Final Progress Report for Research Projects Funded by Health Research Grants

Instructions: Please complete all of the items as instructed. Do not delete instructions. Do not leave any items blank; responses must be provided for all items. If your response to an item is "None", please specify "None" as your response. "Not applicable" is not an acceptable response for any of the items. There is no limit to the length of your response to any question. Responses should be single-spaced, no smaller than 12-point type. The report **must be completed using MS Word**. Submitted reports must be Word documents; they should not be converted to pdf format.

1. **Grantee Institution:** The Pennsylvania State University

2. **Reporting Period (start and end date of grant award period):** 1/1/2010 - 12/31/2013

3. **Grant Contact Person (First Name, M.I., Last Name, Degrees):** John Anthony, MPA

4. **Grant Contact Person's Telephone Number:** 814 935 1081

5. **Grant SAP Number:** 4100050904

6. **Project Number and Title of Research Project:** 15. Activation of STAT3 Protects Liver from Ischemia Reperfusion Injury

7. **Start and End Date of Research Project:** 1/1/2010 - 6/30/2011

8. **Name of Principal Investigator for the Research Project:** Tadahiro Uemura, MD, PhD

9. **Research Project Expenses**.

   9(A) Please provide the total amount of health research grant funds spent on this project for the entire duration of the grant, including indirect costs and any interest earned that was spent:

   $ 62,040

   9(B) Provide the last names (include first initial if multiple individuals with the same last name are listed) of **all** persons who worked on this research project and were supported with health research funds. Include position titles (Principal Investigator, Graduate Assistant, Post-doctoral Fellow, etc.), percent of effort on project and total health research funds expended for the position. For multiple year projects, if percent of effort varied from year to year, report in the % of Effort column the effort by year 1, 2, 3, etc. of the project (x% Yr 1; z% Yr 2-3).

Last Name, First Name	Position Title	% of Effort on Project	Cost
Lucy Xi, Lou	Postdoc Fellow	50%	$20,332

9(C) Provide the names of **all** persons who worked on this research project, but who *were not* supported with health research funds. Include position titles (Research Assistant, Administrative Assistant, etc.) and percent of effort on project. For multiple year projects, if percent of effort varied from year to year, report in the % of Effort column the effort by year 1, 2, 3, etc. of the project (x% Yr 1; z% Yr 2-3).

Last Name, First Name	Position Title	% of Effort on Project
Tadahiro Uemura, MD	Assistant Professor	2.5%
Samuel Shao-Min Zhang, MD, PhD	Assistant Professor	2.5%
John Liang, MD	Assistant Professor	0.0%

9(D) Provide a list of **all** scientific equipment purchased as part of this research grant, a short description of the value (benefit) derived by the institution from this equipment, and the cost of the equipment.

Type of Scientific Equipment	Value Derived	Cost
None		

10. Co-funding of Research Project during Health Research Grant Award Period. Did this research project receive funding from any other source during the project period when it was supported by the health research grant?

Yes_____ No___X_____

If yes, please indicate the source and amount of other funds:

11. Leveraging of Additional Funds

11(A) As a result of the health research funds provided for this research project, were you able to apply for and/or obtain funding from other sources to continue or expand the research?

Yes_____ No____X_____

If yes, please list the applications submitted (column A), the funding agency (National Institutes of Health—NIH, or other source in column B), the month and year when the application was submitted (column C), and the amount of funds requested (column D). If you have received a notice that the grant will be funded, please indicate the amount of funds to be awarded (column E). If the grant was not funded, insert "not funded" in column E.

Do not include funding from your own institution or from CURE (tobacco settlement funds). Do not include grants submitted prior to the start date of the grant as shown in Question 2. If you list grants submitted within 1-6 months of the start date of this grant, add a statement below the table indicating how the data/results from this project were used to secure that grant.

A. Title of research project on grant application	B. Funding agency (check those that apply)	C. Month and Year Submitted	D. Amount of funds requested:	E. Amount of funds to be awarded:
None	☐NIH ☐ Other federal (specify:_____) ☐ Nonfederal source specify:_____)		$	$

11(B) Are you planning to apply for additional funding in the future to continue or expand the research?

Yes_____ No___X_____

If yes, please describe your plans:

12. Future of Research Project. What are the future plans for this research project?

The PI has left the institution.

13. New Investigator Training and Development. Did students participate in project supported internships or graduate or post-graduate training for at least one semester or one summer?

Yes___X_____ No_____

If yes, how many students? Please specify in the tables below:

	Undergraduate	Masters	Pre-doc	Post-doc
Male				
Female	1			
Unknown				
Total	**1**			

	Undergraduate	Masters	Pre-doc	Post-doc
Hispanic				
Non-Hispanic	1			
Unknown				
Total	**1**			

	Undergraduate	Masters	Pre-doc	Post-doc
White				
Black				
Asian	1			
Other				
Unknown				
Total	**1**			

14. Recruitment of Out-of–State Researchers. Did you bring researchers into Pennsylvania to carry out this research project?

Yes_____ No___X_____

If yes, please list the name and degree of each researcher and his/her previous affiliation:

15. Impact on Research Capacity and Quality. Did the health research project enhance the quality and/or capacity of research at your institution?

Yes_____ No____X_____

If yes, describe how improvements in infrastructure, the addition of new investigators, and other resources have led to more and better research.

16. Collaboration, business and community involvement.

16(A) Did the health research funds lead to collaboration with research partners outside of your institution (e.g., entire university, entire hospital system)?

Yes_____ No____X_____

If yes, please describe the collaborations:

16(B) Did the research project result in commercial development of any research products?

Yes_____ No__X_____

If yes, please describe commercial development activities that resulted from the research project:

16(C) Did the research lead to new involvement with the community?

Yes_____ No____X_____

If yes, please describe involvement with community groups that resulted from the research project:

17. Progress in Achieving Research Goals, Objectives and Aims.

List the project goals, objectives and specific aims (as contained in the grant agreement). Summarize the progress made in achieving these goals, objectives and aims for the period that the project was funded (i.e., from project start date through end date). Indicate whether or not each goal/objective/aim was achieved; if something was not achieved, note the reasons why. Describe the methods used. If changes were made to the research goals/objectives/aims, methods, design or timeline since the original grant application was submitted, please describe the changes. Provide detailed results of the project. Include evidence of the data that was generated and analyzed, and provide tables, graphs, and figures of the data. List published abstracts, poster presentations and scientific meeting presentations at the end of the summary of progress; peer-reviewed publications should be listed under item 20.

This response should be a DETAILED report of the methods and findings. It is not sufficient to state that the work was completed. Insufficient information may result in an unfavorable performance review, which may jeopardize future funding. If research findings are pending publication you must still include enough detail for the expert peer reviewers to evaluate the progress during the course of the project.

Health research grants funded under the Tobacco Settlement Act will be evaluated via a performance review by an expert panel of researchers and clinicians who will assess project work using this Final Progress Report, all project Annual Reports and the project's strategic plan. After the final performance review of each project is complete, approximately 12-16 months after the end of the grant, this Final Progress Report, as well as the Final Performance Review Report containing the comments of the expert review panel, and the grantee's written response to the Final Performance Review Report, will be posted on the CURE Web site.

There is no limit to the length of your response. Responses must be single-spaced below, no smaller than 12-point type. If you cut and paste text from a publication, be sure symbols print properly, e.g., the Greek symbol for alpha (α) and beta (ß) should not print as boxes (□) and include the appropriate citation(s). DO NOT DELETE THESE INSTRUCTIONS.

Signal transducers and activators of transcription 3 (STAT3) is a major signaling molecule for a variety of genes in response to cell stimuli and it plays a key role in many cellular processes such as cell growth and apoptosis. Recent studies have suggested that STAT3 activation is involved in protection of hepatocyte from I/R injury. Our goal is to understand the mechanisms of STAT3 in I/R injury. In this project, we hypothesize that STAT3 is an essential factor in protecting liver and in survival from I/R injury. Using STAT3 hepatocyte-specific deficient mice and their wild type control, we will examine this hypothesis in response to partial and total liver ischemia.

Specific Aim 1: To demonstrate that STAT3 has hepatoprotective role from partial hepatic injury. A persistent 90 minutes partial liver ischemia followed by reperfusion will be performed

in both STAT3 hepatocyte deficient mice and wild-type littermates. STAT3 expression, serum transaminase level, liver degeneration (apoptosis) and regeneration (cell cycle reentry) will be monitored by molecular biochemical and immunohistochemical assays. Animals will be sacrificed at 6 hours (injury phase) and 48 hours (repair phase) after reperfusion. Liver enzyme level and liver pathology will be compared between STAT3 deficient mice and wild-type littermates. Histological changes will be examined using liver I/R injury score.

Materials and Methods:

Generation of hepatocyte tissue-specific STAT3 deficient mice:

Classical knockout of the STAT3 gene in mouse results in early embryonic lethality. Using the Cre-loxP system, we have created a conditional STAT3 allele in which exons 18 to 20 are flanked by 2 loxP sequences. Removal of exons 19 and 20 which encode the SH2 domain of STAT3, destroys the function of the protein by blocking its dimer formation. Hepatocyte tissue-specific STAT3 deficiency was generated by crossing STAT3(F/F) to transferrin (TTR)-Cre mice (Strain 4-18). TTR promoter drives a hepatocyte specific expression of Cre recombinase. We have examined the efficiency of Cre activation by crossing the TTR4-18Cre (+/-) mice with a GFP report FloxP mouse line (ZA/G), which allowed us to confirm TTR driven Cre recombinase can specifically delete FloxP in hepatocytes.

Animals:

STAT3(F/F) mice and TTR-Cre (+/-) mice in C57BL/6 background were bred in the Penn State College of Medicine Animal Core, in accordance with the Penn State College of Medicine Institutional Animal Care and Use Committee Guidelines. Mice were housed in pairs in plastic cages in a pathogen-free environment with access to food and water on a 12-hr light-dark schedule.

Genotyping and grouping:

The genotyping of STAT3 (F/F) mice and TTR-Cre (+/-) mice were confirmed at postnatal 21 days by PCR analysis. Male homozygous and wild-type littermates were used for this study. Mice were divided into two groups between STAT3 deficient and control groups. At least 5 animals were used at each point in these experimental groups.

70% partial liver ischemia:

Mice were anesthetized (i.p.) with a mixture of 100mg/kg Ketamine and 10 mg/kg Xylazine. A midline incision was made on the abdomen. The liver was exposed with retractors placed in the flanks. The blood supply to medial largest lobe and lateral lobe of the liver (70% of liver) was temporally interrupted (ischemia) by applying a microclamp (FD562; Aesculap, South San Francisco, CA) to the vascular pedicle (Figure 1). The blood supply was resumed by removing the microclamp after 90 minutes of ischemia.

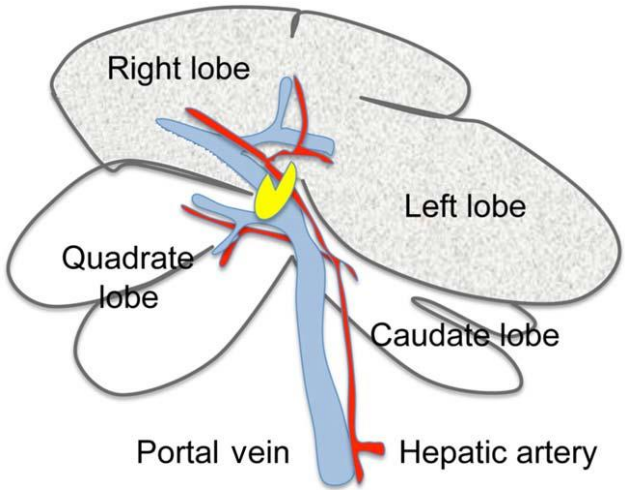

Figure 1. (A) Cartoon of 70% liver warm ischemic model and distribution of ischemic and non-ischemic lobes.

Results:

Immediately increase of STAT3 tyrosine phosphorylation by warm ischemia/reperfusion in vivo

STAT3 is first identified as immediate response gene in liver. To understand the courses of STAT3 activation we have examined expression of STAT3 and its activated form tyrosine phosphorylated STAT3 (pSTAT3) in wild type livers in response to warm I/R injury through temporally interrupted blood supply to medial largest lobe and lateral lobe of the liver (70% of liver). The non-ischemic quadrate lobes of the same livers were also used for the same examinations. As shown in ischemic lobes of Figure 2A and B, the levels of pSTAT3 increased over 6 ($p<0.01$) and 18 ($p<0.01$) hours after ischemia compared to the time point immediately after injury and have a tendency to return to normal level in 48 hours but it still had higher levels ($p<0.01$). A significant increase of total STAT3 protein level was observed with a peak at 18 hours after injury ($p<0.01$). Interestingly a significant and temporally lower level of pSTAT3 was seen at 1 hour after injury ($p<0.01$). As shown in non-ischemic lobes of Figure 2A and C, there are different patterns of pSTAT3 and STAT3 responses compared to the ischemic lobes. A lower but obvious increase of pSTAT3 levels was observed from 1 hour ($p<0.05$) and continued to 48 hours ($p<0.01$) after ischemic injury. A significant increase of total STAT3 protein level was observed after injury ($p<0.01$) with a peak at 48 hours, which was different from the ischemic lobes. These results indicated that STAT3 was a response molecule to liver I/R injury.

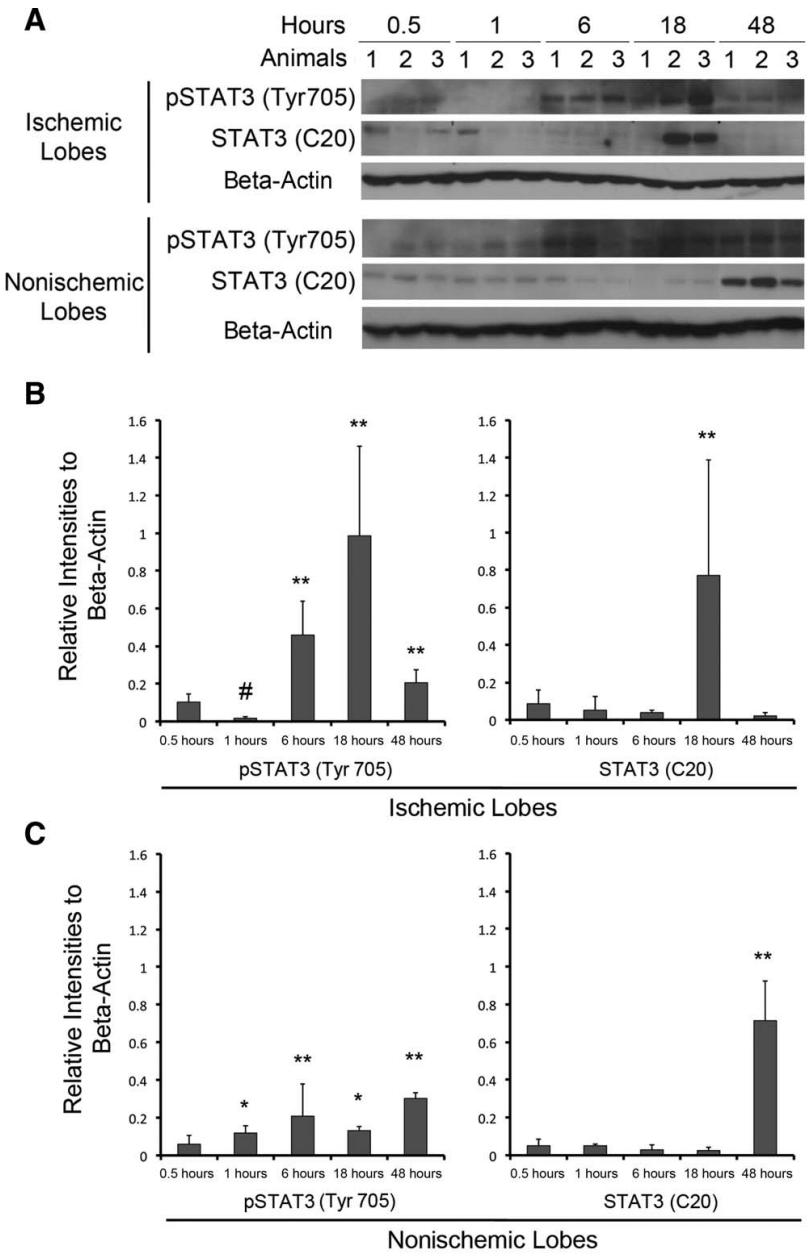

Figure 2. Increase of STAT3 tyrosine phosphorylation by warm ischemia/reperfusion in vivo.
(A) Images of Western blots of STAT3 (C20) and pSTAT3 (Tyr 705) in liver lysates. 1, 2, 3 indicate livers from independent animals. Beta-Actin is used as internal loading control. (B & C) densitometry analysis of Western images, # indicates significantly lower compared to first time point ($p<0.01$); * indicates significantly higher compared to first time point ($p<0.05$); ** indicates significantly higher compared to first time point ($p<0.01$).

Constitutive STAT3 tyrosine phosphorylation in wild type hepatocytes in vivo

Since a significant and temporally lower level of pSTAT3 was seen at 1 hour after injury in ischemic lobes, we asked whether it is a constitutive STAT3 tyrosine phosphorylation in the hepatocytes under rest conditions. Using FloxP-Cre system (Figure 3A&B), we have generated the STAT3 hepatocyte-specific deficient mice. The exons of STAT3 at 18 to 20 encoded SH2

domains were deleted (Figure 3A) following specific expression of Cre in hepatocytes (Figure 3B). As shown in Figure 3C, we examined and compared the levels of pSTAT3 and total STAT3 in STAT3 deficient and wild type livers under rest (control) conditions. A significantly higher level of pSTAT3 (p=0.014) and total STAT3 (p=3.82E-14) proteins compared to the livers from wild type littermates (Figure C&D), suggested a constitutive STAT3 tyrosine phosphorylation in normal hepatocytes in vivo. The faint base line levels of STAT3 and pSTAT3 in the Western blot might reflect the negligible levels of the liver non-parenchymal tissues other that hepatocytes.

Absence of STAT3 tyrosine phosphorylation in liver with hepatocyte STAT3 specific deficiency in response to warm ischemia/reperfusion

On the other hand, following a warm I/R injury almost no expression of pSTAT3 was confirmed in STAT3 deficient livers (Figure 3C&D). Both protein levels of total STAT3 (p=6.82E-10) and pSTAT3 (p=8.0E-17) were significantly increased in wild type livers compared to STAT3 deficient livers. Although about 4-folds increase of total STAT3 protein levels in the STAT3 deficient livers suggested that STAT3 in non-parenchymal tissues of livers were also in response to warm I/R injury, equal levels of pSTAT3 were observed in hepatocyte STAT3 specific deficient livers under both resting and warm I/R conditions (Figure 3D). These results indicated that diminished STAT3 tyrosine phosphorylation in liver with hepatocyte STAT3 specific deficiency in response to warm ischemia/reperfusion.

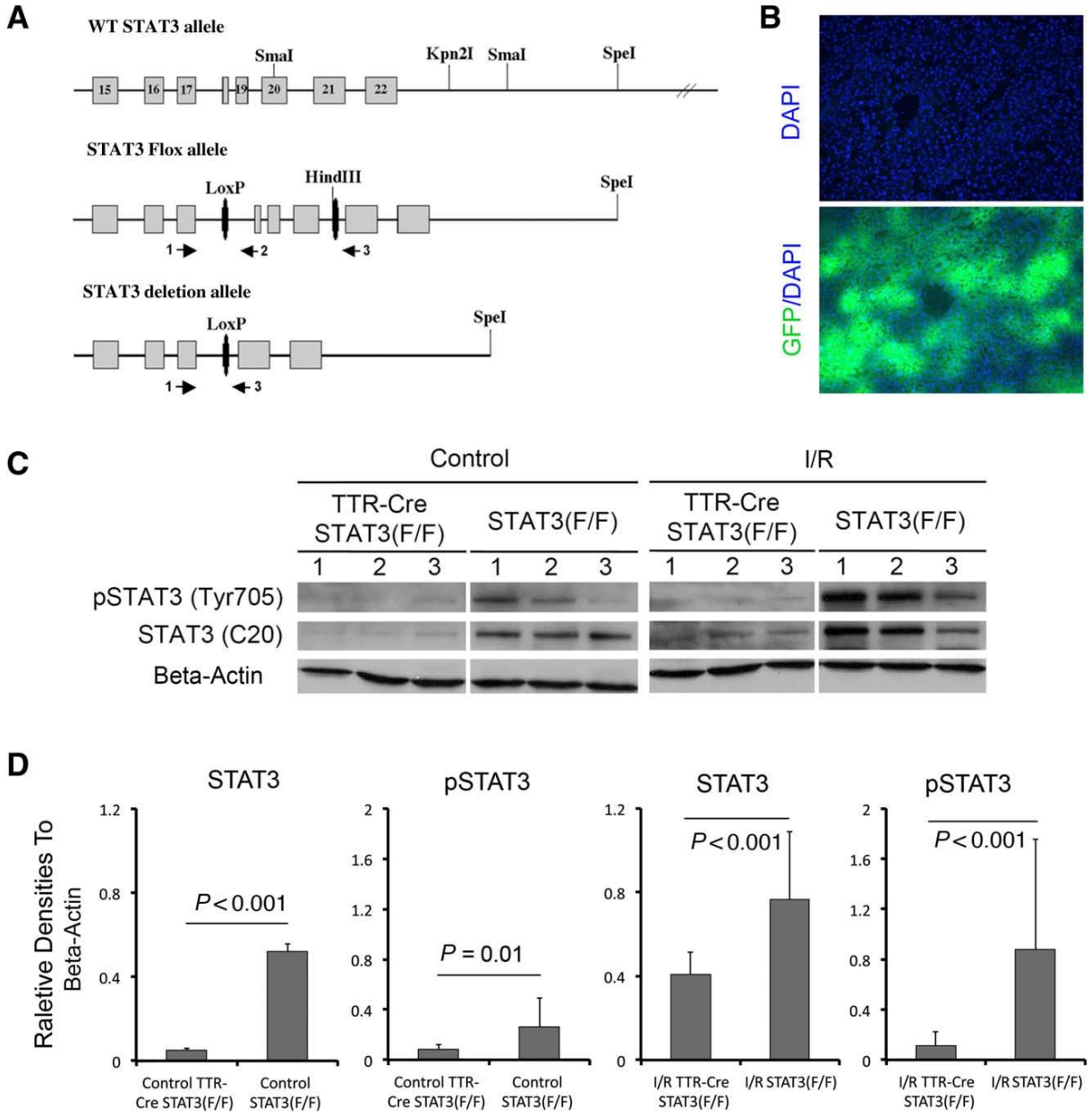

Figure 3. STAT3 hepatocyte-specific deficient livers. (A) Scheme of hepatocyte-specific STAT3 deficient mice. 1, 2, 3 and black closed arrows indicate primer location and direction for mouse genotyping. (B) fluorescence images of livers from TTR-4-18-Cre mated with ZE/G GFP-FloxP reporter animal. Liver sections from ZE/G GFP-FloxP x TTR-4-18-Cre mouse with DAPI staining (upper panel); Liver sections from ZE/G GFP-FloxP x TTR-4-18-Cre mouse with DAPI and GFP imaging (lower panel). GFP shows specifically in hepatocytes X200. (C) images of Western blot from STAT3 hepatocyte-specific deficiency (TTR-CreSTAT3(F/F)) and wild type littermates [STAT3(F/F)]. pSTAT3 (Tyr 705) and total STAT3 (C20) were used for specific protein blotting; beta-Actin serves as control. (D) densitometry analysis of Western images, statistical analysis p values were shown as indicated.

Depletion of STAT3 signaling in hepatocytes aggravates liver damages in response to warm ischemia/reperfusion

To understand any phenotypes associated with the STAT3 deficiency in hepatocytes, we first analyzed the hepatocyte damage measured by ALT (Figure 4A). In control group, ALT levels were 841 ± 433 IU/L and 484 ± 95 IU/L at 3 hours and 6 hours after reperfusion, respectively. In hepatocyte-specific STAT3 deficient group, ALT levels were significantly elevated at 2310 ± 853 IU/L and 1086 ± 231 IU/L at 3 hours ($p=0.011$) and 6 ($p=3.35E-4$) hours after reperfusion, respectively (Figure 4A). Thus, ALT level in STAT3 deficient groups significantly increased compared to their wild type littermates. These liver serum enzyme data correlated with Suzuki's histological grading following warm I/R injury (Figure 4B&C). Hepatocyte-specific STAT3 deficient mice showed moderate-severe sinusoidal congestion ($p=0.02$), cytoplasmic vacuolization ($p=0.01$), and hepatocyte necrosis ($p=0.001$) compared to the livers from their wild type littermates (Figure 4C). These results suggested that liver with STAT3 deficiency specifically in hepatocytes is more susceptible to warm I/R injury compared to wild type groups. Furthermore, we analyzed a number of inflammatory polymorphonuclear neutrophils (PMNs) between wild types and STAT3 deficient groups. PMNs in wild type control group were 59 ±26 and 106±54 and PMNs in STAT3 deficient groups were 51±47 and 118±54 at 3 hours and 6 hours after reperfusion, respectively. There is no change of PMNs counts between these two groups, suggests that endogenous STAT3 signaling in hepatocytes is required for liver protection in response to warm ischemia/reperfusion.

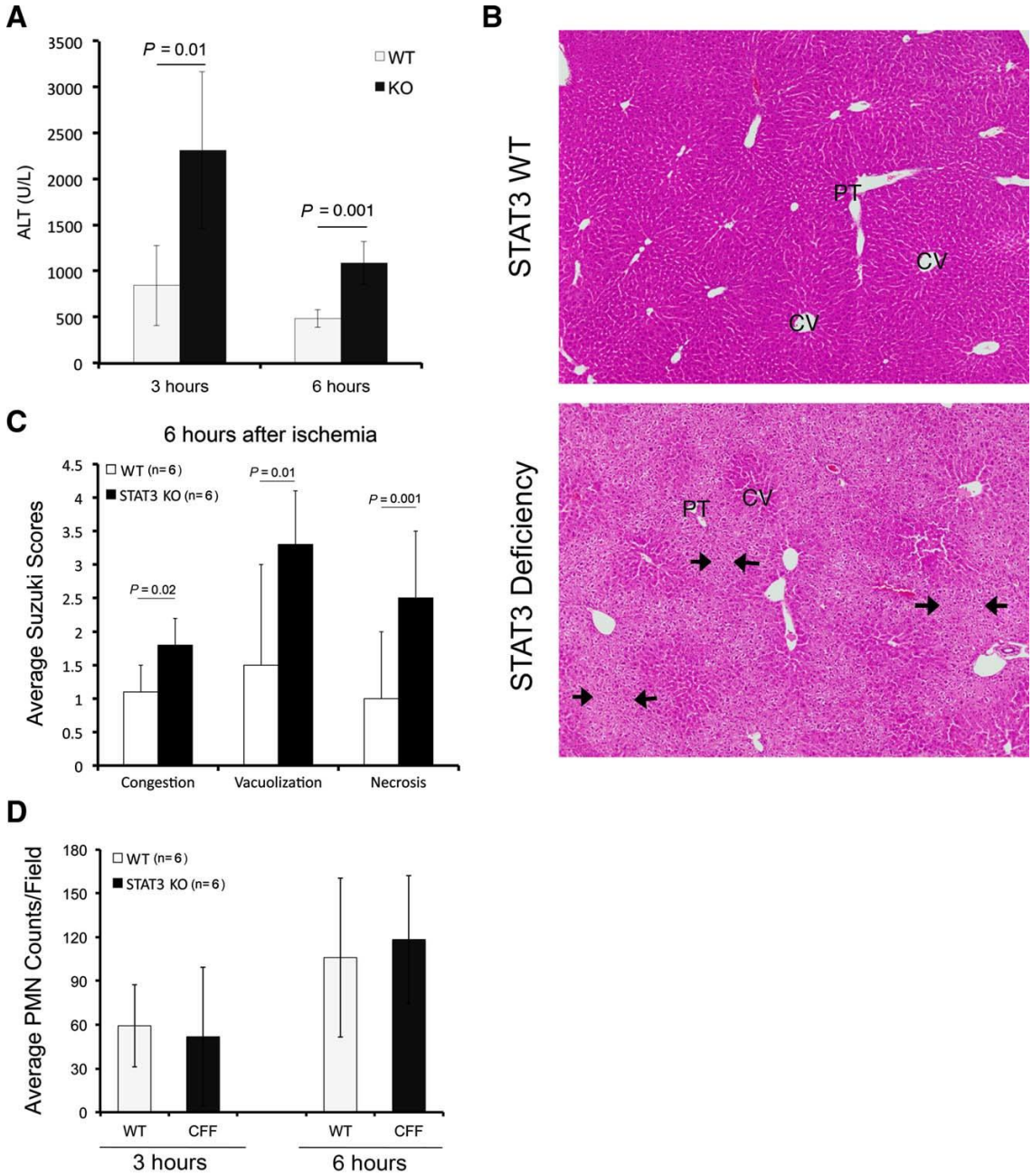

Figure 4. Endogenous STAT3 is required for hepatocyte protection from warm I/R injury. (A) Hepatocellular function evaluated by ALT (IU/L). Mean ± S.D. (n=4-6 samples/group). Mice were subjected to 90 min of partial liver warm ischemia followed by 3 or 6 hours reperfusion, respectively. (B) Panels show H&E stained ischemic liver tissue at 6 hours after 90 min of warm ischemia. Wild type (upper) hepatocyte specific STAT3 knockout mice (lower), hepatocyte specific STAT3 deficient mice showed significant sinusoidal congestion, cytoplasmic vacuolization, and hepatocyte necrosis. (C) statistical analysis of Suzuki's histological grades for hepatocyte specific STAT3 deficient mice (n=13) and their wild type littermates (n=24), statistical analysis p values were shown as indicated. (D) analysis of a number of inflammatory polymorphonuclear neutrophils (PMNs) between wild types and STAT3 deficient groups 3 or 6 hours after warm I/R injury, respectively. No significant differences were observed.

Specific Aim 2: To demonstrate that STAT3 is essential for animal survival from total warm ischemic injury. Total liver ischemia behaves differently from partial liver ischemia. It has been shown that all animals survived 60 minutes of total ischemia, whereas all died after 90 minutes of total ischemia. An intermediate time period of 75 minutes of total liver ischemia followed by reperfusion will be performed in control and hepatocyte specific STAT3 deficient mice. A poor survival outcome is expected in the STAT3 deficient group compared to control group.

This study will provide direct evidence whether STAT3 activation is the essential process in liver protection and survival from I/R injury. In this application, we will be able to show the mechanisms of STAT3 on I/R injury not only at the cellular level but also at the in vivo level.

We could not obtain the results of this specific aim due to instability of the mouse model and limitations on our financial and personnel resources.

18. Extent of Clinical Activities Initiated and Completed. Items 18(A) and 18(B) should be completed for all research projects. If the project was restricted to secondary analysis of clinical data or data analysis of clinical research, then responses to 18(A) and 18(B) should be "No."

18(A) Did you initiate a study that involved the testing of treatment, prevention or diagnostic procedures on human subjects?

_____Yes
__X___No

18(B) Did you complete a study that involved the testing of treatment, prevention or diagnostic procedures on human subjects?

_____Yes
__X___No

If "Yes" to either 18(A) or 18(B), items 18(C) – (F) must also be completed. (Do NOT complete 18(C-F) if 18(A) and 18(B) are both "No.")

18(C) How many hospital and health care professionals were involved in the research project?

_____Number of hospital and health care professionals involved in the research project

18(D) How many subjects were included in the study compared to targeted goals?

_____Number of subjects originally targeted to be included in the study
_____Number of subjects enrolled in the study

Note: Studies that fall dramatically short on recruitment are encouraged to provide the details of their recruitment efforts in Item 17, Progress in Achieving

Research Goals, Objectives and Aims. For example, the number of eligible subjects approached, the number that refused to participate and the reasons for refusal. Without this information it is difficult to discern whether eligibility criteria were too restrictive or the study simply did not appeal to subjects.

18(E) How many subjects were enrolled in the study by gender, ethnicity and race?

Gender:
_____Males
_____Females
_____Unknown

Ethnicity:
_____Latinos or Hispanics
_____Not Latinos or Hispanics
_____Unknown

Race:
_____American Indian or Alaska Native
_____Asian
_____Blacks or African American
_____Native Hawaiian or Other Pacific Islander
_____White
_____Other, specify:_____
_____Unknown

18(F) Where was the research study conducted? (List the county where the research study was conducted. If the treatment, prevention and diagnostic tests were offered in more than one county, list all of the counties where the research study was conducted.)

19. Human Embryonic Stem Cell Research. Item 19(A) should be completed for all research projects. If the research project involved human embryonic stem cells, items 19(B) and 19(C) must also be completed.

19(A) Did this project involve, in any capacity, human embryonic stem cells?
_____Yes
__X___ No

19(B) Were these stem cell lines NIH-approved lines that were derived outside of Pennsylvania?
_____Yes
_____ No

19(C) Please describe how this project involved human embryonic stem cells:

20. Articles Submitted to Peer-Reviewed Publications.

20(A) Identify all publications that resulted from the research performed during the funding period and that have been submitted to peer-reviewed publications. Do not list journal abstracts or presentations at professional meetings; abstract and meeting presentations should be listed at the end of item 17. **Include only those publications that acknowledge the Pennsylvania Department of Health as a funding source** (as required in the grant agreement). List the title of the journal article, the authors, the name of the peer-reviewed publication, the month and year when it was submitted, and the status of publication (submitted for publication, accepted for publication or published.). Submit an electronic copy of each publication or paper submitted for publication, listed in the table, in a PDF version 5.0.5 (or greater) format, 1,200 dpi. Filenames for each publication should include the number of the research project, the last name of the PI, and an abbreviated title of the publication. For example, if you submit two publications for Smith (PI for Project 01), one publication for Zhang (PI for Project 03), and one publication for Bates (PI for Project 04), the filenames would be:

Project 01 – Smith – Three cases of isolated
Project 01 – Smith – Investigation of NEB1 deletions
Project 03 – Zhang – Molecular profiling of aromatase
Project 04 – Bates – Neonatal intensive care

If the publication is not available electronically, provide 5 paper copies of the publication.

Note: The grant agreement requires that recipients acknowledge the Pennsylvania Department of Health funding in all publications. Please ensure that all publications listed acknowledge the Department of Health funding. If a publication does not acknowledge the funding from the Commonwealth, do not list the publication.

Title of Journal Article:	Authors:	Name of Peer-reviewed Publication:	Month and Year Submitted:	Publication Status (check appropriate box below):
1. Endogenous Signal Transducer and Activator of Transcription 3 Is Required for the Protection of Hepatocytes Against Warm Ischemia/ Reperfusion Injury	Lucy Xi Lou, Tadahiro Uemura, Haresh Mani, Chen Yang, Weiyi Li, Zakiyah Kadry, and Samuel Shao-Min Zhang	Liver Transplantation	Jan, 2013	☐Submitted ☐Accepted X Published

20(B) Based on this project, are you planning to submit articles to peer-reviewed publications in the future?

Yes_____ No_____X_____

If yes, please describe your plans:

21. Changes in Outcome, Impact and Effectiveness Attributable to the Research Project. Describe the outcome, impact, and effectiveness of the research project by summarizing its impact on the incidence of disease, death from disease, stage of disease at time of diagnosis, or other relevant measures of outcome, impact or effectiveness of the research project. If there were no changes, insert "None"; do not use "Not applicable." Responses must be single-spaced below, and no smaller than 12-point type. DO NOT DELETE THESE INSTRUCTIONS. There is no limit to the length of your response.

This study demonstrates the role of hepatocyte specific STAT3 in liver protection on I/R injury using conditional model of hepatocyte specific STAT3 knock out. This study supports the possibility that STAT3 targeting therapy could be a therapeutic approach to combating liver I/R injury.

22. Major Discoveries, New Drugs, and New Approaches for Prevention Diagnosis and Treatment. Describe major discoveries, new drugs, and new approaches for prevention, diagnosis and treatment that are attributable to the completed research project. If there were no major discoveries, drugs or approaches, insert "None"; do not use "Not applicable." Responses must be single-spaced below, and no smaller than 12-point type. DO NOT DELETE THESE INSTRUCTIONS. There is no limit to the length of your response.

Liver ischemia/reperfusion injury occurs in many conditions such as liver transplantation, liver surgery, trauma, and shock. We discovered that STAT3 has a protective role in liver ischemia/reperfusion injury which could have beneficial therapeutic applications in preventing liver ischemia/reperfusion injury.

23. Inventions, Patents and Commercial Development Opportunities.

23(A) Were any inventions, which may be patentable or otherwise protectable under Title 35 of the United States Code, conceived or first actually reduced to practice in the performance of work under this health research grant? Yes_____ No____X

If "Yes" to 23(A), complete items a – g below for each invention. (Do NOT complete items a - g if 23(A) is "No.")

a. Title of Invention:

b. Name of Inventor(s):

c. Technical Description of Invention (describe nature, purpose, operation and physical, chemical, biological or electrical characteristics of the invention):

d. Was a patent filed for the invention conceived or first actually reduced to practice in the performance of work under this health research grant?
Yes_____ No____

If yes, indicate date patent was filed:

e. Was a patent issued for the invention conceived or first actually reduced to practice in the performance of work under this health research grant?
Yes_____ No____
If yes, indicate number of patent, title and date issued:
Patent number:
Title of patent:
Date issued:

f. Were any licenses granted for the patent obtained as a result of work performed under this health research grant? Yes_____ No____

If yes, how many licenses were granted?_____

g. Were any commercial development activities taken to develop the invention into a commercial product or service for manufacture or sale? Yes___ No____

If yes, describe the commercial development activities:

23(B) Based on the results of this project, are you planning to file for any licenses or patents, or undertake any commercial development opportunities in the future?

Yes_____ No____X_____

If yes, please describe your plans:

24. Key Investigator Qualifications. Briefly describe the education, research interests and experience and professional commitments of the Principal Investigator and all other key investigators. In place of narrative you may insert the NIH biosketch form here; however, please limit each biosketch to 1-2 pages.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Uemura, Tadahiro	Assistant Professor of Surgery
eRA COMMONS USER NAME Uemura	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
Okayama University Medical School	M.D.	03/94	Medicine
Okayama University Medical School	Ph.D.	03/00	Medicine/Surgery

A. Personal Statement

Liver regeneration is a fascinating phenomenon, and I have been interested in the mechanism since my first experience with liver resection. I studied the mechanism of liver regeneration and atrophy in rodent models for my Ph.D. project. I continued my research career under Dr. Chandrashekhar R. Gandhi at the Thomas E. Starzl Transplantation Institute in Pittsburgh. This experience led me to establish myself as an academic surgeon. I completed Transplant Fellowship at University of Miami and at Baylor University Medical Center in Dallas, Texas. I currently work as a liver, kidney and pancreas transplant surgeon at Penn State University. I am also interested in liver ischemia/reperfusion injury and liver preservation. My goal is to transfer new findings in bench research to patient bedside.

B. Positions and Honors

Positions and Employment

1994- 1994 Junior Resident, Surgery, Okayama University Hospital, Japan
1994- 1996 Junior Resident, Surgery, Himeji Saint Mary's Hospital, Hospital, Japan
1996- 1998 Senior Resident, Surgery, Okayama University Hospital, Japan
1998- 1999 Research Fellow, Thomas E. Starzl Transplantation Institute, Pittsburgh, PA
1999- 2000 Research Associate, Thomas E. Starzl Transplantation Institute, Pittsburgh, PA
2001- 2003 Clinical Fellow, National Shikoku Cancer Center, Japan
2003- 2004 Transplant Fellow, University of Miami, Miami, FL
2004- 2006 Transplant Fellow, Baylor University Medical Center, Dallas, TX
2006- 2011 Assistant Professor of Surgery, Penn State College of Medicine, Hershey, PA
2010- Surgical Director of Pancreas Transplantation, Penn State College of Medicine, Hershey, PA
2011- Associate Professor of Surgery, Penn State College of Medicine, Hershey, PA
2013 Assistant Professor of Surgery, Kyoto University, Kyoto, Japan

Other Experience and Professional Memberships

1994- Member, Japanese Society of Surgery
1994- Member, Japanese Society of Gastroenterological Surgery
1997- 1998 Research Fellow, Department of Cell Biology, Japan
2000- 2000 Visiting Clinical Fellow, Thomas E. Starzl Transplantation Institute, Pittsburgh, PA
2003- 2003 Visiting Clinical Fellow, Kyoto University, Japan

2006- 2006 Visiting Clinical Fellow, Kyoto University, Japan
2005- Member, American Society of Transplant Surgeons
2005- Member, International Liver Transplantation Society

Honors

1994- 1998 Japan Ikueikai Scholarship
2003 Japan-North America Medical Exchange Foundation Scholarship
2007 American Society of Transplant Surgeon (ASTS) Vanguard Prize

C. Selected Peer-reviewed Publications

The most relevant publication

1. Matsumoto H, Hirai R, **Uemura T**, Ota T, Urakami A, Shimizu N. Experimental evaluation of the effects of the intraportal administration of cyclic guanosine monophosphate on ischemia/reperfusion in the porcine liver. *Surg Today*. 1999;29:1158-1163.
2. **Uemura T**, Miyazaki M, Hirai R, Matsumoto H, Ota T, Ohashi R, Shimizu N, Tsuji T, Inoue Y, Namba M. Different expression of positive and negative regulators of hepatocyte growth in growing and shrinking hepatic lobes after portal vein branch ligation in rats. *Int J Mol Med*. 2000;5:173-179.
3. Gandhi CR, **Uemura T**, Kuddus RH. Endotoxin cause up-regulation of endothelin receptors in cultures hepatic stellate cells via nitric oxide-dependent and –independent mechanism. *Br J Pharmacol*. 2000;131:319-327.
4. Gandhi CR, Kuddus R, **Uemura T**, Rao AS. Endothelin stimulates transforming growth factor-□1 and collagen synthesis in stellate cells from control but not cirrhotic rat liver. *Eur J Pharmacol*. 2000;406:311-318.
5. **Uemura T**, Gandhi CR. The inhibition of DNA synthesis in cultured hepatocytes by endotoxin-conditioned medium of activated stellate cells is nitric oxide-independent. *Br J Pharmacol*. 2001;133:1125-1133.
6. Hato S, Urakami A, Yamano T, **Uemura T**, Ota T, Hirai R, Shimizu N. Attenuation of liver and lung injury after hepatic ischemia and reperfusion by a cytokine-suppressive agent, fr167653. *Eur Surg Res*. 2001;33:202-209.
7. Yamano T, Hirai R, Hato S, **Uemura T**, Shimizu N. Delayed liver regeneration and negative regulation of HGF and TGF-β_1 mRNA after portal branch ligation in cholestatic rat. *Surgery*. 2002;131:163-171.
8. Gandhi CR, Murase N, Subbotin VM, **Uemura T**, Nalesnik M, Demetris AJ, Fung JJ, Starzl TE. Portacaval shunt causes apoptosis and liver atrophy despite increase in endogeneous levels of major hepatic growth factors. *J Hepatol*. 2002;37:340-348.
9. Thirunavukkarasu C, **Uemura T**, Wang, L, Watkins S, Gandhi CR. Normal rat hepatic stellate cells respond to endotoxin in LBP-independent manner to produce inhibitor(s) of DNA synthesis in hepatocytes. *J Cell Physiol*. Aug 2005;204(2):654-665. *(Thirunavukkarasu C and Uemura T contributed equally.)*
10. **Uemura T**, Randall HB, Sanchez EQ, Ikegami T, Narasimhan G, McKenna GJ, Chinnakotla S, Levy MF, Goldstein RM, Klintmalm GB. Liver retransplantation for primary nonfunction: analysis of a 20-year single-center experience. *Liver Transplant*. 2007;13:227-233.
11. Bezinover D, Kadry Z, McCullough P, McQuillan PM, **Uemura T**, Welker K, Mastro AM, Janicki P. Release of cytokines and hemodynamic instability during reperfusion of liver graft. *Liver Transpl*. 2011;17(3):324-30.
12. ***Uemura T**, Schaefer E, Hollenbeak CS, Khan A, Kadry Z. Outcome of induction immunosuppression for liver transplantation comparing anti-thymocyte globulin, daclizumab and corticosteroid. *Transpl Int*. 2011;24(7):640-50.

13. Bezinover D, Ramamoorthy S, **Uemura T**, Kadry Z, McQuillan PM, Mets B, Falcucci O, Rannels S, Ruiz-Velasco V, Spiess B Liang J, Mani H, Lou X, Janicki PK. Use of third-generation perfluorcarbon for preservation of DCD rat liver grafts. *J Surg Res*. 2012 Jun 1;175(1):131-7. Epub 2011 Apr 9.
14. ***Uemura T**, Nikkel L, Hollenbeak C, Ramprasad V, Schaefer E, Kadry Z. How can we utilize livers from advanced aged donors for liver transplantation for hepatitis C? *Transpl Int*. 2012 Jun;25(6):671-9. Epub 2012 Apr 6.
*indicates corresponding author