VANDERBILT PRIZE IN BIOMEDICAL SCIENCE LECTURE

LYNNE E. MAQUAT, Ph.D.

NONSENSE-MEDIATED mRNA DECAY AND HUMAN DISEASE:
GENOME GUARDIAN AND EXECUTOR

NOVEMBER 29, 2018
4:00 P.M.
208 LIGHT HALL

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VANDERBILT CUTTING-EDGE DISCOVERY LECTURE

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December 13, 2018
208 Light Hall / 4:00 P.M.
Much progress has been made on how nonsense-mediated mRNA decay (NMD) controls the quality of human gene expression by detecting and rapidly degrading aberrant mRNAs that contain a premature termination codon. Dr. Maquat’s studies of NMD, first reported in 1981, have led to the discovery of the pioneer round of translation and the post-splicing “mark” on newly synthesized mRNAs – later named the exon-junction complex (EJC) in a collaboration with Melissa Moore. Beyond NMD, her lab has also demonstrated the mechanistically related and competing Staufen-mediated mRNA decay pathway, including new roles for short interspersed nuclear elements (SINEs), and most recently a microRNA decay pathway. Dr. Maquat’s group has further tracked individual cellular transcripts in collaboration with Rob Singer to confirm earlier results, indicating that NMD for a number of mRNAs occurs on the cytoplasmic side of the nuclear envelope. The data provide explicit evidence that proteins acquired by newly synthesized mRNAs in the nucleus, including the cap-binding protein CBP80 and constituents of the EJC, are critical for mRNA quality control via translation in the cytoplasm. The Maquat lab has also described the molecular mechanism for how NMD targets are discriminated from other transcripts: the central NMD factor – the ATP-dependent RNA helicase UPF1 – preferentially associates with mRNA 3’-untranslated regions (3’-UTRs) in a way that correlates with 3’-UTR length and the presence of a 3’-UTR EJC. They used this discriminating mark to demonstrate that decay steps during NMD initiate co-translationally and involve the addition of non-templated nucleotides to decay intermediate 3’-ends. Among NMD targets are ~10% of physiologic mRNAs that are key to maintaining cellular homeostasis in a changing environmental milieu. For example, Dr. Maquat reported that a sufficient level of DNA damage induced by common frontline chemotherapeutics inhibits NMD by triggering the caspase-mediated cleavage of sub-stoichiometric amounts of UPF1, thereby upregulating the half-lives of mRNAs that include those encoding proteins for promoting apoptosis. Notably, the modest inhibition of NMD promotes but is not sufficient for programmed cell death.