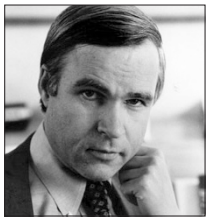

Lloyd John Old 1933–2011

Mark J Smyth

We mourn the passing of Lloyd Old, a visionary, a brilliant mind and the father of modern tumor immunology. He died of prostate cancer at his home in New York City on 28 November 2011, at the age of 78.

When Lloyd Old began his research career in 1958 at Memorial Sloan-Kettering, many of his pupils, like me, were yet to be born and tumor immunology was embryonic. With Baruj Benacerraf, he introduced Bacille Calmette-Guérin (BCG), the tuberculosis vaccine, as a way to stimulate nonspecific resistance to tumor growth. Their results, published in *Nature* in 1959, showed that BCG conferred protection against tumors in experimental mouse models. The paper was one of the first to use the phrase "tumor immunity" in the scientific literature, and today it is considered a classic article in the early history of cancer immunology. Today, BCG is widely used as a first-line treatment for superficial bladder cancer.

The immune system's role in cancer control, development and escape is now a fundamental modern hallmark of cancer, and cancer immunology and immunotherapy are practiced avidly. With hindsight, it can now be appreciated that nearly every major advance, scientist and research program in the field of tumor immunology worldwide can trace its lineage back to Lloyd Old—to his discoveries; his mentorship; the translational research infrastructure he built as director of the Ludwig Institute for Cancer Research (1988–2005); the grant programs he established through the Cancer Research Institute (serving 40 years as its founding Director, 1971–2011); the joint venture he orchestrated in 2001 between those organizations to establish the Cancer Vaccine Collaborative; and the many other ways he worked so tirelessly to raise the credibility and visibility of the field worldwide. His scientific discoveries are seminal contributions that can be assigned to every one of the past six decades. They have, and will continue to have, a lasting effect on the fields of immunology and hematology, autoimmune inflammation, and cancer.

Although he is internationally recognized as one of the major founders and drivers of the field of tumor immunology, his enormous contributions to the discipline of basic immunology should not be overlooked. Early in his career, he turned his attention to the search for tumor-specific antigens. His and Ted Boyse's discovery of the first cell surface antigens introduced the concept of cell-surface differentiation antigens that could be used to distinguish lineage and different functional subsets of leukocytes in mice. First they discovered TL (the thymus-leukemia antigen in mice), which represented the first link between the major histocompatibility complex and a disease state: mouse leukemia. That paved the way for the recognition of the importance of the major histocompatibility complex in the immune response. Later they identified the 'Ly' series. These discoveries led directly to the wide use of cell-surface markers to distinguish and classify normal and malignant cells and directly to the CD (cluster of differentiation) classification. This research laid the groundwork for the identification of the molecular markers on the surfaces of cells that allowed them to be experimentally and diagnostically separated and distinguished, which revolutionized immunology and medicine as it is practiced today.

His serological definition of antigens and establishment of the autologous typing system is legendary. These approaches led to the identification of the first known specific human tumor antigens recognized by antibodies and T cells and the most comprehensive analysis of the humoral immune response to human cancer, which defined the cancer 'immunome' and identified an array of new targets for human cancer vaccines. In addition, at least a dozen monoclonal antibodies developed in his laboratory have been licensed and a large number are in clinical trials—many at Ludwig Institute for Cancer Research sites, including sites in Australia, that he helped establish. More recently, he pioneered the identification and classification of the cancer-testis antigens, which are providing researchers with a unique group of molecules that can be selectively targeted on cancer cells and not healthy cells (except for those in the testis), with NY-ESO-1 being the contemporary prototype that he discovered with Yao-Tseng Chen in 1997.

Beyond immunology, it is essential to mention perhaps his best-recognized discovery, with Elizabeth Carswell, of tumor necrosis factor. This cytokine and its subsequently discovered larger superfamily are now known to be of critical importance in health and many autoimmune inflammatory diseases. Less well known is his coidentification of p53 and demonstration of its overexpression in human tumors. His many additional contributions are too numerous to mention, in over 700 papers published.

To me, his most endearing features were his passion and his kindness. He took genuine responsibility for his students and colleagues and always found time personally and professionally for those in need of help or advice. Regardless of his colleague's status in the field or distance from New York, he would go above and beyond the call of duty to make the effort to deliver or receive advice. His phone calls at any place and hour imaginable left an impression of omniscience, if not a sizeable phone bill. In 2000, with one simple meeting invitation, he single-handedly introduced me to the tumor-immunology community and fostered my long-term collaboration with Robert Schreiber. Lloyd Old had a depth and breadth of knowledge not only in science, but also in literature, philosophy and his first passion, music. Thus, he made a courteous and charismatic host at Cancer Research Institute meetings, charming those new to the field and welcoming them with one of his famous, well-informed and flattering introductions to the other gathered guests. He earned his status as 'father' as much through this kindness as by his scientific exploits. By bringing people together and inspiring the next generation he has been a remarkable scientific catalyst.

When I last spoke to him in September this year, I sensed that phone call might be our final talk. Right to the end he continued to exhibit the same passion and unbridled curiosity, fascinated in the latest data we shared, and despite his own predicament, enthusiastic for the future of cancer sufferers. His legacy of leadership lives on through the Cancer Research Institute and the work of thousands of scientists who have been gifted by his scholarship, generosity and support. I am proud and humble to have shared some of my life with Lloyd Old, my friend and mentor.

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