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Glyco-Forum section

Obituary: Rosalind Hauk Kornfeld (1935–2007)

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On August 10, 2007, the field of Glycobiology lost one of its great pioneers and role models, Rosalind Hauk Kornfeld. Dr. Kornfeld was a Professor of Medicine and Professor of Biochemistry and Molecular Biophysics at the Washington University School of Medicine in St. Louis, where she had served on the faculty for 35 years, before retiring in 2001 due to illness. Born in Dallas, Texas in 1935, Rosalind Kornfeld grew up in Chevy Chase, Maryland and earned her B.S. in Chemistry at George Washington University in 1957. After obtaining her doctorate in biochemistry at Washington University in St. Louis in 1961, she stayed on to do some postdoctoral work there. She then moved to the National Institutes of Health, serving as a postdoctoral fellow and staff fellow during 1963–1965, before finally returning to St. Louis in 1965. There she continued a life-long and fruitful collaboration with her spouse Stuart Kornfeld, which included the training of numerous students and postdoctoral fellows, many of whom have gone on to very successful careers throughout the world. Among other notable achievements, Rosalind Kornfeld was a Scholar of the Leukemia Society of America from 1971–1976, 1991 Chair of the Gordon Research Conference on Glycoproteins and Glycolipids (now the GRC on Glycobiology), and 1993 President of the Society for Glycobiology.

For those of us whom Rosalind mentored and nurtured through our days of training and beyond, it is hard to imagine a world without her winning smile, her cheerful disposition and her no-nonsense can-do attitude toward science and life. Many others who interacted with her over the years undoubtedly feel the same way. Even as we all mourn the loss, we should celebrate her life and achievements, particularly in two areas: setting the foundations of the field of Glycobiology; and, serving as an effective role model for women in science. As Rosalind would undoubtedly have wanted it, let us focus first on her scientific achievements.

During her time at the NIH, Rosalind Kornfeld provided the first evidence for feedback regulation of nucleotide sugar biosynthesis, showing that UDP-GlcNAc inhibits L-Glutamine-D-Fructose 6-phosphate Amidotransferase (GFAT, the first enzyme unique to UDP-GlcNAc biosynthesis), and that CMP-Sialic Acid inhibits the formation of *N*-acetylmannosamine by UDP-*N*-acetylglucosamine 2'-epimerase. She also extended this phenomenon to bacteria, showing that GDP-fucose and GDP-mannose can independently control the rate of synthesis of these nucleotide sugars. Besides being classics in the field of metabolism, this work has had much impact on later research by others. For example, it was subsequently found that the defect in some patients with sialuria is a mutation in the epimerase that results in the loss of this feedback inhibition. Likewise, studies of GFAT have received much attention recently, due to its role in modulation of UDP-GlcNAc levels and regulation of O-GlcNAc formation in diabetes.

"Ros" was also a pioneer in early studies on the nature of glycan ligands for lectins. While many investigators had demonstrated lectin-binding specificity using monosaccharides as inhibitors, she was among the first to show that lectins usually require extended oligosaccharide structures for high affinity binding. For example in 1969–70, the Kornfeld lab showed that an N-linked glycan derived from red blood cell membranes was >20,000-times more potent than galactose or *N*-acetylgalactosamine, and >500-times more potent than Lacto-N-Neotetraose in inhibiting binding of E-PHA. This allowed the conclusion that inner core sugars could influence interactions with this lectin. This concept was extended to studies of the interaction of various oligosaccharides with ConA and pea and lentil lectins. Thus, in the case of the pea and lentil lectins, she showed that a fucose linked to the asparagine-linked GlcNAc was essential for high affinity binding, as were 2 α-linked mannose residues in the core. Further, exposure of the outer *N*-acetylglucosamine residues enhanced binding to lentil lectin, and binding to pea lectin was enhanced by exposure of mannose residues. Based on such observations, she performed one of the first examples of serial lectin affinity chromatography to fractionate mixtures of glycopeptides.

In those early days, there was relatively little known about the exact structures of N-linked glycans on glycoproteins. Taking advantage of her position in a Hematology Division, Rosalind studied N-glycans of monoclonal immunoglobulins that could be obtained in large quantities from the blood of patients with myeloma. These structural analyses (especially of the core sugars) improved as new reagents and techniques became available (such as endo H). The best and most complete studies were of the high mannose-type glycans of human IgM. These were among the first complete structures of N-glycans to be reported. Importantly, these studies also showed that "microheterogeneity" of oligosaccharides existed on otherwise homogeneous proteins secreted by a single clone of cells.

During the next stages of her work Rosalind contributed greatly towards the Kornfeld lab discovery of the N-glycan processing pathway, and then demonstrated an important bypass mechanism for N-linked glycan processing. Using cells deficient in α-glucosidase II, she showed that an endomannosidase discovered by Robert Spiro serves as a bypass route, by cleaving $Glc_{1,2}Man_9GlcNAc_2$ glycans to $Glc_{1,2}Man$ plus $Man_8GlcNAc_2$, thereby allowing complex-type N-glycan synthesis in these mutant cells. She was also involved in providing some of the first evidence for α-mannosidase activity in the ER, distinct from the then known Golgi and lysosomal α-mannosidases.

Although not claiming much credit nor authorship for it, Rosalind also played important roles in the Kornfeld lab discoveries of the mannose 6-phosphate (M6P) pathway for trafficking to lysosomes. For example, the present writer's own contributions to this area would not have been possible without her generous advice and help regarding the structural analysis of glycans and the purification and characterization of enzymes, such as the "uncovering" enzyme, which exposes the M6P ligand for recognition by the M6P receptors. Rosalind later went on to purify and clone this enzyme, showing also that it, unlike most Golgi enzymes, is a Type I membrane protein that resides in the TGN, where it cycles constitutively between that compartment and the plasma membrane.

Last but not least, Rosalind Kornfeld wrote two highly influential reviews that synthesized much information on glycan structure and biosynthesis. The important insight from the 1976 review was the recognition that the high mannose units of species ranging from yeast to man share similarities. To quote: "the striking thing about this group of structures (referring to high mannose-type structures) is that not only are the cores the same, but the branching pattern and linkages in the peripheral region are the same." The review (which was written before the discovery that $Glc_3Man_9GlcNAc_2$–P-P-Dol is the universal donor) went on to say: "Perhaps the constancy of the core structure seen in such a variety of glycoproteins obtained from fungi, hens and humans reflects a common and early evolved synthetic mechanism". This, of course, turned out to be the case, and showed an excellent example of how structural analysis can give insight into biosynthetic pathways. By the time of the 1985 review, N-linked oligosaccharide processing and the Man-6-P recognition system had been elucidated, along with the first purification of glycosyltransferases and the reporting of many more structures. This classic review served to synthesize much of this information in a way that could be understood by people both inside and outside the field. It is still being quoted today (cited almost 3500 times).

Rosalind Kornfeld also contributed to peer review, serving on the Editorial Board of the *Journal of Biological Chemistry* and the Physiological Chemistry Study Section of the NIH. In this regard, her special characteristic was to read the literature carefully and give full credit to contributions by previous investigators, a virtue all too rare these days. This, together with her generous and self-deprecating attitude, and her deep caring for intellectual honesty, scientific accuracy and social justice made her very special to those who had privilege to know her. While Rosalind never made much of the fact, she was also the quintessential role model of the successful female scientists of her era. She succeeded in being fully recognized for her achievements despite the great anti-female prejudices of those days, and even while being a highly successful mother and homemaker. In fact, she was extremely proud of her three children, highlighting them on her CV. Two of them (Kerry Kornfeld and Carolyn Lesorogol) are currently faculty members at Washington University. At the University, Rosalind was Co-Founder and the first President of the Academic Women's Network, created to provide a forum for information sharing, support and advocacy among women faculty members. In 2000, the AWN awarded her with the first of its now annual Mentor Awards. While much still remains to be done to achieve equal opportunity for female scientists (especially those who chose to be mothers), her example should give inspiration to all young women who aspire for success in science in general, and Glycobiology in particular. Meanwhile, let us all celebrate the life and achievements of Rosalind Kornfeld, and continue onward with her mission – to elucidate the structure, biosynthesis and biological roles of glycoprotein glycans, in health and disease.

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