

Neggy Rismanchi...Uncovering the Genetic Basis of Neurological Disease

Individual Agreement MD/PHD student with Pennsylvania State College of Medicine

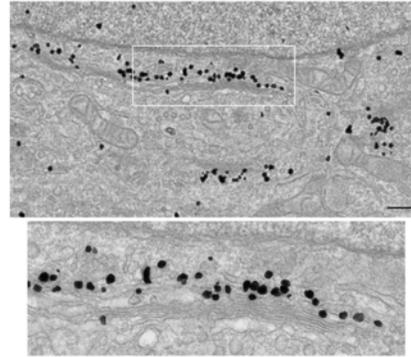
Neggy Rismanchi grew up in Hayward,



California and double majored in Psychology and Neurobiology, Physiology, and Behavior at UC Davis. While there, she discovered her love of the neurosciences and

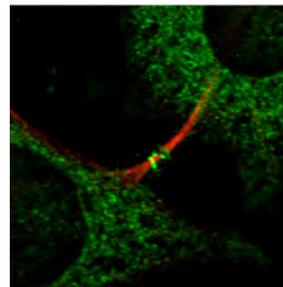
medical research, primarily while working in a traumatic brain injury (TBI) lab. She was awarded funding for an independent project studying the use of bone marrow stromal cells after TBI in rats. She graduated from UC Davis in December 2001 and spent the remainder of the academic year continuing her research at UC Davis.

Soon after starting the MSTP program at Penn State College of Medicine, she learned of the Graduate Partnerships Program at the NIH. She found areas of common interest in the laboratory of Dr. Craig Blackstone, studying both hereditary spastic paraplegia (HSP) and mitochondrial fission/ fusion proteins, and she formed an independent partnership to work in his lab after her second year of medical school. She spent the majority of her first graduate year studying apoptosis and proteins involved in mitochondrial fission, resulting in a second author publication in *Current Biology* and the opportunity to co-author a textbook chapter on mitochondrial dysfunction.



Immunogold electron micrograph showing the localization of the cis-Golgi apparatus marker GM130. The boxed area is enlarged in the lower panel. Bar, 500 nm.

Her interests shifted to protein trafficking and she began characterizing functions of signal transducing adaptor molecules (STAMs). Employing a variety of techniques such as immunocytochemistry, live imaging, immunoprecipitation, electron microscopy, siRNA, and protein overexpression, she identified novel interactions between STAMs and proteins comprising the COPII complex necessary for protein export from the endoplasmic reticulum (ER). Manipulation in STAM levels resulted in alterations in both Golgi structure and secretory trafficking. This work was published in the cell biology journal *Traffic*.



Staining of Spastin (green) and tubulin (red) during cytokinesis

During this time, she was also studying an HSP protein known as atlastin, which is mutated in the second most common cause of HSP. The HSPs are a group of disorders characterized by lower limb weakness and spasticity. Through her investigations, she found that atlastin proteins, part of the dynamin superfamily of large GTPases, were required for formation of the tubular ER network in cells. After publication of an initial study in *Human Molecular Genetics*, a comprehensive functional study of atlastin was published in collaboration with Dr. Tom Rapoport's laboratory at Harvard Medical School, in *Cell*. ER shaping defects are now regarded as one of the principal pathogenic mechanisms for the entire class of HSPs.

After her PhD thesis defense in November 2007, she remained at NIH as a post-doctoral fellow for the remainder of the academic year to complete other projects. One of these projects was identifying and characterizing the protein interactions of spastin, which is mutated in the most common form of HSP, with an ESCRT-III protein known as CHMP1B. In collaboration with the Drs. James Hurley and Jennifer Lippincott-Schwartz at NIH, she helped identify that this interaction is important for midbody localization and membrane abscission during cytokinesis; this data was published in *Nature Structural & Molecular Biology*.

Throughout her time at NIH, Neggy was able to maintain several hobbies, including hiking, running, and travel. Neggy subsequently returned to Penn State to complete her medical training. After completion of a two year pediatrics residency, she will be training at UC San

Diego for her child neurology fellowship.



Visit to the Amazon as part of a trip to Brazil with a friend from a neighboring lab at NIH.



*Dr. Rismanchi with her PhD mentor
Dr. Blackstone on graduation day.*

Publications From Ph.D. work:

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2. **Rismanchi N**, Blackstone C. Mitochondrial function and dysfunction in the nervous system. In: *Molecular Neurology*, Waxman SG, ed. San Diego: Elsevier, 2007; 29-41.
3. **Rismanchi N**, Soderblom C, Stadler J, Zhu P-P, Blackstone C. Atlantin GTPases are required for ER and Golgi morphogenesis. *Hum Mol Genet* 2008; 17:1591-1604.
4. Yang D, **Rismanchi N**, Renvoisé B, Lippincott-Schwartz J, Blackstone C, Hurley JH. Structural basis for midbody targeting of spastin by the ESCRT-III protein CHMP1B. *Nat Struct Mol Biol* 2008; 15:1278-1286. (Faculty of 1000 Biology -- Recommended).
5. **Rismanchi N**, Puertollano R, Blackstone C. STAM adaptor proteins interact with COPII complexes and function in ER-to-Golgi trafficking. *Traffic* 2009; 10:201-217.
6. Hu J, Shibata Y, Zhu P-P, Voss C, **Rismanchi N**, Prinz WA, Rapoport TA, Blackstone C. A class of dynamin-like GTPases involved in the generation of the tubular ER network. *Cell* 2009, 138:549-561. (Faculty of 1000 Biology – Must Read). Highlighted in *Dev Cell* 2009; 17:157-158 and *Curr Biol* 2009; 19:R906-R908.
7. **Rismanchi N**, Blackstone C. Hereditary spastic paraplegias. *Ann Neurol* (Invited Review). In preparation.