THE Flexner DISCOVERY LECTURE SERIES

VANDERBILT CUTTING-EDGE DISCOVERY LECTURE

ERIC P. SKAAR, Ph.D., M.P.H.
Director, Vanderbilt Institute for Infection, Immunology, and Inflammation

DANNY G. WINDER, Ph.D.
Director, Vanderbilt Center for Addiction Research

KATHERINE E. HARTMANN, M.D., Ph.D.
Associate Dean, Clinical & Translational Scientist Development

December 13, 2018
208 Light Hall / 4:00 P.M.

THE Flexner DISCOVERY LECTURE SERIES

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 UNIVERSITY
MEDICAL CENTER

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

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.

LYNNE E. MAQUAT, Ph.D.

J. LOWELL ORBISON ENDOWED CHAIR AND PROFESSOR, DEPARTMENT OF BIOCHEMISTRY AND BIOPHYSICS, UNIVERSITY OF ROCHESTER SCHOOL OF MEDICINE AND DENTISTRY

DIRECTOR, UNIVERSITY OF ROCHESTER CENTER FOR RNA BIOLOGY

CHAIR, UNIVERSITY OF ROCHESTER GRADUATE WOMEN IN SCIENCE

Lynne Elizabeth Maquat is the J. Lowell Orbison Endowed Chair and Professor of Biochemistry & Biophysics in the School of Medicine and Dentistry, Director of the Center for RNA Biology, and Chair of Graduate Women in Science at the University of Rochester, Rochester, NY, USA. After obtaining her PhD in Biochemistry from the University of Wisconsin-Madison and undertaking post-doctoral work at the McArdle Laboratory for Cancer Research, she joined Roswell Park Cancer Institute before moving to the University of Rochester. In 1981, Professor Maquat discovered nonsense-mediated mRNA decay (NMD) in mammalian cells and, subsequently while elucidating the mechanism of NMD, the exon-junction complex (EJC) and how the EJC marks mRNAs for a quality-control "pioneer" round of protein synthesis. She also discovered Staufen-mediated mRNA decay, which mechanistically competes with NMD and, by so doing, new roles for short interspersed elements and long non-coding RNAs. Additional current interests include microRNA decay and functional links between transcription factors and RNA-binding proteins. She is an elected Fellow of the American Association for the Advancement of Science (2006), and an elected Member of the American Academy of Arts & Sciences (2006), the National Academy of Sciences (2011), and the National Academy of Medicine (2017). Lynne was a Batsheva de Rothschild Fellow of the Israel Academy of Sciences & Humanities (2012-2013) and has received the William C. Rose Award from the American Society for Biochemistry & Molecular Biology (2014), a Canada Gairdner International Award (2015), the international RNA Society Lifetime Achievement Award in Service (2010) and in Science (2017), the Federation of American Societies for Experimental Biology (FASEB) Excellence in Science Award (2018), and the Wiley Prize in Biomedical Sciences (2018).