SUMMARY STATEMENT

PROGRAM CONTACT: Personal Info **(Privileged Communication)** ***Release Date:*** **07/11/2017**
Revised Date:

Application Number: **1 R43 TR002231-01A1**

Principal Investigator

CETLIN, DAVID

Applicant Organization: MOCKV SOLUTIONS, INC

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

Meeting Date: **06/30/2017** ***RFA/PA:*** **PA16-302**
Council: **AUG 2017** ***PCC:*** **OSA13**
Requested Start: **10/02/2017**

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: **30-Vertebrate animals involved - no SRG concerns noted**

Project Year	Direct Costs Requested	Estimated Total Cost
1	171,200	233,688
TOTAL	171,200	233,688

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.

1R43TR002231-01A1 Cetlin, David

ADMINISTRATIVE NOTE

RESUME AND SUMMARY OF DISCUSSION: In this resubmission, the applicants aim to utilize a non-infectious virus like particle (VLP)-based kit as a surrogate for minute virus of mice (MVM) clearance prediction that would be BSL-1 compatible (making this a routine test) and more cost efficient in contrast to current kits. They will develop an immuno-qPCR assay to quantify MVM-VLP and then use it for predicting live MVM clearance. The reviewers believed this project would address an immediate market need as there is no low cost viral clearance prediction kit currently available (scientific premise). Additional strengths noted by the reviewers included the preliminary data, the expert team of investigators, a thorough addressing of the comments from the previous review, letters of support showing interest in this project, and the rigorous approach. Though the use of female only mice is not justified as a biological variable in the approach, it was pointed out during the discussion that it is not relevant as female rabbits are being used to generate antibodies, which is a common practice for reagent production. Although the LODs are compatible with market need, the reviewers have concern regarding the needed sensitivity for lower virus concentrations (minor) and reproducibility statistics (scientific rigor). The committee believes this project would have a high probably of success in generating these detection kits that would have a high overall impact on biopharmaceutical manufacturing processes.

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 techniques in a variety of fields that currently rely on expensive and logistically challenging live viruses. We are currently focused on developing a novel series of assay kits which will enable biopharmaceutical scientists to study the efficacy of manufacturing techniques intended to remove or inactive virus; a contaminant of great concern during the production of biopharmaceuticals. In fact, Minute Virus of Mice (MVM) has notoriously contaminated several manufacturing facilities over the past couple decades leading to drug shortages, tremendous costs, and increased regulatory scrutiny. Because of this potential, mammalian derived biopharmaceutics are only approved for clinical or commercial use after their manufacturing processes demonstrate sufficient viral clearance. This is accomplished through small scale “spiking studies” whereby model viruses (ex. MVM) 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 a validation failure. Validation failures lead 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 “MVM-VLP 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 confidentially optimize 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 MVM-VLP Kit would translate into cheaper $/gram manufacturing costs and increase the likelihood of passing regulatory hurdles. Viral clearance is an international regulatory requirement for the ~6,000 mammalian cell derived BP in worldwide development. With the projected cost of a MVM-VLP Kit to be $2,500, we estimate an annual market value of ~$95M/year. To set us on the path toward commercialization, we propose to first develop an Immuno-QPCR assay capable of quantifying MVM-VLP and then utilizing this assay to test the feasibility of accurately predicting live MVM clearance with our non- infectious MVM-VLP surrogate. After successful completion of this Phase I feasibility study we will further optimize and validate the Immuno-QPCR assay. We will then conduct extensive beta testing through a series of Design of Experiments studies, comparing MVM-VLP

clearance to live MVM clearance through variety of purification techniques (chromatography, inactivation, filtration) and representative operating conditions.

PUBLIC HEALTH RELEVANCE: In this Phase I SBIR study, MockV Solutions plans to test the feasibility of accurately predicting Minute Virus of Mice (MVM) clearance through the use of a non-infectious Virus Like Particle Kit. Using this kit, scientists will be able to develop more efficient biopharmaceutical manufacturing processes and predict viral clearance validation failures prior to expensive regulatory testing. These benefits will reduce the $/gram costs of biopharmaceuticals and ensure the timely regulatory approvals of life-altering therapies.

CRITIQUE 1

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

Overall Impact: The viral detection kit proposed here would reduce drug costs by streamlining the discovery, development and production of biologics, a rapidly expanding area for approval of new medicines. In addition to a compelling scientific hypothesis in the proposal, the commercialization plan is clear and means of market penetration logical. The potential impact of the project is high.

1. Significance:

Strengths

- The viral detection kit proposed here would have immediate use in development of purification procedures for biopharmaceuticals produced by mammalian cells and with further development find use in quality control assurances for biopharmaceutical drugs. In both the immediate and eventual uses, the kit would reduce, by months, the time for development of drug production protocols.
- The proposed kit could make an immediate impact because it eliminates the need for specialized biosafety laboratories. The kit could quickly be widely tested and accepted by the biopharmaceutical characterization and production community.
- The low cost of the kit, relative to live spiking experiments currently in use, would allow earlier introduction of virus-elimination testing at earlier stages of the production processes, i.e. stepwise optimization of procedures is more cost effective that testing a developed process.

Weaknesses

- Although suitable for current standard and known viruses, the product may not be suitable, at least in its current form with a detection limit of <10**3 particles/ml, for lower concentrations of virus. This is currently a minor weakness.

2. Investigator(s):

Strengths

- The PI presents reasonable short-term goals for the product by outlining a logical progression for introducing the product.

- The PI is experienced in developing production processes for biopharmaceuticals and in the production of the biopharmaceutical product. The PI played leadership roles in the production of the biopharmaceutical Benlysta (betimunab) for treatment of lupus.
- The assembled team has the expertise required to complete the project.

Weaknesses

- None noted.

3. Innovation:

Strengths

- The PI has developed an I-qPCR assay (Immuno-qPCR) for detection of the MVM-VLP by using a specific antibody conjugated to a double-stranded oligonucleotide. The quantitative immuno-PCR (qIPCR) technology combines the advantages of flexible and robust immunoassays with the exponential signal amplification power of PCR. The antibody is used for detection and the DNA is used for signal generation by quantitative PCR. Because of the efficiency of nucleic acid amplification, qIPCR typically leads to a 10- to 1,000-fold increase in sensitivity compared to an analogous enzyme-amplified immunoassay. While the I-qPCR technology is not novel, a specific assay was developed for this project.

Weaknesses

- None noted.

4. Approach:

Strengths

- The critical reagent for the studies has been validated as a surrogate for live virus. The PI has published studies showing that MVM virus-like particles produced by baculovirus/Sf9 expression have many of the non-infectious properties of the live MVM. The study was conducted in collaboration with CDER scientists at the FDA.
- Quantitative milestones needed to be achieved by the kit to be commercially competitive are clearly stated.
- Possible reasons for pitfalls are clearly stated and alternative approaches are clearly defined. For example, the sources and effects of MVM denaturation are considered in the experimental approach.
- Sex as a biological variable is not relevant for this proposal at this time. Female rabbits will be used to generate antibodies. This is common practice for reagent production.

Weaknesses

- Except for pitfalls noted by the PI, none to add.

5. Environment:

Strengths

- The PI has an established collaboration with scientists at the Office of Biotechnology Products, Office of Pharmaceutical Quality, Center for Drug Evaluation and Research, Food and Drug Administration.
- The Company has or has access to the equipment required for the project. Laboratory space is also suitable.

Weaknesses

- None noted.

Protections for Human Subjects:

Not Applicable (No Human Subjects)

Vertebrate Animals:

YES, all four points addressed

Biohazards:

Not Applicable (No Biohazards)

Resubmission:

- Many of the previous panel's concerns were addressed in a thorough manner. In particular, the PI altered experimental procedures to increase sensitivity, as suggested by the panel.

Authentication of Key Biological and/or Chemical Resources:

Acceptable

- Well-defined and clear plans are presented for authentication of MVM virus-like particles and detection antibodies.

Budget and Period of Support:

Recommend as Requested

CRITIQUE 2

Significance: 2
Investigator(s): 1
Innovation: 1
Approach: 4
Environment: 3

Overall Impact: The goal is to develop a novel series of cost-efficient assay kits to study the efficacy of manufacturing techniques intended to remove or inactivate virus, which will can significantly reduce a risk of viral contamination during biopharmaceutical (BP) manufacturing. The team seems to be experienced in both technology and entrepreneurship. The plan is well laid out, empowered by the use of non-infectious virus like particle (VLP), and is supported by strong preliminary data. The lack of clarity for sex as biological variables and no specific discussion of statistical consideration for reproducibility is concerning but the potential overall impact still remains very strong.

1. Significance:

Strengths

- Viral contamination is a serious and inherent risk during BP manufacturing, and it is regulated extensively. However, the high cost to get "clearance" often results in delaying appropriate

steps to prevent contamination, and eventually leads to validation failures in the late stage of production.

- A low cost viral clearance prediction kit will be extremely valuable. There is no alternative on the market, yet.

Weaknesses

- None noted.

2. Investigator(s):

Strengths

- PI, Mr. Cetlin, seems to have significant experience as "viral clearance specialist" in large biopharmaceutical companies (Human Genome Sciences and GlaxoSmithKline).
- Dr. Dhar seems like an expert in virology.

Weaknesses

- None noted.

3. Innovation:

Strengths

- The use of MVM-VLP as a surrogate to MVM and to predict viral clearance seems novel.
- It was noted that the method was recently granted a notice of allowance (USPTO's intent to issue a patent) for the patent, which should establish strong protection for their IPs.
- The on-site, on-demand, real-time nature of the proposed MVM-VLP Kit will make as an economical and practical tool to develop and optimize manufacturing processes prior to (more expensive) regulatory MVM spiking validation studies.

Weaknesses

- None noted.

4. Approach:

Strengths

- Overall approach seems well laid out, with a clear goal.
- Aim 1: I-qPCR development will enable the detection of VLP which is non-infectious. Preliminary data seems promising (10^5 particles/ml), and the collaboration with MedImmune indicates good progress toward their ultimate goal (<10^4 particles / ml). Also, the use of mAb, instead of pAb, seems to provide additional advantages as more consistent resource.
- Also, recent collaboration with FDA (published) demonstrates that the physicochemical properties of MVM-VLP (ex. hydrodynamic radii, surface charge and hydrophobicity) are comparable to live MVM.
- In Aim 2, the comparison study between MVM and MVM-VLP (spiking experiments) are well laid out.
- Their anticipated global annual marking value of $95M / year seems modest but reasonable for a small business development, with anticipated 50% market penetration.
- Lots of letters of support, including GSK, Millipore, etc. are provided, which demonstrate the existence of their potential markets/customers.

Weaknesses

- Sex as biological variable -- only female mice will be used. No justification given for only female mice.
- No specific discussion of statistical consideration for reproducibility, such as the number of trials and replicates.

5. Environment:

Strengths

- MockV Solutions Inc is very young company but has established strong collaborations with other established companies such as BluePoint, MedImmune, etc, for the project.

Weaknesses

- MockV Solutions Inc does not have their own space, and will sub-lease the spaces from BioHealth Innovation and/or Texcell North America Inc. The company has only 1 full-time employee, Mr. Cetlin.

Protections for Human Subjects:

Not Applicable (No Human Subjects)

Vertebrate Animals:

YES, all four points addressed

Biohazards:

Not Applicable (No Biohazards)

Resubmission:

- The previous critiques are addressed.

Authentication of Key Biological and/or Chemical Resources:

Acceptable

Budget and Period of Support:

Recommend as Requested

Recommended budget modifications or possible overlap identified:

- No detailed budget provided for subcontracts (BluePoint and Texcell North America)

CRITIQUE 3

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

Environment: 3

Overall Impact: This is a strong application that proposes to develop a non-infective viral mimic that can be used in the development of biomolecule purification procedures to test how well those procedures are at clearing potential viruses. The present methods using live MVM require BSL level 2 facilities. The viral-like particles produced here only need BSL-1 facilities that are much cheaper. It will allow the monitoring the effectiveness of purification strategies on viral clearance earlier in production development saving companies potentially millions of dollars and time. The proposal was previously reviewed and the investigators have done a thorough job of revising the proposal in response to these reviews. The investigator team is strong with all of the necessary expertise assembled to successfully carry out the proposed research. Dr. Cetlin has 6 years of previous experience in the area of viral clearance development and has founded this company to specifically overcome the issue he encountered when developing such methods. Dr. Dhar is a molecular virologist experienced in developing non-host virus amplification technology as will be necessary in this proposal. Dr. Dembrow is an Employee of BluePoint Bioscience and has the experience necessary for producing the monoclonal antibodies. The use of the MVM-VLPs is innovative. There are several letters of support from both filtration and biopharma companies attesting to the strong interest in this product. One weakness of the proposal is that MockV does not have a physical presence but will be able to lease the necessary lab space and equipment from Texcell over the duration of the grant should it be successful. A letter verifying this arrangement is in place. The vertebrate mice use is justified and all of the 4 requirements are addressed. Sex as a biological variable is not pertinent for this proposal as the animals are used to produce antibodies and female mice respond better to antigen challenge. This is a strong rigorous proposal that could potentially significantly affect the way viral purification is carried out.

Protections for Human Subjects:

Not Applicable (No Human Subjects)

Vertebrate Animals:

YES, all four points addressed

- Mice are justified to produce the monoclonal antibodies to be used in the study

Biohazards:

Not Applicable (No Biohazards)

Resubmission:

- The investigator has thoroughly and completely responded to the previous review critiques

Authentication of Key Biological and/or Chemical Resources:

Acceptable

- The investigator has provided adequate authentication for all of the biologicals involved in the study.

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 ANIMALS: ACCEPTABLE

COMMITTEE BUDGET RECOMMENDATIONS: The budget was recommended as requested.

ADMINISTRATIVE NOTE:
During the review of this application, reviewers and/or NIH staff noted that one or more biosketches did not comply with the required format (NOT-OD-15-032). An electronic notification has been sent to the contact Program Director/Principal Investigator and Signing Official for this application, to ensure that future applications use the correct biosketch format. NIH has the authority to withdraw such applications from review or consideration for funding.

Footnotes for 1 R43 TR002231-01A1; 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.