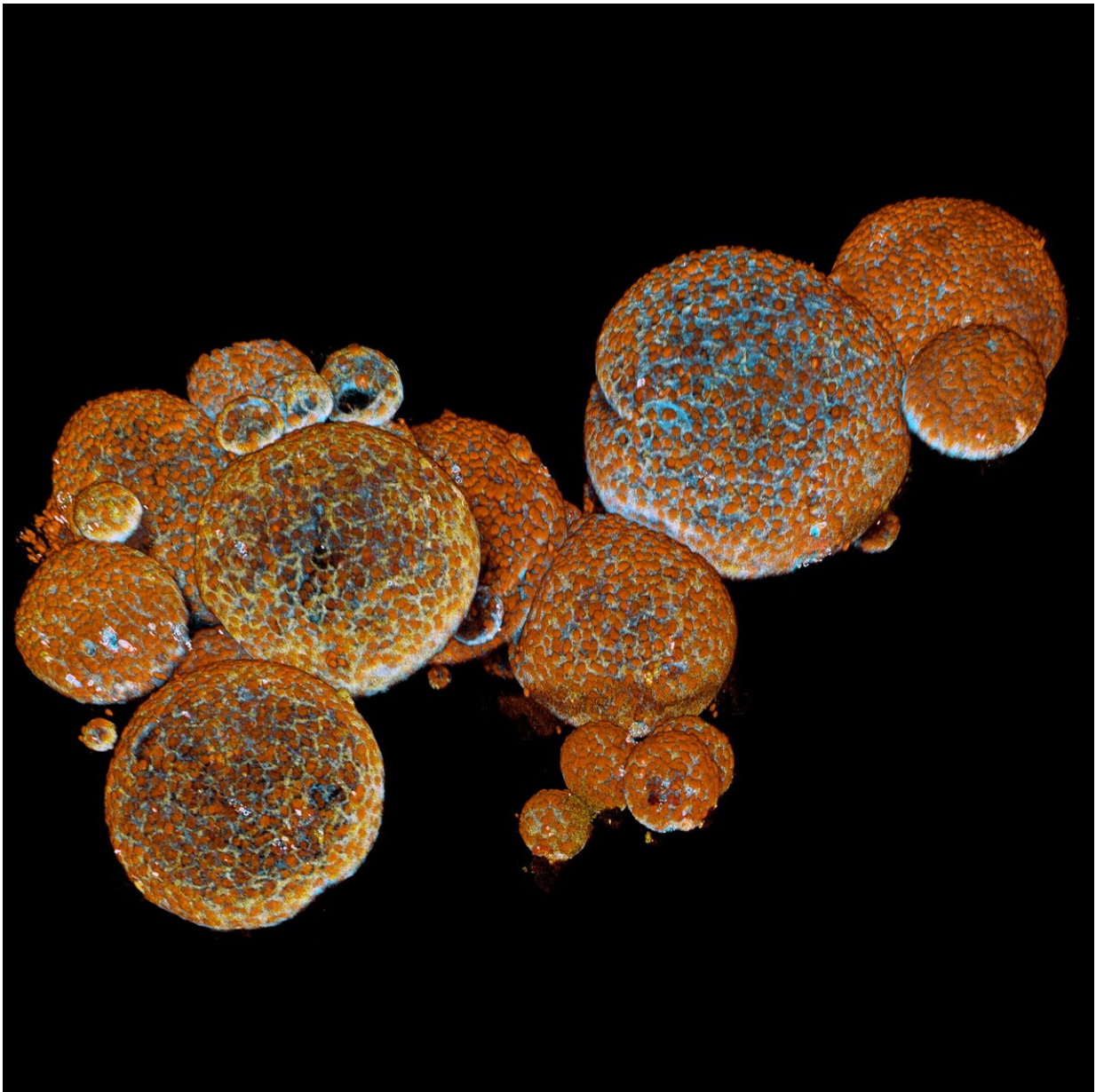


Snake stem cells used to create venom-producing organoids

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Fluorescence microscopy image of snake venom gland organoids. Credit: Ravian van Ineveld, © Princess Máxima Center

Organoids have become an important tool for studying many disease processes and testing potential drugs. Now, they are being used in a surprising and unexpected way: for the production of snake venom. On January 23 in the journal *Cell*, researchers are reporting that they have created organoids of the venom glands of the Cape coral snake (*Aspidelaps lubricus cowlesi*) and that these glands are capable of producing venom.

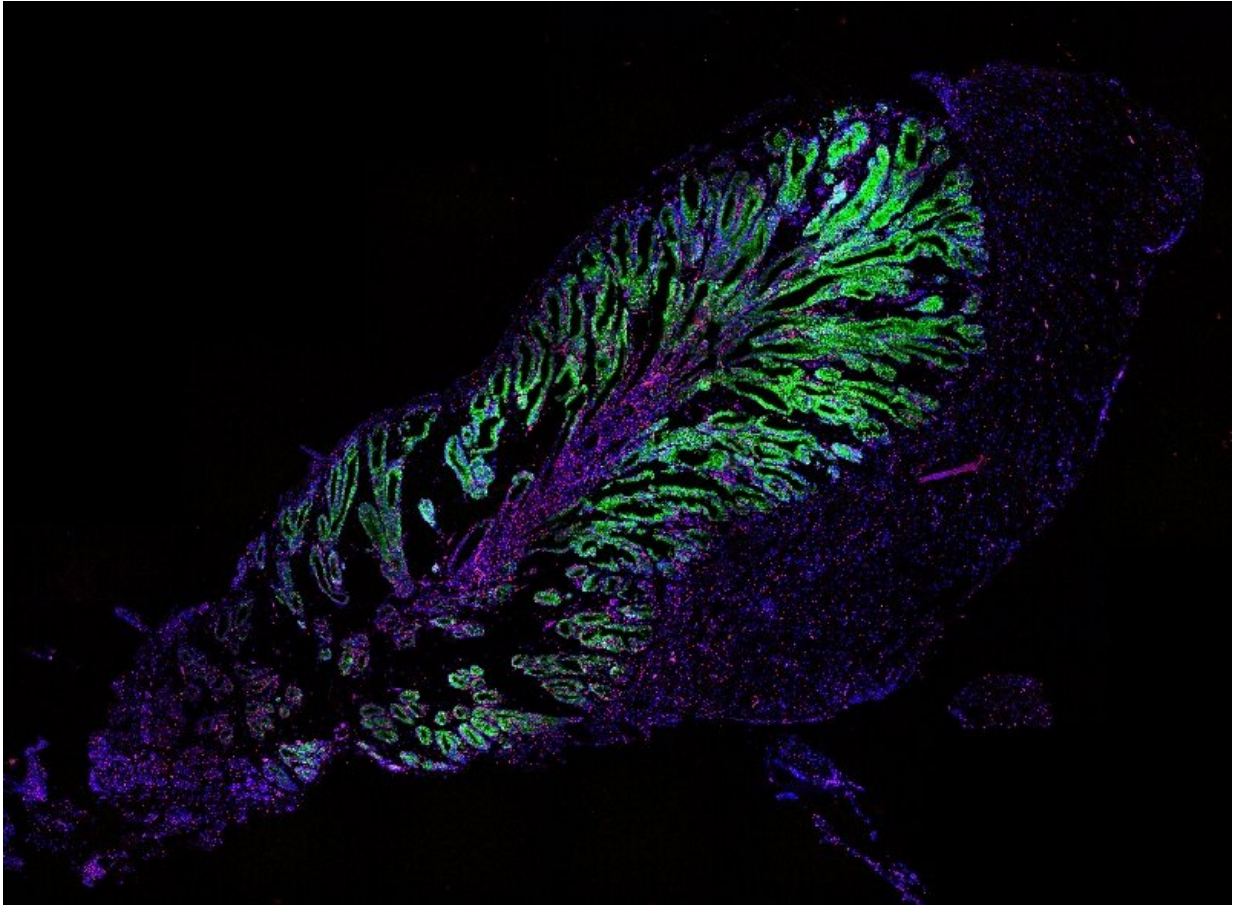
"More than 100,000 people die from [snake bites](#) every year, mostly in developing countries. Yet the methods for manufacturing antivenom haven't changed since the 19th century," says senior author Hans Clevers of the Hubrecht Institute for Developmental Biology and Stem Cell Research at Utrecht University in the Netherlands. "It's clear there is a huge unmet medical need for new treatments."

He adds: "Every snake has dozens of different components in their venom. These are extremely potent molecules that are designed to stop prey from running away. They affect systems as varied as the brain, [neuromuscular junctions](#), blood coagulation, and more. Many of them have potential bioprospecting applications for new drugs."

Clevers' lab traditionally focuses on organoids made from human and mouse cells. But some of his students decided to study stem cells and develop organoids from reptiles. "This is a field that does not exist, so they thought it was interesting to study the most iconic reptilian organ, the snake venom gland," he says. "Once we grew the venom glands as organoids, we realized that they make a lot of venom."

The investigators started with the Cape [coral snake](#) because they knew a breeder who was able to supply some fertilized eggs. The snakes were removed from the eggs before hatching, and small pieces of tissue were removed from various organs and placed into gels, along with growth factors. In addition to the venom glands, the researchers also made organoids of the [snake](#) liver, pancreas, and gut.

"It would have been difficult to isolate [stem cells](#) from these snakes because we don't know what they look like," Clevers explains. "But it turned out we didn't need to. The cells soon began dividing and forming structures." In fact, he says, the venom gland organoids grew so fast that in just one week, they were able to break them apart and re-plate them, generating hundreds of plates within two months. He notes that if it could be commercialized, this method would be much more efficient than the way venom is currently produced—by raising snakes on farms and milking their glands.



Variable toxin production (green and red) in different areas of the snake venom gland. Credit: Joep Beumer, Yorick Post, Jens Puschhof, © Hubrecht Institute

The researchers were able to identify at least four distinct types of cells within the venom gland organoids. They confirmed that the venom peptides produced were biologically active and resembled the components of venom from live snakes.

A challenge of the work was determining gene-expression levels in the [venom](#) gland organoids. "The genomes of most snakes have not been annotated," Clevers says. The investigators were able to identify certain genes that were active under expansion conditions, suggesting that these

pathways—including most importantly the Wnt pathway—may play a role in reptilian stem cell growth.

One of the collaborators on the study was Freek Vonk, a herpetologist and well-known Dutch television host who Clevers calls "the Steve Irwin of Holland." Vonk is affiliated with Leiden University and the Naturalis Biodiversity Center.

More information: Snake Venom Gland Organoids. Yorick Post, Jens Puschhof, Joep Beumer, Harald M. Kerkkamp, Merijn A.G. de Bakker, Julien Slagboom, Buys de Barbanson, Nienke R. Wevers, Xandor M. Spijkers, Thomas Olivier, Taline D. Kazandjian, Stuart Ainsworth, Carmen Lopez Iglesias, Willine J. van de Wetering, Maria C. Heinz, Ravian L van Ineveld, Regina G.D.M. van Kleef, Harry Begthel, Jeroen Korving, Yotam E. Bar-Ephraim, Walter Getreuer, Anne C. Rios, Remco H. S. Westerink, Hugo J. G. Snippert, Alexander van Oudenaarden, Peter J. Peters, Freek J. Vonk, Jeroen Kool, Michael K. Richardson, Nicholas R. Casewell and Hans Clevers. *Cell* 2020. [DOI: 10.1016/j.cell.2019.11.038](https://doi.org/10.1016/j.cell.2019.11.038) , [www.cell.com/cell/fulltext/S0092-8674\(19\)31323-6](https://www.cell.com/cell/fulltext/S0092-8674(19)31323-6)

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