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

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Disclosure

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

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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

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

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

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

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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 ameliorate the quality of life in the subjects affected.

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.

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 ✓

**ANAVEX 2-73**
- Sigma-1 Receptor Agonist
- “Pluripotent Modulator”
- Modulating Ca²⁺
- Reducing mitochondrial dysfunction
- Reducing protein misfolding
- Reducing oxidative stress
- Reducing inflammation

**Parkinson’s#**
- Preclinical validation, MJFF ☐

**Depression**
- Preclinical validation ✓

**Anxiety**
- Preclinical validation ✓

**Epilepsy (seizures)**
- Preclinical validation ✓

**Infantile Spasms (seizures)**
- Preclinical validation ✓

**Multiple Sclerosis (MS)**
- Preclinical validation ✓

# Neurodevelopmental and Neurodegenerative Disease Pipeline

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<tr>
<th>ANAVEX™ 2-73</th>
<th>ALZHEIMER'S</th>
<th>COGNITION IN NEUROPSYCHIATRIC</th>
<th>EPILEPSY</th>
<th>PARKINSON'S</th>
<th>MULTIPLE SCLEROSIS (MS)</th>
<th>RARE DISEASE, FRAGILE X</th>
<th>RARE DISEASE, RETT SYNDROME</th>
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- **US FDA Orphan Designation**
- **In Progress**
- **In Preparation**
- **Alzheimer’s and CNS**
- **Oncology and Pain**

*Image Source: Anavex Life Sciences Corp.*
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
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

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###

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
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$_2$O)
- 20 HET – vehicle (0.25% MC/dH$_2$O)
- 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
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)
The acoustic startle measures an unconditioned reflex response to external auditory stimulation.

Wild type mice have a higher startle response compared to impaired mice.

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** – 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

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<thead>
<tr>
<th></th>
<th>WT vehicle v. Het vehicle</th>
<th>Het vehicle v. Het AV2-73, 10 mg/kg</th>
<th>Het vehicle v. Het AV2-73, 30 mg/kg</th>
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<tr>
<td>Overall</td>
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<tr>
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<td>90, <em>p</em> = 0</td>
<td>53, <em>p</em> &gt; 0.69</td>
<td>62, <em>p</em> &gt; 0.24</td>
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<td>78, <em>p</em> &lt; 0.01</td>
<td>63, <em>p</em> &gt; 0.09</td>
<td>69, <em>p</em> &lt; 0.05</td>
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<td>Paw Features</td>
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<td>91, <em>p</em> &lt; 0.001</td>
<td>52, <em>p</em> &gt; 0.78</td>
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<td>53, <em>p</em> &gt; 0.66</td>
<td>56, <em>p</em> &gt; 0.40</td>
<td>76, <em>p</em> &lt; 0.005</td>
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<td>Body Motion</td>
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<td>60, <em>p</em> &gt; 0.20</td>
<td>81, <em>p</em> &lt; 0.003</td>
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<td>Paw Positioning</td>
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<td>84, <em>p</em> &lt; 0.0001</td>
<td>53, <em>p</em> &gt; 0.57</td>
<td>57, <em>p</em> &gt; 0.36</td>
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*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