Scientist & Postdoctoral Positions Available

Experimental Studies of Ultraconservation and Gene Regulation by Nonsense-Mediated mRNA Decay Induced by Alternative Splicing

Understanding an ultraconserved newly-discovered means of gene regulation

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Project background

Nonsense-mediated mRNA decay (NMD) is a cellular RNA surveillance system that recognizes transcripts with premature termination codons and degrades them. We discovered large numbers of natural alternative splice forms that appear to be targets for NMD, and this has proven to be a mode of gene regulation. We found that all members of the SR family of splice regulators have an unproductive alternative mRNA isoform targeted for NMD. Strikingly, the splice pattern for each is conserved in mouse and always associated with an ultraconserved or highly-conserved region of 100 or more nucleotides of perfect identity between human and mouse. Remarkably, the unproductive splicing and exceptionally conserved sequences seem to have evolved independently in nearly every one of the genes, suggesting that this is a facile mode of regulation.

Project description

Our computational experimental studies have identified thousands of human alternative isoforms that are likely targets of NMD, some of which are associated with ultraconserved elements. This position is for an experimental researcher to understand:

- The regulatory role of alternative splicing coupled to NMD, targeting mRNAs for degradation
- The functional significance and evolutionary mechanisms that underlie ultraconserved elements

This project will use a variety of RNA molecular biology technologies, cell culture, RNA biochemistry, as well as newer approaches including RNA-Seq high-throughput sequencing, microfluidic massively-parallel quantitative real time PCR, and ZFN genome editing.

Position requirements

Candidate should preferably have a Ph.D. in molecular biology or related field with a strong publication record and strong professional references. The ideal candidate will be an expert experimentalist in some area of RNA biology and capable of learning new technologies. As this position will involve writing research papers, grant proposals, and working closely with both experimentalists and computational biologists, communication skills and the demonstrated ability to work independently will be weighted heavily. Work outside of regular business hours and travel are required.

Interested applicants should have statement of interest, CV, transcript, and at least three letters of reference sent to jobs@compbio.berkeley.edu.

For more information, see http://compbio.berkeley.edu/

job posting

The Berkeley academic environment
The Brenner lab is an interdisciplinary research group at the University of California, Berkeley, one of the world's premiere research universities. We are associated with the Department of Plant and Microbial Biology, the Department of Molecular and Cell Biology, the Department of Bioengineering, as well as the University of California, San Francisco and Lawrence Berkeley National Lab.

The University of California, Berkeley ranks first nationally in the number of graduate programs in the top 10 in their fields, according to the most recent National Research Council study. Berkeley is committed to diversity in its staff, faculty, and student body, and invites all qualified people to apply, including minorities and women, veterans and individuals with disabilities. Information about Berkeley's outstanding benefits are at: http://atyourservice.ucop.edu/forms_pubs/misc/benefits_of_belonging.pdf. Please refer to the University's statement on confidentiality, found at http://apo.chance.berkeley.edu/evalltr.html. The University of California is an Equal Opportunity/Affirmative Action Employer.

Relevant papers:
Brooks AN, Aspden JL, Podgornaia AI, Rio DC, Brenner SE. Identification and experimental validation of splicing regulatory elements in *Drosophila melanogaster* reveals functionally conserved splicing enhancers in metazoans. *RNA. 17*:1884-1894.

Brooks AN, Yang L, Duff MO, Hansen KD, Dudoit S, Brenner SE, Graveley BR. 2011. Conservation of an RNA regulatory map between *Drosophila* and mammals. *Genome Research 21*:193-202.

Graveley BR, Brooks AN, Carlson JW, Duff MO, Landolin J, Yang L, et al. 2011. The developmental transcriptome of *Drosophila melanogaster*. *Nature 471*:473-479.

The *Drosophila* modENCODE Consortium, et al. 2010. Identification of functional elements and regulatory circuits in *Drosophila* by large-scale data integration. *Science 33*:1787-1797.

Hansen KD, Brenner SE, Dudoit S. 2010. Biases in Illumina transcriptome sequencing caused by random hexamer priming. *Nucleic Acids Research 38*:e131.

Hansen KD, Lareau LF, Blanchette M, Green RE, Meng Q, Rehwinkel J, Gallusser FL, Izaurralde E, Rio DC, Dudoit S, Brenner SE. 2009. Genome-wide identification of alternative splice forms down-regulated by nonsense-mediated mRNA decay in *Drosophila. PLoS Genetics 5:*e1000525.

Celniker SE et al. 2009. Unlocking the secrets of the genome. *Nature 459*:927-930.

Blanchette M, Green RE, MacArthur S, Brooks AN, Brenner SE, Eisen MB, Rio DC. 2009. Genome-wide analysis of alternative pre-mRNA splicing and RNA binding specificities of the *Drosophila* hnRNP A/B family members. *Molecular Cell 33*:438-449.

Lareau LF, Brooks AN, Soergel DAW, Meng Q, Brenner SE. 2007. The coupling of alternative splicing and nonsense-mediated mRNA decay. in Blencowe B & Graveley B, eds. *Alternative splicing in the postgenomic era.* Landes Biosciences. 190-211.

Lareau LF, Inada M, Green RE, Wengrod JC, Brenner SE. 2007. Unproductive splicing of SR genes associated with highly conserved and ultraconserved DNA elements. *Nature 446*:926-929.

Upcoming papers:
Lareau LF, Brenner SE. Ancient regulation by ultraconserved alternative splicing.