

James & Esther King Biomedical Research Program

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New Investigator (3-year project)*

Project Title: Mechanism of HCV Resistance to Cyclosporine A

Project Summary: The short-term goal of this project is to identify hepatitis C virus (HCV) mutants and lay foundations for molecular characterizations of drug resistance to a new drug candidate by the virus. The broad long-term objectives are to gain better understanding of the virus-host cell interaction and to improve therapy for HCV infection and related liver cancer.

Heavy alcohol use, tobacco smoking, and HCV infection are among the major risk factors for hepatocellular carcinoma (HCC), a serious form of liver cancer that costs many lives and millions of dollars in patient care every year. Cigarette smoking and substance abuse are also important behavioral indicators for high risk of infection by blood-borne pathogens such as HIV and HCV. Furthermore, recent results suggest that tobacco use may in some way influence the susceptibility to infection with HCV, which infects more than 170 million people worldwide, 25–30% of which are reported to be at risk of developing serious liver diseases such as liver cirrhosis and HCC.

Because of the large number of infected people and the tendency of causing chronic diseases, HCV infection presents a grave threat to global human health. Moreover, the currently available treatment and prevention options are scarce and viruses like HCV are well known to quickly develop resistance to single drugs. As a result, there is an urgent and great need for new classes of potent and broad-acting anti-HCV drugs, the development and optimization of which require thorough understanding of the mechanism of actions of the drugs and potential drug resistance. Cyclosporine A (Cs A) is one of new drug candidates that have been tested in recent clinical trials with encouraging results. While both the laboratorial and the clinical studies of Cs A-based inhibition of HCV infection are in the beginning stages, we correctly anticipated and successfully confirmed the emergence of Cs A resistant HCV strains in our lab model of HCV replication, which is called a replicon cell. We then pinpointed the mutations occurred in the drug resistant viral strains. Here we propose to characterize the mechanism of the drug resistance at the molecular and cellular level. Results obtained with this study will not only contribute to better understanding of HCV replication but can also provide guidance to both drug development efforts and the relevant clinical studies.