Introduction

The liver is a major organ for metabolism of foreign substances and also functionally interposed between the site of resorption and the systemic circulation. These condition render the liver not only the most important organ for detoxification of foreign substances but also a major target of their toxicity***.(Chau 2008).***

Drug-induced liver injury (DILI) is a major health problem that challenges not only health care professionals but also the pharmaceutical industry and drug regulatory agencies. According to the United States Acute Liver Failure Study Group, DILI accounts for more than 50% of acute liver failure, including hepatotoxicity caused by overdose of acetaminophen (39%) and idiosyncratic liver injury triggered by other drugs (13%). Because of the significant patient morbidity and mortality associated with DILI, the U.S. Food and Drug Administration (FDA) has removed several drugs from the market, including bromfenac, ebrotidine, and troglitazone. Other hepatotoxic drugs, such as risperidone, trovafl oxacin, and nefazodone, have been assigned " black box " warnings. DILI is the most common cause for the withdrawal of drugs from the pharmaceutical market ***(Michael and Cynthia, 2006).***

The spectrum of DILI is both diverse and complex. Although liver injury is often mild and does not require treatment in these patients, DILI may lead to severe hepatitis with a risk of death. Therefore, adequate initial management after achieving an accurate diagnosis is important for

physicians. Although the incidence of DILI is reported to be increasing, the precise frequency is difficult to estimate because of the lack of a worldwide monitoring system and the lack of a gold standard for diagnosis. Establishment of a worldwide network for monitoring the adverse events of drugs and a universal diagnostic system for DILI are important for accurate diagnosis, and may lead to better management of DILI***. (Kazuto and Yukihiro , 2008)***.

Because available clinical laboratory tests are not ideal biomarker, the diagnosis of drug-induced liver injury (DILI) remains generally one of exclusion and thus is typically time resource intensive. (In the context of medical treatment, a biomarker has been defined as "a characteristic that is objectively measured and evaluated as an indicator of … responces to a therapeutic intervention."). Also, because DILI is a relatively uncommon adverse drug reaction, it is often not possible to confidently identify the specific culprit when DILI is suspected in a patient who is being treated with multiple medications. Finally, in many instances, DILI will resolve despite continuing treatment with the offending drug(s) due to a process termed "adaptation." No current biomarkers can distinguish between patients who are capable of adaptation with continued treatment and patients who will experience progressive liver injury unless treatment is discontinued. Biomarkers that could predict adaptation would be very useful in the treatment of conditions such as tuberculosis, in which DILI is a relatively common occurrence but for which there are limited treatment options. This article reviews the promises and challenges in developing and validating biomarkers that could address these needs and thereby improve the diagnosis and management of DILI. The clinical and

histological presentation of DILI can mimic most types of liver disease, and it is likely that the optimal biomarkers will differ depending on the type of DILI. Hepatocellular liver injury is generally the DILI of greatest concern to patients and physicians. This is because hepatocellular DILI can evolve quickly and be life-threatening before the development of detectable jaundice. For this reason, hepatocellular DILI is the major focus of this review ***(Watkins, 2009).***