Creature column

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Poison frogs

By Billie C. Goolsby, Melody J. Dailey, Luis A. Coloma & Lauren A. O'Connell

Endowed with formidable chemical defenses, spectacular coloration and diverse parental care strategies, poison frogs are a powerful comparative model for understanding how ecology, genetics and neurobiology intersect to shape the evolution of physiology and behavior.

Poison frogs have long captivated people owing to their charismatic coloration, chemical defenses and surprising diversity in social behavior. For centuries, Indigenous tribes from the Chocó region in western Colombia used the toxins of *Phyllobates* poison frogs (known as *kokoi*) to make poison blowgun darts[1]. The common name poison frogs refers to at least two unrelated families, Dendrobatidae and Mantellidae, which live in the Neotropics and Afrotropics, respectively. Long valued in Indigenous knowledge, poison frogs have become comparative model lineages for studying behavior and physiology within an ecological and evolutionary framework.

Towards global collaboration in the evolving study of dendrobatid poison frogs

I (B.C.G.) first encountered poison frogs during my final graduate school interview, when L.A.O'C.'s postdoctoral researcher gave me a tour of the animal facilities at Stanford. It is practically canon across universities that laboratory animal spaces feel sterile, cold and beige – a bit more like lairs than habitats. Yet, when the frog room door swung open, a wall of humid air engulfed me. Lush green vegetation grew in each of the vivaria, accompanied by a chorus of hard-to-place calls. Admittedly, I initially had a hard time finding the frogs, until I saw the bold, brilliant red of an *Oophaga* staring back at me (Fig. 1). She found me first. Anthropomorphism is generally chastised in my field, but I can only describe what the animal evoked in one word: confidence. However tiny, she exuded the sense that I was entering her territory – not the opposite. It was clear that these visually dazzling animals deserved reverence, and I was eager to learn more about them.

Fig. 1 | The diablito poison frog (*Oophaga sylvatica*). Photograph by Elicio Tapa.

Months before I started graduate school, a short documentary specifically on Central and South American poison frogs was released, entitled *Jewels of the Neotropics*; it highlighted conservation work by key leaders in the field, including L.A.C., with whom I was lucky enough to eventually connect years later and to write this Creature Column with. The Global South is home to most poison frog species, and supports efforts in scientific study and the pet trade[2]. In the 1970s, herpetologists from the Global North documented the diversity of poison frogs in Western scientific journals, and the American biochemist John Daly investigated their potent skin toxins and patented epibatidine – a molecule discovered in the Ecuadorian *Epipedobates* frog – as an analgesic in the USA. At that time, the Global South provided biodiversity as the 'raw material', but lacked resources for advanced laboratories or intellectual property control.

During the 1990s, the historical imbalance began to change. Latin American scientists increasingly advanced the field and the early 2000s marked a turning point, when molecular phylogenetics enabled researchers to explore the evolution of coloration and toxicity[3]. Today, more equitable partnerships between Global North and Global South researchers are steadily expanding. These collaborations foster increased participation in big science and high technology from the Global South, and enhance capacity building, conservation efforts and the exchange of knowledge. The evolving study of poison frogs exemplifies how scientific progress depends on innovation, meaningful collaboration, and growing recognition of the vital field knowledge and expertise held by regional researchers. However, fair benefit sharing in bioprospecting partnerships with source nations remains an unresolved challenge.

Dressed for success

Whereas most animals avoid standing out in the rainforest, poison frogs do the opposite. With their brilliant blues, intense oranges and vivid yellows (to name a few), their colors signal to predators that these frogs have chemical defense mechanisms (a phenomenon known as aposematism). Although poison frogs are named for their most famous members, not all dendrobatids are bright and colorful, which reflects their variability in both coloration and toxicity. Indeed, both Batesian and Müllerian mimicry is found within the family, and predator avoidance transfers from models to mimics[4]. Many researchers are exploring the genetic basis of aposematic coloration through transcriptomic approaches, and their work has revealed pigmentation determination pathways similar to those in other taxa[5,6]. Gene-editing tools being developed for amphibians should enable more functional testing of these candidate gene pathways in coloration and patterning.

The dazzling colors and parental care of poison frogs have encouraged a thriving hobbyist community in the Global North. Many hobbyists are considered citizen scientists with a deep knowledge of poison frog behavior and husbandry. Although these pet trade communities allow purchase for academic laboratories in the Global North, there is also illegal poaching of rare and beautiful frogs that has decimated natural populations. It is vital that animal purchases come from legal sources allied with conservation partners in the Global South, where purchases fund ethical biocommerce[7].

You are what you eat

Poison frogs earned their title from their noxious and toxic alkaloids, which are organic molecules with a nitrogen in a circular carbon

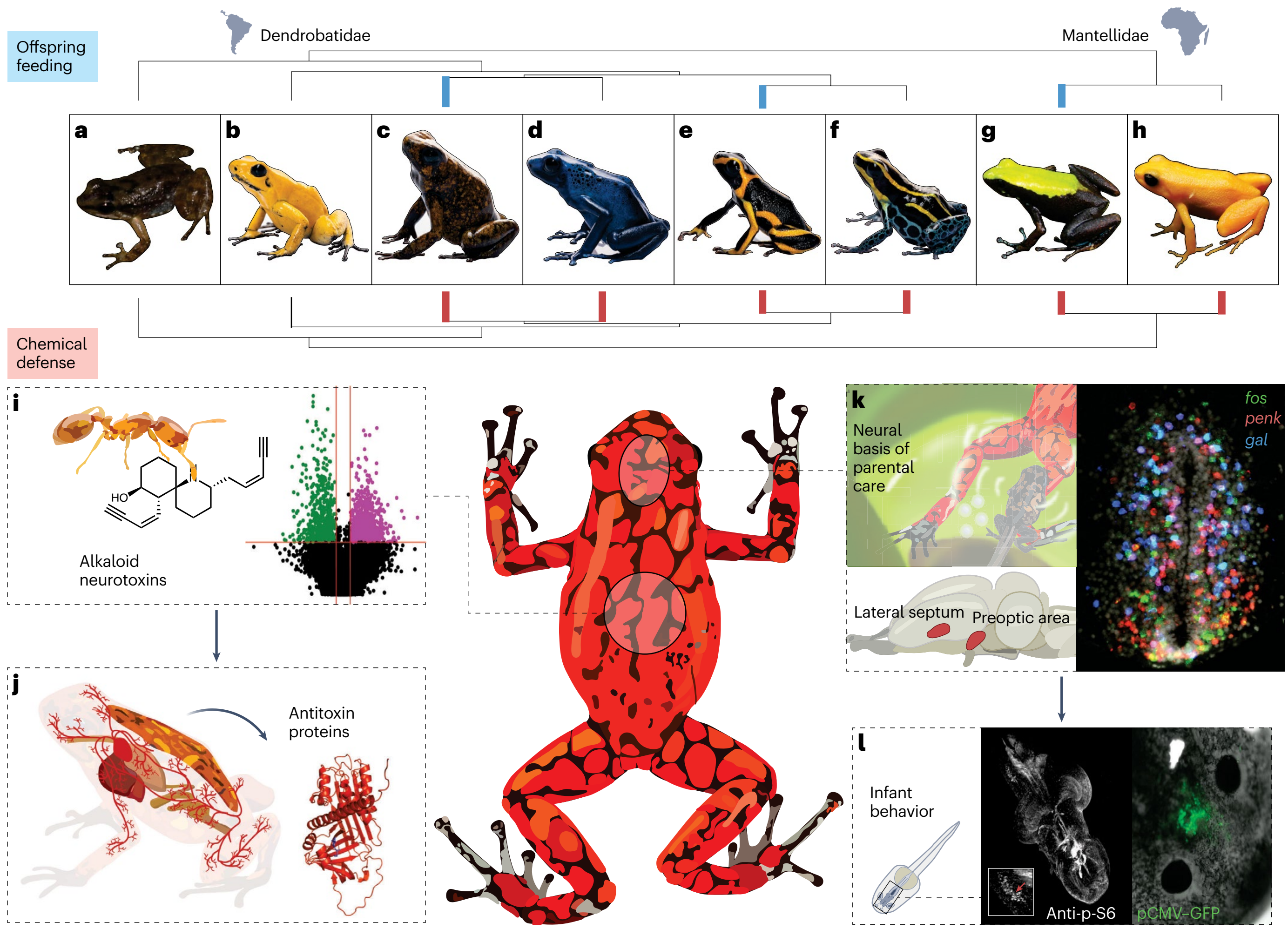

Fig. 2 | Leveraging diverse poison frogs for science. a–h, Examples of where chemical defenses (red on bottom phylogeny) and maternal egg-provisioning behavior (blue on top phylogeny) appeared or were lost in poison frog lineages, such as *Hyloxalus awa* (**a**), *Phyllobates terribilis* (**b**), *Oophaga sylvatica* (**c**), *Dendrobates tinctorius* (**d**), *Ranitomeya imitator* (**e**), *Ranitomeya variabilis* (**f**), *Mantella laevigata* (**g**) and *Mantella aurantiaca* (**h**). **i**,**j**, As poison frogs sequester toxins from their diet, trophic ecology studies can be combined with gene expression meaurements to understand physiological mechanisms of toxin sequestration (**i**) that can be further informed by biochemical analyses of toxin binding proteins (**j**). **k**,**l**, Additionally, brains can be harnessed to understand the evolution of social bonds, such as parent–offspring interactions from both the parental perspective (where ancestral circuits shared with mammals have been found) (**k**) and the offspring perspective, as tadpoles are translucent and tractable model organisms and therefore are beginning to be used in transgenic experiments and whole brain or in vivo imaging (**l**). Photographs by Daniela Pareja Mejía (**a**), Andrew Brodhead (**b**–**f**), Alex Roland (**g**) and Daniel Shaykevich (**h**). Illustrations by Lauren O'Connell (bottom center, **i**,**k**,**l**), Aurora Alvarez Buylla (**j**).

ring (such as cocaine or nicotine) (Fig. 2). Poison frogs do not make these molecules, but instead evolved to sequester toxins from a diverse menu of arthropods (including ants and mites)[8]. Thus, poison frogs in controlled laboratory conditions are nontoxic: dietary manipulations with alkaloids or various prey items enable a stepwise examination of how alkaloid sequestration occurs. Exciting avenues for future studies include mapping how alkaloids shape the trophic interactions among chemically defended arthropods, their frog predators, and their relationships with plants, fungi and microorganisms that are better known for alkaloid production.

More than 800 types of alkaloids have been identified on poison frog skin[1]. These molecules often target ion channels in the nervous system, and have a range that spans from being effectively nontoxic (*Allobates femoralis*) to the potential for a single frog to kill up to 20 people (*Phyllobates terribilis*). Multiomics resources established for poison frogs over the past decade have enabled insights into the physiological machinery that is required for sequestration and the prevention of self-intoxication. As with other chemically defended organisms, poison frogs have mutations in ion channels targeted by their own toxins, which leads to target site insensitivity[9]. However, resistance to toxicity is also found in animals without ion channel mutations. Using proteomics and alkaloid-like photoprobes, dendrobatid frogs have been found to have plasma toxin sponge proteins that bind a range of alkaloids[10]. With new multiomics and gene-editing technologies rolling out for this lineage, the role of these toxin sponge proteins (as well as other transport and metabolism proteins) in both sequestration and autoresistance is being heavily pursued and promises to provide insights into how similar organismal traits have repeatedly evolved.

All kinds of families

One of the most compelling aspects of poison frogs is their extraordinary diversity in parental care strategies[11] (Fig. 2). In some dendrobatid species, only males care for offspring: they provide egg maintenance and defense, and later transport the hatched tadpoles 'piggyback style' to pools of water. In species in which females are involved in offspring care, they perform these typical 'dad duties' as well as provide meals of unfertilized eggs to tadpoles that beg them for food by rapidly vibrating back and forth. Comparative studies have shown that similar brain regions are recruited during offspring transport in both males and females, which suggests a shared neural architecture for parenting[12]. Similarly, there are shared neural signatures of parenting even across South American dendrobatids and Malagasy mantellids[13], in which 'mom' frogs provision their tadpoles with alkaloid-containing egg meals. These parent–offspring relationships rely on different sensory cues: tadpoles recognize their mothers on the basis of smell[14], but parents recognize their offspring on the basis of spatial location[15]. This variability in parent–offspring relationships — as well as the presence of pair bonding, precise spatial memory and variable sociability — make these animal lineages ideal for exploring the neural basis of natural behavior and the ecological drivers that encourage such diversification.

Summary

From their intoxicatingly colored skin to their complex social lives, poison frogs embody the intersection of chemistry, ecology, neurobiology and behavior. As genomics, neuroethology and evolutionary biology converge, these amphibians are no longer just cautionary tales for predators — they are providing insights into fundamental biological questions.

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Competing interest

The authors declare no competing interests.