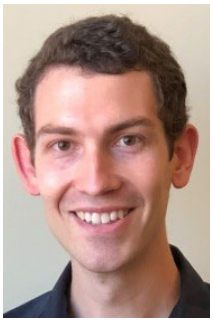
THE HARTWELL FOUNDATION

2020 Individual Biomedical Research Award

Johannes "Joh" Schöneberg, Ph.D.

Assistant Professor
Department of Pharmacology

University of California, San Diego



Fast 3D Time-Lapse Subcellular Imaging in Restoring Mitochondrial Dynamics as a Cure for Drug-Resistant Epilepsy

Childhood epilepsy is a chronic neurologic disorder that results from abnormal brain activity that causes spontaneous recurrent seizures, which may result in uncontrolled convulsive movements, periods of unusual behavior, or simply loss of awareness. The condition can result from brain-related disorders or injury, including family history. It may also be associated with autism. Beyond the manifestation of seizures, epilepsy is compounded by social isolation and loss of self-esteem that often cause lifelong challenges. Unfortunately, while more than 35 anti-seizure drugs have been approved since 1930, about a third of the 50,000 newly diagnosed cases each year in U.S. children under the age of 18 will be refractory to medication (drug-resistant epilepsy). Sadly, drug-resistant seizures that begin early in life are associated with high rates of learning problems and long-term intellectual disability. While surgery is considered a treatment option, postoperative memory deficits are not uncommon. An intriguing alternative is a high-fat/low carbohydrate ketogenic (keto) diet, which has shown remarkable success in reducing the dose and/or range of medications used to control seizures, especially among drug-resistant epileptic children. The downside is it places a dietary restriction on children that requires strict compliance, as seizures may return or worsen if the diet is suddenly stopped. Another disadvantage is that the keto diet requires vitamin and mineral supplements, complicating compliance for a growing child. The unmet need is to determine how the keto diet regimen provides remarkable relief from seizures, which if understood would enable a more targeted, if not also more effective, epilepsy therapy. Clearly, the keto diet must alter cellular metabolism, which Joh believes reflects the involvement of mitochondria — bacteria-sized anatomic structures (organelles), present in large numbers in almost all living cells and responsible for cellular respiration and generating energy. How mitochondria change in response to epilepsy or the keto diet, however, has not been established. Within cells, mitochondria exist as an intricate subcellular three-dimensional (3D) network that may change appearance in a matter of seconds through fission, fusion, and metabolic changes; or remodeled through fluctuation in number and distribution of mitochondria. To profile accurately these dynamics and screen for targeted drug therapies will require rapid acquisition of 3D time-lapse subcellular images. However, existing subcellular imaging technology is limited by tissue induced optical aberrations and can only capture detail in 2D. To overcome this limitation, Joh proposes a novel drug discovery platform to profile mitochondrial dynamics based upon real-time lattice light-sheet microscopy with adaptive optics and machine learning that will provide the required high-resolution imaging. If he is successful, an effective drug therapy will emerge that has the potential to improve the quality of life for children affected with drug-resistant epilepsy.