



ALSFAC 5-YEAR IMPACT REPORT

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Executive Summary

After his daughter-in-law was diagnosed with Amyotrophic Lateral Sclerosis (ALS), Leandro P. (Lee) Rizzuto worked with his son Denis and friend Peter Foss to found ALS Finding a Cure® (ALSFAC) in 2014 to accelerate the development of cures for ALS. Together, they recruited Dr. Merit Cudkowicz, Chair of Neurology at Mass General, to serve as Chief Medical Officer, and convened global leaders in the fields of Neurology, electrophysiology, stem cell biology, neuro-imaging, and other fields, supported by collaborative teams to address major gaps in the scientific understanding of ALS preventing the development of a cure.

ALSFAC was founded with a simple mission: To fund ALS research to find a cure.

At its outset, the organization decided to focus on four key areas: Target Identification, Biomarker/Diagnostic Development, Therapeutic Development, and Research Infrastructure. Over the past 5 years ALSFAC committed over \$30M and leveraged more than \$50M in additional funding towards this goal. This funding supported 36 projects across the four focus areas, 32 of which are now complete.

The impact of ALSFAC has been both broad and deep, catalyzing new scientific collaborations between industry and academic investigators (including a far-reaching collaboration with General Electric), funding critical clinical and scientific infrastructure, and contributing to the development of novel ALS therapies. Through its semi-annual meetings and sponsorship of the annual NEALS clinical conference ALS Finding a Cure® shared its vision and achievements with scientists and clinicians around the world. ALSFAC has engaged 51 industry partners, and over 120 researchers at more than 40 universities. Through its videos, website, public presentations, and via media channels, ALSFAC also inspired and helped ALS patients and their families struggling with the disease.

ALSFAC has contributed to major scientific progress in our understanding of the underlying biology behind ALS. As a direct result of the funded projects, research teams helped develop over 130 pre-clinical models and collect more than 4,440 patient medical records, and more than 8,300 samples. They also have helped identify 2 new ALS genes and one new ALS imaging biomarker. In the past 5 years, ALSFAC-funded teams have initiated 8 clinical trials that enrolled or treated more than 265 patients.



Yet significant gaps still remain. With research institutes and companies increasingly interested in developing and/or testing drugs for ALS, ALSFAC is in a unique position to help accelerate the innovations that could lead to new treatments and someday a cure for ALS including:

1. Ways to diagnose ALS rapidly and definitively and/or track the disease,
2. Efforts to include home-based outcome measures in promising ALS platform trials, thereby enabling more ALS patients to participate,
3. Efficient and effective approaches to provide the necessary chemistry expertise to investigators with promising ALS targets in order to create viable drugs capable of reaching the brain, and
4. The expansion of the critical resources (e.g. databases, sample repositories, standardized operating procedures and documentation, etc.) that underlies human-focused research

As we consider organizational strategic directions for the next 5 years, it helps to look back to see how much ALSFAC has accomplished, and then develop a roadmap to build on Lee's vision and ALSFAC's mission to address the remaining roadblocks along the path to finding a cure for ALS.

Part I: Organizational History

ALS Finding a Cure® (ALSFAC), a program of the Leandro P. Rizzuto Foundation, is focused on identifying and addressing the critical gaps in the scientific understanding of ALS that prevent us from developing a cure. Leveraging the scientific and business acumen of its pre-eminent Executive Committee, and building on emerging technologies from GE Healthcare and other groups, ALSFAC has focused on the pillars of collaboration, non-duplication, data-sharing, transparency, and speed to bring new thought leaders and new technologies to ALS. Once ALS Finding A Cure® identifies a critical gap, it quickly funds the fundamental research necessary to move the field closer to a cure without bureaucracy or red tape.

EXECUTIVE COMMITTEE

Lee Rizzuto, the founder of ALS Finding a Cure®, had a bold vision. He was interested in doing something to help his son and daughter-in-law who were fighting a battle with ALS. Together with friend Peter Foss, he envisioned convening a group of experts from complementary fields to identify and address critical gaps in the scientific understanding of ALS preventing the field from developing a cure. The decision-making body for ALS Finding a Cure® was formed from a mix of world-renowned neurologists, neuroscientists, engineers, health-care leaders, ALS advocates, and corporate officers – all with a common interest in and devotion to finding a cure for ALS. The Board’s deep scientific expertise helped the organization quickly identify and fund promising efforts to advance a cure and attracted prominent new investigators to the ALS field. Through a streamlined grant application process, ALS Finding A Cure® was able to quickly put necessary funds into the hands of top researchers across the country.



DEFINING THE FOUR BUCKETS

The Executive Committee identified four key needs slowing progress in ALS research and development requiring immediate investment: New Targets, Clinical trials/therapeutics, Biomarkers/diagnostics, and Infrastructure.

NEW TARGETS

While great strides had been made in ALS research, many fundamental questions about the disease remained unanswered. For example:

- Why do motor neurons die, as opposed to other neurons or even other cell-types?
- What factors are responsible for the ~90% of all cases of ALS without an identified genetic cause?
- Why do some ALS patients have slowly progressive forms of disease and others have rapidly aggressive forms of disease?

Target identification projects were selected to help address these and other fundamental questions about ALS.

CLINICAL TRIALS/THERAPEUTICS

Because no efficacious therapeutics existed, ALSFAC funding was directed towards new efforts to launch clinical/therapeutic trials covering a broad range of targets and therapeutic classes to more immediately benefit patients and more quickly lead to effective treatments and someday a cure.

BIOMARKERS/DIAGNOSTICS

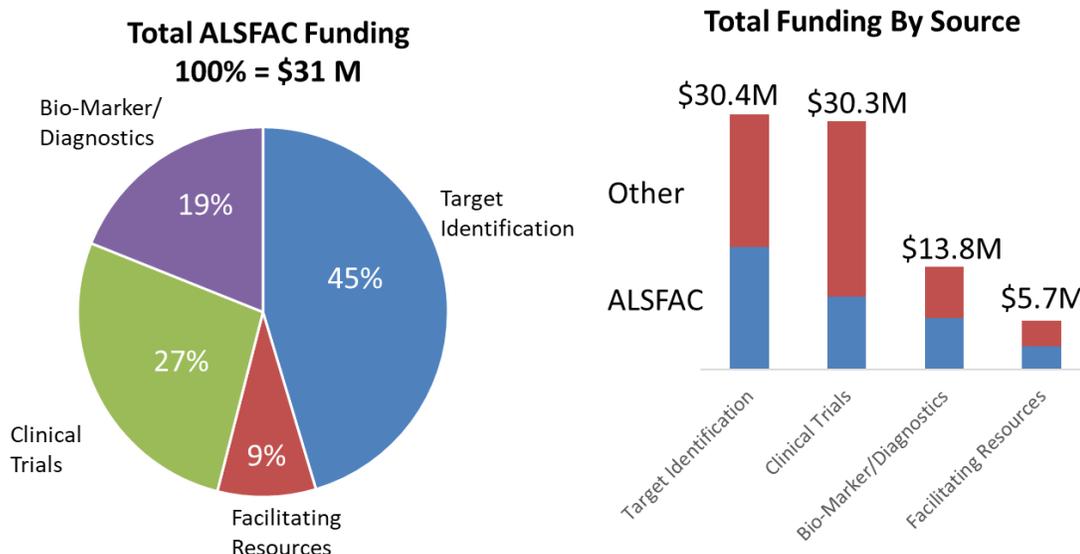
While the disease was first identified in 1869, to date there is still no diagnostic test for ALS, which is a diagnosis of exclusion. It takes on average 12 months in the US (it can take longer in other countries) after onset of first symptoms for a patient to receive an ALS diagnosis. In addition to the lack of diagnostic markers, when ALSFAC was launched there were also no widely accepted biomarkers that could be used to either track progression of disease or measure the beneficial effects of a drug upon the disease. Biomarkers had been identified by industry as a key tool enabling successful drug development across all disease indications, so the Executive Committee identified the need for new biomarkers (including diagnostic biomarkers) as a key gap for ALSFAC funding to address.

RESOURCES

Broad-based efforts to collect, merge, and share data are critical for accelerating progress within a scientific field and ALS is no exception. In addition to access to data, clinical research, as well as target and biomarker research, requires access to large numbers of patient biosamples, and these large infrastructure projects are very challenging to fund, so the Executive Committee identified a significant need for investment in fundamental open-access infrastructure (data and biosample repositories).

PARTNERSHIPS/LEVERAGING EXTERNAL DOLLARS

In addition to transparency, sharing, non-duplication, and speed, another of the key pillars of ALS Finding a Cure® was an interest in leveraging additional dollars for the cause. Over the past 5 years ALSFAC partnered with other major ALS foundations (the ALS Association, Muscular Dystrophy Association, Target ALS, Project A.L.S., Packard Center) on the majority of its programs. ALSFAC funding has also leveraged new funding from the National Institutes of Health and the Department of Defense. While ALSFAC has committed almost \$31M to the programs and projects it supports, these dollars have leveraged an additional \$50M from partners sources towards finding a cure for ALS.

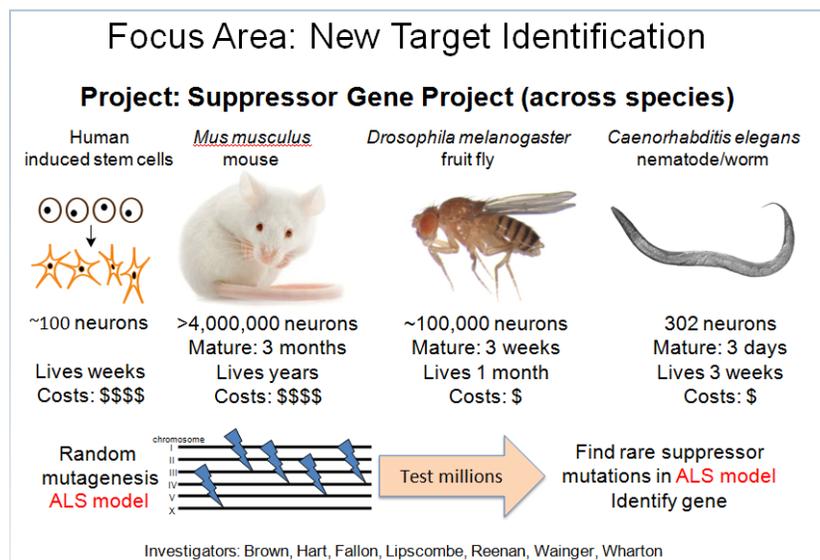


Part II: Organizational Impact

What has been the impact of Lee Rizzuto’s bold experiment of rapid targeted ALS investment over the past 5 years? While it would take hundreds of pages to enumerate all of the impacts (given the 50+ publications alone), this report will present a few highlights (and the summary Dashboard in the next section likewise presents a snapshot).

SCIENTIFIC IMPACTS

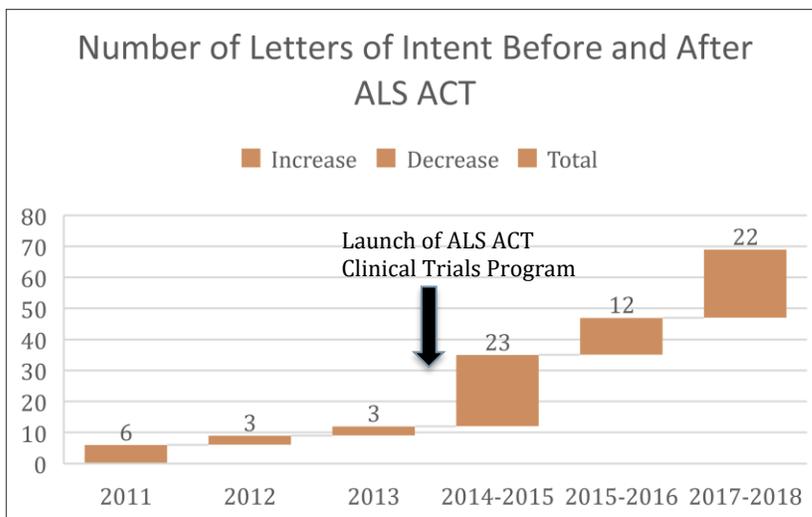
Over the past 5 years ALSFAC has invested almost 45% of its budget in Target Identification efforts designed to help better understand the disease and the disease population. This funding has led to the identification of promising new disease targets, such as members of a major signaling pathway (Accelerating the ID of Suppressors), the nuclear pore component POM121 (Nuclear Pore and ALS), as well as therapeutic targets such as an important gut bacterial species that seems to be lower in ALS patients (Microbiome). ALSFAC has also been a major funder of the Answer ALS initiative to obtain longitudinal clinical and deep biological data on 1000 ALS patients and 100 controls, which should help address questions about the best approaches for utilizing human stem cell-derived motor neurons, in addition to addressing the clinical and scientific challenge of patient stratification. Through its Target Identification funding ALSFAC has also driven the creation of multiple new animal models of disease, which will be useful for unraveling fundamental questions about ALS.



CLINICAL IMPACTS

Over the past 5 years ALSFAC has invested approximately 27% of its funding in clinical trials-related initiatives. Before ALSFAC was launched, the ALS Association in collaboration with Mass General Hospital's Neurological Clinical Research Institute, under Dr. Merit Cudkowicz's leadership, had an initiative to fund early stage ALS clinical trials.

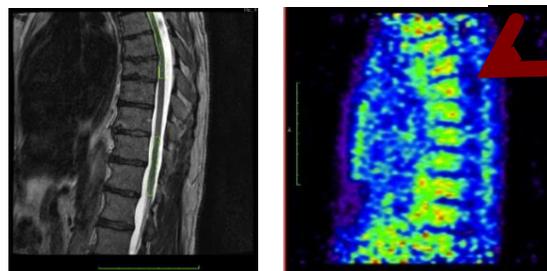
In the 3 years prior to the launch of ALSFAC (and the associated increase in funding for this effort) the ALS ACT Clinical Trials program had received 12 applications. In the 3 years following the launch of ALSFAC this program received 57 new applications. In the 5 years since launch ALSFAC funding has contributed directly to the clinical testing of 8 new potential ALS treatments, and the participation of 270+ ALS patients in the clinical trials of:



- Small molecules: Amylyx, RNS60, Mexiletine
- Cell therapies: CNS10-NPC-GDNF, T-regs
- Biologics: AT1501, Actemra
- Gene therapies: AAV-SOD1

SPINE ALS Project Images

In addition to directly funding clinical trials, ALS Finding a Cure® has also funded the development of the tools necessary for the clinical trials of the future, including imaging biomarkers for both the brain and spinal cord (TRACK ALS, SPINE ALS, and the TDP43 PET Imaging Challenge), home-based outcome measures (AT Home study), development of the infrastructure for future ALS prevention trials (DIALS), and a new method to track levels of SOD1 (the first genetic ALS target ever identified) in people over time, which is currently being considered for incorporation into clinical trials (SOD1 Kinetics).



RESOURCE IMPACTS

Over the past 5 years ALSFAC has invested almost 10% of its funding in two large infrastructure efforts: The ALS Biorepository (collection of human biosamples) and NeuroBANK™ (collection of clinical data from non-industry clinical studies). These vital resources are open access and used by researchers from both industry and academia across the globe for biomarker identification and validation efforts, the linkage between clinical findings and biological data, natural history data, information about concomitant medication use within the ALS populations, and a variety of other important uses. As a snapshot of the impact this investment in infrastructure has had, to date the ALS Biorepository has added more than 10,000 samples to its collection, and distributed 1000s of these to investigators around the world. NeuroBANK™ has incorporated longitudinal, detailed, standardized clinical data from almost 5000 individuals, and has expanded to include more than 20 different clinical studies. Because these infrastructure initiatives are large, complex, resource intensive, and open to everyone they are very challenging to support, and therefore a key contribution from the philanthropic sector to accelerate the efforts of the larger ALS research and drug development community.

PUBLIC IMPACT

ALSFAC has always kept the ALS patient front and center. In addition to its research, clinical, and infrastructure funding, ALSFAC has funded the development of incredible patient resources like the ALS Videos and the Research Access Nurse, a hotline for information and to answer questions about ALS clinical trials (ALS One MAP). ALSFAC funded investigators have also actively disseminated information around ALS clinical and scientific breakthroughs and challenges via print, TV, social media, and through public presentations.

EVALUATING IMPACT

Along the organization's 5-year journey, ALSFAC has been vigilant about tracking its progress, challenges, and successes. All ALSFAC investigators, in addition to submitting quarterly milestone reports, twice a year complete detailed updates on a wide variety of metrics, which can then be summarized in a Dashboard format (as shown in the figure below). In addition, using a methodology developed by Executive Committee member Mr. Tom Gentile and ALSFAC Scientific Consultant Dr. Melanie Leitner, scientific members of the Executive Committee evaluate each project incorporating budget, level of technical certainty, and degree of impact. Project progress is then reviewed on a regular basis by the full Executive Committee.



Input Measures



Project	
• Projects initiated.....	36
• Projects halted.....	2
• Projects evaluated.....	58
• Completed studies/decisions..	18



Funding (in millions)	
• Total Funding.....	\$81M
• From other sources.....	\$50M



Resources Developed	
• Pre-clinical models.....	130+
• Patient medical records.....	4887
• Samples collected.....	8300+



Collaborations	
• Industry Partners.....	51
• Researchers engaged.....	124
• Universities.....	40+

Output Measures



Academic/Industry	
• New grants received.....	30
• Peer reviewed papers.....	50
• Number of posters.....	58
• Academic presentations.....	129



Clinical	
• Identified ALS genes.....	4
• Biomarkers ID'd.....	1
• Clinical trials initiated.....	8
• FDA interactions.....	7
• Patients enrolled/treated.....	265+



Public Relations	
• Videos created.....	16
• Major network appearances..	10
• Major news articles.....	18
• Web page visits.....	300/mo
• Public presentations.....	17



Resource sharing	
• Instances of data sharing.....	100+
• Samples shared.....	1500+

Part III: Remaining Gaps in ALS Research and Drug Development

As part of our effort to identify critical gaps in the ALS landscape, in early 2019 we sent out a survey to 29 ALSFAC-funded investigators. We had a 100% response rate from investigators, with 80% of them feeling qualified to complete the survey. While there was a diverse set of opinions for many of the questions, a strong consensus emerged around three different areas of need for the field: discovery/translational stage gaps (the steps that need to happen even after a drug has been developed in the lab in order to get approval to advance the drug into people), clinical trials gaps, and resource gaps.

DISCOVERY/TRANSLATION

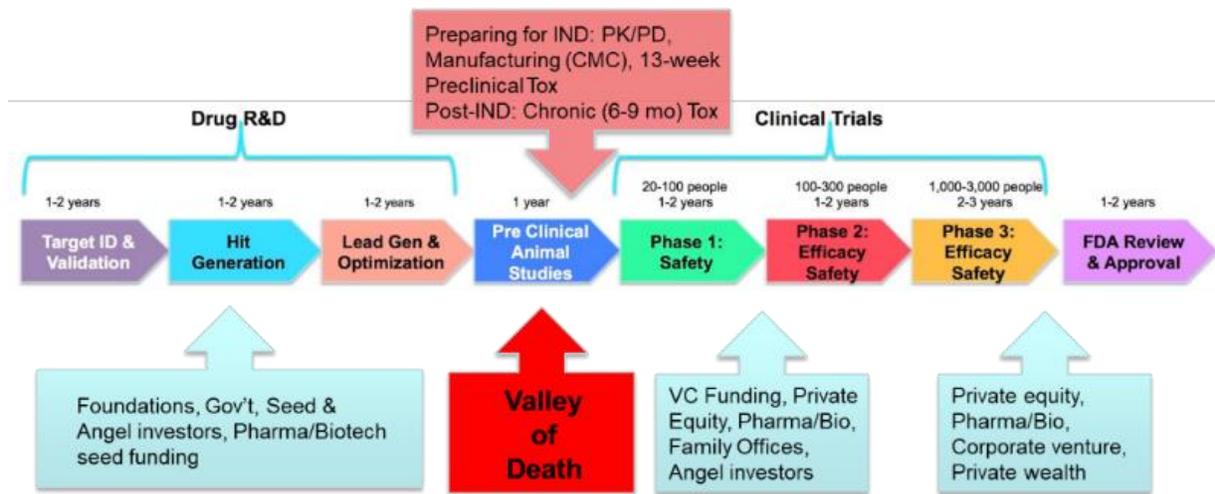
While there has been enormous progress in the identification of novel disease targets for ALS, validation of these targets and the development/identification of chemical compounds that act specifically on these targets (the first step of the long process to eventually developing drugs, shown in the pipeline figure below), remain key areas of need identified by ALSFAC investigators. There are also significant gaps in the process of translating research discoveries into human appropriate therapies particularly in the areas of:

1. Medicinal chemistry (optimizing the identified chemical compounds)
2. Preclinical toxicology (testing safety of the lead compounds in animals)
3. Regulatory guidance (preparing documentation to submit an Investigational New Drug application to the FDA in order to be able to test a compound in people)

An investment of funding into these areas would also have a positive impact on the number and quality of ALS therapies in the pipeline, and make it easier/faster for ALS patients to have access to existing ALS therapies.

CLINICAL TRIALS

Some of ALS Finding a Cure's® greatest successes have been in the area of clinical trials. The survey of ALSFAC investigators did, however, identify a number of critical gaps that continue to slow down progress in drug development even once it has reached the clinical trial stage of testing in people, including an absence of validated, standardized, fit-for-purpose disease progression biomarkers and home-based outcome measures. Also, there has been enormous recent interest from physician scientists, industry, the regulatory agencies, and ALS patients in translating success in clinical trial innovation (particularly platform trials and stratification efforts) from the field of oncology to ALS.



RESOURCES

While ALSFAC has made significant investments in key infrastructure initiatives like the ALS Biorepository and NeuroBANK™, the need to maintain (and in the case of NeuroBANK™ continue to build) these initiatives remain. New clinical research data are continually being generated, and incorporating these new studies (and their associated samples and biological data) into NeuroBANK™ further increases the value of the dataset, thereby leveraging previous investments. As projects like Answer ALS advance, and more is understood about disease subpopulations, the need for biosamples and clinical data will continue to increase. In addition, these samples and accompanying clinical data will be critical for enabling the field to find diagnostic and progression biomarkers (the key gap identified earlier).

Part IV: Looking Forward

In its first 5 years, ALS Finding a Cure made critical investments in four key areas: Target Identification, Biomarker/Diagnostic Development, Therapeutic Development, and Research Infrastructure. At this juncture, given changes in the ALS landscape, we recommend some changes to the ALSFAC portfolio.

TARGET IDENTIFICATION

Given the large investment ALSFAC has already made in Target Identification (45% of funds), the number of other funders who have entered the space, and long time horizon before the impact of many of these studies is realized, going forward ALSFAC may want to consider reprioritizing at least some of its investment away from the identification of new disease targets.

DIAGNOSTIC/BIOMARKERS

Given that there are still no universally accepted fluid-based diagnostic markers for ALS, and it still takes a year on average for an ALS patient to receive the diagnosis, in the interim patients are frequently bounced to multiple doctors, can receive unnecessary surgical procedures and medications, and can become ineligible for clinical trials. With an eye towards improving ALS patient quality-of-life, which starts with a definitive diagnosis, ALSFAC may want to prioritize funding efforts to identify the earliest signs and symptoms of ALS. Related to the need for diagnostic markers, the relative lack of sensitive progression biomarkers in ALS has led to the need for large and prolonged clinical trials, which are slow and expensive and present a hurdle for drug development (and developers). To date ALSFAC has directed approximately 20% of its funds towards biomarker-based efforts. ALSFAC has collaborated with multiple funding organizations to fund several early stage biomarker efforts. ALSFAC may wish to continue to prioritize funding biomarker identification and development as part of this informal biomarker consortium.

THERAPEUTIC DEVELOPMENT

Over the past 10 years there has been significant investment by the biotech and pharmaceutical sectors towards finding a drug for ALS. This has now resulted in a diverse pipeline of candidates, including small molecules, proteins (antibodies), nucleic acids, stem-cell-based therapies, and gene therapies. Many of these candidates have now demonstrated human safety and are poised to be tested in larger ALS trials. In parallel there has been a surge in the development of innovative clinical trial designs. This includes the development of adaptive platform trial approaches where more than



one treatment is tested in a shared infrastructure. This approach, already successful in oncology, cuts time, costs and the number of people needed to determine if a treatment is effective.

Another benefit of platform trials is their ability to serve as endpoint/outcome measure engines to develop and test novel measures that can determine if a therapy is effective at a much earlier stage. This includes the development and testing of home-based measures designed to both ease patient burden and increase the ability to collect valuable data. We are now at a perfect inflection point to pioneer innovation in clinical trial design with the development of an adaptive ALS Platform Trial that can incorporate and test novel outcome measures. Dr. Cudkowicz and her team at the Healey Center at Mass General are developing the first platform trial initiative in ALS. This approach will cut in half the time to develop effective treatments and increase by 2/3rd the proportion of people who receive active treatment. An investment in this initiative will greatly accelerate the ALSFAC mission to find cures for people with ALS. The ALS Platform Trial initiative may be a valuable effort for ALSFAC to prioritize funding towards, in collaboration with other ALS foundations and with industry.

While many of the novel candidates in the pipeline have already transitioned to the stage where they are ready for advancement into human clinical trials, many others are stuck at an earlier stage in the pipeline. As identified in the investigator survey, and in the brainstorming discussions held at the last ALSFAC F2F meeting, the key sticking points appear to be medicinal chemistry support, funding for preclinical toxicology studies, and access to regulatory guidance. As one focus for its next five years, ALS Finding a Cure[®] may want to explore innovative approaches to addressing these important gaps (which to date have not been addressed by other ALS foundations).

RESOURCES

Finally, to date, ALSFAC has invested approximately 10% of its budget in developing and expanding access to critical research infrastructure, enabling multiple research projects in both academia and industry. Building on the data platform of the PRO-ACT (clinical trials) Database, a new clinical visit records database, NeuroBANK™, was developed and launched. This data platform, funded through a collaborative effort between ALSA and ALSFAC, has become the largest existing collection of longitudinal ALS natural history data, providing a critical resource for enabling our understanding of ALS. With ALSFAC funding, NeuroBANK™ has developed capabilities to enable patients to enter and upload their own data.

Over the past 5 years there have been an increasing number of “big data” initiatives that have increased broad-based access to ALS clinical data, leading to increased awareness of and about the disease. As research infrastructure tends to be an area increasingly unfunded by government, and open infrastructure has always been unfunded by biopharma, databases, repositories, and other



large-scale clinical research resources may be an important area for ALS Finding a Cure® to continue funding.

* * *

In conclusion, ALS Finding a Cure® has had an enormous impact on the ALS field in the five years since its founding. While great progress has been made, we still have a way to go in order to achieve the mission of the organization to find a cure. Moving forward, a focus on four new buckets: Biomarkers, Bridging the Translational Gap, Innovation in Clinical Trial Design, and Expanding Access to Resources in the near term will help close the remaining key gaps in ALS research and development, and will bring all of us closer to a future in which we will have found a cure for ALS.