

National Institutes of Health Grant to Copple

Project Information ?

5R01DK073566-09

DESCRIPTION DETAILS RESULTS HISTORY SUBPROJECTS

Project Number: 5R01DK073566-09 **Contact PI / Project Leader:** [COPPLE, BRYAN L](#)
Title: ROLE OF EARLY GROWTH RESPONSE FACTOR-1 IN CHOLESTATIC LIVER INJURY **Awardee Organization:** MICHIGAN STATE UNIVERSITY

Abstract Text:

DESCRIPTION (provided by applicant): Cholestatic liver disease has many causes, including autoimmune destruction of bile duct epithelial cells, genetic disorders, and physical obstruction of the bile duct. Currently, the only approved treatment for many types of cholestatic liver disease is ursodeoxycholic acid, which is only efficacious in a small fraction of patients. Although, several studies indicate an important role for inflammation in the development of hepatocellular injury and fibrosis during cholestasis, glucocorticoids and other potent anti-inflammatory drugs that target classical inflammatory cytokines are only modestly effective at ameliorating liver disease in patients and are often associated with severe side-effects. The failure of current anti-inflammatory treatment regimens to treat cholestatic liver disease underscores the importance of elucidating the mechanism(s) involved in the initiation of hepatic inflammation in this type of liver disease. Our preliminary studies demonstrate that pathological concentrations of the bile acid, taurocholic acid (TCA), stimulate hepatocytes to produce the cytokines, IL-23 and macrophage inflammatory protein-2 (MIP-2). Activation of Akt by TCA is required for upregulation of IL-23 and MIP-2, whereas activation of p38 by TCA inhibits upregulation of these cytokines. IL-23 contributes to hepatic inflammation by stimulating Th17 cells to produce IL-17A. This cytokine inhibits TCA-mediated activation of p38 in hepatocytes leading to enhanced production of MIP-2 and IL-23. Our studies demonstrate further that activation of lysophosphatidic acid receptor 1 (LPA1) is required for upregulation of IL-23 and MIP-2 in TCA-treated hepatocytes, and that LPA1 is activated independent of its ligand, LPA. This indicates that LPA1 is activated by a novel mechanism that may involve direct activation of LPA1 by TCA. Based upon these studies, the central hypothesis of this application is that during cholestasis, elevated concentrations of bile acids activate LPA1 which increases expression of IL-23 and MIP-2, a process which is enhanced by IL-17A-mediated inhibition of p38. The studies in this proposal aim to test the central hypothesis by: (1) determining the mechanism by which bile acids increase expression of IL-23 and MIP-2 in hepatocytes, (2) determining the mechanism by which IL-17A inhibits activation of p38 by TCA, and (3) determine the mechanism by which p38 negatively regulates IL-23 and MIP-2 induction by TCA. Collectively, these studies will increase our current knowledge of regulation of hepatic inflammation during cholestasis, which will allow for the identification of new drug targets to treat cholestatic liver disease.

Public Health Relevance Statement:

PUBLIC HEALTH RELEVANCE: Currently, there are limited therapies for patients with cholestatic liver disease, and therefore, many patients die from this disease. The inflammatory system plays a key role in the development of liver disease during cholestasis. The studies in this proposal will determine the mechanism by which inflammation is initiated in the liver during cholestasis, in order to identify ways to dampen the inflammatory response in patients with this disease.

NIH Spending Category:

Chronic Liver Disease and Cirrhosis; Digestive Diseases; Liver Disease

Project Terms:

Acids; Adverse effects; AKT Signaling Pathway; Anti-inflammatory; Anti-Inflammatory Agents; Autoimmune Process; base; Bile Acids; Bile Duct Epithelium; Cells; chemokine; Cholestasis; CXCL2 gene; cytokine; Development; Disease; Drug Targeting; effective therapy; Epithelial Cells; Failure; FDA approved; Fibrosis; Glucocorticoids; Goals; Grant; Growth; Hepatic; Hepatocyte; Hereditary Disease; Inflammation; Inflammatory; Inflammatory Response; Injury; Interleukin-1 beta; Interleukin-17; interleukin-23; Knowledge; Ligands; Liver; liver development; Liver diseases; Liver Failure; Liver Fibrosis; liver injury; Lysophosphatidic Acid Receptors; macrophage; MAPK14 gene; Mediating; Molecular; new therapeutic target; novel; novel therapeutics; Pathologic; Pathway interactions; Patient-Focused Outcomes; Patients; Pattern; Pharmaceutical Preparations; Phosphoric Monoester Hydrolases; Play; Population; Process; Production; Protein phosphatase; public health relevance; Regulation; response; Role; Signal Transduction; Specificity; System; targeted treatment; Taurocholic Acid; Testing; therapeutic target; TNF gene; Treatment Failure; Treatment Protocols; Up-Regulation; Ursodeoxycholic Acid

Contact PI Information:	Program Official Information:	Other PI Information:
Name: COPPLE, BRYAN L	Name: BURGESS-BEUSSE, BONNIE L	Not Applicable
Email: Click to view contact PI email address	Email: Click to view PO email address	
Title: ASSOCIATE PROFESSOR		

Organization:	Department / Educational Institution Type:	Congressional District:
Name: MICHIGAN STATE UNIVERSITY	PHARMACOLOGY	State Code: MI
City: EAST LANSING Country: UNITED STATES (US)	SCHOOLS OF MEDICINE	District: 08

Other Information:

FOA: PA-13-302	DUNS Number: 193247145	CFDA Code: 847
Study Section: Hepatobiliary Pathophysiology Study Section (HBPP)	Project Start Date: 1-MAY-2007	Project End Date: 31-JUL-2019
Fiscal Year: 2017 Award Notice Date: 14-JUL-2017	Budget Start Date: 1-AUG-2017	Budget End Date: 31-JUL-2019

Administering Institutes or Centers:

NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES

National Institutes of Health Training Grant that funded Roth and Strickland

Project Information ?

2T32ES007255-31

DESCRIPTION DETAILS RESULTS HISTORY SUBPROJECTS

Project Number: 2T32ES007255-31 **Contact PI / Project Leader:** [LAPRES, JOHN J](#)
Title: MULTIDISCIPLINARY TRAINING IN ENVIRONMENTAL TOXICOLOGY **Awardee Organization:** MICHIGAN STATE UNIVERSITY

Abstract Text:

PROJECT SUMMARY/ABSTRACT The multidisciplinary Environmental and Integrative Toxicological Sciences (EITS) Training Program at Michigan State University (MSU) produces scientists with a base knowledge in environmental toxicology coupled with research in a biomedical basic science graduate program. Predoctoral trainees must meet the full PhD requirements of their partnering biomedical doctoral program and complete the coursework, research and interactive aspects of the EITS Doctoral Program administered through the Institute for Integrative Toxicology (IIT). The dual nature of the training is recognized in the biomedical science-environmental toxicology title of the degree awarded (e.g., PhD in "Biochemistry and Molecular Biology-Environmental Toxicology"). Graduates of the program are well equipped to become leaders in their respective fields and conduct research capable of addressing complex environmental toxicological problems that require collaborative, multidisciplinary approaches. Twenty-five training faculty conduct predoctoral training in nine basic science PhD programs (Biochemistry and Molecular Biology, Cell and Molecular Biology, Comparative Medicine and Integrative Biology, Food Science and Human Nutrition, Genetics, Microbiology and Molecular Genetics, Neuroscience, Pharmacology and Toxicology, and Physiology). Added to the basic biomedical science-based education and environmental toxicology research training are didactic, toxicology-oriented courses and other requirements of the EITS Program. This coursework, career development opportunities and multidisciplinary activities provided by the IIT impart a wider scope of knowledge than is available within basic science programs alone. Research topics for trainees span various organ systems and encompass gene-environment interactions and the role of environmental stressors in disease susceptibility and progression. Integrative biology is central to the research training, which emphasizes whole animal, cell-based, molecular and various "omic" methodologies to understand adverse outcomes and mechanisms of toxicity in a collaborative atmosphere. The postdoctoral training program involves not only conducting research in the laboratories of the training faculty but also gaining additional environmental toxicology experience and career-building opportunities by following an individual development plan (IDP). In addition, participation in IIT and University-wide activities is also encouraged to broaden the training experience. This application requests support of seven predoctoral and two postdoctoral trainees, thereby continuing a highly effective multidisciplinary and interactive training program that combines formal and informal approaches to prepare graduates for leadership roles in research that aims to advance our understanding of adverse outcomes from exposure to environmental chemicals.

Public Health Relevance Statement:

PROJECT NARRATIVE An individual's response to exposure to various agents in the environment is dictated by many factors, including co-exposures, age, sex, current health status and underlying genetics. Given the complexities of disease associated with environmental chemicals, reducing the impact of such exposures on human health and devising effective interventions requires public health officials and scientists with interdisciplinary training. This program employs an exceptional, research-intensive faculty experienced in all facets of predoctoral and postdoctoral development within a collaborative environment to train scientists to investigate and address complex environmental toxicology problems.

Project Terms:

environmental toxicology; multidisciplinary; Training

Contact PI Information:	Program Official Information:	Other PI Information:
Name: LAPRES, JOHN J	Name: SHREFFLER, CAROL	Not Applicable
Email: Click to view contact PI email address	A	
Title: ASSOCIATE PROFESSOR	Email: Click to view PO email address	

Organization:	Department / Educational Institution Type:	Congressional District:
Name: MICHIGAN STATE UNIVERSITY	PHARMACOLOGY	State Code: MI
City: EAST LANSING Country: UNITED STATES (US)	SCHOOLS OF VETERINARY MEDICINE	District: 08

Other Information:

FOA: PA-18-403	DUNS Number: 193247145	CFDA Code: 113
Study Section: Environmental Health Sciences Review Committee (EHS)	Project Start Date: 1-JUL-1989	Project End Date: 30-JUN-2024
Fiscal Year: 2019 Award Notice Date: 10-MAY-2019	Budget Start Date: 1-JUL-2019	Budget End Date: 30-JUN-2020

Administering Institutes or Centers:

NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES

Project Funding Information for 2019:

Total Funding: \$338,860	Direct Costs: \$413,581	Indirect Costs: \$26,359
Year	Funding IC	FY Total Cost by IC
2019		\$338,860

NATIONAL INSTITUTE OF ENVIRONMENTAL
HEALTH SCIENCES

History:

Total project funding amount for 31 projects is \$8,034,334*

* Only NIH, CDC, and FDA funding data.

Project Number	Sub #	Project Title	Contact Principal Investigator	Organization	FY	Admin IC	Funding IC	FY Total Cost by IC
2T32ES007255-31		MULTIDISCIPLINARY TRAINING IN ENVIRONMENTAL TOXICOLOGY	LAPRES, JOHN J	MICHIGAN STATE UNIVERSITY	2019	NIEHS	NIEHS	\$338,860
5T32ES007255-30		MULTIDISCIPLINARY TRAINING IN ENVIRONMENTAL TOXICOLOGY	LAPRES, JOHN J	MICHIGAN STATE UNIVERSITY	2018	NIEHS	NIEHS	\$283,415
5T32ES007255-29		MULTIDISCIPLINARY TRAINING IN ENVIRONMENTAL TOXICOLOGY	LAPRES, JOHN J	MICHIGAN STATE UNIVERSITY	2017	NIEHS	NIEHS	\$416,977
5T32ES007255-28		MULTIDISCIPLINARY TRAINING IN ENVIRONMENTAL TOXICOLOGY	LAPRES, JOHN J	MICHIGAN STATE UNIVERSITY	2016	NIEHS	NIEHS	\$427,066
5T32ES007255-27		MULTIDISCIPLINARY TRAINING IN ENVIRONMENTAL TOXICOLOGY	ROTH, ROBERT ANDREW	MICHIGAN STATE UNIVERSITY	2015	NIEHS	NIEHS	\$380,594
2T32ES007255-26		MULTIDISCIPLINARY TRAINING IN ENVIRONMENTAL TOXICOLOGY	ROTH, ROBERT ANDREW	MICHIGAN STATE UNIVERSITY	2014	NIEHS	NIEHS	\$376,865
5T32ES007255-25		MULTIDISCIPLINARY TRAINING IN ENVIRONMENTAL TOXICOLOGY	ROTH, ROBERT ANDREW	MICHIGAN STATE UNIVERSITY	2013	NIEHS	NIEHS	\$381,419
5T32ES007255-24		MULTIDISCIPLINARY TRAINING IN ENVIRONMENTAL TOXICOLOGY	ROTH, ROBERT ANDREW	MICHIGAN STATE UNIVERSITY	2012	NIEHS	NIEHS	\$273,608
5T32ES007255-23		MULTIDISCIPLINARY TRAINING IN ENVIRONMENTAL TOXICOLOGY	ROTH, ROBERT ANDREW	MICHIGAN STATE UNIVERSITY	2011	NIEHS	NIEHS	\$352,134
5T32ES007255-22		MULTIDISCIPLINARY TRAINING IN ENVIRONMENTAL TOXICOLOGY	ROTH, ROBERT ANDREW	MICHIGAN STATE UNIVERSITY	2010	NIEHS	NIEHS	\$363,559
2T32ES007255-21		MULTIDISCIPLINARY TRAINING IN ENVIRONMENTAL TOXICOLOGY	ROTH, ROBERT ANDREW	MICHIGAN STATE UNIVERSITY	2009	NIEHS	NIEHS	\$117,866
5T32ES007255-20		MULTIDISCIPLINARY TRAINING IN ENVIRONMENTAL TOXICOLOGY	ROTH, ROBERT ANDREW	MICHIGAN STATE UNIVERSITY	2008	NIEHS	NIEHS	\$331,038
5T32ES007255-19		MULTIDISCIPLINARY TRAINING IN ENVIRONMENTAL TOXICOLOGY	ROTH, ROBERT ANDREW	MICHIGAN STATE UNIVERSITY	2007	NIEHS	NIEHS	\$332,097
5T32ES007255-18		MULTIDISCIPLINARY TRAINING IN ENVIRONMENTAL TOXICOLOGY	ROTH, ROBERT ANDREW	MICHIGAN STATE UNIVERSITY	2006	NIEHS	NIEHS	\$234,084
5T32ES007255-17		MULTIDISCIPLINARY TRAINING IN ENVIRONMENTAL TOXICOLOGY	ROTH, ROBERT ANDREW	MICHIGAN STATE UNIVERSITY	2005	NIEHS	NIEHS	\$305,176
2T32ES007255-16		MULTIDISCIPLINARY TRAINING IN ENVIRONMENTAL TOXICOLOGY	ROTH, ROBERT ANDREW	MICHIGAN STATE UNIVERSITY	2004	NIEHS	NIEHS	\$309,411
5T32ES007255-15		MULTIDISCIPLINARY TRAINING IN ENVIRONMENTAL TOXICOLOGY	FISCHER, LAWRENCE J	MICHIGAN STATE UNIVERSITY	2003	NIEHS	NIEHS	\$184,501
					2002	NIEHS	NIEHS	\$243,965

5T32ES007255-14		MULTIDISCIPLINARY TRAINING IN ENVIRONMENTAL TOXICOLOGY	FISCHER, LAWRENCE J	MICHIGAN STATE UNIVERSITY			
5T32ES007255-13		MULTIDISCIPLINARY TRAINING IN ENVIRONMENTAL TOXICOLOGY	FISCHER, LAWRENCE J	MICHIGAN STATE UNIVERSITY	2001 NIEHS	NIEHS	\$270,212
5T32ES007255-12		MULTIDISCIPLINARY TRAINING IN ENVIRONMENTAL TOXICOLOGY	FISCHER, LAWRENCE J	MICHIGAN STATE UNIVERSITY	2000 NIEHS	NIEHS	\$222,009
2T32ES007255-11		MULTIDISCIPLINARY TRAINING IN ENVIRONMENTAL TOXICOLOGY	FISCHER, LAWRENCE J	MICHIGAN STATE UNIVERSITY	1999 NIEHS	NIEHS	\$209,703
5T32ES007255-10		MULTIDISCIPLINARY TRAINING IN ENVIRONMENTAL TOXICOLOGY	FISCHER, LAWRENCE J	MICHIGAN STATE UNIVERSITY	1998 NIEHS	NIEHS	\$170,642
5T32ES007255-09		MULTIDISCIPLINARY TRAINING IN ENVIRONMENTAL TOXICOLOGY	FISCHER, LAWRENCE J	MICHIGAN STATE UNIVERSITY	1997 NIEHS	NIEHS	\$210,839
5T32ES007255-08		MULTIDISCIPLINARY TRAINING IN ENVIRONMENTAL TOXICOLOGY	FISCHER, LAWRENCE J	MICHIGAN STATE UNIVERSITY	1996 NIEHS	NIEHS	\$172,981
5T32ES007255-07		MULTIDISCIPLINARY TRAINING IN ENVIRONMENTAL TOXICOLOGY	FISCHER, LAWRENCE J	MICHIGAN STATE UNIVERSITY	1995 NIEHS	NIEHS	\$169,748
2T32ES007255-06		MULTIDISCIPLINARY TRAINING IN ENVIRONMENTAL TOXICOLOGY	FISCHER, LAWRENCE J	MICHIGAN STATE UNIVERSITY	1994 NIEHS	NIEHS	\$187,416
5T32ES007255-05		MULTIDISCIPLINARY TRAINING IN ENVIRONMENTAL TOXICOLOGY	FISCHER, LAWRENCE J	MICHIGAN STATE UNIVERSITY	1993 NIEHS	NIEHS	\$87,847
5T32ES007255-04		MULTIDISCIPLINARY TRAINING IN ENVIRONMENTAL TOXICOLOGY	FISCHER, LAWRENCE J	MICHIGAN STATE UNIVERSITY	1992 NIEHS	NIEHS	\$167,531
5T32ES007255-03		MULTIDISCIPLINARY TRAINING IN ENVIRONMENTAL TOXICOLOGY	FISCHER, LAWRENCE J	MICHIGAN STATE UNIVERSITY	1991 NIEHS	NIEHS	\$171,761
5T32ES007255-02		MULTIDISCIPLINARY TRAINING IN ENVIRONMENTAL TOXICOLOGY	FISCHER, LAWRENCE J	MICHIGAN STATE UNIVERSITY	1990 NIEHS	NIEHS	\$228,076
1T32ES007255-01		MULTIDISCIPLINARY TRAINING IN ENVIRONMENTAL TOXICOLOGY	FISCHER, LAWRENCE J	MICHIGAN STATE UNIVERSITY	1989 NIEHS	NIEHS	\$112,934
Subprojects:							
Project Number	Sub #	Project Title	Contact Principal Investigator	Organization	FY	Admin IC	FY Total Cost by IC
No Subprojects information available for 2T32ES007255-31							

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