AWARD NUMBER: W81XWH-18-9-0009

EGS NUMBER: MT180009

TITLE: Novel cell-based Therapy to Treat Muscle Atrophy Associated with Peripheral Nerve Injury

PRINCIPAL INVESTIGATOR: Dr. Mitchell Zakin

PERFORMING ORGANIZATION: Clear Scientific (previously Nano Terra)

REPORT DATE: 12/01/2020 for Fiscal Year 2 (Oct 2019 – Sep 2020) Activities

TYPE OF REPORT: Annual Report

PREPARED FOR: U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

MTEC
Medical Technology Enterprise Consortium

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Annual Report 2

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6. AUTHOR(S)
Dr. Mitchell Zakin; Dr. Piercen Oliver; Dr. Madeline Vara; Mr. Philip Graf

E-Mail: mzakin@clearsci.com; poliver@clearsci.com; mvara@clearsci.com; pgraf@clearsci.com

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MT180009

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W81XWH-18-9-0009

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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Clear Scientific, LLC
737 Concord Ave
Cambridge, MA 02138

8. PERFORMING ORGANIZATION REPORT
2018-680

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

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13. SUPPLEMENTARY NOTES

14. ABSTRACT
During this performance period, CSInc developed a stable therapeutic formulation which allows for direct and localized injection of human iPSC motoneuron cells, designed to promote motoneuron cell growth and nerve connection, and thus minimize muscle atrophy induced by peripheral nerve injury. This formulation can be readily prepared and injected for studies and treatments. CSInc has continued to work on formulation which can be readily stored in cryogenic conditions (liquid nitrogen) for ease of transport and storage as a viable treatment in hospital settings. In conjunction with our surgical partners at MGH, animal studies were initiated using Lewis rats to monitor and observe the effects of the CSInc therapeutic formulation on sciatic nerve injury (with both repair and no repair) and gastroc muscle atrophy over the course of 28 days. All rats were additionally given daily tacrolimus treatment to inhibit immunorejection of the xenographic motoneuron treatment. Results of the rat studies were quantitatively and qualitatively measured using standard metrics including walking track observations and post-euthanasia gastroc muscle mass comparisons. Rat studies are currently ongoing.

15. SUBJECT TERMS
Peripheral nerve injury; muscle atrophy; muscle wasting; cell therapy; muscle atrophy treatment

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			Clear Scientific, LLC
Unclassified	Unclassified	Unclassified	Unclassified	18	19b. TELEPHONE NUMBER *(include area code)* (617) 621-8500

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MTEC Medical Technology Enterprise Consortium

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Annual Technical Status Report for

Novel cell-based Therapy to Treat Muscle Atrophy Associated with Peripheral Nerve Injury

Research Project No. 2018-680-001

EGS# MT180009

Reporting Period: 01 Oct '19 – 30 Sep '20

MTEC Research Project Awardee

Clear Scientific

Massachusetts General Hospital

Research Project Technical POC

Dr. Mitchell Zakin

737 Concord Ave

Cambridge, MA 02138-1002

617-621-8500

mzakin@clearsci.com

Submitted: 01 Dec '20

1. Project Status

a. Accomplishments

This may include completion of milestones, objectives, and/or tasks, regulatory approval received, publication of papers, presentations at conferences, filing of intellectual property, etc. for this year, followed by date in DD-MMM-YYYY. Write salient bullet points to highlight the requested information.

In the first quarter (October – December 2019), Clear Scientific (CSInc) completed subcontracting negotiations with Massachusetts General Hospital **OCT-2019** and met with MGH and Biomere to determine animal models for *in vivo* experiments **07-OCT-2019**, selecting Lewis rats for the first round of experiments at MGH. Additionally, CSInc/MGH down-selected the therapeutic delivery to direct IM (or, alternatively, near-NMJ) injection, based on the earlier work of Craff, et. al. (2007); this selection significantly simplifies introduction of the therapeutic and enables acceleration of screening of therapeutic candidates **NOV-2019**

In the second quarter (January – March 2020), the MGH Rat IACUC was approved **27-MAR-2020**. During this time, global pandemic COVID-19 began to impact the United States, CSInc continued to work as an essential business under appropriate health and safety guidelines of the CDC and Massachusetts. Non-COVID related animal studies at MGH were temporarily closed in response to the pandemic

In the third quarter (April – June 2020), CSInc and MGH finalized the initial candidate formulation and delivery system for injection into rats **08-MAY-2020**. The rat ACURO protocol was approved **JUN-2020**. MGH reopened for non-COVID related animal studies in June.

In the final quarter of the contracting year, an amendment to the ACURO protocol for the rat study at MGH was approved **10-JUL-2020**. Rat studies began at MGH under the modified protocol, using the formulation and delivery system developed by CSInc **AUG-2020**, **SEP-2020**. Rat studies are ongoing to determine the effects and impacts on the therapeutic system. CSInc is not progressing to NHP studies until positive results are determined from the murine model.

b. Reportable Outcomes

This may include development of a product, prototype, new methodology, or any other similar items that have resulted from this research. Write salient bullet points to highlight the requested information. Please also include a cumulative chronological list of written publications in technical journals, papers, or other presentations at meetings, conferences, seminars, etc.; New discoveries, inventions, or patent disclosures, and specific applications.

During the first quarter (October – December 2019) CSInc/MGH selected to use Lewis rats for screening studies and naïve cynomolgus monkeys for pivotal studies. The team chose to forego porcine studies. Commercially available human motoneuron iPSC cells available from BrainXell were chosen for in vitro studies and planning.

During the second quarter (January – March 2020), CSInc demonstrated with initial formulation/delivery system testing that the viability of neurons do not suffer when injected through 22- or 25-G needle. BrainXell human iPSC-derived motoneurons were sent to VRL for viral analysis in order to submit IACUC. Viral testing of motoneuron source required for rat IACUC and ACRUO came back negative, allowing MGH to move forward with approval submissions. Procedural development with low-speed centrifugation proved to be an effective method to replace BrainXell medium with a GRAS injection medium (PBS) without harming neurons for the formulation. Finally, initial neuron formulation in PBS is stable for at least three hours, and is viable when re-introduced to media that promotes growth.

In the third quarter (April – June 2020), CSInc finalized the method for injecting initial candidate formulation into rats. Initial methods for making the neuron formulation with CryoStor were developed. Additionally, the method for delivery of the neuron formulation to MGH was developed.

In the fourth quarter (July – September 2020), CSInc performed preliminary dry run tests for delivery of neuron formulation and kit materials to MGH. MGH also developed training methods to optimize injection procedure into rats. Simultaneously, CSInc optimized the analysis method to monitor motoneuron viability and cell counts. Rat studies were started at MGH and are continuing into the next year. CSInc will not proceed to NHP studies until positive and conclusive results are demonstrated in the murine model.

c. Progress Detail

Describe each Statement of Work (SOW) task or logical segment of work on which effort was expended during this annual reporting period only. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved or problems encountered. A succinct description of the methodology used shall be provided.

For an award that includes the recruitment of human subjects for clinical research or a clinical trial: (i) report progress on subject recruitment, screening, enrollment, completion, and numbers of each compared to original planned target(s), e.g., number of subjects enrolled versus total number proposed; (ii) report amendments submitted to the IRB and USAMRMC HRPO for review; and (iii) any adverse events.

Since contracting has been changed and updated during the first year, the deliverables described in the Progress Detail section of this report reflect the new and accurate milestones in the updated contract.

Deliverable 2 (Year 1) In-vitro test results for candidate formulation(s)/delivery system combination(s)

CSInc chose to obtain human induced pluripotent stem cell motor neurons from BrainXell (Madison, WI) for use in proposed *in vitro* studies and in rat models. CSInc has formulated an *in vitro* test plan to be conducted at CSInc to confirm that BrainXell's cells follow a similar growth pattern and show viability consistent with previous *in vitro* data obtained at BrainXell and at CSInc. This testing plan will be done in four major parts:

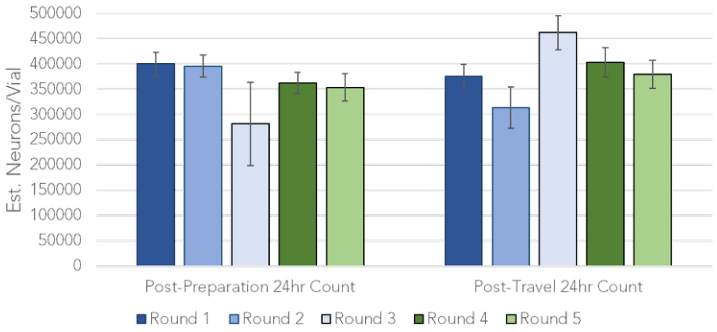
(1) Obtain hiPSC-MNs from BrainXell and obtain Type I collagen gel kits
(2) Test viability of BrainXell MNs in saline solution using live/dead staining as well as observing dendritic extension
(3) Test viability of BrainXell MNs in various collagen gels using live/dead staining as well as observation of dendritic extension
(4) Test viability of BrainXell MNs in saline and collagen when pushed through selected medical disposables including the exact syringes and needles that will be used for rat and NHP studies

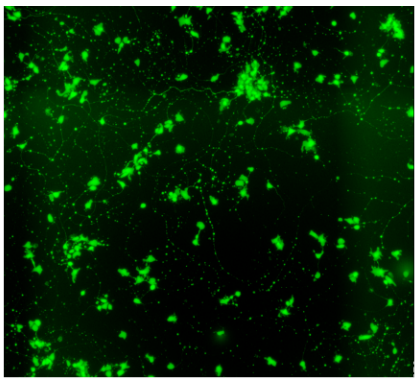
CSInc additionally narrowed down potential type I collagen kits. Type I collagen appears to allow for the best growing conditions for motor neurons compared to other collagen types; type I collagen is used to support similar cell growth to what we are aiming to achieve. CSInc developed a plan to conduct testing of BrainXell's hiPSC-MNs in both saline solution (DMEM/F12-based) as well as in collagen gels of various viscosities. A plan was created to use live/dead stains (Calcein-AM and Ethidium homodimer-1) to determine if the viability of neurons in saline matches the proposed viability suggested by BrainXell then repeat this process with neurons in collagen gel formulations. Previous work done at CSInc with this cell line for this project shows viability within ~10% of viability suggested by BrainXell when seeded at 2,500 viable neurons/well.

Deliverable 3 (Year 2) Rat model motoneuron formulation(s) dosing study results

During this reporting period, CSInc finalized sourcing of the human motoneurons to be used for the studies. Specifically, both in vitro and in vivo work was conducted using iPSC-derived spinal motoneurons purchased commercially from BrainXell (BX-0100). These neurons were derived from peripheral blood mononuclear cells and were reprogrammed using episomal vectors. These motor neurons have >90% purity. Remaining 10% of cells made up of neuronal progenitors that were not fully differentiated. 70-75% of neurons are positive for FOXP1 (motoneuron marker) and the remaining neurons are likely interneurons or other unidentifiable neurons. CSInc tested various cells and gel properties to create the most promising therapeutic mixture for delivery and injection for in vivo studies. Specifically, guidance for the in vivo studies was derived from the based on the earlier work of Craff, et. al. (2007); CSInc determined with MGH to use Lewis rats for the first round of in vivo studies to be conducted with human motoneurons.

The optimal formulation, needle, gauge, and IM delivery method was selected and vetted by CSInc in conjunction with MGH. The final formulation for the decided upon provides a 100 µL injection which should contain approximately 400,000 human motoneuron cells. The injection is delivered with a 27G needle, that is ¾ inch in length. Training tests determined this to be the most efficacious method of delivering the therapeutic into the rat muscle. CSInc monitored the viability and cell count of each delivery by plating cells before an after delivery trips to MGH for 24-hr cell counting, and by monitoring neuron sprouting out to 96-hrs post-plating (**Figure 1**).





Sprouting of neurons confirmed (image taken at 96 hours post-plating)

Figure 1. Neuron viability of the NT therapeutic formulation to be used for *in vivo* studies. On the right, a graph shows the 24-hr viability of five separate rounds of therapeutics prepared for injection and delivery to MGH. The viability targets 400,000 live neurons per injection, which is monitored from the same set of neurons both before and after delivery to MGH. On the left, an image showing a typical neuron sprouting after 96-hrs post-plating, confirming the cell therapy viability.

For the rat study, four main test groups were decided upon. The first control group consists of rats in which the sciatic nerve has been severed and not repaired; in the second control group, the sciatic nerve is severed and then repaired. For both control groups, the rats receive 100 µL injection of PBS to the gastroc muscle (**Figure 2**). Two test groups mimic the sciatic nerve cut with or without repair, followed by injection with the motoneuron therapeutic. The surgery schedule through this reporting period was as follows (**Table 1**):

(1) *Monday, August 17* – 6 rats (all controls; 3 sciatic nerve cut with repair, 3 sciatic nerve cut with no repair)
(2) *Tuesday, August 18* – 6 rats (all controls; 3 sciatic nerve cut with repair, 3 sciatic nerve cut with no repair)
(3) *Monday, September 14* – 6 rats (all experimental; 2 sciatic nerve cut with repair and cell therapy, 4 with sciatic nerve cut with no repair and cell therapy)

(4) *Tuesday, September 15* – 6 rats (all controls; 4 sciatic nerve cut with repair, 2 sciatic nerve cut with no repair)
(5) *Wednesday, September 30* - 6 rats (all experimental; 4 sciatic nerve cut with repair, 2 sciatic nerve cut with no repair)

Table 1. Rat Study Design and Current Status of Surgeries and Necropsies (as of 30-SEP-2020)

Current Status	MGH Rat Study Results			
Experimental Groups	Sciatic Nerve Injury, No Repair (control)	Sciatic Nerve Injury, with Repair (control)	Sciatic Nerve Injury, No Repair + Therapy	Sciatic Nerve Injury, with Repair + Therapy
Number of Rats (n)	12 rats total	12 rats total	12 rats total	12 rats total
Surgeries Performed	10/12 surgeries conducted	10/12 surgeries conducted	8/12 surgeries conducted	8/12 surgeries conducted
Necropsies Performed	6 necropsies performed	6 necropsies performed	*Euthanasia not yet performed*	*Euthanasia not yet performed*

For all groups, rats received regular treatments of tacrolimus (immunosuppressant) for the duration of the experiment, until euthanasia four weeks after the surgery. Rats were monitored for walking track (before and after surgery), tacrolimus levels, and for necropsy and histology (difference in gastroc muscle weight between leg with surgery conducted and control leg, muscle imaging and staining, etc.). Rat studies (surgeries and necropsies) are ongoing into the first quarter of the next reporting period.

At the time of conclusion of this reporting period, control rats from the studies performed on Monday, August 17 and Tuesday, August 18 have been euthanized at the planned 28-day frame. Necropsy procedures and ongoing studies include: mass analysis of treated gastroc muscle as compared to the untreated and healthy gastroc muscle in each rat; preservation of nerve and muscle for histology reports (to be used as a control comparison for cell therapy rats); and tacrolimus blood levels. Initial results from the control group of rats show the expected severe atrophy in the muscles of the control rats, with less atrophy noted in the rats that received sciatic nerve repair (see **Table 2** and **Figure 3**). Rat surgeries conducted in September are ongoing and will not be euthanized and studied until mid to late October, results pending.

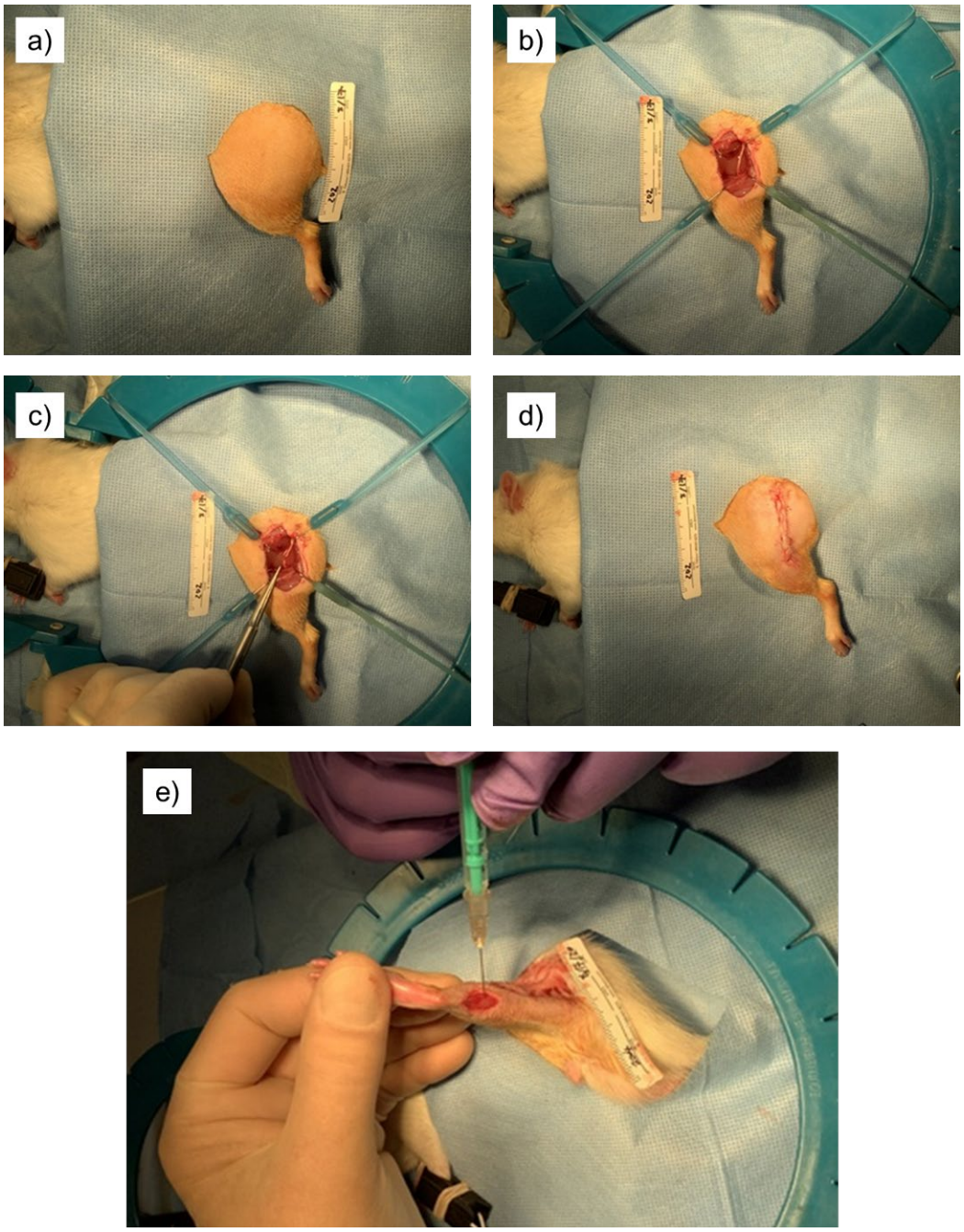


Figure 2. Photographs detailing the surgical procedure for the *in vivo* murine study using Lewis rats. (a-d) Through surgical incision, the sciatic nerve is exposed and severed; the nerve is then either repaired or left severed before suturing the wound closed. (e) After the incision is closed, 100 µL of the therapeutic formulation (containing ~400,000 neurons) or of the control PBS is injection IM to the base of the gastroc muscle to ensure full permeation and spread through the gastroc.

Table 2. Muscle atrophy esults of *in vivo* rat control group studies

Rat Study Group	Atrophy in Gastroc	Standard Deviation
Sciatic Cut, No Repair	-69.3%	±1.6%
Sciatic Cut, Repair	-63.3%	±7.8%

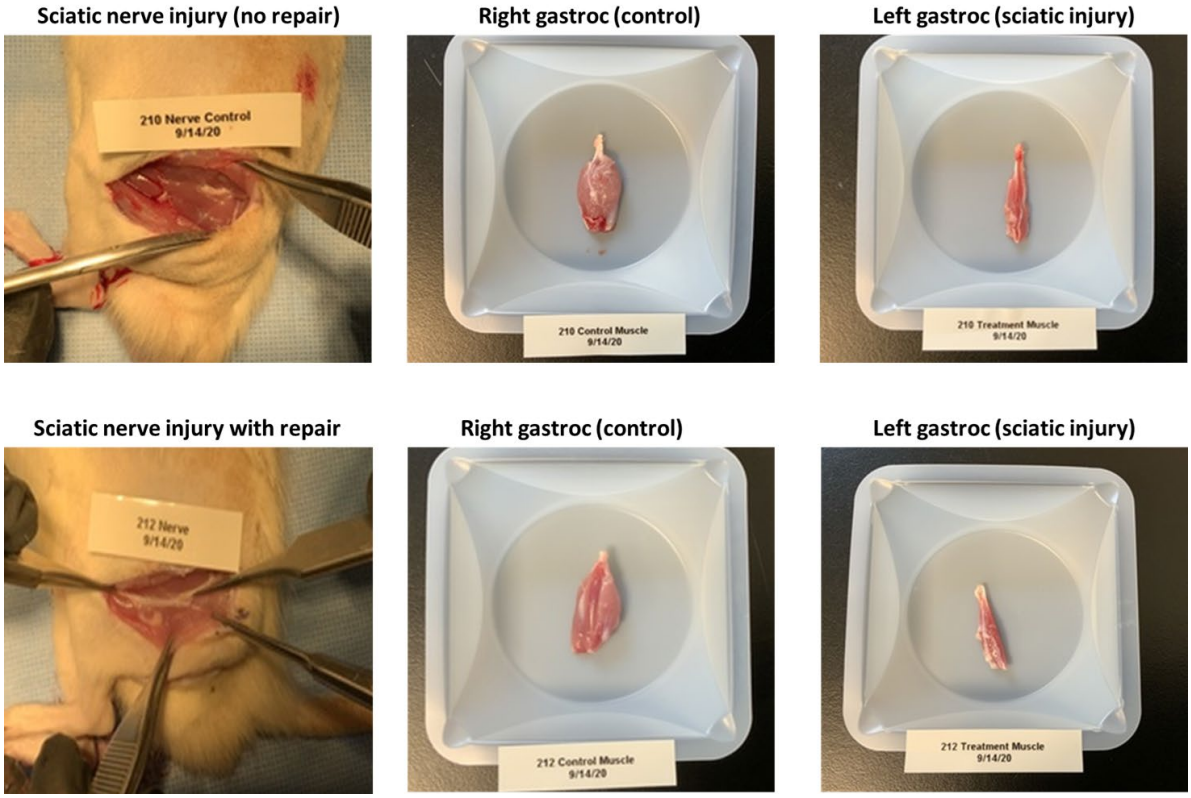


Figure 3. Photographs showing typical necropsy results of the gastroc muscle from control rats. (Top) Images showing a control group rat that had the sciatic nerve severed with no repair, and the comparison of the right gastroc (control, no surgery) to the left gastroc (nerve injury). (Bottom) Images showing a control group rat that had sciatic nerve injury couple with injury surgical repair, and the comparison of the right gastroc (control, no surgery) to the left gastroc (nerve injury with repair).

Deliverable 4 (Year 3): Final motoneuron formulation manufactured under cGMP

While CSInc/MGH believe an FDA-approved, cellulose-based gel formulation will be used in the final formulation, work has not been done to finalize any formulation to date.

Deliverable 5 (Year 3) GLP non-human primate safety/efficacy study results

CSInc and MGH have begun to plan scoping surgeries on NHPs. These surgeries will be done on non-naïve cynomolgus monkeys and include confirming that the bicep is the best muscle to cut as well as mapping out innervation in the NHPs. MGH has also begun to plan longitudinal atrophy studies where the bicep will be deinnervated and muscle mass loss will be measured as a function of time. MGH is also looking into possible sham surgeries as well as control surgeries. These surgeries can take place upon completion of submitted approvals.

Deliverable 6 (Year 3): Submit IND data package

Work has not been done to date on this deliverable.

2. Future Plans

Present a brief statement of plans or milestones planned for the next year. If any of the plans deviate from the original approved SOW (e.g., new or modified tasks, objectives, experiments, etc), they will require review by the Grants Officer's Representative and final approval by USAMRAA Grants Officer through an award modification prior to initiating any changes.

During the first quarter of the next year, CSInc plans to confirm the types of initial testing for Lewis rats that will be conducted. CSInc will submit IACUC and ACCURO approvals for both Lewis rats as well as NHPs. CSInc/MGH will also decide during the first quarter of the next year. In the next year, MGH hopes to complete small animal studies and begin NHP studies.

3. Problems / Issues

Any change that is substantially different from the original approved SOW (e.g., new or modified tasks, objectives, experiments, etc.) will require review by the Grants Officer's Representative and final approval by USAMRAA Grants Officer through an award modification prior to initiating any changes.

a. Current Problems / Issues

Provide a description of current problems or issues that may impede performance or progress of this project along with proposed corrective action. This may include administrative, technical, and/or logistical issues.

For an award that includes the recruitment of human subjects for clinical research or a clinical trial, discuss any problems or barriers encountered, if applicable, and what has been done to mitigate those issues. Discussion may highlight enrollment problems, retention problems, and actions taken to increase enrollment and/or improve retention.

During the second quarter of the second year, SARS-CoV-2 pandemic impacted operations across the globe. MGH temporarily closed all non-COVID-19 related animal studies, which delayed the start of the rat scoping studies. CSInc continues to remain open and fully operational during the pandemic as an essential business, following all State of Massachusetts and CDC recommended guidelines for safe operation of services during this time. We do not anticipate any significant delays in performance milestones and deliverables due to COVID-19 at this time.

b. Anticipated Problems / Issues

Provide a description of anticipated problems or issues that have a potential to impede performance or progress. Also provide course of actions planned to mitigate problems or to take should the problem materialize.

None

4. Financial Health

Comment on the financial health of the study. Was the study financially on track during this annual reporting period and cumulatively for completion as proposed within the period of performance? If not, describe the cause(s), whether this will have a short-term or long- term impact, the likelihood this can be overcome, and provide remediation strategy. Provide amount expended this year and cumulatively. State if there was any major equipment procured, sub-award implemented, and/or travel conducted.

a. This is a Cost Reimbursable, Cost Sharing Milestone effort. The spending for the year of October 2019 - September 2020 was $713,209.79. The cumulative program total is $1,158,919.05 of the $2,327,616 total government funded award. There has been $0 in cost share out of a total budgeted amount of $23,774. We have $1,168,696.95 (50.2%) of the government funded base period remaining in the award.

5. Personnel Effort

Provide names of current staff along with their roles and percent effort of each on this project. Add additional rows if necessary to list the complete team. If there is more than one project on this award, breakdown according to each project (one table per project).

Personnel	Role	Percent Effort
Allison Tierney	Scientist	41%
Philip Graf	Product Manager	5%
Piercen Oliver	Director R&D	16%
Xinhua Li	EVP Chemistry	14%
Shekar Shetty	CEO	8%
Mitchell Zakin	CSO	16%
Michael White	Director R&D	1%
Madeline Vara	Senior Scientist	7%
Amanda Code	Scientist	8%

6. Protocol and Activity Status

For awards involving the use of human subjects, use of human cadavers, and/or use of animal subjects, prepare a summary in accordance with the following subsections. For all other awards, including those involving the use of human anatomical substances (such as tissue or cells or identifiable private information), mark as directed below.

a. Human Use Regulatory Protocols

TOTAL PROTOCOLS:

"No human subjects research will be performed to complete the Statement of Work."

b. Use of Human Cadavers for RDT&E, Education or Training

TOTAL ACTIVITIES:

"No RDT&E, education or training activities involving human cadavers will be performed to complete the Statement of Work (SOW)."

c. Animal Use Regulatory Protocols

TOTAL PROTOCOLS: The total number of animal use protocols required to complete the Statement of Work is still being determined. It is anticipated there will be 3 animal use research protocols required.

PROTOCOLS:

Rat in-vivo to-be-determined

Non-human primate in-vitro to-be-determined

Protocol [ACURO Assigned Number]: Log MT180009.e001
Title: Rat in-vivo (to-be-determined)
Target required for statistical significance: In-progress
Target approved for statistical significance: In-progress
Submitted to and Approved by:
Provide bullet point list of protocol development, submission, amendments, and approvals (include IACUC in addition to ACURO).

- Both IACUC and ACURO for rat studies has been approved.
- IACUC Assigned Number: 2020N000005

STATUS: Provide bullet point list of performance and/or progress status relating to the above protocol and discuss any administrative, technical, or logistical issues that may impact performance or progress of the study (e.g. animal use protocol need revision to minimize animal suffering, animal protocol modification to include additional staff) for the above ACURO approved protocol.

- Both rat IACUC and ACURO protocols have been approved

Protocol [ACURO Assigned Number]: Not yet submitted
Title: Non-human primate in-vivo (to-be-determined)
Target required for statistical significance: In-progress
Target approved for statistical significance: In-progress
Submitted to and Approved by:
Provide bullet point list of protocol development, submission, amendments, and approvals (include IACUC in addition to ACURO).

- Protocol being developed

STATUS: Provide bullet point list of performance and/or progress status relating to the above protocol and discuss any administrative, technical, or logistical issues that may impact performance or progress of the study (e.g. animal use protocol need revision to minimize animal suffering, animal protocol modification to include additional staff) for the above ACURO approved protocol.

- Initial protocol being developed

Annual Business Status Report for

Novel cell-based Therapy to Treat Muscle Atrophy Associated with Peripheral Nerve Injury
Research Project No. 2018-680-001
EGS# MT180009
Reporting Period: 01 Oct '19 – 30 Sep '20

MTEC Research Project Awardee
Clear Scientific
Massachusetts General Hospital

Research Project Technical POC
Dr. Mitchell Zakin
737 Concord Ave
Cambridge, MA 02138-1002
617-621-8500
mzakin@clearsci.com

Submitted: 01 Dec '20

1. CURRENT STAFF

Personnel	*% of Effort on project*
Scientist	41%
Product Manager	5%
Director R&D	16%
EVP Chemistry	14%
CEO	8%
CSO	16%
Director R&D	1%
Senior Scientist	7%
Scientist	8%

2. CURRENT EXPENDITURES

A. Cost Reimbursable Contracts: Complete only if your contract is Cost Reimbursable or Cost Plus Fixed Fee.

Expenditures should be reflective of cost incurred to date, not exceeding awarded project ceiling. Expenditures should coincide with the latest invoice for the reporting period. For cost reimbursable contracts please use the table below.

Contract Expenditures	Current Year Expenditures	*Cumulative To Date Expenditures*
Labor (Personnel and Fringe)	$225,711.89	$412,383.25
Supplies/Materials	$38,443.77	$54,655.76
Travel	$26.10	$26.10
Equipment	$0	$0
Subcontractors and Consultants	$148,831.21	$148,831.21
Other Direct Costs	$0	$0
Indirect Costs	$300,196.82	$543,022.73
Total	**$713,209.79**	**$1,158,919.05**

B. Cost Share Contributions: Complete only if you're reporting Cost Share:

Cost sharing includes any costs a reasonable person would incur to carry out (necessary to) proposed projects' statements of work not directly paid for by the Government. There are two types of cost sharing: **(1) Cash**: Outlays of funds to perform the proposed project. Cash includes labor, materials, new equipment, and relevant subcontractor efforts. Sources include new IR&D funds, profit or fee from another contract, overhead or capital equipment expense pool. (**2) In-Kind:** Reasonable value of in-place equipment, materials or other property used in performance of the proposed project. All cash or in-kind cost sharing availability must be clearly and convincingly demonstrated by the Offeror. The Offeror will be required to provide financial reporting with appropriate visibility into expenditures of Government funds vs. private funds.

Funding Source (Cash)	This Period	Cumulative to Date
Cash	$0.00	$0.00
Labor Dollars	$0.00	$0.00
Indirect Labor Rates (Overhead/Fringe Benefits)	$0.00	$0.00
Travel	$0.00	$0.00
General & Administrative Services	$0.00	$0.00
Equipment (New)	$0.00	$0.00
Material	$0.00	$0.00
Other Direct Costs	$0.00	$0.00
Other *	$0.00	$0.00
Sub-Total	$0.00	$0.00
Funding Source (In-Kind)	**This Period**	**Cumulative to Date**
Use of Existing Equipment (Estimated fair market value)	$0.00	$0.00
Use of Existing Software (Estimated fair market value)	$0.00	$0.00
Intellectual Property (Estimated fair market Value)	$0.00	$0.00
Space (Land or buildings)	$0.00	$0.00
Sub-Total	$0.00	$0.00
Cost Share Total	$0.00	$0.00

3. STATUS OF MILESTONES – FILL OUT FOR ALL CONTRACT TYPES (all project milestones are to be included)

All project milestones from the Milestone Payment Schedule, in the project award, should be accounted for below. Milestones reported below are from the MPS approved via email on 3/20/20, which have been submitted but not yet included in a contract modification.

MTEC Milestone Number	Milestone Description	Due Date	% Completed this Reporting Period	Cumulative % Complete
1	**Project Kick Off**	**9/30/2018**	0%	100%
2	Quarterly Reports 1 (October-December, Technical and Business Reports)	1/25/2019	0%	100%
3	Quarterly Reports 2 (January - March, Technical and Business Reports)	4/25/2019	0%	100%
4	Quarterly Report 3 (April - June, Technical and Business Reports)	7/25/2019	0%	100%
5	Annual Report 1	10/25/2019	0%	100%
6	Quarterly Report 4 (October-December, Technical and Business Reports)	1/25/2020	100%	100%
7	Determination of commercially available human motoneuron source	2/29/2020	100%	100%

8	Development of initial formulation(s) using human motoneurons in PBS	2/29/2020	100%	100%
9	HRPO approval	4/25/2020	100%	100%
10	Quarterly Report 5 (January - March, Technical and Business Reports)	4/25/2020	100%	100%
11	Rat IACUC approved for in vivo studies	6/30/2020	100%	100%
12	Rat ACURO submitted for in vivo studies	6/30/2020	100%	100%
13	Quarterly Report 6 (April-June, Technical and Business Reports)	7/25/2020	100%	100%
14	NHP IACUC approved for in vivo studies	7/31/2020	25%	25%
15	NHP ACURO submitted for in vivo studies	7/31/2020	0%	0%
16	Rat ACURO approved for in vivo studies	9/30/2020	100%	100%
17	Annual Report 2	10/25/2020	100%	100%
18	NHP ACURO approved for in vivo studies	10/31/2020	0%	0%
19	Initial rat dosing studies using Task 1.3 formulation(s)	11/30/2020	86%	86%
20	Pre-FDA meeting to guide NHP work	11/30/2020	0%	0%
21	Determination of initial formulation(s) for use in NHP	12/31/2020	0%	0%
22	Quarterly Report 7 (October-December, Technical and Business Reports)	1/25/2021	0%	0%
23	Procurement of FDA/GRAS carrier materials (on-going)	3/31/2021	82%	82%
24	Development of adapted human motoneuron formulation(s) (on-going)	3/31/2021	50%	98%
25	Determination of final human motoneuron formulation(s)	3/31/2021	15%	15%
26	Initial NHP efficacy studies using Task 3.3 formulation(s)	3/31/2021	18%	18%
27	Quarterly Report 8 (January-March, Technical and Business Reports)	4/25/2021	0%	0%
28	Additional rat dosing studies using Task 1.4 formulation(s) (on-going)	4/30/2021	0%	0%
29	Determination of additional formulation(s) for use in NHP (if required, on-going)	4/30/2021	0%	0%
30	Data Package for initial FDA meeting based on data from Task 4.1	4/30/2021	0%	0%
31	FDA meeting	5/31/2021	0%	0%
32	Quarterly Report 9 (April-June, Technical and Business Reports)	7/25/2021	0%	0%
33	Additional NHP efficacy studies using Task 3.4 formulation(s) (if required, on-going)	7/31/2021	0%	0%
34	Additional FDA meetings (on-going)	9/29/2021	0%	0%
35	Final motoneuron formulation manufactured under cGMP	9/29/2021	0%	0%
36	IND Filed	9/29/2021	0%	0%
37	Final Reports (Business and Technical)	9/29/2021	0%	0%

4. DEVIATION FROM PROJECT PLAN

Any major deviations from the agreed to project plan shall be explained with a discussion of proposed actions to address the deviations.

Transfer of program from Nano Terra, Inc to Clear Scientific, LLC is in progress.
Contracting of updated MTEC Milestones is in progress.

Milestone references in report reflect approved milestones that are yet to be contracted.