



XENON

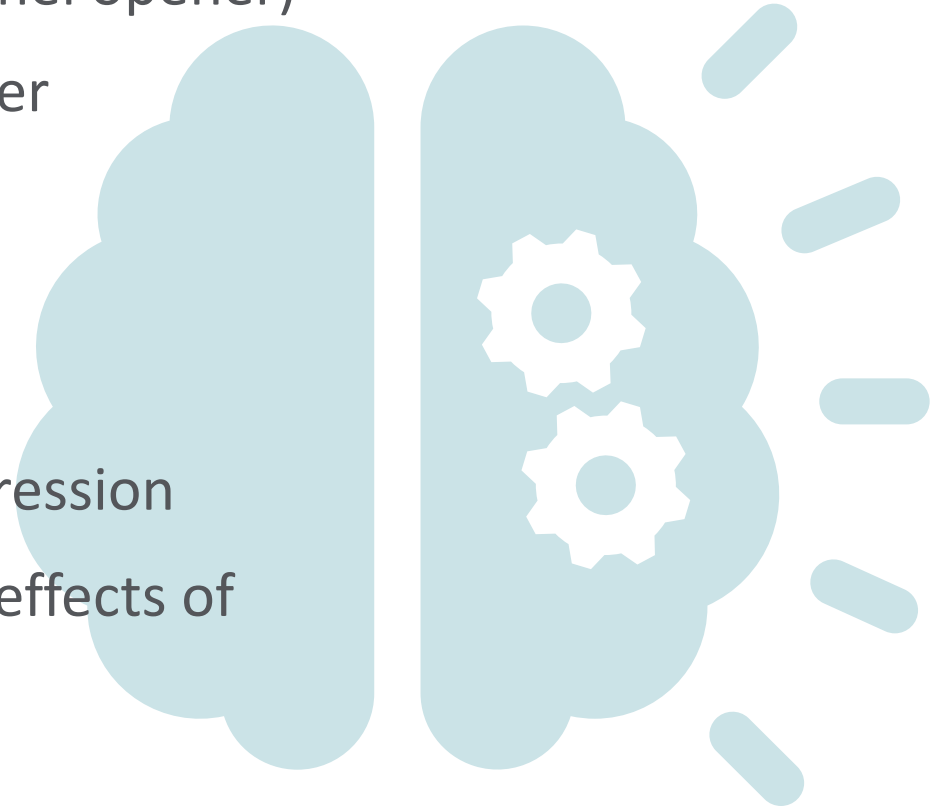
5th Neuropsychiatric
and Psychedelic Drug
Development Summit

Overview: Novel K_v7 Mechanism of Action for Depression

OCTOBER 31-NOVEMBER 2, 2022 | BOSTON, MA

Discussion Topics

- Overview of K_v7 mechanism of action (potassium channel opener)
- XEN1101: a novel, “next-gen” potassium channel opener
 - Compelling clinical efficacy results in epilepsy
- Pre-clinical K_v7 data in models of depression
- Clinical research of K_v7 (ezogabine) in MDD
- Current XEN1101 clinical development program in depression
- Recent pre-clinical research examining antidepressant effects of Ketamine (by upregulating K_v7)



XEN1101 is a Novel “Next-Gen” K_v7 Channel Modulator

Potential “only-in-class” K_v7 potassium channel modulator to treat adult focal seizures

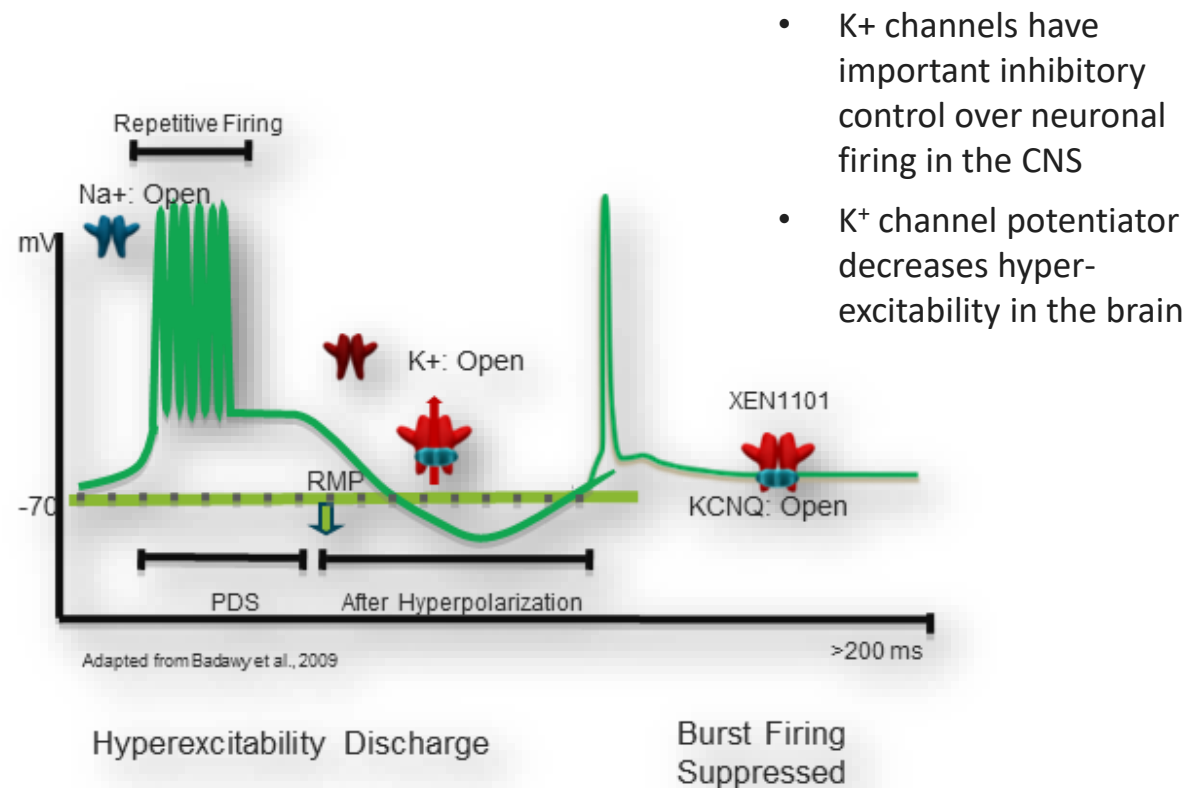
Addresses **limitations** of first-gen K_v7 modulator, ezogabine; cannot form **pigmented dimers**

Novel MOAs needed for rational **polypharmacy approach**

Potential efficacy for **common comorbidity of depression**

Covered by patents up to ~2040

Mechanism of Action Previously Validated with Ezogabine



XEN1101 Summary



Novel Mechanism

Differentiated “next generation” K_v7 potassium channel opener being developed for the treatment of epilepsy and other neurological disorders

Preclinical models and clinical studies suggest K_v7 channel openers may have broad anti-seizure activity in patients with focal and generalized epilepsy



XEN1101 Clinical Experience

Positive results from the Phase 2b X-TOLE trial demonstrate statistically significant seizure reduction in a difficult-to-treat FOS patient population

Additional X-TOLE and X-TOLE OLE analyses support differentiated clinical profile

Alignment with FDA regarding use of X-TOLE to support NDA submission and planned Phase 3 program in FOS



XEN1101 Commercial Opportunity

In market research, physicians reacted positively to the XEN1101 profile:

- Broad spectrum benefits with rapid onset and no titration
- Novel MOA that can be used in polypharmacy
- QD dosing



XEN1101 Expansion Opportunities

PGTCS are life-threatening seizures, with fewer ASMs available resulting in significant unmet need

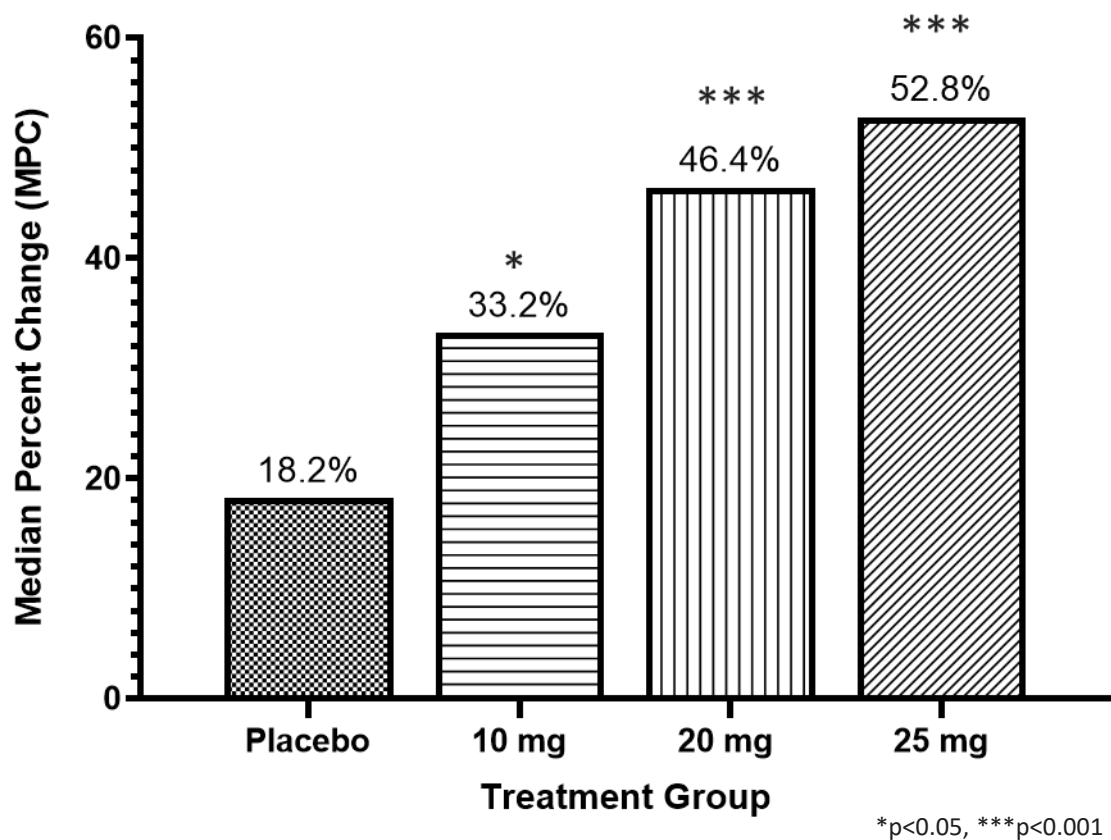
- Single Phase 3 X-ACKT clinical trial; a randomized, placebo-controlled, double-blind trial in PGTCS

Depression represents a key co-morbidity associated with FOS

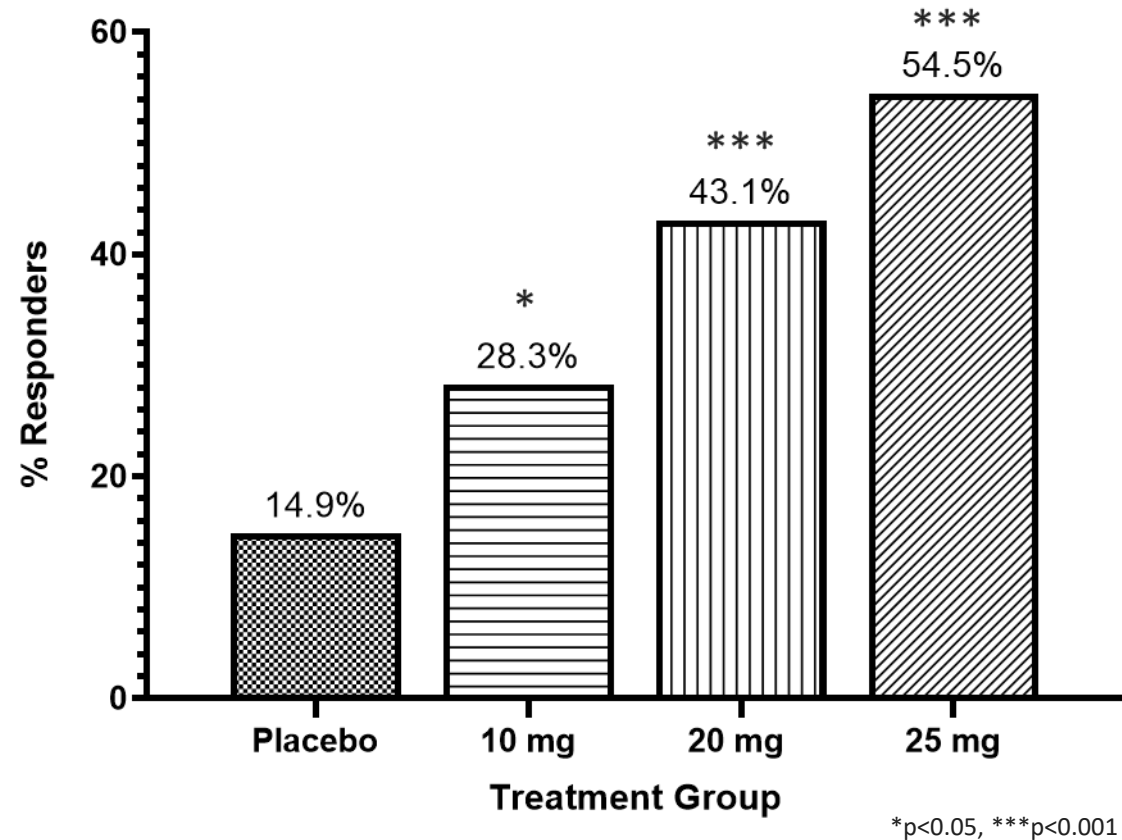
- Phase 2 X-NOVA POC clinical trial ongoing in MDD to understand impact on depression and anhedonia

XEN1101's Compelling Phase 2b Efficacy Results

Change from Baseline in Seizure Frequency



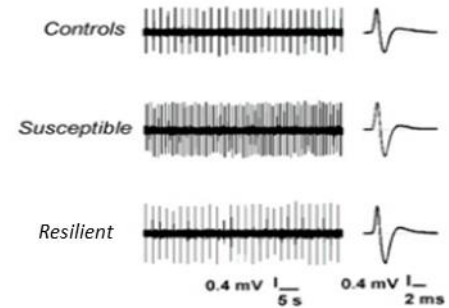
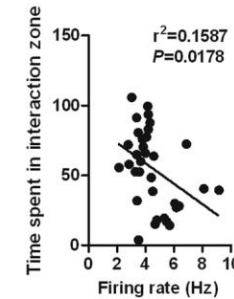
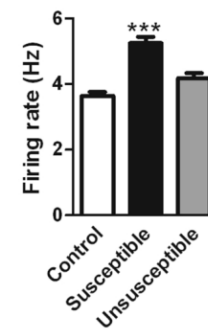
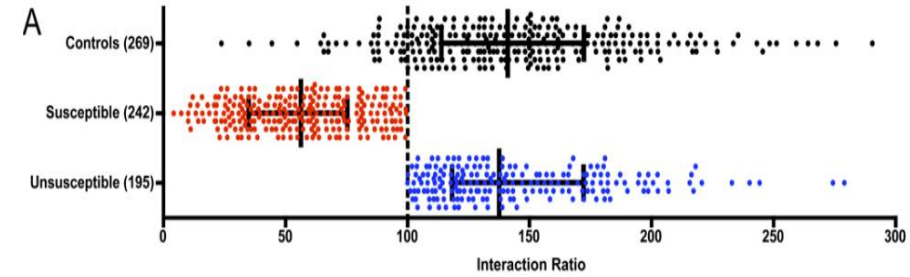
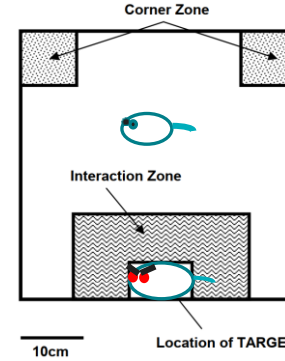
Responder Rate (RR50)



Highly significant and dose dependent reduction in seizures

K_v7 Channels and Resilience to Chronic Social Defeat Stress

- Model of stress related depression
- Discordant behavioral outcomes to CSDS resulting in susceptible and resilient animals
- Studied to understand the molecular basis of resilience in stress induced depression
- Tonic firing rather than hyperexcitability of the VTA in the reward system leads to resilient mice
- Gene expression studies showed upregulation of potassium channel including K_v7.3 (KCNQ3) correlate with resilient phenotype
- Suggests resilience to CSDS is an active molecular process of stress-coping



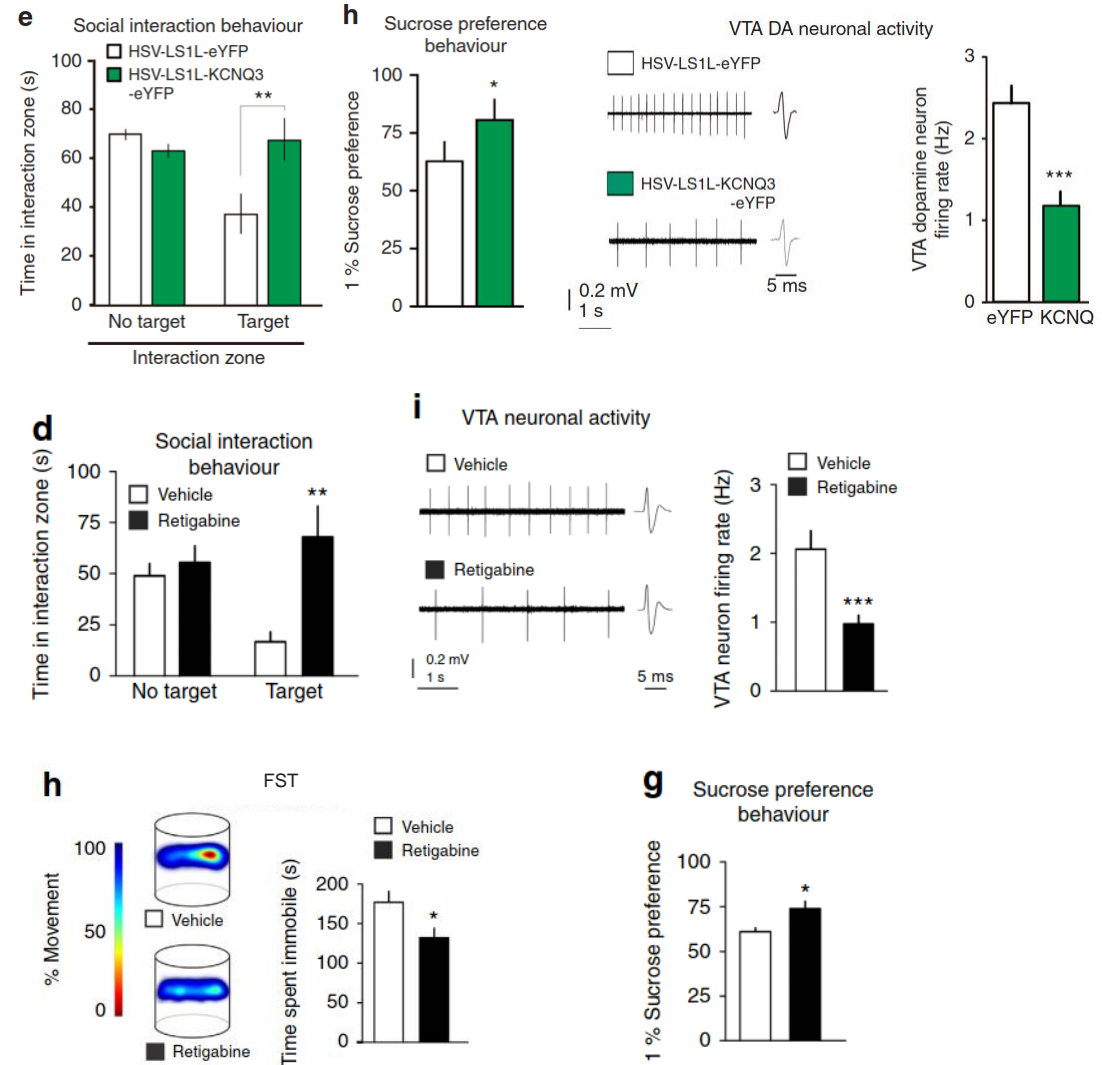
Ventral Tegmental Area

| Gene (Definition) | Susceptible | Unsusceptible |
|--|-------------|---------------|
| <i>Gal</i> (Galanin) | ↑ | ↔ |
| <i>Gdnf</i> (Glial derived neurotrophic factor) | ↔ | ↑ |
| <i>Kcnf1</i> (Voltage gated K ⁺ channel F1) | ↔ | ↑ |
| <i>Kcnh3</i> (Voltage gated K ⁺ channel H3) | ↔ | ↑ |
| <i>Kcnk4</i> (K ⁺ channel K4 [TRAAK]) | ↔ | ↑ |
| <i>Kcnq3</i> (Voltage gated K ⁺ channel Q3) | ↔ | ↑ |
| <i>Kif1b</i> (Kinesin family member 1B) | ↔ | ↓ |
| <i>Lcn2</i> (Lipocalin-2) | ↑ | ↑ |

Krishnan, Cell 2007; Cao, J Neuroscience 2010

K_V7 Channels' Role in Active Resilience

- K_V7.3 forms heterotetramers with K_V7.2 to effect the M-current and blunt VTA hyperexcitability
- Viral expression of K_V7.3 in VTA reverses the CSDS susceptible phenotype and hyperexcitability and improved anhedonia
 - Blunted VTA hyperexcitability and normalized social interaction
 - Improved sucrose preference a measure of anhedonia
- K_V7 opener (ezogabine/retigabine) dosed 8-days (1 mg/kg ip) reversed the susceptibility phenotype mimicking the resilient phenotype
 - Blunted VTA hyperexcitability and normalized social interaction
 - Improved sucrose preference a measure of anhedonia

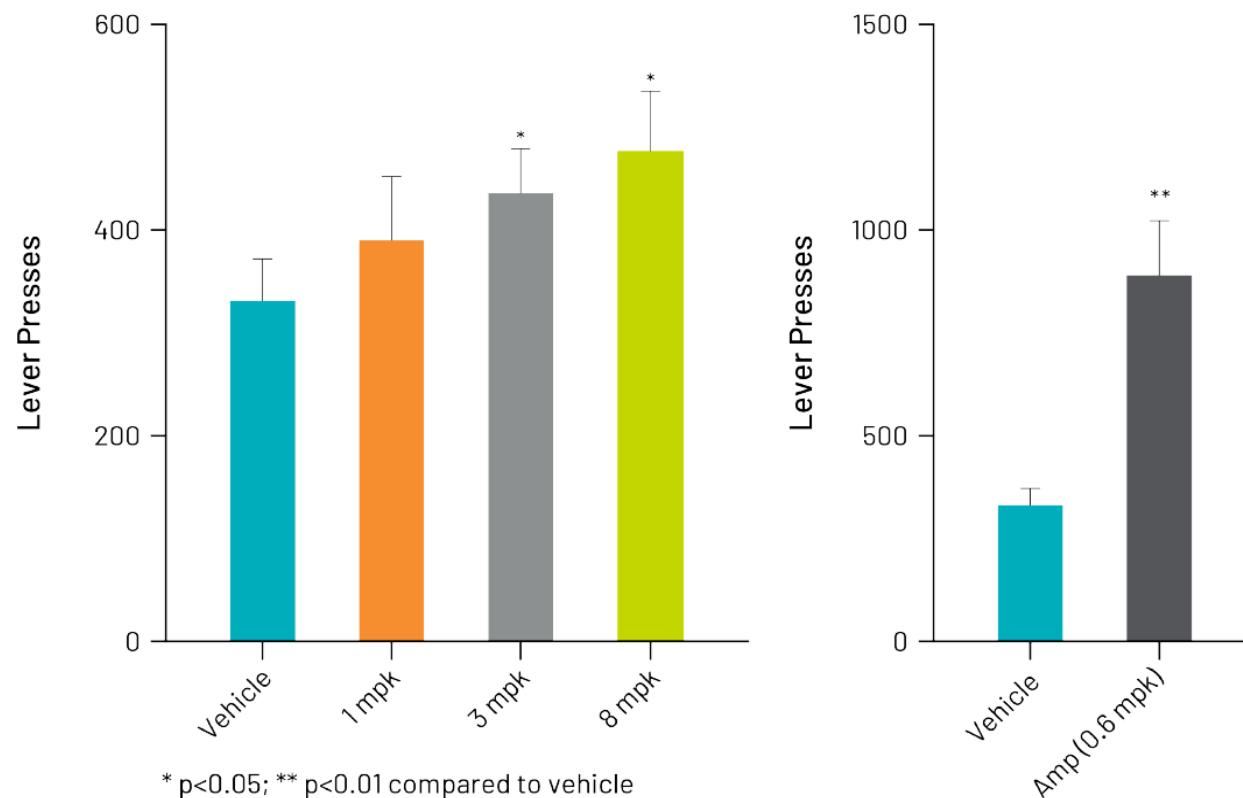


Friedman, Nature Communications 2016

Supportive Pre-Clinical XEN1101 Data

- Encouraging pre-clinical activity data with XEN1101
- XEN1101 was assessed in the progressive ratio test (PRT)
 - protocol evaluates motivational performance and decisional anhedonia in rats
- In this test XEN1101 increased the total number of lever presses, indicating improved motivation versus vehicle

Results of the Progressive Ratio Test

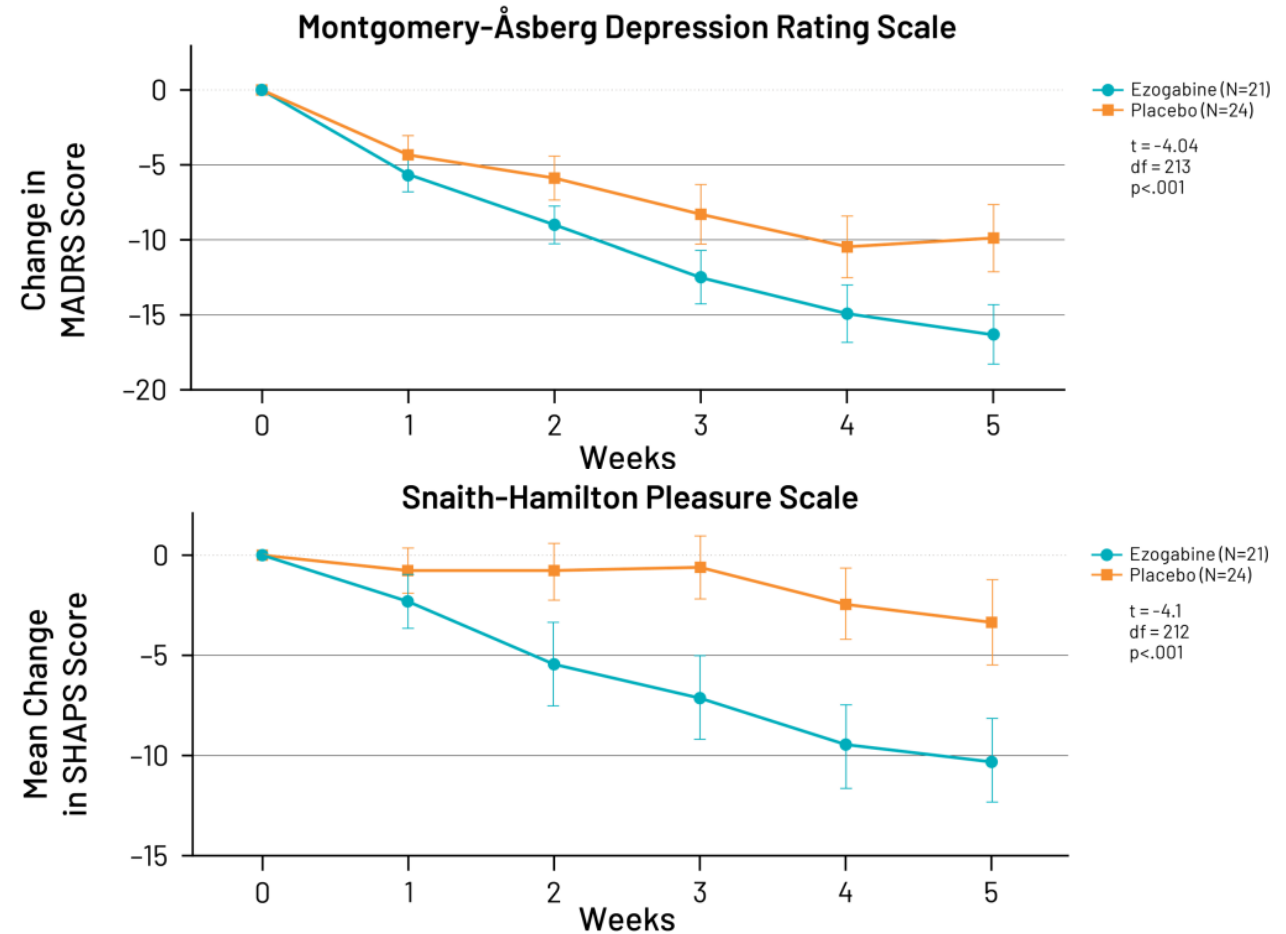


Rats were trained to respond for food made available under a progressive schedule of reinforcement in which the number of lever presses required to obtain a food reward increased for each successive reward. In a cross-over design, rats received a single dose of 1, 3, 8 mpk XEN1101 or vehicle (n=32). Total number of lever presses in the test session were measured. The stimulant amphetamine was used as a positive assay control.

Promising Clinical Data with Ezogabine in MDD

- Promising clinical results with ezogabine dosed 300 mg TID as a treatment for Major Depressive Disorder (MDD) and anhedonia
- Ezogabine, compared with placebo, was associated with:
 - an increase in activation to reward anticipation during the flanker test from baseline to week 5 ($p=0.07$). Ezogabine (N=18) Placebo (N=22)
 - a large improvement in depression as measured by the Montgomery-Åsberg Depression Rating Scale (MADRS score change from placebo: -7.9 ± 3 , $p<.001$)
 - a large improvement in hedonic capacity as measured by the Snaith-Hamilton Pleasure Scale (SHAPS score change from placebo: -6.9 ± 3.2 , $p<.001$)

Figures reproduced from Costi et al. Depression symptoms assessed by the Montgomery-Åsberg Depression Rating Scale. Anhedonia symptoms assessed by the Snaith-Hamilton Pleasure Scale.



Costi et al, Am J Psychiatry 2021

XEN1101 Phase 2 POC Studies in Major Depressive Disorder

Company-sponsored “X-NOVA” XEN1101 Phase 2 Clinical Trial Underway

Primary Objective: Assess the efficacy of 10 mg and 20 mg doses of XEN1101 compared to placebo on improvement of depressive symptoms in ~150 subjects diagnosed with MDD using MADRS score change through week 6

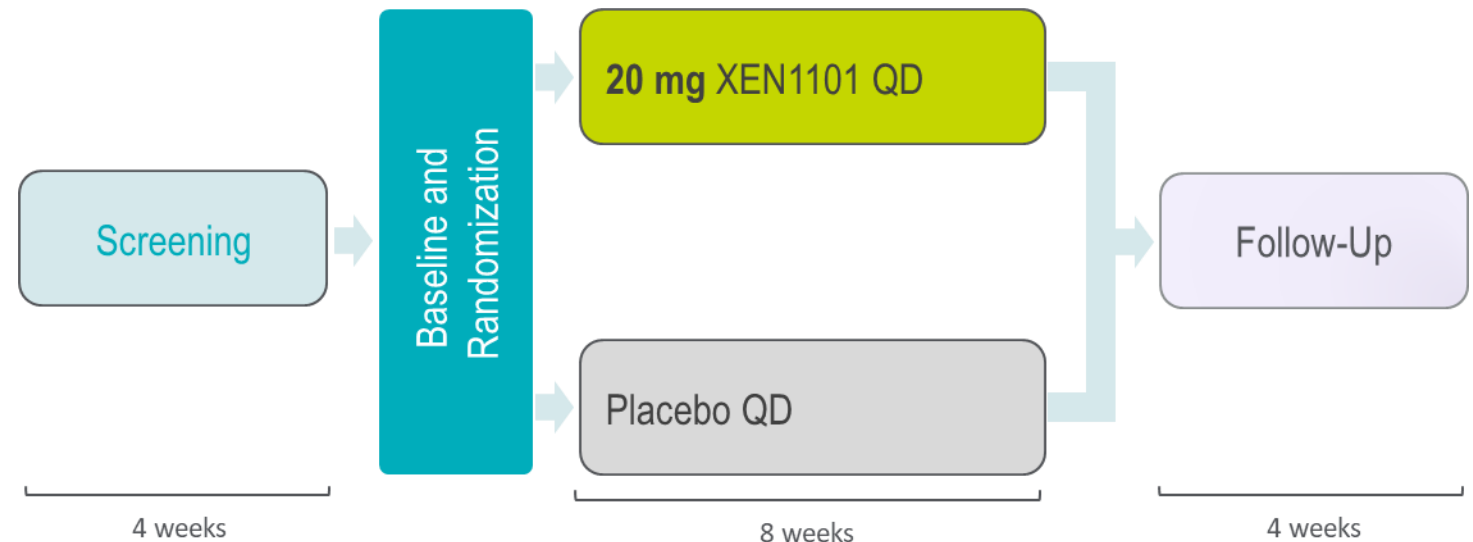


| Inclusion Criteria |
|---|
| 1. Male or female, aged 18 through 65 years (inclusive) with a body mass index (BMI) ≤ 35 kg/m ² . |
| 2. Subject must meet the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for major depressive disorder (MDD) and currently be experiencing a moderate to severe major depressive episode (MDE), confirmed using the Mini International Neuropsychiatric Interview (MINI). |
| 3. Current MDE duration ≥ 2 months and < 24 months at the time of screening. |
| 4. Current illness severity that is at least moderate, defined as a score of ≥ 20 on the Hamilton Depression Rating Scale, 17-Item (HAM-D17) at screening and on Day 1. |
| 5. Score ≥ 20 on the Snaith-Hamilton Pleasure Scale (SHAPS) at screening and on Day 1. |
| Exclusion Criteria |
| 1. A primary psychiatric diagnosis other than MDD as defined by DSM-5 (comorbid anxiety disorders are allowed). |
| 2. Concomitant use of antidepressants and/or other disallowed pharmacotherapy (including benzodiazepines). |
| 3. History of schizophrenia or other psychotic disorder, MDD with psychotic features, bipolar I or II disorder, or MDD with mixed features. |
| 4. History of non-response to > 1 antidepressant drug due to lack of efficacy in the current MDE. |
| 5. Failing > 3 antidepressant drug trials, for any reason, in the current MDE. |
| 6. Active suicidal plan/intent in the past 6 months, or > 1 lifetime suicide attempt. |
| 7. Meets criteria for a substance use disorder within the past 12 months, with the exception of tobacco use, and/or has a positive urine toxicology screen for drugs of abuse. |

XEN1101 Phase 2 POC Studies in Major Depressive Disorder

Mount Sinai Investigator Initiated Trial of XEN1101 for Major Depressive Disorder

- Sample size: 60 (30 per arm)
 - 2 sites (Mt Sinai and Baylor)
- Similar design to Xenon's MDD study, with some differences:
 - Primary endpoint: Change in activation within the bilateral ventral striatum, assessed through the incentive flanker task during fMRI
 - 8-week treatment duration
 - Only 20 mg dose and placebo arms
 - Subjects excluded if non-response to >4 adequate antidepressant trials in the current episode

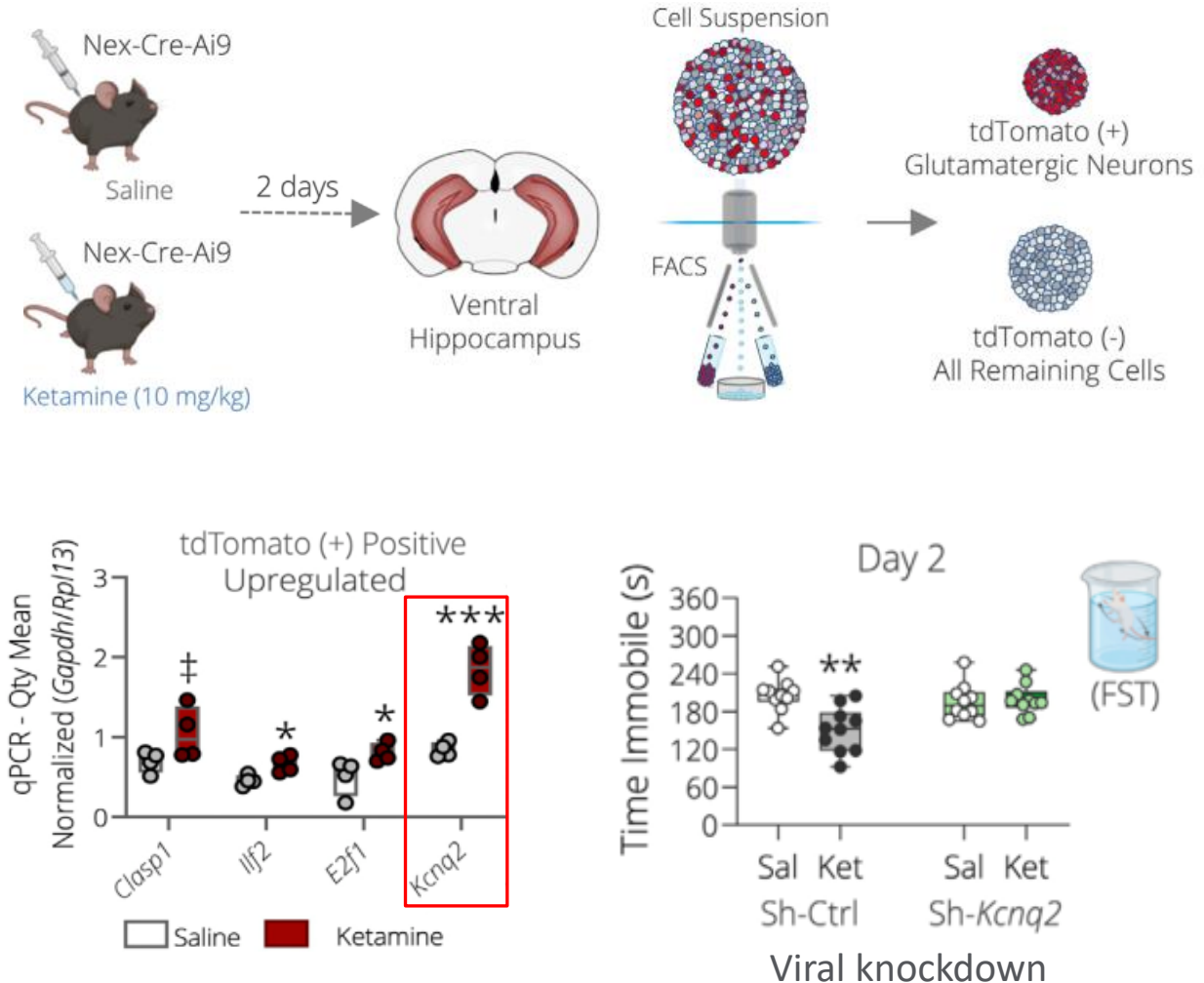


- Investigator-initiated study
- Financed by NIMH grant
- Xenon to provide XEN1101 and matching placebo

Sustained Antidepressant Response of Ketamine

Ketamine Exerts its Sustained Antidepressant Effects via Upregulation of Kv7 (Kcnq2)

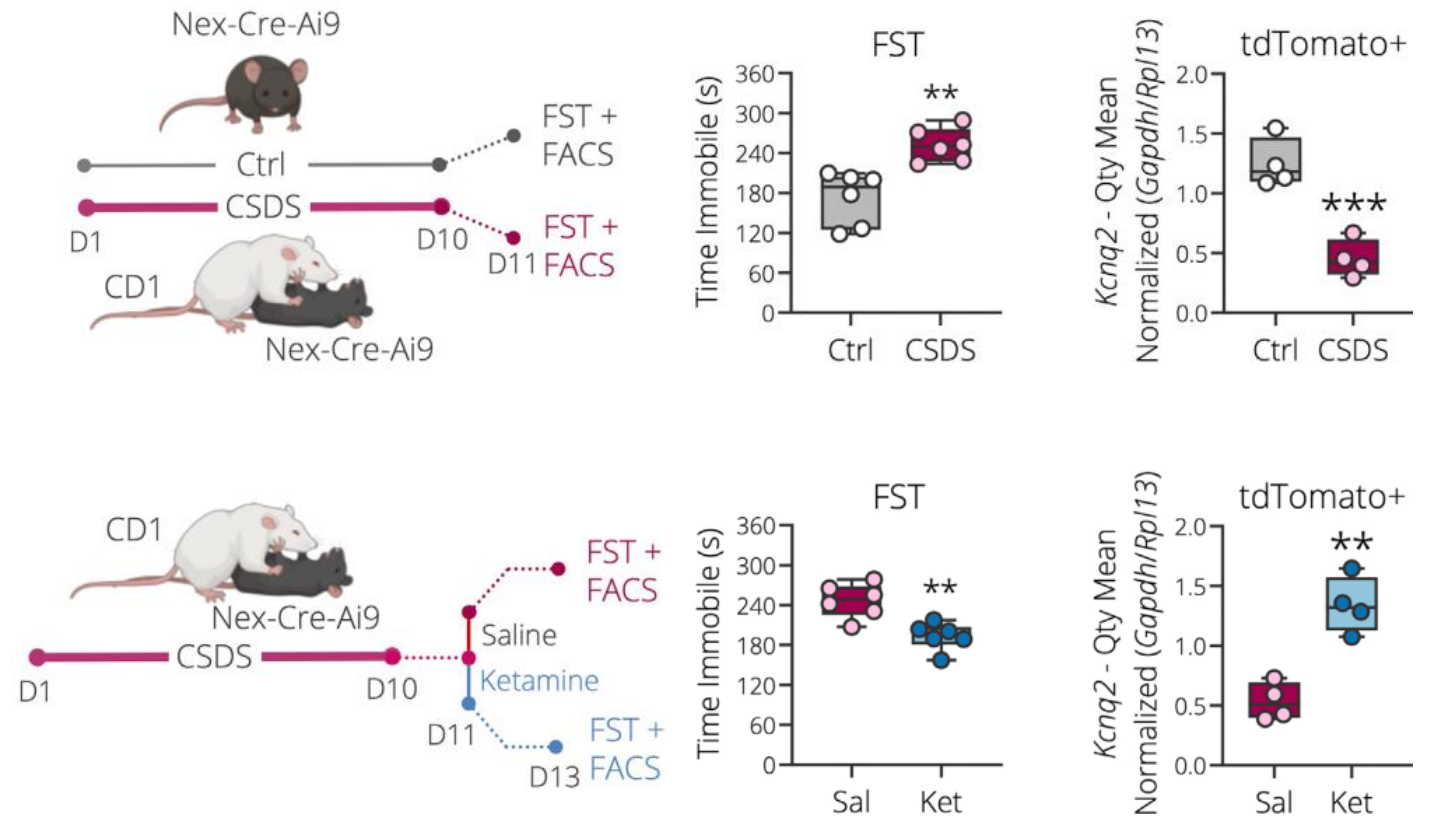
- A single sub-anesthetic dose of ketamine, a glutamate N-methyl-D-aspartate (NMDA) receptor blocker, produces a rapid (hours) yet sustained (days) antidepressant response long after its metabolism ($t_{1/2}$ 2-4 h)
 - Suggests activation of downstream signaling cascades causing long-lasting and sustained adaptations in neural circuits
- Through RNA seq, Lopez et al. identified *Kcnq2* as a gene that is upregulated by ketamine in labeled glutamatergic neurons in the ventral hippocampus
- Viral knockdown of *Kcnq2* in vivo diminishes anti-depressant effects of ketamine in FST



Ketamine's Sustained Antidepressant Effects Associated with an Increase in Kcnq2 Expression

Chronic Stress Exposure and Ketamine Modulate Kcnq2 mRNA in the Ventral Hippocampus

- After 10 days in a chronic social defeat stress (CSDS) model, mice have increased time immobile in the FST
- Correlates with a decrease in Kcnq2 expression in glutamatergic ventral hippocampal neurons
- 2 days after a single ketamine injection, CSDS mice performance in the FST improves, which is concurrent with an increase in Kcnq2 expression in labeled glutamatergic neurons



Conclusions

- XEN1101 is a novel, “next-gen” K_v7 channel opener which has shown compelling clinical efficacy results in epilepsy
- Encouraging pre-clinical activity data supports potential therapeutic utility in depression
- Ezogabine, an earlier generation K_v7 opener, demonstrated clinical efficacy on MDD symptoms
- Based on this evidence, there are currently two ongoing proof-of-concept studies of XEN1101 in MDD
- Recent pre-clinical research suggests that the antidepressant effects of ketamine are mediated via upregulation of K_v7 gene expression
- Taken together, XEN1101 is a promising candidate for further development for treatment of depression

Thank you!

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