
Seth Lederman, M.D.
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Certain statements in this presentation regarding strategic plans, expectations and objectives for future operations or results are “forward-looking statements” as defined by the Private Securities Litigation Reform Act of 1995. These statements may be identified by the use of forward-looking words such as “anticipate,” “believe,” “forecast,” “estimate” and “intend,” among others. These forward-looking statements are based on Tonix’s current expectations and actual results could differ materially. There are a number of factors that could cause actual events to differ materially from those indicated by such forward-looking statements. These factors include, but are not limited to, the risks related to failure to obtain FDA clearances or approvals and noncompliance with FDA regulations; delays and uncertainties caused by the global COVID-19 pandemic; risks related to the timing and progress of clinical development of our product candidates; our need for additional financing; uncertainties of patent protection and litigation; uncertainties of government or third party payor reimbursement; limited research and development efforts and dependence upon third parties; and substantial competition. As with any pharmaceutical under development, there are significant risks in the development, regulatory approval and commercialization of new products. The forward-looking statements in this presentation are made as of the date of this presentation, even if subsequently made available by Tonix on its website or otherwise. Tonix does not undertake an obligation to update or revise any forward-looking statement, except as required by law. Investors should read the risk factors set forth in the Annual Report on Form 10-K for the year ended December 31, 2023, as filed with the Securities and Exchange Commission (the “SEC”) on April 1, 2024, and periodic reports and current reports filed with the SEC on or after the date thereof. All of Tonix's forward-looking statements are expressly qualified by all such risk factors and other cautionary statements.
Outline

1. History of horsepox as a smallpox vaccine – Edward Jenner
2. Development and characterization of the new horsepox vaccine TNX-801*
3. Reconstructing the evolution of “Jenner’s vaccinia” (horsepox-like) to “circa 1960 vaccinia”
4. Vaccination of NHPs with TNX-801 to protect against lethal monkeypox challenge
5. Vaccination of NHPs with TNX-1800* (SARS-CoV-2 spike expressing horsepox) to protect against SARS-CoV-2 challenge
6. Assessment of horsepox virulence *in vitro* and *in vivo*
7. Conclusion and future directions

*TNX-801 and TNX-1800 are experimental biologics and are not approved for any indication

Disclosures: Dr. Lederman is CEO and an employee of Tonix Pharmaceuticals and holds stock and options in Tonix
Live Virus Vaccines: Historical Perspective and Development Rationale

Control of smallpox, measles, mumps, rubella, chickenpox and other viral conditions
- Prevent forward transmission
- Mucosal immunity after percutaneous vaccination

Effective in eliciting durable or long-term immunity
- T cell (“cell-mediated”) immunity

Economical to manufacture at scale
- Low dose because replication amplifies dose in vivo
- Single dose administration

Standard cold chain required for shipping and storage

Live virus vaccines are the oldest vaccine technology
- Starting with Edward Jenner’s smallpox vaccine, the first vaccine, eradicated smallpox
In 1796, Edward Jenner Successfully Used Vaccination to Protect Against Smallpox

- Jenner observed milkmaids were protected from smallpox
- A mild illness (low reactogenicity) provided protection (immunity)
  - “Cowpox” was the name of a disease in cows that could transfer to humans and cause sores
  - Jenner “vaccinated” (from vacca, Latin for “cow”) a patient with pustule matter from “cowpox” sores on a milkmaid’s hands; that patient remained healthy when challenged with smallpox virus
- Jenner suspected that the agent causing cowpox, which he called **vaccinia** originated in horses and had been transferred from horses to cows’ udders by the hands of farriers
“There is a disease to which the **Horse** from his state of domestication is frequently subject. The Farriers have termed it *the Grease*. It is an inflammation and swelling in the heel, from which issues matter² possessing properties of a very peculiar kind, which seems capable of generating a disease in the Human Body (after it has undergone the modification³ I shall presently speak of), which bears so strong a resemblance to the Small Pox, that I think it highly probable it may be the source of that disease.”

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¹Jenner, E. "An Inquiry Into the Causes and Effects of the Variolae Vaccinae, a Disease Discovered in Some of the Western Counties of England, Particularly Gloucestershire, and Known by the Name of the Cow Pox" (p 2-3.)

²Vaccine virus

³Passage in cows
“In this Dairy Country a great number of Cows are kept, and the office of milking is performed indiscriminately by Men and Maid Servants. One of the former having been appointed to apply dressings to the heels of a Horse affected with the Grease, and not paying due attention to cleanliness, incautiously bears his part in milking the Cows, with some particles of the infectious matter adhering to his fingers. When this is the case, it commonly happens that a disease is communicated to the Cows, and from the Cows to the Dairy-maids, which spreads through the farm until most of the cattle and domestics feel its unpleasant consequences. The disease has obtained the name of the Cow Pox.”

1 Jenner, E. *An Inquiry Into the Causes and Effects of the Variolae Vaccinae, a Disease Discovered in Some of the Western Counties of England, Particularly Gloucestershire, and Known by the Name of the Cow Pox* (p 3.)
Loy’s “Account of some experiments1 (1801)

“This fact induces me to suspect, that two kinds of Grease exist, differing from each other in the power of giving disease to the human or brute animal: and there is another circumstance which renders this supposition probable. The horses that communicated the infection to their dressers, were affected with a general, as well as a topical, disease. The animals, at the commencement of their disease, were evidently in a feverish state, from which they were relived as soon as the complaint appeared at their heels, and an eruption upon their skin. The horse, too, from whom the infectious matter was procured for inoculation, had a considerable indisposition, previous to the disease at his heels, which was attended, as in the others, with an eruption over the greatest part of his body: but those that did not communicate the diseases at all, had a local affection only.”

1Loy JG. An account of some experiments on the origin of the cow-pox: Whitby; 1801. (p 20-21.)
Both Jenner and Loy used vaccine from horses; subsequently “Equination” was used in Europe in parallel with “vaccination”
- Jenner believed that his “cowpox” or “vaccinia” came from horses with “Grease”

Horsepox isolated from a sick horse in Mongolia in 1976
- Like many other poxviruses, natural host is likely rodents (mice or voles)
- No cases reported in >30 years, some believe it to be extinct; eliminated through improved animal husbandry

Construction of an infectious horsepox virus vaccine from chemically synthesized DNA fragments

Ryan S. Noyce¹, Seth Lederman², David H. Evans¹*

¹ Department of Medical Microbiology & Immunology and Li Ka Shing Institute of Virology, University of Alberta, Edmonton, Alberta, Canada, ² Tonix Pharmaceuticals, Inc., New York, New York, United States of America

Genome Assembly (212 kbp): TNX-801 Core Genome is Based on HPXV Strain MNR-76¹,²

https://doi.org/10.1371/journal.pone.0188453

Sequence: GenBank entry DQ792504; DNA: GeneArt
Vaccination with TNX-801 (rHPXV): Immunity with Low Reactogenicity (i.e., Better Tolerability)

Efficacy and safety of TNX-801 compared to Dryvax ("circa 1960 vaccinia" strain)\(^1\):
- Mice (5 per group) infected with Dryvax lost up to 15% of their body weight because of illness induced by the vaccine, but mice infected with TNX-801 did not experience any weight loss or illness.
- TNX-801 protected mice from a lethal dose (LD) of vaccinia (VACV), like Dryvax.
- TNX-801 may be safer (less reactogenic) than "circa 1960 Vaccinia" vaccines without sacrificing immune protection (efficacy).

Horsepox Compared to Cowpox and Vaccinia Strains\textsuperscript{1}: Consistent with Near “Primordial” Strain Status

\textsuperscript{1}Evans, D. U. of Alberta (2018) with permission
Recent studies (particularly from José Esparza & colleagues) demonstrate that horsepox and horsepox-like viruses were used as smallpox vaccines in the 1800s1-3

Civil War-era vaccines are genetically diverse, with some strains having 1 or both ITRs intact

One recently identified strain, VK05, was found to be **99.7% similar to HPXV** across the whole genome

The 1902 Mulford vaccine is similar to both horsepox (99.7% similar core sequence) and vaccinia (similar ITR deletions)

Selected for WHO Eradication Intensification Program (1967)

Horsepox environmental isolate sequenced in 2006 shares a common ancestor with vaccinia and could be considered a strain of vaccinia
- Similar to cowpox with “intact” inverted terminal repeats (ITRs) – could be considered a primordial strain of vaccinia
- TNX-801 has strong homology in core with Mulford 1902 vaccinee\(^1\)
- TNX-801 has 99.7% colinear identity with “circa 1860 vaccinia” smallpox vaccine VK05, including the LTRs/ITRs that contain host control elements\(^2,3\)

Genetic analysis of early vaccines indicates that “horsepox” is closely related to Edward Jenner’s vaccinia from 1796
- Strong evidence linking a horsepox-like virus as progenitor to circa 1960 vaccinia
- circa 1960 “vaccinia” evolved during the 220 years it was propagated by primitive methods –Propagated for over 120 years before “viruses” were characterized
- Selected for reactogenicity and growth (replication)

\(^1\)Schrick, L. et al An Early American Smallpox Vaccine Based on Horsepox, N Engl J Med 2017; 377:1491
\(^3\)Brinkmann A et al, Genome Biology 2020; 21:286 https://doi.org/10.1186/s13059-020-02202-0
Deduced Relationship of Horsepox with “Jenner’s Vaccinia” and “circa 1960 Vaccinia” Vaccines

Horsepox Progenitor

→

“Jenner’s Vaccinia”

→

Arm-to-arm

1860 US Civil War Vaccine VK05

→

1976 Mongolian Field Isolate

Molecular Biology

→

TNX-801
Less Virulent

“Vaccine Farms”
Cow production started ~1875: Selection for Growth, Reactivity or Increased Virulence

Deletions

→

“circa 1960 Vaccinia”
More Virulent
TNX-801 (Live HPXV for Percutaneous Administration)

Vaccine based on sequence of isolated horsepox (HPXV) clone

- Synthesized since 1976 isolate was not available outside of the U.S. Centers for Disease Control and Prevention (CDC)
- No new gene elements
- Coding sequence identical to HPXV

Small plaque size in culture

- Appears identical to U.S. CDC publication of 1976 horsepox isolate

Question: will “horsepox” perform as a vaccine similar to “Jenner’s vaccinia”?

- Need to evaluate tolerability and activity in animal models

Survival: 100% of TNX-801 Vaccinated NHPs Survived Lethal MPXV Clade 1 Intratracheal Challenge

No deaths in Tonix-801 vaccinated groups
TNX-801 Vaccination/MPXV Clade 1 Challenge: No Lesions Were Observed After TNX-801 Vaccination


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TNX-801 Vaccination: Minimal MPXV Virus Shedding


Potential to Reduce Forward Transmission
Conclusions from NHP MPXV Challenge Study

- A single dose of TNX-801 (rcHPXV) vaccination was well tolerated
  - No severe adverse events

- TNX-801 vaccination via traditional route (scarification) was immunogenic

- Provided near complete protection against virus shedding, viremia, and weight loss

- No clinical disease was observed (lesions)

- All NHPs (TNX-801 and rVACV vaccinated) survived lethal challenge
Risk of Spread and Lethality

- Case Fatality Rate (CFR): 0.1% to 3.6% → Lower compared to Clade I
- Primarily spread through sexual contact among MSM
- Rapid and significant spread beyond endemic regions → Over 90,000 cases reported in more than 100 countries by the end of 2022
- Systemic symptoms and rash leading to medical interventions in up to 40% of cases

Total Cases: 95,912; 92,982 were in locations that have not historically reported Mpox
Total Location: 118; 111 has not historically reported Mpox
Do We Need Additional One-Dose Mpox and Smallpox Vaccine?

Vaccine effectiveness of JYNNEOS against mpox ranges from 36%–75% for 1-dose vaccination and 66%–89% for 2-dose vaccination.

### U.S. Mpox Vaccine Coverage in High-Risk Groups (CDC)

- **1-dose:** 38.8%  
  **2-dose:** 24.3%  
  **37% Drop Out**

ACIP Oct 25, 2023
Smallpox and other orthopoxviruses pose significant threats to the United States and the world due to their potential for weaponization, accidental release, and vulnerability of populations who stopped routinely vaccinating against smallpox in the 1970s.¹

(2-2) Smallpox vaccines that have improved safety across different population subgroups and are available as a single dose would support faster and more effective response to contain smallpox and other orthopoxvirus outbreaks. The development of novel smallpox vaccines using multi-vaccine platforms (i.e., use common vaccine vectors, manufacturing ingredients, and processes) would improve the capacity for rapid vaccine production in response to a smallpox event and reduce the need for stockpiling in the SNS at current levels.
M kapsam 2023-24: Clade I and Current State of the Mpox Epidemic in Congo

Risk of Spread and Lethality
- Higher CFRs → 1.4% to over 10%
- From January 1, 2023, to April 14, 2024, DRC reported 19,919 suspected cases and 975 deaths (4.9% CFR) in 25 out of 26 provinces
- Children under 15 years old account for 70% of total cases and 88% of total deaths in DRC
- Significant impact on sex workers in mining areas and LGBTQ+ communities
- Global travel amplifies the spread of risk

The New York Times
C.D.C Warns of a Resurgence of Mpox

A health official investigating and treating a probable case of Mpox at the Yalolia health center in Tshopo, DRC

Number of suspected clade I Mpox cases, by province, DRC, January 1, 2023–April 14, 2024

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https://www.cdc.gov/mmwr/volumes/73/wr/mm7319a3.htm
Brief Report

Immunogenicity and Tolerability of a SARS-CoV-2 TNX-1800, a Live Recombinant Poxvirus Vaccine Candidate, in Syrian Hamsters and New Zealand White Rabbits

Mayanka Awasthi, Anthony Macaluso, Scott J. Goebel, Erin Luea, Ryan S. Noyce, Farooq Nasar, Bruce Daugherty, Sina Bavari and Seth Lederman

Recombinant SARS-CoV-2 Vaccine Generation (TNX-1800* Expresses Spike)

Development of HPXV as a recombinant Delivery Vector Platform

Non-Essential Viral Genes

Left Terminal Region 60Kbp

HPXV Genes 001-062

Δ095 (TK)

Essential Viral Genes

Central General Region 36Kp - 146Kbp

HPXV Genes 063-145

Non-Essential Viral Genes

Right Terminal Region 147-212 kbp

HPXV Genes 146- 207

Left Flanking Arm

Pox E/L Promotor

Right Flanking Arm

SARS-CoV-2 WA-2020 Spike Protein Gene

Recombinant Generation
Rescue virus: TNX-1800

*TNX-1800 has not been approved for any indication.
Immunogenicity and Efficacy of TNX-1800, A Live Virus Recombinant Poxvirus Vaccine Candidate, against SARS-CoV-2 Challenge in Nonhuman Primates

Mayanka Awasthi¹, Anthony Macaluso¹, Dawn Mysofski¹, Jon Prigge², Fusataka Koide³, Ryan S. Noyce⁴, Siobhan Fogarty⁵, Helen Stillwell⁶, Scott J. Goebel¹, Bruce Daugherty⁷, Farooq Nasar¹, Sina Bavari¹ and Seth Lederman⁸.*

Immunogenicity: All NHPs in TNX-1800 Vaccinated Group Had Neutralizing Antibody Response

NHPs were vaccinated day 0 and challenged day 41
Vaccination with TNX-1800 results in the inhibition of SARS-2 Replication in Vaccinated NHPs

NHPs were vaccinated day 0 and challenged day 41; “Day 47” is 6 days after challenge
Tonix Pharmaceuticals’ Vaccine Candidate, TNX-1800, Selected by NIH/NIAID Project NextGen for Inclusion in Clinical Trials

Published
Nov 2, 2023 8:00AM EDT

NIAID is conducting early phase clinical trials on select next generation COVID-19 vaccine candidates with the intent to identify promising vaccine candidates.

TNX-1800, a live virus percutaneous vaccine candidate, is based on Tonix’s recombinant pox virus (RPV) platform.

Phase 1 clinical trial of TNX-1800 expected to start in the second half of 2024.

NIAID will cover the full cost of the clinical trial; Tonix will supply the vaccine candidate.
Title: Recombinant chimeric Horsepox Virus (TNX-801) is attenuated relative to Vaccinia Virus Strains in Human Primary Cell Lines and in Immunocompromised Mice

Stephanie V Trefry¹, Christy N Raney¹, Amy L Cregger¹, Chase A Gonzales¹, Brittney L Layton¹, Robert N Enamorado¹, Nelson A Martinez¹, Deborah S Gohegan¹, Tinoush Moulaei¹, Natasza E Ziólkowska¹, Scott J Goebel¹, Seth Lederman¹, Sina Bavar¹, Farooq Nasar¹

Trefry, SV et al. bioRxiv 2023.10.25.564033; doi: https://doi.org/10.1101/2023.10.25.564033
TNX-801 has Reduced Virulence Relative to “circa 1960 Vaccinia”

Comparisons in vitro:
1) Plaque phenotype: VACV (~3-4 mm) vs. TNX-801 (~1-2 mm)
2) Multi-step growth kinetics:
   ▪ Immortalized cell lines: TNX-801 ~10- to 100-fold less virulent
   ▪ Human primary cell lines: TNX-801 ~10- to 100-fold less virulent

Comparisons in vivo:
1) Assessed TNX-801 attenuation in immunocompromised murine models (C57BL/6 ifnar^-/- and C57BL/6 ifnar^-/-ifngr^-/-) :
   ▪ TNX-801 is >100- to 1,000-fold less virulent than VACV strains
   ▪ TNX-801 is indistinguishable from mock treated animals in immunocompromised model
Conclusion: TNX-801 is 10-to-1000-fold Less Virulent than “circa 1960 Vaccinia” (VACV)’’
## Approved Recombinant Poxvirus-Based Commercial Products

<table>
<thead>
<tr>
<th>Product</th>
<th>Application / disease</th>
<th>Location</th>
<th>Poxvirus vector</th>
<th>Host restricted?</th>
<th>Doses released to environment</th>
</tr>
</thead>
<tbody>
<tr>
<td>TROVAC-AIV H5N1</td>
<td>Agriculture/avian influenza</td>
<td>Mexico, Central America</td>
<td>TROVAC-AIV H5N1</td>
<td>No Replication competent</td>
<td>2 billion (as of 2006)</td>
</tr>
<tr>
<td>Purevax FeLV</td>
<td>Companion animals (cats)/FeLV</td>
<td>US, others</td>
<td>ALVAC-FeLV Gag/Pol</td>
<td>Yes Replication incompetent</td>
<td>Unknown</td>
</tr>
<tr>
<td>Purevax Rabies</td>
<td>Companion animals (cats)/rabies</td>
<td>US, others</td>
<td>ALVAC-RG</td>
<td>Yes Replication incompetent</td>
<td>Unknown</td>
</tr>
<tr>
<td>Recombitek</td>
<td>Companion animals (dogs)/canine distemper</td>
<td>US, others</td>
<td>ALVAC-HA, F</td>
<td>Yes Replication incompetent</td>
<td>Unknown</td>
</tr>
<tr>
<td>Raboral V-RG Rabisin</td>
<td>Wildlife control of rabies</td>
<td>US, Europe, Israel</td>
<td>Vaccinia Copenhagen RG</td>
<td>No Replication competent</td>
<td>250 million doses 5 million doses/year</td>
</tr>
</tbody>
</table>

Certain Gene Factors Make Modern Cowpox and “circa 1960 Vaccinia” More Virulent Than HPXV

Replicative capacity equates to the ”fitness” or competitive advantage of the virus

*This is a conceptual view to illustrate whether these genes are active or not and does not indicate the actual number, size, or location of the genes
†Stripes indicate regions among different vaccinia strains that are present in some but absent in others

Horsepox Balances Tolerability and Reactogenicity Relative to Other Pox-based Vaccines

Conventional view holds that replicative capacity correlates with reactogenicity and protection.

Well tolerated, requires high dose, 2 vaccinations

Non-propagating

Optimal Replicative Capacity

Horsepox (TNX-801)

Moderately Propagating

Circa 1960 smallpox vaccines

Dryvax
Lister
TianTan

Copenhagen
Tashkent

~1 death per million
~10 deaths per million

Robustly Propagating

MVA
NYVAC
Canarypox
Fowlpox

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Horsepox Activity and Tolerability Potentially Decouples Protective Immunity from Reactogenicity

Protective immunity is not necessarily related to reactogenicity
- Reactogenicity was a basis for testing vaccine activity prior to the understanding that vaccinia was a virus

“Real World Evidence” supports efficacy of horsepox-like vaccines
- Effectiveness of archaic vaccines (from the 1800’s) support the belief that horsepox will be protective against smallpox
- Historical evidence that horsepox-like vaccines prevented forward transmission

For “circa 1960 vaccinia”, the process of “Passage” through cows or birds was a primitive form of genetic engineering

− “Passage” through cows resulted in gene deletions that may have increased virulence relative to “circa 1860 vaccinia” (circa 1960 “vaccinia” deleted regulatory genes)
− MVA: “Passage through birds resulted in extensive gene deletions that decreased replication in humans (“non-replicating”)

Horsepox data: More Genes may be better than Fewer Genes

− Horsepox appears to have preserved regulatory genes that confer tolerability
TNX-801 is Potential Vaccine for Mpox and Smallpox

Platform to express other viral antigens

Animal studies show TNX-801 protects against mpox
- Appears to provide mucosal immunity after percutaneous vaccination (May prevent forward transmission)

Single dose efficacy
- May elicit durable or long-term protection by stimulating T cell (“cell-mediated”) immunity

Economical to manufacture at scale
- Low dose because replication amplifies dose \textit{in vivo}

Standard cold chain believed to be sufficient for shipping and storage

Jenner’s vaccinia is the oldest vaccine technology – can now be engineered with payload antigens
- “Jenner’s vaccinia” and its descendants “circa 1960 Vaccinia” eradicated smallpox
- “Circa 1960 vaccinia” kept mpox out of the human population in Africa
- Horsepox and vaccinia express transgenes with high fidelity
Live Virus Vaccine Platform: Recombinant Pox Vaccine (RPV) Platform

Monkeypox and Smallpox

COVID-19

Future Pandemics & New Infectious Diseases (“Hard Targets”)

Biodefense

Oncology

RPV VECTOR BELIEVED SIMILAR TO EDWARD JENNER’S VACCINE1-3

2Esparza, J. Vaccine. 2020 Jun 19; 38(30): 4773–4779. doi: 10.1016/j.vaccine.2020.05.037

Using Proven Science To Address Challenging Disease States, We Have Created A Programmable Technology Platform Aimed At Combating Future Threats To Public Health
A Canarypox Prime (ALVAC) was the Basis of a Successful HIV Vaccine Trial – RV144\(^1\)

**Prime-Boost Regimen**

- Recombinant canarypox vector vaccine (ALVAC-HIV [vCP1521]) plus two booster injections of a recombinant glycoprotein 120 subunit vaccine (AIDSVAX B/E)
- ~16,000 patients
- Conducted by US Army in collaboration with Thailand

**26-31% Efficacy**

- The only successful adequately controlled HIV vaccine trial to date

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