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TALES FROM THE CELLULAR UNDERWORLD:
mRNA DECAY AND DISEASE

DECEMBER 6, 2012
4:00 P.M.
208 LIGHT HALL

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Upcoming Discovery Lecture:

THOMAS C. SUDHOF, PH.D.
Stanford University
December 13, 2012
208 Light Hall / 4:00 P.M.

VANDERBILT  UNIVERSITY
MEDICAL CENTER

TALES FROM THE CELLULAR UNDERWORLD: mRNA DECAY AND DISEASE

In mammalian cells, two different messenger ribonucleoproteins (mRNPs) serve as templates for protein synthesis. Newly synthesized CBP80-CBP20 (CBC)-bound mRNPs initially undergo a pioneer round of translation (Maquat et al., 2010). One purpose of this round of translation is to ensure the quality of gene expression, as exemplified by nonsense-mediated mRNA decay (NMD). NMD largely functions to eliminate mRNAs that prematurely terminate translation, although NMD also contributes to proper gene control, and it targets CBC-bound mRNPs (Sato et al., 2008; Isken et al., 2008). CBC-bound mRNPs are remodeled to eIF4E-bound mRNPs as a consequence of the pioneer round of translation as well as independently of translation by importin- β binding to importin- α -associated CBC (Sato and Maquat, 2009). eIF4E-bound mRNPs support the bulk of cellular protein synthesis and are the primary targets of mRNA decay mechanisms that conditionally regulate gene expression, such as Staufen1-mediated mRNA decay (Gong et al., 2009).

Mechanistic aspects of NMD will be discussed, including how CBP80, which is acquired by the 5' caps of newly synthesized transcripts within nuclei, promotes NMD at multiple steps by promoting specific mRNP rearrangements (Hwang et al., 2010). Mechanistic aspects of SMD will also be described, including the formation of Staufen1-binding sites not only by intramolecular base-pairing within an mRNA 3'-untranslated region but also by intermolecular base-pairing between the Alu element of an mRNA 3-untranslated region and a partially complementary Alu element within a long noncoding RNA (Gong and Maquat, 2011). These are new functions for Alu elements and for long noncoding RNAs, which we call $\frac{1}{2}$ -sbsRNAs.

Gong, C., Kim, Y. K., Woeller, C.F., Tang, Y. and Maquat, L.E. (2009) SMD and NMD are competitive pathways that contribute to myogenesis: Effects on PAX3 and myogenin mRNAs. *Genes & Dev.* 23:54-66.

Gong, C. and Maquat, L.E. (2011) lncRNAs transactivate Staufen1-mediated mRNA decay by duplexing with mRNA 3'UTRs via Alu elements. *Nature*, 470:284-288.

Hwang, H., Sato, H., Tang, Y., Matsuda, D. and Maquat, L.E. (2010) UPF1 association with the cap-binding protein, CBP80, promotes nonsense-mediated mRNA decay at two distinct steps. *Mol. Cell* 39:396-409.

Isken, O., Kim, Y.K., Hosoda, N., Mayeur, G.L., Hershey, J.W.B. and Maquat, L.E. (2008) Upf1 phosphorylation triggers translational repression during nonsense-mediated mRNA decay. *Cell* 133:314-327.

Maquat, L.E., Tarn, Y.-W. and Isken, O. (2010) Specialized features and functions of the pioneer round of translation. *Cell*, 142:368-374.

Sato, H., Hosoda, N. and Maquat, L.E. (2008) Efficiency of the pioneer round of translation affects the cellular site of nonsense-mediated mRNA decay. *Mol. Cell* 29:255-262.

Sato, H. and Maquat, L.E. (2009) Remodeling of the pioneer translation initiation complex involves translation and the karyopherin importin β . *Genes & Dev.* 23:2537-50.



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Lynne E. Maquat is the J. Lowell Orbison Endowed Chair and Professor of Biochemistry & Biophysics, Director of the Center for RNA Biology, and Chair of Graduate Women in Science at the University of Rochester. Her research focuses on nonsense-mediated mRNA decay (NMD) and Staufen-mediated mRNA decay (SMD), which led to defining a rule for which termination codons trigger NMD, the exon-junction complex, the pioneer round of translation, and new roles for long noncoding RNAs and Alu elements. She is recipient of the RNA Society's Lifetime Achievement Award in Service and an elected member of the American Academy of Arts & Sciences, the American Association for the Advancement of Science, and the National Academy of Sciences. Dr. Maquat is also a 2012 Batsheva de Rothschild Fellow of the Israel Academy of Sciences and Humanities.