

"Mis-regulation of Protein Translation in the Pathogenesis and Treatment of Cancer"

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Abstract: In the last several years it has become increasingly apparent that the mis-regulation of protein translation plays a critical role in cell transformation, tumorigenesis, and the resistance of cancer cells to cytotoxic therapies. A wide variety of human tumors have been shown to depend on activated signal transduction pathways that control protein translation (i.e. PI 3-kinase and mTor pathways), and inhibition of mTor-driven protein translation by the drug rapamycin is now in clinical trials as a cancer treatment. Similarly, many human tumors over-express one or more translation initiation factors (i.e. eIF4E, 4G and 4A), and experimental overexpression of these proteins in non-transformed cell lines directly leads to cell transformation in culture and tumor formation in transgenic mouse models. However, the identities of many of the mis-translated proteins that contribute to oncogenesis, metastasis, and resistance to therapy are unknown, because until now there has been no unbiased method by which to identify them in cancer cells in a proteome-wide manner. In this proposal we will implement, modify, and adapt a novel technology - Bio-Orthogonal Non-Canonical Amino Acid Tagging - for the non-biased mass-spectrometry-based mapping of actively translated proteins (hereafter referred to as the 'translatome'). We will utilize this approach to identify mis-translated proteins in human breast cancer cells compared with normal human breast cells, as well as proteins whose translation is upregulated in cancers that show enhanced metastatic potential or resistance to chemotherapy and radiation treatment.