

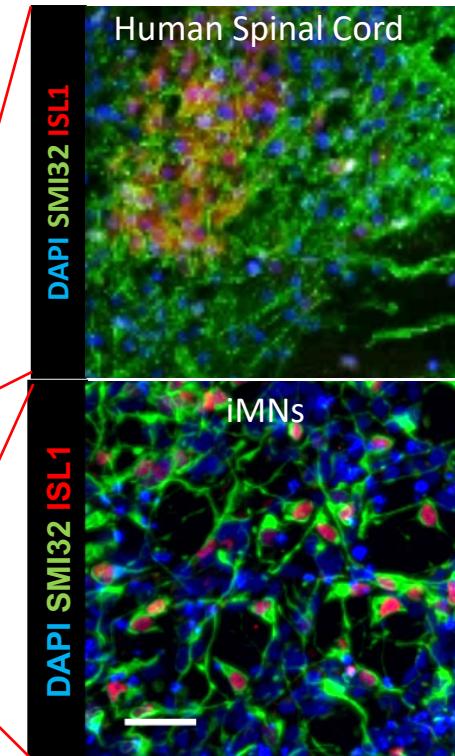
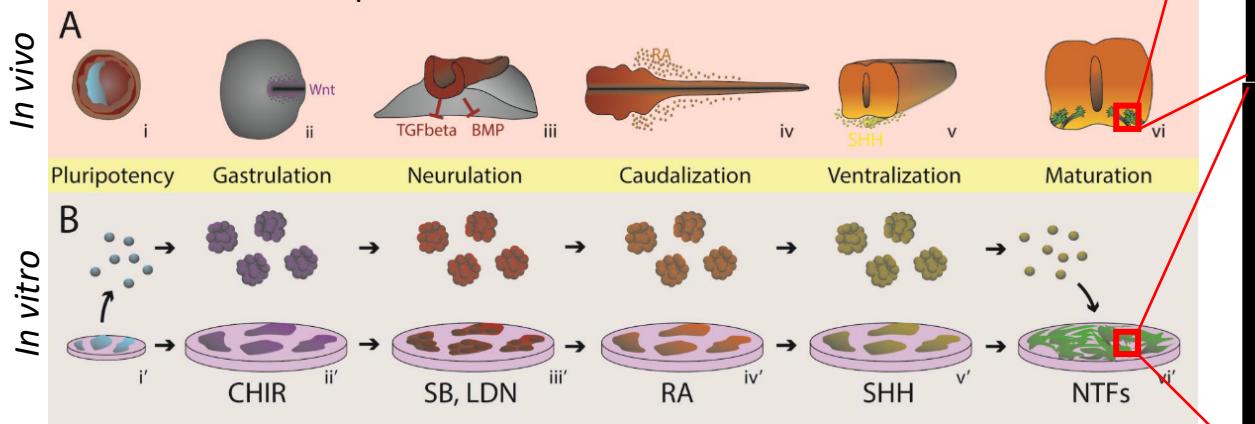
Answer ALS

Recreating Amyotrophic Lateral Sclerosis *in vitro* using iPSCs.

Generation of Spinal Motor Neurons (iMNs)

- iPSCs are directed to neural fate by blocking mesoderm and endoderm.
- Neural progenitors are then patterned to caudal and ventral origins.
- Mixed neural cultures contain ISL1/SMI32 positive neurons.

Differentiation of Spinal Motor Neurons



Modeling sporadic ALS in iPSC-derived motor neurons identifies a potential therapeutic agent

Koki Fujimori¹, Mitsuaki Ishikawa¹, Asako Otomo^{2,3,4}, Naoki Atsuta⁵, Ryoichi Nakamura⁵,

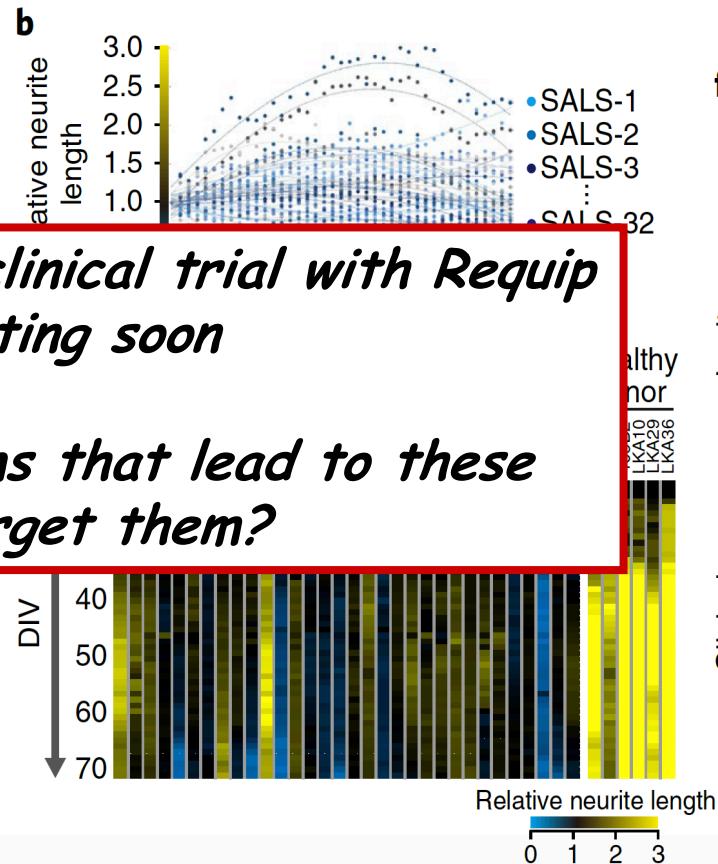
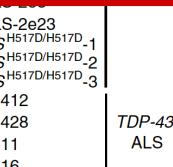
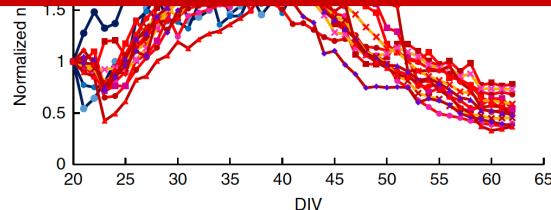
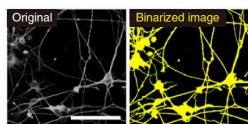
Tetsuyuki
and Hiroyuki

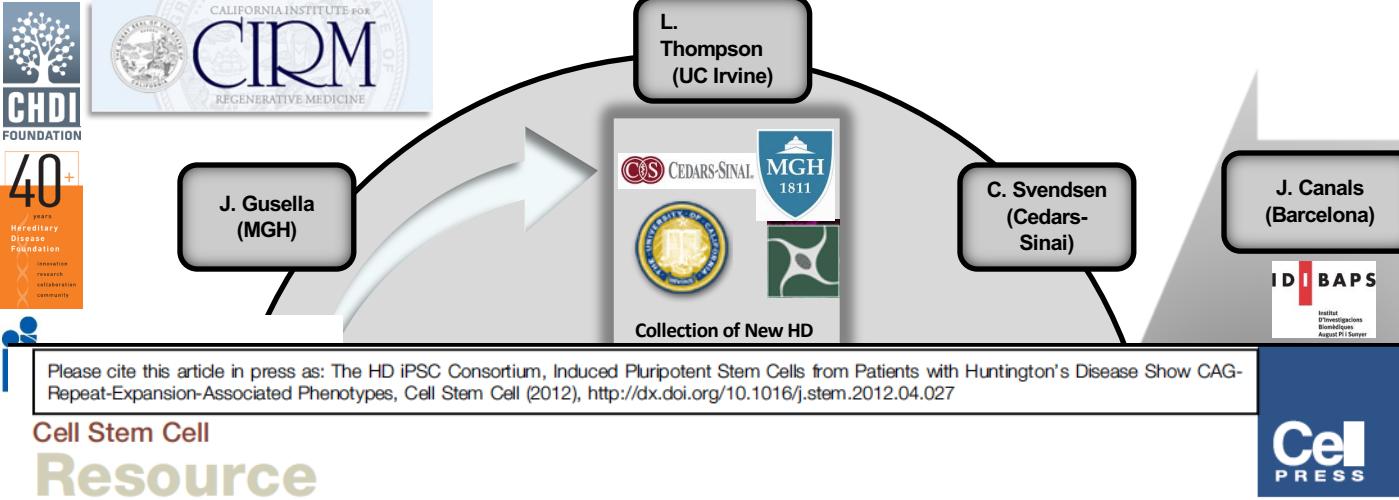
Screening using this system led to new clinical trial with Requip (Ropinirole) in Japan - starting soon

c
Differentiation

DIV
2

Time-course analysis of neurite length





Induced Pluripotent Stem Cells from Patients with Huntington's Disease Show CAG-Repeat-Expansion-Associated Phenotypes

The HD iPSC Consortium^{1,*}

¹Membership of the consortium is provided in Document S2

*Correspondence: clive.svendsen@cshs.org
<http://dx.doi.org/10.1016/j.stem.2012.04.027>



Modeling ALS using iPSCs and big data

Leslie
Thompson



UCIrvine
University of California, Irvine

Jeff Rothstein



JOHNS HOPKINS
MEDICINE

Steve
Finkbeiner



UCSF
University of California
San Francisco

Jenny Van Eyk

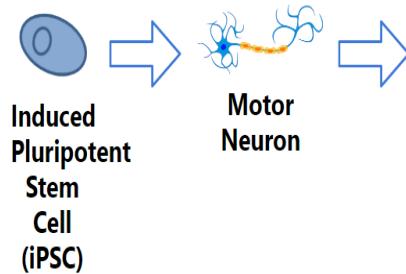
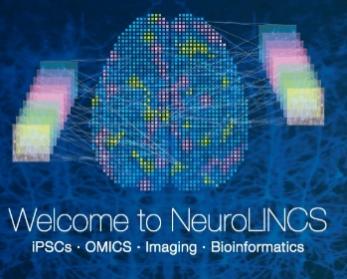


CEDARS-SINAI®

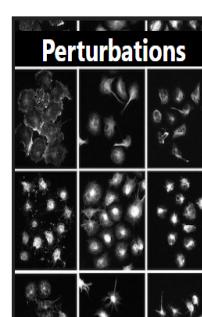
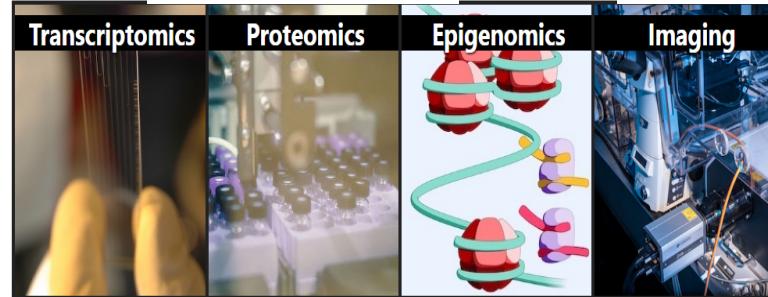
Clive
Svendsen



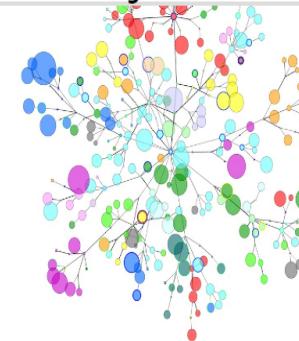
NEUROLINCS



Total RNA-Seq Data Independent ATAC-Seq Acquisition (SWATH) - MS



Integrative Network Analyses and Cellular Signature Generation



FRAENKEL LAB NEUROLINCS TEAM



**Brook
Wassie**



**Pamela
Milani**



**Miriam
Adam**



**Johnny
Li**



**Divya
Ramamoorthy**

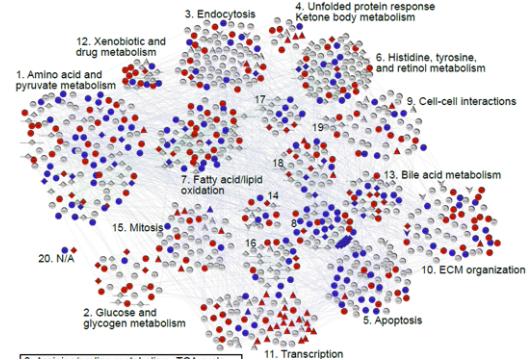
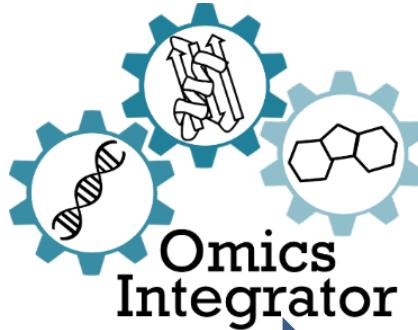
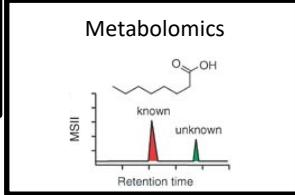
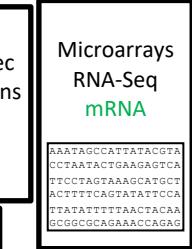
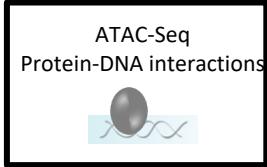
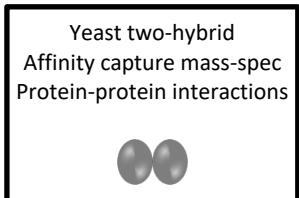
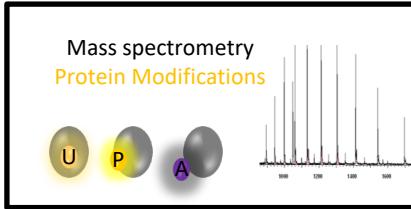


**Alex
Lenail**



**Karen
Sachs**

Data Integration



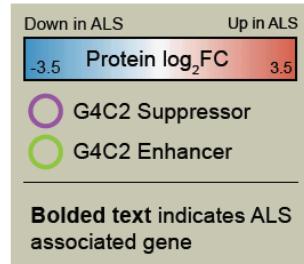
**Johnny
Li**

Output filtered for robustness and statistical significance

Nature Methods. doi: 10.1038/nmeth.3940.

PLoS Computational Biol. 2016 doi: 10.1371/journal.pcbi.1004879.

C

**Translation**

SRP14 FAU
Ribosomal proteins
Eukaryotic initiation factor proteins
Ubiquitin RPS6KB1

EGF EGFR
GRB2 CBL
PTPN11 BRAF APC
CRK PRKACA
RHOQ RHOA EZR ANXA8

C9ORF72
RBP/splicing
WDR77 hnRNPs
snRNPs PRMT5
PABPC1 Spliceosome Assembly

Nucleocytoplasmic Transport
Nucleoporins
RANBP2

Microtubules

Heat shock proteins
MAP kinases

Response to stress

Mitochondrial

Catenins Cadherins
AJUBA JUP CGN

Adhesion

Vesicle transport

ECM

Rab proteins DBI AP2 complex
GD1 HIP1 Clathrin
LAMC1
DMD
LMOD1 CALD1 RAC proteins
PPP1CB Sorbins Actins CDC42
Tropomyosin Myosin PAK2

DNA repair/chromatid interactors

Secreted/ECM

Transcriptional regulation

Actin cytoskeleton

Causal pathways

Compensatory pathways



GLADSTONE INSTITUTES

Answer ALS

An Individualized ALS Therapeutic Initiative

Jeffrey D. Rothstein, Director
Clive Svendsen, Co-Director
Merit Cudkowicz, Co-Director

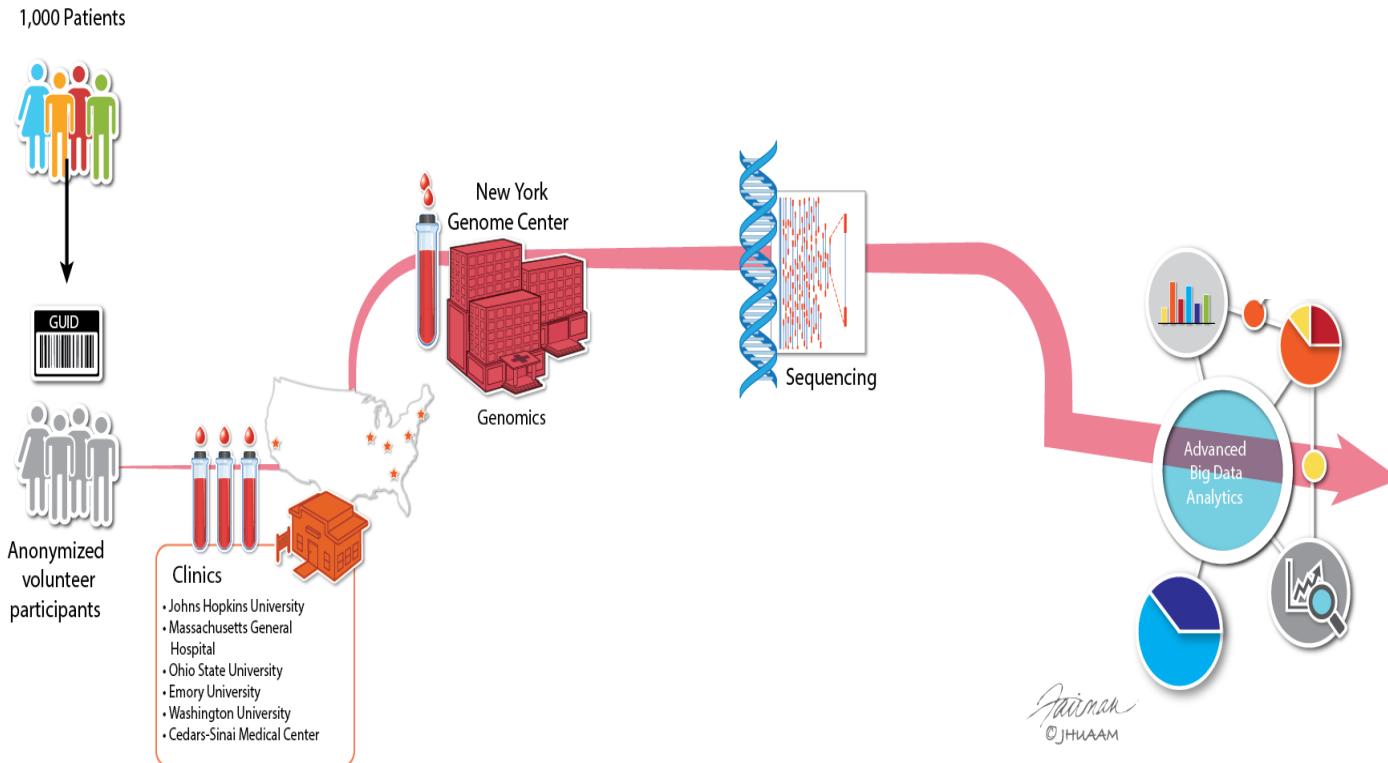
Leslie Thompson
Steve Finkbeiner
Ernest Fraenkel



alsFINDINGaCURESM

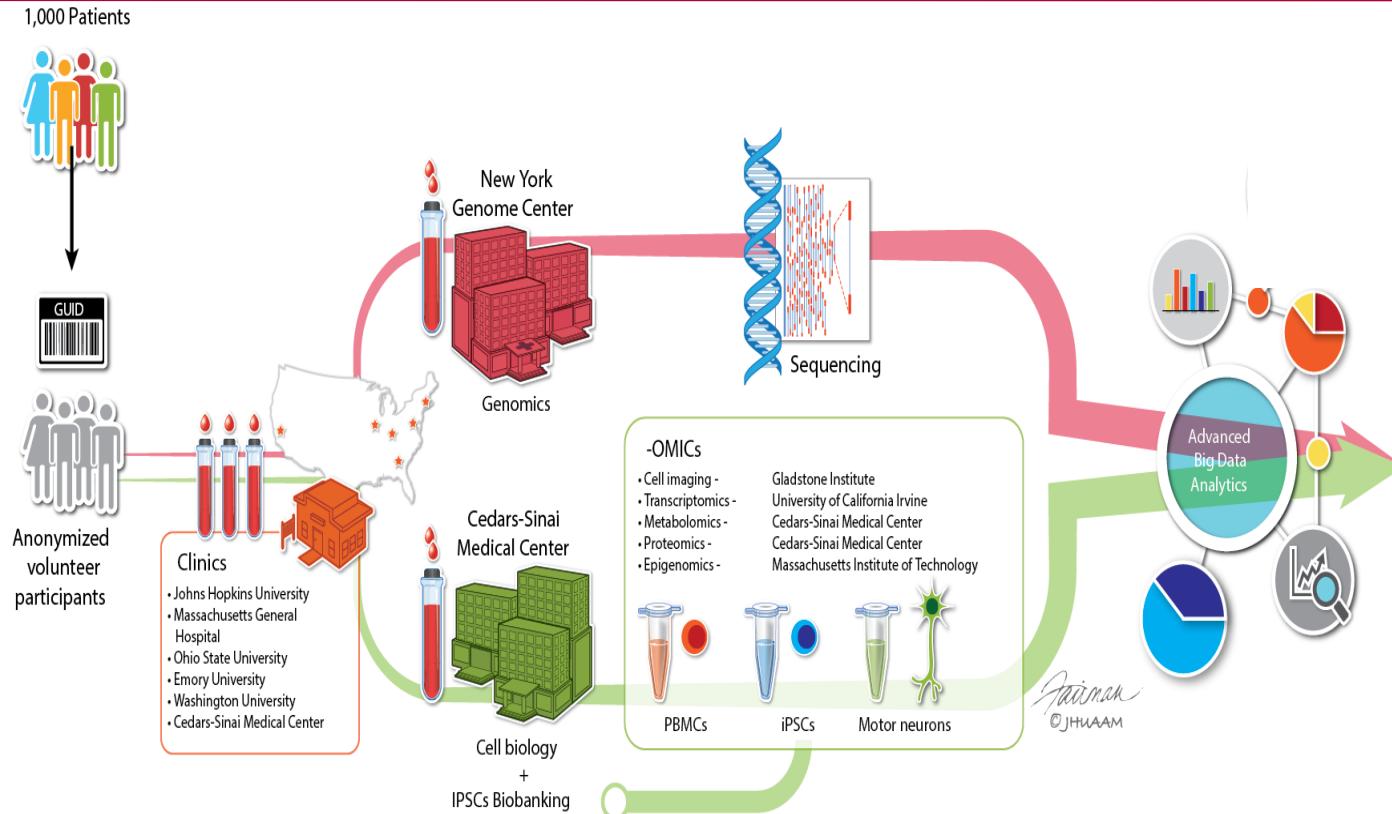


Stratifying ALS patients will lead to personalized medicines



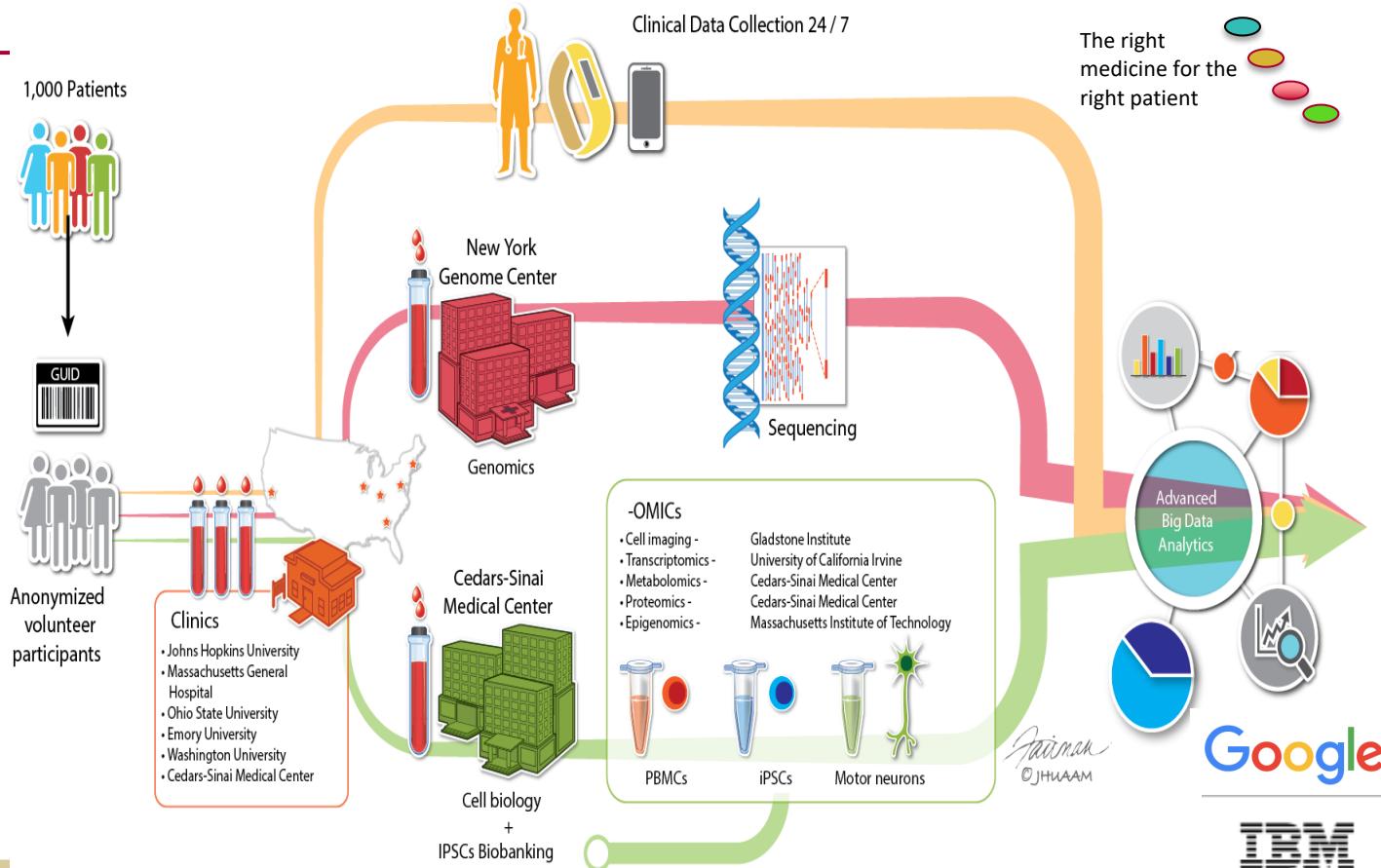
CEDARS-SINAI®

Stratifying ALS patients will lead to personalized medicines



CEDARS-SINAI®

Stratifying ALS patients will lead to personalized medicines



CEDARS-SINAI®

Answer ALS iPSC repository

Type “Cedars-Sinai iPSC core” into Google



Answer ALS Data Portal

Home

Search



als FINDING A CURE™

Answer



Answer ALS Data Portal

This data portal
is organized by:

- The Home Page takes you to the Partition and Dashboard.
- The Search bar allows you to search for specific iPSC lines.

Partition

Dashboard

This data portal
The development

Patient Sample

Condition

ALS Asymptomatic ALS Gene carrier

Sex

Male Female Unknown

Age



Age Onset



Consciousness

AnswerALS

- Fill out the Cedars-Sinai MTA Questionnaire

- Select "I am REQUESTING items from the iPSC Core" from the dropdown menu.

- Enter the cell lines you wish to request under the "Cell Lines" section.

- The iPSC Core will contact you with the next steps.



CEDARS-SINAI®

project	patient	sample	experiment	omic
aals	AALS_03B7A8	CGND-HDA-	WGS	genomics
		CS7VCZIALS		
	AALS_08FD03	CGND-HDA-	WGS	genomics
		CS2MXHIALS		
	AALS_09B455	CGND-HDA-	WGS	genomics
		CS5AFMIALS		
	AALS_0B0218	CGND-HDA-	WGS	genomics
		CS5LJ8iALS		
	AALS_0CF2F4	CGND-HDA-	WGS	genomics
		CS2UNGIALS		
	AALS_0D18B3	CGND-HDA-	WGS	genomics
		CS3AJYIALS		
	AALS_0DC376	CGND-HDA-	WGS	genomics
		CS6DKFIALS		
	AALS_0DDDB62	CGND-HDA-	WGS	genomics
		CS6ZLDiALS		
	AALS_0E60F9	CGND-HDA-	WGS	genomics
		CS2XWCIALS		
	AALS_0FBAA4	CGND-HDA-	WGS	genomics
		CS3FYFIALS		
	AALS_1209AF	CGND-HDA-	WGS	genomics
		CS4UCEIALS		
	AALS_18E5E63	CGND-HDA-	WGS	genomics
		CS2XRCIALS		

Search

Search for a specific ID...

Actions

Request to Download Data

Download All Metadata

Download Filtered Metadata

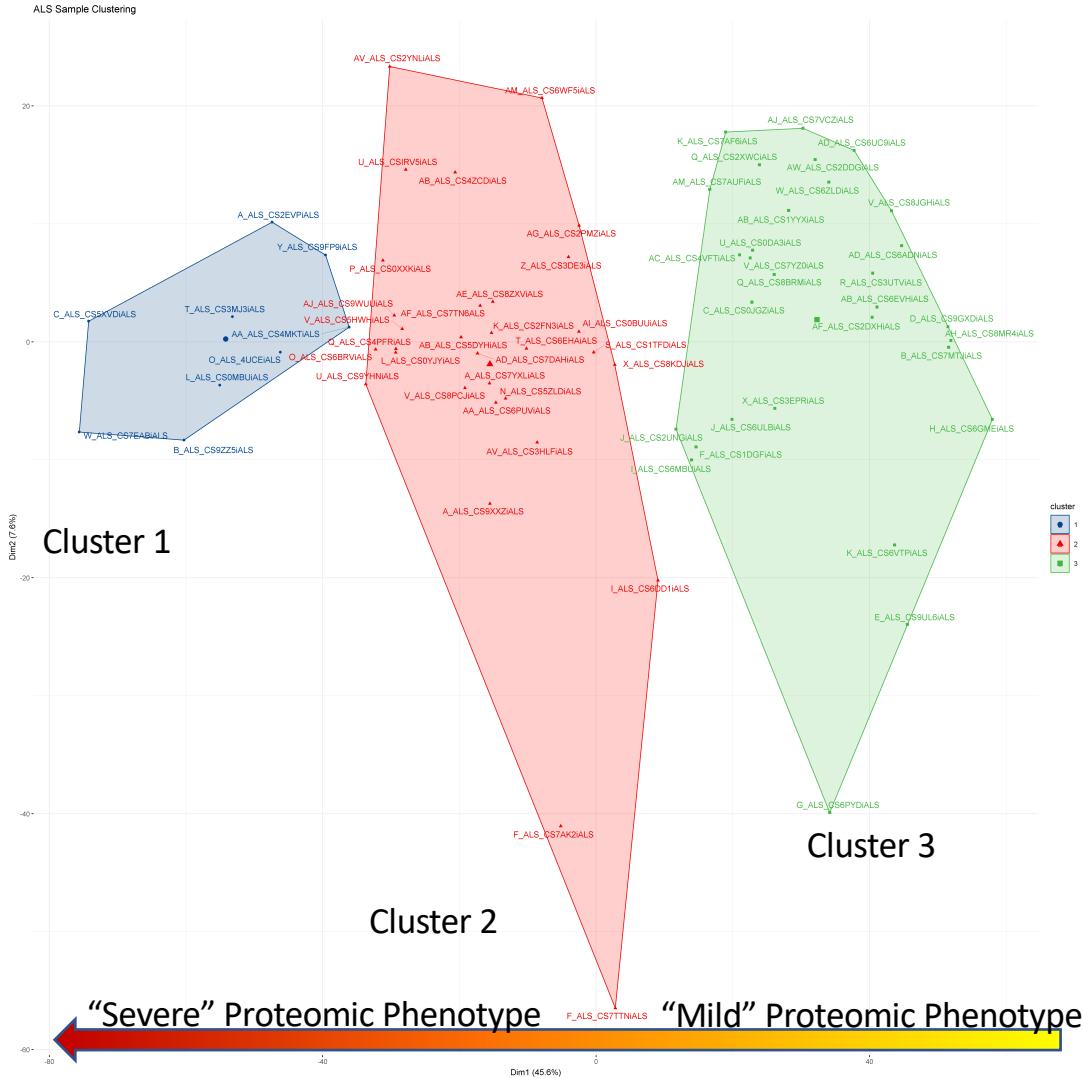
Download Filtered Data

Order Filtered iPS Cell Lines

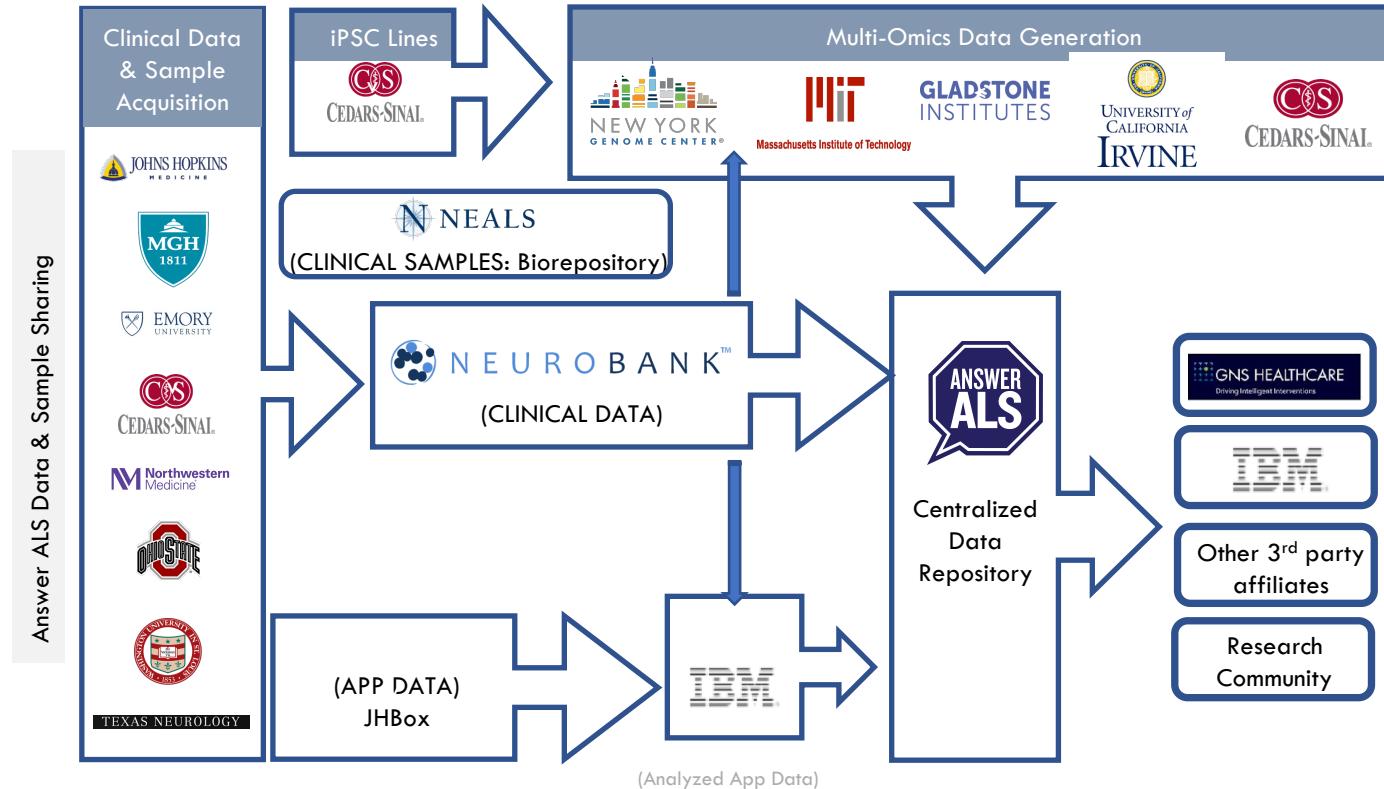
Submit Feedback About This Portal

Details

100 ALS iPSC lines
differentiated to
motor neurons:
Three clusters
identified



Answer ALS: Operational Structure





Answer ALS: Progress Highlights



- Target enrollment of **1000 participants in 3 years** met and exceeded
- **450 whole genomes** sequenced
- Development and roll-out of **genetic return of results** sub-study
- **>500 IPS cell lines** successfully initiated
- **> 400 IPS cell lines available** for request through Cedars-Sinai Core (with associated clinical data)
- >100 MN cell lines examined by **multi-omics**
 - ***3 biological subgroups identified in early proteomic analytics!***
- Custom-designed **app to monitor ALS disease progression** built and deployed
- Answer ALS **data portal** built
- First **public release of data**

NeuroLincs and Answer ALS Team and Support



Johns Hopkins Univ

Jeffrey D. Rothstein

Nick Maragakis

Emily Baxi

Betsy Mosmiller

John Krakauer

Mass General/Harvard

Merit Cudkowicz

James Berry

Alex Sherman

Cedars-Sinai

Clive Svendsen

Dhruv Sareen

Bob Baloh

Jenny Van Eyke

MIT

Ernest Fraenkel

UC Irvine

Leslie Thompson

Terri Thompson

Gladstone/UCSF

Steve Finkbeiner

Emory

Jon Glass

Stanford

Karen Sachs

Washington Univ

Tim Miller

Ohio State

Steve Kolb

Northwestern Univ

Senda Ajroud-Driss

Texas Neurology

Daragh Heitzman

Core Collaborators

Lucie Bruijn- ALSA

Hemali Phantami- NY Genome

IBM Watson

Marg Sutherland- NINDS/NIH

MDA

Project Managers &

Technical staff

> 50



FISHMAN
FAMILY



Les Turner ALS Center



Existing Neurodegeneration Focused Consortia

- PPMI – Parkinson’s Progression Markers Initiative
- FOUNDIN-PD – Foundational Data Initiative for PD
- IPDGC – International Parkinson’s Disease Genomics Consortium
- NDC – The Neurodegeneration Consortium
- Answer ALS <https://www.answerals.org>
- NeuroLINCS (NINDS) <http://neurolinacs.org>
- NeuroNext <https://neuronext.org/>
- LINCS (NIH Common Fund) <http://www.lincsproject.org>
- AMP (Accelerating Medicines Partnership NIH) <https://www.nih.gov/research-training/accelerating-medicines-partnership-amp>
- ADNI (Alzheimer’s Disease Neuroimaging Initiative) <http://adni.loni.usc.edu>
- ENIGMA (human brain mapping and genetics) <http://enigma.ini.usc.edu>
- The Brain Initiative (NIH) <https://www.braininitiative.nih.gov>
- FOS – Current Friends of Stacie, Alzheimer’s focus

