BRAINSTORMING NEURODEGENERATION

Leveraging Genomics, Stem Cells, Gene Therapy and Novel Clinical Trials for Field-wide Advancement

Ideation Workshop

San Francisco Airport Marriott Waterfront

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CIRM "Brainstorming Neurodegeneration" Outcomes

Progress in neurodegenerative disease research and development has been fraught with difficulties in translating research findings into clinical success. The typical analogy of blind individuals attempting to describe an elephant through their own limited exposure to the parts (tail, feet, trunk) has been told and retold countless times in the context of neurodegeneration. Though common, there remains an element of truth in the analogy where often key discoveries are made in isolation from wholistic perspective.

In April 2019, CIRM hosted a pan-neurodegeneration workshop meeting bringing together ~50 key opinion leaders from a diverse global cross section of regenerative medicine, stem cell research and development, disease foundations, academia, industry, funding bodies and the FDA. The main goal of this meeting was to enable a free-flowing discussion or "brainstorming session" where the attendees would tackle issues experienced in the development of neurodegenerative therapies by applying current state of the art techniques and platforms to reconfigure discovery and development pipelines and find synergies with groups/consortia. The meeting was held over 2 days and covered topics ranging from leveraging genomics data and patient derived induced pluripotent stem cell models for discovery research to a discussion of clinical development strategies and regulatory paradigms specific to a new generation of therapies.

The meeting opened with a dynamic and provocative keynote presentation from Carlos Bustamante Ph.D. (Stanford) giving an overview of how precision medicine and genomics can be employed to advance clinical development and increase success rates. Dr. Bustamante illustrated key differences between the current knowledge base created through datasets generated from populations of European descent and important gaps with the knowledge base of underrepresented populations intended for treatment. Examples of where these gaps have ultimately led to a disproportionately high morbidity rate for diseases of interest were used to highlight slow success rates in development.

The main stated goals of the meeting were as follows:

- Discuss novel models to accelerate therapeutic development for neurodegenerative diseases (NDs).
- Discuss proof of concept examples where genomics and large datasets have enabled progress in NDs.
- Prioritize elements of common utility.
- Explore benefits and considerations for a neutral collective effort across NDs.
- Discuss incentive structures to encourage alignment.
- Propose an operational framework(s) to move from concept to reality.

Session discussions were led by a Chair with selected panelists addressing a set of pre-defined "anchoring questions". The following summary provides an overview of each session theme, discussion questions and content from the discussants.

Session I: Leveraging Genomics and Big Data

- *Chair: Carlos Bustamante*
- *Panelists: Joshua Stuart, Ernest Fraenkel, Howard Federoff*

Anchoring Questions and Summary of Discussion:

- ***What can the Neurodegeneration community glean from current genomics approaches?***

The panelists stressed the importance of appropriately applying genomics based technologies by first determining whether genomics (specifically) is the "correct/best" omics approach for a given disease. Making this determination requires an understanding of the extent to which germline vs. somatic cells are the most appropriate tissue source to study for a given indication. Cancer research often sees greater success when utilizing somatic data, for example.

Determination of exactly what should be measured was also stressed. Genomics data alone may not be sufficient to generate a complete and relevant (disease) profile. Again, the oncology field often finds that phosphorylation data can be more useful for predicting disease than straight sequencing for some patients. Panelists agreed that employing a multi-omics approach is likely optimal at this stage.

The significant potential of direct to consumer commercial genomics data acquisition (i.e. 23andMe) was discussed. Having profiled 20 million people to date, this dataset eclipses all institution-based studies and is invaluable for population-based research. While current population-based studies appear powerful, a caveat exists when these approaches lack appropriate diversity with respect to minority representation, which are often the most affected populations for certain diseases. This highlighted an overall need to increase minority representation in database creation and expansion.

Finally, an acknowledgement was made that standardization of datasets (analysis, format, etc.) is key and all data and should be put into common coordinates to make it useful for a multi-center or consortium-based analysis.

- ***What should the Neurodegeneration community look to model? What should be avoided?***

Pre-clinical animal model data has repeatedly demonstrated a low predictive value for clinical success in Neurodegenerative disease clinical trials. As a result, the panel felt that current approaches should seek to employ disease models that contain features that are concurrent with the pre-symptomatic clinical disease state. A valuable new route for study should include patient derived induced pluripotent stem cells (iPSC) as a segment of the screening funnel.

Multiple sessions featured a recurring theme on the need for improved standardization practices across the field. "Target ALS" was discussed as an example of patient sample collection performed in a well-controlled and curated manner, thereby increasing the value/utility of the sample bank. Target ALS banking practices tackle standardization by utilizing accessible donor IDs linked to an associated database which is recognized as an asset to the collection. Having such standardized information easily accessible and visible to researchers was stated as a significant value factor. Without standardization, consortium data is difficult to analyze collectively due to the nature of multiple contributors to a collection, and the value of the output suffers.

Furthermore, a mechanism for standardization of clinical readout while integrating other data streams was recognized as important, with home monitoring stated as both an accepted and useful addition. Studies do not need to be mutually exclusive (either or) – multiple datasets can be very beneficial.

Another important factor to consider in bank or consortium establishment is to maintain some degree of flexibility to pilot and adapt, iterate and scale as needed. Ultimately, this ability for adaptation makes a consortium much more successful.

- ***Where have industry efforts failed and is there an opportunity for current data platform technologies to augment probability of success?***

Multiple high-profile clinical failures in targeting amyloid for the treatment of Alzheimer's Disease (AD) is often the preferred case study for reconsidering clinical approach and target selection. The panel came to a consensus that the focus on amyloid to the exclusion of other disease mechanisms based on its association as a neurological hallmark of the disease has driven a conservative approach by the pharmaceutical industry. The attraction to the amyloid pathway is largely due to the existence of a tremendous dataset supporting the approach. Multiple

examples of clinical programs exist showing that amyloid reduction has produced, at best modest improvements in cognitive function, yet the pathway remains attractive. It remains a possibility that such interventions may not be early enough in the course of AD, and/or amyloid isn't ultimately driving pathology/dysfunction. Therefore, the field arrives at a conundrum of risk vs. investment: where to place crucial R&D funds in an unpredictable landscape. Refining the patient population has produced unclear connections between the familial AD data and sporadic AD cases which in turn slows development.

How can a diverse and occasionally disparate field make real progress in this space? The panelists cited the emergence of novel targets and data sharing as drivers for transforming development. Failures need deep post-hoc analysis to gain an understanding of factors driving results. Ultimately this is an ethical obligation for investigators. Data transparency around clinical failure is critically important and mechanisms for sharing with the field need to be developed to make progress.

Panelists expanded this concept above by also citing the failure of NIH funded trials in Parkinson's Disease (PD). As an outcome of these failures, multiple teams have joined in sharing information from both failures AND successes which has served to advance the field. Given that the majority of clinical trials are sponsored by the pharmaceutical industry, mechanisms to incentivize data sharing from this work need to be developed. Currently, data sharing is less of an issue with academic center sponsored trials. Funding agencies such as CIRM and the NIH have encouraged public private partnerships which may be one possible solution for data sharing.

Session II: iPSC Models, Creating Standards, Utilizing Banks

- *Chair: Lorenz Studer*
- *Panelists: Kristin Baldwin, Clive Svendsen, Genie Jones, Stuart Lipton*

Anchoring Questions and Summary of Discussion:

- ***Do we know enough to create standards? Can more complex models (i.e., CNS organoids, chip-based approaches) be standardized at this time?***

No two iPSC lines are identical. This heterogeneity ultimately leads to challenges with the reproducibility of results. One source of this variability is the differential effects that genetics have on the specific cell type under study (or affected by disease). An approach that helps mitigate this variability is the utilization of multiple iPSC lines in a given set of experiments. While cell line heterogeneity is a major source of variability, technical aspects of bank preparation are also key to managing variability. A recommendation was made to cryopreserve initial donor samples, allowing the bank to be re-made should significant technological evolution occur. The example was given of a CiPA (Comprehensive In Vitro Proarrhythmia Assay) study using iPSC-derived cardiomyocytes that showed distinct differences in drug response across individual cell lines. Cardiac cells represent one relatively homogenous cell type and clearly neuronal population complexity and heterogeneity are well documented. This heterogeneity undoubtedly contributes to variability seen in small sample sets.

The ability to standardize is tied to the scientific study goals. Robust sets of biomarkers/signals for conditions like Parkinson's Disease may make standardization possible, however other ND diseases like ALS pose challenges due to a weak signal (identifier linking the cell to the disease). The discussion continued to touch on knowledge around ND disease biology informing standardization and occasions where field "standards" like Ngn2 for Parkinson's have been adopted but do not reflect disease pathology and may be misleading. The recurring theme of identifying the "signal" and its contribution to standardization continued with comments around optimization/standardization of the disease system relative to the signal tied to the ND. While the signal may evolve as mechanistic understanding improves, it is important to optimize around the strongest signal with the lowest degree of system noise possible.

Finally, though much of the discussion centered around ND patient iPSC neurons, a recognition that multiple cell types (i.e. the contribution of neuroinflammation, glial cells etc.) and the importance of model systems including co-culture systems and organoid cultures serve a purpose. However useful organoid systems may be though, challenges around the significant complexity of these systems make them difficult to standardize. Value

may be derived from this technology by exerting some control of their development and applying learnings from 2D culture, or topographically organizing them with a patterned substrate.

- ***How do we utilize existing banks and establish requirements for future banks?***

Not addressed by the meeting participants

- ***Where could consolidated efforts be useful to the community?***

Not addressed by the meeting participants

Session III: Exploring a Neurodegeneration Consortium Model

- *Chair: Clive Svendsen*
- *Panelists: Lucie Bruijn, Margaret Sutherland, Leslie Thompson*

Anchoring Questions and Summary of Discussion:

- **What can be learned and broadly applied from the Answer ALS model?**

The origins of Answer ALS began with the NIH funded NeuroLINCS collaborative effort and the team viewed this as a pilot for the expanded Answer ALS effort. One of the strongest highlighted features cited for the Answer model was the flow scheme for sample acquisition coupled to a network of distribution and analysis sites. This completely integrated approach will result in iPSC lines from 1000 patients, which will be linked to clinical and other metadata allowing a "big data" analytics approach (lines from 500 patients made to date). Samples include whole genome sequencing data, iPSC lines and iPSC derived motor neurons. From a technical perspective, biological variability is minimized by a single cell pellet being split amongst multiple labs for RNA, Protein and ATAC- seq rather than using the product of multiple expansions. Using the same starting material from same source (Cedars-Sinai performs does iPSC line generation and motor neuron derivation) has resulted in a quality dataset. Current results of initial proteome analyses suggest 3 novel subtypes of ALS that have been previously unseen.

Additionally, having trained and experienced scientists and staff contributing to a consortium effort has been a strength in advancing the science behind Answer ALS. Another aspect cited as beneficial to the consortium is the maintenance of open communication between the "working" scientists (grad students and post-docs) across member institutions and with consortium leadership.

- **What is the existing ND-specific consortium landscape? What are the features & assets?**

Some of the major assets discussed for the Answer ALS project included key centralizing features and the spoke and hub concept, however specific consortia needs and goals should dictate structure. Another key, but possibly overlooked strength of a consortium is the eagerness of the patient population to participate. Having an engaged patient population can significantly enhance efforts. Answer ALS has had enthusiastic patient involvement and has been driven by patient support.

- **Where are the gaps left by existing consortia? How could a new combined approach address those gaps?**

As with any developing field, gaps are often identified mid-stream. As such, some discussion time was devoted to taking an objective look at existing consortia and identification of areas for improvement. A common recurring theme which seems inherent to modern research is the disconnect between the generation of large datasets and the analytical tools and algorithms applied to them. One such example mentioned was the concept of how best to utilize datasets for disease sub-typing. It is often hypothesized that many neurodegenerative diseases exist on a spectrum or are syndromes which may be more effectively treated with appropriate patient stratification. While the datasets exist, a definitive deconvolution for this data has yet to be developed.

Another gap that was touched on again in this session was the need for standardization across multiple functions in a combined research effort. Reproducibility of datasets across different patient populations and

variability across 'omics experiments lead to a lack of understanding that may be due to inherent patient heterogeneity, or lack of standardization across different points in the experimental pipeline. It is ultimately important to implement quality control (QC) standards and checkpoints in the consortium system to avoid such variability leading to uninformative outputs. A Parkinson's biofluids focused effort similarly collected & studied by 'omics, has constructed a QC standard to ensure the patient sample under study is representative of the assumed patient identity. The panel felt that standardization was a significant need prior to generating large datasets as output.

While there are multiple global efforts focusing on specific neurodegenerative indications, there was a group consensus that a coordinated effort to identify common biological mechanisms was lacking. For example, there are known linkages to mitochondrial dysfunction and /or neuroinflammation across ND, however these mechanisms were thought not to be granular enough to develop a therapy. Nonetheless, such linkages might be used to cure an epiphenomenon at this level.

It was also felt that existing consortia would benefit from additional coordination across member institutions. One significant gap that limits the pace of development is the lack of a simplified Material Transfer Agreement (MTA). Paperwork can often impede the pace or even completion of activities.

In the spirit of providing recommendations on how these above gaps could be addressed by the formation of a new consortium, the panel felt that success would come to an effort with an unbelievably clear mandate, and without overreach or over-specificity. Methods, data, quality, tools and, intellectual property (IP) are all great to share, even without specific and granular mechanisms - since this is what will bring people together. Building on existing efforts rather than establishing a consortium *de novo* would drive value by leveraging current successful work. One example of a broad coordinated effort included the Dementia Discovery Fund which consists of a diverse set of investors including Bill Gates, UK government and AARP. This contains a broad mandate with a focused dementia overlap covering AD, Huntington Disease (HD), PD, Amyotrophic Lateral Sclerosis (ALS), and frontotemporal dementia (FTD). With such a coordinated effort there is an allowance for shared dementia elements that are not restricted solely to AD.

A second line of discussion on specific needs of a consortium focused on the generation of a new set of patient derived iPSC and the specific needs of creating a new repository. Aspirations for the practical aspects of such a repository included standardization of iPSC lines in conjunction with some determination of quality, which could take the form of well annotated metadata linked to each sample (including clinical data). Additionally, the utility of generated data could be enhanced through simplification of data use agreements, MTAs and an easily accessible shared information portal.

Session IV: Accelerating Drug Development Based on Patient Data

- *Chair: Ernest Fraenkel*
- *Panelists: Mark Frasier, Ralph Kern, Omar Khwaja, Merit Cudkowicz, David Higgins*

Anchoring Questions and Summary of Discussion:

- ***How can the ND community leverage genomic and clinical data, patient-derived iPSCs, etc. to accelerate drug development? What are the challenges?***

Not specifically addressed by the meeting participants

- ***Are there current exemplars in other disease areas that the ND community should look to model?***

Not specifically addressed by the meeting participants

- ***Does industry perceive value in a consortium approach utilizing pooled data sets?***

The group discussion for this session evolved to address questions as they emerged with input from both the panel and audience. Several key themes arose that the group felt would greatly accelerate clinical development. As was evident in prior sessions, the idea of enhancing data quality, collection, curation and analysis was a major focus.

What data do we need?

Central to expanding the value of datasets would be the inclusion of multiple disease (specific) collections including non-diseased controls and "blue card" outliers. In order for clinical trials to produce meaningful results, data expansion around patient relevant endpoints needs to be developed. A patient relevant endpoint was explained by the patient advocates as a disease symptom meaningful to improving the patient's overall quality of life. The example of using tremor as an endpoint for Parkinson's was referenced as not being at the top of a patient's concerns. In the same sense, expanding knowledge around the linkage between biomarkers and secondary disease processes rather than only the proximal cause, and linking these biomarkers to patient specific data relative to disease course was perceived as a high value addition. Standardization of disease stage was stressed as a shortcoming in current practice where there is often a misuse of categorization terminology such as "early in disease". As classification of disease stage is clearly impacted by the rate of disease progression, patient disease trajectory should be a component included in classification.

An important distinction was made regarding the quality and use of data from industry sponsored trials. While some in the discussion felt that the volume of trial data needed expansion, industry discussants maintained the opinion that the gap lies more in the understanding and interpretation of data from failed trials and the need for incentivizing sharing of this failure data broadly with the field.

What can we do to overcome gaps?

In the spirit of addressing deficiencies with solutions, the group considered various methods of incentivization that would foster data sharing. Important to the discussion was what types of data would lend themselves to sharing, including redacted data and results from placebo arms, etc., which could be valuable to share. However, mechanisms of incentivizing data sharing may differ depending on the sponsor (i.e. industry vs. academic) It was mentioned that Cytokinetics agreed up front to donate failure data to the field via an agreement with Answer ALS and it would appear that foundations have been doing a good job to encourage sharing and data distribution.

What could CIRM do to support (acceleration)?

Discussion on this question centered around expanding the workforce and understanding of disease mechanisms. Also important was enabling a deeper understanding of the molecular mechanisms behind trial failure. This could be accomplished by (funding), training programs and disease specific initiatives that link patient trajectories to an agnostic biomarker-based approach. There was a sense that such an expanded effort would require recruiting additional data scientists into the field of biology. Importantly, the data scientists need to be paired with clinical scientists. Input from data scientist discussants indicated that tools are under development for dealing with emerging data, but there are difficulties in getting the tools to where stakeholders are able to get what they need from it.

Session V: Clinical Trials in Regenerative Medicine – Benefits of a Consortium

- *Chair: Abla Creasey*
- *Panelists: Malin Parmar (ESC-based), Jun Takahashi (iPSC-based), Howard Federoff (Gene Therapy)*

Anchoring Questions and Summary of Discussion:

- **What could a cell or gene therapy approach offer that is different from traditional/past approaches?**

Using the clear rationale for the mechanism of action (MOA) of dopamine cell replacement for Parkinson's as a disease specific example, there is a value proposition for cell therapy where the major pathology is due to degeneration of one type of neuron in fairly small population localized in one area of brain. Therefore, achieving a localized, physiologically responsive dopamine release can overcome limitations of oral drugs. Cell therapy clinical trials like TRANSEURO may see a positive clinical effect, but limitations inherent to fetal cells impact the product given manufacturing/supply issues will impede broad use. An alternative approach/solution using PSC derived dopaminergic (DA) neurons has shown that they function similarly to fetal DA neurons based on the work of multiple labs.

However, cell therapy alone cannot stop the underlying disease driving pathology, it can only reverse the symptoms/degeneration. Disease modifying therapy can stop or slow the disease process, but it cannot reverse the symptoms/degeneration. Perhaps future strategies utilizing multiple modalities can be combined to improve patient outcome.

The nascent field of gene therapy for central nervous system (CNS) indications has been enabled largely due to new adeno-associated virus (AAV) serotypes that cross the blood brain barrier and are more bioavailable. CNS targets that were historically unapproachable may now be more tractable and may not require invasive dosing techniques like intracranial delivery. The Voyager Therapeutics viral delivery AADC Deficiency trial contained several groundbreaking elements. Delivering the largest dose in cohort 3 with substantial use of a co-administered tracer to help guide delivery enabled accounting for anatomical variation and verification of depot placement. This was an open label study and despite being open label, there has been a decrease in the UPDRS clinical endpoint and a dose dependent reduction in levodopa use. Positive data for the time spent without troubling dyskinesia has been seen. Though results will also have to be validated in later trials, it is important to consider that Parkinson's disease trials typically see the largest placebo effects and this novel therapeutic strategy has shown unprecedented results to date.

- **Are there approaches in other disease areas that the ND community should look to model?**

G-Force was cited as a unique platform/consortium where competitors are collaborating together developing similar therapies for the same indication. Ultimately, whether this approach is successful will be demonstrated by the output of G-Force members. One potential rationale for collaboration is that individual failure of G-force's member approach ultimately impacts his/her competitors (i.e. failure of platform?).

Pulling in successes and failures from related approaches can greatly inform new neurodegeneration efforts. The concurrent development of multiple Dry/Wet AMD cell therapy products can inform GMP manufacturing across the field. CNS targeted stem cell therapies can and should learn from the fetal transplantation field with regard to dosing, delivery and patient follow up. Additionally, looking beyond CNS indications, cell therapy can be informed by successful trials of advanced technologies in cancer.

Session VI: Taking Regenerative Medicine ND Candidates to the Clinic

- *Chair: Daniela Bota*
- *Panelists: Wilson Bryan, Robert Pacifici, Marg Sutherland, Walter Koroshetz*

Anchoring Questions and Summary of Discussion:

- **Regulatory considerations and challenges for consortium sponsored trials**

Information below reflects the conversation; however, the key questions were not directly addressed.

With this session the focus of the meeting shifted to mechanisms of innovating the clinical development paradigm. It was well recognized that clinical development in the neurodegenerative space is fraught with challenge. Innovations in trial design and expanded mechanistic understanding of disease biology will certainly be required to improve the probability of clinical success.

Some time was spent emphasizing the importance of quality science in supporting a clinical hypothesis. Investing in quality biomarkers can open a path for expanded endpoints. An understanding of the therapeutic target, and what to measure is key to success. A sentiment was expressed that trial results would certainly improve with better animal models, surrogate endpoints and/or innovative trial designs, etc. Ultimately these aspects are of limited value if the science informing the therapeutic approach isn't robust. A deep understanding of disease mechanisms relevant to the target and pursuing targets that represent well defined stages of the neurodegenerative disease will ultimately have more impact on trial outcomes than simple evolution of how they are clinically tested.

A recommendation and an example were given with the Genetic Modifiers of Huntington's Disease (GeM-HD) Consortium, which found modifier genes associated with mismatch repair, leading to a mechanistic hypothesis.

This was accomplished by making observations in the clinical population intended for treatment and effectively understanding what's broken before trying to fix it. This took the form of a large HD registration trial consisting of 20,000 people, collecting data and samples prospectively and assigning a unique linked identifier for each subject.

Overall, the consensus was that expansion of efforts on a global scale would benefit consortium sponsored trials.

- **What regulatory advantages or potential challenges would a consortium model pose to the development of novel endpoints, access to expedited regulatory designations and the use of adaptive trial design for ND?"**

A need exists to expand information sets to include as many patients as possible. Of the 20 different initiatives targeting, ALS, Alzheimer's, HD, PD, would it be possible to link smaller efforts to help drive at accelerating endpoint development and the regulatory process?

- **What are the key infrastructure gaps preventing advancement of regenerative ND candidates to the clinic?**

Comments included that there have been significant infrastructure hurdles with some of the larger ND disease focused efforts (i.e. HD), however no specific examples of needy components were given.

- **What solutions could be applicable (e.g., data platforms for imaging and surrogate measures, registries and data repositories, etc.)?**

Not directly addressed

Session VII: Would an ND Consortium Accelerate Therapy Development: Considerations for a Path Forward

- Chair: Ekemini Riley
- Panelists: Katja Brose, Mark Frasier, Walter Koroshetz, Maria Millan

Anchoring Questions and Summary of Discussion:

- **Taking the breakout discussions into consideration, what could a path forward look like?**

Panelists were asked to address the series of questions shown below. A summary of answers is provided.

What programs are most relevant to this group?

Panelists were asked to highlight the overall impact of their projects.

- Katja Brose; The Chan Zuckerberg Initiative (CZI) organization is disease agnostic, exclusively focused on basic science and ND is first disease area they have taken on. There is much to be learned by thinking of ND as a class of disorders. They have formed the Neurodegeneration Challenge Network, a small-scale collaborative network as a test for how you can motivate community to progress; people (new talent), collaborations, tools and technology and open science. The Cell Atlas project is another key program in which they partner via 3 open RFAs. The first two provided small scale pilot funding around protocols and benchmark data, computational tool development.
- Mark Frasier said that Michael J Fox Foundation (MJFF) is supporting biomarker and tool development. The first project is the Parkinson Progression Marker Initiative, or PPMI, to develop biomarkers(s) to guide decision making at phase 2 clinical trial stage. This started as a natural history study and has grown to include carriers, 1300 individuals. There has been a lot of clinical data collected along with biospecimens with a 5-year longitudinal collection plan. Outcomes have included a few markers being identified that appear to track with disease progression, but secondary to this is an opportunity to study PD at the

molecular level. The initiative currently has data for ~200 people including patient linked iPSCs. Data emerging from this initiative is open access. The other story for MJFF is a partnership with the Alzheimer's association to identify commonalities and fund analysis of open access data sets such as ADNI (Alzheimer's Disease Neuroimaging Initiative). The goal is to monitor imaging changes over time, genetic data sets, etc.

- Walter Koroshetz referenced the NINDS public/partnership with MJFF, professionals, (i.e. Verily) in the data space and companies, and they are optimistic that this may be a potential solution to problems faced at NIH. They have an interest in applying this approach to others therapeutic areas besides PD. Trying to understand disease phenotypes and relationships to human cell models is attractive for the institution. Ideally, he feels that they need a "Center without Walls"
- Maria Millan discussed the level of money invested by CIRM in the neurology space, which has primarily focused on discovery and translation stage projects, but a few have progressed to clinical development. CIRM's value proposition is the pipeline funding model.

What are the barriers and challenges to forming partnerships?

This panel echoed the sentiment expressed in earlier sessions that a partnership (or consortium) needs a clear and articulate goal to be successful. Making sure all stakeholders are aligned toward this goal is critical. Restrictions on how funding can be spent/utilized can have a negative impact on initiative-based efforts. An NIH example of a public/private partnership looking at the effect of alcohol on health was ultimately determined to be inappropriate for existing funding mechanisms through the federal government. The NIH solution has involved some work being funded by the NIH Foundation, which has different requirements/limitations deploying funds. Similarly, seeking private or commercial investment in a consortium effort also comes with unique restrictions which can be minimized by focusing on a clear goal for the effort.

Another perceived challenge was dissemination of knowledge. The example was given for recruiting new scientists to a field that don't know how and where to get resources. This has been shown to directly impact productivity and the pace of work. Reproducibility is also a huge issue once a project advances beyond the innovators and the early adopters. How do cutting edge and paradigm shifting tools end up in the hands of the average scientist? There was a sense that existing biobanks are dramatically underused due to this lack of dissemination. Researchers don't know how to find and use a needed sample. These are operational problems however, not scientific.

A suggestion was made that making dissemination of information surrounding initiative/consortium activity mandatory could be considered as a component of the funding requirements. This may ultimately incentivize the practice and by being creative, it could help by targeting areas that aren't typically funded.

On the theme of incentivizing data sharing

While data sharing has been in the mandate of some institutions, this can be difficult to implement in a way that avoids impacting the careers of young investigators. Though this is a recognized problem, no one has a good solution. Additional practical issues also need to be taken into consideration. In order for shared data to be of value, curation is a key component. Understanding the needs of the end users (researchers, clinicians) complicates this due to differing needs.

On the subject of a training gap

The panel agreed that the gap in the pool of trained staff experienced in PSC based research is a recurring theme.

Cellular Dynamics International (CDI) reported that they spend a significant portion of time teaching non-PSC scientists to use the iPSC lines, which was not accounted for in their sales model originally. An ideal solution would be to direct those in need to a pre-identified resource, but the means to do this is currently non-existent. Discussants from academic institutions referenced their own internal training programs but cited limited space for expansion. Virtual solutions have been explored with online journals like JOVE, but this has not been enough to

cover the significant need and has been deemed as largely unsuccessful. The Stem Cell COREdinates consortium of human pluripotent stem cell-focused core facilities was also mentioned as a group attempting to disseminate expertise across the field that appears to be experiencing some success.

On the subject of how broad a ND consortium should be

The exploration of the value in a pan-neurodegeneration consortium opened with a reflection on Pharma and venture investment in the ND space being difficult due to the risk associated with the space. Perhaps investment could be encouraged from a shared risk perspective in a broad effort, but would require clarifying how this investment benefits individual members.

What form would such an effort take? This could be something other than an aggregator, curator, standardizer, etc. A few discussants felt that there wasn't an overwhelming need for a broad consortium, but based on multiple session discussions, a significant need for standardization in the field is evident, and perhaps some entity could bring this together. Still, others felt that their own success in the ND field has come from looking across common pathways and investigating "low hanging fruit". It was also recognized that in order for a broad consortium to work, it would require some degree of disease specific infrastructure. In this sense, a consortium would be valuable in aggregating/centralizing data for such work.

The value of a consortium-based approach was highlighted by citing the current success with using a curated platform of iPSCs for ALS. The recognition that this iPSC platform contains a high-quality dataset has resulted in increased use by the field. Ultimately, this will provide a service to the community that is able take the lines and make organoids while referring to the data as a standard.

A consortium built on the successes of current efforts like ANSWER ALS and the MJFF may beneficial. If such an effort were initiated, industry perspective was that not only the goals need to be clear, but the output of the effort also needs to be defined including a time component. By incorporating time bound deliverables in the goals, obtaining industry investment may be feasible. This output (clearly linked to the mission/goals of the consortium) would also need to have a clear end in sight. It was perceived by the group that focused testing of a hypothesis or the establishment of go/no go success criteria for an effort would have a tremendous value and minimize wasted effort long term.

Infrastructure; Cell Phenotypes- what else do we need?

Discussants felt that a broad integrated approach as had been described throughout the course of the meeting could be applied in disease areas outside of the ND field, but that implementing for ND provided a high value due to the recognized unmet need, associated emerging technology platforms including cell/gene therapy, big data/Artifical Intelligence (AI) analytics and the possibility of leveraging these to gain a better understanding of ND biology.

Infrastructure was also a recurring theme as a gap needing to be addressed, beginning with something as basic as how to practically connect all the pieces identified in various sessions. As industry is not likely to take the lead, there is an obvious role for academic, government, nonprofit organizations.

The concept of having a well-defined goal was repeated and expanded to include implementing checkpoints allowing for course correction based on progress. An agile and responsive strategy was considered useful. The value for a broad effort comes from having multiple perspectives provided by a diverse group of consortia rather than an unchallenged dogmatic approach to a problem.

The idea of expanding the Answer ALS effort was voiced as a mechanism to generate large banks (1000 donors each) across several ND diseases. Requests for Funding (RFAs) could be issued targeting specific questions for the banks, including phenotyping, drug discovery etc.