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PERSPECTIVE

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In memoriam: Jefferson Foote

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ABSTRACT
In a scientific career that spanned over three decades, Dr. Jeff Foote made seminal contributions to antibody humanization and the biophysical aspects of antibody recognition. In this Perspective, we discuss his life and work.

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Jefferson (Jeff) Foote sadly passed away of pancreatic cancer on January 17, 2020 at the age of 64. He was a leading figure in physical immunochemistry and antibody humanization, a polymath of broad interests, and a wonderful friend and colleague. Jeff was born in Chicago and grew up in Tarrytown, NY. Following graduation from Harvard University where he worked in the laboratory of William Lipscomb, he earned his Ph.D. at Berkeley with Howard Schachman, studying the canonical aspartate transcarbamylase system. In 1985 he moved to the Laboratory of Molecular Biology (LMB) in Cambridge, where he worked with (now Sir) Greg Winter and then with Cesar Milstein. During his time in Cambridge, Jeff applied his understanding of protein biophysics and interaction kinetics to address problems in immunochemistry, increasingly leveraging the availability of the first emerging crystal structures of antibody-antigen complexes. This was before the BIAcore/surface plasmon resonance era that started in the early 1990s, and the work required a comprehensive knowledge of the inner workings of fluorometers, including stop-flow, and the associated mathematical tools. Jeff imported a Macintosh ("Mac") culture to the laboratory, which was well-received by other local Mac fans in days when benchtop computers were still something of a novelty and there was a threat of other personal computer models becoming the norm.

Whilst at the LMB, Jeff made significant contributions in areas ranging from state-of-the-art antibody engineering to fundamental aspects of B cell biology, including the first description of the CDR grafting, or humanization, of an antibody specific for a hapten.[1] Jeff applied his expertise to determine the affinities of the test grafts, enabling the design principles of the engineered antibodies to be verified in precise, quantitative terms. This seminal study formed the foundation for the subsequent avalanche of therapeutic antibody humanizations, the first of which was the CD52-specific antibody Campath-1 (Alemtuzumab) generated in the Winter/Waldmann laboratories and used to treat chronic lymphocytic leukemia and multiple sclerosis. In addition, Jeff used the first antibody to be structurally solved in complex with antigen, the anti-lysozyme antibody D1.3, to define how framework residue modifications could restore binding behavior close to that of the donor (rodent) antibody to a humanized antibody.[2] As well as the biophysical characterization of framework mutants, he was also the first to synthesize a "consensus" framework.[2,3]

In parallel to Jeff's work on antibody humanization, he carried out an extensive analysis with Cesar Milstein on how the maturation of the immune response is accompanied by an increased on-rate of antibodies for binding to their antigen. This study led to the paradigm that the selection of the "fittest" B cells is driven by interaction kinetics.[4] Subsequently, in a second publication with Cesar, Jeff observed that antibodies could undergo switching between different conformations ("conformational isomerism"), resulting in bi- or triphasic interaction kinetics.[5] This not only provided a molecular mechanism for the further diversification of antibodies, but also challenged the longstanding axiom that each lymphocyte produces an antibody with a single combining site.

Jeff was one of those more civilized members of the LMB who drove into work, rather than arriving with the appearance of a half-drowned rat following a cycle ride in the wintry, wet days that were common in Cambridge. Whilst working with Greg Winter in the tiny 5–6 person laboratory known as T4, Jeff relished being in the thick of the day-to-day, frequently frenetic activities. The day usually started with copious quantities of "Java", an almost toxic, viscous dark brown liquid that kept the group members charged and running. Given that antibody humanization and, subsequently, antibody repertoire work were ongoing in the laboratory at this time, there was rarely a dull moment.

Jeff returned to the US in 1992 to take up a faculty position at the Fred Hutchinson Cancer Research Center ("the Hutch") in Seattle. He was a one of the founding members of the Hutch's Structural Biology Program and a valued colleague, in particular, of Barry Stoddard and Roland Strong. He continued to work on problems related to the molecular aspects of antibody recognition, particularly using mutants of

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Jeff Foote with his Mac at the MRC Laboratory of Molecular Biology, Cambridge (ca. 1986). Photo courtesy of Kathleen Foote.

the anti-lysozyme antibody D1.3 in work with the "Foote Lab's" first member, the talented x-ray crystallographer Meg Holmes.[6] (It was a great shock to the entire Center when in 2010 Meg was diagnosed with glioblastoma, and sadly, she passed away about a year later.) Jeff was always keen to try and improve antibody humanization, with an interest in reducing the potential for immunogenicity. He developed a modified CDR grafting technique which he called "Superhumanization".[7] The members of his laboratory tried to talk him out of using this name, but his wry sense of humor would have none of it.

Whilst at the Hutch, Jeff also advanced the concept of buffering of drug concentrations by anti-drug antibodies to prolong their persistence in the body. This important work formed the basis of several publications in which he described, in quantitative terms, the ability of antibody buffering to stabilize drugs that otherwise are rapidly cleared.[8] Despite the emerging promise of antibody-based therapeutics, funding for immunochemistry was scarce, and Jeff was a leader of the charge to muster greater investment in this area. In 2003, he left the Hutch to set up his own biotechnology company named Arrowsmith Technologies, focusing in part on enhancing the local persistence of drugs in the brain by intrathecal delivery of drug-specific antibodies. The name Arrowsmith, from the 1925 novel by Sinclair Lewis featuring creative, obsessive scientists pursuing their work wherever it led, was very appropriate to Jeff's way of thinking.

Jeff not only made major scientific contributions, but he was a superb companion who had a wonderfully engaging way of telling stories. He was highly cultured and had a wide array of extracurricular interests, including photography, music, ballet, coaching of youth soccer, and the philosophy of science. If his interest was piqued by something, he would research the topic in great detail, becoming remarkably knowledgeable. He was an extraordinarily entertaining and well-informed host; one of us once visited an ice cave, a salmon ladder, a marina, a public garden, and the grave of Bruce Lee with him during a single weekend in Seattle.

Jeff loved his son Ulysses above all else, and once proudly shared the gel of Ulysses' first site-directed DNA mutant. He had many friends, who remember him as a visionary known for acts of kindness. Consequently, he was beloved by his laboratory members at the Hutch even long after the laboratory itself had been disbanded. His wry sense of humor was enjoyed by many; for example, he jokingly carried the Swedish for "Thank you, your Highness" as a note in his wallet, to be ready for his anticipated Nobel prize. Jeff was always available to be a caring, thoughtful sounding board. His correspondence was carefully crafted and could be highly amusing, even as he bravely faced the adversity of his diagnosis (notably, he delayed telling one of us of his illness until the day after Christmas, so as not to spoil their holiday). The world is a better place for his having been in it, and he is very much missed by all who knew him.

Abbreviations

CDR	complementarity-determining region
LMB	Laboratory of Molecular Biology

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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