

## George Klein (1925–2016) A Prescient, Luminous Voice

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George Klein

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George Klein, and his wife, Eva Klein, made discoveries that were fundamental to cancer immunology and cancer biology. George passed away December 10, 2016, at the age of 91.

George and Eva Klein's 1960 article in *Cancer Research* (1) was something of a big bang, whose reverberations are still palpable, and arguably central, in this still rapidly expanding universe of cancer immunology. That article, along with the sense of its times, is best described in George Klein's own words from 2001 (2):

"All of us who . . . worked with inbred mice - still a minority around 1955 or thereabouts - became convinced that tumor immunology did not exist. The immune system regarded tumor cells as "self" in the primary host and there was nothing more to it."

Ludwik Gross had "performed some not too well controlled experiments suggesting that chemically induced mouse sarcomas could be immunogenic in syngeneic mice. Subsequently, Prehn and Main confirmed this in critically controlled experiments in 1957 and showed that methylcholanthrene-induced sarcomas, but not spontaneous mammary carcinomas, could induce relatively weak but regularly repeatable rejection reactions. Their data also indicated that the chemically induced tumors did not cross react with each other in rejection tests and that each tumor was thus individually distinct by the rejection criterion. . . ."

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"We were still die-hard skeptics at this time. We suspected - wrongly - that even the experiments of Prehn and Main may have been flawed. Obviously, the ultimate evidence had to be based on experiments with the primary, autochthonous tumor host. We did these rather laborious experiments and published them in 1960 in *Cancer Research*. Yes, it was all true."

The "it" that "was all true" consisted of two observations: that tumors could elicit protective immunity against themselves in syngeneic hosts, and that such immunity was specific to the individual tumor. These observations were extensively reproduced and critically dissected (see ref. 3 for a review). They were also the key ammunition of those who argued in the 1990s that, contrary to the enthusiasm of that time for the shared protective antigens of cancers, the protective antigens of human cancers were likely to be individually unique (4). The current excitement about neoepitopes (5, 6) is a direct descendant of that reasoning, whose origins go back all the way to Klein, as well as Richmond Prehn, who too passed away at the age of 93, a month before Klein.

Klein (with his then student Hans Olof Sjögren) also discovered the common transplantation antigens of the mouse polyoma virus (7). That work with viral antigens led George and Eva Klein to their interests in Burkitt lymphoma and their landmark observation connecting that lymphoma and nasopharyngeal carcinoma to Epstein-Barr virus (8). The activation of proto-oncogenes by chromosomal translocations was among his major discoveries (9). During 1975 to 1976, G. Klein and his then protégé Rolf Kiessling, along with Hans Wigzell, reported the discovery of the natural killer (NK) cells (10). Klaus Karre and Rolf Kiessling would later go on to formulate the "missing self" hypothesis to explain the mechanism of action of NK cells (11). The reach of George Klein's discoveries, and those of his trainees, is vast.

Descendant of a Hungarian Jewish family and a survivor of the Holocaust, George Klein was endowed with rare personal and intellectual courage and, therefore, originality. The tales

of his discoveries are a lasting testament to that originality. In addition to his prolific scientific writings, he wrote several books on the themes of humanism, atheism, religion, and the Holocaust. His most recent book, *Resistance*, received the Gerard Bonnier Prize for the best essay collection of 2015. His luminous, prescient voice continues to reverberate

in the farthest reaches of cancer biology and cancer immunology.

#### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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