

## BEAMLINE

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## PUBLICATIONS

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## FOR MORE INFORMATION

Günter Blobel or André Hoelz, Laboratory, Cell Biology, Howard Hughes Medical Institute, The Rockefeller University  
blobel@rockefeller.edu  
hoelza@rockefeller.edu

## Nucleoporin Crystal Structure Suggests Flexible Pore Diameter by Intermolecular Sliding

I. Melčák, A. Hoelz, and G. Blobel

Laboratory of Cell Biology, Howard Hughes Medical Institute, The Rockefeller University

*The exchange of macromolecules across the nuclear envelope is mediated through the nuclear pore complex (NPC). During the cargo translocation, the central channel of the NPC is thought to alter its diameter. We present the atomic structure of nucleoporin Nup58/45, a component of a central channel. In the crystal structure of an  $\alpha$ -helical region of Nup58/45, we identified distinct tetramers of different conformations. These conformations reveal that dimer subunits of Nup58/45 tetramers may slide against one another over a distance of  $\sim 11$  Å. The lateral displacement of  $\alpha$ -helices is accompanied by formation of an alternative hydrogen-bond network. We suggest that these data may provide an explanation for the adjustable transport channel.*

The nuclear pore complex (NPC) embedded in the nuclear envelope gates macromolecular traffic between the nucleus and cytoplasm. The central conduit channel is formed by an eight-fold symmetrical assembly composed of a set of proteins called nucleoporins. To accommodate the passage of cargo, large-scale structural rearrangements might occur to adjust the central channel diameter. However, the molecular details of such structural changes are unknown.

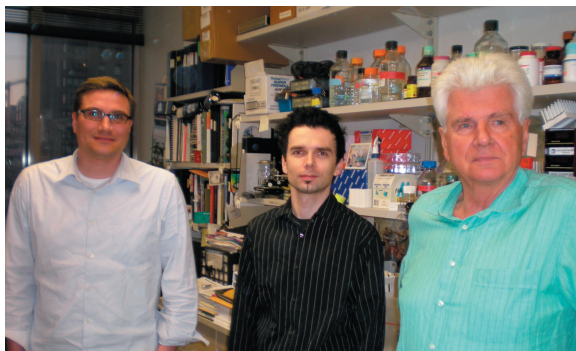
The central channel of the NPC is lined by the Nup62 complex, which consists of Nup62, Nup54, Nup58, and Nup45. The minimal core domains of Nup58 and Nup45 are identical  $\alpha$ -helical regions (referred to as Nup58/45) and are sufficient for Nup62 complex assembly.

We identified two similar, structurally distinct Nup58/45 tetramers in two independent crystal forms that result from the dimerization of identical dimers (**Figure 1A**). Each protomer folds

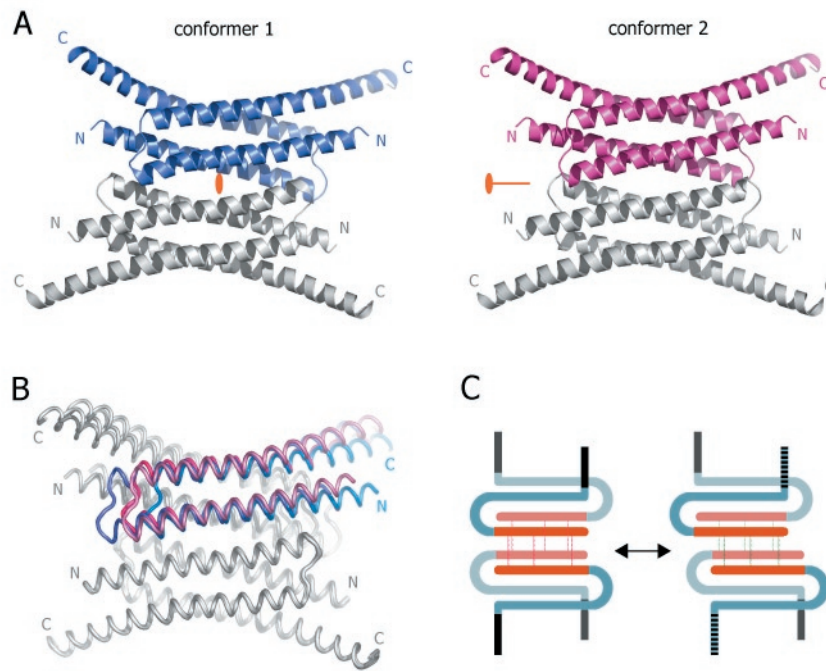
into an antiparallel hairpin structure and the protomers dimerize to form a four-helix bundle. The dimers interact with each other in a "head-to-head" orientation with their N helices. The tetramerization interface is formed by an extensive side-chain hydrogen bond network that ties the N-helices of the four protomers together. Most of the interactions occur within each pair of aligned, anti-parallel N-helices, involving polar and/or charged side-chains. The two conformers differ by an  $\sim 6$  Å lateral displacement of their dimer subunits along the long axis of the tetramerization interface. By superposition of all

four pairs of N-helices, four different configuration states can be discerned that exhibit a maximum lateral displacement of  $\sim 11$  Å (**Figure 1B**). The rearrangement of the dimer-dimer interaction surface results in the formation of alternative hydrogen-bond networks. The identification of multiple interaction states in which rigid Nup58/45 dimers are sequentially shifted along the dimer-dimer suggests an intermolecular sliding mechanism. The residues of the sliding surface have two major features: (i) propensity of switching interaction partners by acting alternatively as either hydrogen-bond donors or acceptors, or as both, (ii) sampling capability of the flexible long side chains.

The mutual arrangement of subunits within a single sliding module can be altered by a distance of at least  $\sim 11$  Å (**Figure 1C**). We propose that circumferential sliding of Nup58/45 in the channel perimeter results in an adjustable diameter as cargo passes across.



Authors (from left to right) André Hoelz, Ivo Melčák and Günter Blobel



**Figure 1.** Structures of tetrameric Nup58/45 assemblies. (A) Ribbon representations of the two tetrameric conformers. The different coloring of dimers (blue, conformer 1; purple, conformer 2) illustrates the alternative tetrameric configurations of the two conformers. The crystallographic two-fold axes (orange) are indicated. (B) Superposition of the two tetrameric Nup58/45 conformers. The unique protomers of the two tetrameric assemblies are superimposed to highlight the lateral shift between the different conformers. For clarity, only one protomer of each superposition is colored. (C) Schematic representation of the Nup58/45 sliding module. The four N helices that generate the tetramerization interface (orange) and the C helices (light blue) are indicated. The sliding of the Nup58/45 dimer surfaces formed by the N helices is facilitated by an alternative hydrogen bond network (red and green thin lines).