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IN MEMORIAM

In memoriam: Richard O. Hynes

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The passing of Richard Olding Hynes on January 6, 2026, from complications of cancer is a great loss to science and an even greater loss to his many friends, students, and colleagues. Richard was born in Nairobi, Kenya, where his biologist father and physics teacher mother had relocated for a research project. The family returned to Liverpool, UK, where he spent most of his childhood before attending Cambridge University for bachelor's and master's degrees in biochemistry. He earned his PhD with Paul Gross at MIT studying the developmental biology of sea urchins, then did postdoctoral research at the Imperial Cancer Research Fund in London (now part of the Crick Institute) before returning to MIT in 1973 as an assistant professor. He worked at MIT for the remainder of his career, serving at various times as chair of the Biology Department, director of the MIT Cancer Center, an investigator of the Howard Hughes Medical Institute, and as holder of the Daniel K. Ludwig Chair in Cancer Research. Richard retired in 2024 but continued as a professor emeritus until his death. Among his many honors are membership in the Royal Society, the National Academy of Sciences, the Canada Gairdner Award, the E.B. Wilson Medal from the American Society of Cell Biology, and the Lasker Award in Basic Medical Research.

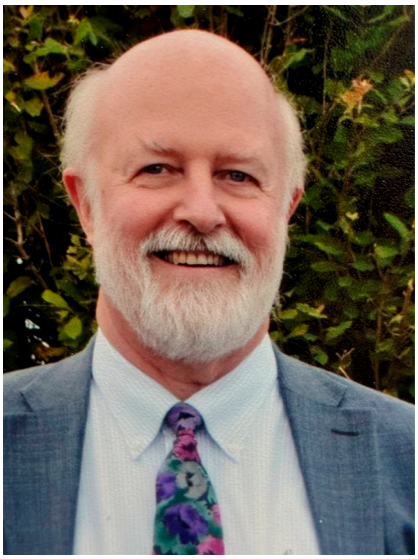

Photo courtesy of Fleur Hynes.

Richard's lifelong scientific journey began in earnest with a simple experiment carried out as a postdoc at the Imperial Cancer Research Fund: using a recently invented method to label cell surface proteins with radioactive iodine, he found that hamster fibroblasts had a ~225-kD protein on their outer surfaces that nearly vanished when these cells underwent oncogenic transformation (Hynes, 1973). He named it large external transformation sensitive or LETS protein, which was later renamed fibronectin. Similar findings using different methods were reported about the same time by Erkki Ruoslahti in Helsinki and Ken Yamada at the NIH (Ruoslahti et al., 1973; Yamada and Weston, 1974).

Following on from these observations, Richard's lab at MIT showed that adding purified protein back to transformed, cancerous cells shifted their cytoskeletal organization, shape, and adhesive properties toward those of normal cells, though it did not reverse their uncontrolled growth (Ali et al., 1977). Using another newly developed method, called immunofluorescence, they then found that LETS protein organized into fibrils on the cell surface, which co-aligned with actin filament bundles on the inside of the cell (Hynes and Destree, 1978). Further, these two filament systems were functionally connected, with the disruption of either one causing loss of the other (Hynes et al., 1978). These studies established the central concept that the extracellular matrix guides the organization of the cytoskeleton and cell functions, setting the stage for the next 50 years of research. Moreover, they illustrate Richard's general approach to discovery: exploiting newly developed methods, obtaining clear results, interpreting those results within the context of his encyclopedic knowledge, and identifying the critical next steps that moved the field forward.

The cloning and molecular characterization of fibronectin represent a case in point. Jean Schwarzbauer in the Hynes lab took advantage of local MIT expertise to set up a λgt11 rat hepatocyte cDNA expression library, which she then used to screen with anti-fibronectin antibodies. The resultant cloning of the fibronectin gene was not only a major achievement at the time

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but surprisingly revealed the expression of multiple fibronectin isoforms arising from a single gene, thus providing an early demonstration of regulated alternative splicing (Schwarzbauer et al., 1983).

Over the next few years, the Hynes lab made notable contributions to our understanding of wound healing and blood clotting, but the most important direction in the field was the identification of receptors for fibronectin and other matrix proteins. A number of groups had identified bands on SDS-PAGE gels for proteins that bound to ECM proteins and had begun raising antibodies and other reagents. Rick Horwitz's lab, in collaboration with Clayton Buck and Carolyn Damsky at The Wistar Institute, raised a monoclonal antibody that caused chick myoblasts and fibroblasts cultured on ECM-coated substrates to round up and detach (Neff et al., 1982). This antibody, which recognized a 120–140-kD complex of cell surface proteins, enabled John Tamkun to screen a λgt11 chick embryo cDNA library, resulting in the cloning of the β1 integrin subunit (Tamkun et al., 1986).

This finding opened the field to rapid consolidation. The chicken β1 gene was subsequently found to be homologous to several other adhesion receptors, forming a gene family with related functions, as described in Richard's remarkable synthesis of the available information at this stage, published as a review article in *Cell* (Hynes, 1987). This review was enormously influential, essentially announcing the arrival of the integrin field and the establishment of multiple subfamilies of integrin heterodimers.

Subsequent work revealed Richard's roots in developmental biology and interest in morphogenesis. He often noted that cancer represents aberrant development or the redeployment of normal developmental programs, reflecting his view that insights into disease must ultimately be grounded in understanding of normal functions. Thus, the next major direction in the lab used the newly developed gene knockout technology to delete fibronectin in mice. This experiment revealed profound defects in mesoderm formation, neural tube closure, and vascular development (George et al., 1993). Following on, the next target was the integrin α5 subunit of the main fibronectin receptor α5β1. Surprisingly, α5-deficient embryos survived longer and presented a distinct spectrum of defects, revealing that fibronectin functions in development could not be explained simply by a single receptor and instead reflected interactions with multiple integrins (George et al., 1993; Yang et al., 1999).

Additional integrin knockouts in mice and other systems reinforced this complexity. Integrin α5β1, a major fibronectin receptor, is highly expressed in the developing vasculature, yet its specific deletion in endothelial cells produced no overt phenotype (van der Flier et al., 2010). Knockouts of integrins αv, β3, and β5 did not produce the predicted defects in vascularization (Bader et al., 1998; Reynolds et al., 2020). Instead, a thorough analysis of KO mice revealed fascinating and complex roles in vertebrate biology and tumor angiogenesis (McCarty et al., 2002; Reynolds et al., 2004).

In subsequent years, Richard became increasingly fascinated by the evolutionary origins of ECM proteins. He addressed this problem using cutting-edge genomic analyses to identify and annotate ECM components across species, including systematic comparisons between normal and transformed cells (Naba et al., 2012; Whittaker et al., 2006; Whittaker and Hynes, 2002). Having characterized the ECM genes, the Hynes lab took the logical next step, harnessing the advances in mass spectrometric proteomic methods to characterize the ECM proteome, (Naba et al., 2012), again providing the ECM community with both a resource and insightful analysis that has been of value across a range of disciplines.

For Martin, "Working in Richard's lab was challenging but rewarding. Standards were uncompromising, but he offered his fullest support. It was done in a matter-of-fact way that did not draw attention, but Richard's generosity of spirit was unmistakable. Indeed, for many of us, Richard's support and calm advice remained part of our scientific lives. And if his lab was demanding, it also provided an incredible environment where we learned from one another and the surrounding labs."

For Sophie, "the most important advice Richard gave was when I was leaving to start my lab at Weill Cornell. He said that in grad school and postdoc training, there is a 50/50 male/female ratio, but when it comes to faculty, some women tend to drop out because they are less likely to tolerate academic nonsense. He meant this as a way to encourage me to persevere despite the challenges. He also offered advice when the tsunami of academic challenges hit, once even calling me from the airport while he was traveling, to offer words of support and advice on how to deal with things. He offered unwavering support for women in science, supporting female candidates when hiring faculty at MIT and supporting many of the women trained in his lab after they got their academic appointments. Maybe this is one reason why so many female scientists who came through Richard's lab are in academia."

For Doug, "Richard was not only a remarkable scientist but also a lasting role model. He brought to mentoring, teaching and service—the same gifts that distinguished his research: extraordinary breadth of knowledge, a rare ability to synthesize disparate observations, intellectual rigor, and a deep sense of responsibility to the scientific community. He was demanding, but always in the service of clarity and discovery. I vividly experienced these qualities after our paper reporting the first integrin sequence appeared (Tamkun et al., 1986). Richard urged me to attend an upcoming talk at the Dana Farber Cancer Institute by Tim Springer because he had already grasped, from his command of the emerging literature and the underlying biology, that the leukocyte adhesion proteins Springer was studying were likely related to our just-reported integrin story. For me, seeing appear on the screen what we now recognize as conserved cysteine repeat motifs of integrin β-subunits was both a moment of great excitement and relief and a lasting lesson in how Richard thought: boldly, creatively, and always a step ahead. Many of us have spent our careers trying to emulate what he modeled."

Richard taught that one should boldly formulate and test a hypothesis, but never be disappointed if it does not bear out. The key was to look at the data objectively, without discarding inconvenient points. Richard was a generous mentor who illuminated not only what was known but also the mysteries that remained to be solved. One enduring mystery he often

highlighted was the need to understand the roles of ECM proteins beyond their presumed function as mere mechanical support for tissues. While his work and ideas have shed considerable light on the functions of fibronectin and its receptors in development and tumorigenesis, many enigmas persist. For years to come, Richard's insights will continue to guide us, and the hypotheses he inspired will continue to drive the field forward.

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