microscope. After looking at many images of negative clones, I was very excited to observe nice punctate signals in the nucleus, suggesting a positive clone. I remember that I cried in the dark room. By continuing this experiment, we found many constitutive centromere proteins, which are now called 'CCAN' proteins. This series of experiments determined the direction of my research career.

Do you continue to study centromeres/kinetochores? Yes. In the two decades since this experiment, we have continued to look for components of kinetochores, and I believe that most components have been identified. The next question is how these proteins are organized to generate functional kinetochores. Since there are over 100 different kinetochore proteins, it is not easy to address this question. At the same time, several researchers, including our lab, began to reconstitute a part of the kinetochore structure. Although this is a very important experiment, we had to first understand the organization of the native kinetochore structure. I believe that understanding kinetochore structure and function is the best way to understand how chromosomes segregate equally into daughter cells. There are many important general questions that we should address in biology. You might feel that studies on chromosome segregation or kinetochore structure are a bit restricted or limited, but that is not true. If we continue our studies in this field, we may find answers to unexpected new questions, because chromosomes are the fundamental structures in every cell. For this reason, I would like to encourage young scientists to join this field. I am sure that we will still get to reveal several unexpected phenomena in this area of science.

Is Japan a good place to conduct research? This is a difficult question. Of course, we have a strong tradition of chromosome research, and there are many researchers in Japan working on chromosomes. Needless to say, though, the centers of scientific research are based in the USA and Europe. For example, major journals are published in the USA or Europe. Therefore, we must communicate with scientists in the USA or Europe. Today, as communication tools are well developed, it is possible to talk easily with scientists abroad using Skype or email. However, it is still much better to talk with colleagues in person, and these opportunities are limited. In addition, many talented students and postdocs want to join labs in the USA or Europe. Considering this, I cannot say that Japan is the best country in which to conduct science. However, there are clear merits in Japanese science. For example, Japanese people are good at teamwork, and individual abilities of Japanese students are not less than those of students in the USA. Although we are generally not very skilled at writing manuscripts or responding effectively to hard reviews, we can learn many things from the scientific communities in the USA and Europe through this process. I have actually received many useful suggestions from reviewers, and this process trained me quite well, and could also be done in Japan. If I organize a good team in Japan, utilizing these merits in Japanese science, I believe that we can produce better scientific achievements from Japan. I recently moved to a new place (Osaka University). Here, I will try to organize the best team possible.

Since I have been supported by the Japanese scientific community, I feel obligated to train young Japanese scientists to be active in scientific research as part of the world community. In recent years, the Japanese government has been promoting globalization. True globalization is possible if each scientist is active and recognized in his or her research field.

Recently, the Japanese government has also demonstrated a trend towards supporting medical science rather than basic science in the field of biology. However, as I learned early on, excellent research in the field of applied science (including medical science) requires a deep understanding of basic science. Since Japan has a strong background in chromosome research, I hope that the Japanese government will continue to support our basic research, which will contribute to the overall development of medical research and help to train excellent 'global' young scientists.

Graduate School of Frontier Biosciences, Osaka University, Suita, Osaka 565-0871, Japan.
E-mail: tfukagawa@fbs.osaka-u.ac.jp

Quick guide

Predatory grasshopper mice

Ashlee H. Rowe* and Matthew P. Rowe

What are grasshopper mice? Grasshopper mice are big-eared, big-eyed, nocturnal rodents closely related to deer mice. They are relatively small (they are mice, after all!), only 120–190 mm long, about the length of a pencil, including their stubby, fat tail; adults typically weigh between 20 and 50 grams, the weight of about eight pennies for a small individual, 20 pennies for a bruiser. There are just three species, all in the genus *Onychomys*, the southern, northern, and Mearns' (or Chihuahuan) grasshopper mouse, respectively. Their geographical distribution is restricted to the short-grass prairies, shrub deserts, and desert grasslands of the western United States and northern Mexico, with the range of one species, the northern grasshopper mouse, extending into the northern Great Plains of south-central Canada.

Why are they called 'grasshopper mice'? The mice earned this epithet because they aren't the timid, hide-in-the-corners, seed-eating, cheese-stealing pantry pests many people think of when they hear the label 'mouse'. They are top-level carnivores, ferocious killers little different, besides their diminutive size, from a cheetah, coyote, or stoat. Early explorers of the American west ascribed two equally common names to the mice once their predatory lifestyles had been recognized — grasshopper mouse in some regions, and scorpion mouse in areas with an abundance of these arachnids. While grasshopper mice eat some plant material, and have been recorded killing and eating lizards, birds, and even other mice, a significant majority of their diet is arthropods including, obviously, grasshoppers and scorpions (Figure 1).

Are they the only carnivorous rodents? Actually, no. Indeed, the common perception of rodents as primarily herbivorous is erroneous. Many rodents are omnivorous and some, like ground squirrels, frequently include

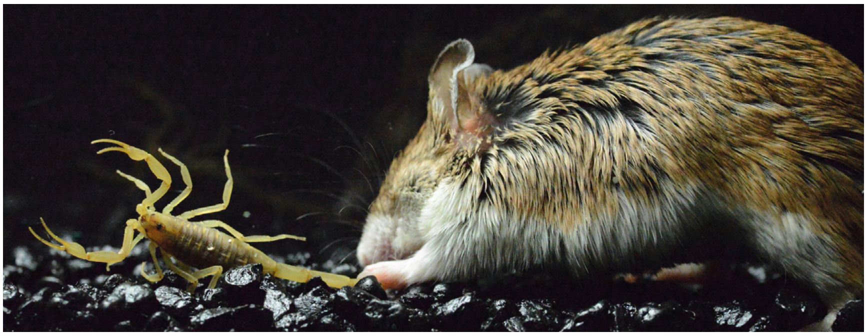

Figure 1. Southern grasshopper mouse capturing an Arizona bark scorpion.
Photo by Matthew and Ashlee Rowe.

insects, bird eggs, carrion, and other animal matter in their diet. Even deer mice (genus *Peromyscus*), the closest relatives of grasshopper mice, enjoy an arthropod snack or two when available. What distinguishes grasshopper mice from most other rodents, including their deer mice cousins, is their reliance on, and specializations for, a meat-based diet. While deer mice are opportunistic predators, grasshopper mice are obligate carnivores, a difference apparent in the behavior, morphology, and physiology of the two genera of mice. Experiments show that a grasshopper mouse, even an inexperienced juvenile, will voraciously attack almost any moving object that isn't substantively larger than itself; deer mice, in contrast, are more hesitant to attack, especially when facing novel prey items, and are less proficient at killing when they do. The skulls of grasshopper mice have evolved to deliver more forceful bites than deer mice, and their stomachs are better adapted for dealing with the lacerating edges of finely masticated arthropod exoskeletons. Even the fingernails of grasshopper mice appear modified for their predatory habits; *Onychomys* means 'clawed mouse', a trait thought to provide the mice with a better grasp on their often slippery, frequently struggling-to-escape prey (Figure 2).

Adaptations for their carnivorous lifestyle are also evidenced by the kinds of prey eaten by grasshopper mice, and the manner in which the prey are killed. Many desert arthropods, tarantulas and scorpions, for example, are protected by venomous bites and stings, while others, like pinacate beetles, possess toxic sprays. Grasshopper mice are known to eat all of these species and, with practice, learn how best to neutralize the defensive capabilities of a given prey by, for example, biting off the tail of a scorpion or burying the abdominal tip of a pinacate beetle, the noxious squirt-gun end, harmlessly in the sand. This does not mean, however, that grasshopper mice are never stung by scorpions or sprayed in the face by pinacate beetles during an attack — they are. But here, too, the mice show interesting specializations, with the best evidence provided by recent studies of their interactions with bark scorpions (genus *Centruroides*).

But aren't the stings of bark scorpions potentially lethal? Some of them, yes. There are approximately 1500+ species of scorpions on the planet, roughly three dozen of which possess neurotoxic venoms capable of killing an adult human; the stings from most species, however, are basically harmless, apart from an allergic reaction, although stings from many can be painful. Scorpions in the genus *Centruroides* reflect this variability in dangerousness. There are 40 or so species, all restricted to the New World, a handful of which are among the most deadly scorpions in the world, while others possess stings no more bothersome than a honeybee. Two species, the Arizona bark scorpion and the striped bark scorpion, are sympatric with grasshopper mice in the southern US and northern Mexico, and they too reflect this interesting variability in venom toxicity. The Arizona bark scorpion, while not the most lethal of the genus, is nonetheless of medical significance as its sting can kill a human infant or young child. Stings from the striped bark scorpion are less toxic and pose no risk to humans, although it too has neurotoxic venoms potentially lethal to small mammals. And both species have very painful stings. Yet grasshopper mice eat them with impunity.

What traits enable grasshopper mice to prey on such potentially deadly and painful scorpions? Answering this question requires a quick foray into the world of scorpion toxins. Scorpion venoms are usually a cocktail of small proteins (toxins) and salts designed to quickly immobilize prey and deter predators. Bark scorpions produce toxins that bind to sodium (Na^+) and potassium (K^+) ion channels in nerve and muscle tissue, producing hyperexcitable cells that disrupt normal physiological functioning in the neuromuscular and peripheral sensory systems. The effect on the nerves and muscle in these systems is analogous to hitting the gas pedal and cutting the break line on a car. Toxins that kill animals work by targeting ion channels in the nerve and muscle tissues that regulate lung function, causing asphyxiation. Pain-inducing toxins activate ion channels in peripheral sensory neurons, initiating the transmission of pain signals to the brain.

Grasshopper mice have evolved resistance to lethal and pain-inducing toxins via structural and functional modifications to their neuromuscular- and sensory-expressed ion channels that reduce the effects of the toxins. In fact, instead of inducing pain in grasshopper mice, in a paradoxical twist of evolution, the ion channels in grasshopper mice sensory neurons bind toxins and use them to block the pain signals that the venom is trying to transmit.

Is there evidence of an arms race? Predator–prey arms races are a form of coevolution, that is, reciprocal selection, wherein a trait in the predator leads to an evolutionary response in the prey, which leads in turn to an adaptation in the predator to counter the evolved trait in the prey. Repeated iterations, a ratcheting up, generate an arms race. In the grasshopper mouse-bark scorpion system, for example, evidence that resistance by the grasshopper mouse to the pain-inducing components in bark-scorpion venom has led to selection for even more painful venom constituents in the scorpion would provide evidence of reciprocal selection.

Preliminary support of the coevolution hypothesis is provided by geographic covariation, not in venom painfulness, but in its toxicity. Mearns' grasshopper mice in the Chihuahuan Desert can feed on sympatric striped bark scorpions because the mice are sufficiently resistant to the lethal constituents in the scorpion's venom. But a Mearns' grasshopper mouse would be killed if it happened upon, attacked, and was stung by the more toxic Arizona bark scorpion from the Sonoran Desert. Southern grasshopper mice sympatric with Arizona bark scorpions are, in contrast, sufficiently resistant that they show no ill effects from multiple stings delivered by their local, more lethal *Centruroides*. There appears to be some cost to such resistance, as southern grasshopper mice allopatric with Arizona bark scorpions are significantly less resistant, perhaps as a result of relaxed selection. This geographic covariation in venom toxicity in the scorpions and venom resistance in the mice is consistent with an arms race.

Are there other animals that feed on bark scorpions? Pallid bats, elf owls, gray shrews, whiptail lizards, and ring-tailed cats are just a few of the predators whose geographical ranges overlap with *Centruroides* and that are known to feed on scorpions. Whether any of these predators actually feed on bark scorpions and, like grasshopper mice, are resistant to the debilitating toxins in bark scorpion venom awaits more detailed exploration.

Are there other venomous critters the mice feed on? There are many other biochemically protected creatures sharing the desert with grasshopper mice, including the aforementioned tarantulas and pinacate beetles, joined by, among others: a giant centipede longer than the mice, with huge fangs and neurotoxic venom; vinegaroons, a large, prehistoric-looking arachnid, protected by a spray of concentrated acetic acid (vinegar, hence their name); and tobacco hornworms, a caterpillar rendered unpalatable to most predators by the nicotine the larvae sequester when feeding on their host plant. Grasshopper mice are known to eat several of these biochemically protected prey — whether the mice use the same or different mechanisms employed to render bark scorpions harmless also merits additional investigation.

Figure 2. Mearns' grasshopper mouse eating a striped bark scorpion in New Mexico.
Photo by Jillian Cowles.

Are there any other interesting facts regarding grasshopper mouse natural history? Yes, too many for a Quick Guide! One of the more frustrating factoids, at least for scientists who study them, is that grasshopper mice are notoriously difficult to catch — not because they are too clever to be lured into a trap baited with dry cat food (they aren't), but because they are uncommon. Top-level predators are rare, in part because they typically require large territories, and grasshopper mice are no exception. While the home ranges of deer mice vary from a few hundred to a few thousand square meters, those of grasshopper mice measure in the tens of thousands. And grasshopper mice, like many predators, are solitary and territorial, which explains another curious observation — they 'howl' like wolves. It's not actually a howl *per se*, but a pure-tone whistle that they use, like wolves, to proclaim their territory. As a practical matter for the field biologist hoping to catch a grasshopper mouse or two, this scarcity of grasshopper mice means she must bait 200, 300, or 400 live traps just to have a chance of catching a single mouse.

What are grasshopper mice good for? Well, there is one aspect of grasshopper mouse biology some people might label as 'bad' — northern grasshopper mice appear to be a reservoir maintaining the plague bacterium in prairie dog colonies in the Great Plains. But the mice's appetite for grasshoppers, crickets, beetles, and caterpillars likely benefit gardeners and farmers, and one early explorer of the American west actually kept a pair of grasshopper mice in his basement as an effective form of ‘cockroach control’, opening the door to their cage each evening, closing the door when the mice returned, contentedly satiated, in the morning. And although still a long way off, the novel mechanism evolved by the mice for dealing with the intense and prolonged pain from a bark scorpion sting could lead to the development of a completely new class of analgesics, perhaps one lacking the unfortunate side effects of opiates — the benefits for people suffering chronic pain would be incalculable.

But maybe we should rethink the question. Most biologists consider *all* species ‘good’ in the sense that every plant, animal, fungus, virus, and bacterium is interesting and thus meritorious in its own right, worthy of our curiosity, investigation, and respect. Many species, if not most, may also play some critical role in their community we don’t understand until it is too late — dodos, for example, appear to have been important to forest regeneration on Mauritius, while sea otters serve a keystone function promoting healthy kelp beds in the Pacific. Who knows what critical roles grasshopper mice might play in the deserts and grasslands they currently patrol, howling?

Where can I learn more about grasshopper mice?

Bailey, V., and Sperry, C.C. (1929). Life history and habits of grasshopper mice, genus *Onychomys*, USDA Techn. Bull. *145*, 1–19.
Horner, B.E., Taylor, J.M., and Padykula, H.A. (1965). Food habits and gastric morphology of the grasshopper mouse. J. Mamm. *45*, 513–535.
Langley, W.M. (1994). Comparison of predatory behaviors of deer mice *(Peromyscus maniculatus)* and grasshopper mice *(Onychomys leucogaster)*. J. Comp. Psychol. *108*, 394–400.
Rowe, A.H., and Rowe, M.P. (2006). Risk assessment by grasshopper mice (*Onychomys* spp.) feeding on neurotoxic prey (*Centruroides* spp.). Anim. Behav. *71*, 725–734.
Rowe, A.H., and Rowe, M.P. (2008). Physiological resistance of grasshopper mice (*Onychomys* spp.) to Arizona bark scorpion (*Centruroides exilicauda*) venom. Toxicon *52*, 597–605.
Rowe, A.H., Xiao, Y., Rowe, M.P., Cummins, T.R., and Zakon, H.H. (2013). Voltage-gated sodium channel in grasshopper mice defends against bark scorpion toxin. Science *342*, 441–446.

Neuroscience Program and Department of Integrative Biology, Michigan State University, 293 Farm Lane, Room 108 Giltner Hall, East Lansing, MI 48824, USA.
*E-mail: roweashl@msu.edu

Quick guide

Poison frogs

Jennifer L. Stynoski[1], Lisa M. Schulte[2], and Bibiana Rojas[3]

What are poison frogs? Poison frogs, also commonly called ‘dart poison frogs’ or ‘poison arrow frogs’, are charismatic amphibians forming a spectacular adaptive radiation, comparable to that of African cichlids. Many of the diurnally active species have skin toxins and bright coloration (Figure 1), and display numerous terrestrial reproductive modes including elaborate parental care and complex social behaviors. The most diverse and well-studied group, superfamily Dendrobatoidea, consists of two families, Dendrobatidae and Aromobatidae, and is found from Nicaragua to northern South America. Although less popular, other groups known as poison frogs exist in South America (family Bufonidae, genus *Melanophryniscus*), Madagascar (family Mantellidae) and Australia (family Myobatrachidae, genus *Pseudophryne*), as well as two species in Cuba (family Eleutherodactylidae). Here, we focus on the traditional ‘poison frogs’, the dendrobatids.

Are they called poison dart frogs, poison arrow frogs, dart-poison frogs, or just poison frogs? There are three species of poison frog (genus *Phyllobates*) to which common names including ‘arrow’ or ‘dart’ can be justly attributed. The epithet comes from the use that some Colombian native tribes made of these species’ secretions, which when rubbed on darts provide a lethal hunting weapon. The exudate of a single golden arrow frog (*Phyllobates terribilis*) — one of the most toxic vertebrates — can kill up to six humans.

Why are poison frogs interesting? Besides being poisonous, many species display bright colors and unique behaviors. Exceptional polymorphism and variation in coloration is due to both natural and sexual selection. Predator learning and recognition, as well as mating preferences in different species for novel, brighter, or familiar colors, have both played a role in producing a brilliant spectrum of color and pattern across the family. Coloration is an honest indicator of toxicity in some species, but not in others, and is associated with territorial aggressiveness and boldness in some cases. Recently, one Peruvian species, *Ranitomeya imitator*, was found to be a true Müllerian mimic of sympatric congeneric species. In addition, the males and females of several species are territorial and have particularly good orientation and homing ability. Male communication includes both acoustic (calls) and visual (vocal sac inflation) signals (Figure 1H); each of these signals is not as effective to repel intruders as the multimodal signal.

How do they reproduce? Several species guard mates and some are completely monogamous. These strategies are associated with the most striking behavior observed in poison frogs: elaborate parental care. Parents guard terrestrial egg clutches and transport newly hatched tadpoles to water bodies (Figure 1G). Some species transport all tadpoles at once to small streams or puddles (Figure 1E,K). Other species transport tadpoles to very small pools in plants (phytotelmata; Figure 1C) where there is less predation risk (Figure 1F). Parents that place offspring in smaller pools generally transport tadpoles individually to separate pools to avoid competition for scarce food resources and even larval cannibalism (Figure 1B). Parents assess the quality and potential danger of tadpole deposition sites via chemical or visual cues. In some species, parental care goes a step further: after deposition, adults feed tadpoles with unfertilized eggs. In addition to providing food in resource poor environments, this behavior supplies tadpoles with alkaloids to protect them from predators. Hungry tadpoles distinguish between mothers and predators using visual and tactile cues, and then proceed to communicate with mother frogs by vibrating vigorously (Figure 1I), which appears to stimulate egg laying. Parental care can be performed by mothers, fathers or both parents, depending on the species.