

new
organ
LIVER PRIZE



NEW ORGAN LIVER PRIZE RULES

The Methuselah Foundation

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Section 1

EXECUTIVE SUMMARY

New Organ's goal is to advance the day when no one dies from lack of a healthy organ. Our initial prize, the New Organ Liver Prize, is the first step toward that goal. It's the first in what will be a series of challenges and awards to accelerate whole organ regeneration, engineering, and preservation.

The New Organ Liver Prize will award \$1,000,000 to the first registered team that creates a regenerative or bioengineering solution to replace the native liver of a large animal, enabling the host to recover in the absence of native liver function and survive 90 days with a normal lifestyle during the last month of the trial.

The New Organ management team aspires to define prizes for all of the solid organs. Due to the complexity of creating solutions to the other organs, at the present time, we have decided to limit this initial prize to solutions that replace the liver.

Section 2

NEW ORGAN LIVER PRIZE AT A GLANCE

<i>Guidelines</i>	<i>Requirements</i>
Type of Host	Large animal (pig, rabbit, cow, or sheep), excluding rodents (rats, mice, etc.)
Duration	A minimum of 90 days survivability
Organ/Tissue	Any regenerative or bioengineered solution is allowed; must be biological rather than non-biological
Immunosuppression	Immunosuppression is allowed in allotransplants; immunosuppression is allowed in xenotransplants; no immunosuppression is allowed in homotransplants
Multiple Successes	A minimum of 3 successful trials are required
Success Rate	A minimum of 3 out of 4 trials must be successful (75% success)
Functionality	The animal must survive the duration of the 90-day survival trial based on the solution alone; no other support (natural or artificial) can be provided; during the last month of the trial the animal must exhibit specific liver functions and “lifestyle” functions
Deadline	The trials must be completed by December 31st, 2018
Judging	The team’s trials will be evaluated by a technically-proficient and fully-independent judging committee
Award(s)	The first registered team to meet all requirements will win the \$1,000,000 award and receive significant marketing recognition

Section 3

DEFINITIONS & ASSUMPTIONS

1. Immunosuppressive drugs – any drug that suppresses the immune reaction for the purpose of counteracting the rejection of the team’s implanted solution.

2. Survival Functionality – to win the prize, we are asking for teams to create a regenerative or bio-engineered solution that allows the host animal to survive a minimum of 90 days based solely on the function provided by the team’s solution. Recognizing that “survival” itself can mean many things, we use the following functions and lifestyle markers to define “survival” for this prize.

[Note that the following liver and lifestyle functions are under review for potential refinement.]

1. *Liver Organ Functions* – for the purpose of this prize we define normal liver functionality as keeping albumin and bilirubin within the ranges listed for each potential animal host:

	Pig	Rabbit	Cow	Sheep
Albumin (g/dL)	1.8 to 3.4	2.7 to 4.6	2.8 to 3.8	2.4 to 3.0
Bilirubin (mg/ dL)	0 to 0.7	0.2 to 0.7	0.1 to 0.4	0.1 to 0.3

Source: <http://www.ahc.umn.edu/rar/refvalues.html>

2. *Lifestyle Functions* - the following functions are required to be demonstrated for the last month of the 90-day survival trial. Prior to this, the animal may exhibit lower than normal lifestyle functions as it recovers from the trial’s surgery.

1. The host must maintain and demonstrate regular mobility patterns within +/- 20% of its original mobility patterns.
2. The host must maintain regular weight within +/- 20% of its starting “healthy” weight.
3. The host must maintain regular dietary patterns as defined by not requiring any dietary supplements or forced feeding.

Section 4
RESTRICTIONS

The following items are requirements that must be met by the team and verified by the judging committee in order for the team to win the New Organ Liver Prize:

1. Organ/Tissue Type – Only solutions restoring liver functionality will be considered.

2. Animal Host

1. Teams must implement their solution in an allowable animal host defined in the table in Section 3. Explicitly excluded from this prize are rats and mice and other rodents. Rabbits are not defined as rodents and are allowable hosts for this study.
2. The team must follow the approved animal handling and care practices of their host institution, or those of their governing nation.
3. The animal must be beyond its neonatal development stage at the start of the 90-day survival trial.
4. The animal host must be kept on its regular diet with no special dietary restrictions or supplements.
5. If the team is using non-human cells for their trial, the team must not use immunodeficient hosts. The hosts must have an active, natural immune system. If the team is using human hepatocytes, then the team may also use immune deficient hosts.
6. The animal host must not be a genetically manipulated animal, or other genetically defective animal. It must be a “wildtype” host animal.

3. Duration – Teams must demonstrate that the host animal survives for a minimum of 90 days after the start of the survival trial.

4. Implant & Surgery Restrictions

1. *Multiple Implants* – the team may implant their solution as many times as they like before the 90-day survival trial begins; however, once the trial has started, no additional implants or surgeries of any kind are allowed.
2. *No Transplantation* – teams may not transplant fully-functioning pieces of liver from another host, however, decellularization/recellularization techniques are allowed. The implant must be grown in vitro, or in vivo to become functioning liver tissue.

5. Immunosuppression Restrictions

1. If using allotransplants, immunosuppression is allowed.
2. If using xenotransplants, immunosuppression is allowed.
3. If using homotransplants, immunosuppression is not allowed.

6. Mechanical Limitations

1. Approaches that rely upon mechanical solutions to produce the liver's functions (e.g. dialysis machine) will not be eligible for this award.

7. Multiple Successes – The team must demonstrate the successful implementation of the solution in a minimum of three animal hosts.

8. Success Rate – teams must have a 75% success rate where at least three out of four hosts survive. For example:

1. *Team A:* Conducts three trials and all three animals survive. This team wins the prize.
2. *Team B:* Conducts three trials and only two survive. The team must conduct a fourth trial where the host survives (three out of four = 75% success rate) to win. If the fourth host dies, they must conduct additional trials.
3. *Team C:* Conducts three trials. None of their hosts survive. The team then conducts three more trials and all of the hosts survive. This team will win the prize after these six trials because the last four trials produced three out of four hosts surviving (meeting a 75% success rate in the last four trials).

9. Functional Requirements – The team's solution must meet all functional requirements listed in Section 3. Teams must demonstrate once per week during the last month of the trial that the functions stay within the ranges listed in Section 3. During the last week, teams must show acceptable function ranges at the beginning of the week and at the conclusion of the trial.

10. Survival Trial

1. The 90-day survival trial will begin when the host organ can no longer produce the function to keep the animal alive. This loss of function can be achieved in either of two ways:

1. *Total hepatectomy of the original liver* – the hepatectomy can be conducted in multiple stages allowing for the implanted solution to grow to support the required functions; however, the three-month survival trial will only begin when the native liver has under-gone a 100% hepatectomy.

2. *Induced liver failure* – the team must provide a method of validating that the animal would not survive after the liver failure has been induced by the team. This could be through control trials or other verification means, but the method used must be presented to the judging committee and accepted as validation of native liver failure to the point that the host animal will die without an intervention. The 90-day survival trial will begin only after validation that the host animal's native liver is at a state where it cannot produce the function to keep the animal alive.

2. The solution may be implanted prior to starting the survival trial, and allowed to grow inside the host, but must meet all functionality requirements during the last month of the 90-day trial.

3. The team must gather data on the functional performance of the host animal at least once per week during the 90-day trial, and demonstrate during the last month of the trial that the functions stay within the ranges listed in Section 3. During the last week of the trial, teams must also show acceptable function ranges at the beginning of the week and at the conclusion of the trial.

11. Cell Types – All cell types will be allowed, so long as the final product meets all other requirements.

12. No Liver Support Interventions – During the 90-day survival trial, the host animal must not receive any plasma exchange, filtering, or any other liver support intervention of any kind whether introduced externally or internally beyond normal activities, such as eating, playing, mating, sleeping, etc.

13. Internal Solutions – Eligible solutions must be completely internal to the host animal's body. No external-to-the-body devices, products, tissues, or solutions will be allowed.

14. No Teratoma Formation – The team must demonstrate through histology that no teratomas are formed in the tissue at the end of the 90-day survival trial.

15. Deadline – All trials must be completed (including 90 days of host survival after implantation) by December 31st, 2018.

Section 5

SAFETY & CARE

All teams must follow the proper animal care and use policies identified by their host institution, or those identified by a governing body of their home nation. If the team's institution, or governing nation does not have such policies, the team will be required to adhere to the requirements for animal welfare listed in the National Institutes of Health, Office of Laboratory Animal Welfare that are required for an institution to receive an "Animal Welfare Assurance." Details of these requirements are found at: <http://grants.nih.gov/grants/olaw/olaw.htm>

Section 6

REGISTRATION & REQUIREMENTS

To officially register, teams are required to:

1. Submit an Intent to Participate – Teams must submit a notice that they intend to participate to New Organ management. Teams can submit an Intent to Participate anytime after the launch of the prize and must submit it at least one month prior to signing the official Team Agreement. The Intent to Participate must be a written statement to the Methuselah Foundation (New Organ's host charity) expressing your interest in being recognized as an official Team. The statement must include:

1. Who your team leader is expected to be
2. The host institution(s) of your team members
3. A brief summary, no more than 500 words, describing the techniques you plan to use to win the prize

2. Executive Summary & Team Agreement – Teams invited to officially register for the challenge based on their Intent to Participate will be recognized as an official team once they have submitted an Executive Summary and the Team Agreement is co-signed by Methuselah Foundation and the Team.

1. *The Team Agreement* – all details on how New Organ management and the team will interact. It defines and protects the intellectual property of the teams and the rights of New Organ to promote their work. The Team Agreement governs the following items between New

Organ and the Team:

1. Award Disbursement
2. Media and PR rights
3. Reporting Requirements
4. IP ownership (stating that Methuselah Foundation takes no IP of the teams)
5. Insurance protection and liability waiver requirements for New Organ Judging Committee members

2. *Executive Summary* – Along with the Team Agreement, each team must submit a summary defining the team members, leader, and the process being pursued by the team to win the New Organ Liver Prize. The Executive Summary must be submitted prior to being recognized as an Official Team participating in the challenge.

3. Submit a Team Trial Application – This document covers the details of how the team will conduct the trials. It must be approved by the judging committee as described below in Section 7.

Section 7

JUDGING

New Organ management will form an independent committee of highly-qualified experts to serve as the judging committee for the New Organ Liver Prize. This committee will conduct judging of a team's trials to ensure that all judging review criteria listed below are met. The judging committee's determination on the success or failure of a team to meet these criteria is final. The judging process and evaluation will be conducted following the steps listed below.

1. Judging Review Process

1. ***Team Trial Application Submission*** – To begin the judging process, each team must submit a Team Trial Application to the judging committee. This document will be reviewed by the committee to determine if all criteria are met to launch the team into the Trial Oversight process. The Team Trial Application document must be submitted to the New Organ Liver Prize Judging Committee no later than 90 days prior to the date the team will begin their trials. The Team Trial Application must include:

1. *Executive Summary*: An overview of all key techniques and milestones in your process.

2. *Process Description*: A step by step description of all details to conduct the team's trials including a list and description of all tests to verify the performance of the team's product with sufficient detail to allow someone skilled in the art to reproduce the experiments. The tests described in this section must provide enough data for the judging committee to verify all Judging Review Criteria mentioned above in this section. The testing procedures must also include a process for the judges to verify that the animal reviewed at the end of the trial is the same as the animal that received the bioengineered solution. The information contained in this description will be held in confidence by our judges during the prize process. Teams are encouraged to seek IP protection prior to release.

3. *Materials List*: A table listing all materials used in the process of creating the team's solution, and in conducting the team's trial. This information will be held in confidence by our judges during the prize process.

4. *Process timeline & key milestones*: A table identifying key milestones and timing of all tests and experiments required in the team's trial.

2. Team Trial Application Review and Approval – The judging committee will review the process described by the team and make one of three determinations based on their review of the application:

1. *Rejection* – the team's application will be rejected if the judging committee determines that they have not developed a process capable of successfully completing all requirements listed in the rules.

2. *Conditional Approval* – the team's application will be Conditionally Approved, if the judging committee determines that the team has developed a process capable of meeting all the requirements in the rules, but has not included enough tests or experiments to provide the data required to determine whether or not the team has won the prize.

3. *Approval* – the team's application will be Approved if the judging committee determines that they have developed a process capable of meeting all the requirements in the rules, and they have included adequate tests or experiments to provide the data required to determine whether or not the team has won the prize.

For each team application, the judging committee will provide feedback on the application within one month of receiving it. If accepted, the team and judging committee will then finalize all details for the oversight process for the trials. The judging committee and team will each verify the final “Replication & Oversight” procedures required to gather all data needed to declare the team a winner of the New Organ Liver Prize.

1. *Trial Oversight* – Judging committee members will conduct site visits to oversee the key parts of the team’s process to ensure that the process reviewed is implemented and that all requirements and restrictions noted in the rules are met. The oversight procedures for each team will be developed based on the needs of that team as determined by the judging committee. If the team is found to not comply with any of the agreed upon steps in the Team Trials Application, the team will be disqualified from the trials. Teams must include continuous video capture of the animal throughout the 90-day trial, for judge review only.

2. *Determination of a Winner* – Upon completion of the team’s trials, the team must produce a final report on the trial detailing all processes used, experiments conducted, and the results of those experiments. This report will be reviewed by the judging committee. This report and the committee’s own oversight notes will be used to determine whether or not the team has won the New Organ Liver Prize. Determination of the New Organ winner(s) is at the sole discretion of the judging committee.

2. Winning Criteria – In order for the team to receive a favorable decision by the judging committee, they must:

1. Provide the results to all tests, measurements, and experiments agreed upon in the accepted Team Trial Application.
2. Be able to demonstrate and verify that their solution meets all restrictions listed in Section 4 of the Rules.
3. Be able to demonstrate and verify that their solution provides the functionality requirements identified in Section 3 of the Rules.
4. Be able to demonstrate and verify that the host animal is surviving on the engineered replacement alone.
5. They have complied with all other restrictions and regulations listed in the Rules.

3. Determination of Placement – If multiple teams submit a Team Trial Application prior to a team being accepted as the prize winner, the committee will consider the team that has their application

either Conditionally Approved, or Approved first, to be the first in line for winning the prize, so long as the team begins the trial within 90 days from their application being accepted. If the team does not begin their trial within 90 days time, their application will need to be re-approved and their effective time of application reset to the new date.

Section 8

TIMELINE AND MILESTONES

The timeline for the New Organ Liver Prize is very fluid between the launch of the challenge and the final deadline. Between these end points there will be milestones that must be achieved, but most milestones will be conducted on a rolling basis. These milestones include the following:

- 1. Prize Launch** – December 2013
- 2. Intent to Participate** – teams wishing to participate in the challenge must first submit an Intent to Participate statement to the Methuselah Foundation. This can be submitted at any date after the launch of the prize and at least seven months before the Team expects to begin their survival trial.
- 3. Team Registration** – groups invited to be recognized as an Official Team participating in the challenge must first submit the Team Agreement and Executive Summary. These items must be submitted a minimum of six months before the team wishes to begin their trials.
- 4. Team Trial Application Submission** – the team must submit their Team Trial Application documents to the judging committee a minimum of 90 days before they wish to start their trial.
- 5. Trials** – the team will begin the trial for the New Organ Liver Prize at an agreed upon date with the judging committee.
- 6. Deadline** – teams must complete all trials necessary to win the prize (including the 90-day survival period for the animal host) before December 31st, 2018.

Section 9

ELIGIBILITY, DISQUALIFICATION & APPEAL

- 1. Eligibility** – any incorporated organization is eligible to register as a team for the New Organ

Liver Prize. The officially recognized team will be the organization and members listed on the signed Team Agreement.

2. Disqualification – all teams must adhere to the following guidelines to remain eligible for the prize. If at anytime the team is found to be in violation of one of these requirements, they will be disqualified by the judging committee.

1. *Ethical Behavior* – if the team is found to be mistreating animals by breaking the ethical behavior and animal treatment rules of their institution or those of their host nation, the team will be disqualified. In the absence of relevant guidelines from their host nation or institution, the guidelines from the National Institute of Health, listed in Section 5 of the rules, must be followed.

2. *Falsification or Misrepresentation of Data* – if the team is found to have falsified data that is used in any part of the New Organ Liver Prize, the team will be disqualified.

Disqualification of teams is at the sole discretion of the judging committee.

3. Appeal – Disqualified teams may appeal to the judging committee to be allowed to participate in the challenge. Appeals will be considered for each team only once. For an appeal to be successful, the team must demonstrate to the judging committee that: (a) the committee has been misinformed of the actual behavior or falsification of data by the team, or (b) the team has adequately amended their processes to remove any offending items. The determination of appeal by the judging committee is final.

Section 10

AWARDS

The New Organ Liver Prize will provide a First Place Award of \$1,000,000 to the team that can first achieve all of the requirements in the rules. In addition the winning team will receive significant worldwide recognition for their accomplishment, which will increase recognition for every team engaged in the New Organ Initiative.

The team leader will have the option of determining how their award will be disbursed: as a lump-sum payment, as a series of payments over a set number of years, or as a donation to an organization to support further research.

Additional awards will be added as funding allows.



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