2022. Proceedings of the Indiana Academy of Science 130(2):179–185

136th ANNUAL ACADEMY MEETING[1]
Presidential Plenary by Eric M. Rubenstein[2]
Clearing the Way: How Cells Unclog Clogged Channels

The following text is a summary of the plenary presentation delivered by Eric M. (VJ) Rubenstein at the 136th annual meeting of the Indiana Academy of Science. Citations have been added.

It is my pleasure to share work performed by the excellent high school, undergraduate, and master's students in my lab at Ball State University concerning how cells unclog clogged channels. Channels – tubes through which a substance is transmitted from one end to another – make life easier. We are familiar with many channels that enable everyday life, such as straws, highway tunnels passing through mountains, and drainpipes. As long as they remain functional, we often take these channels for granted. However, when these channels become clogged or dysfunctional, we become acutely aware of the purposes they serve. Living systems also possess channels that must be maintained in an unclogged and functional state. These include macroscopic channels, such as the human digestive tract, and microscopic channels that permit the movement of substances across otherwise impermeable cellular membranes.

My lab is broadly interested in understanding cellular and molecular mechanisms underpinning human health and disease. However, fundamental experimentation on human subjects is not always technically feasible, ethically advised, or financially possible. Therefore, many cell and molecular biology labs rely on model organisms, which are well-characterized species that have a number of important genetic and mechanistic similarities with humans. The organism my research team uses to study how cells unclog clogged channels is *Saccharomyces cerevisiae*, or budding yeast [1]. You are probably familiar with some of budding yeast's delicious applications, including beer and bread. My team uses budding yeast for basic research.

All eukaryotic cells share features that are necessary for life. Many of the molecules, structures, and processes that exist in human cells also exist in yeast. For example, yeast and humans have the same types of macromolecules, membranes, and organelles. Yeast can be infected by viruses. Yeast perform metabolic reactions, and they respond to their environment. Yeast undergo cell division; in fact, virtually everything we know about cancer (a disease characterized by unregulated cell division) is based in some way on foundational studies performed on yeast cells [2]. If you have visited a doctor and been prescribed a medication, the research leading to that drug's approval almost certainly included basic biological research conducted on yeast. In addition to being used to study fundamental biological processes, yeast are used as factories for therapeutic molecules and biofuels. For example, using technology pioneered at Eli Lilly, yeast can be used as a highly efficient insulin-producing system for patients with diabetes [3, 4].

Many molecular systems that fail and give rise to disease in humans also fail in yeast cells. Scientists can study the consequences of these molecular failures as well as investigate ways cells resolve these failures. This may provide insights for the development of treatments for human disease. Yeast have played an important role in understanding the novel coronavirus. In particular, investigators used yeast as a tool to efficiently reconstruct the coronavirus genome (without the need for human cells) [5], and yeast have been used to understand how the coronavirus spike protein interacts with human ACE2 receptor, an early step in coronavirus infection [6]. Very recently, yeast have been engineered to produce large quantities of a cost-effective coronavirus vaccine that is being shared with lower-income countries [7, 8]. With the rise in baking in 2020, yeast even

[1] Due to COVID-19, the 136th Annual Academy Meeting was a virtual meeting.

[2] Professor of Biology, Ball State University, Department of Biology, Ball State University, Muncie, IN 47306; 765-285-8805 (phone); emrubenstein@bsu.edu.

played an important role in *coping with* the coronavirus pandemic [9].

My research group uses yeast as a model to understand cellular traffic [10]. Rather than tracking how cars or bikes get from point A to point B, our team studies how proteins get from the place in the cell they are synthesized to where they ultimately function. Many proteins are made on the outer surface of a cellular compartment called the endoplasmic reticulum, or ER. These proteins are "trafficked", or moved, into the ER and through a series of membrane-bound compartments to reach one of several different final destinations, such as the Golgi apparatus or the lysosome. Proteins destined to be secreted to the outside of the cell, such as insulin, begin their journeys at the ER. To enter the ER, proteins must cross an otherwise impenetrable membrane surrounding the ER. Proteins crossing the ER membrane face a similar challenge to cars crossing a mountain. Cars cut through mountains by moving through tunnels; proteins cross the ER membrane by moving through narrow molecular tunnels called translocons [11]. A protein synthesized on the outer surface of the ER must be threaded through a translocon to reach the interior of the ER. Once the protein has reached the ER interior, it twists and turns and assembles (or "folds") into a three-dimensional structure, which is its functional form. The protein is then trafficked to its final destination inside or out of the cell.

As with cars moving through a tunnel where an occasional break down causes a traffic jam, proteins can also "break down" as they pass through translocons, effectively jamming the tunnel [12]. This may occur if a protein begins to fold prematurely. As a result, a portion of the protein on one side of the translocon adopts a structure that is too big to pass through the narrow tunnel [13]. As a graduate student at the University of Pittsburgh, I became very familiar with the consequences of clogged tunnels. Cars would become backed up on the highway, and many people were late to work. Likewise, clogged translocons cause cellular traffic buildups, leading to accumulation of proteins outside of the ER, unable to reach their final destinations [14].

Clogged translocons and other forms of translocon dysfunction have been linked to human disease, including Type II Diabetes and certain forms of cancer [15, 16]. Therefore, if we can learn how translocons become clogged, and the mechanisms by which cells unclog translocons, we may be better able to understand and treat human disease. Translocon structure and function are highly similar in yeast and mammals (such as humans) [17]. Thus, my research group's central goal is to understand how cells unclog clogged translocons using yeast as a model system.

To study how cells unclog clogged translocons, we stage engineered channel-clogging proteins in translocons and monitor how long it takes cells to identify and destroy these proteins [18, 19]. By way of analogy, if one wanted to study how well a city handles cars that have broken down in a tunnel, they might send nearly broken-down jalopies on the brink of failure into a tunnel and monitor how long it takes tow trucks to arrive and clear the scene.

In work that began during my postdoctoral fellowship at Yale University and continues in my research lab at Ball State University, my students and I investigate how cells extract and destroy translocon-clogging proteins. We use a technique called cycloheximide chase analysis to characterize the rates at which cells degrade proteins engineered to reliably break down in and clog translocon channels [20]. In healthy yeast cells, most of these translocon-clogging proteins are destroyed within an hour [19–21].

We tested the hypothesis that an enzyme called Hrd1 (a member of a class of enzymes called ubiquitin ligases, found in both yeast and humans), which is located near translocons, contributes to unclogging clogged translocons [18, 21]. Indeed, using cycloheximide chase experiments, yeast engineered to lack Hrd1 destroy translocon-clogging proteins at a much slower rate than yeast that possess Hrd1. In essence, Hrd1 functions as a "molecular tow truck" (Fig. 1).

Translocons are essential for cellular life. In fact, mutations that reduce translocon function cause cells to become sick [22]. This is analogous to what happens if a highway tunnel is blocked or if traffic is reduced to a single lane; the impacts are widespread – many commuters will be late to work at various locations throughout the city! Having identified Hrd1 as a molecular tow truck, we hypothesized that cells that lack Hrd1 would be as unfit as cells with translocon defects. Given how important translocons are, we reasoned that the Hrd1 quality control enzyme that maintains translocon function would also be important for cellular fitness.

Our lab measures cellular fitness by comparing growth rates of yeast cultures [23]. We compared

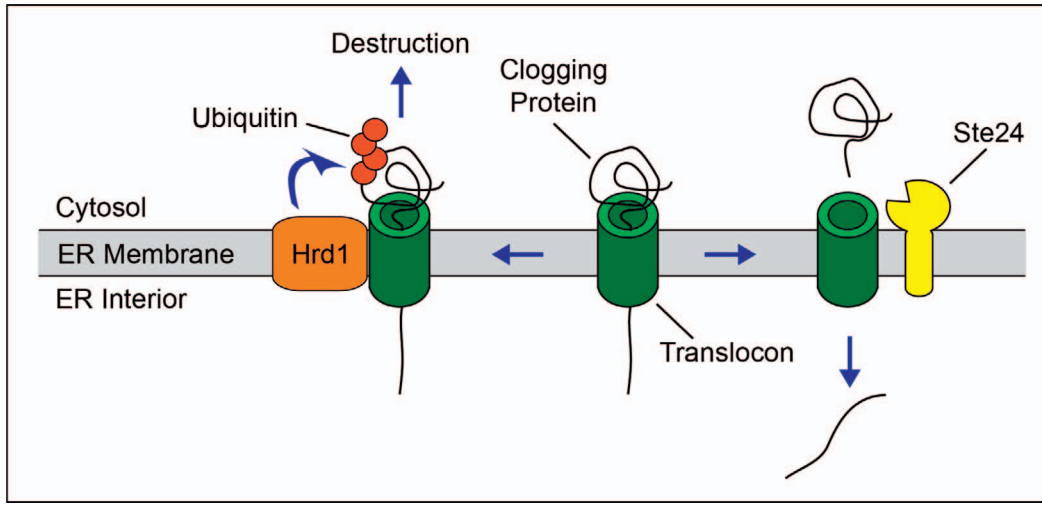

Figure 1.—Hrd1 and Ste24 have overlapping function in unclogging clogged translocons. Clogged translocons may be resolved by the ubiquitin ligase Hrd1 (left) or Ste24 (right). Hrd1 attaches multiple copies of the small protein ubiquitin to the surface of target proteins. These ubiquitin molecules flag the tagged protein for destruction. Ste24 cleaves target proteins into multiple fragments.

the growth of healthy yeast cells possessing Hrd1 to yeast cells engineered to lack Hrd1. In contrast to our hypothesis, yeast grew at the same rate regardless of whether they possess Hrd1 [19, 24–26]. This vexed us for some time. If translocon channels are so important, why was this quality control mechanism that surveys these channels not similarly essential for cellular fitness?

A clue came when we reevaluated our cycloheximide chase experiments where we tracked the degradation rate of translocon-clogging protein in cells possessing or lacking Hrd1 [19, 21]. When Hrd1 was missing, the clogging protein was strongly stabilized, but it was still degraded over time, albeit at a substantially reduced rate. This suggested there must be at least one additional quality control mechanism resolving clogged translocons! This made intuitive sense: perhaps translocon function is *so* important to cellular health that there is inbuilt redundancy. This would be analogous to a city having contracts with two different tow truck companies to ensure traffic does not grind to a halt if drivers for one of the companies do not come to work.

We commenced a search for additional molecular tow trucks that maintain functional translocons. As we conducted our investigations, another lab led by Dr. Maya Schuldiner at the Weizmann Institute of Science in Rehovot, Israel was also investigating how cells maintain functional translocons. The Schuldiner lab found that a second enzyme called Ste24 (previously implicated in other aspects of cell signaling) functions as a molecular tow truck to extract translocon-clogging proteins [13]. Ste24 is a member of a class of enzymes called metalloproteases found in both yeast and humans; it is believed to cut translocon-clogging proteins into smaller fragments prior to their extraction from translocons (Fig. 1).

We were very excited to compare the function of Hrd1 and Ste24. The Schuldiner lab was gracious in sharing yeast strains and reagents with our lab. We first tested whether loss of Ste24 affected cellular health. We hypothesized that Ste24 was the primary molecular tow truck and that cells would suffer if we mutated the gene that encoded it. However, similar to loss of Hrd1, loss of Ste24 proved to be tolerated by yeast cells [19]. Yeast possessing Ste24 and yeast lacking Ste24 grow at similar rates, suggesting Ste24 is not required for cellular health.

Hrd1 functions as a molecular tow truck to unclog translocons but is not required for cellular health. Ste24 functions as a molecular tow truck but also is not required for cellular health. We therefore hypothesized that either one of these enzymes is sufficient to promote degradation of translocon-clogging proteins and maintain cellular fitness. We analyzed degradation of translocon-clogging proteins in healthy yeast possessing both Hrd1 and Ste24, yeast lacking Hrd1 but possessing Ste24, yeast lacking Ste24

but possessing Hrd1, and yeast lacking both Hrd1 and Ste24. Translocon-clogging proteins were rapidly destroyed in healthy cells possessing both Hrd1 and Ste24. When Hrd1 was missing, clogging proteins were partially stabilized (as we previously observed) [19, 21]. Similarly, when Ste24 was missing, clogging proteins were also partially stabilized (as previously observed by the Schuldiner lab) [13, 19]. However, when both Hrd1 and Ste24 were absent, clogging proteins were more abundant and stable than when either tow truck protein was individually missing [19].

These experiments provided the first direct evidence that cells possess two redundant translocon quality control enzymes. Each is able to recognize and degrade broken-down proteins that clog translocon channels. This redundancy likely reflects that critical nature of maintaining functional translocons for cellular health. We next analyzed the impact of simultaneous loss of both Hrd1 and Ste24 on cellular fitness. As previously observed, cells engineered to lack either Hrd1 or Ste24 exhibited no impairment of cellular fitness. However, simultaneously removing genes encoding both enzymes dramatically reduced cell fitness; these double mutant yeast exhibited a substantially reduced growth rate compared to either healthy yeast or single mutants [19]. In our highway tunnel model, this is analogous to a situation in which workers for both tow truck agencies go on strike; traffic would grind to a halt, and the city would suffer.

Hrd1 and Ste24 are multifunctional enzymes. In addition to extracting and degrading translocon-clogging proteins, Hrd1 and Ste24 process a number of different cellular proteins [27, 28]. We hypothesized that the reduced fitness observed when both enzymes are missing reflects defective translocon surveillance; however, it was alternatively possible that reduced fitness was due to loss of other, translocon-unrelated functions of Hrd1 and Ste24. To test this hypothesis, we asked whether Hrd1 and Ste24 remain essential for maximum fitness when translocon clogging is reduced by other means. To this end, we evaluated fitness of yeast cells that either possess or lack *both* Hrd1 and Ste24 enzymes. We introduced an additional, unrelated mutation into these yeast cells that reduces the frequency of clogging events (breakdowns) in translocon tunnels. This mutation is equivalent to a reduced speed limit in a mountain tunnel; if all cars move just a little more slowly, crashes occur less frequently. In yeast with this additional mutation, translocons become clogged much less frequently.

Our results were striking. In the context of the additional mutation that reduces the frequency of translocon clogging, the absence of Hrd1 and Ste24 no longer impaired cellular fitness [19]. By reducing the speed limit of proteins moving through translocons, fewer crashes occur, and the need for molecular tow trucks is greatly diminished. When everyone in the city drives carefully, the tow trucks are not so important! This result strongly suggests that the fitness defect of cells lacking both Hrd1 and Ste24 is linked to their function at the translocon (and not to their functions unrelated to translocon surveillance).

In summary, my students and I have discovered that Hrd1 and Ste24 are "molecular tow truck" enzymes with overlapping function in unclogging clogged translocons (Fig. 1). The presence of either Hrd1 or Ste24 is sufficient to maintain cellular health, but eliminating both enzymes dramatically impairs fitness. If translocon clogging is prevented from occurring in the first place, the cellular need for Hrd1 and Ste24 is dramatically reduced. Drawing an analogy to another important channel de-clogger, if a toilet is never clogged, the plunger is merely decorative.

This work leaves us with several unanswered questions. First, we do not yet understand how Hrd1 and Ste24 "see" clogged translocons and distinguish whether a particular protein is clogged in a translocon rather than being in the process of moving through a channel. Second, recent data from our lab indicate that translocon unclogging functions are impaired during specific forms of cellular stress (similar to cellular stress experienced in some human diseases, including several neurodegenerative conditions) [29, 30]. How stress impairs translocon unclogging remains uncharacterized. Further, the crucial nature of Hrd1 and Ste24 for cellular function suggests clogging is likely to be a frequent occurrence; however, we know little about which proteins or types of proteins are most likely to clog translocon channels. We presently have knowledge of a limited number of naturally occurring translocon-clogging proteins (e.g. [31]). Improved mechanistic understanding of how cells relieve traffic jams will be enhanced by characterization of additional proteins that clog translocons and contribute to human diseases. Finally, given that translocon clogging and dysfunction have been linked to Type II Diabetes, some forms of cancer, and other disorders [15, 16], can the human versions of Hrd1

and Ste24 be targeted therapeutically? Further investigation of translocon quality control is likely to reveal novel, fundamental cell biology and may lead to enhanced intervention in human disease.

ACKNOWLEDGMENTS

The experiments discussed in this manuscript were performed by Kyle A. Richards, Avery M. Runnebohm, Courtney Broshar Irelan, Samantha M. Turk, Halie E. Vitali, Christopher J. Indovina, and Eric M. Rubenstein. The author acknowledges Molly Dolan, Julia Niekamp, Seth Horowitz, Brian Voas, Kelsey Woodruff, Kamryn Kennedy, and Mahmoud Daraghmi for generating reagents and providing lab assistance. This study is described in greater detail in [19]. This work was supported by Indiana Academy of Science Senior Research grants, Ball State University ASPiRE research grants, and National Institutes of Health Grant GM111713. The author wishes to acknowledge current and former Indiana Academy of Science members and Ball State University colleagues Dr. Kemuel Badger, Dr. Heather Bruns, Dr. Clare Chatot, Dr. David LeBlanc, Dr. James Olesen, Dr. Susan McDowell, and Dr. Donald Ruch for mentorship and advice.

LITERATURE CITED

1. Duina, A.A., M.E. Miller & Keeney. 2014. Budding yeast for budding geneticists: a primer on the *Saccharomyces cerevisiae* model system. Genetics 197:33–48.
2. Hartwell, L.H. 2004. Yeast and cancer. Bioscience Reports 24:523–544.
3. Nielsen, J. 2013. Production of biopharmaceutical proteins by yeast: advances through metabolic engineering. Bioengineered 4:207–211.
4. Ho, P.W., S. Piampongsant, B. Gallone & A. Del Cortona. 2021. Massive QTL analysis identifies pleiotropic genetic determinants for stress resistance, aroma formation, and ethanol, glycerol and isobutanol production in *Saccharomyces cerevisiae*. Biotechnology for Biofuels 14:211.
5. Thi Nhu Thao, T., F. Labroussaa, N. Ebert, P. V'kovski, H. Stalder, J. Portmann, J. Kelly, S. Steiner, M. Holwerda, A. Kratzel, M. Gultom, K. Schmied, L. Laloli, L. Hüsser, M. Wider, S. Pfaender, D. Hirt, V. Cippà, S. Crespo-Pomar, S. Schröder, D. Muth, D. Niemeyer, V.M. Corman, M.A. Müller, C. Drosten, R. Dijkman, J. Jores & V. Thiel. 2020. Rapid reconstruction of SARS-CoV-2 using a synthetic genomics platform. Nature 582:561–565.
6. Starr, T.N., A.J. Greaney, S.K. Hilton, D. Ellis, K.H.D. Crawford, A.S. Dingens, M.J. Navarro, J.E. Bowen, M.A. Tortorici, A.C. Walls, N.P. King, D. Veesler & J.D. Bloom. 2020. Deep mutational scanning of SARS-CoV-2 receptor binding domain reveals constraints on folding and ACE2 binding. Cell 182:1295–1310 e20.
7. Chen, W.H., J. Pollet, U. Strych, J. Lee, Z. Liu, R.T. Kundu, L. Versteeg, M.J. Villar, R. Adhikari, J. Wei, C. Poveda, B. Keegan, A.O. Bailey, Y.-L. Chen, P.M. Gillespie, J.T. Kimata, B. Zhan, P.J. Hotez & M.E. Bottazzi. 2022. Yeast-expressed recombinant SARS-CoV-2 receptor binding domain RBD203-N1 as a COVID-19 protein vaccine candidate. Protein Expression and Purification 190:106003.
8. Bush, E. 2022. From Texas to India, a Patent-free Covid Vaccine Looks to Bridge Equity Gaps. NBC News. At: https://www.nbcnews.com/science/science-news/texas-india-patent-free-covid-vaccine-looks-bridge-equity-gaps-rcna10911. (Accessed 19 January 2022).
9. Guyunn, J. & K. Tyko. 2020. Dry Yeast Flew off Shelves During Coronavirus Pantry Stocking. Here's When You Can Buy It Again. USA Today. At: https://www.usatoday.com/story/money/food/2020/04/23/coronavirus-pantry-baking-yeast-shortage/3004274001/. (Accessed 19 January 2022).
10. Feyder, S., J.-O. De Craene, S. Bär, D.L. Bertazzi & S. Friant. 2015. Membrane trafficking in the yeast *Saccharomyces cerevisiae* model. International Journal of Molecular Sciences 16:1509–1525.
11. Aviram, N. & M. Schuldiner. 2017. Targeting and translocation of proteins to the endoplasmic reticulum at a glance. Journal of Cell Science 130:4079–4085.
12. Wang, L. & Y. Ye. 2020. Clearing traffic jams during protein translocation across membranes. Frontiers in Cell and Developmental Biology 8:610689.
13. Ast, T., S. Michaelis & M. Schuldiner. 2016. The protease Ste24 clears clogged translocons. Cell 164:103–114.
14. Izawa, T., T. Tsuboi, K. Kuroha, T. Inada, S. Nishikawa & T. Endo. 2012. Roles of Dom34:Hbs1 in nonstop protein clearance from translocators for normal organelle protein influx. Cell Reports 2:447–453.
15. Kayatekin, C., A. Amasino, G. Gaglia, J. Flannick, J.M. Bonner, S. Fanning, P. Narayan, M.I. Barrasa, D. Pincus, D. Landgraf, J. Nelson, W.R. Hesse, M. Costanzo, AMP T2D-GENES Consortium; C.L. Myers, C. Boone, J.C. Florez & S.Lindquist. 2018. Translocon declogger Ste24 protects against IAPP Oligomer-Induced Proteotoxicity. Cell 173:62–73 e9.

16. Sicking, M., S. Lang, F. Bochen, A. Roos, J.P.H. Drenth, M. Zakaria, R. Zimmermann & M. Linxweiler. 2021. Complexity and specificity of Sec61-Channelopathies: human diseases affecting gating of the Sec61 complex. Cells 10(5):1036.
17. Rapoport, T.A., L. Li & E. Park. 2017. Structural and mechanistic insights into protein translocation. Annual Review of Cell and Developmental Biology 33:369–390.
18. Rubenstein, E.M., S.G. Kreft, W. Greenblatt, R. Swanson & M. Hochstrasser. 2012. Aberrant substrate engagement of the ER translocon triggers degradation by the Hrd1 ubiquitin ligase. Journal of Cell Biology 197:761–773.
19. Runnebohm, A.M., K.A. Richards, C.B. Irelan, S.M. Turk, H.E. Vitali, C.J. Indovina & E.M Rubenstein. 2020. Overlapping function of Hrd1 and Ste24 in translocon quality control provides robust channel surveillance. Journal of Biological Chemistry 295:16113–16120.
20. Buchanan, B.W., M.E. Lloyd, S.M. Engle & E.M. Rubenstein. 2016. Cycloheximide chase analysis of protein degradation in *Saccharomyces cerevisiae*. Journal of Visualized Experiments 2016(110):53975.
21. Engle, S.M., J.J. Crowder, S.G. Watts, C.J. Indovina, S.Z. Coffey & E.M. Rubenstein. 2017. Acetylation of N-terminus and two internal amino acids is dispensable for degradation of a protein that aberrantly engages the endoplasmic reticulum translocon. PeerJ 2017.**5**:e3728.
22. Stirling, C.J., J. Rothblatt, M. Hosobuchi, R. Deshaies & R. Schekman. 1992. Protein translocation mutants defective in the insertion of integral membrane proteins into the endoplasmic reticulum. Molecular Biology of the Cell 3:129–142.
23. Watts, S.G., J.J. Crowder, S.Z. Coffey & E.M. Rubenstein. 2015. Growth-based determination and biochemical confirmation of genetic requirements for protein degradation in *Saccharomyces cerevisiae*. Journal of Visualized Experiments 2015:e52428.
24. Runnebohm, A.M., M.D. Evans, A.E. Richardson, S.M. Turk, J.B. Olesen, P.J. Smaldino & E.M. Rubenstein. 2020. Loss of protein quality control gene UBR1 sensitizes *Saccharomyces cerevisiae* to the aminoglycoside hygromycin B. Fine Focus 6:76–83.
25. Niekamp, J.M., M.D. Evans, A.R. Scott, P.J. Smaldino & E.M. Rubenstein. 2019. TOM1 confers resistance to the aminoglycoside hygromycin B in *Saccharomyces cerevisiae*. microPublication Biology 2019.
26. Woodruff, K.A., K.A. Richards, M.D. Evans, A.R. Scott, B.M. Voas, C.B. Irelan, J.B. Olesen, P.J. Smaldino & E.M. Rubenstein. 2021. Inner nuclear membrane Asi Ubiquitin Ligase Catalytic Subunits Asi1p and Asi3p, but not Asi2p, confer resistance to aminoglycoside hygromycin B in *Saccharomyces cerevisiae*. microPublications Biology 2021:10.
27. Phillips, B.P. & E.A. Miller. 2021. Membrane protein folding and quality control. Current Opinion in Structural Biology 69:50–54.
28. Goblirsch, B.R. & M.C. Wiener. 2020. Ste24: an integral membrane protein zinc metalloprotease with provocative structure and emergent biology. Journal of Molecular Biology 432:5079–5090.
29. Buchanan, B.W., A.B, Mehrtash, C.L. Broshar, A.M. Runnebohm, B.J. Snow, L.N. Scanameo, M. Hochstrasser & E.M. Rubenstein. 2019. Endoplasmic reticulum stress differentially inhibits endoplasmic reticulum and inner nuclear membrane protein quality control degradation pathways. Journal of Biological Chemistry 294:19814–19830.
30. Yoshida, H. 2007. ER stress and diseases. FEBS Journal 274:630–658.
31. Mitchell, D.M., M. Zhou, R. Pariyarath, H. Wang, J.D. Aitchison, H.N. Ginsberg & E.A. Fisher. 1998. Apoprotein B100 has a prolonged interaction with the translocon during which its lipidation and translocation change from dependence on the microsomal triglyceride transfer protein to independence. Proceedings of the National Academy of Sciences (USA) 95:14733–14738.

Manuscript received 16 January 2022, revised 21 June 2022.

Eric "VJ" Rubenstein is Professor of Biology and Co-Director of the Biotechnology Certificate program at Ball State University, where he has been a faculty member since 2012. He obtained his PhD in Biochemistry and Molecular Genetics at the University of Pittsburgh School of Medicine, where he investigated mechanisms of glucose sensing. He completed postdoctoral research in the Department of Molecular Biophysics and Biochemistry at Yale University, where he initiated studies of protein quality control in *Saccharomyces cerevisiae*. At Ball State, Dr. Rubenstein teaches Cell Biology courses and continues to investigate conserved mechanisms of protein quality control. Discoveries in his lab have potential implications for neurodegenerative conditions, diabetes, and cholesterol-related pathologies. Dr. Rubenstein and his students have shared their research in 30 presentations at the Indiana Academy of Sciences Annual Meetings, in presentations at international conferences, and in peer-reviewed journal articles. His work has been supported by grants from the Indiana Academy of Science and the National Institutes of Health. Dr. Rubenstein has previously served as Chair and Vice Chair for the Cell Biology section of the Academy. A former amateur competitive eating champion, Dr. Rubenstein enjoys running, hiking, reading, and watching television in his spare time.