BIOGRAPHICAL MEMOIRS

Günter Blobel

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A Biographical Memoir by Karl S. Matlin, Larry Gerace, and Qais Al-Awqati

Günter Blobel in the lab in 1999 after receiving the Nobel Prize.

Günter Blobel is one of the most important cell biologists of the twentieth century. Through his ingenuity, enthusiasm, and ambition he played a major role in the transformation of modern cell biology from a discipline employing a strategy of morphological analysis integrated with cell fractionation into a true molecular science. He accomplished this through the development and application of a novel cell-free experimental system that retained important aspects of the cell itself. Use of this system to investigate what he called the "signal hypothesis" enabled him and his associates to explain at the molecular level the biological processes of protein targeting and translocation across the endoplasmic reticulum membrane.[1] Though best known for his work on the signal hypothesis, for which he was awarded the Nobel Prize in Physiology or Medicine in 1999, Blobel also made major contributions to our understanding of nuclear organization and macromolecular transport into and out of the nucleus.[2]

Early Life and Education

Blobel was born in 1936 in Silesia, a part of Germany that is now located in Poland, to a large and prominent family. His village of Waltersdorf in the county of Sprottau, where his father Bruno worked as a large animal veterinarian, was rural and idyllic. Blobel and his siblings often traveled by horse-drawn wagon to his nearby grandparents' farm, where they helped to harvest vegetables, churn butter, and prepare sauerkraut. Bruno was drafted into the German army in 1939 at the outset of World War II and was stationed in Finland with other veterinarians to care for horses used in the war. Even as destruction spread throughout Europe, the area where Blobel and his family lived was largely unaffected until near the end of the conflict.

In January 1945, Blobel, his mother, and most of his siblings fled west ahead of the advancing Soviet Red Army to seek shelter with distant relatives in Reichenbach in Saxony. On the way, they passed through Dresden which, at the time, was relatively untouched by the war. Even at his young age Blobel was impressed with the beauty of the baroque

city and was horrified when he observed from a distance its destruction by firebombing in February 1945. His family was further touched by tragedy when Blobel's oldest sister Ruth was killed in a bombing raid near Schwandorf in Bavaria in April 1945.

After the war, the reunited Blobel family remained in Reichenbach for four years until they settled near Dresden in the Saxon town of Freiberg, where he continued his education. For a small town, Freiberg was culturally rich, and Blobel was immersed in the music of Johann Sebastian Bach and Wolfgang Mozart and the poetry of Wolfgang von Goethe. But the oppressive East German government considered the Blobel family to be bourgeoise and, when they refused to join the communist party, the children were prevented from seeking higher education. Consequently, beginning in 1947, the entire family successively moved to West Germany. At this time, prior to the construction of the Berlin Wall in 1960, it was possible to travel to West Germany from the east. Blobel himself left Freiberg in 1954, joining his brothers Reiner and Karl in the west, arriving in Frankfurt on Goethe's birthday, something Blobel always believed to be a positive omen.

Once in West Germany, Blobel decided to study medicine, a six-year program that began in the first year of university. By the time he graduated from the University of Tübingen in 1960 with his medical degree, Blobel had decided that he was more interested in medical research than clinical medicine. Encouraged by his brother Hans, who had studied veterinary medicine in the United States and was now on the faculty of the University of Wisconsin, Blobel enrolled in the doctoral graduate program at Wisconsin to study biochemistry and molecular biology. Potential mentors included future Nobel laureate and nucleic acid chemist H. Gobind Khorana and cancer biologist and biochemist Van R. Potter. Blobel chose to work with Potter in late May 1962, a fortuitous decision because of Potter's close connections to the cell biologists at the Rockefeller University.

At Wisconsin, Blobel's research foreshadowed topics that would later become his consuming interests. One paper with Potter detailed a procedure for isolating intact nuclei from rat liver.[3] The bulk of his work, however, focused on mammalian ribosomes and what was sometimes called the ribosome cycle.[4,5,6] Although it was well known at the time that some ribosomes were free in the cytoplasm and others were bound to the endoplasmic reticulum membrane, the identity of these two populations and the processes by which they circulated from bound to free were unclear. In prescient remarks made in one of a series of papers published in the *Journal of Molecular Biology* soon after Blobel completed his Ph.D. degree, he and Potter stated, "The question of *why* ribosomes are bound to the membrane cannot be answered until it is known *how* they are bound."[7] Later in the same paper, after casting doubt on other models, they said, "As to the functional significance of the binding of ribosomes to membranes, we suggest as a working hypothesis that the ribosome has a specific binding site which interacts with a ribosome specific receptor on the membrane."[8]

Rockefeller University and the Signal Hypothesis

Although Blobel originally planned to return to Germany, during his graduate studies he became familiar with the work of Philip Siekevitz, David Sabatini, and George Palade at New York's Rockefeller University on ribosomes and the endoplasmic reticulum and decided to go there for postdoctoral work. Potter, who had previously sent biochemists including Siekevitz to work with the cell biologists at Rockefeller, made the connection, and Blobel arrived in New York in late 1966. At Rockefeller, work on membrane-bound ribosomes had shifted from Siekevitz and Palade to Sabatini, an Argentinian M.D. who had been promoted to assistant professor after completing a Ph.D. at Rockefeller. With complementary skills, Blobel and Sabatini soon joined forces to investigate the interactions between ribosomes, messenger RNA (mRNA), and nascent polypeptide chains with the endoplasmic reticulum membrane.

Their studies grew from the long-term efforts by Palade and Siekevitz to understand how secretory proteins, those proteins destined after their synthesis for release from cells, entered the intracellular secretory pathway, a sequence of membrane bounded organelles that includes the endoplasmic reticulum, Golgi complex, and secretory granules. In cells of the exocrine pancreas, the focus of their studies, the synthesis, transport, and secretion of digestive enzymes destined for the small intestine dominated all other cellular activities.

By late 1970, Blobel and Sabatini had developed a hypothetical model proposing how the complex of mRNA, ribosomes, and secretory proteins undergoing synthesis was specifically targeted to the endoplasmic reticulum in preparation for transport of the proteins across the membrane. The model was indirectly dependent on the specific mRNA but more directly involved "a common sequence of amino acids" coded by the mRNA at the amino terminus of the nascent polypeptide chain that mediated directly or indirectly (with a proposed factor) interaction with the membrane. Blobel presented this model, along with a hand-drawn sketch, at a small meeting in 1971, and it was published soon afterwards in the accompanying symposium volume.[9] (Fig. 1a)

Blobel and Sabatini, along with graduate students and postdoctoral fellows in their joint laboratory, focused on experiments related to this model until Sabatini left Rockefeller in 1972 for New York University Medical School. Blobel then

continued the work on his own with the goal of designing a refined cell-free assay that could yield definitive results. His efforts were spurred on by the publication in 1972 of a short paper in *Nature New Biology* from the Cambridge University laboratories of Cesar Milstein and George Brownlee.[10] In the paper, which was based upon the graduate work of Timothy Harrison and contributions from Michael Matthews (both coauthors), they reported the discovery of a putative precursor of the immunoglobulin light chain that possesses a short extension of the polypeptide chain at the amino-terminus. Because the possible precursor was only detected when the light chain was synthesized in vitro in the absence of membranes, they suggested that the extension might be a transient "signal" that helps direct polyribosomes synthesizing light chain to the endoplasmic reticulum.

Blobel believed that to prove that a secretory protein precursor existed and to demonstrate its involvement in targeting the protein to the endoplasmic reticulum membrane, a well-defined reconstituted cell-free system was required. As he stated in a brief communication published in 1974:

> [A] system containing stripped [endoplasmic reticulum] membranes, ribosomal subunits and either globin mRNA (in vivo translated on free ribosomes) or immunoglobulin mRNA (in vivo translated on membrane-bound ribosomes) should, under protein synthesizing conditions in vitro, lead to ribosome attachment and to vectorial discharge of the nascent chain into a proteolysis resistant location of the membrane only in the case of immunoglobulin mRNA. Such a result would constitute unequivocal evidence for in vitro reconstitution.[11]

By the end of 1974, Blobel had the first positive results with such a system, and by the end of 1975 he and postdoctoral fellow Bernhard Dobberstein published two key papers.[12,13] The revised scheme that appeared in the papers was similar to the original 1971 model except that the stretch of amino-terminal amino acids, the "signal" part of what was now called the signal hypothesis, was now cleaved from the nascent secretory protein as transport across the membrane proceeded. (Fig. 1b) The steps illustrated in the model were strongly supported by the data generated with the cell-free system. Blobel also proposed the existence of a transmembrane proteinaceous "tunnel" assembled during translocation to address the problem of how a hydrophilic secretory protein is able to cross a hydrophobic membrane.

Subsequent work in Blobel's laboratory quickly developed along two parallel lines. One was a deeper investigation of the mechanisms of targeting and translocation by identifying key factors associated with bound ribosomes or the endoplasmic reticulum. The other aimed to determine if signal-mediated

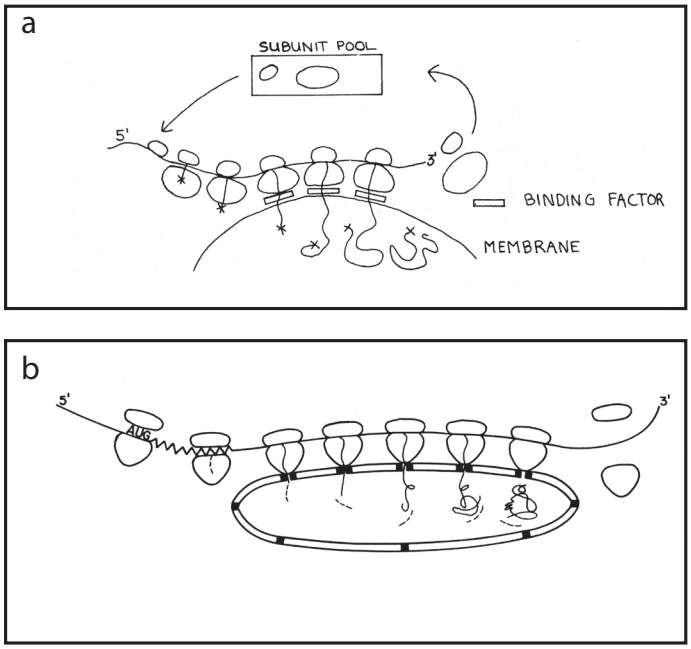

Figure 1 Models of the signal hypothesis. The diagram in *a* is the original speculative model published in *Biomembranes* in 1971. The diagram in *b* is the revised model published in the *Journal of Cell Biology* in 1975. Diagram *a* used with permission of Günter Blobel. Diagram *b* © Günter Blobel and Bernhard Dobberstein 1975. Originally published in *Journal of Cell Biology* 67(3):852-862.

targeting and translocation was a general and well-conserved mechanism valid for a variety of secretory proteins, tissues other than the pancreas, and even for proteins from diverse non-mammalian species.

The first factor identified was the proteolytic enzyme signal peptidase, which removed the signal sequence from nascent polypeptides as they traversed the endoplasmic reticulum membrane.[14] Unexpectedly, and more significantly, a complex of proteins and a small RNA molecule was discovered by Peter Walter, a graduate student in Blobel's laboratory, that was capable of binding to signal sequences, ribosomes, and a receptor on the endoplasmic reticulum membrane.[15] This complex, named the signal recognition particle (SRP), insured that nascent polypeptides with signal sequences were correctly targeted to the endoplasmic reticulum via the SRP receptor, a membrane protein.

Although SRP was not predicted in the 1975 model of the signal hypothesis, its discovery helped explain how secretory proteins reached the surface of the endoplasmic reticulum membrane. What it did not explain was how such proteins crossed the membrane. Blobel's speculation that a proteinaceous tunnel through the membrane was necessary was controversial and not yet supported by evidence. Beginning in 1989, Blobel and his postdoctoral fellow Sandy Simon used an electrophysiological approach to detect a tunnel, or channel, as it was now called.[16,17,18] In the next few years, other laboratories marshalled genetic and biochemical evidence for

the channel, eventually resulting in its purification, functional reconstitution, and structural analysis.[19–25]

The discovery of the channel demonstrated that all of the essential features of Blobel's proposed signal hypothesis were correct. As secretory proteins are synthesized by ribosomes and mRNA, the signal sequence is extruded from the ribosome and is bound by SRP, which pauses translation. When SRP binds its receptor on the surface of the endoplasmic reticulum membrane, SRP is released, and the nascent polypeptide is transferred into the channel and translocated across the endoplasmic reticulum membrane as synthesis is completed. Signal peptidase, located on the inside of the membrane, cleaves the signal sequence during translocation, completing the protein's entry into the secretory pathway.

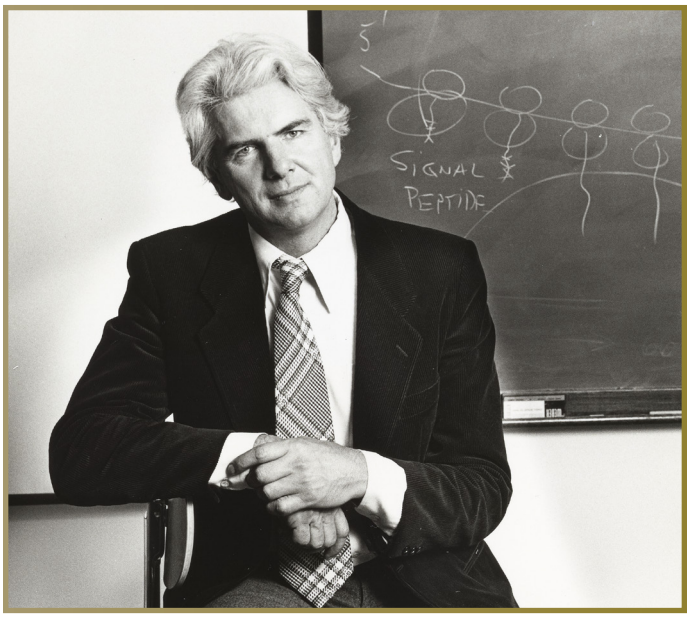

Figure 2 Günter Blobel in 1982. © Ingbert Grüttner/The Rockefeller University. Used with permission.

In parallel with this work, Blobel and his laboratory colleagues demonstrated that the signal hypothesis applied not only to secretory proteins but also to integral membrane proteins, proteins intercalated into the membrane's lipid bilayer.[26] The latter are targeted to the endoplasmic reticulum identically to secretory proteins, but their transfer across the membrane stops partway, integrating them into the membrane itself. Blobel's group and others also showed that the signal hypothesis operated not only in a variety of secretory tissues and non-mammalian species, such as fish, but also in organisms as distinct as bacteria and yeast. In these cases, the details of the mechanism were often different, but the fundamental idea of signal-sequence-mediated targeting and translocation was the same.

A variation on the theme was discovered through Blobel's collaborations with the laboratories of Gottfried Schatz and Nam-Hai Chua. Schatz and Chua were interested in how certain proteins synthesized in the cytoplasm are specifically targeted to mitochondria (in all cells) and chloroplasts (in plant cells). What they found was that such proteins are synthesized with an amino-terminal extension that is removed during transport of the proteins into the organelles.[27,28] The mechanism for this is distinct from mechanisms used to target proteins to the endoplasmic reticulum in that the amino acid sequences of these "signals" are different from secretory proteins and the targeting and transport processes occur *after* synthesis is completed, not during synthesis.

In a 1980 paper, Blobel proposed that, in general, most proteins synthesized in cells possess certain topogenic sequences that provide information about their ultimate location in the cell.[29] According to this idea, the signal sequences found on secretory and certain membrane proteins determine that those proteins enter the secretory pathway, and, subsequently, other sorting sequences on the same proteins dictate the proteins' final destinations in the cell. Similarly, the amino terminal sequences on mitochondria and chloroplast proteins determine that these proteins are targeted to these organelles, whereas other sequences in these proteins direct them to their specific final locations within the organelles. Blobel's proposal was significant because it suggested how sequence information encoded in the genome contributes to the spatial distribution of proteins in the cell and, consequently, the overall three-dimensional spatial organization of the cell itself. It also highlighted the continuity of the cell's spatial organization because specific proteins capable of correctly interpreting topogenic information had to be prepositioned in the cell and distributed to daughter cells as the cell divides. When Blobel was awarded the Nobel Prize in 1999, commentaries emphasized the fundamental nature of the concept of protein addresses or zip codes.

The Nucleus

In the mid-1970s, as work on the signal hypothesis was expanding, Blobel began pursuing a parallel project on the nucleus. His interests in the nucleus and endoplasmic reticulum had broad thematic similarities, in that both involved transport of macromolecules across the boundaries of intracellular membrane compartments. Nuclear-cytoplasmic transport, however, was quite different from endoplasmic reticulum translocation. The nucleus is surrounded by a double membrane, or nuclear envelope, with the outer leaflet facing the cytoplasm and continuous with the endoplasmic reticulum membrane and the inner leaflet facing the nuclear contents. At the time that Blobel began this work, it was

suspected that transport into and out of the nucleus occurred through nuclear pore complexes, giant electron-dense structures that spanned the nuclear envelope at nuclear pores in regions where the inner and outer nuclear membranes were periodically fused. The nuclear pore complexes were fairly well-described morphologically and were similar across a broad range of eukaryotes. At the outset of his studies, however, nothing was known about their molecular constituents.

In an effort to isolate nuclear pore complexes, Blobel purified the intact nuclear envelope with associated pore complexes free of chromatin and extracted it with detergent to dissolve the membranes.[30,31] Surprisingly, the pore complexes remained morphologically intact, appearing in the electron microscope attached to a fine filamentous network. (Fig. 3) The lamina was believed to correspond to a structure, called the fibrous lamina by some morphologists, that was visible in certain cell types as a discrete layer lining the inner nuclear membrane. The polypeptide composition of the pore complex lamina, as they called it, was complex but was dominated by three major polypeptides of approximately 60-70kD. In 1978, Blobel and his graduate student Larry Gerace, using an immunocytochemical approach, reported that these polypeptides were the major constituents of the lamina and demonstrated that they became diffusely distributed throughout the cytoplasm as the nuclear envelope disassembled during mitosis.[32] In subsequent work, they demonstrated that the lamins, as Gerace and Blobel named them, were members of a new class of intermediate filament proteins that formed polymeric arrays at the inner nuclear membrane. Moreover, they found that mitotic disassembly and subsequent reformation of the lamina was driven by reversible lamin phosphorylation, a process that likely potentiated the parallel breakdown and reconstitution of the nuclear envelope.[33]

Over the next several decades, Blobel continued intensive work on the nucleus and nuclear transport. Although he did not dominate the nuclear transport field in the way that he had the targeting and translocation of proteins into the endoplasmic reticulum, Blobel continued to make substantive contributions throughout the rest of his career. Proteins destined for transport into and out of the nucleus contain nuclear localization sequences and nuclear export sequences, respectively. These are classes of topogenic sequences (or signals, as they are often called) originally predicted by Blobel.[34,35] A very significant finding was his co-discovery of the GTPase Ran, which defines the directionality of transport dictated by these sequences and indirectly provides the energy source for nuclear transport.[36] Blobel and coworkers also extensively characterized the cargo specificities of various nuclear transport receptors, called karyopherins, that recognize nuclear localization and export sequences and also provided some of the first X-ray structures of this receptor family.

In other contributions, Blobel's laboratory characterized many nucleoporins, constituents of the nuclear pore complexes that he originally sought, and, by determining the X-ray structure of nucleoporin oligomers, helped to elucidate the three-dimensional structure of the nuclear pore complexes at high resolution. He also determined how integral membrane proteins of the inner nuclear envelope, which are synthesized in the cytoplasm but cannot pass through the aqueous nuclear pore channel, are transported into the nucleus in yeast.[37] Apparently, following their insertion into the endoplasmic reticulum membrane, such proteins bind karyopherins through their nuclear localization sequences and then move laterally in the lipid bilayer until they reach a nuclear pore. Here they are bound to constituents of the pore and carried inside where Ran-GTP releases them inside the nucleus.

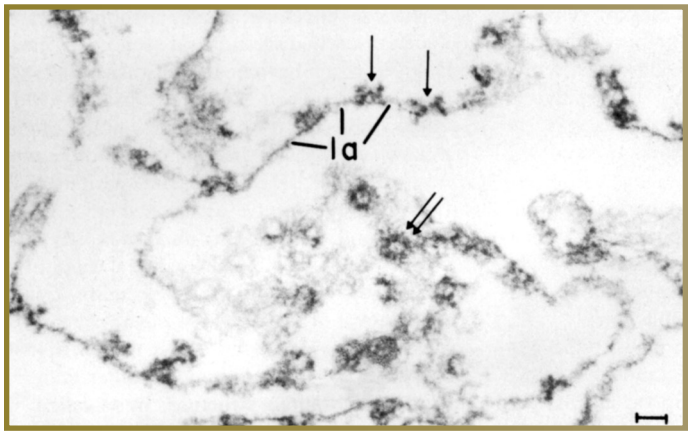

Figure 3 The nuclear pore complex lamina. © 1976 Nancy Dwyer and Günter Blobel. Originally published in the *Journal of Cell Biology* 70:581-591. (la: lamina; single arrow: lateral view of pore complex; double arrow: frontal view of pore complex; x44,000, bar denotes 0.1 µm)

In 1985, Blobel published a paper entitled "Gene Gating: A Hypothesis" that proposed that gene expression is in part controlled by the three-dimensional arrangement of the genome in the nucleus, as is, consequently, the differentiated state of cells.[38] According to this idea, interaction of "transcribable" parts of the genome with nuclear pore complexes leads to specific transcripts being transported, or "gated," through the pores into the cytoplasm. In contrast, compacted and inactive chromatin associates with the nuclear lamina that lines all parts of the inner nuclear envelope exclusive of the pores. The concept associated with this hypothesis, while not accurate in specific terms, was prescient overall, anticipating by many years our understanding of the importance of the three-dimensional organization of chromatin in the regulation of gene expression and the recognition that there is a close coupling between events of transcription and nuclear export.

Blobel: Art, Fantasy, and the Imaginative Spirit

Blobel's outlook on culture was very much that of the nineteenth-century Romantic era (and its preceding *Sturm und Drang* movement) with its emphasis on beauty, the role of inspiration, and the unity of the creative process in art, music, and science. He was deeply knowledgeable about the work of leaders of that movement, particularly poet, dramatist, and scientist Wolfgang von Goethe, and he knew many of Goethe's poems by heart. In addition, he shared Goethe's adoration of Nature, so evident in all his poems. Blobel's almost encyclopedic knowledge of the names of different trees and flowers was impressive, likely inspired by his childhood nanny, who would take the children out for walks in the nearby forests and point out the names of plants. His daily morning walk in Central Park was a mandatory activity, and he related to the trees along his path with great intimacy.

Music, another powerful part of the Romantic imagination, was an early and lifelong passion, beginning when Blobel was a choirboy at the Freiberg Cathedral, known for its magnificent organ built by local master (and the greatest organ builder of the Baroque era) Gottfried Silbermann. Organ music remained an intense interest, but it led to some political and bureaucratic problems. In Dresden, Blobel contributed funds from his Nobel Prize to help reconstruct the Frauenkirche, which was destroyed by firebombing during World War II.[39] When the restoration was nearly complete, he rallied many politicians and especially musicians and musicologists in a letter-writing campaign to ensure that the organ for the rebuilt church would be a replica of its original Silbermann that had been played at the church's inauguration by Bach himself. It was a major disappointment (he called it defeat) when the church authorities opted for a modern instrument. In New York, Blobel was a frequent presence at concerts and was always noticeable, given his height and shock of white hair and his rather un-Germanic late arrival. Afterwards, he loved talking about the performances at late dinners, many of them held at his wife Laura Maioglio's restaurant, Barbetta, in New York's theater district.

Another of Blobel's passions was baroque architecture, especially that of Germany and Austria, an interest likely stimulated by his first walk through Dresden as a child. His knowledge was so thorough that, following a dinner with architectural historians at a friend's residence, one guest was so impressed that he asked to attend Blobel's course on the subject, not realizing that Blobel's field was cell biology.

Like Goethe, Blobel was enamored of Italy, visiting it as often as he could. Laura Maioglio, whom he married in 1976, was Italian-American. During their travels, their base was her ancestral village of Fubine in Italy's Piedmont region. He was an ideal tourist guide to Venice, Florence, and Rome, knowledgeable about arcane aspects especially when, as so often was the case, the music, architecture, and history were part of the same narrative. His enthusiasm for these was infectious, as was his insatiable curiosity and thirst for new knowledge about these subjects. It is likely that Blobel's romantic "southern" side juxtaposed with his German "northern" side was, like his idol Goethe and German Nobel laureate Thomas Mann, important elements of his imagination and creativity. When asked once what the arts contributed to his scientific research, he had a one-word answer: *fantasy*. Blobel passed away in Manhattan on February 18, 2018.

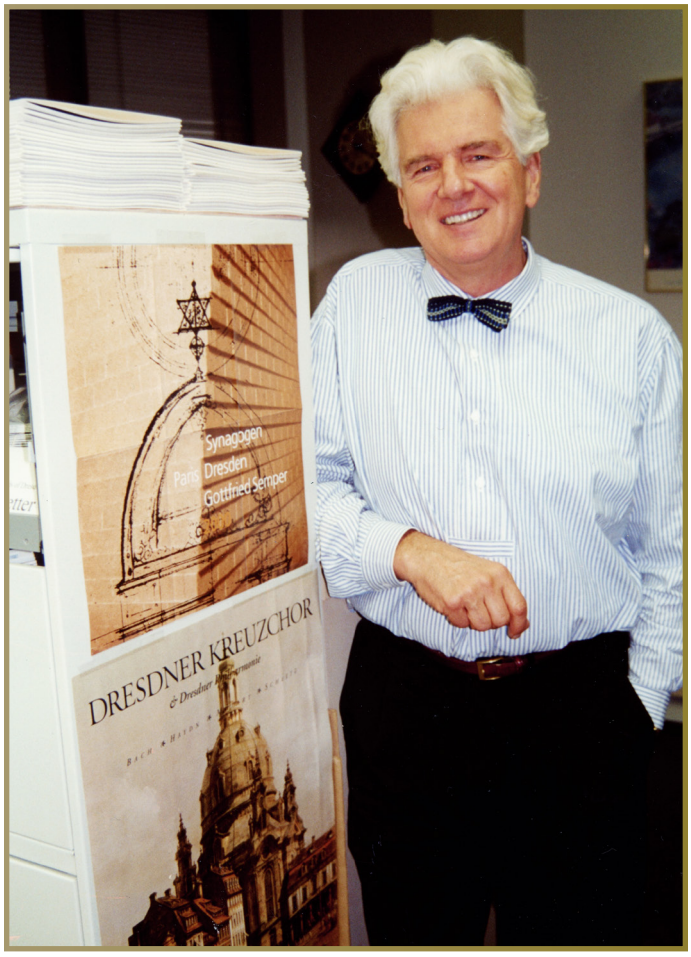

Figure 4 Günter Blobel next to posters promoting events at the new Dresden synagogue and the reconstructed Dresden Frauenkirche. © I. Hargittai/The Rockefeller University. Used with permission.

Acknowledgments

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