Conotoxinology with Dr. Joshua Torres & Dr. Sabah Ul-Hasan
Ologies Podcast
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Oh hi, it's me, the guy in the grocery store parking lot who pointed out that the moon looked cool, Alie Ward. We're back with an aquatic, toxic episode of *Ologies*. It was so mysterious, so dangerous, so hopeful, we had to have two ologists for it. One studies the chemistry and the molecular composition of this very niche, but trust me, intriguing sea snail venom. And then another who investigates what microbes have to do with the whole shebang. Because there are roughly 1,000 species of cone snail. Who are they? What are they doing? They each have, perhaps, their own signature venom. And today, we're going to make you care about every single one of them, and not just because they could kill you, they could also save your life... if they don't kill you first, as one researcher found out. We'll get into it.

But first, to the lifesavers out there, thank you to everyone at Patreon.com/Ologies for submitting your questions and always supporting the show. You also can join for as little as a dollar a month. And for no money, you can rate the show, you can subscribe so that you always get new episodes. Or you can review, because you know I read them all; every single one. Like for example, such as, Steve Musical Arts, who this week left a review that said:

> *Ologies is hope and dares us to be curious instead of fearful. Thank you for the intrepid pursuit of wonder.*

And Steve, thank you. Also... this one is fearful; I'm scared of cone snails. But I'm definitely in wonder of them as well, as you will be too. Also, KL_Neuro left a three-star review because the Urology episode was skipping on you... KL_Neuro, I love you, that's a Wi-Fi and a streaming issue, AKA, that's a you problem, my babies. But if you have spotty Wi-Fi, just let her download fully, I'm just saying... love you.

Okay, conotoxinology. The word, as far as I can tell, has been used legitimately, one time in a 2001 publication called, "Conotoxins, in retrospect" which happened to be authored by a certain Dr. Toto Olivera, more on him in a bit. But essentially, I found out about it, it was on.

So, get ready to hear about patterned shells, poisoned proboscises, tong-less diving, near-death experiences, how doctors use a snail painkiller 1,000 times more powerful than morphine, what bugs have to do with it, Rembrandt's enchantment with cone snails, and why working together is better, with Conotoxinologists, Dr. Joshua Torres and Dr. Sabah Ul-Hasan.

Sabah: I'm Sabah Ul-Hasan and my pronouns are they/them/theirs.

Joshua: I'm Joshua Torres, my pronouns are he/him.

Alie: And okay, this ology, we've gone back and forth, what do you both think the best ology for cone snail venom would be?

Sabah: We were trying to figure out a one-word term. Conotoxinology came pretty close but then we also want to talk about venom microbes a little bit as well, and so figuring out how to do that, that's the tricky part. We're deferring to you Alie, you're the ology expert. [*Alie groans*] The pressure is on you. I liked the Conotoxinology one. [*"Well... it's decided then."*]

Alie: How big is the cone snail toxicology venomology community? How many people are working on this?

Sabah: Ooo, that's a good question.

Joshua: I'm pretty sure there's more than 50 groups around the world. I just moved to Copenhagen in Denmark, and we just had our first venom conference here, and I'd say there are a lot of people working in different aspects of cone snail venoms here. And in Asia as well, where actually I'm originally from, I'm from the Philippines, there's a lot of groups doing cone snail venoms.

Alie: Well, perhaps then it fairs asking, where are cone snails? Where around the world do we find these critters?

Sabah: I'm going to defer to Joshua to answer since he is from one of the hotspots for finding cone snails.

Joshua: Most of the cone snails, you'll find them in the warm waters of the world, so you're looking at tropical regions of the world. But you could also find them in temperate waters and even in the Mediterranean.

Alie: So, we would not find them, say, off the coast of California, say. But maybe Hawaii too?

Sabah: There is one species off the coast of California; that's the one I'm working on. [*laughs*]

Alie: Reaaally?

Aside: So, quick back up. At a venom conference, Sabah saw a video on brown recluse spiders and got captivated by microbes in venom. They got their PhD from the University of Merced in 2019 with the thesis, "The utility of marine snail *Californiconus californicus* as a model system for venom." And that species name struck me, because I don't want a Cone Snail 2.

Alie: Where off the coast in California? I'm only asking because I'm based in California, and because I have feet.

Sabah: You can find *Californiconus californicus,* which is the California cone snail, the only cone snail species currently known that is endemic to the California coast, so you can find it as far north as about Monterrey. But I would say mainly Monterrey area, down south through Baja California, you start to see overlap with other species there, a few other species, once you get more south.

Joshua: And the other side of the US as well, in Florida, I know you'll find a lot of them. In Hawaii, especially in Guam. I've been to those places collecting these things.

Aside: So, Joshua had been a research assistant in the Philippines and the lab there was partnered with one in the States. So, in 2020, got his PhD in Medicinal Chemistry at the University of Utah, where he met Sabah, and they both had connections through faculty and researchers there including famed Filipino biochemist and cone snail expert, Dr. Toto Olivera and Dr. Eric W. Schmidt of the Marine Natural Products Laboratory. So, their cone snail partnership was born... in Utah?

Sabah: I thought I was going to go swimming in the Indo-Pacific collecting cone snails and they're like, "No actually, we work with fishermen and they're going to give those samples for it." And I was like, "Oh, okay." [*Sabah and Alie laugh*]

Aside: But since then, of course, they've both gotten to do plenty of fieldwork and lab work. Sabah even started a group called The Initiative for Venom Associated Microbes and Parasites, which is a bunch of cool researchers helping each other out.

Alie: So, does one of you have to analyze the components of the venom from a molecular level and then do you try to grow the microbes to see what's living in there? Where do you pass the baton?

Sabah: So, in my case, I was able to get funding and support. And I did want to do things kind of from scratch, so I collected the majority of the animals myself and then I collaborated with people to do the processing, depending on what I was interested in; if it was proteomics, if it was microbiomes, if it was transcriptomics. I didn't get a chance to do as much with as I would have liked, but just trying to collaborate to paint a holistic picture of basically the venom as a microenvironment. And then I think in Joshua's work, he did a lot of really good microscopy follow-up, which is really important to kind of visualize where those microbes were in the venom.

Aside: So, those are very exquisite science terms that mean studying their proteins and what instructions their RNA is giving out. Now, what about Joshua?

Joshua: It started because I joined the ICBG group, it's called the International Cooperative Biodiversity Group program, that's funded by the NIH. And it's a really big group that does bioprospecting and drug discovery in weird places in the world. For this particular group that I was in, we were mostly interested in the drug discovery in marine animals, and this is where the cone snails come in. So, I started studying the microbes in these animals to see what compounds they can produce, and the overall arching theme of my work back then was to really figure out how are they made, and what are they making, and can we use it for something?

Alie: Let's start with what a cone snail is. I figure they're called a cone snail because of their shell. Is that correct?

Joshua: That's true.

Alie: It is!

Joshua: It is true. They got the name because of what they look like, it's a shell that looks like a cone. [*Joshua and Alie laugh*]

Alie: But don't so many shells look like cones? I mean, I feel like there's so many other snails out there being like, "Excuse me, have you seen...?"

Sabah: Yeah, that's a good point. I feel it's one of those things... and I don't know what your thoughts are on this Joshua, but I feel it's one of those things where once you see it you can't unsee it. It's just more conelike, I guess you could say, than a regular cone. There might be more waves to it or curves to it. So, I would just say it's more conelike, and once you see it, you'll go to any shell shop and be like, "Oh, that's a cone snail."

Alie: Really?

Joshua: They come in different colors and shell patterns, but like what Sabah said, they have less flair on the whorls. They're basically like a cone, it always reminds me of a Cornetto, that's basically what the cone snail looks like. If it looks like that, then it must be a cone snail.

Sabah: Once you see it, you can't really unsee it, and then you see it everywhere and you notice this thing of… they're very, kind of, clean in being this desirable color and pattern and they kind of stay that way even after they dry.

Aside: So, cone snails. I was picturing pointy, pointy sharp shells, kind of like a high heel. But no, cone snail shells, they're more like a broad V, or like a teeny waffle cone, but shellacked and patterned, and with rounder edges. Or like a Cornetto, which is a Drumstick of ice cream, I learned today. So just Google Image search it and you're going to be like, "Ohhh yes, one of those shells that you would see glued onto an accent mirror, or a lamp at your rich aunt's beach house. Got it." But with predatory venomous, sneaky smart cone snails, it's about what's inside those shells... or flooping around just outside of them.

Alie: And their venom, let's talk about why they have it because there are a lot of snails out in the oceans and lakes that don't have venom. Can you explain what their hunting style is like?

Joshua: So, generally, cone snails would have to have venom. I don't think there's any cone snail out there that doesn't have a venom. They make it in this particular organ, we call it the venom gland. [*"Naturally."*] And they use it to actually hunt either fish, other types of mollusks, or shelled things, and marine worms. So, those practically are their diet, so they would make several forms of these venoms and tailor it according to the diet that they would like.

Alie: Each individual snail can do that?

Joshua: Yeah.

Alie: Really?

Joshua: That's true. It's not just one venom in there, the gland would make several hundreds of these. So, it comes out as a cocktail of things.

Alie: Wait that's ins– that's like, incredibly fucked up and cool. That's like one of those soda machines where you're like, "Do I want a Minute Maid Light with a shot of Cherry and some Dr. Pepper?" What the fuck?

Joshua: Yeah, [*laughs*] that's true. You know, my background is in chemistry and my fascination about these snails really… The idea that these little things can actually make so many different components in a venom and tailor it according to what they want and how they actually use it, which is the really interesting part for us, for people who try to make drugs out of these things.

So, what they do primarily is to actually load the venom into what we call a radula, you could think of it as a harpoon. It's like a hypodermic needle that shoots out [*Alie laughs nervously*] and targets a fish, or a worm, or another snail, and instantaneously paralyzes them. Other cone snails would just have to open its mouth really big and lace the surrounding water with this venom and then the fish, usually fish, would just be paralyzed, and it could not move. It's like an opium den that they cannot escape and then the snail would just swallow it.

And other things that we just figured out just last year, part of the venom are also mimics of sex pheromones that the worms use, so they would hijack that horny process during a full moon.

Alie: [*laughs*] That is low, that is so low.

Sabah: They're really clever.

Aside: So, these little fuckers can shoot a syringe of paralyzing poisons at you, or they can release an aquatic cloud of sedatives and swallow you whole, or they can use venom to seduce hornt up worms and then just be like, "Psych, you're my dinner."

Sabah: So, the California cone snail, it's considered an extreme generalist. So, what Joshua was mentioning about, they can be fish hunters, worm hunters, they can eat other mollusks. So, the California cone, it's really weird in that it hunts in groups, otherwise cone snails are fairly solitary. So, it hunts in groups, it can scavenge, and then it can also eat multiple types; it can eat fish, it can eat mollusks, all of the above.

There was an experiment I did where we starved the animals and then... I always feel bad doing these experiments, but I guess it's… you gotta do what you gotta do. But we starved the animals and then we exposed them to different prey types. [*"Would you like to hear tonight's speciale?"*] And so, I was reading that they usually capture their prey within 5 to 10 minutes, and we had the starved animal as a control, just regular fed animals as another control, and then we had them exposed to three different types. One was shrimps, so those would be in one category, then we had another that was snails, another that was fish. And we see a different proteomic profile, so that corresponds to their venom profile, and that was only after 5 minutes of exposure. But at an individual level, they can basically gear up their little harpoon and get it lodged and ready for whatever they're wanting to eat, which is an interesting thing.

Alie: This harpoon, you mentioned it was a radula. Is that essentially a tooth that they're using as a harpoon?

Joshua: You could think of it, but it's generally made out of chitin so it's like a harpoon that's hollow inside. You can think of it as a hypodermic needle where they could load the venom into that thing and it ejects out; it comes out of that really long proboscis and ambushes a fish or something like that.

Sabah: Yeah, I like to think of it, if you look at an aquarium and you see the little snails just scraping off the algae, just to piggyback off of Joshua, that's the radula. It is different from a tooth, but I guess you can think of it as it's scraping stuff off and using it to eat. It's some kind of tool that helps them eat.

In the cone snail's case, it's like a little purse, the radula sack, it's a little purse it carries around, filled with little harpoons, and then it gets one ready to lodge. Or depending on its predatory scheme, if it's using the netting scheme that Joshua mentioned, or another scheme, could be slightly different.

Alie: Why isn't every school team named The Cone Snails? What a little badass.

Sabah: That's what we want to know.

Alie: [*laughs*] I love that that's what you're investigating, is why doesn't every high school archery team or football team...? [*laughs*]

This is amazing. So, of course it's easy to get obsessed with them, which is good for two people who research them because day in, day out, it's cone snail o'clock for you. But when we're talking about this incredible ability to dial in the venom that they want, how do the microbes come into play? What's living in the venom?

Joshua: I've studied a good deal of what kinds of microbes can be found on every conceivable, dissectible part of a cone snail. The venom gland was really interesting for me because there's some form of diversity there, but there's one consistent group of microbes that's always in there, regardless of where you get the species. For the same species that you'd get from Hawaii, or in the Philippines, or in Guam, you'll find the same microbe there. We look at where exactly they are localized in the venom duct, it's a really long duct anyway. I did sections of that, did microscopy, and you know, they're there.

But what they're doing exactly is still a mystery, for me at least. [*"What are you doing here?" "What are YOU doing here?"*] I don't really know what they're doing there. It's almost tempting to suspect that they might have to do something with venom production but that remains to be tested.

Aside: But even he isn't sure, and he is one of the world's experts in this, having authored the 2021 paper, "Small molecule mimicry, hunting strategy in the imperial cone snail, *Conus imperialis*," which explains that fish-hunting cone snails use venom that targets vertebrate ion channels and receptors, which is why the FDA and the pharma world sees promise in similar chemical pathways for pain medicines.

And one article which was in *The Atlantic* was written by Katherine J. Wu, and it bore the headline, "Cone Snails are Liars and Murderers: They lure their prey with the promise of sex and then kill them cold." And in that article, they of course quoted Joshua who said, "Cone snails have mastered chemistry. They are smarter than we are." And I'm starting to believe that too.

Sabah: So, Josh's paper is really cool and extensive, so I definitely encourage people to check it out, and he's a nice person so if you have any questions just ask him. Eric is also pretty nice. So, basically, from my end, I was coming in a little bit on the microbial ecology side or like, that was the angle I was taking, trying to collect the animals from the field, focus on the California cone snail species as a potential model system for looking at venom microbes, and then seeing if that aligned, generally, with what Josh was seeing too.

It was exciting in that I also kind of independently was seeing that there are definitely microbes you see only in the venom that you don't see in other parts of the body, that you don't see in the seawater or the sediment, and these animals, they can bury in the sediment too. That's why we just want to encourage people, you know, yeah, venom microbes! Because there's very few venom microbiome studies generally, which is crazy when you think about, there's hundreds of thousands of venomous animals, there's so many different types of microbes out there, and we know so little. Maybe there's five explicit venom microbiome studies, one just came out this past year. But there's very few that are these comprehensive, high-throughput sequencing, venom microbiome studies, and Josh's is one of them which is great.

But then also, in terms of, what are they doing there? So, you see certain groups that are in certain parts of the venom gland and so like Josh mentioned, it's really long. I got curious and if you stretch out, at least for a California cone, if you stretch out the venom ducts of the animal, it ends up being two to three times the size of the animal.

Alie: Oh, wow!

Sabah: So, California cone, it's probably on a range of an inch to three inches, depending on where you go. So, if you stretch these out, it ends up being two to three times the size of the animal. And then think about what's in the human body, what is really, really long if

you stretch it out? The gut, the GI. We know a lot about human gut microbiomes generally at this point, but we know very, very little about venom glands and venom microbiomes, which is kind of interesting when you think about this parallel of the venom gland is an incredibly specialized organ, convergently evolved across very different animals; you have snakes, you have spiders, you have cone snails, you have marine, you have terrestrial. They're very, very different, and yet, you still see these very specialized organs, and yet we only have a few studies that are explicit venom microbiome studies.

So, going back to Josh making the comment of what are they doing there? So, one interesting thing that is speculative I would say, still, is with the California cone, I was trying to do kind of a multi-omic study – so you have genomics, you have transcriptomics, et cetera, et cetera – but what I was able to do with the time I had was really looking at the microbiome or kind of a general microbial community.

Aside: So, Sabah's analyses focus not just on the chemistry of the venom, which can include over 100,000 different bioactive compounds, but also, which tiny, tiny critters, which microbes, are hanging out in the venom? And what molecules and metabolites are floating around?

Sabah: So, what we saw, there was one experiment that I did where I wanted to basically sterilize the animals and see what happened when the animals were in a sterile environment and what microbes they retained. So, you can think of this as analogous to, if you go to the hospital, hospitals are very sterile environments. And then in aquaculture, people use antibiotics for making sure that the fish are healthy enough, or don't get sick, so that they can be used for seafood. So, one of the main antibiotics people use in aquaculture is tetracycline, so that's what I used for my experiment.

So, I had three groups, three categories. One was just a wild type with the natural seawater, I was able to use a facility in San Diego thanks to collaborators there, where I had access to fresh flowing seawater and the population of the animals were also from San Diego. So, I had fresh flowing seawater and then I had sterile seawater that I synthetically made and then introduced to the animals, so it's clean and there's no microbes in there, hypothetically. And then I had another category that was the sterile sea water with the tetracycline added. And then we looked at what the microbial profile was, what the proteomic profile was for the venom, and what the metabolomic profile was.

And then I was looking at the results and I was like, "This can't be right, did I contaminate something?" So, I added tetracycline, the antibiotic, to only one group and I was seeing tetracycline in the metabolomic profile actually be present in the wild type controls as well, the wild type and the sterile controls. I was like, this can't be right, I'm sure I didn't contaminate it, what's going on? And then I was like, wait a second, how is tetracycline made? It's made from *Streptomyces*, which is a part of this group actinobacteria. And then I looked at the microbe profile in the cone snails and I also saw *Streptomyces*.

So again, this is a speculative, it needs to be reproduced and re-done, but it was kind of a hypothesis that potentially, the microbes could be contributing to keeping the integrity of the venom gland to prevent other microbes from coming in and basically messing up the environment. So, if they're naturally making tetracycline, which is this antibiotic, in the venom gland, then maybe they're keeping other pathogenic microbes out, as competition.

Aside: So wait, they didn't contaminate their sample with tetracycline, the call was coming from inside the house. But yes, making microbe friends means cone snail DIY antibiotics. And Sabah said that the researcher Dr. Michelle Quezada has done great work in this area and a lot more experimentation can be done to figure out why they do it, why the microbes are making tetracycline. They could be making antibiotics to keep their niche competition-free of other microbes; they could be making compounds that enhance the venom itself; or they might serve as natural medicines for the cone snail to have a clean venom duct... which is why medical chemists, and me, are getting stoked. So, antibiotics, possibly anesthetics or analgesics. I mean, don't kill me cone snails, but please kill my germs and my pain.

Sabah: So, I was really curious about why are there, basically, little to no, or so few, venom microbiome studies? Right, because coming in from the angle of where I was really interested in microbes, microbiomes, microbial ecology, I was like, "What? Microbes are everywhere!" Why are people not looking at venom?

So, generally, people in the venomics community are really interested in drug discovery and natural products, and in tandem, another big issue right now is antibiotic resistance, right? So, you have these groups, *E. coli*, staph, et cetera, they're called the escape groups and you see them a lot in hospitals, where there are superbugs that are antibiotic resistant, and you have to take a lot of different combinations of antibiotics to kill them off in hospital settings. So, people are really trying to look for solutions for this. I think one popular solution that's coming is phage therapy.

Aside: Phage therapy, side note, is when specific antibacterial viruses are deployed, kind of like tiny hitmen for bacteria. So, that's one idea. But...

Sabah: But then also people are looking at other types of natural products from different sources such as venoms. So, when you look in the literature, one thing that comes up a lot in the literature is that people are looking at venoms as a source for killing off these antibiotic superbugs in hospitals. But then they're doing these experiments where they're taking the venom and they're saying, "Can I kill off this strain of staph from a hospital?" But they're not looking at what's already in the venom. So in these studies, they're isolating certain venom toxins but they're not looking at the holistic picture, which makes sense in the context of what they're doing, but then there's just a whole other side of the story that could also be helpful in this fight against antibiotic resistance.

So, that's where we're thinking that, okay maybe there are so few studies on this topic because people have this cultural thought that because we've found so many compounds in venom toxins that have antibiotic properties, that means the venom is sterile. And that's just not true from what we know from a microbial perspective because microbes live everywhere. So, just kind of, having more of these studies pop up to show that okay, there are microbes there and what are they doing?

Joshua: We have almost a decade of work on the microbes of not just cone snails but a lot of different snails in the marine world. And on the other hand, we also work on the venom itself which is, of course, another different field of work, not for the antimicrobials but for what Alie alluded to for analogy's sake, the venoms are really nice platforms to build peptides that can be used to treat pain and other types of diseases, human diseases. In fact, one of the earliest compounds from the marine world that made it into the clinics is actually from a cone snail. [*"You don't say."*]

Aside: So, this is called Ziconotide, or Prialt, and it works by blocking calcium channels in these pain-screaming, nerve cells. And it was formulated from discoveries made right in the same University of Utah lab. It was approved by the FDA in 2004. Now, can you pick some up at CVS alongside tampons and chocolate? No, you cannot. It's administered directly into the spinal fluid, straight to the dome. But it's said to be 1,000 times more powerful than morphine. From a frickin' cone snail!

Joshua: Prialt, it's just short for primary alternative for morphine. Unlike opioids or morphine, it does not develop tolerance which is really great. A lot of us are really finding the next Prialt and even the other types of peptides that are found in the venom like insulin, even certain types of hormones that are similar to humans are being clinically developed for medicinal purposes.

Sabah: You know, evolutionary medicine is becoming more popular, which I think is really exciting and really great. Because when you think about it from an evolutionary biology perspective, you know, these animals, these cone snails, they're considered in the category *Neogastropoda*, which means new gastropods, or that they're more recently evolved, compared to others that are evolutionary relatives. You have got spiders, snakes, all sorts of groups that kind of range across this evolutionary timeline. These are animals that have these systems that have been evolved for millions if not hundreds of millions of years. Of course, there's going to be really good resources in there that we could then apply to these more recent, within 10, 20, 30 years for antibiotic resistance issues, for example, that we can use to tackle, that have already been, you could say, perfected, in an evolutionary context.

Alie: I mean, I was here thinking we were going to learn about how they can kill us, but really, they can end up helping us.

Sabah: Kill and cure.

Alie: Yeah. Can I ask you some questions from listeners?

Joshua: Sure.

Sabah: Sure.

Alie: Okay, amazing.

Aside: And before we dig into your questions, let's spend some money on some good causes chosen by the ologists. Sabah selected HelpingWomenPeriod.org, which is a nonprofit committed to supplying menstrual health products to people that menstruate who are either unhoused or low income.

And Joshua chose the OCA National Center. Founded in 1973, the OCA Asian Pacific American Advocates is the second oldest civil right organization dedicated to advocating for social, economic, and political well-being of all Asian Americans and Pacific Islanders. And May happens to be Asian American and Pacific Islander Heritage month, which celebrates community milestones but also remembers the adversity endured in the past and today. So, I will include links to both of those great charities in the show notes. Those donations were made possible by sponsors of the show.

[*Ad Break*]

Okay, you had questions patrons. Let's dive into the cone zone.

Alie: Here we go, you ready?

Sabah: Let's do it.

Joshua: Go!

Alie: Okay, they're not scary, they're not as scary as a cone snail might be. And on that note Jess Swann wants to know: Do you have a sense of where the cone snail sting might fall in comparison to the jellyfish? I guess there's a Schmidt Sting Pain index. But, any idea, how much does it hurt? Have you ever been stung by one?

Sabah: I have not.

Joshua: I haven't either. But I don't think you'd want to be stung by cone snails just because there are certain species of cone snail that can actually kill people and that have been recorded.

Alie: Really?

Joshua: There's no antivenom for that, unlike snakes. So, even if you're really close to the hospital, if you got stung by a geographer snail, *Conus geographus*, that's going to kill you.

Sabah: And that's one that's nicknamed cigarette cone, right?

Joshua: It's like a colloquial thing that they say, if a cigarette snail or a cigarette cone, just because...

Sabah: You can enjoy a last cigarette before you die. [*Alie lets out a small cry/laugh*]

Joshua: But I think you'd actually last more than that. I don't know how quick a cigarette is actually, maybe like 15 minutes?

Sabah: I think in terms of lethality to humans, the Irukandji or the box jelly is the quickest death for humans, in terms of lethal dose. And then cigarette cone is I think the second most.

Aside: For more on jellyfish and their venom, you can see the Medusology episode with Dr. Rebecca Helm, and the companion episode, Toxinology about jellyfish venom with Anna Klompen. It will bust so many myths, especially about peeing on your friends' legs, and I'm going to link those on the web page for this episode.

But yeah, the box jelly sting will escort you to heaven in about two minutes. But what about this cigarette snail? Okay, so I looked it up. The average amount of time it takes to smoke a cigarette is six minutes and the good news is, if you do get harpooned by one of these *Conus geographus* snails, in a shallow reef somewhere in the Indian Ocean, or off the coast of Australia, or the Red Sea, or in the Indo-Pacific region, you can actually smoke at least 10 cigarettes, maybe even 50 cigarettes, because it actually takes about one to five hours to die. That's great! What a relief.

Sabah: But then California cone, if you get stung by a California cone, I have some friends that have been, and they said it's like a bee sting. I haven't ever been stung because I choose safety. But yeah, there are people out there who do... there's a subgenre of people who are really interested in intentionally injecting themselves with venom – some of those people are scientists, I don't know – but that is some controversial stuff. I choose life, so I don't do that.

Joshua: If I may add, because this is sort of a really interesting question because people would say that cone snails are deadly. I'd like to add, most of the cone snails that would eat fish or whose diet is mainly fish are the ones that's going to sting, hurt really bad. It's just because the components of those venoms, snail-hunting cone snails can actually be good

substrates or ligands to the kind of sodium channels or receptors or target that we, as humans, also have.

Aside: I didn't know what any of those words meant, so I was just going to cut that part out, but you know what? We're here to learn some shit. So, a ligand is a chemistry term, and it means a molecule or an atom that binds things together. And a substrate is a molecule that an enzyme acts on. So, Dr. Torres, someone with a PhD in medical chemistry is saying that cone snail venoms that act on fish can also act on us, because we're made of the same stuff.

Joshua: Our receptors are related to those receptors in fish. So, you'd expect it to be more lethal or potent when you get stung by a fish-hunting cone snail versus a worm-hunting cone snail.

Sabah: Evolution! Vertebrates.

Alie: Yes! [*laughs*] And do they use it for self-defense at all, or is it just predation?

Joshua: So, most of the known documented cases of cone snails that actually harm humans is because people would pick them up, or I guess some stupid person would look at it, "This really looks good so I'm just going to take this out while diving, put it under my wetsuit." That's going to get you into trouble. But if you work on the snails, they have certain types of personalities really. I've observed that for the years that I've been looking at the snails.

Alie: Really?

Joshua: Yeah! There are snails that are quite aggressive. And these are the really venomous ones; the geographer snail and the magician snail, which is *Conus magus*, they are really temperamental, I think. I guess that's the word. When you really poke them or hold them, you'd see the proboscis, that's where the harpoon comes out, would literally be pointing where it feels like the threat is coming from. But most of them are really docile, the worm-hunting ones, if you touch them, they would just hide in their shells. The shells themselves are really tough for some of these species. So, they would try to just be hiding if any danger. But for some, they're really aggressive and they're going to put up a fight.

Aside: Which is why researchers when collecting, use tongs: keeping their distance, preserving their lives. But what if you are clueless and/or tongless? Well, patrons including Lisa Inglese, Christian Krupp, and first-time question-asker, BlueRehn, AKA, Emma Wren asked about first-aid tips, if the grim reaper happens to saunter up to you with a cone snail in his pocket.

Alie: Gerald Thompson wants to know: What should you do if you are stung by a cone snail? Don't pee on it, you don't have to pee on it. Do you have to pee on a cone snail sting or no?

Joshua: There are no standard protocols for life-saving measures if you've been stung by one. I know there is a protocol that has been developed at the University of Utah Hospital because there was one case where someone actually got stung by the cone snail.

Sabah: In the lab... I think I did hear about that. [*laughs*]

Joshua: Yes, and I think what they did, the hospital – unlike snakes, there's snake antivenom – I think what they did was to rehydrate, or I think they had to wait. [*laughs*] If the person is going to make it or not.

Sabah: Yeah, I think you're right. I think I remember because I think I was at UU when that happened actually, and I think I might remember who it was. [*laughs*] Oh my god, just sit. But yeah, we could probably ask them.

But I would agree with Josh. I would say the nice thing in this is that it's one of those things where it's like, enjoy and look at nature but don't touch, right? It's one of those things where if you leave them alone, they leave you alone. For the most part that's how it is. Josh mentioned there are ones that have personalities but unless you're going and diving or snorkeling and you're touching everything, and you're really low to the ground, it's very low risk. A lot of these cases where people get stung it's because they pick something up, they want to take it home. It's one of those things, just respect the environment, that's what I would say, and you'll be fine.

Joshua: And you really have to think, it's a very energetic process, they're going to use a lot of their resources in trying to come up with this venom cocktail, and they would not just use it on something that's really big that they could not even swallow, like a human or something like that. [*all laugh*] That would take a lot of venom to knock a human out. So generally, they would try to evade danger into the shell. And they're really docile, except for, really, when you provoke them.

Alie: That's good to know. They're like, "If I want to protect myself, I'm not going to give you my Minute Maid Cherry-Dr. Pepper cocktail. I'm going to hide in this incredibly tough shell I have. That's why I have a shell."

Joshua: [*laughs*] Exactly, right. "But if you're going to pick me up and do something where it's crushing my shell or something, you're going to have it."

Sabah: And to that end too, I was wondering, with the California cone snails, I had all these questions of how often do they even eat? They're a pretty hardy species. And I'm not encouraging anything here, but they're a pretty hardy species. They're pretty tolerant, they can withstand a lot. If they're living healthily off the LA coast in whatever waters, they're doing okay, I guess.

But I kind of tested a little bit and you could think of them, similar to a boa or something where they don't seem to need to eat that often. I think to Josh's comment, that it does take energy for them to make these venoms, and so okay, how often do they actually need to use that and what is that process for them? That's something to consider. Similar with snakes too, it's like, how much do they want to be using that all the time? Just respecting animals and not provoking them is a good way to go. It's low probability. With stingrays for example, it's usually because you're not doing the shuffle and you step on one by accident, which I think is a reasonable reaction. If I got stepped on by something, I'd probably fight back a little bit too.

Alie: It's so funny that it's called "the shuffle." [*laughs*] It's something that marine scientists just know about, you know? [*Sabah laughs*] The shuffle.

Aside: Looked this up, and yes, keep your feet in the sand as you walk because, one, the vibrations will scare the stingrays away. And two, you don't want to Godzilla down onto an unsuspecting flippy flappy, who is forced to say, "No, dude" via their venomous tail spines. Don't surprise them.

Also, I did reach out to the researcher who was stung. I got their name, I found their email and confirmed that yes, they are okay, they preferred to remain nameless but told me – I got the whole scoop – that they were studying the fish-hunting, *Conus magnus,* and

one managed to land a harpoon right through their latex glove, which is unsurprising they said, because they can penetrate fish scales.

At first it felt like a bee sting, but they immediately knew, "I am in life-threatening trouble," because no antivenom exists. They had numbness and paralysis of the stung hand, and they felt it progressing into their arm when they were getting to the ER. And they said that they lost 30-40% of breathing capacity during this episode and had a really dangerous heart rate, all over the place. But they say that they survived because, luckily, they just must not have gotten a lethal dose of the venom and they had the ER and the medical center right there, which were ready to intubate them in case they stopped breathing or in case their heart stopped.

So, they say they barely survived and let that be a lesson: if you work with cone snails, always be careful; and if you see a cone snail, just leave it be. But what a champ, what a story to live to tell.

Alie: We mentioned Anna Klompen who is a Toxinologist who was in the Jellyfish Venom episode and in all caps wrote in: I'M SO EXCITED ABOUT THIS. And wants to know about the process of "milking" the venoms from these animals. And Summer Foovay said: I'm sure we've all seen the videos of rattlesnakes being milked, but how do they extract snail venom? And Julie Burton wrote in and said: There's a lab in South Carolina that milks cone snails for venom and even weirder, the cone snail has learned to trade the venom for food... My god, I had no idea, when you say weird, you are not fooling around. Have you heard of any of that? How is the milking happening?

Joshua: So, there are two ways to actually milk, that I know, two ways to milk venom out of the cone snail. First requires that you actually have to sacrifice the cone snail. You open them up. I guess that's a really safe one because if you want to take out the gland and work on it, the snail has to be dead, at least preventative measures for you being stung by a snail.

We haven't really described what the venom gland is, but you can picture it like something as long as a spaghetti noodle and that has a kidney bean at the other end. But the venom itself is made on that really long spaghetti, the kidney bean. We think it's just some form of muscle that can contract and push away, you know, squeeze out the venom into those radulas, into those hypodermic needles. But the venom itself, the fluid itself, is found in that spaghetti noodle. So, you open up one snail, take it out, and just squeeze it through. That's how you get most of the venom.

And the other way that the commenter was alluding to is milking it from a live cone snail. So, what they do is they get an epitube, it's just a small tube, they actually put fish in there or something, usually it's fish meat, and then wrap one end of the tube with the plastic film. And that's how the cone snail would realize there's some form of food in the epitube, it bites that film that covers the lining of the tube and milks it out.

Aside: So yes, the old, "Hey, you want a snack? JK, it's a tube covered in Saran wrap. Thank you." Now, do cone snails have enemies that are not researchers trying to milk them? Well, patron Eli Jonathan had a two-part question. Firstly asked: WHAAAAAAAT? Secondly asked: Do they use their venom on other snails (be they cone snails, or vanilla, non-venomous ones)?

Alie: What about other cone snails? Are other cone snails susceptible to being venomized? Or are they so immune that it doesn't even phase them?

Sabah: You mean attacking each other?

Alie: Yeah. Is that used in mating at all? Is there an aphrodisiac?

Joshua: The other type of cone snail, the one that actually hunts for other gastropods, their venom is specialized for hunting other mollusks underwater, including other cone snails. We've actually seen this in laboratory settings wherein you accidentally put a snail-hunting cone snail in another tank that has a snail in it, and it actually eats that cone snail.

Alie: Oh wow.

Joshua: So, you have to be really careful when you have a collection and you have live snails, bringing them into the lab. You really need to separate those snail-hunting cone snails from the rest of the cone snails because they're going to eat it. So, the worm-hunting snail would go well with the fish-hunting snail, but never with snail-hunting cone snails because you're basically giving them food. [*"Yeah, but who wants to eat snails for breakfast?"*]

Alie: Well, you know, on that note of eating cone snails, Timothy Hwang, Kelley Uhlig, and Talia Dunyak all wanted to know: Can we eat them? Are they tasty? Talia wanted to know: If I eat one, would it kill me or just be vaguely spicey?

Joshua: Yes, you can eat cone snails, I've tried it before.

Alie: Whaaaat?

Joshua: Yeah! But not all parts of it. You can't eat shells I guess, right? [*laughs*]

Sabah: Only eat the venom. [*all laugh*]

Alie: Well, if anyone is going to be prepared to actually cut that up with a scalpel and take out the venom, it would be you, Joshua. Who else is going to be in the kitchen like, "I got this, I got this spaghetti noodle filled with poison, and just gently put that aside"?

Joshua: The edible part, at least from my experience, was actually the foot of the cone snail.

Alie: That makes sense; that makes sense.

Joshua: So, that's actually a really nice part of the snail that people can eat. You don't want to eat the stomach and stuff like that. But the foot is something that you can eat from the really big snails like the geographer snail. And they taste like any other mollusk that we eat, like a squid, or the tentacle of an octopus. The texture is like that.

Alie: A little chewy.

Joshua: Yeah, they're chewy.

Alie: I'm glad that at least one of us on this call has eaten them, so we know.

Sabah: I would also caution people because there are certain species that are endangered, or they take a while to develop and things like that. So, just like with other seafood, I would encourage people... California cone snail is an incredibly common species, you can find it pretty much anywhere, you don't have to worry about putting an end to its population any time soon. There are some papers that have come out that even with research that scientists have done, we've made a dent in cone snails and their populations from all these collections we do for our research. So yeah, I definitely encourage people to check that out. The IUCN website is a good place you can see if you want to try a cone snail and see that it's going to be okay to eat them without feeling as much guilt.

Aside: So that is the IUCN, the International Union for Conservation of Nature, which is a global authority on what species are doing okay and which ones are getting a raw deal, from species of Least Concern, to Vulnerable, Endangered, Critically Endangered, Extinct in the Wild, Extinct, et cetera. And this website, I poked around, it's kind of like a sad yearbook, checking on people's statuses. But I was relieved to see that a lot of the cone snails seem to be doing okay. But for inexperienced hunters, I would not put them high on your list of favorite munchies.

Joshua: It has been something that has been done in the past. Culturally there are places in the world that would actually eat them, like the Philippines where I grew up. And even cone snails have been part of culture already, they've been used for jewelry, as means of money, and even Rembrandt has a painting, has an etching of a cone snail.

Alie: Really? Where did he see a cone snail? When was that guy out hanging around cone snails?

Joshua: Cone snails were mostly, like, prized possessions because it was really hard to trade something from outside of your... that's how they actually got these snails before. It's an etch by Rembrandt, it's called The Shell. [*laughs*] And it's the only still live etching that he did, it's a marbled cone, it's *Conus marmoreus*.

Alie: Wow, that's a great pop cultural reference.

Joshua: There's a lot of pop cultural references of cone snails, even dating way, way, way, way back. Cone snails were even expensive back then, like certain collectors and shell items would actually fetch so much. There's a species of cone snails... we're really digressing with the question.

Alie: No, no this is a great question. Mary C wants to know if you're aware of any movies, books, et cetera, where cone snails are used as a plot point and if it was realistic? So, anything in pop culture that's cone snails, we're here for it.

Joshua: Okay, so I'll continue. So, shell collectors, there's this particular cone snail species, it's called *Conus gloriamaris*, or Glory of the Sea. It's so nice, it's like a mathematically perfect cone snail, they would say, if you look it up. It used to fetch, like, back then... the price, if you compare it to now, would be around a million US dollars because it was so rare. [*"I'm rich."*] But then in the 1960s, they actually found out there's a lot of these in the warm waters of the Pacific. [*Alie laughs*] But they're still expensive a little bit. Right now you can see them on eBay, they would fetch less than a hundred dollars [*"I'm not rich."*] per shell. But that was the most expensive cone snail, *Conus gloriamaris*.

Alie: The Beanie Babies of the mollusk world. People are like, "This is going to be my investment for retirement."

Joshua: People don't know about this, or only a few people know about this, I guess. There was a mention of cone snails in Jurassic *Park*, the movie.

Alie: Really? [*Joshua laughs*] Really?

Sabah: Oh, I need to rewatch that.

Joshua: Yes. There was a part, I think it's *The Lost World,* the newer ones with Jeff Goldblum. I think they were trying to kill one of the dinosaurs and this one guy actually gave him a gun and it has been loaded with a toxin from *Conus purpurascens*. It's supposed to kill the dinosaur. [*everyone laughs*]

Sabah: I love that.

Alie: That's really cool.

Sabah: Some scientist was like, this is a really good... what's it called, Easter egg?

[*clip from The Lost World:* Jurassic *Park*]

Eddie Carr: Lindstradt Air Rifle. Requires a subsonic Fluger impact delivery dart.

Ian Malcolm: Does it work any better than your satellite phone?

Eddie Carr: That's funny. I loaded it with the enhanced venom of Conus purpurascens, South Sea cone shell. Most powerful neurotoxin in the world, acts within a 2,000th of a second, which is faster than the nerve conduction velocity. So, the animal is down before it even feels the prick of the dart.

Ian Malcolm: *Is there an antidote?*

Eddie Carr: What do you mean? Like, if you shot yourself in the foot? Don't do that. You'd be dead before you even realized you had an accident.

Joshua: The way they delivered the line was so convincing, but totally BS.

Aside: The world needs an action hero who uses weaponized cone snails. Am I right? And both doctors agree. Sabah says that both they and Joshua are available for consulting and also nominates comedian Julio Torres to be that action hero, which they say would be really sweet. Speaking of sweet...

Alie: Last listener question, Julie Burton wants to know: Is it true that some cone snails shoot insulin at prey fish to make their blood sugar plummet? And also, how are they seducing each other? Is it through a similar method?

Joshua: We'll go with the easy one first, the shortest answer. For how they would attract... Cone snails are hermaphrodites, so they would just lay eggs by themselves. [*laughs*]

Alie: Really?

Joshua: So, there are also instances where there are male and female...

Sabah: I think California cone are male and female, yeah.

Joshua: But have you seen it mate? Nobody...

Sabah: So yeah, I have seen... Basically, they just have like a cone snail orgy. [*laughs*]

Joshua: Oh wow! [*everyone laughing*]

Sabah: You'll see piles of them. [*"That's cool, where's the party?"*] Whenever I've seen it, it's usually between, I would say, April to June that you see them in the water, there are just these piles. [*laughs*]

Alie: Wow.

Sabah: And then you see them following each other's traces too, the little slime trails. Because they are a bit more social, I would say, versus the other cone snail groups. They do seem to kind of socialize. They hunt in groups so that might be a distinction that I would say is a little unique from regular cone snail groups. But they do follow each other's trails, I've noticed.

Alie: That's so cute. So cute!

Joshua: And to answer the other question, for the insulin. That is true; they make insulins. They have endogenous, the insulin that they use for this system, but they've also recruited this insulin gene that they make for themselves into their venom ducts and evolved it to look like insulin of a fish. And they use that as part of their venom to actually cause hypoglycemia in their prey fish.

So, what we think is happening, or how they use this is that they would make those fish-like insulins that have been weaponized, this is like the first instance that an insulin was weaponized by a predator. So, they open their mouths, and they just lace the water around them. You could imagine that the insulin, because they target fish, it would just go through their gills, directly to the bloodstream, and would just cause the hypoglycemic shock. You should see the videos of this wherein the fish is just like… not a zombie, but you know, it's just not moving. The mouth of the cone snail is so big, it's so impossible that the fish could not see it, the eyes are still open, you can still see the gills breathing, the eyes moving, but it's not swimming away, and it's slowly being engulfed by this really big mouth.

Alie: Wow, that is bananas. Such cool creatures! I didn't know that I had a favorite snail. Now I do, you guys!

Sabah: That was our mission this entire time.

Alie: I'm Team Cone Snail.

Joshua: You're Team Cone Snail now. [*laughs*]

Alie: Last questions I always ask, there must be something that sucks about them, there must. Or something that sucks about working on them. Any petty annoyances you have? Complaints you'd like to file with the cone snail department?

Joshua: I think I have one, if Sabah doesn't have any. I wish they would produce more of the toxins because you know, they produce so little and we have to study them, we really have to stretch out the venom for science.

Sabah: If they could just make their own cell line for us, that would be really helpful because I don't want to go through that work. And then you know, we don't have to kill them really as much, and they could just... you know, if they could just work on that in the admin department, that would be good.

Aside: Now, for Sabah, having started in Dr. Toto Olivera's lab with molecular biology and then entering the fields of biochemistry, neuroendocrinology, microbial ecology, venom microbes, and even biomedical database creation, they say the most exciting aspect about their job is collaboration with other scientists. And while cone snails may be called liars and murderers, other scientists are your friends.

Sabah: A good piece of advice that a mentor had told me was, you know, when you're doing something, just let people know, because then people know you're doing it and even if something happens, where somebody publishes on the same stuff you're working on, there's always more ideas and you're going to learn a lot more than what you would just on your own. I think that's really good advice, especially now that I basically do all my research just open source and open to the public.

I think for me the really exciting thing about this, which is maybe not specifically on the cone snails, but the really exciting thing about this for me has just been... I just started asking around, I would read a paper and cold email people or be at a conference, I'm like,

"Hey, I'm looking at microbes in venom, if anyone out there wants to do this let me know!" And you know, that's how I chatted with Josh, that's how I chatted with a lot of people in the venom microbe group that we have now. People have just been really great and open. For me, it's almost like a reinforcement that sharing knowledge and being collaborative is really in the best interest of good science as well. For me, that's a really exciting part, because at the end of the day it's about the science and I think good science comes from being open about this kind of stuff and it's been really exciting.

Aside: Hence, they started The Initiative for Venom Associated Microbes and Parasites, because the more we help each other along the way, the farther we'll all go. We're one big social pile of snails. Now, what about Joshua?

Joshua: My life's goal, really, in trying to study these things is actually to discover compounds or peptides that are medically useful for humans. Really what drives me every day to go to the lab are those tiny... not tiny, but seldom once-in-a-lifetime moments, when you get to discover something. That's a really, really good feeling. I remember when I had elucidated my first new molecule, when I understood what the pheromone mimics were for it was just like... for the first time, nature shared with you her secrets and nobody in the world knows about it but you.

Alie: Oh wow, that is so cool.

Joshua: Right? I remember it... It dawned on me at like, 3am. I was in Salt Lake, I could not sleep. My brain was like, over-sensitized. I couldn't sleep because I solved something, I solved something. And probably nobody cares about it in the world [*"I care. I care a lot."*] but that kind of fascination was really... was a high. It was enough for me to go for another year with the series of frustrations, you know. I go to the lab, ending up with bad results… I eat frustration for breakfast, I would always say that. [*Alie laughs*] But those once-in-a-while discoveries... Augh, it's going to wipe it all away, those frustrations. I think that's why I really like doing this.

Alie: Oh my gosh, what good life advice is: collaborate, reach out, eat frustration for breakfast, and just keep going. This has been so, so fun. I am 100% on your cone snail PR team now; if you need anything, let us know. I think you just turned a lot of people into cone snail fanatics.

So, ask quality people, aquatic snail questions. Really, you have nothing to lose and all of the caution to gain. So, thank you, Dr. Ul-Hasan, Dr. Torres, and all the researchers and cone snails out there who are making better medicines for us. There's a link in the show notes to our website at AlieWard.com/Ologies/Conotoxinology and that will have links to research papers, and social media handles, and the charities the ologists chose, and more.

And we are @Ologies on Twitter and Instagram, I'm @AlieWard on both. You can join us on Patreon.com/Ologies to submit questions for the ologists, it costs a dollar a month to join; our hearts are cheap. Also, hello the *Ologies* Podcast Redditers, and the *Ologies* Podcast Facebook page. That's adminned by Erin Talbert, with help from Shannon and Boni from the podcast *You Are That*. Thank you to Emily White of The Wordary who makes and oversees the transcripts, and Caleb Patton who bleeps episodes. Those can be found for free at AlieWard.com/Ologies-Extras. Susan Hale and Noel Dilworth handle so much *Ologies* business from scheduling to accounts payable. Thank you, Zeke Rodrigues Thomas, of Mindjam Media for handling the shortened, kid-friendly *Smologies* episodes that come out every few weeks. Apologies to him that we're a little behind

because of some family emergencies. Thank you all for your patience on that. Steven Ray Morris assists on those. Thanks Kelly R. Dwyer for website design; she can make yours too. And giant love darts to lead editor, Jarrett Sleeper of Mindjam Media, who puts these all together each week. Nick Thorburn made the music.

And if you stick around to the end, I tell you a secret. And this week it's that I just found out... Nobody ever told me that when you do laundry and you have that sticky cup of soap that you use for your detergent, apparently you can just throw the cup into the washer with your clothes, especially if it's one of those really rubbery silicone ones, you just toss it in there and then you don't have a drippy cup, it just gets cleaned in the wash. Nobody tells us this shit! Nobody. It's boggling. I'm forever changed, I hope you are too. Okay. Berbye.

Transcribed by Aveline Malek at TheWordary.com

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Image of Rembrandt's "The Shell"

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