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OBITUARY

Guido Tarone, Ph.D. (1951–2015)

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Guido Tarone's premature death on 17 May has shocked and saddened not only his many immediate friends and colleagues, but also the European cell biology community and investigators working on cell adhesion across continents. Guido made important contributions to our understanding of the molecular basis of cell adhesion but also profoundly influenced the development of this field through his generosity and collegiality.

Guido acquired his expertise in immunochemistry and membrane biology during his postdoctoral training with Vincent Marchesi at Yale. After returning to Torino in 1978, he established his own laboratory in the Institute of Anatomy and Histology of the University of Torino, where Salvador Luria, Renato Dulbecco and Rita Levi-Montalcini had developed their passion for cell and tissue biology before World War II in the lab of the great Italian anatomist Giuseppe Levi. In this environment, Guido became fascinated with the emerging field of matrix adhesion and decided to work towards the identification of the fibronectin receptor. In an elegant series of experiments, his newly established laboratory provided evidence that the fibronectin receptor is a membrane glycoprotein resistant to trypsin cleavage. Guido and colleagues then developed adhesion-blocking antibodies and identified as their primary target on trypsin-treated mouse fibroblasts an αβ dimer with a molecular mass and SDS-PAGE migration properties that are typical of an integrin dimer. During a brief sabbatical in Clayton Buck's laboratory at the Wistar Institute in 1983, Guido and Caroline Damsky obtained evidence that the adhesion-blocking monoclonal antibody CSAT, which had been developed by Rick Horwitz, recognized a group of proteins on chick cells, including the αβ dimer that Guido's laboratory had identified on mouse cells. Returning to Torino and now working with Filippo Giancotti – then a junior graduate student – Guido provided evidence that the mouse β component was cleaved by trypsin in the presence of mild reducing agents, and this correlated with loss of adhesion to fibronectin. Moreover, affinity-purified antibodies against this component blocked cell adhesion to fibronectin and stained focal contacts in adherent cells.

In parallel and pioneering work, Erkki Ruoslahti's group had identified the cell attachment site in fibronectin and, in work published in 1985, they had used synthetic peptides comprising its core determinant, the RGD sequence, to competitively elute a similar αβ dimer from a fibronectin column loaded with a human placenta extract. Liposome reconstitution experiments demonstrated that this dimer was sufficient to mediate attachment to fibronectin, thereby providing definitive evidence that it comprised the fibronectin receptor. These were exciting times. By the following year, Erkki and colleagues had identified additional RGD-dependent and -independent heterodimeric matrix receptors, and several labs – including those of Mark Ginsberg, Martin Hemler,

Tim Springer and Michael Wilcox – had provided evidence that identical and similar heterodimers were expressed in multiple mammalian cell types, including leukocytes and platelets, as well as in *Drosophila*, where they participated in a variety of adhesive interactions. Richard Hynes' laboratory exploited the newly established λGT11 method to clone the β subunit of the CSAT antigen, which they aptly named integrin from its ability to link (integrate) fibronectin to the intracellular cytoskeleton. Shortly thereafter, Erkki's laboratory sequenced the fibronectin receptor α chain. Additional molecular characterization studies by several groups confirmed the relationship between the multiple αβ dimers, marking the official birth of the integrin field. The original, high-affinity and fibronectin-specific receptor became – perhaps inconspicuously – known as the α5β1 integrin. By then, the field had grown to include many prominent and large laboratories that had come to realize that they were also working on integrins. Remarkably, during this pivotal time, Guido's laboratory also made several additional and important contributions to the cell adhesion field. He and colleagues identified CD44 as a cytoskeleton-associated glycoprotein that is able to bind to hyaluronic acid. Furthermore, they discovered that Rous-sarcoma-virus-transformed fibroblasts form peculiar feet-like matrix-interaction contacts, which they named podosomes. Wen-Tien Chen and colleagues later located the matrix metalloproteases MMP1 and MMP2 to these structures, and named them invadopodia. These protrusions have a prominent role in tumor invasions and are still alternatively referred to as podosomes or invadopodia.

In 1987, Guido moved his laboratory from the Institute of Anatomy and Histology to the Department of Genetics, Biology and Biochemistry. In the ensuing two decades, he remained an important contributor to the integrin field. His laboratory elucidated mechanisms of signal transduction and of cooperation with growth factor receptors, identified and studied new splice variants of the β1 subunit, and studied integrin function in angiogenesis, neural differentiation and neoplastic transformation. Guido's work was always characterized by a high

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degree of rigor, inspired by his strong sense of right and wrong. For example, although he had contributed to the identification of the integrin β1B variant, he quickly realized that it lacked physiological significance and proposed that it be used as a tool for dominant-negative inhibition of integrin function. More importantly, Guido worked tirelessly to further the independence of talented junior investigators he had recruited to the newly established Molecular Biotechnology Center of the University of Torino, including amongst others Paola Defilippi, Emilio Hirsch and Mara Brancaccio. Guido was so disinterested in self-promotion that he would not accept to serve as last author on several papers, although he had inspired or – in large part – designed the experiments that were being reported. During meetings, his comments were often the most insightful, yet he never came across as arrogant. His humility and generosity were genuine and there was no second motive. In a striking example, while on sabbatical in Erkki Ruoslahti's laboratory in 1989, he discovered the αvβ1 integrin and worked with Bruce Vogel to characterize its biochemical properties. Yet, he did not want to be the first author on the paper reporting the findings. Guido clearly derived more satisfaction from seeing his collaborators shine than from being recognized as a leader in the field. Yet, he clearly was one, and from the start.

Guido was a main driving force for the creation of the Molecular Biotechnology Center of the University of Torino, which opened its doors in 2006 and now hosts several vibrant laboratories working in the area of molecular and cellular biology. At the Center, he worked tirelessly to create an open environment where junior investigators could thrive. He organized and inspired seminars, symposia and collaborative grants that helped to put the Center on the map of the European science. More recently, Guido's interest was piqued by cardiac hypertrophy. He and his colleagues identified the scaffold protein melusin as a muscle-cell-specific interactor of the integrin β1 subunit, and demonstrated that it facilitates ERK activation in response to integrin-dependent mechanotransduction. Guido was now exploring ways to interfere with melusin's function to ameliorate cardiac hyperthrophy. In 2012, he was appointed Director of the Department of Molecular Biotechnology and Health Sciences and elected to the Senate of the University of Torino. To these jobs, he was bringing passion and continuing dedication to the future of young scientists.

Guido loved biking, skiing, and good food and wine. To many, it is difficult to accept that Guido had a fatal accident while indulging his passion, biking through the Baldissero woods near Torino. He leaves his wife Fiorella Altruda, a companion in work and life for 45 years, and his 30-year-old son Enrico. With them, we mourn the passing of an esteemed and extraordinarily generous colleague and friend.