Vaccines for Treating Opioid Use Disorder

ACTTION Meeting • November 21-22, 2019 • Washington, DC

Columbia University and NYSPI

Columbia University Department of Psychiatry

New York State of Opportunity. New York Psychiatric Institute

University of Minnesota, Minneapolis

Pharmacology

University of Minnesota Center for Immunology

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NIDA National Institute on Drug Abuse

Investigative Team

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University of Minnesota, Minneapolis

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☐ Scott Winston, PhD	Consultant

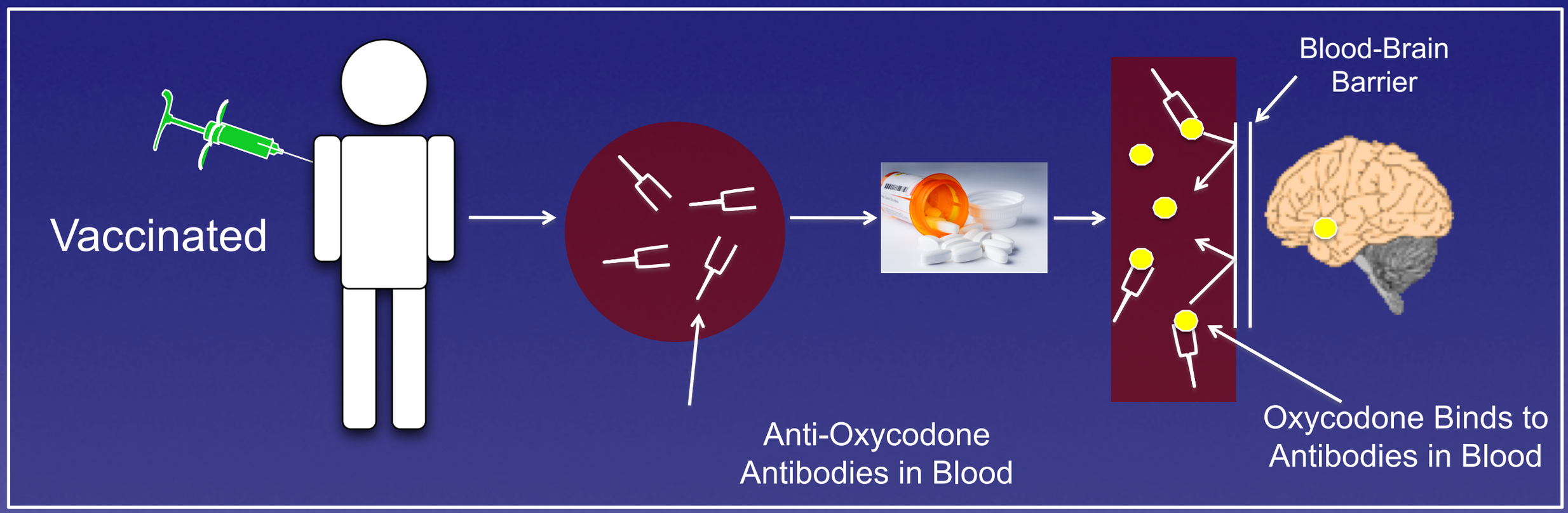
Clinilabs

☐ Gary Zammit, PhD	President & CEO, **Sub-award PI**
☐ Eileen McAuley	Chief Operating Officer
☐ Veronica (Ronni) Spanola	Manager, CRU Operations

Why Vaccines?

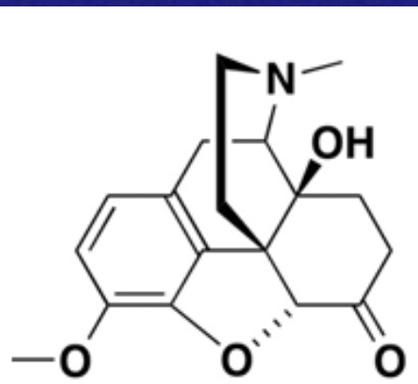
- We have effective medications for treating OUD (buprenorphine, methadone, naltrexone) and overdose (naloxone) so why develop vaccines?
- What are the clinical advantages?
- What are the potential concerns?
- What are the regulatory hurdles?

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

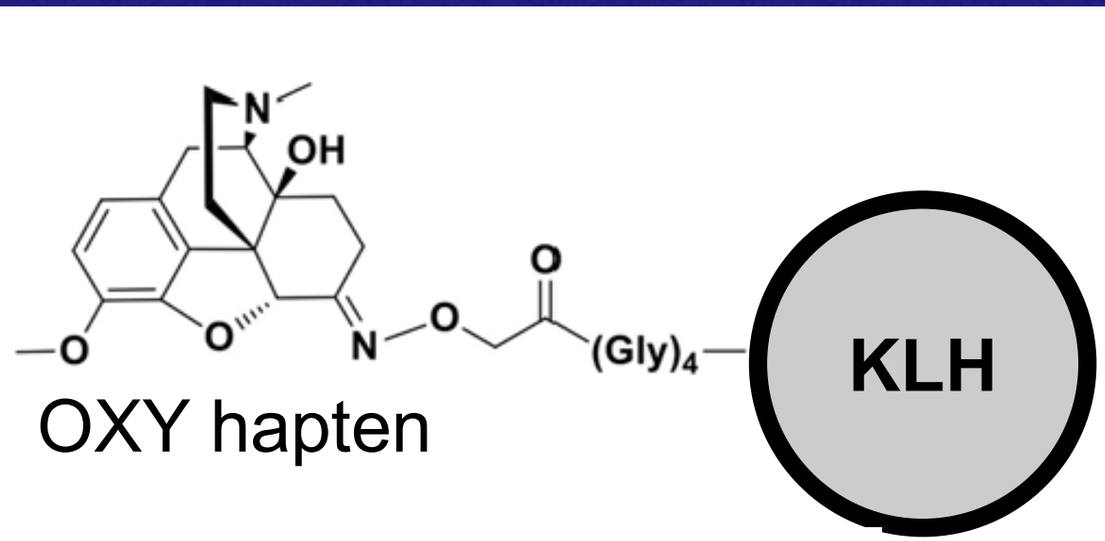


A series of injections are given over several months in order to achieve maximal antibody production

Candidate vaccines for heroin and prescription opioids

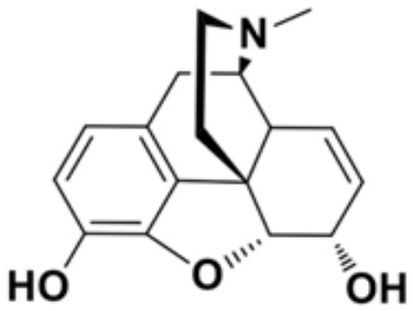


Oxycodone

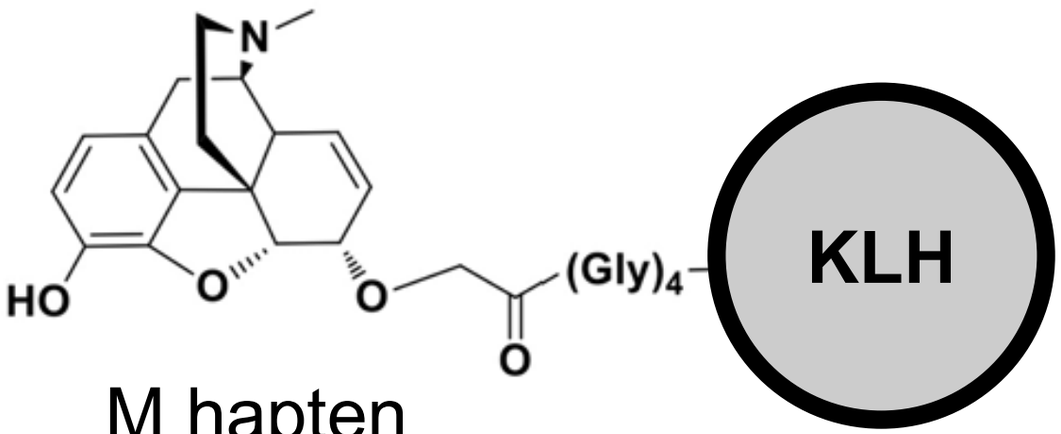


OXY hapten

OXY-KLH targets oxycodone, hydrocodone, oxymorphone



Morphine



M hapten

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

Multivalent Vaccine Concept

Heroin,
Morphine

Oxycodone,
Hydrocodone

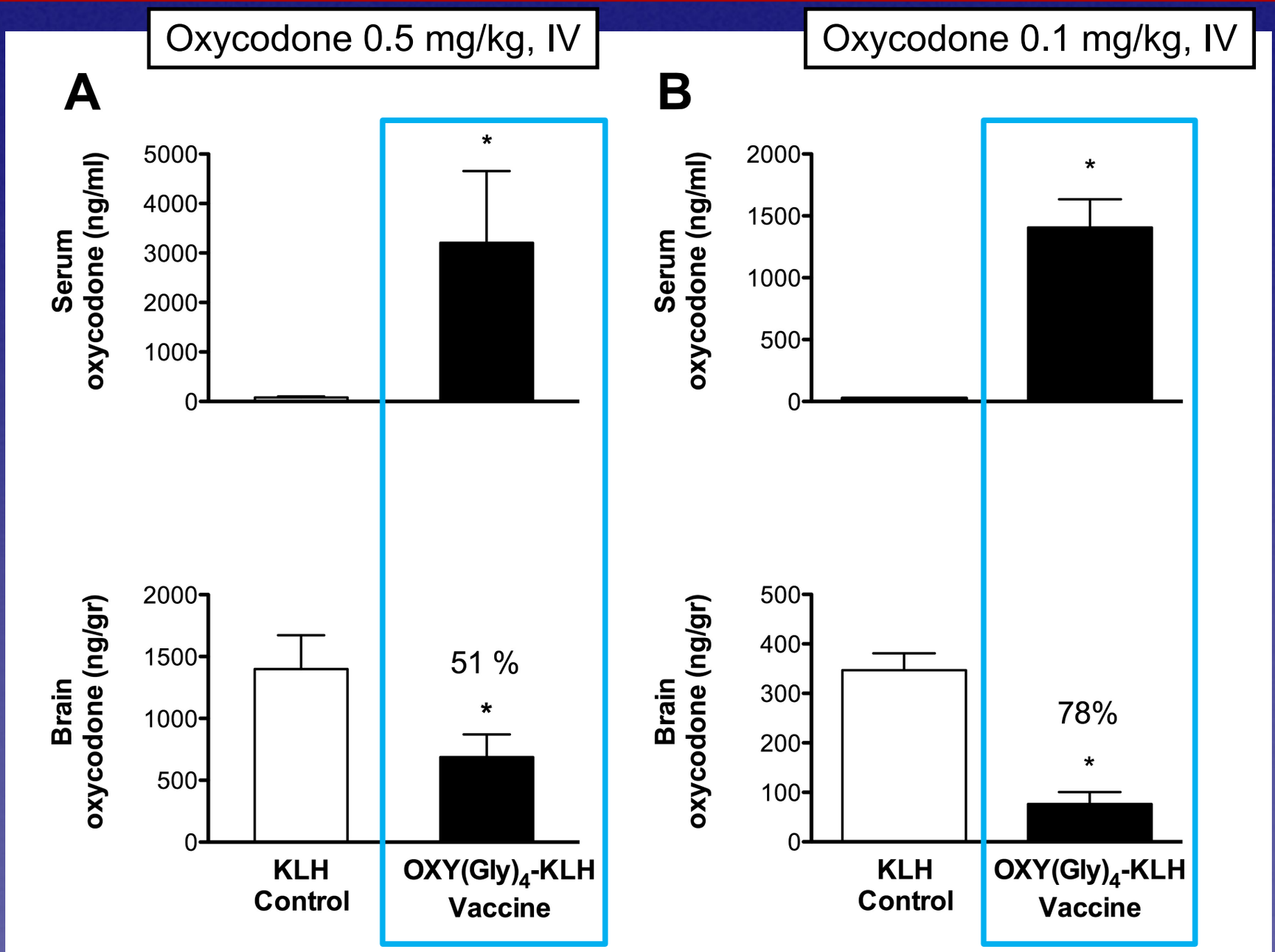
Fentanyl,
Analogs

Multivalent
Vaccine

X?

Y?

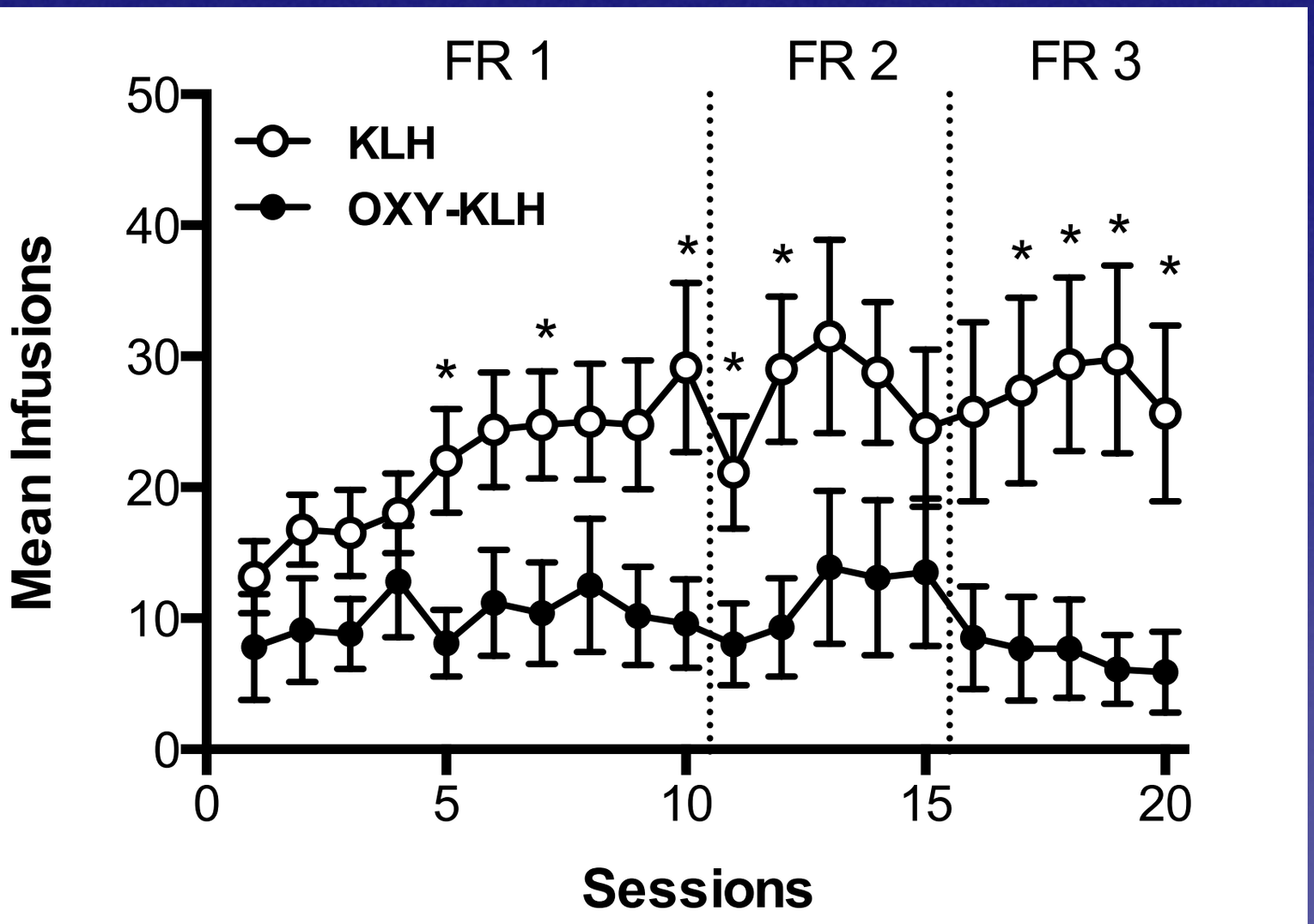
Mechanism of action. Antibodies decrease opioid distribution to the brain in a dose-dependent fashion

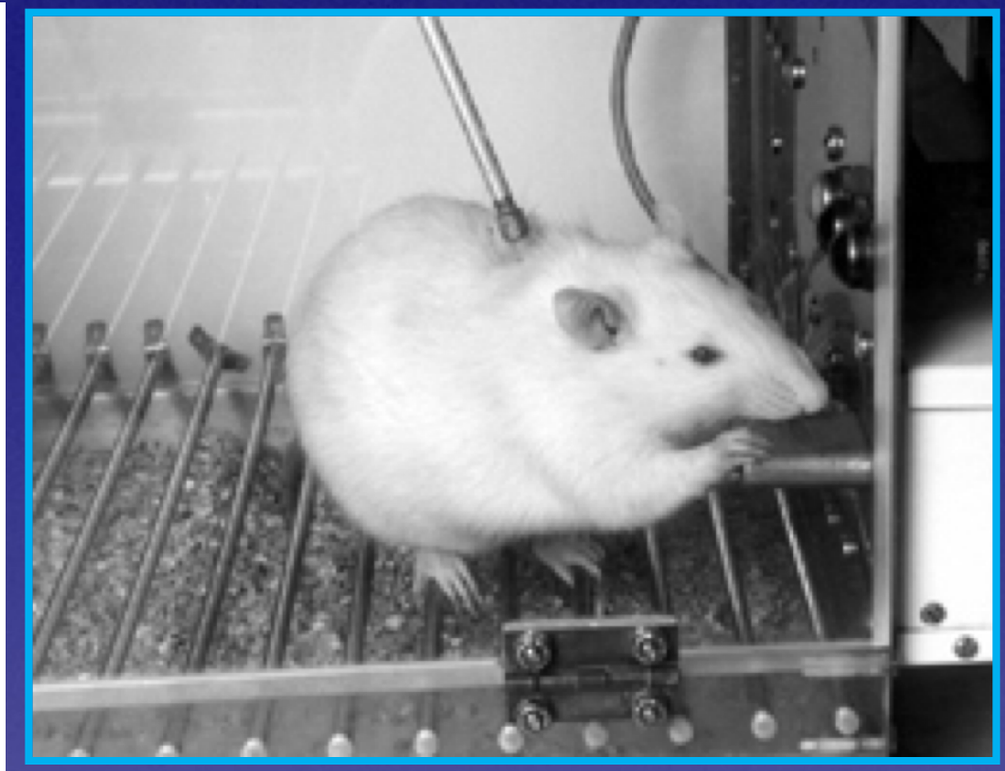


Efficacy depends on antibody response, dose and route of exposure, target opioid

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



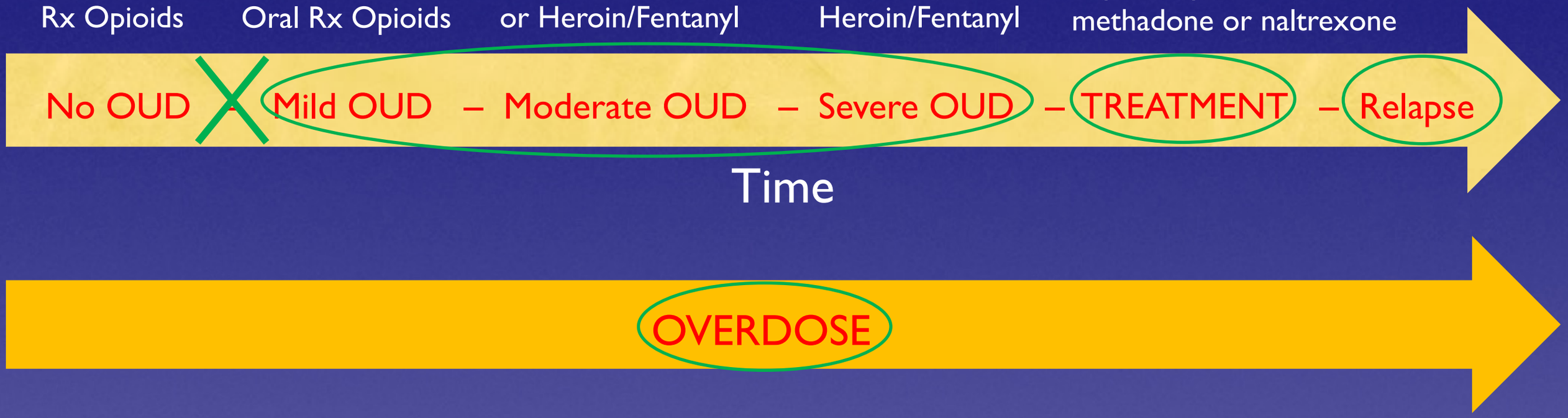


Pravetoni et al., PLOSone 2014

Vaccination with OXY-KLH generated serum IgG antibodies with high affinity for oxycodone

Fixed ratio (FR)= number of active lever presses to deliver i.v. oxycodone

How does a vaccine fit into treatment options for OUD?



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

Pro's and Con's of Approved Medication Therapies vs a Vaccine

Agonist	Sustained-release Naltrexone	Opioid Vaccine
Effective	Effective	???
Easy to transition from heroin	Must detox patients	??? Should be easy
Risk of OD low if relapse	Risk of OD low if relapse	???
Good medication compliance	Good medication compliance	???
Patient convenience poor (methadone)	Patient convenience good	???
Risk of diversion/misuse	No risk of diversion/misuse	No risk of diversion/misuse
Sedation/cognitive impairment during dose changes	Not sedating	Not sedating
Respiratory depression risk during dose titration (methadone)	No respiratory depression risk	No respiratory depression risk
Child safety risk	No child safety risks	No child safety risks

History of Interactions with the FDA on Trial Design

- 2014 – Initial Pre-IND meeting
- 2018 – UG3/UH3 grant funded, leadership change
- 2019 – Pre-IND meeting to discuss Phase 1a/1b

Initial FDA (CBER) Concerns

- Potential of vaccine to block endogenous peptides
- Potential of vaccine to block the rewarding effects of opioids but not their respiratory depressant effects
- Compensatory use of opioids that will result in increased toxicity
- Altered opioid PK/PD in vaccinated individuals
- Choice of subject population

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
  - Antibody titer, concentration, affinity, specificity
- AIM 3 – PRELIMINARY EFFICACY
  - Mean peak ratings of Drug Liking

PARTICIPANTS:
OXY-KLH Vaccine

- INCLUSION CRITERIA:
  - Male or female aged 18-59 years
  - DSM 5 criteria for moderate-severe OUD and physical dependence on opioids (no physical dependence on alcohol or any other drugs, with the exception of nicotine and caffeine)
  - Not currently seeking treatment for drug use

PARTICIPANTS: OXY-KLH Vaccine

- Selected EXCLUSION CRITERIA:
  - Opioid of choice is oxycodone or structurally related opioids
  - Sensitivity, allergy, or contraindication to opioids, alum, or any components of the vaccine
  - Acute HIV, active tuberculosis, or other immunocompromising diseases
  - Previous serious or unexpected adverse reaction to a vaccine, including Guillain-Barre syndrome
  - Use of inhaled corticosteroids, antihistamines, immunosuppressive agents or other medications within 30 days prior to administration of investigational product that might interfere with an immune response

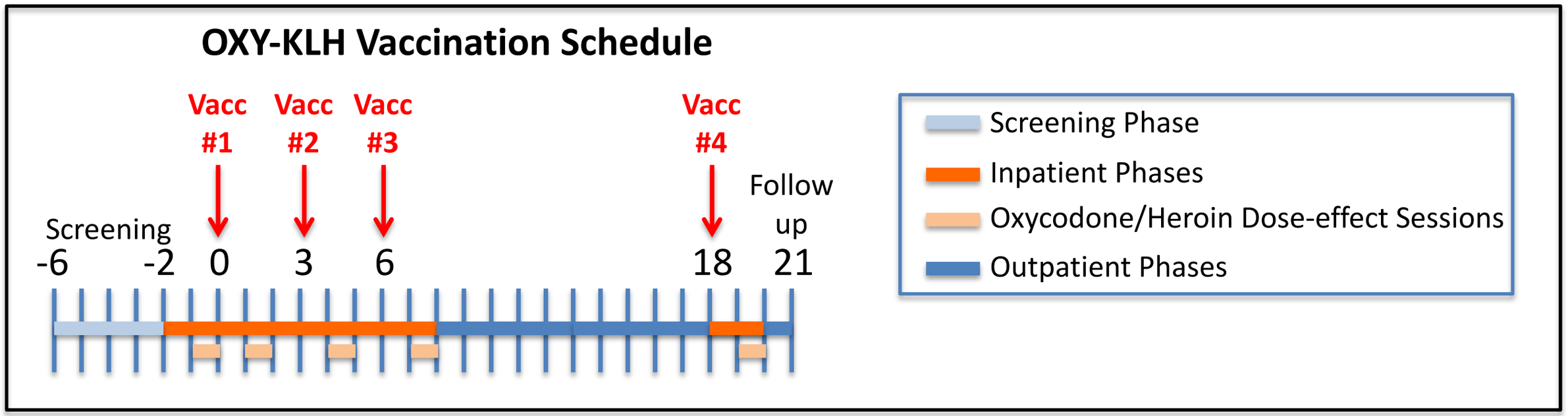
EXPERIMENTAL DESIGN: OXY-KLH Vaccine

- Mixed within and between subjects
  - Within – Each subject will serve as his or her own control (pre-vaccination and repeated post-vaccination assessments will be made)
  - Between – 3 different doses of the vaccine will be tested in ascending order (placebo (n=15), low dose OXY-KLH (n=15), and high dose OXY-KLH (n=15)

EXPERIMENTAL DESIGN: OXY-KLH Vaccine

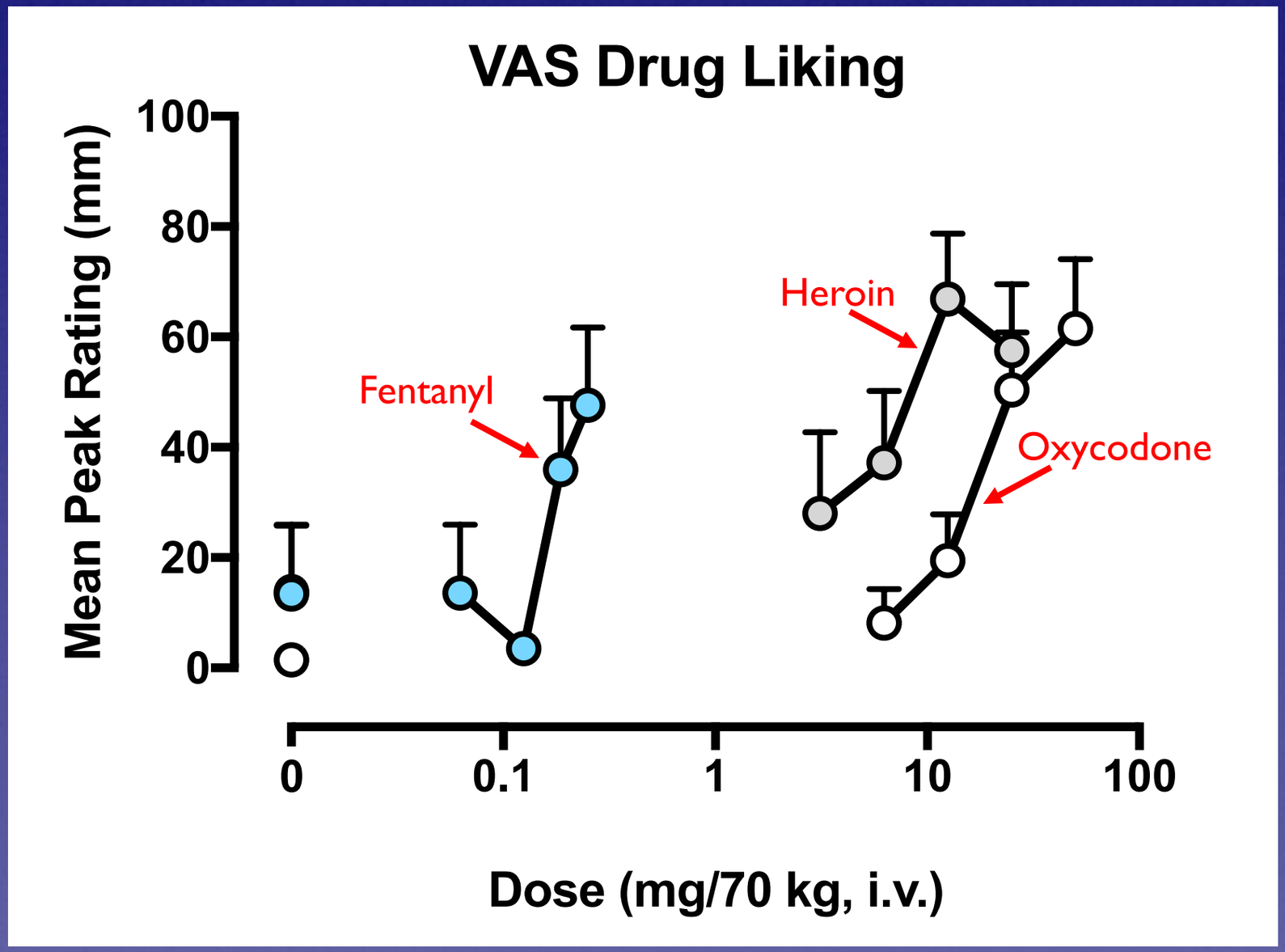
- Both INPATIENT and OUTPATIENT periods
- During INPATIENT periods, the following drugs/doses will be administered
  - ✓Oxycodone: 25, 50, and 100 mg/70 kg, i.n. (target drug)
  - ✓Fentanyl: 250 ug/70 kg, i.n. (positive control)
  - ✓Placebo: lactose powder, i.n. (neutral control)
- Multi-site at Columbia University (Comer) and Clinilabs (Zammit)
- Monitoring of immunological and pharmacokinetic responses (Pravetoni, UMN)

Planned 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 FENTANYL (250 μg IN)

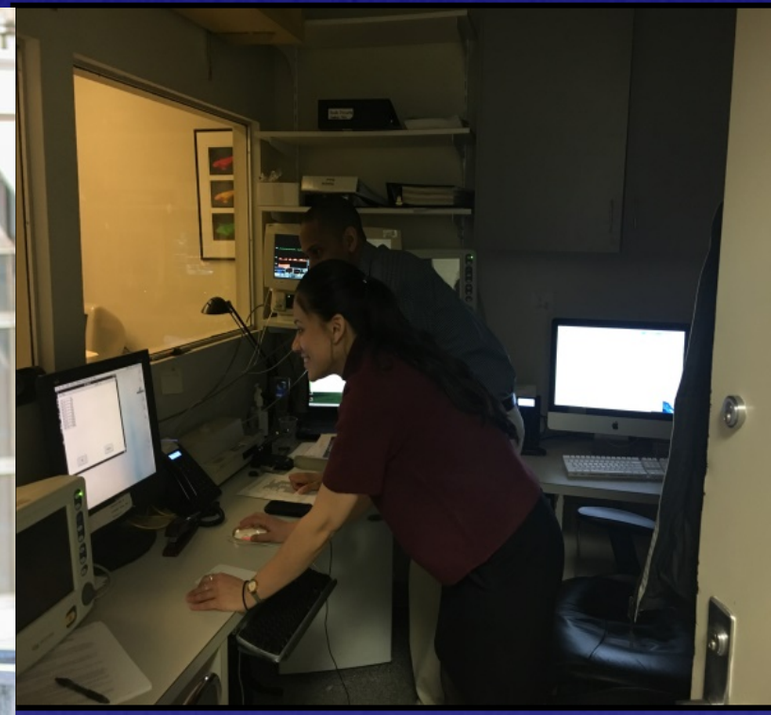
PREVIOUS DATA: Fentanyl, Heroin, Oxycodone



Comer et al. 2008

DEVELOPMENT PLAN

- Submit IND application — Dec 2019
- Receive FDA approval — Jan 2020
- IRB Approval — Conditional approval now, final approval Feb 2020
- Initiate OXY-KLH study (UG3) — Feb 2020
- Complete OXY-KLH study — Dec 2021
- Initiate M-KLH study (UH3) — Jan 2022



THANK YOU!

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ACTTION CURES, November 21st, 2019

Vaccines for treating opioid use disorders: exploring predictive biomarkers



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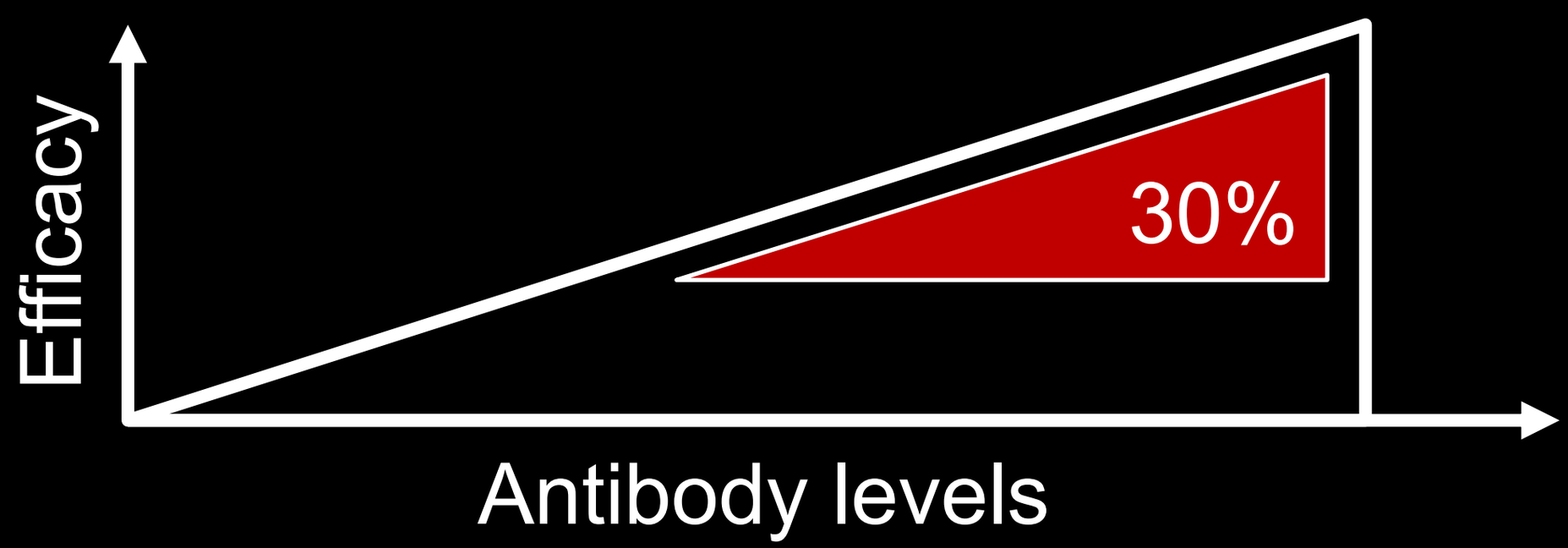
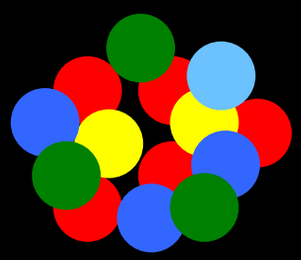
Challenge. Identify immunological mechanisms and biomarkers of vaccine efficacy to accelerate translation

First-generation nicotine and cocaine vaccines showed clinical proof of efficacy in ~30% of immunized subjects that achieved highest antibody levels



Opportunity. Clinically effective antibodies are the endpoint of successful activation of B and T cell lymphocytes

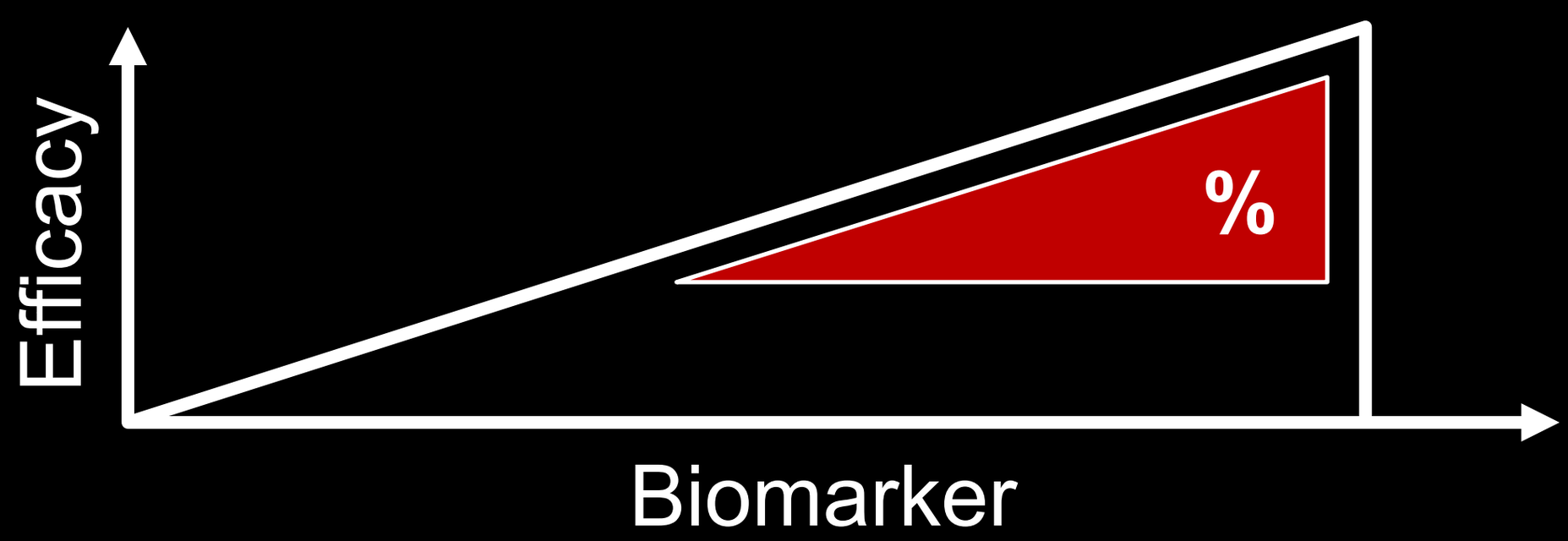
Before Vaccination
Naïve B and T cell pool



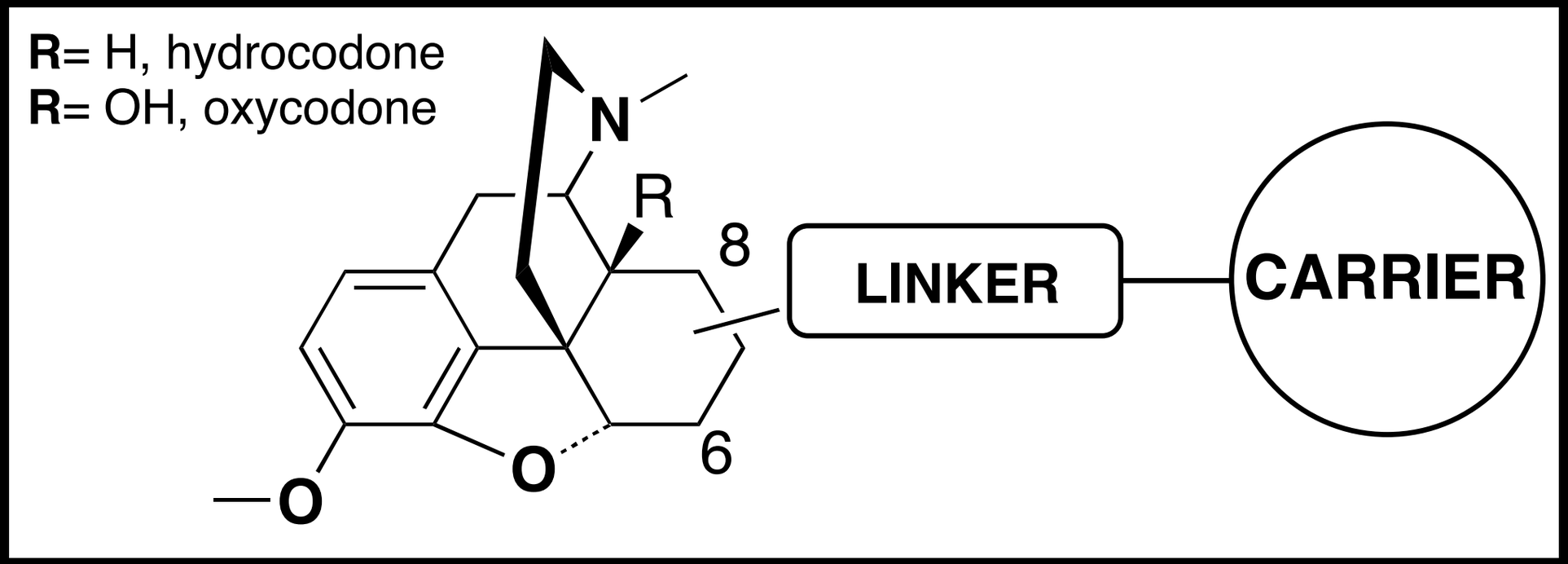
After Vaccination
Innate immunity
Adaptive immunity
Antibodies
Molecular pathways

Anti-Drug Antibody

Vaccine Efficacy
Reducing
Drug distribution to Brain & drug-induced Behavior



Vaccine components are critical for optimal activation of innate and adaptive immunity

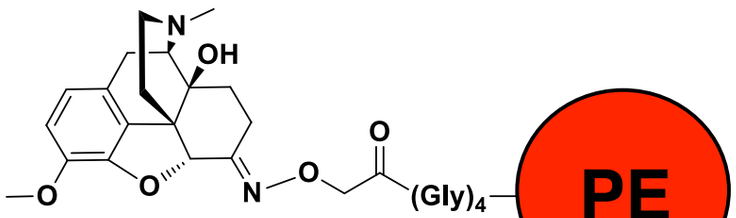


Taylor et al. JIM 2014

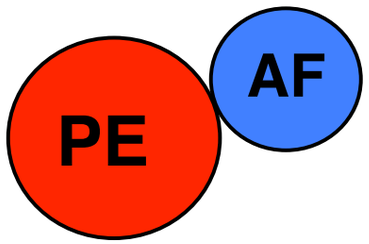
Technology. Antigen-based magnetic enrichment for flow cytometry analysis of hapten-specific B cell lymphocytes

B CELL ENRICHMENT

Spleen & lymph nodes
~200 x 10^6 cells
↓
Incubate with:
1. Alexa Fluor 647-PE
2. Hapten-PE
↓
Incubate with:
anti-PE microbeads
↓
Enrichment of all PE positive B cells by magnetized column



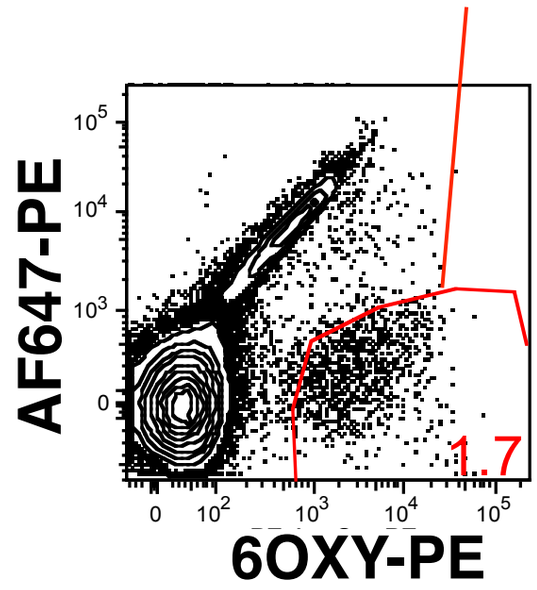
6OXY-PE
(λ= 575 nm)



AF647-PE
(λ= 670 nm)

FLOW CYTOMETRY ANALYSIS

Hapten-specific B cells



Fluorescent protein phycoerythrin (PE)
Florochrome Alexa Fluor647 (AF)

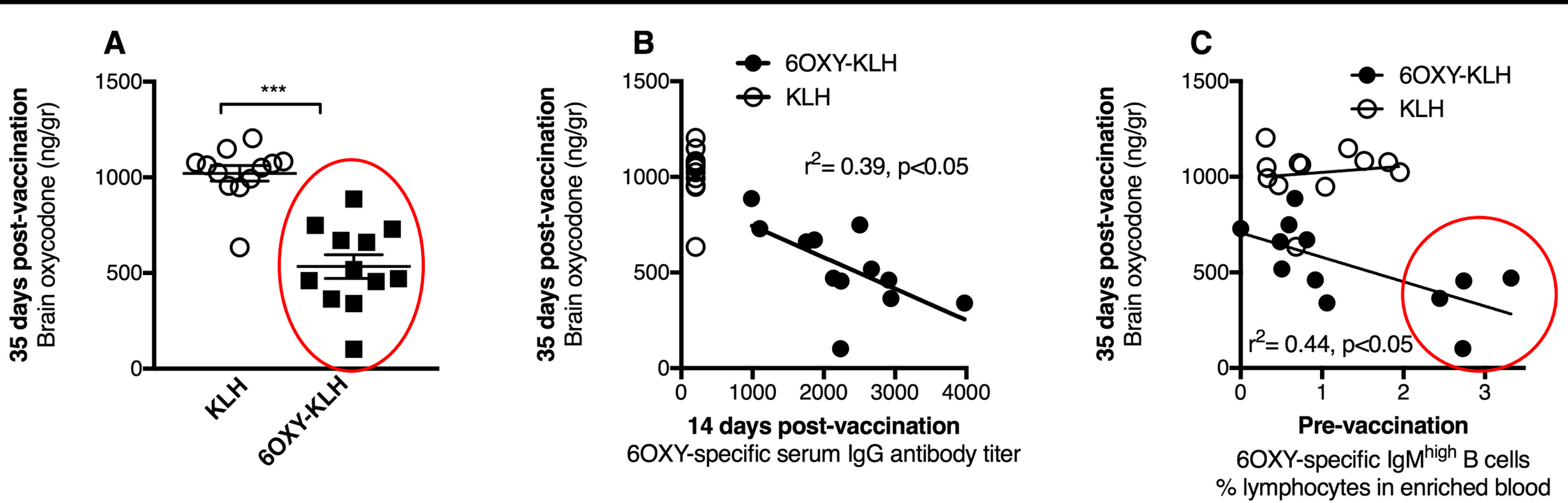
Needle in a haystack: ~2 x 10^8 nucleated cells in peripheral lymph nodes and spleen
In a naïve mouse, OXY-specific IgM$^+$ B cells 2,950±455 in spleen and 125±20 in 0.2ml blood
(mean±SEM, n=24, Balb/c, from Laudenbach et al., J. Immunol. 2015)

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

A. OXY-KLH efficacy in blocking oxycodone to brain

B. Antibody titers vs. efficacy

C. B cell frequency vs. efficacy

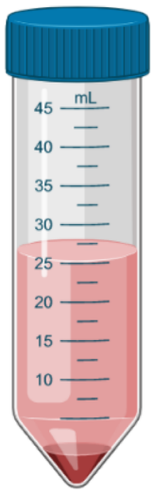


Laudenbach et al., J. Immunology 2015
Laudenbach et al., Vaccine 2015
Taylor et al., J. Immunol. Methods 2014

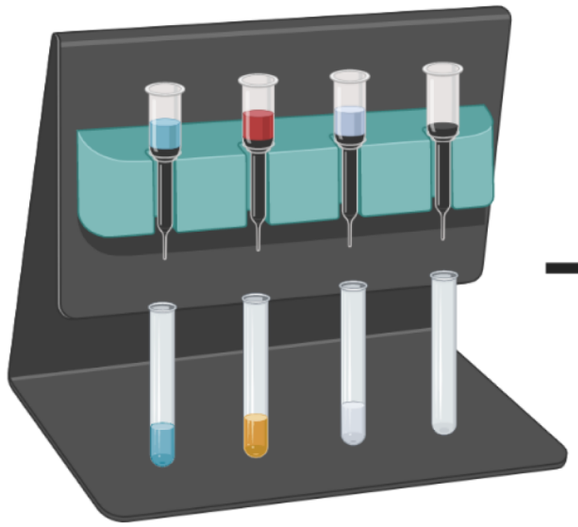
Viable biomarkers to select or stratify patients?

Strategy. Opioid-specific B cell frequency, B cell receptor sequencing, and monoclonal antibody isolation in human

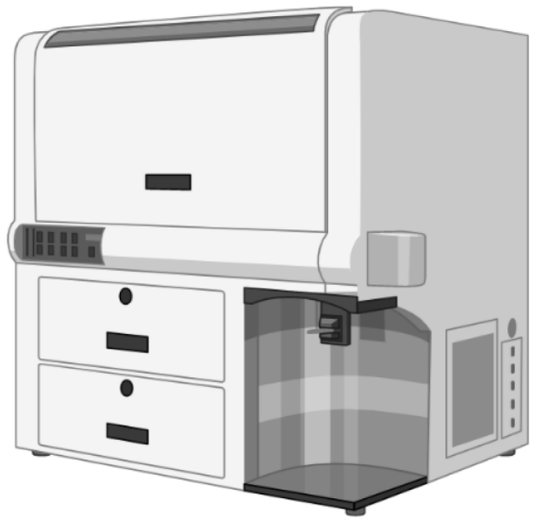
Blood collected from opioid-naïve individuals and individuals diagnosed with OUD



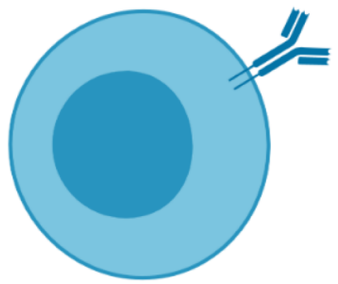
PBMC extraction via ficoll gradient



Opioid-specific B cell isolation by magnetic enrichment



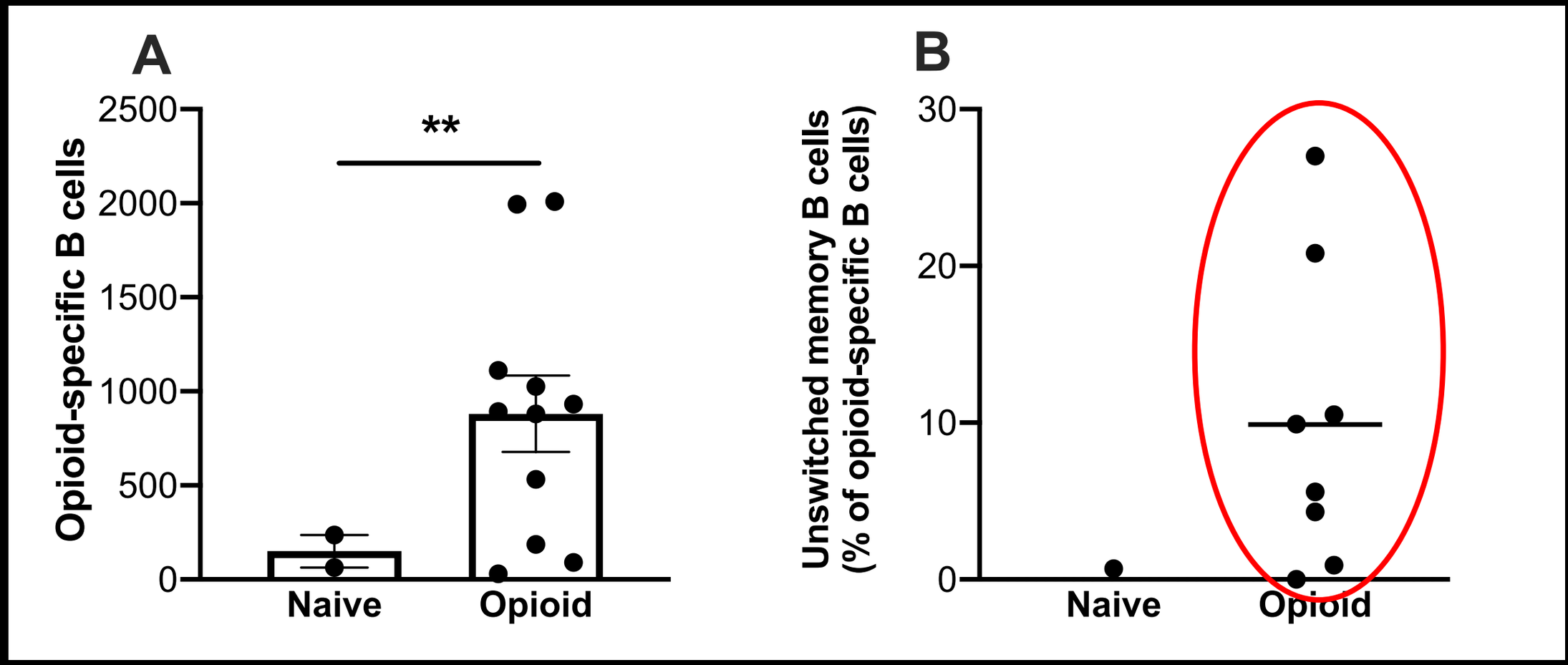
Determination of opioid-specific B cell subtype frequency by flow cytometric analysis



B cell receptor sequencing

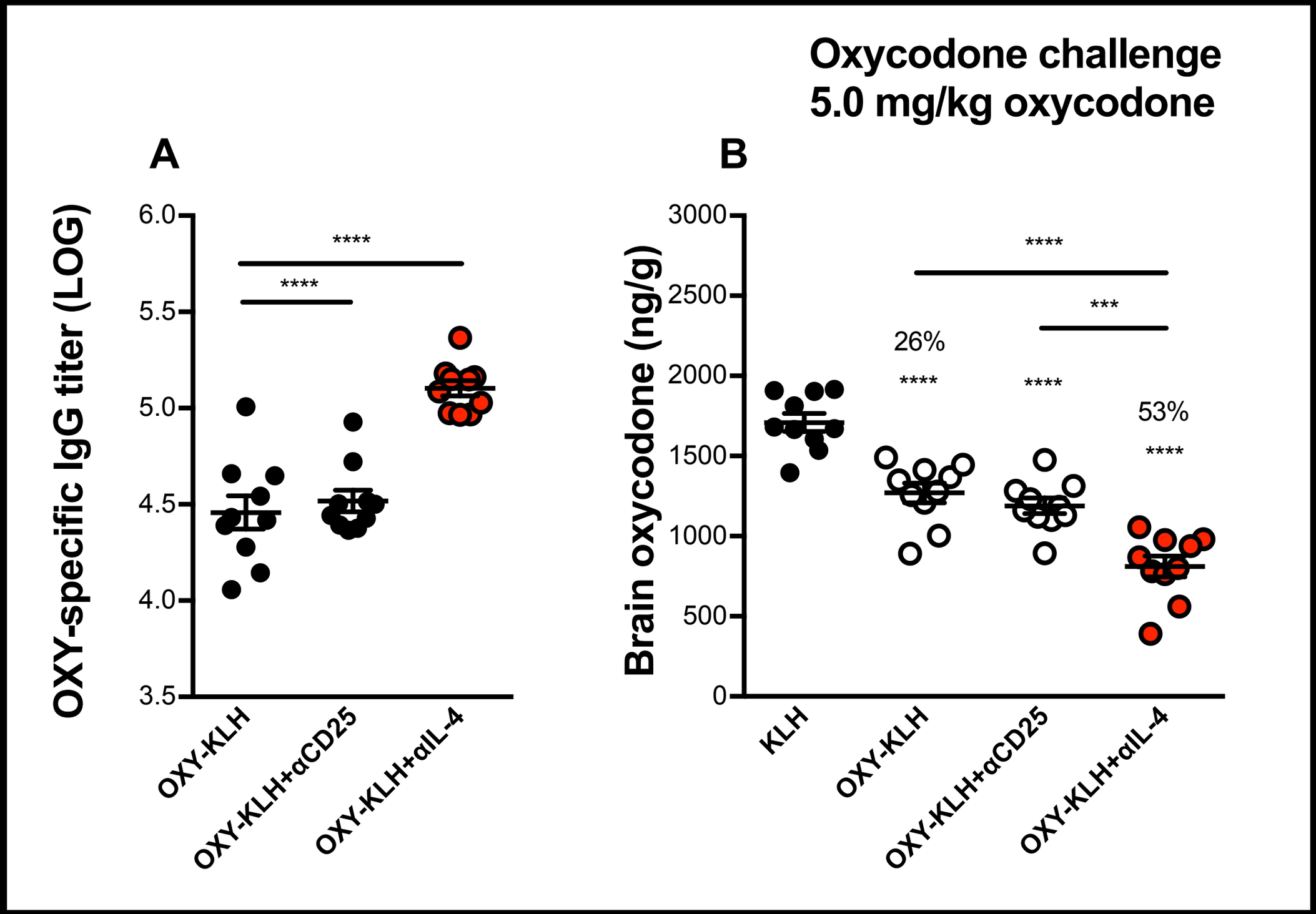
Generation of opioid-specific mAbs

Opioid users show greater number and frequency of opioid-specific B cells than opioid naïve individuals



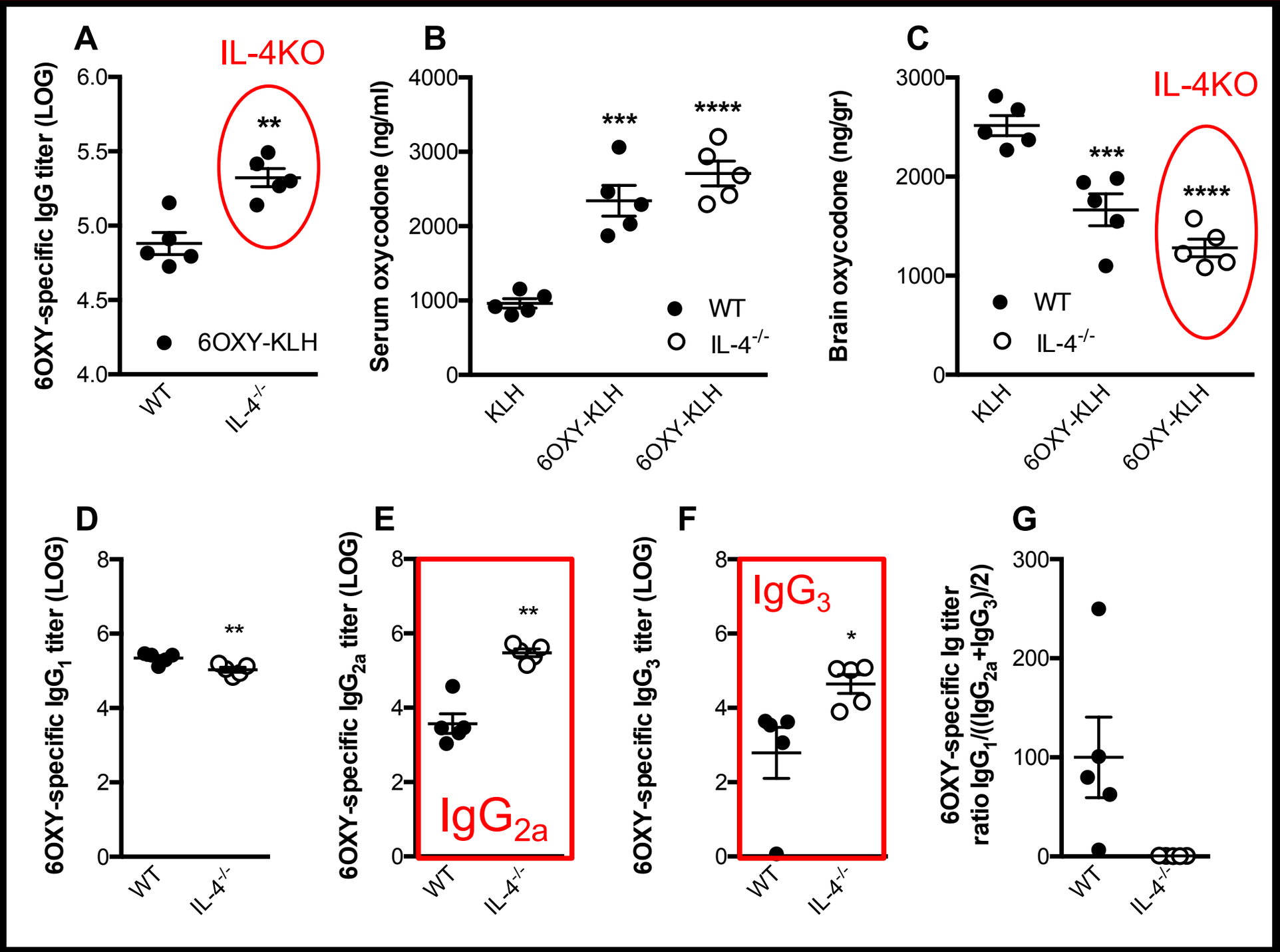
Are opioid-specific B cells viable biomarkers to predict vaccine clinical efficacy?

Biomarker. Efficacy of OXY-KLH is increased by neutralizing mAb against interleukin 4 (αIL-4)



Laudenbach et al., Sci. Rep, 2018

IL-4 knockout mice show increased OXY-KLH efficacy



Is IL-4 a viable biomarker?

Pre-clinical data support use of biomarkers predictive of vaccines efficacy against opioids

- Sex
- B or T cells
- IgG subclasses
- Toll-like receptor (TLR)
- Interleukin 4 and other cytokines
- Unknown ???

Team

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