Example Summary Statement 2R44TR002231-02A1 Redacted

SUMMARY STATEMENT

PROGRAM CONTACT: Personal Info **(Privileged Communication)** ***Release Date:*** **07/19/2019**
Revised Date:

Application Number: **2 R44 TR002231-02A1**

Principal Investigator

CETLIN, DAVID

Applicant Organization: MOCKV SOLUTIONS, INC

Review Group: **ZRG1 IMST-F (10)**
Center for Scientific Review Special Emphasis Panel
Small Business: Biological Chemistry, Biophysics and Assay Development

Meeting Date: **07/09/2019** ***RFA/PA:*** **PA18-574**
Council: **AUG 2019** ***PCC:*** **3SB14**
Requested Start: **10/01/2019**

Project Title: **Demonstrating Utility of a Non-Infectious Minute Virus of Mice Virus Like Particle for Predicting Viral Clearance during Biopharmaceutical Process Development**
SRG Action: Impact Score
Next Steps: **Visit https://grants.nih.gov/grants/next_steps.htm**
Human Subjects: **10-No human subjects involved**
Animal Subjects: **10-No live vertebrate animals involved for competing appl.**

Project Year	Direct Costs Requested	Estimated Total Cost
2	639,970	929,937
3	581,989	845,685
TOTAL	1,221,959	1,775,622

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.

2R44TR002231-02A1 Cetlin, David

RESUME AND SUMMARY OF DISCUSSION: This resubmitted Phase II SBIR application proposes to develop Mock Virus Particles (MVP), an assay kit for validating effective removal of viral particle contaminants in biopharmaceuticals. If successful, the proposed research would develop viral surrogate particles, optimize scale of production and validate the utility of the surrogates in evaluating the clearance of viral particles in biomanufacturing processes. The assigned reviewers expressed high to high-moderate enthusiasm for the proposal, with agreement that given the current renaissance in bioprocessing, there is an unmet need for effective viral clearance standards in manufacturing biopharmaceuticals that elevates the significance and innovation of achieving effective viral clearance analysis at lower biosafety levels. There are additional strengths in rigorous Phase I studies supporting the proposed aims, a scientifically robust research plan and well-written commercial plan. Many of prior review's concerns have been addressed in the resubmission. The research team is well qualified, although the role of collaborators is less clear, and geographical separation of the investigators could pose logistical difficulties. Weaknesses noted during discussion mostly centered on the lack of confidence in the effectiveness of the surrogate particles to report viral clearance, which some reviewers perceived as an inadequately addressed lingering concern from the initial review. The business plan does not consider how the assay metrics compare with FDA regulatory requirements, and some panelists were skeptical that viral clearance targets could be achieved and would be adequately scalable for commercial launch. There are also concerns about the commercialization plan that understates the realities of revenue projection. Discussants weighted the noted caveats differently and those who were more enthusiastic were compelled by the significance and commercialization potential of the asay. Following discussion, this was evaluated as a very strong proposal that is expected to make a high impact on the field.

DESCRIPTION (provided by applicant): MockV Solutions, Inc. (MockV) is an early stage company creating viral-surrogate tools that solve the unmet needs of scientists as they develop and optimize products and techniques in a variety of industries that currently rely on expensive and logistically challenging live virus analysis. Virus is a contaminant of great concern during biopharmaceutical production. Because of this concern, international regulatory agencies require proof that manufacturing steps such as chromatography or nanofiltration can effectively remove virus. This is accomplished through small scale "spiking studies" whereby model viruses (ex. Minute Virus of Mice) are artificially introduced into biopharmaceutical material and removed or inactivated by purification techniques. These studies require specialized Biological Safety Level laboratories (BSL) and trained personnel resulting in costs that can soar well above $100,000. Due to these hurdles, most companies delay assessments, thereby increasing the risk of failure leading to cost over-runs and delayed regulatory approval which can cost a company valuable revenue/patent life and cost patients timely access to therapies. MockV is developing a BSL-1 compatible, low cost MVM clearance prediction kit based on the novel use of Virus Like Particles (VLP's) as non-infectious surrogates to live infectious MVM. Utilized during manufacturing process development, the "MVP Kit" would provide scientists with a unique tool to generate "real time" data on MVM clearance. With a "Quality by Design" approach, these scientists could more efficiently engineer their manufacturing process to clear MVM and determine the efficacy of process steps before investing significant resources in costly validation studies. The time and resources saved by the MVP Kit would translate into manufacturing cost of goods and increase the likelihood of passing regulatory hurdles. This project will fund efforts to advance the MVP Kit toward commercialization through product development and applications testing efforts. First, we will optimize MVP production through small scale cell expression screening experiments and downstream chromatography process development efforts. We will also establish analytical MVP Quality Control metrics. After scale-up, we will produce MVP to support applications testing. In this phase of the project, we will be collaborating with REGENX BIO and Chromatan, to assess the utility of MVP for gene therapy and continuous processing applications. During this phase, spiking studies will be conducted to compare the removal of MVP vs live MVM. The data generated could support the use of the MVP Kit in these two emerging and important markets. Finally, we will develop a second-generation

proximity ligation assay for quantifying MVP in high throughput screening applications. After successful completion of this Phase II study we will conduct extensive beta testing prior to commercialization.

PUBLIC HEALTH RELEVANCE: In this Phase 2 SBIR study, MockV Solutions plans to demonstrate the ability of its MVP Kit to predict viral clearance during gene therapy and continuous processing applications. Using this kit, scientists will be able to engineer more efficient biopharmaceutical manufacturing processes and predict viral clearance validation failures prior to expensive regulatory testing. These benefits will reduce biopharmaceutical manufacturing costs of goods and help ensure the timely regulatory approvals for life-altering therapies.

CRITIQUE 1

Significance: 4
Investigator(s): 3
Innovation: 3
Approach: 4
Environment: 3

Overall Impact: While the project is very significant overall, there are a number of minor issues that add up to dampen the enthusiasm for this proposed effort. There is no proof that what their detection can achieve in terms of the number of particles removed will clearly indicate effective virus removal, or at least sufficient virus removal for acceptance by relevant regulatory agencies. The Phase I results leave some questions as to the effectiveness of the method. Questions also remain about the commercialization plan, though eventual acceptance of the product or a competing product is expected. Collaborations and consultants add to the proposal, but does the applicant organization have the personnel and facilities/equipment necessary to achieve their part of the effort? The approach is detailed with expected problems and potential solutions outlined, but the basic issue of “will the product provide relevant data” is not really presented.

1. Significance:

Strengths

- Development of a BSL-1 method for measurement of viral clearance from cell culture produced products is a worthwhile goal.
- The proposed project develops both the particles and the assay for monitoring of the particles to be sold as a kit.
- Second AAV based therapy just approved by FDA and more will be forthcoming, providing a basis for this product.
- Very detailed commercialization plan. Support letters from a number of potential users, though no actual commitments.

Weaknesses

- The total addressable market provided in the commercialization plan is based on use of this kit for all antibody and gene therapy products, and at the $5,000 price point, which does not reflect potential competition, especially by 2027, and the potential lack of willingness to implement this type of product.
- It is hard to imagine that the company can go from 180K in sales to 5.5M in sales in two years, where does this estimate come from?

- This sales increase would take a significant increase in the amounts of MVP and quantitation reagents being produced. The company has not provided the space or personnel expansion plan necessary to achieve this kind of rapid expansion of kit sales.
- Phase I data is not completely convincing that assay will perform as required.

2. Investigator(s):

Strengths

- PI has the experience and background for the proposed work, and the applicant organization already has a related product on the market.
- Good collaborators and organizations with whom this project will be fully evaluated.

Weaknesses

- It is not clear who is qualified on the team to lead the optimization of the proximity ligation assay development effort.
- Two consultants indicate they are providing services for a Phase I project.
- Letters of commitment list indicates one from Dr. Dhar, which is not present.

3. Innovation:

Strengths

- Replacement of real virus in clearance testing assays with a mock virus is an excellent innovation.
- Transition to continuous flow processing is well conceived.
- Improvement in detection assay is good innovation.

Weaknesses

- Aim 1 is simply about decreasing the cost of production and bringing the production in-house.

4. Approach:

Strengths

- Procedure for Aim 1 is well thought out and clearly presented.
- Specific Aim 2 studies will be needed to validate this potential method. Method is well thought out.
- Transitioning the assay for continuous processing in Aim 3 is also worthwhile since batch processing is slowly being replaced with continuous methods.
- Improving the performance of the quantitation assay is needed to reduce the limit of detection, it was surprising Aim 4 was not Aim 2, as this seems very important, and is scheduled to be performed before Aim 2.
- Scientific rigor of experimental testing appears to be present.

Weaknesses

- MVP concentration is to be calculated based on TEM measurements. At expected concentrations greater than 1E13/mL, this is a lot of dilution or a lot of counted particles, but likely both. Is this process automated?
- Text indicates that 3 worse case runs will be conducted with MVP for both AAV serotypes, but Table 2 indicates only a single run under these conditions, which is correct?

- Aim 2 analysis for MVP will use I-qPCR and threshold cycle values, but Figure 1 suggests any particle concentration below 1E5/mL would not be detected.
- The authors indicate an LRV value for MVP ≥ 4 is okay, but if the process shows an LRV of 4 at 1E9/mL loading, does that also mean it will show an LRV of 4 at an MVP loading of 1E7/mL?
- It is not clear why a FBS based media is being used for Sf9 cell growth and particle production when serum free media formulations are available.

5. Environment:

Strengths

- Collaborators and subcontract organization have excellent facilities for the work to be performed by these organizations.

Weaknesses

- Lab and office for applicant organization are 20 miles apart, and collaborators are spread across an even wider area.
- Concern remains over the use of shared equipment with Bluepoint. While applicant indicates that no issues have arisen thus far, the previous work had production of the MVPs outside of the company. Bringing this endeavor inside the company will require a great deal of use of the shared facilities, particularly hoods and cell culture equipment.
- A number of the necessary cell culture instrumentation components are not present, and would need to be purchased, delivered and set up in the facility, which is not included in the 24 month schedule.
- It is not clear why the board of directors is listed under the equipment and facilities.

Phase II (Type 2 R42 and Type 2 R44 applications):

Unacceptable

- The Phase I efforts resulted in a significant advancement in the development of the mock virus particle and assay, and show the necessary scientific rigor. My concern is for the data shown in figure 1, in which a 10 fold dilution series was analyzed, but only the results from the first 5 fold dilutions are reported along with the blank. While the 1E5 can clearly be distinguished from the blank, it is not clear how lower virus particle concentrations performed. In addition, it is not clear that 1E5/mL is an acceptable performance, as this still indicates that 100 virus particles are present in each 1 µL of solution. The proposal text indicates that particles were found to be completely removed at centerpoint conditions and at pH 8.0, but it is not clear what "completely removed" actually means based on the data reported.
- Commercialization plan is included and is detailed, but with a few weaknesses.

Protections for Human Subjects

Not Applicable (No Human Subjects)

Vertebrate Animals:

Not Applicable (No Vertebrate Animals)

Biohazards:

Acceptable

- BSL-2 virus will only be utilized in appropriate laboratories.

Resubmission:

- PI has addressed most of the concerns raised by the previous reviewers. The issue of geographical separation and much of the necessary equipment being outside of the applicant organization control were not truly addressed.

Resource Sharing Plans:

Acceptable

Authentication of Key Biological and/or Chemical Resources:

Unacceptable

- To produce the mock particles using the Sf9 cloning system the baculovirus had to be genetically modified to incorporate the necessary proteins. No mention of continued monitoring of the baculovirus stock was included in the authentication plan.

Budget and Period of Support:

Recommend as Requested

CRITIQUE 2

Significance: 3
Investigator(s): 3
Innovation: 4
Approach: 4
Environment: 3

Overall Impact: In this Phase II SBIR proposal, MockV seeks to move its lead viral clearance prediction kit toward commercialization. Specific objectives include: (1) optimization of mock virus particle production, (2) optimization of a high-throughput mock virus particle quantitative assay that builds on Phase I successes and allows end users to implement the kit in existing lab hardware systems, and (3) demonstration of the kit in gene therapy and continuous processing applications. The estimated current market for the “MVP kit” is $61M, and the projected addressable market it $204M, based on reasonable estimates of mAb and gene therapy market growth. MockV has begun to protect its market position through securing its IP, with one US patent awarded. The premise of the proposed effort is that a non-infectious, virus-free means of assessing viral clearance from biotherapeutics at the point of manufacture would enhance throughput and safety in biopharmaceutical production, and a well-reasoned commercialization plan is presented. The MockV team is large and their backgrounds and capabilities are diverse. The team has developed an approach that will yield valuable insight into virus clearance in biopharmaceuticals at the point of manufacture. The scientific rigor demonstrated in Phase I is convincing and bodes well for a continuation of the effort. While the proposed effort has many strengths, it also has weaknesses, some of which were carried forward from the previous Phase II submission: It is not clear that the cost savings claimed (relative to a Minute Virus of Mice assay) would be as large as claimed, or that the advantages of this approach would justify the change in process required for biopharmaceutical manufacturers who have already emplaced MVM approaches. The ChromaTan collaboration team is larger than appears to be needed given the scope of work

required of them. The scientific approach lacks novelty, and no convincing argument was offered for the selection of batch mode affinity chromatography for VLP purification.

1. Significance:

Strengths

- The premise of the proposed effort is that a non-infectious, virus-free means of assessing viral clearance from biotherapeutics at the point of manufacture would enhance throughput and safety in biopharmaceutical production. This is a well-reasoned premise.
- The use of a virus-like particle rather than a virus, even a benign virus, would enhance safety.
- The commercialization plan is thorough and well-reasoned.

Weaknesses

- It is not clear that the cost savings claimed (relative to a Minute Virus of Mice assay) would be as large as claimed, or that the advantages of this approach would justify the change in process required for biopharmaceutical manufacturers who have already emplaced MVM approaches.

2. Investigator(s):

Strengths

- The MockV team is large and their backgrounds and capabilities are diverse. The PI has significant relevant experience and is appropriately equipped to lead the effort.

Weaknesses

- The ChromaTan collaboration team is larger than appears to be needed given the scope of work required of them.

3. Innovation:

Strengths

- It is clear that MockV has developed an approach that will yield valuable insight into virus clearance in biopharmaceuticals at the point of manufacture.
- MockV has started to protect its technology, with one US patent to date.

Weaknesses

- The approach lacks novelty.

4. Approach:

Strengths

- The production approach for virus-like particle manufacture is solid.
- The scientific rigor demonstrated in Phase I is convincing and bodes well for a continuation of the effort.

Weaknesses

- The VLP production purification methodology, as described, was not sufficiently convincing to indicate that batch mode affinity chromatography is in fact the best method. A comparison of alternative approaches that are more scalable (or continuous), given the claimed market volume, is needed.

5. Environment:

Strengths

- The facilities and equipment available to the group is appropriate to the tasks outlined in the proposal.

Weaknesses

- The breadth of participating organizations raises concern that management of the project to ensure timely progress will be a challenge.

Phase II (Type 2 R42 and Type 2 R44 applications):

Acceptable

- MockV effectively utilized its Phase I project opportunity to collect confirmatory data that support the objectives outlined for Phase II.

Protections for Human Subjects

Not Applicable (No Human Subjects)

Vertebrate Animals:

Not Applicable (No Vertebrate Animals)

Biohazards:

Acceptable

- The proposal adequately addresses handling of applicable biohazardous materials.

Resubmission:

- This resubmission adequately addresses some of the concerns raised in the previous review. Inadequately addressed concerns include: lack of provision of quantitative metrics for Specific Aim 3, and lack of fit with continuous processing methods.

Resource Sharing Plans:

Not Applicable (No Relevant Resources)

Authentication of Key Biological and/or Chemical Resources:

Acceptable

- A plan was provided for regularly authenticating key chemical/biological resources.

Budget and Period of Support:

Budget Modifications Recommended (in amount/time)

Recommended budget modifications or possible overlap identified:

- Equipment items 1 and 2 (Cell Viability Analyzer and cell culture analyzer) are insufficiently justified. It is recommended that an alternative to the purchase of these items (a lease, or contracting of services) be found and that these items be removed from the budget.

- The ChromaTan project component and subaward are not well justified, and it is not clear that all of the support requested for this project component is needed. It is recommended that this line item in the budget be reduced by 50% and the scope of work assigned to ChromaTan be reduced equivalently. The inclusion of five personnel and two CCTC systems is not well justified.

CRITIQUE 3

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

Overall Impact: This proposal seeks to commercialize a noninfectious viral-like particle kit for quantitatively evaluating viral clearance in bioprocess operations. This Phase II application addresses an ongoing challenge in bioprocessing, viral clearance in individual processing steps, that is difficult to evaluate during process development due to the current need for live virus and BSL-II facilities to conduct clearance assays. This resubmission includes a summary of the successful Phase I work previously conducted, a strong business plan, and an approach that includes quantitative metrics by which experiments in all aims will be evaluated. The approach is ambitious but has the backing of key partners that will make its execution within 24 months feasible. Both the previous work and the proposed work include the quantitative and statistical analyses needed to achieve high levels of rigor and reproducibility, which is critical for the proposed application. While the application is generally strong, one weakness of the application is the risk that the MVP will not adequately mimic actual viral infections under all potential process conditions. One example of this is seen in Figure 3 of the application, where log reduction values in “Run 6” were statistically distinct between MVP and MVM experiments. However, quantitative comparisons between MVP and MVM infections could provide guidance as to the conditions that will lead to differences in log reduction values. In summary, this is a very strong application that addresses an important unmet need in bioprocessing in an era where the diversity of emerging bioprocesses will require extensive validation using robust but cost-effective characterization techniques.

1. Significance:

Strengths

- This application addresses the important bioprocessing challenge of viral clearance, which is currently too costly for systematic evaluation. The availability of a robust tool for evaluating viral clearance could lead to major improvements in the rigorous evaluation of viral contamination and clearance in a field that is rapidly expanding into several new product areas (major).

Weaknesses

- None noted.

2. Investigator(s):

Strengths

- The PI invented the mock viral particles that form the basis for the kit, and is ably seeing through the development of the technology (major).

- The research team has an extremely strong background in bioprocess engineering and is fully prepared to perform the work (major).

Weaknesses

- None noted.

3. Innovation:

Strengths

- The proposed kit would be the first of its kind for the entire bioprocess industry (major).

Weaknesses

- None noted.

4. Approach:

Strengths

- The research plan is based on rigorous, reproducible previous research conducted by the company and shown in the application (major).
- The research plan in this resubmission includes detailed plans for generating extensive data that meets high standards of rigor and will readily enable reproducibility (major).

Weaknesses

- There is the risk that the MVP will not adequately mimic actual viral infections under all potential process conditions of interest. One example of this is seen in Figure 3 of the application, where log reduction values in “Run 6” were statistically distinct between MVP and MVM experiments. This concern may be alleviated by the rigorous proposed sets of evaluations to be pursued (see also strengths) (major).

5. Environment:

Strengths

- Strong bioprocess facilities at all proposed performance sites (major).

Weaknesses

- The sites are separated by some distance, requiring the PI to travel in order to coordinate efforts (minor).

Phase II (Type 2 R42 and Type 2 R44 applications):

Acceptable

- The Phase I studies reported in the application appear to have been successful, the business plan for Phase II appears to be sound, and there appears to be strong commercialization potential as evidenced by a growing number of industry interest and collaborations.

Protections for Human Subjects

Not Applicable (No Human Subjects)

Vertebrate Animals:

Not Applicable (No Vertebrate Animals)

Biohazards:

Acceptable

- BSL-2-qualified facilities will be used for all work involving infectious viral particles (MVM versus MVP studies).

Resubmission:

- This resubmission carefully considers and addresses the reviewer comments from the previous round of reviews.

Resource Sharing Plans:

Acceptable

Authentication of Key Biological and/or Chemical Resources:

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:

COMMITTEE BUDGET RECOMMENDATIONS: The budget was recommended as requested.

Footnotes for 2 R44 TR002231-02A1; PI Name: Cetlin, David

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.