

## **AVI KREMER ALS TREATMENT PRIZE**

### **Abstract:**

Patients with Amyotrophic Lateral Sclerosis (ALS or Lou Gehrig's Disease) urgently need therapeutic candidates capable of increasing their survival time. Prize4Life is looking for novel treatments that have been shown to be effective in ALS mouse models, an important preclinical validation step prior to initiation/consideration of human clinical trials and a critical hurdle for potential therapies.

### **Summary:**

ALS patients urgently need therapies capable of increasing their lifespan. This prize challenge aims to encourage the identification of therapies that have been experimentally validated in mouse models of the disease. To be eligible to win the Avi Kremer ALS Treatment Prize, a proposed therapy must meet the criteria outlined below under Detailed Description & Requirements. One million USD will be awarded for an experimentally validated ALS therapy showing significant efficacy in mouse models of the disease. Intellectual property (IP) rights for this therapy will remain with the team making the submission (please refer to section on Intellectual Property Terms below for a detailed explanation of Prize4Life's position on IP).

All submissions must include a detailed description and experimental validation of the therapy in at least two of the mouse models described below. All biological correlate(s) need to be thoroughly characterized. This description and validation should be accompanied by a solid scientific rationale supported by mainstream literature precedents. Awarding of the prize will be contingent upon experimental validation of the results by Prize4Life using an independent research laboratory (Prize4Life will pay for this validation step). Practicality of translation of the proposed therapy to patients will be a key selection criterion.

### **Launch Date:**

Tuesday October 21, 2008

### **Closing Date:**

Submissions will be considered on a rolling basis immediately following the launch date and up until either the Prize is awarded or the close date of October 15, 2010.

**DETAILED DESCRIPTION & REQUIREMENTS:**

**Background:**

ALS is a fatal neurodegenerative disorder characterized by death of motor neurons in the brain and spinal cord. This loss leads to muscle weakness, atrophy, and gradual paralysis. At present, there is no effective therapy for the disease and patients usually die within 2-5 years of the onset of symptoms.

Several transgenic mouse models have been developed over the past decade, facilitating both investigations of ALS disease mechanisms and development of possible therapies for ALS. The majority of these models express a form of the human mutant cytosolic Cu/Zn superoxide dismutase (SOD1), a protein known to be the cause of an inherited form of ALS, underlying approximately 2% of all ALS cases.

As no effective therapy currently exists, Prize4Life is interested in promoting the identification of novel candidate therapies for treatment of ALS, as determined by a highly significant positive outcome for efficacy in mouse models of the disease.

**Objective:**

For this challenge, the aim is to develop an ALS therapy that reliably increases the lifespan of SOD1 ALS mice by at least 25%.

**Requirements:**

There are **five (5)** basic requirements that the proposed therapy must meet in order to be considered for the prize.

- 1) **Animal Model:** the treatment must extend life by at least 25% in the mutant SOD1 models utilized :
  - a) Mouse Model
    - i) the G93A mouse
      - (1) hSOD1 G93A C57BL6/SJL (Gurney) background (high copy number)  
**OR**
      - (2) hSOD1 G93A C57BL6 isogenic background (high copy number)
    - ii) as well as one of the following types of ALS mice (the submitting team may select which one):
      - (1) hSOD1 G85/86R
      - (2) hSOD1 G37R
      - (3) hSOD1 D90A
      - (4) hSOD1 G127X
  - b) Rat Model
    - i) G93A rat (either Taconic or Aoki models are acceptable)
- 2) **Experimental design:** the experimental design of the mouse trials must be conducted according to the following requirements:
  - a) Study Design (ALS-TDI publication as reference: Ref #5 below):

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- i) Minimum of 24 mice per cohort (if effect size is large enough and inter-litter variability low enough that smaller cohorts can be justified, Prize4Life will consider such requests on a case by case basis)
  - ii) Match gender across treatment groups
  - iii) Pair litter mates across treatment groups
  - iv) Eliminate from consideration all animals (and if possible their littermate controls if using a congenic strain) that die for reasons other than ALS and be explicit regarding exclusion criteria used (e.g. failure to demonstrate expected neurological decline prior to death). Report numbers of excluded animals.
- b) Outcome measures:
- i) Overall life span increased by 25% (compared to untreated controls and correlated with known average lifespan for a given model)
- c) Onset measures<sup>1</sup>:
- i) Peak body weight (if you desire to use an earlier measure of onset you must prove this measure of onset to our satisfaction)
  - ii) Treatment must begin at or after disease onset
- d) Endpoint measure:
- i) Inability of the mouse to right itself in 30 seconds when placed on its side
- e) Other measures
- i) Provide basic data on pharmacokinetics of the compound
    - (1) Absorption (solubility and justification of mechanism of delivery)
    - (2) Distribution (show evidence of penetrance to brain and spinal cord)
  - ii) Any other measures that reviewers can use to confirm the validity of the reported findings and the experimental rationale (i.e., motorneuron counts, measures of astrogliosis, behavioral observations, etc.)
- 3) **Data on biological correlates**, if applicable i.e. if proposed survival explanation involves increased proliferation of mitochondria, provide direct measure indicating such (mitochondrial counts in drug vs. controls) or if proposed survival explanation involves increase in autophagy, provide direct measure indicating such
- 4) **Transgene copy number**: to control for spontaneous deletion of the transgene, you must present quantitative expression data on transgene copy number for all animals used. We recommend that teams additionally keep DNA from all treated animals in case any more sensitive post-test confirmation is deemed valuable.
- 5) **Statistical package**: use Cox Proportional Hazards model (see ALSTDI reference) when assessing significance of detectable differences.

Given the urgency of the need for effective ALS treatments, Prize4Life will review submitted solutions as they are received (on a rolling basis following the prize launch) up until the prize has been awarded or the closing date of **October 15, 2010**. For those submissions indicating a robust effect in studies using the proper design and controls (as described above), Prize4Life will undertake (and cover the costs of) independent validation experiments in the G93A SOD1 model using BL6SJL (Gurney) ALS mice.

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<sup>1</sup> Peak body weight is simple and reproducible (need to know average body weight at disease onset to initiate treatment; this info is available for different models).

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Validation experiments will be conducted by ALSTDI, PsychoGenics, or The Jackson Laboratory at Prize4Life's discretion.

The first treatment that meets the solution requirements and shows successful independent validation will be awarded the prize at the discretion of Prize4Life. Prize4Life wishes to make clear that the intended outcome of this Prize Challenge is a treatment appropriate for future clinical development. Therefore all proposed therapies must be practical and feasible in humans and practicality of a given solution will be taken into account by the scientific review committee when awarding the prize.

Please feel free to submit any questions regarding the ALS Treatment Prize to us at: [contact@prize4life.org](mailto:contact@prize4life.org)

### REFERENCES:

1. Boillee, S., Vande Velde, C., and Cleveland, D.W. *ALS: A Disease of Motor Neurons and Their Nonneuronal Neighbors*. *Neuron* **52**: 39–59 (2006).
2. Bruijn, L.I., Miller, T.M., and Cleveland, D.W. *Unraveling the mechanisms involved in motor neuron degeneration in ALS*. *Annu Rev Neurosci*. **27**: 723–49 (2004).
3. Cleveland, D.W. and Rothstein, J.D. *From Charcot to Lou Gehrig: deciphering selective motor neuron death in ALS*. *Nat Rev Neurosci* **2**: 806–819 (2001).
4. Pasinelli, P., and Brown, R.H. *Molecular biology of amyotrophic lateral sclerosis: insights from genetics*. *Nat Rev Neurosci* **7**: 710–723 (2006).
5. Scott, S., et al., *Design, power, and interpretation of studies in the standard murine model of ALS*. *Amyotrophic Lateral Sclerosis* **1**, 1–12 (2008).
6. Schnabel, J. *News Feature: Standard Model*. *Nature* **454**: 682–685 (2008).

### INTELLECTUAL PROPERTY TERMS:

Prize4Life will notify all participants as promptly as possible as to whether or not a proposed treatment (a "Proposal") has been selected as the prize winning Proposal. Prize4Life has absolute and sole discretion in determining the prize winning Proposal. A Proposal meeting the criteria for a Proposal established by Prize4Life does not mean that the Proposal will be selected by Prize4Life as the prize winning Proposal. In the event that your Proposal is not selected by Prize4Life as the prize winning Proposal, Prize4Life will not retain any rights to your Proposal or any work product relating thereto (the "Work Product"). If your Proposal is selected by Prize4Life as the winning Proposal and payment of the \$1,000,000 US prize is made to you (the "Award"), you hereby agree, as a precondition to the receipt of any Award, to permit Prize4Life to generally publish the results of your Proposal to the interested public either concurrently with the payment of an Award to you or within a reasonable period of time thereafter (as shall be reasonably determined by Prize4Life after consultation with you) as may be necessary to enable you to establish patent or other ownership rights in the subject matter of the Proposal. You acknowledge that under no circumstances will Prize4Life agree to forego publication of a Proposal for which an Award was granted beyond the period of time reasonably

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necessary to enable you to establish patent or other ownership rights in the subject matter of your Proposal.

Upon payment of the Award, there will be no further obligations between you and Prize4Life with respect to the Proposal or the Work Product

### **SUBMISSION INSTRUCTIONS**

All submissions must be in English and must conform to the following format:

1. **General:**  
The submission text must be 12-point type Arial or Times New Roman font. It can be single spaced. Figures, charts, tables, figure legends, and footnotes must be readily legible and incorporated into the overall page limits. Images must be no less than 10.5 and no more than 18.0 cm wide. Numbers, letters, and symbols should be no smaller than 6 point and no larger than 12 point. Composite figures must be preassembled. Each item should have a brief title. There must be an adequate border of at least 0.5 inches around each figure, chart or table. Page margins, in all directions, must be at least 0.5 inches. The complete application should be submitted as a PDF.
2. **Maximum Length:**  
The total submission package can be no more than 20 pages (not including references). No section may be longer than the limits provided below.
3. **Title and Abstract (1 page):**  
Please submit a title and abstract for your proposal. The abstract should be no longer than 300 words and should summarize your proposed solution, the rationale and the methods on which it is based.
4. **Background, introduction and rationale (1 page):**  
Describe the background, introduction and rationale for your proposed solution, including relevant scientific literature.
5. **Preliminary data from you and others (2 pages):**  
Describe existing preliminary data from you and others as it relates to your proposed solution.
6. **Main text (16 pages):**  
Describe in detail your proposed solution and how it was realized. Be careful to explain in detail how your solution fulfills the basic requirements of the Treatment Prize challenge as specified above.
7. **References (must be included but will not count toward 20 page limit):**  
Use a standard scientific reference format including author, title, and full details of the source (such as journal name, volume, year and page number).
8. **Your completed package will adhere to the following format:**  
Page 1: Title and abstract  
Page 2: Introduction, background and rationale

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Pages 3-4: Preliminary data

Pages 5-20: Main text

Pages xx-xx: References