Safety and Efficacy of TNX-801 Vaccine Platform

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Abstract

TNX-801 is a live attenuated orthopoxvirus vaccine platform capable of delivering multiple heterologous antigens and inducing protective immunity against emerging infectious diseases. The safety profile of TNX-801 in *in vivo* models has demonstrated that the platform is ~10- to 100,000-fold more attenuated than historical (VACV)-based vaccine strains used in the eradication of smallpox. A single dose of TNX-801 administered via percutaneous, subcutaneous, intradermal, or intramuscular routes elicited IgG and/or neutralizing antibody responses in mice, rabbits, and cynomolgus macaques. These immune responses conferred protection against clinical disease, as measured by lesion counts, and resulted in 100% survival following lethal challenge with monkeypox virus (MPXV) clade Ia, clade IIa, or rabbitpox virus (RPXV).Additionally, as a “proof of concept”, the TNX-801 platform was engineered to express single or multiple heterologous antigens. A single-dose vaccination elicited both humoral and cellular immune responses, and conferred protection against viral pathogens in multiple nonhuman primate models. These data highlight the potential of the TNX-801 platform to enable development of multivalent constructs engineered to encode multiple heterologous antigens, capable of providing protection against multiple infectious agents following a single vaccination. In summary, TNX-801 demonstrates an improved safety profile relative to traditional VACV-based smallpox vaccine strains and provides protection against disease and/or lethality across multiple animal models. These data support advancement of the TNX-801 platform into clinical development for mpox, as well as multivalent vaccines targeting emerging infectious diseases.

Background

Poxviridae Family

- Double-stranded DNA genome ranging from ~128–456 kb
- Enveloped, brick-shaped virion: 220–450 nm long × 140–260 nm wide × 140–260 nm thick
- 2 Subfamilies
- 24 Genera
- Genus *Orthopoxvirus:* monkeypox and variola

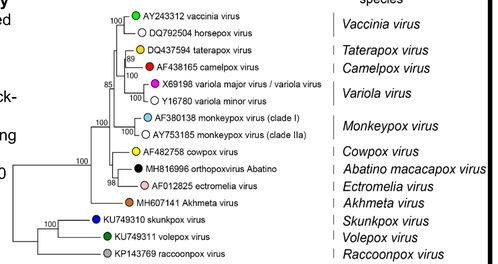

Figure 1. Phylogenetic tree of Genus *Orthopoxvirus.*

Variola Virus (smallpox)

- Variola Virus: case fatality rate of ~30–50%
- Estimated 200–500 million deaths in 20th century
- Eradicated in 1980 following widespread vaccination with vaccinia vaccine

Monkeypox virus (mpox)

- Endemic in Central and West Africa; divided into two clades with four subgroups (Ia, Ib, IIa, IIb)
- Clade Ia carries the highest case fatality rate at ~11%
- Largest outbreak in 2022
- Clade IIb spread to 147 countries, accumulating ~180,000 cases globally

Vaccine Need & Approach

- Global outbreak scale underscores the urgent need for an effective vaccine
- Tonix Pharmaceuticals is developing a novel orthopoxvirus vaccine based on horsepox virus (TNX-801)

Rescue of Recombinant TNX-801

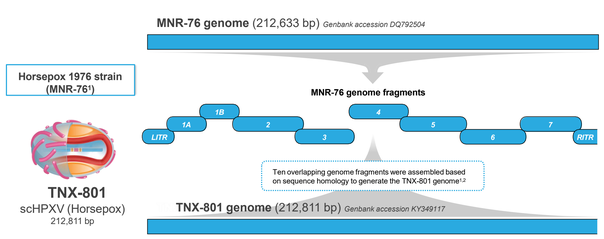

Figure 2. Schematic of recombinant TNX-801 rescue.

Safety of TNX-801

TNX-801 Lacks Lethality Associated With Older Smallpox Vaccine Strains

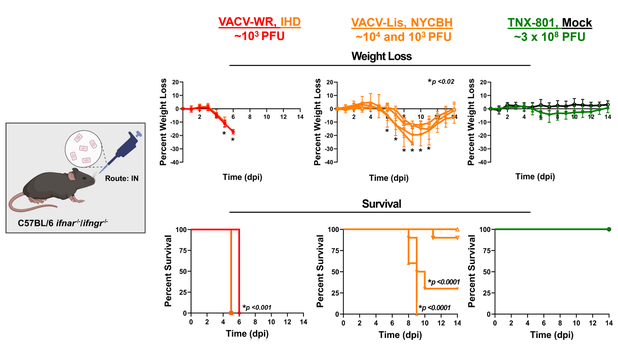

Figure 3. TNX-801 cannot cause severe disease in immunocompromised mice. In contrast, older vaccina virus-based vaccines (VACV-Lister, VACV-NYCBH) utilized in the eradication of smallpox can cause severe disease.

TNX-801 Displays Limited Replication

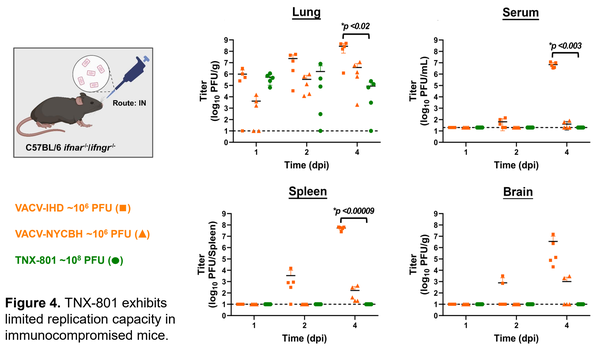

Figure 4. TNX-801 exhibits limited replication capacity in immunocompromised mice.

Immunogenicity and Efficacy of TNX-801

TNX-801 Protects Against Respiratory MPXV Clade IIa Challenge In Mice

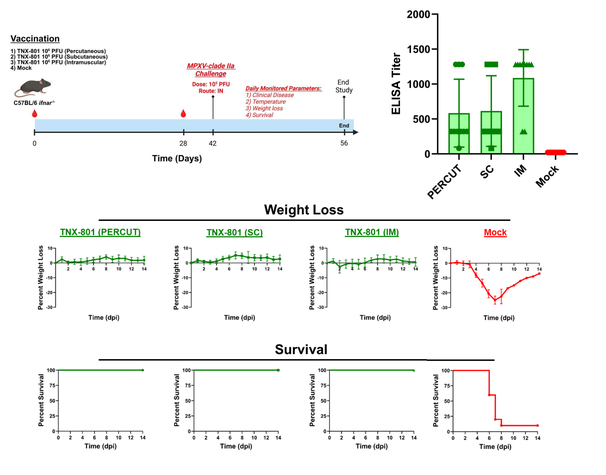

Figure 5. TNX-801 is immunogenic in C57BL/6 *ifnar*$^{-/-}$ mice following vaccination via percutaneous (PERCUT), subcutaneous (SC), or intramuscular (IM) routes. TNX-801 provides complete protection against lethal MPXV clade IIa challenge via the intranasal route.

TNX-801 Protects Against Lesions from Monkeypox Clade Ia Challenge in NHPs

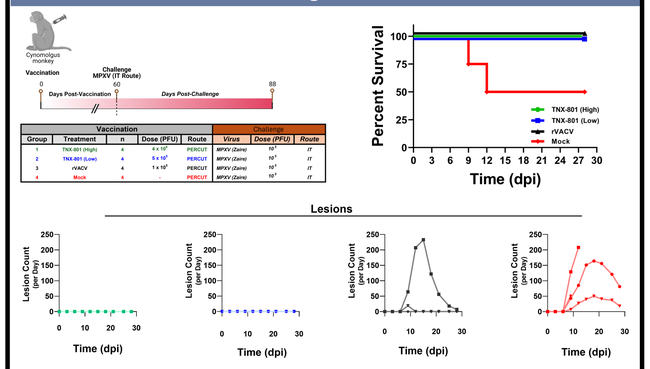

Figure 6. TNX-801 vaccination provides complete protection against lesion development and lethal disease in cynomolgus macaques following MPXV clade Ia challenge via intranasal/intratracheal route.

TNX-801 Protects Against Lesions Development Following RPXV Challenge in Rabbits

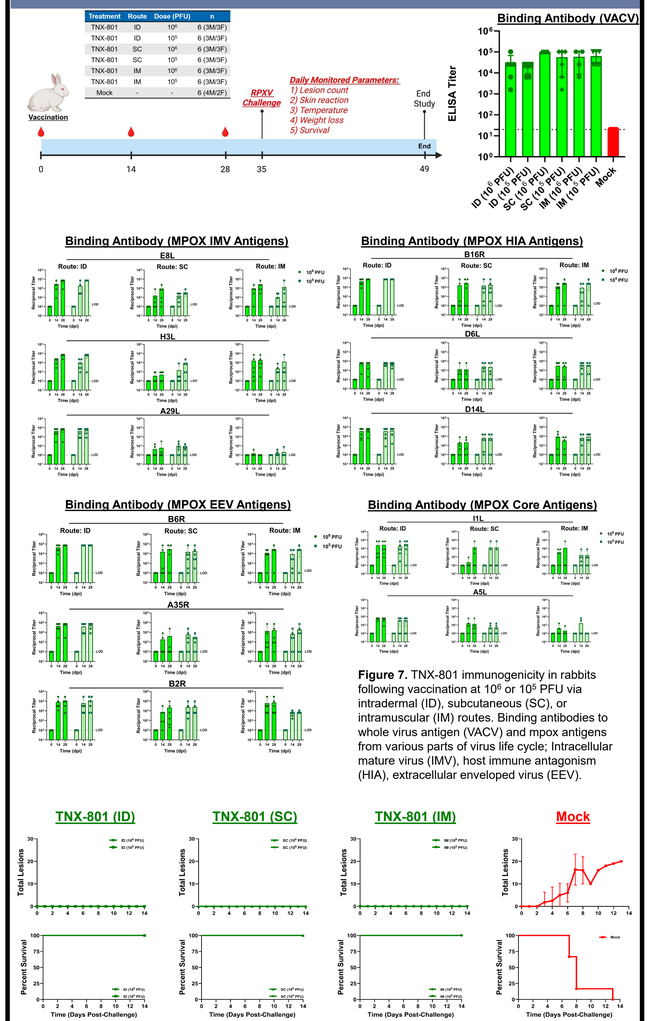

Figure 7. TNX-801 immunogenicity in rabbits following vaccination at 10^6 or 10^5 PFU via intradermal (ID), subcutaneous (SC), or intramuscular (IM) routes. Binding antibodies to whole virus antigen (VACV) and mpox antigens from various parts of virus life cycle; Intracellular mature virus (IMV), host immune antagonism (HIA), extracellular enveloped virus (EEV).

Figure 8. TNX-801 vaccination provides complete protection against lesion development and lethal disease following rabbitpox virus challenge via ID route at 35 days post-vaccination.

Durability of TNX-801

Efficacy Against RPXV Challenge 6-Months Post-Vaccination

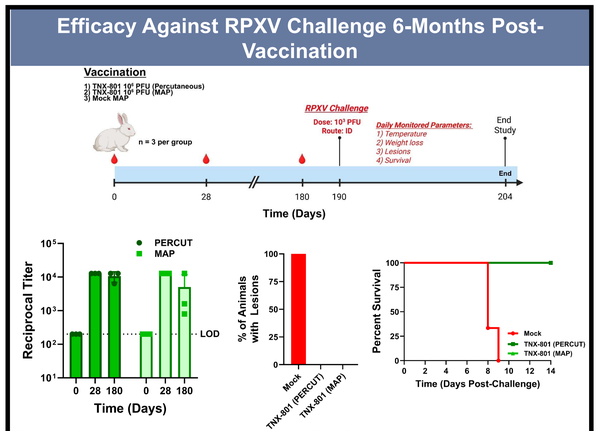

Figure 9. TNX-801 vaccination via percutaneous (PERCUT) or microneedle patch delivery induced durable binding antibody response and provides complete protection against lesion development and lethal disease following rabbitpox virus challenge at 6-months post-vaccination.

Efficacy Against RPXV Challenge 14-Months Post-Vaccination

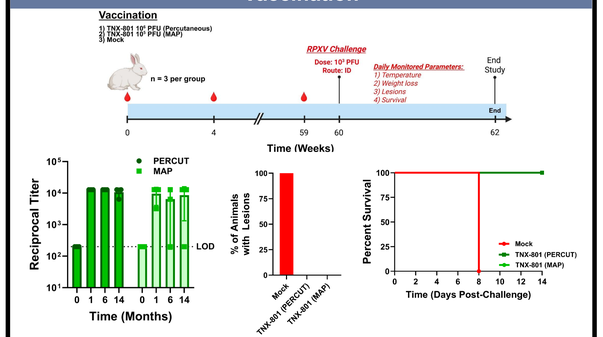

Figure 10. TNX-801 vaccination via percutaneous (PERCUT) or microneedle patch delivery induced durable binding antibody response and provides complete protection against lesion development and lethal disease following rabbitpox virus challenge at 14-months post-vaccination.

Discussion

Safety:

- Well-tolerated in mice, rabbits, and NHPs
- Minimal or no disease in immunocompromised murine models
- Up to *100,000-fold* more attenuated than VACV-based vaccines
- Minimally replicates at site of delivery

Immunogenicity:

- Evaluated in multiple animal models [Mouse, Rabbit, and NHP (Cynomolgus)]
- Single vaccination
- Various routes: percutaneous, subcutaneous, intradermal, intramuscular, microneedle
- Antigen breadth: binding antibody to >12 mpox antigens
- TNX-801 minimally replicates, yet elicits immune responses to antigens from various parts of the virus life cycle

Efficacy:

- Models: Mouse, Rabbit, and NHP
- Viruses: VACV, RPXV, MPXV clade Ia and IIa
- Provides 100% protection against lesion development & lethal challenge
- Elicits robust binding antibody response (6- or 14-months post-vaccination)
- Provides 100% protection against lesion development (6- or 14-months post-vaccination)
- Provides 100% protection against lethal challenge (6- or 14-months post-vaccination)

“Proof of concept” monovalent TNX-801 vaccine candidates

- Expressed Spike protein of SARS-CoV-2
- Immunogenic and provided protection against SARS-CoV-2 replication in cynomolgus and African Green macaques

Future Direction

- Engineering monovalent and multi-valent TNX-801 vaccines against high consequence emerging infectious diseases

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