Abstract – David M. Center, MD

The Interleukin 16 gene is located on Ch 15q26.3 and codes for two isoforms, one exclusively of neuronal origin and the second widely distributed in many organs, most notably in immunocytes. In T cells, IL-16 is synthesized as an 80 kDa precursor, which contains a phosphorylation-regulated nuclear localization motif (CcN) and three PDZ intermolecular binding domains, which target HDAC3 to a GABP transcriptional site resulting in silencing of Skp2 transcription. Without Skp2-dependent degradation of p27, the levels of p27 remain high and transition out of G1 is inhibited. Pro-IL-16 is constitutively expressed in the nucleus of resting T cells and is rapidly degraded following T cell activation. This results in dissociation of HDAC3 from GABP binding domains permitting transcription of Skp2, degradation of p27 and T cell cycle progression. Sezary T cells lack nuclear Pro-IL-16 as the result of mutations in regions that bind the nuclear chaperone hsc70. Reintroduction of the normal Pro-IL-16 gene is sufficient to completely inhibit the growth of Sezary T cells and all T cell lines derived from CTCLs. This lecture will chronicle the science behind these observations and the path from *in vitro* molecular biology to evaluation of patients with disease.

Learning objectives:

At the end of the lecture individuals will have a working knowledge of the role of Skp2 and p27 in control of the T cell cycle; the function of PDZ proteins; mechanisms of translocation of proteins from cytoplasm to nucleus; and the concepts of scaffold proteins for highly selective nuclear targeting of histone deacetylases to transcriptional elements. They will learn about mutations not previously described in Ch15 universally associated with Sezary cutaneous T cell lymphomas.

Disclosures:

Dr. Center is the scientific co-founder of Abkine Pharmaceuticals, Inc and the inventor of 11 patents owned by Boston University on products and uses derived from the secreted cytokine Interleukin 16.