TARGET ALS FOUNDATION, INC.

Financial Statements and Supplementary Information

Year Ended December 31, 2023

(With Independent Auditors' Report Thereon)

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Certified Public Accountants and Business Consultants

TARGET ALS FOUNDATION, INC.

FINANCIAL STATEMENTS AND SUPPLEMENTARY INFORMATION

Year Ended December 31, 2023

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INDEPENDENT AUDITORS' REPORT

To the Board of Directors of Target ALS Foundation, Inc.:

Opinion

We have audited the accompanying financial statements of Target ALS Foundation, Inc. (a not-forprofit organization) (the Foundation), which comprise the statement of financial position as of December 31, 2023, and the related statements of activities, functional expenses, and cash flows for the year then ended, and the related notes to the financial statements.

In our opinion, the financial statements referred to above present fairly, in all material respects, the financial position of Target ALS Foundation, Inc. as of December 31, 2023, and the changes in its net assets and its cash flows for the year then ended in accordance with accounting principles generally accepted in the United States of America.

Basis for Opinion

We conducted our audit in accordance with auditing standards generally accepted in the United States of America. Our responsibilities under those standards are further described in the Auditors' Responsibilities for the Audit of the Financial Statements section of our report. We are required to be independent of the Foundation and to meet our other ethical responsibilities in accordance with the relevant ethical requirements relating to our audit. We believe that the audit evidence we have obtained is sufficient and appropriate to provide a basis for our audit opinion.

Responsibilities of Management for the Financial Statements

Management is responsible for the preparation and fair presentation of these financial statements in accordance with accounting principles generally accepted in the United States of America; and for the design, implementation, and maintenance of internal control relevant to the preparation and fair presentation of financial statements that are free from material misstatement, whether due to fraud or error.

In preparing the financial statements, management is required to evaluate whether there are conditions or events, considered in the aggregate, that raise substantial doubt about the Foundation's ability to continue as a going concern for one year after the date that the financial statements are available to be issued.

Auditors' Responsibilities for the Audit of the Financial Statements

Our objectives are to obtain reasonable assurance about whether the financial statements as a whole are free from material misstatement, whether due to fraud or error, and to issue an auditors' report that includes our opinion. Reasonable assurance is a high level of assurance but is not absolute assurance and therefore is not a guarantee that an audit conducted in accordance with generally accepted auditing standards will always detect a material misstatement when it exists. The risk of not detecting a material misstatement resulting from fraud is higher than for one resulting from error, as fraud may involve collusion, forgery, intentional omissions, misrepresentations, or the override of internal control. Misstatements, including omissions, are considered material if there is a substantial likelihood that, individually or in the aggregate, they would influence the judgment made by a reasonable user based on the financial statements.

In performing an audit in accordance with generally accepted auditing standards, we:

- Exercise professional judgment and maintain professional skepticism throughout the audit.
- Identify and assess the risks of material misstatement of the financial statements, whether due to fraud or error, and design and perform audit procedures responsive to those risks. Such procedures include examining, on a test basis, evidence regarding the amounts and disclosures in the financial statements.
- Obtain an understanding of internal control relevant to the audit in order to design audit procedures that are appropriate in the circumstances, but not for the purpose of expressing an opinion on the effectiveness of the Foundation's internal control. Accordingly, no such opinion is expressed.
- Evaluate the appropriateness of accounting policies used and the reasonableness of significant accounting estimates made by management, as well as evaluate the overall presentation of the financial statements.
- Conclude whether, in our judgment, there are conditions or events, considered in the aggregate, that raise substantial doubt about the Foundation's ability to continue as a going concern for a reasonable period of time.

We are required to communicate with those charged with governance regarding, among other matters, the planned scope and timing of the audit, significant audit findings, and certain internal control related matters that we identified during the audit.

Report on Summarized Comparative Information

We have previously audited the Foundation's 2022 financial statements, and we expressed an unmodified audit opinion on those audited financial statements in our report dated June 7, 2023. In our opinion, the summarized comparative information presented herein as of and for the year ended December 31, 2022, is consistent, in all material respects, with the audited financial statements from which it has been derived.



Supplementary Information

Our audit was conducted for the purpose of forming an opinion on the financial statements as a whole. The information on Supplemental Schedule I is presented for purposes of additional analysis and is not a required part of the financial statements. Such information is the responsibility of management and is of a non-accounting nature. The information has not been subjected to the auditing procedures applied in the audit of the financial statements and, accordingly, we express no opinion on it.

Kahn, Litwin, Renya ¿ Co. Ltd.

April 19, 2024

TARGET ALS FOUNDATION, INC. STATEMENT OF FINANCIAL POSITION December 31, 2023 (With Comparative Totals at December 31, 2022)

	2023	2022
Assets		
Cash	\$ 25,815,121	\$ 38,202,262
Investments	38,537,227	3,099,063
Receivables:		
Grants, net	79,111,867	52,487,810
Pledges, net	37,060,511	21,728,583
Prepaid expenses	48,235	44,750
Total Assets	\$ 180,572,961	\$ 115,562,468
Liabilities and Net Assets		
Liabilities:		
Grants payable	\$ 3,030,383	\$ 1,735,469
Accounts payable and accrued expenses	18,396	13,921
Total liabilities	3,048,779	1,749,390
Net Assets:		
Without donor restrictions	59,872,935	34,360,343
With donor restrictions	117,651,247	79,452,735
Total net assets	177,524,182	113,813,078
Total Liabilities and Net Assets	\$ 180,572,961	\$ 115,562,468

TARGET ALS FOUNDATION, INC. STATEMENT OF ACTIVITIES Year Ended December 31, 2023 (With Comparative Totals for the Year Ended December 31, 2022)

	2023	2022
Change in Net Assets Without Donor Restrictions:		
Revenue and Support:		
Contributions and grants	\$ 31,472,735	\$ 31,335,271
Investment earnings, net	403,757	22,235
Other income	4,197	2,249
Net assets released from restrictions	9,477,586	7,693,442
Total revenue and support	41,358,275	39,053,197
Expenses:		
Research	12,536,830	7,275,438
Management and general	2,714,125	1,264,090
Development	594,728	732,461
Total expenses	15,845,683	9,271,989
Change in net assets without donor restrictions	25,512,592	29,781,208
Change in Net Assets With Donor Restrictions:		
Contributions and grants	47,676,098	67,021,314
Net assets released from restrictions	(9,477,586)	(7,693,442)
Change in net assets with donor restrictions	38,198,512	59,327,872
Change in Net Assets	63,711,104	89,109,080
Net Assets, beginning of year	113,813,078	24,703,998
Net Assets, end of year	\$ 177,524,182	\$ 113,813,078

TARGET ALS FOUNDATION, INC. STATEMENT OF FUNCTIONAL EXPENSES Year Ended December 31, 2023 (With Comparative Totals for the Year Ended December 31, 2022)

	Research	Management and General	Development	2023 Total	2022 Total
Research awards	\$ 11,786,738	\$ -	\$ -	\$ 11,786,738	\$ 6,463,758
Personnel and related:					
Salaries	-	1,494,830	91,112	1,585,942	980,025
Payroll taxes and employee benefits	-	420,398	13,893	434,291	245,916
Total personnel and related	-	1,915,228	105,005	2,020,233	1,225,941
Other expenses:					
Advertising and promotion	-	-	169,568	169,568	184,839
Conferences, conventions and meetings	750,092	-	-	750,092	512,994
Office expenses	-	28,785	-	28,785	35,924
Professional services	-	654,847	320,155	975,002	510,229
Travel	-	48,260	-	48,260	1,376
Meals	-	4,054	-	4,054	418
Telephone and internet	-	62,951	-	62,951	37,824
Business loss	-	-	-	-	298,686
Total other expenses	750,092	798,897	489,723	2,038,712	1,582,290
Total Expenses	\$ 12,536,830	\$ 2,714,125	\$ 594,728	\$ 15,845,683	\$ 9,271,989

TARGET ALS FOUNDATION, INC. STATEMENT OF CASH FLOWS Year Ended December 31, 2023 (With Comparative Totals for the Year Ended December 31, 2022)

2023	2022
\$ 63,711,104	\$ 89,109,080
(403,757)	(22,235)
(2,034,407)	(1,061,172)
(1,084,414)	18,708,686
(25,000,000)	(55,750,000)
(15,871,571)	(24,430,000)
(3,485)	36,977
1,294,914	258,542
4,475	(10,754)
20,612,859	26,839,124
(33,000,000)	-
(33,000,000)	
(12,387,141)	26,839,124
38,202,262	11,363,138
\$ 25,815,121	\$ 38,202,262
\$ 2,034,407	\$ 1,061,172
	\$ 63,711,104 (403,757) (2,034,407) (1,084,414) (25,000,000) (15,871,571) (3,485) 1,294,914 4,475 20,612,859 (33,000,000) (33,000,000) (12,387,141) 38,202,262 \$ 25,815,121

1. Nature of Operations

Target ALS Foundation, Inc. (the Foundation), a not-for-profit Delaware corporation operating in New York, New York, was incorporated on December 3, 2015 to promote, support, and further the funding of medical and scientific research to accelerate drug discovery and development for Amyotrophic Lateral Sclerosis (ALS). The Foundation pursues its mission by awarding grants to fund ALS - related research.

2. Summary of Significant Accounting Policies

This summary of significant accounting policies of the Foundation is presented to assist the reader in understanding the Foundation's financial statements. The financial statements and notes are representations of the Foundation's management, who is responsible for their integrity and objectivity. These accounting policies conform to accounting principles generally accepted in the United States of America and have been consistently applied in the preparation of the financial statements.

Comparative Financial Information

The accompanying financial statements include certain prior year summarized comparative information without accompanying note disclosures and certain functional expense information. Such information does not include sufficient detail to constitute a presentation in conformity with accounting principles generally accepted in the United States of America. Accordingly, such information should be read in conjunction with the Foundation's financial statements and related notes to the financial statements for the year ended December 31, 2022, from which the summarized information was derived.

Financial Statement Presentation

The Foundation prepares its financial statements on the accrual basis of accounting and, in accordance with authoritative guidance, reports information regarding its financial position and activities according to two classes of net assets: net assets without donor restrictions, and net assets with donor restrictions.

Net Assets without Donor Restrictions

Net assets without donor restrictions are available for use at the discretion of the Board of Directors (the Board) and/or management for general operating purposes. From time to time, the Board may designate a portion of these net assets for specific purposes which make them unavailable for use at management's discretion.

Net Assets with Donor Restrictions

Net assets with donor restrictions consist of assets whose use is limited by donor-imposed time and/or purpose restrictions. Other donor-imposed restrictions are perpetual in nature, where the donor stipulates that resources be maintained in perpetuity. The Foundation had no net assets to be maintained in perpetuity as of December 31, 2023.

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Donor-restricted contributions are reported as increases in net assets with donor restrictions. When a restriction is satisfied, net assets are reclassified from net assets with donor restrictions to net assets without donor restrictions in the statement of activities.

Investments and Fair Value Measurement

The Foundation measures its investments at fair value. Fair value is the price that would be received to sell an asset or paid to transfer a liability in an orderly transaction between market participants at the measurement date. A fair value measurement assumes that the transaction to sell the asset or transfer the liability occurs in the principal market for the asset or liability or, in the absence of a principal market, the most advantageous market. Valuation techniques that are consistent with the market, income or cost approach, as specified by authoritative guidance, are used to measure fair value.

The fair value hierarchy prioritizes the inputs to valuation techniques used to measure fair value into three broad levels:

Level 1 inputs are quoted prices (unadjusted) in active markets for identical assets or liabilities the Foundation has the ability to access.

Level 2 inputs (other than quoted prices included within level 1) are observable for the asset or liability, either directly or indirectly.

Level 3 inputs are unobservable inputs for the asset or liability and rely on management's own assumptions about the assumptions that market participants would use in pricing the asset or liability. The unobservable inputs are developed based on the best information available in the circumstances and may include the Foundation's own data.

The Foundation reports investments at fair value on a recurring basis. The investments are classified as level 1 within the fair value hierarchy.

Level 1 investments owned by the Foundation and listed on a National Securities Exchange are valued at the last recorded sales price as of the financial statement reporting date, or in the absence of recorded sales, at the last quoted bid price reported as of the financial statement reporting date.

Realized and unrealized gains and losses on investments are reported as changes in net assets without donor restrictions, unless gains and losses on investments are restricted by a donor's explicit stipulation or by a law that extends a donor's restriction.

Dividends and interest are recorded as received, which does not differ materially from the accrual basis. Purchases and sales of securities are recorded on the trade date.

Grants and Pledges Receivable

The Foundation carries its receivables at net realizable value. Pledges receivable consist of unconditional promises to give. Amounts that are expected to be collected within one year are recorded at net realizable value. Receivables expected to be collected after more than one year are recorded at the present value of the estimated future cash flows to be received. On a periodic basis, the Foundation evaluates its receivables and establishes an allowance for credit losses, based on historical experience, current conditions, and reasonable and supportable forecasts.

The Foundation does not accrue interest on receivables. A receivable is considered past due if payment has not been received within stated terms. The Foundation will then exhaust all methods in-house to collect the receivable. Once all practical resources to collect the receivable have been utilized without success, the receivable is deemed uncollectible and charged against the allowance for credit losses. At December 31, 2023, management determined that no allowance for credit losses was necessary.

Grants Payable

Unconditional research grants are recognized in the financial statements when they are recommended and approved by the Independent Review Committee (IRC) and the Chief Advisor of the Foundation. Conditional research grants are expensed by the Foundation as the researchers substantially meet the terms and conditions of the grant during the grant period.

Revenue Recognition

The Foundation recognizes contributions and grant income in the year in which the contribution or grant is made. Conditional promises to give are recognized in the period in which the condition is met. Contributions and grants are recorded either as without donor restrictions or with donor restrictions depending on the existence and/or nature of any donor-imposed restrictions. However, it is the policy of the Foundation to recognize restricted contributions and grants that are both received and fully expended during the same fiscal year as net assets without donor restrictions.

Donated assets are recorded as contributions at their fair value on the date of donation.

Allocation of Expenses

The Foundation's operating costs have been allocated between research, management and general, and development based on direct identification when possible, and allocation if a single expenditure benefits more than one program or function. Expenditures that require allocation are allocated based on personnel cost. Development expenses consist of fundraising expenses.

Income Taxes

The Foundation is exempt from income taxes as a public charity under Section 501(c)(3) of the Internal Revenue Code. The Foundation is considered a Private Foundation under Section 170(b); therefore, it pays an excise tax on its net investment income at either 1% or 2%, depending on the ratio of qualifying disbursements to the fair value of Foundation assets. The qualifying disbursements include amounts paid to qualifying charities. Management believes that the Foundation operates in a manner consistent with its taxexempt status. The Foundation has notified the Internal Revenue Service (IRS) of its intention to convert to a public charity, and the IRS has ruled that grantors and contributors may consider Target ALS Foundation, Inc. a public charity for the purpose of making contributions to the Foundation.

The Foundation annually files IRS Form 990-PF, *Return of Private Foundation*, reporting various information that the IRS uses to monitor the activities of private foundations. The Foundation currently has no tax examinations in progress.

Estimates and Assumptions

The preparation of financial statements in conformity with accounting principles generally accepted in the United States of America requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities and disclosure of contingent assets and liabilities at the date of the financial statements and the reported amounts of revenues and expenses during the reporting period. Accordingly, actual results could differ from those estimates.

Reclassifications

Certain amounts in the 2022 financial statements have been reclassified to conform to the 2023 financial statement presentation.

Subsequent Events

The Foundation has evaluated subsequent events through April 19, 2024, which is the date these financial statements were available to be issued.

3. Liquidity and Availability

Financial assets available for general expenditure, that is, without donor or other restrictions limiting their use, within one year of the statement of financial position date, comprise the following at December 31, 2023:

Financial assets:	
Cash	\$ 25,815,121
Investments	38,537,227
Grants receivable	79,111,867
Pledges receivable	37,060,511
Total financial assets	180,524,726
Less: financial assets unavailable for general expenditure: Receivables scheduled to be collected in more than one year Required to satisfy donor purpose restrictions within one year Total financial assets unavailable for general expenditure	 91,885,508 1,478,869 93,364,377
Financial assets available to meet cash needs for general expenditures within one year	\$ 87,160,349

The Foundation has a policy to structure its financial assets to be available as its general expenditures, liabilities and other obligations come due. In addition, as part of its liquidity management, the Foundation manages its liquidity by developing and adopting annual operating budgets that provide sufficient funds for general expenditures in meeting its liabilities and other obligations as they come due. Actual performance is reported and monitored monthly in comparison to budgets. Adjustments are made to the policy as needed to ensure adequate liquidity.

Included within the cash balance above is \$15,060,250 of grant funding maintained within a separately designated account at the Foundation's financial institution. These funds can be utilized to support the Foundation's mission, as defined in the grant agreement.

4. Investments

Investments consisted of the following:

Level 1:	
Money market funds	\$ 19,676,681
Mutual funds	18,366,323
Common stock – financial services	494,223
Total investments	\$ 38,537,227

5. Pledges and Grants Receivable

Pledges receivable consist of unconditional promises to give from contributors to support the Foundation's mission.

The present value of pledges and grants receivable has been calculated using interest rates of 3.88% to 4.23%, which approximate the Federal Reserve five-to-ten year Treasury bill rates.

Grants receivable are due as follows:

Year Ending	
December 31, 2024	\$ 17,000,000
December 31, 2025	13,000,000
December 31, 2026	12,750,000
December 31, 2027	12,500,000
December 31, 2028	12,500,000
Thereafter	23,000,000
	90,750,000
Less present value component	11,638,133
Grants receivable, net	\$ 79,111,867

Pledges receivable are due as follows:

6.

Year Ending	
December 31, 2024	\$ 7,286,870
December 31, 2025	5,456,000
December 31, 2026	5,341,000
December 31, 2027	5,286,000
December 31, 2028	4,324,000
Thereafter	15,740,000
	43,433,870
Less present value component	6,373,359
Pledges receivable, net	\$ 37,060,511
Net Assets	
A summary of net assets is as follows:	
Net Assets without Donor Restrictions	
Undesignated – available for operations	\$ 59,872,935
Total net assets without donor restrictions	59,872,935
Net Assets with Donor Restrictions	
Subject to expenditure for specified purposes:	
In Vivo Target Validation Studies	500,000
Spatial Genomics Resource Project	500,000
Biorepository Initiative	200,000
Gates Ventures Grant	153,457
Biogen Collection Project	100,412
TDP-43 Biomarker Initiative	25,000
	1,478,869
Subject to time restriction	116,172,378
Total net assets with donor restrictions	117,651,247
	·)) ·
Total net assets	\$177,524,182

In Vivo Target Validation Studies

Funds have been restricted to support In Vivo Target Validation RFAs. The Foundation partners with contract research organizations to enable evaluation of novel therapeutics for target engagement and disease-modifying potential in ALS. Results from these studies have the potential to catapult ALS drug candidates from preclinical to clinical pipelines, accelerating development of novel therapeutics.

Spatial Genomics Resource Project

Funds have been restricted to support research at Columbia University and the New York Genome Center aiming to uncover novel shared cellular mechanisms that cause both ALS and FTD. The team is leveraging powerful spatial transcriptomics and proteomics technology to study post-mortem tissue in detail. These results will not only provide valuable information for the development of biomarkers and treatments for ALS but will also provide a framework for understanding neurodegenerative disease that can be broadly applied.

Biorepository Initiative

Funds have been restricted to support the acquisition of and the data migration to the BioLims biorepository database. The database will centralize samples and associated clinical data available for use by the neurodegenerative research community to further clinical research.

Gates Ventures Grant

Funds have been restricted to accelerating the development of Biofluid-based Biomarkers that are applicable to ALS, Alzheimer's disease and frontotemporal lobar degeneration. Gates Ventures will provide \$1,000,000 to the Foundation to support this initiative; however, the Foundation will also be required to contribute \$1,400,000 to investigators that are part of the approved collaborative consortia.

Biogen Collection Project

Funds have been restricted to support the biofluid core sites that collect patient specimens for clinical research.

TDP-43 Biomarker Initiative

Funds have been restricted with the goal of developing improved immunoassays that can accurately measure and quantify TDP-43 in human biofluids, which would have tremendous impact on clinical research and therapeutic development for ALS and other neurodegenerative diseases.

The Foundation enters into conditional commitments annually to award scientific research grants. All research distribution-making decisions are made by the IRC and are reviewed by the Conflict-of-Interest Committee to ensure the IRC has no stake in the projects selected. Subject to the annual review and reapproval process, these distributions generally cover a period of one to two years. Research commitments at December 31, 2023 are reported as grants payable in the accompanying statement of financial position. Subsequent to year-end, the Foundation committed to future research distributions in the amount of approximately \$1,620,000 for the year ending December 31, 2024.

Except as previously provided for by restricted gifts, the Foundation's ability to meet these distribution commitments may be dependent on future contributions to be received.

8. Retirement Plan

The Foundation sponsors a defined contribution plan under Internal Revenue Code Section 403(b). The plan covers all employees over 21 years old, excluding temporary employees. In addition, the Foundation elects to make a noncontributory match equal to 5% of total wages. Employer contributions of approximately \$76,000 were made to the plan during the year ended December 31, 2023.

9. Concentrations of Risks

Financial instruments that potentially subject the Foundation to concentrations of credit risk consist principally of cash, grants and pledges receivable and investments.

The Foundation maintains its cash balance in one financial institution. The balance is insured by the Federal Deposit Insurance Corporation up to \$250,000. At year-end, the uninsured portion of this balance was approximately \$25,314,800. The Foundation monitors its exposure with regard to cash and cash equivalents and has not experienced losses on such accounts.

At December 31, 2023, the Foundation's grants receivable were due from five contributors, two of which represent approximately 98% of grants receivable. At December 31, 2023, the Foundation's outstanding pledges receivable were due from fifty-four contributors, two of which represent approximately 41% of pledges receivable. Management has performed an analysis of these receivables at year end and does not believe that there is a significant credit risk related to those receivables.

Investment securities are exposed to various risks, such as interest rate, market and credit risks. Due to the level of risk associated with certain investment securities, it is possible that changes in values of investment securities could occur in the near term and that such changes could materially affect investment balances and activity included in the financial statements. At year end, management does not believe that significant credit risk exists relative to the investments.

TARGET ALS FOUNDATION, INC. PROGRAM ACCOMPLISHMENTS (UNAUDITED) Year Ended December 31, 2023

The Foundation continues to make strides toward its mission to promote, support and further the funding of medical and scientific research to accelerate drug discovery and development for ALS. Select accomplishments during 2023 include the following:

- Our precompetitive biomarker initiative that involves experts from 15 pharma/biotech companies, a panel of academics and 6 not-for-profit organizations is continuing to move two active projects forward.
- Continued to expand the Foundation's core facilities, which are comprised of a network of academic centers and contract research organizations that, for the first time in the history of the disease, provide access to critical ALS research tools and resources to scientists.
 - *Postmortem tissue (PMT) core:* The PMT core has integrated a new BioLims data platform that enables efficient inventory management and expedites fulfillment of tissue requests.
 - *TDP-43 Immunoassay development:* Mass spectrometry to determine TDP-43 Species in biofluids.
 - *Treatment of Ultra-rare Forms of ALS: Partnership with n-Lorem Foundation:* The Foundation's goal is to expand this program to enable more ALS patients with ultra-rare forms of ALS to benefit from ASO-based treatments.
 - Grant from Chan Zuckerberg Initiative (CZI): Based on the work and impact of the PM core, the Foundation was invited to submit a proposal to CZI to help modernize neuropathology. We received a grant from CZI to generate and digitize stained neuropathology slides from brain and spinal cord tissue of all PM core cases (ALS and ALS/FTD). The digitized dataset will be made accessible through platforms that will also offer support for analysis. We have received an additional grant from CZI to enable participation of underrepresented communities and minorities. Two initiatives will be launched under this grant at the Barrow Neurological Institute.
 - *Longitudinal biofluid repository:* This core was launched in November 2020. There are currently ten sites participating in this effort.

TARGET ALS FOUNDATION, INC. PROGRAM ACCOMPLISHMENTS (UNAUDITED) Year Ended December 31, 2023

- *Collaboration with FBRI:* A collaboration is being forged with FBRI to analyze longitudinal biofluid samples to generate unbiased proteomics, lipidomics and metabolomics datasets. These datasets will be integrated with the detailed demographic and clinical information from these cases along with the whole genome sequencing data.
- Collaboration with Broad Institute/Bloomberg L.P.: A critical aspect of this effort is to ensure that this data can be accessed and analyzed by any investigator worldwide to further ALS research. We are working with the Broad Institute and a team of software engineers from Bloomberg L.P. to build a unique data platform that will allow integration, access, and the ability to analyze these datasets.
- *Genomic datasets core:* Whole genome sequencing (WGS) and bulk RNAseq datasets are now being generated from all PM cases.
- In vivo Target Validation Core: We have now initiated all five projects that were identified for support by the independent review Committee.
- C9orf72 BAC-based transgenic mouse model: The BAC transgenic model characterization is being completed at Jackson labs. This mouse model presents abundant C9Orf72 RNA foci pathology, affecting major brain regions.
- TDP43 models: Knock- in of a single base change, K181E in RRM1 domain: Several cohorts of mice were evaluated for TDP43-related pathology at 3-, 6and 9- months of age, while data from the 12-month time point is pending. Key hallmarks of ALS including pTDP43 accumulation and neurodegeneration have not been detected.
- *Knock-in of mutant NLS domain:* Original technical approaches taken to develop this mouse line in 2021 were unsuccessful due to lethality of the mutation. A different technical approach to develop a conditional knock-in line targeting the ES cells is being evaluated. To-date, this approach has not been successful due to incorrect targeting in ES cells or to poor transmission of targeted allele. The remaining ES cell clones are all being injected and in vitro fertilizations on existing low chimeric founder animals will replace traditional breeding. Alternative methods to create ES clones and to perform blastocyst injections are being evaluated.