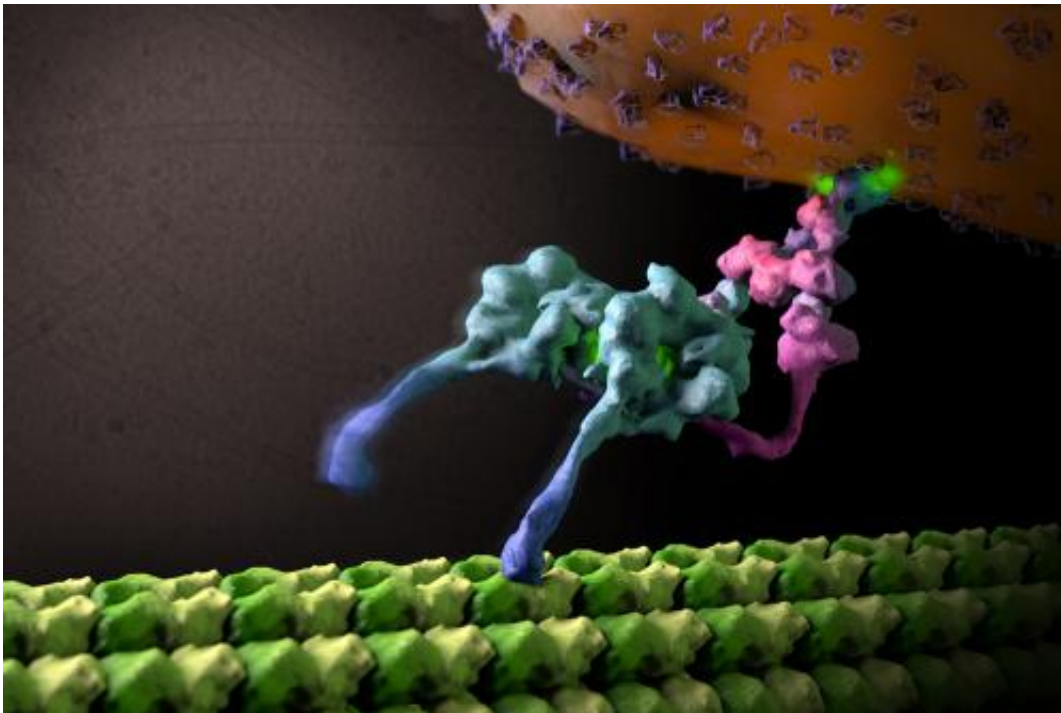


Scientists reveal structural secrets of nature's little locomotive

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A team led by scientists at The Scripps Research Institute has determined the basic structural organization of a molecular motor that hauls cargoes and performs other critical functions within cells. The complex's large size, myriad subunits and high flexibility have until now restricted structural studies to small pieces of the whole. Credit: Lander lab, The Scripps Research Institute.

A team led by scientists at The Scripps Research Institute (TSRI) has determined the basic structural organization of a molecular motor that hauls cargoes and performs other critical functions within cells.

Biologists have long wanted to know how this [molecular motor](#)—called the "dynein-dynactin complex"—works. But the complex's large size, myriad subunits and high flexibility have until now restricted structural studies to small pieces of the whole.

In the new research, however, TSRI biologist Gabriel C. Lander and his laboratory, in collaboration with Trina A. Schroer and her group at Johns Hopkins University, created a picture of the whole dynein-dynactin structure.

"This work gives us critical insights into the regulation of the dynein motor and establishes a structural framework for understanding why defects in this system have been linked to diseases such as Huntington's, Parkinson's, and Alzheimer's," said Lander.

The findings are reported in a *Nature Structural & Molecular Biology* advance online publication on March 9, 2015.

Unprecedented Detail

The proteins dynein and dynactin normally work together on microtubules for cellular activities such as cell division and intracellular transport of critical cargo such as mitochondria and mRNA. The complex also plays a key role in neuronal development and repair, and problems with the dynein-dynactin motor system have been found in brain diseases including Alzheimer's, Parkinson's and Huntington's diseases, and amyotrophic lateral sclerosis (ALS). In addition, some viruses (including herpes, rabies and HIV) appear to hijack the dynein-dynactin transport system to get deep inside cells.

"Understanding how dynein and dynactin interact and work, and how they actually look, is definitely going to have medical relevance," said Research Associate Saikat Chowdhury, a member of the Lander lab who

was first author of the study.

To study the dynein-dynactin complex, Schroer's laboratory first produced individual dynein and dynactin proteins, which are themselves complicated, with multiple subunits, but have been so highly conserved by evolution that they are found in almost identical form in organisms from yeast to mammals.

Chowdhury and Lander then used electron microscopy (EM) and cutting-edge image-processing techniques to develop two-dimensional "snapshots" of dynein's and dynactin's basic structures. These structural data contained unprecedented detail and revealed subunits never observed before.

Chowdhury and Lander next developed a novel strategy to purify and image dynein and dynactin in complex together on a microtubule—a railway-like structure, ubiquitous in cells, along which dynein-dynactin moves its cargoes.

"This is the first snapshot of how the whole dynein-dynactin complex looks and how it is oriented on the microtubule," Chowdhury said.

Pushing the Limits

The structural data clarify how dynein and dynactin fit together on a microtubule, how they recruit cargoes and how they manage to move those cargoes consistently in a single direction.

Lander and Chowdhury now hope to build on the findings by producing a higher-resolution, three-dimensional image of the dynein-dynactin-microtubule complex, using an EM-related technique called electron tomography.

"The EM facility at TSRI is the best place in the world to push the limits of imaging complicated molecular machines like these," said Lander.

More information: "Structural organization of the dynein-dynactin complex bound to microtubules," [DOI: 10.1038/nsmb.2996](https://doi.org/10.1038/nsmb.2996)

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