Vaccines for Treating Opioid and Stimulant Use
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How do vaccines work?
What are the implications for treatment?
What are the challenges?
Vaccines for illicit drug use generate antibodies that bind drug in plasma and block entry to the brain.

A series of injections are given over several months in order to achieve maximal antibody production.
Candidate vaccines for heroin and prescription opioids

OXY-KLH targets oxycodone, hydrocodone, oxymorphone

M-KLH targets heroin, 6-AM, and morphine

F-CRM targets fentanyl and its analogs
## Stimulant (Cocaine and Methamphetamine) Use Disorder Medication Pipeline

<table>
<thead>
<tr>
<th>Early Preclinical T2L: (&gt; 12 years)</th>
<th>Late Preclinical (10 – 12 years)</th>
<th>Phase I (6 – 10 years)</th>
<th>Phase Ib (5 – 9 years)</th>
<th>Phase II (4 – 6 years)</th>
<th>Phase III (3 – 5 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ SBI-0069330 / SBI-0801315 mGluR2 PAM</td>
<td>□ IXT-m200 Long-duration anti-meth mAb</td>
<td>□ dAdGNE Anti-cocaine vaccine</td>
<td>□ Mirtazapine NE/SHT antagonist</td>
<td>□ NS2359* DAT/NET/SERT inhibitor</td>
<td></td>
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<tr>
<td>□ NOP/Kappa/Mu ligands</td>
<td>□ Methamphetamine conjugate vaccine</td>
<td>□ Cocaine hydrolase gene therapy</td>
<td>□ Duloxetine &amp; Methylphenidate NET/SERT inhibitor &amp; CNS stimulant</td>
<td>□ IXT-m200 Anti-meth mAb</td>
<td></td>
</tr>
<tr>
<td>□ PTPRD ligands</td>
<td>□ IXT-v100 Methamphetamine vaccine</td>
<td>□ h2E2 Anti-cocaine mAb</td>
<td>□ Pomaglumetad methionil mGluR2/3 agonist prodrug</td>
<td>□ Bupropion DAT/NET inhibitor</td>
<td></td>
</tr>
<tr>
<td>□ Peptidic KOR agonists</td>
<td></td>
<td></td>
<td>□ Clavulanic acid GLT-1 activator</td>
<td>□ Mavoglurant* mGluR5 non-competitive antagonist</td>
<td></td>
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<tr>
<td>□ GLT-1 up-regulator</td>
<td></td>
<td></td>
<td>□ Ketamine NMDA antagonist</td>
<td>□ EMB-001 Metyrapone &amp; oxazepam GC synth inhibitor &amp; benzodiazepine</td>
<td></td>
</tr>
<tr>
<td>□ Methamphetamine vaccine</td>
<td></td>
<td></td>
<td>□ Pioglitazone PPAR-γ agonist</td>
<td>□ Guanfacine d2A agonist</td>
<td></td>
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<tr>
<td>□ Cocaine catabolic enzyme</td>
<td></td>
<td></td>
<td>□ Naltrexone SR injection &amp; oral Bupropion Mu antagonist &amp; DAT/NET inhibitor</td>
<td></td>
<td></td>
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<tr>
<td>□ VMAT-2 inhibitor</td>
<td></td>
<td></td>
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</tbody>
</table>

**KEY:**
- □ – NME
- ○ – New Indication
- △ – Biologic
- △ – Gene Therapy
- □ – cocaine
- □ – meth
- □ – both cocaine and meth

* Not currently supported by NIDA
Multivalent Vaccine Concept

- Oxycodone, Hydrocodone
- Heroin, Morphine
- Fentanyl, Analogs
- Methamphetamine
- Cocaine

Multivalent Vaccine
Mechanism of Action

In vaccinated rats, serum oxycodone levels increase and brain oxycodone levels decrease compared to control rats.

**Efficacy. Vaccines prevent opioid self-administration**

Vaccination with OXY-KLH generated oxycodone-specific serum IgG antibody conc. of \(450 \pm 65 \mu g/ml\), with high affinity for oxycodone (\(K_d < 50 \text{ nM}\) and \(IC_{50} < 20 \text{nM}\)).

**Fixed ratio** (FR) = number of active lever presses to deliver i.v. oxycodone 0.06 mg/kg/inf; session= 120-min.

*Pravetoni et al., PLOSone 2014*
### Increased Overdose Death Rates During COVID-19 Pandemic

12-months Ending July 2020 Compared to 12-months Ending July 2019

<table>
<thead>
<tr>
<th></th>
<th>ALL DRUGS</th>
<th>HEROIN</th>
<th>NAT &amp; SEMI - SYNTHETIC</th>
<th>METHADONE</th>
<th>SYNTHETIC OPIOIDS</th>
<th>COCAINE</th>
<th>OTHER PSYCHO-STIMULANTS (mainly meth)</th>
</tr>
</thead>
<tbody>
<tr>
<td>July 2019 *</td>
<td>75,687</td>
<td>14,793</td>
<td>12,203</td>
<td>2,875</td>
<td>33,704</td>
<td>15,031</td>
<td>14,941</td>
</tr>
<tr>
<td>March 2020*</td>
<td>86,001</td>
<td>14,427</td>
<td>13,259</td>
<td>3,315</td>
<td>50,122</td>
<td>19,542</td>
<td>20,406</td>
</tr>
<tr>
<td>July 2020*</td>
<td>92,018</td>
<td>14,470</td>
<td>13,619</td>
<td>3,266</td>
<td>50,122</td>
<td>19,542</td>
<td>20,406</td>
</tr>
<tr>
<td>July 2019-July 2020 Change</td>
<td>+24.2%</td>
<td>-2.5%</td>
<td>+8.7%</td>
<td>+15.3%</td>
<td>+48.7%</td>
<td>+30.0%</td>
<td>+36.6%</td>
</tr>
</tbody>
</table>

Fentanyl Vaccine: Preclinical Data

**A**
- Serum levels increase

**B**
- Brain levels decrease

- Respiratory depression is reversed
- Naloxone reversal is unaffected

Raleigh et al. JPET 2019; Robinson et al. JMC 2020
How does a vaccine fit into treatment options for SUD?

- Prevent SUD
- Treat SUD as stand-alone medication
- Adjunct to other medications
- Reduce fatal overdoses

Maintenance on buprenorphine, methadone or naltrexone

No SUD – Mild SUD – Moderate SUD – Severe SUD – TREATMENT – Relapse

What about illicit stimulant use?

OVERDOSE
Clinical Study Design: OXY-KLH Phase 1

• AIM 1 - SAFETY
  • Physical examinations, self-reported side effects, routine blood and urine chemistries, reactogenicity, and signs/symptoms of opioid withdrawal

• AIM 2 – IMMUNE RESPONSE
  • Titers, concentrations, affinity, and specificity of oxycodone-specific serum antibodies

• AIM 3 – PRELIMINARY EFFICACY
  • Mean peak ratings of Drug Liking
Vaccination Schedule for Each Participant

**OXY-KLH Vaccination Schedule**

- Vacc #1
- Vacc #2
- Vacc #3
- Vacc #4

- Screening Phase
- Inpatient Phases
- Oxycodone/Heroin Dose-effect Sessions
- Outpatient Phases

- Screening Phase: 0, 3, 6, 18, 21
- Inpatient Phases: 0, 3, 6
- Oxycodone/Heroin Dose-effect Sessions: 0, 3, 6, 18, 21
- Outpatient Phases: 0, 3, 6, 18, 21

- **Inpatient Maintenance: Oral MORPHINE (30 mg QID)**
  - not expected to interact with vaccine response

- **Test: Intranasal OXYCODONE (0, 25, 50, 100 mg IN) and HEROIN (100 mg IN)**
PREVIOUS DATA: Fentanyl, Heroin, Oxycodone

Comer et al. 2008
Challenge. Identify immunological mechanisms and biomarkers of vaccine efficacy to accelerate translation.

First-generation nicotine and cocaine vaccines showed clinical proof of efficacy in ~30% of immunized subjects that achieved highest antibody levels.
Biomarker. Vaccine efficacy is predicted by early antibodies and pre-immunization B cell frequency in mice

A. OXY-KLH efficacy in blocking oxycodone to brain

B. Antibody titers vs. efficacy
   IgG subclasses vs. efficacy

C. OXY-specific B cell frequency vs. efficacy

Phase I trial includes exploratory biomarkers to select or stratify patients

Laudenbach et al., J. Immunology 2015
Laudenbach et al., Vaccine 2015
Comparison of **opioid users and naïve** individuals' opioid-specific B cells and TNF$\alpha$ expression

- Significant difference in the frequency of opioid-specific B cells
- No difference in the expression of TNF$\alpha$
- Correlation between TNF$\alpha$ expression and opioid-specific B cells only for **opioid users**

Is TNF$\alpha$ a viable biomarker to predict vaccine clinical efficacy?
CONCLUSIONS

✓ Do vaccines work?
  • Preclinical studies support good immunogenicity and safety
  • Preclinical studies demonstrate proof-of-concept
  • Preclinical studies show good vaccine selectivity for the target opioid and no interference with approved MOUDs
  • OXY-KLH has been well tolerated thus far in our clinical study

✓ Implications for treatment
  • Prevent the progression to a SUD
  • Stand-alone or adjunct maintenance medication
  • Overdose

✓ Potential challenges
  • Vaccination regimen
  • Duration of protection
  • Inter-subject variability in immunogenicity
THANK YOU!

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