UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 8-K

CURRENT REPORT

Pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934

Date of report (date of earliest event reported): September 6, 2024

TONIX PHARMACEUTICALS HOLDING CORP.

(Exact name of registrant as specified in its charter)

Nevada	**001-36019**	**26-1434750**
(State or Other Jurisdiction of Incorporation)	**(Commission File Number)**	**(IRS Employer Identification No.)**

26 Main Street, Chatham, New Jersey 07928
(Address of principal executive offices) (Zip Code)

Registrant's telephone number, including area code: (862) 904-8182

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions (see General Instruction A.2. below):

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)
☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)
☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))
☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Stock	TNXP	The NASDAQ Capital Market

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§ 230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§ 240.12b-2 of this chapter).

Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 7.01 Regulation FD Disclosure.

On September 6, 2024, the Company presented data (the "Presentation") at a symposium hosted by the Department of Medical Microbiology & Immunology and the Li Ka Shing Institute of Virology (the "Symposium") regarding the Company's vaccine platform, including its TNX-801 vaccine candidate for preventing mpox. A copy of the press release which discusses this matter is furnished hereto as Exhibit 99.01, and incorporated herein by reference. A copy of the Presentation is furnished hereto as Exhibit 99.02, and incorporated herein by reference.

The information in this Item 7.01 of this Current Report on Form 8-K, including Exhibits 99.01 and 99.02 attached hereto, shall not be deemed "filed" for purposes of Section 18 of the United States Securities Exchange Act of 1934 (the "Exchange Act") or otherwise subject to the liabilities of that section, nor shall they be deemed incorporated by reference in any filing under the United States Securities Act of 1933 or the Exchange Act, except as shall be expressly set forth by specific reference in such a filing.

Item 8.01. Other Events.

On September 6, 2024, the Company presented data at the Symposium from a manuscript showing that TNX-801 is highly attenuated relative to 20th century vaccinia vaccines. The presentation also included data showing improved tolerability in immunocompromised animals and that it did not spread to the blood or tissue, even at a 100-fold higher dose than 20th century vaccinia vaccines. Scientists at the Company's Research and Development Center in Frederick, Maryland have shown that monkeypox clade IIb from a 2022 isolate in Massachusetts is 10,000- to 100,000-fold more attenuated than clade IIa isolates from 2003. The attenuation of clade II monkeypox in the recent outbreak may have led to its greater dissemination. Similar analyses of the new and more lethal clade I monkeypox have not yet been reported.

Forward- Looking Statements

This Current Report on Form 8-K contains certain forward-looking statements within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934 and Private Securities Litigation Reform Act, as amended, including those relating to the Company's product development, clinical trials, clinical and regulatory timelines, market opportunity, competitive position, possible or assumed future results of operations, business strategies, potential growth opportunities and other statement that are predictive in nature. These forward-looking statements are based on current expectations, estimates, forecasts and projections about the industry and markets in which we operate and management's current beliefs and assumptions.

These statements may be identified by the use of forward-looking expressions, including, but not limited to, “expect,” “anticipate,” “intend,” “plan,” “believe,” “estimate,” “potential,” “predict,” “project,” “should,” “would” and similar expressions and the negatives of those terms. These statements relate to future events or our financial performance and involve known and unknown risks, uncertainties, and other factors which may cause actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements. Such factors include those set forth in the Company’s filings with the SEC. Prospective investors are cautioned not to place undue reliance on such forward-looking statements, which speak only as of the date of this press release. The Company undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise.

Item 9.01 Financial Statements and Exhibits.

(d)

Exhibit No.	Description.
99.01	Press Release of the Company, September 9, 2024
99.02	Using Synthetic Biology to Battle Mpox
104	Cover Page Interactive Data File (embedded within the Inline XBRL document)

SIGNATURE

Pursuant to the requirement of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned thereunto duly authorized.

TONIX PHARMACEUTICALS HOLDING CORP.

Date: September 9, 2024

By: /s/ Bradley Saenger
Bradley Saenger
Chief Financial Officer

Exhibit 99.01

Tonix Pharmaceuticals Presented Data on the Potential Mpox Vaccine TNX-801 in "Using Synthetic Biology to Battle Mpox" Talk at Immunology Symposium at the University of Alberta

TNX-801 vaccination demonstrated efficacy in protecting animals from lethal challenge with clade I monkeypox and is in development as an mpox vaccine

New data show improved tolerability in immunocompromised animals and no evidence of spreading to blood or tissues even at high doses

Tonix's synthetic horsepox vaccine platform has been selected by NIH's Project NextGen for clinical testing

CHATHAM, N.J., September 9, 2024 – Tonix Pharmaceuticals Holding Corp. (Nasdaq: TNXP) (Tonix or the Company), a fully-integrated biopharmaceutical company with marketed products and a pipeline of development candidates, today announced data presented at a symposium hosted by the Department of Medical Microbiology & Immunology and the Li Ka Shing Institute of Virology to celebrate the career and honor the retirement of Tonix's collaborator, David Evans, Ph.D., FCAHS, Emeritus Professor, Department of Cell Biology, University of Alberta. A copy of the Company's presentation is available under the Scientific Presentations tab of the Tonix website at www.tonixpharma.com.

The presentation titled, "*Using Synthetic Biology to Battle Mpox*", detailed the Company's vaccine platform, led by TNX-801 (horsepox, live virus vaccine for percutaneous administration) for preventing mpox (formerly known as monkeypox). TNX-801 is an attenuated live-virus vaccine based on synthesized horsepox that has been shown to provide single-dose immune protection against a monkeypox challenge with better tolerability than 20th century vaccinia live-virus vaccines in animals.

TNX-801 is structurally closer to 19th century live-virus vaccinia vaccines than 20th century versions. [1-3] Genomic sequencing of archaic smallpox vaccines has shown that vaccines used prior to 1900 would be called 'horsepox' today. [1-3] While effective against smallpox as single-dose vaccines, 20th century vaccines have diverged from horsepox-like progenitors to have greater virulence and toxicity than TNX-801 in animals. The U.S. Food and Drug Administration (FDA) recently approved ACAM2000® from Emergent Technologies for preventing mpox.[4] ACAM200 is a live-virus vaccine derived from a 20th Century vaccinia vaccine. ACAM2000 carries a Black Box warning on its package insert labeling warning of tolerability issues, including myocarditis and pericarditis, encephalitis, encephalomyelitis, encephalopathy, progressive vaccinia, generalized vaccinia, severe vaccinial skin infections, erythema multiforme major, eczema vaccinatum resulting in permanent sequelae or death, and risks in certain individuals that may result in severe disability, permanent neurological sequelae and/or death.[5]

The Jynneos® vaccine from Bavarian Nordic is a non-replicating vaccinia vaccine that is FDA-approved for mpox with a two-dose regimen requiring sterile injection.[6] Single-dose TNX-801 has advantages over non-replicating vaccinia vaccines which require two doses. Percutaneous TNX-801 has advantages over vaccines which require sterile injection.

The durability of protection from 19th century live-virus vaccinia vaccines was believed to last decades or even be live-long. Consequently, single-dose TNX-801 is believed to stimulate long-lived T cell immunity. Consequently, TNX-801 will not require multiple repeated doses at six-month intervals like mRNA vaccines. [7] Also, the stability of live-virus vaccines, particularly in lyophilized form, eliminates the need for ultra-cold storage which complicates the widespread use of mRNA vaccines in Africa, where they are needed most right now.

Tonix's focus on single-dose vaccines adheres to recommendations by the Bipartisan Commission on Biodefense[8], and the U.S. National Academies of Science (NAS).[9] For example, the NAS report highlights the difficulty of a case-contact or "ring" vaccination strategy with even a two-dose regimen.[9]

In the presentation, Tonix highlighted positive preclinical efficacy data, demonstrating that TNX-801 protected animals against lethal challenge with intratracheal clade I monkeypox virus.[10] An outbreak of Clade I mpox has recently been declared a Public Health Emergency of International Concern (PHEIC) by the World Health Organization (WHO).[11,12] Starting from an outbreak in the Democratic Republic of the Congo, clade I mpox has spread to several Central African Countries and cases have been reported in Sweden, Thailand and Singapore. According to the U.S. Centers for Disease Control and Prevention (CDC), and other experts, there is a significant risk that clade I strain may appear in the U.S.[13] Clade I mpox is typically associated with higher case fatality rates than clade II mpox.

After a single dose vaccination, TNX-801 prevented clinical disease and lesions and also decreased shedding in the mouth and lungs of animals challenged with clade I monkeypox.[10] These findings are consistent with TNX-801 inducing mucosal immunity and suggest TNX-801 has the ability to block forward transmission, similar to Dr. Edward Jenner's vaccinia vaccine, descendants of which eradicated smallpox and kept mpox out of the human population.

The presentation at University of Alberta included results from Tonix scientists at the Research and Development Center (RDC) in Frederick, Md. Data from a manuscript showed that TNX-801 is highly attenuated relative to 20th century vaccinia vaccines in in immunocompromised animals.[14] New data showed TNX-801 is unable to spread in blood or tissues in these animals, even at an approximately 100-Fold higher dose than 20th century vaccinia vaccines.

In addition to characterizing TNX-801's activity and tolerability, Tonix scientists have explored the characteristics of the monkeypox virus. The prior 2022 global clade IIb mpox outbreak, affected over 90,000 persons in countries where mpox previously had not been endemic, including Europe and the US. The spread of clade IIb strain mpox in 2022 underscores the pandemic potential of mpox. Data presented show that monkeypox clade IIb from a 2022 isolate in Massachusetts is 10,000- to 100,000-fold more attenuated than clade IIa isolates from 2003. The attenuation of clade II monkeypox in the recent 2022 outbreak may have contributed to its greater dissemination. The new and more lethal clade I monkeypox has not yet been analyzed.

"We are excited to develop TNX-801 to prevent mpox and control mpox epidemics," said Seth Lederman, M.D., Chief Executive Officer of Tonix. "TNX-801 has conferred protective immunity to animals with single-dose administration. We believe TNX-801 can be manufactured at scale economically with standard shipping and storing requirements. Evidenced by the second WHO declared PHEIC involving an mpox epidemic since 2022, viral diseases are rapidly evolving and our methods to developing effective vaccines must evolve just as rapidly. Synthetic biology is an important technology for vaccine development. We believe the potential of TNX-801 is supported by real world evidence based on the success of horsepox-like vaccines prior to 1900 in protecting against smallpox and containing smallpox outbreaks. When smallpox vaccination with live-virus vaccinia vaccines was employed in Africa prior to eradication, mpox was kept out of the human population."

Dr. Lederman continued, “We recently announced a collaboration to develop GMP manufacturing processes for TNX-801 with Bilthoven Biologics (Bbio), part of the world’s largest vaccine manufacturer, the Cyrus Poonawalla Group, which also includes the Serum Institute of India. In addition, TNX-801 has the potential to be used as a viral vector platform, for which recombinant versions, like TNX-1800 for COVID-19[11,12], can be developed to protect against other infectious diseases that may emerge from this ever-evolving viral landscape. We are excited for TNX-1800’s inclusion into the U.S. National Institute of Health’s (NIH’s) Project NextGen.”

About TNX-801*

TNX-801 is a live replicating attenuated vaccine based on horsepox that is believed to provide immune protection with better tolerability than 20th century vaccinia viruses. As previously disclosed, TNX-801 protected animals against lethal challenge with intratracheal clade I monkeypox virus.[10] After a single dose vaccination, TNX-801 prevented clinical disease and lesions and also decreased shedding in the mouth and lungs of non-human primates.[10] The Findings are consistent with mucosal immunity and suggest the ability to block forward transmission, similar to Dr. Edward Jenner’s vaccinia vaccine, which eradicated smallpox and kept mpox out of the human population. On August 26, 2024, Tonix announced a collaboration to develop GMP manufacturing processes for its mpox vaccine with Bilthoven Biologics (Bbio), part of the world’s largest vaccine manufacturer, the Cyrus Poonawalla Group, which also includes the Serum Institute of India.

On the horsepox platform, Tonix is developing TNX-1800 (horsepox expressing SARS-CoV-2 spike protein) for protecting against COVID-19. TNX-1800 is an engineered version of horsepox that expresses the spike protein of SARS-CoV-2. In preclinical studies of TNX-1800 highlighted in the presentation, TNX-1800 was tested for immunogenicity and efficacy of TNX-1800 in nonhuman primates following a SARS CoV-2 challenge.[14,15] TNX-1800 vaccination results in a neutralizing antibody response that was associated with significant reduction in virus replication/shedding in the respiratory tract and tolerability.[11,12] TNX-1800 was selected by the NIH’s, Project NextGen for inclusion in clinical trials as part of a select group of next generation COVID-19 vaccine candidates with the intent to identify promising vaccine platforms. NIH plans to conduct a Phase 1 trial of TNX-1800 and cover the full cost of the study, while Tonix provides the vaccine candidate.

About Mpox*

On August 14, 2024, the WHO determined that the upsurge of mpox in a growing number of countries in Africa constitutes a public health emergency of international concern, the second such declaration in the past two years called in response to an mpox outbreak. The current outbreak was caused by clade I monkeypox virus, while the 2022 outbreak was clade II monkeypox virus. The global mpox outbreak, which commenced in 2022 has affected over 90,000 persons in countries where mpox had previously not been endemic, including Europe and the US. The spread of clade IIb strain mpox in 2022 underscores the pandemic potential of mpox. Unlike clade IIb mpox, the clade I strain of mpox appears to be spreading to countries neighboring the Democratic Republic of the Congo. Clade I mpox is typically associated with approximately twenty times the case fatality rates than Clade IIb mpox in Africa. According to the U.S. Centers for Disease Control and Prevention (CDC), and other experts, there is a significant risk that the deadlier clade I strain may appear in the U.S.[13]

Tonix Pharmaceuticals Holding Corp.*

Tonix is a fully-integrated biopharmaceutical company focused on developing, licensing and commercializing therapeutics to treat and prevent human disease and alleviate suffering. Tonix recently announced the U.S. Department of Defense (DoD), Defense Threat Reduction Agency (DTRA) awarded it a contract for up to $34 million over five years to develop TNX-4200 small molecule broad-spectrum antiviral agents targeting CD45 for the prevention or treatment of infections to improve the medical readiness of military personnel in biological threat environments. Tonix owns and operates a state-of-the art infectious disease research facility in Frederick, MD. The company’s Good Manufacturing Practice (GMP)-capable advanced manufacturing facility in Dartmouth, MA was purpose-built to manufacture TNX-801 and the GMP suites are ready to be reactivated in case of a national or international emergency. Tonix’s development portfolio is focused on central nervous system (CNS) disorders. Tonix’s priority is to submit a New Drug Application (NDA) to the FDA in the second half of 2024 for TNX-102 SL, a product candidate for which two statistically significant Phase 3 studies have been completed for the management of fibromyalgia. The FDA has granted Fast Track designation to TNX-102 SL for the management of fibromyalgia. TNX-102 SL is also being developed to treat acute stress reaction. Tonix’s CNS portfolio includes TNX-1300 (cocaine esterase), a biologic in Phase 2 development, designed to treat cocaine intoxication that has Breakthrough Therapy designation. Tonix’s immunology development portfolio consists of biologics to address organ transplant rejection, autoimmunity and cancer, including TNX-1500, which is a humanized monoclonal antibody targeting CD40-ligand (CD40L or CD154) being developed for the prevention of allograft rejection and for the treatment of autoimmune diseases. Tonix also has product candidates in development in the areas of rare disease and infectious disease, including a vaccine for mpox, TNX-801. Tonix Medicines, our commercial subsidiary, markets Zembrace® SymTouch® (sumatriptan injection) 3 mg and Tosymra® (sumatriptan nasal spray) 10 mg for the treatment of acute migraine with or without aura in adults.

*Tonix’s product development candidates are investigational new drugs or biologics and have not been approved for any indication.

This press release and further information about Tonix can be found atwww.tonixpharma.com.

[1]Schrick L, et al. *N Engl J Med.* 2017;377(15):1491-1492

[2]Duggan AT, et al. Genome Biol. 2020;21(1):175.

[2]Brinkmann A, et al. Genome Biol. 2020;21(1):286.

[4]August 30, 2024. Reuters. “US FDA approves Emergent's smallpox vaccine for people at high risk of mpox”. https://www.msn.com/en-us/health/other/us-fda-approves-emergent-s-smallpox-vaccine-for-people-at-high-risk-of-mpox/

[5]FDA Package insert ACAM2000, https://www.fda.gov/media/75792

[6]Zaeck LM, et al. Low levels of monkeypox virus-neutralizing antibodies after MVA-BN vaccination in healthy individuals. Nat Med. 2023 Jan;29(1):270-278. doi: 10.1038/s41591-022-02090-w. Epub 2022 Oct 18. PMID: 36257333; PMCID: PMC9873555.

[7]Mucker et al., (in press) Comparison of protection against mpox following mRNA or modified vaccinia Ankara vaccination in nonhuman primates, Cell (2024), https://doi.org/10.1016/j.cell.2024.08.043

[8]Bipartisan Commission on Biodefense. Box the Pox: Reducing the risk of Smallpox and Other Ortho poxviruses, Washington:2024

[9]U.S. National Academies of Science. Future State of Smallpox Medical Countermeasures. Washington:2024

[10]Noyce RS, et al. *Viruses*. 2023 Jan 26;15(2):356. Doi: 10.3390/v15020356. PMID: 36851570; PMCID: PMC9965234

[11]WHO Press Release August 14, 2024. “WHO Director-General declares mpox outbrfeak a public health emergency of international concern”. URL:www.who.int/news/item/14-08-2024-who-director-general-declares-mpox-outbreak-a-public-health-emergency-of-international-concern (accessed 8-15-24)

[12]McQuiston JH, et al. *U.S. Preparedness and Response to Increasing Clade I Mpox Cases in the Democratic Republic of the Congo* 2024, MMWR Morbi Mortal Wkly Rep: United States. p. 435-440

[13]CDC. 2022-2023 Mpox: US Map and Case Count. https://www.cdc.gov/poxvirus/mpox/response/2022/us-map.html

[14]Trefry, SV et al. bioRxiv 2023.10.25.564033; doi: https://doi.org/10.1101/2023.10.25.564033

[15]Awasthi M, et al. *Viruses*. 2023 Oct 21;15(10):2131. Doi: 10.3390/v15102131. PMID: 37896908; PMCID: PMC10612059.

[16]Awashti M et al *Vaccines* (Basel). 2023 Nov 2;11(11):1682. Doi: 10.3390/vaccines11111682.PMID: 38006014

Forward Looking Statements

Certain statements in this press release are forward-looking within the meaning of 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,” “expect,” 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, risks related to the failure to obtain FDA clearances or approvals and noncompliance with FDA regulations; risks related to the failure to successfully market any of our products; 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. Tonix does not undertake an obligation to update or revise any forward-looking statement. 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 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. The information set forth herein speaks only as of the date thereof.

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TONIX PHARMACEUTICALS

Using Synthetic Biology to Battle Mpox

Symposium to Honor Prof. David Evans on His Retirement

Seth Lederman, M.D.

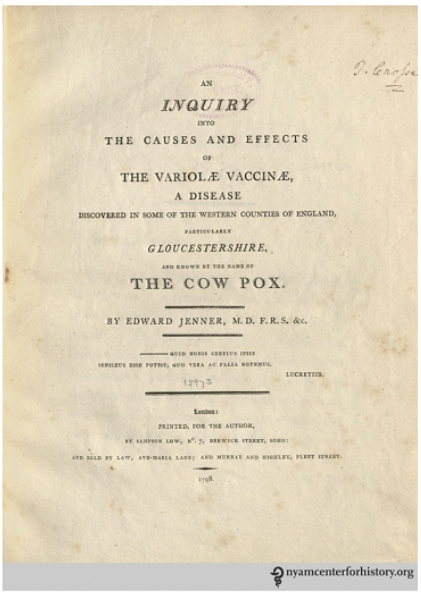
Version P0594 Sept 6, 2024 (Doc 1505)

Cautionary Note on Forward-Looking Statements

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.

In 1798, Dr. Edward Jenner Described the "Virus" that Causes Cow Pox and Identified its Utility in Preventing Smallpox

- Jenner, E. (1798) "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"
- Known as "The Inquiry"…
- Jenner observed milkmaids were protected from smallpox
- Cow Pox was a mild illness in humans that provided protection (later known as *immunity*)
  - "Cow Pox" was the name of a disease in cows that could transfer to humans and cause sores


AN
INQUIRY
INTO
THE CAUSES AND EFFECTS
OF
THE VARIOLÆ VACCINÆ,
A DISEASE
DISCOVERED IN SOME OF THE WESTERN COUNTIES OF ENGLAND,
PARTICULARLY
GLOUCESTERSHIRE,
AND KNOWN BY THE NAME OF
THE COW POX.
BY EDWARD JENNER, M.D. F.R.S. &c.
LUCRETIUS.
London:
PRINTED, FOR THE AUTHOR,
nyamcenterforhistory.org

Edward Jenner Successfully Used *Vaccination* to Protect Against Smallpox

- Jenner "vaccinated" healthy individuals with material from the lesions, which he called "vaccine" (from *vacca*, Latin for "cow")
- The pustule matter from "cow pox" sores on a milkmaid's hands; conferred protection against future challenges with smallpox virus inoculation
- Jenner suspected that the agent ("infectious principle") causing cow pox, which he called **vaccinia** originated in horses and had been transferred from horses to cows' udders by the hands of farriers

The College of Physicians of Philadelphia. Accessed July 15, 2021. https://www.historyofvaccines.org

First Live Virus Vaccine: Edward Jenner's *Inquiry*[1] (1798) – 1/2

"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 matter[2] possessing properties of a very peculiar kind, which seems capable of generating a disease in the Human Body (after it has undergone the modification[3] 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."

[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 2-3.)
[2]Vaccine virus
[3]Passage in cows

First Live Virus Vaccine: Edward Jenner's *Inquiry*[1] (1798) – 2/2

"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 experiments*[1] (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."

[1]Loy JG. An account of some experiments on the origin of the cow-pox: Whitby; 1801. (p 20-21.)

Equination[1]: Use of Smallpox Vaccines Directly from Horse Lesions (Without Passage Through Cows)

Both Jenner and Loy used vaccine from horses; subsequently "Equination" was used in Europe in parallel with "vaccination"

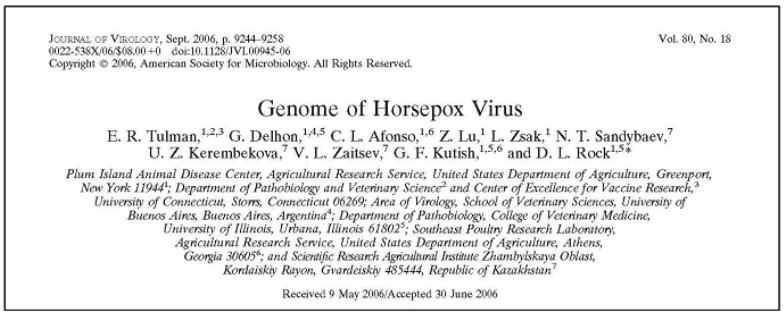
- –Jenner believed that his "cowpox" or "vaccinia" came from horses with "Grease"

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

[1]Esparza J, Schrick L, Damaso CR, Nitsche A. Equination (inoculation of horsepox): An early alternative to vaccination (inoculation of cowpox) and the potential role of horsepox virus in the origin of the smallpox vaccine. *Vaccine*. 2017 Dec 19;35(52):7222-7230. doi: 10.1016/j.vaccine.2017.11.003. Epub 2017 Nov 11. Review. PMID:29137821

2006 Sequence and Analysis of the Horsepox Genome[1]



JOURNAL OF VIROLOGY, Sept. 2006, p. 9244–9258 Vol. 80, No. 18
0022-538X/06/$08.00+0 doi:10.1128/JVI.00945-06

Genome of Horsepox Virus

E. R. Tulman,[1,2,3] G. Delhon,[1,4,5] C. L. Afonso,[1,6] Z. Lu,[1] L. Zsak,[1] N. T. Sandybaev,[7] U. Z. Kerembekova,[7] V. L. Zaitsev,[7] G. F. Kutish,[1,5,6] and D. L. Rock[1,5]*

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"It is likely that a once naturally circulating but now rare VACV-like virus(s) from which current strains are derived was introduced as a vaccine virus, and the agent of horsepox has been surmised as a likely candidate (Baxby, D 1981[2]). Indeed, apparently Edward Jenner believed that his vaccine originated from the "grease" infection found in the heels of horses, and the use of horse-derived material for use as vaccines is documented (Baxby, *ibid.*, Fenner F, 1989[3])."

[1]Tulman ER, et al. 2006. Genome of horsepox virus. *J Virol* 80:9244–9258.
[2] Baxby, D. 1981. Jenner's smallpox vaccine: the riddle of vaccinia virus and its origin. Heinemann Educational Books Ltd., London, United Kingdom.
[3] Fenner, F., R. Wittek, and K. Dumbell. 1989. The orthopoxviruses. Academic Press, Inc., San Diego, Calif.

2015 Genetic Analysis of Vaccinia Vaccines: Horsepox-like Virus Ancestor?[1]

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Evolution of and Evolutionary Relationships between Extant Vaccinia Virus Strains

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"The biological origin of VACV is uncertain, although it has been suggested that a horsepox-like virus was an ancestor, even though a surviving horsepox virus (HPXV) genome harbors many extra genes (Tulman ER, 2006[2]). This hypothesis is supported by Jenner's report that he obtained his later inocula from an infection in horses called "grease" (Baxby D, 1977[3])"

[1]Qin, L., Favis, N., Famulski, J. & Evans, D. H. Evolution of and evolutionary relationships between extant vaccinia virus strains. *J. Virol.* **89**, 1809–1824 (2015)
[2]Tulman ER, et al. 2006. Genome of horsepox virus. *J Virol* 80:9244–9258.
[3]Baxby D. 1977. The origins of vaccinia virus. J Infect Dis 136:453– 455. http://dx.doi.org/10.1093/infdis/136.3.453.

David Evans[1]: Speciation and Gene Loss in Vaccinia

Evans in (Qin et al): , "…the process of speciation appears to be associated with gene loss."

−Larger virus

−"**Relationship between DPP25 and horsepox virus.** An important aspect of poxvirus evolutionary modeling concerns the hypothesis that as viruses spread into new biological niches, the process of speciation appears to be associated with gene loss (3). If this is true, then the simplest evolutionary scheme would involve a DPP25-like virus evolving from an even larger virus. Horsepox virus (HPXV) is the largest known example of what is still clearly a vaccinia virus, if one defines this assignment based upon a relationship supported by phylogenetic trees, and perhaps retains some resemblance to a hypothetical common ancestor. By using a dot matrix plot, it can be seen that HPXV and DPP25 share the same gene content and gene order from DVX_014 (vaccinia virus growth factor) to DVX_213 as well as from ORFs DVX_214 to DVX_216 (containing fragments of a Kelch-like protein) (Table 3). However, DPP25 also encodes duplicated segments of DNA bearing the genes DVX_010 to DVX_013 inboth the right and left TIRs, whereas this sequence is found only in the right end of HPXV (Fig. 3A, deletion 3). Compared to HPXV, DPP25 also bears a 10.7-kbp deletion near the left TIR boundary and a 5.5-kbp deletion near the right TIR boundary (Fig. 3A, deletions 1 and 2, respectively). (The 5.5- and 10.7-kbp deletions differentiate HPXV from all other vaccinia virus strains and are discussed in greater detail below.) Collectively, these data suggest that DPP25/CL3 shares a unique sequence with HPXV, located near the right TIR boundary, but that the overall genome structures have been impacted by events that have changed the location of the TIR boundaries, inverted and duplicated sequences now located in the TIRs, and deleted two large segments of DNA."

[1]Qin, L., Favis, N., Famulski, J. & Evans, D. H. Evolution of and evolutionary relationships between extant vaccinia virus strains. *J. Virol.* **89**, 1809–1824 (2015)

Synthesis of Horsepox (HPXV, TNX-801) 2018[1]

PLOS ONE

RESEARCH ARTICLE

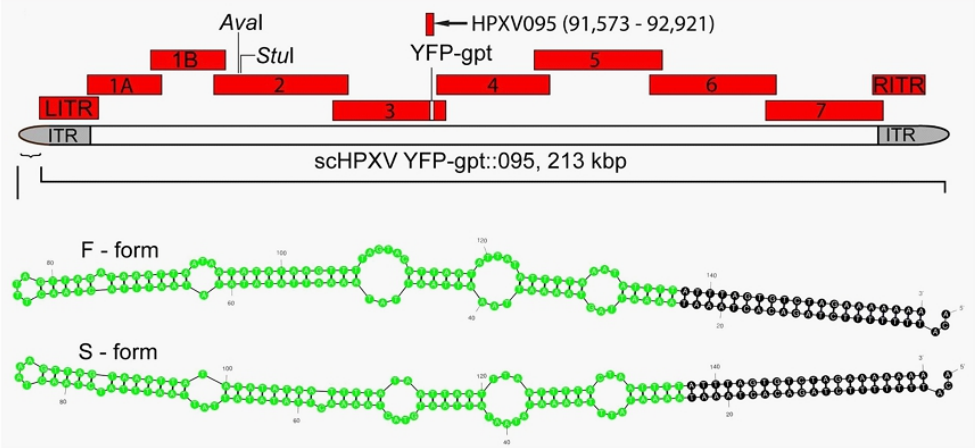
Construction of an infectious horsepox virus vaccine from chemically synthesized DNA fragments

Ryan S. Noyce[1], Seth Lederman[2], David H. Evans[1]*

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

[1]Noyce RS, Lederman S, Evans DH. *PLoS One*. 2018 Jan 19;13(1):e0188453. doi: 10.1371/journal.pone.0188453. PMID: 29351298; PMCID: PMC5774680.

Genome Assembly (212 kbp): TNX-801 Core Genome is Based on HPXV Strain MNR-76[1,2]



Sequence: GenBank entry DQ792504; DNA: GeneArt

[1]Noyce, RS, Lederman S, Evans DH. PLoS ONE. 2018; 13(1): e0188453
https://doi.org/10.1371/journal.pone.0188453
[2]Tulman ER, et al. Genome of horsepox virus. *J Virol*; 2006 80(18):9244-58.PMID:16940536

TNX-801 (Live HPXV for Percutaneous Administration)

Vaccine based on sequence of isolated horsepox (HPXV) clone[1]

- Synthesized[2] 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[3]

Question: will "horsepox" perform as a vaccine similar to "Jenner's vaccinia" and 20th century vaccinia vaccines?

- Need to evaluate tolerability and activity in animal models

[1]Tulman ER, et al. *J Virol*. 2006 80(18):9244-58.PMID:16940536
[2]Noyce RS, et al.. *PLoS One*. 2018 Jan 19;13(1):e0188453
[3]Trindade GS, et al. *Viruses* 2016 Dec 10;8(12). pii: E328. PMID:27973399 PMCID: 10.3390/v8120328

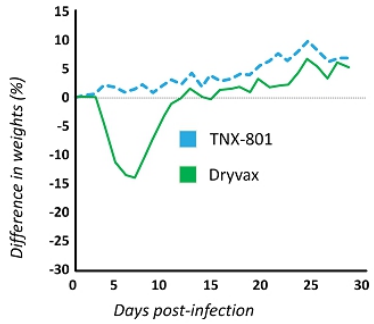
Vaccination with TNX-801 (horsepox): Protective Immunity with Low Reactogenicity (*i.e.*, Improved Tolerability)

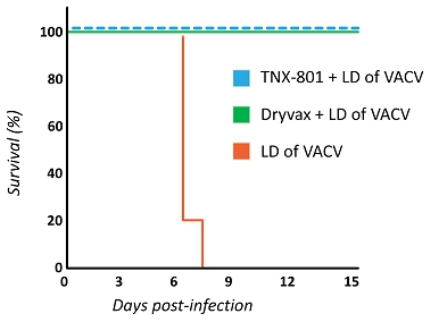
Efficacy and safety of TNX-801 compared to Dryvax ("circa 1960 vaccinia" strain)[1]:

–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

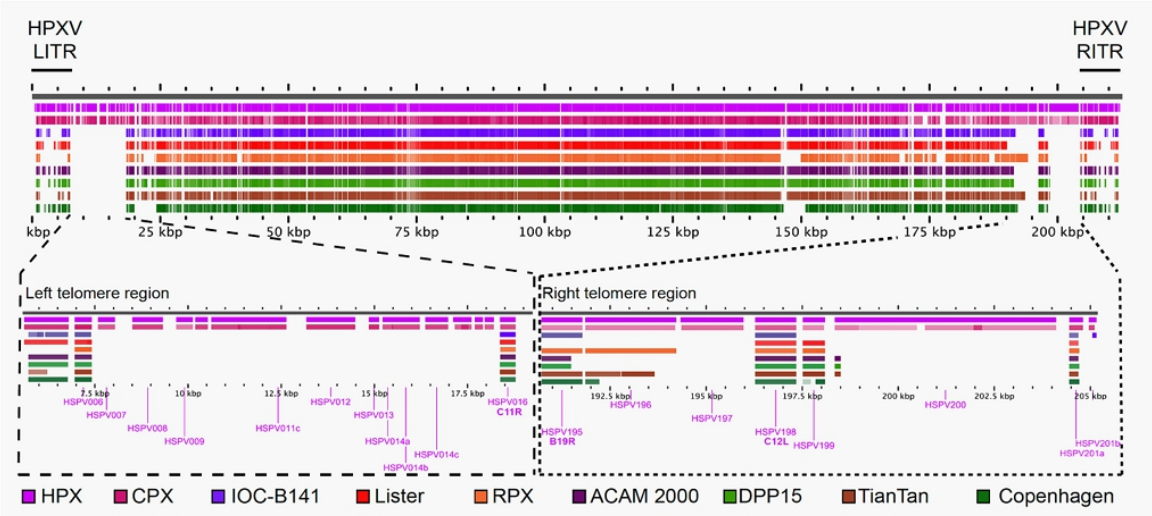
–**TNX-801 may be safer (less reactogenic) than "circa 1960 Vaccinia" vaccines without sacrificing immune protection (efficacy)**





[1]Noyce RS, et al.. Construction of an infectious horsepox virus vaccine from chemically synthesized DNA fragments. *PLoS One*. 2018 Jan 19;13(1):e0188453.

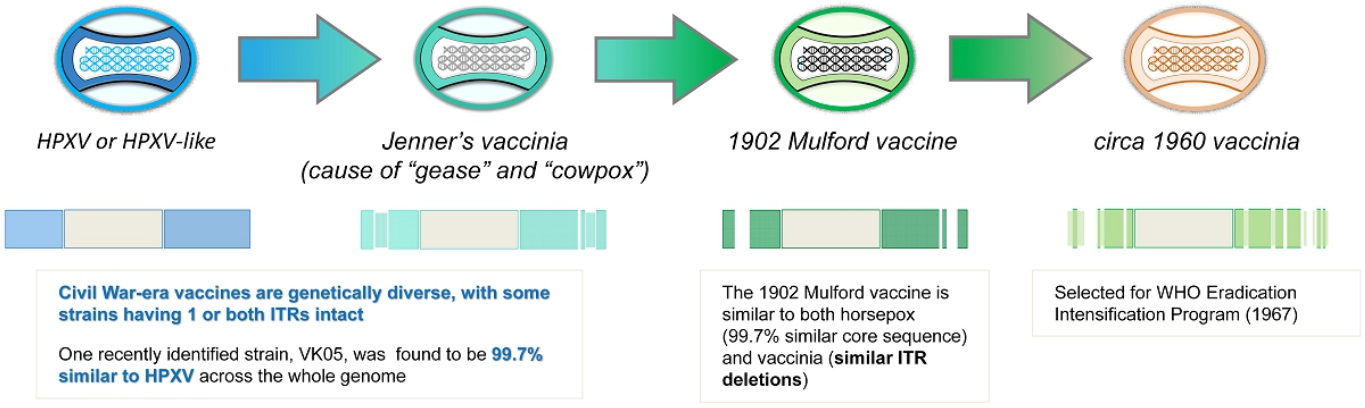
Horsepox Compared to Cowpox and 20th Century Vaccinia Strains[1]: Consistent with Near "Primordial" Strain Status



[1]Evans, D. U. of Alberta (2018) with permission

Evolution of the Vaccinia Genome

Recent studies (particularly from José Esparza & colleagues) demonstrate that horsepox and horsepox-like viruses were used as smallpox vaccines in the 1800s[1-3]



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)

[1]Schrick L, et al. *N Engl J Med.* 2017;377(15):1491-1492
[2]Duggan AT, et al. Genome Biol. 2020;21(1):175.
[2]Brinkmann A, et al. Genome Biol. 2020;21(1):286.

Horsepox: Relationship to Jenner's Vaccinia

Horsepox environmental isolate sequenced in 2006 shares a common ancestor with vaccinia and could be considered a strain of vaccinia

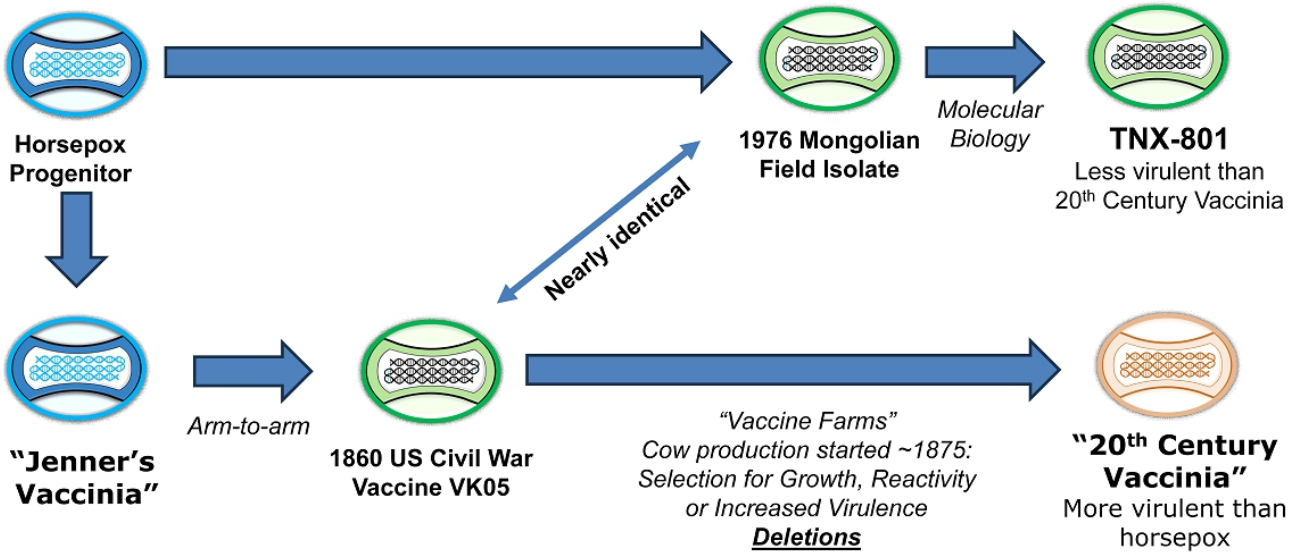
- –Similar to cowpox with "intact" inverted terminal repeats (ITRs) – could be considered a primordial strain of vaccinia
- –TNX-801 has strong homology in **core** with Mulford 1902 vaccinee[1]
- –TNX-801 has 99.7% colinear identity with "**circa 1860 vaccinia**" smallpox vaccine VK05, **including the 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
[2]Tulman ER, et al. Genome of horsepox virus. *J Virol*; 2006 80(18):9244-58.PMID:16940536
[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 "20th Century Vaccinia" Vaccines



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TNX-801 Immunogenicity and Efficacy in Macaques - 2023

viruses

MDPI

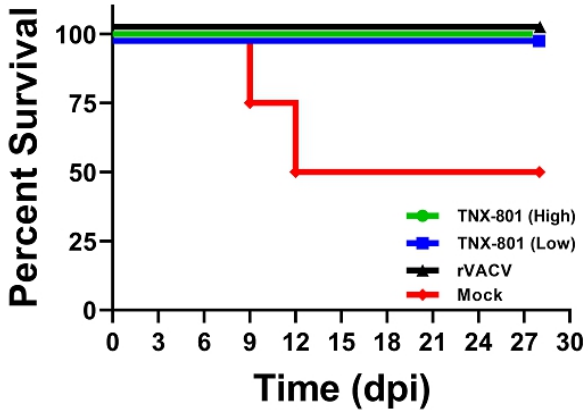
Article

Single Dose of Recombinant Chimeric Horsepox Virus (TNX-801) Vaccination Protects Macaques from Lethal Monkeypox Challenge

Ryan S. Noyce [1], Landon W. Westfall [2,†], Siobhan Fogarty [3], Karen Gilbert [2], Onesmo Mpanju [4], Helen Stillwell [3,‡], José Esparza [5], Bruce Daugherty [3], Fusataka Koide [2], David H. Evans [1] and Seth Lederman [3,*]

Noyce RS, et al. *Viruses*. 2023 Jan 26;15(2):356. doi: 10.3390/v15020356. PMID: 36851570; PMCID: PMC9965234.

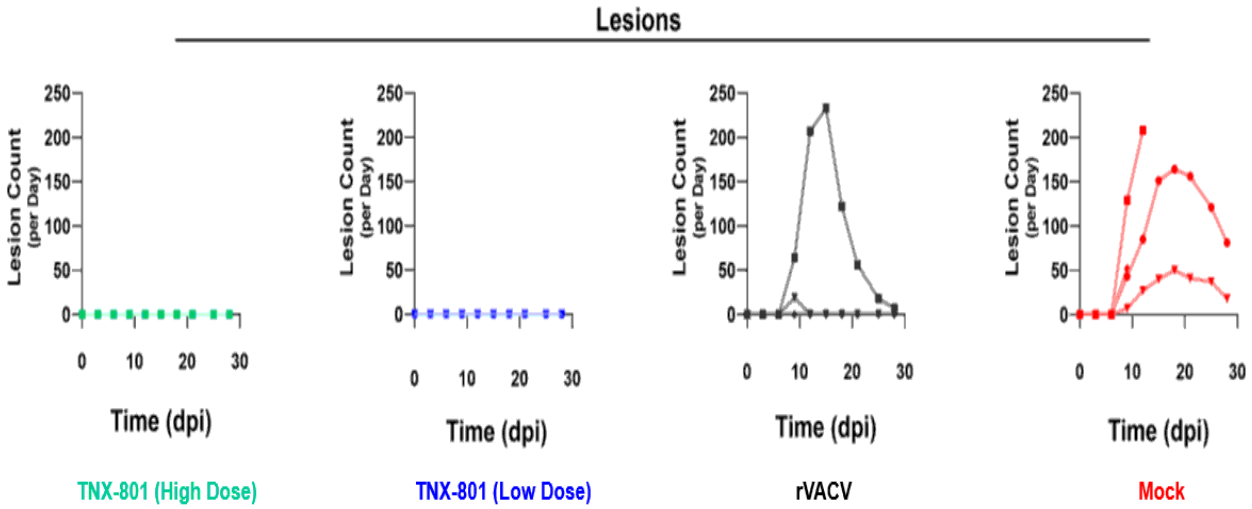
Survival: 100% of TNX-801 Vaccinated Macaques Survived Lethal MPXV Clade 1 Intratracheal Challenge



No deaths in TNX-801 vaccinated groups

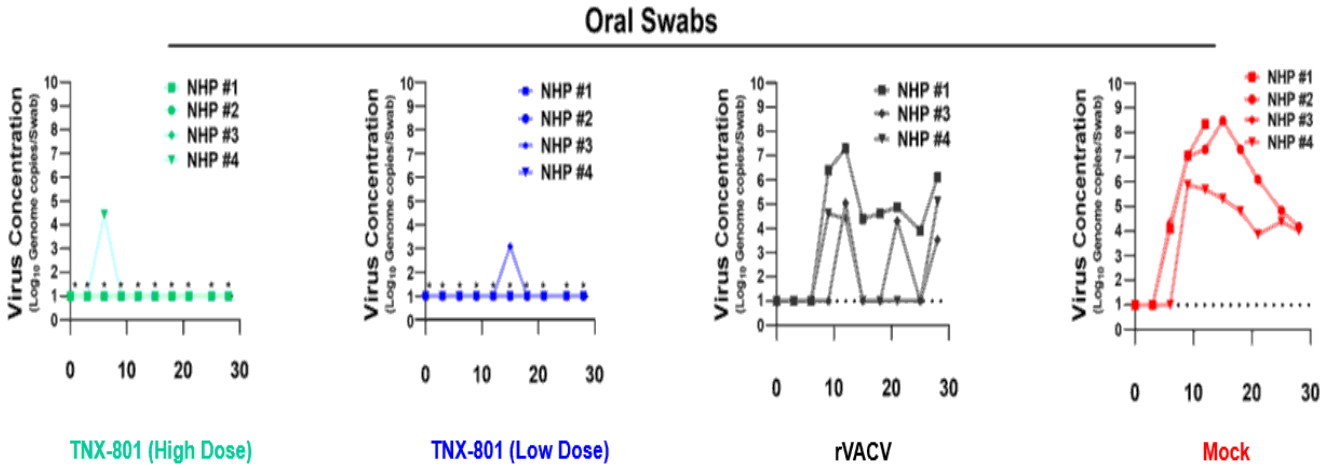
Noyce *et al*. Viruses. 2023 Jan 26;15(2):356.

TNX-801 Vaccination/Monkeypox Clade 1 Challenge: No Lesions Were Observed After TNX-801 Vaccination



Noyce *et al*. Viruses. 2023 Jan 26;15(2):356.

TNX-801 Vaccination: Minimal Monkeypox Virus Shedding



Potential to Reduce Forward Transmission

Noyce *et al*. Viruses. 2023 Jan 26;15(2):356.

Conclusions from Macaque Monkeypox Challenge Study

- A single dose of TNX-801 (horsepox) vaccination was well tolerated
  - No severe adverse events
  - Tolerability compares favorably to ACAM2000 – recently approved by US FDA for mpox[1]
- TNX-801 vaccination via traditional route (scarification) was immunogenic ("take")
- All NHPs (TNX-801 and rVACV vaccinated) survived lethal challenge
- No clinical disease was observed (lesions)
- Provided strong protection against virus shedding, viremia, and weight loss
  - Activity compares favorably to MVA (non-replicating)[2] vaccinia or recent mRNA vaccine[3]

[1]August 30, 2024. Reuters. "US FDA approves Emergent's smallpox vaccine for people at high risk of mpox". https://www.msn.com/en-us/health/other/us-fda-approves-emergent-s-smallpox-vaccine-for-people-at-high-risk-of-mpox/
[2]Zaeck LM, et al. Low levels of monkeypox virus-neutralizing antibodies after MVA-BN vaccination in healthy individuals. Nat Med. 2023 Jan;29(1):270-278. doi: 10.1038/s41591-022-02090-w. Epub 2022 Oct 18. PMID: 36257333; PMCID: PMC9873555.
[3]Mucker et al., (in press) Comparison of protection against mpox following mRNA or modified vaccinia Ankara vaccination in nonhuman primates, Cell (2024), https://doi.org/10.1016/j.cell.2024.08.043

TNX-801 in Primary Cell Lines and Immunocompromised Mice – 2023 *(BioRxiv)*

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 Trefry[1], Christy N Raney[1], Amy L Cregger[1], Chase A Gonzales[1], Brittney L Layton[1], Robert N Enamorado[1], Nelson A Martinez[1], Deborah S Gohegan[1], Tinoush Moulaei[1], Natasza E Ziółkowska[1], Scott J Goebel[1], Seth Lederman[1], Sina Bavari[1], Farooq Nasar[1*]

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 "20th Century Vaccinia Vaccines"

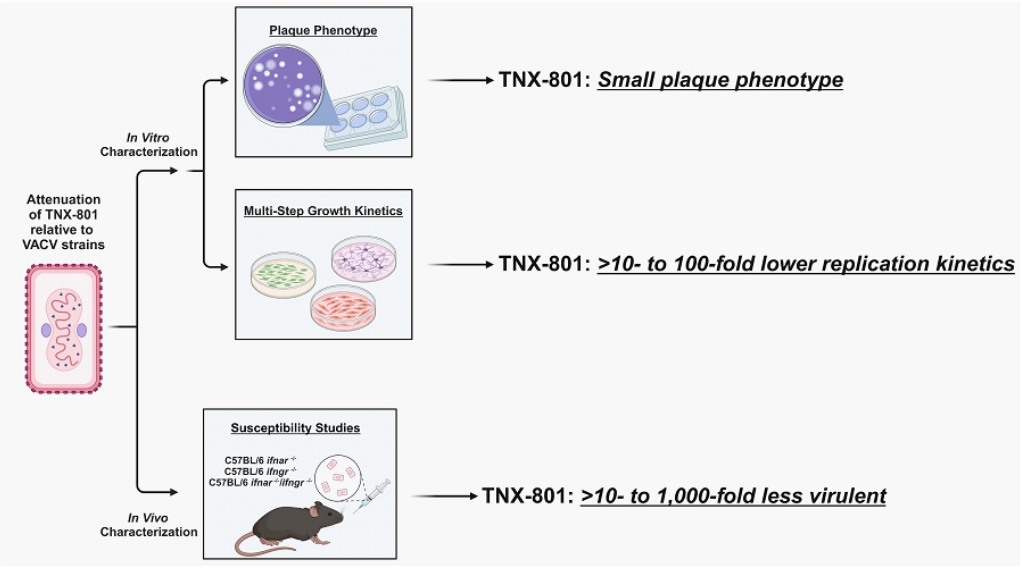
Comparisons *in vitro:*

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

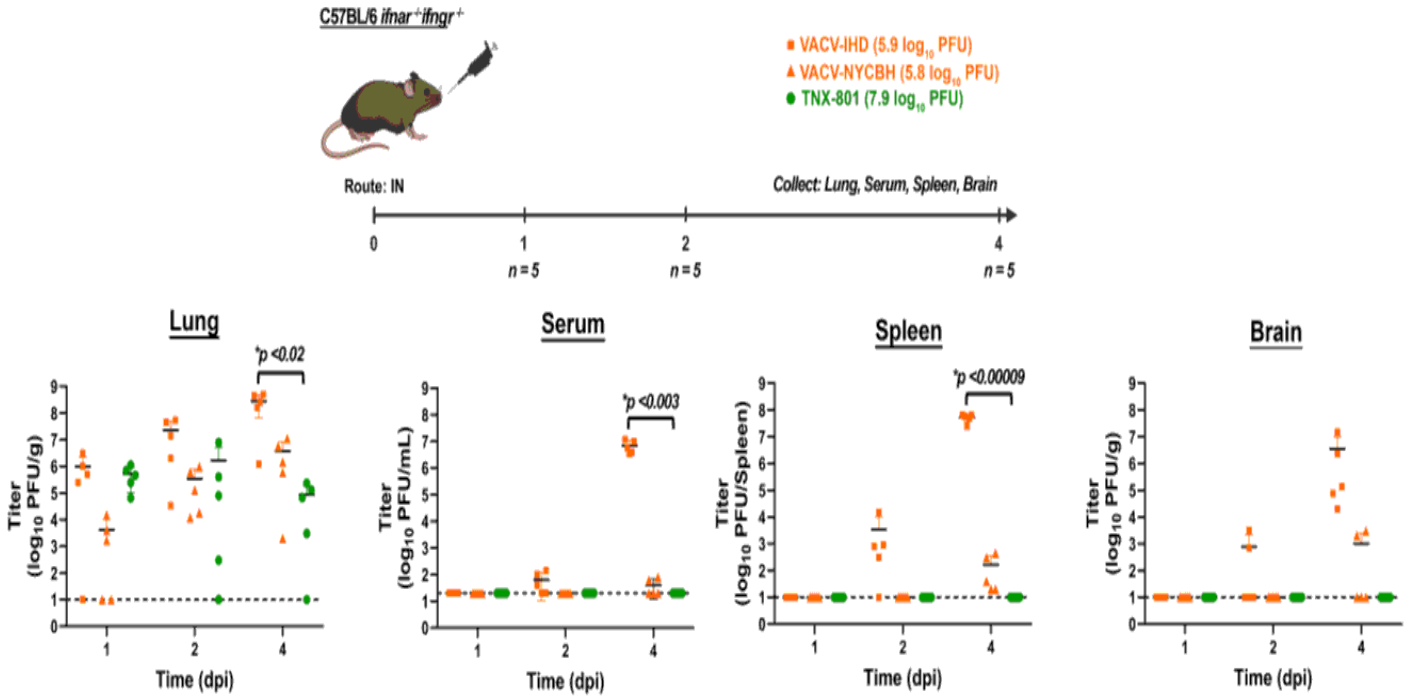
Comparisons *in vivo*:

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 20th Century Vaccinia (VACV) Vaccines



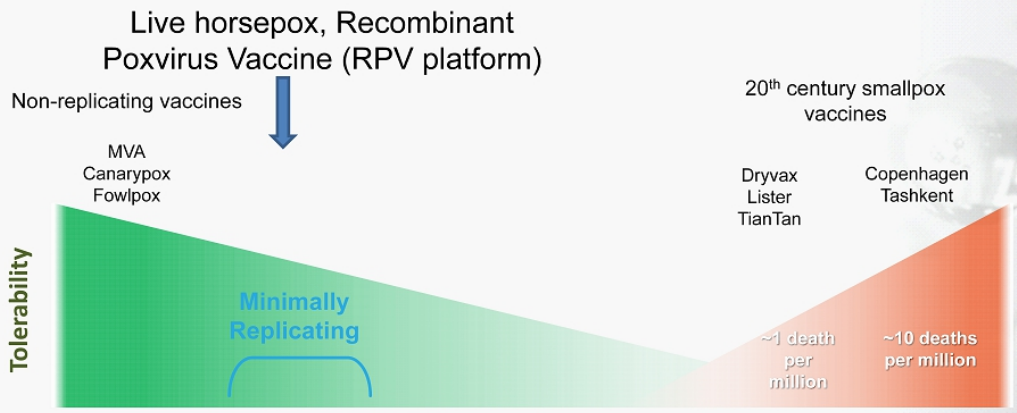
High Dose TNX-801 is Unable to Cause Disseminated Infection in Double KO IFN-αR$^{-/-}$ and IFN-γR$^{-/-}$ mice



IND strain was deposited by the US Army in 1963

Farooq Nasar et al, Tonix unpublished data

Illustrative Safety Spectrum Of Pox-based Vaccine Vectors Optimizing Live Virus Vaccines



Replicative Capacity	Non-replicating	Minimally-replicating			Robustly replicating
#-of doses	Two	Single-dose			Single-dose
Durability of protection	waning	long			decades
Transgene expression	Poor	robust			robust

INFECTIOUS DISEASE PORTFOLIO

TONIX PHARMACEUTICALS

Horsepox Protection and Tolerability in Animals Potentially Decouples Protective Immunity from Reactogenicity

Conventional view holds that reactogenicity correlates with protection

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 or 19th century) support the belief that horsepox will be protective against smallpox

–Historical evidence that horsepox-like vaccines prevented forward transmission

[1]Schrick, L. et al An Early American Smallpox Vaccine Based on Horsepox *N Engl J Med* 2017; 377:1491
[2]Tulman ER, et al. Genome of horsepox virus. *J Virol*; 2006 80(18):9244-58.PMID:16940536
[3]Brinkmann A et al, *Genome Biology* 2020; 21:286 https://doi.org/10.1186/s13059-020-02202-0

Horsepox: More (Regulatory) Genes Confer Tolerability

"20th Century vaccinia vaccines" evolved through a process of "Passage" through cows or birds that was a primitive form of genetic engineering

- –"Passage" through cows resulted in gene deletions that may have increased virulence relative to "circa 1860 vaccinia" (20th century "vaccinia" have 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

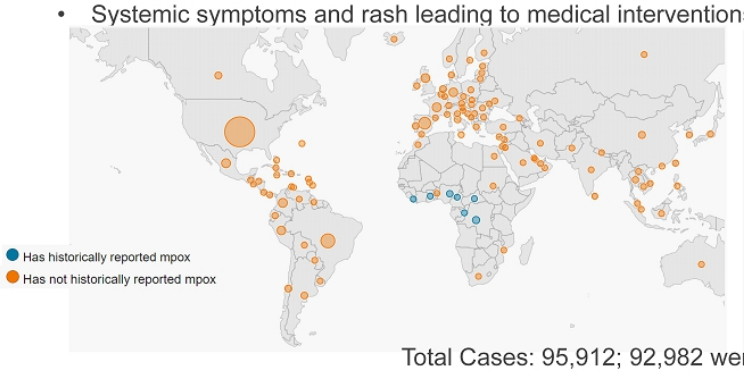
- –Horsepox appears to have preserved regulatory genes that confer tolerability, while preserving immune protection

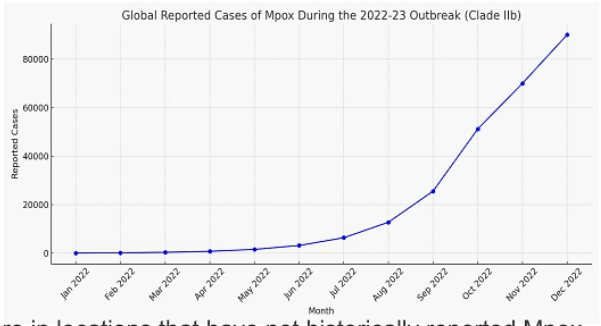
[1]Schrick, L. et al An Early American Smallpox Vaccine Based on Horsepox *N Engl J Med* 2017; 377:1491
[2]Tulman ER, et al. Genome of horsepox virus. *J Virol*; 2006 80(18):9244-58.PMID:16940536
[3]Brinkmann A et al, *Genome Biology* 2020; 21:286 https://doi.org/10.1186/s13059-020-02202-0

Mpox Outbreak 2022-23: Clade IIb: WHO Declared a Public Health Emergency of International Concern (PHEIC)

Risk of Spread and Lethality of Clade IIb

- Case Fatality Rate (CFR): 0.1% to 3.6%→Lower compared to Clade I
- Primarily spread through sexual contact among MSM (men who have sex with men)
- 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

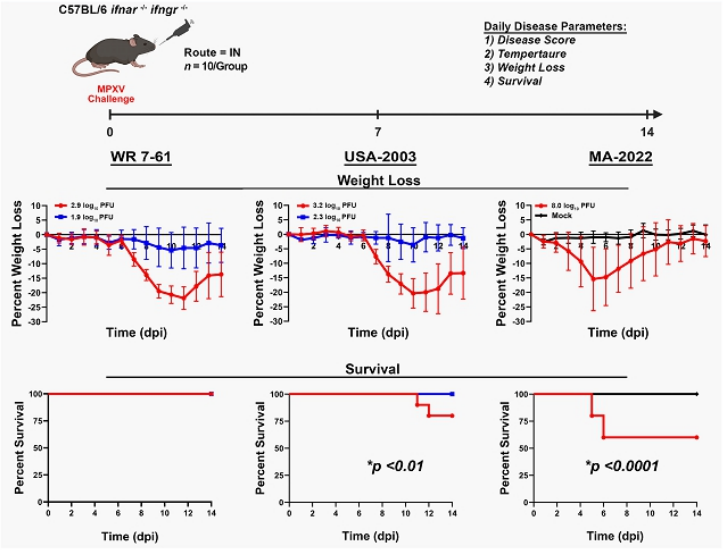
Sources: WHO, European CDC, US CDC, and Ministries of Health
2022 U.S. Map and Case Count | Mpox | Poxvirus | CDC
WHO = World Health Organization
FDA = U.S. Food and Drug Administration

Monkeypox Clade IIb (U.S. Isolate) is 10,000- to 100,000-fold More Attenuated Than Clade IIa

Double KO IFN-αR$^{-/-}$ and IFN-γR$^{-/-}$ mice

Clade IIb:
MA-2022

Clade IIa:
WR 7-61 and US-2003

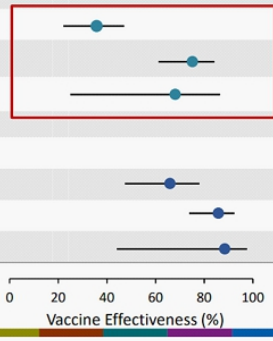


Farooq Nasar et al, Tonix unpublished data

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

	Cases	Controls	Adjusted* VE (95% CI)
1-dose JYNNEOS			
Epic Cosmos case-control study	146	1000	36% (22–47)
Multi-jurisdictional case-control study	58	237	75% (61–84)
New York State case-control study	10	23	68% (25–86)
2-dose JYNNEOS			
Epic Cosmos case-control study	25	335	66% (47–78)
Multi-jurisdictional case-control study	14	122	86% (74–89)
New York State case-control study	2	19	89% (44–98)



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

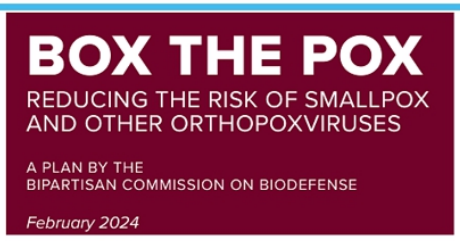
Mpox and Smallpox Reports by U.S. Agencies & Institutions

- **Multiple recent statements by U.S. Agencies warning about smallpox and monkeypox[1-6]**

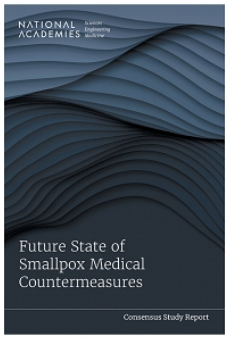
- **U.S. National Academy of Sciences Consensus Report (March, 2024)[6]**
  - *"Additionally, safer, single-dose vaccines and a diverse set of therapeutic options against smallpox would improve the U.S. readiness and response posture for immediate containment and long-term protection in a smallpox emergency.*
  - *"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.*
  - *"Given the lack of commercially available orthopoxvirus diagnostics, vaccines, and therapeutics, planning for logistics and supply chain management considerations is critical. Efforts could give consideration to developing plans to increase the number of smallpox vaccine and therapeutics manufacturers as well as optimizing current manufacturing capacities should they be needed in the shorter term."*

[1] Office of Science and Technology Policy (OSTP). American Pandemic Preparedness: Transforming Our Capabilities. September 2021
[2] National Biodefense Science Board (NBSB). Prioritization of Product Attribute Categories to Maximize Access for Next Generation COVID-19 Vaccines and Therapeutics. August 2023
[3] Office of Science and Technology Policy (OSTP). American Pandemic Preparedness: Transforming Our Capabilities. September 2021
[4] National Biodefense Science Board (NBSB). Prioritization of Product Attribute Categories to Maximize Access for Next Generation COVID-19 Vaccines and Therapeutics. August 2023
[5] BARDA Strategic Plan 2022-2026.
[6] U.S. National Academy of Sciences. March 28, 2024. "Consensus Study Report: Future State of Smallpox Medical Countermeasures." https://nap.nationalacademies.org/catalog/27652/future-state-of-smallpox-medical-countermeasures

U.S. Recognizes Smallpox Preparedness as a Priority
National Stockpile Expansion is Recommended by Experts



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.

Mpox Outbreak 2023-24: Clade I and Current State of the Mpox Epidemic in Congo

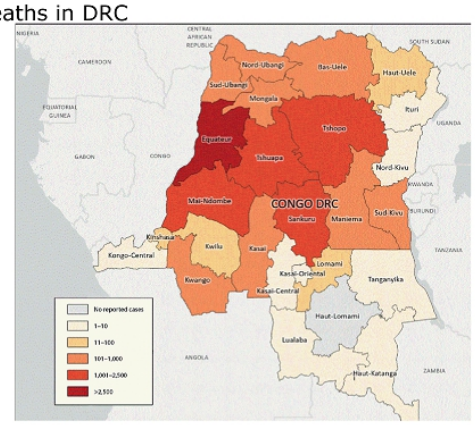
Risk of Spread and Lethality

- 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

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

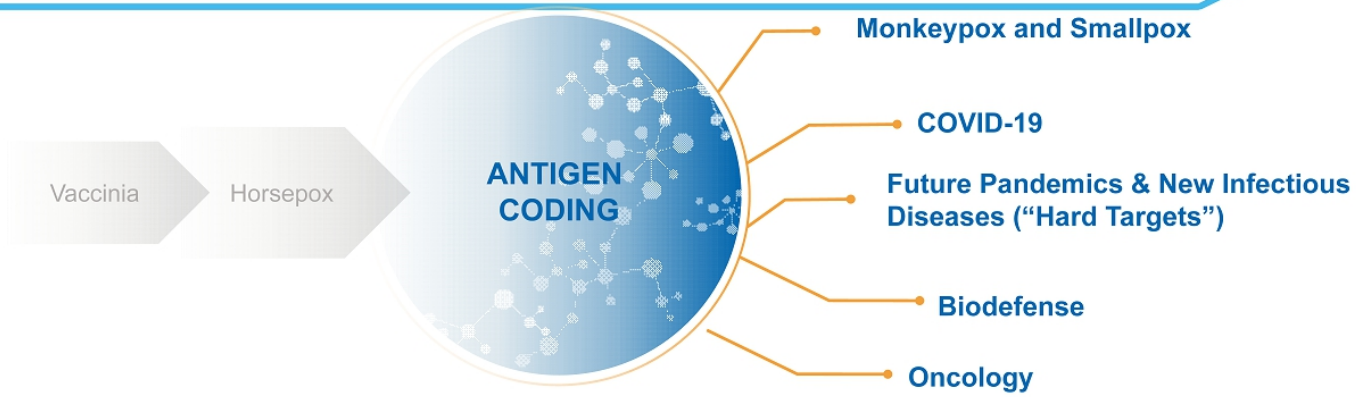
Mpox Declared Public Health Emergency of International Concern (PHEIC) by WHO* on August 14, 2024: New Clade I

- **Clade I - first wave in Democratic Republic of Congo (DRC)**
  - ~10% mortality,
  - Affects children
- **Additional emerging mutation**
  - Potentially lower mortality
  - Affects both MSM (men who have sex with men) + heterosexual transmission primarily in adults
- **2024 mpox epidemic in DRC has led to >20,000 cases by mid-August**
  - Spread to 12 countries in Africa, recently includes Kenya
- **First cases of Clade I identified in Sweden, Thailand, Singapore**
- **Two FDA**-approved vaccines:**
  - Jynneos® (Bavarian-Nordic)
    - Requires 2-dose regimen, durability of neutralization antibody titers being studied[1,2]
  - ACAM 2000 (Emergent)
    - Single-dose, reactogenic, provides durable protection[3]

*WHO = World Health Organization
**FDA = U.S. Food and Drug Administration

[1]Zaeck LM, *Nat Med.* 2023 29(1):270-278. doi: 10.1038/s41591-022-02090
[2]Berens-Riha N, et al. *Euro Surveill.* 2022 27(48):2200894. doi: 10.2807/1560-7917.ES.2022.27.48.2200894.
[3]August 30, 2024. Reuters. "US FDA approves Emergent's smallpox vaccine for people at high risk of mpox". https://www.msn.com/en-us/health/other/us-fda-approves-emergent-s-smallpox-vaccine-for-people-at-high-risk-of-mpox/

Live Virus Vaccine Platform: Recombinant Pox Vaccine (RPV) Platform



RPV VECTOR BELIEVED SIMILAR TO EDWARD JENNER'S VACCINE[1-3]

Using Proven Science To Address Challenging Disease States, We Have Created A Programmable Technology Platform Aimed At Combating Future Threats To Public Health

[1]Shrick, L. *N Engl J Med* 2017; 377:1491-1492. DOI: 10.1056/NEJMc1707600
[2]Esparza, *J. Vaccine*. 2020 Jun 19; 38(30): 4773–4779. doi: 10.1016/j.vaccine.2020.05.037
[3]Brinkmann, A. *Genome Biol*. 2020; 21: 286. doi: 10.1186/s13059-020-02202-0

TNX-1800 (SARS-CoV-2 spike – Expressing HPXV) Immunogenicity in Hamsters and Rabbits - 2023

viruses

MDPI

Brief Report

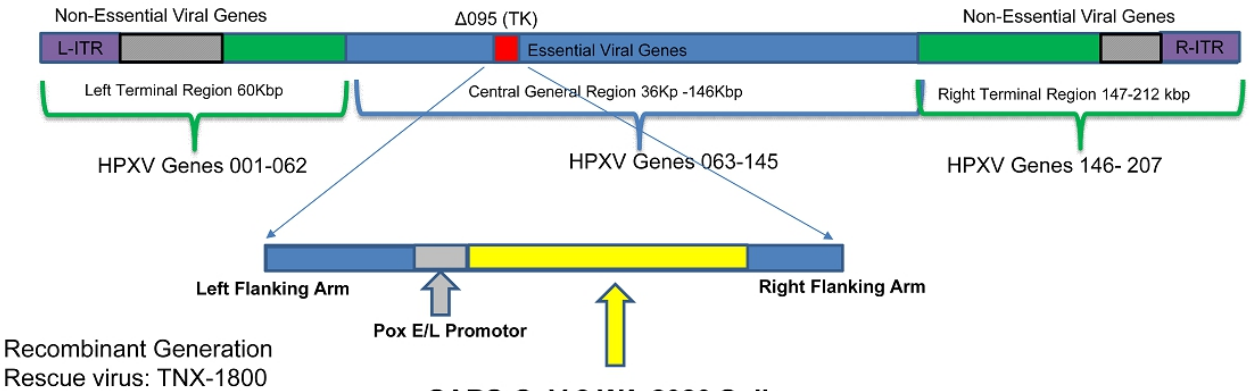
Immunogenicity and Tolerability of a SARS-CoV-2 TNX-1800, a Live Recombinant Poxvirus Vaccine Candidate, in Syrian Hamsters and New Zealand White Rabbits

Mayanka Awasthi [1], Anthony Macaluso [1], Scott J. Goebel [1], Erin Luea [2], Ryan S. Noyce [3], Farooq Nasar [1], Bruce Daugherty [4], Sina Bavari [1] and Seth Lederman [5,*]

Awasthi M, et al. *Viruses*. 2023 Oct 21;15(10):2131. doi: 10.3390/v15102131. PMID: 37896908; PMCID: PMC10612059.

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

Development of HPXV as a recombinant Delivery Vector Platform



Recombinant Generation
Rescue virus: TNX-1800

SARS-CoV-2 WA-2020 Spike Protein Gene

*TNX-1800 has not been approved for any indication.

TNX-1800 Immunogenicity and Efficacy in NHPs - 2023

vaccines

MDPI

Article

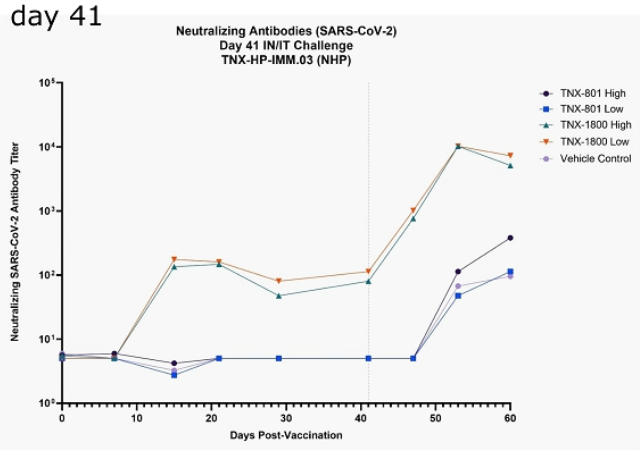
Immunogenicity and Efficacy of TNX-1800, A Live Virus Recombinant Poxvirus Vaccine Candidate, against SARS-CoV-2 Challenge in Nonhuman Primates

Mayanka Awasthi [1], Anthony Macaluso [1], Dawn Myscofski [1], Jon Prigge [2], Fusataka Koide [3], Ryan S. Noyce [4], Siobhan Fogarty [5], Helen Stillwell [6,7], Scott J. Goebel [1], Bruce Daugherty [7], Farooq Nasar [1], Sina Bavari [1] and Seth Lederman [8,*]

Awasthi M, et al. *Viruses*. 2023 Oct 21;15(10):2131. doi: 10.3390/v15102131. PMID: 37896908; PMCID: PMC10612059.

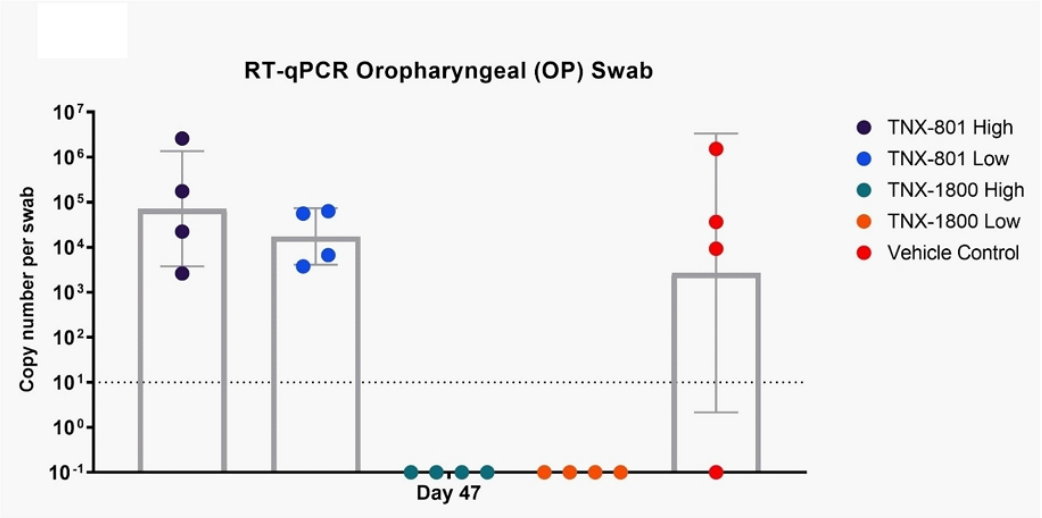
Immunogenicity: All NHPs in TNX-1800 Vaccinated Group Had Neutralizing Antibody Response

NHPs were vaccinated day 0 and challenged day 41



Vaccination with TNX-1800 results in the inhibition of SARS-CoV-2 Replication in Vaccinated NHPs

NHPs were vaccinated day 0 and challenged day 41; "Day 47" is 6 days after challenge



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

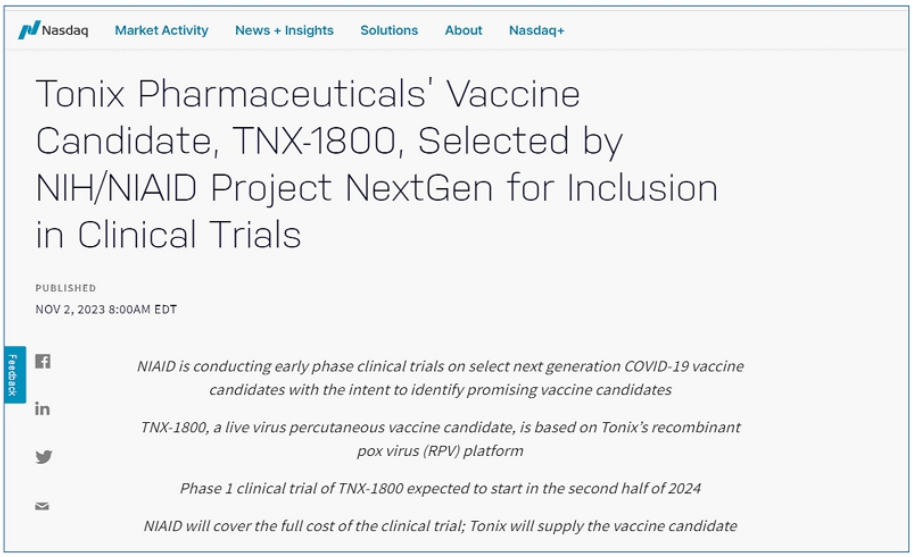
- −Low dose because replication amplifies dose *in vivo*

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
- −“20th century vaccinia” kept mpox out of the human population in Africa
- −Horsepox and vaccinia express transgenes with high fidelity

Tonix Platform Selected by NIH/NIAID : Project NextGen COVID



Nasdaq Market Activity News + Insights Solutions About Nasdaq+

Tonix Pharmaceuticals' Vaccine Candidate, TNX-1800, Selected by NIH/NIAID Project NextGen for Inclusion in Clinical Trials

PUBLISHED
NOV 2, 2023 8:00AM EDT

Feedback

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

TNX-801: Pre-IND Ready Candidate Mpox Vaccine

- Based on synthetic horsepox-vector, believed related to first smallpox vaccine reported by Dr. Edward Jenner in 1798
- Single-dose percutaneous
- Attenuated live virus for durable T-cell immunity
- Believed will be thermo-stable in ultimate lyophilized formulation
- Eventual presentation may use Micro Array Patch technology

R&D Center- Maryland
Operational BSL-3 capable

Advanced Manufacturing Center- MA
GMP-manufacturing capability*

*GMP Suites currently decommissioned

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