Vaccines for Treating Opioid and Stimulant Use

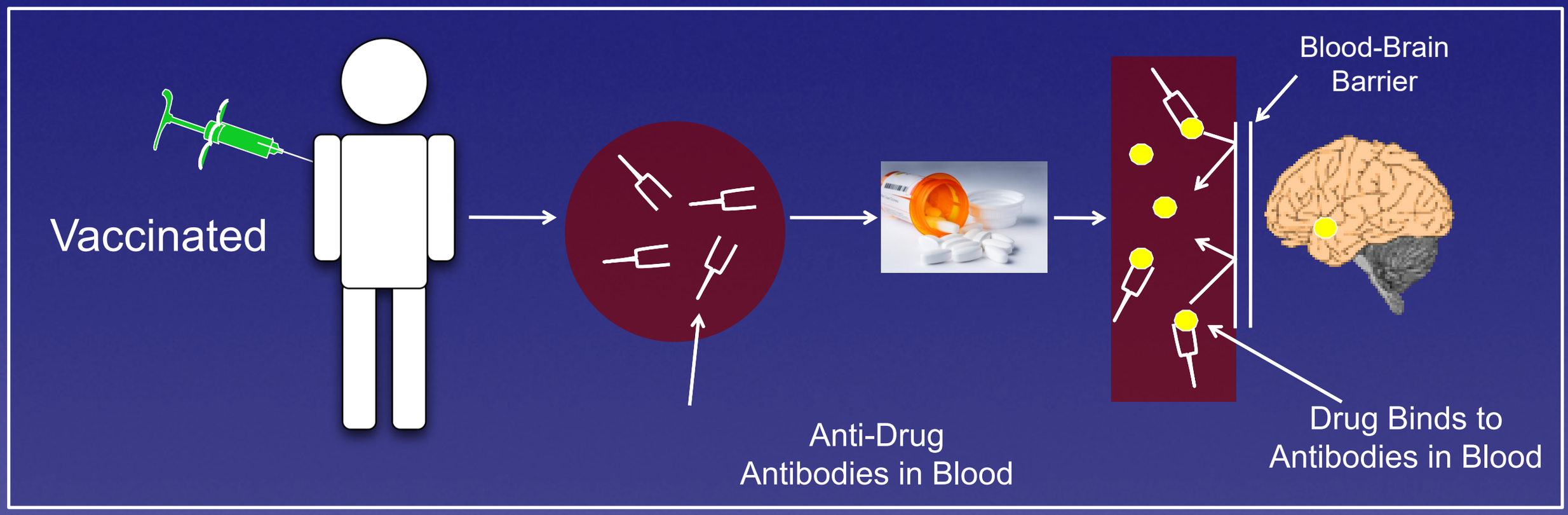
NIH HEAL Meeting • April 14, 2021

Sandra D Comer, PhD
Professor of Neurobiology
Department of Psychiatry
Columbia University and NYSPI
New York, NY

OUTLINE

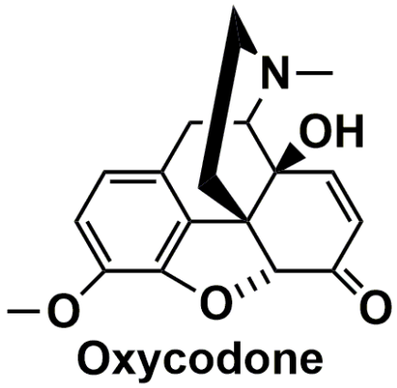
- ✓ How do vaccines work?
- ✓ What are the implications for treatment?
- ✓ What are the challenges?

Vaccines for illicit drug use generate antibodies that bind drug in plasma and block entry to the brain

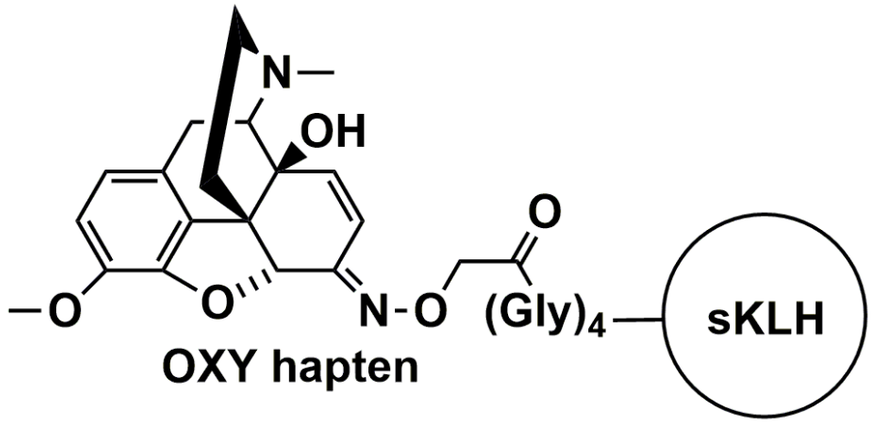


A series of injections are given over several months in order to achieve maximal antibody production

Candidate vaccines for heroin and prescription opioids

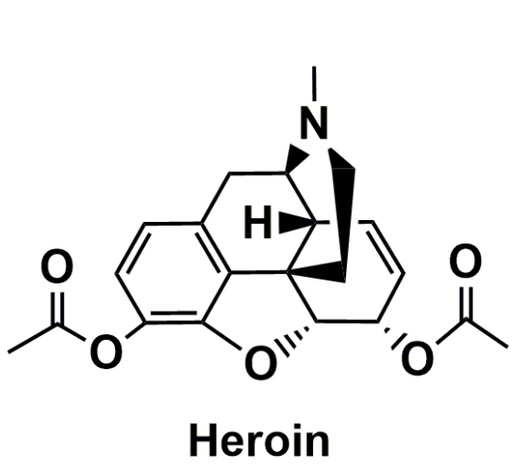


Oxycodone

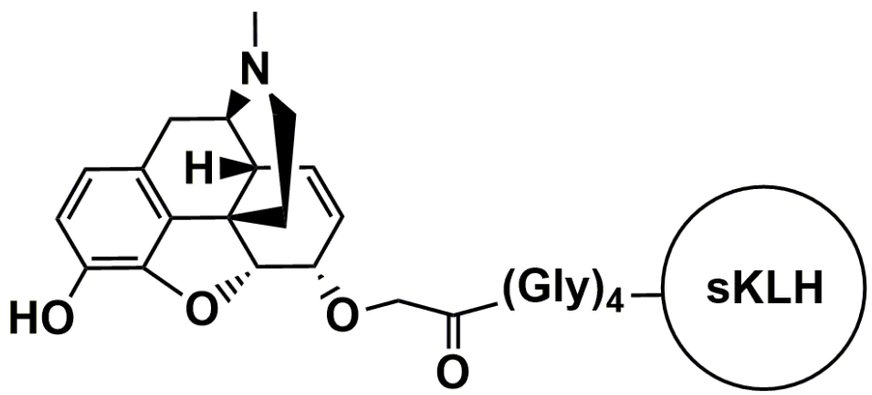


OXY hapten

OXY-KLH targets oxycodone, hydrocodone, oxymorphone

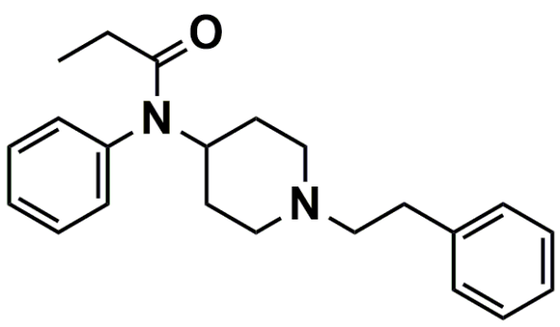


Heroin

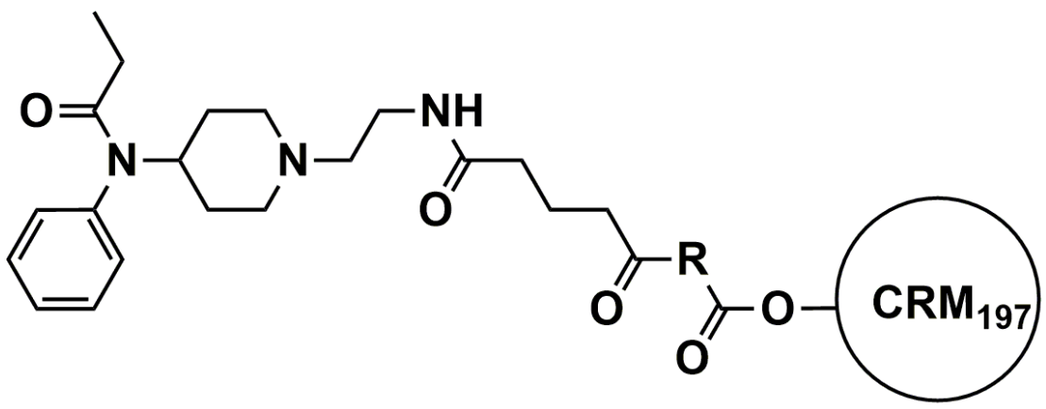


MOR hapten

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



Fentanyl



F hapten

F-CRM targets fentanyl and its analogs

NIDA Development Pipeline

Courtesy of Kurt Rasmussen, PhD

Director, Division of Therapeutics and Medical Consequences

Stimulant (Cocaine and Methamphetamine) Use Disorder Medication Pipeline

Early Preclinical T2L: (> 12 years)	Late Preclinical (10 – 12 years)	Phase I (6 – 10 years)	Phase Ib (5 – 9 years)	Phase II (4 – 6 years)	Phase III (3 – 5 years)
SBI-0069330 / SBI-0801315 mGluR2 PAM	IXT-m200 Long-duration anti-meth mAb	dAdGNE Anti-cocaine vaccine	Mirtazapine NE/5HT antagonist	NS2359* DAT/NET/SERT inhibitor	
NOP/Kappa/Mu ligands	Methamphetamine conjugate vaccine	Cocaine hydrolase gene therapy	Duloxetine & Methylphenidate NET/SERT inhibitor & CNS stimulant	IXT-m200 Anti-meth mAb	
PTPRD ligands	IXT-v100 Methamphetamine vaccine	h2E2 Anti-cocaine mAb	Pomaglumetad methionil mGluR2/3 agonist prodrug	Bupropion DAT/NET inhibitor	
Peptidic KOR agonists			Clavulanic acid GLT-1 activator	Mavoglurant* mGluR5 non-competitive antagonist	
GLT-1 up-regulator			Ketamine NMDA antagonist	EMB-001 Metyrapone & oxazepam GC synth inhibitor & benzodiazepine	
Methamphetamine vaccine			Pioglitazone PPAR-γ agonist	Guanfacine α2A agonist	
Cocaine catabolic enzyme				Naltrexone SR injection & oral Bupropion Mu antagonist & DAT/NET inhibitor	
VMAT-2 inhibitor					

KEY:

– NME – New Indication – Biologic – Gene Therapy | – cocaine – meth – both cocaine and meth

* Not currently supported by NIDA

Multivalent Vaccine Concept

Heroin,
Morphine

Oxycodone,
Hydrocodone

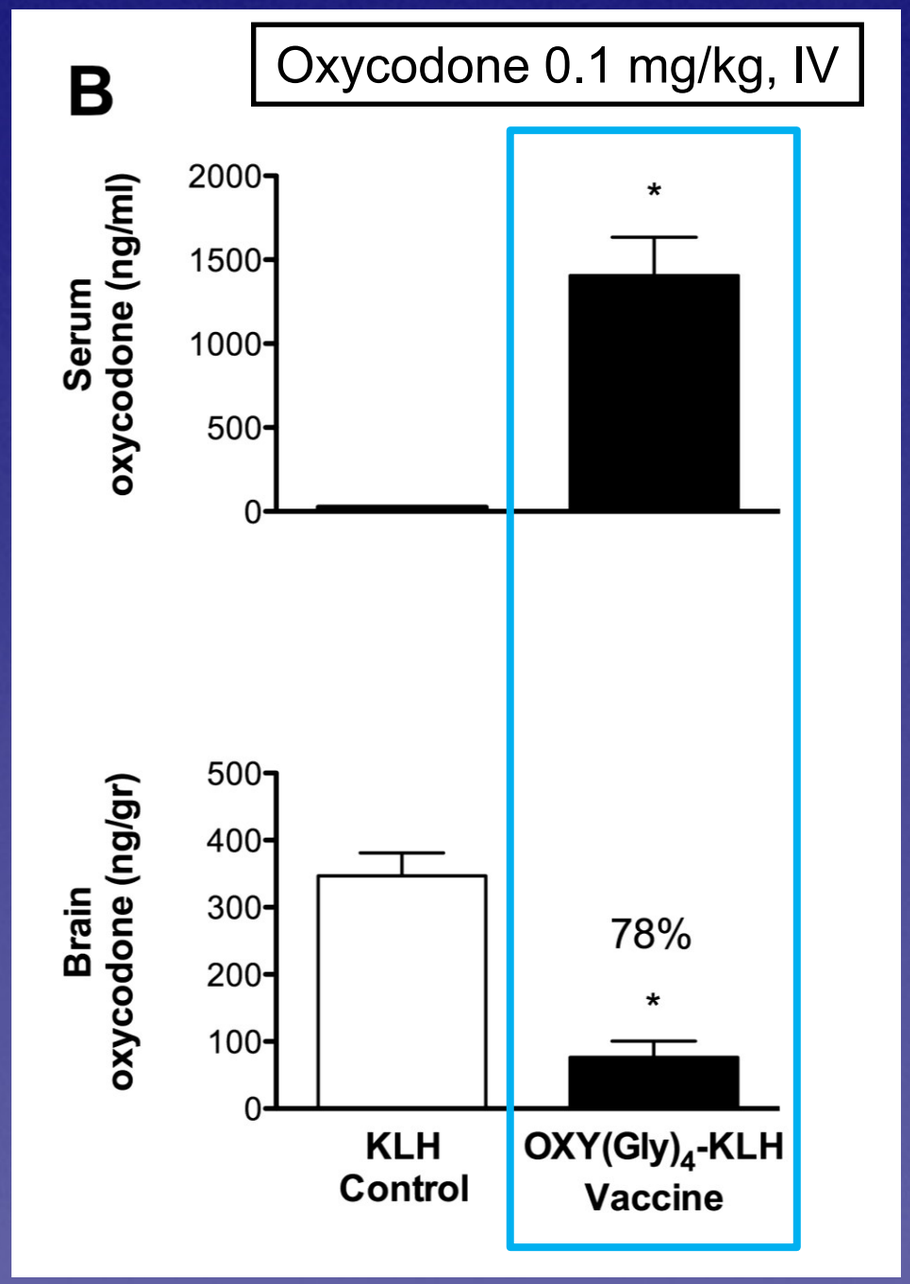
Fentanyl,
Analogs

Multivalent
Vaccine

Methamphetamine

Cocaine

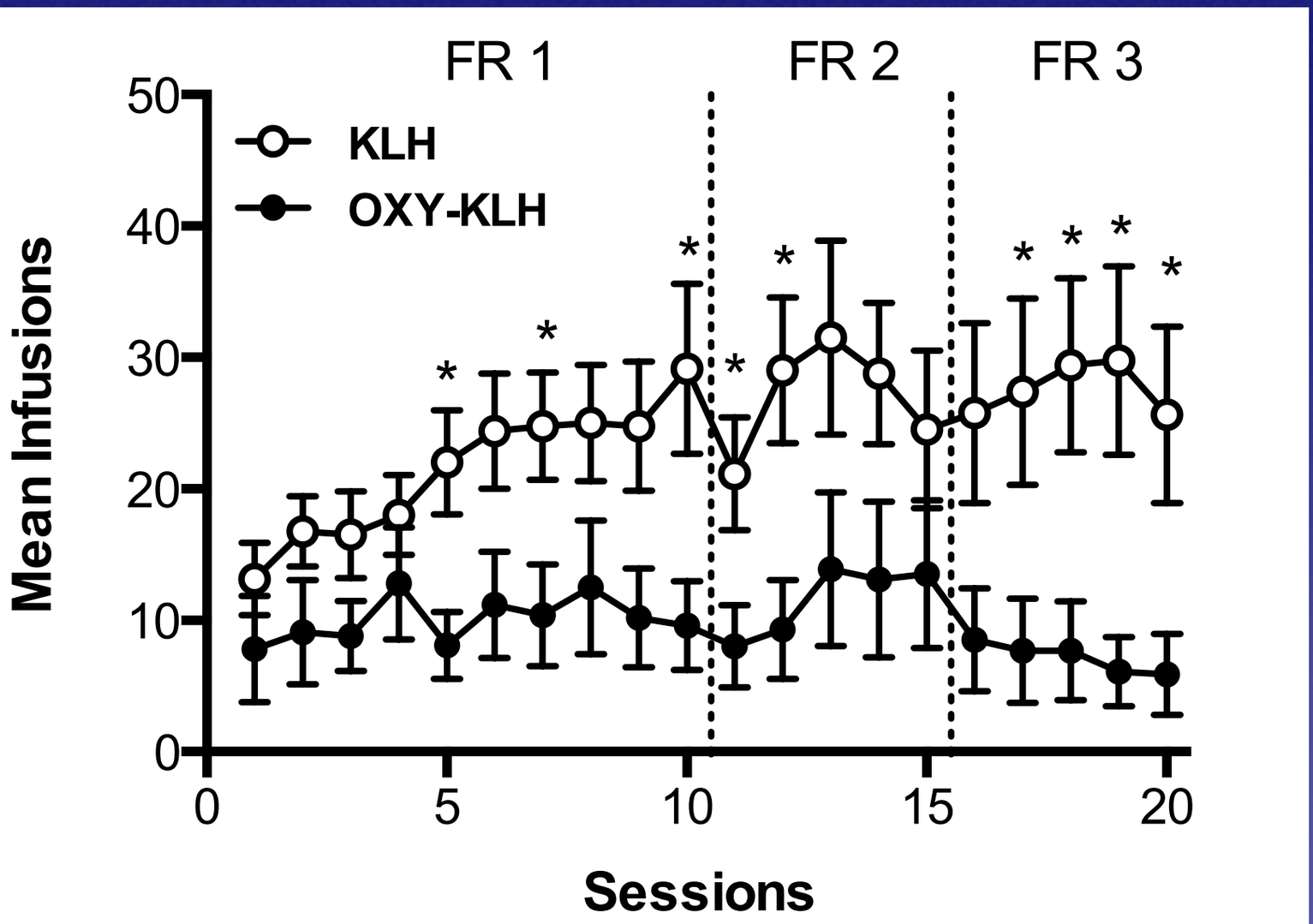
Mechanism of Action

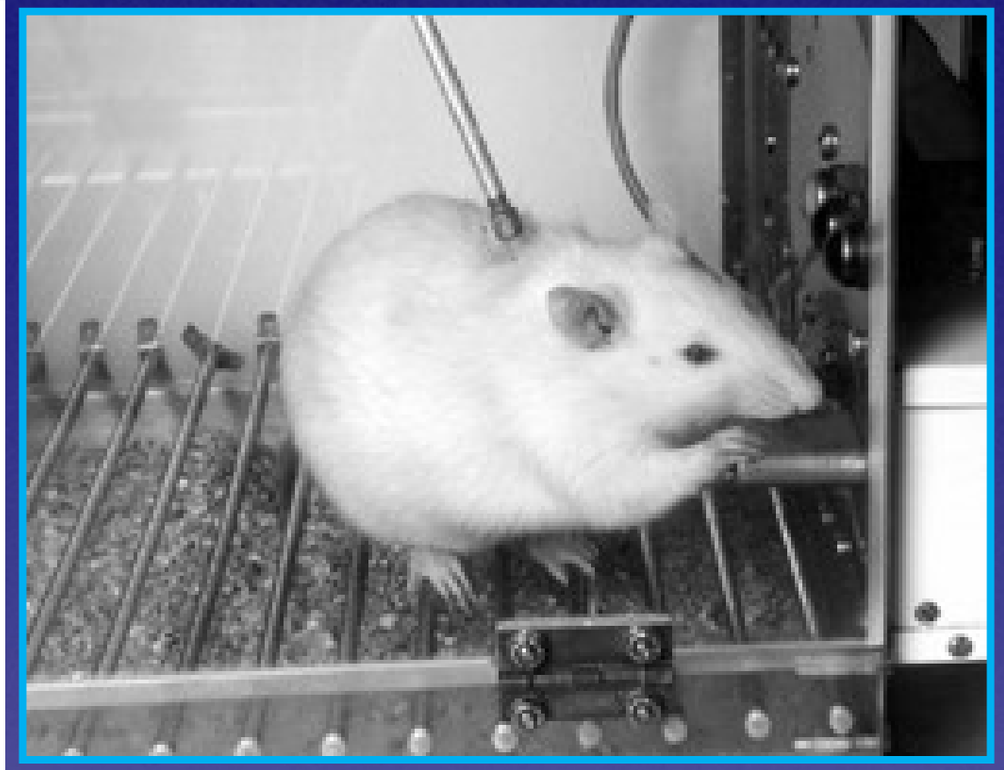


In vaccinated rats, serum oxycodone levels increase and brain oxycodone levels decrease compared to control rats

Pravetoni et al., JPET 2012, Pravetoni et al., J. Med Chem 2013, Raleigh et al. JPET 2018, Baruffaldi et al., Mol. Pharm. 2018 & 2019

Efficacy. Vaccines prevent opioid self-administration





Pravetoni et al., PLOSone 2014

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

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

Increased Overdose Death Rates During COVID-19 Pandemic

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

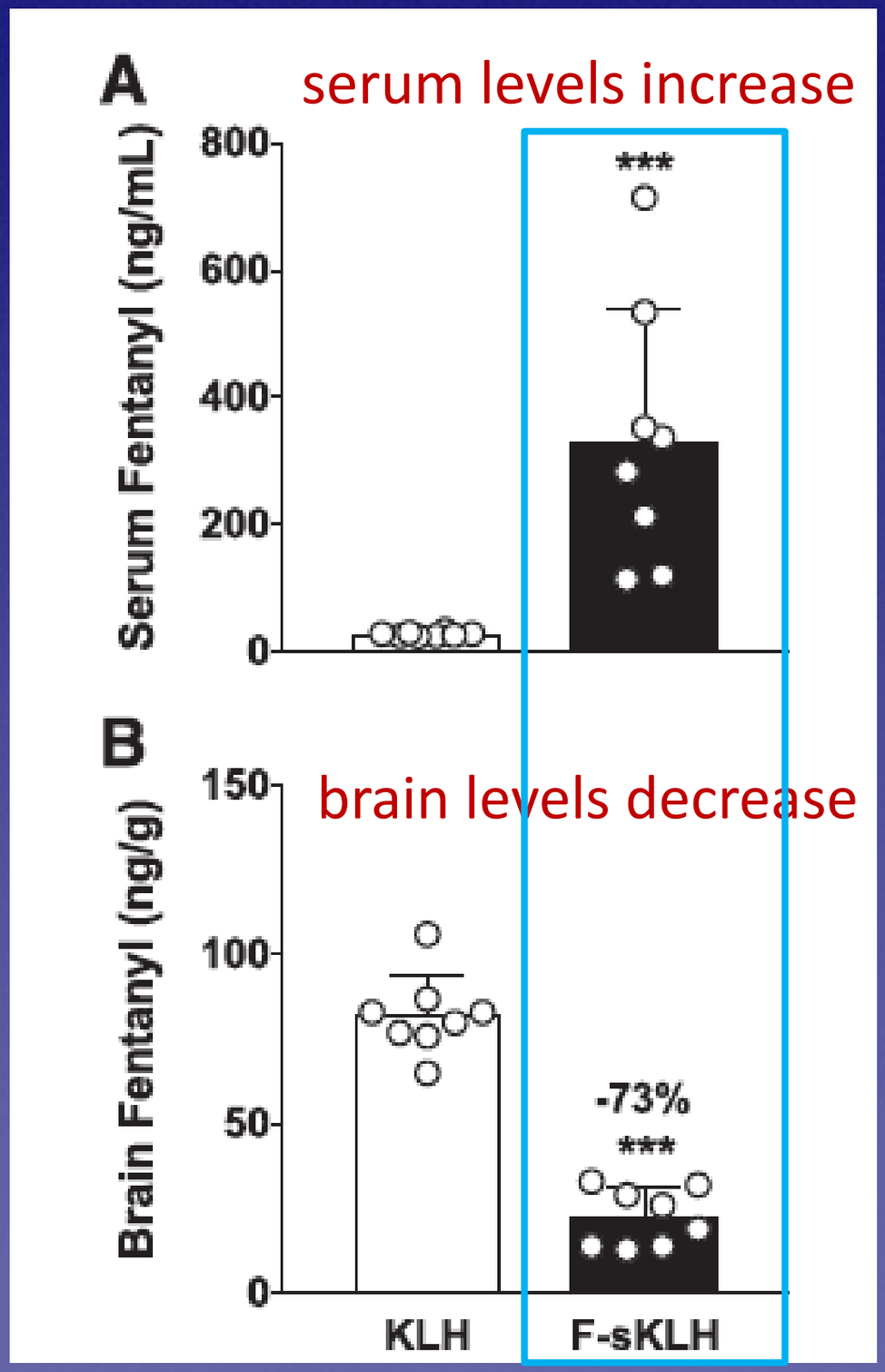
	ALL DRUGS	HEROIN	NAT & SEMI – SYNTHETIC	METHADONE	SYNTHETIC OPIOIDS	COCAINE	OTHER PSYCHO-STIMULANTS (mainly meth)
July 2019 *	14,793	12,203	2,875	33,704	15,031	14,941	
March 2020*	75,687	14,145	12,349	2,837	40,756	17,465	18,033
July 2020*	86,001	14,427	13,259	3,315	50,122	19,542	20,406
July 2019-July 2020 Change	**+24.2%**	**-2.5%**	**+8.7%**	**+15.3%**	**+48.7%**	**+30.0%**	**+36.6%**

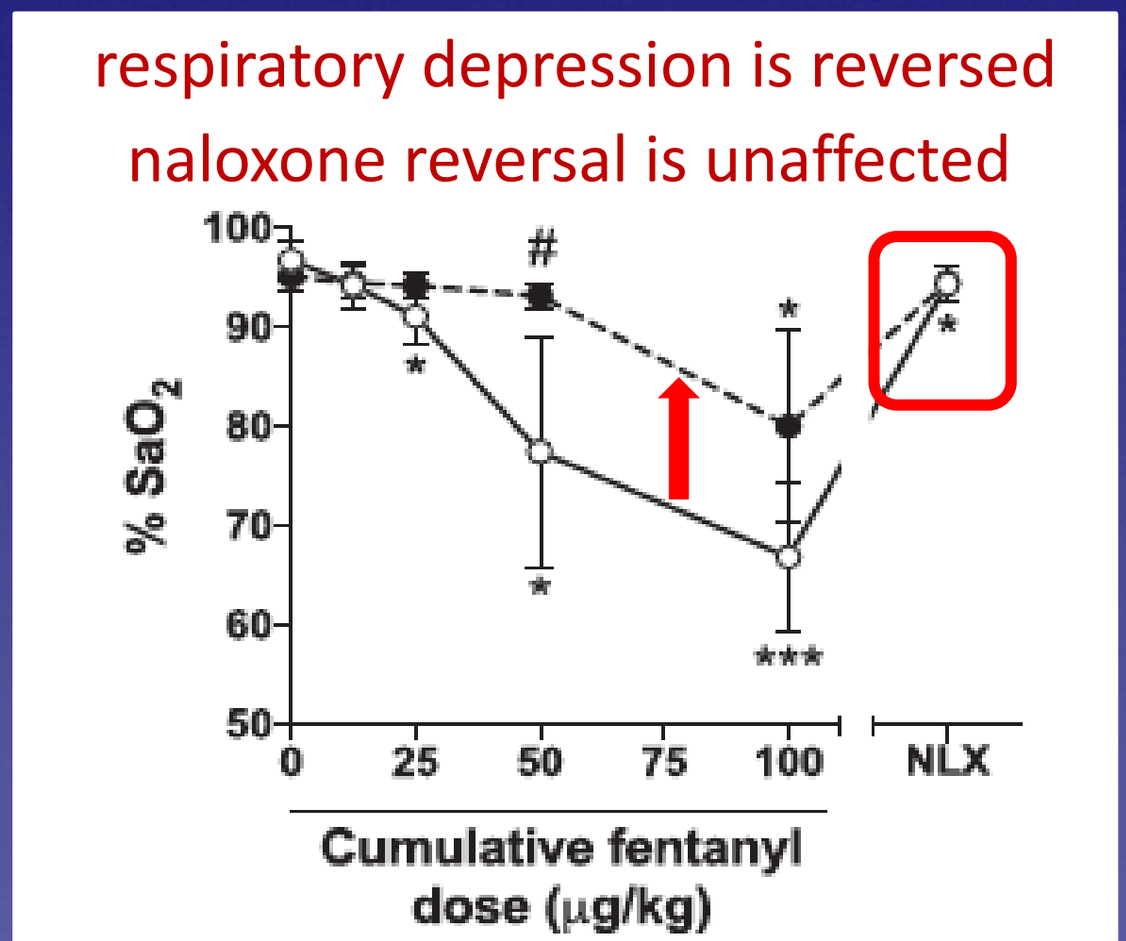
NIH National Institute on Drug Abuse
Advancing Addiction Science

*NCHS Provisional Drug Overdose Death Counts: *https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm*

(Volkow, 2021)

Fentanyl Vaccine: Preclinical Data





Raleigh et al. JPET 2019; Robinson et al. JMC 2020

How does a vaccine fit into treatment options for SUD?

What about illicit stimulant use?

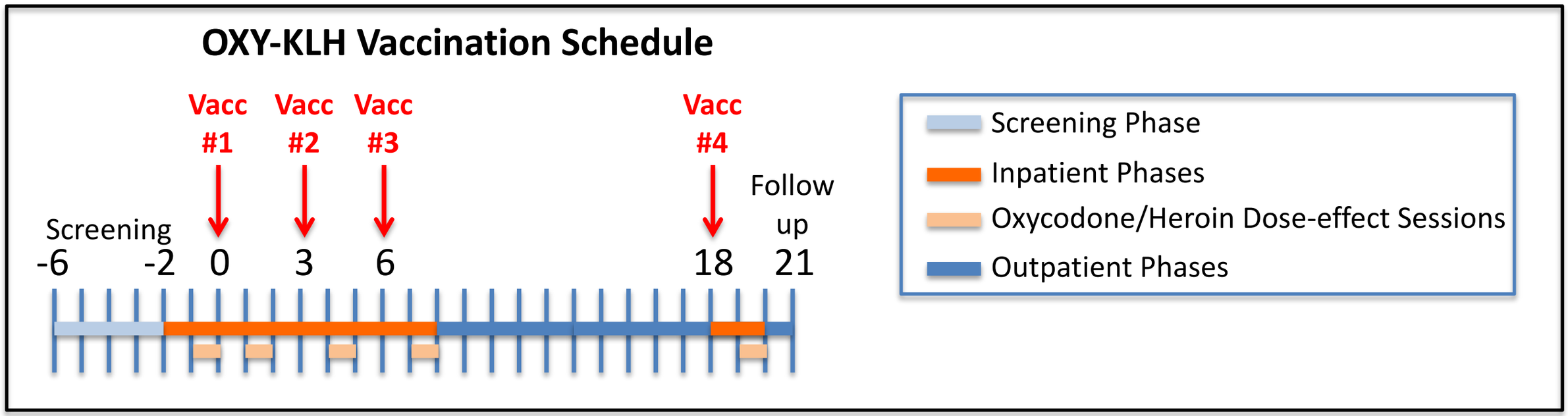
OVERDOSE

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

Clinical Study Design: OXY-KLH Phase 1

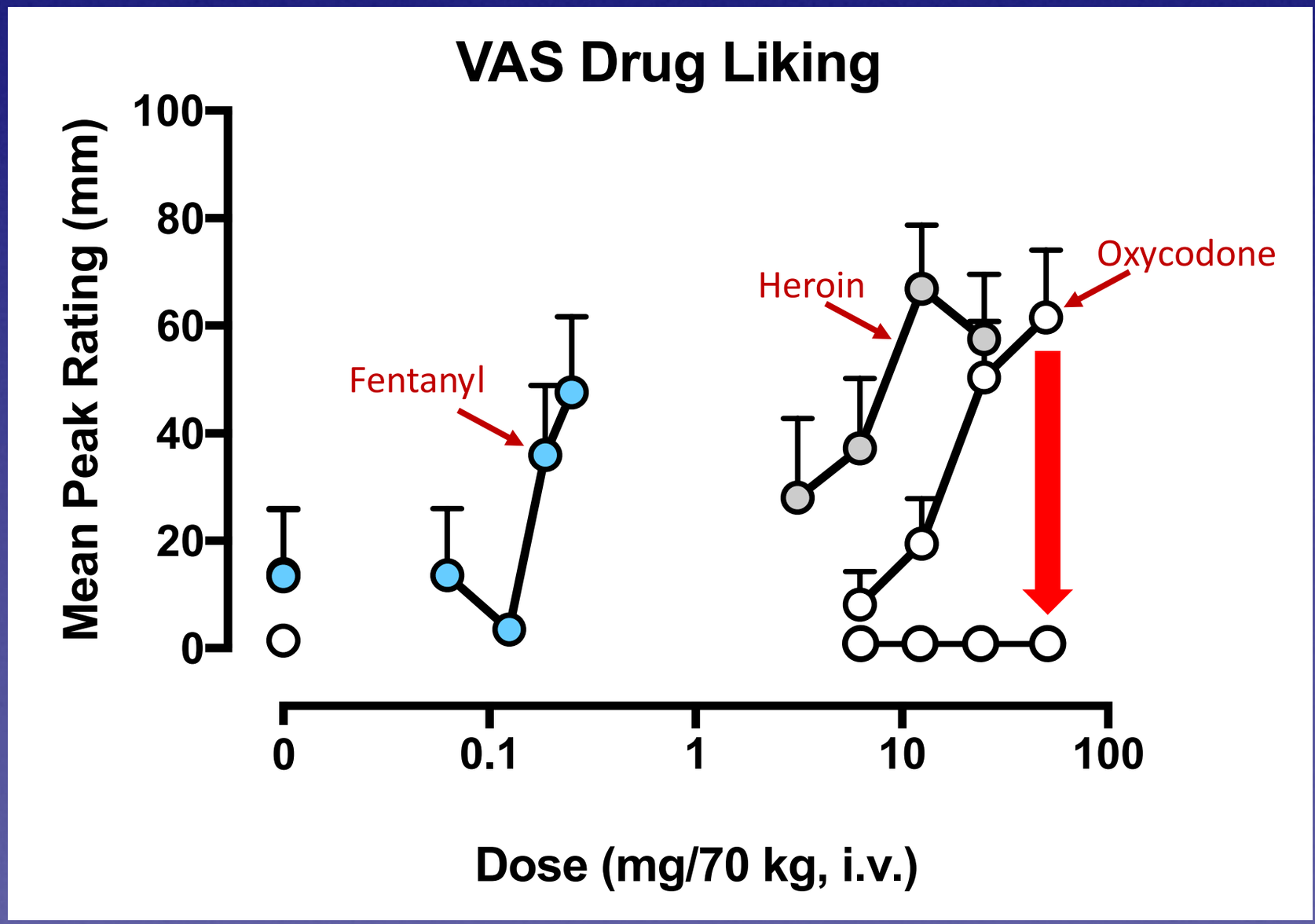
- AIM 1 - SAFETY
  - Physical examinations, self-reported side effects, routine blood and urine chemistries, reactogenicity, and signs/symptoms of opioid withdrawal
- AIM 2 – IMMUNE RESPONSE
  - Titers, concentrations, affinity, and specificity of oxycodone-specific serum antibodies
- AIM 3 – PRELIMINARY EFFICACY
  - Mean peak ratings of Drug Liking

Vaccination Schedule for Each Participant



- 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)

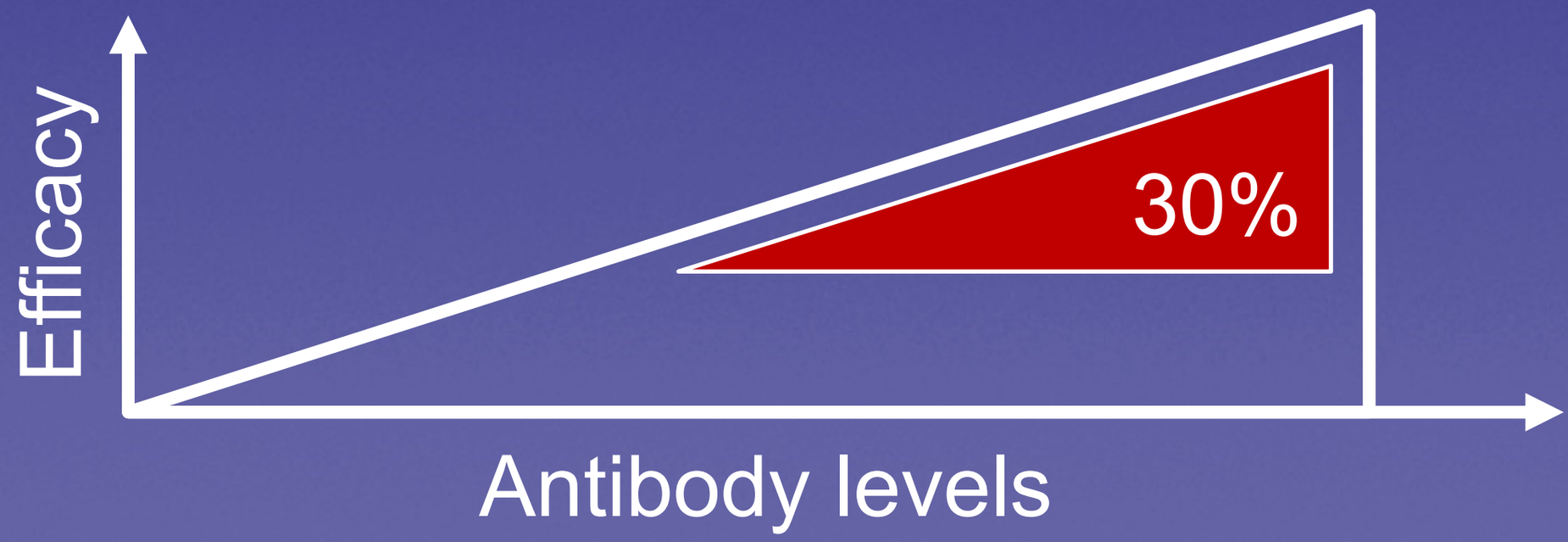
PREVIOUS DATA: Fentanyl, Heroin, Oxycodone



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

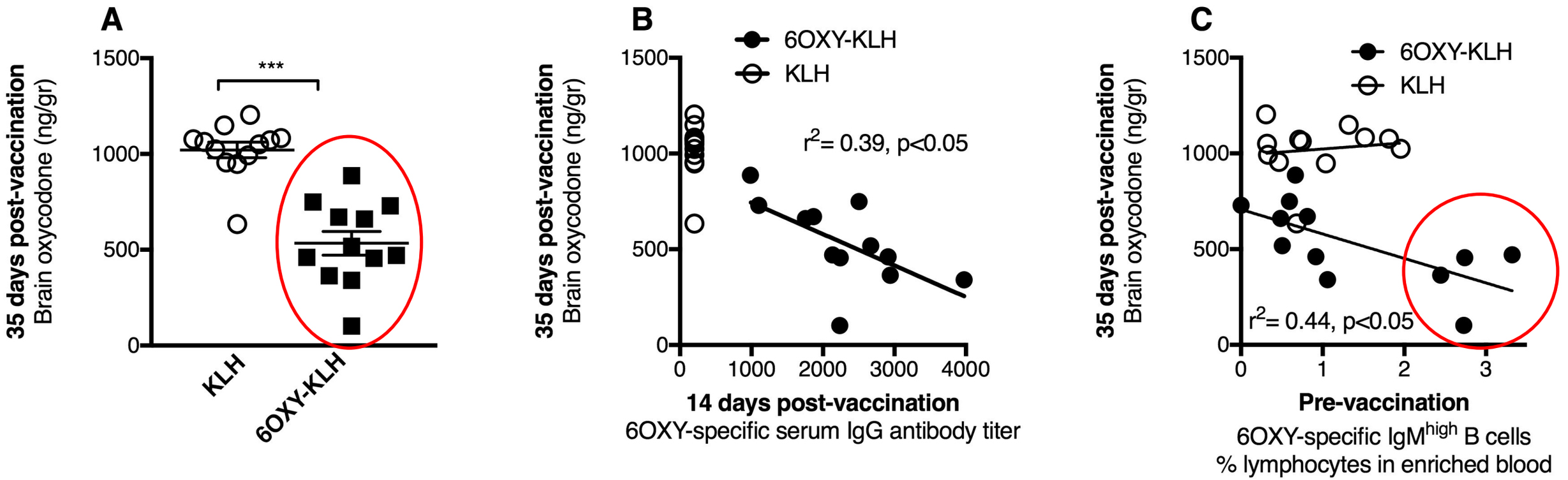


Biomarker. Vaccine efficacy is predicted by early antibodies and pre-immunization B cell frequency in mice

A. OXY-KLH efficacy in blocking oxycodone to brain

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

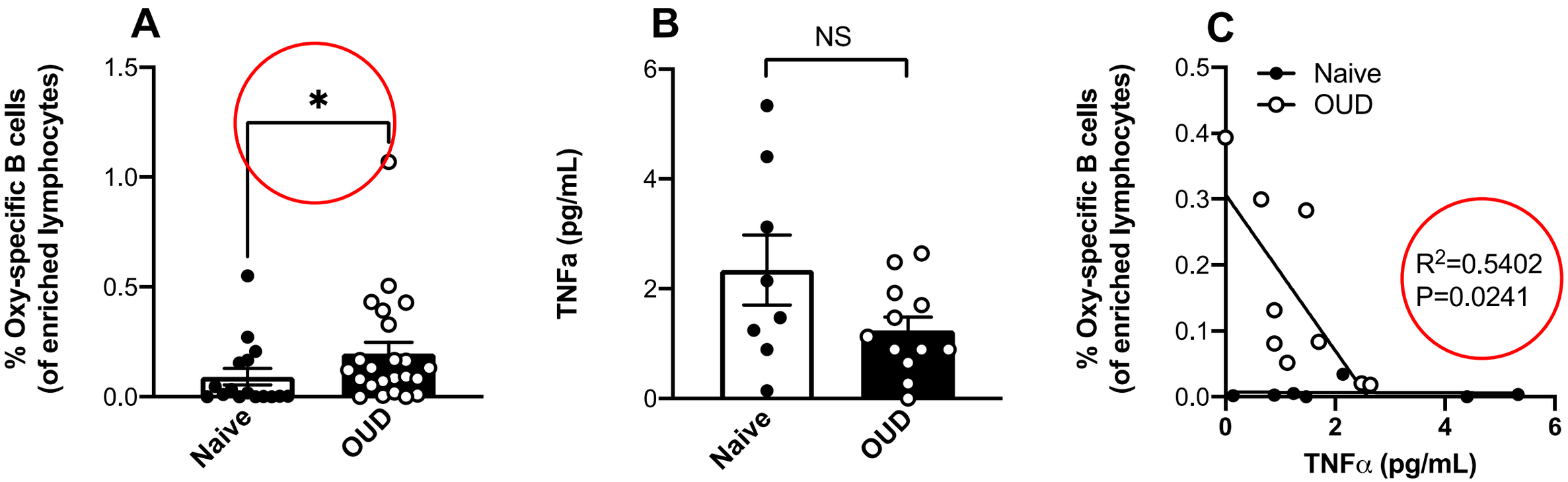
C. OXY-specific B cell frequency vs. efficacy



Laudenbach et al., J. Immunology 2015
Laudenbach et al., Vaccine 2015
Taylor et al., J. Immunol. Methods 2014

Phase I trial includes exploratory biomarkers to select or stratify patients

Comparison of opioid users and naïve individuals' opioid-specific B cells and TNFα expression



- Significant difference in the frequency of opioid-specific B cells
- No difference in the expression of TNFα
- Correlation between TNFα expression and opioid-specific B cells only for opioid users

Is TNFα 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!

Jermaine Jones, PhD
Rachel Luba, PhD
Jeanne Manubay, MD
Shanthi Mogali, MD
Felipe Castillo, MD
Claudia Tindall, NP
Janet Murray, RN
Nicholas Allwood, BS
Rebecca Abbott, BS
Freymon Perez, BS

UG3DA047711 (Comer)
T32DA007294 (Levin)

NIDA
NATIONAL INSTITUTE
ON DRUG ABUSE

Pravetoni Lab at University of Minnesota

NIH funding. U01DA038876, R01DA041730, UG3DA048386, UG3DA047711, UG3 DA048775, HHSN272201800048C, U01DA051658, DAIT-75N93019R00009, and T32DA007097