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# Inhibition of Sterile Inflammation by Digoxin in Alcoholic Hepatitis

| Project Number | Contact PI/Project Leader | Awardee Organization |
|---|---|---|
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## Description

### Abstract Text

ABSTRACT: Alcoholic hepatitis (AH) is a major liver disease, and has an inpatient mortality of between 25-40%. Liver inflammation is a key feature of AH, yet the factors which drive this inflammatory response are not known. We have identified novel key drivers of liver inflammation which are the subject of this application. We have also identified novel proteomic and molecular markers in AH which will be used to predict prognosis. We have shown that activation of the nuclear (hypoxia inhibitory factor 1- : HIF-1 ) pathway was required for the development of sustained sterile inflammation, which suggested that inhibition of HIF-1 may be therapeutic in AH[1]. In a high throughput screen cardiac glycoside were identified to have significant ability to inhibit HIF-1 [2]. The preliminary data demonstrates i) Up-regulation of HIF-1 dependent genes in liver tissues from early AH, as compared to severe AH, from the InTeam consortium ii) Ability of digoxin to reduce tissue damage in a model of alcohol, and others forms of liver injury. iii) Digoxin binds to the enzyme pyruvate kinase M2 (PKM2), iv) Digoxin reduces PKM2 binding to the HIF-1 promoter and limits up-regulation of HIF-1 , and HIF-1 response genes. v) An aptamer based proteomic analysis of serum shows that in patients with the AH and the systemic inflammatory response (SIRS) there is an increase in tumor necrosis factor related proteins, low affinity immunoglobulin gamma Fc region receptor II, complement components, kallikrein and fibroblast growth factors. vi) Serum DNA is known to be a pro-inflammatory ligand and serum DNA levels correlated with peripheral blood white cell count in AH. Aim 1. Obtain clinical data supporting the therapeutic use of digoxin in alcoholic hepatitis. Aim 2. Identify dominant and novel targets that are regulated by PKM2 in alcoholic hepatitis. Aim 3. Obtain plasma proteomic and molecular data to allow for early identification of patients with SIRS. Collectively this will allow us to obtain the necessary data towards clinically testing low dose digoxin in AH. In addition, it will allow us to identify novel protein markers and pro-inflammatory signals in the serum of patients with AH. Finally, we will be able to identify if any of the novel protein markers are associated with the novel PKM2 pathway we have identified.

### Public Health Relevance Statement

Project Narrative. Alcohol driven liver injury is a major health problem with no known therapy. We have identified a new pathway that is responsible for liver damage and identified an old drug which can protect the liver. In this application, we will develop the steps necessary to test this in a clinical trial.

### NIH Spending Category

Alcoholism, Alcohol Use and Health
Biotechnology
Chronic Liver Disease and Cirrhosis
Clinical Research
Clinical Trials and Supportive Activities
Digestive Diseases
Genetics

Health Disparities Hepatitis Liver Disease Minority Health Substance Abuse Women's Health

## Project Terms

Affinity Alcohol consumption Alcoholic Hepatitis Alcohols Aptamer Technology Bacteremia Binding Cardiac Glycosides Clinical Clinical Data Clinical Trials Complement Complication DNA Data Development Digoxin Dose Early identification Enzymes Ethanol Fibroblast Growth Factor Gene Proteins Gene Targeting Genes Grant Health Heavy Drinking Hepatocyte Human Hypoxia Immune Inflammation Inflammatory Inflammatory Response Inpatients Kininogenase Laboratory Markers Ligands Liver Liver diseases Mitochondrial DNA Modeling Molecular Nuclear Oral Oxides

## Details

No information available for 5U01AA026962-02

## Sub Projects

No Sub Projects information available for 5U01AA026962-02

## Publications

Disclaimer

No Publications available for 5U01AA026962-02

## Patents

No Patents information available for 5U01AA026962-02

## Outcomes

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No Outcomes available for 5U01AA026962-02

## Clinical Studies

No Clinical Studies information available for 5U01AA026962-02

## News and More

### Related News Releases

No news release information available for 5U01AA026962-02

## History

No Historical information available for 5U01AA026962-02

## Similar Projects

No Similar Projects information available for 5U01AA026962-02