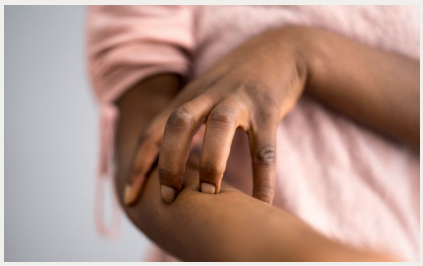
## Itch receptor OSMR attracts industry



Credit: Andriy Popov / Alamy Stock Photo

In August, Genentech entered into an exclusive agreement with Kiniksa Pharmaceuticals for the rights to develop and commercialize a monoclonal antibody (mAb) targeting the oncostatin M receptor-β (OSMRβ) for treating pruritus. The Hamilton, Bermuda-based biotech will receive $100 million up front plus milestones of up to $600 million and potential sales royalties.

The pathophysiology of pruritus is poorly understood, and the condition remains difficult to treat. Kiniksa's mAb vixarelimab (KPL-716) is a first-in-class fully human mAb that blocks OSMRβ. In the skin of patients with chronic pruritus, the cytokine OSM is highly expressed, as it is secreted by immune cells. It signals through OSMRβ, but to generate itch sensations it must partner with interleukin-31 (IL-31), made by T helper 2 cells. It is thought that pruritus is induced when IL-31 signals through the IL-31 receptor — which forms a heterodimer with OSMRβ — on keratinocytes and mast cells. These activated cells in turn mediate neuroimmune communications that transmit itch sensations to the central nervous system.

Vixarelimab has breakthrough designation for treating pruritus associated with prurigo nodularis, a chronic inflammatory skin condition with severely itchy lumps, and is in phase 2 testing. Genentech will also continue the preclinical development of the mAb to treat fibrosis, an indication where OSM-mediated signaling is an important driver of pathogenesis.

Published online: 9 September 2022
https://doi.org/10.1038/s41587-022-01481-1

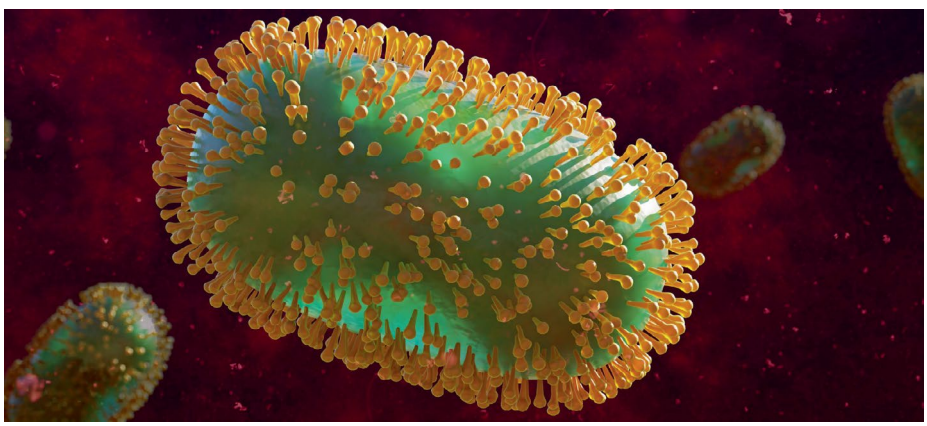
# Monkeypox response relies on three vaccine suppliers

Biodefense stockpiles are helping to curb the monkeypox outbreak, but the vaccines are based on old technology with significant side effects. Are other vaccines on the horizon?

When the World Health Organization declared on 23 July the global spread of the monkeypox virus a public health emergency, the question over vaccines to prevent disease became a pressing one. Monkeypox virus is closely related to the better known variola or smallpox virus. Three vaccines, all developed and initially approved by three small vaccine developers to treat smallpox, are thought to be about 85% effective against human monkeypox infection as a result of similarities between these two large double-stranded DNA orthopoxviruses. But existing vaccines — most of them stockpiled and ready to deploy — haven't been directly tested against the disease in people. What's more, they are made with old technologies and have safety drawbacks.

The health emergency demands prompt action, and the availability of ready-made vaccines is reassuring. In July, the European Medicines Agency recommended the smallpox vaccine made by Danish biotech Bavarian Nordic be authorized for monkeypox disease. The product, Imvanex (Jynneos in the United States and Imvamune in Canada), has been approved in the European Union since 2013 for smallpox. The US Food and Drug Administration had given the vaccine the go-head in 2019 to protect from smallpox or monkeypox infection. Bavarian Nordic's vaccine is made from live non-replicating virus, a modified strain of the vaccinia virus named Ankara that is closely related to smallpox or monkeypox but is less virulent. It was developed largely through funding from the US government's Biomedical Advanced Research and Development Authority (BARDA) program and is the World Health Organization's vaccine of choice in the current outbreak; as yet around 95% of the available 16.4 million doses are yet to be filled into vials and finished. The efficacy of smallpox vaccines can no longer be tested in the field, but phase 3 results testing Ankara as a standalone smallpox vaccine show that it provokes immune responses similar to those of established smallpox vaccines.

Another approved vaccine is from Emergent BioSolutions. The vaccine ACAM2000 was purchased from Sanofi in 2017 for $97.5 million plus milestone payments. It is a live vaccinia vaccine derived from a single clone of the original smallpox vaccine Dryvax, and is given by scarification (applied to repeatedly scratched skin). Although this vaccine currently has the widest availability as part of national stockpiles (with ~100 million doses), it is associated with rare but serious cardiac side effects and the potential to cause progressive vaccinia, in which the attenuated virus spreads to the whole body. Moreover, Emergent's vaccine cannot be used in people with HIV or who are immunocompromised.



The monkeypox virus is a double-stranded DNA virus endemic to Central and West Africa. Credit: dotted zebra / Alamy Stock Photo

A third approved vaccinia vaccine is made by the Kumamoto, Japan-based KM Biologics. It is stockpiled and available only in Japan for use against bioterrorism. LC16m8 is an attenuated smallpox vaccine derived from vaccinia strain Lister. It was developed to lack the B5R envelope protein gene to attenuate its neurotoxicity but still strongly protect with a single dose, as demonstrated in animal models.

Although vaccinia has an extensive safety history in humans, cardiac effects such as myocarditis and pericarditis are still a concern.

For this reason, several other companies are looking toward non-vaccinia strategies. For example, Tonix Pharmaceuticals is heading toward clinical trials with TNX-801, a live vaccine that uses a horsepox virus developed in collaboration with the University of Alberta. TNX-801 was assembled from synthetic DNA fragments and has genetic differences from vaccinia vaccines, such as complete left and right inverted terminal repeats. In non-human primate, TNX-801 blocks the formation of monkeypox lesions, and in mice it is less virulent than old vaccinia strains, which Tonix CEO Seth Lederman thinks will translate to better tolerability in humans.

Lederman says that horsepox is closer to the pox strain used by vaccine pioneer Edward Jenner and avoids mutations that have accumulated over centuries of pox-based vaccine manufacture. "Jenner's live-virus vaccine is the most successful vaccine ever. It eradicated smallpox and provides nearly lifelong immunity with no booster," he says.

Jenner's vaccine and nineteenth- and early twentieth-century smallpox vaccines are now known to be closer to horsepox than cowpox. During Jenner's time in the early nineteenth century, inocula derived from either cowpox or horsepox were used interchangeably for smallpox vaccination, taking advantage of what we now know: that all poxviruses lead to cross-species immunity. Yet surprisingly, the true origin of modern post-1930s vaccinia virus used in today's vaccines is unknown — the vaccinia virus has only ever been found in vaccine form.

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Most clinical studies are done in non-human primates, but Tonix expects to test TNX-801 in collaboration with the Kenya Medical Research Institute in 2023. Although cases of human monkeypox have not been reported in Kenya, it is close to regions where a high-mortality clade is endemic, and spread is anticipated. "The vaccine strategies that are being played out now in the United States and Europe don't apply in African countries — there's currently no vaccine for them," he says. Lederman anticipates robust clinical trial data from Kenya's healthcare system that he says has high participation, robust data analysis and excellent infrastructure.

Because attenuated whole-virus vaccines have been so successful, target-defined DNA vaccines against smallpox have had little backing to date. Even so, one such candidate is EpiVax's VennVax — a DNA-based vaccine that is designed to contain just T cell epitopes, with the aim of providing protective immunity. In a 2011 paper, the company showed that the vaccine used as a DNA-prime/peptide-boost strategy protected vaccinated mice from a lethal vaccinia challenge.

EpiVax CEO and University of Georgia Professor Annie De Groot thinks the vaccine will drive T cell responses similar to those thought to underlie a large part of the efficacy of COVID-19 mRNA vaccines and prevent morbidity and mortality. But she hasn't found a partner to trial this, despite having reached out to larger vaccine companies. "I'm sure the lack of positive response is because they view the market as being tiny compared [with] COVID," she says.

Lack of funding and demand also meant that Inovio Pharmaceuticals shelved its synthetic smallpox or human monkeypox DNA vaccine, according to a company spokesperson. A 2011 study showed that the vaccine, directed to specific mature and enveloped virion antigens, protected non-human primates from lethal monkeypox challenge. The company has no immediate plans to resurrect this program.

For now at least, DNA vaccines for human monkeypox must wait to be tested clinically. Yet this might be the right thing to do in the current outbreak, according to Lederman, where the aim of science should be to mobilize a vaccine. "We have a solution [in live-virus vaccines] with compelling real-world evidence that can save lives. It seems prudent to go in that direction," he says. Moderna, however, announced on 5 August that, in response to concerns about vaccine supply and the public health situation, it has begun a preclinical program investigating possible mRNA vaccines for monkeypox. ❐

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Published online: 9 September 2022
https://doi.org/10.1038/s41587-022-01463-3