



TRAN & Clinical Neuro Portfolio Update

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- CIRM Neurology Classification Glossary
- Current CIRM TRAN & Clinical Neurology Portfolio
- CIRM Neurology Awards - Progression Events
- Neurology Landscape Clinical Highlights:
 - Approved Neurology Cell & Gene Therapies
 - Neurology Drugs - Pending FDA Decisions
 - Neurology Clinical trials shaping medicine in 2023
- CIRM Key Findings

❖ **Neurodegenerative disorders,**

Alzheimer's disease (AD) and other dementias.
Parkinson's disease (PD) and PD-related disorders.
Prion disease.
Motor neuron diseases (MND)
Huntington's disease (HD)
Spinocerebellar ataxia (SCA)
Spinal muscular atrophy (SMA).



❖ **Neuropsychiatric disorders**

Schizophrenia spectrum and other psychotic disorders
Bipolar and related disorders
Depressive disorders
Anxiety disorder
Trauma- and stressor-related disorders
Dissociative disorders
Somatic symptom and related disorders
Feeding and eating disorders
Sleep–wake disorders
Sexual dysfunctions
Substance-related and addictive disorders

- ❖ **Neurodevelopmental disorders** such as (as per DSM-5): Intellectual disability disorders, communication disorders, Autism Spectrum Disorders (see DSM-5 definition), (Aspergers, childhood disintegrative disorders, and pervasive developmental disorder not otherwise specified (PDD-NOS), ADHD, motor disorders (encompasses developmental coordination disorder, stereotypic movement disorder, and the tic disorders including Tourette syndrome)
- ❖ **Vascular disorders**, stroke, transient ischemic attack (TIA), subarachnoid hemorrhage, subdural hemorrhage and hematoma, and extradural hemorrhage
- ❖ **Traumatic brain injuries**, to include the neurodegenerative condition chronic traumatic encephalopathy, or CTE.
- ❖ **Some diseases of the eye**, those that affect the retina and optic nerve.
- ❖ **Diseases that affect other sensory inputs**, such as hearing loss, provided that the primary defect affects CNS and not somatic tissues.
- ❖ **Structural disorders**, such as brain or spinal cord injury, Bell's palsy, cervical spondylosis, carpal tunnel syndrome, brain or spinal cord tumors, peripheral neuropathy, and Guillain-Barré syndrome
- ❖ **Functional disorders**, such as headache, epilepsy, dizziness, and neuralgia
- ❖ Cancers that affect the brain and central nervous system
- ❖ "Diseases of the Brain and CNS" as listed in the CIRM coding system (*)



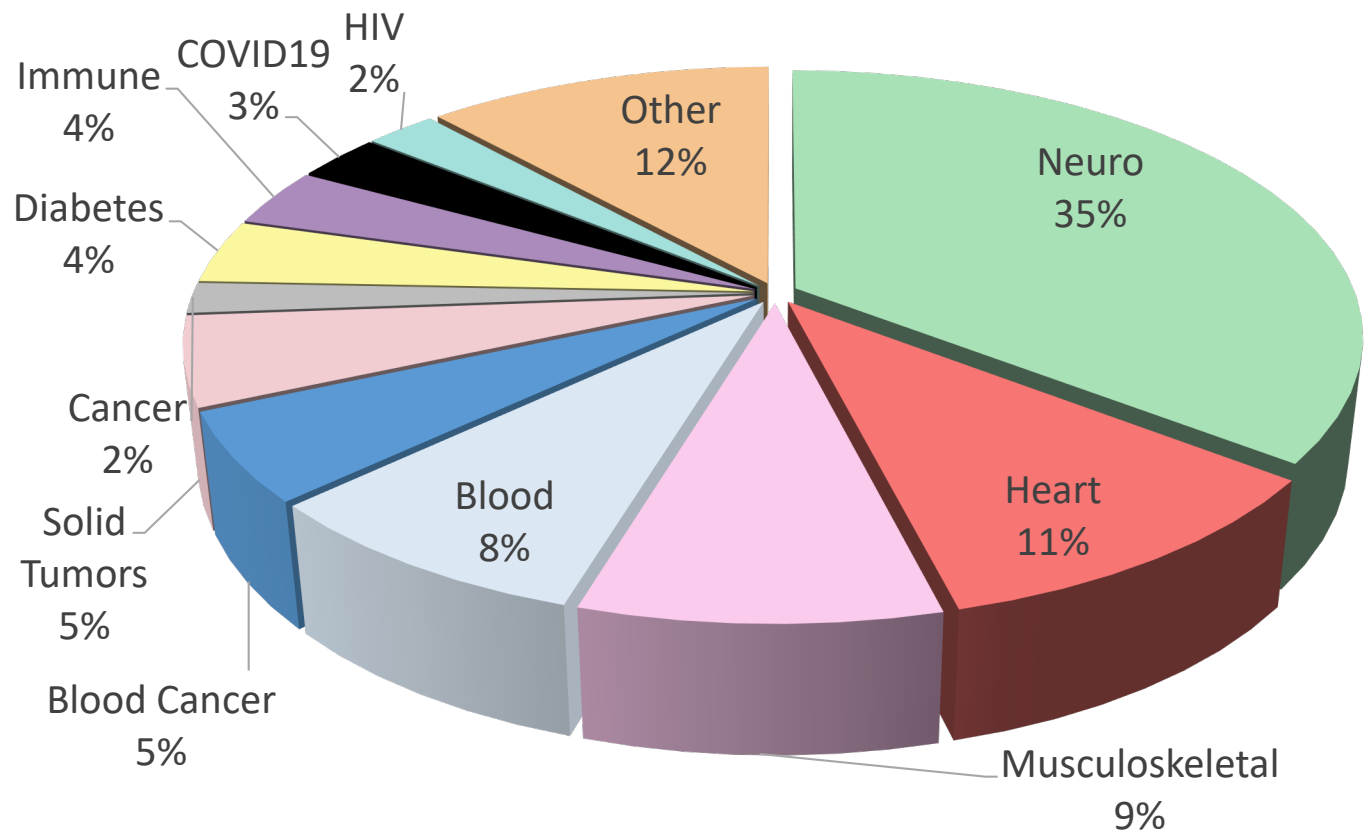
(*) This list includes ALS, Dementia, Alzheimer's, Parkinson's, Huntington's, chronic and acute and chronic stroke, spinal cord injury, autism, mental disorders, multiple sclerosis, neuropathy, Rett's syndrome and SMA

Current Translational and Clinical Portfolio Phases

Pre-IND Meeting Prep	IND-Enabling	Early Clinical	Mid-Clinical	Pivotal-Late Clinical
35.5%	11.2%	34.6%	13.1%	5.6%

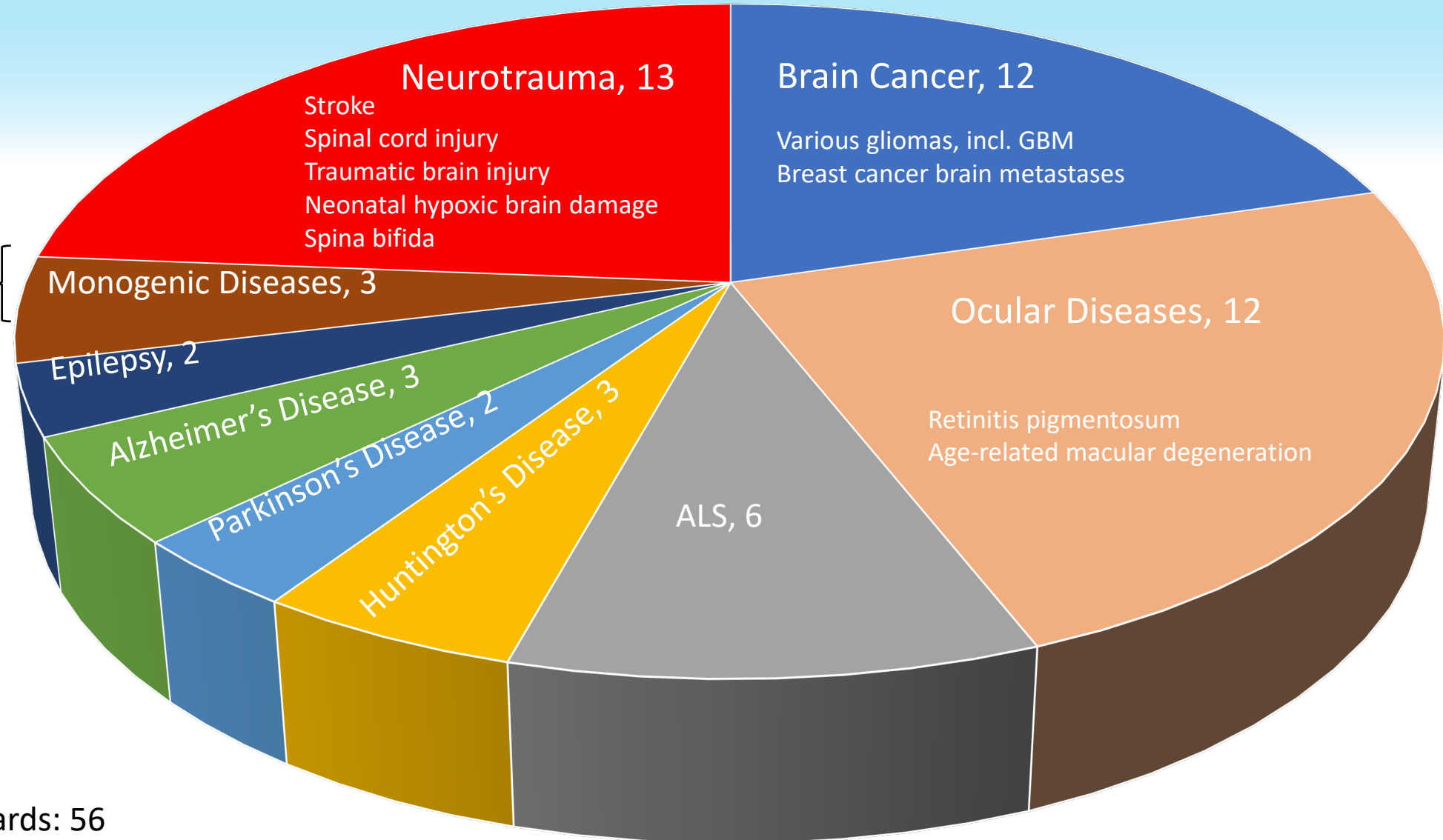
81.3% of our current portfolio = de-risking projects

As of September 2022.
% Total R&D awards



All TRAN and CLIN stage awards, neurology

Tay-Sachs disease
Canavan's disease
Friedreich's ataxia



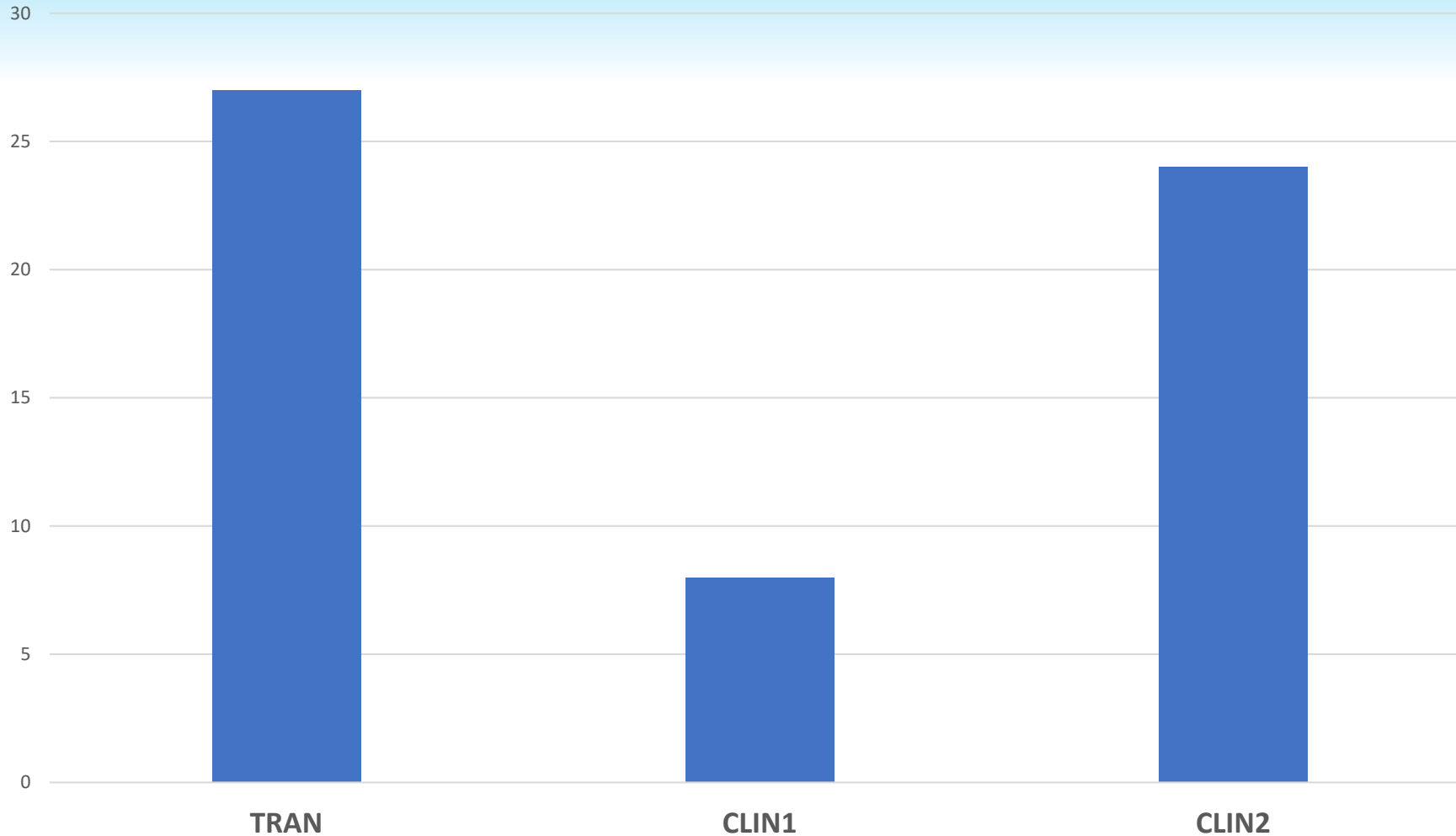
Total awards: 56

Number of Projects

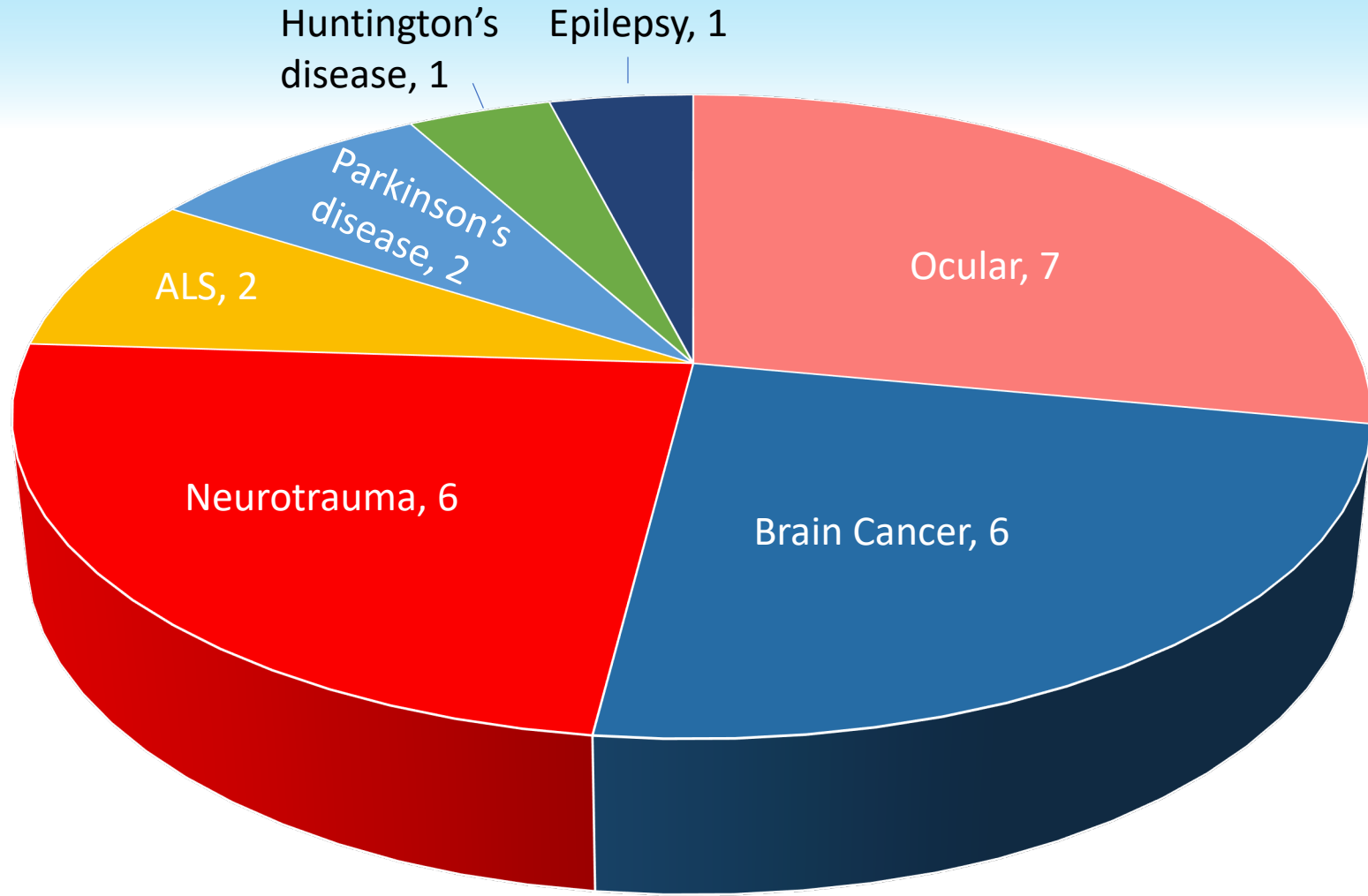
All (active or closed) TRAN, CLIN1, CLIN2 and equivalent awards as of January 2023

Neurology Awards by Stage

Number of neuro awards (active and closed)



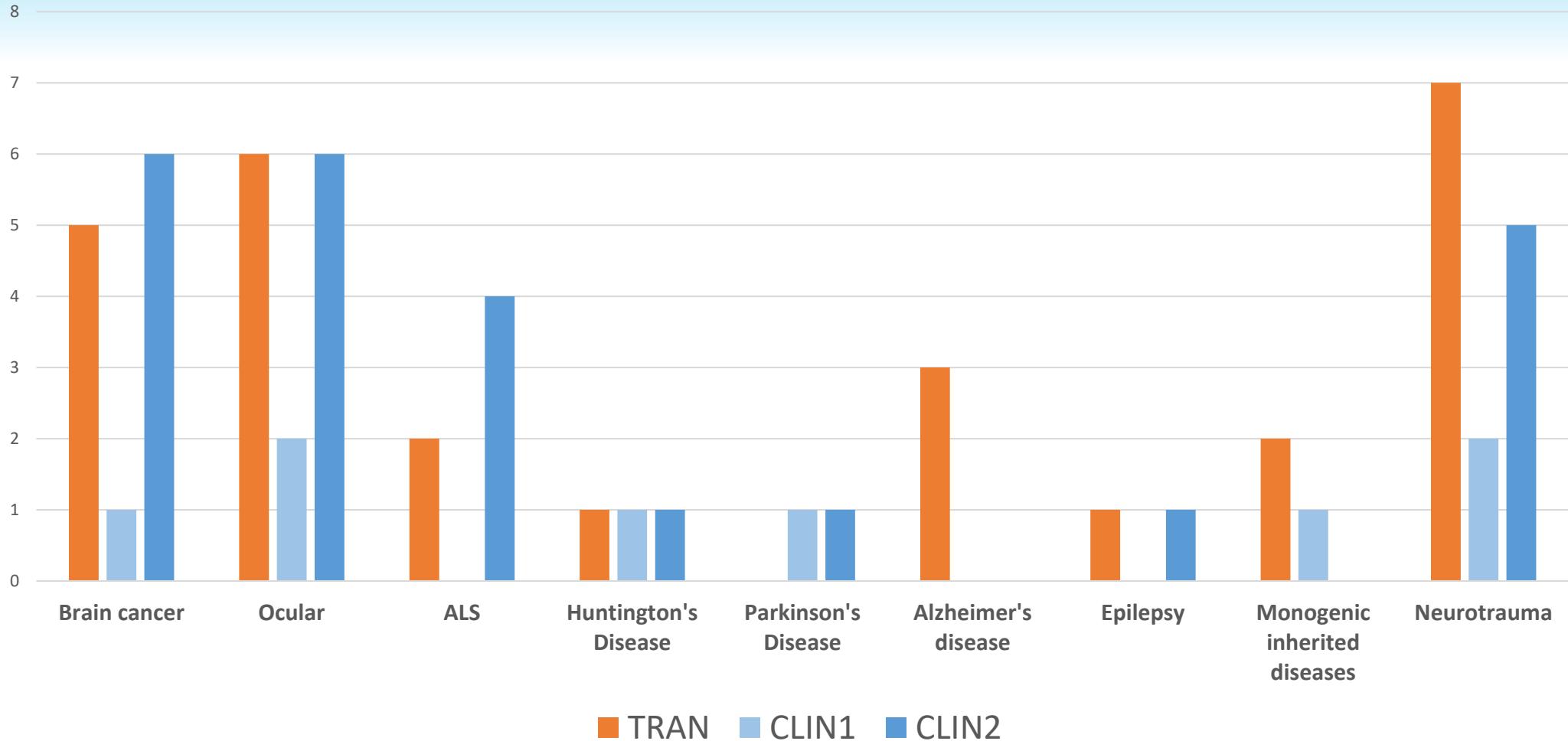
Active and Closed TRAN, CLIN1, CLIN2 and equivalent awards as of January 2023



Total awards: 25

Number of Projects

Number of Awards



Disease Areas	Investigator	Organization	Trial Status	Target Enrollment	Alpha Clinics
ALS	Clive Svendsen	Cedars-Sinai Medical Center	Recruiting	16	
Parkinson's Disease	Krystof Bankiewicz	Brain Neurotherapy Bio	Recruiting	12	
Spina bifida	Diana Farmer	University of California, Davis	Recruiting	35	UC Davis
GBM	Christine Brown	City of Hope, Beckman Research Institute	Active, not recruiting	82	COH
High grade glioma	Jana Portnow	City of Hope, Beckman Research Institute	Launching	36	
Breast cancer brain metastases	Saul Priceman	City of Hope, Beckman Research Institute	Recruiting	39	COH
Pediatric glioma	Leo Wang	City of Hope, Beckman Research Institute	Recruiting	18	COH
Diffuse gliomas	Crystal Mackall	Stanford University	Recruiting	54	
Stroke	Gary Steinberg	Stanford University	Recruiting	30	
Epilepsy	Cory Nicholas	Neurona Therapeutics	Recruiting	40	

Disease Areas	Investigator	Organization	Trial Status	Target Enrollment	Alpha Clinics
Retinitis pigmentosum	Clive Svendsen	Cedars-Sinai Medical Center	Recruiting	16	

Disease Areas	Investigator	Organization	Trial Status	Target Enrollment	Alpha Clinics
Ophthalmology	Henry Klassen	jCyte, Inc	Complete Closed	84	UCI
Ophthalmology	Henry Klassen	jCyte, Inc	Complete Closed	35	UCI

Disease Areas	Investigator	Organization	Trial Status	Target Enrollment	Alpha Clinics
Neurobiology	Ralph Kern	BrainStorm Cell Therapeutics	Complete Closed	263	UCI

PI	Institution	Indication	DISC	TRAN	CLIN1	CLIN2	CLIN2
Gary Steinberg	Stanford	Stroke					
Leslie Thompson	UC Irvine	Huntington's Disease					
Kris Bankiewicz	UCSF	Parkinson's Disease					
Diana Farmer	UC Davis	Spina bifida					
Clive Svendsen	Cedars-Sinai	ALS					
Henry Klassen	Jcyte	Retinitis pigmentosum					
Christine Brown	City of Hope	GBM					
Saul Priceman	City of Hope	Breast cancer brain mets					
Clive Svendsen	Cedars-Sinai	Retinitis pigmentosum					
Cory Nicholas	Neurona	Epilepsy					

* Grants that progressed from either Discovery, TRAN, or CLIN1 to Clinical Trials

- **Luxturna** for Leber congenital amaurosis (retinal disease), 2017
- **Zolgensma**- Spinal Muscular Atrophy , 2019
- **Libmeldy** (ex vivo HASPC gene Therapy) for Metachromatic Leukodystrophy , 2020*
- **Upstaza** for aromatic L-Amino Acid decarboxylase (AADC) Deficiency, 2022

* Approved in EU; US BLA filing planned 2023

5 Pending FDA Decisions in Neurology for 2023

Drug	Indication & Status
Friedreich Ataxia: Omaveloxolone (Reata Pharmaceuticals)	An oral, once-daily activator of molecular pathways that promote resolution of inflammation; potential approval data of February 28, 2023; first treatment for Friedreich ataxia (FA), a rare degenerative neuromuscular disorder.
Rett syndrome: Trofinetide (Acadia Pharmaceuticals)	A novel synthetic analog of the amino-terminal tripeptide of IGF-1 designed to potentially reduce neuroinflammation and supporting synaptic function. If approved by FDA on March 12, 2023, it will become the first approved therapy for Rett syndrome, a rare genetic disorder of brain development
SOD1 ALS: Tofersen (Biogen)	An antisense agent in development for the treatment of SOD1 amyotrophic lateral sclerosis (ALS), currently has a PDUFA date of April 25, 2023, could be the first targeted therapy for SOD1-mediated ALS.
Parkinson disease: IPX203 (Amneal Pharmaceuticals)	A novel, oral formulation of carbidopa/levodopa (CD/LD) extended-release capsules intended to treat patients with Parkinson disease (PD). Expected approval June 30, 2023.
Cervical dystonia: DaxibotulinumtoxinA (Revance Therapeutics)	Novel botulinum toxin type A formulation for cervical dystonia. PDUFA date, August 19, 2023; promising results from two separate trials as the basis for the agent's new biologics license application (s BLA).

Table 1 | Clinical trials to watch in 2023

Treatment	Organization	Description	Phase	Lead indication
Exenatide	University College London	Neuroprotective effect of exenatide, used to treat type 2 diabetes, over a 2-year follow-up period	3	Parkinson's disease
Diet and exercise	European Research Council	Long-term effect of a weight-loss intervention based on a reduced-calorie Mediterranean diet, physical activity and behavioral support	3	Obesity and metabolic syndrome
Lecanemab	Eisai/Biogen	Monoclonal antibody to amyloid-β, for the treatment of mild cognitive impairment with Alzheimer's disease	3	Alzheimer's disease
mRNA-1273 and bivalent vaccine	South Africa Medical Research Council	Efficacy of vaccines against COVID-19 in people with HIV	3	COVID-19
Mirvetuximab soravtansine	Immunogen	ADC that targets tumors with high expression of folate receptor-α	3	Recurrent platinum-resistant ovarian cancer
Fexinidazole	Drugs for Neglected Diseases	Efficacy of the oral drug fexinidazole for <i>rhodesiense</i> sleeping sickness versus that of the existing drugs melarsoprol and suramine	2/3	Stage 2 <i>T. brucei rhodesiense</i> infection
CTX001	CRISPR Therapeutics and Vertex Pharmaceuticals	Autologous CRISPR-Cas9-modified CD34 ⁺ human hematopoietic stem and progenitor cells	1/2/3	Sickle-cell disease
GenPHSat	Charité-Universitätsmedizin Berlin	Base editing to repair a mutation in muscle stem cells, to rebuild muscle	1/2	Muscular dystrophy
Digoxin	ETH Zurich	Dissociation of CTC clusters	1	Metastatic breast cancer
PSA, kallikrein panel, MRI, and prostate biopsy	Tampere University	A new screening approach that reduces harm from PSA screening while maintaining mortality reduction	Population-based randomized trial	Prostate cancer
HPV DNA testing and liquid-based cytology	Australian Centre for the Prevention of Cervical Cancer	HPV testing versus Pap smears to detect early-stage cervical cancer	Population-based randomized trial	Cervical cancer

← Neuro

← Neuro – accelerated approval on Jan 6

MRI, magnetic resonance imaging.

- Neuro composes about 35% of the Translation and Clinical portfolio
- All Active Neuro Trials (11/11) are in Phase 1- early clinical development
- Several are in rare diseases consistent with the field