Research Project 2 [1]

The Role of Airborne PCBs in Adipogenesis, Adipose Function, and Metabolic Syndrome

An overarching goal of Project 2 is to determine how airborne PCBs affect the development of metabolic syndrome (MetS), a cluster of conditions that includes obesity, hypertension, dyslipidemia, and hyperglycemia, which increase the risk of heart disease, stroke, and type II diabetes. Project 2 will determine how airborne PCBs affect the development of MetS in adolescence, specifically through their effects on adipose tissue. WE will be doing this by:

1) Elucidating the functional consequences of airborne PCB exposure on adipogenesis and adipocyte function. Using a stepwise screening process with immortal and primary human preadipocytes in our
organoid model system, we will assess how volatile PCBs (single congeners or in relevant mixtures), or their human PCB-metabolites dissolved in media and exposed to cells, affect adipogenesis and adipokine secretion. As different fat depots play different physiological roles, we will test whether there are differences in the responses between preadipocytes derived from subcutaneous and visceral white adipose tissue (WAT). Similarly, we will use adipocytes matured in our 3D culture system to determine how volatile PCBs or PCB-metabolites cause hypertrophy and inflammation in adipose tissue and whether this leads to changes in adipose-specific transcriptional pathways, adipokine secretion, thermogenic response, and insulin resistance.

2) Developing a human adipose-liver biomimetic on-chip that allows for facile and accurate testing of the effects of environmental toxicants on adipose function. We will utilize our 3D adipose organoid system to build a functional adipose tissue-on-chip biomimetic that incorporates liver cells to allow metabolism of PCBs \textit{in vitro}. PCBs that we know to affect adipogenesis or adipocyte function will then be tested on these devices for their effects on the secretion of factors from adipose and liver. We will use this unique system to assess how volatile PCBs, identified by the ISRP as present in school building air, affect adipose and liver tissue.

3) Determining how airborne PCBs affect adiposity and metabolism \textit{in vivo}. As a
model for exposure in schools, adolescent male and female rats will be chronically exposed to airborne PCBs and assessed for changes in adiposity and metabolism. We will determine the extent of proinflammatory response to PCB exposure and how it alters signaling pathways in adipose tissue, transcriptional regulation, and biochemical metabolite profiles.

We will determine how the PCBs affect liver steatosis and overall fat deposition through
NMR studies. We will assess systemic energy metabolism, including insulin and glucose tolerance and lipid and adipokine profiles. ISRP studies will determine distribution and levels of PCB congeners and metabolites in adipose tissue.

**Aloysius Klingelhutz, Ph.D., Project Leader**

Dr. Klingelhutz is a Professor of Microbiology and Immunology with expertise in preadipocyte immortalization and preadipocyte/adipocyte cell culture, 3D organoid culture, and assessment of parameters related to adipocyte function. He will be responsible for overall direction and management of Project 2, and will work closely with Ankrum to coordinate different aspects of this study, organize weekly meetings, and to supervise budget, data analysis, and dissemination of experimental findings through presentations, manuscripts, and progress reports. As Project Leader, he will serve on the ISRP Executive Committee and ensure all Project 2 activities are well integrated with the ISRP and supportive of the specific aims of all components.

**James Ankrum, Ph.D., Co-Investigator**

Dr. Ankrum is an Associate Professor of Bioengineering with expertise in bioengineering of cells, mesenchymal stem cells, and 3D organoid cultures. He will share leadership responsibilities with Klingelhutz and oversee the tissue-on-chip experiments. In addition to supervising and participating in daily activities in his laboratory relevant to Project 2, he will work closely with Klingelhutz to coordinate the overall project, manage experiments, analyze data, and disseminate experimental findings through presentations, manuscripts, and progress reports.

**Larry Robertson, PhD, Other Significant Contributor**

Dr. Robertson will work with Dr. Klingelhutz to design and interpret the rat studies as well as to provide guidance on in vitro PCB exposure studies. Dr. Robertson was a Project Leader for previous ISRP studies and was Director of the Iowa Superfund Research Program for 12 years.