



PedsFocus

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NEUROLOGY

Basic Science and Translational Research on Neurogenetic Disorders

Rady Children's Hospital-San Diego and the Gleeson laboratory's Center for Brain Development at the University of California, San Diego have developed a program to identify patients with likely neurogenetic etiology, perform whole genome sequencing, and study basic mechanisms of disease in patient-derived neurons. Along this spectrum of disease are structural brain defects, microcephaly, and inherited forms of autism and epilepsy.

Most children with neurological disease cannot receive a genetic diagnosis, which limits treatment options. Although several neurological disorders have genetic etiology already solved, there are many more such disorders yet to be connected to specific gene function. The Gleeson lab seeks to connect neurological disorders to specific genes and thus develop a deeper understanding of causes of this class of disease. Although most neurological conditions are considered to be untreatable, recent work from the Gleeson lab and other labs are beginning to change this paradigm. Research has shown that such conditions might be targets for safe and effective gene-specific therapies.

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ONCOLOGY

Target Discovery for Cancer Metastasis

The Durden laboratory at Rady Children's Hospital-San Diego and the University of California, San Diego Moores Cancer Center, using mouse genetic models, has identified a master control switch that regulates the process of metastasis. The discovery provides a new target for treating or preventing metastasis and has the potential to transform cancer therapeutics.

Using mouse genetics and data from many years of analysis of mammalian signaling pathways in cancer, the lab has uncovered a specific signaling pathway required for cancer cells to metastasize. Removing a protein (Rac2) involved in this pathway prevented metastasis from occurring. Most important, the lab has identified a kinase upstream of Rac2 that, when inhibited, blocks this metastasis signaling pathway in mice. The next steps are to validate this discovery in human tumor samples (pediatric and adult) and to present this data to the pharmaceutical company that developed the kinase inhibitor for potential clinical application as a Phase II trial. The scientific process described here, called "target discovery," will help to improve and individualize cancer therapy in coming years.

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PULMONARY/RESPIRATORY MEDICINE

Effects of Hypoxia on Cell Function and Development

The Haddad laboratory at Rady Children's Hospital-San Diego and the University of California, San Diego Department of Pediatrics studies the effect of hypoxia on cell function and development, with a particular interest in the molecular mechanisms that underlie susceptibility to injury, especially in the brain, neurons and glia.

Mammalian tissues are extremely sensitive to the stress of hypoxia and can only survive for relatively short periods of time – about five to 10 minutes if O₂ is severely deprived. To examine the susceptibility to tissue injury, Dr. Haddad and his team use a rodent model (mouse) and invertebrate model (*Drosophila melanogaster*).

Years ago, the Haddad lab discovered that the adult fruit fly is tolerant to low oxygen conditions, and unlike mammals, can survive hours in environments with no oxygen. Using a variety of screens and mutational analysis, the lab has been able to dissect and evaluate the genetic basis of tolerance in fruit flies to low oxygen. With an understanding of how fruit flies endure such conditions, they are studying how mammalian cells could be changed genetically to resist hypoxic effects. Currently, the lab is investigating the roles of a number of genes and genetic pathways in hypoxia tolerance in fruit flies as well as mammals, including humans. These humans live at high altitudes or have a condition in which hypoxia is a major component of the pathogenesis of their disease.

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