

## Role of the NMD RNA Decay Pathway in Maintaining the Stem-Like State

### Grant Award Details

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Role of the NMD RNA Decay Pathway in Maintaining the Stem-Like State

**Grant Type:** Basic Biology IV

**Grant Number:** RB4-06345

**Project Objective:** This project explores the role of nonsense-mediated RNA decay (NMD) in hESC and hNPC, elucidating its contribution to self-renewal and differentiation potential, and the pathology that results when NMD factor UPF3B is defective.

**Investigator:**

<b>Name:</b>	Miles Wilkinson
<b>Institution:</b>	University of California, San Diego
<b>Type:</b>	PI

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**Disease Focus:** Neurological Disorders

**Human Stem Cell Use:** Embryonic Stem Cell

**Cell Line Generation:** iPS Cell

**Award Value:** \$1,360,450

**Status:** Closed

### Progress Reports

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**Reporting Period:** Year 1

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**Reporting Period:** Year 2

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**Reporting Period:** Year 3

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Reporting Period: NCE (Year 4)

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## Grant Application Details

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**Application Title:** Role of the NMD RNA Decay Pathway in Maintaining the Stem-Like State

**Public Abstract:** A subset of intellectual disability cases in humans are caused by mutations in an X-linked gene essential for a quality control mechanism called nonsense-mediated RNA decay (NMD). Patients with mutations in this gene—UPF3B—commonly have not only ID, but also schizophrenia, autism, and attention-deficit/hyperactivity disorder. Thus, the study of UPF3B and NMD may provide insight into a wide spectrum of cognitive and psychological disorders. To examine how mutations in UPF3B can cause mental defects, we will generate and characterize induced-pluripotent stem cells from intellectual disability patients with mutations in the UPF3B gene. In addition to having a role in neural development, our recent evidence suggests that NMD is important for maintaining the identity of ES cells and progenitor cells. How does NMD do this? While NMD is a quality control mechanism, it is also a well characterized biochemical pathway that serves to rapidly degrade specific subsets of normal messenger ribonucleic acids (mRNAs), the transiently produced copies of our genetic material: deoxyribonucleic acid (DNA). We have obtained evidence that NMD preferentially degrades mRNAs that interfere with the stem cell program (i.e., NMD promotes the decay mRNAs encoding proteins that promote differentiation and inhibit cell proliferation). In this proposal, we will identify the target mRNAs of NMD in stem and progenitor cells and directly address the role of NMD in maintaining the stem-like state.

**Statement of Benefit to California:** iPS cells provide a means to elucidate the mechanisms underlying diseases that afflict a growing number of Californians. Our proposed project concerns making and testing iPS cells from patients with mutations in the UPF3B gene, all of whom have intellectual disabilities. In addition, many of these patients have autism, attention-deficit disorders, and schizophrenia. By using iPS cells to identify the cellular and molecular defects in these patients, we have the potential to ultimately ameliorate the symptoms of many of these patients. This is important, as over 1.6 million people in California have serious mental illness. Moreover, a large proportion of patients with UPF3B mutations have autism, a disorder that has undergone an alarming 12-fold increase in California between 1987 and 2007.

The public mental health facilities in California are inadequate to meet the needs of people with mental health disorders. Furthermore, what is provided is expensive: \$4.4 billion was spent on public mental health agency services in California in 2006. Mental health problems also exert a heavy burden on California's criminal justice system. In 2006, over 11,000 children and 40,000 adults with mental health disorders were incarcerated in California's juvenile justice system. Our research is also directed towards understanding fundamental mechanisms by which all stem cells are maintained, which has the potential to also impact non-psychiatric disorders suffered by Californians.

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