Beth Levine 1960–2020

The untimely death of Dr. Beth Levine has robbed the autophagy community of a remarkable leader, mentor and human being. Beth was a leading investigator in the field of autophagy, a process by which cells remove unwanted organelles and macromolecules by delivering them to the cellular dustbin, the lysosome. In the late 1990s, Beth Levine burst onto the autophagy field with the power of a supernova. She identified the Bcl-2-interacting protein Beclin 1 as the mammalian homolog of yeast Atg6/Vps30, a protein required for autophagy and vacuolar protein sorting. At that time, autophagy genes had been identified in yeast, with only a few homologs (e.g., ULK1, ATG5, and ATG12) being reported in mammals. Remarkably, Beth noticed that the *beclin 1* gene is often deleted monoallelically in cancers and thus proposed a link between autophagy and tumour suppression in her 1999 *Nature* paper. One of the cancers Beth linked to mutations in autophagy was breast cancer, the disease to which she tragically succumbed. This study was a true landmark in autophagy research, causing a "phase transition" from basic cell biology to biomedical research.

As a leading physician scientist, Beth was motivated to conduct cross-disciplinary research on the underlying mechanisms and physiological significance of autophagy in health and disease, resulting in seminal studies in cancer, infectious diseases, aging, and metabolism. In 2003, she showed that mutant mice heterozygous for *beclin 1* spontaneously develop lung adenocarcinomas, hepatocellular carcinomas, and lymphomas, confirming the tumour-suppressing activity of *beclin 1*. This work attracted the attention of researchers both within and outside the autophagy field by bridging autophagy with medicine and inspiring many translational studies harnessing the autophagy pathway.

Trained as an infectious disease doctor, Beth had a special passion for virology. Consistent with her enthusiasm for studying viral pathogenesis, she demonstrated a molecular link between autophagy and viral infection. When several laboratories later found that bacteria are also targeted by autophagy, it was Beth who coined the term "xenophagy" for the selective autophagic elimination of intracellular pathogens. She also revealed how viruses could evade autophagy by identifying a herpes simplex virus type 1-encoded neurovirulence protein that interacts with and blocks Beclin 1 activity, thereby inhibiting autophagy.

Credit: Image courtesy of Brian Coats

Beyond her work on cancer and infectious diseases, Beth was a pioneer in recognising the connection between autophagy and aging. In 2003, Beth's group found that the *Caenorhabditis elegans bec1/beclin 1* homolog is required for dauer development and lifespan extension. More recently, by developing knock-in mice that harbour a *beclin 1* allele resistant to Bcl2-mediated inhibition ($Becn1^{F121A}$), members of her laboratory made the remarkable discovery that enhancing autophagy improves lifespan and healthspan in mammals. Autophagy is now recognised as one of the main pillars supporting cellular and organismal youth, and its modulation represents a promising approach to reverse aging.

Beth made myriad important contributions to the field of autophagy, including the identification of autophagy-regulating factors (e.g., eIF2α, SMURF1, Fanconi anaemia pathway proteins, and prohibitin 2), the study of an autophagy-dependent form of cell death that she called "autosis", and molecular links between exercise and autophagy. Not only did she establish much of our understanding of the beneficial effects of autophagy, but also developed methods to modulate autophagy in vivo. One unique approach was the use of a cell-permeable Tat-beclin 1 peptide that induces autophagy by disabling an autophagy inhibitor. This peptide improves the clinical course of viral infection in mice and has potential as a human therapeutic.

Beth was born in Newark, New Jersey in 1960. After graduating magna cum laude from Brown University in 1981, she received her medical degree from Cornell University Medical College in 1986, which was followed by a residency in internal medicine at the Mount Sinai Hospital in New York. She was a postdoctoral fellow in infectious diseases and virology at the Johns Hopkins School of Medicine from 1989 to 1992. Whilst she loved clinical practice, her heart and head resided in research. Beth became Assistant and then Associate Professor at Columbia University. In 2004 she was recruited by UT Southwestern to be the Chief of Infectious Diseases and became the Director of the Center for Autophagy Research in 2011. An Investigator with the Howard Hughes Medical Institute since 2008, an elected member of the American Society of Clinical Investigation, the American Association of Physicians, and the National Academy of Sciences, and an awardee of the 2014 ASCI Stanley J. Korsmeyer award, Beth Levine will be remembered by colleagues as a brilliant, innovative, and inspiring woman and scientist.

A mesmerizing speaker and an exquisite writer with an unrelenting work ethic, Beth often worked late into the night and early morning hours. She excelled in her creative vision and intellectual rigour, mentoring over 50 graduate students and postdoctoral researchers, many of whom continue her legacy through their own distinguished careers. Her qualities as a mentor are illustrated by one of her mentees who recalls that Beth explained in over 100 words in the margin why she had changed one word in the edited version of a grant application.

Through her leadership, Beth helped shape the autophagy field into one of the most stimulating and collegial scientific fields, including catalysing and organizing the inaugural Keystone and Gordon conferences on autophagy. With the rare combination of being quietly unassuming and humble yet fierce and rigorous, she easily and effortlessly commanded respect (high heels included), while generously welcoming newcomers (such as one of us) and old friends to the field that she helped to create. Despite this combination of

shyness and authority, her colleagues in the autophagy field, including the many women she inspired and supported, describe their personal encounters with her as kind, warm, and encouraging. She combined family and career with unflagging passion and had a reverence for the mother's role which was wholly relatable and hugely encouraging, creating the "autophagy sisterhood".

Beth is survived by her husband, Dr. Milton Packer, and their two children, Rachel, aged 26, and Ben, aged 25. Many of us remember private conversations with Beth that centred around her family. During her Shiva, the Jewish mourning ritual held in her honour, her brother described her most movingly as having "the command without abusing it and the beauty without the vanity".

Autophagy and biomedical research have lost a brilliant star. Beth will be profoundly missed. ❐

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