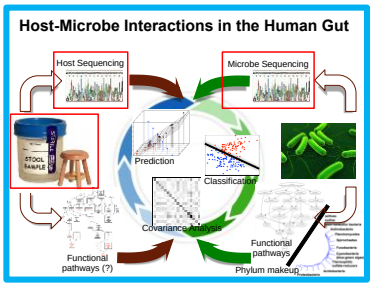
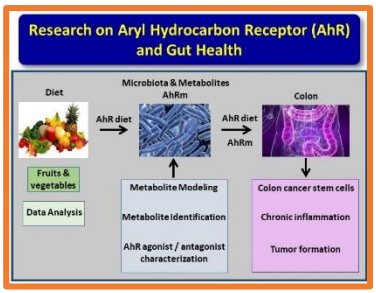
Dr. Robert S. Chapkin – Distinguished Professor and National Cancer Institute Outstanding Investigator Awardee, leads the **Program in Integrative Nutrition & Complex Diseases at TAMU.** Work in the Chapkin lab focuses on dietary prevention of colon cancer and chronic inflammatory diseases. The central goal is to (1) understand cancer chemoprevention at a fundamental level, and (2) to test pharmaceutical agents in combination with dietary/microbial countermeasures to the "Western diet" to more effectively improve gut health and reduce colon cancer and chronic inflammatory diseases. Since diet influences gut microbial composition and metabolite production, to unravel the interrelationships between gut health and the structure of the gut ecosystem, we are in the process of evaluating (using transgenic mice, fruit fly models, and humans) how gut microbes modulate intestinal stem cells (the origin of cancer). As part of this endeavor, we are modeling at the molecular level the dynamic relationship between diet and gut microbe-derived metabolites which modulate the cellular organization of the intestine, e.g., stem cell niche. Work in the lab focuses on four specific areas:

HOST-MICROBE INTERACTION



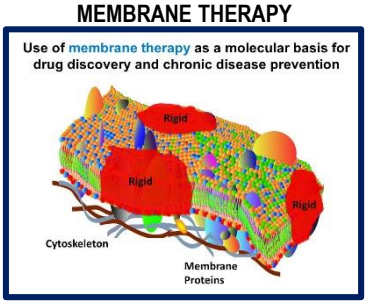
DEVELOPMENT OF NOVEL (EXFOLIATED CELL) NONINVASIVE METHODOLOGY TO MONITOR HOST/MICROBE INTERACTIONS IN THE GUT. Early detection can be considered a method for prevention in the sense that it can reduce morbidity and mortality. To address this need, our team has identified **novel noninvasive early detection biomarkers in feces containing exfoliated cells shed from the gut**. We use these biomarkers to classify/predict host chronic inflammation, metabolism, immune status, and gut barrier function on a molecular level in mouse models and humans. Mathematical models are used to determine dynamical system behavior for the purpose of deriving therapeutic strategies. Outcomes include the prediction of new cancer targets based on intracellular signaling pathways. Cutting edge applications include: (i) the influence of diet and gut microbes on host gene expression in neonates and adults, and (ii) analysis of gut microbe (prokaryotic) and host (eukaryotic) crosstalk.

RESTORING AhR SIGNALING



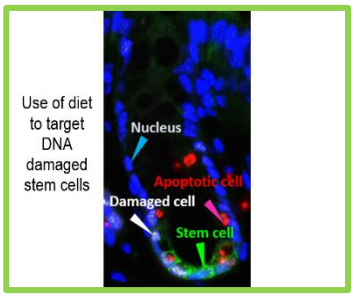
ROLE OF DIET AND MICROBES AS MODIFIERS OF STEM CELLS AND COLON CANCER. Projects in this research area are designed to assess how microbe-derived tryptophan metabolites mediate Aryl hydrocarbon receptor (AhR)-dependent intestinal stem cell function. Since transformation of adult stem cells is an extremely important route towards initiating intestinal cancer, we are interrogating the effects of diet and microbe-derived AhR mediators on intestinal stem cell homeostasis and colon cancer using tissue and stem cell-specific AhR transgenic mice. This objective is supported by our novel preliminary data indicating that microbe-derived AhR ligands have a direct effect on intestinal stem cells. **Collectively, our results provide a critical new paradigm in understanding the molecular mechanisms through which diet and gut microbes modulate colon cancer risk.**

MEMBRANE THERAPY



USE OF MEMBRANE THERAPY AS A MOLECULAR BASIS FOR DRUG DISCOVERY AND CANCER PREVENTION. Although cellular membranes are the environment in which many cancer related mutated proteins function, it is now apparent that protein assemblies can be organized to form distinct nanodomains that facilitate signaling events. Interestingly, cell membrane composition is altered during human disease processes such as cancer and obesity. For example, an increased rate of cholesterol synthesis in cancerous tissues has long been recognized as an important aspect of the rewired metabolism of transformed cells. However, the contribution of cholesterol to cellular function in disease models is not yet fully understood. Since diet is a major modulator of cell membrane composition, we are examining scenarios in which **diet-induced changes in membrane composition modulate cancer-causing mutated protein interactions (nanoclustering) in the plasma membrane, thereby impacting downstream signaling and human health.**

TARGETED DELETION OF CANCER STEM CELLS



USE OF DIET TO ENHANCE TARGETED DELETION OF CANCER STEM CELLS. We are assessing how nutritional combinations of fish oil and fermentable fiber (**Pesco-vegetarian diet, PVD**) uniquely reduce colon cancer risk in humans. This PVD effect is mediated in part by its ability to up-regulate the targeted death (**ferroptosis**) of DNA damaged stem cells in the gut, thereby reducing cancer risk. Our novel findings indicate that highly fermentable fiber, which generates butyrate in the colon, has a protective effect when combined with long chain n-3 polyunsaturated fatty acids (PUFA) found in fish oil. From a mechanistic perspective, n-3 PUFA and butyrate (a microbial fermentation product in the gut) synergistically induce a novel p53-independent, GPX4-phospholipid oxidation-ferroptosis mediated pathway. These findings emphasize the **need to examine both the fat and fiber composition of diets as a means of promoting the targeted deletion of cancer stem cells in the gut.**