
JANET DAVISON ROWLEY



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DR. JANET ROWLEY was internationally renowned for her studies of chromosome abnormalities in human leukemia and lymphoma. A woman of tremendous grace and beauty, she distinguished herself not only for her historic scientific discoveries but also with her sustained efforts to support the careers of others—including myself.

Janet Davison Rowley was born in New York City on 5 April 1925, the only child of Hurford and Ethel Davison, both graduates of The University of Chicago. In 1940, after 2 years at a Catholic girls' high school, Janet, 15, won a scholarship to enroll in the Hutchins College at The University of Chicago, which combined the last 2 years of high school with the first 2 years of college. She completed a Bachelor of Philosophy degree in 1944 and was accepted into the University's medical school, but the quota—three women for a class of 65—was already filled. "I had to wait 9 months," she said in an interview. "I was only 19 at the time, so it wasn't a great tragedy."

Janet was married to Donald Rowley, MD, the day after she graduated from medical school on 18 December 1948. She would spend the next 20 years raising their four sons while working part time, including at a Chicago clinic for children with Down's syndrome. It was not until her husband's sabbatical at Oxford University in 1962 that Janet's interest and focus shifted to chromosomes and cancer, and she learned the laboratory techniques that she would later use to change the scope of cancer diagnosis and treatment. She made her first major discovery at 47, when she identified the first consistent chromosome translocation in any human cancer, namely the 8;21 translocation in acute myeloid leukemia (AML).

In a landmark paper in 1973, Janet described the identification of the 9;22 translocation (Philadelphia chromosome) in chronic myeloid leukemia (CML). Subsequently, she identified more than a dozen different recurring translocations in children and adults with leukemia and lymphoma. These discoveries changed the view of cancer researchers regarding the critical importance of recurring chromosome abnormalities in cancer cells and facilitated identification of novel oncogenes at the breakpoint junctions. In fact, it is reasonable to say that her early discoveries galvanized the scientific community in support of the Human Genome Project and influenced a whole generation of cancer geneticists like myself who came of age in the golden era of cytogenetics.

Janet taught us the importance of collaboration to accomplish greater scientific goals. She was always willing to share. She described five very important translocations and/or inversions, including the 15;17 translocation in acute promyelocytic leukemia (APL-M3); the

6;9 translocation in AML; the inversion and translocation involving chromosome 3 [inv(3)/t(3;3)] in AML associated with increased platelet counts; the inversion and translocation involving chromosome 16 [inv(16)/t(16;16)] in acute myelomonocytic leukemia with abnormal eosinophils (AMMoL-M4EO); and the 14;18 translocation in follicular lymphoma. Her work led to the recognition that chromosome translocations were specifically associated with particular morphologic subtypes of leukemia and lymphoma.

A series of International Workshops on Chromosomes in Leukemia provided critical information regarding the phenotypes associated with specific translocations in large numbers of patients and showed that recurring chromosomal abnormalities were independent predictors of response to therapy in AML and acute lymphoblastic leukemia (ALL). This finding led to “risk-adapted” therapy for adult and childhood leukemia. Although it is now widely accepted that genomic analysis plays a critical role in the diagnosis, subclassification, and selection of therapy for patients with cancer, Janet, sitting behind her microscope, was ahead of the curve.

Janet’s work has had a profound global impact. Her early work on the t(9;22) in CML culminated in the most successful example of targeted therapy and provided a new paradigm for using molecular diagnosis to define therapy in oncology. The BCR-ABL fusion protein is located on the cytoplasmic surface of the cell membrane and acquires a novel function in transmitting growth-regulatory signals to the nucleus via the RAS/MAPK, PI3K/AKT, and JAK/STAT signal transduction pathways. The tyrosine kinase activity of the BCR-ABL fusion protein can be specifically inhibited by imatinib mesylate (Gleevec/STI571, Novartis Pharmaceuticals). Imatinib has shown remarkable activity in all phases of CML and is the preferred therapy for most patients with newly-diagnosed CML who can now expect to live the course of a normal life on therapy. All Trans-Retinoic Acid (ATRA) as treatment for the 15;17 translocation in acute promyelocytic leukemia also provides highly effective therapy with minimal side effects and represent the cutting edge of molecularly targeted therapeutics. Janet was an innovator. Her rapid application of spectral karyotyping (1997) resolved new chromosomal rearrangements associated with leukemias opening up yet another series of discoveries.

Janet recognized that the cellular oncogenes mapped to chromosome bands contain the breakpoints of the recurring translocations, and she proposed that chromosomal translocations represented one mechanism by which the function of cellular oncogenes is altered. She and her

colleagues initially mapped a number of genes relative to translocation breakpoints. They then started to clone translocation breakpoints, beginning with the t(14;19) in chronic lymphocytic leukemia. The gene on 19 is BCL3, which has been shown to be a critical regulatory component in the IKB-NFKB family. She and others cloned the t(8;14) in T cell acute lymphoblastic leukemia (T-ALL) involving the T cell receptor alpha (TCRA) and the MYC oncogene, as well as the t(10;14) and the t(1;14) in T-ALL, which involve a T cell receptor gene on 14 and either HOX11 on chromosome 10 or LCK on chromosome 1. She collaborated in the cloning of the t(8;21) fusion gene (RUNX1/AML1-ETO) by using fluorescence in situ hybridization to show that one of several candidate yeast artificial chromosome clones on chromosome 21 was split in patients whose leukemic cells contained a t(8;21). Her laboratory was the first to demonstrate the association of the 3;21 translocation with CML in blast crisis and with t-AML and t-MDS. She determined that the same gene on chromosome 21, AML1, was involved in the 3;21 translocation. Her laboratory then cloned a series of genes at the breakpoint on chromosome 3 (MDS1/EVI1) that are involved in complex variable splicing of fusion mRNAs. This translocation is important because it is seen almost exclusively in patients who had previously received anthracycline therapy for a primary malignant disease.

Her group cloned the gene at the translocation breakpoint of the common translocations of 11q23, as did several other laboratories. She called this gene MLL, for myeloid-lymphoid leukemia (others called it ALL-1, Htrx, or HRX) and she showed that it was involved in 24 different translocations detected in her laboratory alone. Identification of this gene is important because it is likely involved in the critical decision stage in which differentiation into B lymphocytes or monoblasts is determined. Janet demonstrated that breaks in MLL occur in an 8.3-kb breakpoint cluster region (BCR) encompassing exons 5 through 11, and that 75% of patients with de novo AML have breakpoints in MLL in the centromeric half of the BCR between two scaffold-associated regions (SAR), whereas 75% of the t-AML patient breakpoints mapped to the telomeric half of the BCR within a strong SAR. This work paved the way for cloning close to 50 MLL partner genes and for molecular detection of the MLL translocations for diagnosis. Because of the association of MLL rearrangements and prior treatment with topoisomerase II inhibitors, she determined the location of topoisomerase II consensus binding sites, scaffold attachment regions and Alu sequences in MLL with the precise position of the breakpoints in both de novo and t-AML patients. The data suggested that chromatin structure of the MLL BCR might influence the location of DNA breaks in both de novo and therapy-related

leukemias. Moreover, she proposed a model for a common mechanism leading to chromosome translocations mediated by non-homologous recombination occurring in unstable or “hot-spot” regions in both de novo and t-AML patients.

Throughout her illustrious career, Janet was a stubborn advocate for science. She provided leadership to the field and fostered public understanding of science. She served as a member of The President’s Council on Bioethics, where she was one of the most effective members championing the need for a strong national program supporting responsible human embryonic stem cell research. Her patience and wisdom allowed the committee to survive intact for 8 years before President Obama signed an Executive order permitting stem cell research in 2009. With her long-term scientific partner and friend Felix Mitelman, she co-founded and was co-editor of *Genes, Chromosomes and Cancer*, the premier cancer cytogenetics journal worldwide. She served on scientific and public boards. Through these activities, Janet provided enormous opportunities for her mentees and promoted the careers of others.

Janet was the recipient of the National Medal of Science (1998) and the Albert Lasker Clinical Medicine Research Prize (1998), the Benjamin Franklin Medal from the American Philosophical Society (2003), the Gruber Prize in Genetics (2009), and the Presidential Medal of Freedom (2009). The Medal of Freedom recognizes “an especially meritorious contribution to the security or national interests of the United States, world peace, cultural, or other significant public or private endeavors.”

Janet continued to direct an active and productive laboratory until her death. I marveled as she rode her bike to work every day, and when she could no longer do so, she organized laboratory meetings in her home. Janet was restless, ambitious, and kind. She was an avid gardener and a phenomenal athlete who climbed mountains and swam in Lake Michigan most summer days. She enjoyed the opera and traveled to exotic corners of the world. Janet was a devoted mother and grandmother. She was a pillar in the University of Chicago community, a most beloved mentor, and a scientific mother who will be terribly missed.

OLUFUNMILAYO FALUSI OLOPADE¹

Walter L. Palmer Distinguished Service Professor
Director, Center for Clinical Cancer Genetics & Global Health
The University of Chicago

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