Cell Systems
Letter

From Yeast to Patients: The Audacity and Vision of Susan Lindquist

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In this issue of *Cell Systems*, we present two papers (Chung et al., 2017; Khurana et al., 2017) that bring together 15 years of effort from the laboratory of Susan Lindquist, a visionary biologist we were privileged to call our mentor. Susan passed away from complications of cancer on October 27, 2016, just as the final revisions of these manuscripts were being submitted.

This body of work meant a good deal to Susan because it provided a glimpse of how basic questions she had worked on for decades might play out one day to make a difference in the clinic. A basic biologist to the core, Susan was also a deeply engaged and empathic human being. It is thus not surprising that driving basic biological insights for the betterment of patients and humanity became an all-consuming goal for her in the latter part of her career.

Many moving obituaries have been written recently by her colleagues, friends and fellow Lindquist laboratory alumni (Bevis, 2017; Fuchs, 2016; Hartl, 2016; Hightower, 2017; Shorter and Gitler, 2016; Siegel, 2017; Whitesell and Santagata, 2016). Here, we present a brief scientific history of this pair of papers colored by our own personal experiences in working with her.

Alpha-synuclein: From Yeast to Neurons

In 2003, Susan's laboratory published a paper that modeled a key pathology of Parkinson's disease (PD) in simple baker's yeast cells by over-expressing the protein alpha-synuclein (Outeiro and Lindquist, 2003). The reductionist work was met with some surprise and consternation in the field. PD was (and often still is) considered a disease resulting from depletion of the neurotransmitter dopamine in the highly complex basal ganglia circuity of the brain. How was this to be modeled in a unicellular organism without neuronal specialization, let alone a nervous system? Baker's yeast did not even have a clear ortholog of alpha-synuclein.

As it often was, Susan's take on the PD problem was different. Exciting advances in the late 1990s had identified causal mutations at the alpha-synuclein gene locus and defined alpha-synuclein aggregation as the hallmark pathology of PD. Susan wagered that understanding proteotoxicity and the cellular response to it would unlock fundamental disease mechanisms. Her pioneering work on yeast prions and chaperones convinced her that these responses were likely to be highly conserved across evolution. Baker's yeast cells attracted her as living eukaryotic test tubes in which mysterious biological problems like neurodegeneration could be dissected with unbiased genetic tools (Khurana and Lindquist, 2010). To her, there was no organism better suited to advance testable hypotheses into neurons and higher organisms.

The 2003 paper delivered the first unbiased genome-wide screen against alpha-synuclein cytotoxicity and unexpectedly tied it to perturbed lipid metabolism and protein trafficking. Subsequent papers from the Lindquist lab showed that key mechanisms of toxicity at play in yeast were conserved in neurons of metazoans, from worms to flies to rodents (Cooper et al., 2006; Gitler et al., 2009). That body of work sharpened the field's focus on protein trafficking as a central player in PD.

As this work proceeded, advances in human genetic analysis were delivering a first glimpse of the genetic landscape of parkinsonism, a phenotype commonly but not always associated with alpha-synucleinopathy. Remarkably, many of the emerging genes were highly conserved across evolution, suggesting that insights could indeed be delivered in simple organisms (Brás et al., 2015).

Never one to shy away from her own convictions, Susan tenaciously pursued her efforts in yeast against a backdrop of continued skepticism for her approach. Her determination recalled the pure grit with which she responded to her NIH study section upon rejection of her first R01 renewal: "I believe I initially proposed the right next experiments; therefore, in revising the application I have not changed one word" (D. Cleveland, personal communication). This was not arrogance, but honesty. That time, she was awarded the grant. Often she wasn't so lucky, but she always found a way to keep going if the data continued to support her convictions.

Increasingly sophisticated tools in her laboratory were developed and began to reveal connections between seemingly disparate genetic risk factors for parkinsonism (Gitler et al., 2009). Indeed, over the years, human genetic analysis provided strong support for perturbed protein trafficking as a central cellular mechanism underlying PD (Hunn et al., 2015), a finding that had been heralded in 2003 by Susan's group in those first experiments in humble yeast. Importantly, genetic screens in yeast against other proteinopathies, including TDP-43 and beta-amyloid, revealed very distinct consequences from alpha-synuclein. Just as known parkinsonism risk factors had emerged in the alpha-synuclein screens, AD risk factors emerged in a beta-amyloid screen (Treusch et al., 2011) and novel genetic risk factors for ALS were discovered through a yeast TDP-43 screen (Elden et al., 2010; Johnson et al., 2008).

Fired up by the knowledge that genetic screens in a lowly organism could specifically uncover human disease genes, Susan became convinced that insights from yeast could one day lead to therapies. It was at this time that the three of us were recruited to her group to build multi-faceted human-induced pluripotent stem cell (V.K.), neuronal assay (C.Y.C.) and target identification (D.T.) platforms that could deliver on that potential. Breathtaking advances in somatic cell reprogramming and genome editing enabled us to utilize insights from yeast genetic screens to uncover early, innate pathologies attributable solely to alpha-synuclein mutations in patient-derived neurons. Genetic modifiers and drug-like compounds reversed pathologies in yeast and could do the same in patient-derived cells (Chung et al., 2013). Moreover, yeast genetic tools could uncover the targets of these molecules, providing a workaround for target identification, a major stumbling block for any cellular phenotypic screens (Tardiff et al., 2013; 2014).

In the current studies, we bring to bear the tools of systems biology to map at proteome-scale the cellular consequences of alpha-synuclein toxicity (Khurana et al., 2017), and its spatial location in living neurons (Chung et al., 2017). A surprising number of parkinsonism and neurodegeneration genes are molecularly linked to alpha-synuclein. An overlap between genetic determinants of alpha-synuclein toxicity and proteins neighboring alpha-synuclein in neurons intimately tied together the physiology of this protein and the toxic consequences of its misfolding. We hope the work ushers in approaches that will aid patient stratification and precise targeting of underlying molecular defects.

Writing, and Final Days

By the time we came to write this current pair of papers, Susan had become very ill—terminally ill, as it turned out. But she never once refused to move forward with writing. The science was her salve, tumor be damned! We watched in awe the day before a major surgery as she sat with razor-sharp focus on our manuscript, quizzing us on the science and sharpening our message. To her, science was powerless if it was not communicated properly and made accessible. She called into meetings, or invited lab members home, and even offered to revise manuscripts while receiving chemotherapy. Her last voicemail admonished us to "get these two papers out!" In her final days, she continued to design experiments to combat her tumor and even delivered the Albany Medical Prize in Medicine lectureship from her hospital bed. But, despite the intense focus on science, our final conversations struck a much more personal tone. She asked about the well-being of *our* family, offered sagely advice for our careers, and advised us to "always think about how you want to be remembered." Her years of mentorship culminated in a final, yet premature, heartfelt hug and "good-bye", one of the hardest moments of our lives. If the true measure of a person is the way they face a challenge, then we will remember Susan by the way she continued to live until the very last with dignity, grace, and in complete control. She left, as she lived, on her own terms.

Susan's legacy will thrive through her paradigm-shifting publications and the work of more than a hundred mentored trainees. Her extraordinary contributions to women in science have been memorialized in the recent endowment by Johnson and Johnson of the Susan Lindquist Chair for Women in Science at the Whitehead Institute. Students and postdoctoral fellows flocked from all quarters to join her laboratory, thrilled to sit in the cockpit with her for a time and catch an aerial glimpse of biology. The three of us help shepherd her vision of making a difference to patients through our work in the laboratory and the clinic, and at Yumanity Therapeutics, a company led by Tony Coles and Ken Rhodes that we co-founded with Susan in 2014. Where will this journey from yeast to humans lead? In short, we don't know. Naturally, we believe in the potential of these approaches, but we won't trumpet their value until the day they deliver a therapeutic that prevents, slows, or reverses neurodegeneration in a patient. We continue to fight the good fight, spurred on by memories of a transformative woman and the uncommonly beautiful biology she brought back from a billion years ago.

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