SUMMARY STATEMENT
(Privileged Communication)

Principal Investigators (Listed Alphabetically):
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SAMULSKI, RICHARD J PHD

Applicant Organization: UNIV OF NORTH CAROLINA CHAPEL HILL

Review Group: **GDD**
Gene and Drug Delivery Systems Study Section

Meeting Date:	10/21/2015	*RFA/PA:*	PA13-302
Council:	JAN 2016	*PCC:*	I2F
Requested Start:	04/01/2016		
		Dual IC(s):	HL, DK

Project Title: **Enhance AAV Liver Transduction with Capsid Immune Evasion**

SRG Action: **Impact Score: 20   Percentile: 2**
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		Estimated Total Cost
1	███████		████████
2	███████		████████
3	███████		████████
4	███████		████████
5	███████		████████
TOTAL	██████		█████

ADMINISTRATIVE BUDGET NOTE: The budget shown is the requested budget and has not been adjusted to reflect any recommendations made by reviewers. If an award is planned, the costs will be calculated by Institute grants management staff based on the recommendations outlined below in the **COMMITTEE BUDGET RECOMMENDATIONS** section.

1R01AI117408-01A1 Li, Chengwen

BUDGETARY OVERLAP

RESUME AND SUMMARY OF DISCUSSION: The applicants propose to identify methods to prevent immune system clearance of hepatocytes transduced with adeno-associated virus (AAV) vectors by examining the role of empty capsids in the immune response, modifying AAV capsid antigen presentation and identifying new AAV vectors capable of avoiding the capsid-specific cytotoxic T lymphocyte (CTL) response through a directed evolution approach. The research was thought to be highly significant because of the importance of overcoming the immune response to AAV gene therapy for successful treatment of diseases such as hemophilia. The innovative concepts of exploring the CTL response and the role of empty capsids in the AAV immune response, thorough experimental plan and outstanding investigative team that includes a world leader in AAV gene therapy are among the other strengths of the application discussed by the panel. Questions were raised about the suitability of mouse models for identifying immune responses that will be relevant to humans. Reviewers disagreed about the necessity for testing multiple capsid mutants. Overall, reviewers agreed that the strengths outweigh the weaknesses and rated the application likely to have high impact on the field of AAV gene therapy.

DESCRIPTION: Adeno-associated virus (AAV) vector has been successfully applied in phase I clinical trials in hemophilia B patients with liver targeting. However, these studies have suggested that AAV capsid specific cytotoxic T lymphocytes (CTL) have the potential to eliminate AAV transduced hepatocytes and result in the therapeutic failure. Our prior studies have demonstrated that AAV capsid antigen presentation is dose-dependent and requires capsid ubiquitination for proteasome mediated degradation. The contamination of empty virions in AAV preparation inhibits transduction from full particles of AAV vectors and potentially increases the risk of virus capsid antigen load. In this proposal we will investigate capsid antigen presentation from AAV empty virions and the effect of empty particles on antigen presentation from full virus transduction (Aim 1). To decrease antigen presentation on AAV transduced cells for avoiding capsid specific CTL-mediated elimination, it has been proposed to modify the AAV capsid surface or apply proteasome inhibitors to enhance AAV transduction while lowering the effective dose or to escape capsid ubiquitination. We will study the effect of AAV mutants and proteasome inhibitors on AAV capsid antigen presentation (Aim 2). It is well-known that the transduction of AAV vectors in mouse models does not always translate into the human. Finally, we will explore the directed evolution approach combined with a rational design strategy to isolate AAV vectors with human hepatocyte specific tropism and the ability to evade a capsid specific CTL response in humanized mice (Aim 3). Elucidation of AAV empty capsid antigen presentation in vivo and the development of an AAV vector with enhanced human liver transduction and CTL immune-evasion will allow us to design safer and more effective strategies that address the current clinical complications for human liver gene therapy using AAV.

PUBLIC HEALTH RELEVANCE: Having demonstrated that AAV capsid antigen presentation is dose-dependent and requires proteasome mediated degradation, and modification of the AAV capsid surface induces enhanced AAV transduction while lowering the effective dose or decreases capsid antigen presentation, we will explore to develop AAV mutants with the ability to evade capsid specific CTL mediated elimination and with human hepatocyte tropism. This study will allow us to design safer and more effective strategies for human liver gene therapy using AAV.

CRITIQUE 1:

Significance: 3
Investigator(s): 2
Innovation: 3
Approach: 3
Environment: 1

Overall Impact: The investigators hypothesize that the AAV-mediated T cell response is dependent on the capsid dose response. The investigation will evaluate these types of responses and determine if they can be mitigated by reducing the empty capsids present in rAAV vector preparations. In addition, these T cell responses are dependent on capsid proteasome interactions and capsid ubiquitination. The investigators will use AAV capsid libraries that will lead to the creation of vectors with optimized human hepatocyte transduction and reduced immunogenicity. To do this, the investigators will study AAV antigen (Ag) presentation after exposure to various doses of empty capsids and or empty/full capsids. They will establish class I vs. II Ag presentation via use of two different knockout mouse strains. The importance of proteasome inhibitors and capsid ubiquitination will be evaluated. Ultimately novel AAV capsids will be isolated in a humanized mouse models. Variants found to be robust at transducing human hepatocytes in these mouse models will be further evaluated in B6 mice for their antigenicity. There is enthusiasm for attempting to define the parameters that are responsible for the T cell-mediated response in humans infused with various AAV vectors. There is real concern that the immune responses observed in the mouse models will not accurately predict the human condition as mice or any other animal models tested to date do not stimulate similar responses. Nevertheless, this proposal may ultimately provide additional insights into this important yet unexplained process as well as provide new AAV vectors that may have reduced immunogenicity in humans.

1. Significance:

Strengths

- The cell-mediated immune response in humans treated with AAV vectors remains a challenge and a better understanding of how AAV induces such responses will be an important step forward in developing a means to overcoming this limitation.

- While it may be obvious to some, the value of removing empty capsids from clinical grade AAV vectors remains controversial. Thus, providing solid data to support the removal of empty capsids is important to the field.

- Evaluating the T cell response in mice may provide important insights with the caveat listed below.

Weaknesses

- Although there has been great effort, no one has created an animal model that recapitulates the events that occur in humans. Thus it is not possible to know whether the events studied will be relevant to humans.

- The parameters that reduce antigen presentation may be inherently linked to efficacy and if so, capsids that have reduced immunogenicity may have reduced transduction.

2. Investigator(s):

Strengths:

- Dr. Samulski is a world leader in AAV vector biology. Dr. Li did two post docs, the last ended with Dr. Samulski in 2004. Together they have a strong publication record with Dr. Li as first author.

Weaknesses

- Is Dr. Li has few senior author papers. He has been a faculty for 10 years yet most if not all of his publications are with Dr. Samulski– many of which Dr. Samulski is the senior author.

3. Innovation:

Strengths

- Identifying effective humanized AAV variants that are resistant to ubiquitination result in a lower risk for activation of T cells is the most innovative feature of the proposal.

Weaknesses

- Most of the methods and approaches are not highly innovative because it involves approaches and methods that are relatively well established.

4. Approach:

Strengths

- The experiments are well described and the logical progression through each of the aims is easy to follow.

- To provide experimental support to show the proportion of empty capsids may influence the immune response is important. This is especially true because, as the investigators point out, not all of the T cell responses are dose dependent.

- The use of two serotypes, AAV-2 and AAV-8, are important because they have very different transduction efficiencies in mice.

Weaknesses

- The AAV-2 and AAV-8 variants, while having different transduction in mice, appear to have similar transduction in humans. The same may be true for the various capsid variants described herein.

- One mouse inbred strain is studied and the immune parameters measured may have nothing to do with the human condition.

- How is the capsid load ultimately removed from the cell if ubiquinition and other degradation pathways are blocked -- especially in terms of alternate processing and ultimate alternative antigen loading processing?

- The fumarylacetoacetate hydrolase deficiency (FRG) humanized mice are extremely difficult to generate. The data in Figure 10 suggests there is almost no reconstitution with human hepatocytes (70ng/ml at best).

5. Environment:

Strengths

- Very strong AAV environment.

Weaknesses

- This study lacks input from a bona-fide immunologist.

- Can they generate humanized mice as stated?

Vertebrate Animals:

Is the proposed research involving vertebrate animals scientifically appropriate, including the justification for animal usage and protections for research animals described in the Vertebrate Animal section?

YES, all fine points addressed

- OK

Biohazards:

Acceptable

- OK

Resource Sharing Plans:

Acceptable

Budget and Period of Support:

Recommend as Requested

Recommended budget modifications or possible overlap identified:

- Both the Principal Investigators have multiple NIH grants, some shared, that are related to AAV immune responses and/or capsid shuffling. Should be checked for overlap.

CRITIQUE 2:

Significance: 1
Investigator(s): 1
Innovation: 2
Approach: 2
Environment: 1

Overall Impact: In this resubmission, the investigators have focused on many of the gray areas of rAAV gene therapy including the effects of empty vector particles and antigen presentation mechanisms. The immune response to rAAV vectors, particularly the CTL response, remains one of the greatest obstacles to effective gene therapy, yet the most poorly understood. The investigators will explore the novel concept that efficient transduction is negatively correlated with efficient antigen presentation due to trafficking through different subcellular compartments. If these pathways can be manipulated using proteosome inhibitors or ubiquitination mutants (Aim 2), it would have a profound

impact on the field. Based on the hypothesis that empty vector capsids are trafficked differently than full capsids, the investigators will test their effects on transduction and CTL response in Aim 1. In Aim 3, they will use humanized mouse models to select for hepatotropic capsid mutants, and further characterize ubiquitination of these mutants in the xenograft model. Together, success in these aims could help overcome this significant obstacle to more effective liver-directed rAAV gene therapy.

1. Significance:

Strengths

- The primary focus of the proposal is on gene delivery to the liver, which has broad therapeutic applications in genetic diseases.

- The CTL response to rAAV gene therapy has had a greater impact on efficacy in clinical trials than the Ab response, given that patients with low levels of neutralizing Ab were selected for these trials. The CTL response is currently poorly understood.

- Understanding the role of empty vector capsids in the immune response will guide ongoing development of production methods and also increase the understanding of rAAV immune processing in general. The investigators have highlighted a great deal of conflicting information in the literature regarding the immune response to empty vectors and the role of proteosome inhibition. If these conflicts are convincingly resolved, there is a potential to greatly improve the efficacy of rAAV gene therapy.

- There is a significant potential that intervention with proteosome inhibitors at the time of gene delivery could both improve transduction efficiency and reduce the CTL response.

Weaknesses

- As pointed out by the investigators, it is unlikely to be feasible to study the CTL response in mice previously exposed to AAV, and retaining memory T-cells, due to the inhibitory effects of neutralizing Ab.

2. Investigator(s):

Strengths

- The lead Principal Investigator, Dr. Li, has made significant contributions to all aspects of the immune response in relation to the efficacy of rAAV gene therapy, with a strong record of productivity. Dr. Samulski, the other Principal Investigator, has been a pioneer in the design and development of rAAV as a gene therapy vector, and continues to have a great impact on the field. They are highly likely to complete the proposed studies.

Weaknesses

- None.

3. Innovation:

Strengths

- The goal of selecting for CTL evasion is highly innovative, as most rAAV engineering has been geared toward evasion of neutralizing Ab and increasing transduction.

- Combined doses of wild type and OVA/empty and full capsids is an innovative approach to determine the differential effects of empty and full capsids on transduction and antigen presentation.

- The thorough exploration of the effects of proteosome inhibitors and ubiquitination inhibiting mutations on transduction efficiency and the CTL response is novel.

Weaknesses

- The use of the humanized mouse liver as a means to select for hepatocyte tropism is not novel, although characterizing the CTL response in this context remains innovative.

4. Approach:

Strengths

- The systematic analysis of the immune response to empty capsids and the interrelationships between empty and full capsids and vector transduction are likely to yield valuable results.

- The use of the mice lacking either class I or class II antigen presentation is likely to be revealing in terms of understanding the CTL response in liver.

- The combination of proteosome inhibitor and capsid ubiquitination mutants is highly complementary and likely to shed light on crucial Ag presentation pathways.

- Alternative approaches are carefully considered in all 3 aims.

Weaknesses

- The evaluation of the CTL response to rAAV capsids will be limited to naive animals because in mice previously exposed to rAAV, and retaining memory T-cells which may be important in CTL-mediated immune clearance, the pre-existing Ab levels would preclude vector transduction.

5. Environment:

Strengths

- The research environment at University of North Carolina (UNC) and the UNC gene therapy center are outstanding.

Weaknesses

- None.

Protections for Human Subjects:

Not Applicable (No Human Subjects)

Vertebrate Animals:

Acceptable

- The 5 points are addressed and a thorough rationale for animal numbers is presented.

Biohazards:

Acceptable

- rAAV is a BSL1 agent and biohazard risks are easily manageable.

Resubmission:

- The investigators have responded to the previous review by combining two of the previous aims and adding an innovative new aim to select capsids that retain hepatocyte tropism in the context of humanized mouse liver, and then use this model to determine patterns of capsid ubiquitination related to antigen presentation.

- In response to the concern that insertion of the OVA peptide used to assay the capsid CTL response may interfere with vector transduction, the investigators propose an alternate approach using CTLs induced by AAV capsid delivered in the context of an adenovirus vector.

Resource Sharing Plans:

Acceptable

Budget and Period of Support:

Recommend as Requested

CRITIQUE 3:

Significance: 2
Investigator(s): 1
Innovation: 3
Approach: 3
Environment: 1

Overall Impact: This is a revised multiple Principal Investigator application with due modifications submitted by Dr. Chengwen Li. Here the investigators have proposed to tackle the issue of antigen cross-presentation which is a major limiting factor for successful gene therapy for liver diseases using AAV. The investigators have proposed to develop AAV mutants that will avoid capsid ubiquitination and proteasomal degradation thereby decreasing AAV capsid antigen presentation and possibly minimizing CTL-mediated elimination, thereby leading to enhanced hepatocyte transduction. The mechanism of capsid antigen presentation from empty virions and full AAV particles will be elucidated using TAP-/- and Cat S-/- mice. Further, the investigators will explore directed evolution and rational design strategy to isolate AAV vectors with preferential hepatotropism and their ability to evade capsid specific CTL response in humanized mice. If successful, it will enable the development of potentially safer AAV vectors for hepatic gene therapy.

1. Significance:

Strengths

- Gene therapy using current AAV vectors suggest that capsid-specific CTLs eliminate AAV transduced hepatocytes thereby leading to suboptimal results. Therefore, the proposed strategy to develop new AAV capsids that bypass the host immune response is exciting.

Weaknesses

- Although TAP-/- and Cat S-/- are very useful to determine molecular mechanisms involved in AAV immunogenicity, it would be necessary to employ Rag2gamma-/- mice reconstituted with humanized immune system.

2. Investigator(s):

Strengths

- The lead Principal Investigator has research expertise in studying immunogenicity as well as the development of AAV vectors.

- Dr. Samulski is an established leader in the field of AAV gene therapy. His extensive research expertise in AAV vector development significantly strengthens the proposal.

- Drs. Li and Samulski have established collaborations.

Weaknesses

- None

3. Innovation:

Strengths

- TAP-/- and Cat S-/- are very useful to determine molecular mechanism involved in AAV immunogenicity.

- Directed evolution and rational design strategy to develop AAV capsids that are hepatotropic but significantly less immunogenic.

Weaknesses

- It would be extremely important to perform these studies in humanized immune system reconstituted mice as it will mimic the human immune cell interaction with AAV.

4. Approach:

Strengths

- Use of TAP-/- and Cat S-/- mice to study AAV immunogenicity is impressive.

- Development of hepatotropic AAV capsids by directed evolution and rational design is very useful.

- Real-time in vivo bioluminescence imaging (BLI) will provide valuable information on new hepatotropic AAV capsids.

Weaknesses

- It is not clear what promoter is driving AAT expression.

- No consideration given for performing these studies in humanized immune system reconstituted mice as it will mimic the human immune cell interaction with AAV.

- The details of AAV2, 2G9, 2i8, 2i8G9, AAV9 luc vectors are not provided as a result it becomes extremely difficult to interpret the results.

- A strong rationale for generating multiple complex mutations in AAV capsid is not only time consuming and technically challenging but also appears highly ambitious.

- The BLI signal cannot accurately predict the organ source and the depth of AAV transduction. It is important to perform immunohistochemical analysis of multiple organs to accurately determine the degree of transduction and presence of APCs in addition to BLI.

- It is unclear why use of primary human hepatocytes instead of transformed HepG2 cells for in vitro studies has not been proposed.

- The proposal lists use 3490 mice. This number is impractical and requires careful evaluation of the experimental strategy.

- What is the need for testing several AAV capsid mutants instead of testing few potentially more useful select caspids?

5. Environment:

Strengths

- The University of North Carolina Chapel Hill Gene Therapy Center has excellent research facilities to carry-out proposed research.

- The investigators have full access to shared equipment at the core facilities and collaborators' lab and in the Gene Therapy Center.

- Overall the scientific environment at the North Carolina Chappell is very conducive for the research proposed in this proposal.

Weaknesses

- None.

Protections for Human Subjects:

Not Applicable (No Human Subjects)

Vertebrate Animals:

Is the proposed research involving vertebrate animals scientifically appropriate, including the justification for animal usage and protections for research animals described in the Vertebrate Animal section?

NO, animal welfare concerns or incomplete

- The proposal requires 3490 mice. This number is simply too large. What is need for testing several AAV capsid mutants?

Biohazards:

Acceptable

Resubmission:

- This is a revised R01 application.

Resource Sharing Plans:

Acceptable

Budget and Period of Support:

Recommend as Requested

THE FOLLOWING SECTIONS WERE PREPARED BY THE SCIENTIFIC REVIEW OFFICER TO SUMMARIZE THE OUTCOME OF DISCUSSIONS OF THE REVIEW COMMITTEE, OR REVIEWERS' WRITTEN CRITIQUES, ON THE FOLLOWING ISSUES:

VERTEBRATE ANIMAL (Resume): ACCEPTABLE. Concerns raised by one reviewer about the number of animals to be used were mitigated during discussion by other reviewers who argued that the numbers are thoroughly justified.

BUDGETARY OVERLAP: Reviewers noted that possible overlap exists between the studies proposed in this application and funded grants awarded to both Principal Investigators.

COMMITTEE BUDGET RECOMMENDATIONS: The budget was recommended as requested.

NIH has modified its policy regarding the receipt of resubmissions (amended applications). See Guide Notice NOT-OD-14-074 at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-074.html. The impact/priority score is calculated after discussion of an application by averaging the overall scores (1-9) given by all voting reviewers on the committee and multiplying by 10. The criterion scores are submitted prior to the meeting by the individual reviewers assigned to an application, and are not discussed specifically at the review meeting or calculated into the overall impact score. Some applications also receive a percentile ranking. For details on the review process, see http://grants.nih.gov/grants/peer_review_process.htm#scoring.

MEETING ROSTER

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CENTER FOR SCIENTIFIC REVIEW
GDD
October 21, 2015 - October 22, 2015

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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.