present knowledge of science into a future realization of clinical improvements.

Here to Help: Vascular Biology

"The NIH Program Officers are here to assist you and other investigators," Sonia said, continuing, "Do you understand the difference between the Program and the Center for Scientific Review?" This began what was perhaps the earliest conversation I had with Dr. Skarlatos. The year was 1994, and I had recently submitted my first NIH R01 proposal. At a national vascular biology meeting, Dr. David Robinson, Sonia's then boss and leader of the Vascular Research Program, had taken an interest in my laboratory's work. Dr. Robinson and I discussed how much there was to be learned about smooth muscle differentiation and how important that topic was to a variety of medical problems. David then followed up by introducing me to Sonia, who

was his protégé. During the next year or two, I found myself at multiple scientific meetings and eventually involved in review panels with Sonia, who was always interested in chatting with the investigators and hearing about the latest advances. During our first several meetings, I would ask her about how this or that aspect of NIH worked and gradually came to understand the overall structure better. She also made it clear to me that the NIH program officers would welcome visits to their offices, and so I made it a point to visit NIH on occasions when I was in Washington. What initially seemed an inscrutable structure became more and more understandable.

Vascular Biology and Gene Therapy, Too

During those early visits in 1994–1995, I shared with Sonia my great interest in advancing therapeutic gene approaches into the context of the vascular system. I was fascinated by the theory that dysregulation of growth factors and oncogenes played a role in the development of atherosclerosis and restenosis and wanted to employ local delivery of viral vectors both to test this concept as well as to attempt to modify the courses of these diseases, at least at a specific location. It turned out that Sonia was also very intrigued by gene therapy in general and by its possibilities in vascular applications in particular. This shared interest sparked many discussions. In 1996, based on early work and collaborations characterizing gene transfer kinetics as related to and modified by the dynamics of the vascular system (March et al., 1995; Mittereder et al., 1996), I was offered an opportunity to assemble and edit what was to be the first book on cardiovascular gene therapy (March, 1997). The task of organizing material in this rapidly advancing field led me to seek Sonia's advice on the structure of the book. I was delighted to find that she was always willing to help and modeled kind, insightful, and collegial interactions.

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During the next several years, I was called upon to serve the NIH on numerous study sections, including those reviewing program projects, the “parent committee,” so-called special emphasis panels, and Small Business Innovative Research (SBIR) groups. Like many other investigators called upon to be reviewers, I shared the privilege of reviewing much superb science in the areas of cardiovascular biology and gene therapy. These review opportunities were both challenging and rewarding and were provided by Sonia and her team, who recommended a cadre of scientists interested in and excited by these fields. The relationships of Sonia and her colleagues with many leading scientists in the field were foundational to the review and development of programs that fostered a complementary mix of basic work along with a prescient emphasis on the importance of identifying grants with translational relevance.

Dr. Skarlatos was also interested in ways that local delivery might be significant for practical aspects of gene therapy and for other treatments in the cardiovascular system. We continued to discuss the direction of the field in this arena, and I came to recognize her depth of understanding and her desire to be a lifelong learner, always ready to consider new advances and positioned to advocate for them. This advocacy was particularly manifested as she developed several programs within NHLBI focused on gene therapy, which were further fostered by the 2005 appointment of Dr. Elizabeth Nabel, one of the early cardiovascular gene therapy explorers, as NHLBI director.

Cell Therapy in the Cardiovascular System: A National Network is Born

Following early descriptions of circulating cells with a selection of proangiogenic characteristics (e.g., Asahara, 1997), several leading cardiovascular colleagues and groups around the world vigorously proposed and expanded exploration of the young field of cardiovascular cell-based treatments. Within the NIH, Dr. Skarlatos tracked these developments attentively and began to work toward the realization of a set of programs to facilitate these early explorations with an eye toward eventual translation into clinical trials. Her efforts informed a series of strategic meetings, which started in 2005, and created a recommendation for a national clinical trial network focused on development and evaluation of cardiovascular cell therapy. This was ultimately to become the Cardiovascular Cell Therapy Research Network (CCTRN) (Simari et al., 2009), led by Sonia as its program officer. Numerous reviewers were brought together in 2006 to evaluate dozens of grant proposals from institutions eager to bring ideas for cell-based trials forward. After this process, I received an unexpected call from Sonia, asking me to chair the cell therapy component of the Cell and Gene Therapy Data Safety and Monitoring board for the newly created CCTRN group. Upon agreeing to this commitment, I had the privilege once again to witness the adept and thoughtful manner in which Sonia and her network of colleagues led the early national forays into trials addressing cardiovascular therapeutics from a cellular perspective.

In 2009, Dr. Skarlatos was appointed to the position of deputy director of the Division of Cardiovascular Sciences at NHLBI, her position at the National Institutes of Health

prior to her unexpected illness and death in August 2013. She had successfully ushered many investigations and investigators through interlinked programs of excellence in cardiovascular biology and the emerging translational fields of gene therapy and cell therapy. Many of these programs (CCTRN, PACT, SMARTT) and others, as described in more detail in this issue (see McDonald, 2013, pages 899–905), are vibrant and ongoing, in the prime of their life, just as Sonia had been.

Indeed, her final major program, the renewed and expanded Cardiovascular Cell Therapy Research Network (CCTRN-II) commenced operations in 2012. Sonia’s tireless leadership on behalf of the network is eloquently recognized in a memorial focused on her efforts to form and advance it (CCTRN, 2013). The efforts of the CCTRN investigator group will continue to develop programs and multiple clinical trials in the burgeoning area of cardiovascular cell therapy, which promise to bear the translational fruit for which these investigators and their NIH colleagues, including Sonia, have hoped.

Gentle Guidance, Cautious Optimism

While Sonia and many investigators have been optimistic and have held high hopes for these new fields and the possibility that they would lead ultimately to new therapies for diseases with limited treatment options, Sonia has also shown a consistent understanding that the investigations of the last decade or so in cell and gene therapy were among the first of their kind, and that the development timeline for these gene and cell therapies would be lengthy, perhaps decades long. In fact, she projected the critical awareness that there was much indeed to be learned; that these first efforts should be viewed as creating initial foundations upon which programs of the future would be built; and that negative outcomes were not to be rejected but to be expected and used as platforms to design the next basic and clinical studies.

Many of the world’s leading programs in vascular biology, gene therapy, and cell therapy continue on as a testimony to Sonia, her patient efforts, and the vision she collegially helped so many to develop. The investigative teams critical to these efforts, including the national group of dozens of investigators, coinvestigators, coordinators, and staff are committed to working all the more diligently *in memoriam* of Sonia Skarlatos, PhD.

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