LAB OVERVIEW

Our lab is interested in developing zebrafish models of human diseases to interrogate the disease mechanisms and to identify potential therapeutics against these diseases. Using both transgenesis and several gene-editing nuclease technologies that we have developed in our lab, we can generate unique disease models in zebrafish, enabling high-throughput chemical screening for small molecules that modify the disease phenotypes in a whole organism.

Selected review articles:


SCIENCE
Currently, there are four major projects in our lab.

1. Use a chemical suppressor screen to identify novel pathways involved in leukemogenesis

AML1-ETO is the fusion product of t(8;21) chromosomal translocation that can be found in approximately 12% of the acute myelogenous leukemia (AML) patients. AML1-ETO, as many other leukemic oncogenes, causes dysregulation of hematopoietic differentiation. Current treatments against AML rely heavily on non-specific cytotoxic drugs that kill proliferating cells, resulting in unbearable side effects, and yet most of the patients relapse after a brief remission. Compared to conventional cytotoxic therapeutics, targeted cancer therapies hold great promise to be more effective and less toxic. Thus, we generated a zebrafish model of AML by inducing AML1-ETO expression in zebrafish embryos, and showed that AML1-ETO exerts AML-like hematopoietic differentiation defects within just hours. We have developed a chemical suppressor screen using this zebrafish model of AML. Several classes of chemical suppressors have been identified in the screen and they are currently being evaluated for therapeutic potential using human cells and mouse models of AML.
Figure 1. A chemical suppressor screen conducted in the zebrafish model of AML1-ETO identifies a potential role for COX-2 in AML leukemogenesis. (a) Expression of AML1-ETO results in a hematopoietic differentiation defect, suppressing the erythroid cell fate in zebrafish embryos. This effect can be readily detected using the erythroid cell marker, gata1. Each panel shows five zebrafish embryos per well in a 96-well screening plate after gata1 staining. (b) We found that COX-2 inhibitors reverse the hematopoietic defect caused by AML1-ETO, pointing to potential therapeutic benefits of COX inhibitors for treating AML.

Selected publications:


2. Develop gene-editing nuclease technologies for the generation of targeted mutations in zebrafish

In collaboration with the Joung lab in the Department of Pathology and the Peterson lab in the Cardiovascular Research Center of MGH, we have developed several customizable nucleases platforms, including the zinc finger nucleases (ZFNs), the transcription activator-like effector (TALE) nucleases and the CRISPR-Cas system, that can be used for generating targeted mutations in zebrafish. We have created a number of zebrafish mutant lines for the studies of iron homeostasis, angiogenesis and neurological/psychiatric disease mechanisms. By exploiting the unique capabilities of the zebrafish for disease modeling and small molecule screening, these zebrafish mutant lines will provide powerful tools for dissecting signaling pathways involved in a broad range of biological processes and may uncover promising new therapeutic approaches for treating human diseases.
Figure 2. The ZFN technology facilitates the creation of human disease models in zebrafish for the discovery of novel therapeutic agents. First, we engineer gene-specific zinc-finger nucleases (ZFNs) for generating zebrafish mutants of interest. Second, we identify zebrafish mutant lines that manifest specific disease phenotypes similar to humans. Third, zebrafish mutant embryos are subjected to large-scale chemical screening to identify compounds that can modify the disease phenotypes. Lastly, we identify the compounds’ underlying mechanisms of action, which may provide new insights into the development of therapeutic agents.

Selected publications:


3. **Investigate the roles of metabolic oncogenes and tumor suppressor genes**

Cancer metabolism is a field currently under intensive investigations partly due to the recent discoveries of cancer-causing mutations in several metabolic genes, such as IDH1 and IDH2 in glioblastoma and AML, FH in hereditary leiomyomatosis and renal cell cancer (HLRCC) and SDH in paraganglioma and phaeochromocytoma. Mutations in these genes can affect not only metabolism, but also DNA methylation, histone methylation and cellular hypoxia response due to the important roles of α-KG-dependent dioxygenases in these processes (Figure 3). Understanding the metabolic transformation mechanisms may shed light on new and promising targeted therapeutic approaches. Interestingly, these mutations are only found in some specific cancer types, suggesting their tissue-specific functions. We are interested in investigating the disease mechanisms of these mutations using zebrafish models in conjunction with human cell culture systems.

**Figure 3. Metabolic oncogenes and tumor suppressor genes in cancer.** Gain-of-function mutations in isocitrate dehydrogenase 1 (IDH1) and IDH2 as well as loss-of-function mutations in succinate dehydrogenase (SDH) and fumarate hydratase (FH) have been found in human cancers. The diagram depicts the subcellular localizations of the enzymes encoded by these genes and their normal enzymatic functions in the Kreb Cycle. The dashed box shows a mitochondria. A nucleus is indicated by a green oval. It has been shown that accumulations of fumarate, succinate and 2-hydroxyglutarate in the presence of FH, SDH and IDH mutations, respectively, can suppress the activities of α-KG-dependent enzymes.

4. **Use zebrafish to identify dietary modulations that may reduce hyperlipidemia**

The circulating metabolites in the blood may represent the well-being of an individual and report for certain disease states. However, diets and changes in plasma metabolites can also play causative roles in disease mechanisms. Previously, our collaborator Dr. Gerszten’s group in the Cardiovascular Research Center at MGH has discovered several plasma metabolites that show significant associations with various metabolic risk factors including hyperlipidemia (Circulation 2012; 125(18):2222-31). Using zebrafish, we plan to identify how certain amino acids may affect triglycerides/cholesterol profiles in a whole organism.
Figure 4. The associations between plasma amino acids and metabolic traits in the Framingham Heart Study participants. β coefficients and P values generated from age- and sex-adjusted regression analyses of the relation of each metabolite (standardized and log transformed) with insulin resistance phenotypes and metabolic traits (standardized) in the Framingham Heart Study sample. BMI indicates body mass index; WC, waist circumference; HOMA, homeostasis model assessment; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; HDL, high-density lipoprotein. (Cheng, et al. Circulation 2012; 125(18):2222-31.)

Selected publications: