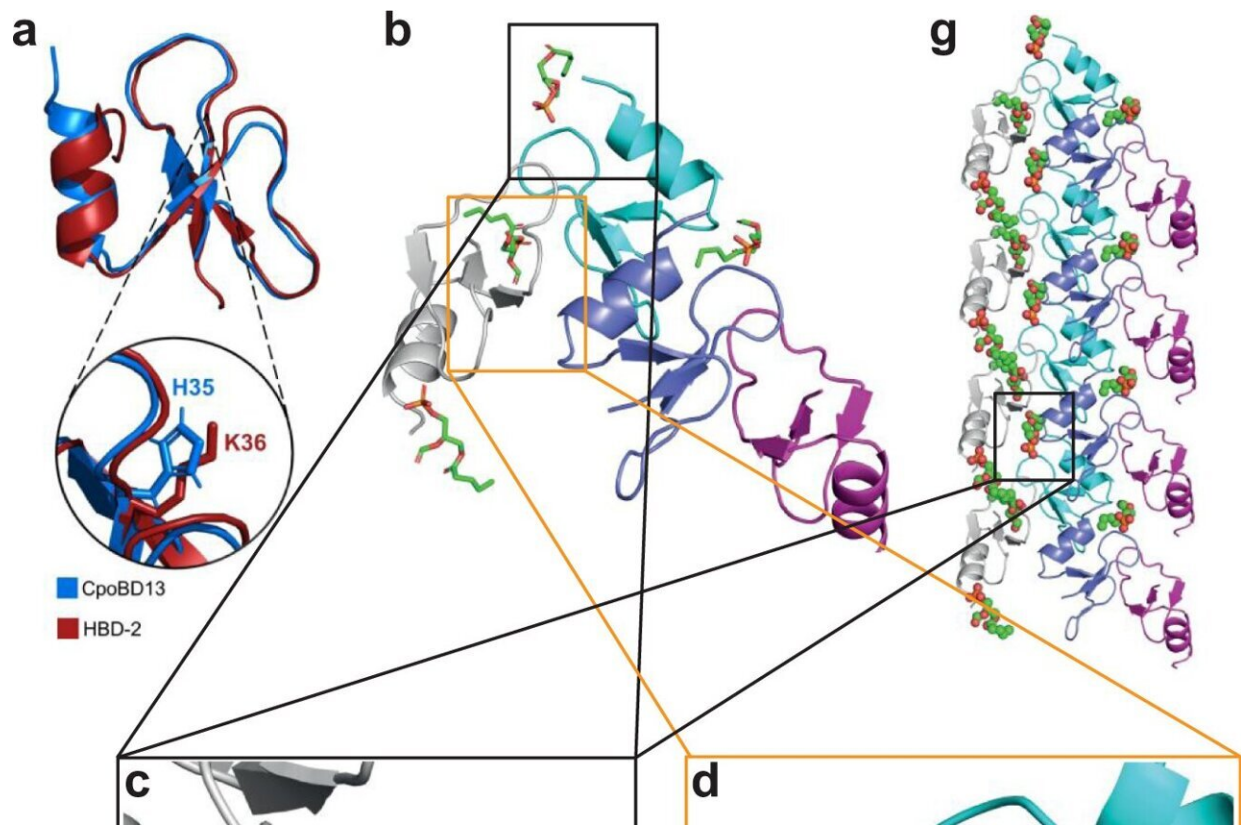


Crocodiles could save us from deadly infections

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Crystal structure of the CpoBD13:PA complex. a Three-dimensional structure of CpoBD13 determined by X-ray crystallography superimposed with HBD-2 (PDB ID 1FD3). Zoomed in region shows the substitution of K36 (a crucial residue for membranolytic activity) in HBD-2 for H35 in CpoBD13. b Four CpoBD13 chains are found in the asymmetric unit (white, cyan, steel blue and magenta cartoon), bound to four PA molecules shown as green sticks. c Type I and d Type II PA binding sites. Key interacting residues are shown as sticks. Hydrogen bonds or ionic interactions are marked as black dashed lines.

Schematic representation of the e Type I and f Type II PA binding sites. g CpoBD13:PA complex forms a single-stranded left-handed helix. The coil shown comprises the content of four asymmetric units. The location of a single type I PA binding site is boxed in black. Credit: *Nature Communications* (2023). DOI: 10.1038/s41467-023-36280-y

A new study by La Trobe University researchers reveals how crocodiles resist fatal fungal infections using a unique pH sensing mechanism despite living in filthy water.

Published in *Nature Communications* the research could be used to create targeted treatment for fungal infections in humans which are becoming increasingly frequent due to growing antibiotic resistance.

Lead author from La Trobe University, Scott Williams, focused on the [crocodiles'](#) defensins—small proteins that detect and announce an [infection](#) to the [immune system](#).

"We solved structures of crocodile defensins and they look surprisingly like the same proteins in humans, which means we could use them as a template to treat fungal infections in humans," Scott Williams said.

"Crocodiles have great antifungal defenses and hopefully we'll be able to adapt their defense to our own needs."

Scott Williams said it's the first time this function has been found in any plant or animal.

"We haven't seen the pH sensing mechanism in any other animal or plant. The defensins are able to change their activity based on the pH environment, so we could engineer other defensins to turn off or on

depending on the presence of infection," Scott Williams said.

"Some therapeutic treatments act on [healthy cells](#) by accident whereas this mechanism could help to reduce these off-target effects and focus on what's harmful."

Senior author Professor Mark Hulett said that the study is also the first to document the structure of the defensin membrane attack in high resolution.

"Using the power of the Australian Synchrotron, together with co-author Prof Marc Kvensakul, we were able to generate structural data to define how defensins attack and kill [fungal pathogens](#)," Professor Hulett said.

"Consequently, our findings provide a model for understanding the anti-microbial activity of other defensins including those in humans."

For this study, Professor Hulett harvested the crocodile tissue with the help of John Lever and John McGrath from the Koorana Crocodile Farm in Yeppoon, Queensland, the first commercial crocodile farm in Australia.



(L-R): Professor Mark Hulett, lead author and PhD candidate Scott Williams, Dr Fung Lay. Credit: La Trobe University

Future therapeutics that could targeting infections

The findings of the study could allow researchers in the future to engineer defensins with pH-dependent activity in biotechnology and therapeutic applications, like treating serious infections in humans.

Saltwater crocodile defensin CpoBD13 harbors an intriguing antimicrobial activity dependent on environmental pH which is key to the body recognizing which area or cells are infected.

Based on the pH level of the cell's outer wall, CpoBD13 will recognize

and attack [fungal infections](#).

What are defensins?

Defensins are proteins in plants and animals that form an important part of our innate immune system to protect against infection by microbial pathogens such as bacteria, fungus and viruses.

They were first discovered in the 1980s and more recently have been attracting attention as potential therapeutics for the treatment infectious disease and cancer.

Although most research effort has focused on human and plant defensins, very little is known about defensins from other species that could harbor unique and useful functions.

The Hulett Lab at La Trobe University is leading research to understand the function of plant and animal defensins towards their application as novel therapeutics for treating human disease.

More information: Scott A. Williams et al, Crocodile defensin (CpoBD13) antifungal activity via pH-dependent phospholipid targeting and membrane disruption, *Nature Communications* (2023). [DOI: 10.1038/s41467-023-36280-y](#)

Provided by La Trobe University

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