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TITLE: Identification and Utilization of Upper Motor Neuron Biomarkers for ALS

PRINCIPAL INVESTIGATOR: Hande Ozdinler, PhD

CONTRACTING ORGANIZATION: Northwestern University, Chicago, IL

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8. PERFORMING ORGANIZATION REPORT NUMBER

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14. ABSTRACT

This proposal is a collaborative effort between (a) a clinical team at Massachusetts General Hospital/Harvard Medical School, who have created the world's largest platform for ALS clinical trials; and (b) a multi-disciplinary team at Northwestern University, composed of scientists who have developed ways to detect proteins in blood with unprecedented precision and clarity, and scientists who have extensive knowledge of the biology of upper motor neurons (UMN) and their role in ALS. This multi-institutional team will apply its expertise and resources towards the goal of identifying UMN biomarkers in ALS. These studies will be used to determine whether specific patterns of protein in blood can be used to diagnose ALS, develop more precise and sensitive clinical trials, and provide a reliable measure of the impact of treatment on the cortical component of ALS more quickly and accurately. The development of biomarkers for UMN degeneration has the potential to substantially improve the diagnosis, treatment and prognosis of individuals with ALS.

15. SUBJECT TERMS
Amyotrophic Lateral Sclerosis, Upper Motor Neurons, Biomarkers, Diagnosis

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1. INTRODUCTION:

ALS is both rare and heterogeneous. It involves both the cortical and the spinal component of the motor neuron circuitry. Previously, due to technical challenges, the cortical component of ALS has been somewhat neglected. For example, upper motor neurons (UMNs) are harder to derive from iPSC and UMN clinical signs are more difficult to detect. However, biomarkers of cortical health is required to stratify patients based on the origins of disease and provide an index of the stage and progression of UMN degeneration. Even though peripheral benzodiazepine receptor positron emission tomography (PBR-PET) imaging correlate with UMN dysfunction, currently, there are no biomarkers that allow quantitative and reliable measures to assess the extent of UMN loss in ALS patients. Consequently, clinicians rely solely on reflex examination to establish a diagnosis of ALS. Furthermore, UMN dysfunction may correlate with stages of ALS that would be more or less amenable to a given therapeutic. The health and stability of UMNs in ALS could be a trial outcome measure if it were quantitative. The development of quantitative biomarkers of UMN dysfunction could assist with ALS diagnosis, help target novel therapies to an appropriate stage of disease, and act as ALS trial outcome measures, with enough validation. The first step in that pathway is identification of such biomarkers.

2. KEYWORDS:

ALS, Upper motor neurons, biomarker, proteomics, bottom-up proteomics, top-down proteomics

3. ACCOMPLISHMENTS:

What were the major goals of the project?

STATEMENT OF WORK
START DATE – 09/01/2022

Task	Completed	Northwestern Univ.	MGH
Major Task 1: Enable transfer of Patient Serum and Blood Samples from MGH to Northwestern for purposes of this projec100%			
Subtask 1: Coordinate with Sites for material transfer agreements (MTAs)	100%		
Subtask 2: Coordinate with Sites for nondisclosure agreements (NDAs).	100%		
Subtask 3: Coordinate with Sites for IRB protocol submission. *Note:* IRB approvals already in place at MGH and samples previously collected.	100%	IRB Determination of Not Human Subjects Research	X
Subtask 4: Coordinate with Sites for USAMRDC review (ORP/HRPO)	100%		
Subtask 5: Coordinate with Sites for annual IRB report for continuing review	N/A		
Milestone Achieved: Local IRB approval at MGH	100%		X
Milestone Achieved: HRPO approval for all protocols and local IRB approval through MGH	100%		
Specific Aim 1: Determine the protein profile of serum and plasma samples isolated from ALS patients with prominent UMN loss, ALS patients with minimal cortical involvement, and age and sex-matched healthy controls. Determine whether identified "key proteins" are specific to ALS patients with prominent UMN loss, or also observed in HSP and PLS patients.			
Major Task 2: We hypothesize that there is a protein signature in serum and/or plasma samples, that is aligned with UMN loss in ALS patients. Our ability to detect and reveal the precise distribution of these proteins will help identify the ALS patients with prominent UMN loss. Depending on the identity of proteins, this information can also help suggest the underlying cause of the disease.			
Subtask 1: Serum and plasma samples collected from ALS patients with prominent UMN involvement (n=30; n=15 female; n=15 male) and serum and plasma samples collected from ALS patients with minimal UMN involvement (n=30; n=15 female; n=15 male) and serum and plasma samples collected from sex and age matched healthy controls who do not have any neurodegenerative diseases (n=20; n=10 female; n=10 male) sent to Northwestern by MGH.	100%		
Subtask 2: Samples blinded and distributed for proteomics analysis according to study design	100%		
Sample 3: Sample preparation	100%		

Subtask 3: Label-free quantitation (LFQ) with bottom-up proteomics	70%		
Subtask 4: Statistical analyses of proteomics data	0%		
Subtask 5: Proteins that are differentially present in ALS patients with prominent UMN involvement will be determined. The levels of these proteins in the serum and plasma of HSP and PLS patients will be determined either by ELISA or SRM strategy to investigate whether these proteins are specific to ALS patients or also present in other UMN disease patients.	0%		
Milestone Achieved: Identification of the presence of key proteins that are differentially identify ALS patients with prominent UMN involvement.	5%		
Specific Aim 2: Determine whether serum/plasma protein profiles can be used to reliably and accurately assess disease progression and response to treatment. We will quantitate changes in proteins and their isoforms over time in alignment with clinical markers of UMN involvement and in response to disease progression and/or therapeutic intervention.			
Major Task 3: When investigating proteins, one must consider the proteoform of proteins, which include their splice variations and post-translational modifications. We hypothesize that different proteoforms of proteins will be informative as "biomarkers" because splicing defects are frequently observed in ALS. In an effort to identify pharmacodynamic biomarkers, one needs to investigate whether these distinct proteoforms change quantitatively and structurally with disease progression.			
Subtask 1: Serum and plasma samples isolated from ALS patients with prominent UMN loss over time (at least 3 time points/patients and each sample separated by 6 months) organized from samples sent by MGH	100%		
Subtask 2: Samples blinded and distributed for proteomics analysis according to study design	50%		
Subtask 3: Subject samples to tandem mass tag quantitation by bottom up proteomics to determine the changes in the quantity of key proteins with respect to healthy controls.	50%		
Subtask 4: Statistical analysis of proteomics data.	0%		
Subtask 4: The identified proteins, together with the selected proteins from Aim 1 will be subjected to	0%		

top-down proteomics to investigate the presence of splice variations and/or post-translational modification defects, which will be quantitatively assessed for all 3-time points.			
Milestone Achieved: Identification of the dynamic changes of proteins and their proteoforms in serum and plasma of ALS patients with prominent UMN involvement.	0%		

What was accomplished under these goals?

This is a two-year DoD grant and the first year was important for receiving samples from MGH, deciding which sample goes to which study and which controls to be used. The bottom-up proteomics were going to be the focus of the first year and the top-down proteomics was going to be the focus of the second year. By the end of the first year, we have preliminary results from both the top-down proteomics approach and the bottom-up approach.

A. Top-down proteomics approach:

To date, the analysis of multiply-glycosylated intact glycoproteoforms by denatured-mode top-down (TD) or native mass spectrometry (nMS) is largely restricted to isolated glycoproteins. Omics-scale processing of glycoproteoforms is challenged by the high dynamic range in protein concentration and physiochemical properties, sample buffer complexity, and lack of bioinformatics resources that discriminate Fuc:Hex:GlcNAc:SA mass isomers allowing unambiguous assignment of 10-100s glycoproteoforms for each protein in an unbiased manner (Figure 1). Major activities related to our work have sought to report on how we have addressed this challenge through a dedicated omics-scale bioanalytical pipeline for the characterization of intact glycoproteins from tissues or biofluids from humans or animal models (**Figure 1**).

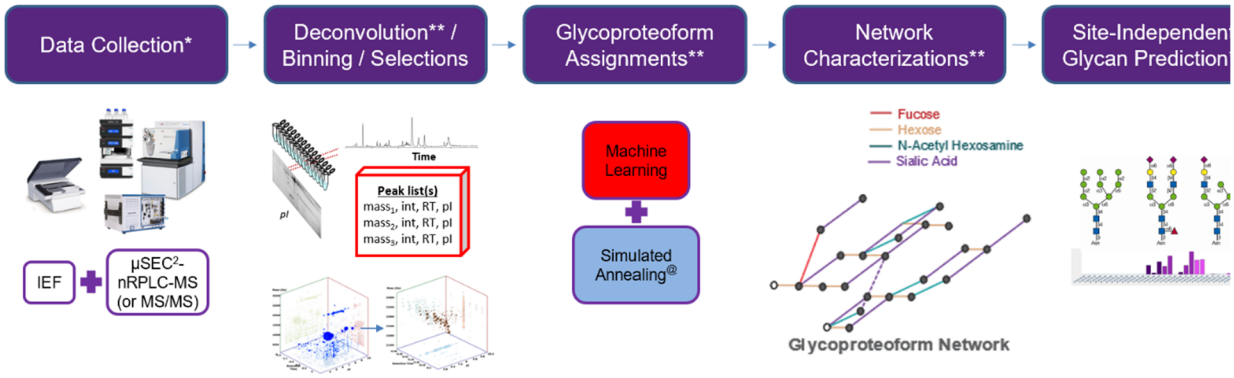


Figure 1: Omics-Scale Top-Down Mass Spectrometry of Multiply-Glycosylated Intact Glycoproteins by Online High/Low Pass Microflow Size-Exclusion Chromatography and Proteoform Network Analysis

In an investigation of the figures of merit associated with intact protein/proteoform measurements using a multidimensional proteomics workflow composed of off-gel isoelectric focusing (IEF) and superficially porous liquid chromatography (SPLC) with Fourier transform mass spectrometry (FTMS) we were able to rigorously and robustly quantify proteins and proteoforms, achieving physicochemical property measurements between proteome replicates with inter-replicate variances of ±3 ppm mass error for proteoforms <30 kDa, ±1.1 Da for proteins >30 kDa, ±12 s retention time error, and ±0.21 p*I* units. This workflow subsequently took an evolutionary step forward for non-targeted glycoproteoform investigations in our animal model studies through the recent online implementation of our tandem High/Low Pass (HP/LP) microflow size-exclusion chromatography (SEC) with nano-LC-MS/MS (μSEC^2-nLC-MS/MS). The work coupled μSEC to nanoLC through a novel injection volume control (IVC) strategy of inserting protein traps, pre- and post-μSEC columns, to enable injection of dilute samples in high volumes without loss of sensitivity or resolution (**Figure 2**).

implementation of our tandem High/Low Pass (HP/LP) microflow size-exclusion chromatography (SEC) with nano-LC-MS/MS (µSEC^2-nLC-MS/MS). The work coupled µSEC to nanoLC through a novel injection volume control (IVC) strategy of inserting protein traps, pre- and post-µSEC columns, to enable injection of dilute samples in high volumes without loss of sensitivity or resolution (**Figure 2**).

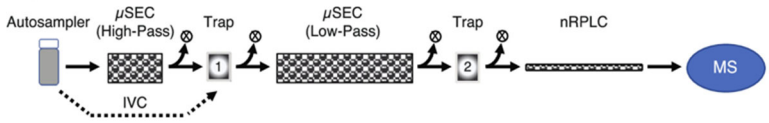


Figure 2: Injection Volume Control (ICV) overcomes SEC injection volume limits.

The sensitivity of this discovery-workflow for glycoproteins from 5-155 kDa was assessed, comparing 10-100 µL human, rat, and cynomolgus monkey cerebrospinal fluid (CSF) and 5-50 µL normal human pooled plasma (NPP) fractionated by OFFGEL IEF (pI 3-10). Through automated desalting via HP-µSEC and ICV, and concentration of the target proteins or MW range via LP-µSEC, the platform substantially increased proteoform detection from sample requirements that were ~100-150x less than previous reports. The workflow permits simultaneous detection of more abundant biofluid glycoproteins with 10s-100s of glycoproteoforms each (e.g., beta-haptoglobin, L-PGDS, transferrin, heavy-chain IgG) from as little as 10 µL CSF and 5 µL NPP. The improvements were aided by inclusion of detergents (e.g., triton X) in the IEF buffers, highlighting the importance of online HP-µSEC in TD investigations for effective removal of small molecule interferences.

We have worked to overcome another analytical challenge related to identification of intact glycoproteins from complex mixtures. Identification of glycoproteins using conventional data dependent data acquisition events is challenging because of the extreme glycoproteoform heterogeneity which leads to low signal to noise spectra on a chromatographic timescale. To overcome this challenge, we adapted our custom continuous elution bioinformatics procedure for data-independent in source dissociation (ISD) data acquisition across the LC run**)** When applied to IEF separated glycoproteoforms from biofluids (e.g., plasma) we can now routinely identify glycoproteins detected across the IEF separation space at FDR <0.05 (**Figure 3**).

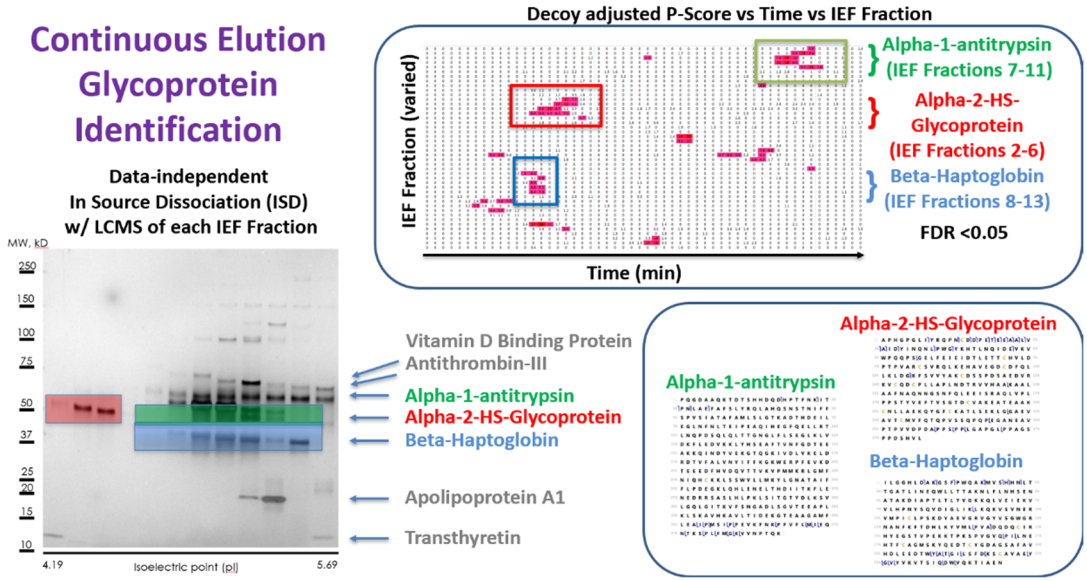


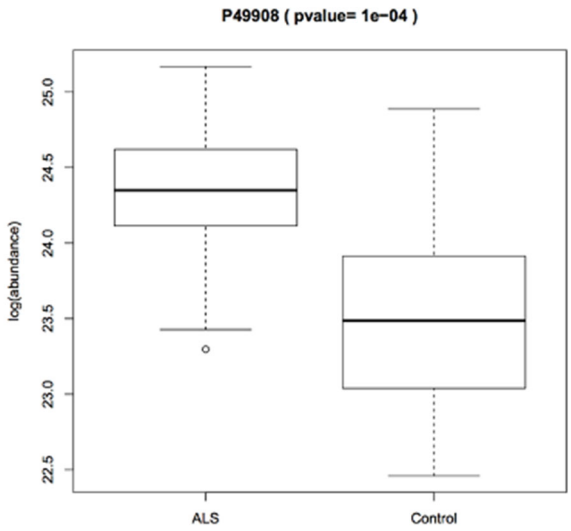
Figure 3. A custom continuous elution bioinformatics procedure for data-independent in source dissociation (ISD) data acquisition events across the LC run is a reliable way to identify intact glycoproteins from biofluids with high confidence (FDR <0.05).

Along with IEF, we have also been working towards developing orthogonal enrichement and chromatography strategies that allow us to reduce sample volumes approaching 10 uL of plasma or serum. For example, we began to use lectin affinity columns (e.g., WGA or CONA) to improve detection of glycoproteins from plasma. Plus, we have been utilizing complementary HILIC, capillary electrophoresis and nano-reversed phase liquid chromatography to help resolve groups of glycoproteoforms that share specific glycosylation structural elements.

In summary, we made important progress in the optimization of topdown proteomics to detect and assess the glycosylated forms of proteins, which are an important form of post-translational protein modification. We also made progress in their detection in smaller amounts of samples.

B. Bottom-up Approach:

We are still in the process of completing our bottom-up proteomics. Currently, all proteins are precipitated by acetone to remove salts, and resolubilized prior to digestion with Lys-C and trypsin for all serum and plasma samples. Peptides are concentrated prior to mass spectrometry. Peptides are resuspended and 150 samples are injected onto a trap column coupled with a nanobore analytical column. Peptides are separated and MS data are being obtained on a mass spectrometer fitted with a custom nanospray ionization source. The top 20 m/z species will be isolated within the ion trap and fragmented using collisionally induced dissociation (CID). A small percentage of data is analyzed with MaxQuant software (version 1.6.0.16) using the SwissProt Homo Sapiens database, and full data analyses is expected to be completed by November 2023. False discovery rates are adjusted to 1% at the peptide level using Scaffold 4.4 (Proteome Software) using standard Benjamini-Hochberg methods. Our initial studies using serum and plasma isolated from ALS patients revealed the presence of about 450-600 proteins within the confident level of significance and background subtraction. Among those proteins, some appear to be significantly higher in ALS patients with prominent UMN loss. We find for example that Sepp1 protein is significantly increased in the serum of ALS patients with prominent UMN involvement. This seem to be true for both male and female subjects. Selenoprotein P is an extracellular selenium binding protein that containts 10 selenocysteines. It is suggested to be a free radical scavenger. It reduces phospholipid hydroperoxide such as 1-palmitoyl-2-(13-hydroperoxy-cis-9,trans-11-octadecadienoyl)-3-phosphatidylcholine hydroperoxide, as well as glutathione, dithiothreitol, mercaptoethanol, cysteine, and homocysteine. Therefore, selenoprotein P functions as a phospholipid hydroperoxide glutathione peroxidase.



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

This had been a collaborative effort and many team members received training and professional development thanks to this proposal and grant. For example, Dr. Mukesh Gautam, Dr. Nathaniel Henning benefitted from the training activities. Dr. Gautam is invited to give a talk at the Les Turner ALS Symposium, he is invited to review grants at the NIH and he applied to his own independent grant as a young faculty. Dr. Henning learned new approaches for top-down proteomics, and he is in part supported by the Cornew Award given to CLP members at Northwestern. Kate Paus, an undergraduate student working with and helping Dr. Gautam, also received training and now she is accepted to the PhD program in Neuroscience at the Kentucky School of Medicine.

Postdoctoral fellow Jua Lee has regular one-on-one meetings with Dr. Patrie as well as opportunities to present her research formally to the Kelleher group as a whole a couple of times per year. She also participates in subgroup meetings where she has more opportunities to present to a smaller group and learn new techniques and strategies from other members. She also attended the American Society for Mass Spectrometry (ASMS) annual conference in the last year.

How were the results disseminated to communities of interest?

We have not yet disseminated any result to the community.

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

Next reporting period will be very important as we will have the bottom-up proteomics data both on the serum and on the plasma, and we will also have the top-down proteomic results collected by that time. When both of these analyses are completed, we will have a better understanding of the proteins and their isoforms and their quantitative distribution in the serum and/or the plasma of ALS patients with prominent upper motor neuron involvement and other UMN disease patients, such as the PLS patients. I anticipate that the next reporting period will have better analyzed data with proper statistics.

4. IMPACT:

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

We have not completed data generation and analyses, we only have preliminary results and even our initial investigations began to reveal the presence of key proteins that are present at high levels in patients with UMN involvement. We think this has an immense impact on the future clinical trials that will include ALS patients with predominant UMN involvement.

What was the impact on other disciplines?

Technologies are being improved and developed. As can be seen in the "Accomplishments" section, the top down proteomic approaches are being improved to detect proteins with glycosylation modification using low quantity of samples.

What was the impact on technology transfer?

We have not yet filed any tech transfer agreements.

What was the impact on society beyond science and technology?

We think the results of this proposal will have an immense impact on the design of future ALS clinical trials, so that patients with predominant UMN can also be included in the study. It is even possible to initiate novel clinical trials only for UMN disease patients, and this would be an immense impact to the society.

5. CHANGES/PROBLEMS:

We unfortunately ran into couple unforeseen problems during the first grant period. First, obtaining serum and plasma samples were delayed by 2-3 months, and even the grant period started in September, we were able to obtain the samples only towards the end of November. Pulling samples and collecting samples from different resources took longer than we anticipated. In addition, even though we were told 15 samples of HSP patients are available, in fact only 7 were in the repository. We waited for other centers to search for their biorepository to see if they have any HSP samples. I contacted UPenn, Northwestern University and I found 3 more samples from Northwestern University, and this delayed the experimental design and the initiation of bottom-up experiments.

As we were blinding samples, performing randomization and getting them ready for the bottom-up proteomics, we unfortunately received the sad news that the spouse of our Proteomics Center director unexpectedly passed away. The director took time off and then after two months we were informed that she will not be returning back. This was a major limitation on the timing of our planned experiments, and it also had a negative impact on our first-year reporting. I had a meeting with our program officer and shared this unexpected and sad development, and how it affected our workflow.

Actual or anticipated problems or delays and actions or plans to resolve them.

After we realized that we will not be able to share our samples with the proteomics core here, I had to find another resource for the bottom-up studies to be performed. We chose to work with Dr. Young Ah Goo, who was the previous director of the Northwestern Proteomics Core facility and now is the Director at University of Washington at St. Louis. We were able to send serum and plasma samples to be analyzed in June of 2023, with much delay. The samples are still being analyzed and as we write this progress report, we still have not yet received the complete result. However, we are confident that the samples are prepared in the best way and the experiments will be completed soon. We anticipate receiving the first results in October, 2023.

We also solved our sample number issue as we received other samples from other centers in the United States.

Changes that had a significant impact on expenditures

No, we did not have an impact on expenditures.

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

Significant changes in use or care of human subjects

There has not been a significant change on the use or care of biosamples isolated from human subjects.

Significant changes in use or care of vertebrate animals

Not applicable for this grant.

Significant changes in use of biohazards and/or select agents.

There has been no significant change in this regard.

6. PRODUCTS:

- **Publications, conference papers, and presentations**
  Journal publications.

We have not yet published our findings.

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

We have not yet published our findings.

Other publications, conference papers and presentations.

We have not yet published our findings, but we used our preliminary result to apply for an NIH R21 grant.

- **Website(s) or other Internet site(s)**

Not applicable.

- **Technologies or techniques**

The optimization of the glycoprotein detection system with minimal amount of serum and plasma resulted thanks to this application. We have not yet shared this technology with the public.

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

We have not yet disclosed our inventions in the form of a patent or license. We expect this to be at the end of the second year.

- **Other Products**

None yet. We are still in the data collection phase.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name: Hande Ozdinler, PhD
Project Role: PI
Researcher Identifier:
Nearest person month worked: 1
Contribution to Project: Overseeing all of the experiments and major tasks of the proposal.

Name: Jua Lee
Project Role: Postdoctoral Fellow
Researcher Identifier:
Nearest person month worked: 3
Contribution to Project: Working with Drs. Patrie and Kelleher for in method development and execution of top-down proteomics

Name: Robert Parish
Project Role: Instrument Technician
Researcher Identifier:
Nearest person month worked: 1
Contribution to Project: Maintenance of mass spectrometers and supplies used for bottom-up and top-down proteomics assays of patients' serum samples.

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

CHANGES IN ACTIVE SUPPORT

OZDINLER, P. HANDE, PhD

ACTIVE (# indicates change)

#New Award

CDMRP/USAMRDC – W81XH-21-ALSRP-TIA 05/01/2022 – 04/30/2024
1.20 CM
Ozdinler (PI)

Developing Cell-Based and Mechanism-Focused Preclinical Platforms with Diseased Upper Motor Neurons

We will develop a semi high-throughput drug discovery/verification platform that utilizes diseased UMNs and obtains data directly from their cellular responses to treatment allow the establishment of cell-based and mechanism-focused drug discovery. These studies will help identify the most effective treatment strategy for a distinct underlying cause or pathology.

- Specific Aim 1:. Develop a semi high-throughput platform to define the baseline characteristics of UMNs diseased due to mSOD1 toxicity, TDP-43 pathology, lack of alsin function, profilin mutations, and Spastin mutations in vitro with respect to healthy UMNs.
- Specific Aim 2:. Investigate the extent of diseased UMN's response to compound treatment in vitro.
- Specific Aim 3: Investigate the impact of compound treatment on neuro-immune modulation and UMN health.

Sponsor Contact

Dr. Sarah Dougherty

sarah.e.dougherty5.civ@mail.mil

Overlap: This is the award being reported on.

#New Award (THIS AWARD)

CDMRP/USAMRDC – W81XWH-21-ALSRP-CDA 09/01/2022 – 08/31/2024 0.84 CM

Ozdinler (PI)

Identification and Utilization of Upper Motor Neuron Biomarkers for ALS

This multi-institutional team will apply its expertise and resources towards the goal of identifying UMN biomarkers in ALS. These studies will be used to determine whether specific patterns of protein in blood can be used to diagnose ALS, develop more precise and sensitive clinical trials, and provide a reliable measure of the impact of treatment on the cortical component of ALS more quickly and accurately. The development of biomarkers for UMN degeneration has the potential to substantially improve the diagnosis, treatment and prognosis of individuals with ALS.

- Specific Aim 1: Determine the protein profile of serum and plasma samples isolated from ALS patients with prominent UMN loss, ALS patients with minimal cortical involvement, and age and sex-matched healthy controls. Determine whether identified "key proteins" are specific to ALS patients with prominent UMN loss, or also observed in HSP and PLS patients.
- Specific Aim 2: Determine whether serum/plasma protein profiles can be used to reliably and accurately assess disease progression and response to treatment. We will quantitate changes in proteins and their isoforms over time in alignment with clinical markers of UMN involvement and in response to disease progression and/or therapeutic intervention.

  Sponsor Contact

  Dr. Sarah Dougherty

  sarah.e.dougherty5.civ@mail.mil

Overlap: None

Stealth BioTherapeutics, Inc. 08/01/19 - 07/31/23 1.20 CM

Ozdinler (PI)

SRA: Preclinical Investigation of SBT Discovery Compounds in Upper Motor Neuron Cell Based Model of ALS

The aim of this grant is to investigate whether compounds at reduced protein aggregation will be beneficial for neurodegenerative diseases.

• Specific Aim 1: We will investigate putative neuroprotective effects of two discovery stage mitochondrial therapies in a primary cell culture model of ALS.

Sponsor Contact
Name: Dennis Keefe

Fax: N/A
Email: dennis.keefe@stealthbt.com

Overlap: None.

Spastic Paraplegia Foundation, Inc. 07/16/20 - **#09/29/2023 (NCE)** 0.60 CM
Ozdinler (PI)

Directed Gene Delivery to Upper Motor Neurons

The aim of this grant is to investigate the approaches for directed gene delivery to the upper motor neurons.

- Specific Aim 1: We will investigate AAV-mediated gene delivery approached to the motor cortex such that selective transduction of upper motor neurons can be achieved with a one-time motor cortex injection. Studies will be made on the motor cortex in a mouse model and the macaque monkey with the goal of translational efforts being developed in the near future. We will collaborate with Dr. Hatsopoulous at University of Chicago, an expert on cortical connectivity in non-human primates.

Sponsor Contact
Name: Mark Weber
Fax: N/A Email:

Overlap: None

NIH/NIA - R01 AG061708 08/01/19 - 04/30/24 4.80 CM
Ozdinler (PI)

Novel Protein Aggregation Inhibitors and Upper Motor Neuron Stabilizers for ALS and other Neurodegenerative Diseases

Upon successful completion, our proposal will result in the development of a novel drug discovery platform and will identify new drug candidates for amyotrophic lateral sclerosis (ALS) and, more broadly, for other age-related neurodegenerative diseases in which protein aggregation is the underlying cause, such as Alzheimer's disease, Parkinson's disease, and ALS/FTD.

- Specific Aim 1: To synthesize new analogues of pyrazolone and cyclohexane-1,3-dione compounds that inhibit protein aggregation.
- Specific Aim 2: To identify the target of action of our pyrazolone class of compounds, including edaravone, and our cyclohexanediones.
- Specific Aim 3: Investigate the impact of selected compounds on their ability to improve the health and stability of diseased UMNs *in vitro*.
- Specific Aim 4: To investigate whether compounds of interest improve overall motor neuron function and motor neuron health *in vivo*.

Sponsor Contact
Name: Coryse St.Hillaire-Clarke

Fax: +1 301 496-1494 Email:

Overlap: None

#New Award

Spastic Paraplegia Foundation, Inc. **12/22/2022 – 12/21/2024** 0.60 CM

Ozdinler (PI)

Investigation of NU-9 and its impact on upper motor neurons diseased by spastin mutations in HSP

This proposed research is an investigation of NU-9 and its impact on disease models, which recapitulate HSP disease, an upper motor neuron disease. All experiments will be performed in the Ozdinler Lab, and all experiments are tissue culture experiments to reveal the underlying mechanism of action.

- Specific Aim 1: To investigate the optimum concentration of NU-9 to improve the health of upper motor neurons diseased due to mutations in the spastin gene (SPG4)
- Specific Aim 2: To investigate the cellular mechanisms by which NU-9 improves the health of diseased CSMN with Spastin mutations.

Sponsor Contact

Name: Mark Weber

Fax: N/A

Email: markw732@yahoo.com

Overlap: None

#New Award

NIH/NINDS – R21 NS125465 **09/01/2022 - 08/31/2024** 1.20 CM

Ozdinler (PI)

Profiles of Common and Unique aspects of Upper Motor Neuron degeneration in HSP and ALS

Using pure populations of upper motor neurons that are diseased due to HSP and ALS pathologies, the goal of the project is to investigate the dynamic changes in their gene expression profile and metabolomic alterations during presymptomatic and symptomatic stages of neurodegeneration. Our results will reveal the common and unique aspects of upper motor neuron vulnerability and progressive degeneration in ALS and HSP, and will lay the foundation for future detailed therapeutic strategies for these upper motor neuron diseases.

- Specific Aim 1: Identify the dynamic changes in gene expression profiles of UMN that become diseased due to HSP and ALS.
- Specific Aim 2: Identify the dynamic changes in protein profiles of UMN that become diseased due to HSP and ALS.

Sponsor Contact

Name: Karrah Benson Fax:
N/A

Email: karrah.benson@nih.gov

Overlap: None

#New Award
Revalesio Corporation - RC AGMT 10/19/22 10/19/2022 - 10/18/2024 0.24 CM
Mukesh Gautam, PI
Preclinical Investigation of RNS60 Discovery Compounds in TDP-43^{A315T} mouse model of ALS The goal of the study is to investigate putative neuroprotective effects of RNS60 mitochondrial therapy in an ALS mouse model of TDP-43 pathology.

- Specific Aim1: Phase I: In vivo treatment of prpTDP-43^{A315T}-UeGFP mouse with a predetermined dose of RNS60 to investigate its effect on mitochondria and UMN health

- Specific Aim 2: Phase II: Assessment of mitochondrial function in prpTDP-43A315T-UeGFP upper motor neuron in vivo at optimized doses of RNS60

Sponsor Contact:
Name: Supurna Ghosh
Fax:
Email: sghosh@revalesio.com

Overlap: None

#New Award
Spastic Paraplegia Foundation, Inc. 07/1/23 - 06/30/2025 0.24 CM
Mukesh Gautam, PI
Revealing ultrastructural defects in the motor cortex of PLS patients with and without TDP-43 pathology
The aim of this grant is to targets the PLS patient population.

- Specific Aim 1: To reveal the ultrastructural defects within the motor cortex of primary lateral sclerosis (PLS) patients with and without TDP-43 pathology.
- Specific Aim 2: To investigate organelle-specific defects in motor cortex of PLS patients with respect to TDP-43 pathology.

Sponsor Contact
Name: John Cobb

Fax: N/A
Email: johncobb00@gmail.com
Overlap: None

BERRY, JAMES

Active (# indicates change)

#New Award (This Award)
Title: Identification and Utilization of Upper Motor Neuron Biomarkers for ALS
Project Number: W81XWH2210166/AL210134
Time Commitments: 0.36 calendar

Supporting Agency: CDMRP/USAMRDC
Contracting/Grants Officer: Dr. Sarah Dougherty
Performance Period: 09/01/2022-08/31/2024
Level of Funding:
Project Goal: The overall goal of this collaborative, interdisciplinary research project is to identify novel biomarkers that will help to identify patients with prominent UMN loss, point towards the underlying cause, and most importantly, can illuminate the extent of UMN degeneration and response to therapeutic intervention.
Specific Aims: Determine the protein profile of serum and plasma samples isolated from ALS patients with prominent UMN loss, ALS patients with minimal cortical involvement, and age and sex-matched healthy controls. Determine whether identified "key proteins" are specific to ALS patients with prominent UMN loss, or also observed in HSP and PLS patients.
Specific Aim 2: Determine whether serum/plasma protein profiles can be used to assess disease progression and respond reliably and accurately to treatment. We will quantitate changes in proteins and their isoforms over time in alignment with clinical markers of UMN involvement and in response to disease progression and/or therapeutic intervention.
Overlap This is the award being reported on

#New Award
Title: An Expanded Access Protocol of Intravenous Trehalose Injection 90 mg/mL Treatment of Patients with Amyotrophic Lateral Sclerosis
Time Commitments: 2.4 CM
Supporting Agency: National Institutes of Health – National Institute of Neurological Disorders and Stroke
Address:
9000 Rockville Pike
Bethesda, MD, 20892
Contracting/Grants Officer: Russell Blaisdell
Performance Period: 09/28/2022-08/31/2025
Level of funding:
Project Goals: The proposed expanded access would provide 6 months of access to trehalose (SLS-005), an investigational product that is currently being tested in a randomized clinical trial for ALS, the HEALEY ALS Platform Trial. This expanded access would provide broad and long-term safety, biomarker, and real-world efficacy data to supplement the eventual new drug application (NDA) submission by the drug manufacturer, Seelos Therapeutics. By providing a model for following safety, biomarker changes, and clinical efficacy in this program, we are helping to treat participants in this project, and also creating a blueprint for the design of scientifically relevant, patient-centric expanded access protocols.
Specific Aims: To present award-winning project to the MGH research community at our annual Celebration of Science
Overlap: None

#New Award
Title: Pilot Trial of Baricitinib for ALS Patients and Asymptomatic Mutant C9ORF72 Carriers Including Novel Peripheral Immune Cell Profiling and CSF Biomarkers
Time Commitments: .12 CM

Supporting Agency: US Army Medical Research Acquisition Activity
Address:
1077 Patchel Street
Ft. Detrick, MD 21702
Contracting/Grants Officer: Stephanie Stone
Performance Period: 06/01/2022-05/31/2025
Level of funding:
Project Goals: To examine the efficacy of Baricitinib in ALS patients.
Specific Aims: To act as both a coordination center for the overall study, and a site that enrolls participants as outlined in the protocol.
Overlap: None

#New Award
Title: Development of novel NLRP3 inflammasome inhibitors for Alzheimer's disease
Time Commitments: .12 CM
Supporting Agency: Virginia Commonwealth University
Address:
701 West Broad Street Richmond, VA 23284
Contracting/Grants Officer: Stephanie Stone
Performance Period: 06/01/2022-05/31/2027
Level of funding:
Project Goals: To provide expertise in clinical trial design.
Specific Aims: Specifically, the overall goal of the project will be focused on identifying and characterizing potential molecules that specifically and safely inhibit NLRP3 inflammasome from a viable library generated by Dr. Shijun Zhang, which may ultimately provide as potential therapeutics of Alzheimer's disease (AD). To be analyzed for the efficacy in ameliorating disease related pathologic changes using disease models, the candidate molecules will be evaluated by a series of studies that can display clinical potentials as well as desirable drug-like properties for AD.
Overlap: None

#New Award
Title: A Geospatial and Toxicological Evaluation of Massachusetts ALS Registry Patients
Time Commitments: 1.2 calendar
Supporting Agency: Dartmouth Hitchcock Medical Center
Address:
289 Country Road
Windsor, VT 05089
Contracting/Grants Officer: Adam Carlson
Performance Period: 09/01/2021-08/31/2026
Level of Funding:
Project Goal: To provide samples from ALS brains from the Massachusetts Alzheimer's Disease Research Center and from several control brains. To correlate toxin levels from ALS brains and compare to controls in a manner so that statistical analysis and machine learning techniques can be employed by Dartmouth researchers.
Specific Aims: To act as a study site to provide postmortem tissue for toxin level testing.

Overlap None

#Expired Award
Title: A Phase 3, Randomized, Double-blind, Placebo-controlled Multicenter Study to Evaluate Efficacy and Safety of Repeated Administrations of NurOwn® (Autologous Mesenchymal Stem Cells Secreting Neurotrophic Factors) in Patients with Amyotrophic Lateral Sclerosis (ALS).
Time Commitments: 0.01 calendar
Supporting Agency: BrainStorm Therapeutics
Address:
12 Bazel Street
Kiryat Arieh, Petach-Tikva
Israel, 4900101
Contracting/Grants Officer: Uri Yablonka
Performance period: 04/03/2017-04/02/2022
Level of funding:
Project Goals: The purpose of this study is to be a clinical trial site and determine the efficacy and safety of repeat administrations of intrathecal injections of NurOwn® as compared to placebo in patients with ALS
Specific Aims: To evaluate the safety and efficacy of NurOwn® (MSC-NTF cells) vs. placebo as measured by the proportion of patients whose disease is stabilized or improved with a 100% or greater improvement in post-treatment slope vs. pre-treatment slope ALSFRS-R.
Overlap: None

#Expired Award
Title: Expanded Population of Regulatory T-Cells (EPAR T-Cells) for People with ALS
Time Commitments: 0.01 calendar
Supporting Agency: ALS Finding a Cure
23 Barry Place
Stamford, CT 06902
Contracting/Grants Officer: Chris Collins
Performance period: 08/01/2018-12/31/2021
Level of funding:
Project Goals: The primary goal of this study is to evaluate the biological activity of IV infusion of an expanded population of autologous regulatory T-lymphocytes and low-dose IL-2 in people with ALS by evaluation of Treg number and suppressive function.
Specific Aims: To characterize the effects of EPAR T-Cells and low-dose IL-2 on clinical outcome measures of ALS
including Appel ALS Scale (AALS) and ALS Functional Rating Scale-Revised (ALSFRS-R) scores.
Overlap: None

#Expired Award
Title: CTA: A Phase 1, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability and Pharmacokinetics of Single Doses of AT-1501 in Healthy Adults and ALS patients
Time Commitments: 0.12 calendar
Supporting Agency: Anelixis Therapeutics Inc

Address:
300 Technology Square
Suite 400
Cambridge, MA 02139
Contracting/Grants Officer: Maeve McNally
Performance period: 10/23/2018-10/22/2023
Level of funding:
Project Goals: The primary goal of this study is to enroll participants to determine safety, efficacy and tolerability of AT-1501.
Specific Aims: To evaluate the effectiveness of AT-1501 at three sequential ascending doses of AT-1501 (0.5, 1.0, or 5.0 mg/kg) or placebo.
Overlap: None

#Expired Award
Title: Phase II Clinical Trial to Evaluate Safety, Tolerability, and Biomarker Engagement of AMX0035 in Patients with ALS
Time Commitments: 0.2 Calendar
Supporting Agency: Amylyx Pharmaceuticals
Address:
43 Thorndike St
Cambridge, MA 02141
Contracting/Grants Officer: Josh Cohen
Performance period: 03/15/2017-06/30/2022
Level of funding:
Project Goals: MGH is a site for a Phase II clinical study to enroll subjects for study participation.
Specific Aims: To determine the safety, efficacy and tolerability of AMX0035.
Overlap: None

#Expired Award
Title: CTA for Amylyx CENTAUR Open Label Extension
Time Commitments: 0.1 Calendar
Supporting Agency: Amylyx Pharmaceuticals
Address:
43 Thorndike St
Cambridge, MA 02141
Contracting/Grants Officer: Josh Cohen
Performance period: 03/12/2018-03/11/2023
Level of funding:
Project Goals: MGH is a site for the Open Label portion of the Phase II clinical study.
Specific Aims: To extend participation in the study to determine the safety, efficacy and tolerability of AMX0035.
Overlap: None

#Expired Award
Title: Development and validation of novel biofluid biomarker immunoassays employing SupraAntigenTM induced antibodies to detect TDP-43-associated neuropathologies in ALS

Time Commitments: 0.36 Calendar
Supporting Agency: Target ALS Foundation Inc.
Address:
PO Box 1598
New York, NY, 10101
Contracting/Grants Officer: Kenneth Devaney
Performance period: 11/01/2020-10/31/2022
Level of funding:
Project Goals: MGH is a compassionate use site for the Open Label portion of the Phase II clinical study.
Specific Aims: To extend participant access to AMX0035.
Overlap: None

#Expired Award
Title: The development and validation of a novel tool for the assessment of bulbar dysfunction in ALS
Time Commitments: 0.24 calendar
Supporting Agency: Sunnybrook Research Institute
Address:
75 Francis Street
Boston, MA 02115
Contracting/Grants Officer: Stephanie Stone
Performance period: 07/20/2018-06/30/2023
Level of funding:
Project Goals: Major goal is to operate a clinical study site for the project
Specific Aims: Processing, shipping and storing clinical information and biofluid samples from people with ALS.
Overlap: None

#Expired Award
Title: Digital Quantitative Measurements in ALS
Time Commitments: 0.12 calendar
Supporting Agency: Biogen
Address:
250 Binney Street
Cambridge, MA 02142
Contracting/Grants Officer: Peter Bergethon
Performance period: 11/07/2018-12/19/2022
Level of funding:
Project Goals: We aim to investigate the utility of digital tools to quantify aspects of the neurological examination in a clinic setting for use as quantifiable biomarkers of neurological change over time in people with ALS.
Specific Aims: Processing, shipping and storing of information from people with ALS.
Overlap: None

#Expired Award

Title: Targeting pro-inflammatory mediators to restore Treg homeostatic expansion and function in ALS, in vitro studies as surrogates for in vivo applications.
Time Commitments: 0.30 calendar
Supporting Agency: Department of Defense Congressionally Directed Medical Research Program
Address:
75 Francis Street
Boston, MA 02115
Contracting/Grants Officer: Jessel Lawson
Performance period: 06/01/2021-05/31/2023
Level of funding:
Project Goals: To match sample collection techniques with each experiment, so that we can efficiently identify compounds that will enhance Treg function in people with rapidly progressing ALS cases.
Specific Aims: Processing, shipping and storing of information from people with ALS.
Overlap: None

#Expired Award
Title: Neuron-derived Exosomes as a Biomarker Platform for Amyotrophic Lateral Sclerosis.
Time Commitments: 0.24 calendar
Supporting Agency: Target ALS Foundation, Inc.
Address:
PO Box 1598
New York, NY, 10101
Contracting/Grants Officer: Kenneth Devaney
Performance period: 11/01/2020-10/31/2022
Level of funding:
Project Goals: Together, proposed experiments will evaluate the ability of NDEs to accurately reflect the "disease status" of human neurons, human autopsied tissue, and plasma samples collected over 1-2 years.
Specific Aims: We propose to build on our preliminary findings by analyzing NDEs from both sALS and familial (f)ALS. In a mixed cohort of sALS and fALS (C9ORF72 and SOD1) patients from the Answer ALS study and equal number of non-ALS controls plasma samples will be analyzed using ExoSORT^{TM} for biomarker discovery.
Overlap: None

#Expired Award
Title: Metabolomics to Identify Targets in ALS: Improving ALS subtyping through integrative analysis of molecular pathways
Time Commitments: 0.36 calendar
Supporting Agency: Massachusetts Institute of Technology
Address:
600 Technology Square
Cambridge, MA 02139
Contracting/Grants Officer: Victoria Grafflin
Performance Period: 04/01/2021-03/31/2023
Level of Funding:

Project Goal: To act as a study site for the project.
Specific Aims: Oversight of the study conduct, oversight of biospecimen processing, and assurance of the study integrity.
Overlap None

HOLLAS, MICHAEL

ACTIVE (# indicates change)
#New Award (This Award)
CDMRP/USAMRDC W81XWH2210166 09/01/2022 – 08/31/2024 0.51 CM
Ozdinler (PI)
Identification and Utilization of Upper Motor Neuron Biomarkers for ALS
This multi-institutional team will apply its expertise and resources towards the goal of identifying UMN biomarkers in ALS. These studies will be used to determine whether specific patterns of protein in blood can be used to diagnose ALS, develop more precise and sensitive clinical trials, and provide a reliable measure of the impact of treatment on the cortical component of ALS more quickly and accurately. The development of biomarkers for UMN degeneration has the potential to substantially improve the diagnosis, treatment and prognosis of individuals with ALS.

- Specific Aim 1: Determine the protein profile of serum and plasma samples isolated from ALS patients with prominent UMN loss, ALS patients with minimal cortical involvement, and age and sex-matched healthy controls. Determine whether identified "key proteins" are specific to ALS patients with prominent UMN loss, or also observed in HSP and PLS patients.
- Specific Aim 2: Determine whether serum/plasma protein profiles can be used to reliably and accurately assess disease progression and response to treatment. We will quantitate changes in proteins and their isoforms over time in alignment with clinical markers of UMN involvement and in response to disease progression and/or therapeutic intervention.

Sponsor Contact
Dr. Sarah Dougherty
sarah.e.dougherty5.civ@mail.mil

Overlap: None

#New Award (#Hollas added mid project period)
NIH/NIGMS / P41 GM108569 06/01/2020 – 05/31/2025 7.20 CM
Kelleher, Neil L. (PI)
National Resource for Translational and Developmental Proteomics
The National Resource for Translational and Developmental Proteomics (NRTDP) will advance technology development for whole protein mass spectrometry in denaturing LC-MS mode while applying high performance proteomics to timely needs in biomedical research.

- Specific Aim 1: To advance biomedical research through implementing precise measurement of proteins on timely biomedical projects in basic and clinical research.
- Specific Aim 2: To develop and deploy robust technology for next-generation proteomics required by collaborative projects that can be adopted by others.
- Specific Aim 3: To engage the community of practitioners, collaborators and consumers of proteomics through Consortia, an on-site Training Center, and a series of informative videocasts disseminated via digital media.

Sponsor Contact
Charles Ashley Barnes

ashley.barnes@nih.gov
Overlap: None

#New Award (#Hollas added mid project period)
NIH/NIDA / P30 DA018310 07/15/2019 – 05/31/2024 2.00 CM
Sweedler, Jonathan (PI)
UIUC Neuroproteomics and Neurometabolomics Center on Cell to Cell Signaling
The major goals are to develop proteomic approaches applicable to proteins in the mammalian brain and interface with leading researchers in studies of how drug abuse affects the brain and long term behavior.

- Specific Aim 1: Characterization of the neuropeptides/hormones from selected samples—ranging from brain regions and defined nuclei to specific cells—using both directed and global measurement approaches. These include localization via discrete cell isolation for MS imaging, the measurement of activity dependent release and quantitative level changes as a function of activity/exposure to drugs, and other user-requested measurements.
- Specific Aim 2: Measurement of the neurometabolome, which can include transmitters, lipids, and metabolites, from samples ranging from entire brain regions to the cytoplasm of individual patch-clamp-selected cells.
- Specific Aim 3: Brain proteomics measurements performed with bottom-up, top-down and native top-down mass spectrometry including innovative structure-based proteomics of macromolecular assemblies.
- Specific Aim 4: High level bioinformatics and data analytics support to create curated catalogs of metabolites, prohormones, neuropeptides, proteoforms, and user-friendly web services that integrate descriptive, analytic, and predictive tools for hypothesis testing and data mining of highly dimensional proteomic, metabolomic, genomic, and transcriptomic data, and community support through web platforms.

Sponsor Contact
Jonathan D. Pollock
jpollock@nida.nih.gov

Overlap: None

KELLEHER, NEIL L.

ACTIVE (# indicates change)
#New Award
NIH/NIGMS / T32 GM149439 07/01/2023 – 06/30/2028 0.90 CM
Kelleher (PI)
Chemistry of Life Processes Predoctoral Training Program
The mission of the proposed Chemistry of Life Processes (CLP) Predoctoral Training Program at Northwestern University is to recruit, train and advance a diverse cohort of students who are prepared to lead the next wave of innovation and discovery at the interface of chemistry and biology. Trainees are appointed to the grant starting in the fall of their second year and are supported throughout the

course of the second and third years of graduate education. Ten additional students will be supported by one year university fellowships, enabling the participation of well qualified and diverse international students. The program deploys a team-based approach to program leadership that leverages the unique skill sets of its members and the administrative expertise of the Chemistry of Life Processes Institute to enhance program development and training. The CLP Training Program will address multiple dimensions of the training ecosystem and is aligned with NIGMS goals for predoctoral training: student-centered skills acquisition, trainee wellness and retention, mentor development, diversity, equity and inclusion, and assessment and improvement. The CLP Program will provide students with the opportunity to integrate graduate studies in chemistry and the life sciences to a degree beyond.

Sponsor Contact
Michelle Rueffer Bond
bondmr@nigms.nih.gov

Overlap: None

#New Award
CZ Biohub Chicago, LLC 07/01/2023 – 06/30/2025 0.09 CM
Kelley (PI)
Sampling and Sensing Technologies for Spatiotempo
Our ultimate goal is to reveal molecular alterations linked to skin inflammation and learn how to target inflammation to restore tissue health.

- Specific Aim 1: Integration of Skin/Sampling & Sensing Technologies
- Specific Aim 2: Spatial Proteomics and Metabolomics for the discovery of inflammatory signatures

Sponsor Contact
Victor Colunga

Contact: https://www.czbiohub.org/contact/
Overlap: None

#New Award (This Award)
Department of the Army / W81XWH2210166 09/01/2022 – 08/31/2024 0.18 CM
P. Ozdinler (PI)
Identification and Utilization of Upper Motor Neuron Biomarkers for ALS
This multi-institutional team will apply its expertise and resources towards the goal of identifying UMN biomarkers in ALS. These studies will be used to determine whether specific patterns of protein in blood can be used to diagnose ALS, develop more precise and sensitive clinical trials, and provide a reliable measure of the impact of treatment on the cortical component of ALS more quickly and accurately. The development of biomarkers for UMN degeneration has the potential to substantially improve the diagnosis, treatment and prognosis of individuals with ALS.

- Specific Aim 1: Determine the protein profile of serum and plasma samples isolated from ALS patients with prominent UMN loss, ALS patients with minimal cortical involvement, and age and sex-matched healthy controls. Determine whether identified “key proteins” are specific to ALS patients with prominent UMN loss, or also observed in HSP and PLS patients.

- Specific Aim 2: Determine whether serum/plasma protein profiles can be used to reliably and accurately assess disease progression and response to treatment. We will quantitate changes in proteins and their isoforms over time in alignment with clinical markers of UMN involvement and in response to disease progression and/or therapeutic intervention.

  Sponsor Contact

  Dr. Sarah Dougherty

  sarah.e.dougherty5.civ@mail.mil

Overlap: None

#New Award

NIHAID / R43 AI174407-01 03/15/2023 – 02/29/2024 0.24 CM

Kelleher (PI)

Multi-Omics and Synbio Enabled Discover of Antifungal Fernene Triterpenes

For this subcontract, Prof. Neil Kelleher will work with Varigen Biosciences to perform metabolomics analysis on their fungal strains utilizing our established NP/BCG discovery pipeline and provide raw files for them to complete their analysis. This work shall include some growth and extraction of fungal strains as well as sample preparation for LCMS/ MS analysis on our Q-Exactive Plus mass spectrometer with UPLC. The goal of this project is to perform metabolomics analysis on fungal strains utilizing our established NP/BCG discovery pipeline and provide raw data to Varigen Biosciences.

- Specific Aim 1: Advance a second generation of triterpene antifungal analogs into the research and clinical marketplace.

  Sponsor Contact

  Baoying Liu

  baoying.liu@nih.gov

Overlap: None

#New Award

NIHAID / R01 AI170728-01A1 08/17/2023 – 07/31/2027 0.09 CM

Tambur, Anat R. (PI)

The Immunogenicity and Pathogenicity of HLA-DQ in Solid Organ Transplantation

This research proposal is relevant to public health because it aims to maximize utility of a scare resource – organs donated for the purpose of life-saving transplantation. Our work aims to provide fundamental knowledge of mechanisms underlying rejection of the transplanted organs. Upon conclusion, this knowledge will enhance transplant allograft survival, reduce medical and financial ramifications associated with the need to treat rejection, and will improve transplant recipients' quality of life.

- Specific Aim 1: we will define the immunogenicity of HLA-DQ mismatches that lead to the development of donor-specific HLA-DQ antibodies in transplant recipients. We will use computational and experimental approaches including adsorption/elution and site directed mutagenesis studies to prognosticate qualitative characteristics of HLA-DQ epitopes.
- Specific Aim 2: we will compare immune activation pathways triggered by ligation of different HLA class II molecules

  Sponsor Contact

Shilpa S. Kulkarni
shilpa.kulkarni@nih.gov

Overlap: None

#New Award

NIH/NCCIH / R01 AT009143 08/05/2022 – 05/31/2027 0.50 CM
Kelleher (PI)

Mapping and Understanding Production of Natural Products in Fungi

The goal of this project is to improve a genome-driven, correlation-based platform to unearth and then produce new bioactive compounds from fungi. This platform and research will deliver access to a large repertoire of fungal natural products, which historically have been a great source of new medicines and tool compounds. Typical estimates have natural products and their derivatives accounting for ca. 75% of the currently used antibiotics and nearly 60% of anti-cancer drugs along with numerous antiviral, antiparasitic, antifungal and immunosuppressive medicines. Despite their historical successes, traditional screening programs have been severely curtailed due to declining numbers of promising new candidates and lack of ready access to new compounds. At the same time, analysis of over one thousand fungal genomes suggests that tens of thousands of high-value natural products have yet to be identified and put into screens. Thus, new technologies are needed and here we describe an integrated plan to systematical tap into this vast potential of fungal metabolites through genomics, metabolomics and molecular biology. In the previous funding period, we developed an untargeted approach called 'metabologenomics' that correlates genomic content with metabolite output to uncover new hundreds of natural products and their gene clusters from soil actinobacteria. Activities described in this proposal will reduce technical barriers by establishing optimal workflows, improving experimental methodology and refining scoring metrics to create a discovery platform with the ability to unlock the medicinal potential of natural products in the fungal kingdom.

- Specific Aim 1: Propose to extend the method to 250 fungi advancing the field in the process
- Specific Aim 2: Focus on the targeted capture and expression of BGCs in specific euchromatic loci in a widely used host for natural product heterologous expression, Aspergillus nidulans.

Sponsor Contact
Craig Hopp

hoppdc@mail.nih.gov

Overlap: None

Chicago Biomedical Consortium / C202128982 10/01/2021 – 09/30/2024 0.18 CM
N. Kelleher / B. Murphy (PI)

Establishing Two New Bacterial Phyla to Produce the Next Generation of Biomedical Drug Leads

This project involves the analysis of bacterial extracts by mass spectrometry and coordination of this data with genomic sequencing to identify promising biomedical drug targets.

- Specific Aim 1: Use of an automated colony picker to construct a library of Acidobacteria and Planctomycetes isolates (Murphy lab).
- Specific Aim 2: Genome sequencing, mass spectrometry-based metabolomics, and optimization of omics correlation metrics to mine for NP leads. (Kelleher/Thomson labs).

Sponsor Contact
Kimberly Corn

k-corn@northwestern.edu

Overlap: None

NIH/NIDA P30 DA018310 07/15/2019 – 05/31/2024 1.00 CM
J. Sweedler (PI)
UIUC Neuroproteomics and Neurometabolomics Center on Cell to Cell Signaling
The major goals are to develop proteomic approaches applicable to proteins in the mammalian brain and interface with leading researchers in studies of how drug abuse affects the brain and long term behavior.

- Specific Aim 1: Characterization of the neuropeptides/hormones from selected samples—ranging from brain regions and defined nuclei to specific cells—using both directed and global measurement approaches. These include localization via discrete cell isolation for MS imaging, the measurement of activity dependent release and quantitative level changes as a function of activity/exposure to drugs, and other user-requested measurements.
- Specific Aim 2: Measurement of the neurometabolome, which can include transmitters, lipids, and metabolites, from samples ranging from entire brain regions to the cytoplasm of individual patch-clamp-selected cells.
- Specific Aim 3: Brain proteomics measurements performed with bottom-up, top-down and native top-down mass spectrometry including innovative structure-based proteomics of macromolecular assemblies.
- Specific Aim 4: High level bioinformatics and data analytics support to create curated catalogs of metabolites, prohormones, neuropeptides, proteoforms, and user-friendly web services that integrate descriptive, analytic, and predictive tools for hypothesis testing and data mining of highly dimensional proteomic, metabolomic, genomic, and transcriptomic data, and community support through web platforms.

Sponsor Contact
Jonathan D. Pollock
jpollock@nida.nih.gov

Overlap: None

NIH/NIA RF1 AG063903 08/15/2019 – 03/31/2024 0.50 CM
N. Kelleher (PI)
Defining native proteoform landscape for amyloid-beta in Alzheimer's disease
Our strong multidisciplinary team will leverage decades of experience in advanced proteomics and pioneering the amyloid-beta oligomer (AβO) hypothesis to provide a completely fresh look at Aβ. The work will lead to fundamental insights on downstream spatial/temporal signaling leading to neurocognitive decline, as well as, inform most Aβ research tracks, including hypothesis testing in relation to in vivo targeting of Aβ by, e.g., imaging probes or diagnostic or therapeutic antibodies.

- Specific Aim 1: **Elucidating the Aβ proteoform landscape of AβOs.** Little is known about how the brain environment shapes the Aβ proteoform landscape. To overcome this knowledge gap, samples will be selected that probe the maximal chemical landscape of Aβ proteoforms comprising AβOs in human subjects compared with animal models that are physiologically similar (non-human primates, NHP) and distant (mice). This will be achieved by implementation

of a nTDMS screen with enhanced liquid handling, automated data acquisition, and aligned native-state bioinformatics and statistical procedures that provide order-of-magnitude improved dynamic range for descriptive investigations on Aβ proteoforms within a single sample, with a duty cycle that promises hundreds of samples in a given year.

- Specific Aim 2: **Meta-analysis ascribes pathological phenotypes to Aβ proteoform signatures measured by highly parallelized nTDMS and cell-based neurotoxicity screens.** With highly parallelized immunoassays, cell-based neurotoxicity screening technologies, and nTDMS assays, we will correlate distinct sets of Aβ proteoforms that comprise AβOs and are observed in a spatiotemporal manner with cellular phenotypes and histological and biomolecular features in AD. This knowledge will inform on possible function of distinct Aβ proteoform sets and rational development of Aβ-targeting therapeutics or diagnostics.
- Specific Aim 3: **Quantitation of Aβ proteoform signatures at milestone transition points in 5XFAD mice.** As in human AD, data from the 5XFAD model suggests proteoform-level alterations in Aβ (pyroglutamylated-, N-truncated-, metal-Aβ) that occur in a manner that correlate with AβO solubility and neurotoxicity, often in an age-, and therefore disease-dependent manner. Here, a quantitative nTDMS analysis of select Aβ proteoform families will reveal connections between Aβ PTMs with disease pathogenesis, such as AβO membrane association and neurotoxicity phenotypes.
- Specific Aim 4: **Implement Proteinopathy Proteoform Knowledgebase (PPK) framework.** Proteoform sciences have immense potential for biomedical data and data-related innovation to advance human health. Here, in partnership with the neuroscience community, we propose to aggregate and disseminate proteoform-level insights from the brain to the greater neuroscience community, providing unique perspectives on disease drivers that are defined beyond those conventionally searched at the DNA, RNA, and protein levels.

Sponsor Contact
Austin Jyan-Yu Yang
yangj13@mail.nih.gov

Overlap: None

NIH/NIGMS P41 GM108569 06/01/2020 – 05/31/2025 2.00 CM
N. Kelleher (PI)

National Resource for Translational and Developmental Proteomics

The National Resource for Translational and Developmental Proteomics (NRTDP) will advance technology development for whole protein mass spectrometry in denaturing LC-MS mode while applying high performance proteomics to timely needs in biomedical research.

- Specific Aim 1: To advance biomedical research through implementing precise measurement of proteins on timely biomedical projects in basic and clinical research.
- Specific Aim 2: To develop and deploy robust technology for next-generation proteomics required by collaborative projects that can be adopted by others.
- Specific Aim 3: To engage the community of practitioners, collaborators and consumers of proteomics through Consortia, an on-site Training Center, and a series of informative videocasts disseminated via digital media.

Sponsor Contact
Charles Ashley Barnes

ashley.barnes@nih.gov
Overlap: None

HU0001-22-2-0006 05/01/2022 – 04/30/2024 0.45 CM
Uniformed Services University of the Health Sciences
N. Kelleher (PI)
Top Down Proteomics of Laser Capture Microdissected Samples for the Cancer Moonshot
Label-free quantitative top-down proteomics of APOLLO tissue samples will be performed using the top-down proteomic pipeline that has been developed in the National Resource for Translational and Developmental Proteomics. Benchmark and streamline a Quantitative Spatial LMD Top-Down Proteomics workflow at Pilot Scale.

- Specific Aim 1: Over a timeframe of 4 months (36-40 m), a staff scientist at the PCE will develop methods for proof-of-concept experiments and data analysis on a Quantitative Spatial LMD Top-down Proteomics workflow using 10 LMD samples that are spatially collected across one tumor.
- Specific Aim 2: Phase 6: Perform Quantitative Spatial LMD Top-Down Proteomics on 100 samples across 10 tumors.
- Specific Aim 3: Over a timeframe of 8 months (40-48 m), the Quantitative spatial LMD Top-Down Proteomics workflow will be performed on 100 samples that are spatially collected across 10 tumors (10 samples/tumor) by a staff scientist at the Proteomics Center of Excellence. This phase will commence after the Phase 5 experiments.

Sponsor Contact
Shiloh Davis
sdavis@hjf.org

Overlap: None

NIH/NIAID / U01 AI163081 09/06/2021 – 06/30/2028 0.18 CM
J. Levitsky (PI)
Utility of Biomarkers of Rejection and Kidney Injury in Tailoring Liver Transplant Immunosuppression
Biomarkers in the blood can be used to detect signs of certain diseases to guide treatment strategies aimed at preventing them, and in the case of this application, rejection and kidney injury in liver transplant recipients. This project will test if the biomarkers we developed in a prior CTOT study can predict rejection and kidney injury and therefore help us use anti-rejection medications in a more successful way. This study will also provide a deeper understanding of the pathways that lead to rejection and kidney injury and improve our ability to avoid these complications.

- Specific Aim 1: Clinical Trial – We aim to conduct a multicenter trial assessing the utility of validated biomarkers of rejection and kidney injury in tailoring immunosuppression management in liver transplant recipients.
- Specific Aim 2: Mechanistic Studies – We aim to gain deeper mechanistic insights into the effect of early calcineurin inhibitor withdrawal on immune responses and kidney function in liver transplant recipients.

Sponsor Contact
Deborah Hayes

dhayes@niaid.nih.gov
Overlap: None

NIH / R01 NS127204 06/17/2022 – 05/31/2027 0.45 CM
P. Opal (PI)
Elucidating cellular mechanisms underlying neurodegeneration
The goal is to understand the cellular pathogenesis of giant axonal neuropathy with a view to inspiring novel treatment strategies.
Sponsor Contact Glen Nuckolls
nuckollg@mail.nih.gov

Overlap: None

PAGANONI, SABRINA

Active (# indicates change)

#New Award (This Award)
Title: Identification and Utilization of Upper Motor Neuron Biomarkers for ALS
Project Number: W81XWH2210166/AL210134
Time Commitments: 0.36 calendar
Supporting Agency: CDMRP/USAMRDC
Contracting/Grants Officer: Dr. Sarah Dougherty
Performance Period: 09/01/2022-08/31/2024
Level of Funding:
Project Goal: The overall goal of this collaborative, interdisciplinary research project is to identify novel biomarkers that will help to identify patients with prominent UMN loss, point towards the underlying cause, and most importantly, can illuminate the extent of UMN degeneration and response to therapeutic intervention.
Specific Aims: Determine the protein profile of serum and plasma samples isolated from ALS patients with prominent UMN loss, ALS patients with minimal cortical involvement, and age and sex-matched healthy controls. Determine whether identified "key proteins" are specific to ALS patients with prominent UMN loss, or also observed in HSP and PLS patients.
Specific Aim 2: Determine whether serum/plasma protein profiles can be used to assess disease progression and respond reliably and accurately to treatment. We will quantitate changes in proteins and their isoforms over time in alignment with clinical markers of UMN involvement and in response to disease progression and/or therapeutic intervention.
Overlap This is the award being reported on

#New Award
Title: An Expanded Access Protocol of Intravenous Trehalose Injection 90 mg/mL Treatment of Patients with Amyotrophic Lateral Sclerosis
Time Commitments: 2.4 CM
Supporting Agency: National Institutes of Health – National Institute of Neurological Disorders and Stroke

Address:
9000 Rockville Pike
Bethesda, MD, 20892
Contracting/Grants Officer: Russell Blaisdell
Performance Period: 09/28/2022
Level of funding:
Project Goals: The proposed expanded access would provide 6 months of access to trehalose (SLS-005), an investigational product that is currently being tested in a randomized clinical trial for ALS, the HEALEY ALS Platform Trial. This expanded access would provide broad and long-term safety, biomarker, and real-world efficacy data to supplement the eventual new drug application (NDA) submission by the drug manufacturer, Seelos Therapeutics. By providing a model for following safety, biomarker changes, and clinical efficacy in this program, we are helping to treat participants in this project, and also creating a blueprint for the design of scientifically relevant, patient-centric expanded access protocols.
Specific Aims: To present award-winning project to the MGH research community at our annual Celebration of Science
Overlap: None

#New Study
Title: CTA: A Phase 3, Multi-Center, Double-Blind, Randomized, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Reldesemtiv in Patients with Amyotrophic Lateral Sclerosis
Supporting Agency: Cytokinetics, Inc.
Address:
Cytokinetics, Inc. 527 Madison Ave
New York, NY **Contracting/Grants**
Officer: Stacy Rudnicki
Performance Period: 10/01/2021 -
10/01/2026 **Level of funding:**

Project Goals: To assess the effect of reldesemtiv versus placebo on functional outcomes in ALS.
Specific Aims: To assess the effect ofreldesemtiv versus placebo on combined functional and survival outcomes.
Person Months per budget period: 0.12
Overlap: None

#Study Closed
Title: PLS Natural History Study
Time Commitments: 0.00 CM
Supporting Agency: Trustees of Columbia University in the City of New York
Address:
154 Haven Ave. 2nd Floor
New York, NY 10032
Contracting/Grants Officer: Rosa Rivera
Performance Period: 07/15/2020 – 07/14/2022
Level of funding:
Project Goals: To enroll participants and collect information from them at three visits: a baseline

visit and two follow-up visits at 6 months and 12 months after baseline. Arrange for the collection of urine by providing participants with urine collection and facilitate the scheduling of interviews and questionnaires if needed.
Specific Aims: Collect and analyze study data.
Overlap: None

#Study Closed
Title: Multi-Center 18-Week Open Label of Safety and Efficacy Trial of Dalfampridine in PLS
Time Commitments: 0.00 CM
Supporting Agency: Hospital for Special Surgery
Address:
535 East 70th Street
New York, NY 10021
Contracting/Grants Officer: Dale J. Lange
Performance Period: 09/26/2017 - 12/31/2021
Level of funding:
Project Goals: This study will comprise a three site 18-week, open label safety and efficacy trial. A total of 35 subjects with PLS will be enrolled. After being screened for inclusion/exclusion criteria, signing informed consent, and undergoing a baseline laboratory evaluation, a complete neurological and physical examination, and transcranial magnetic stimulation will be performed.
Specific Aims: To determine the efficacy of Dalfampridine on the speed of walking in 35 people with primary lateral sclerosis (PLS) as measured by consistent improvement in the timed 25-foot walk test; assess the safety of Dalfampridine when used in people with PLS; determine the effect of Dalfampridine on consistent response to testing different characteristics of gait (endurance and coordination) and hand dexterity as measured in the 2-minute walk, timed up and go, foot and finger tapping tests and purdue pegboard test (PPT), respectively; determine the effect of Dalfampridine on the magnitude of improvement in gait speed, endurance, coordination, and hand dexterity; determine the effect of Dalfampridine on quality of life and function status as measured in the MSWS-12, CGI, SGI, and ALSFRS-R; determine if Dalfampridine causes a change in cortical excitability as measured by the resting RMT and SICI.
Overlap: None

#Study Closed
Title: CRSA: CENTAUR Open Label Extension Study 231344
Time Commitments: 0.12 CM
Supporting Agency: Amylyx Pharmaceuticals, Inc
Address:
Amylyx Pharmaceuticals, Inc.
210 Broadway, # 201
Cambridge, MA 02139
Contracting/Grants Officer: Joshua Cohen
Performance Period: 08/01/2017 – 07/31/2022
Level of funding:
Project Goals: The Coordination Center at the Neurological Clinical Research Institute (NCRI) will design the Open Label Extension phase of the CENTAUR trial.
Specific Aims: Aims include developing study protocol, informed consent, schedule of activities,

per subject fee, designing electronic database capture system for the open-label extension phase and will be responsible for the submission of the study to the central institutional review board. Staff will work with the study Sponsor and the CENTAUR team on study start-up activities including contacting vendors and sites to ensure materials, supplies and processes are in place to facilitate transition of participants from CENTAUR to the Open Label Extension.
Overlap: None

#Study Closed
Title: IAM ALS Expanded Access Protocol
Time Commitments: 0.12 CM
Supporting Agency: IAM ALS
Address:
1200 Pennsylvania Ave, NW, #14135,
Washington, DC 20044
Contracting/Grants Officer: Danielle Carnival
Performance Period: 11/13/2020 – 1231/2022
Level of funding:
Project Goals: To build an EAP Program in parallel to the Platform Trial by partnering with colleagues at Duke University and Northwestern University.
Specific Aims: The EAP program will offer access to one of the Platform Trial drugs to patients who are not eligible for the trial at the three participating sites (Duke University, Mass General, and Northwestern University). The drug, verdiperstat, will be donated and the manufacturer, Biohaven Pharmaceuticals, will match this grant donation.
Overlap: This grant award is being matched by Bio Haven in support of the EAP project.

#Study Closed
Title: CTA: Digital Quantitative Measurements in ALS
Time Commitments: 0.12 CM
Supporting Agency: Biogen
Address:
250 Binney Street
Cambridge, MA 02142
Contracting/Grants Officer: Peter Bergethon
Performance Period: 11/07/2018 – 12/19/2022
Level of funding:
Project Goals: We aim to investigate the utility of digital tools to quantify aspects of the neurological examination in a clinic setting for use as quantifiable biomarkers of neurological change over time in people with ALS.
Specific Aims: Processing, shipping and storing of information from people with ALS.
Overlap: None

#Study Closed
Title: Trial of Sodium Phenylbutyrate-Taurursodiol for Amyotrophic Lateral Sclerosis
Time Commitments: 4.06 CM
Supporting Agency: MGH ECOR Martin Prize
Address:

125 Nashua Street, Suite 822
Boston, Massachusetts 02114-2554
Contracting/Grants Officer: Katherine Brook
Performance Period: 04/01/2021 – 03/31/2022
Level of funding:
Project Goals: Award received in support of clinical research paper "Trial of Sodium Phenylbutyrate-Taurursodiol for Amyotrophic Lateral Sclerosis," which was published in the *New England Journal of Medicine.*
Specific Aims: To present award-winning project to the MGH research community at our annual Celebration of Science
Overlap: None

#Study Closed
Title: Imaging of Inflammation in PLS and HSP
Time Commitments: .12 CM
Supporting Agency: Spastic Paraplegia Foundation, Inc.
Address:
4 Sherwood Hill Road
Sherman, CT 06784
Contracting/Grants Officer: Mark Weber
Performance Period: 04/15/2018 – 04/21/2022
Level of funding:
Project Goals: To develop these novel neuroimaging techniques into powerful measure of target engagement that can accelerate PLS clinical trials. In the meanwhile, the project will have immediate impact for PLS and HSP patients by providing a new diagnostic and prognostic tool.
Specific Aims: Determine whether neuro-inflammation is present in the brain of people with HS; Determine the feasibility of using PET-MR with [11C]-PBR28 as a diagnostic tool for Upper Motor Neuron Syndromes; Determine the contribution of neuro-inflammation to PLS severity and disease progression
Overlap: None

#Study Closed
Title: Neuron-derived Exosomes as a Biomarker Platform for Amyotrophic Lateral Sclerosis
Time Commitments: 0.60 calendar months
Supporting Agency: Target ALS
Address:
PO Box 1598
Radio City Station
New York, New York 10101-1598
Contracting/Grants Officer: Martha Jones
Performance Period: 11/01/2020 – 13/31/2022
Level of Funding:
Project Goal: The goal of this project is to develop a streamlined reliable procedure (ExoSORT^{TM}) that provides selective insights into exclusively neuronal component of blood plasma by highly selective capture of neuron-derived EVs (NDEs) for biomarker analysis.
Specific Aims: Biomarker discovery, hypothesis-driven and unbiased approaches; iPSC-based

validation of the ExoSORT platform for the detection of ALS pathology and response to treatment; Longitudinal analysis of NDE biomarkers in human samples for prognostic validation and stratification.
Overlap: None

#Study Closed
Title: CRSA: An Intermediate Expanded Access Protocol for Amyotrophic Lateral Sclerosis with Verdiperstat
Time Commitments: 0.12 CM
Supporting Agency: Bio Haven Pharmaceuticals, Inc.
Address:
Biohaven Pharmaceuticals, Inc.
215 Church St.
New Haven, CT 06510

Contracting/Grants Officer: Irfan Qureshi
Performance Period: 02/19/2021 – 02/18/2026
Level of funding:
Project Goals: Based on the success of the EAP Program at the Healey Center and the unique opportunity to leverage the upcoming launch of the HEALEY ALS Platform Trial nationwide, this study proposes to build an EAP Program in parallel to the Platform Trial by partnering with colleagues at Duke University and Northwestern University.
Specific Aims: To offer access to one of the Platform Trial drugs to patients who are not eligible for the trial at the three participating sites (Duke University, Mass General, and Northwestern University).
Overlap: Bio Haven has matched the grant support provided by IAM ALS.

PATRIE, STEVEN M.

ACTIVE (# indicates change)

#New Award (This Award)
CDMRP/USAMRDC W81XWH2210166 09/01/2022 – 08/31/2024 0.51 CM
Ozdinler (PI)
Identification and Utilization of Upper Motor Neuron Biomarkers for ALS
This multi-institutional team will apply its expertise and resources towards the goal of identifying UMN biomarkers in ALS. These studies will be used to determine whether specific patterns of protein in blood can be used to diagnose ALS, develop more precise and sensitive clinical trials, and provide a reliable measure of the impact of treatment on the cortical component of ALS more quickly and accurately. The development of biomarkers for UMN degeneration has the potential to substantially improve the diagnosis, treatment and prognosis of individuals with ALS.

- Specific Aim 1: Determine the protein profile of serum and plasma samples isolated from ALS patients with prominent UMN loss, ALS patients with minimal cortical involvement, and age and sex-matched healthy controls. Determine whether identified "key proteins" are specific to ALS patients with prominent UMN loss, or also observed in HSP and PLS patients.

- Specific Aim 2: Determine whether serum/plasma protein profiles can be used to reliably and accurately assess disease progression and response to treatment. We will quantitate changes in proteins and their isoforms over time in alignment with clinical markers of UMN involvement and in response to disease progression and/or therapeutic intervention.

Sponsor Contact

Dr. Sarah Dougherty

sarah.e.dougherty5.civ@mail.mil

Overlap: None

#New Award

NIH/NIGMS - 5R21GM147847-02 08/05/2022 – 07/31/2024 1.00 CM

Patrie (PI)

Exploring the sepsis-delirium connection through glycoproteomics

Protein glycosylation is programmed in both time and space with factors such as environment, age, and disease shaping the final glycan repertoire. The goal of this research is to develop next generation resources that rapidly quantify hard to predict chemistry in blood-based biospecimens in the context of normal physiology as well as molecular heterogeneity for sepsis sub-phenotypes/endotypes.

- Specific Aim 1: Investigate best practices for blood-based glycoproteoform investigations, including Glyco-Proteoform Network Analysis (PNA) resources in proteome-wide and targeted screens (R21, yrs 1-2).
- Specific Aim 2: Meta-analysis ascribes gp signatures to critically ill and septic patients from the DECODE-Sepsis and BRAIN-ICU-1 studies (R33, yrs 3-4).
- Specific Aim 3: Disseminate research resources through the Sepsis Glycoproteoform Knowledgebase (SGK).

Sponsor Contact

Xiaoli Zhao

Xiaoli.zhao@nih.gov

Overlap: None

NIH/NIDA - 5P30DA018310-20 07/15/2019 – 05/31/2024 2.00 CM

Sweedler, Jonathan (PI)

UIUC Neuroproteomics and Neurometabolomics Center on Cell to Cell Signaling

The major goals are to develop proteomic approaches applicable to proteins in the mammalian brain and interface with leading researchers in studies of how drug abuse affects the brain and long term behavior.

- Specific Aim 1: to provide neurobiologists with the ability to benefit from proteomics experiments
- Specific Aim 2: to build a cadre of proteomics experts who will develop expertise in analyzing neural tissues
- Specific Aim 3: to develop new or improve existing proteomics technologies as they relate to neurobiology or tissues of the nervous system

Sponsor Contact

Kiran Vemuri

Kiran.vemuri@nih.gov
Overlap: None

NIH/NIA - 1R01AG063903 08/15/2019 – 03/31/2024 1.65 CM
Kelleher, N. (PI)
Defining native proteoform landscape for amyloid-beta in Alzheimer's disease
Our strong multidisciplinary team will leverage decades of experience in advanced proteomics and pioneering the amyloid-beta oligomer (AβO) hypothesis to provide a completely fresh look at Aβ. The work will lead fundamental insights on downstream spatial/temporal signaling leading to neurocognitive decline, as well as, informs most Aβ research tracks, including hypothesis testing in relation to in vivo targeting of theranostic agents such as Aβ imaging probes or diagnostic or therapeutic antibodies.

- Specific Aim 1: will describe the spatial pattern of native Aβ proteoforms in demented patients and animal models relative to controls. Data mining will describe signatures of Aβ related by covalent PTMs or non-covalent interactions, correlating the signatures to pathological co-variables
- Specific Aim 2: will utilize data mining to define proteoform signatures that associate with cellular phenotypes (e.g., synapse binding and neuroinflammation)
- Specific Aim 3: will describe the temporal variability of Aβ proteoforms relative to distinct neuropathological features in animal models. Partnering with neuroscientists
- Specific Aim 4: we will create a Proteinopathy Proteoform Knowledgebase that aggregates proteoform data in a manner that links subsets of proteoforms to disease relevant phenotypes (e.g., Aβ pathologies) or other clinical data

Sponsor Contact Austin
Jyan-Yu Yang
Yangj13@mail.nih.gov

Overlap: None

NIH/NIGMS - 5P41GM108569 06/01/2020 – 05/31/2025 3.00 CM
Kelleher, N. (PI)
National Resource for Translational and Developmental Proteomics
The National Resource for Translational and Developmental Proteomics (NRTDP) will advance technology development for whole protein mass spectrometry in denaturing LC-MS mode while applying high performance proteomics to timely needs in biomedical research.

- Specific Aim 1: To advance biomedical research through implementing precise measurement of proteins on timely biomedical projects in basic and clinical research.
- Specific Aim 2: To develop and deploy robust technology for next-generation proteomics required by collaborative projects that can be adopted by others.
- Specific Aim 3: To engage the community of practitioners, collaborators and consumers of proteomics through Consortia, an on-site Training Center, and a series of informative videocasts disseminated via digital media.

Sponsor Contact
Charles Ashley Barnes

ashley.barnes@nih.gov
Overlap: None

#New Award
NIH/NINDS - 5R01NS114409 11/01/2022 – 06/30/2025 1.00 CM
L. Brundin (PI)
The contribution of the vermiform appendix to Parkinson's disease
In this subcontract, Northwestern Proteomics scientists will be using top-down mass spectrometry to characterize proteoforms of alpha synuclein. These proteoforms are thought to be involved in the progression of Parkinson's disease. Dr. Brundin will send samples to Northwestern the PCE. Here Dr. Patrie and his team will perform a sample workup, which includes the analysis of immunoprecipitated samples from over 100 samples along with data analysis and statistical workup.

- Specific Aim 1: What gene regulatory changes are prominent in the PD appendix compared to that of healthy controls
- Specific Aim 2: The specific truncated forms of α-syn enriched in the PD appendix and their capacity to seed further aggregation
- Specific Aim 3: The consequences of initiating α-syn pathology in the appendix on the subsequent development of PD-like pathology in the brain, in vivo

Sponsor Contact
Beth-Anne
Sieber
sieberb@ninds.nih.gov
Overlap: None

What other organizations were involved as partners?

Organization Name: Massachusetts General Hospital
Location of Organization: Boston, MA
Partner's contribution to the project (identify one or more): Collaboration
Dr. Berry's and Dr. Paganoni's role on this project is to facilitate provision of matched serum and plasma samples from both PLS and HSP patients, as well as matched serum and plasma samples from ALS patients. They work with Dr. Ozdinler's team to coordinate sample shipment, and assist in the interpretation of study results.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

QUAD CHARTS:

N/A

9. APPENDICES:

None.