Günter Blobel 1936–2018

Few scientists are capable of forging fundamentally new directions for their field of study during the course of their careers. Günter Blobel was one such person. He was a founder of the molecular era of cell biology, revealing the mechanistic basis for how proteins are directed to various intracellular compartments. His work provided a new understanding of many basic cell biological processes and opened the way to a cornucopia of new diagnostics and therapeutics. Günter Blobel died on 18 February, 2018, at the age of 81.

Growing up in Silesia, then in the eastern part of Germany, Günter was fortunate in his early years to be spared much of the impact of the terrible events in Germany at that time¹. He grew up in a rural environment, enjoying summers of carriage rides and winters of sleigh rides. However, all of this changed toward the end of World War II, and the family became refugees. Fleeing west via Dresden, Günter was awestruck by the baroque beauty of the city, and it was from the outskirts, just a few days later, that Günter saw Dresden's destruction, an event that made an indelible impact on him and inspired much of his later philanthropy.

Though Günter's family largely regrouped in Freiberg at war's end, the oppression of the new East German regime made life increasingly difficult. In order to gain a higher education, Günter left, initially graduating with a degree in medicine from University of Tübingen, but then, finding himself more interested in the scientific problems of medicine rather than its practice, he joined the laboratory of Van Potter in the University of Wisconsin as a graduate student. There, he isolated and analyzed different pools of ribosomes from rat liver and so began his lifelong studies of how subcellular machineries manage and organize living processes of the cell. Several years later he moved to the Rockefeller University for his postdoctoral training with George Palade, who had by that time established an outline of how cellular proteins are synthesized and secreted, being made on the endoplasmic reticulum (ER) before being shuttled in vesicles to the plasma membrane. However, the molecular machineries involved in these processes remained completely unknown. Günter took on the task—starting in Palade's lab, but later in his own group—of cataloging these machineries and uncovering the principles upon which they functioned. In the process, Günter was promoted to the faculty and so made the Rockefeller University his scientific home for more than 50 years.

Credit: The Rockefeller University

Usually, major scientific discoveries are uncovered by the gradual accumulation of understanding, through long study of important biological processes. However, occasionally, a flash of deep insight can lead to the rapid uncovering of a fundamental principle, which must then be tested through hard bench research. The latter was the case for Günter Blobel and his colleague David Sabatini. It was known that mRNAs encoding secreted proteins become sequestered with their translating ribosomes on the surface of the ER. However, despite searching, they and others could find no obvious differences between ribosomes on the surface of the ER and those free within the cytosol that produced non-secreted proteins. Günter hypothesized that the difference wasn't in the ribosomes, or even the mRNA, but in the nascent proteins being made by these ribosomes. In an intuitive leap, Günter and David Sabatini proposed the existence of a signal sequence uniquely present in proteins destined for secretion and positioned at the amino terminus so that it protruded from the translating ribosome and directed the translating ribosome, via a 'binding factor', to a protein-conducting channel embedded in the ER's membrane². There, the translating protein would wind through this channel into the ER lumen, and from there, move on to secretion. Although the idea was elegant, at the time it was—as Günter admitted—little more than 'pure speculation', which garnered a cool reception from numerous other researchers. However, evidence began to emerge that the idea might be correct, including observations from

Cesar Milstein's laboratory in Cambridge³. As definitive evidence was still lacking, Günter teamed with postdoctoral researcher Bernhard Dobberstein to see if they could systematically assemble a completely *in vitro* system to directly test this 'signal hypothesis'. In a series of groundbreaking publications, they described a cell-free system in which isolated mRNA, ribosomes, and ER-derived microsomes devoid of ribosomes could be combined to produce signal-sequence-dependent protein translation and translocation into the microsomes, with concomitant removal of the signal peptide to generate a mature luminal protein^{4,5}. Günter's achievement was thus twofold. First, he had this rare insight. Second, and just as importantly, he then doggedly pursued the experimental evidence to test this idea, going so far as to develop an entirely unprecedented type of cell-free, reconstituted system in the process. And eventually, he proved the signal hypothesis to be true. For this fundamental discovery, Günter was awarded the Nobel Prize in Medicine in 1999, and over his long career, he received many other accolades for his discoveries, including the Canada Gairdner International Award, the ASCB Wilson Medal, and the Albert Lasker Basic Medical Research Award.

Günter was a multitasking scientist with a wide variety of interests beyond the ER protein secretory mechanism and made seminal scientific contributions to many other fields. He went on to correctly extend the principle of localization and targeting sequences embedded in proteins to other organelles and compartments;

Credit: The Rockefeller University

indeed, protein targeting to peroxisomes, chloroplasts, mitochondria, and even into and out of the nucleus depends upon the presence of a signal sequence on the proteins being targeted. He was also fascinated by the construction, composition, and functions of nuclear pore complexes (NPCs), the mediators of nuclear cytoplasmic transport, and by the architecture of the nuclear lamina, the filamentous array immediately beneath the nuclear envelope of many cells and the organizer of the distribution of NPCs and of a large proportion of chromatin. His laboratory developed a procedure to isolate intact NPCs that remain associated with the lamina, which helped open up these assemblies to molecular characterization⁶.

One passion of Günter's that is particularly fitting for this journal, and intimately linked with his love of art and architecture, was his desire to understand the molecular structure of subcellular assemblies. The late 1990s marked the Blobel Lab's entry into twenty-first-century structural biology; Günter often joked (proudly) that he had transformed his cell biology laboratory into a structural biology laboratory, and indeed, in many ways, he had. Günter drew tremendous inspiration from electron micrographs that documented the discoveries of major structures within the cell. We remember his excitement when he brought out Fawcett's book, *The Cell*, which he did often, to show us these beautifully complex images and his fervor to understand

how the subcellular structures they depicted were assembled. He felt that they revealed a structural beauty every bit as real as that in any great painting or magnificent building. His fascination with micron-scale structures in cells complemented his molecular analysis of cellular functions and transitioned very naturally to the appreciation of structures at the molecular and atomic levels. Günter's first foray into structural biology was a 1971 negative-stain EM study of the ribosome's structure⁸. Twenty-six years later, his discoveries of protein targeting to the ER came full circle with his laboratory's visualization of the Sec61 protein-conducting channel attached to a ribosome poised to translocate protein. This revealed how a ribosomal channel harboring the nascent protein chain aligns with the Sec61 channel to guide the nascent chain across the ER membrane into the ER lumen⁹. To complement this work, he also published the structure of the β subunit of the eukaryotic signal recognition particle receptor¹⁰. In a series of publications spanning two decades, his laboratory also revealed one of the first structures of a karyopherin- β nuclear import receptor, the atomic structures of numerous nucleoporins (component proteins of the NPC), and, most recently, structures of the cholesterol transport machinery including a sterol reductase that is homologous to the Lamin B receptor¹¹. Günter's flavor of structural biology was a little different from the one that most traditional structural biologists

with chemistry or physics backgrounds bring to the table; Günter's contexts for the molecules were the electron micrographs that he had examined closely for decades and the functions that he was analyzing. He was most excited about the shapes of proteins and how they fitted together into larger assemblies. He loved to predict how they could come together and apart like highly choreographed moves of a ballet, performances of which he and his wife Laura Maioglio regularly enjoyed.

While Günter's scientific discoveries have been eulogized in the days following his passing, the incredibly fertile incubator for generations of scientists that was the Blobel Laboratory has perhaps received less attention. In five decades, Günter mentored well over one hundred trainees, many of whom are today's leaders in cell and structural biology and who continue to work in various aspects of intracellular trafficking in health and disease. The successes of the many women and men who trained in his laboratory were largely due to the freedom of thinking and exploration that Günter encouraged, the egalitarian, exciting, and rigorous scientific environment of his laboratory, and Günter's fertile imagination. The success of these many trainees was also due in no small part to Günter's generous principle of letting them take their projects to seed their own laboratories. Many of us kept in close contact with Günter for years after leaving his laboratory, returning to enjoy a dose of his captivating and vivacious personality, his passion for science combined with dramatic analogies, and his ability to inspire us once again in our own efforts to conduct research. It seems to us that with his passing, the world has lost some of its brilliance. □

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