

## IN MEMORIAM

# Bill Weis (1959–2023): Pioneering structural biologist and biochemist who revolutionized our understanding of cell adhesion and Wnt signaling

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In October 2023, cell biology lost one of its brightest stars, Bill Weis, gone too soon at the age of 64. Bill was a masterful biochemist and structural biologist who made landmark contributions to a remarkable number of fields, most notably cell–cell adhesion, Wnt signaling, and signaling by G-protein coupled receptors (GPCRs).

Bill grew up in a middle-class family in Queens and on Long Island, with grandparents who emigrated from Russia and Ukraine (Weis, 2000). His family encouraged their children to follow their own paths—his brothers are a lawyer and a bagel baker. He did his undergraduate studies at Princeton, receiving a degree in biochemistry in 1981. He loved the science there, and had a supportive scientific mentor, Dr. Meredith Applebury, but was put off by the “WASPy (White Anglo-Saxon Protestant) elitist” attitude of many undergraduates (Weis, 2000). His family had to stretch financially to afford Princeton, and Bill had jobs in a hospital, the campus library, and a work-study lab job to help pay the bills—it wasn’t until after starting his faculty job that he was finally able to pay off the student loans.

He then joined the PhD program in biochemistry and molecular biology at Harvard, as a graduate school classmate of one of us (M. Peifer). In our first year, we got a rigorous grounding in biochemical and molecular approaches in a problem-set-based class taught by two of the faculty, Don Wiley and Steve Harrison. Bill went on to join the Wiley lab—Wiley and Harrison led parallel groups in a shared space that became one of the world-renowned centers of structural biology. During Bill’s time there, he was surrounded by a remarkable set of future leaders of the field, including Pam Bjorkman, Ian Wilson, Jim Hogle, Tomas Kirchhausen, Cynthia Wolberger, and Peter Sorger. However, Bill also remembered it as a challenging time, with the high-pressure environment and the intellectual arrogance of the department providing an experience that shaped his own very different approach to mentoring and lab climate (Weis, 2000).



Bill Weis. Image courtesy of Sherin Halfon.

There Bill solved the structure of the influenza virus hemagglutinin complexed with its receptor, sialic acid (Weis et al., 1988). He continued his structural studies of hemagglutinin in a short postdoc at Yale, and then began a second postdoc in Wayne Hendrickson’s lab at Columbia. He described his time in the Hendrickson lab as “best four years of [his] life.” Hendrickson “would...work very closely with everyone on their particular problems. He really left you alone, but when you wanted help and advice, he was there. And he was always really constructive” (Weis, 2000). This experience changed Bill’s views on lab management and mentoring. It was at Columbia that Bill began his first independent research focus, studying lectins, proteins that mediate protein–carbohydrate interactions, a project Hendrickson was generous enough to let him take with him. This led

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to a pioneering set of publications (e.g., [Weis et al., 1992](#)) and a position as an assistant professor of structural biology at Stanford Medicine in 1993.

It was during his time as an assistant professor that Bill's interests diversified, and he began the multiple strands of investigation that continued for the rest of his career. He was able to broaden his focus with funds from a Pew Scholars Award ([Weis, 2000](#)). Inspired by his neighbor James Nelson, a world leader in studying cell-cell adhesive junctions, Andy Huber and Bill solved the structure of  $\beta$ -catenin in 1997 ([Huber et al., 1997](#)). By that point, we knew that  $\beta$ -catenin had dual functions—it functions at the plasma membrane as a key component of cadherin-based cell-cell adhesive junctions, and it has a separate role in the nucleus as the regulated effector of the canonical Wnt signaling pathway, acting as a transcriptional co-activator. Andy and Bill's structure of  $\beta$ -catenin ultimately provided key insights into both of these functions and also revealed how Wnt signaling is regulated. As someone who had worked on the *Drosophila* homolog Armadillo for nine years at that point (M. Peifer), and had named its signature Armadillo repeats, Bill sharing the structure with me was a career highlight.

Bill and his lab took this work in two directions. First, they dug into the mechanisms that regulate Wnt signaling.  $\beta$ -Catenin, the key Wnt effector, is regulated by modulating its stability. A protein complex including the tumor suppressor proteins APC and Axin and the kinases GSK3 and CK1, termed the “destruction complex,” captures and phosphorylates  $\beta$ -catenin, priming it for recognition and ubiquitination by an E3 ubiquitin ligase and degradation by the proteasome. Wnt signaling inactivates the destruction complex, stabilizing  $\beta$ -catenin and allowing it to enter the nucleus. In a remarkable series of publications, Bill's lab defined the structural and biochemical basis for destruction complex assembly and function. They determined the mechanisms by which APC binds Axin ([Spink et al., 2000](#)) and by which APC binds  $\beta$ -catenin ([Eklof Spink et al., 2001](#); [Ha et al., 2004](#)). In doing so, they pioneered studies of the function of intrinsically disordered regions, just as the term was coming into our scientific discourse. His lab also provided important insights into the mechanisms by which the T cell factor/ $\beta$ -catenin complex plays dual roles as a transcriptional activator and repressor ([Daniels and Weis, 2002, 2005](#)), and into how Wnt ligand interactions with their receptors are regulated ([Ahn et al., 2011](#); [Stamos et al., 2014](#)). Recently, the Weis lab and collaborators built on this foundation, beginning to assemble the destruction complex from purified proteins to probe questions about its assembly state and regulation ([Kan et al., 2020](#)).

Bill's impact on our understanding of cell-cell adhesion was even more central. This rested on a decades-long collaboration with cell biologist James Nelson and more recently biophysicist Alex Dunn (AD). Bill's work was central to revealing how cell-cell adhesive junctions link to the actomyosin cytoskeleton. In the field's original model, the linkage was simple and direct, with  $\beta$ -catenin binding both the cadherin cytoplasmic tail and  $\alpha$ -catenin, and  $\alpha$ -catenin binding actin. Building on their structure of  $\beta$ -catenin's central domain, Bill and his lab defined the structural basis of  $\beta$ -catenin/ $\alpha$ -catenin ([Pokutta and Weis, 2000](#)) and  $\beta$ -catenin/E-cadherin interactions ([Huber and Weis, 2001](#)).

However, their next steps would shatter this long-held paradigm. The Nelson and Weis labs set out to directly test the hypothesis that the junction-cytoskeleton connection was simple and direct. In a pair of papers, they found that while  $\alpha$ -catenin binds actin with high affinity, particularly when dimerized, when they assembled the cadherin-catenin complex, its affinity for actin was quite low ([Drees et al., 2005](#); [Yamada et al., 2005](#)). This revolutionized our field, stimulating us all to think more deeply about the nature and complexity of these interactions. One change in our view of junction-cytoskeletal connections was to bring more proteins into the picture. Bill and his lab were part of this, defining interactions between  $\alpha$ -catenin and Afadin ([Pokutta et al., 2002](#)). The second key insight, facilitated by adding the Dunn lab (AD) to the team, was their demonstration that the cadherin-catenin complex acts a mechanosensor, with the minimal cadherin-catenin complex switching to high-affinity actin interactions when force was exerted on it ([Buckley et al., 2014](#)). This led them to define the functional differences between monomeric and dimeric  $\alpha$ -catenin and to explore potential cadherin-independent functions of  $\alpha$ -catenin ([Benjamin et al., 2010](#); [Bianchini et al., 2015](#)). They found that mechanosensitive “catch bond” behavior was exhibited by additional junction:cytoskeletal linkers, vinculin and talin ([Huang et al., 2017](#); [Owen et al., 2022](#)), and they defined the structural basis for the switch in  $\alpha$ -catenin ([Xu et al., 2020](#)). Together, these insights re-shaped our view of cell adhesion and morphogenesis, as we unravel the complex network of mechanosensitive proteins that mediates junction:cytoskeletal linkage via multivalent interactions. Along the way, Bill and his lab also provided important insights into the second major cell-cell junction, the desmosome (e.g., [Choi et al., 2002](#); [Choi and Weis, 2005](#)), and explored the diversity and evolution of catenin functions in organisms as far afield as *Dictyostelium* ([Dickinson et al., 2011, 2012](#)).

Bill's scientific contributions, documented in his almost 200 scientific publications, go far beyond these, including important contributions to protein trafficking (e.g., [Hattendorf et al., 2007](#); [Misura et al., 2000](#)) and to the methodology underlying structural biology. Bill also provided key assistance to Brian Kobilka, who as a new assistant professor wanted to solve the structures of GPCRs. Kobilka acknowledged this, noting, “Bill played an essential role in these studies that led to me to be awarded a Nobel Prize in chemistry. Bill knew much more about my primary focus than I knew about his primary focus. That's just the kind of person he was; he was really engaged in science beyond his own research” ([Moskal, 2023](#)). This led to one of the first GPCR structures ([Rasmussen et al., 2007](#)) and a series of many additional co-authored publications.

Bill's many scientific achievements were matched by his qualities as a colleague, mentor, and friend. At Stanford, he served as chair of the Department of Photon Science, the Department of Structural Biology, and of the Graduate Program in Biophysics. He approached these tasks with energy, good humor, and tact. Bill's understated but effective leadership played a key role in recruiting multiple junior colleagues to the university, to the maintenance of a National Institutes of Health-funded graduate student training grant, now in its 34th year,

and most recently to the initiation of the Stanford-SLAC CryoEM Center, which has rapidly developed into a leading center for cryo-electron microscopy. The energy and foresight with which he pursued these tasks improved the lives of many colleagues in very tangible ways.

Although these and many other accomplishments are undoubtedly important, Bill was, for his students and colleagues, a completely remarkable human being. He was a quintessentially great advisor—available when needed, but secure enough to give his lab members space to develop their own ideas and to learn from mistakes. Bill also displayed a remarkable degree of compassion and psychological insight, and was known as a source of wise advice for students and colleagues alike. His perceptive advice on both science and mentorship was particularly appreciated by one of us (AD). This is only one of many personal and professional relationships that were touched by Bill's penetrating scientific insight and personal wisdom. Outside the lab, Bill shared his life with his spouse, Sherin Halfon, a biotechnology scientist, and his pit bull rescue, Kermit. They enjoyed travel, dining at fine restaurants, cooking, and renovating their midcentury home in Palo Alto.

In thinking about how to capture Bill's essential brilliance, his wisdom and compassion, his excellent sense of humor, and his essential generosity, it is perhaps easiest to share one concrete memory: Bill on the edge of his chair, eyes alive, completely pleased by an exceptionally clean and delightfully unexpected new result. One of many such moments, unrecorded, but etched in the minds of those fortunate enough to know him.

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full interview is at: <https://digital.sciencehistory.org/works/pet9ht9>.

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