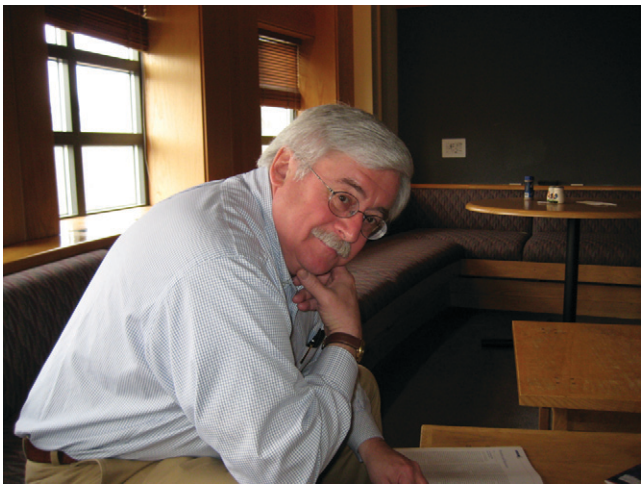

Thomas J. Silhavy

The 2008 Novitski Prize

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THE recipient of the inaugural Novitski Prize of the Genetics Society of America is Thomas J. Silhavy, a world-renowned bacterial geneticist. The award, named in honor of influential Drosophila geneticist Edward Novitski (1918–2006) and supported through the generosity of his family, was established to recognize an extraordinary level of creativity and intellectual ingenuity in solving significant problems in biological research through the application of genetic methods. The scientific accomplishments of Tom Silhavy truly represent the kind of achievements in research that stand out because of their innovativeness and because of the deep insights about all cells that have sprung from his discoveries using the enteric gram-negative eubacterium *Escherichia coli* as his model organism. It can indeed be said that Tom Silhavy's path-finding research into fundamental mechanisms of protein secretion, membrane assembly, and sensing of environmental cues established basic paradigms that are now the content of all modern textbooks of microbial genetics and cell biology. Most importantly, the clever selections and screens used to identify the gene products and underlying mechanisms involved in these processes that were and are being used by Tom Silhavy are brilliant examples of the beauty and ingenuity that can be brought to bear when genetics is used as a tool for scientific discovery, as recounted below.

It was not always clear that Tom's path would lead him to the door of genetics to carry out his major life's work because he manifested early on an aptitude for the chemical side of biology. He received his B.S. *summa cum laude* in Pharmacy from Ferris State College in Big Rapids, Michigan, in 1971. He then entered the graduate program of the Department of Biological Chemistry at Harvard Medical School in Boston, where he had the good fortune to elect to carry out his doctoral dissertation research under the guidance of Winfried Boos, whose group was situated then in the Biochemical Research Laboratory at Massachusetts General Hospital. In a remarkable series of nine articles published in the mid- to late 1970s, in the midst of which Tom moved with Winfried briefly to the Institut Pasteur in Paris (1974–1975) and then to Germany when Winfried accepted a faculty position at the University of Konstanz (where he has remained ever since), Tom made major strides in investigating the protein machinery necessary for the active transport of galactose, galactosides, and other carbon sources into *E. coli*, especially the role of periplasmic substrate-binding proteins. This work ran the gamut from organic synthesis of an all-purpose galactoside analog to the development of convenient assays for transport kinetics to ligand-binding measurements to the electrophoretic analysis of the composition of purified membranes. So, it seemed that Tom was at risk of holding legitimate credentials as a gifted biochemist. However, during that same period, Tom also devised and applied a clever selection procedure to isolate mutants defective in the *E. coli* transport system for β-methylgalactosides—and, thenceforth, he was hooked on the value of genetics to get to the beating heart of a biological problem. This growing penchant for genetics was strongly reinforced during his time in Paris by his further training and exceptionally productive collaborations with Maxime Schwartz and his circle of colleagues at the Institut Pasteur.

After receipt of his M.A. (1974) and Ph.D. (1975) in record time, and following his stay in Europe, Tom irrevocably sealed his fate as a molecular geneticist by returning to Boston and Harvard Medical School to receive further postdoctoral training (1975–1977) with legendary bacterial geneticist Jonathan R. Beckwith, in whose lab he was supported by a prestigious postdoctoral fellowship from the Jane Coffin Childs Memorial Fund for Medical Research. It was with Jon Beckwith that Tom was instrumental in establishing the use of gene fusions as an incisive experimental tool for a

variety of genetic applications, a methodology that is now part of the repertoire of practically every biological scientist who works at the molecular and cellular level. In fact, that experience and subsequent collaborative efforts led to two now-classic books written by Tom Silhavy, *Experiments with Gene Fusions* (with Mike Berman and Lynn Enquist) in 1984 and *The Power of Bacterial Genetics* (with Jon Beckwith) in 1992, both published by the Cold Spring Harbor Laboratory Press. After spending another 2 years as an Instructor in the same department (Microbiology and Molecular Genetics), Tom was recruited away from Harvard Medical School in 1979 to serve as the Head of the Genetics of Membrane Biogenesis Section of the relatively newly established National Cancer Institute–Frederick Cancer Research Center in Frederick, Maryland, where he then was named Director of the Laboratory of Genetics and Recombinant DNA (in 1981) and remained until 1984. He was lured back to academia in 1984 to become a founding member of the Department of Molecular Biology at Princeton University, where he now holds the Warner–Lambert Parke–Davis Professorship.

Tom is an especially deserving candidate for the honor of the Novitski Prize because, for more than 30 years, he and his students have used *E. coli* genetics as a powerful tool to discover the essential components and dissect the molecular apparatuses that cells use for protein secretion, membrane biogenesis, and prokaryotic cell signal transduction. In every instance, this work has been characterized by the use of a variety of clever genetic approaches of unique design. Proteins destined for secretion are made initially as precursor forms with a typical signal sequence at the amino terminus that directs them to the cellular secretion machinery. Tom's lab was the first to isolate signal sequence mutations. Bootstrapping from those mutations by selections for suppressors, Tom's group was the first to identify a component of the *E. coli* protein secretion machinery, an integral membrane protein that later was found to be a core component of the protein translocation channel that directs protein secretion from the cytoplasm to the outside of the bacterial cell. Thus, in large part on the basis of Tom's discoveries, we now know that both signal sequences and the mechanism of protein secretion are conserved from bacteria to humans.

Tom and his colleagues also discovered the first two-component signal-transduction system. It is now recognized that two-component systems form the major family of regulators that bacteria use to sense a wide variety of environmental cues and then transduce the information to regulate transcription, thereby achieving an appropriate pattern of gene expression. For example, Tom's work on the Cpx stress-response pathway has shown that this two-component system senses a variety of cellular stresses, including misfolded proteins, and then responds by upregulating the expression of protein-folding and trafficking factors. The CpxA component resides in the inner membrane and has both protein kinase and phosphatase activities. CpxR, the response regulatory component, resides in the cytoplasm and transduces the CpxA signal by activating transcription of stress-responsive genes.

In very exciting recent work, some of it conducted in collaboration with a former Princeton colleague (Dan Kahne), Tom investigated the structure, function, and spatial organization of the Omp85/YaeT family of integral membrane proteins that are conserved from bacteria to humans. These proteins are pivotal and essential components of the molecular machines that catalyze insertion and assembly of porins and other β-barrel proteins into the outer membranes of gram-negative bacteria (and into the outer membranes of mitochondria and chloroplasts too). These current studies certainly represent one of the most major findings in bacterial cell biology in recent years. In addition to the areas of research mentioned above, current work in the Silhavy lab is also focused on the regulatory systems that sense and respond to nutrient limitation and evoke the responses that allow *E. coli* cells to survive starvation. Overall, Tom has authored close to 200 primary research articles on all of these subjects, many of them considered groundbreaking in their respective fields.

In recognition of his scientific accomplishments, Tom has received many other well-deserved accolades, in addition to his receipt of the 2008 Novitski Prize. These awards include an honorary Doctor of Sciences degree from his undergraduate alma mater (1982), election as a Fellow of the American Academy of Microbiology (1994), a MERIT Award from the National Institutes of Health (1999), election as a Fellow of the American Association for the Advancement of Science (2004), and election as a Member of the American Academy of Arts and Sciences (2005) and of the National Academy of Sciences (2005). It is especially noteworthy that his commitment to teaching has been formally recognized by the President's Award for Distinguished Teaching at Princeton (1993), the Graduate Microbiology Teaching Award of the American Society for Microbiology (2002), and the Graduate Advising Award at Princeton (2003).

Jeremy W. Thorner