



Optimization of Preclinical Animal Models

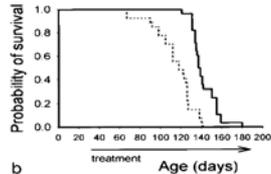
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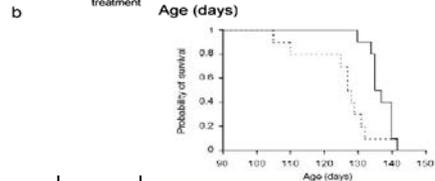


Historical Issue with Pre-clinical Animal Model Development and Validation

First Mutation Associated with ALS Identified: SOD1 Gene, 1993

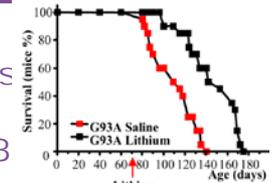


Celebrex Slows Disease & Improves Survival in SOD1 Mouse Model, 2002



Minocycline Slows Disease & Improves Survival in SOD1 Mouse Model, 2004

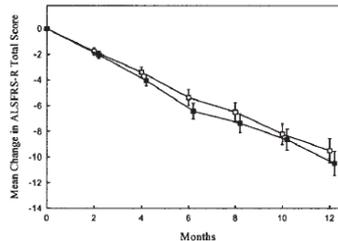
Lithium Slows Disease & Improves Survival in SOD1 Mouse Model, 2008



Experimental Design for Preclinical Drug Screening in the ALS Mouse Model, 2007

1993 1995 1997 1999 2001 2003 2005 2007 2009 2011 2013

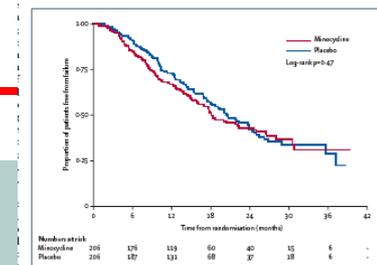
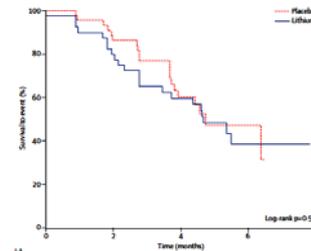
Transgenic mouse model expressing human mutant SOD1, 1997



Celebrex ALS Clinical Trial Fails in Phase III, 2006

Lithium ALS Clinical Trial Fails in Phase III, 2010

Minocycline ALS Clinical Trial Fails in Phase III, 2007

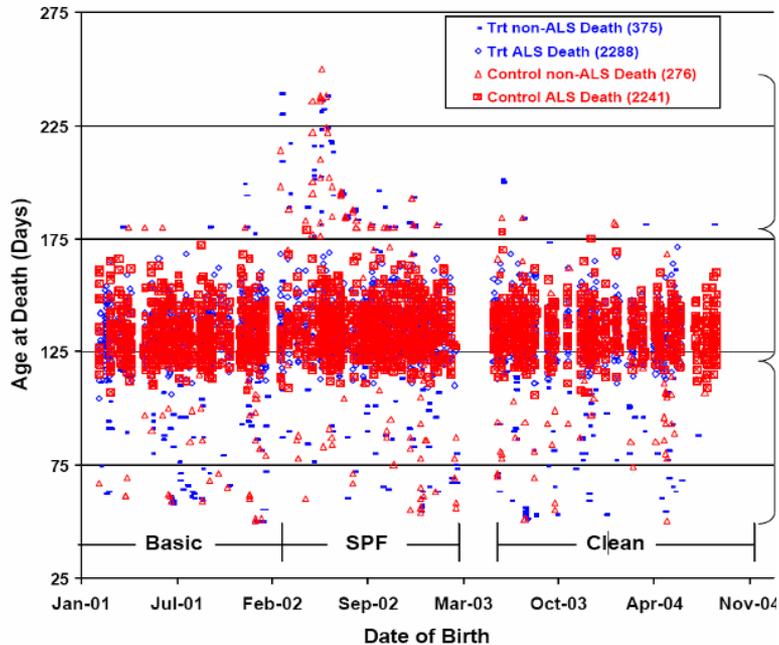


4 Years
To make the Model

10 Years

To Validate the Model

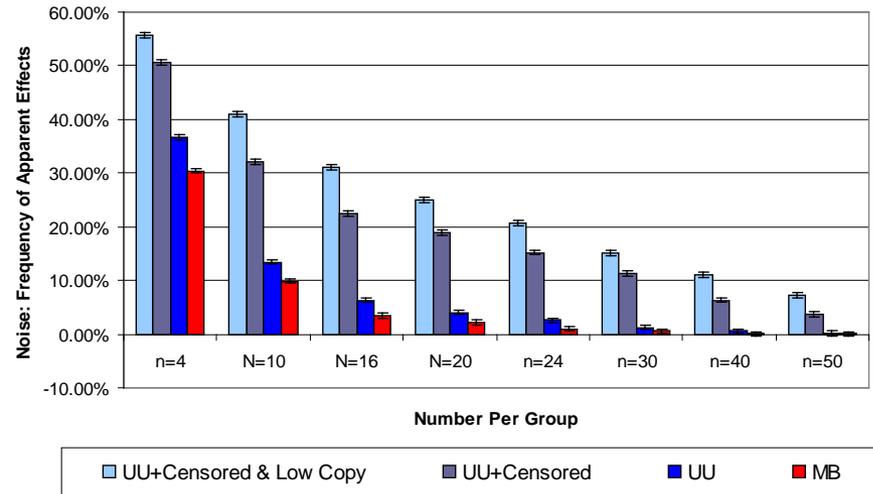
How to Validate a Pre-clinical Model



Identify Noise Variables

- Variable #1: Exclusion Criteria
- Variable #2: Low Copy Animals
- Variable #3: Gender
- Variable #4: Litter

Effect of increasing 'n' on Noise for Each Study Design Variable



Optimized Study Design

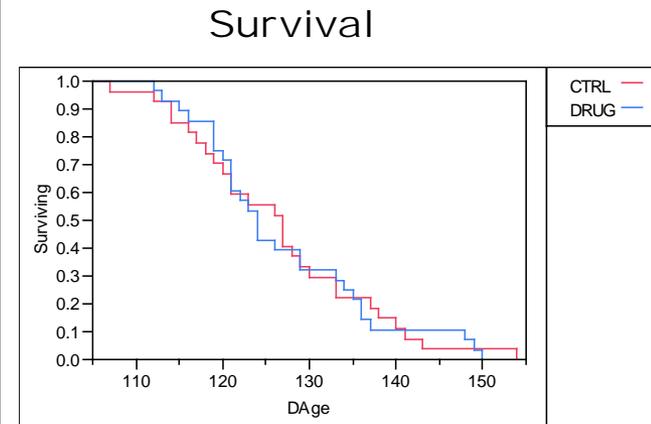
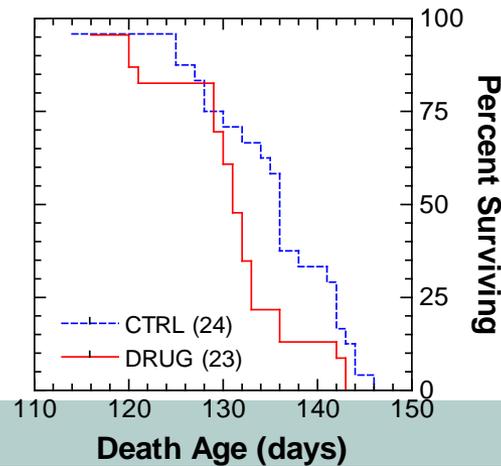
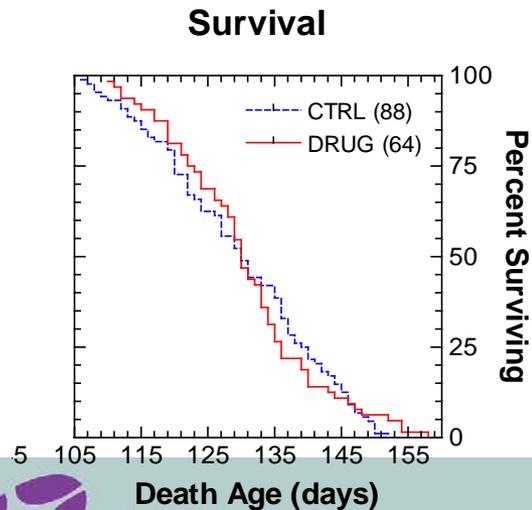
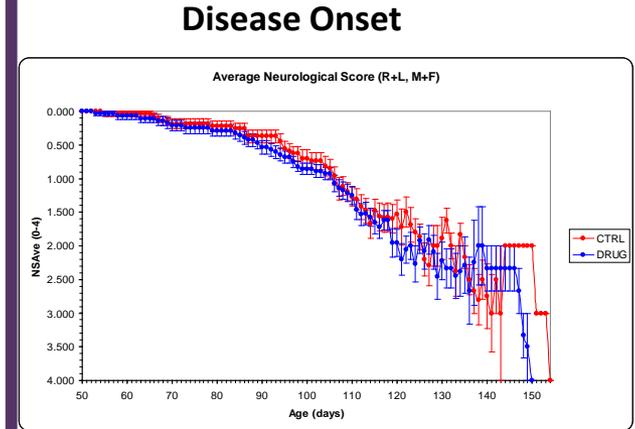
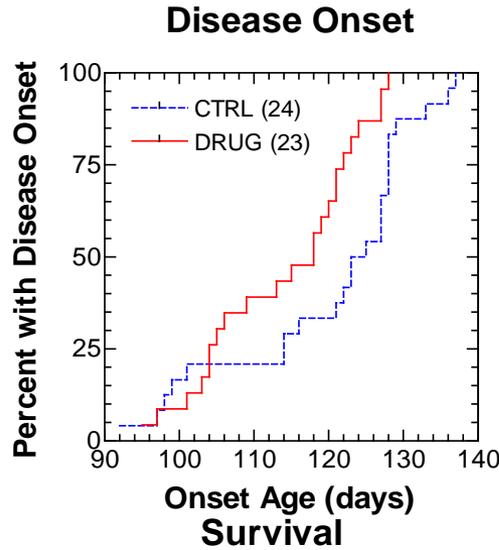
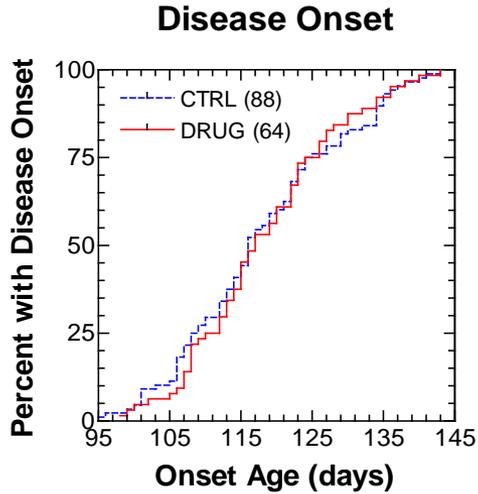
1. 48 mice (Tx group 12m+12f; Control group 12m+12f)
2. Gender & litter matching
3. Confirm transgene copy number
4. Censor non ALS deaths; Blinded scoring
5. Log rank and Cox proportional hazard model

In Properly Designed Studies these Compounds Failed in the SOD1 Model

Celebrex

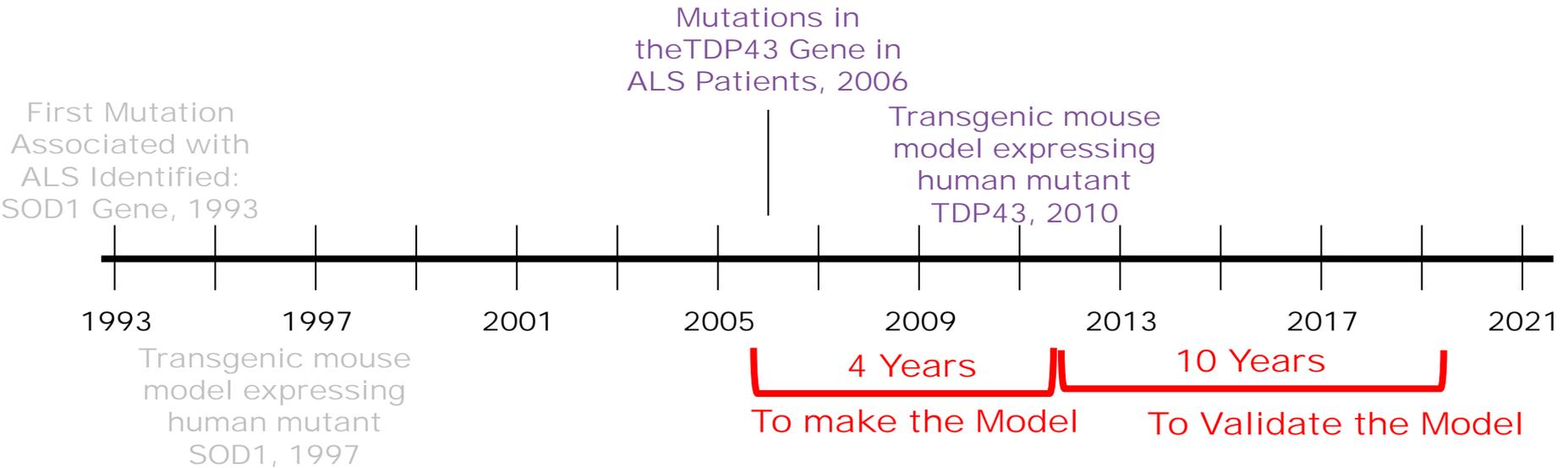
Minocycline

Lithium



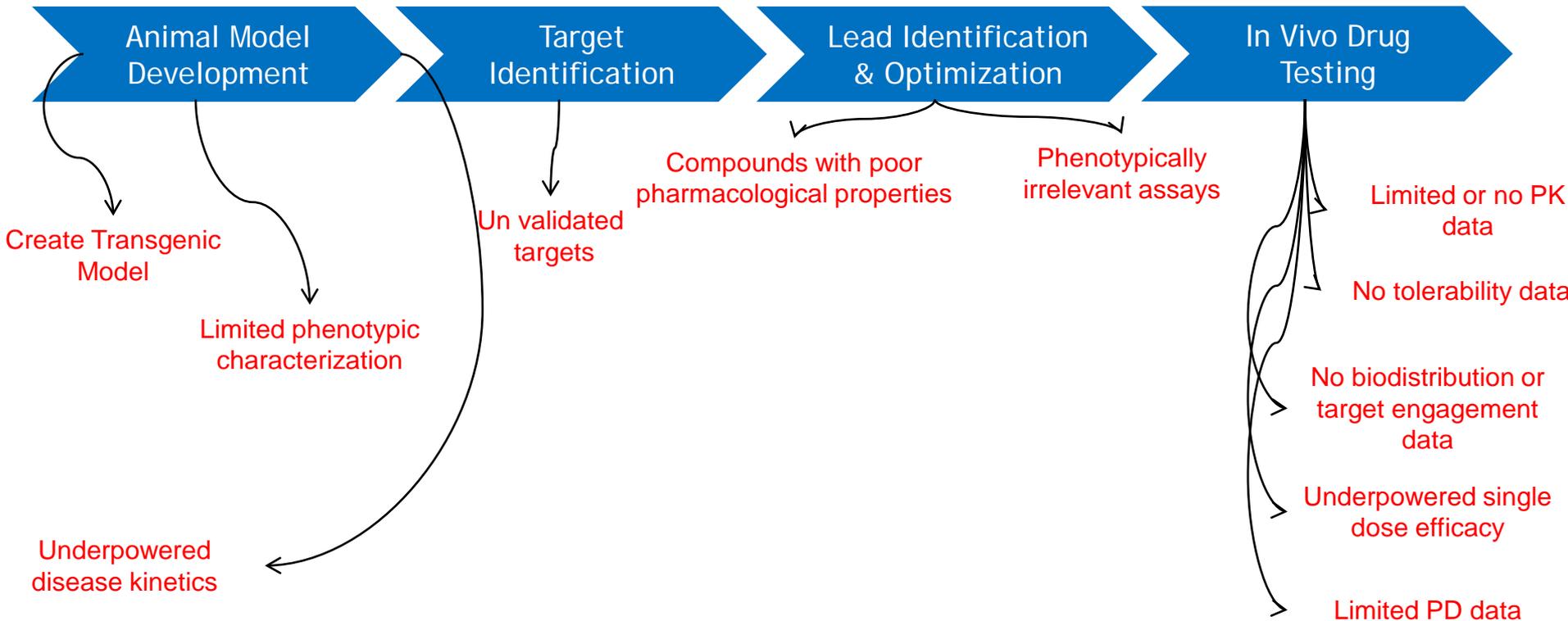
Historical Issue with Preclinical Animal Model Development and Validation

TDP43 Mutations in ALS: déjà vu?

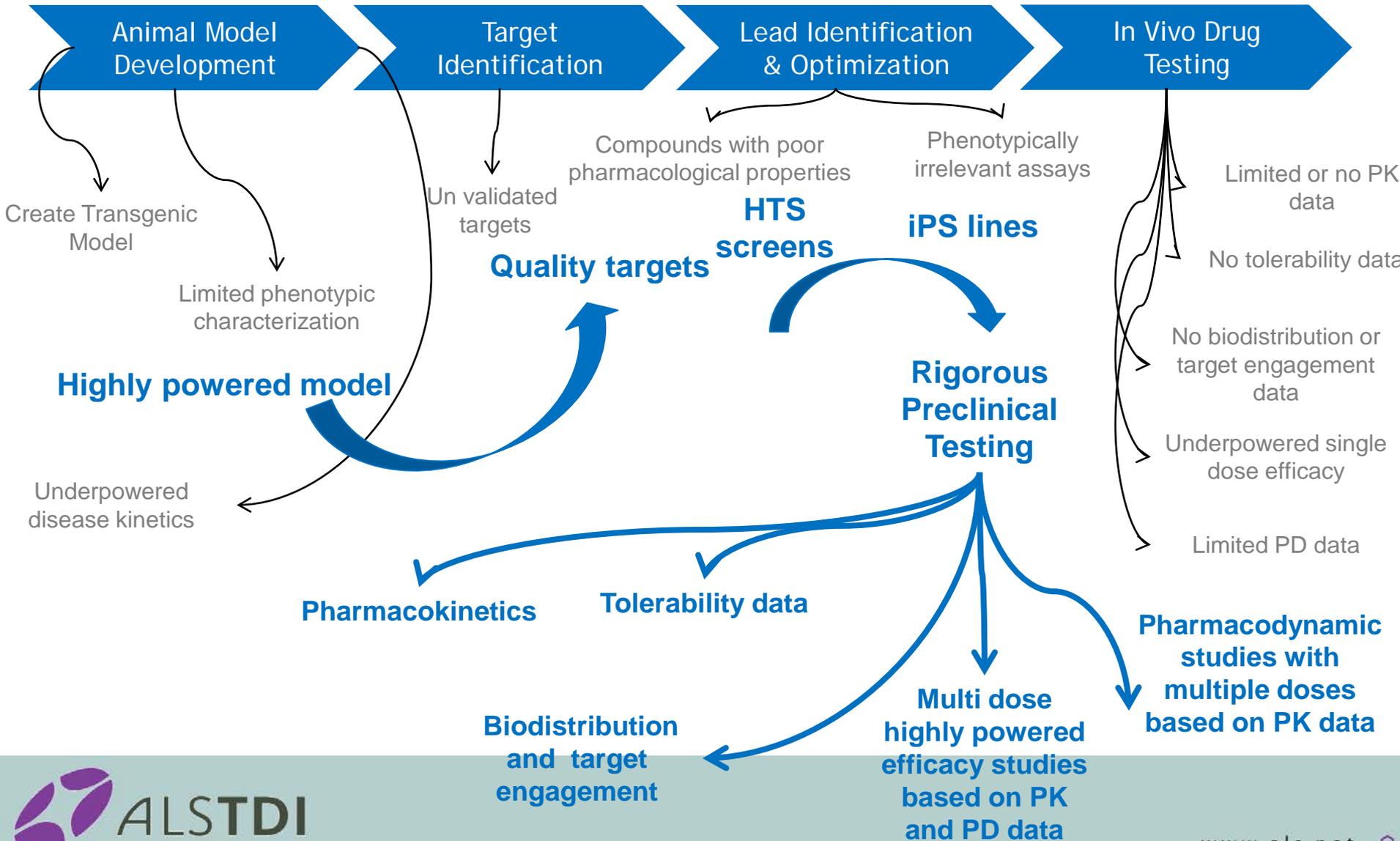


Does it have to take 10 Years to Validate the Model ?

Current Preclinical Model Development Paradigm



Current Preclinical Model Development Paradigm





Preclinical Animal Model Development Consortium

- Validate 50 preclinical models with high priority in neurological disease
- Governance
 - Steering committee from academia, industry, stakeholders and funding agencies
 - Animal model selection
 - Oversight of milestones and budget
- Validation Scheme
 - Analysis of genetic variance
 - Power analysis for disease onset, progression, and survival where applicable
 - Highly powered histological analysis in the CNS and periphery as defined for a model
 - May encompass neuron loss in brain regions and cord, microglial and astrocyte activation, axon counts, neuromuscular junction loss ect
- Budget
 - \$25-\$30M: Precompetitive consortia from pharma, non profits, government
- Need a better acronym?