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# Grants Working Group Public Review Summary

## Human Liver Regeneration Using Adipocyte Stem Cells

| Application Number: LSP1-08292 #2 | Review Date: July 28, 2015 |
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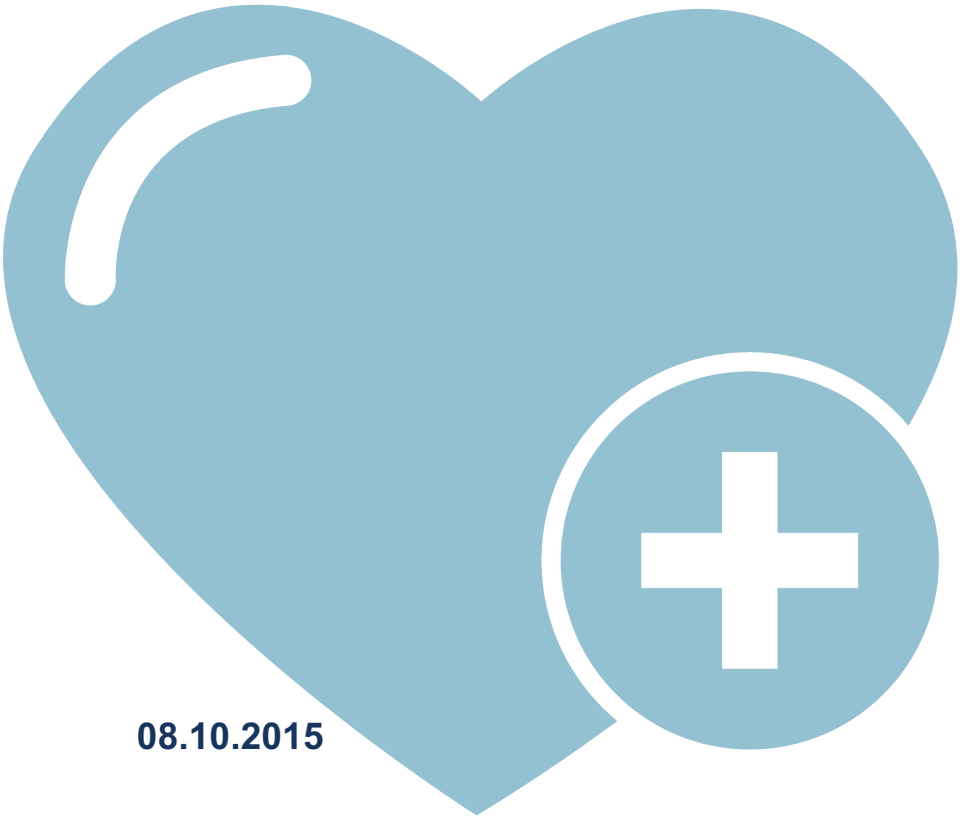
15-01: Late Stage Preclinical Project Proposal



**08.10.2015**

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# Human Liver Regeneration Using Adipocyte Stem Cells

**APPLICATION NUMBER: LSP1-08292 #2**

**REVIEW DATE: July 28, 2015**

**PROGRAM ANNOUNCEMENT: Late Stage Preclinical Projects (15-01)**

## Therapeutic Candidate

Stem cells present in fat, converted into hepatocytes

## Indication

Alcohol-Induced Liver Failure

## Unmet Medical Need

Liver transplantation is now the only treatment for severe liver injury or end stage liver disease but its utility is severely limited by the lack of donor organs. This project will develop a procedure for liver regeneration using stem cells present in fat.

## Major Proposed Activities

Develop method for monitoring the function of transplanted hepatocytes in human subjects.

Demonstrate the efficacy and safety of induced hepatocytes for liver regeneration.

Implement a method compatible with FDA guidelines for production of induced hepatocytes from stem cells present in fat.

## Funds Requested

$2,990,293 ($0 Co-funding)

## Recommendation

Score: 3

Votes for Score 1 = 0 GWG members

Votes for Score 2 = 0 GWG members

Votes for Score 3 = 13 GWG members

- A score of “1” means that the application has exceptional merit and warrants funding;
- A score of “2” means that the application needs improvement and does not warrant funding at this time but could be resubmitted to address areas for improvement;
- A score of “3” means that the application is sufficiently flawed that it does not warrant funding, and the same project should not be resubmitted for review.

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## Review Overview

Reviewers thought it premature to move this candidate toward clinical testing given the lack of data demonstrating that functional and engraftable hepatocytes can be generated using the described manufacturing process. Furthermore reviewers thought the patient population proposed for the first-in-human (FIH) clinical trial to be inappropriate, and the trial unlikely to be informative as designed. Reviewers strongly recommend that the applicant focus their work on demonstration of hepatocyte identity and then work closely with regulatory and clinical advisors to generate data supporting late stage preclinical development.

## Review Summary

**Does the project hold the necessary significance and potential for impact?**

**a) Consider whether the proposed therapy fulfills an unmet medical need.**

- Acute liver failure represents a large unmet medical need for which the only available treatment is liver transplantation. Given the shortage of available livers development of a readily available source of hepatocytes for transplantation would be valuable.
- The intended Phase I trial targets patients with acute alcohol-induced liver failure without pre-existing cirrhosis, a small and heterogeneous patient population whose frequency is overestimated by the investigator.
- The proposed therapy may be better utilized in a different patient population than the one proposed for the clinical study.

**b) Consider whether the approach is likely to provide an improvement over the standard of care for the intended patient population.**

- There is little evidence provided that transplantation of the proposed cell product will improve standard of care in patients with acute liver failure.

**c) Consider whether the proposed therapeutic offers a sufficient, impactful, and practical value proposition for patients and/or health care providers.**

- The value proposition for the therapeutic is dependent upon the production of an adequate quantity of hepatocytes that both engraft and provide meaningful support of liver function. There is little evidence that the proposed cell product can do either.

**Is the rationale sound?**

**a) Consider whether the proposed project is based on a sound scientific and/or clinical rationale, and whether it is supported by the body of available data.**

- The applicant does not provide convincing data that the proposed manufacturing process results in the production of bona fide hepatocytes that provide the necessary secretory and metabolic function to support a patient in acute liver failure.
- Primary hepatocytes have demonstrated promise in early stage trials, providing a clinical rationale for a cell replacement approach in liver disease. However, the applicant does not provide sufficient data demonstrating that the proposed cell product is comparable to primary hepatocytes and instead seems to assume this will be true.



- Even for primary hepatocytes achieving adequate engraftment is a bottleneck to clinical success, particularly in the inflammatory environment of alcohol poisoning. Reviewers were unconvinced that the engraftment challenge has been solved for the candidate therapeutic, especially since, despite claims to the contrary, the proposed clinical method of injection via the portal vein was not used in the preclinical setting.
- The provided efficacy data is not convincing as the selected preclinical models do not mimic the condition of the proposed FIH patient population.
- The proposed product is not pure and other cells in the product have not been characterized despite an FDA request to do so.
- Supporting publications are in low impact journals.

**b) Consider whether the data supports the continued development of the therapeutic candidate at this stage.**

- The project is premature for this stage of funding and much of the proposed activities should have been completed prior to applying for the Late Stage Preclinical Project Program Announcement.
- Until there is convincing data that engraftable and functional hepatocytes can be generated under this protocol it is difficult to justify moving the candidate toward testing in humans. Reviewers recommended the applicant continue working towards generating such data.

**Is the project well planned and designed?**

**a) Consider whether the project is appropriately planned and designed to meet the objective of the program announcement and achieves meaningful outcomes to support further development of the therapeutic candidate.**

- The proposed preclinical studies are unlikely to inform the proposed trial as the highly permissive preclinical model does not reflect the inflammatory environment and engraftment challenges of the targeted FIH disease state and do not address the potential impact of allogeneic rejection of the large number of the transplanted cells.
- The studies as designed are unlikely to provide convincing data that functional hepatocytes have been generated by the applicant team.
- There were several concerns regarding the patient population proposed for the clinical trial. The population described by the inclusion criteria may be too rare to reasonably recruit, are vulnerable to infections, and could be harmed by the proposed immunosuppression. They may also have additional challenges that render follow up difficult after discharge (as proposed by the applicant). For these reasons, reviewers doubted the trial would be informative.
- The novel assay proposed to track in vivo engraftment remains to be developed and it's unclear whether it has been discussed with the FDA.
- Assumptions in the application regarding function and required dosing of the cell product are not based upon data with the proposed therapeutic and are therefore insufficient and unlikely to be predictive.

**b) Consider whether this is a well-constructed, quality program.**

- The program is not of appropriate quality to support clinical testing as the project plan is not sufficient to demonstrate that the candidate therapeutic has potential to provide liver function necessary to rescue a patient in liver failure.

**c) Consider whether the project plan and timeline demonstrate an urgency**

**that is commensurate with CIRM's mission.**

- The timeline does demonstrate an urgency, but the proposed project plan is unlikely to lead to an outcome that impacts CIRM's mission.

**Is the project feasible?**

**a) Consider whether the intended objectives are likely to be achieved within the proposed timeline.**

- The applicant can likely complete the proposed studies in the proposed timeframe, and the work is technically feasible.
- Given the scope of work still necessary to convincingly support the hypothesis that these cells can rescue liver failure, the ongoing process development, the immature state of the GMP manufacturing plan, and the need for additional work in relevant preclinical models to select an appropriate first-in-human indication, filing of an approvable IND in two years seems unlikely.

**b) Consider whether the proposed team is appropriately qualified and staffed and whether the team has access to all the necessary resources to conduct the proposed activities.**

- The bulk of the experience of the Principal Investigator (PI) does not appear to be focused upon liver disease and the team does not have sufficient expertise in liver transplantation.
- The time committed by the assembled team, predominantly consisting of consultants and research associates, appears small for the body of work proposed.
- The regulatory correspondence suggests a lack of familiarity with regulatory terminology, the requirements of an IND, and the extent to which FDA advises sponsors.
- The proposed GMP facility and quality infrastructure at the host institution is not well described and does not appear to be fully functional. Delayed access to such a facility represents a significant barrier to success. Furthermore, the application lacks a budget for use of the GMP facility, a significant oversight.

**c) Consider whether the team has a viable contingency plan to manage risks and delays.**

- Contingency plans are poorly described in the application, and potential delays are not addressed.
- Reviewers found the proposed second model of liver failure a poor solution to potential challenges in the first.

## CIRM Recommendation

The CIRM team met after the GWG to consider its recommendation to the Application Review Subcommittee. This section will be posted publicly.

**RECOMMENDATION:** Do Not Fund and Do Not Allow Reapplication (CIRM concurs with the GWG recommendation)