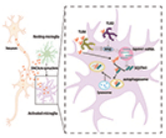
Autophagy



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MEMORIAM

Beth Levine in memoriam

Beth Levine
In memoriam

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Beth Levine was born on 7 April 1960 in Newark, New Jersey. She went to college at Brown University where she received an A.B. Magna Cum Laude, and she attended medical school at Cornell University Medical College, receiving her MD in 1986. She completed her internship and residency in Internal Medicine at Mount Sinai Hospital in New York, and her fellowship in Infectious Diseases at The Johns Hopkins Hospital. Most recently, Beth was a Professor of Internal Medicine and Microbiology, Director of the Center for Autophagy Research, and holder of the Charles Sprague Distinguished Chair in Biomedical Science at the University of Texas Southwestern Medical Center in Dallas. Beth died on 15 June 2020 from cancer. Beth is survived by her husband, Milton Packer, and their two children, Rachel (26 years old) and Ben (25 years old).

Dr. Levine was as an international leader in the field of autophagy research. Her laboratory identified the mammalian autophagy gene *BECN1/beclin 1*; identified conserved mechanisms underlying the regulation of autophagy (e.g. BCL2-BECN1 complex formation, insulin-like signaling, EGFR, ERBB2/HER2 and AKT1-mediated BECN1 phosphosphorylation); and provided the first evidence that autophagy genes are important in antiviral host defense, tumor suppression, lifespan extension, apoptotic corpse clearance, metazoan development, Na,K-ATPase-regulated cell death, and the beneficial metabolic effects of exercise. She developed a potent autophagy-inducing cell permeable peptide, Tat-beclin 1, which has potential therapeutic applications in a range of diseases. She was a founding Associate Editor of the journal *Autophagy* and an editorial board member of *Cell* and *Cell Host & Microbe*. She has received numerous awards/honors in recognition of her scientific achievement, including: The American Cancer Society Junior Faculty Research Award (1994); election into the American Society of Clinical Investigation (2000); the Ellison Medical Foundation Senior Scholars Award in Global Infectious Diseases (2004); elected member, American Association of Physicians (2005); appointment as a Howard Hughes Medical Institute Investigator (2008); Edith and Peter O'Donnell Award in Medicine (2008); elected fellow, American Association for the Advancement of Science (2012); election into the National Academy of Sciences (2013); election into the Academy of Medicine, Engineering and Science of Texas (2013); the ASCI Stanley J. Korsmeyer Award (2014); Phyllis T. Bodel Women in Medicine Award, Yale University School of Medicine (2018); recipient, Barcroft Medal, Queen's University Belfast (2018).

Beth Levine's research

Beth's work filled the void between fundamental cellular biology and real-world human disease. Her keen unwavering focus on fundamental biological concepts swept through biomedical research to influence many scientific disciplines and inform our understanding of clinical conditions. Her meticulous dissection of autophagy has provided the mechanistic insight required to advance the field toward targeted therapeutic strategies that are applicable to a wide range of diseases. This was key to understanding how to intervene and form the basis for several autophagy-inducing therapeutic strategies that are currently under

development (e.g., Tat-beclin 1 peptide and BCL2 disruptor) and many other pharmacologically tractable yet unexplored mechanisms for the field to pursue for years to come. Her work has made an indelible impact on colleagues and the field at large.

Autophagy and organismal health

The spectrum of health and disease has extreme ends and many states in between. Disease makes more sense when framed in the context of health. Beth's lab had an equal focus on the mechanisms of health (not just disease), which was a refreshing perspective. The early, seminal discovery from the Levine lab that BECN1 functionally connects autophagy and cell survival pathways (*J. Virol*., 1998) was the result of a bold discovery initiative that became a pattern in the lab's approach to challenging questions. In a series of landmark papers, the Levine lab discovered BECN1 as a direct binding partner of BCL2 in a yeast two-hybrid screen and went on to demonstrate that BCL2 asserts anti-autophagy function by binding to BECN1 and inhibiting formation of the BECN1-PIK3C3/VPS34 complex and its associated class III PtdIns3K activity (*Cell*, 2005). Overexpression of BCL2 inhibits starvation-induced autophagy in cardiac muscle, and BECN1 mutants unable to bind BCL2 induce autophagy in cancer cells. The Levine lab went on to expand these findings by generating a mouse model to genetically disrupt the BECN1-BCL2 interaction by means of a point mutation in BECN1 (F121A) (*Nature*, 2018). Remarkably, these mice exhibit prolonged lifespan associated with healthy aging and reduced incidences of spontaneous cancers. The Levine lab had previously demonstrated the requirement for autophagy in lifespan extension in a *C. elegans* model (*Science*, 2003), but improving healthspan in a mammalian system with the $BECN1^{F121A}$ mutation was a monumental accomplishment with important implications for understanding health in humans. In an orthogonal approach to modulating autophagy *in vivo*, the Levine lab generated a mouse model expressing a BCL2 phospho-defective mutant (BCL2 AAA) that prevents stimulus-induced release of BECN1 and induction of autophagy (*Nature*, 2012). These BCL2 AAA mice exhibit defective exercise-induced autophagy in skeletal and cardiac muscle, decreased endurance, and impaired regulation of glucose metabolism. As the Levine lab further pursued these key discoveries, they meticulously dissected the pathways controlling exercise-induced autophagy and their associated health benefits. In another landmark study, the Levine lab discovered a link between inflammation and metabolism by demonstrating that the innate immune receptor TLR9 interacts with BECN1 to activate AMPK in exercise-induced autophagy (*Nature*, 2020). Collectively, these findings provide a detailed mechanistic explanation for the benefits of exercise in human health.

Fifteen years after their first report regarding BECN1, the Levine lab identified a novel mammalian-specific BECN1 family member, called BECN2 (beclin 2; *Cell*, 2013). BECN2 is an essential autophagy protein in mammalian cells and also plays a critical role in regulating degradation of certain G protein-coupled receptors and glucose homeostasis. These findings highlight the functional and mechanistic diversity of BECN family members in the integration between two crucial distinct lysosomal degradation pathways (autophagy and endolysosomal trafficking) in eukaryotic cell biology.

Cancer and tumor suppressors

The seminal discovery from the Levine lab that BECN1 operates at the intersection of autophagy and cell survival pathways formed the basis for new paradigms in cancer biology. Beth was one of the first investigators to recognize the significance of *BECN1* monoallelic deletion, which occurs in 40–75% of sporadic breast, ovarian, and prostate cancers (*Nature*, 1999; *J. Clin. Invest*., 2003). At this time, it was not widely appreciated that tumor suppressor function can be overturned by loss of heterozygosity. The Levine lab provided compelling evidence in a series of papers demonstrating that complementation of BECN1 in haploinsufficient MCF7 breast carcinoma cells restores autophagy and reduces proliferation (*Nature*, 1999). Shortly thereafter, the Levine lab generated a *Becn1* haploinsufficient mouse model to conclusively demonstrate the tumor suppressor function of BECN1. In these mice, loss of a single allele of *Becn1* was sufficient to increase the frequency of spontaneous malignancies and to accelerate the development of premalignant lesions induced by hepatitis B virus (*J. Clin. Invest*., 2003). After making these discoveries, the Levine lab proceeded to systematically identify novel mechanisms by which oncogenic signaling pathways suppress autophagy through direct regulation of BECN1. As the field of cancer genomics advanced, the importance of autophagy in breast cancer has come into clear focus. In particular, the Levine lab found that ERBB2/HER2-enriched, mainly triple negative, breast cancers tend to exhibit lower expression of *BECN1* mRNA relative to other subtypes (*EBioMedicine*, 2015). They further demonstrated that ERBB2/HER2 interacts with BECN1 and that tyrosine kinase activity of ERBB2/HER2 is required for inhibition of autophagy (*PNAS USA*, 2018). Remarkably, $BECN1^{Y121A}$ mice exhibit increased mammary epithelial autophagy and show reduced tumorigenesis in the ERBB2/HER2 MMTV transgenic model. A similar mechanism was uncovered for the related oncogene EGFR in non-small cell lung cancer (NSCLC). Work from the Levine lab demonstrated that EGFR phosphorylates BECN1 to inhibit autophagy, and EGFR tyrosine kinase inhibitors relieve autophagy inhibition to reduce growth of tumor xenografts (*Cell*, 2013).

The concept of oncogenic pathways converging on autophagy at the level of BECN1 is a recurring theme in cancer biology. AKT phosphorylates BECN1 to inhibit autophagy (*Science*, 2012), whereas MAPK8/JNK1 phosphorylates BCL2 leading to dissociation of BECN1 and induction of autophagy (*Mol. Cell*, 2008). These key findings demonstrating that BECN1 is a tumor suppressor raise the question of how autophagy mediates cell-growth control. The Levine lab approached this difficult question head on and clarified several long-standing issues in the field by characterizing a novel mechanism of autophagy-dependent programmed cell death termed autosis (*PNAS USA*, 2013). In an elegant study, the Levine lab performed a screen using an annotated library of small molecule bioactives to demonstrate that the Na^+/K^+-ATPase is required for autotic cell death. Taking this finding one step further, the Levine lab demonstrated that autophagy controls energy-dependent engulfment signals required for clearance of cellular corpses (*Cell*, 2007). Taken together, the body of work contributed by the Levine lab firmly established autophagy as a central regulator of cell-growth control and tumor suppression.

Innate immunity

Early in her research career, to understand the mechanism by which BCL2, an apoptosis regulator, protected mice from fatal Sindbis virus-induced encephalitis, Dr. Levine's group used a yeast two-hybrid screen for BCL2-interacting proteins. They discovered BECN1, which through a BCL2 binding domain-specific interaction confers resistance to in vivo Sindbis virus infections (*J. Virol*., 1998). This key finding led to a follow-up study by her group demonstrating that BECN1 was functionally homologous to the Vps30/Atg6 core autophagy protein found in the yeast *Saccharomyces cerevisiae*, and was the first gene shown to be involved in autophagy in mammalian cells (*Nature*, 1999). These studies suggested that expression of BECN1 and interaction with BCL2 coordinates autophagy and cell survival pathways, and that activation of the autophagy pathway through dissociation of BECN1 can inhibit viral replication and tumorigenesis (*J. Virol*., 1998; *Nature*, 1999; *Cell*, 2005a). Dr. Levine later went on to coin the term xenophagy to distinguish selective autophagy targeting intracellular pathogens from classical nonselective autophagy (*Cell*, 2005b). Her lab has continued to make critical discoveries in the fields of xenophagy and virophagy, or viral-selective autophagy.

As cumulative data have shown, autophagy is an important innate immune response to intracellular pathogens, and several pathogens, including *Legionella pneumophila, Mycobacterium tuberculosis* and *Listeria monocytogenes*, have evolved mechanisms to elude the host autophagic clearance mechanism (*PNAS USA*, 2009). In fact, in 2006, studies had suggested that xenophagy could degrade bacterial pathogens; however, Dr. Levine's lab first demonstrated that viruses, such as Herpes Simplex virus type 1 (HSV-1), could also be targeted by selective autophagy for lysosomal degradation (*Autophagy*, 2006). Their previous study had suggested that the HSV-1 neurovirulence protein ICP34.5 mediated virulence by inhibiting the antiviral response mediated by the EIF2AK2/PKR pathway (*PNAS USA*, 2002). However, this subsequent report demonstrated that HSV-1 could be detected within double-membraned autophagosomes dependent upon expression of EIF2AK2/PKR, and that HSV-1 ICP34.5 could inhibit host autophagic degradation, demonstrating a novel antiviral innate immune response, and more importantly, revealed a novel mechanism by which a virus subverts the host autophagy pathway for its own benefit (*Autophagy*, 2006). Furthermore, Dr. Levine's lab elucidated the mechanism by which HSV-1 ICP34.5 inhibits antiviral autophagy, or virophagy, through direct binding to BECN1 (*Cell Host Microbe*, 2007). By engineering BECN1 binding-deficient ICP34.5 virus, they demonstrated that ICP34.5 mutant viruses were unable to inhibit autophagy in vitro and had an attenuated in vivo phenotype in wild-type mice, but virulence was restored in mice deficient in EIF2AK2/PKR signaling. Finally, to directly interrogate the role of essential autophagy genes in mammalian host antiviral response, Dr. Levine's group demonstrated that ATG7 and ATG5 promote clearance of viral proteins and survival of Sindbis virus-infected cells in in vitro and in vivo models, respectively (*Cell Host Microbe*, 2010). This study also suggested a critical role for the autophagy receptor protein SQSTM1/p62 in viral protein clearance. Collectively, these studies provided the first evidence of virophagy and a mechanism for virus-directed inhibition of the host innate immune response.

In addition to her significant contributions to the study of host innate immune responses to viral infections, Dr. Levine's discoveries using genetic screens and model organisms advanced our understanding of other forms of selective autophagy, including xenophagy and mitophagy. As the field of selective autophagy and its role in targeting and degrading intracellular pathogens, damaged organelles and protein aggregates has grown, her group developed systematic screening approaches to identify novel genes required for selective autophagy (*Nature*, 2011). A genome-wide siRNA screen identified hundreds of candidate genes required for targeting core autophagy machinery to Sindbis virus capsid protein. Many of which are also required for PRKN/parkin-mediated mitophagy. This first report focused on characterizing the role of SMURF1, a ubiquitin ligase, required for targeting selective autophagy components to viruses and damaged mitochondria, but not for basal autophagy functions. Her group later demonstrated the requirement of SMURF1 ubiquitin ligase activity in antibacterial targeting to phagophores, and further demonstrating its role in controlling *Mycobacterium tuberculosis* infection in in vivo models (*Cell Host Microbe*, 2017). Other genes identified by the siRNA screen included three Fanconi anemia (FA) pathway genes, *FANCC, FANCF* and *FANCL*, revealing a cytoplasmic role of FA pathway genes in selective autophagy, which were previously known to be essential for the nuclear DNA damage response (*Cell*, 2016; *Oncotarget*, 2016; *J. Cell Sci*., 2017). Similarly, Dr. Levine's group identified and described the role of peroxisomal proteins, PEX3 and PEX13, in virophagy and mitophagy suggesting that these functions may contribute to the pathogenesis of fatal peroxisome biogenesis disorders. Furthermore, a mitophagy-directed biochemical screening approach implicated PHB2 (prohibitin 2), a mitochondrial inner membrane protein, as a receptor for mitochondrial degradation, linking the prohibitin complex to this protective cellular process (*Cell*, 2017). Using a variety of approaches, Dr. Levine's group has made significant contributions to the foundational understanding of selective autophagy and its role in human diseases.

The Levine lab also had an extensive interest in unraveling autophagy-independent roles of essential autophagy genes in immunity. They demonstrated the role of BECN2 as a novel cellular regulator of viral G protein-coupled receptors (GPCRs) and as a host suppressor of Kaposi's sarcoma-associated herpesvirus-encoded GPCR-driven tumorigenesis in vivo (*PNAS USA*, 2016). This discovery indicates that BECN2-mediated endolysosomal trafficking and degradation of an oncogenic viral protein may represent a novel cellular mechanism in innate immunity (by defending against microbial virulence factors) and in tumor suppression (by degrading microbial oncogenic factors).

Therapeutics

Devoting her career to studying and understanding fundamental biological processes as a means of improving health, and using her extensive knowledge encompassing many scientific disciplines, Dr. Levine sought to develop therapeutics addressing diseases, including cancer, neurodegenerative and infectious diseases. In an effort to induce selective autophagy, the Levine lab used insights from mechanisms used by viral pathogens to avoid host-directed autophagy, to develop Tat-

beclin 1, an autophagy-inducing peptide molecule (*Nature*, 2012). The human immunodeficiency virus (HIV)-1 Nef protein inhibits autophagy through interaction with host BECN1 (*Nature*, 2013), which was mapped to a short peptide found in the evolutionarily conserved domain. This BECN1 peptide was fused to the HIV-1 Tat protein transduction domain to generate the cell permeable Tat-beclin 1 peptide, which induces autophagy in both in vitro and in vivo models, as well as improves clinical outcomes for neonatal mice challenged with chikungunya and West Nile virus infections. Using an alternative therapeutic strategy, the Levine lab also screened collections of small molecules for novel inhibitors of BECN1-BCL2 interactions (*Nature*, 2018). Three BECN1-BCL2 selective candidate molecules were identified and found to induce autophagy in in vitro assays. Development of these molecules, as well as the Tat-beclin 1 peptide, by Dr. Levine and her colleagues represents successful and innovative therapeutic starting points for the treatment of a broad range of human diseases based on extensive research in basic science.

Recollections about Beth

Zhenyi An; Assistant Professional Researcher, University of California, San Francisco (Former graduate student)

Beth meant a lot to scientists working in the biomedicine field, the autophagy community, and to me personally. She was a great mentor, and what she taught me will serve me well for many years to come.

I first met Beth when I joined her lab as a graduate student. On my first day in the lab, she welcomed me with a big smile. She was such a dedicated mentor, spending lots of time guiding me through the research projects and addressing all my questions patiently. She was always there to help. Beth was very hard-working. Once she spent hours in the microscopy room on her birthday, taking pictures of immunohistochemistry slides for a publication. When she got beautiful pictures of the slides, she was so happy and said that was the best birthday gift. Beth was also very sweet and considerate. She arranged a celebration on each lab member's birthday, and sent Christmas gifts to our homes each year.

Dear Beth, hopefully I will be able to pass on what I have learned from you to others. I will miss you so much.

Andrea Ballabio; Professor, University of Naples "Federico II", Italy

A few years ago, I attended my first autophagy meeting. I think it was in Whistler Canada in 2011. It was there where I met Beth for the first time. I was immediately impressed both by her science and by her style and attitude. Being a physician, I was struck by her studies in the context of human physiology and of disease mechanisms. Since then, we have seen each other at many scientific meetings and each time she would ask me about my research with an extremely kind attitude and, at the same time, with vivid scientific curiosity. At one of these meetings something happened that I will never forget. We were at Il Ciocco in Tuscany, it was quite late in the evening and I was informed that Beth was sick and she needed to be taken to a hospital. So, she got into my car, together with Skip Virgin and Vojo Deretic, and I drove (pretty fast) in the middle of the night along a winding country road looking for a hospital. We finally found a small hospital and she was really impressed by how fast and efficient the hospital clinicians and nurses were and then she thanked and cheered everybody there. Fortunately, she got better pretty soon but I realized that she had a bad disease (nobody had told me before then).

Since then Beth and I have met more and more often. She is the one who, together with Skip, "brought me" to Casma Therapeutics and I owe her for this.

Beth is definitely one of brightest and determined women that I have ever met. She is one of my science heroes.

Lynda Bennett; Assistant Professor, UT Southwestern Medical Center

In the year that I have had the enormous privilege of working with and learning from Beth, I came to realize that her passion for science was equaled by her desire to take great care of everyone.

I witnessed Beth's approach to mentoring her trainees as being professional, respectful and, above all, kind. She genuinely cared about her trainees' future by helping them to develop what she described as "career-building" projects to secure their successful transition into independence.

As exceptionally busy as she always was, Beth made her lab members a priority. Her time was a most valuable gift that she gave freely to everyone in her lab. She would make sure to meet frequently to discuss their science without ever making anyone feel that she was pressed for time or that she needed to be somewhere else. Indeed, my impression was that talking about science with her trainees was one of the things Beth enjoyed the most. Of course, conversations would very often turn to matters other than research projects because Beth was genuinely concerned for the wellbeing and happiness of the whole person.

I know that I am speaking for Beth's lab family when I say that we truly admired, respected and loved her. We all wish that we could have had considerably more time to learn from an exceptional scientist and mentor. We all greatly admired her tremendous gift for language and her tireless, all-on approach to everything she did. We also enjoyed her sense of humor and her love for hosting parties. Beth considered karaoke to be an essential part of her holiday party so that (in her own words) "people will stay and have a good time" (Figure 1).

Beth said on many occasions that for her, it wasn't all about the science, but she truly endeavored to develop something, a treatment, that was going to benefit people and cure disease.

Figure 1. Beth hosting one of her famous karaoke holiday parties, December 2019.

Beth Levine is irreplaceable, no one can fill her shoes, but we will strive to fulfill some of the dreams that she had.

Patricia Boya; Scientific Investigator, Centro de Investigaciones Biologicas Margarita Salas, CSIC, Spain

Dear Beth,

I will always remember the day I met you. This strong and elegant woman that organized the first Gordon Conference on Autophagy in 2003, when I was just starting as a postdoc in the field. You have been a reference in the field for us, as a woman and as a scientist.

Your many key contributions to Autophagy have been so important that have influenced generations of scientists. You will be also be remembered as an outstanding mentor. It is a pleasure to hear what they say about you.

With warm regards from Spain.

Francesco Cecconi, Gerry Melino and Mauro Piacentini; Professors, University of Rome Tor Vergata, Italy

Dear Beth, what is important is the message you leave around yourself, behind, and the young scientists you train with your own enthusiasm and energy. Definitely, your presence in the field has been pivotal and a crucial driver to establish this field in the center of cell biology, with its crucial implication in human diseases. We have to thank you for bringing our scientific community to the next level, and even more for allowing the growth of new young leading scientists. Just as an example, the discovery of *Beclin 1* has allowed the definition of the underlying molecular mechanisms of autophagy, and its interactions with the programmed cell death machinery. We do believe that your seminal work has inspired all of us, and we will never forget the good times we shared with you in many meetings all over the world.

Daniel Wei-Chung Chiang; Assistant Professor National Yang-Ming University, Taiwan (former postdoctoral fellow)

Not long ago, I was thinking about the possibility of inviting Beth to the next international conference in Taiwan. She used to tell me that she enjoyed white wine from Sancerre, France. I was planning, if she is visiting, sharing a bottle of white wine from Sancerre with her would be a great idea, isn't it?

I still remember vividly the scene when she passionately showed me a piece of nitrocellulose membrane in a broken petri dish that she kept for many years. This is THE membrane on which she initially identified Beclin 1 back in the 1990s at Columbia University. Beth told me about the story of this artifact, how it was accidentally trashed into the dumpster when the lab was moving to Texas, and then how it was miraculously rescued by lab members. I was amazed by such a small item – it marked an iconic moment in Levine lab history and turned out to be one of the important discoveries in the field of autophagy research. It was an inspiring experience that I will always keep in mind.

Thanks to her training and support, I had the opportunity to work in a top research university in Taiwan. Starting fresh as an assistant professor back in Taiwan is not an easy job. Facing many decisions on the research projects, I reminisce and think about the days when I was in Beth's lab. Every discussion, every conversation. I looked back and seek guidance from my experience with her. I often wonder: If she were in my place, what will she do?

In every way, Beth's passion and attitude toward science have greatly influenced me. I often tell my students about the story of my best mentor and I will continue to inspire them with our "Levine lab spirit" like when she passionately showed me that piece of membrane in her drawer.

Beth, it is hard to let you go. Thanks for everything you have done for us. It is a great pleasure and privilege to be your trainee.

Patrice Codogno; Research Director Emeritus, INSERM, Université Paris, France; ; and Sophie Pattingre, Senior Scientist, University of Montpellier, France

A scientific community is like a human being: it is born, grows and develops by welcoming other people. This is the case with the international research community on autophagy. Unfortunately, as happens for human beings, death has taken a person who was much treasured by this community. Beth Levine was very much loved and respected, a very special person. A great lady, "une Grande Dame", always elegant, like one of these New York ladies who can be found in the books by F. Scott Fitzgerald and Truman Capote. Yet, clothes are not enough to make a great person, and Beth was one mainly because of her dignity, her intellectual rigor, her interest for others, and her courage during her disease. She did not make a show of her courage, out of discretion, but it was emanating from her person. She was a solar person due to her brilliant intelligence, sharp as a diamond.

Everybody attending a seminar given by Beth was touched by her intensity. We were all mesmerized! Like both of us, during our first meeting with her in 2000 for organizing the 2nd International Symposium on Autophagy at Aix-les-Bains. One was an organizer and the other a PhD student in charge of the slides (a bygone time … !). Beth had always kept a special memory of this symposium: her first invitation as a speaker in front of the autophagy community. We think that it is not necessary to list here her contributions to the autophagy field after her discovery of beclin 1. We all know her outstanding scientific career filled with discoveries that go beyond our field and that have been influencing different research fields, from microbiology, immunology, and biology of aging, to cancer development and the control of cell survival and death.

Over time, a deep friendship has developed between Beth and Sophie, and Beth and Patrice, and also among the three of us. It has always been a pleasure to talk with her, in English, sometimes peppered by some words in French, a language that she could understand well because she followed French classes at university and worked as a physician in France during her medical course. Short or long conversations, a few words, some glances, we could understand each other.

Her daily life was to understand and accompany the members of her laboratory, to protect them and to push them to give their best with kindness. Hearing her steps, so recognizable, in the corridors was reassuring and stimulating at the same time.

Yes … it is a great person who left us and we are honored by her friendship (Figure 2). She has opened many research paths that will allow many future generations of researchers to continue her work that, sadly, has been interrupted too early.

We met her for the first time at Aix-les-Bains, on the shore of Lake Bourget that inspired Lamartine. She loved poetry. These lines from a poem by Lamartine accompany her now:

"And so! Pushed constantly toward new coasts,
Swept away into eternal night, with no return,
Can we never on the ocean of ages
Throw down an anchor for a single day?"

Figure 2. Goodbye to an exceptional person.

Maria Isabel "Marisa" Colombo (on behalf of the Autophagy South American Network); Professor, Universidad Nacional de Cuyo-CONICET, Argentina

A tribute to one of the pioneers in the study of autophagy

With deep sorrow we regret to communicate the loss of one of the pioneer scientists in the study of autophagy, Dr. Beth Levine.

Beth focused in the field of autophagy, more specifically in its regulation and its role in diverse diseases, including cancer and infectious diseases. One of her major contributions includes the discovery of the mammalian autophagy gene *beclin 1* and its role in tumor suppression, longevity, and antimicrobial host defense. Thanks to her collaborative spirit and generosity, many laboratories that work on autophagy, including our lab at the IHEM, Mendoza, Argentina, have been able to dissect and provide detailed molecular studies of this pathway both in vitro and in vivo.

The scientific community will remember her as one of the researchers that gave a substantial and quantitative leap in the knowledge of autophagy and its relationship with disease. Beth's legacy should be an inspiration for all of us, especially young researchers, to follow her footsteps and always hold to her very high standards and try to do the best in our research.

Dear Beth, you will always be a model to follow for all the ones which were very fortunate to know you either personally or through your outstanding work. We will miss you!!

Un homenaje a una de las pioneras en el estudio de la autofagia

Con profundo pesar lamentamos la pérdida de una de las científicas pioneras en el estudio de la autofagia, la Dra. Beth Levine.

Su campo principal de estudio fue la autofagia; más específicamente su regulación y su papel en diversas enfermedades, incluido el cáncer y las enfermedades infecciosas. Una

de sus principales contribuciones incluye el descubrimiento de uno de los genes reguladores de la autofagia en mamíferos, *beclin1* y su papel en la supresión tumoral, la longevidad y la defensa antimicrobiana del huésped. Gracias a su espíritu colaborador y su generosidad, las investigaciones de muchos de los laboratorios que trabajan en autofagia, incluido el nuestro en el IHEM, Mendoza, han podido describir con certeza y rigurosidad científica el rol de esta vía tanto en estudios *in vitro* como *in vivo*.

La comunidad científica la recordará como una de las investigadoras que le dio un salto cuantitativo al conocimiento de la autofagia y su relación con la salud y la enfermedad. El legado de Beth debería ser una inspiración para todos nosotros, especialmente los investigadores jóvenes, para seguir sus pasos y siempre tratar de avanzar con excelencia en nuestra investigación.

Querida Beth, siempre serás un ejemplo a seguir para todos los que tuvimos la suerte de conocerte ya sea personalmente como por tus trabajos. Te extrañaremos!!

Ana Maria Cuervo; Professor, Albert Einstein College of Medicine

You hear Beth Levine and you think autophagy, beclin, xenophagy, autosis … but for all of us in the autophagy field, you hear her name and we think way beyond her amazing science. We think of an authentic **pioneer** who was able to make a major splash in the biomedical research community with the word "autophagy", that back in 1999, was only familiar to a very small community of cell biologists. We think of a **visionary**, that thought of organizing the first GRC on autophagy and bringing the most multidisciplinary crowd to advance this field. We think of this **very elegant lady** (always with her high heels!) that showed up in a small autophagy meeting in a remote place in France and blew us all away with her first connection of autophagy with cancer. We think of this **amazing colleague**, always on target with her questions, passionate about "her" beclin, always finding a way to bring balance to the most disparate opinions. We think of this **dedicated mentor** that has given the field the next generation of creative and enthusiastic scientists to carry her torch … because yes … you need a whole group of gifted minds to continue was she has been doing in that effortless manner through the years. I am personally delighted that over the past years, I have had the opportunity to evolve from being utterly intimidated by Beth, to consider her a beloved colleague and friend. Our expeditions in search for "diet coke" in the most remote places during conferences, truly helped me to lose the "fear" of being in the presence of a unique mind and, instead, feel fortunate for having the opportunity to talk, discuss and always learn something new from her. You will think of auto-phagy when you hear her name, but I will forever think of an amazing person to whom we, as a field, and me as a woman scientist, will be always in debt.

Jayanta Debnath; Professor, University of California, San Francisco

I have vivid memories of first meeting Beth when she chaired the first autophagy Gordon conference in Maine in 2003. From the beginning, I was struck by her creativity, her attention to detail, her incisive intellect, and curiosity across a broad spectrum of physiologies and models. The Maine GRC was an epiphany for me and I would argue for many of us who started our incredible journeys in autophagy research, now nearing two decades, during those hot and humid summer days at Colby College. Over the years, I have watched in admiration the many amazing discoveries that Beth made and the accolades that she so deservingly achieved. I've also had the pleasure of coauthoring some reviews and commentaries with Beth, which allowed me to experience first-hand her incredible talent as a writer and communicator. But what I cherish most are the casual conversations over many years at our scientific meetings around the world, where I have benefited from her generosity as a mentor and friend. She has been among the first to cheer my scientific discoveries and to offer candid advice about everything in science and in other aspects of life. Sometimes I am asked why I enjoy autophagy meetings so much. For me, the answer is very simple – the friends and colleagues all over the world. To Beth, I am so grateful to you for starting me on this path and for being a such a wonderful friend and colleague for many years.

Vojo Deretic; Professor, University of New Mexico

Beth Levine was a dear friend and colleague who epitomized everything I liked about science and scientists. Dr. Levine was a pioneer, a true champion of autophagy. Unquestionably, her seminal opus of studies on mammalian autophagy has made the field what it is today. She infused the science of autophagy and the autophagy community with her immense intellect and humanity. She was a great role model for all of us and I can only imagine the impact she made as a role model for women in science. She endowed the field with her gracefulness, ethos, vision, leadership, and with her superbly high impact publications. With each of her outstanding studies she has made autophagy shine brighter and moved the field forward. Inestimable is her impact in generating magnetism both as a role model and through her publications ever attracting the new talent to the field as attested to by the volume of autophagy science that we all contributed to.

Beth Levine's impact on the field of autophagy is immense and represents a thread of significant historic and current discoveries, often setting the (autophagic) dots on the map for the rest of us to connect them. Beth always knew where the true North is both scientifically and personally. I will miss writing an occasional review with her and most of all the moments when we would gather as a circle of friends that included my scientist wife, having both fun and substantive discussions at autophagy meetings. I will also miss reading the next big story from her group, always pushing the envelope.

Figure 3. Beth Levine, International Symposium on Autophagy, China, 2015.

We have lost a dear friend and the world of science has lost one of its brightest lights but her persona and work will stay with us and will be treasured forever.

Ivan Dikic; Professor, Goethe University Frankfurt, Germany

From the first day I met Beth Levine, at the EMBO conference in 2009, she has been an exemplary scientist – a tireless torch that has led the autophagy community with her science and visionary personality. My first conversations with Beth in Ascona were about scientific conferences. She was enthused by how science could bring different people and disciplines together to address questions and challenges we normally would not come across. Beth was convinced this is the best way of encouraging creative science, and that conferences are places where critical connections are established. This spirited discussion resulted in regular meetings, frequently at remote and distant places around the world, such as Argentina, Japan, Canada, Croatia, Norway and many others (Figure 3). Over the course of these meetings, Beth became a close colleague and a good friend.

She was always elegant, thoughtful and smiling, particularly when surrounded by a large group of autophagy specialists and friends. Beth was also a peerless educator and supporter of new generations of scientists, especially women and those just joining the autophagy field. Her energy and passion to bring people together, and her captivating personality – sometimes shy, but always deeply warm and caring – will always be cherished.

We all remember and celebrate Beth the scientist – her discoveries, papers, and scientific breakthroughs, as well as her original and creative mind and her stimulating lectures. But we will equally remember Beth the woman. There was a personal touch that Beth added to her work and interactions that will stay with us. It has been a privilege to know her and spend time together – both as a scientist and a friend.

Keith Dionne; CEO, Casma Therapeutics

Dr. Beth Levine is known around the world as a pioneer in autophagy research and she brought that expertise to the founding of Casma Therapeutics to develop novel, lifesaving medications based on autophagy activation. But Beth brought more than her science to Casma, she also brought her passion for research and for developing treatments that could benefit patients. Beth's passion for science was on display the first time I met her. As she drove us from the hotel to her lab at UTSW, she stopped the car in the middle of the street to turn and describe her latest findings on autophagy. I was terrified, but I learned early on where Beth's priorities lay. Beth's belief in the healing powers of autophagy was not confined to the laboratory. When Beth was first diagnosed with breast cancer, in addition to the chemotherapy and radiation, Beth ran 5–6 miles every day. Why? To turn on autophagy. Beth practiced what she believed. Beth will be missed, but her passion and her drive to find cures for patients continue to inspire scientists at Casma to turn her vision into therapeutics that will benefit patients suffering from a host of diseases ranging from rare genetic disorders to neurodegeneration.

Xiaonan Dong; Assistant Professor, UT Southwestern Medical Center (former trainee)

Beth is a very thoughtful mentor and great scientist-educator who has made tremendous impacts on her mentees and every coworker. Her scientific impact is way beyond leading pioneering research. More importantly, she has been passing on the curiosity, enthusiasm and excitement of scientific inquiry to the new generation of researchers. She has always shed light on critical questions of each era and encouraged the new generation of researchers to take on the challenging conundrums. She often shares her own stories, particularly what happened before she became a world-renowned scientist. She said to me that "Xiaonan, you may not believe, when I began my independent research career, I had a very small lab space and a small startup; however, I never lost my belief and discovered beclin 1 afterward". She also said that she keeps those two-decade-old original yeast two-hybrid plates leading to the discovery of beclin 1, as they are her most precious souvenir for her career. In her philosophy, a researcher should never lose his/her dream and give in to the brutal reality.

Beth is undoubtedly one of the best writers in the scientific community. Her writings are so elegant and enjoyable, no matter it is a research article or a review. However, what the majority of the audience does not know is that she was also a wonderful teacher with great patience and humor. She made great efforts to teach junior researchers like me how to write a good article. She did not simply polish my writing, instead, she always included detailed comments to explain why her edits would read better. It was not unusual at all that she wrote a one-hundred-word explanation for only a single word substitution. It would definitely save her a lot of time if not doing so, but she told me that it is her obligation to teach her mentees how to fish instead of fishing for them.

Many people know how hard Beth usually worked in research, while fewer people know that she has also spent

a considerable amount of time on caring for the life of lab members. She considered the lab as a family. At a couple of weeks prior to my daughter's arrival (although Beth had a very tight schedule as always), we had two personal meetings and numerous e-mail conversations to discuss just one single question: the given name of my daughter. She said naming a baby is as critical as launching a new project and all her blessings were involved in the name she chose. She means a lot to myself and my family, and we cherish every single piece of our memories of her.

Zvulun Elazar; Professor, Weizmann Institute, Israel

Beth Levine was one of the founders of the emerging field of autophagy and a worldwide top biomedical scientist. She was a truly gifted investigator who has been directly responsible for foundational scientific discoveries in several areas, most notably autophagy, a cellular process with very important implications for human infectious diseases, neurodegeneration, cancer, and metabolic disease.

Dr. Levine was a wonderful collogue and a trustworthy friend. She was always open for scientific discussions and was willing to help, especially young scientists, in any possible way. Her wisdom and knowledge were extraordinary and together with her outstanding scientific achievements, placed her early on as a true leader of our field of research. Her strong personality together with the gentle and elegant manner by which she was treating her peers led to a large number of fruitful collaborations and friendships around the globe. It is much to her credit that the scientific atmosphere among the autophagy research community is uniquely warm and open for new ideas. She was a source of inspiration for many of us.

Lorenzo Galluzzi; Assistant Professor, Weill Cornell Medical College

Dear Beth,

I first met you around 2010, at a Parisian conference my dwindling memory cannot identify now. What I instead distinctively remember is that you came to me – impeccably dressed – during one of the breaks, and asked if I was really Lorenzo, as you expected someone looking way more senior than myself (back then in my 30s, most likely wearing a pair of old jeans and one of the very few polos I have ever owned) or even that Lorenzo Galluzzi would be a fictional name for Guido's ghost writer. That was a funny way to break the ice, but was followed by the most unexpected and unsettling question: "I'm looking to hire someone like you, would you consider moving to Texas?" It was such an honor for me that you – THE Beth Levine that I had studied, cited, and ultimately learnt from so much – were actually offering me a job. I blabbered how much I admired your work and that I would consider your offer, although I already knew deep inside that I would not take it. I was not ready for such a free jump.

Since then, we stayed in touch over e-mail, worked together on a few review articles and met quite regularly (most often at Keystone or Gordon conferences). At each of these occasions, your grace, kindness and supportiveness invariably came across, even when the unfair fight you had engaged with cancer was the toughest to endure. Your support was especially important when I finally decided to take that jump and accepted an Assistant Professor position at WCM in 2017. It was with the deepest sadness that I learnt about you a couple of days ago. Sadness not just because the entire planet has lost an irreplaceable scientist, an authentic *illuminée* (to use the language that you loved so much), but because we have lost a great woman, caring friend, passionate mentor. You are leaving two huge voids behind, Beth, and your scientific legacy will fill only one of them.

Frank Gentile; Chief Operating Office, Casma Therapeutics

I am grateful for the opportunity to write about my perspective of Beth Levine. My words are inadequate to truly capture my feelings toward her. My particular relationship with her was both very scientific and professional and also being deeply personal. I had the good fortune of meeting Beth in early 2016. She was at that time dealing with the effects of breast cancer therapy (chemotherapy and radiation) while she was pitching the idea of a company focused on the autophagy-lysosomal pathway to me and two others at Third Rock Ventures. She was indefatigable in her preparation for that meeting and in her scientific AND clinical passion that a new company focused on this pathway could bring about cures and therapies for a great many devasting diseases. We worked together for 4 years. Two of those were in incubating and refining the ideas that would eventually become Casma Therapeutics and two were after Casma was launched with a nearly 60 million USD investment. Beth was the cornerstone of Casma. There were other founders involved. All are amazing scientists in their own right (Andrea Ballabio, Jim Hurley, and Skip Virgin), but Beth and her work were the cornerstone of Casma. Beth gave three things to the creation of Casma. First was her time, perspective and amazing discoveries related to the field. Second, was her attitude that she would do anything to help get this enterprise off the ground and third, that she was willing to educate and mentor a group of VC's and young scientists on the wonders and importance of this pathway. I hope that one of her many permanent legacies will be the life-saving drugs that are developed in this company.

While working with Beth in those early years, I came to see another side of her. This was her ability to create deep and lasting friendships. I recall one conversation in the summer of 2017. My family was going through our own devasting health crisis with one of our children. I was speaking with Beth about a company incubation issue when she asked if there was something wrong with me. She could just tell in my voice. I confided in her this very personal and confidential family pain and she responded with equal candor about things she and her own family had been through. She was completely vulnerable with me and it not only shocked me that she was willing to trust me with something so personal but I cannot

describe how much peace I experienced then that someone like Beth who was a Howard Hughes Medical Investigator, a member of the National Academy of Sciences, a holder of an endowed professorship at UTSW and someone in the scientific history books would even take the time to talk to me about this at all. Beth gave me some of her strength so I could move forward.

Several months later, I myself became very sick with a tick-borne pathogen (not uncommon in Massachusetts). I was supposed to see Beth in Dallas the week I wound up in a hospital. When she found out, she spent a great amount of time looking at my lab results as she was trained as an infectious disease doctor. She insisted that I see the Department Head of Infectious Diseases at Massachusetts General Hospital and even made the appointment happen for me through her professional network.

So, my personal tribute to Beth is to point out not only what she has done for me professionally by being a founder of Casma Therapeutics, but also what she has done for me personally during some very difficult periods of my life. I wish I could have repaid any of that back while she bravely faced the end of her life. I mourn her and miss her. She taught me that there is always time to reach out to others with empathy and I am so sorry her time was so short among us.

With deep gratitude for my friend.

Diane E. Griffin; Professor, Johns Hopkins Bloomberg School of Public Health

Beth was an infectious diseases fellow at Johns Hopkins with little basic research experience who came to do her research training in my laboratory, and I was lucky to have her as a fellow – smart, motivated, hard-working and quick to identify important questions and devise approaches for answering them. My laboratory was (and still is) working on alphavirus encephalomyelitis in mice, and her contributions to this project are well known: identification of antibody as an important mechanism for virus clearance from neurons (*Science*, 1991), and apoptosis as a mechanism of virus-induced cell death (*Nature*, 1993). Luckily for both of us, Marie Hardwick was a laboratory colleague with molecular virology skills that Beth quickly learned, resulting in construction of a very useful double subgenomic recombinant virus for expression of host cell proteins in infected cells – a tool that is still widely used. However, not all of our important scientific endeavors led to high profile publications: In 1991, Beth, Richard (Dick) Johnson, a neurovirologist who was my mentor and Director of the Department of Neurology, and I spent a week in Pergamino, Argentina investigating patients with "late neurologic syndrome" a complication of immune plasma treatment for Argentine hemorrhagic fever. Evidence was that this was due to virus reactivation in the nervous system 3–4 weeks after treatment – the data still need to be published!

Malene Hansen; Professor, Sanford Burnham Prebys Medical Discovery Institute

I met Beth Levine at my first international conference in Mexico in 2011, where she invited me to give my very first talk to the autophagy community. This was a milestone for me, noting that Beth's lab several years earlier had published the first direct link between autophagy and lifespan extension in the nematode *C. elegans*. Coming from the *C. elegans* aging research field, this was a truly inspirational event given that the intersection between autophagy and aging was to become the future focus of my new research laboratory. I remember she welcomed me warmly, listened carefully to our research ideas, and provided much valued feedback. As a newcomer to the autophagy field, this meant so much to me, and Beth continued to be a genuine mentor/sponsor and a strong role model to myself and my lab members, something I will forever be grateful for. Many other scientific conferences followed, with travel to wonderful places, and a much-valued friendship grew on top of our professional relationship – during these trips and a number of delightful dinners, she would share many personal stories. One particularly memorable one was when she learned that exercise not only would increase autophagy in muscle but also in the brain, she went and bought a treadmill and started exercising! A lovely story that shows just how passionate she was about her truly inspirational research and its tremendous impact, ranging over many different fields of biology. My last personal interaction with Beth was also at a conference. It was last summer in Scotland, where she gave a dazzling talk, went on a cool conference tour to the Stirling castle, and joyfully learned Scottish dancing at the close of the meeting with her "family" of beloved colleagues and new autophagy researchers. I cannot think of a more wonderful memory of this unique and creative scientist, an admired role model especially for women, and a truly inspiring human being.

J. Marie Hardwick; Professor, Johns Hopkins University

Beth was a fellow with Diane Griffin studying antibody-mediated virus clearance from neurons (Science 1991) and virus persistence in the brain (*J. Virol.*, 1992). My lab next door was studying the BCL2 homolog of Epstein-Barr virus (BHRF1), using BCL2 as a control. Both proteins had been discovered only a few years earlier. Beth had a vision that challenged the very core of our understanding of viral neuropathogenesis – she cloned BCL2 into the Sindbis virus genome to illustrate that mammalian BCL2 could dramatically alter the outcome of virus infection (*Nature*, 1993; *PNAS USA*, 1996). Beth had impeccable foresight that focused her work to yield high impact science. I learned a lot from her, she had a big influence on my career. Beth elevated the atmosphere in the lab with her fashion and style – I saw her many times working in the hood in a designer cocktail dress – beautiful person in so many ways.

Sad to lose her – so many are shocked and saddened to learn the news.

Congcong He; Assistant Professor, Northwestern University (former postdoctoral fellow)

I am very fortunate to have worked with Beth as a postdoctoral fellow from 2009 to 2013. Her passion for science is intense. I still remembered her unconcealable joy talking about some unexpected discoveries during my interview. I then joined her lab, wanting to study the role of autophagy in metabolism and metabolic diseases. While Beth herself is a cancer researcher and infectious disease expert, she welcomed bold ideas and gave me incredible freedom and independence to pursue the new field. She was even more excited than I was on every trivial finding along the way. She never wanted to miss any chance discussing new data and experimental progress, evidenced by e-mails routinely written at 3 AM or at a corner on Earth during her vacations. When our first paper revealing the unexpected function of autophagy in exercise got published in *Nature*, she proudly announced that she installed a treadmill in her house so she could practice the science and confirm the findings herself at home.

Being resilient is another valuable thing I learned from her, even 6 years after I have started my own lab. At those moments that were emotionally catastrophic (for example, harshly negative review on papers/grants), she was there to support and encourage, and help me bring back the enthusiasm by soothing and mood-lifting words or texts. This is extremely important for one's growth and maturation in academia.

Yet sometimes, I feel that Beth is still like a youngster, when it comes to her creativity, her straightforwardness and energy, her sharp yet witty conversations at numerous lab lunches/dinners, and her vivid usage of emojis in e-mails. I sorely miss her as a great and very fun person, mentor, and pioneer. She is truly a charismatic role model for female scientists like me (and males as well).

Shu-Yi Huang; Assistant Researcher, National Taiwan University Hospital, Taiwan (former postdoctoral fellow)

Dr. Levine has been my role model as a female scientist. She is always sharp on scientific discussions but was never harsh. She has a very high standard for the quality of evidence and has great attention to detail even with her crazy schedule. She was like a superwoman when we were preparing our manuscript; she replied to my e-mails so quickly that I didn't know if she slept at all. In addition to science, she always remembered to ask me about my family when we had our one-on-one meetings and gave me great advice on work-life balance and even how to raise a kid.

I left her lab and moved back to Taiwan in 2012 due to family reasons. It took me a few years to finally get back to research, but now I don't have enough time to prove myself to her. The International Symposium on Autophagy was held in Taiwan last year but she accidentally missed it. I didn't realize that was the last chance for us to meet again. I'll always remember her elegance and kindness.

James Hurley; Professor, University of California, Berkeley

I read Beth's papers long before I met her, and they inspired me to start a new research direction in the lab, on the structural biology and biochemistry of Beclin and mammalian autophagy. It took off. After I got to know her, she was kind enough to have me join her in founding a company to discover new autophagy inducers and cure diseases. Sometimes I'm inspired to write a poem. Now is one of those times. Here's a haiku for Beth:

From Beclin to cures
Elegant, perfect, composed
Icon of our field

William T. Jackson; Associate Professor, University of Maryland School of Medicine

Beth is the kind of scientist who inspires not with platitudes or buzzwords but by doing. By doing the best science in the field, not in fits and spurts, but every time. Reading a paper with Beth's name on it is like reading a preview of a future textbook. It's not just cutting edge, it's *right*, in the satisfying I-could explain-this-to-a-student way of the very best science.

At a Keystone Meeting years ago, Beth was the one who taught me, a green postdoc, how to pronounce "autophagy." The Editor in Chief of this very journal notwithstanding, she was as right about that as she is about everything else.

Cindy Jozefiak; Division Manager, UT Southwestern Medical Center

It has been my honor and privilege to work for Beth Levine for the last 14 years. She and I were as different as two people could be. She, a scientist from New York and I, a tried and true Texan; one of our first conversations was a debate about what "BBQ" means. We learned, over the course of time, to speak each other's language and developed a friendship that I will forever cherish. We shared celebrations and tribulations about our children during their younger years while growing up and I was always impressed with the loving mother that Beth was. She always made sure she was home for dinner when her kids were growing up. She was devoted absolutely to her family.

Beth was intimidating if you didn't know her and it could take some time to *get* to know her. I believe she was terribly shy, although she probably wouldn't admit it. Beth had a presence about her. She was professional, sophisticated and classy. I was reminded this morning how she could move like the wind in her 4-inch stiletto heels. Once, when she broke her elbow, I was assisting her to the car and noticed she was wearing 2-inch block-heeled shoes. I said, "Beth, you need to be wearing flats." She said, "These *are* my flats."

I have seen Beth's extraordinary contributions to science and I know the world has lost a giant in the field and the benefit of her future discoveries. I cannot imagine UT Southwestern without Beth. She was a selfless mentor and adviser to her trainees. Beth truly cared about the lives and careers of her lab members and did all she could to ensure they succeeded beyond her lab. Beth held people to high standards but she held herself to even

higher standards. She had a strong moral compass and was generous beyond measure.

It is difficult to put into words the depth of my admiration and affection for Beth. I'm afraid that I cannot do her memory justice no matter how much I say. She was truly an amazing person and I will miss her terribly. We shared many laughs and I will treasure my time with her always. Beth has made an everlasting impression on my life.

Richard N. Kitsis; Professor, Albert Einstein College of Medicine

Dear Beth,

First and foremost, I will miss you. It has been a long time. I think we first met in the early – 90s when you were an assistant professor at Columbia going off in a completely novel and exciting direction. I remember that I was giving a seminar there, and you took me to my next appointment, and then just disappeared. You were a little shy then. But, under the shyness, was tremendous resolve and the sheer guts to figure out things about nature that no one knew or suspected. Your contributions were so important to the development of a new field. It was not just the novelty of the work. It was the solidness of the discoveries, and your uncompromising standards. You have made a real difference in science – in how many people view the world. You have made a real difference in my life. So, this note ends just as it started – I will miss you.

Daniel J. Klionsky; Professor, University of Michigan

"Unfortunately, the fear I have been living with for the past four years has materialized into reality – I have metastatic disease." Beth wrote these words to me on January 12, thus beginning the first of several months when I found it difficult to stop thinking about her. Yet, now that I am trying to write a tribute that sums up her life, it seems to be a nearly impossible task – at least for one person, and confined to the pages of a single tribute; Beth embodied very many things to a wide range of people. One aspect of Beth that is eminently clear is that she was a fighter. Indeed, I do not know anyone who was so determined as Beth. Almost until the last possible moment she was working on writing a review article with Noboru Mizushima, about to start on a new grant proposal with Ana Maria Cuervo, and had agreed to an interview with me to sum up her life's work. If only I'd had the chance for that interview I might have been able to write this with some confidence that I had accurately summed up such a rich life, ended much too early.

I first met Beth at the International Symposium on "Lysosomal Transport in Health and Disease," which took place in Aix-les-Bains, France, in September, 2000. I think this was the first time for most people in the autophagy field to meet her, because her seminal *Nature* paper on the connection between autophagy and BECN1 (beclin 1) was published in December 1999. Beth was an unassuming person, considering that she had just written a paper that was about to revolutionize the field, providing the first evidence for a role of autophagy in tumor prevention – and the first paper that provided what would turn out to be the major direction of the autophagy field for the following two decades, the role of autophagy in health and disease. We now know that autophagy has an infamous "double-edged" role in either promoting or preventing cancer, due to an incredible number of papers on this topic. But it is difficult today to remember where the field of autophagy research stood at that time – very few people had even heard of autophagy.

I would like to step back and consider that time a little more carefully. The first International Symposium on Autophagy was held in Japan in 1997. Although the Gordon Research Conference (GRC) on Lysosomes/Molecular Membrane Biology had started to include a session devoted to autophagy, Beth was concerned that there was no specific conference focused on this topic in the United States. In addition to helping advance the science in this area, Beth wanted to have a venue where it was easier for students and postdocs in the USA to attend (i.e. with reduced cost relative to international conferences). Thus, she contacted me with the proposition that we apply for our own GRC series. The GRCs have substantial logistical support from the main office, which provides a certain level of funding. However, it is anticipated that the organizers will also raise funds to pay for speaker travel costs, food, etc. Imagine my dismay when calling various companies to see if they would be interested in funding a conference on autophagy. Typically, there were a few moments of silence as the person on the other end of the line tried to figure out if they had heard me correctly, what I was talking about, and how to quickly end the conversation. If not for Beth's efforts in fundraising, the conference would not have succeeded. In fact, Beth was able to raise enough money to largely fund the second GRC as well. At any rate, the first GRC on Autophagy in Stress, Development and Disease was held June 22–27, 2003 at Colby College, Maine. Beth was the chair, and I was the vice chair. In 2007, Beth, Noboru Mizushima and I were the co-chairs of the first Keystone Symposium on Autophagy in Health and Disease. Again, Beth was the driving force behind the development and organization of this conference. Now, there are numerous autophagy conferences held around the world, and several societies with annual meetings devoted to this topic, but the first conference devoted to autophagy in the USA was primarily due to Beth's efforts.

With all due respect to some of the early pioneers in the autophagy field, such as Per Seglen, Fred Meijer and Patrice Codogno, to many people in the 1990s, autophagy was largely considered a garbage pathway used to remove cellular debris. For the significance section, my own grant applications at that time referred to the work of Richard Lockshin on the physiological role of autophagy in insect metamorphosis. Then, Beth's *Nature* paper appeared and "significance" took on an entirely new meaning – autophagy was involved in cancer. For those of us applying to the NIH for funding, this was big news indeed. However, I am jumping ahead in terms of talking about Beth's publications. Certainly, for the autophagy field that *Nature* paper was very important, but it was hardly the only one that can be described in that way, and it was far from her first published paper.

Beth had developed an interest in infectious diseases. During medical school, she spent three summers working in Haiti, where she studied with Dr. Jean Pape, the founding Director of the Haitian Group for the Study of Kaposi's Sarcoma and Opportunistic Infections/GHESKIO. (As an aside, it was during her time in Haiti that Beth developed fluency in the Creole dialect, to complement her love of the French language.) Beth's work in Haiti led to her being a second author on a paper by Pape et al., published in *The American Journal of Tropical Medicine and Hygiene* in 1987. This was followed by three first-author papers in medically oriented research journals. Thus, even at this early stage of her career (she started medical school at Cornell University Medical College in 1986), she was interested in research. According to her husband, Dr. Milton Packer, Beth's path was always directed toward research, not to the practice of clinical medicine, "She loved clinical care, but that was not where her heart and head resided."

As a result, Beth spent four years, from 1989–1992 after her residency as a Clinical and Research Fellow, working with Dr. Diane Griffin at the Johns Hopkins Hospital. At that time, she focused on alphaviruses including Sindbis virus. This marked the beginning of a seemingly nonstop series of papers in high-profile journals such as *Science* and *Nature*, which has continued until the present day. Beth's work with Sindbis virus had a lasting effect on her career, as evidenced by a critical paper written by Xiao Huan Liang, a former postdoc in Beth's lab: *Protection against fatal Sindbis virus encephalitis by Beclin, a novel Bcl-2-interacting protein* was published in the *Journal of Virology* in 1998. The abstract of that paper states: "We identified a novel 60-kDa coiled-coil protein, Beclin, which we confirmed interacts with Bcl-2 in mammalian cells" and "These findings demonstrate that Beclin is a novel Bcl-2-interacting cellular protein that may play a role in antiviral host defense." I doubt that at that moment even Beth realized what a wild ride she was about to begin, because it was of course her work on BECN1/Beclin 1 that led her into autophagy research.

According to the Human Genome Nomenclature Committee, the official name for Beclin is BECN1. Beth named it Beclin for "BCL2 interacting". I remember once, for some unrelated reason, that I asked Beth about her name, and she mentioned that her middle initial was "C" (I do not think she ever used it on her papers; she used her full name on her first two patents, and then used her middle initial on all subsequent ones). She then quickly pointed out that she did not choose the name Beclin to match her name, "Beth C. Levine", which had not occurred to me at that moment. In fact, I had the impression that Beth was embarrassed to think that anyone might have that thought, because such an action would have been uncharacteristic. This coincidence between beclin and Beth's initials was confirmed by Milton Packer, who noted that Beth was actually surprised when he pointed out the parallel in the letters. Just for the record, I also note that, although her own official name is "Beth", she used the name "Elizabeth" for some time during medical school. Thus, the name on her first paper is actually listed as "E. Levine".

From my perspective, the late 1990s and early 2000s was an exciting time for research in general, at least for cell and molecular biologists. One of the reasons I state this is because DNA sequencing had just reached a state where it was becoming possible to sequence entire genomes. For example, the complete genome of *Saccharomyces cerevisiae* was published in 2000. Thus, sequence information started to become more widely available in the preceding year. Beth had published that first paper on Beclin in 1998, which included as Figure 1, the sequence of the protein. For this reason, she was contacted by Dr. Matthew Seaman, a former postdoc from the lab of Dr. Scott Emr. Dr. Emr's lab had identified and characterized many of the *VPS* (vacuolar protein sorting) genes, including *VPS30* (also referred to as *ATG6*). Dr. Seaman noticed a sequence similarity between Vps30 and Beclin, and he mentioned this to Beth. Such is the stuff through which history is made. In 1999, Beth's lab published the seminal *Nature* paper: *Induction of autophagy and inhibition of tumorigenesis by* beclin 1. This paper demonstrated the role of Beclin 1 as a haplo-insufficient tumor suppressor that was "mono-allelically deleted in 40–75% of sporadic human breast cancers and ovarian cancers." Furthermore, she demonstrated that *beclin 1* could restore autophagy in the yeast *vps30Δ* strain. I think it is difficult to overstate the importance of this work, which focused attention on autophagy just as the molecular analysis of this process was in its infancy. The subsequent explosion in the number of autophagy-related publications, mostly due to papers demonstrating the connection between autophagy and a growing list of human diseases, attests to the impact of this one manuscript.

Beth's lab, first at Columbia University College of Physicians & Surgeons and then at the University of Texas Southwestern Medical Center, continued to make significant contributions centering around autophagy, but connected to a wide range of other topics. One aspect of Beth's research that I found quite intriguing was the fact that she used so many different model systems – mammalian cell culture, mice, *C. elegans*, even yeast – to answer the questions that she wanted to explore. Although it is easy to get caught up in the many high-profile papers, it is important to remember that Beth was a meticulous researcher who was interested in understanding how cells worked. Thus, her publishing opus includes a large number of papers that focus on mechanistic aspects including the nature of the BECN1-BCL2 interaction. In addition, Beth was highly sought after for collaborative work, which further expanded the topics of her research.

According to Milton Packer, "[Beth] reasoned that cells must have a mechanism of clearing viruses, and her work led her to propose autophagy as the clearance mechanism. But autophagy captured her spirit and her soul. Once she began to focus on it, her interest in virology (and infectious diseases) waned considerably." Nonetheless, I think that Beth never entirely lost interest in infectious diseases, and much of her recent focus was concerned with the role of autophagy in the cellular response to microbial infection. This interest, coupled with her work on BECN1, led to another important discovery, Tat-beclin 1. The potential for using this peptide, or derivatives, to induce autophagy as part of the immune response to invasive pathogens led, in part, to the launching of Casma

Therapeutics, which was scientifically founded by Beth, Andrea Ballabio, James Hurley and Skip Virgin.

For me, Beth was always a reliable, generally calming influence. The only time I can remember seeing Beth particularly upset was at a conference when someone gave a presentation that she considered to be sub-par, not due to the style of the presentation, but rather because of the data. At any rate, Beth was one of the original three associate editors of the journal *Autophagy*, along with Patrice Codogno and Yoshinori Ohsumi, and she has remained on the board ever since. Ron Landes, the original publisher, had asked me if I was interested in starting a journal devoted to this topic. I asked Beth, Patrice and Yoshinori for advice about whether this was a good idea. Each of them responded with a resounding "No". They argued that it was too early to start a journal on autophagy, and that it would minimize the field if we published papers in this unknown journal. Thus, I informed Ron Landes that it was too early. However, Beth also suggested that if I wanted to be an editor as the next step in my professional career – meaning, if that was something I was interested in doing – she was supportive. Thus, when Ron called back three months later to see if it was still too early, I agreed to go ahead. Beth has been a staunch supporter of the journal, and helped me maintain an appropriate perspective. She was a great sounding board on the occasions when I wanted to write an editor's corner excoriating a paper published elsewhere that had faulty science; I would furiously write an article, send it to Beth for comment, and get back a measured response along the lines of, "Now that you have gotten that out of your system, let me explain why you do not want to publish it." For each of the guidelines papers that we published, Beth was one of the early signatories. In fact, I sought her out for the very reason that I knew having her name on the paper would lend it dignity and encourage other authors to participate. When I mentioned this to Beth, her response was typical, "Hah".

So, we know Beth primarily as a stellar researcher. However, I knew there was another side to this intensely private person, and one that I hoped others could at least glimpse, through various anecdotes. I want to conclude with some comments from her husband (note that in part this was a response to a question I asked in regard to an e-mail I received from Beth some time ago, that was written at 2:00 am – I wondered if she ever slept):

"Beth was focused on two things in her life: her research and her family. Her family always came first, but her commitment to her work was extraordinary. It was not unusual for her to work late hours. That was actually part of our family routine. We both had a lot of work after "normal hours", but we took regular breaks during the evening to spend time together, and then, often returned to work before going to bed. Depending on the evening, we usually went to sleep around midnight or 1am. Sometimes, when the evening was filled with some activity, the first opportunity to go through e-mails might occur at 2am.

"But family was always first, especially when our kids were young and living with us. We never missed a childhood event – never ever. Our son played Little League baseball. I was the head coach, and Beth was the official scorekeeper. We never missed a game, and we often left a conference in another city early so we would be able to catch a flight in time for the first pitch. The same principles applied to our daughter's school events. (Beth was also the official scorekeeper for our family's Scrabble games.)"

Guido Kroemer; Professor, University of Paris Descartes, France

To Beth Levine: A timeless word of love

Dear Beth,

You have been dedicating most of your scientific life to autophagy, the name of which is a neologism derived from ancient Greek.

Most modern European languages including English, your native tongue (spiced, in your case, with some Yiddish and a few Hebrew words), and French, a language that you were particularly fond of (you even majored in French studies), have reduced their vocabulary with respect to ancient Greek. For example, for love (*amour* in French), Greeks use three totally separable words: eros (which has lost all its poetical connotation in modern English or French), agape (caring for others in an altruistic way) and philia (affection among friends and for immaterial values, yielding the prefix for philosophy and philanthropy). For time (*temps* in French), Greeks used three expressions: chronos (the time that relentlessly consumes itself), aeon (or "eon", a long period that reflects the cycles of generations) and kairos (the opportune moment).

For us, Beth, you have been embodying the essentials of these sophistications, like an ancient but humane Goddess, mythic but close.

You had many facets, Beth, but for most people you were best known as an overtly brilliant scientist, engaged in your everyday live by your impetuous strive for knowledge (philia) and your fight against infectious diseases and age-associated health deterioration (chronos), fueled by medical altruism (agape).

For many years, you invested most if not all of your energy in discovering new elements of the process, that you were the first to appreciate for its pro-health effects, autophagy, taking advantage of your kairos. You discovered that a human gene encoding an essential autophagy protein, Beclin 1, is involved in malignant disease. You pioneered the idea that autophagy – in principle – has antiviral properties, but that infectious pathogens may perfidiously subvert or even harness autophagic pathways to replicate themselves. You discovered that caloric restriction increases life span via the induction of autophagy. You found that exercise reduces diabetes by activating autophagy. You discovered a myriad of molecular connections between autophagy and distinct human diseases. You were a giant of biomedical research, because you discovered that insufficient or excessive autophagy precipitates pathological manifestations. In addition, you identified several actionable targets to correct pathogenic deviations in autophagy.

You were elegant in your style, appearance, expression and verb, impersonating a close-to-intimidating perfection, especially when you were giving public lectures. But when you stepped down from the pedestal, divinity gave room to cordiality

and fragility. You were sympathetic (another Greek word) because you made us understand that all of us are suffering from the same afflictions: modern society (to which you were so much opposed) with its collateral superficiality, mediocrity and greed: no grandeur without dollars; no medical care without credit cards; no promotion without profit.

You were ambitious for Humanity and for patients, not for yourself. You cared for your family, friends, colleagues and alumni more than for yourself. You defended principles, not yourself. Instead of vanitous recognition that would fade away with chronos, you earned love for eons. Love is endless.

Alfred J. Meijer; Associate Professor Emeritus, University of Amsterdam, The Netherlands

In the nineties, when I entered autophagy as a research area, I noticed that the field was dominated by a few scientists who I greatly admired (and I still do). Beth was one of them. She was very bright, critical, original in her ideas and, perhaps more importantly, extremely nice. My background as a researcher was in the field of metabolism, and I had hoped that one day research in autophagy, which in the nineties was not very popular yet, would eventually lead to clinical applications. Beth was the first to make the breakthrough in 1999 with her discovery of the connection between autophagy and cancer. We now know that defective autophagy is also implicated in many other diseases. Which is the reason why popularity of autophagy as a research subject has increased exponentially ever since.

During one of the meetings of autophagy, I think it was in 2003 at the 1st Gordon Conference on Autophagy in Stress, Development and Disease (Colby College, Waterville, Maine), I had a long conversation with Beth, not related to autophagy but to my family background, in particular my own experiences as a child during and after the war. This is not a subject I generally talk about, and certainly not at scientific meetings. I am not sure why and how we started the conversation, but it struck me that she was so much interested in my family history. She listened with deep understanding. I have always remembered this.

After my retirement in 2005 I still followed the literature on autophagy research, and that of Beth in particular, with great interest. She has always been an example for me. The last time I met her was at a CFATG meeting in Paris, November 2017. It is beyond comprehension that Beth is not among us anymore.

The world has lost a great scientist.

Alicia Meléndez; Professor, Queens College and The City University of New York (former postdoctoral fellow)

I joined Beth's group in 2000, and I began studies on the role of the BEC-1 protein in *Caenorhabditis elegans* development and aging. Beth had just discovered the human protein Beclin 1, and she was interested in studying the role of this protein in a genetic model system. I had trained in Drosophila and *C. elegans* genetics and immediately found the *C. elegans* ortholog of Beclin 1, and decided to investigate its role in *C. elegans* dauer development and longevity.

When I think of Beth, I am so grateful for the independence that she afforded me. I deeply treasure Beth's willingness to let me pursue my own ideas, and the support that she provided. She believed in me and took me seriously. Beth was passionate about the process of scientific discovery, and her wisdom and guidance were exemplary throughout my time in her lab, as well as years later. Beth was a highly creative, and generous spirit. She was an out-of-the-box thinker, with a unique intuition as to the right biological question to ask. As a mentor, she valued the members of her lab greatly, and was generous with her time. We often compared notes about our children, as they were of similar age. She loved her family and was very supportive of women in science having their own family. She was a great role model on how to be a scientist and a mother. If I have to sum it up in a few words: I certainly would not be where I am, if it were not for Beth.

Noboru Mizushima; Professor, The University of Tokyo, Japan

I clearly remember the first time I met Beth. It was at the 2nd International Symposium on Autophagy in France in 2000. Beth was in a suit, unlike other autophagy researchers. And, she gave a perfect presentation, unlike other autophagy researchers. Beth admits that she is a perfectionist, which I think many people would agree with. But this is only one aspect of her. She is also caring and generous. She nurtures friendships in the autophagy field. During my discussions with Beth, she often prefaced a statement with "I am sorry but I am too American …." I think she was concerned about being too direct to Japanese people. But this was never the case; she was always kind, thoughtful and fair.

Beth organized the first Gordon Research Conference on Autophagy in 2003, which was a truly memorable event. Not only were the scientific sessions excellent, the excursion was also wonderful. She brought many gloves and organized a baseball match she called "Yeasts v.s. Mammals". She started with teaching baseball rules to the European researchers. She really enjoyed playing baseball and shared her enthusiasm for the sport with us freely. But she was actually far from "perfect" in baseball. She was completely different from the Beth we saw at conferences. I think both are the true Beth.

Beth has contributed tremendously to the field of autophagy research, not only with her high impact scientific discoveries but also as a strong, kind and impartial leader and mentor. I would like to express my heartfelt gratitude to Beth as one of the recipients of her intellect and kindness over the years.

Leon O. Murphy; Chief Scientific Officer, Casma Therapeutics

I first met Beth at a Gordon Research Conference in Tuscany in 2005, my first autophagy meeting. While it was indeed daunting for me to approach Beth after her talk, she was interested in my questions and especially interested to know why an industry scientist was attending the conference. It was apparent to everyone at that meeting that here was someone who was pioneering the field of mammalian autophagy and its relevance for human disease. She really stood out. In the years that followed we got to interact at subsequent workshops and meetings, and

I always benefitted from Beth's intellect, feedback and support. Then, in 2017, I became involved in the creation of Casma Therapeutics, a biotechnology company that Beth along with Skip Virgin, Andrea Ballabio and Jim Hurley helped create. Despite her many institutional responsibilities and ongoing health issues, Beth was so extremely generous with her time in working with me and the Casma team. She helped us discover new things about topics I considered to be dogma and on occasion when we did not agree, Beth was thoughtful, respectful and always maintained focus on developing therapies for patients. On two separate visits to Dallas I got to experience what a gracious host Beth was. She and Milton entertained us at their wonderful home and demonstrated that it is possible for scientists to converse about non-science topics over dinner! At UTSW we also experienced the wonders of Texas BBQ washed down with copious amounts of Diet Coke. I will miss Beth's intensity and her ability to engage on a whole range of topics that have an impact on the world today. Her drive and fighting spirit remain an inspiration to help us develop autophagy medicines.

Ralph Nixon; Professor, New York University School of Medicine, and the Nathan Kline Institute

My first personal encounter with Beth was sitting next to her in Osaka at the pre-meeting dinner for the third ISA meeting. This was when I learned that she was actually my neighbor in Westchester, not next-door to us, but to our former next-door neighbors and close friends. This coincidence and the sharing of a circle of common local acquaintances became a special bond at subsequent autophagy meetings. After Beth moved with family to Texas, my updates on schoolmates of her daughter became, I think, a memory trace that brought her fondly back to her life in New York.

That first autophagy meeting in Japan also introduced me to the perfectionism that was one of Beth's scientific trademarks. This first ISA presentation and every talk of hers thereafter unfolded a new autophagy concept that had been meticulously dissected and comprehensively validated. What for some might have represented the culminating scientific achievement of their career was for Beth just her latest, annual or semi-annual, inspiring gift to our autophagy community. Meeting to meeting, year to year, Beth's latest achievement served as a model of scientific rigor that guided many of us and later inspired the many young scientists drawn into the autophagy field by the excitement Beth and her collaborators created. Perfectionism in science also extended to Beth's signature attention to fashion. Whether in the ultra-relaxed environs of Il Ciocco or at a fancier venue, Beth always managed to be impeccably dressed, adding another element of class to our meetings. While it likely didn't happen this way, I can easily accept as true a memory of Beth walking trails in the Yellow mountains of China in a designer outfit and high heels.

I will always be grateful to Beth for championing a (then) controversial line of Alzheimer's research we had published and standing up to a vocal group of mainstream dogmatists. It was the quality of the science, not the politics, that mattered. It was always all about the science. We as a community are lucky to have known Beth and to be forever inspired by her research and dedication.

Anthony Orvedahl; Instructor, Washington University in St. Louis School of Medicine (former graduate student)

As the first graduate student to successfully defend a PhD thesis in the lab of Beth Levine, MD, I feel extremely privileged to hold this distinction. This is not only due to the immense generosity shown by Dr. Levine with her time and resources, both professionally and personally, but also because it occurred during a period of palpable excitement in the lab and exponential growth of the autophagy field. This excitement was first piqued and memorialized with a note that I jotted down as a first year MD, PhD student during a seminar from another investigator at UT Southwestern, Joseph Hill, MD, PhD. As shown, in this seminar I learned that a world-renowned expert in the new (at least to me) and exciting field of autophagy had recently been recruited to UT Southwestern (Figure 4). This expert was, of course, Beth Levine, and this serendipitous event forever altered the arc of my scientific and professional career. Much of my success as a Pediatric Infectious Diseases physician-scientist traces back to my training with Dr. Levine. The indelible scientific mark left by Beth Levine's work is widely chronicled in the scientific literature and I will not attempt to do it any justice by summarizing it here. Rather, I would like to take this opportunity to highlight my experiences as a mentee of Dr. Levine and how they have shaped my career.

My first exposure to the mentorship of Dr. Levine was during a summer lab rotation in 2005. I was impressed that Beth took the time to personally show me the technique of intracranial injection of herpes virus in a murine model of HSV encephalitis. This project was a continuation of findings from a previous postdoctoral associate in the lab, Zolt Tallóczy, PhD, and was assisted by a technician in the lab, Qihua Sun. ICP34.5 was the first viral virulence factor found to inhibit autophagy to promote disease, and we found the mutant virus was complemented by host PKR deficiency. From this experience I learned multiple things: the importance of persevering with an important finding when studies may be disrupted by personnel changes or moving institutions; the power of animal models and host genetics to reveal mechanisms of disease; and not just the rigor necessary to publish high quality scientific manuscripts but also the need to be meticulously detail-oriented in their writing. More importantly, I learned how much Beth valued the success of her trainees by being not only a dedicated mentor but also by acting as an advocate for their advancement. Experiences in those early days drove me to pursue a PhD in her lab.

One of the important unanswered questions in the autophagy field at the time of starting my thesis work was the mechanism by which viruses were targeted to phagophores. During this work (from 2006–2010), Beth taught me the importance of asking important questions and taking novel approaches when the tools do not exist to answer those questions. We developed a fluorescence image-based high-content siRNA screen to identify human genes required

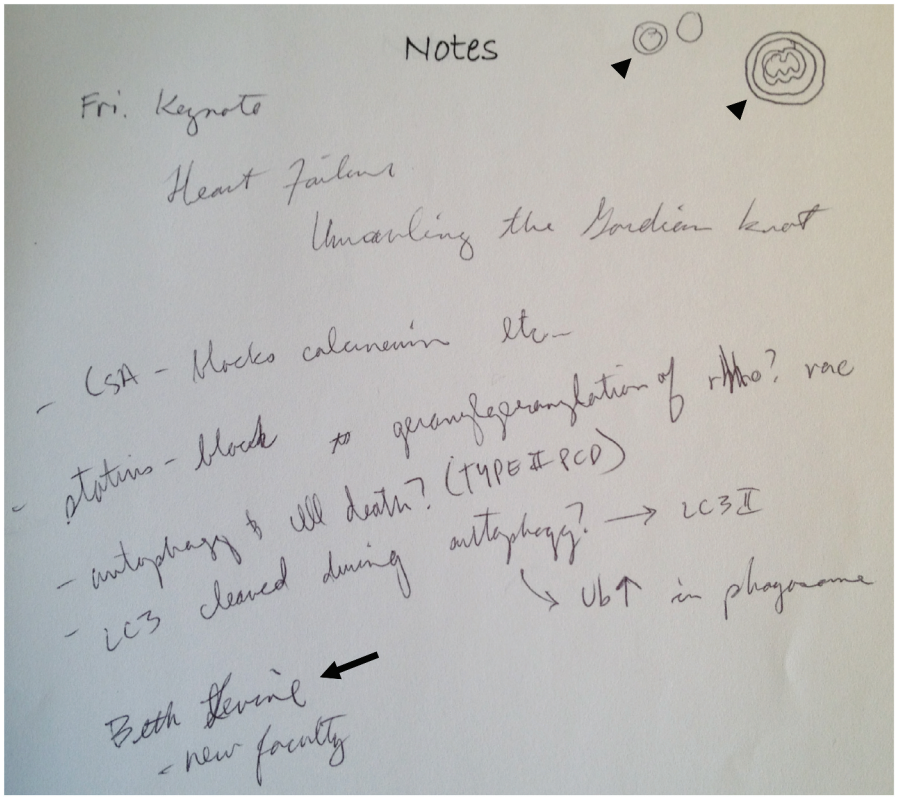

Figure 4. A note from the author's archives (c. 2004). Arrowheads: autophagosome-lysosome fusion event and mitophagosome. Arrow: alert to the arrival of an incredible scientist and mentor.

to target Sindbis virus capsids to phagophores. This screen revealed numerous factors, including SMURF1, which we found was also important for targeting damaged mitochondria by mitophagy.

In addition to developing the intellectual and technical skills to complete this work under Beth's mentorship, I learned the importance of developing personal connections in science. One example of an important personal connection facilitated by Beth, was the introduction to Herbert "Skip" Virgin, MD, PhD, with whom I eventually went on to perform a post-doctoral fellowship at Washington University in St. Louis. Beth continued to act as a mentor to me in searching for faculty positions and funding opportunities during this time. During my graduate work, I was also fortunate to overlap and collaborate with Rhea Sumpter, MD, PhD, a postdoctoral fellow in the lab, on the SMURF1 project. This provided an opportunity to gain not only a valuable colleague but also a good friend. I am incredibly fortunate to have been given the opportunity to work in the environment provided by Dr. Levine during this time. Discovering novel genes and studying their role in a fascinating area of biology with such talented scientists has been a highlight of my scientific and professional career. The generosity of Beth is most evident in her promotion of students and postdoctoral fellows, encouraging attendance at national and international meetings and facilitating publication of high impact papers. Equally telling of this quality is the story of when Rhea Sumpter once suggested half-jokingly to Beth that a mariachi band should perform at my thesis defense celebration. Naturally, a full ensemble was there to round out the festivities at her home.

As I advance toward the position of an independent investigator, I consider my time training with Beth Levine and lessons learned there among my most valuable. I continually strive to uphold the ideals that Beth modeled with great ease. Think big, while always maintaining scientific rigor. Give generously and stay dedicated to the success of your trainees. And, foster interpersonal relationships as a key element to any worthy endeavor.

Sophie Pattingre; Senior Scientist, University of Montpellier, France (former postdoctoral fellow)

My very Dear Beth,

I met you twenty years ago in France, in Aix les Bains, in the first autophagy meeting you had been invited to. I was a second year PhD student and I had a feeling that I had only one time in my professional life. In France, we call that "un coup de foudre", a love at first sight … Then I took one of the most important decisions of my life, personal and professional, I decided to do all possible to join your lab for a post doc.

Twenty years later, one of your presents, a frame, is still hanging in my house allowing me to be reminded of you every day, to remind me how important you are for me.

You changed my life because you belonged to those rare people who make you believe that everything is possible. When you were around, we (me and your people) felt safe, strong, confident and supported and this feeling stays inside

you for your entire life. With you, with your help and support, I learned so much as a scientist but also as a human being.

You were the most inspiring, supportive, passionate mentor one could ever have. Always with a lot of discretion, you were watching me, caring for me. I remember so many details about my life in the US. I remember when we accidently discarded the membrane of the yeast two hybrid that allowed the discovery of Beclin 1/Bcl-2 interaction. You were so sad that I spent hours in the basement of Columbia to snoop in the trash and finally find it. I also remember this flight from New York to Dallas when the lab moved. You absolutely wanted to fly with me and that I sit next to you. You knew how sad I was to leave my friends and you wanted to comfort me during the flight. I am smiling because I am remembering that special day in June 2005 when our *Cell* paper was finally accepted. I was working on my computer in the lab and I heard your so characteristic footstep sound. You entered brutally into the room and just told me "your *Cell* paper is accepted" and you left me slamming the door. I ran into your office and asked "Are we not supposed to be the happiest people in the world?". Gently, you told me "Of course yes, but it also means that you will leave the lab". I came back to France, but I missed you so much all these years, my post doc is one of the happiest periods of my life.

I would love that you know how much you meant to me, how lucky, privileged and proud I felt to know someone like you, someone so special.

With all my love.

Fulvio Reggiori; Professor, University of Groningen, The Netherlands

The first word that comes into my mind when thinking about Beth Levine is *Inspirational*. Beth has set the bar in the field of autophagy to a high that has become a stimulus, a motivation and a goal for a lot of us, especially for the youngest. Saying that this is because of the creative and groundbreaking research that she has been carrying out over the years, is not giving the right credit to the caliber of scientist and person that she has been. Smart, sharp, to the point, modest, kind, open, collaborative, generous, supportive, friendly, … it is very difficult or impossible to fully describe the incredible gift, the privilege that she has been for an entire community. A true leader on multiple aspects, not with words, but with facts, and a unique positive and pro-positive attitude. Truly *inspirational*.

Theodora Ross; Vice President of Translational Medicine, Merck

A synonym for Beth is Friend. From the first day I arrived at UT Southwestern, Beth was there to help solve scientific, political or personal problems. I can't think of a time when she didn't call within 24 hours when one of my SOS signals was sent.

When she was diagnosed with breast cancer, it was an honor to help her navigate the treacherous cancer path she was on. Her legacy as a great scientist, wise friend and collaborative colleague will last forever.

She even forgave me for loudly pronouncing autophagy like a Michigander – Auto-fagee … . She liked to say that sounded like a special type of Ford vehicle. That's a true friend.

David C. Rubinsztein; Deputy Director, Cambridge Institute for Medical Research, United Kingdom

Beth Levine was greatly admired by her colleagues. Her science set the highest standards for novelty, impact, quality and rigor and contributed critical discoveries. However, her influence on the autophagy field has been much greater than this. She has been an inspirational and generous leader and encouraged her colleagues in a way that is very rare. As a personal example – when I mentioned to Beth that we were thinking about clinical trials with autophagy-inducing agents in neurodegenerative diseases, she put me in contact with her husband, an expert clinical trialist, in order to help me develop my strategies. I have heard younger scientists speak with great enthusiasm about the mentoring they had received from Beth at meetings. She has served as an inspiration to me both as a scientist, as well as a person.

Kevin Ryan; Professor, Cancer Research UK Beatson Institute, United Kingdom

When we think about the contribution of Beth Levine to our field it is honestly very difficult to know where to start. We all know her as a great pioneer in the field, but for me it was her continued inspired inventiveness that really stands out, with seminal discoveries linking autophagy to aging, cancer, exercise and infection to name but a few! Her presence and contributions at meetings were also iconic; always ready with the incisive questions and never afraid to raise an issue and to defend an opinion even if many in the room did not share her view – ultimately isn't this what meetings are for?

I think to many Beth could appear intimidating with her immaculate dress, business-style approach and her quick mind – she was always on point! As I got to know her, however, I got to know the other side of Beth who liked to laugh and to talk about her family and her travels. I remember one time in Bern and we were lost. Nobody that we asked for directions could understand us. Beth said no problem, I can speak French (another one of her talents), and so she proceeded to ask for directions in French, only to receive a reply in German! The realization that we were not quite in the right part of Switzerland for French was met with much laughter. Beth then spent much of that evening discussing with me the nuances of British humor – I never really quite explained (I'm not sure you can), but the questions together with laughter kept coming no end! A great mind, always questioning, never intimidated and an inspiration to so many in our field and beyond.

Junichi Sadoshima; Professor, Rutgers New Jersey Medical School

Dear Beth,

I enjoyed so much having the opportunity to get to know you through our Leducq network and to collaborate with you directly through the years – most recently on autosis in the

heart. Knowing you was a true honor. I remember when I first emailed you in 2005 and was thrilled when you responded right away and suggested that we talk. I have been admiring you ever since. You kindly commented on my papers every time I sent them to you. I always appreciated your interest, collegiality, and kindness. I have loved reading your papers. The clarity with which you write, your ability to make us understand the functional relevance and importance, is unmatched. Your presence in our network had a tremendous influence on me and others not only because of the quality of science you demonstrated but also because of your spirit to drive the field to the next level. You showed me how our scientists should behave. I can't thank you enough. I will miss you.

Stuart L. Schreiber; Professor, Harvard University and the Broad Institute

Dear Beth,

You rewired our brains scientifically but you will always live in our hearts.

Frederick Scott; Research Scientist, UT Southwestern Medical Center

About 5 years ago I took my three-year-old Grandson up to work with me over the Christmas holidays. He left my office ran down the hall and right into Beth as she was leaving her office. She calmly knelt down in front of him and with a smile told him why he shouldn't be running in the hall as she patted him on his back. I remember watching the brief encounter and thinking wow not only is she a brilliant scientist but she must be a great Mom. She then held his hand as she walked him back to me. Over the next several years she would often ask me about how he was doing.

There are other examples, but this is the one that has always meant the most to me.

Salwa Sebti; Instructor, UT Southwestern Medical Center (former postdoctoral fellow)

I remember the raw happiness and excitement I first felt when Beth Levine gave me the opportunity to join her lab. It has been such an honor to be part of her team, learn from her and see her turn time and effort into knowledge and discoveries.

Beth Levine was the kind of outstanding researcher whose vision inspires people around her. But she was equally fantastic on a personal level. She was open minded in her conversation, she was strong and kind, she was a perfectionist and did everything with integrity.

I will miss hearing her genuine laughter. It would always put a smile on my face. I will miss hearing her heels on the floor with that distinctive rhythm of determination. I will miss our long conversations about the intricacies of an experiment. And I will miss our sometimes-longer conversations about the beauty of a cultural experience.

I will forever remember Beth Levine, as an extraordinary mind wrapped in elegance and kindness. Thank you for everything you have done and the legacy you leave behind.

Michael Shiloh; Associate Professor, UT Southwestern Medical Center

Throughout my life and career, there are few people who have made such a profound and lasting impression on me as Beth. From the moment she intervened to defend me from a heckler at my job talk, to all the time she spent mentoring me, I always knew she had my best interest at heart. Beth truly strove to elevate and promote the success of everyone around her, and gave willingly of her most precious commodity, time. For example, in my first few months as an Assistant Professor, she encouraged me to write my first grant even though I felt I wasn't ready to do so. She didn't mess around and gave it to me straight. "Michael, you work on a very slow growing organism and haven't even started your biosafety level 3 work. How much more data will you have in a year that you don't already have?" When I had to admit that the answer was "not much", I started writing that day. To her credit, she didn't leave me to sink or swim. She spent many hours, often with e-mails timestamped at 2 A.M., to help me craft my first grant.

At first, I was exasperated by her exacting demands. I chaffed at revising my grants and papers again and again or repeating complicated experiments not just 3 but 4 times. Ultimately, I learned to appreciate the value of her meticulous attention to detail. She not only conveyed complex ideas with an incomparable clarity, but also approached her science with a rigor that was unmatched, and that I now strive to emulate.

But my fond memories are not all work related. Beth loved to host her lab at her home over the holidays, and I was fortunate to be invited as well. The last few years she organized karaoke as entertainment. My lab, and, I have to admit, I as well, looked forward to this party for the food, drink, and especially the karaoke. My greatest joy was, together with Milton, encouraging a reluctant Beth to sing at the past two parties, and we belted out rousing versions of Billy Joel's "Piano Man" and Simon and Garfunkel's "America". Seeing Beth let loose and have fun turned her party into a real "simcha".

I will forever cherish the memories of and lessons learned from Beth. I know that Beth's impact on me and you, her colleagues and friends, will be everlasting. To paraphrase Simon and Garfunkel, "If you need a friend, she'll be sailing right behind."

Sanae Shoji; Pharmacist, Valstagardel Hospital, Japan (former postdoctoral fellow)

I was a post-doc researcher in Dr. Beth Levine's lab. I really respect her as a researcher and a woman. I sometimes felt that she was an elder sister.

She taught me difficult research-related things and thoughtfully advised me on my life. The discussion with her was a great lesson for me, which made my thinking much more sophisticated. When I was disappointed with a lot of negative data, she told me that you should work and study much harder than usual in a tough situation if you want to go ahead more than others. I think that what she told me is true. She also strongly recommended that I have a child. I was not sure that I could do research and raise a child. She said, "You

can do both of them!" When I was pregnant, she gave me a book, "What to Expect When You're Expecting".

When she e-mailed me that she was struggling with breast cancer, I believed that she definitely would be cured. I did not think that she would pass away soon. I should have talked with her. I will continue to make efforts in my career and life as she advised me.

Anne Simonsen; Professor, University of Oslo, Norway

Beth Levine has always been a huge inspiration to me, both scientifically and as an excellent female role model. Her 1999 *Nature* paper linking, for the first time, autophagy to cancer was instrumental for my entry into the autophagy field. I had just cloned a novel PI3P binding protein (ALFY) and Beth's finding that Beclin1, a component of the PI3-kinase complex, was important for induction of autophagy made me investigate whether ALFY would play a role in autophagy. My first personal interaction with Beth was at the Gordon Research conference in Il Ciocco, Italy in 2005. At first, she could seem a bit intimidating, but I soon learned to know Beth as a very nice, fun and supporting person. Her scientific contributions to the field of autophagy are tremendous. In addition to her outstanding publications linking autophagy to human pathophysiology, aging and infection biology, she always gave excellent talks and had the ability to clearly summarize and discuss the most important findings in the field in several landmark review articles.

Haley Smith; Division Administrator, UT Southwestern Medical Center

Anyone who has ever worked with Beth knows that she accepts nothing less than perfection. She was an incredible leader that demanded the most of her team and herself (Figure 5). More impressive than her determination to excel in her science, Beth set a standard as a human being that most will fall short of.

That said, I fear nothing I can put on paper will do her justice, but I will start from the beginning.

I began working for Dr. Levine in 2011. While I was young and had some experience, I had no idea how much I still had to learn until I began working for Beth! Her standards were high and I discovered quickly that only the best was good enough. She saw my potential and made sure I lived up to it. She taught me many things in life and work. Among those was the art of being thorough. She had a keen eye for detail. No matter who it was or how many times it was proofread, she would always identify errors within a nanosecond of eyeballing a document and she was always spot on. We are similar in that we are not the type to quickly open up to others. However, over the years we grew very close; we shared many joys, some sorrows, and countless hours of frenzied stress perfecting manuscript submissions, grant applications, meeting/conference plans, and much more. It was always gratifying and done in each other's company.

Dr. Levine's commitment to excellence and integrity on every single occasion makes all those around her better. In the recruiting season, I often received one common question from faculty and postdoctoral candidates. Some would sheepishly ask, "I hear Dr. Levine is demanding to work for?" I loved receiving this question. It gave me the opportunity to proudly share with a smile, that yes, although her standards are high, the knowledge and personal growth achieved by working with her is a rare opportunity, and if their goal was to improve then they would not find a better mentor anywhere.

Nobody has made a bigger impact on me as a person. I cannot possibly list the many lessons I have learned or the joy I have experienced by working with her in the last ten years. After suffering such a loss as Dr. Levine, I will practice the principles that she taught me: to be brave and direct in what you want, to be humble, to be virtuous, and to always, always do things to the absolute best of your ability, while doing so with sophistication and style. Dr. Levine was my boss and mentor, but most importantly, she was my dear, dear friend. I will deeply treasure the years I had with her and consider her friendship one of the greatest gifts I have received in this life.

Figure 5. Levine lab, December 2019.

Kathryn M. Sumpter (on behalf of Rhea Sumpter, Jr., former postdoctoral fellow, d. 6-12-19)

Beth was an exceptional mentor to Rhea, both in science and in life. He admired and strove to emulate her style of investigation, blending solid scientific judgment with elegant esthetic sense in articulating questions. Like many postdoctoral fellows, his passion for discovery could lead him to bounce from one exciting hypothesis to another and juggle too many projects at once. With patient persistence, Beth tempered this sometimes-irrational exuberance with her intentional discipline. She demanded excellence, both of herself and those on her team, but she also celebrated successes enthusiastically, often with a party at her home complete with karaoke or mariachis. Although her intellect, no-nonsense demeanor, and stiletto heels could be intimidating, Beth was profoundly compassionate and empathetic. As a mentor, she was committed to supporting and developing the whole person, not just the scientific trajectories of her trainees. She did not hesitate to invest time or provide assistance, even when doing so was unlikely to advance her own career.

As the spouse of a postdoc, I knew Beth from a different perspective. Soon after we met, I saw her at a departmental holiday party. Without even thinking, I let my Texas roots take over and gave her a hug. She initially stiffened and I was sure I had committed a serious faux pas. From that day on, however, she initiated the hug every time I saw her. Our happiness and success were important to her, and her actions showed it. I feel forever indebted to Beth for her love and support over so many years. She will be greatly missed.

Craig B. Thompson; President and CEO, Memorial Sloan Kettering Cancer Center

Beth was an inspirational leader, colleague, and friend to so many of us. I first got to know Beth when she was in Marie Hardwick's lab and we collaborated on a paper studying the differential role of Bcl-2-related proteins in regulating cell death in response to Sindbis virus infection. Beth became convinced from these studies that there were additional regulators beyond the Bcl-2 family that limit Sindbis virus propagation and cell death.

When I had the opportunity to visit Beth at Columbia soon after she started her laboratory there, she had already discovered Beclin 1 and identified its homology to Vps30/Atg6, a critical autophagy protein in yeast. With her studies of Beclin 1, she established autophagy as an important mechanism in regulating cell survival. Her work not only launched a full assault on studying the role of autophagy in mammalian biology, but also established that there were pathways in addition to apoptosis which can regulate the life-and-death decisions of cells.

Over the last 20 years, Beth was a major scientific leader, meeting organizer, and mentor. To some, she was a larger-than-life figure. But to me, she will always be that excited and inspirational scientist I met with at Columbia who had discovered something new and couldn't wait to tell the world about it. She will be missed.

Andrew Thorburn; Professor, Colorado University School of Medicine

Beth's seminal paper in *Nature* in 1999 showing that Beclin 1 interacts with BCL-2 and then connecting that to cancer was one of the first papers about autophagy that I read. I did so because of my interest in cell death and cancer, and that paper drew me into what has been an astonishingly exciting field. Two decades later, it is humbling to see how important Beth's many contributions have been to the science, especially in showing how physiological and pathological processes interact with the autophagy pathway. Equally, perhaps more, important is her vision and leadership. How many people have started studying autophagy because of Beth? The number is huge. Our field is exciting because the biology is so interesting and exciting. But, we know that the biology is so exciting in very large part because of Beth. Her impact on all of us will go on and on.

Michael Thumm; Professor, Georg-August-Universitaet, Germany

I remember well the 1999 *Nature* paper from Beth Levine, where she showed a direct link of Beclin 1 and tumorigenesis. At this time several yeast labs had identified a couple of autophagy proteins, but the medical relevance of autophagy was not generally known. Her study was a great leap for the whole field and the first connection between a severe disease and mutations within an autophagy gene. She presented her data at a conference at Aix-les Bains, where I met her the first time. Her data draw a lot of attention to the autophagic field and helped to make it the interesting topic it is now. Over the years it was a pleasure to listen to her brilliant talks; she always had some exciting new findings. And, if I remember right, she always used to have a bottle of Coke.

Sharon Tooze; Senior Group Leader, Francis Crick Institute, United Kingdom

In 2003 I met Beth in her lab at Columbia University and since that visit, Beth has been one of the constant stalwarts in my scientific life, a constant source of inspiration both scientifically and personally. I can honestly say that her seminal *Nature* paper in 1999 changed the direction of my scientific career. Meeting Beth in person at Columbia that day she gave me the first glimpse of her amazing scientific talent as she explained the aging experiments in worms and was so full of ideas, thoughts, and probing questions about my intentions and interests. From that meeting Beth was a constant source of inspiration, and my admiration grew every time we met. Beth led us, the autophagy community, with vice chair Dan Klionsky to the first GRC in Colby Maine in 2003. Beth combined sophisticated elegance with a steely determination which was embodied by her amazing ability to walk on high heeled shoes up podium steps, through uneven ground, where she needed to go or be, often carrying a massive black bag on her shoulder. Over the years as we met in many different venues in many different countries, encountering many different challenges and memorable events, Beth was unfailingly kind,

generous with her time (and medical supplies) and always supportive of me and the wider family of autophagy colleagues.

Maria I. Vaccaro; Professor, University of Buenos Aires, Argentina

I deeply regret the loss of Beth. I remember that she was so excited to travel to Buenos Aires for the 2017 Conference on Autophagy, and she made efforts up to the last minute to get medical permission to travel.

Beth was an outstanding researcher. Her discoveries were groundbreaking and inspired all of us. She always encouraged us and gave really useful advice and feedback to improve our work. She was also very affectionate. We will certainly miss Beth!

Herbert W. "Skip" Virgin; Executive Vice President, Chief Scientific Officer, Vir Biotechnology, and Adjunct Professor, Washington University School of Medicine

Beth Levine, passing of a leader and friend.

Beth Levine is now, was, but shall remain for me, the best scientist I know, and a close friend for decades. I will miss her. Her science came within the context of her as a person (more on that below), but the combination of the science and the person is a diamond without compare. She is, in my view, the founder of the field of mammalian autophagy, and a leading light in linking autophagy to disease and the human suffering that diseases bring to so many. I first met Beth at a virology meeting in the mid-1980s and have been a friend and collaborator of Beth's for many years. I came to know her as a special talent with many attributes to which I aspire. She was brave in facing her illness, literally planning for her own passing in a way that protected her trainees. Admirable to the end.

Beth published a lot of papers, and received many deserved honors, but I want to focus on something a little bit different, which is the KIND of discoveries she made. Beth was given to bouts of remarkable scientific intuition and insight about biology. She was eclectic in thought, allowing linkage of things that others did not see because they operate in a smaller intellectual space than Beth. Beth's science lived in a galaxy of possibility, while other thinkers live in the atmosphere of a single planet. I have been asked over the years to review the field, and each time I am surprised by the singular brilliance of her insights.

Who first linked cell death to viral pathogenesis and persistence? Beth Levine. Who showed that antibodies to a viral antigen can clear a virus out of an already infected neuron? Beth Levine. Who showed that the "apoptosis" protein Bcl-2 interacts with and regulates the first described (with functional data) mammalian autophagy gene? Beth Levine. Who showed that interferon pathways regulate autophagy? Beth Levine. Who showed that autophagy genes are antiviral using plant models? Beth Levine. Who showed in mammalian systems that viruses as so afraid of autophagy that they have developed potent countermeasures? Beth Levine. Who proved that autophagy protects CNS neurons from viral infection? Beth Levine. Who demonstrated that an autophagy gene can suppress tumorigenesis in an animal, documenting an entirely new tumor suppressor pathway? Beth Levine. Who found that autophagy genes regulate aging? Beth Levine. Who linked autophagy genes to development? Beth Levine. Who has mapped the existence of more autophagy regulatory factors and linked them to physiology and disease than any other? Beth Levine. Who used viral protein function to create an autophagy-inducing drug? Beth Levine. Who founded one of the first companies to create autophagy-inducing drugs? Beth Levine. Who linked exercise to autophagy and thus to metabolic disease? Beth Levine. Who showed that Toll receptors link autophagy genes and metabolic signaling to muscle function and organism-level physiology? Beth Levine. Through our shared role in a Center for Excellence in Translational Research grant, I can tell you that there are many more such discoveries as yet unpublished.

I can go on and on (as many of you have experienced), but that is not the point. Consider instead of the litany, the linkages. Often these linkages came between COMPLETELY DISPARATE areas of biology. Somehow, this unique person and scientist managed to understand the WHOLE cell and organism in a way that allowed her to cross boundaries, create new fields, see and document linkages that others simply could not imagine. She had the near-unique capacity to link disparate facts into a tapestry of truth. This ability, which can only be called genius, is a legacy that cannot be underestimated, and that I deeply admired and respected in Beth.

But not all geniuses have the capacity to bring people together as Beth did. Over many years and through many grants and letters and nominations and meetings, I can say that she was totally fair and completely aboveboard with constant unswerving integrity forming the core of her personal actions. Beth was also brilliant, was incisive, bragged about her children, loved to laugh with Vojo Deretic and Sharon Tooze, was a real doctor, was a caring and a strong mentor and advocate for her people, was rigorous, was decent, was a good friend and advisor, thought in the language of multisystem biology with alacrity, was precise, had a lifelong dedication to curing suffering and death from diseases including cancer, was a feminist who succeeded with unquestionable exceptionalism, had an eidetic memory, was joyful, could somehow always tell what Ramnik Xavier was saying, maintained high standards without arrogance, was an exquisite experimentalist, wrote prolifically and led the field intellectually through her writings, was visionary and fearless and, always, exhibited an unspoiled child-like curiosity about biology and medicine. She was a leader that people gladly followed, including me.

This type of leadership leaves its imprint on people and creates legacy. I have great confidence that Beth's story, the story of autophagy and disease, will continue to be told, and that we, her friends, will honor that.

Fei Wang; Assistant Professor, UT Southwestern Medical Center

Sadness has been proven profounder than happiness or hope in this world, again and again. However, at this stage, I still

hoped for a miracle, which I have truly believed and will keep believing should have spared Beth from her illness.

I know Beth first from her legendary scientific work in the field of Autophagy, which inspired me to apply to, and in 2017 join, the Center for Autophagy Research as a junior faculty. During our first phone call of my job interview she described to me the future of the center that she was establishing at UTSW, her plan to recruit talented people with genuine interests in both basic and clinical aspects of autophagy research, and her commitment to create an environment for everybody to breathe, to react and to thrive. The chat was so relaxing and inspiring that it became the most pleasant job interview experience of mine. In the next three years, after I started my lab in UTSW, I had been so impressed, each time after chatting with her. Those chats were clearly delivered with very detailed suggestions, always, as well as her care, consideration and expectation. I kept seeing the picture she drew in our first phone call, being polished by her unique personality and leadership.

Beth was a great scientist. She had astonishing instinct in outlining big pictures of biological science as well as outstanding ability to handle tremendous details without losing focus. At our center's bi-weekly journal club, she always took the discussion to a new level, which inspired not only the trainees but also the faculty a lot. This was only possible because she was so knowledgeable of the literature and knew so well of everybody's expertise/shortage in the meeting room. In her presence, discussing a scientific topic was so fun that very often a journal club could take much longer than planned and people just chatted on the topic in small groups even after it ended. In addition to supervising people, Beth loved doing experiments. I had seen her so many times operating a microscope in the darkroom, a mission almost impossible from my opinion given how many responsibilities were on her on a daily basis. Her scientific leadership established a sturdy foundation for the Center for Autophagy Research at UT Southwestern Medical Center, and it will never be the same without her.

Beth was a great mentor. As a junior faculty, it is countless how many times in my thus far three years' UTSW faculty career she guided me through mazes, from hiring to building a lab culture, from ordering to grant writing. On every detail, she worried, on my behalf. It is so vivid in my memory how she walked me through an empty lab that has been assigned to me, giving me suggestions on how to fill the space, while she smiled. That is the first day when I was in my lab at UTSW. Since then, it had been such a great relief, for me to be so sure that she watched on my tenure track, when the pressure was on. Her watching, warms the track up, making it less stressful and more meaningful. She watched, and she helped. Among numerous things she did for me, it is hard to pick one and not the other as an example. But I guess she would pick grants. She spent so much effort in helping me with grant applications, and she saw every small improvement I made. Every grant I wrote had been edited by her, word by word, sentence by sentence, to fix grammar and to provide detailed suggestions for enhancement of its scientific impact. Many times, she returned her edits in the late nights and early mornings. Every time, I replied by saying "Thank you" to her. She did not know that it is not just an appreciation. It is a lot more than that. Beth set a great admiring example for me, at every level, as a researcher, a mentor and a friend. In fact, her landmark gift to the Autophagy Research Center at UT Southwestern is beyond her influence as a scientist, a colleague and a leader. She was the soul of the center. She had such a sincere and deeply felt commitment to helping people to reveal their potential. I am so grateful to have been among those and look forward to fulfilling that commitment in the future.

Eileen White; Professor, Rutgers Cancer Institute of New Jersey

I have known Beth for the past 15 years as a leader of the autophagy field, to which she made seminal contributions. She contributed greatly to many discoveries that propelled the autophagy field forward, from the beginning to the point now there are hundreds of labs all over the world working on it. Beth, however, also stood out in the graceful and elegant way she carried herself, her deep love for science, and the beauty of her scientific presentations. I was fortunate to get to know Beth personally. She had a deep love of her family and we spoke often about our kids and being mothers while doing science, and she served as a role model for women physician scientists. We had great fun together at autophagy meetings all over the world, and I will particularly remember swimming in Tulum, the Sake party in Nara, and various Keystone meetings endured with insufficient oxygen. We also spoke about cancer, and her cancer battle. I have dedicated my career to eliminating the pain and suffering caused by cancer, and this represents yet another terrible example where we have come up short. We must work harder to overcome this disease, as here it leaves a void in our field and in our hearts.

Ramnik J. Xavier; Core Institute Member, Broad Institute

Beth's achievements and accomplishments brought her high honors and national recognition: she was an HHMI investigator and member of the National Academies of Science and Medicine to name a few. Her scientific legacy will undoubtedly continue to lead to breakthroughs, as she established autophagy as a basis of cognitive health, healthy aging, and many diseases.

I realized after my last call with Beth, hope was less distinct and medicine, its outcome, failed us in our expectations.

In many ways, Beth's life exemplified a joy for science. She maintained the highest standards and held her friends to the same standards. She was always thorough and always driven by the pursuit of excellence. Generous with her time, she dedicated many hours to long conversations that enriched the accomplishments of those around her. Personally, I am a better scientist. Displaying enormous dignity and courage despite recurrent symptoms, Beth continued to work on advancing science and ensuring that CETR program in Autophagy would continue forever. Her commitment to science is rivaled only by her commitment to friendship, and she will be missed dearly.

I will miss a very dear friend.

Tamotsu Yoshimori; Professor, Osaka University, Japan

I met Dr. Beth Levine for the first time in 2000 at the 2nd International Symposium on Autophagy (ISA) held in Aix-Les-Bains, France, just after the publication of her seminal *Nature* paper on Beclin 1. Then I met her innumerable times during the last two decades; she was my long-time colleague and dear friend.

She had been leading the autophagy field, especially mammalian autophagy. She provided many amazing unexpected insights into mechanisms and physiological relevance of mammalian autophagy. Our present understanding of this important cellular function is profoundly affected by her distinguished achievements.

She has also affected the atmosphere in the field. The community of the autophagy field is quite cooperative and friendly. Dr. Levine was always kind and supportive to other researchers in the field. Indeed, I obtained nice advice several times about submission of papers. She definitely contributed to foster the good vibes in the field.

The loss of our dear friend and outstanding scientist is leaving us in deep grief and broken-hearted. However, her soul and achievements will stay with us forever. If people continue to remember her, she will never die.

Junying Yuan; Professor, Harvard Medical School

Even though we are becoming numb to hearing about someone passing away prematurely in 2020, the news of Beth Levine in hospice was still shocking and devastating. Beth was so strong and vivacious, the word "sick" is incompatible with Beth in my mind. A few years back, I heard that Beth had breast cancer. However, there was no doubt in my mind then that Beth would be able to overcome as she was so strong. It was devastating that such a wonderful life can come to the end so prematurely. It reminds us how precious and fragile life is.

Beth's works contributed significantly to our understanding of autophagy in cancers. Beth discovered Beclin 1 as a novel interacting protein of Bcl-2 in mammalian cells (*Nature*, 1999). She found that Beclin 1 shared high homology with yeast autophagy gene product Vps30/Atg6, a part of the class III PtdIns 3-kinase complex critically involved in promoting autophagy. Beth found that the gene for Beclin 1 was frequently mono-allelically deleted or silenced in human breast cancers and ovarian cancers. Her work provided the first insight into the function and molecular mechanism of autophagy in cancers. Her subsequent work systematically characterized this Beclin 1-Bcl-2 axis in cancer, glucose metabolism and longevity, and investigated the possibility to target this interaction pharmacologically.

I got to know Beth because we shared some common views in science. I wrote a review on the topics of alternative cell death mechanisms (*Neuron*, 2003). This review discussed the literature on the morphological evidence for the existence of non-apoptotic cell death, including necrosis and autophagic cell death, and proposed the possible existence of a necrotic cell death mechanism, which we later named necroptosis. However, this review concluded that autophagy was a predominantly cell survival mechanism, which was a view shared by Beth. She then invited me to co-write another review on this point which was titled "Autophagy in cell death: an innocent convict?" (*J. Clin. Invest*., 2005).

I invited Beth and Dan Klionsky to speak at the 2006 Fawcett Lecture series in the Department of Cell Biology, Harvard Medical School. During that period, I saw Beth frequently at various autophagy meetings (Keystone, Gordon, etc. [Figure 6]). Beth impressed me as a dedicated scientist with boundless energy. Once I counted that Beth wrote no less than 17 reviews on autophagy during a three-year period (2009 to 2011). Beth was a loving mother devoted to her family. We would chat endlessly about our children. As we mourn for the loss of a precious colleague, Beth can be assured that her legacy will be carried on by her children and those of us who continue to work in the autophagy field.

Zhenyu Yue; Professor, Icahn School of Medicine at Mount Sinai

On one summer afternoon in 2003, while I was a postdoc fellow and working on my experiments at Rockefeller University,

Figure 6. Beth Levine (center) with Patrice Codogno (turned), David Rubinsztein (left), Junying Yuan (right) and Han-Ming Shen (second right) at the 2007 Keystone meeting on autophagy.

I received a phone call from Beth Levine, who was then a junior faculty at Columbia University. She first complimented my work that was just published about the findings of Beclin 1-mediated autophagy in a neurodegeneration mouse model. Then she told me that her lab had created *beclin 1* knockout mice, and further offered her mutant Beclin 1 mice for collaboration in testing the role for Beclin 1 in neurodegeneration. That was the first time I spoke to Beth.

I was pleased at Beth's call – not only because she reached out to me for collaboration, but also the fact that she discovered Beclin 1, which was the first mammalian autophagy gene ever reported and could open a door to reveal many secrets of autophagy functions in biology.

Interestingly, back then I had also generated the similar Beclin 1 mutant mice, in which I found the haploinsufficiency of Beclin 1 linked to tumor suppression. After I thanked her for her generosity in offering her mice, I told her my findings in our mice. Beth was a bit surprised at my unpublished study in *beclin 1* knockout mice, but she was happy to know that my work in the Beclin 1 mutant mice reproduced quite well her observations. Eventually both her work and ours in Beclin 1 mutant mice were published back-to-back in 2003, highlighting the role of autophagy in cancer. Our work together marked the beginning of the study of mammalian autophagy using animal models. I recalled many years later, when we exchanged e-mails about the past, she graciously commented that, "My congratulations to you, … . our paper and your paper published in 2003 actually represented the first autophagy mouse knockout and provided a genetic evidence that autophagy gene deficiency was linked to disease. Of course, you have continued to go on to make so many important contributions since then … ." Indeed, Beth's series of pioneering studies in Beclin 1 had made a significant impact on the autophagy research community and shaped my future research direction when I became independent and had my own research laboratory.

I have since then followed closely Beth's work. Beth had demonstrated a great vision for the research of autophagy. She soon became a leader in the autophagy research community with creative ideas and outstanding publications showing the physiological functions of autophagy. I have always enjoyed reading her papers with insightful findings and clarity of the message. I have met Beth many times in a number of autophagy conferences and other occasions. Her lectures have always been elegant, enlightening, and inspiring. She was a role model for many young woman scientists that as a mother who can also maintain an extremely successful scientific career. I can see her genuine passion in research discovery and tireless effort in the mentoring of future scientists. I am immensely grateful for her advice and encouragement as she wrote to me in an e-mail, "Keep up the great work and let's all continue to work together to move forward on the exciting journey."

Beth will be sorely missed as a great mentor, friend and colleague!

Qing Zhong; Professor, Shanghai Jiaotong University School of Medicine, China

I always counted Beth as a mentor and friend. Beth was the most elegant female scientist in my opinion, a role model for many young female students and junior faculty members. She is a legend in the autophagy field and was the main reason that I joined UTSW in 2013. I was her first faculty recruit since she set up the Center for Autophagy Research at UTSW. I was so lucky to exchange research ideas, write papers and reviews, compose grants, and chat about daily life with her for years. She showed me how glorious and elegant a human being could be. Beth was a great leader with principle and warmth. Beth pursued science with highest quality and rigor. All of the young faculty around her benefited from her unselfish help. She was very well respected and loved in the campus. Her contribution to autophagy has been invaluable to this scientific community.

My words cannot express my deep sorrow.

Acknowledgments

Ramnik Xavier was instrumental in summarizing Beth's research contributions. Apologies to the many friends and colleagues who were not included due to considerations of space and time.

Disclosure statement

No potential conflict of interest was reported by the authors.