Bacteriophage virus-like particle based vaccines targeting opioids

Isabella Murphy[1], Susan Core[1], Andzoa Jamus[1], Bryce Chackerian[1], Kathryn M. Frietze[1,2]

[1]University of New Mexico Health Sciences, School of Medicine, Department of Molecular Genetics and Microbiology, Albuquerque, NM
[2]University of New Mexico Health Sciences, Clinical & Translational Science Center, Albuquerque, NM

ABSTRACT

Opioid use disorder (OUD) and opioid overdose are growing problems. Opioid vaccines are a novel treatment approach for OUD, but current vaccine strategies are slow to elicit antibodies and require multiple immunizations. Here, we report our efforts to engineer opioid vaccines that could elicit high-titer, long-lasting antibodies with a single dose. We used bacteriophage Q beta virus-like particles (VLPs) as a platform to display oxycodone in a highly immunogenic format. Opioid drugs of interest were chemically modified to include a short peptide linker (G-G-G-G-C). This allowed for the chemical conjugation of the opioid drugs to the surface of the Q beta VLPs. These drug-VLP conjugates were then used to immunize mice one time intramuscularly. Sera was collected from the immunized mice at days 3, 7, and 14 post immunization. Sera were then assessed by enzyme-linked immunosorbent assay (ELISA) for antibodies against oxycodone to determine the kinetics of the antibody response elicited by our vaccines. Additionally, mice were challenged with a lethal overdose of oxycodone at day 16 post immunization and survival of immunized and control mice were compared. Sera from mice immunized with Q beta oxycodone elicited antibodies as quickly as 3 days post-immunization. Male, but not female, mice challenged with a lethal overdose of oxycodone showed statistically significant protection. Future studies will investigate our vaccination strategy for other opioids, the impact of boost on protection, and protection from drug-induced antinociception upon sub-lethal oxycodone administration.

RATIONALE

- Previous efforts to generate vaccines against opioid drugs have shown that antibodies elicited by the vaccines bind the the drug in the blood and prevent its passage into the CNS.

- Traditional protein carrier approaches tend to require multiple immunizations and exogenous adjuvants to reach peak, effective titers, and elicited antibody responses are not long-lived

- Opioid vaccines were proposed as a long-term strategy for addressing OUD and opioid epidemic (Collins and Volkow, 2017)
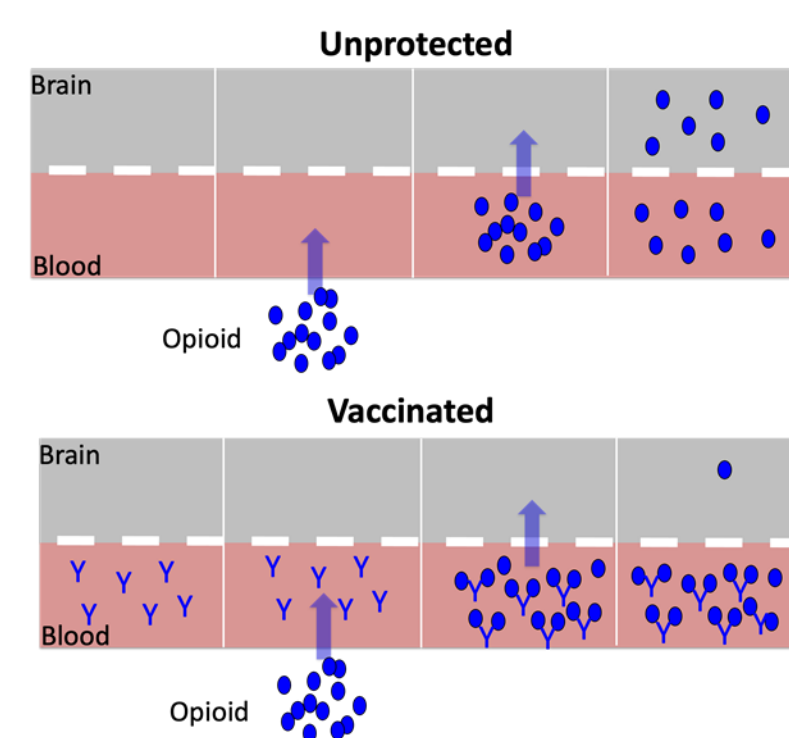

GOAL

- **Develop bacteriophage virus-like particle vaccines against opioids**

## Engineering a Qβ virus-like particle vaccine against oxycodone
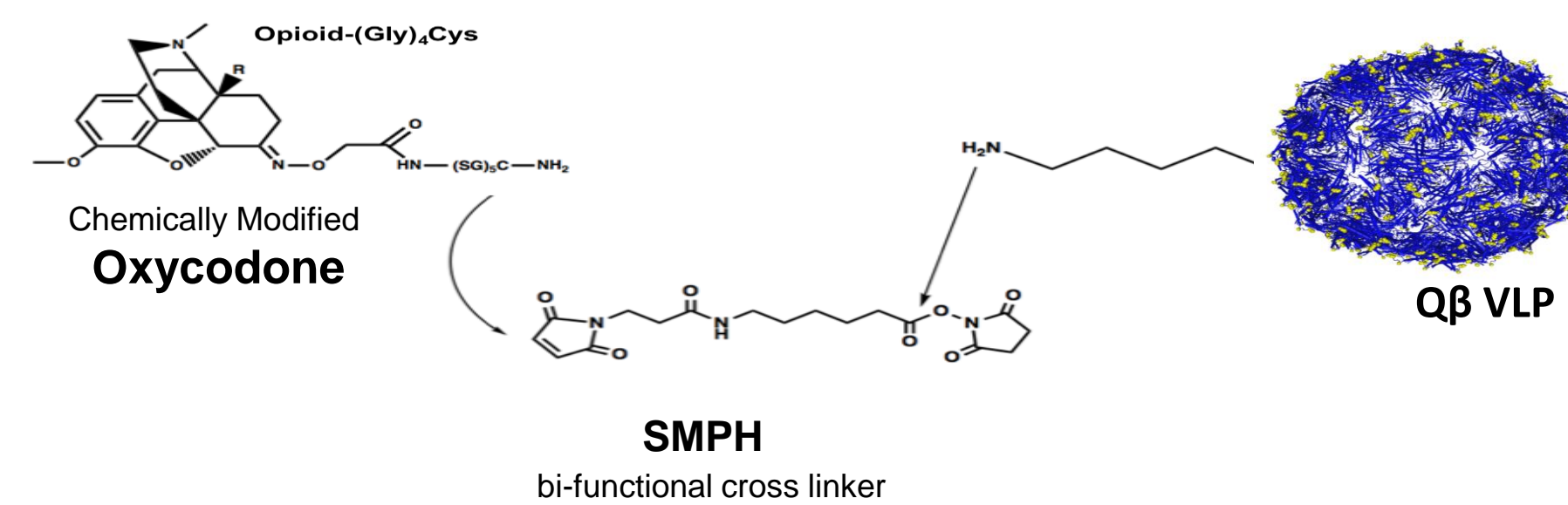
Drugs are chemically modified to include a short peptide linker sequence (GGGGC), allowing chemical conjugation to the surface of bacteriophage virus-like particles on surface-exposed lysines. This results in high-density display of the drug of interest (>720 exposed lysines available for conjugation).

Qβ-Oxycodone vaccine elicits high titer IgG in mice
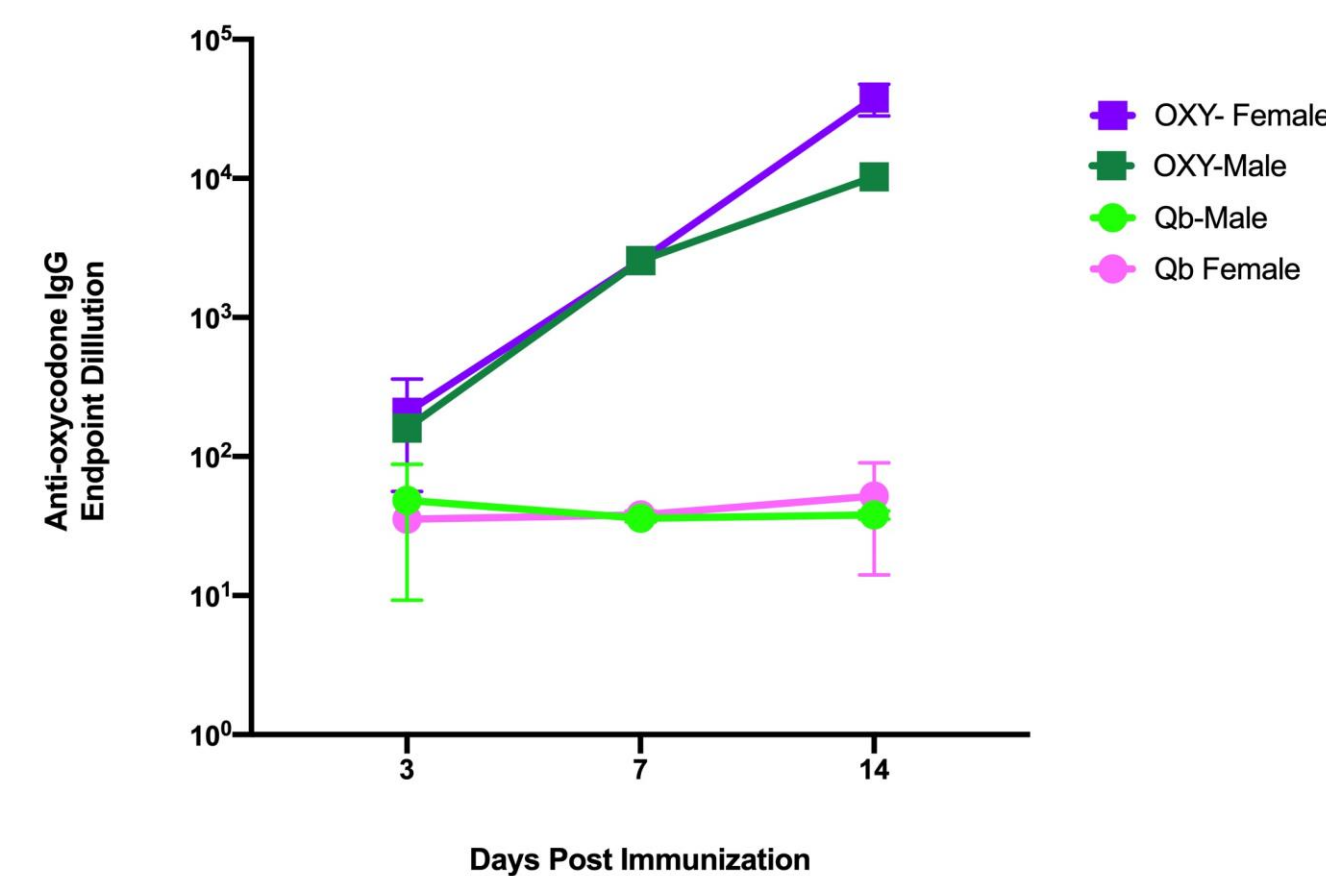
Balb/c mice (n=10) received a single 20ug intramuscular of Qbeta-oxycodone vaccine or Qbeta control and were assessed for serum IgG. Mice generated anti-oxycodone antibodies as soon as 3 days post immunization, and reached peak titers by day 14

Qβ-Oxycodone protects mice against oxycodone challenge
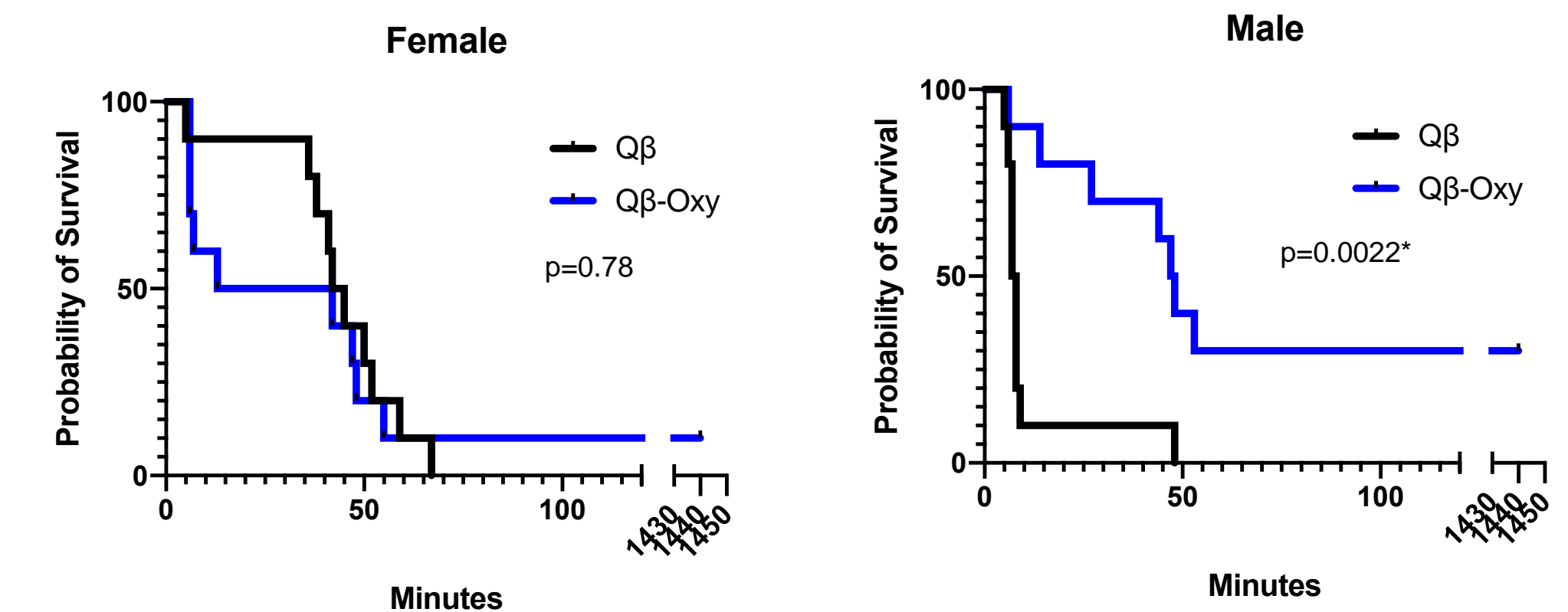
Mice (n=10 per group) were immunized one time, intramuscularly 20ug of VLP-oxycodone vaccine. Mice were then challenged subcutaneously with 426mg/kg oxycodone and monitored for survival continuously for 2 hours and then at 24 hours post challenge. Survival curves were analyzed by Log-Rank (Mantel Cox) and p values are reported above.

CONCLUSION & FUTURE DIRECTIONS

- Here, we investigated the kinetics of the antibody response to a bacteriophage VLP-based vaccine against oxycodone and the ability of these vaccines to protect against lethal overdose in mice
- We observed detectable antibody responses within 3 days of a single intramuscular immunization and peak antibody titers at 14 days post immunization We found that vaccinated male mice had statistically significant prolonged survival when administered a subcutaneous lethal overdose of oxycodone.
- Future studies will investigate the efficacy of this vaccine against drug seeking behavior in animal models and protection against sub-lethal doses of oxycodone
- Additional vaccines are being developed against other opioids using this strategy

FUNDING