

An Award for Cell Biology

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"This Is an Award for the Entire Field of Cell Biology."

This remark, made by Günter Blobel on American television after winning the 1999 Nobel Prize for Physiology or Medicine, was hardly uncharacteristic: the six-foot, snowy-haired Rockefeller University professor was typically, generously, extending his prize to all of us who toil 'midst the microscopes.

Perhaps more importantly, he was granting the relatively quiet field of cell biology its fifteen minutes of fame or, at least, national attention. As Blobel told his interviewer, even though this is the era of prime-time PCR and cloned sheep, it is the field of cell biology that is entering into another golden age. Although the genomes of many different organisms have been, or are about to be, sequenced, we remain largely unaware of how most proteins function. How they do so in the context of the cell, he maintained, is essential for understanding many human diseases. As the interview progressed, Blobel, like a medieval wizard, spoke as much with his hands as with his voice, conjuring images of cells and their compartments; many in the TV audience surely went to bed that night with images of zip codes and mail carriers dancing in their heads. It is a further testament to his charm and eloquence that Blobel also managed to slip in an impassioned, persuasive plea for increasing federal funds for basic research.

English, however, is not Blobel's native tongue. He was born 63 years ago in the small German farming town of Waltersdorf. This cosmopolitan figure, equally at ease donning a tuxedo as tossing balls to his beloved dogs, had never even glimpsed a city until he was eight years old. It was at the end of WWII in Germany, fleeing



Blobel with members of his laboratory.

oncoming Russian troops, when his family passed through the then-beautiful town of Dresden. Blobel was captivated by the place, particularly by the structure and organization of its buildings. Three days later, Blobel and his family watched from a distance as Dresden was firebombed and very nearly destroyed.

Years later, Blobel went on to earn a medical degree at the University of Tübingen. He then went to the Wisconsin lab of Van R. Potter where he got his Ph.D., training in the art of cell fractionation by purifying cell nuclei. Next, he went to New York for a post-doctoral fellowship at The Rockefeller University. There, Drs. George Palade, Phil Siekevitz, David Sabatini, and Colvin Redman had just demonstrated that secretory proteins and cytosolic proteins start their syn-

thesis from a common pool of ribosomes, but secretory proteins start to translocate across the membrane of the endoplasmic reticulum as they are being made. Along with the rest of the Palade lab, Blobel began to concentrate on the question of what could be responsible for targeting these proteins.

In 1971, together with Sabatini, Blobel proposed the "signal hypothesis," the idea that secretory proteins are synthesized with an amino terminal extension that is recognized by a cytosolic factor and that, together, they are responsible for targeting to the endoplasmic reticulum. At the time, there was no experimental data to support the hypothesis. However, it allowed Blobel to make a number of very clear predictions that could be tested experimentally: 1, the signal

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for targeting a protein to the endoplasmic reticulum, and therefore secretion, was an amino terminal extension, a signal sequence; 2, there are cytosolic factors that engage the signal sequence; 3, there are proteins in the membrane of the endoplasmic reticulum involved in the translocation; and 4, proteins translocate across the membrane through aqueous protein-conducting channels. The next three decades of his life were devoted to testing these predictions.

The first experimental evidence came from laboratories of Philip Leder, Cesar Milstein, and Israel Schechter, who demonstrated that when a secretory protein (the light chain of IgG) was made in a cell-free system, it migrated slower on a gel. This could be the predicted signal sequence. However, *in vitro* translations could be unfaithful. Was this shift in apparent molecular weight the predicted amino terminal extension or was it an artifact of an *in vitro* system? Blobel resolved that the issue could best be addressed using the same tools that had revealed the mysteries of intermediate metabolism: fractionation and reconstitution. If he could fractionate the machinery of protein synthesis and the endoplasmic reticulum and then reconstitute the targeting and translocation reaction, he would be able to test the hypothesis. This was a statement of belief that was to be tested. Blobel used many of the known sources of endoplasmic reticulum, and they always inhibited protein synthesis. Different organs from different species were systematically tested. It took four years before the Blobel lab published a pair of papers in the *The Journal of Cell Biology* demonstrating reconstitution of protein targeting and translocation. These papers introduced the assays and controls that are, to this day, still the gold standard for translocation.

Thanks to the work of Blobel and his colleagues, the model was deepened by studies on biochemical and biophysical mechanisms: the cytosolic factor for targeting to the endoplasmic reticulum, the signal recognition particle, its receptor, and the signal peptidase were identified (see Fig. 1). Their functions were elucidated and the protein-conducting channels were characterized. The

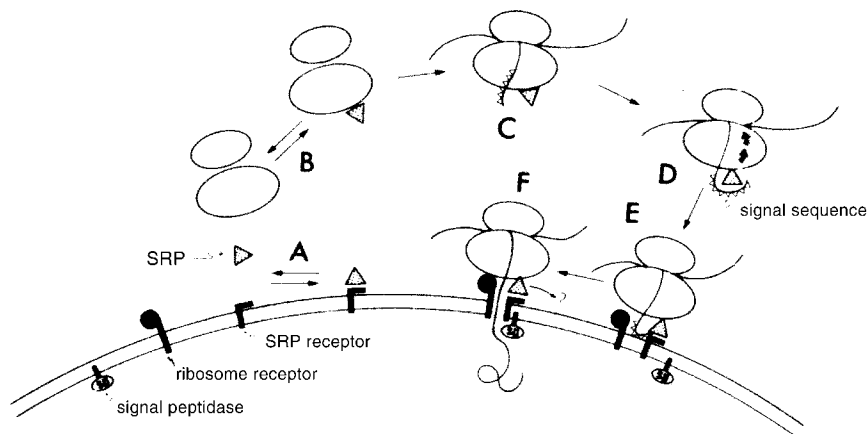


Figure 1. Model for the function of SRP in the translocation process. Reprinted from Walter, P., and G. Blobel. 1981. Translocation of proteins across the endoplasmic reticulum. III. Signal recognition protein (SRP) causes signal sequence-dependent and site-specific arrest of chain elongation that is released by microsomal membranes. *J. Cell Biol.* 91:557-561.

model was widened to include the synthesis of membrane proteins and the targeting of proteins to other membranes, such as the mitochondria, the chloroplast, the bacterial inner membrane, as well as transcytosis and import and export from the nucleus. In the process, Blobel evolved the hypothesis into a general model for the topogenesis of membrane proteins.

Albert Claude, together with Palade, Keith Porter, Christian deDuve, and Siekevitz, built the laboratories of cell biology at Rockefeller. Together, they systematically broke the cell apart and analyzed its components. For this work, Palade, Claude, and deDuve received the Nobel Prize in 1974. During his 30 years at Rockefeller, Blobel has devoted his efforts to rebuilding the cell, asking how these separate fractionated pieces work together. As a result, he has contributed a molecular understanding of how cells direct their bricks and girders to make their own beautiful structures.

Blobel's obsessions with structures began with the beautiful buildings he first encountered as a young boy in Dresden. Unfortunately, those structures were soon destroyed. Throughout his life, Blobel has dreamed they might one day be rebuilt. In what is a most fitting twist of fate, the money that Albert Nobel earned from the creation of dynamite is now being used to rectify the acts of war: in a Nobel gesture, Blobel has contrib-

uted his prize money to the rebuilding of two magnificent structures, the Frauenkirche church and the synagogue that used to illuminate the historic center of Dresden.

Blobel has also contributed to building the structure of the cell biology community. He has served as president of the American Society for Cell Biology and as an Associate Editor at *The Journal of Cell Biology*. The community of cell biologists is populated by many scientists who have trained in his lab and who still pursue the cell biology questions that first captivated them when working with Blobel.

Blobel has received scores of prestigious scientific awards, but, in keeping with his down-to-earth persona, has maintained an irreverent attitude toward honorifics. Once, a friend's infant was crawling around his office. The child yanked a volume of the Harvey Society Lecture Series down from the shelf. Blobel insisted the child continue, laughing: "They need rearranging." When the child reached for a collection of Nobel Lectures and proceeded to rip out some of the pages, Blobel calmly reassured the parent: "They need editing."

Blobel's fascination with structure, triggered as a young boy, led him to "the discovery that proteins have intrinsic signals that govern their transport and localization in the cell."¹ The Nobel prize now brings him full-circle to rebuilding those structures that fed the fantasies of his youth.

¹Quotation is from the official announcement of the Nobel Committee.