AWARD NUMBER: W81XWH-20-1-0212

TITLE: Nuclear Pore Complexes in the Maintenance of Skeletal Muscle Integrity and Function

PRINCIPAL INVESTIGATOR: Maximiliano D'Angelo, PhD

CONTRACTING ORGANIZATION: Sanford Burnham Prebys Medical Discovery Institute, La Jolla

REPORT DATE: MAY 2023

TYPE OF REPORT: Annual Technical Report

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

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
MAY 2023	Annual Technical Report	1MAY2022 - 30APR2023

4. TITLE AND SUBTITLE

Nuclear Pore Complexes in the Maintenance of Skeletal Muscle Integrity and Function

5a. CONTRACT NUMBER
W81XWH-20-1-0212

5b. GRANT NUMBER
W81XWH-20-1-0212

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Maximiliano D'Angelo

E-Mail: mdangelo@sbpdiscovery.org

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Sanford Burnham Prebys Medical Discovery Institute
10901 North Torrey Pines Rd.
La Jolla, CA 92037-1005

8. PERFORMING ORGANIZATION REPORT NUMBER

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

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

Skeletal muscle homeostasis is the result of proper maintenance of differentiated muscle fibers and continuous repair of muscle tissue by satellite cells. Alterations in both, or either, of these processes results in progressive muscle damage leading to excessive loss of muscle mass and/or to the development of muscular dystrophies. The identification and characterization of the basic regulators of skeletal muscle maintenance is critical to comprehend the mechanisms that lead to the deterioration of muscle integrity, and a necessary step in the development of therapies to enhance muscle performance and treat muscle diseases. In our previous work we discovered that the nuclear pore complex component Nup210 is an important regulator of muscle physiology. Of particular importance for this project, we identified that mice lacking Nup210 show a progressive deterioration of muscle structure and function. Yet, the muscle processes that are affected by the absence of Nup210, and the causes of such muscle alterations are poorly understood.

15. SUBJECT TERMS
Musculoskeletal Disorders - Tissue Regeneration

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRDC
U	U	U	UU	18	19b. TELEPHONE NUMBER *(include area code)*

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

TABLE OF CONTENTS

1. **INTRODUCTION:**

Muscle growth, maintenance and repair in adulthood requires the constant regeneration of muscle fibers. As we age or in pathological conditions, the deterioration of muscle maintenance mechanisms contributes to the loss of muscle mass (sarcopenia (1)), to reduced muscle repair in response to injury, and to the development of muscular dystrophies. Understanding the basic regulators of skeletal muscle homeostasis is crucial to prevent muscle wasting and to develop new therapies to promote muscle regeneration and treat muscle disorders. Our previous work uncovered that Nup210, a tissue-specific nuclear pore complex (NPC) component, plays a critical role in myoblast differentiation, and in the maturation and survival of skeletal muscle fibers. We also identified that Nup210 knockout mice show progressive deterioration of skeletal muscle structure and function, with features reminiscent of inflammatory muscle disorders. The main goals of this proposal are to understand in detail the skeletal muscle alterations that result from Nup210 depletion, to identify their causes, and to establish if increasing Nup210 levels can promote muscle repair and function in healthy mice and in a model of Duchenne Muscle Dystrophy (DMD).

2. **KEYWORDS:**

Nuclear pore complex, Nup210, skeletal muscle, regeneration, repair, muscle dystrophy, inflammation, vacuoles, immune system

3. **ACCOMPLISHMENTS:**

- **What were the major goals of the project?**

Our hypothesis, based on our previous findings, is that Nup210 is an important regulator of muscle maintenance and that increasing its activity can enhance muscle repair and function. The overarching goal of this project is to establish how inhibiting Nup210 affects the integrity and function of skeletal muscle and to define if modulating its levels could be exploited to enhance muscle performance and regeneration. Below is the list of the major goals of the project pertaining to this reporting period as stated in the project timeline approved SOW and:

Aims/Tasks	Months
Specific Aim 1: Characterize the age-dependent deterioration of skeletal muscle in Nup210 knockout animals.	
Major Task 1: Employ immune profiling, histological, and functional analyses to characterize in detail the age-dependent alterations in the skeletal muscle tissue of Nup210 knockout animals and determine if they represent features of inflammatory myopathies, particularly sIBM	
Subtask 3: Characterize the immune infiltrates of muscles from Nup210 knockouts of different ages	6-9
Subtask 5: Identify the muscle functional abnormalities of Nup210 knockout mice	6-9
Specific Aim 2: Identify the origin/s of muscle alterations in Nup210$^{-/-}$ animals.	
Major Task 2: Combine tissue-specific knockouts in which Nup210 is specifically ablated either in the immune system or in skeletal muscle, with pharmacological interventions to determine the contribution of Nup210 malfunction in each tissue to skeletal muscle degeneration. Investigate if Nup210 loss results in a progressive deterioration of muscle stem cell function and/or in the maturation and survival of differentiated muscle cells.	
Subtask 1: Compare the muscle alterations of constitutive and muscle-specific Nup210 knockouts using histology and muscle function assays.	4-6
Specific Aim 3: Define if Nup210 up-regulation can stimulate muscle regeneration.	
Major Task 3: Generate and use different mouse models that allow to increase Nup210 levels in skeletal muscle to evaluate if increasing its activity can enhance the endurance,	

strength, and regeneration capacity of healthy and dystrophic muscle.	
Subtask 2: Breed conditional Nup210 knockin mouse line with muscle-specific constitutive and inducible CRE lines (*HSA1-CRE* and *HSA1-CRE^{ERT2}*)	6-9
Subtask 3: Characterize mouse lines overexpressing Nup210 in muscle	4-6
Subtask 4: Asses muscle regeneration in mouse lines overexpressing Nup210 in muscle (healthy and DMD)	12-15
Subtask 5: Analyze muscle endurance and strength in mouse lines overexpressing Nup210 in muscle (healthy and DMD)	12-15

- **What was accomplished under these goals?**

Major Task 1: Employ immune profiling, histological, and functional analyses to characterize in detail the age-dependent alterations in the skeletal muscle tissue of Nup210 knockout animals and determine if they represent features of inflammatory myopathies, particularly sIBM

Subtask 3: Characterize the immune infiltrates of muscles from Nup210 knockouts of different ages

The specific objective of this subaim to characterize if Nup210 ablation affects immune infiltration in skeletal muscle. The major activities for this goal have been to set up the conditions and test different methods to examine the presence of different immune cells in muscle from control and Nup210 knockout mice. As described in previous reports, using qPCR approaches and histology approaches we initially detected increased levels of $CD8^+$ cells and macrophages in muscles without Nup210. For a more detailed characterization of the immune infiltrates of Nup210 knockout muscle we initially proposed to performed flow cytometry analyses, but the low numbers of different immune cell populations and the variability among animals and between different ages prevented us to obtain results of acceptable significance. As an alternative approach to identify immune cells that might accumulate in skeletal muscle when Nup210 is depleted and to better understand the function of this nucleoporin in maintaining skeletal muscle homeostasis we analyzed control and Nup210 knockout muscles by RNAseq. This whole genome analyses not only allowed us to uncover processes that might be regulated by Nup210 to maintain skeletal muscle integrity but also indirectly identify potential immune cells affected by analyzing the expression levels of different immune cell markers such as CD4 and CD8 for example. We found that numerous genes were deregulated upon Nup210 ablation (Figure 1A). Notably, Ingenuity Pathway Analyses (IPA) of genes changing expression levels by at least 1.5-fold showed enrichment for cell adhesion/cytoskeletal and immune signaling pathways (Figure 1B). The alterations in cell adhesion/cytoskeletal genes observed in Nup210 knockout muscles is consistent with previous studies (1-3), while the immune signature is likely related to the inflammation induced by the increased muscle damage we observe in these animals. It is worth mentioning that many of the immune genes deregulated in Nup210 knockout muscles are downstream targets of the transcription factor Mef2C that we previously identified to function with Nup210 in the regulation of cell adhesion and structural genes (2).

Subtask 5: Identify the muscle functional abnormalities of Nup210 knockout mice

The specific goal of this task is to characterize the muscle functional defects of Nup210 knockout mice. In previous years we determined that Nup210 knockout mice have reduced strength and running endurance. One phenotype that we noticed with animals lacking Nup210 was that many mice had intermittent running with periods of high running activity separated by periods pf low activity. This is different from control animals that showed a more constant running pattern (Figure 2A). Notably, we also noticed that Nup210 some knockout mice tend to keep running once the lights came on while control mice stop running as expected (Figure 2B). This suggest that Nup210 depletion might affect the animal's circadian rhythm. Because the circadian rhythm plays a key role in skeletal muscle growth and repair (4), these findings provide novel insights into the potential mechanisms of action of Nup210 in muscle.

Major Task 2: Combine tissue-specific knockouts in which Nup210 is specifically ablated either in the immune system or in skeletal muscle, with pharmacological interventions to determine the contribution of Nup210 malfunction in each tissue to skeletal muscle degeneration. Investigate if Nup210 loss results in a progressive deterioration of muscle stem cell function and/or in the maturation and survival of differentiated muscle cells.

Subtask 1: Compare the muscle alterations of constitutive and muscle specific Nup210 knockouts using histology and muscle function assays.

In previous preliminary studies of $Nup210^{-/-}$ mice we have observed that while constitutive Nup210 ablation led to reduce running distances, depletion of Nup210 only in muscle seem to have no effect no the running activity of mice (Figure 3A, B). This was partially puzzling as depletion of this nucleoporin in muscle shows similar alterations in muscle integrity as constitutive knockouts (Figure 3C). On possible explanation is that the muscle-specific knockout mice were trained for longer periods before the experiment was carried out. To be able to directly compare the running alterations to the constitutive knockout mice we repeated these experiments with exact amount of pre-running training. Under these conditions we observed that mice with a muscle specific depletion of Nup210 also showed reduced running distances and a more intermittent running pattern (Figure 3D). These experiments support a muscle intrinsic function for Nup210.

Major Task 3: Generate and use different mouse models that allow to increase Nup210 levels in skeletal muscle to evaluate if increasing its activity can enhance the endurance, strength, and regeneration capacity of healthy and dystrophic muscle.

Subtask 2: Breed conditional Nup210 knockin mouse line with muscle-specific constitutive and inducible CRE lines (*HSA1-CRE* and *HSA1-CRE^{ERT2}*)

The specific goals of subtask 1 and 2 of this aim is to generate mouse lines that allow us to increase Nup210 levels in muscle and investigate if it can improve muscle function. In the previous report we showed that Nup210 overexpressing mice with one or two copies of the overexpression cassette resulted in very high levels of expression that led to the misclocalization of this nucleoporin in muscle and other tissues. In these animals we observed no differences in muscle integrity or regenerating capacity. The major activities of the past year have been to obtain a mouse line overexpressing Nup210 in more physiological levels to avoid potential issues due to mislocalization. To do this we crossed our mouse lines to obtain homozygous Nup210 knockout mice with one copy of the overexpression cassette.

Subtask 3: Characterize mouse lines overexpressing Nup210 in muscle

The specific goals of subtask 3 is to characterize mouse lines overexpressing the nucleoporin Nup210. As mentioned above, our analysis of the wild type mice lines that we previously generated to express one or two copies of Nup210 produced high levels of this nucleoporin (see previous report) which resulted in its mislocalization and potentially malfunction. During the past year we generated a mouse line that expresses one copy of the Nup210 overexpression cassette in a null Nup210 background ($Nup210^{-/-}$). To validate the functionality of ectopically expressed Nup210 in this mouse line, we analyzed its ability to rescue the loss of CD4 T cells associated with Nup210 knockout. Flow cytometry analyses of blood in showed that expression of one copy of Nup210 is sufficient to rescue CD4 cells to normal levels (Figure 4A-C). Notably, increased expression of Nup210 in a wild type background did not further increase the number of circulating T cells. These findings validate the function of Nup210 in this overexpression mouse line.

Subtask 4: Assess muscle regeneration in mouse lines overexpressing Nup210 in muscle (healthy and DMD) and Subtask 5: Analyze muscle endurance and strength in mouse lines overexpressing Nup210 in muscle (healthy and DMD)

The specific goal of subtask 4 and 5 is to establish if increasing Nup210 levels could enhance muscle function and regeneration. For this, we have tested the ability of Nup210 overexpressing animals to regenerate muscle in response to $BaCl_2$ injury as previously described. We found that no differences with control levels in the regeneration response (data not shown) suggesting that increased Nup210 levels did not significantly accelerated the process. Interestingly, we noticed that even though muscles seemed to regenerate similar to controls, they have an increased number of Pax7+ progenitor cells (Figure 5A, B). The physiological relevance of this finding is currently unknown. Like with muscle regeneration, overexpression of Nup210 did not seem to increase running performance, as overexpressing animals seem to run the same distances as control mice (Figure 5C, D).

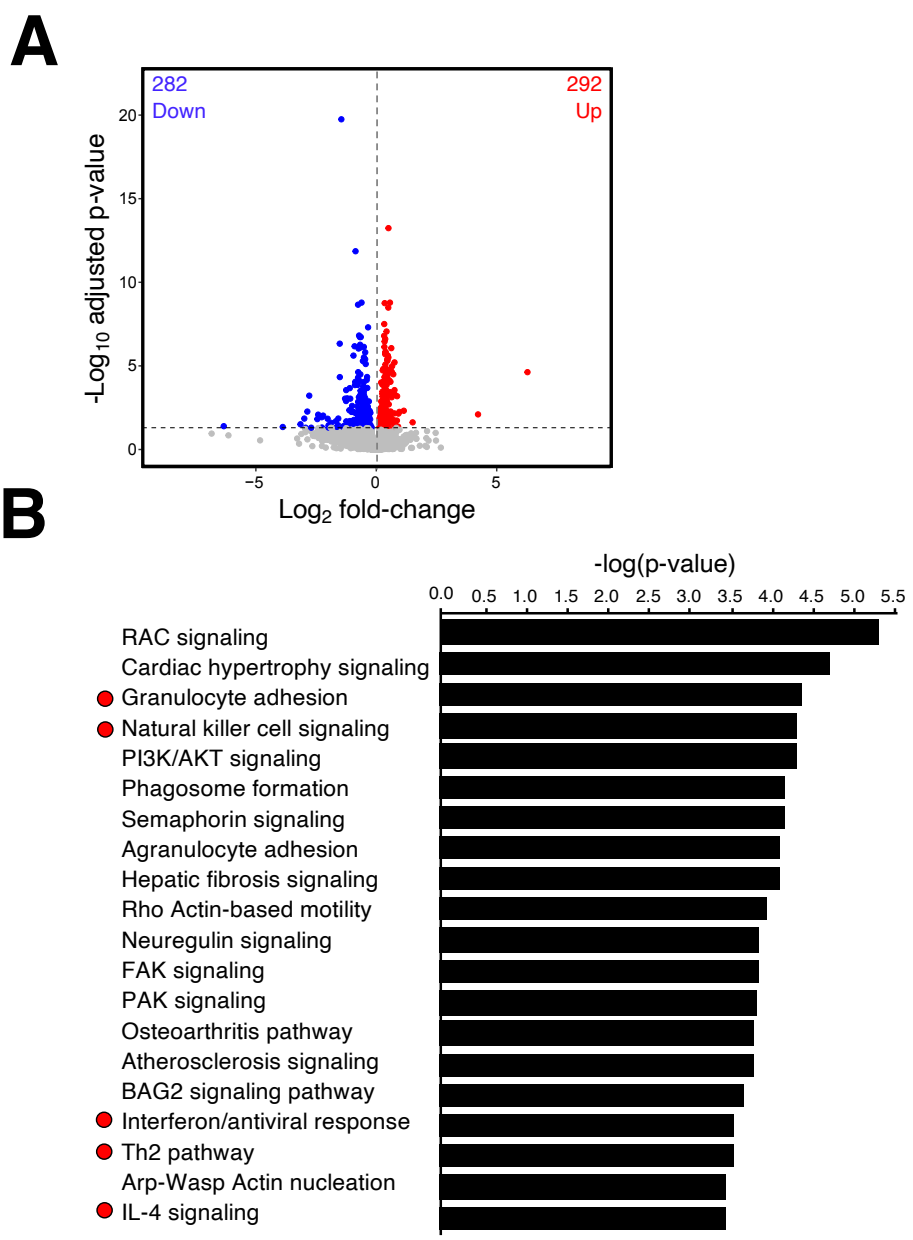

Figure 1: A) Volcano plot of RNA-seq transcriptome data for Nup210 knockout quad muscle relative to control muscle. Significantly up- and downregulated genes are reported as red and blue dots, respectively (q< 0.05). Genes not changing expression are represented as gray dots. **B)** Ingenuity Pathway Analysis (IPA) of genes deregulated in Nup210 knockout quad muscle (>1.5 fold, q<0.05). The top 20 pathways are shown. Red dots show immune-related pathways.

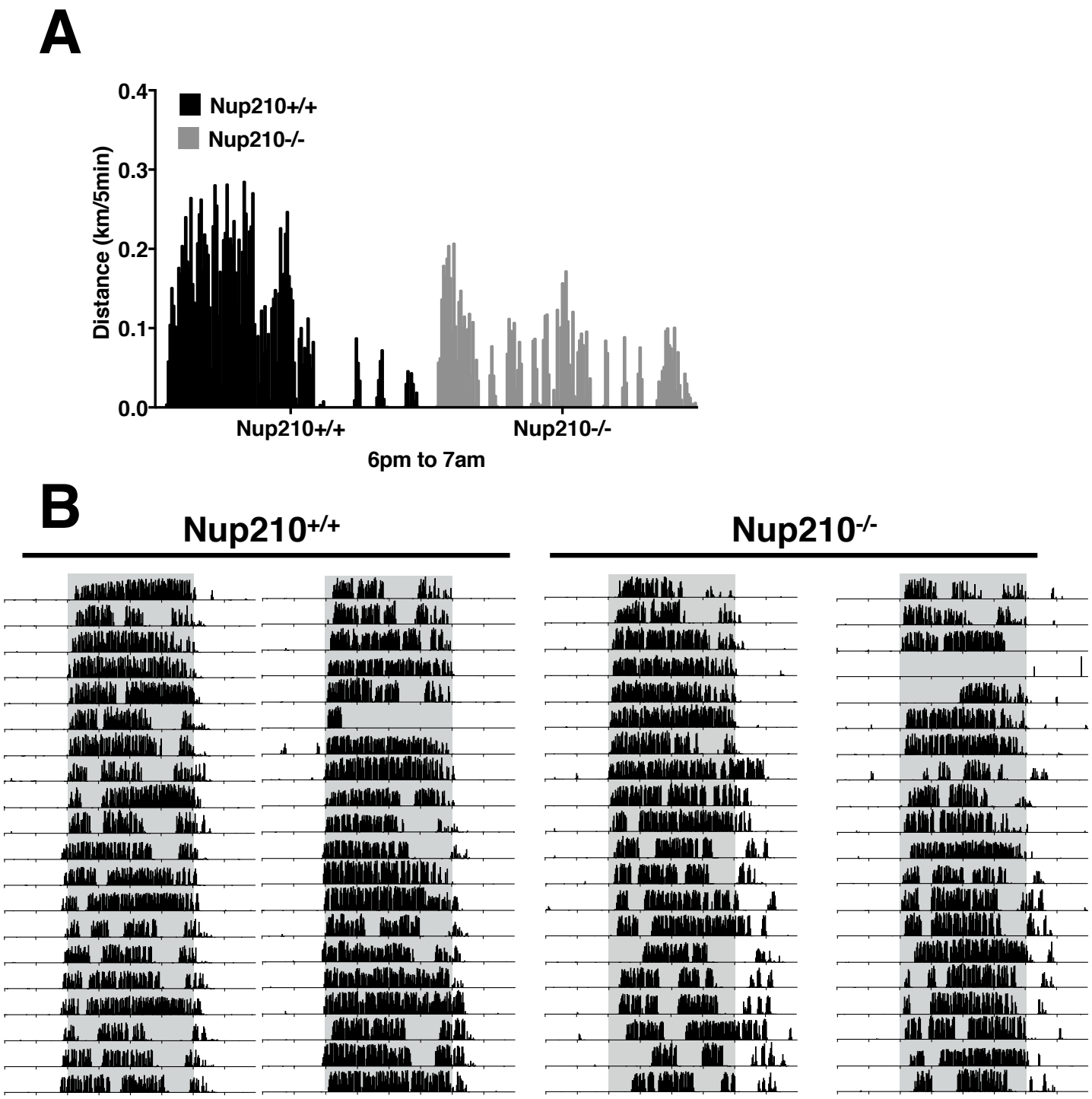

Figure 2: A) Running distance by hour for control and Nup210 knockout mice during dark hours. **B)** Daily running distance by hour over 20 days for control and Nup210 knockout mice. Highlighted gray area represents night hours.

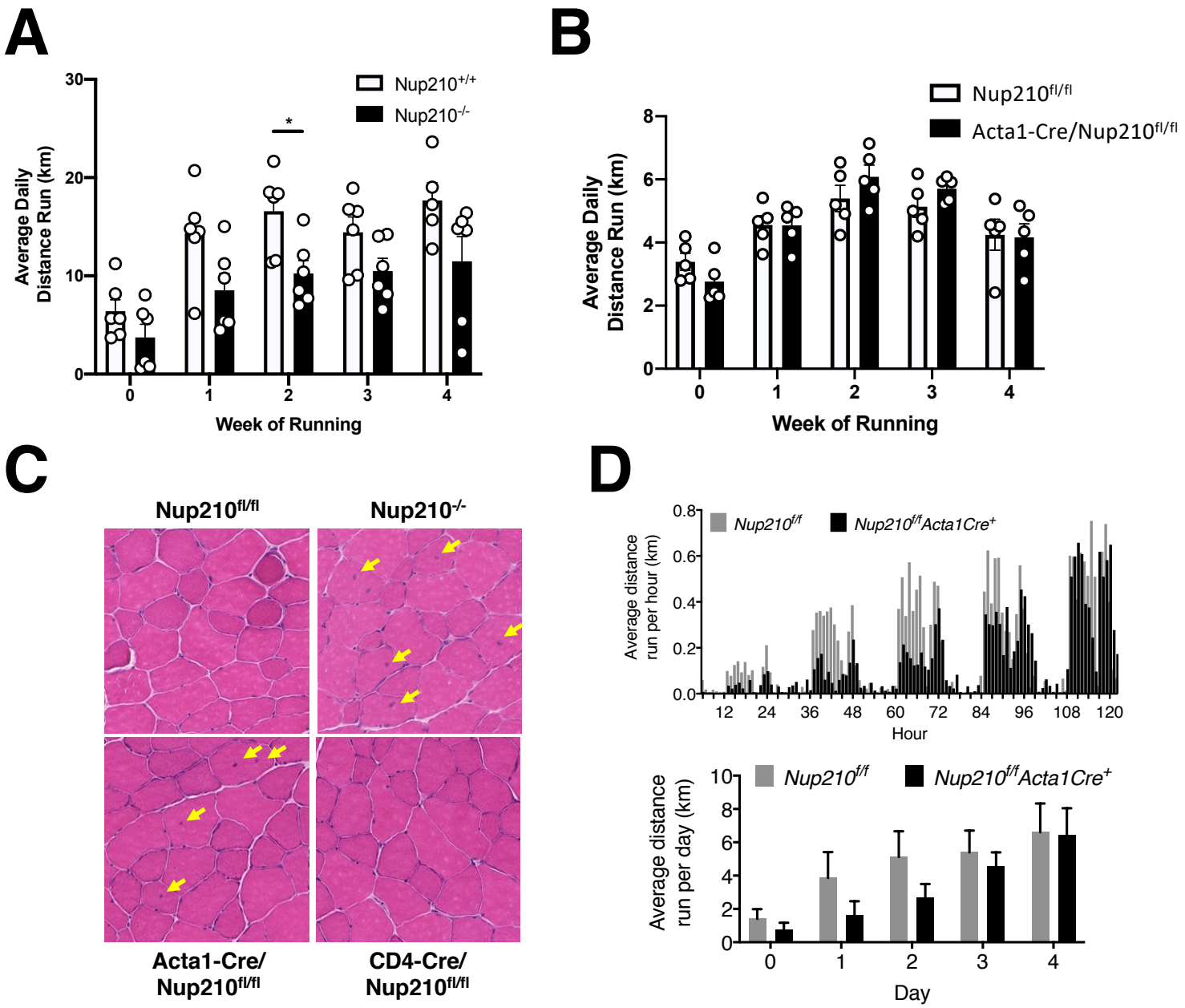

Figure 3: A) Average daily distance ran by control and constitutive Nup210 knockout mice over 4 weeks of voluntary running. **B)** Average daily distance ran by control and muscle-specific (Acta1-Cre) Nup210 knockout mice over 4 weeks of voluntary running. Note than muscle specific knockout mice have a longer training time on the running wheel before the experiment compared to constitutive mice (2 weeks vs 1 week) . **C)** H&E analyses of control, and constitutive ($Nup210^{-/-}$), muscle-specific (Acta1-Cre/ $Nup210^{fl/fl}$) and T cell-specific (CD4-Cre/ $Nup210f^{fl/fl}$) Nup210 knockouts show centrally nucleated fibers result from muscle-intrinsic defects of Nup210 ablation. **D)** Average hourly and daily distance ran by control or Control and muscle-specific (Acta1/HSA1-Cre) Nup210 knockout mice after receiving the same training regimen (1 week) than constitutive Nup210 knockout mice.

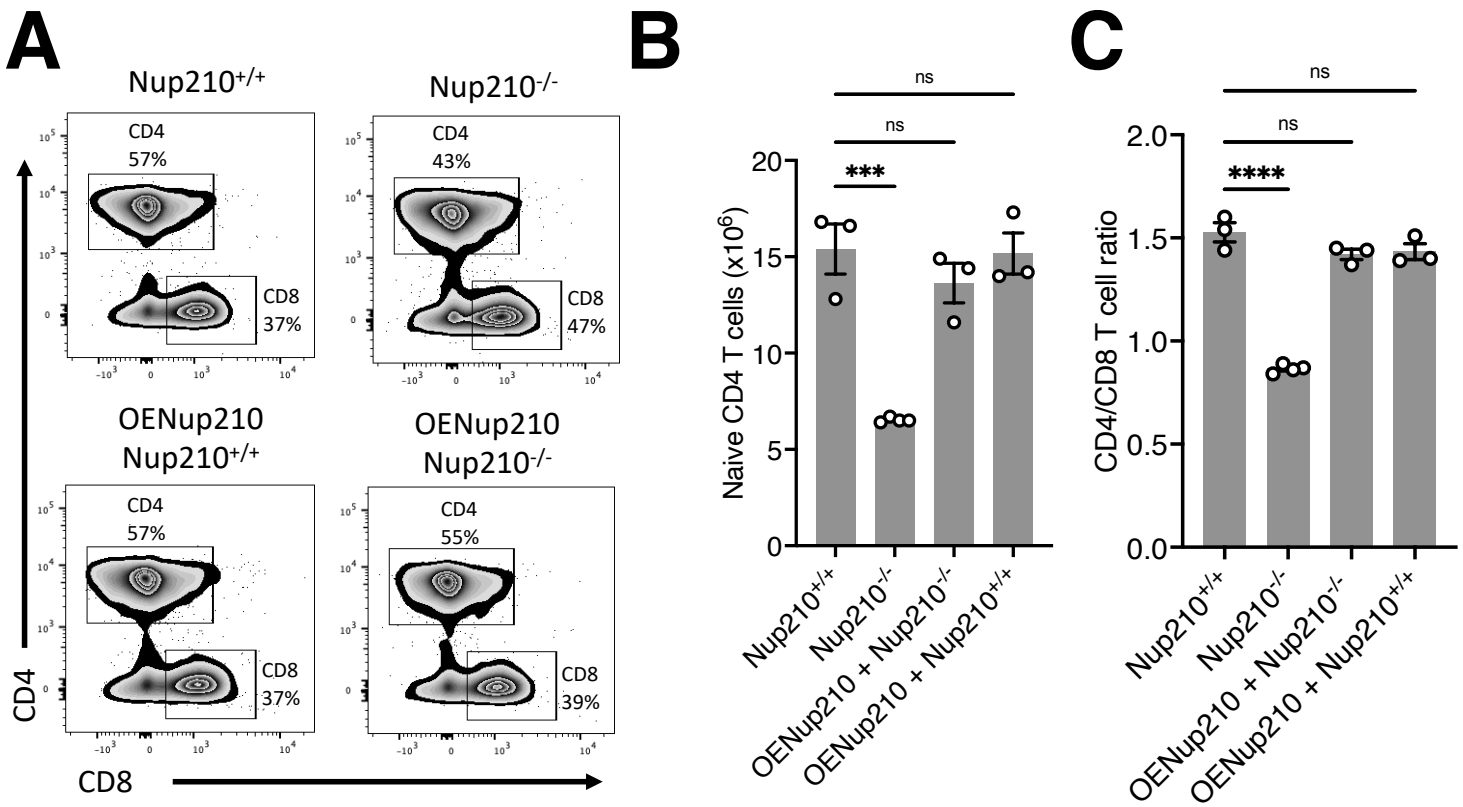

Figure 4: A) Blood of Nup210$^{+/+}$, Nup210$^{-/-}$, and Nup210$^{+/+}$ or Nup210$^{-/-}$ mice carrying one copy of the Nup210 overexpression (OE) cassette were analyzed for CD4 and CD8 T cells by flow cytometry. **B)** Quantification of naive CD4 T cells in the blood of these mice. **C**) Quantification of the CD4/CD8 T cell ratio.

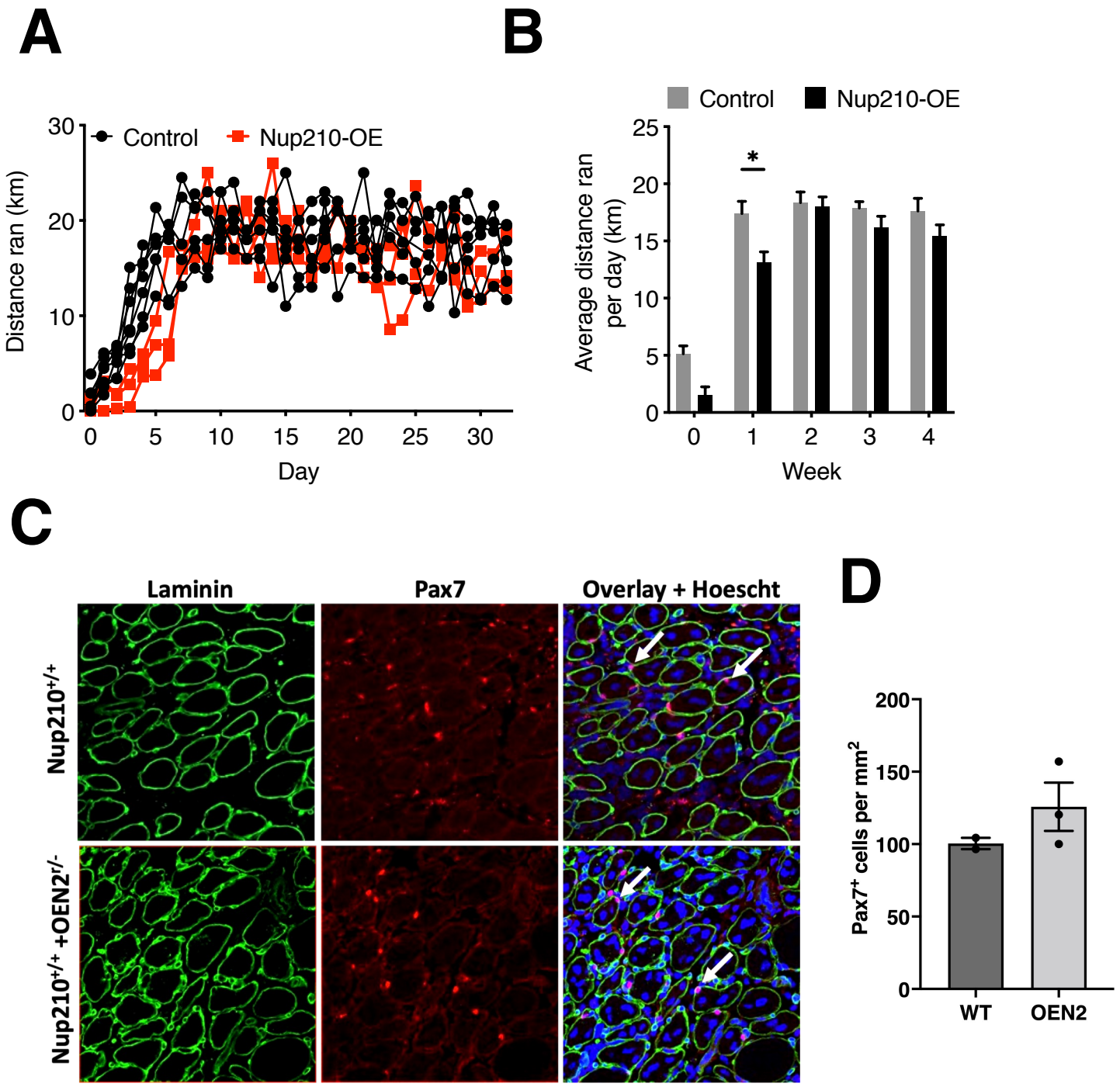

Figure 5: A, B) Average daily and weekly distance ran by control or Nup210 overexpressing mice (OE) mice over 4 weeks of voluntary running. **B)** Control and Nup210 OE mice were subjected to BaCl2 muscle injury and muscle was collected 7 days after injury. Muscle sections were stained against laminin and Pax7. White arrows show some of the $Pax7^{+}$ stem cells in the muscle sections. **D)** Quantification of $Pax7^{+}$ cells.

References

1. D'Angelo MA, Gomez-Cavazos JS, Mei A, Lackner DH, Hetzer MW. A change in nuclear pore complex composition regulates cell differentiation. Developmental Cell. 2012;22(2):446-58. Epub 2012/01/24. doi: 10.1016/j.devcel.2011.11.021. PubMed PMID: 22264802; PMCID: 3288503.
2. Raices M, Bukata L, Sakuma S, Borlido J, Hernandez LS, Hart DO, D'Angelo MA. Nuclear Pores Regulate Muscle Development and Maintenance by Assembling a Localized Mef2C Complex. Developmental Cell. 2017;41(5):540-54 e7. doi: 10.1016/j.devcel.2017.05.007. PubMed PMID: 28586646.
3. Amin R, Shukla A, Zhu JJ, Kim S, Wang P, Tian SZ, Tran AD, Paul D, Cappell SD, Burkett S, Liu H, Lee MP, Kruhlak MJ, Dwyer JE, Simpson RM, Hager GL, Ruan Y, Hunter KW. Nuclear pore protein NUP210 depletion suppresses metastasis through heterochromatin-mediated disruption of tumor cell mechanical response. Nat Commun. 2021;12(1):7216. Epub 2021/12/15. doi: 10.1038/s41467-021-27451-w. PubMed PMID: 34903738; PMCID: PMC8669001.
4. Chatterjee S, Ma K. Circadian clock regulation of skeletal muscle growth and repair. F1000Res. 2016;5:1549. Epub 2016/08/20. doi: 10.12688/f1000research.9076.1. PubMed PMID: 27540471; PMCID: PMC4965692.

- **What opportunities for training and professional development has the project provided?**

Graduate Students:

The Sanford Burnham Prebys Medical Discovery Institute's (SBP) Graduate School of Biomedical Sciences (GSBS) oversees and coordinates an annual individual development planning (IDP) process for all graduate students in the SBP GSBS program. The focus of the IDP process within GSBS is the development of the educational pathway of the student through identification of the skills, knowledge, and accomplishments that will be necessary for the student to obtain a Ph.D. degree, and selection of educational and professional development opportunities that are available for the student to obtain the skills and knowledge identified as needed. GSBS provides guidance and advising to both students and PIs throughout the student's education with respect to developing IDPs and preparing for a successful transition to the next career level post-graduation.

The SBP GSBS IDP process includes two components:

1) Student Mentor Annual Reports. Each year students are required to submit an annual progress report in collaboration with their mentor. This report focuses on the educational goals accomplished through the past school year, highlights the scientific research progress and other accomplishments made by the students, and outlines an academic and research plan for the following year. Students and their mentor complete this form together and each complete sections providing feedback on the topics above. These reports are reviewed by the Graduate Program Executive Committee (GPEC) each year.

2) Annual Thesis Committee Meetings. Beginning in year two of studies, students are required to hold annual Thesis Committee meetings between June – October of each year. At these meetings, the student outlines their current specific aims for their thesis project, reports progress made in the previous year and outlines a plan for the future of the project. The thesis committee members provide the student feedback and guidance on the progression of the research project and may suggest additional coursework or training if needed. At the completion of the meeting, the student submits a report signed by the faculty mentor containing a summary of the work they presented, the committee's feedback, and plans for continuance to the GSBS Office. This report is then reviewed by GPEC.

Postdocs:

The Sanford Burnham Prebys Medical Discovery Institute (SBP) Office of Education, Training & International Services (OETIS) oversees and coordinates an annual individual development planning (IDP) process for all

postdocs at the Institute. The focus of the IDP process at Sanford-Burnham is the career goal of the postdoc; identification of what skills, knowledge, and accomplishments will be necessary for the postdoc to obtain a desired independent position following training; and identification of training and professional development opportunities that are available for the postdoc to obtain the necessary skills and knowledge. OETIS provides guidance and advising to both postdocs and PIs throughout the postdoc's training with respect to developing IDPs and preparing for a successful transition to independence post-training. OETIS also maintains webpages containing comprehensive resources on career path identification, career planning, and creating an IDP that can be utilized in conjunction with the formal annual IDP process.

The SBP IDP process includes two components:

1) First-Year IDP. Within the first 3 months of beginning postdoctoral training at SBP, all postdocs receive and fill out an initial "planning and expectations" document to discuss with their PI. This document serves as the foundation for their postdoctoral IDP and is designed to facilitate discussion between the PI and new postdoc regarding goals and expectations for the first year of training, as well as stimulate initial discussions about long-term career goals and training plans.

2) Postdoctoral IDP. At the end of the first year of training SBP postdocs receive notification that it is time to update their IDP, and they receive the information they included in their first-year planning and expectations document in the form of a full IDP that they can update with their accomplishments over the past year and their goals for the coming year, mid-term future, and long-term future. Each subsequent year of their postdoctoral training, postdocs will receive notification and the previous year's IDP form to update and expand. The IDP forms are designed to build upon each previous year as well as provide a solid foundation from which a postdoc can easily build his or her CV/resume.

- **How were the results disseminated to communities of interest?**

Nothing to Report

- **What do you plan to do during the next reporting period to accomplish the goals?**

For the next reporting period, we expect to finish most of the remaining experiments proposed in these studies. We also expect to characterize in more detail our mouse line expressing the single Nup210 overexpression cassette in the knockout background and establish how this affects muscle performance. We expect to perform additional analyses of muscle integrity, including the localization and levels of overexpressed Nup210, regeneration studies, and muscle function (voluntary running and treadmill assays) studies as performed with control and Nup210 knockout mice. If we find that Nup210 in this overexpression mouse line behaves as expected, we plan to breed this line with the DMD mouse line and investigate if it can rescue some of the disease-associated phenotypes. We will also continue to characterize the immune infiltrates of Nup210 knockout muscles by confirming our RNAseq findings using qPCR. Additionally, we will further analyze our RNAseq data to dissect the mechanisms through which Nup210 functions to maintain the integrity of the skeletal muscle tissue. Understanding how this nucleoporin prevents the deterioration of skeletal muscle tissue could lead to the development of novel therapeutic strategies to improve muscle physiology in disease and aging.

IMPACT:

- **What was the impact on the development of the principal discipline(s) of the project?**

  Nothing to Report

- **What was the impact on other disciplines?**

  Nothing to Report

- **What was the impact on technology transfer?**

  Nothing to Report

- **What was the impact on society beyond science and technology?**

  Nothing to Report

4. **CHANGES/PROBLEMS:**

- **Changes in approach and reasons for change**

  Nothing to Report

- **Actual or anticipated problems or delays and actions or plans to resolve them**

  Nothing to Report

- **Changes that had a significant impact on expenditures**

  Nothing to Report

- **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**

  Nothing to Report

- **Significant changes in use or care of human subjects**

  Nothing to Report

- **Significant changes in use or care of vertebrate animals**

  Nothing to Report

- **Significant changes in use of biohazards and/or select agents**

  Nothing to Report

5. **PRODUCTS:**

- **Publications, conference papers, and presentations**

  Nothing to Report

- **Journal publications**

  Nothing to Report

- **Books or other non-periodical, one-time publications**

  Nothing to Report

- **Other publications, conference papers, and presentations**

Nothing to Report

- **Website(s) or other Internet site(s)**
  Nothing to Report

- **Technologies or techniques**
  Nothing to Report

- **Inventions, patent applications, and/or licenses**

  Nothing to Report

- **Other Products**

  Nothing to Report

6. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

- **What individuals have worked on the project?**
  - Maximiliano D'Angelo, PI – No change
  - Valeria Guglielmi, Postdoctoral Associate – No change
  - Stephen Sakuma, Graduate Student – No change
  - Davina Lam, Research Assistant I– 6.37 calendar months
  - Madeleine Liu, Research Assistant I– 3.08 calendar months
  - Marcela Raices, Staff Scientist– 2.00 calendar months

- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

Yes, current support for Dr. D'Angelo is attached.

- **What other organizations were involved as partners?**

  Nothing to Report

7. SPECIAL REPORTING REQUIREMENTS

Nothing to Report

8. APPENDICES:

Changes to PI active support are attached.

CHANGES TO ACTIVE SUPPORT

Name of Individual: D'Angelo, Maximiliano
Current Appointment: Associate Professor, Sanford Burnham Prebys Medical Discovery Institute

Other Support – Project/Proposal

ACTIVE

Title:	Characterizing the Nuclear Pore Complex-T Cell Receptor Connection
Major Goals:	The main goal of this project is to dissect the molecular mechanisms through which nuclear pore complexes regulate TCR signaling.
Specific Aims:	1. Establish the mechanisms that connect TCR activation with Nup210 function at the nuclear envelope. 2. Identify the role of Nup210 in the regulation of NFATc1 and STAT3 activity. 3. Characterize Cav2 function in Nup210 regulation of T cell gene expression
Project Number:	R01 AI148668
Name of PD/PI:	D'Angelo, Maximiliano
Source of Support:	NIH/NIAID
Primary Place of Performance:	Sanford Burnham Prebys Medical Discovery Institute
Project Performance Period:	12/2019 – 11/2024
Total Award Amount:	(total direct costs)
Time Commitment:	3.60 calendar months
Agency POC:	Jordan A Kindbom
Overlap:	None

Title:	Nuclear Pore Complexes in the Maintenance of Skeletal Muscle Integrity and Function
Major Goals:	The goal of this project is to characterize in detail the muscle degeneration that results from Nup210 ablation in mice and to establish how this nucleoporin regulates different muscle processes critical for muscle maintenance.
Specific Aims:	1. Characterize the age-dependent deterioration of skeletal muscle in Nup210 knockout animals. 2. Identify the origin/s of muscle alterations in Nup210-/- animals. 3. Define if Nup210 up-regulation can stimulate muscle regeneration.
Project Number:	W81XWH-20-1-0212
Name of PD/PI:	D'Angelo, Maximiliano
Source of Support:	Department of Defense
Primary Place of Performance:	Sanford Burnham Prebys Medical Discovery Institute
Project Performance Period:	05/2020 – 04/2023
Total Award Amount:	(total direct costs)
Time Commitment:	3.00 calendar months
Agency POC:	Brittany N. Hebb
Overlap:	None

Title:	Cancer Center Support Grant (CCSG)
Major Goals:	The mission of Sanford Burnham Prebys Medical Discovery Institute's Cancer Center is to be a national leader in the effort to overcome cancer as a cause of human suffering and death. Our vision is to make paradigm shifting discoveries that will underlie novel therapeutic modalities by

	creating, translating, and disseminating exceptional basic cancer science.
Project Number:	P30 CA030199
Name of PD/PI:	Ronai, Ze'ev
Source of Support:	NIH/NCI
Primary Place of Performance:	Sanford Burnham Prebys Medical Discovery Institute
Project Performance Period:	05/2020 – 04/2025
Total Award Amount:	(total direct costs)
Time Commitment:	2.40 calendar months
Agency POC:	Candace M Cofie
Overlap:	None

INACTIVE

Title:	Nup210 Roles in Cell Survival and Leukemia
Major Goals:	The goal of this project is to establish the role that nuclear pore complexes play in the development of blood malignancies.
Specific Aims:	1. Determine if increased Nup210 levels enhance the survival, proliferation and invasion capacities of normal and transformed hematopoietic progenitors. 2. Establish the role of Nup210 in leukemia initiation and progression. 3. Uncover the molecular mechanisms of Nup210 function in leukemic transformation.
Project Number:	RSG-17-148-01-CCG
Name of PD/PI:	D'Angelo, Maximiliano
Source of Support:	American Cancer Society
Primary Place of Performance:	Sanford Burnham Prebys Medical Discovery Institute
Project Performance Period:	01/2018 – 12/2022
Total Award Amount:	(total direct costs)
Time Commitment:	1.80 calendar months
Agency POC:	Charles Saxes, Ph.D.
Overlap:	None