Inaugural Scholars:

Laura Lackner, PhD
Assistant Professor of Molecular Biosciences

Identifying new ways to inhibit mitochondrial division, a process essential for cancer cell proliferation and metastasis

Mitochondrial division is emerging as a promising yet under-utilized therapeutic target for the treatment of cancer. Many types of cancer are associated with the inappropriate stimulation of mitochondrial division. As increased rates of this division are linked to the spread of the disease, inhibiting mitochondrial division is an appealing therapeutic approach. To develop strategies to control division, Dr. Laura Lackner and her group need to fully understand the mechanism and regulation of mitochondrial division in healthy cells and how this critical cellular process is dysregulated in disease states. To this end, she and her team propose to identify and functionally characterize the complement of proteins that execute and regulate division of mitochondria. They then will examine how the dysregulation of these proteins contributes to cancer. By doing so, Dr. Lackner and her team will identify novel therapeutic targets and strategies for cancers in which the inhibition of mitochondrial division is predicted to prevent or alleviate disease progression and pathology.

Marcus Ernst Peter, PhD
Professor of Medicine-Hematology/Oncology

Killing cancer cells by targeting tumor suppressors

Fas/CD95 and Fas ligand (FasL) are proteins that are involved in the induction of apoptosis, a form of programmed cell death. Immune cells use FasL to kill cancer cells. One can therefore consider Fas and FasL as tumor suppressors. Surprisingly, however, Dr. Marcus Peter and his group recently found that all cancer cells die when either Fas or FasL are eliminated by a novel form of cell death called DICE (for death induced by CD95/CD95L elimination). This validates their hypothesis that these tumor suppressors are so important that they need to be maintained by cells to prevent cancer formation and, conversely, that induction of DICE could be used to treat cancer. When the relevance of the expression of the tumor suppressors Fas and FasL for cancer cells was recognized, Dr. Peter’s group questioned whether other tumor suppressors could also be essential for the survival of cells to make it less likely that they are lost (i.e. during cancer formation). This resulted in the discovery of a set of now 17 genes that Dr. Peter calls Cancer indispensable Tumor Suppressors (CiTS).
With crucial support from the Liz and Eric Lefkofsky Innovation Research Award, Dr. Peter and his group plan to validate all 17 CiTS that they have identified. They will knock them down, one by one, in a set of cancer cell lines and test whether cells die after the knockdown. Dr. Peter and his team expect to complete this testing by autumn 2015. All CiTS that are essential for survival will be compared to Fas and FasL proteins. Dr. Peter and his group will compare the cell death observed after knockdown of any of the CiTS to DICE to determine whether each tumor suppressor protects cancer cells from a different form of cell death. They plan to complete an initial analysis of the type of cell death observed in cells after knockdown of the CiTS by the end of 2015.

Athanasios Vasilopoulos, PhD
Assistant Professor of Radiation Oncology

Acetylation of KRAS Lysine 147 is a novel oncogenic post-translational modification directed by SIRT2

One of the fundamental observations in oncology is that increasing age is the strongest statistical variable that predicts for carcinogenesis, the process by which normal cells turn into cancer cells. A fact that has emerged over the last several years is that aging is a complex process that appears to be regulated, at least in part, by sirtuins, a relatively new gene family that has been identified in multiple species. These observations raised the question whether sirtuins may be the mechanistic link between aging and tumorigenesis by orchestrating mechanisms involved in both processes. To specifically address this idea, preliminary studies conducted by Dr. Athanasios Vasilopoulos and his team showed that one of the primary anti-aging genes, SIRT2, plays a role in the development of pancreatic adenocarcinoma by using a genetic murine model. More importantly, its role in human pancreatic adenocarcinoma was further supported by the finding that SIRT2 levels are decreased in pancreatic tumors as compared to a normal pancreas.

Within the next year, Dr. Vasilopoulos’s goal is to dissect how SIRT2 modifies the activity of the KRAS gene. KRAS is essential in normal pancreatic cell function (cell growth and proliferation). However, it has been demonstrated that the modification of KRAS is an essential step in the development of many cancers and that this modified KRAS is present in 95% of all pancreatic adenocarcinomas. Acetylation is a type of gene modification and the acetylation of KRAS at lysine 147 has been directly linked to pancreatic adenocarcinoma. Therefore, Dr. Vasilopoulos has hypothesized that SIRT2 interferes with the acetylation of KRAS causing it to be inactive. He and his team aim to determine the mechanism by which this happens. Their results may have implications in the development of novel targeted therapeutic interventions involving KRAS.