Significance of the proposed research: There is an urgent, unmet need to understand the mechanisms underlying the predisposition to obesity and related disorders. Obesity currently adds more than $200 billion to US healthcare costs annually, and the number of obese individuals is increasing.[38] Evidence implicating environmental influences on obesity is mounting, but the mechanisms through which obesogens interact with established risk factors such as diet composition remain largely unexplored. We showed that descendants of obesogen-exposed individuals may respond to calories differently, storing more of the calories they consume as fat and resisting losing this fat, even when fasting. An important human study links blood levels of per-fluorinated obesogens with lower resting metabolic rates and regained weight faster after dieting.[70] These observations have important implications for the treatment of obesity. The proposed work will build on our established model, illuminating understanding of the molecular mechanisms through which obesogen exposure interacts with diet and how key metabolic tissues become dysregulated by this exposure. This research will identify how dietary composition might be expected to interact with obesogen exposure. A conservative estimate of the impact of three obesogens on the price of obesity in the EU put the annual cost at €18 billion;[66] a comparable study estimated the cost in the US at $5.9 billion.[1] The extent to which exposure to TBT or any of the ~50 other obesogens impacts the human obesity epidemic in the US is unknown, but likely substantial.

3b. Innovation: The obesogen hypothesis opened a new area of research into obesity by connecting EDC research with developmental origins of disease. There is a dearth of research data in this area, particularly on mechanisms, transgenerational effects, and obesogen interactions with diet. Few labs are prepared to answer questions related to transgenerational induction of obesity by obesogens and fewer still can combine cutting edge multi-omics and physiological analyses with transgenerational studies of obesity. Our demonstration of transgenerational obesity was innovative, and our recent publication showing that ancestral TBT exposure leads to a transgenerational thrifty phenotype is novel and relevant to human health.[19] Thus, our research team is uniquely suitable to carry out the proposed studies. Successful completion of the proposed work will reveal molecular mechanisms underlying the role of EDCs in transgenerational obesity by employing our well-defined transgenerational model, TWD, deep physiological analysis, and advanced genomic methods to provide insights into how the obesity epidemic may be curtailed. This is an important and timely public health issue.