Much progress has been made on how nonsense-mediated mRNA decay (NMD), which we first described for humans in 1981, controls the quality of gene expression by detecting and rapidly degrading aberrant mRNAs that contain a premature termination codon (PTC). Our studies of NMD have led to the discovery of the pioneer round of translation, the post-splicing “mark” on newly synthesized mRNAs – later named the exon-junction complex (EJC) in a collaboration with Melissa Moore – and the mechanistically related Staufen-mediated mRNA decay pathway. More recently, we tracked individual cellular transcripts in collaboration with Tatjana Trcek and Rob Singer to confirm our results from the mid-1990’s indicating that NMD for a number of mRNAs occurs on the cytoplasmic side of the nuclear envelop. Our 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. We have 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. Importantly, NMD also targets ∼10% physiologic mRNAs that are key to maintaining cellular homeostasis in a changing environmental milieu. In this regard, we have found that a sufficient level of DNA damage induced by commonly used frontline chemotherapeutics inhibits NMD by triggering the caspase-mediated cleavage of sub-stochiometric amounts of UPF1, thereby upregulating the half-lives of mRNAs that include those encoding proteins promoting apoptosis. Notably, the modest inhibition of NMD promotes but is not sufficient for programmed cell death. These and other results will be discussed.


About the Speaker:

Lynne Maquat is the J. Lowell Orbison Endowed Chair, Professor of Biochemistry & Biophysics, 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. Professor Maquat discovered nonsense-mediated mRNA decay (NMD) in 1981 and, subsequently, the exon-junction complex (EJC) and how the EJC marks mRNAs for a quality-control “pioneer” round of protein synthesis. She is an elected Fellow of the American Association for the Advancement of Science (2006), an elected Member of the American Academy of Arts & Sciences (2006) and the National Academy of Sciences (2011), and a Batsheva de Rothschild Fellow of the Israel Academy of Sciences & Humanities (2012-3). She received the William C. Rose Award from the American Society for Biochemistry & Molecular Biology (2014) and a Canada Gairdner International Award (2015).