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NIH 102
(NIH 101: The sequel)

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NIH 101 outline:

September 5, 2019

- NIH mission as an agency
- NIH IC missions and budgets
- Success rates
- Common funding mechanisms and when they are appropriate
- NIH funding updates (Common Fund)

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NIH 102 follow-up:

- Where should a grant proposal be targeted?
- How do I get it there?
- Whom do I contact to help me answer these questions?
- What should I do to help my proposal be reviewed well?
- What is in a summary statement and what does it mean?

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NIH 102 follow-up:

- Where should a grant proposal be targeted?
  - How do I get it there?

What is your problem?
What gap are you filling?

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Targeting:

What is the problem?

What has been done already to address this problem?

What is the gap that still remains (your north star)?

How do you propose to address this gap?

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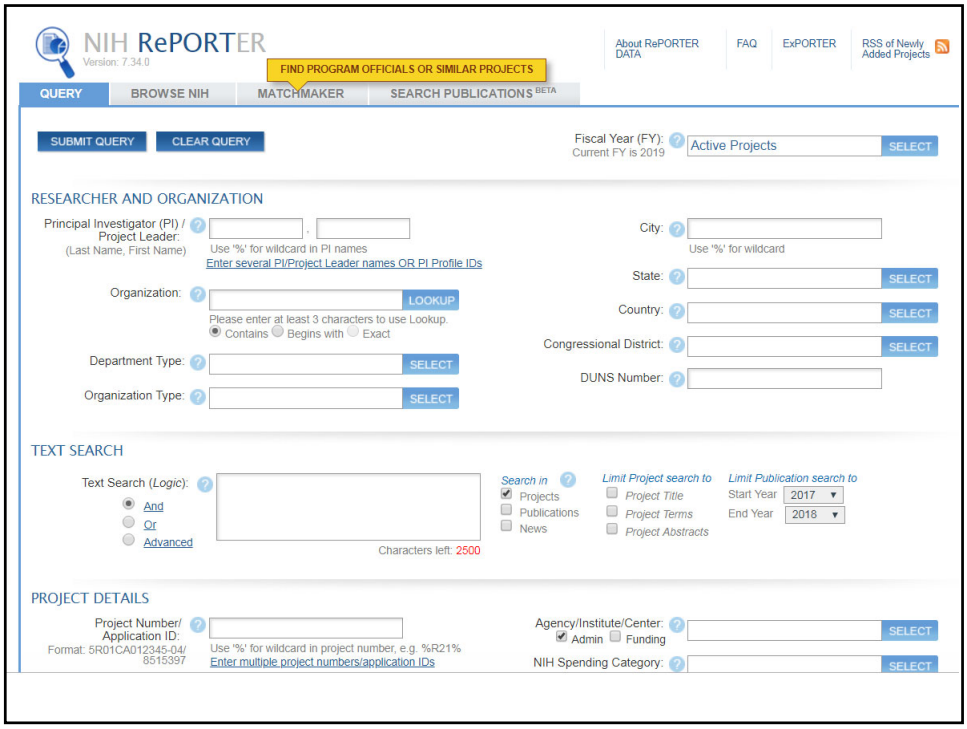
Dorothy Teegarden (NIH R01 CA232589-01A1; Obesity, Metabolism, and Breast Cancer Metastasis)

What is the problem? What has been done already to address this problem?
What is the gap that still remains? How do you propose to address this gap?

PROJECT SUMMARY

While significant evidence has demonstrated that obesity increases the risk of metastasis, the molecular mechanisms by which obesity contributes to the metastatic progression of breast cancer are unclear. Further, recent research in cancer development and progression has highlighted the role of metabolic reprogramming, which results in an increased supply of the cellular building blocks necessary for the increased cell proliferation and in adaptations required for cell survival in changing nutrient- and oxygen-containing environments. Research from our team and others demonstrates that the metabolic enzyme, pyruvate carboxylase, is upregulated during obesity and that this upregulation correlates strongly with breast cancer progression. Additional studies suggest that leptin, an adipokine whose expression is increased during obesity and whose receptor's expression is enhanced in metastatic cells, drives pyruvate carboxylase expression in breast cancer cells. Importantly, recent studies demonstrate that genetic depletion of pyruvate carboxylase drastically inhibits breast cancer metastasis in several syngeneic mouse models. Despite the supporting evidence that pyruvate carboxylase contributes to breast cancer metastasis under obese conditions, the mechanisms by which this enzyme exerts this effect remain poorly understood. In the proposed studies, the research team will evaluate the mechanistic basis by which pyruvate carboxylase regulates obesity-driven breast cancer metastasis. They will test the **hypotheses** that leptin increases pyruvate carboxylase expression in mammary tissue during obese states, and that pyruvate carboxylase is critical for both migration and survival of extracellular matrix detachment, providing metabolic flexibility (e.g., glucose utilization and fatty acid metabolism) during metastasis. These hypotheses will be tested through completion of the following aims: 1) define the mechanisms of PC expression during metastasis; 2) elucidate the metabolic mechanisms by which PC promotes metastasis; and 3) establish the mechanisms by which leptin-regulated PC expression contributes to obesity-driven metastasis. Completion of these studies will result in valuable mechanistic information that could guide future development of evidence-based recommendations for those who are overweight and obese and that will help reduce breast cancer metastasis.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Agency/Institute/Center:
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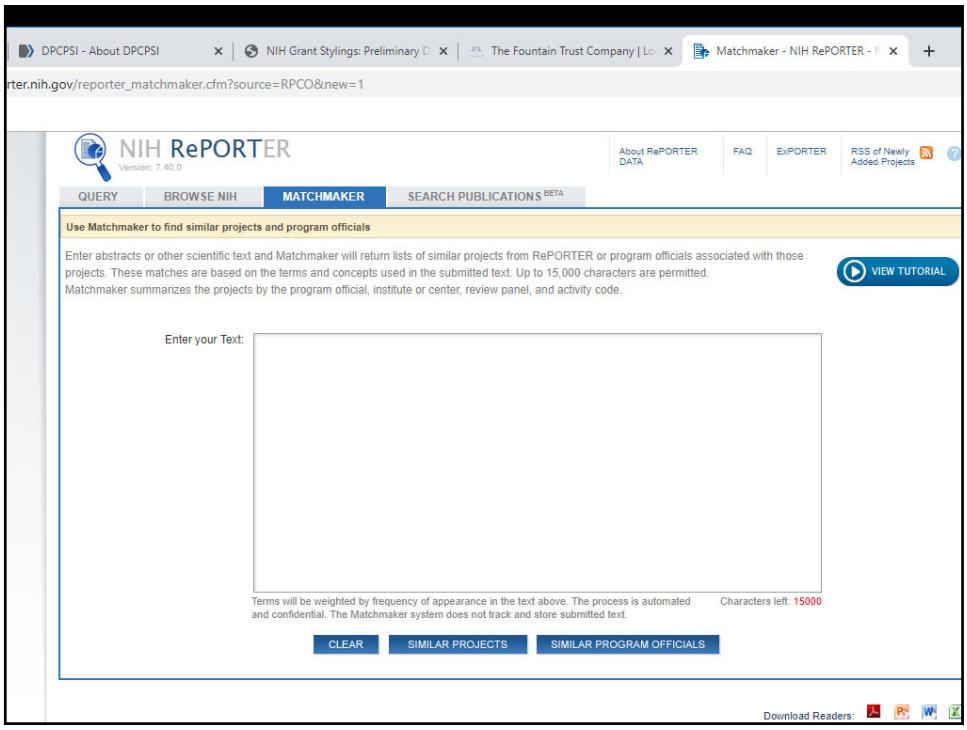
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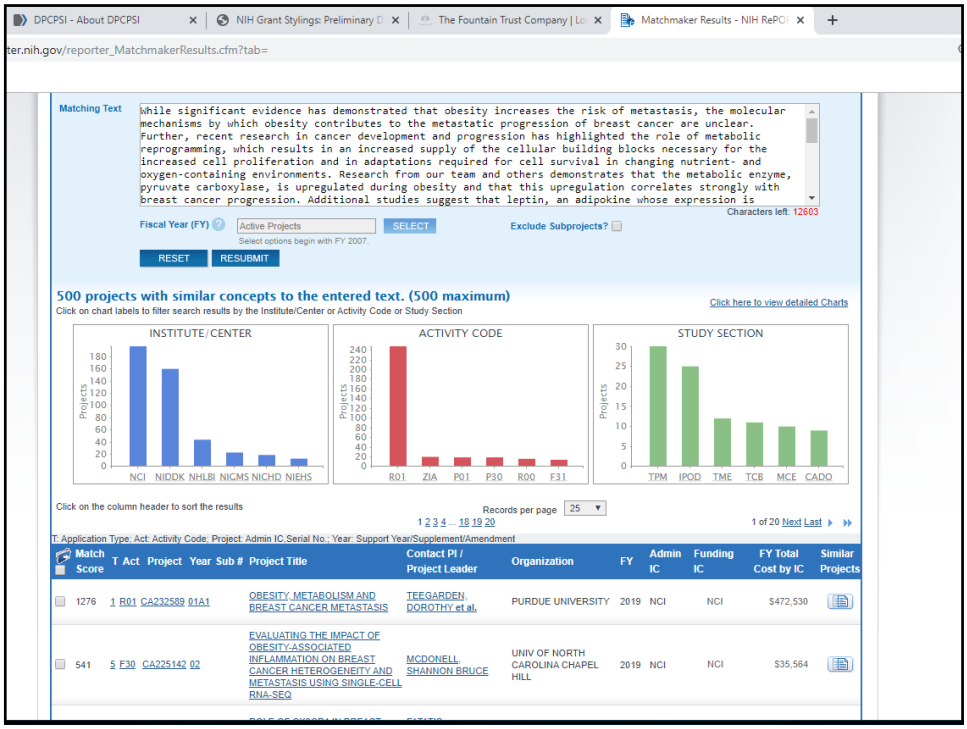
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while significant evidence has demonstrated that obesity increases the risk of metastasis, the molecular mechanisms by which obesity contributes to the metastatic progression of breast cancer are unclear. Further, recent research in cancer development and progression has highlighted the role of metabolic reprogramming, which results in an increased supply of the cellular building blocks necessary for the increased cell proliferation and in adaptations required for cell survival in changing nutrient- and oxygen-containing environments. Research from our team and others demonstrates that the metabolic enzyme, pyruvate carboxylase, is upregulated during obesity and that this upregulation correlates strongly with breast cancer progression. Additional studies suggest that leptin, an adipokine whose expression is
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T Act Project Year Sub # Project Title
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Organization
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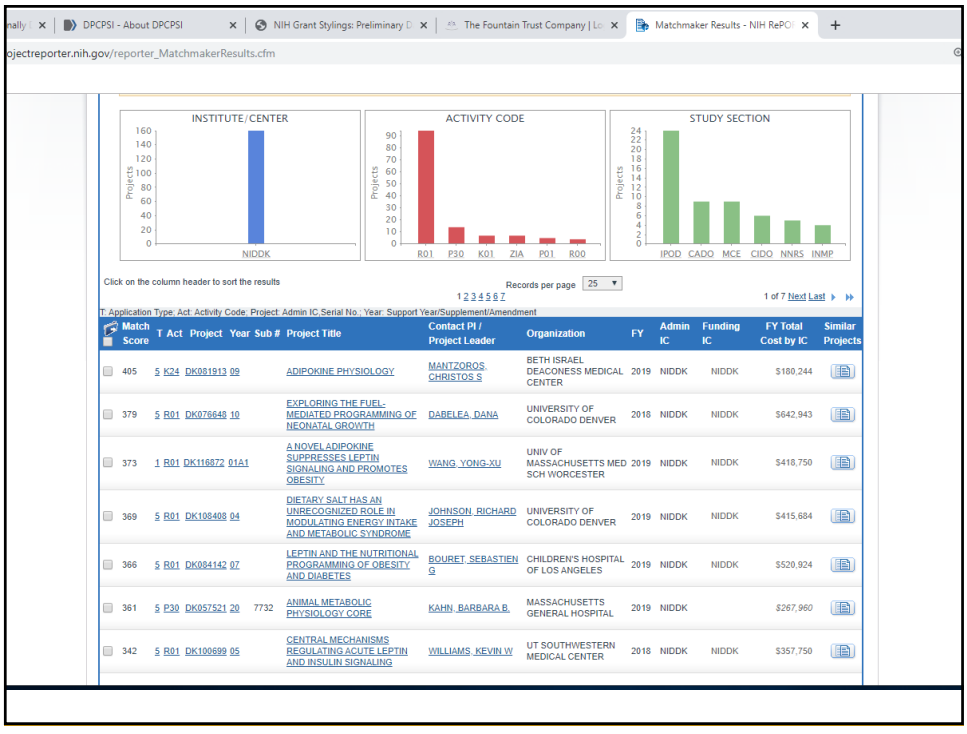
Admin IC
Funding IC
FY Total Cost by IC
Similar Projects
1276 1 R01 CA232589 01A1 OBESITY, METABOLISM AND BREAST CANCER METASTASIS TEEGARDEN, DOROTHY et al. PURDUE UNIVERSITY 2019 NCI NCI $472,530
541 5 F30 CA225142 02 EVALUATING THE IMPACT OF OBESITY-ASSOCIATED INFLAMMATION ON BREAST CANCER HETEROGENEITY AND METASTASIS USING SINGLE-CELL RNA-SEQ MCDONELL, SHANNON BRUCE UNIV OF NORTH CAROLINA CHAPEL HILL 2019 NCI NCI $35,564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ACTIVITY CODE
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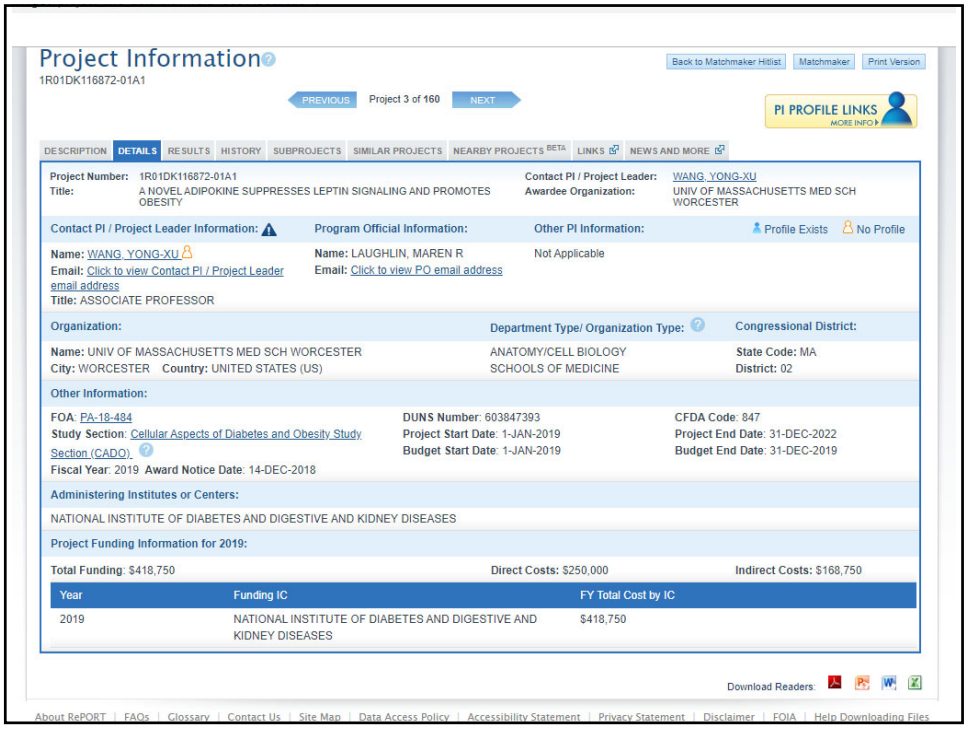
Match Score
T Act Project Year Sub # Project Title
Contact PI / Project Leader
Organization
FY
Admin IC
Funding IC
FY Total Cost by IC
Similar Projects
405 5 K24 DK081913 09 ADIPOKINE PHYSIOLOGY MANTZOROS, CHRISTOS S BETH ISRAEL DEACONESS MEDICAL CENTER 2019 NIDDK NIDDK $180,244
379 5 R01 DK076648 10 EXPLORING THE FUEL-MEDIATED PROGRAMMING OF NEONATAL GROWTH DABELEA, DANA UNIVERSITY OF COLORADO DENVER 2018 NIDDK NIDDK $642,943
373 1 R01 DK116872 01A1 A NOVEL ADIPOKINE SUPPRESSES LEPTIN SIGNALING AND PROMOTES OBESITY WANG, YONG-XU UNIV OF MASSACHUSETTS MED SCH WORCESTER 2019 NIDDK NIDDK $418,750
369 5 R01 DK108408 04 DIETARY SALT HAS AN UNRECOGNIZED ROLE IN MODULATING ENERGY INTAKE AND METABOLIC SYNDROME JOHNSON, RICHARD JOSEPH UNIVERSITY OF COLORADO DENVER 2019 NIDDK NIDDK $415,684
366 5 R01 DK084142 07 LEPTIN AND THE NUTRITIONAL PROGRAMMING OF OBESITY AND DIABETES BOURET, SEBASTIEN G CHILDREN'S HOSPITAL OF LOS ANGELES 2019 NIDDK NIDDK $520,924
361 5 P30 DK057521 20 7732 ANIMAL METABOLIC PHYSIOLOGY CORE KAHN, BARBARA B. MASSACHUSETTS GENERAL HOSPITAL 2019 NIDDK $267,960
342 5 R01 DK100699 05 CENTRAL MECHANISMS REGULATING ACUTE LEPTIN AND INSULIN SIGNALING WILLIAMS, KEVIN W UT SOUTHWESTERN MEDICAL CENTER 2018 NIDDK NIDDK $357,750



Project Information
1R01DK116872-01A1

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PI PROFILE LINKS MORE INFO

DESCRIPTION | DETAILS | RESULTS | HISTORY | SUBPROJECTS | SIMILAR PROJECTS | NEARBY PROJECTS BETA | LINKS | NEWS AND MORE

Project Number: 1R01DK116872-01A1
Title: A NOVEL ADIPOKINE SUPPRESSES LEPTIN SIGNALING AND PROMOTES OBESITY

Contact PI / Project Leader: WANG, YONG-XU
Awardee Organization: UNIV OF MASSACHUSETTS MED SCH WORCESTER

Contact PI / Project Leader Information:
Name: WANG, YONG-XU
Email: Click to view Contact PI / Project Leader email address
Title: ASSOCIATE PROFESSOR

Program Official Information:
Name: LAUGHLIN, MAREN R
Email: Click to view PO email address

Other PI Information: Not Applicable

Profile Exists | No Profile

Organization:
Name: UNIV OF MASSACHUSETTS MED SCH WORCESTER
City: WORCESTER **Country:** UNITED STATES (US)

Department Type/ Organization Type:
ANATOMY/CELL BIOLOGY
SCHOOLS OF MEDICINE

Congressional District:
State Code: MA
District: 02

Other Information:
FOA: PA-18-484
Study Section: Cellular Aspects of Diabetes and Obesity Study Section (CADO)
Fiscal Year: 2019 **Award Notice Date:** 14-DEC-2018
DUNS Number: 603847393
Project Start Date: 1-JAN-2019
Budget Start Date: 1-JAN-2019
CFDA Code: 847
Project End Date: 31-DEC-2022
Budget End Date: 31-DEC-2019

Administering Institutes or Centers:
NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES

Project Funding Information for 2019:
Total Funding: $418,750 **Direct Costs:** $250,000 **Indirect Costs:** $168,750

Year	Funding IC	FY Total Cost by IC
2019	NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES	$418,750

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NIH 102 follow-up:

- **What should I do to help my proposal be reviewed well?**

Preliminary/feasibility data
Judicious use of figures
Grammar and consistency of outline

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The need for preliminary data

- Demonstrate that your proposed research is promising
- Demonstrate a credible ability to carry it out your proposal
- The more surprising the results the more data you will need to convince the reviewers
- Must convince the reviewers of a high likelihood of success
- Demonstrate that you can interpret or analyze data correctly
- The preliminary data must address your north star*. Do not include data that does not help you address the north star of the proposal
- Sometimes it is feasibility data
- Insert it in the proposal where it is relevant

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*north star = the gap you are addressing

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NIH 102 follow-up:

- What should I do to help my proposal be reviewed well?

Judicious use of figures

Grammar and consistency of outline

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What should I do to help my proposal be reviewed well?

- Co-PIs, co-investigators, consultants
- Early stage investigators and/or new investigators
- "A hammer in search of a nail" versus innovation or merging into a new field

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NIH 102 follow-up:

- What is in a summary statement and what does it mean?

SUMMARY STATEMENT

PROGRAM CONTACT: [redacted] **(Privileged Communication)** ***Release Date:*** **12/12/2016** ***Revised Date:***

Application Number: **2 R01 AI098472-06**

Principal Investigator

GANDHI, MONICA

Applicant Organization: UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

Review Group: **BSCH**
Behavioral and Social Consequences of HIV/AIDS Study Section

Meeting Date: **11/15/2016** ***RFA/PA:*** **PA16-160**
Council: **JAN 2017** ***PCC:*** **A23E**
Requested Start: **04/01/2017**
Dual IC(s): **HD**

Project Title: **"Hair Extensions": Using Hair Levels to Interpret Adherence, Effectiveness and Pharmacokinetics with Real-World Oral PrEP, the Vaginal Ring, and Injectables**
SRG Action: **Impact Score:15 Percentile:1**
Next Steps: **Visit http://grants.nih.gov/grants/next_steps.htm**
Human Subjects: **30-Human subjects involved - Certified, no SRG concerns**
Animal Subjects: **10-No live vertebrate animals involved for competing appl.**
Gender: **1A-Both genders, scientifically acceptable**
Minority: **5A-Only foreign subjects, scientifically acceptable**
Children: **1A-Both Children and Adults, scientifically acceptable**
Clinical Research - not NIH-defined Phase III Trial

Project Year	Direct Costs Requested	Estimated Total Cost
6		
7		
8		
9		
10		
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.

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.

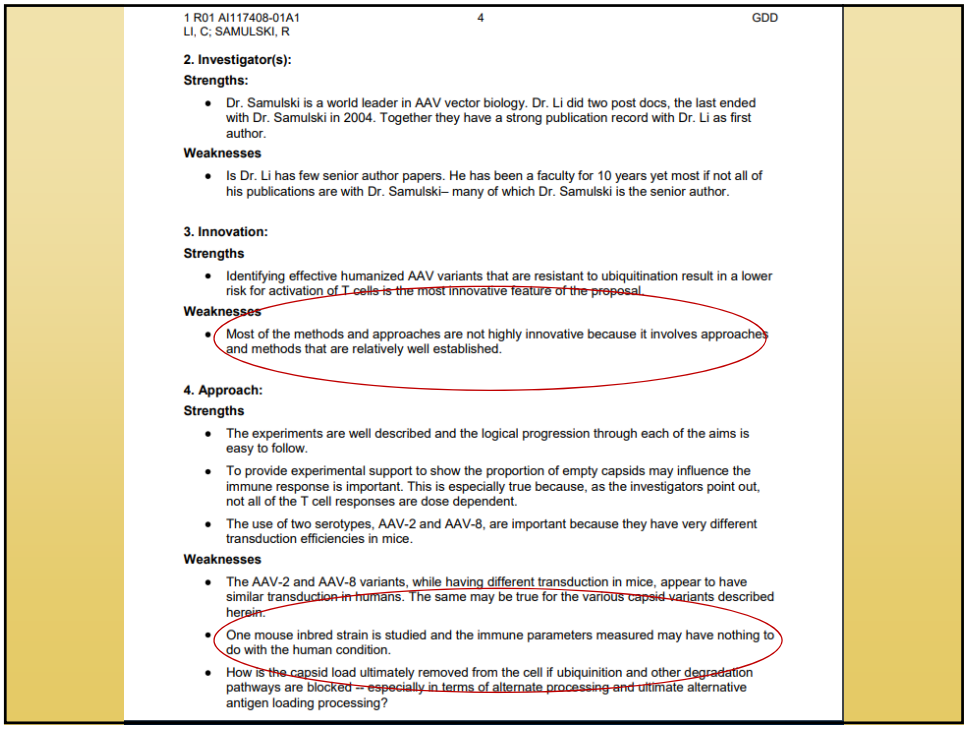
1. Significance:

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.



1 R01 AI117408-01A1 4 GDD
LI, C; SAMULSKI, R

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?