Development of $M_5$ Muscarinic Acetylcholine Receptor Negative Allosteric Modulators for the Treatment of Opioid Use Disorder

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VCNDD has advanced a Selective M₁ PAM VU319 into Clinical Development for Cognitive Impairments in Alzheimer’s Disease

**VCNDD Primary GOAL:** De-risk innovative novel approaches for CNS disorders to facilitate full discovery and development in industry.

Received FDA permission to proceed to Phase I clinical trials with VU319 with Dr. Paul Newhouse, Director of the Vanderbilt Center for Cognitive Medicine.

Ongoing Phase I Single Ascending Dose study in healthy volunteer participants has progressed to cohort 3. No Adverse Dose-limiting effects observed in cohorts 1 and 2.
Development Novel Treatment Approach for Opioid Use Disorder

Selective M₅ NAMs

1R01 DA037207-01A1 NIH/NIDA ‘Discovery of mAChR5 Modulators for Use in Rodent Models of Cocaine Addiction’ with Dr. Craig Lindsley

Gunter et al. in press Addiction Biology 2017

Ongoing Collaboration:
Dr. Danny Winder
Director, Vanderbilt Center for Addiction Research
FDA Approved treatment options for Opioid Use Disorder

**Detox therapies**
- Methadone
- Buprenorphine
- Alpha-2 agonists
  - Clonidine

**Maintenance therapies**
- Methadone
- Buprenorphine
  - Combined with Naloxone (Suboxone)
- Extended release Naltrexone
  - Antagonist
- Most effective when combined with counseling

**Limitations**
- High Abuse Liability
- Dependence
- Tolerance
- Respiratory Depression
- Constipation

***Majority approved treatments still target the mu opioid receptor***
Drug-exposure procedures and animal behavioral models can effectively approximate the human addiction cycle.

The reinforcing effects of drugs of abuse are mediated by the mesolimbic dopamine circuit

Opioid Mechanism of Action: Disinhibition of Mesolimbic DA Circuitry

**Targeting M₅ muscarinic acetylcholine receptor for OUD**

| M₁ | High Density in CNS-cortex, striatum, hippocampus |
| M₂ | Medium Density in CNS-caudal regions of brain, heart |
| M₃ | Low Density in CNS-endocrine glands, GI tract |
| M₄ | High Density in CNS-cortex, striatum, hippocampus |
| M₅ | Low Density in CNS, but enriched in VTA, substantia nigra |

$M_5$ KO mice exhibit reduced morphine conditioned place preference

Localization of $M_5$ mAChR within the mesolimbic DA circuitry?
High Cellular co-distribution of $M_5$- and TH- positive cells within the VTA

Studies ongoing to optimize a selective radioligand for assessment of the distribution and levels of $M_5$ protein within the mesolimbic DA Circuitry after acute and chronic opioid exposure.
Development of Subtype Selective M₅ NAMs as an alternative to orthosteric antagonists

• Subtype selective orthosteric antagonists historically more difficult to develop due to high conservation of the orthosteric ACh binding site across M₁-M₅

ML375 (M₅ NAM)

hM₅ IC₅₀ = 300 nM
rM₅ IC₅₀ = 790 nM
r/h M₁ - M₄ IC₅₀s > 30 μM

Suitable DMPK profile using systemic dosing for *in vivo* studies (long *t*½)

Methods for Assessment of M₅ NAMs on Opioid schedules of reinforcement in Rats

**Progressive ratio**
- Assess reinforcing “strength”
- Each subsequent reinforcer requires a greater number of responses
  (e.g. PR: 1, 3, 10, 30, 100, etc)

*Changes in Breakpoint or the limit to the amount of "work" that a subject is willing to perform to obtain a reinforcer.*
ML375 reduces breakpoints for long-acting mu opioid agonist oxycodone

**Oxycodone Dose 56 µg/kg/infusion**

<table>
<thead>
<tr>
<th>Dose</th>
<th>Reinfers earned (BP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mg/kg ML375</td>
<td>12 (50)</td>
</tr>
<tr>
<td>18 mg/kg ML375</td>
<td>10 (32)</td>
</tr>
<tr>
<td>30 mg/kg ML375</td>
<td>8 (20)</td>
</tr>
<tr>
<td>0.3 mg/kg Naltrexone</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Vehicle</td>
<td>2 (2)</td>
</tr>
</tbody>
</table>

RM 1-way ANOVA, n = 7
* p < 0.05 compared to vehicle

**Oxycodone dose (µg/kg/inf) vs. Reinfers earned (BP)**

- **Vehicle**: 10 mg/kg ML375 (15 min PT)
- 30 mg/kg ML375 (15 min PT)
- 0.3 mg/kg Naltrexone

RM 2-way ANOVA n = 5/data point
* 10 mg/kg, * 30 mg/kg, & 0.3 mg/kg p < 0.05 compared to vehicle
Reinstatement of Responding following Oxycodone SA

Method: Cue Reactivity/Reinstatement of Responding following Oxycodone SA

Acquisition of self-administration Oxycodone

Cue light during infusion

Rats stay in home cage
No exposure to operant Chamber or oxycodone

48 hr abstinence

Active lever Inactive lever

Cue light, no infusion

Active lever Inactive lever
ML375 attenuates the cue-induced reactivity following 48 hr forced abstinence from oxycodone self-administration

1-way ANOVA
p < 0.05 compared to vehicle
n = 7-8/treatment
ML375 has no analgesic properties alone nor does it affect oxycodone-induced analgesia

Abuse deterrence?

Similar effects observed in Tail Flick Test
M₅ NAMs as a novel treatment approach for opioid use disorder: Paths for the future

Current Focus:

*NIDA requested Submission of a U19 application for National Cooperative Drug Discovery/Development Groups (NCDDG) for development of a novel treatment for OUD.*
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Discovering new roads to recovery