

# ALS/MND Alliance Meeting 2010

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CEO and CSO

ALS Therapy Development Institute

# ALS-TDI: A Non Profit Biotech

- History

- Founded 1999 by Heywoods
- Annual budget of ~\$10 million
- 48 employees
- 30 full time scientists
- 4.0 charity rating by Charity Navigator

- Mission

- Bridge the gap of ALS therapeutic development and facilitate the clinical development and commercialization of therapeutics for ALS patients

- Combines power of a 501(3)c non-profit with the best practices of a for-profit biotech or pharmaceutical company

# Fund Raising Objectives

- Growth plan of 20% annually
- Drivers
  - Events
  - Major Donors
  - Philanthropic Foundations
  - DOD
  - NIH
  - Corporate sponsorship
  - Pharmaceutical partnerships
  - For profit business model

# young faces of {ALS}

## 2010 Location

Oakland

San Francisco

San Diego

Texas Rangers

Chicago White Sox

Braves

Brewers

Seattle

LA Dodgers

LA Angels

Cardinals

Indians

Blue Jays



# Leadership Summit Recap



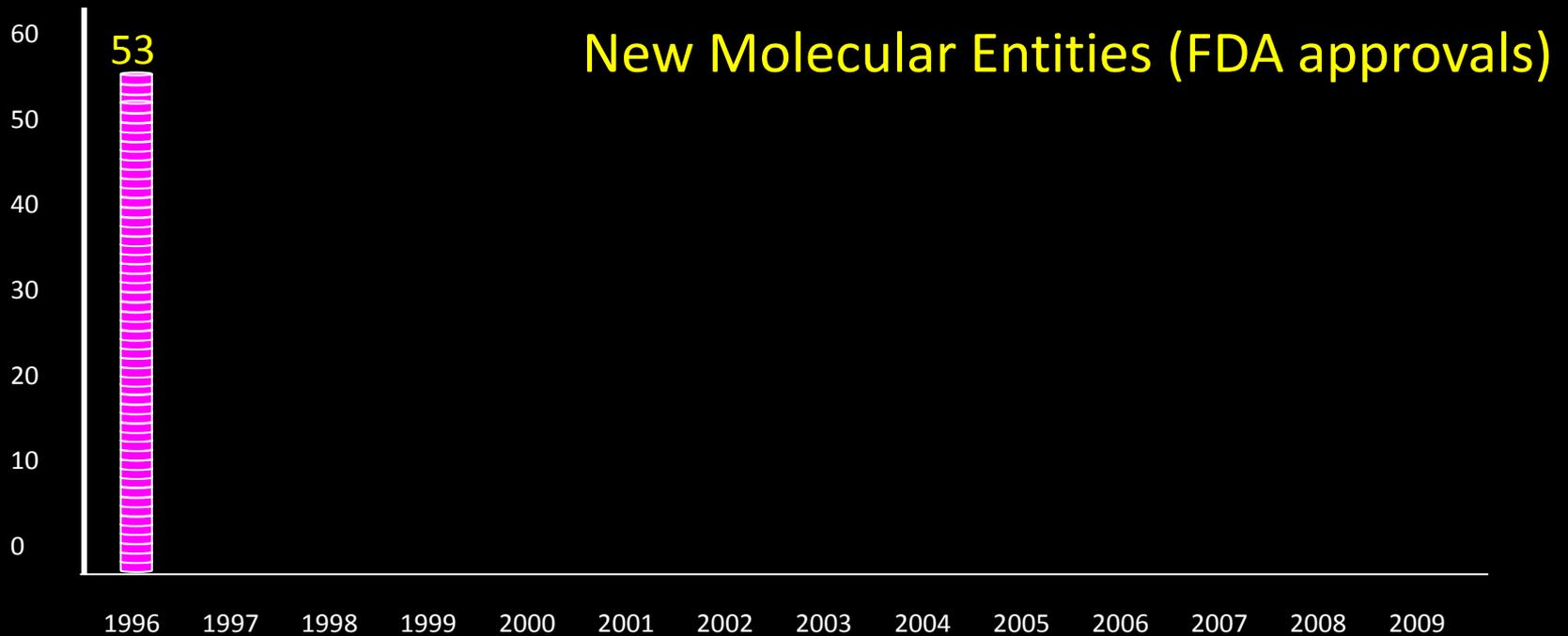
- 100 people in room, another 50 online
- Attendance shifted dramatically, to include more academics, researchers and industry people.
- Several new families attended summit and toured lab. (several donations afterward)



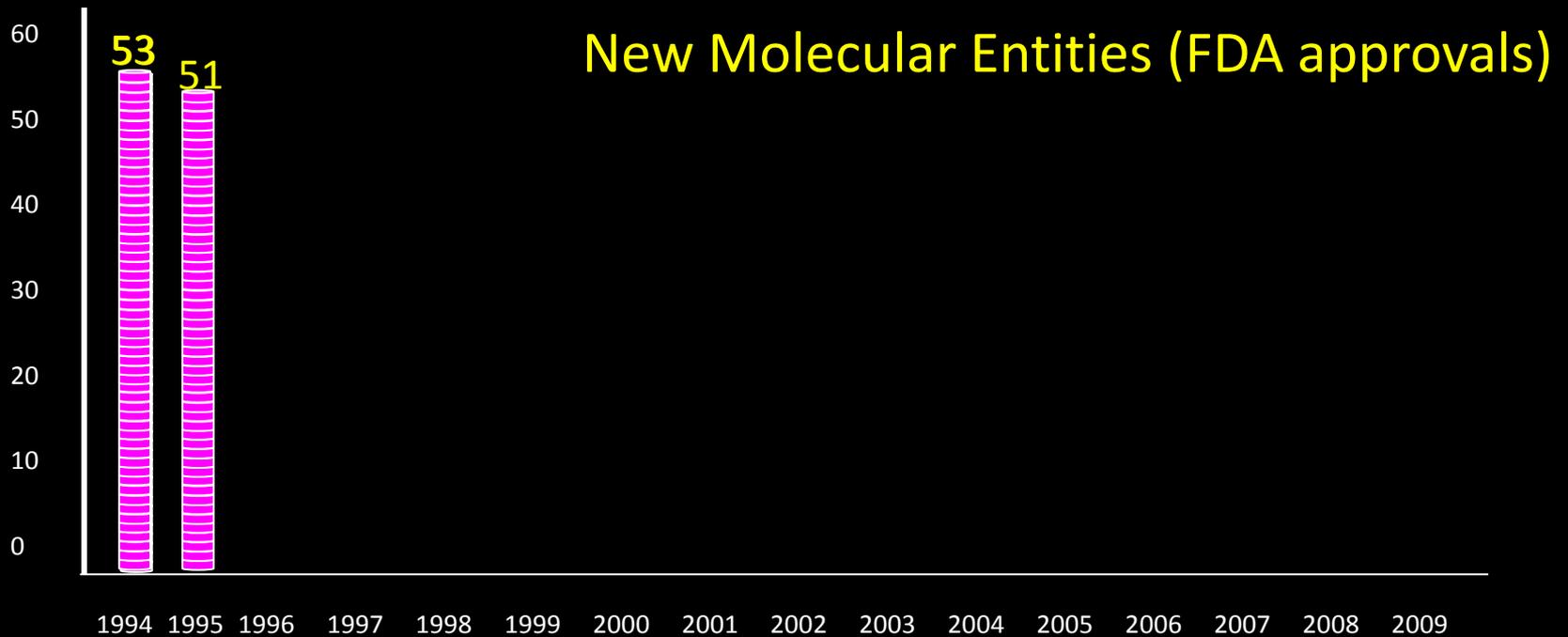
# Poor Productivity Has Created “A Gap” In the Clinical Development Process

- Non Profits & Foundations are Poised to Fill the Gap
- Limited discovery research is being performed in biotech and pharmaceutical organizations to close this gap.
  - Pharmaceutical pipelines are poorly resourced
  - R&D budgets are strapped and discovery is being down sized
- Most academic laboratories have excellent expertise in a selected discipline
  - Target discovery and therapeutic development requires inter disciplinary teams
- Lack of well validated targets for therapeutic development in neurodegenerative disorders and ALS in particular.

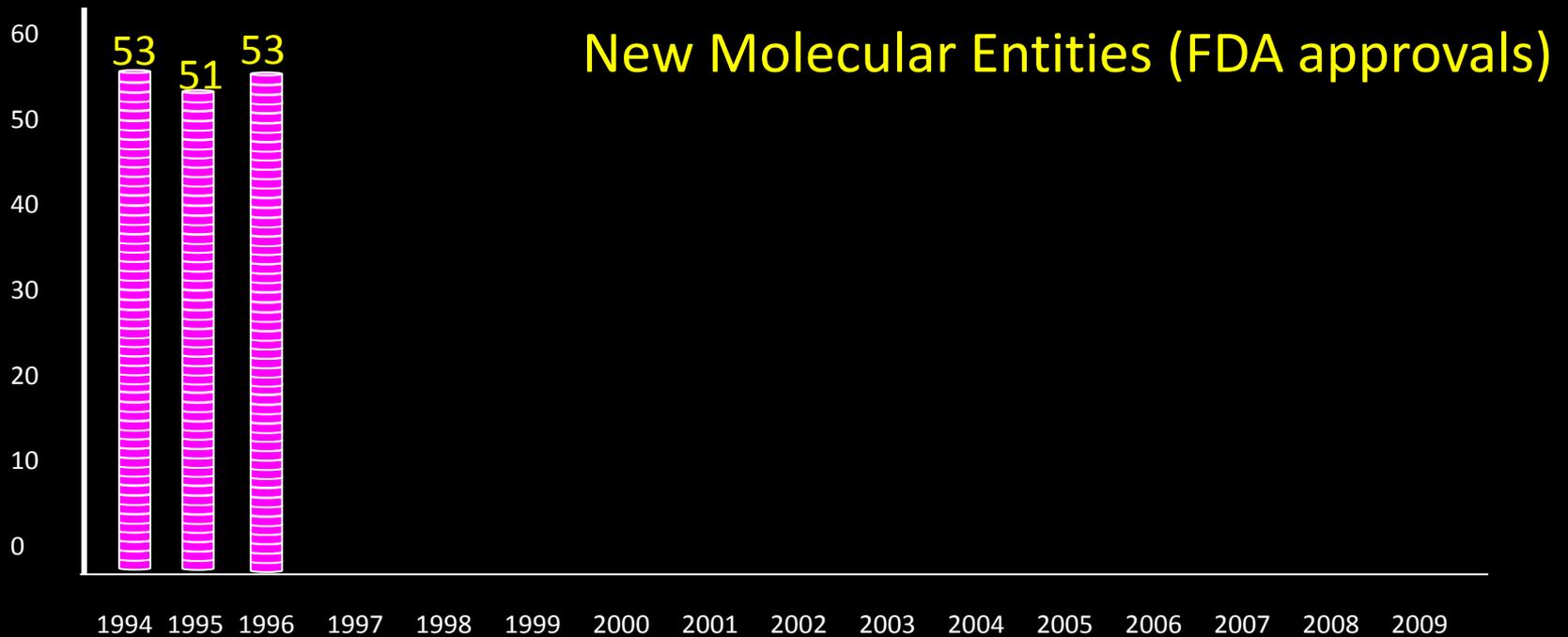
# New Era of Drug Development.....?

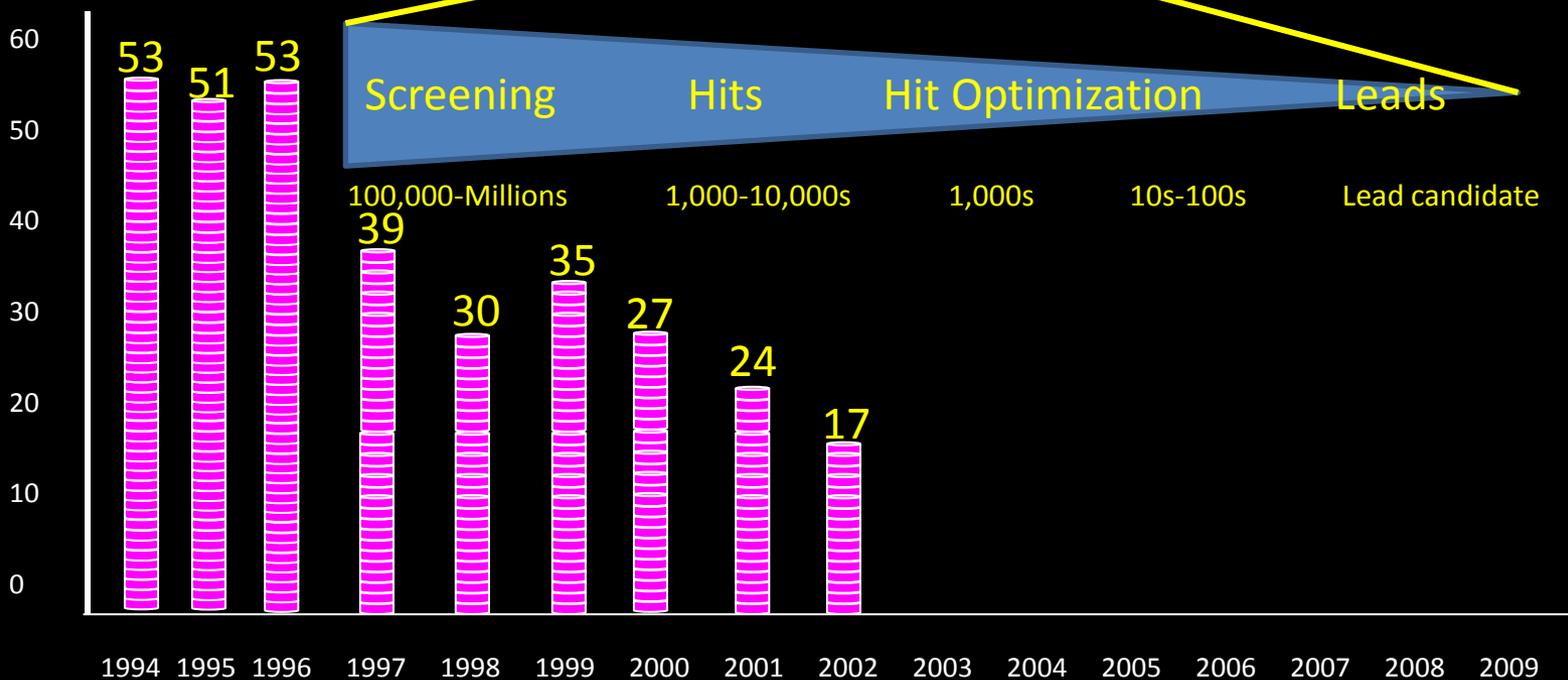
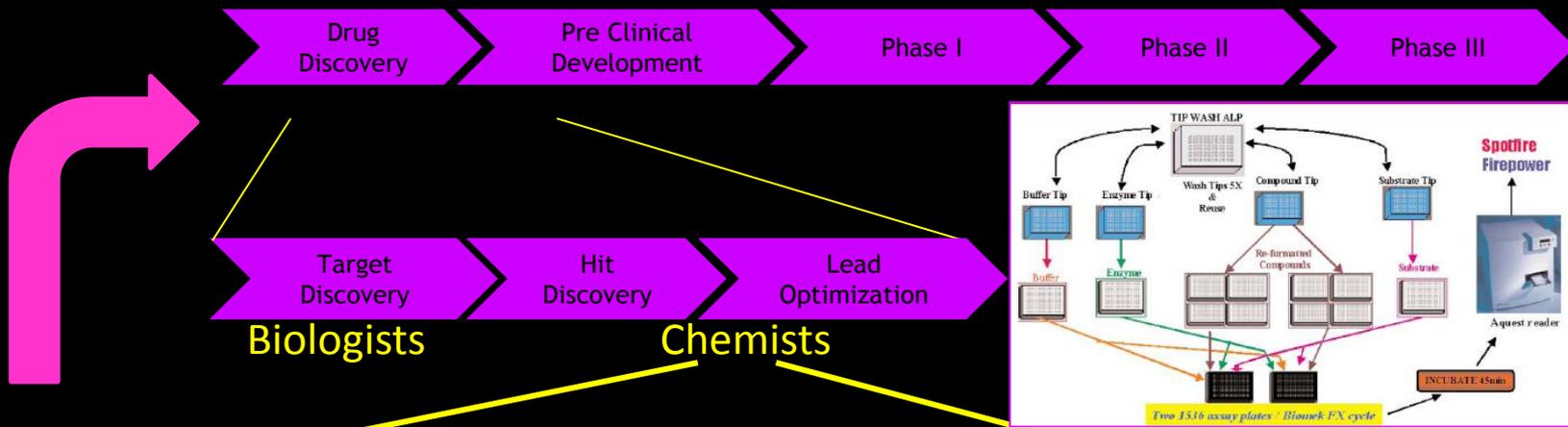


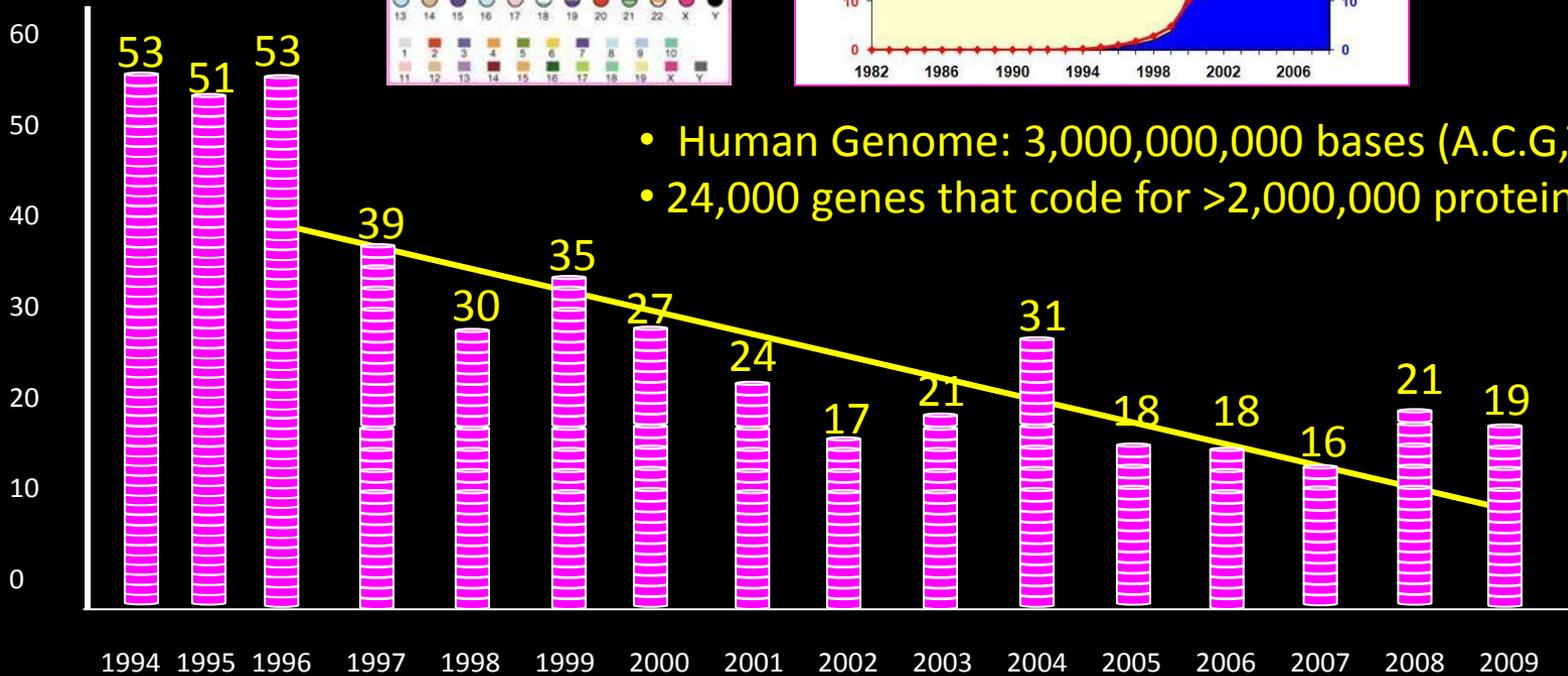
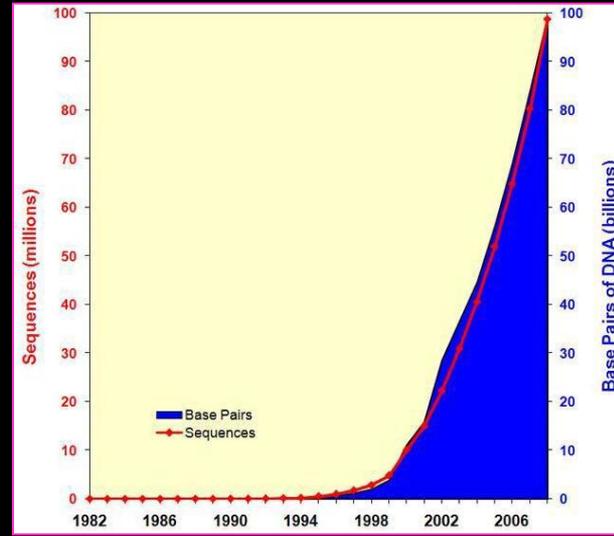
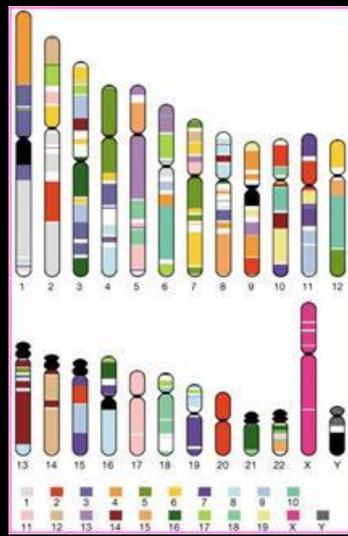
# New Era of Drug Development.....?



# New Era of Drug Development.....?







- Human Genome: 3,000,000,000 bases (A.C.G,T)
- 24,000 genes that code for >2,000,000 proteins

- 1977: 1.5 Kbbp/person/year
- 1998: 20 Mb bp/person/year
- 2008: 150 Gbbp/person/year
- 2010: 2.000 Gbbp/person/year

# R&D Productivity Model

	Target ID	Hit	Lead Optimization	Preclinical Validation	Phase I	Phase II	Phase III	Submission Launch
P(TS)	80%	75%	85%	69%	54%	34%	70%	91%
WIP per Launch	24.3	19.4	14.6	12.4	8.6	4.6	1.6	1.1
Cost per WIP per Phase	\$1	\$2.5	\$10	\$5	\$15	\$40	\$150	\$40
Cycle Time (Years)	1.0	1.5	2.0	1.0	1.5	2.5	2.5	1.5
% Total Cost per NME	3%	6%	17%	7%	15%	21%	27%	5%
Cost per Launch	\$94	\$166	\$414	\$150	\$273	\$319	\$314	\$48

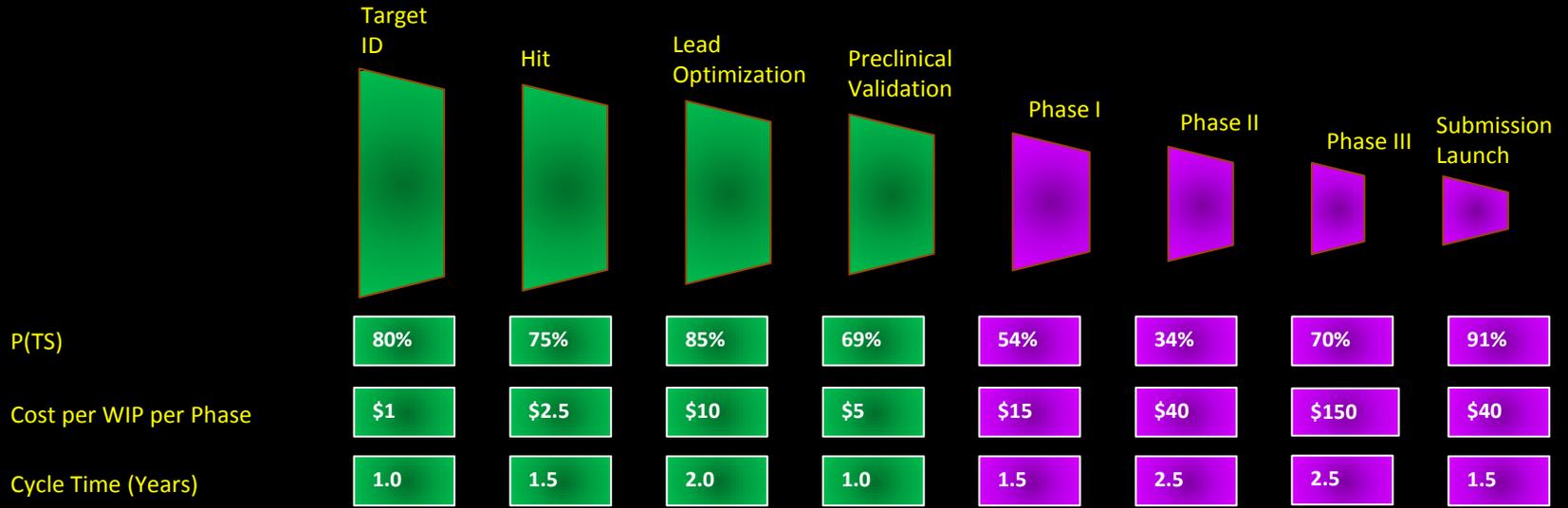
Preclinical Cost per NME  
 Average: \$18.5M  
 Capitalized: \$824M  
 Cycle time: 5.5 years

Clinical Cost per NME  
 Average: \$245M  
 Capitalized: \$954M  
 Cycle time: 8 years

$$\text{R\&D Productivity} = \frac{\text{P(TS)} \times \text{WIP} \times \text{V}}{\text{CT} \times \text{C}}$$

- P(TS) : probability of technical success
- WIP : work in progress
- V : value
- CT : cycle time
- C : cost

# R&D Productivity Model



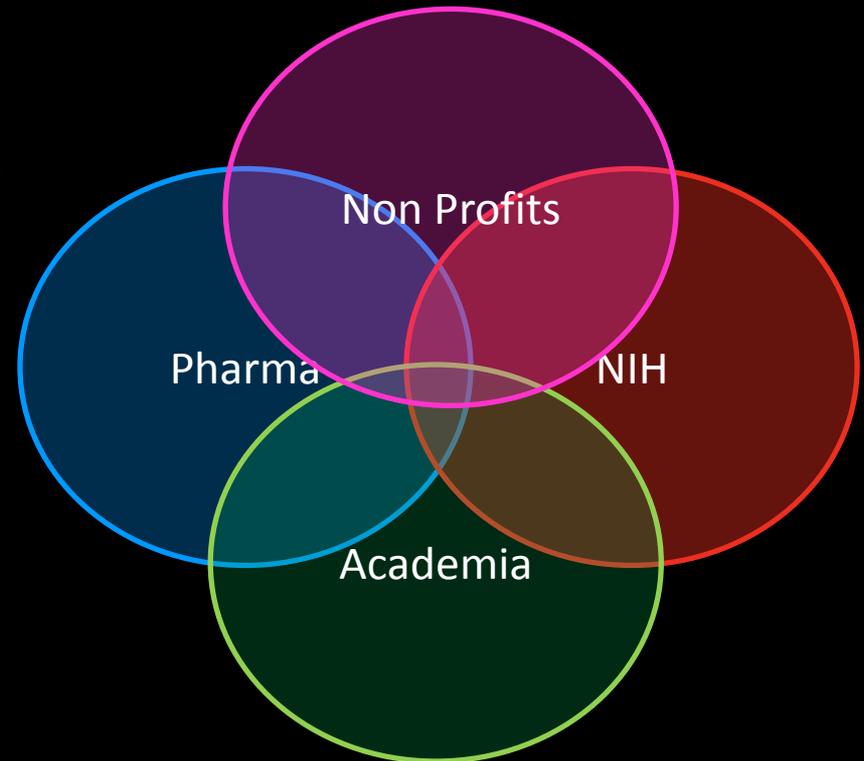
# New R&D Productivity Model Innovation & Efficiency



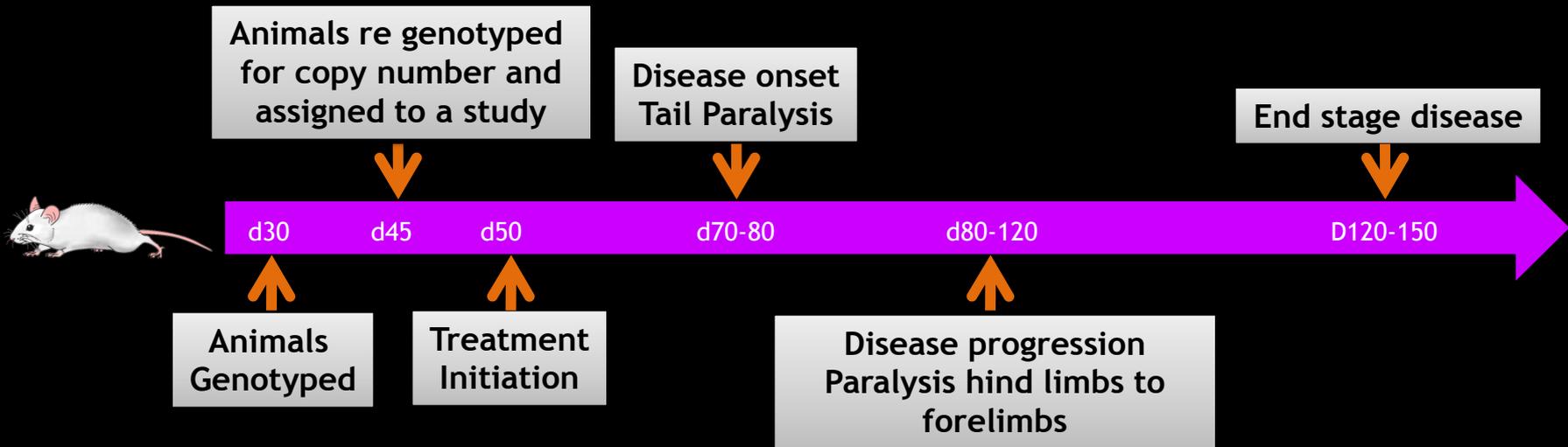
# New Era of Drug Development.....!



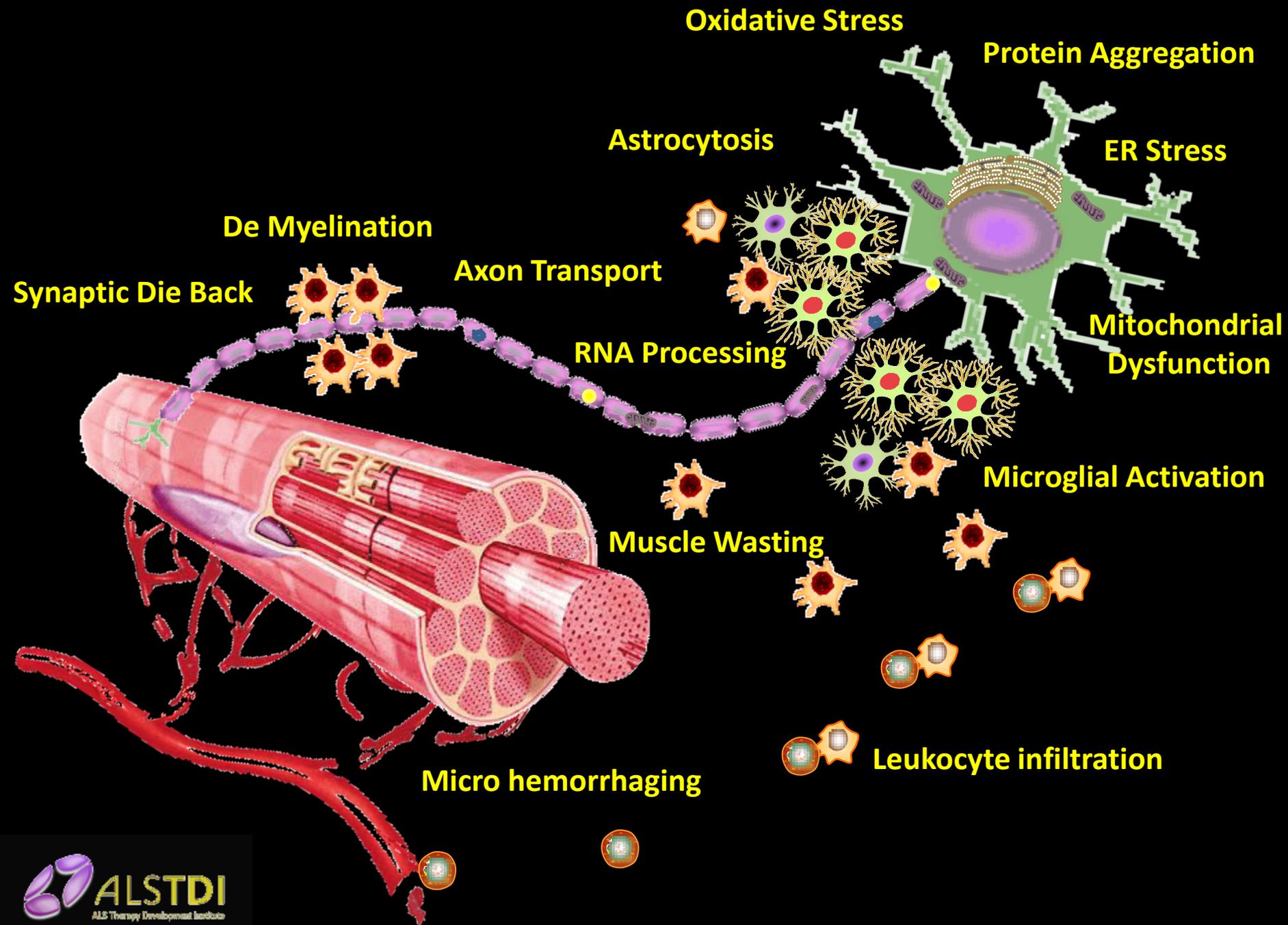
## • Role of the Non Profits ....



# Study Design: *Whole Genome Expression Profiling SOD1 Mice*



- 5 non transgenics, 5 SOD1<sup>G93A</sup> and 5 wtSOD1 transgenic animals per group
- Groups harvested at 10 day intervals starting at day 50
- Tissues extracted and flash frozen on dry ice
- Brain, spinal cord, skeletal muscle, brown fat, white fat, sciatic nerve, blood
- Laser captured motor neurons and surrounding tissue
- Profiled on Affymetrix MOE430vII gene chips and Affymetrix Ex1.0 exon arrays

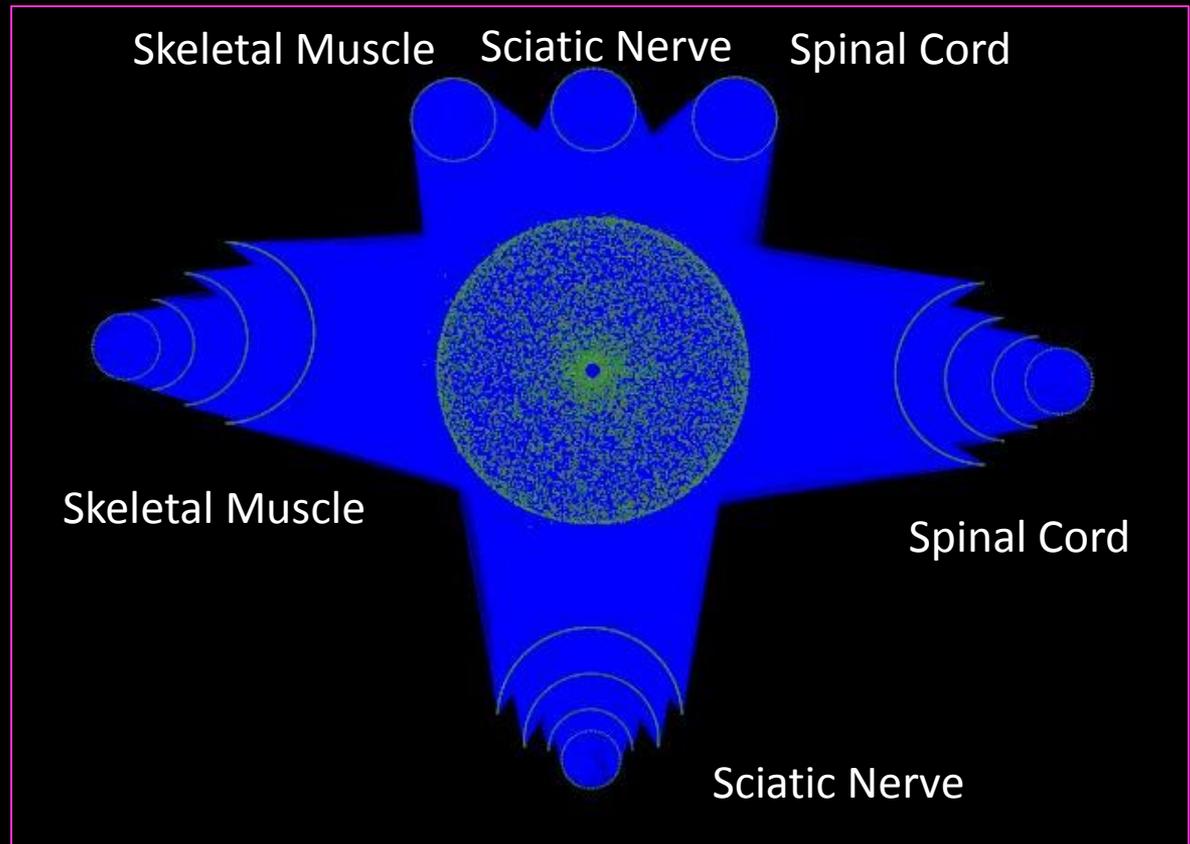


# SOD1<sup>G93A</sup> Tissue Interactome

- 3 Tissues:
  - muscle
  - spinal cord
  - sciatic nerve
- 8 time points:
  - days 30, 50, 60
  - 80, 90, 100, 110, 120
- 45,000 genes
  - Affy: MOE430vII
- SOM Clustering of TxP
  - 100 clusters per tissue
- 498 biological pathways
  - kegg, biocarta
- Drug bank interactions
  - 10,500 drugs
- 22,830 nodes
- 52,857 interactions

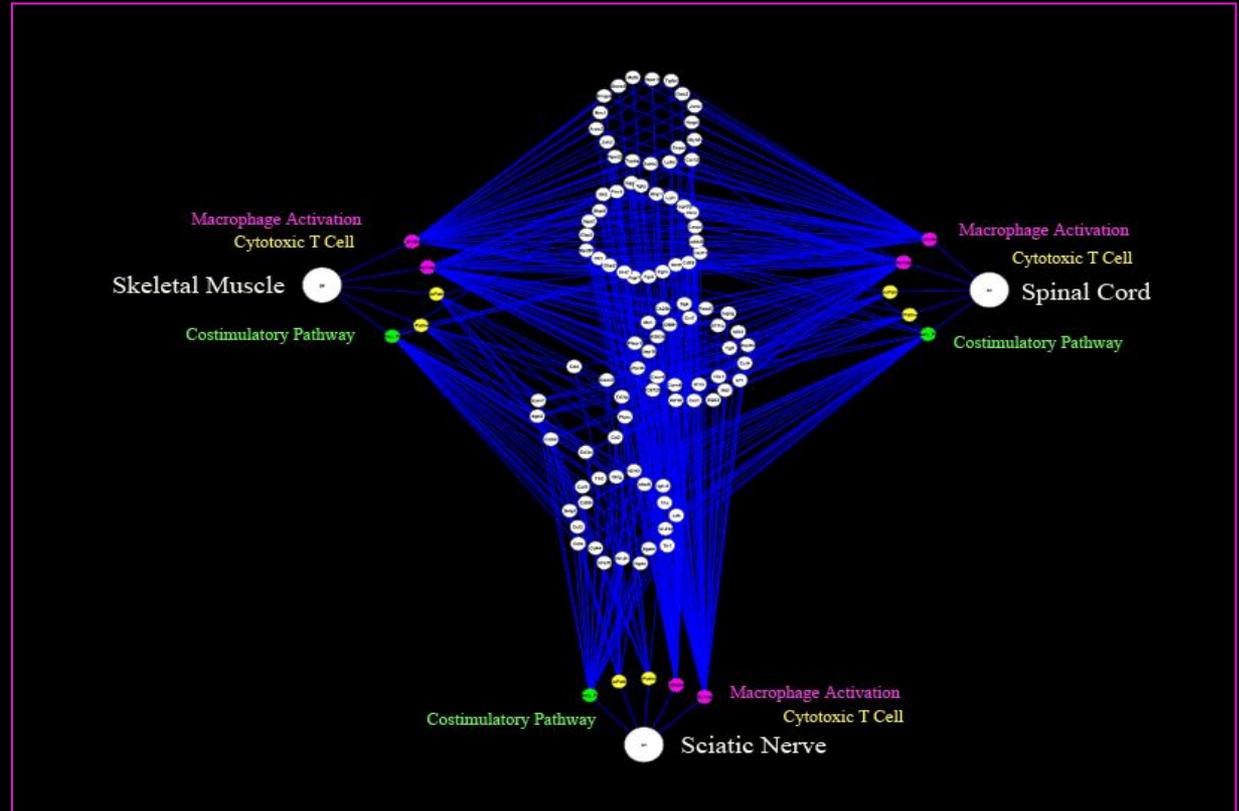
## •Statistics

- Limma package (R)
  - Estimate changes in mRNA
- GlobalTest (R)
  - Estimate changes in biological pathways based on geometric mean

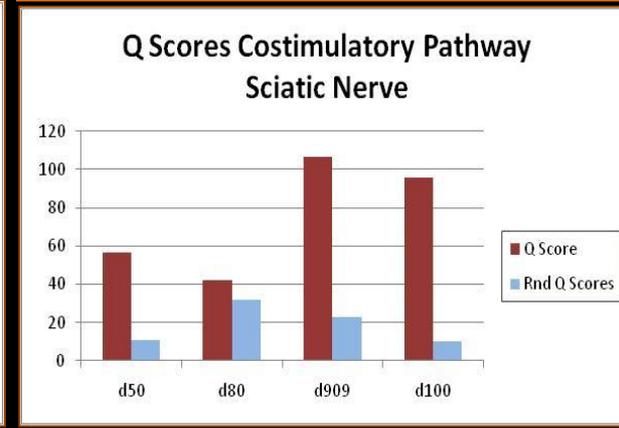
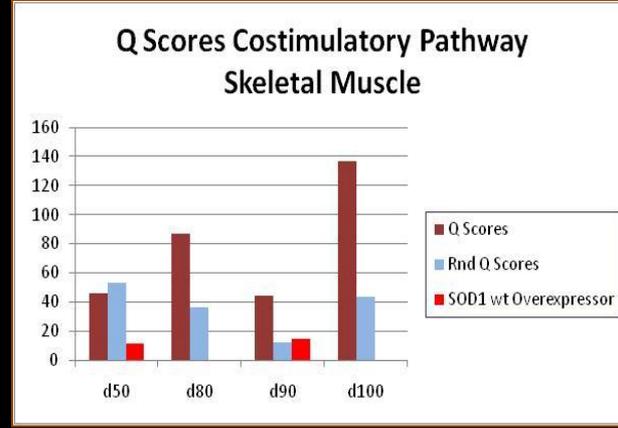
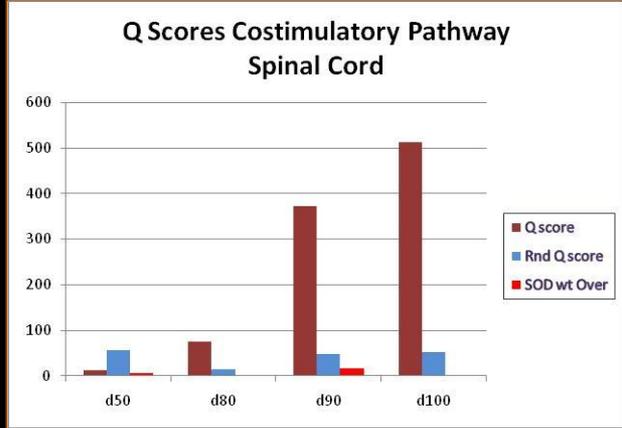
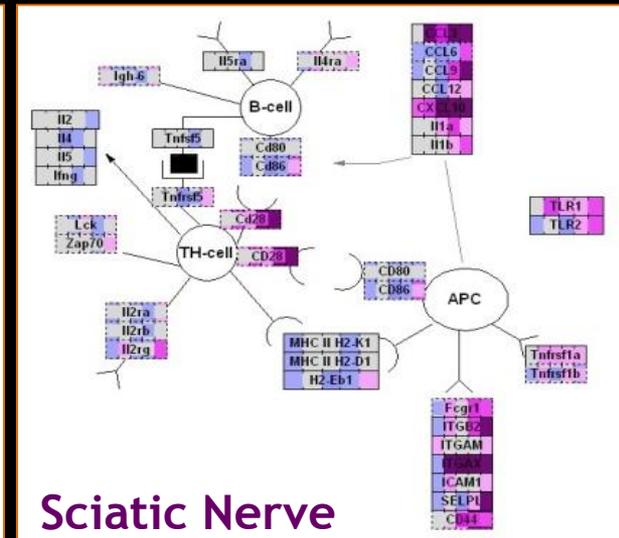
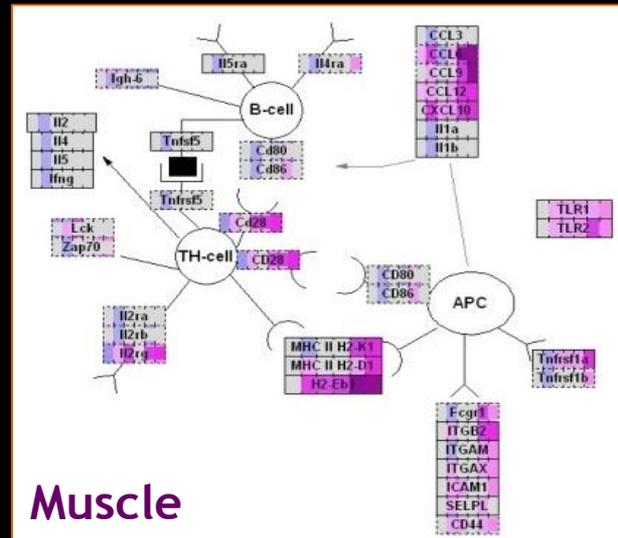
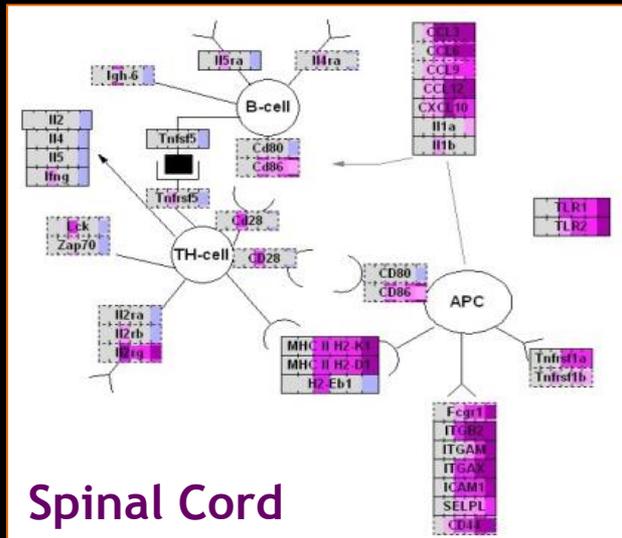


# SOD1<sup>G93A</sup> Tissue Interactome

- Query
- Pathways at days 80 and 90
  - Q score >40
  - All 3 tissues
- Cut off of 40 is significant
- Determined by sample randomization
- 5 pathways pass filter
- 95 genes total
- Related biological function
- Activation of the costimulatory Pathway and humoral response

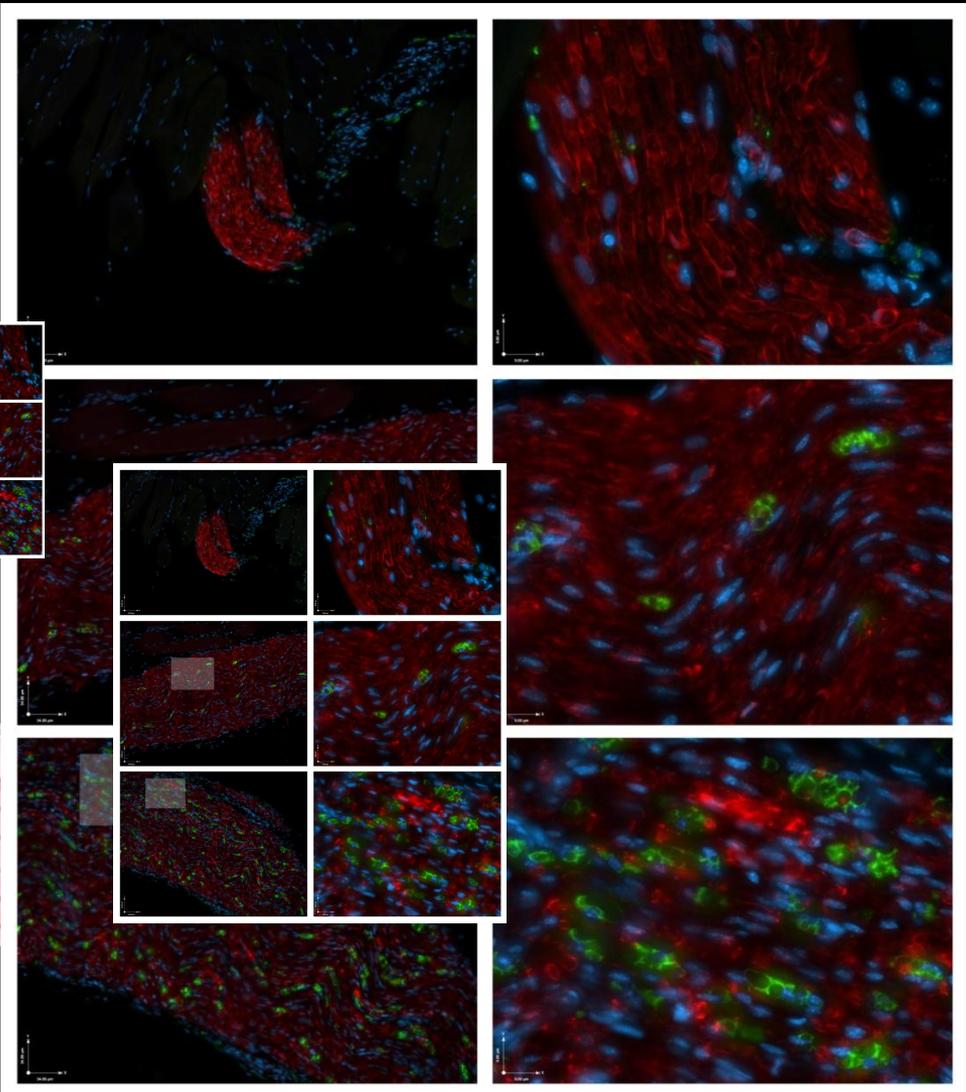
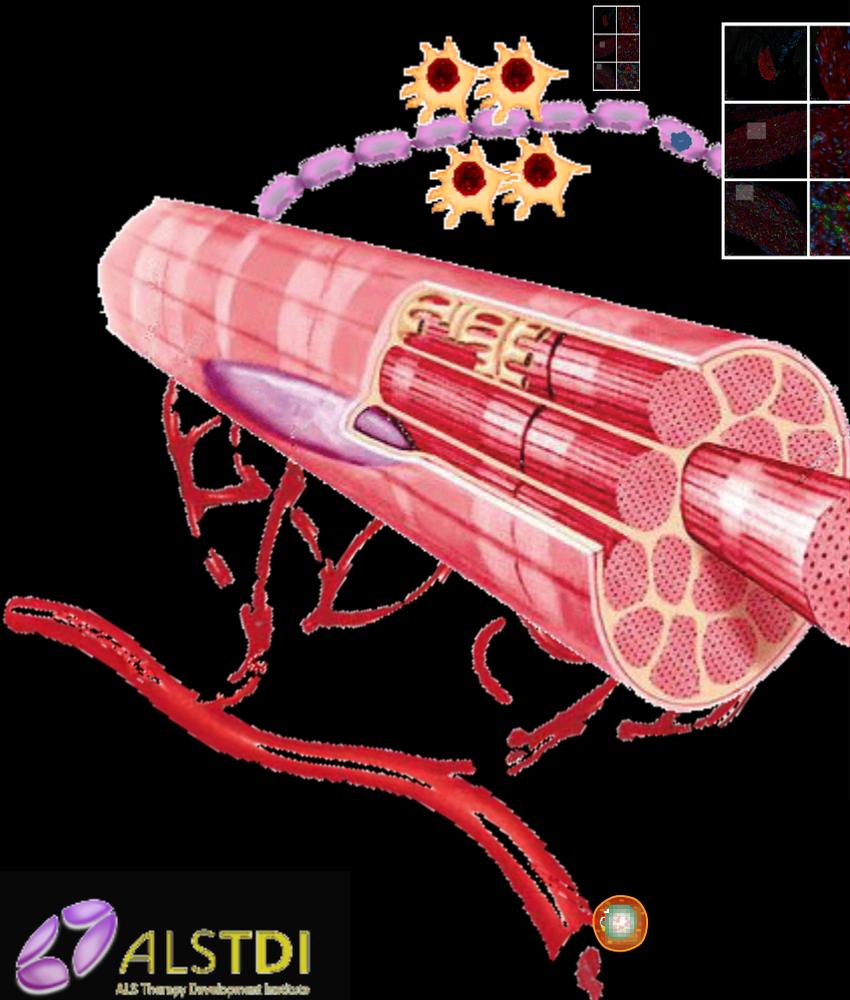


# Activation of Costimulatory Pathway



• Drugable pathway present in 3 diseased tissues in the hSOD1 preclinical model

# Tie the Genomics..... to the Biology.....



Distal Nerve: SOD1  
Red: S100b  
Green: CD68  
Blue: DAPI



# Anti CD40L Treatment is Efficacious in SOD1<sup>G93A</sup> Mice

## Females:

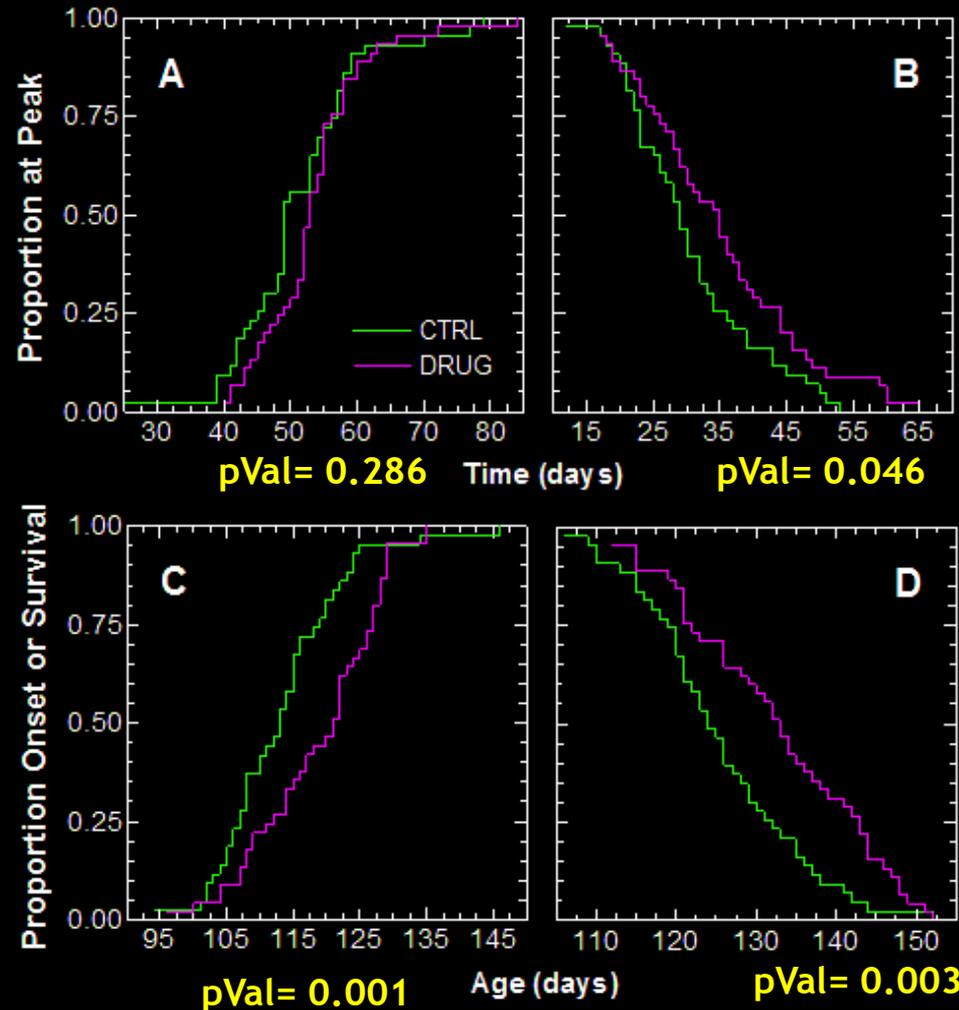
5.22 mg/kg loading dose  
1 mg/kg weekly IP

## Males:

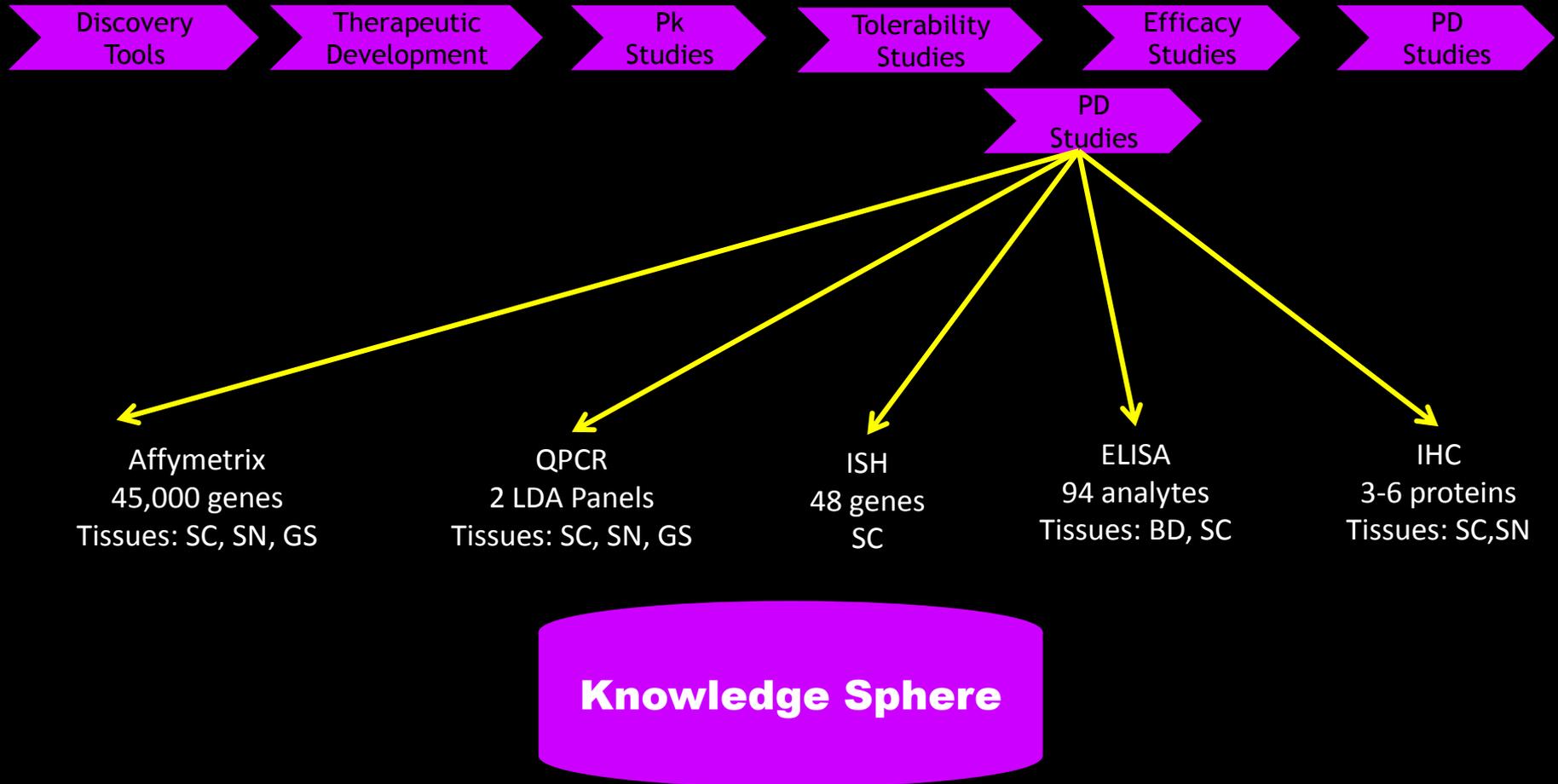
6.75 mg/kg loading dose  
1.34 mg/kg weekly IP

Day 50 start

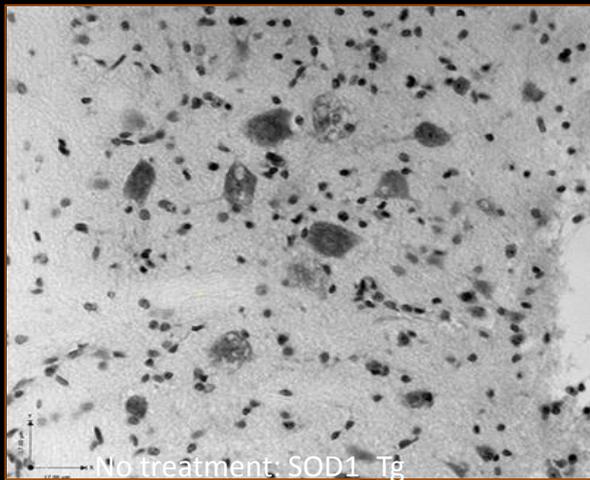
- A. Time required to attain peak body weight. Time to peak was not significantly changed
- B. Time from peak body weight until death. BW maintenance was significantly improved
- C. Time to disease onset (Ns =2). Disease onset was significantly delayed by
- D. Survival was significantly prolonged



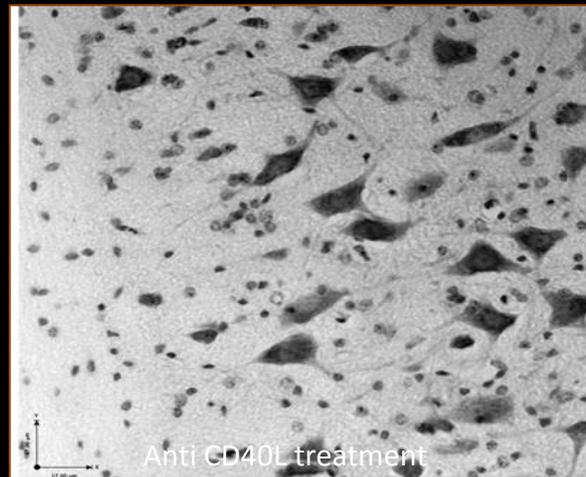
# Standardized PD Design



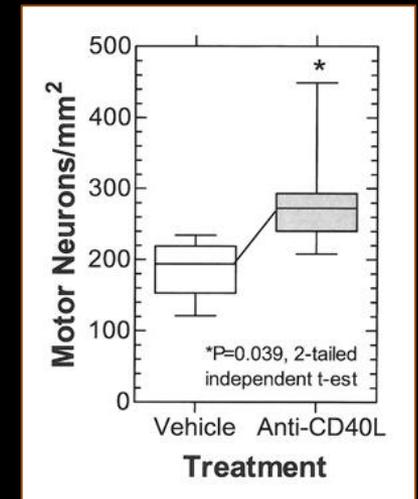
# Anti CD40L Treatment Improves Motor Neuron Survival



Control

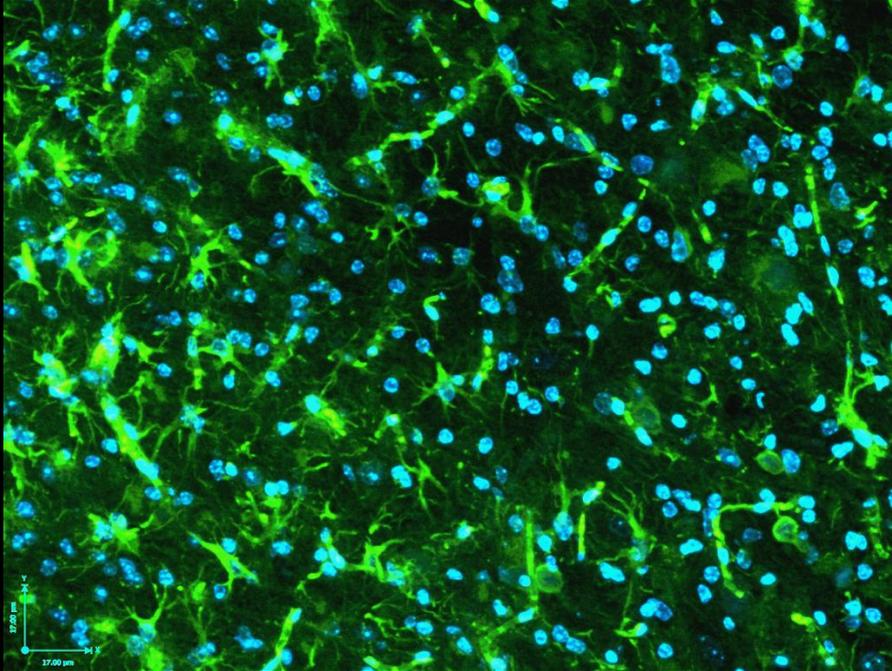


Anti-CD40L

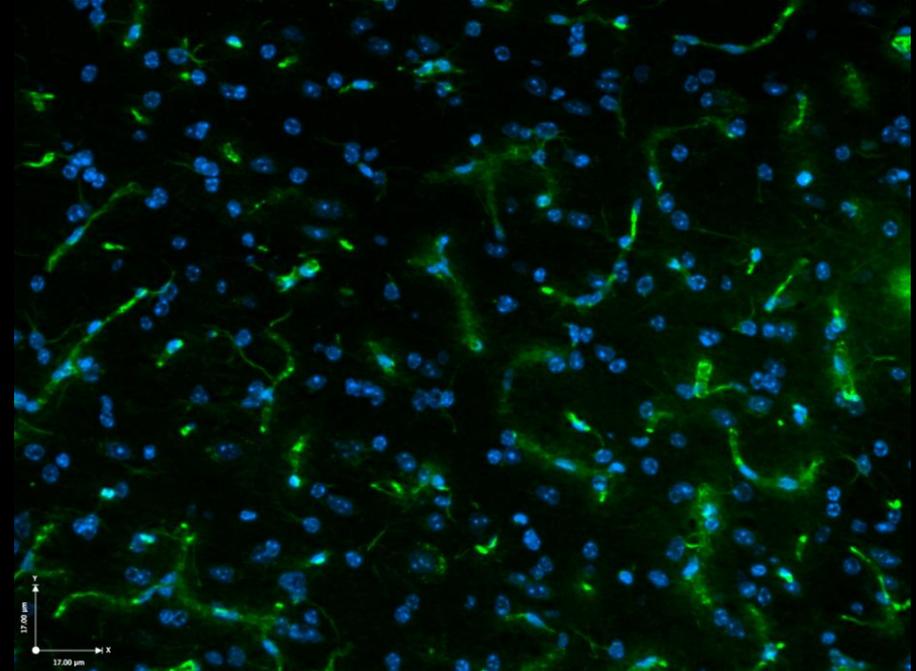


- Lumbar Spinal Cord
- 103 days,
- 53 days treatment 1mg/kg

# Anti CD40L Treatment Decreases Astrocytosis in the Lumbar Spinal Cord



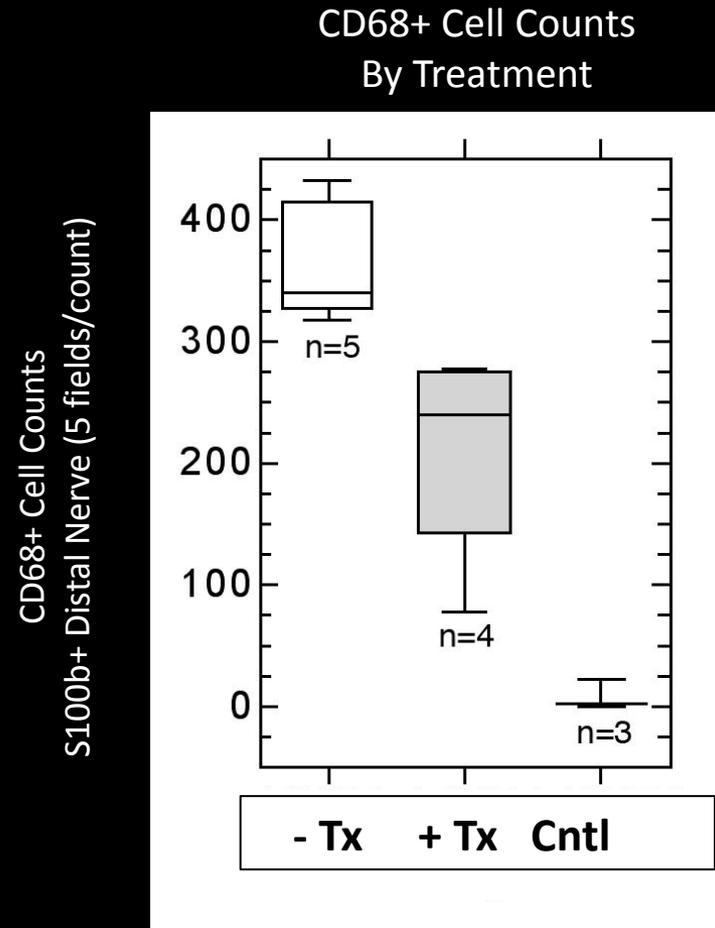
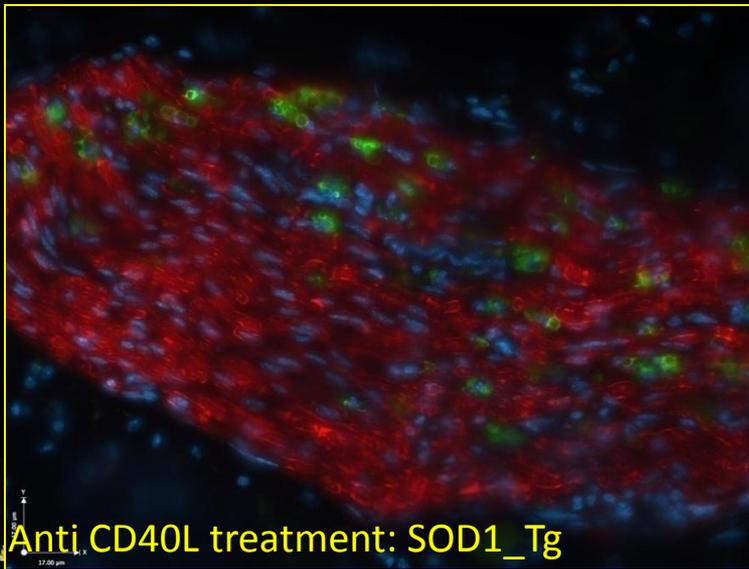
Control



Anti-CD40L

- GFAP, Dapi
- Lumbar Spinal Cord
- 103 days,
- 53 days treatment 1mg/kg

# Anti CD40L Treatment Reduces Axonal Recruitment of Macrophages



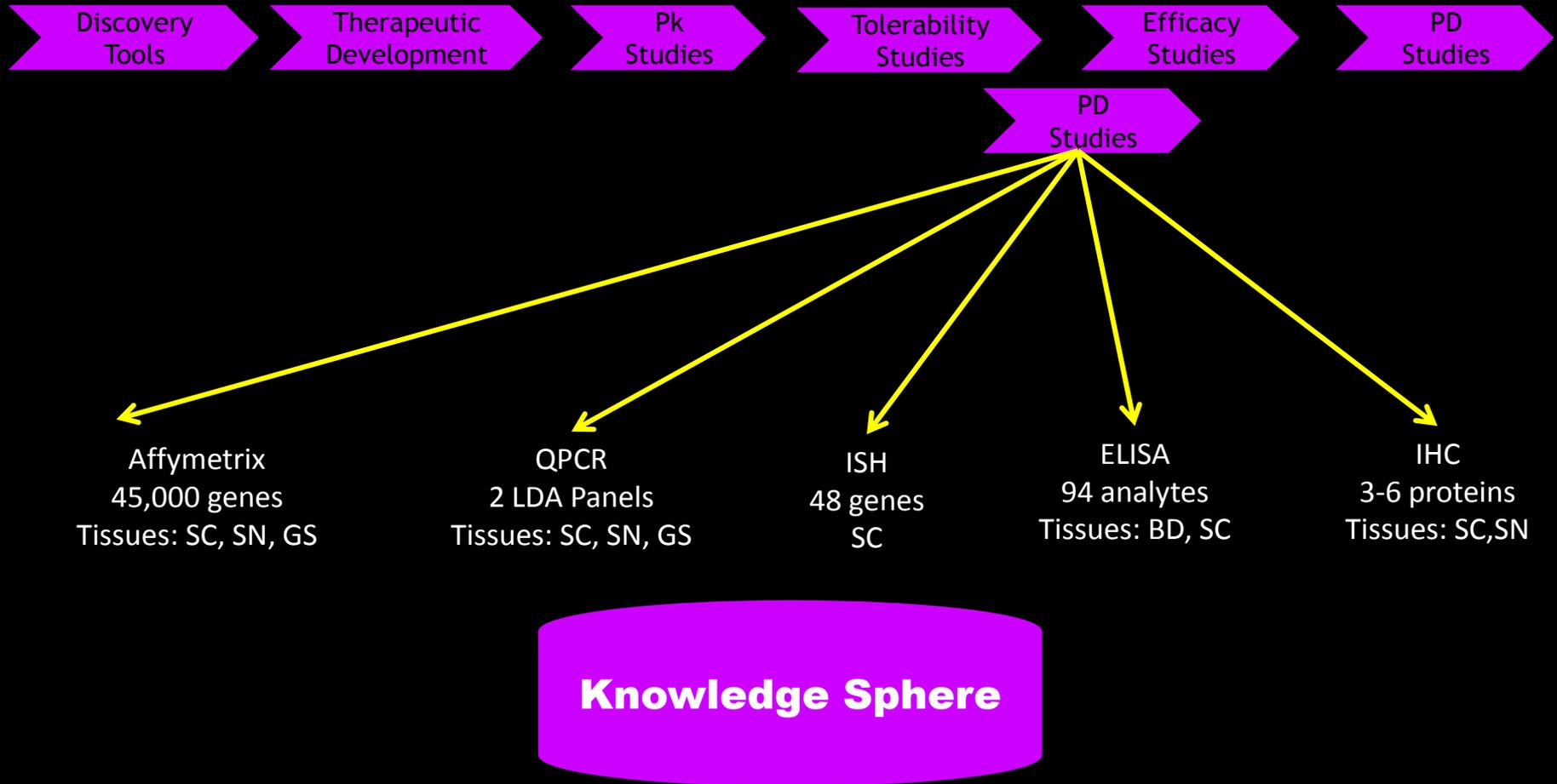
All age matched females, 1 mg/kg /week, i.p.  
50 day start, sacrificed at 103 days  
Biological replicates; double blind analysis



# ALS TDI Drug Development Pipeline

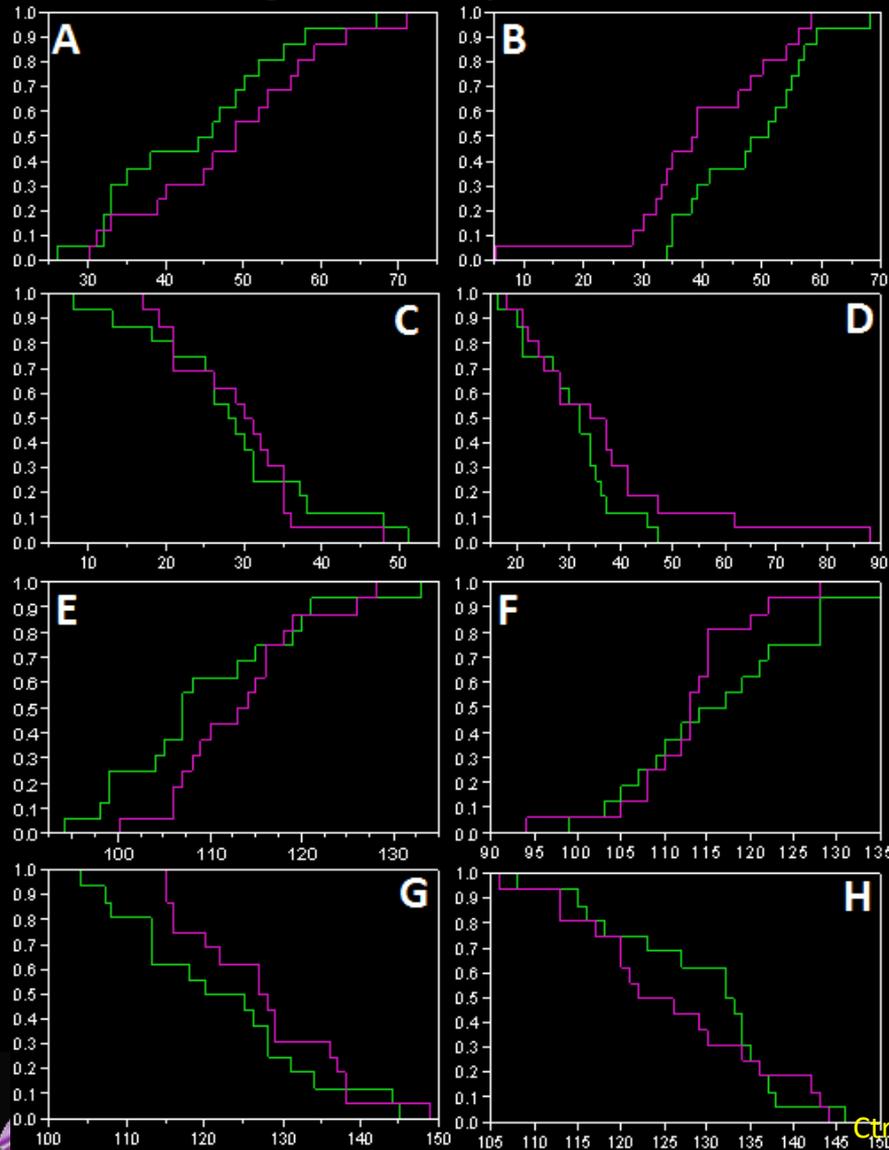
Target ID	Biological Process	Target Validation	Drug Manufacturing	In Vitro Assay Development	Pk & biodistribution	Pd and biomarker	Efficacy Testing	IP Filing
ALS TDI 00898	Metabolism							
ALS TDI 00897	Metabolism							
ALS TDI 00883	Cellular Stress							
ALS TDI 01006	Complement Inhibition							
ALS TDI 00847	Complement Inhibition							
ALS TDI 01002	Complement Inhibition							
ALS TDI 01001	Immune Modulation							
ALS TDI 00879	Immune Modulation							
ALS TDI 00846	Immune Modulation							
ALS TDI 00900	Immune Modulation							
ALS TDI 00878	Immune Modulation							
ALS TDI 00903	Immune Modulation							
ALS TDI 00894	Immune Modulation							
ALS TDI 01004	Immune Modulation							
ALS TDI 01005	Immune Modulation							
ALS TDI 01003	Immune Modulation							
ALS TDI 00904	Synapse Remodeling							
ALS TDI 00874	Synapse Remodeling							

# Standardized PD Design

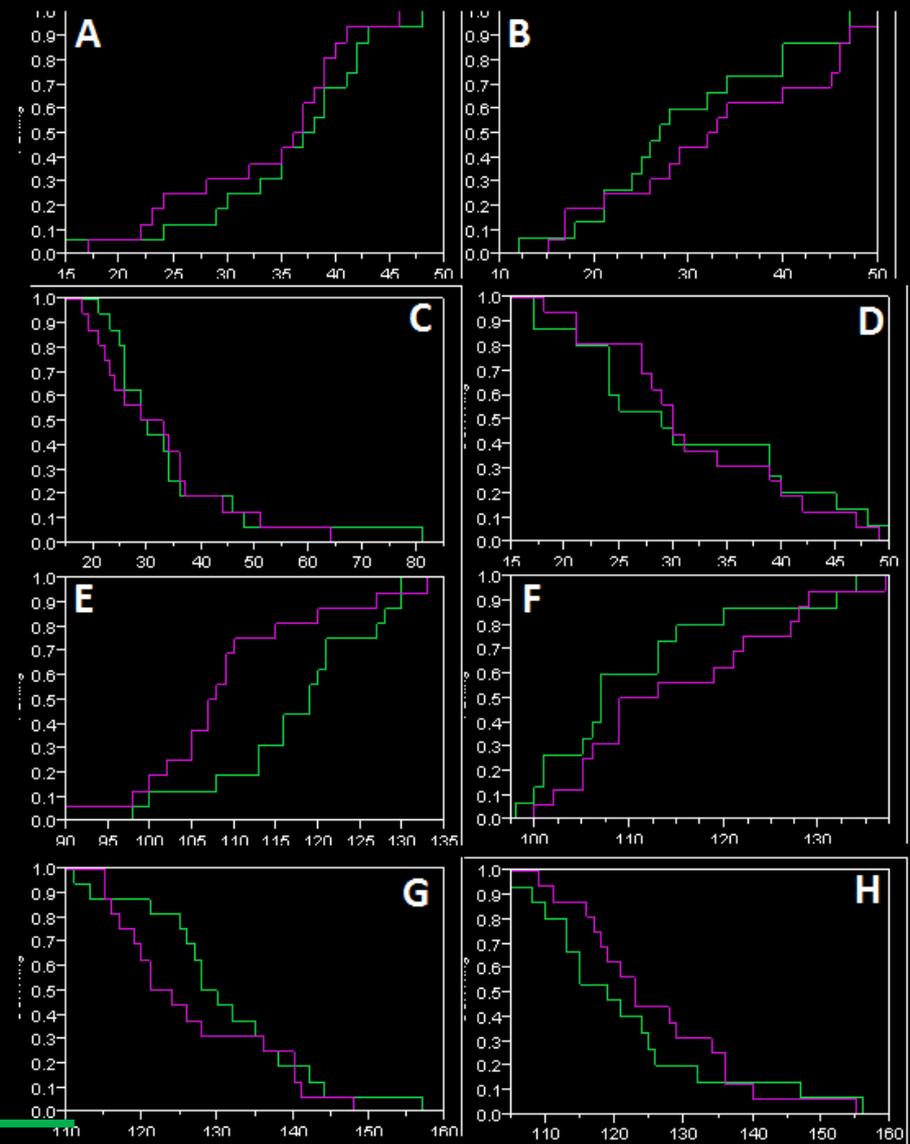


# ALS TDI 00903 Day 50 Start

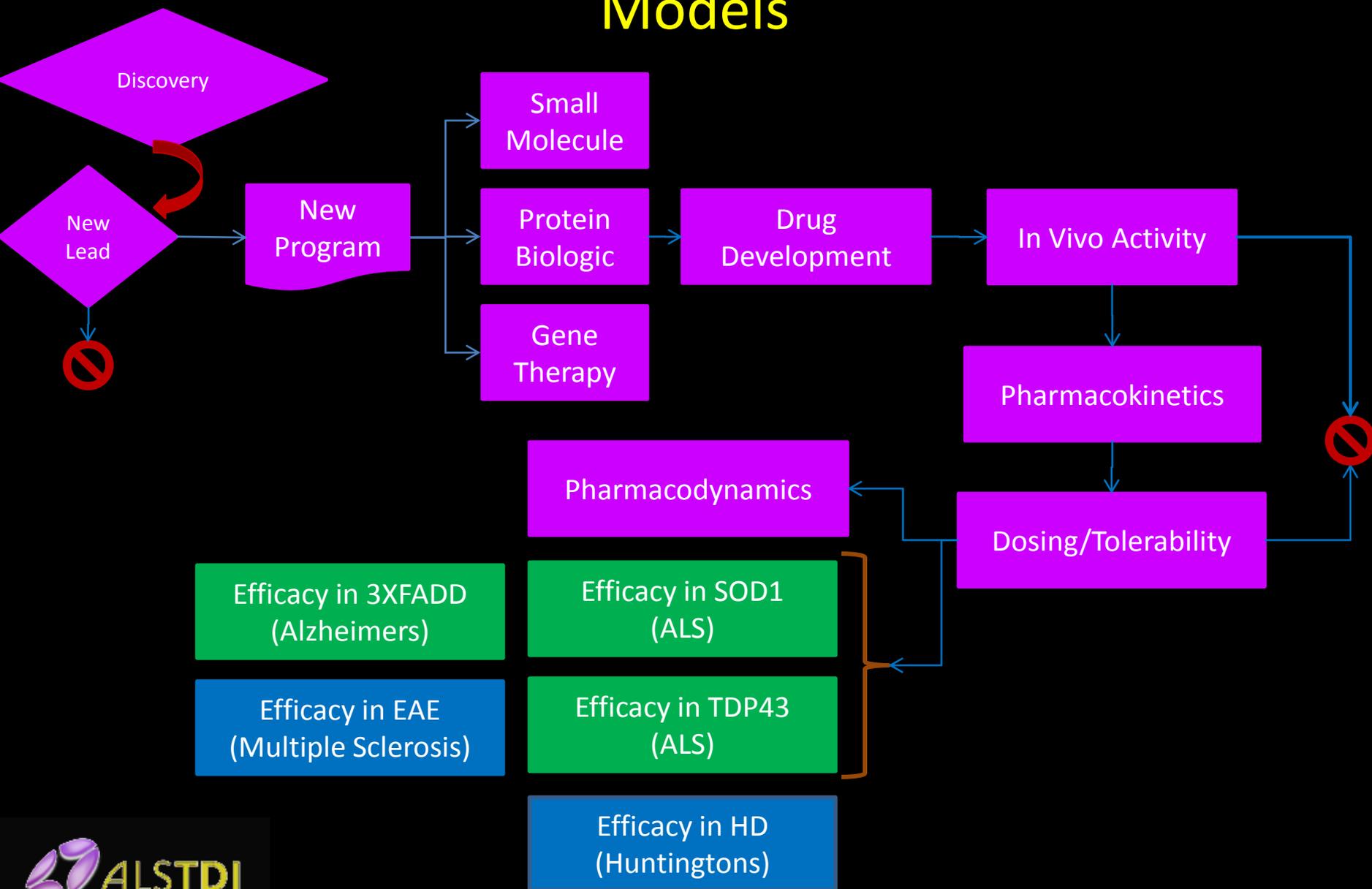
• Single dose day 50



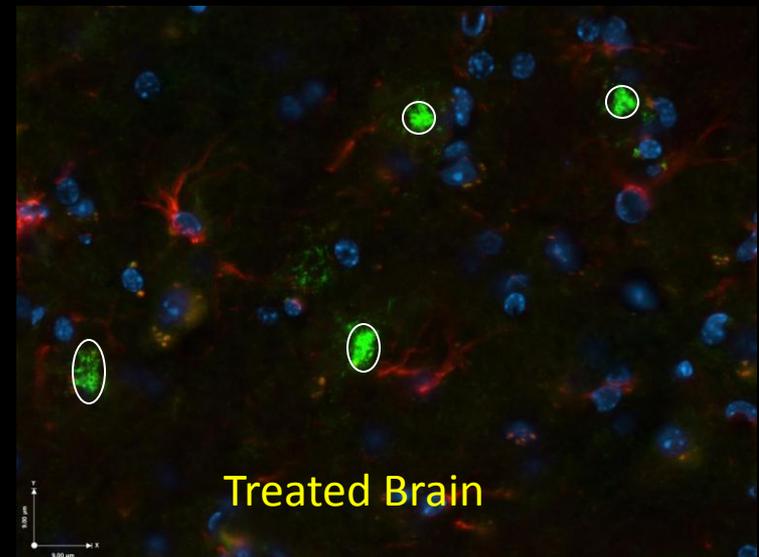
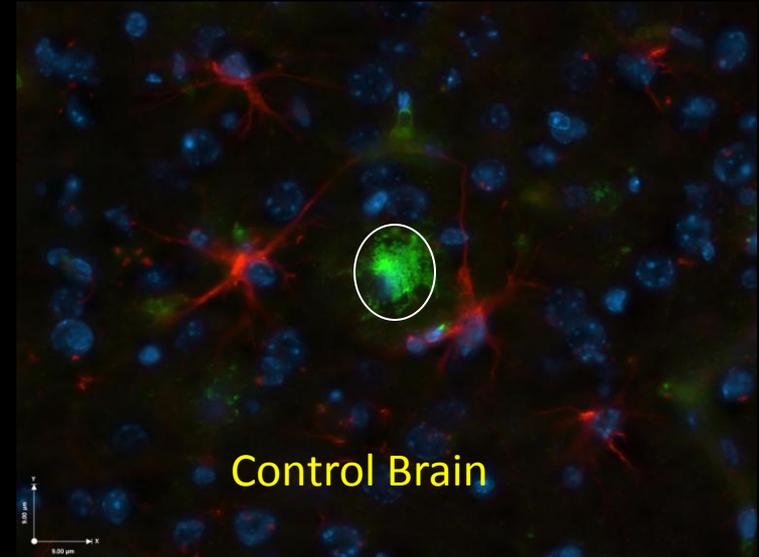
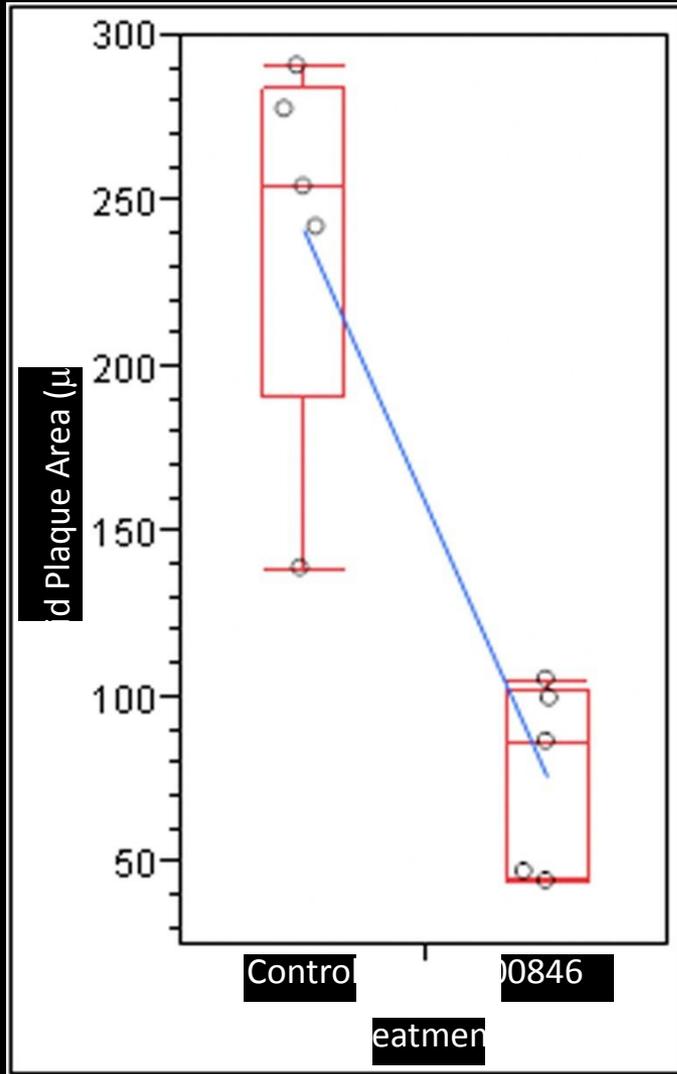
• Single dose day 70



# Preclinical Repurposing in Neurodegenerative Models



# ALSTDI 00846 Therapy Reduces Inflammation and Plaque Size in Alzheimer's Disease Mouse Model



# Summary



- As a community we need to continue to work together
- All our missions have a common thread

# Summary



- No one organization can accomplish this alone
- The process is too complicated and too expensive

# How can We Succeed

- Paradigm shift in Alliance Meeting
  - Strategy Meeting:
    - Increase awareness
    - Increase fund raising efforts
    - Unified drug development approach
      - International centers of excellence
      - Single governing body of stakeholders
      - Joint fund raising efforts
      - For profit business model