TR2-01857: Liver Cell Transplantation

Recommendation: Recommended for funding
Scientific Score: 66
First Year Funds Requested: $1,271,316
Total Funds Requested: $5,199,767
Public Abstract (provided by applicant)

Because there is still considerable morbidity and mortality associated with the process of whole liver transplantation, and because more than a thousand people die each year while on the liver transplantation list, and tens of thousands more never get on the list because of the lack of available livers, it is evident that improved and safer liver transplantation would be valuable, as would approaches that provide for an increased number of transplantations in a timely manner. A technology that might address these issues is the development of a human liver cell line that can be employed in liver cell transplantation or in a bioartificial liver. Developing such a cell line from human embryonic stem cells (hESC) would provide a valuable tool for pharmacology studies, as well as for use in cell-based therapeutics. The objective of this proposal is to focus a team effort to determine which differentiated hESC will be the most effective liver-like cells in cell culture and in animal studies, and to then use the best cells in clinical trials of cell transplantation in patients with advanced liver disease. In the proposed studies, the team will differentiate hESC so that they act like liver cells in culture. Once it has been established that the cells are acting like liver cells by producing normal human liver proteins, and that they do not result in tumors, the cells will be assessed in clinically-relevant models using techniques that can then be adapted to future human clinical trials. One of the ways cells can be evaluated is to label the cells which will provide a means to monitor them with various imaging systems. The intent in these studies is to determine which will be the most effective cells to use in human clinical trials. Once this is determined, the best cells can then be employed in human patients. If the studies are successfully undertaken, we will have established a clinically useful and viable liver cell line that could be used to repopulate an injured liver in a safer and less expensive manner than with whole liver transplantation. Moreover, all people who have liver failure or an inherited liver disease could be treated, because there would be an unlimited supply of liver cells.
Statement of Benefit to California (provided by applicant)

In California, as in all parts of the US, there are not enough livers available for transplantation for all the people who need them. The result is that many more people die of liver failure than is necessary. One way to improve this situation is the transplantation of liver cells rather than whole organ transplantation. We are attempting to develop liver cell lines from stem cells that will act like normal liver cells. If the cells that we develop function well and do not act like cancer cells in culture, the cells will be assessed in clinically-relevant models using techniques that can then be adapted to future human clinical trials. In our studies, we will compare

human embryonic stem cells with other stem cells to determine which will be the most effective cells to transplant into people. In the future, we will employ the best cells in clinical trials in humans. If the studies are successfully undertaken, we will have established a clinically useful and viable liver cell line that could be used to repopulate an injured liver in a safer and less expensive manner than with whole liver transplantation. Moreover, all people who have liver failure or an inherited liver disease could be treated, because there would be an unlimited supply of liver cells.

Review

This Development Candidate (DC) proposal seeks to develop human embryonic stem cell (hESC) derived hepatocytes, hEDH, as a therapy for liver failure. These cells would be indicated for patients suffering acute failure and patients who require such large resections as to leave inadequate residual liver tissue to permit survival until regeneration. The team proposes to establish differentiation methods that consistently generate high purity, metabolically active hEDH. The applicants will then employ genetic and sorting strategies to eliminate residual pluripotent cells and thereby minimize teratoma risk. The hEDH will then be tested for oncogenic potential in an immunocompromised model and engraftment in an immunocompetent preclinical in vivo model. An immunocompromised model of liver failure will be used to assess both efficacy and liver specific function. The applicants also plan to develop GMP master and working hESC cell banks.

Reviewers praised this project's focus and found its rationale well supported overall. However, they raised some serious questions regarding specific elements of the plan. Most notably, reviewers unanimously agreed that the rationale for utilizing the proposed relevant preclinical in vivo models was flawed and found them unnecessary to achieve the proposal's aims. They found the prenatal model irrelevant to the goals of the proposal and the immunocompetent model inadequately supported by convincing preliminary data. Further, the objective of these particular experiments was unclear, since go/no go success criteria and the project's further progress did not depend on results from this experimental series. The panel also noted that the applicant should define the hEDH engraftment level required for effective regenerative benefit in man. Reviewers were enthusiastic about the potential impact an unlimited supply of safe and metabolically functional human hepatocytes would make on severe life-threatening disease.

Reviewers found the preliminary data substantiating the applicant's ability to successfully differentiate hESCs into hepatocyte-like cells compelling. In particular, they appreciated the relative metabolic maturity of these cells and the plans to compare hEDH to primary human hepatocytes. Reviewers also supported the proposed use of a karyotyped hESC seed stock. However, elements of the plan led reviewers to question the feasibility of achieving a DC in three years. As proposed, this DC is both a xenotransplant and a gene therapy and therefore faces a very

complex regulatory path. The applicants did not address the extensive testing required to ensure safety of xenotransplant material. Reviewers were unconvinced of the necessity and efficacy of the proposed genetic approach to eliminate residual hESCs. They cautioned that a foreign protein could trigger an immune response and impose an additional regulatory burden. Further, reviewers felt the applicants should have addressed the limitations of methods for sorting cells at a scale needed for clinical application. They noted tumorigenicity studies would be most useful if performed with the final DC under GLP conditions, and, as such, this activity would be outside of the scope of this RFA. Finally, reviewers were concerned that the proposed models do not reflect the chronic fibrotic liver disease suffered by the vast majority of patients awaiting liver transplantation. Other than the above concerns, the applicant acknowledged potential pitfalls and provided alternative plans. Moreover, reviewers agreed that the remaining research milestones provided clear, and quantifiable endpoints to assess the project's progress. Taken together, reviewers remained supportive of the project's potential, but felt that the research group could not accomplish all the activities required to achieve a DC ready for IND enabling development within three years.

Reviewers agreed that the PI and key members of the research team are outstanding scientists and possess the expertise needed to successfully conduct the proposed studies. Moreover, they noted that the PI has a strong record of achievements supporting his/her qualifications to lead the proposed translational effort. Collaborations are appropriate, documented and critical to the project's success. Reviewers praised the administrative core, as well as the external scientific advisory board that will be implemented to facilitate communication and coordination among team members. Resources, facilities, and major equipment critical to the success of the project are available for conducting the proposed work, and there is a strong institutional support for translational research.

In summary reviewers supported the concept of hEDH for liver failure and identified many strengths in the proposal including the scientific rationale, preliminary data, and PI and research team. However, they felt the plan as proposed would not achieve a DC in three years.

PROGRAMMATIC REVIEW

A motion was made during Programmatic Review to move this application into Tier 1, Recommended for Funding, as a Development Candidate Feasibility (DCF) Award (instead of a DC Award) on the condition that the proposed relevant preclinical model studies, GMP cell banking and other elements not required for establishing the feasibility of the development candidate be excluded and the budget adjusted accordingly. Programmatic discussion clarified that the proposed therapy was indeed intended for acute liver failure and as a bridge to enable survival following very large resections. This allayed reviewers concerns about the lack of chronic liver disease models in the proposal as well as concerns regarding the use of chronic

immune suppression. Further, reviewers were unanimous that liver regeneration is a huge unmet medical need and that inclusion of this program would benefit CIRM's portfolio. The motion carried.

The following Working Group members had a conflict of interest with this application:

* Charles ffrench-Constant