

## Thomas Maciag: *In praise of an open mind*

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### Obituary

In my office, I have a painting. It depicts a waterway in Venice that is flanked by a row of eight buildings that recede diagonally from the foreground on the right to the background on the left. In the middle distance, a lone boatman plies his way inward along the canal. Blue- or red-and-white barber pole moorings demarcate the water's edge. Each edifice rising from the water is architecturally detailed, with its own unique collection of pitched roofs, porticos, balustrades, niches, and statuettes. Rows of doors, windows, and balconies punctuate each façade. The colors are bold — a saturated reddish-brown invests each structure, setting it apart from the sky's ethereal blue and the water's murky gray. There is a strong sense of perspective in this picture, but the eye is drawn to a vanishing point that lies not within the watercolor image itself but off to the left, beyond the confines of the frame. The artist was Tom Maciag, who died on March 8, 2004. Tom was born November 19, 1946 in Bayonne, New Jersey. He served in the US Army Medical Corps (1969–1971) and then received a Ph.D. in Molecular Biology and Biochemistry from the University of Pennsylvania (1975). After a year of postdoctoral work at Penn, he became a senior research investigator at Collaborative Research Inc. in Waltham, [...]

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## Thomas Maciag

### *In praise of an open mind*

In my office, I have a painting. It depicts a waterway in Venice that is flanked by a row of eight buildings that recede diagonally from the foreground on the right to the background on the left. In the middle distance, a lone boatman plies his way inward along the canal. Blue- or red-and-white barber pole moorings demarcate the water's edge. Each edifice rising from the water is architecturally detailed, with its own unique collection of pitched roofs, porticos, balustrades, niches, and statuettes. Rows of doors, windows, and balconies punctuate each façade. The colors are bold — a saturated reddish-brown invests each structure, setting it apart from the sky's ethereal blue and the water's murky gray. There is a strong sense of perspective in this picture, but the eye is drawn to a vanishing point that lies not within the watercolor image itself but off to the left, beyond the confines of the frame. The artist was Tom Maciag, who died on March 8, 2004.

Tom was born November 19, 1946 in Bayonne, New Jersey. He served in the US Army Medical Corps (1969–1971) and then received a Ph.D. in Molecular Biology and Biochemistry from the University of Pennsylvania (1975). After a year of postdoctoral work at Penn, he became a senior research investigator at Collaborative Research Inc. in Waltham, Massachusetts (1976–1979), and then a research fellow in Medicine (1979–1980) and assistant professor of Pathology at Harvard Medical School (1980–1983). He returned to the biotech arena as director of Cell Biology at the Revlon Biotechnology Research Center in Rockville, Maryland (1983–1986), which was acquired by Rorer Pharmaceuticals in 1985. He was invited to lead the Department of Molecular Biology at the Jerome H. Holland Laboratory for Biomedical Sciences at the American Red Cross in 1986, a post he held for the next 11 years. In 1997, he was recruited to establish the Center for Molecular Medicine at Maine Medical Center Research Institute, where he remained for the next seven years.

A gifted scientist, Tom contributed a remarkable series of new concepts to the field of developmental vascular biology. In 1979, he discovered an activity in

bovine hypothalamus that was mitogenic for human umbilical vein endothelial cells and distinct from the previously described bovine brain growth factor, later known as basic fibroblast growth factor (bFGF, FGF-2) (1). He was the first to demonstrate that “endothelial cell growth factor,” subsequently dubbed acidic FGF or FGF-1, supported the long-term propagation of human endothelial cells in culture, thus laying the groundwork for dozens of inves-



tigators who followed (2–4). He completed the biochemical characterization of FGF-1 (5–7), delineated its heparin-binding properties (8–10), pointed out its chemotactic characteristics (11), and identified its high affinity tyrosine kinase receptor (12, 13). His laboratory was instrumental in the cloning of the FGF-1 cDNA (14), and he was also first to demonstrate the ability of FGF-1 to support neoangiogenesis in vivo (15). These studies (16), carried out with Michael Stemerman, Robert Weinstein, Gayle Hoover, Robert Friesel, Wilson Burgess, and Todd Rosengart, prompted research that would reveal the crucial role of FGFs in angiogenesis, wound healing, and atherogenesis.

From this detailed framework of FGF biology, Tom began his most visionary set of experiments. In the 1990s, he and his group, including Anthony Jackson, Francesca Tarantini, Carla Mouta Carreira, Matteo Landriscina, Igor Prudovsky, Raffaella Soldi, Anna Mandinova, and Lazar Mandinov, reported that FGF-1, which lacks a classical signal sequence for secretion, was released from cultured cells in response to heat shock (17). He subsequently char-

acterized an FGF-1 “release complex” that requires cysteine-mediated FGF-1 homodimerization in response to copper oxidation (18–20), interaction with phosphatidyl serine (21), binding to the extravesicular domain of synaptotagmin-1 (22, 23), and association with S100A13, a member of the S100 family of calcium-regulated proteins (24–26). He developed an animal model to show the ability of an oral copper chelator to reduce neointimal thickening following aortic balloon injury in the rat (27), and he postulated a “molten globule” model of FGF-1 release whereby a polypeptide traverses the plasma membrane in a partially unfolded high energy conformation (28). These experiments suggested that cells can respond to metabolic stress by releasing bioactive mediators that may stimulate mitosis, recruit inflammatory cells, or reorganize the extracellular milieu.

Tom's work also defined the interrelationships among the inflammatory response, atherogenesis, and angiogenesis. With Timothy Hla, he showed that cyclooxygenase and endothelial differentiation gene (EGD-1) are immediate-early genes induced by interleukin-1 or phorbol ester in the endothelial cell (29–32). With Elizabeth and Gary Nabel, he showed that recombinant FGF-1 promotes intimal hyperplasia and angiogenesis in arteries in vivo (33). With Ann Zimrin, Radiana Trifonova, Deena Small, and Lucy Liaw, he showed that the notch-jagged signaling system inhibits FGF-1-dependent cellular transformation (34–37). These studies identified new scenarios for rational drug design.

In the end, Tom Maciag's creativity transcended his art and permeated his science. In both disciplines, he sought order in the midst of apparent chaos. He celebrated ideas — the new, the surprising, the iconoclastic. But, though he thought “outside the box,” he maintained a true perspective. In his life and work, Tom inspired us to look beyond the landscape of the familiar toward something more distant and unexplored. He will be greatly missed.

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