UNITY • STRENGTH • HOPE

RETTSYNDROME.ORG • EAGLEWOOD RESORT, ILLINOIS • 2016

RESEARCH SYMPOSIUM (JUNE 22-24)

Nothing replaces the experience of meeting face-to-face

14th Rettsyndrome.org Rett Syndrome Symposium, an international, interdisciplinary meeting focused on recent advances in Rett syndrome research

Rettsyndrome.org
ACCELERATING RESEARCH. EMPOWERING FAMILIES.

The 401 Project
CURE MECP2 DUPLICATION SYNDROME

International Foundation For CDKL5 RESEARCH
HOPE • LOVE • CURE

INTERNATIONAL FOXG1 FOUNDATION

anavex LIFE SCIENCES Corp.™

ANAVEX 2-73 as a Potential Treatment for Rett Syndrome and Other Pediatric or Infantile Disorders with Seizure Pathology

N. REBOWE[1], J SPROUSE[1], D. BRUNNER[2], P. KABITZKE[2], L. VELISEK[3], M. BENSON[3], J. VELISKOVA[3], C. MISSLING[1]
[1]Anavex Life Sciences, New York, NY; [2]Psychogenics, Tarrytown, NY; [3]New York Medical College, Valhalla, NY

2016 Rett Syndrome Symposium June 22-24, 2016

Rettsyndrome.org ACCELERATING RESEARCH. EMPOWERING FAMILIES.

The 4O1 Project CURE MECP2 DUPLICATION SYNDROME

International Foundation For CDKL5 RESEARCH HOPE • LOVE • CURE

INTERNATIONAL FOXG1 FOUNDATION

Disclosure

- Employee of Anavex Life Sciences
- Shareholder of Anavex Life Sciences
- Options of Anavex Life Sciences

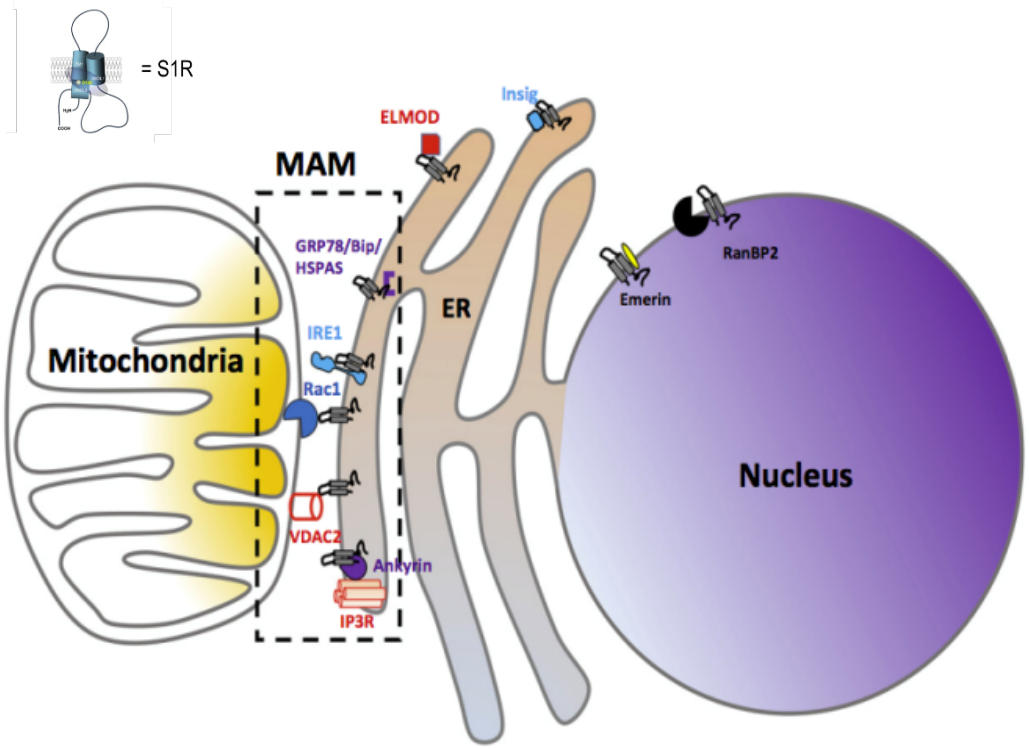
Safe Harbor

This presentation contains forward-looking statements made within the meaning of the Private Securities Litigation Reform Act of 1995 by Anavex™ Life Sciences Corp. and its representatives. These statements can be identified by introductory words such as ``expects,'' ``plans,'' ``intends,'' ``believes,'' ``will,'' ``estimates,'' ``forecasts,'' ``projects'' or words of similar meaning, and by the fact that they do not relate strictly to historical or current facts. Forward-looking statements frequently are used in discussing potential product applications, potential collaborations, product development activities, clinical studies, regulatory submissions and approvals, and similar operating matters. Many factors may cause actual results to differ from forward-looking statements, including inaccurate assumptions and a broad variety of risks and uncertainties, some of which are known and others of which are not. Known risks and uncertainties include those identified from time to time in the reports filed by Anavex Life Sciences Corp. with the Securities and Exchange Commission, which should be considered together with any forward-looking statement. No forward-looking statement is a guarantee of future results or events, and one should avoid placing undue reliance on such statements. Anavex Life Sciences Corp. undertakes no obligation to update publicly any forward-looking statements, whether as a result of new information, future events or otherwise. Anavex Life Sciences Corp. cannot be sure when or if it will be permitted by regulatory agencies to undertake clinical trials or to commence any particular phase of clinical trials. Because of this, statements regarding the expected timing of clinical trials cannot be regarded as actual predictions of when Anavex Life Sciences Corp. will obtain regulatory approval for any ”phase” of clinical trials. We also cannot be sure of the clinical outcome for efficacy or safety of our compounds. Potential investors should refer to the risk factors in our reports filed on Edgar.

ANAVEX™ 2-73

- Currently in a Phase 2a clinical trial for Alzheimer's disease (AD)
- ANAVEX 2-73 is an **orally available** small molecule targeting protein misfolding, oxidative stress, mitochondrial dysfunction, inflammation and cellular stress, factors in **neurodegenerative and neurodevelopmental** diseases through activation of the **Sigma-1 Receptor**
- Phase 2a (PART A) results demonstrate favorable safety and bioavailability; Positive dose-response curve and tolerability/risk profile
- Supportive evidence indicates a cognitive benefit associated with ANAVEX 2-73 (Cogstate, MMSE, EEG/ERP statistically significant improvement at 5 weeks of treatment)
- Guidance received from the FDA supports the Company's plan to advance ANAVEX 2-73 for the treatment of Alzheimer's disease in a larger double-blinded, randomized, placebo-controlled Phase 2/3 trial
- Phase 2a PART B 52 week extension trial is ongoing
- Additional data, including updates on PART B, to be presented at upcoming scientific meetings

Sigma-1 Receptor: Upstream Pluripotent Modulator

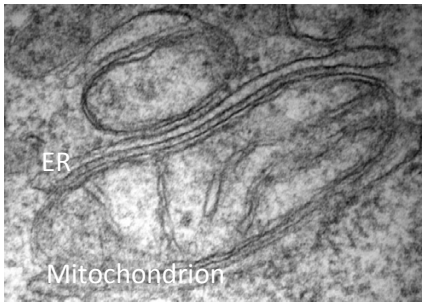


- Reducing mitochondrial dysfunction
- Reducing protein misfolding
- Modulating Ca^{2+}
- Reducing oxidative stress
- Reducing inflammation
- Enabling neuroprotection

Su et al., Trends Pharmacol Sci. 2016 Feb 8. pii: S0165-6147(16)00004-3; Cauli et al., Neuroscience, Volume 190, 2011, Pages 27-36; Miki et al, Dec 9. doi: 10.1111/neup.12080 Neuropathology 2013; Glembotski et al., Circulation Research. 2007;101:975-984

Common in Neurodegenerative Diseases: ER-Mitochondria Axis Disruption … Sigma-1R Restores Association …

Disease situation



Normal situation

Endoplasmic reticulum (ER)-Mitochondria associations are disrupted in neurodegenerative diseases …[#]

… Sigma-1R restores association[##]

[#] Cause of disruption is multifactorial,e.g. Abeta oligomers build-up inside ER; Source: Meli et al. NATURE COMMUNICATIONS | DOI: 10.1038/ncomms4867; Miller et al. Trends in Neurosciences, March 2016, Vol. 39, No. 3; [##] Lahmy et al. Neuropsychopharmacology (2013) 38, 1706–1723

Mitochondrial Dysfunction: Convergence of Pathological and Genetic Lesions in Neurodevelopmental and Neurodegenerative Diseases

Neuroscience and Biobehavioral Reviews 46 (2014) 202–217

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review

Mitochondrial dysfunction as a central actor in intellectual disability-related diseases: An overview of Down syndrome, autism, Fragile X and Rett syndrome

Daniela Valenti[a], Lidia de Bari[a], Bianca De Filippis[b], Alexandra Henrion-Caude[c], Rosa Anna Vacca[a,*]

[a] Institute of Biomembranes and Bioenergetics, National Council of Research, Bari, Italy
[b] Section of Behavioural Neuroscience, Department of Cell Biology and Neurosciences, Istituto Superiore di Sanità Roma, Italy
[c] INSERM U781 Hôpital Necker – Enfants Malades, Paris, France

ARTICLE INFO

Article history:
Received 2 July 2013
Received in revised form 5 November 2013
Accepted 13 January 2014
Available online 15 February 2014

Keywords:
Intellectual disability
Mitochondria
Mitochondrial dysfunction
Oxidative phosphorylation
Neurogenesis
Neuroplasticity
Down syndrome
Rett syndrome
Autism
Fragile X
Oxidative stress
Drug development
Epigallocatechine-3-gallate

ABSTRACT

Clinical manifestations typical of mitochondrial diseases are often present in various genetic syndromes associated with intellectual disability, a condition leading to deficit in cognitive functions and adaptive behaviors. Until now, the causative mechanism leading to intellectual disability is unknown and the progression of the condition is poorly understood.

We first report latest advances on genetic and environmental regulation of mitochondrial function and its role in brain development. Starting from the structure, function and regulation of the oxidative phosphorylation apparatus, we review how mitochondrial biogenesis and dynamics play a central role in neurogenesis and neuroplasticity. We then discuss how dysfunctional mitochondria and alterations in reactive oxygen species homeostasis are potentially involved in the pathogenesis of various neurodevelopmental syndromes with a special focus on Down, Rett, Fragile X syndromes and autism spectrum disorders. Finally, we review and suggest novel therapeutic approaches aimed at improving intellectual disability by activating mitochondrial function and reducing oxidative stress to amiliorate the quality of life in the subjects affected.

Trends in Neurosciences

CellPress

Review

There's Something Wrong with my MAM; the ER–Mitochondria Axis and Neurodegenerative Diseases

Sebastien Paillusson,[1,3] Radu Stoica,[1,3] Patricia Gomez-Suaga,[1] Dawn H.W. Lau,[1] Sarah Mueller,[1] Tanya Miller,[2,*] and Christopher C.J. Miller[1,*]

Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis with associated frontotemporal dementia (ALS/FTD) are major neurodegenerative diseases for which there are no cures. All are characterised by damage to several seemingly disparate cellular processes. The broad nature of this damage makes understanding pathogenic mechanisms and devising new treatments difficult. Can the different damaged functions be linked together in a common disease pathway and which damaged function should be targeted for therapy? Many functions damaged in neurodegenerative diseases are regulated by communications that mitochondria make with a specialised region of the endoplasmic reticulum (ER; mitochondria-associated ER membranes or 'MAM'). Moreover, several recent studies have shown that disturbances to ER–mitochondria contacts occur in neurodegenerative diseases. Here, we review these findings.

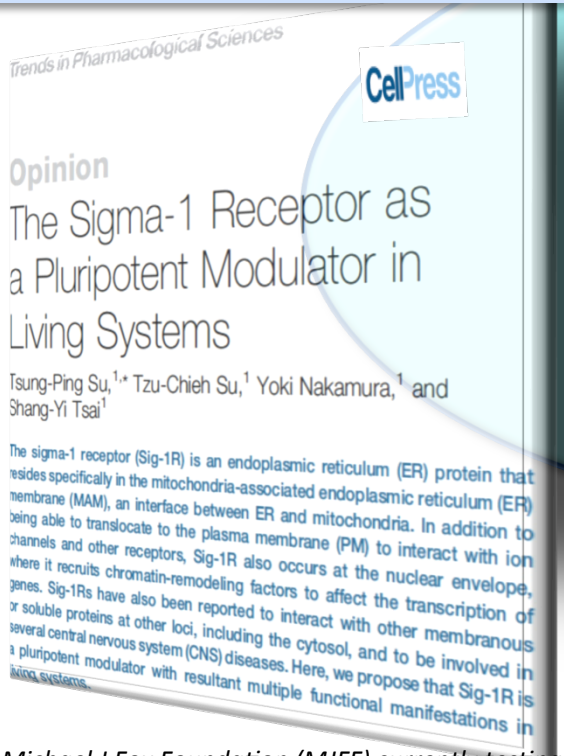
Sources: Vacca et al. Neuroscience and Biobehavioral Reviews 46 (2014) 202–217; Miller et al. Trends in Neurosciences, March 2016, Vol. 39, No. 3

ANAVEX™ 2-73: Confirmed Targeted Indications: From Rare Disease Indications to Largest CNS Indication …

Rett Syndrome (RTT)
Rare neurodevelopmental disease
Preclinical validation, RettSyndrome.org ☑
Planning blinded controlled Phase 2 ☐

Alzheimer's Disease (AD)
Neurodegenerative disease
Clinical validation Phase 2a ☑
Planning blinded controlled Phase 2/3 ☐

Fragile X Syndrome (FXS)
Preclinical validation ☑


Trends in Pharmacological Sciences

CellPress

Opinion

The Sigma-1 Receptor as a Pluripotent Modulator in Living Systems

Tsung-Ping Su,[1,*] Tzu-Chieh Su,[1] Yoki Nakamura,[1] and Shang-Yi Tsai[1]

The sigma-1 receptor (Sig-1R) is an endoplasmic reticulum (ER) protein that resides specifically in the mitochondria-associated endoplasmic reticulum (ER) membrane (MAM), an interface between ER and mitochondria. In addition to being able to translocate to the plasma membrane (PM) to interact with ion channels and other receptors, Sig-1R also occurs at the nuclear envelope, where it recruits chromatin-remodeling factors to affect the transcription of genes. Sig-1Rs have also been reported to interact with other membranous or soluble proteins at other loci, including the cytosol, and to be involved in several central nervous system (CNS) diseases. Here, we propose that Sig-1R is a pluripotent modulator with resultant multiple functional manifestations in living systems.

ANAVEX 2-73
Sigma-1 Receptor Agonist
"Pluripotent Modulator"

Modulating Ca^{2+} Neuroprotective
Reducing mitochondrial dysfunction
Reducing protein misfolding
Reducing oxidative stress
Reducing inflammation

Depression
Preclinical validation ☑

Anxiety
Preclinical validation ☑

Epilepsy (seizures)
Preclinical validation ☑

Infantile Spasms (seizures)
Preclinical validation ☑

Multiple Sclerosis (MS)
Preclinical validation ☑

Parkinson's#
Preclinical validation, MJFF ☐

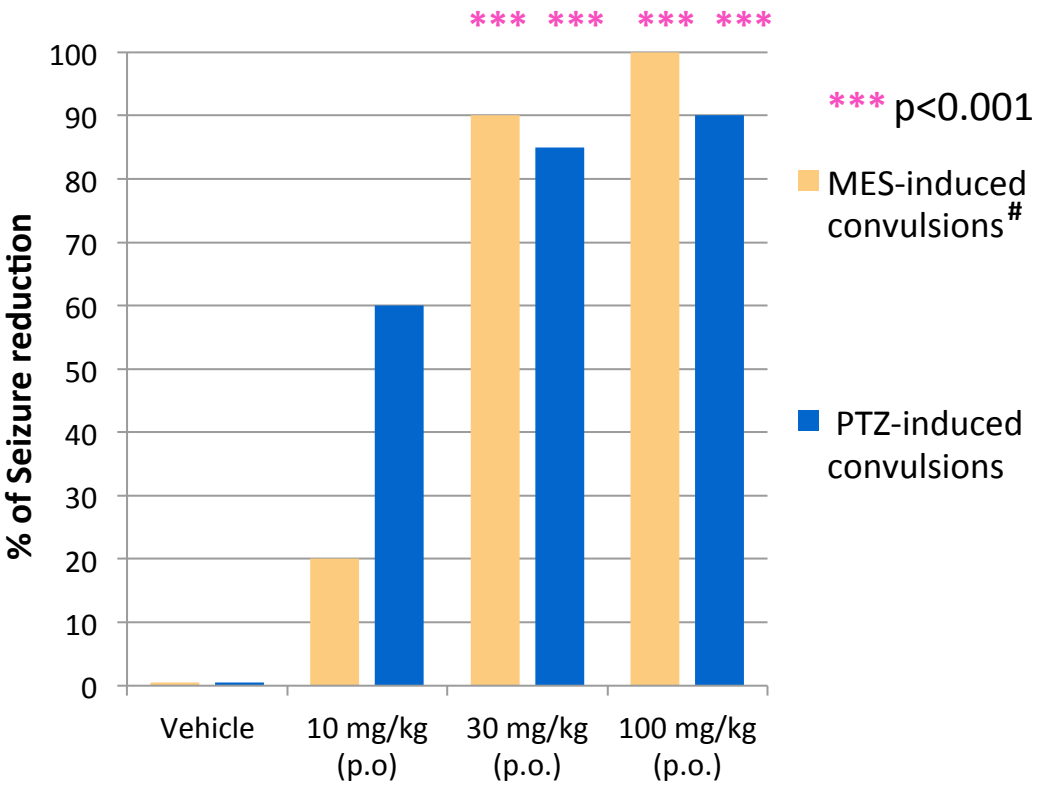
 # Michael J Fox Foundation (MJFF) currently testing ANAVEX 2-73 in Parkinson's disease models; Su and Tsai et al. Trends Pharmacol Sci. 2016 Apr;37(4):262-78. doi: 10.1016/j.tips.2016.01.003. Epub 2016 Feb 9.

anavex LIFE SCIENCES Corp.™

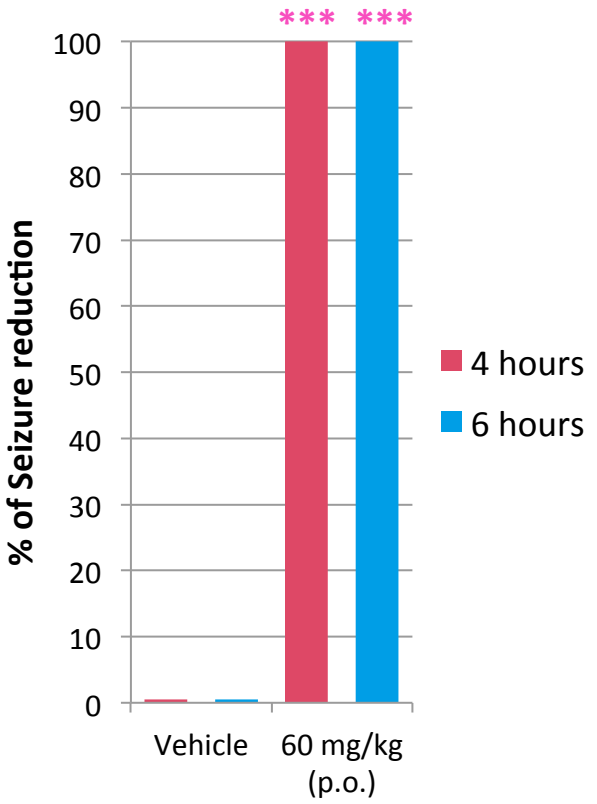
Neurodevelopmental and Neurodegenerative Disease Pipeline

ANAVEX™ 2-73 Pre-Clinical Epilepsy Data

Significant Seizure Reduction with ANAVEX2-73 in both MES and PTZ-Induced Seizure Models



Long-Lasting Effect Shown in PTZ-Induced Seizures

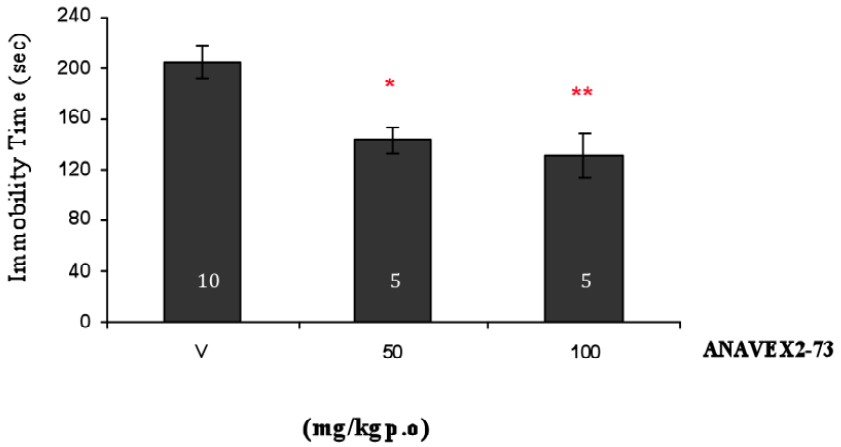


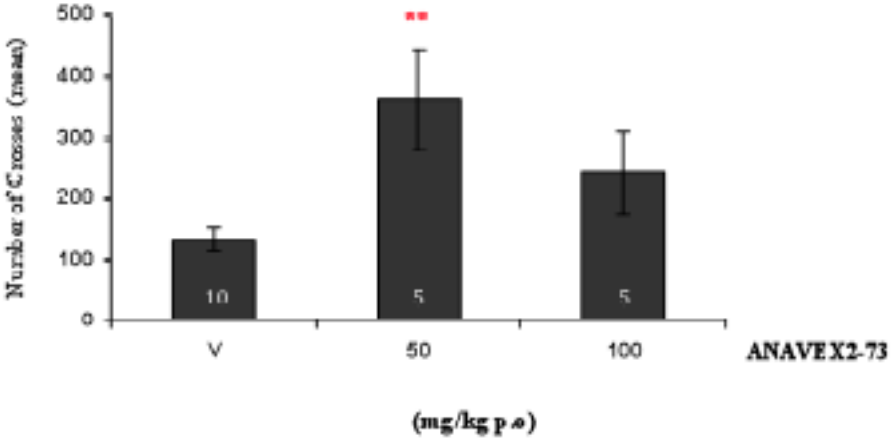
ANAVEX 2-73 also shows *synergistic* activity with three generations of epilepsy drugs currently on the market: ETS (Zarontin®), VPA (Depakene®) and Gabapentin (Neurontin®)

Presented at AES Meeting 2015; # Results have been confirmed by the NINDS screening program

Anti-Depressant and Anti-Anxiety Effect of ANAVEX™ 2-73 in Porsolt Swim Test (PST) and in Open Field Test

No observed "sedative" effect of ANAVEX 2-73





- Effect of ANAVEX2-73 on immobility time on PST. P<0.01, *p<0.05 and **p<0.01 for 50 and 100 mg/kg vs vehicle treated group. Statistical analysis performed with ANOVA followed by Dunnett's post-hoc test

- Effect of ANAVEX2-73 on the number of crosses (motility-exploratory behavior) in the Open Field Test. Statistical analysis performed with ANOVA followed by Dunnett's post-hoc test. P<0.05, **p<0.01

Presented at AES Meeting 2015

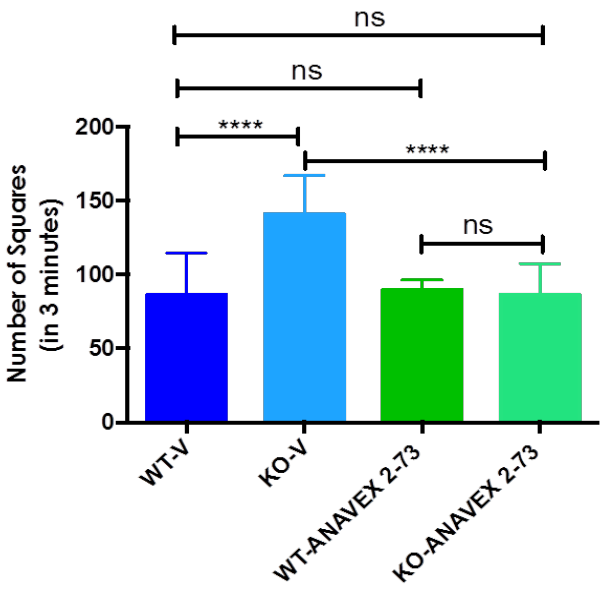
Autism Spectrum Disorders and Fragile X Syndrome

- Autism spectrum disorders (ASD) occur in up to 2/3 of males and 1/3 of females with Fragile X syndrome (FXS)
- FXS is the most common form of inherited intellectual disability and the most frequent single gene cause of autism, affecting approximately 1 in 4,000 males and 1 in 6,000 females
- In addition to the clinical overlap between FXS and ASD, there is likely a substantial overlap in the molecular pathology of the two disorders
- Molecules aimed at targets in these shared pathways are expected to have therapeutic overlap in subsets of individuals with ASD or neurodevelopmental disorders
- The Fragile X gene FMR1 is coding the FMR1 protein. In the brain FMR1 protein is highly expressed in neurons its main function appears to be the regulation of protein synthesis. Insufficient expression of FMR1 protein leads to deregulated translation and a broad array of effects on cellular signaling pathways, ultimately leading to abnormalities in brain connectivity and neurodevelopmental processes[#]

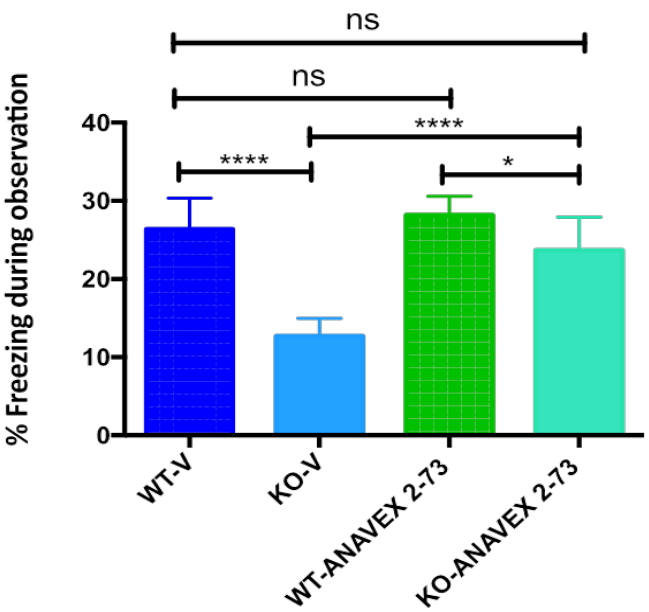
[#] *Grossman AW et al 2006, Bhakar AL et al 2012*

ANAVEX 2-73™ Significantly Reverses the Hyperactivity and Deficits in Learning and Memory in Fragile X – Autism-Related Disorders Model

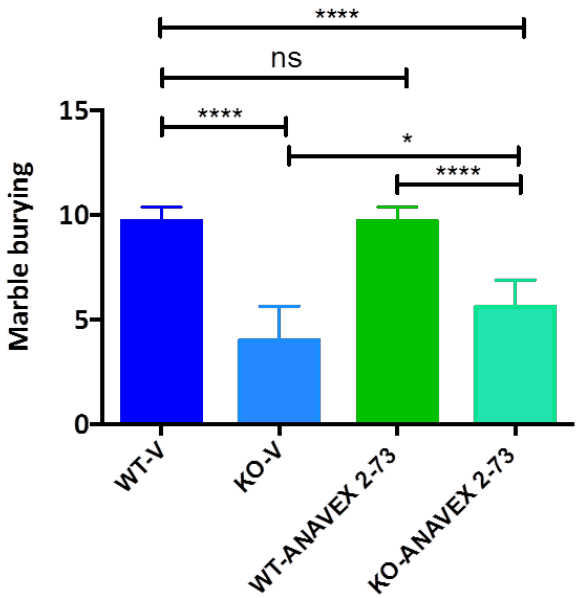
AV2-73 Reverses Hyperactivity of Fmr1-KO2 mice to Normal



AV2-73 Normalizes the Impairment in Associative Learning Characteristic of Fmr1-KO2 mice



AV2-73 Reduces Impairments in Species-Specific Behavior in Fmr1-KO2 Mice



Chronic treatment with ANAVEX 2-73 to Fmr1-KO2 mice has a robust effect on their characteristic hyperactivity and deficits in learning and memory. At the dose tested, ANAVEX 2-73 also yielded a partial effect on species-specific behavior in the form of marble burying

Presented at the Gordon Conference 2016; Study supported by FRAXA

Infantile Spasms

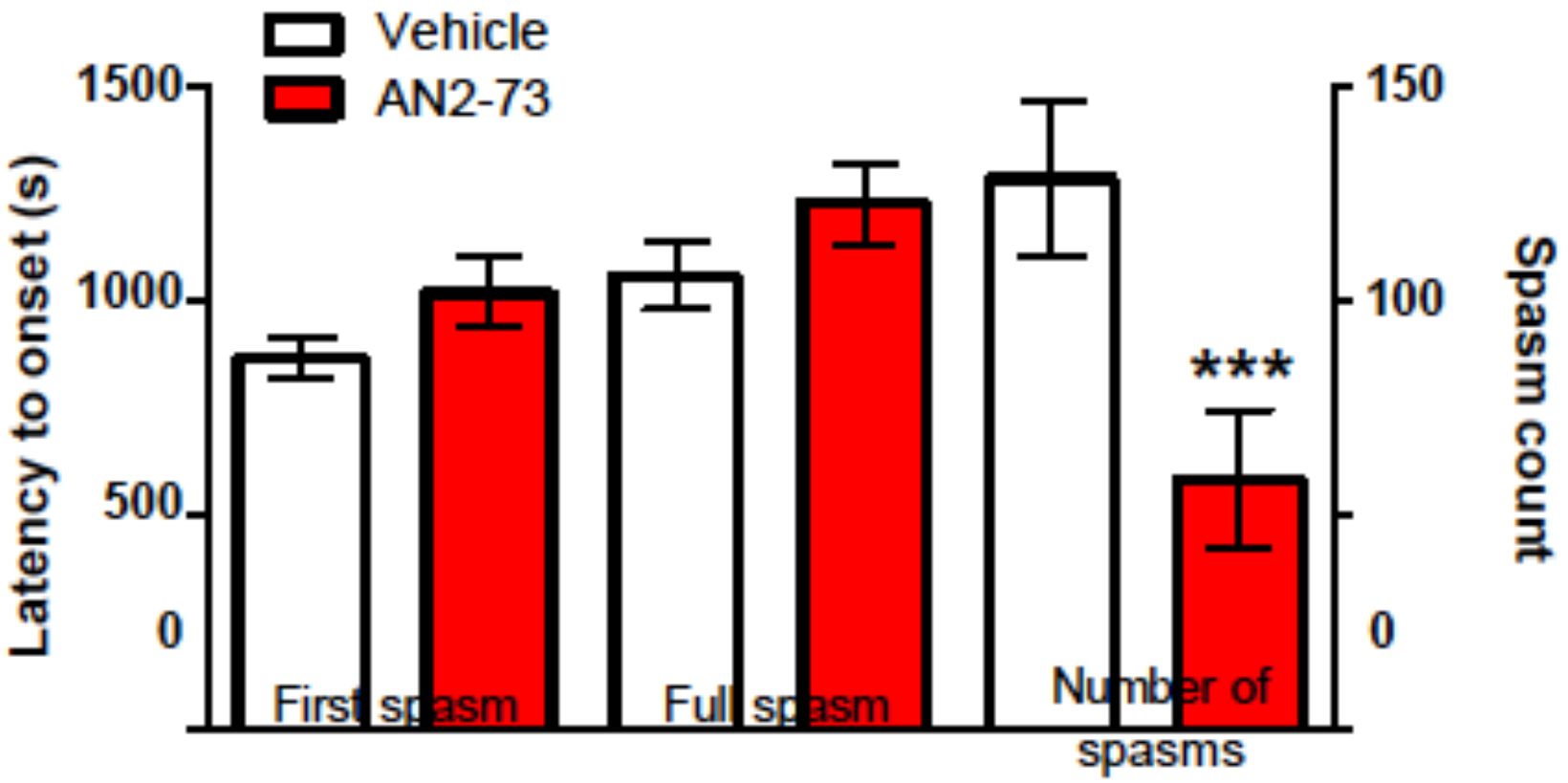
- A rare yet devastating condition, infantile spasms (IS) is a seizure disorder that typically occurs during the first 4-11 months of childhood
- Children who develop IS are at great risk for developmental disability and autism
- Most children who have infantile spasms will have a very abnormal electroencephalogram (EEG) pattern called hypsarrhythmia or modified hypsarrhythmia
- Infantile spasms usually stop by age five, but may be replaced by other seizure types
- Many underlying disorders, such as birth injury, metabolic disorders, and genetic disorders can give rise to spasms, making it important to identify the underlying cause

Preclinical Infantile Spasms

- The infantile spasms rat model represents a clinically relevant animal model of infantile spasms since the phenotype is developmentally specific and semiologically similar to human infantile spasms, including clustering of spasms[#]
- The phenotype of spasms persists only up to 21 days of age in rats (correlating with human infancy and early childhood)
- Further, EEG features correspond well to human infantile spasms, with interictal high amplitude asynchronous waves similar to hypsarrhythmia and ictal EEG suppression similar to electrodecrements
- Following prenatal priming with betamethasone (gestational day 15) in infant rats, 60 minutes later NMDA (15 mg/kg i.p.) was administered to trigger spasms[##]
- Infant rats received a single pretreatment of ANAVEX 2-73 (30 mg/kg i.p.) on postnatal day 15
- Spasms were recorded for 90 minutes following postnatal trigger of spasms with NMDA injection
- The protective effects of ANAVEX 2-73 were assessed[###]

[#] Tsuji, M., et al., Epilepsia, 2016; [##] Chachua, T., et al., Epilepsia, 2011. 52(9): p. 1666-77; Velisek, L., et al., Epilepsia, 2010. 51 Suppl 3: p. 145-9; [###] Study supported and performed by Libor Velisek, MD, PhD, Professor of Cell Biology & Anatomy, Pediatrics, and Neurology and his laboratory at New York Medical College (NYMC)

ANAVEX 2-73™ Significantly Reduces the Number of Spasms in an Infant Rat Model of Infantile Spasms

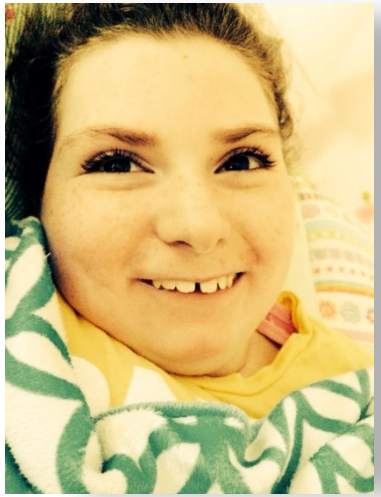


Treatment with ANAVEX 2-73 significantly reduced the number of spasms by 55 percent compared to vehicle (p=0.0002)

Rett Syndrome

What is Rett Syndrome?

- Rare non-inherited genetic postnatal progressive neurodevelopmental disorder
- Caused by mutation of *MECP2* gene
- Occurs almost exclusively in girls and leads to severe impairments
- One in 10,000 to 15,000 girls
- Seizures
- Anxiety disorder
- Cognitive impairment
- Loss of speech
- Loss of purposeful hand movements and development of stereotypic hand movements
- Balance and coordination issues, decrease or loss of ability to walk



Experiment to Study ANAVEX 2-73 in *MECP2* Rett syndrome disease mouse model supported by Rettsyndrome.org

Image Source: RettSyndrome.org, patient Jilly

Preclinical Rett Syndrome

Breeding info

- Female mice with heterozygous (HET) *MECP2*-null mutation[#]
- A mouse with a *MECP2*-null mutation causes neurological symptoms that mimic Rett syndrome
- Breeding done at Jackson Laboratories, mice provided at 4-5 weeks of age

MECP2 females testing at 8 and 12 weeks of age

- 20 WT[##] – vehicle (0.25% MC/dH_2O)
- 20 HET – vehicle (0.25% MC/dH_2O)
- 20 HET – AV2-73 (10 mg/kg)
- 20 HET – AV2-73 (30 mg/kg)

- Chronic dosing (p.o.) daily, starting at ~5.5 weeks of age and continuing through the 12-week behavioral testing time point 60 min pre-treatment during behavioral testing[###]

[#] HET = (B6.129P2(C)-MECP2(tm1.1Bird); [##] WT = wild type; [###] Study supported by RettSyndrome.org and performed by PsychoGenics, Inc.

Clasping

- Mice are lifted gently by the tail with front limbs remaining on surface
- Clasping of hind legs is noted (normal is a spread in the hind legs)

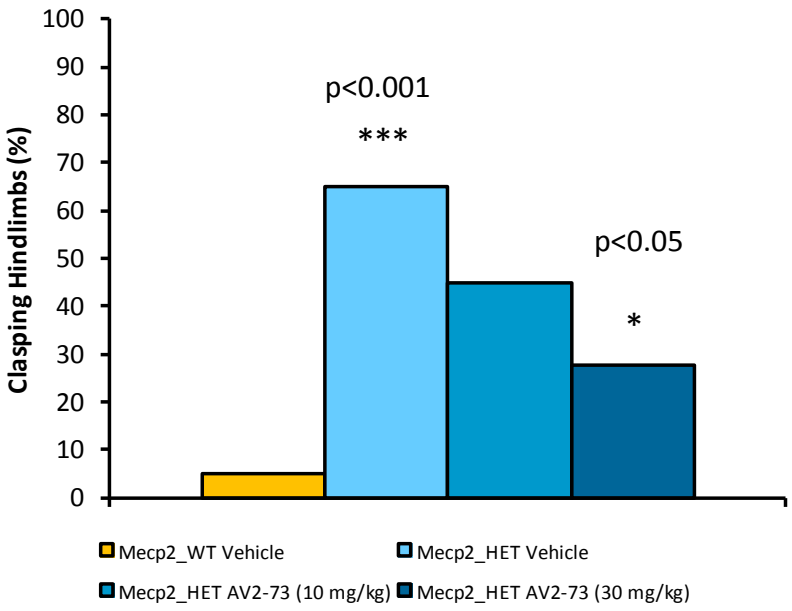
Normal

Impaired

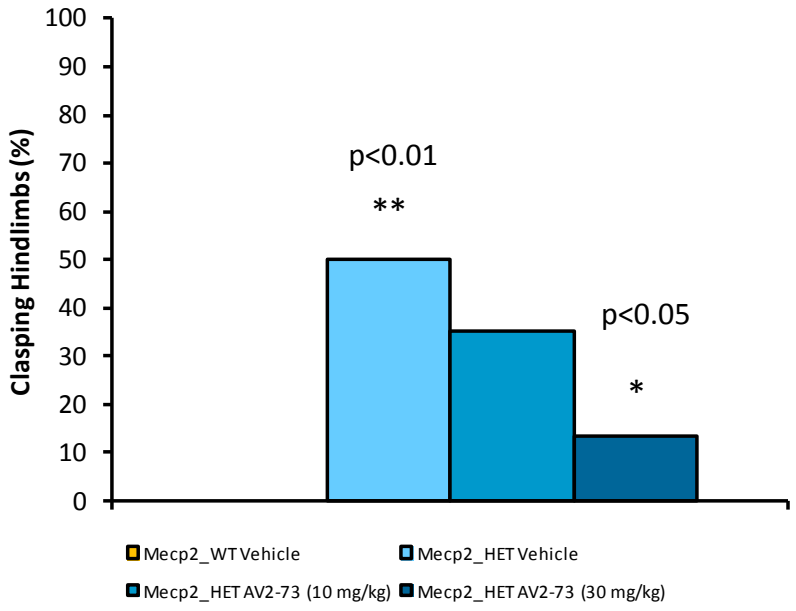
Clasping at 8 and 12 Weeks

- Vehicle-treated mutant (HET) mice clasped more than vehicle-treated wild type (WT) mice ($p<0.001$ at 8 weeks; $p<0.01$ at 12 weeks)
- Mice treated with AV2-73 (30 mg/kg) clasped less than vehicle-treated mutant mice ($p<0.05$ at 8 and 12 weeks)

Clasping at 8 weeks



Clasping at 12 weeks



Startle

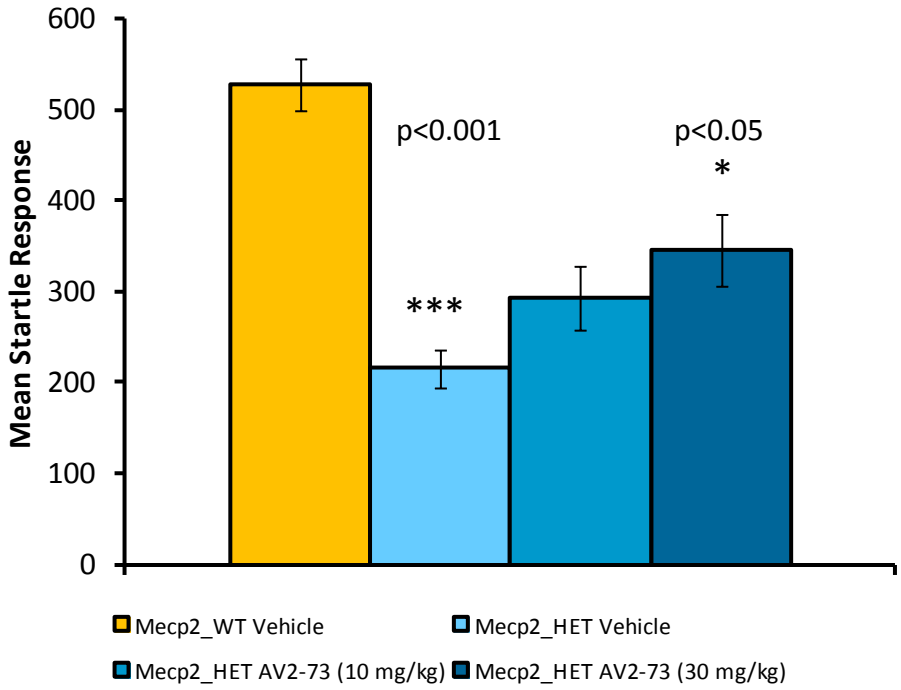
- The acoustic startle measures an unconditioned reflex response to external auditory stimulation
- Wild type mice have a higher startle response compared to impaired mice

Image: www.med-associates.com

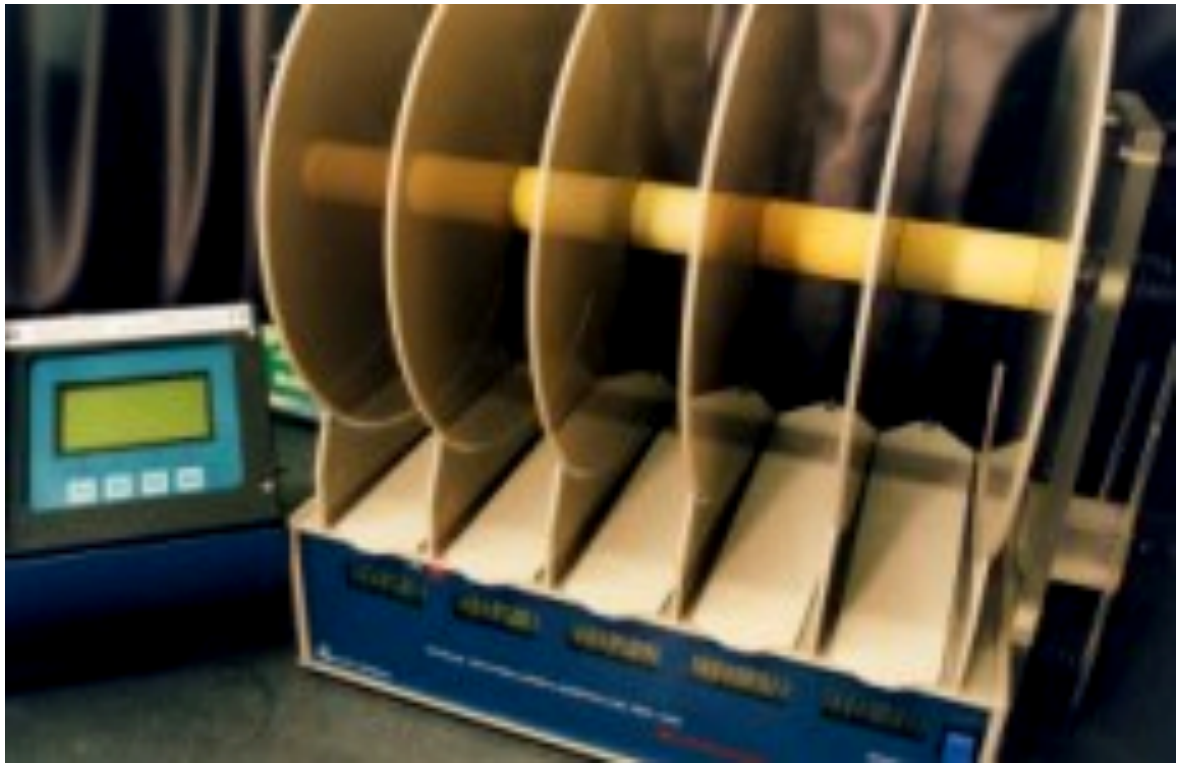
Source: PsychoGenics, Inc.

Startle at 8 Weeks

- Vehicle-treated mutant (HET) mice startled less compared to vehicle-treated wild type (WT) mice ($p<0.001$)
- AV2-73 (30 mg/kg) treated mice showed an increased startle response compared to vehicle-treated mutant mice ($p<0.05$)



Rotarod

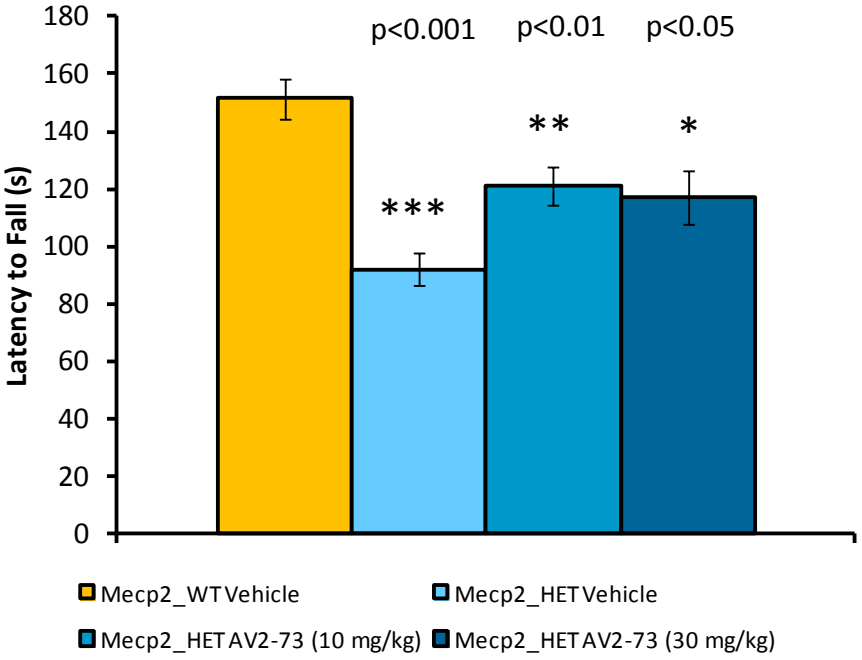


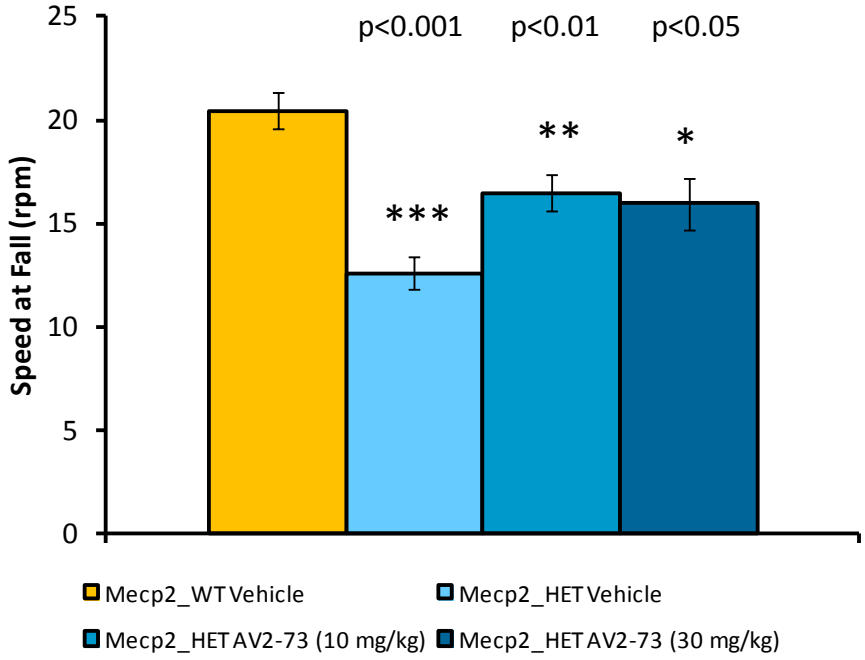
Source: PsychoGenics, Inc.

Rotarod at 12 Weeks

- Vehicle-treated mutant (HET) mice fell significantly more rapidly and at lower speeds compared to vehicle-treated wild type (WT) mice (p<0.001)

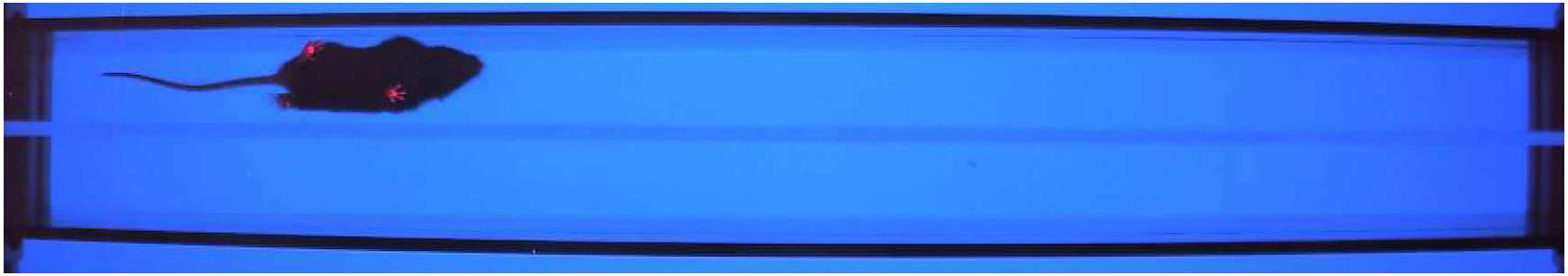
- AV2-73-treated mice at both doses (10 and 30 mg/kg) took significantly more time to fall off the rod and fell at higher speeds compared to vehicle-treated mutant mice (p<0.01 and p<0.05)





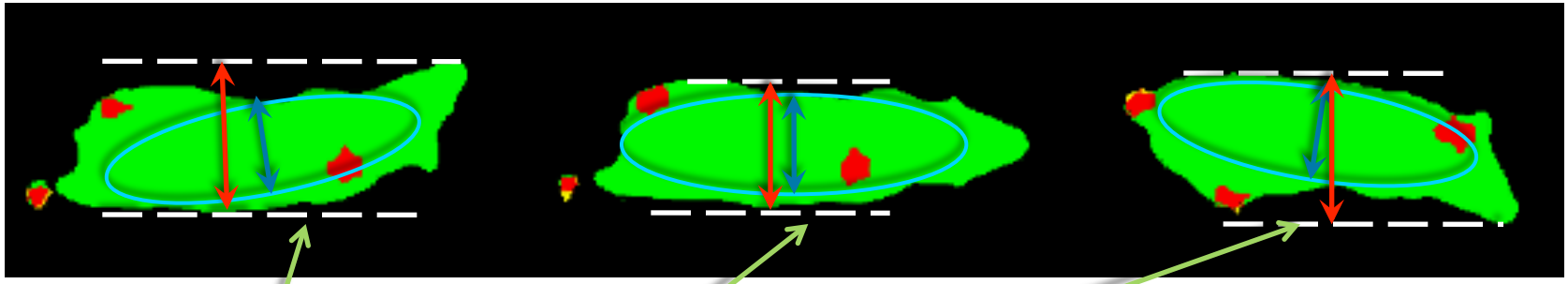
NeuroCube

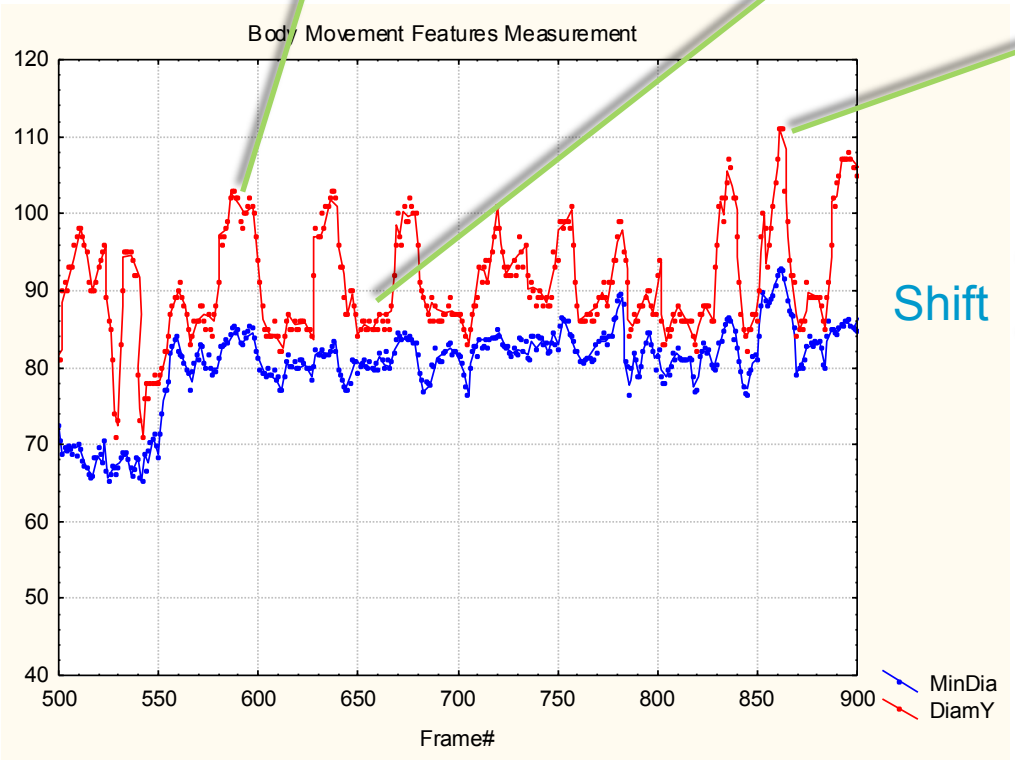
- A platform that employs computer vision to detect changes in gait geometry and gait dynamics in rodent models of neurological disorders, pain & neuropathies
- Mice are allowed to walk in the chamber for 5 min
- When the paw touches the screen, LED light reflects creating bright spots
- Images are captured and processed using proprietary computer vision and bio-informatics data mining algorithms



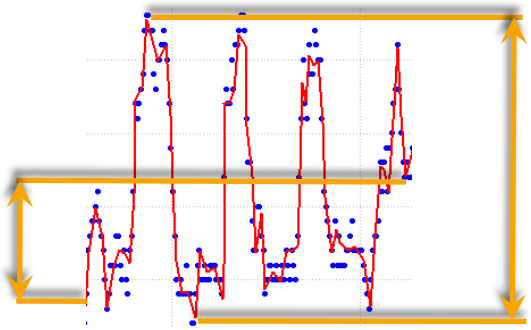
Source: PsychoGenics, Inc.

NeuroCube Body Motion Features





Shift



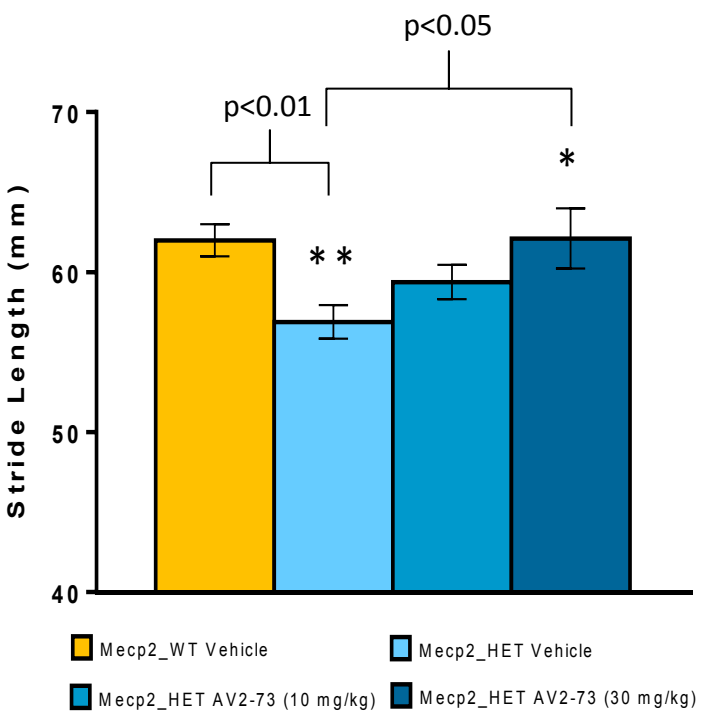
Amplitude

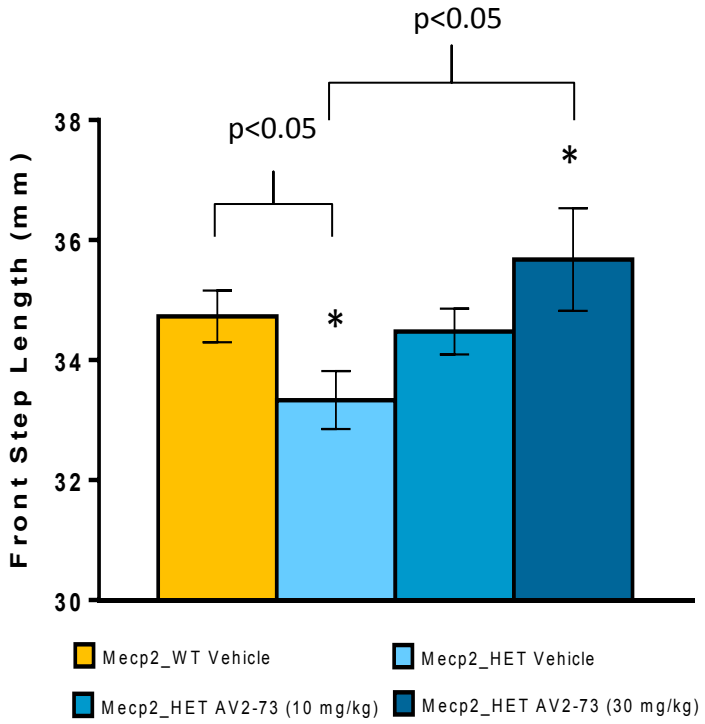
- Shift – the difference between the first and the last values
- Amplitude – the difference between maximal and minimal values
- Volatility = Shift / Amplitude

Source: PsychoGenics, Inc.

NeuroCube at 8 Weeks

Some gait differences appear to be rescued





NeuroCube at 8 Weeks

Comprehensive Analysis:

Gait, Correlation, Body Motion demonstrate significant improvement

	WT vehicle v. Het vehicle	*Het vehicle v. Het AV2-73, 10 mg/kg*	*Het vehicle v. Het AV2-73, 30 mg/kg*
Overall			
	90, *p=0*	53, *p*> 0.69	62, *p*> 0.24
GAIT			
	78, *p*< 0.01	63, *p*> 0.09	**69, *p*< 0.05**
Paw Features			
	91, *p*< 0.001	52, *p*> 0.78	55, *p*> 0.56
Correlation			
	53, *p*> 0.66	56, *p*> 0.40	**76, *p*< 0.005**
Body Motion			
	71, *p*< 0.02	60, *p*> 0.20	**81, *p*< 0.003**
Paw Positioning			
	84, *p*< 0.0001	53, *p*> 0.57	57, *p*> 0.36

Bold represents significance

Summary

- Administration of ANAVEX 2-73 results in both significant and dose related improvements in an array of behavioral paradigms in the *MECP2* HET Rett syndrome disease model
- These behavioral paradigms measure different aspects of muscular coordination, balance, motor learning and muscular strengths, some of the core deficits observed in Rett syndrome
- The efficacy of ANAVEX 2-73 in additional different disease-relevant models – Infantile Spasms and Fragile X, Autism-related Disorders – in combination with existing clinical safety data supports exploration of ANAVEX 2-73 as a potential therapeutic in these disorders
- Clinical efficacy may also be evident in patients with CDKL5 mutations given that this gene has been implicated in both Rett Syndrome and X-linked Infantile Spasm Syndrome

Coupled with positive human safety and clinical cognition data, as well as preclinical anti-seizure and anti-anxiety data, ANAVEX 2-73 might be a potential drug candidate to investigate in Rett syndrome