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# Live Virus Smallpox and Monkeypox Vaccine

## *Presentation to World Vaccine & Immunotherapy Congress*

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# 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, 2021, as filed with the Securities and Exchange Commission (the “SEC”) on March 14, 2022, 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.

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# Live Virus Vaccines: Development Rationale

- **Control of smallpox, measles, mumps, rubella, chickenpox and other viral conditions**
  - Prevent forward transmission
- **Effective in eliciting durable or long-term immunity**
- **Economical to manufacture at scale**
  - Low dose because replication amplifies dose *in vivo*
  - Single shot 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

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# First Live Virus vaccine:
## Edward Jenner's *Inquiry*[1] (1796) – 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

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# First Live Virus vaccine:
## Edward Jenner's *Inquiry*[1] (1796) – 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.)

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# 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.)

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# Equination[1]: Use of Smallpox Vaccines from Horse Lesions

- **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"

- **Producers of "vaccinia" may have supplemented or refreshed stocks with horsepox periodically"**
  - Methods of propagating vaccine in the 19th Century were not based on understanding of microbiology

- **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

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# Horsepox: Development Rationale

- **Horsepox clone 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
- **U.S. vaccine from Mulford 1902 was found to be 99.7% similar to horsepox in core viral sequence[1,2]**
  - TNX-1800 has 99.7% colinear identity with circa 1860 smallpox vaccine[2,3]
  - Strong evidence linking a horsepox-like virus as progenitor to modern vaccinia
  - Effectiveness of older vaccines support belief that horsepox will e protective against smallpox
- **Genetic analysis of early vaccines indicates that “horsepox” is closely related to Edward Jenner’s vaccinia from 1796**
  - Modern “vaccinia” evolved during the 220 years it was propagated by primitive methods – for over 120 years before “viruses” were identified
  - Prevents forward transmission
  - Edward Jenner’s “cowpox”/”vaccinia” smallpox vaccine eradicated smallpox

[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 Biol*ogy 2020; 21:286 https://doi.org/10.1186/s13059-020-02202-0

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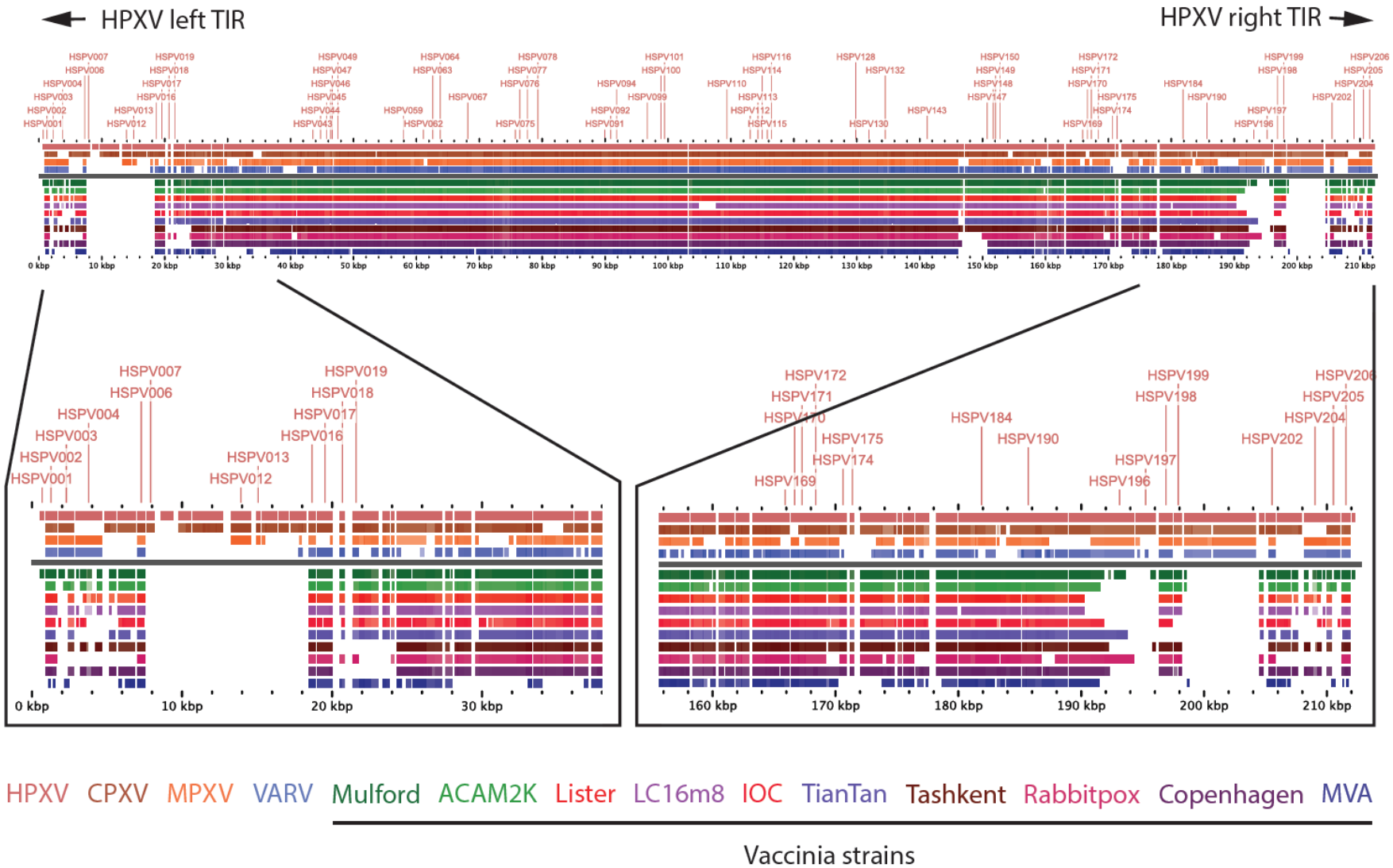
# Horsepox Compared to Cowpox and Vaccinia Strains[1]
## Consistent with Near "Primordial" Strain Status




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



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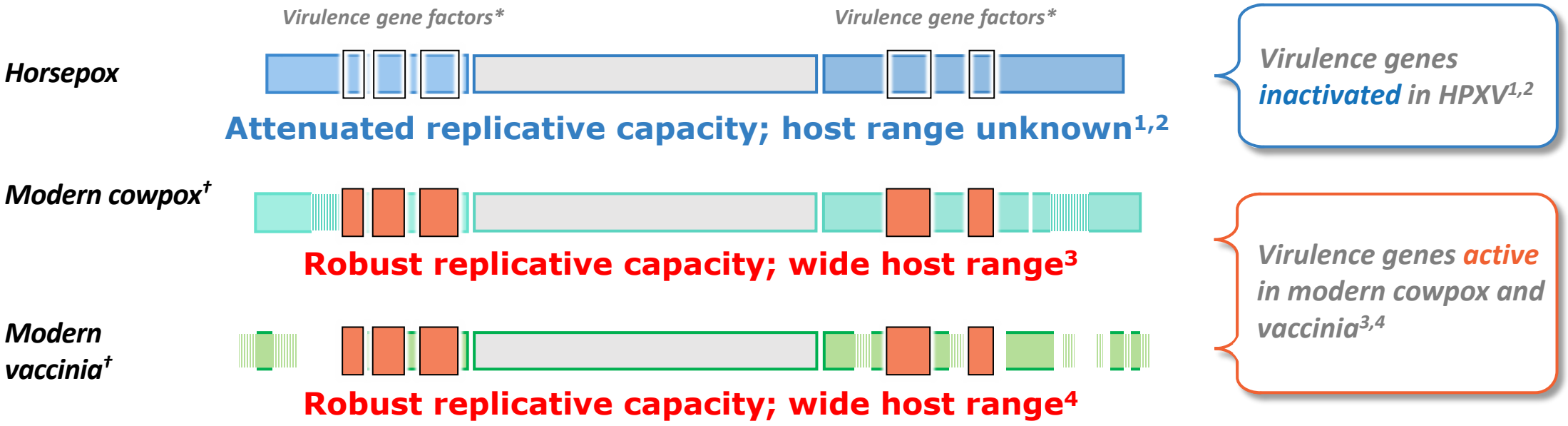
# Certain Gene Factors Have the Potential to Enhance Virulence of Vaccinia and Cowpox Relative to Horsepox




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


[1]Schrick L, et al. *N Engl J Med.* 2017;377(15):1491-1492.
[2]Dabrowski PW, et al. *PLoS One*. 2013;8(12):e79953.
[3]Tulman ER, et al. *J Virol.* 2006;80(18):9244-9258.
[4]Qin L, et al. *J Virol.* 2015;89(3):1809-1824.

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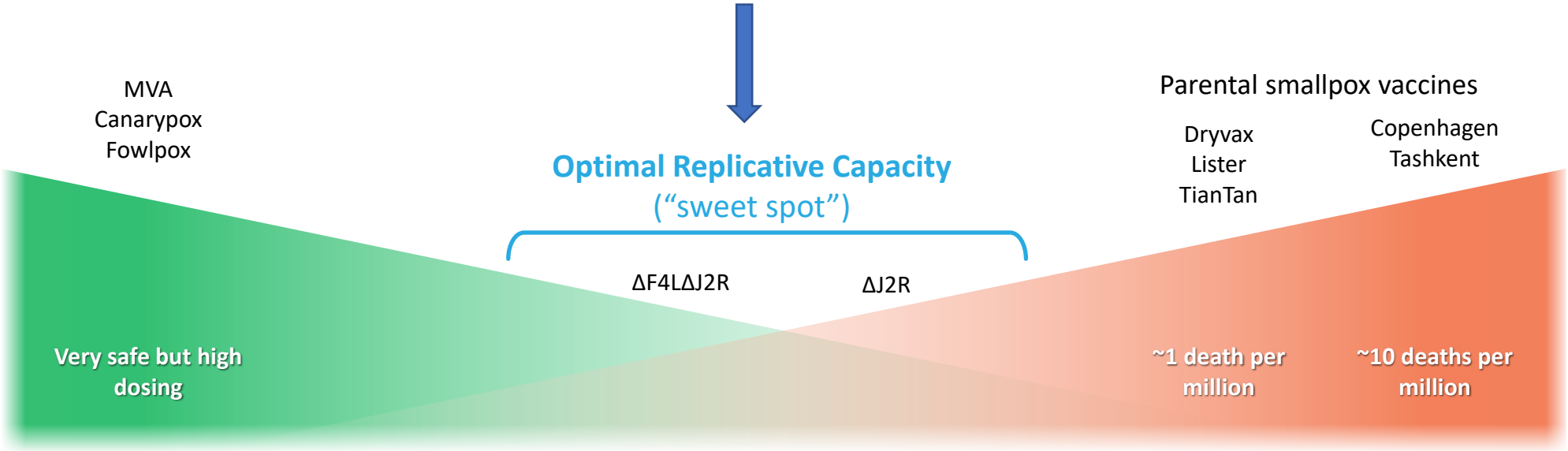
# Historical Safety Spectrum Of Pox-based Vectors
## Optimizing Live Virus Vaccines

New Recombinant Pox VACCINE (RPV)




***Nonreplicating***
***Poor Transgene immunogenicity***

***Intermediate Replicative Capacity***
***Ability to elicit robust immunological responses to Transgene***

***Robust Replication***
***Risk for adverse vaccination events***

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# Commercial Applications of Licensed Recombinant Poxvirus-Based Vaccines

## Agriculture[1,2]

- Newcastle disease virus (NDV) TROVAC (**recombinant fowlpox**)
- Avian influenza (AIV) TROVAC (**recombinant fowlpox**) (H5N9 and H5N1)

## Cats[3]

- **Recombinant canarypox** rabies vaccine (ALVAC-RG) and feline leukemia (ALVAC-FeLV)

## Dogs[4]

- RECOMBITEK® C4 **recombinant canarypox** vector expressing the HA and F glycoproteins of canine distemper virus; modified live adenovirus type 2, parainfluenza virus, and parvovirus

[1]Taylor J, et al. *Avian Dis.* 1996;40(1):173-180.
[2]The Poultry Site. March 14, 2005. Accessed July 9, 2021. https://www.thepoultrysite.com/news/2005/03/merial-launches-new-h5n1-avian-influenza-vaccine-provides-new-hope-for-avian-flu-epidemic
[3]Boehringer Ingelheim. Accessed July 9, 2021. https://www.boehringer-ingelheim.com/animal-health/companion-animals-products/purevax
[4]Larson LJ, et al. *Vet Ther.* 2007;8(2):101-106.

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# Approved Recombinant Poxvirus-Based Commercial Products[1-3]

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

[1]Boehringer Ingelheim. Accessed July 15, 2021. https://www.boehringer-ingelheim.com/animal-health/products
[2]Bublot M, Pritchard N, Swayne DE, et al. Development and use of fowlpox vectored vaccines for avian influenza. *Ann N Y Acad Sci*. 2006;1081:193-201.
[3]Maki J, Guiot AL, Aubert M, et al. Oral vaccination of wildlife using a vaccinia-rabies-glycoprotein recombinant virus vaccine (RABORAL V-RG®): a global review. *Vet Res*. 2017;48(1):57.

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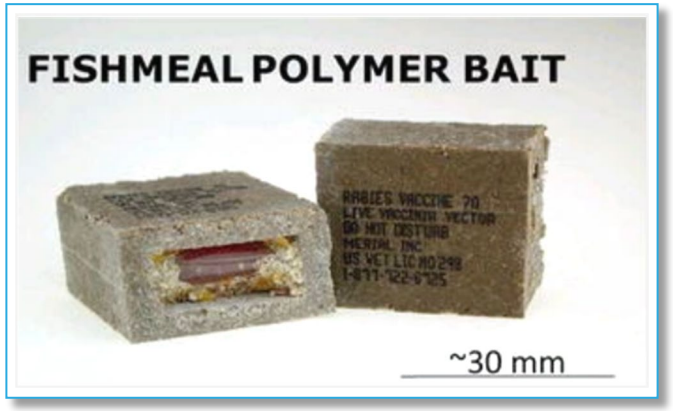
# Environmental Distribution: Vaccinia Released Aerially as Rabies Vaccine

- **RABORAL V-RG® is an oral vaccine based on vaccinia–rabies-glycoprotein recombinant virus used to prevent the spread of rabies among wildlife populations[1-3,*]**
  - RABORAL has been in continuous use since 1987
  - Approximately **250 million doses** in the form of animal baits have been aerially distributed across Europe, Israel, Canada, and the US at a rate of about 5 million baits per year
  - Species targeted include skunks, racoons, foxes, and coyotes
  - Jordona Kirby, the rabies field coordinator for the USDA's National Rabies Management Program was interviewed about dropping Raboral out of low-flying planes and helicopters to control rabies in the East Coast of the US[4]





*A registered trademark of Boehringer Ingelheim Animal Health

[1]Raboral V-RG®. Accessed July 9, 2021. https://www.raboral.com/about-rabies/raboral-v-rg
[2]Kieny MP, et al. *Nature.* 1984;312(5990):163-166.
[3]Maki J, et al. *Vet Res.* 2017;48(1):57.
[4]Science Friday : NPR Sept 30, 2022 NPR's program "Science Friday" at 30:02 in the podcast www.npr.org/podcasts/583350334/science-friday

# 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 CDC publication of 1976 horsepox isolate[3]
- **Substantially decreased virulence in mice[2] and efficacy in NHPs to protect against monkeypox[4]**
  - Non-human primate study showing protection from monkeypox presented at 2020 ASM Biothreats conference

[1]Tulman ER, et al. Genome of horsepox virus. *J Virol*. 2006 80(18):9244-58.PMID:16940536
[2]Noyce RS, et al.. Construction of an infectious horsepox virus vaccine from chemically synthesized DNA fragments. *PLoS One*. 2018 Jan 19;13(1):e0188453
[3]Trindade GS, et al. Serro 2 Virus Highlights the Fundamental Genomic and Biological Features of a Natural Vaccinia Virus Infecting Humans. *Viruses* 2016 Dec 10;8(12). pii: E328. PMID:27973399 PMCID: PMC5192389 DOI: 10.3390/v8120328
[4]Noyce, RS, et al. Synthetic Chimeric Horsepox Virus (scHPXV) Vaccination Protects Macaques from Monkeypox* Presented as a poster at the American Society of Microbiology BioThreats Conference - January 29, 2020, Arlington, VA. (https://content.equisolve.net/tonixpharma/media/10929ac27f4fb5f5204f5cf41d59a121.pdf )

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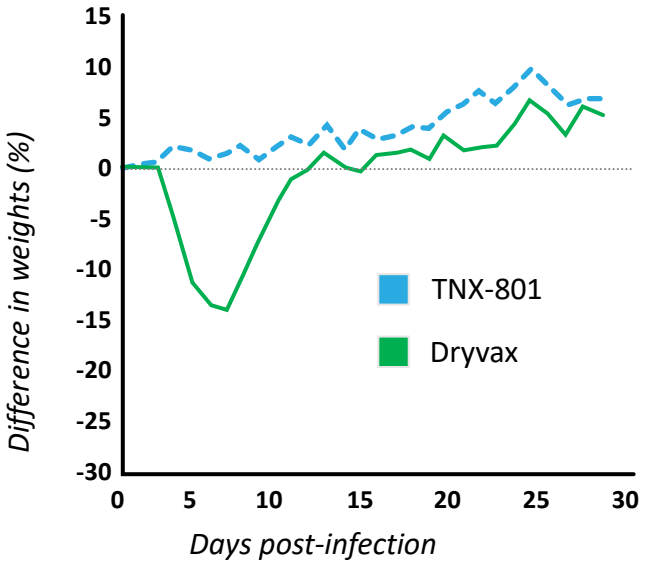
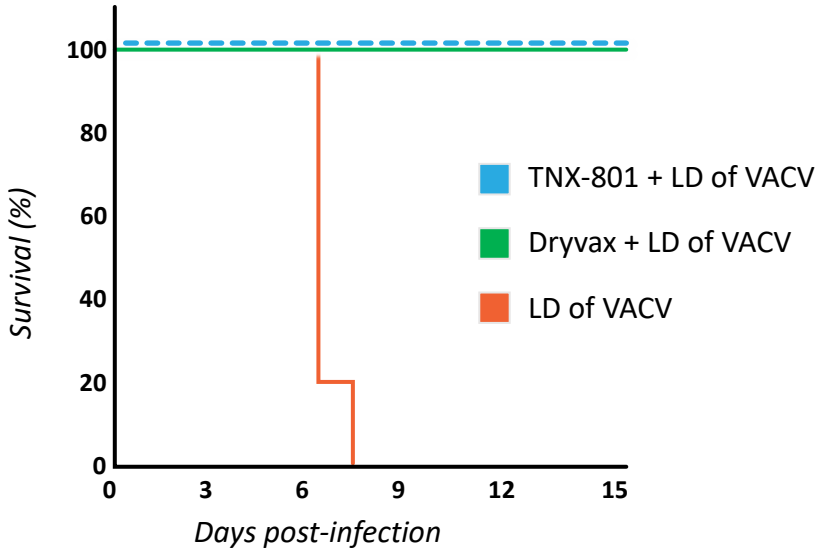
# Vaccination with TNX-801 (rHPXV) Improves Upon the Tolerability Profile of Modern Vaccines in Animals

- **In a study that compared the efficacy and safety of TNX-801 to Dryvax[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 equally well as Dryvax from a lethal dose (LD) of vaccinia (VACV)
  - TNX-801 may be safer than current vaccines without sacrificing 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.

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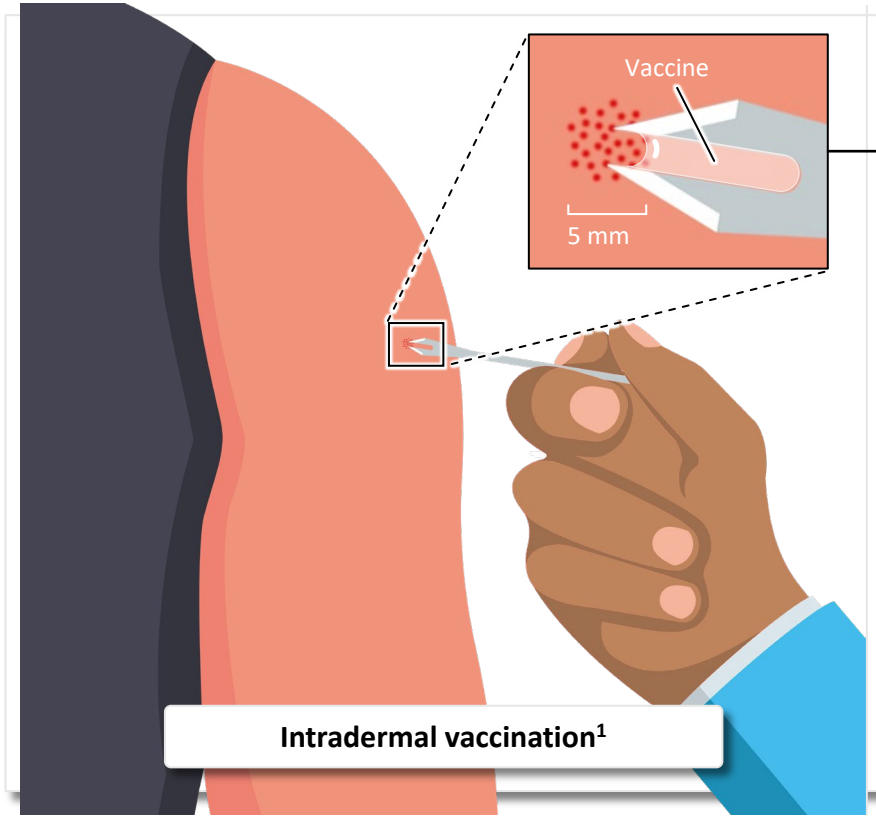
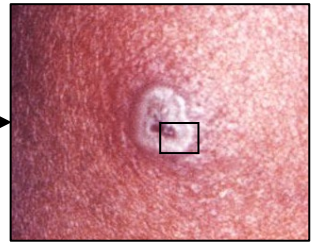
# Vaccinia Induces a Skin Reaction Called "Take" – Described by Dr. Edward Jenner



Take[2]

- **Biomarker of protection**
  - Smallpox was eradicated using this marker
  - Revaccination indicated for recipients without "take"
- **Measure of T cell immunity**
  - No need for blood draws or complex laboratory studies
  - No other functional T cell assay is approved or in clinical use for vaccination

*Example of major cutaneous reaction, or "take," resulting from a replication-competent live-virus vaccine with intradermal delivery, indicating successful vaccination[1,2]



[1]Fulginiti VA, et al. *Clin Infect Dis.* 2003;37(2):241-250.
[2]Centers for Disease Control and Prevention. Accessed April 15, 2020. https://phil.cdc.gov/Details.aspx?pid=3276



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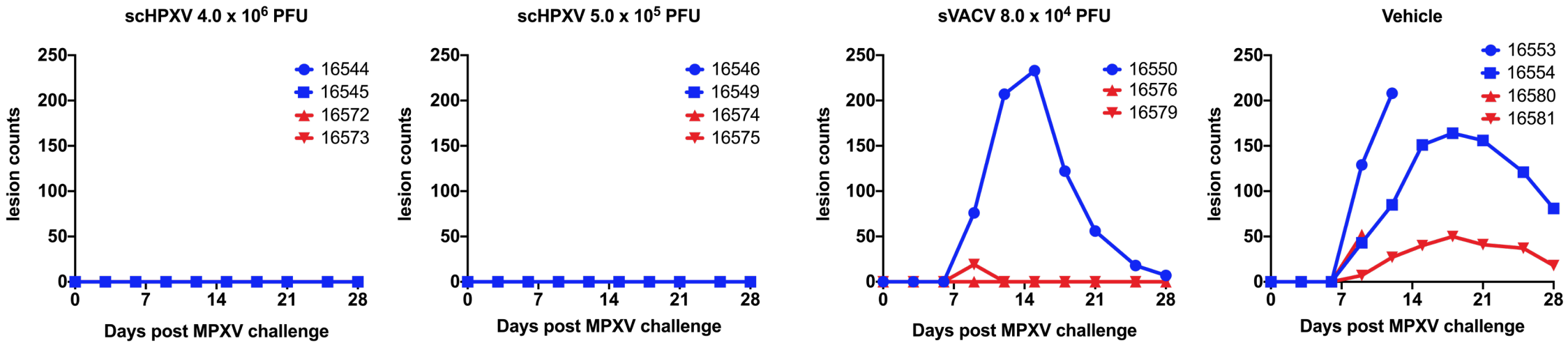
# No Overt Clinical Signs Observed in TNX-801 Vaccinated Macaques After Monkeypox (MPVX) Challenge[1]

## No monkeypox lesions observed after monkeypox (MPXV) challenge in any of the eight animals vaccinated with TNX-801




Legend: Cynomolgus macaques (4 per group), were vaccinated *via* scarification using a bifurcated needle. Two different doses of TNX-801 (scHPXV) vaccine were tested (panel a. and b.); one dose of TNX-1200 (sVACV)(panel c.); or vehicle (panel d). After monkeypox (MPXV) challenge, no lesions were seen in any of the 8 animals vaccinated with TNX-801 (panel a and b.). One animal in the TNX-1200 arm died from unrelated causes, and two of three remaining animals showed lesions by Day 69 (panel c.). All four vehicle vaccinated animals developed lesions (panel d.) Clinical signs of systemic monkeypox infections were seen in all 4 vehicle-vaccinated animals (panel d.) by Day 69, but TNX-801 and TNX-1200 vaccinated animals were protected. In Panels a-d, blue symbols are male animals and red are female.

Methods: 4 of 4 animals in the $4x10^6$ PFU dose, and 3 of 4 animals in the $5x10^5$ PFU dose groups exhibited a "take" at Day 7 after a single vaccination. A take is a biomarker of protective immunity. In the TNX-1200 (sVACV) arm only 1 of 4 animals exhibited a take after a single vaccination. The animals that did not present a take were revaccinated on Day 14: the one TNX-801 animal was revaccinated with $5x10^5$ PFU TNX-801 and the 3 TNX-1200 animals were revaccinated with $2.4x10^5$ PFU TNX-1200. All but one of the TNX-1200 animals subsequently produced a take. Tolerability was comparable for TNX-801 and TNX-1200.

[1]Noyce, RS, et al. Synthetic Chimeric Horsepox Virus (scHPXV) Vaccination Protects Macaques from Monkeypox* Presented as a poster at the American Society of Microbiology BioThreats Conference - January 29, 2020, Arlington, VA. (https://content.equisolve.net/tonixpharma/media/10929ac27f4fb5f5204f5cf41d59a121.pdf )

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# Monkeypox Outside of Africa

- **First case reported May 7th, more than 25,000 cases observed outside of Africa[1]**
  - West African strain found outside of Africa, low mortality in Africa (<1%)
  - Mortality in Africa believed to be 3-6%; strain prevalent in Congo has higher mortality (~10%)
  - Skin to skin transmission
  - In latest outbreak most cases outside Africa were linked to linked to a events in Spain and Belgium
  - Last outbreak outside of Africa was 2003 when infected prairie dogs led to 70 cases in the US
- **Resurgence believed due to cessation of routine smallpox vaccination**
  - Smallpox vaccination with live virus vaccinia protects against monkeypox[2]
- **US Stockpile includes Jynneos®[3], 2-dose regimen of non-replicating MVA vaccinia strain that protects NHPs from monkeypox[4]**
  - US has ordered more Jynneos – CDC considering ring vaccination and vaccinating first responders, but Jynneos requires two dose regimen
  - ACAM2000®[3] - live replicating 1-dose regimen also recommended but not FDA approved

[1] *The Economist* May 25th 2022, "Monkeypox is not covid mk2, but it needs to be nipped in the bud: The illness can be dangerous for children, pregnant women and the immunocompromised":
URL: Monkeypox is not covid mk2, but it needs to be nipped in the bud | The Economist
[2] https://www.cdc.gov/smallpox/pdfs/revaccination-memo.pdf
[3] Jynneos is a trademark of Bavarian Nordic and ACAM2000 is trademark of Emergent BioSolutions
[4] Rao, AK. et al. May 27, 2022. US CDC MMWR 71 "Use of JYNNEOS (Smallpox and Monkeypox Vaccine, Live, Nonreplicating) for Preexposure Vaccination of Persons at Risk for Occupational Exposure to Orthopoxviruses: Recommendations of the Advisory Committee on Immunization Practices — United States, 2022"
www.cdc.gov/mmwr/volumes/71/wr/mm7122e1.htm?s_cid=mm7122e1_w

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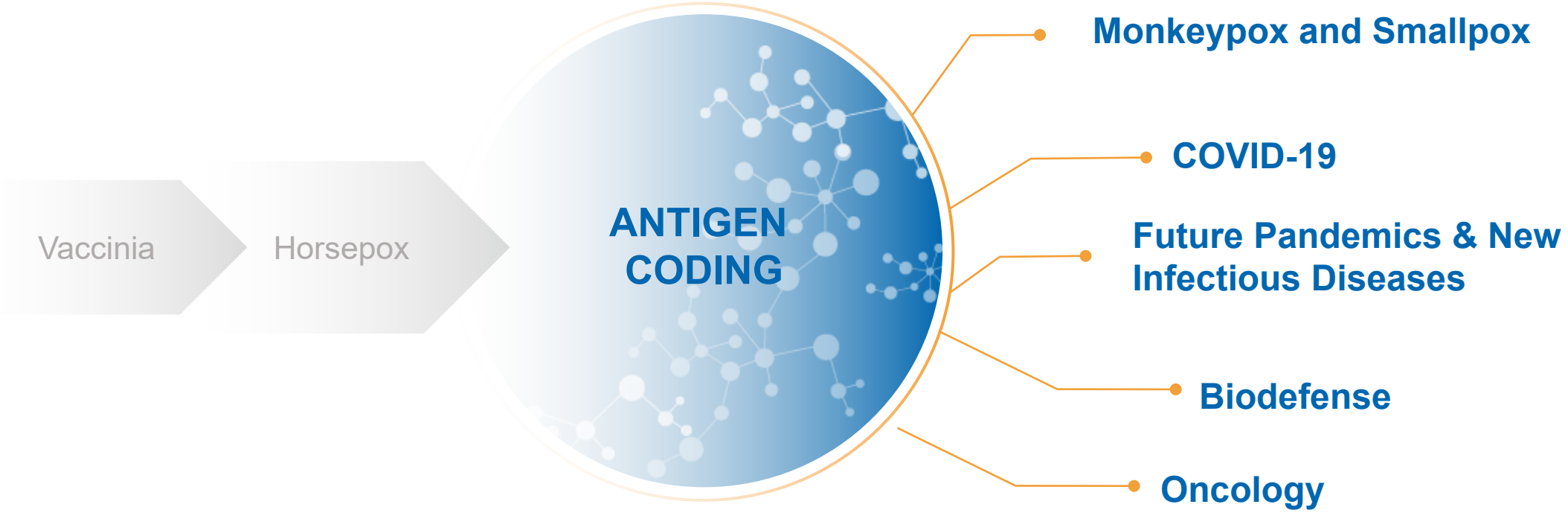
# Live Virus Vaccine Platform: Recombinant Pox Vaccine (RPV) Technology for Emerging Infectious Diseases and Oncolytics




**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



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# Live Virus RPV Platform
# Internal Development & Manufacturing Capabilities

## Infectious Disease R&D Center (RDC) – Frederick, MD

- Function: Accelerated development of vaccines and antiviral drugs against COVID-19, its variants and other infectious diseases
- Description: ~48,000 square feet, BSL-2 with some areas designated BSL-3
- Status: Operational

## Advanced Development Center (ADC) – North Dartmouth, MA

- Function: Development and clinical scale manufacturing of biologics
- Description: ~45,000 square feet, BSL-2
- Status: Operational


## Commercial Manufacturing Center (CMC) – Hamilton, MT

- Function: Phase 3 and Commercial scale manufacturing of biologics
- Description: ~44 acre green field site, planned BSL-2
- Status: Planning for site enabling work

*Architectural Rendering*

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# Investigators and Collaborators

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# THANK YOU