SUMMARY STATEMENT

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(Privileged Communication) ***Release Date:*** **03/12/2014**

Application Number: **1 R21 DK103205-01**

Principal Investigator

CHAUDHURY, ARUN

Applicant Organization: HARVARD UNIVERSITY (MEDICAL SCHOOL)

Review Group: **HBPP**
Hepatobiliary Pathophysiology Study Section

Meeting Date: **02/10/2014**
Council: **MAY 2014**
Requested Start: **07/01/2014**

RFA/PA: **PA12-139**
PCC: **NAS LITA**

Project Title: **Biliary pathophysiology and prevention by "Somah" during liver preservation**

SRG Action: **++**
Next Steps: **Visit http://grants.nih.gov/grants/next_steps.htm**
Human Subjects: **10-No human subjects involved**
Animal Subjects: **30-Vertebrate animals involved - no SRG concerns noted**

Project Year	Direct Costs Requested
1	150,000
2	125,000
TOTAL	275,000

++NOTE TO APPLICANT: Members of the Scientific Review Group (SRG) were asked to identify those applications with the highest scientific merit, generally the top half. Written comments, criterion scores, and preliminary impact scores were submitted by the assigned reviewers prior to the SRG meeting. At the meeting, the more meritorious applications were discussed and given final impact scores; by concurrence of the full SRG, the remaining applications, including this application, were not discussed or scored. The reviewers' comments (largely unedited by NIH staff) and criterion scores for this application are provided below. Because applications deemed by the SRG to have the highest scientific merit generally are considered for funding first, it is highly unlikely that an application with an ND recommendation will be funded. Each applicant should read the written critiques carefully and, if there are questions about the review or future options for the project, discuss them with the Program Contact listed above.

1R21DK103205-01 Chaudhury, ARUN

DESCRIPTION (provided by applicant): Liver transplantation is the only definite therapy for both acute and chronic liver failure. However, graft dysfunction occurs due to non-physiological states during storage. A major feature of post-transplant complication is related to biliary dysfunction, including intraluminal biliary casts and non-anastomotic biliary stricture. Traditionally, livers are stored in University of Wisconsin (UW) solution. An improvised organ storage solution, "Somah", with rationally designed components to maintain perfusion and high energy phosphates have been recently demonstrated to provide superior status of storage of solid organs like heart in vitro. Preliminary data demonstrated biliary ductular reactive changes and mucosal injury in porcine DCD (donation after cardiac death) livers cold-stored in UW solution as early as 6 hrs. However, these histopathological changes could not be visualized in livers cold-stored in Somah for even 72 hrs. We hypothesize that the ability of Somah to restore intracellular ATP levels in vitro is the basis for preservation of cholangiocyte integrity during preservation. The current proposal aims to examine the pathophysiological basis for biliary dysfunction of livers stored in vitro and explore rational basis for biologically preconditioning storage solutions to prevent cholangiocyte cellular injury. In biliary epithelial cells, the solute carrier protein, SLC17A9-positive vesicles, store and secrete ATP in bile. ATP in bile stimulates chloride and water secretion and decreases bile viscosity and facilitates bile flow. We hypothesize that when biliary ATP is deficient, bile stasis may damage to mucosa of cholangiocytes. In vitro storage of livers in ischemic conditions has also been reported to damage actin within cholangiocytes. We plan to examine whether cytoskeletal injury disrupts SLC17A9 vesicular trafficking. We hypothesize that restoration of intracellular high energy phosphates by the novel organ storage solution, "Somah", prevents biliary damage by supplying the substrate ATP for effective actomyosin action (myosin II is an ATPase) and vesicular content, i.e., ATP, of SLC17A9 micropinosomes (SLC17A9 is a VNUT, a vesicular nucleotide transporter). The specific aims aimed to test our hypotheses are: (a) Aim 1# To examine whether extracellular ATP secretion is impaired and SLC17A9 containing vesicles is decreased in biliary epithelium during in vitro liver storage and (b) Specific Aim 2# To examine whether non-muscle myosin II (NMMII) isoforms are diminished in biliary epithelium during in vitro liver storage Anticipated outcome is that livers stored in Somah will have intact functional SLC17A9 positive vesicles that can traffic to cholangiocyte membrane post-stimulation for release of contents.

PUBLIC HEALTH RELEVANCE: Liver transplantation is a life-saving surgery for numerous conditions in which the liver, the body's main organ for detoxification, fails to function. However, a major obstacle is availability of high quality organs, as there is lack of rationally designed storage solutions which may provide physiologic protection in vitro. Here we show the efficacy of a novel solution Somah ("elixir of life", in Sanskrit), in protection of liver structure and function for 3 days ex vivo, which will facilitate storage for a long period of time and organ transfer between geographically separated sites.

CRITIQUE 1:

Significance: 4
Investigator(s): 5
Innovation: 4
Approach: 6
Environment: 3

Overall Impact: The current R21 proposal from a junior neurobiologist aims to examine the pathophysiological basis for biliary dysfunction of livers stored in vitro and explore a rational basis for biologically preconditioning storage solutions to prevent cholangiocyte cellular injury. The objective is to identify the mechanisms of cellular changes related to the damage of intrahepatic biliary ductules that occurs during the in vitro storage of the liver. The proposed studies aim to evaluate the pathophysiological basis for biliary dysfunction of livers stored in vitro and to explore the basis for

biologically preconditioning storage solutions to prevent biliary cellular injury. The rationale for the proposed studies is based on the fact that in cholangiocytes, the solute carrier protein, SLC17A9-positive vesicles, store and secrete ATP in bile. ATP in bile stimulates chloride and water secretion and decreases bile viscosity and facilitates bile flow of small ductules. The PI hypothesizes that when biliary ATP is deficient, bile stasis may damage the mucosa of cholangiocytes. The PI plans to examine whether cytoskeletal injury disrupts SLC17A9 vesicular trafficking. They hypothesize that restoration of intracellular high energy phosphates by the organ storage solution, “Somah”, prevents biliary damage by supplying the substrate ATP for effective actomyosin action (myosin II is an ATPase) and vesicular content, i.e., ATP, of SLC17A9 micropinosomes (SLC17A9 is a VNUT, a vesicular nucleotide transporter). The PI proposes that in the livers stored in Somah there are intact functional SLC17A9 positive vesicles that can traffic to cholangiocyte membrane post-stimulation for release of contents. Potentially, the proposal may have clinical relevance since it is important to develop new tools to prevent biliary damage during in vitro storage of the liver before transplantation. However, this R21 grant proposal has been submitted by a PI and his assembled team of scientists who do not have enough experience in liver pathophysiology. The impact of the proposed studies is decreased by the fact the PI does not extend the experimental approach of the proposed studies, and does not propose mechanistic studies aimed to demonstrate how “somah” prevents the loss of ATP secretion and the expression of non-muscle myosin II (NMMII) isoforms in bile ductules during in vitro liver storage. Furthermore, the proposal is rather descriptive. The scope of the experimental approach is very limited. Also, it is unclear why the PI uses secretin and somatostatin (know modulators of cAMP but not calcium) as modulators of ATP, since ATP is regulated by calcium but not cAMP. Purinergic receptor agonists or other agonists stimulating calcium and ATP should be used to modulate ATP secretion and to prevent/retard the functional damage of bile ductules. Overall, the confidence for the completion of the proposed studies is low.

1. Significance:

Strengths

- Liver transplantation is a life-saving surgery for numerous conditions in which the liver, the body’s main organ for detoxification, fails to function. However, a major obstacle is availability of high quality organs, as there is a lack of rationally designed storage solutions, which may provide physiologic protection in vitro. The current proposal aims to identify the cellular mechanisms related to the damage of intrahepatic biliary ductules that occurs during the in vitro storage of the liver. It is being increasingly recognized that bile ductular damage is one of major reasons for delayed dysfunction after orthotopic liver transplantation.
- The proposal has translational significance since it is important to understand how to prevent biliary damage during in vitro storage of livers before transplantation. The proposed studies could potentially result in a paradigm shift in harvesting and storing DCD (donation after cardiac death) livers.
- The proposal could potentially address the critical issues of shortage of organ supply and provide high quality livers for transplantation. The PI proposes that ATP is a major determinant for the maintenance and preservation of liver in vitro. Thus, modulation of ATP in the damaged bile ductules may be a key component for a better preservation of biliary function.

Weaknesses

- Numerous weaknesses decrease the significance of the proposed studies. For example, the PI does not extend the experimental approach of the proposed studies much beyond the preliminary data and does not propose mechanistic studies of how “somah” prevents the loss of ATP secretion and the expression of non-muscle myosin II (NMMII) isoforms in bile ductules during in vitro liver storage.

- It is unclear why they use secretin and somatostatin (known modulators of cAMP and not calcium) as modulators of ATP since ATP is regulated by calcium and not cAMP. Purinergic receptor agonists or other agonists stimulating calcium and ATP should be used (rather than secretin and somatostatin) to modulate ATP secretion and to prevent/retard the functional damage of bile ductules.
- It is very difficult to assess the impact and significance of the proposal due to the cardiac specificity of the organ storage solution, “Somah” because of the functional difference between heart and liver. Furthermore, the significance of each specific aim is disconnected based on the provided information.

2. Investigator(s):

Strengths

- Dr. Chaudhury is a member of The Harvard Clinical and Translational Science Center (Harvard CATALYST) and Instructor, Department of Surgery, Brigham and Women’s Hospital. The PI has been productive and has the experience with the proposed tools.
- Dr. Hemant Thatte, M.D., Co-Investigator, will supervise all aspects of the study and provide consultation as needed at any level. He is the PI of one VA Merit Review Award and one DOD grant. Dr. Thatte has a joint appointment with Harvard Medical School and the VA Boston Healthcare System.

Weaknesses

- The PI has the technical experience to accomplish the proposed studies but he has very limited experience in biliary/liver pathophysiology. Similarly, the other investigators are also inexperienced in liver pathology. A scientist with expertise in biliary disorders is needed.
- A publication record in liver pathophysiology is absent. This raises serious concerns regarding the feasibility of the proposed studies.

3. Innovation:

Strengths

- It has been demonstrated that a newly formulated organ storage solution, “Somah”, counterbalanced many of the impairing factors encountered by porcine and rat solid organs like hearts and kidneys during prolonged cold static storage and at higher temperatures.
- Somah provided cell protection by maintenance of high-energy phosphate levels, and preserved structure and function of cardiac myocytes and endothelium in hearts and kidneys obtained from BHD and DCD donors during short-term hypothermic storage as well as long-term storage.
- The concept that “somah” may exert protective effects on bile ductules during in vitro preservation of the liver is innovative.

Weaknesses

- The innovation is dampened somewhat by the fact that the foundation for the proposed studies is the heart, and a critical link between “somah” and liver storage, instead of heart storage, is not well developed.
- The translational significance is not obvious in the current proposal since only animal studies instead of human-based studies were proposed.

- Concerns exist regarding the experimental approach that is limited and does not go much beyond the interesting feasibility studies on how somah prevents the loss of ATP and biliary damage.
- Innovation is dampened by the use of secretin and somatostatin as agents (rather for example purinergic receptor agonists) to modulate ATP. Indeed, secretin and somatostatin exert their functions on biliary secretion through cAMP and not calcium/ATP-dependent signaling.

4. Approach:

Strengths

- In aim 1, the reduction in ATP transporter SLC17A9 or its function may be the fundamental pathology that contributes to diminished extracellular release of ATP in the bile and the cyclical biochemical events that follow to cause biliary stasis and structural damage to bile ductules.
- Cholangiocyte SLC17A9 pump failure will likely be demonstrable in livers stored ex vivo in UWS but may not occur in tissues stored in Somah.
- In aim 2, preconditioning storage media using recently available pharmacologic activators of myosin II like omecamtiv mecarbil may contribute to prevention of biliary epithelial damage during in vitro storage of livers.
- An anticipated outcome is that livers stored in Somah will have intact functional SLC17A9 positive vesicles that can traffic to cholangiocyte membrane post-stimulation for release of contents.
- Good preliminary data regarding the protective effect of “somah” on the damage of heart.
- The concept that “somah” may exert protective effects on bile ductules during in vitro preservation of the liver is good.

Weaknesses

- Overall limited experimental approach and very descriptive study. More detailed information about the proposed experiments and their outcomes should be provided.
- The potential link between protective effects on bile ductules and liver function during in vitro preservation of the liver should be established.
- Because of the functional difference between heart and liver, the application of somah in liver storage may have other side effects such as the induction of metabolic dysfunction.
- In aim 1, it is unclear why they use secretin and somatostatin (know modulators of cAMP and not calcium) as modulators of ATP since ATP is regulated by calcium and not cAMP. Other agonists such as purinergic receptor agonists or agonists stimulating calcium and ATP should be proposed rather than secretin that does not affect ATP.
- In aim 2, the PI does not extend the experimental approach of the proposed studies much beyond the preliminary data and does not propose mechanistic studies how “somah” prevents the loss of ATP secretion and the expression of non-muscle myosin II (NMMII) isoforms in bile ductules during in vitro liver storage.
- Both aims may be more important for heart storage instead of liver storage. The function of non-muscle myosin II is more important in heart than the liver. The biliary specific signaling pathways such as cAMP/calcium dependent mechanisms should be investigated.
- It is not readily apparent that the knowledge generated from the project will provide novel therapeutic strategies for human liver storage.

5. Environment:

Strengths

- Dedicated lab space for the work will be provided by the co-I, Dr. Hemant Thatte.
- Laboratory and office space including computers are available for conducting the experiments and analyses.
- In addition, dedicated animal facilities are available for maintaining animals proposed for the experiments.
- The scientific environment is appropriate. All of the equipment and physical resources available to the investigators are adequate for the proposed project.

Weaknesses

- The hepatobiliary research environment at the Harvard Clinical and Translational Science Center (Harvard CATALYST) is potentially not as strong as expected, since not much teamwork in the liver/biliary project was apparent.

Vertebrate Animals:

Acceptable

- No vertebrate animal concerns.

Budget and Period of Support:

Recommend as Requested

CRITIQUE 2:

Significance: 2
Investigator(s): 5
Innovation: 2
Approach: 4
Environment: 3

Overall Impact: This is an R21 application from a new investigator to examine the mechanisms by which an organ preservation solution, Somah, prevents biliary tract damage during organ preservation. The proposal addresses a topic of very high significance, and the concepts to be examined are novel. However, the proposed studies and the environment are poorly described, and the experience of the PI is limited. The proposal may have benefitted from inclusion of individuals with the relevant expertise that would have been able to provide scientific guidance and in proposal writing. Nevertheless, there is a moderate level of enthusiasm for studies in this area given their high significance.

1. Significance:

Strengths

- The availability of organs is a limiting factor for liver transplantation. The use of marginal organs may be improved by reducing biliary tract damage arising from ischemia during organ storage.

Understanding the mechanisms by which a novel organ preservation solution, somah, functions to preserve biliary integrity is of importance. Thus, the significance of these studies is very high.

Weaknesses

- None noted.

2. Investigator(s):

Strengths

- The PI is a Research Fellow and Instructor in surgery at Harvard Medical School. His previous experience as a post-doctoral fellow has been in neuronal cell biology and neurotransmission.
- Dr. Hemant Thatte is an Associate Professor of Surgery at Harvard Medical School who has been a pioneer and involved in development of organ storage solutions and the invention of the Somah solution for cardiac donor organs. He has VA Merit funding to study this solution in heart donor organs, and industry funding to explore its use in other solid organs. He will provide supervision for the studies.
- Haiyan Cao and Xiu-Gui Lu are both Instructors in surgery with expertise in gene transfer and cell biology who will assist with the studies as needed.

Weaknesses

- The PI has very limited prior experience, and no publications in the field of organ preservation solutions, or biliary tract pathobiology. Although a senior investigator, Dr. Thatte has experience in the former, much of the focus has been in the area of cardiac donor organ preservation.

3. Innovation:

Strengths

- The concept that organ storage in Somah will preserve functional SLC17A9 positive vesicles and their trafficking to cholangiocyte membranes post-stimulation is novel.

Weaknesses

- None noted.

4. Approach:

Strengths

- This is a proposal to examine the ability of an organ storage solution, somah, to preserve cholangiocyte integrity during organ preservation. The hypothesis is that loss of biliary ATP results in cholangiocyte mucosal damage due to bile stasis, and that restoration of phosphates by Somah enables actomyosin action, and vesicular ATP within micropinosomes.
- Aim 1 will examine whether extracellular ATP secretion is impaired and the vesicular nucleotide transporter SLC17A9 containing vesicles are decreased in biliary epithelium during in vitro storage. Aim 2 will examine whether non-muscle myosin II isoforms are reduced in biliary epithelium during in vitro liver storage.

Weaknesses

- The proposal is difficult to read and follow, with some information presented in a disjointed manner.
- The aims have been poorly developed, and the rationale could be more cohesively explained.

5. Environment:

Strengths

- Harvard Medical School is a well-respected institution.

Weaknesses

- The resources should have been described in greater detail to allow for a determination of their appropriateness and adequacy for the proposal. Without this, the environment cannot be adequately assessed.
- Laboratory space will be provided by Dr. Thatte, but the space that will be provided is not described and a letter from Dr. Thatte to verify this should be provided.

Vertebrate Animals:

Acceptable

- Adequately addressed.

Budget and Period of Support:

Recommend as Requested

CRITIQUE 3:

Significance: 4
Investigator(s): 5
Innovation: 5
Approach: 8
Environment: 2

Overall Impact: This proposal explores the pathophysiologic basis for the observation that the Somah solution for organ preservation is superior to the standard UW solution with respect to biliary epithelial cell integrity. The investigators propose that high energy phosphates in the Somah solution allow biliary ATP levels to be maintained through salutary effects on SLC17A9 microvesicular function/ exocytosis which may be linked to preserved non-muscle myosin II function. The clinical implications of adaptation of the Somah solution are significant. Nevertheless, the data from this project is unlikely to have a bearing on whether this solution will find a role in clinical practice. The strengths of the proposal include the clinical significance of the field; the experience of the investigators with respect to the Somah solution and organ transplantation; and the environment. The Somah solution is innovative as an organ preservation solution, and the concept of expanding the scope of its use from hearts to livers is a logical progression. Weaknesses include the prosaic nature of the approach which is descriptive rather than mechanistic; a weak justification for using two different animal models; lack of prior experience of the investigators in biliary epithelial cell biology; and the lack of expertise with respect to hepatobiliary pathology. The proposal is deemed to have a low impact.

1. Significance:

Strengths

- Expanding the donor pool of livers for transplantation would have a significant impact on liver disease treatment. The Somah solution proposed by the investigators shows promise as an alternative to solutions currently in use.

Weaknesses

- Mechanistic insights into why Somah is superior to UW solution, while intellectually appealing, may not matter from a clinical standpoint as much as its clinical efficacy. Therefore, clinically relevant data such transplant outcomes will be a stronger determinant of significance.

2. Investigator(s):

Strengths

- Dr. Thatte, the Co-investigator, is an inventor of the Somah solution which has been studied for preservation of hearts intended for transplantation. He possesses several patents for tissue preservation solutions.

Weaknesses

- The PI has no published experience in the field of cholangiocyte biology or liver preservation. The proposal encompasses a new area of investigation without a clear connection to his expertise in the field of neurobiology of the GI system.
- The collaborator, Dr. Thatte, is a cell biologist and biochemist with expertise relating to cardiothoracic surgery. There is no prior published experience with hepatobiliary pathophysiology.
- There is a lack of expertise among the investigators with respect to hepatobiliary pathology. Analysis of liver pathology would benefit from the expertise of a hepatobiliary pathologist.

3. Innovation:

Strengths

- The Somah solution is innovative as an organ preservation solution, and the concept of expanding the scope of its use from hearts to livers is a logical progression.

Weaknesses

- There is little conceptual or technical innovation in the proposal.

4. Approach:

Strengths

- Experimental techniques are within the expertise of the investigators.
- Investigators have expertise in ex vivo organ perfusion with livers and small animal surgery.

Weaknesses

- The justification for using both pigs and rats for the proposed experiments is weak.
- The methodologies described to test the hypotheses will yield data that is descriptive. The proposed experiments do not promise to yield significant novel mechanistic insights into biliary epithelial cell biology.

5. Environment:

Strengths

- Facilities and resources are adequate for the proposed studies.

Weaknesses

- None noted.

Vertebrate Animals:

Acceptable

- No concerns noted.

Biohazards:

Acceptable

- No concerns noted.

Budget and Period of Support:

Recommended budget modifications or possible overlap identified:

- The budget should be adjusted if the animal model experiments are reduced as suggested in this critique.

MEETING ROSTER

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Digestive, Kidney and Urological Systems Integrated Review Group
CENTER FOR SCIENTIFIC REVIEW
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February 10, 2014 - February 11, 2014

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* Temporary Member. For grant applications, temporary members may participate in the entire meeting or may review only selected applications as needed.

Consultants are required to absent themselves from the room during the review of any application if their presence would constitute or appear to constitute a conflict of interest.