Andrew Saintsing: You're tuned into 90.7 FM KALX Berkley. I'm Andrew Saintsing. And this is The Graduates, the interview talk show where we speak to UC Berkeley graduate students about their work here on campus and around the world today, I'm joined by Sarah Guth, from the Department of Integrative Biology. Welcome to the show, Sarah.

Sarah Guth: Thanks so much for having me. It's great to be here.

Saintsing: It's great to have you here. You've been away for a while, right? And you just got back into the country.

Guth: Yeah, I was in Madagascar for eight months. I'm working with a team of researchers that are studying bat-borne zoonoses.

Saintsing: What did you say?

Guth: Bat-borne zoonosis are diseases that are transmitted between animals and people like the coronavirus that we're currently experiencing.

Saintsing: You're not studying coronavirus though.

Guth: I'm not specifically no, though the bats we study in Madagascar, do have beta coronaviruses we think, but we haven't isolated them. So we don't know the exact, exact type of beta coronavirus. It's probably not COVID-19 but it may be something similar.

Saintsing: So beta coronavirus, that's a, that's a big group of coronaviruses that there's a lot of differences among beta coronaviruses?

Guth: There is. Yeah. So there's four general groups of Coronaviruses. There're the beta coronaviruses, the alpha coronaviruses, then I think delta and gamma. Um, I'm not exactly sure, but, uh, COVID-19 is a beta coronavirus. The beta and alpha coronaviruses are typically found in rodents and bats. So it's a large group of coronaviruses though. I I've read that coronaviruses are very diverse, so you can have a very diverse set of beta coronaviruses in a particular bat species, which is part of the reason why they're so susceptible to recombination and spilling over into not full hosts like humans.

Saintsing: And that's just because there's so many different kinds of coronaviruses living in the same bat that they can just get close to each other and share information.

Guth: That's yeah. That's my understanding

Saintsing: You're not really studying the coronaviruses though. Are you studying a particular virus that the bats have?

Guth: So, our group has historically looked at serological evidence of filoviruses and henipaviruses. So

Saintsing: Serological evidence being blood?

Guth: Yeah. Taking blood samples and looking for antibodies to look at past exposure to specific pathogens or specific groups of pathogens, because oftentimes there can be cross-reactivity between pathogens in our particular group. So you can't, we can't say, as of up to this point, we haven't been able to isolate specific pathogens in the bats, but we know that there has been exposure to pathogens in the group known as filo viruses. So a Ebola is in the group of filoviruses. So yeah, my dissertation is not going to focus specifically on Corona viruses, more focused on filo viruses and henipaviruses.

Saintsing: What are henipaviruses?

Guth: So henipaviruses, some examples you may have heard of. So Nipah virus is, and these are not viruses that I've ever come to the US but Nipah spills over from bats to pigs, to humans in Malaysia and from bats to humans in Bangladesh. And this happens quite regularly in Bangladesh because, um, it's shed in bat urine and bats, well bat urine gets into date palm sap and humans consume that sap. And so it happens actually annually.

Saintsing: Like pretty bad or?

Guth: Uh, yeah, it does. It is, um, the case fatality rate. I'm not sure exactly what it is, but it's, it's higher than COVID-19. I think it's almost as, or around as virulent as the SARS epidemic we saw in the early 2000s, but yeah, I'm not sure exactly what the case fatality rate is.

Saintsing: Is it, it's been known for a while, or like when was the first time they recorded cases of it in humans?

Guth: Uh, it's a good question. I think it was in the late 19 hundreds was the first outbreak of Nipah. Um, but I, I don't remember exactly. I want to say the 1990s and the first outbreak was in Malaysia.

Saintsing: Okay. And these are viruses that'll kind of burn out in human populations.

Guth: The outbreaks are limited in human populations. Um, you'll have it's, it's not anything like we're seeing now with, uh, COVID-19. You need to have regular spillovers from the reservoir host, which is the bat, uh, to have any sort of prolonged epidemic.

Saintsing: Right. But you're kind of less interested in the viruses themselves and more interested in like how they're sustained in the bat populations and how they're moving through that population.

Guth: So, I'm a, I'm a disease ecologist, which means that we're interested in the dynamics of disease transmission as opposed to, I mean, sometimes so we're, we often use epidemiological models and sometimes we do integrate information from the molecular

level, but we're generally more focused on dynamics as opposed to understanding what's going on, on a within-host level, on a molecular level,

Saintsing: Right. You look at, you look at a bunch of blood samples from a bunch of different bats to kind of see how widespread maybe these viruses have been in a bat population?

Guth: We take blood samples from bats every month. Um, and we put the from three different species, uh, and we put the blood samples in a centrifuge and we spin them down. So you separate into a serum and a blood pellet, which has as, you know, the wipe, all the blood cells, uh, and then using that, we send that serum sample to collaborators in Singapore, and they do, what's called a Luminex assay to, uh, look at the serology, to look at for serological evidence of exposure to henipaviruses, um, or if you live viruses. And so then we know, you know, what bats have been exposed to these pathogens. And what I'm interested in, one of my collaborators are interested in is figuring out the average age at which an individual becomes first infected, because once you know that you can infer the rate of transmission within that population. So then you can build what's called these, these age or prevalence models to then model the dynamics of transmission within that population.

Saintsing: You want to know the average age at which the bat gets infected.

Guth: Yeah. So we get the, and when we're looking at the age at which a bat becomes exposed, as we're looking at serology, um, so we get serology from blood samples and then we get age. Um, what I'm currently working on now is trying to get age from, uh, DNA samples. So we take a piece of the wing tissue and we extract DNA. And we're trying to look at the level of DNA methylation and correlate that with chronological age. So we can have this sort of epigenetic clock to determine the age of any bat. And there's a group that is actually building this, this clock using wing tissue for other bat species. And we're going to try to apply their clock. But right now I'm trying to figure out the, essentially like the lab pipeline to get that done. Um, because it's not going to be easy to, to, to sequence, um, or to detect DNA methylation specific parts of the genome without spending tons of money.

Saintsing: Okay. I gotta ask some questions about some of the things you just said. Okay. So DNA methylation. So can you explain that just a little bit? Just like briefly.

Guth: Yeah. Yeah. So I'm, I'm going to disclaimer, I'm pretty new to, um, Oh, this world of genomics. Um, and that's what I'm spending a lot of time doing, but yeah, so DNA methylation is when, um, a methyl group is added to the, the DNA of the bat. Um, and people have found that the rate at which this happens is correlated with age. Um, and it's, it's a pretty new, um, this is a pretty new field. We don't know why, or whether there is a reason for this, like whether it plays there's evidence that may play a role in the aging process, but we're not sure, but the point is that it's been shown across many different species that you can. Um, so this often happens at, at what are called CPG sites. So it's just when you have a cytosine followed by a guanine. Um, and there are specific sites that are, um, have levels of DNA methylation that are often correlated with

chronological age. So you have to find those sites and then you measure the level of DNA methylation at those sites and you can calculate age.

Saintsing: Okay. So you, so there's DNA methylation. And you're saying, we don't really know like why it's happening. Um, but it is like shown to correlate well with age. Um, and then you said it was like CPG, those, the C's and the G's, those are like two examples of the bases you can have for DNA. Um, and those are when C's when G's follow C's, those are particularly susceptible to methylation.

Guth: Yeah. Yeah. Sorry. I didn't explain that very clearly. Um, the methyl groups are added to the site, are added to C and that opens happened where you have a C followed by a G, and DNA methylation is, um, I mean, it's epigenetic, so it's linked to gene expression, but there's this, um, there has been this other trend to kind of discover that it can be, we think it's involved in the aging process. We don't know exactly what the link is. Um, yeah, that's still being characterized.

Saintsing: And you know, that often happens where C's are followed by G's, but you don't really know like what the deal is. So is that just something like, that's a pattern you've seen and that's helpful because then you can know where if you sequence the genome, like you can like target those spaces to look for methylation. And that's like, why you care that it's C's followed by G is not necessarily because there's anything, you know, like mechanistically that's happening when C's follow G's.

Guth: Mostly we're using, um, this other group is, is building an epigenetic clock for bats. Um, and so they're picking out, they're focusing on these CPG sites because we know that, uh, you're more likely to find DNA methylation that's correlated with age at those sites. Um, and since we don't want to spend a lot of money, we're going to target that the same sites that they identify. Um, so we're trying to figure out first how to take our, our DNA genomes, how to, um, extract the, the CPG sites and then further extract the CPG sites that, um, that this other group have identified as being correlated with chronological age or biological age in bats.

Saintsing: Right. And so that's why when you say chronologically - biological age, that's like, that's like saying like some bats might develop different, like develop at different rates basically. Is that why you say biological age instead of chronological age?

Guth: Yeah. So there is, there's been a lot of research in this field that, um, have looked at rates of aging as shown by DNA methylation versus rates like, you know, our chronological age, which is what we, something that you might know before you look at the DNA methylation age, um, and have found that in some species or in some, some diseases in humans even, um, will result in the acceleration of DNA methylation age or biological age. And we think that since, like I said before, um, we think that DNA methylation may play a role in aging because it is involved in gene expression. So you may see some genes turned off as we age. Um, and so maybe, you know, having a disease, for example, like cancer may accelerate your, the, the, the stress on your DNA, the rate of aging

biologically. Um, and so there is that people do make that, um, do distinguish between biological and chronological age in this field.

Guth: Um, but we're, uh, our project is not going to make that distinction because we, we do have, um, previously would be taking teeth from bats, uh, to get at their age. So if you, um, if you cut a tooth in half, um, you can actually count the rings. Yeah. So the bats put down, um, they put down layers in their teeth annually kind of like a tree. So when you cut that tooth in half, you can count the rings and get their age. Um, but it's a really time consuming and stressful process for both the researchers and the bat. Um, more so for the bat, obviously. Uh, and we only did it on a subset of adult bats. So, um, we're trying to get away from that method. So we don't have chronological age for every bat. Um, and there also is quite a bit of variation in, or quite a bit of error in getting aged from teeth. It's not a precise process. Um, so it wouldn't be fair to compare, um, or we don't think it would be fair to compare the DNA methylation, biological age with the chronological age.

Saintsing: I see. Okay, you do all of this. You look at the DNA methylation, um, in your blood samples, just mostly to establish the ages of the bats that you've drawn blood from. And then you're also simultaneously looking for evidence of, uh, exposure to different viruses. And so you want to compare to say like, okay, this bat is this old and it has been exposed. So the earliest we can say that it was exposed was at this age.

Guth: Yeah, exactly. So we're not gonna be able to say, you know, when in the history of that bat has, has it been exposed, but across the entire data set, we can then identify, you know, at what age do we see that bats start becoming exposed the average age at bats, we start becoming exposed. And then you can build these age seroprevalence models where you can infer the transmission rate in the population and disease dynamics,

Saintsing: The transmission rate. It's like,

Guth: It's as simple as one divided by the average age at which a bat becomes infected is the rate at which bats become infected. And then you can multiply that by the susceptibility of the population and the infectiousness of the population and get a sense of what's called the force of infection. And that's kind of our larger, it incorporates both the, the rate of transmission and the contact rate between susceptibles and infected

Saintsing: And the susceptibility. What does that measure?

Guth: So the susceptibility of the population is the proportion of individuals that are susceptible. But so these age seroprevalence models don't take that into account specifically. It's yeah, it's, it's more dependent on that, that, um, one divided by the average age of infection.

Saintsing: Right. And so that, that model is like what you're focused on. Like you're not really focused on the force of infection. That's like something that will come after.

Guth: It's a different way of calculating the force of infection, but they're just kind of general the point is that you can, um, yeah, the main point is I, by getting the average age of infection, dividing, you know, one dividing one, by that average age, you can get the, this transmission, you can get a sense of a transmission rate.

Saintsing: You're looking at two different types of viruses, right? Like the filoviruses and what was the other type of virus?

Guth: Henipaviruses.

Saintsing: And so, are you, are you trying to like draw comparisons between these groups? Is that why you have multiple?

Guth: So just because we're, we're doing serological assets for those. And then also, um, the, we still don't really understand disease dynamics in bats. Um, that's have really, and you probably read about this with COVID-19. Um, they have really remarkable immune systems. Um, we don't really understand how, um, bats can sustain these infections in their population. Um, you know, when, like I said, when Nipah spills over into people, it's a very limited outbreak because you don't have enough. There isn't enough transmission in the population because people that become infected aren't mobile and they don't, they aren't able to infect new susceptible hosts. So yet we don't really understand how that's our sustaining these infections. So we build these epidemiologic models to get a better sense of what's going on. And so the goal is, you know, I mean the more models you can build, maybe the easier it would be to get at the rules.

Saintsing: Oh yeah. Like bats, they're so weird. Are there any, I mean, viruses that are actually, you know, that actually have a negative impact on bats, it just seems like all of the viruses you hear about like rabies, Ebola, coronavirus, Nipah, they all kind of just live in bats and don't really affect them.

Guth: So, rabies actually does have, um, that's can die from rabies and that's still, that's kind of a complicated, we don't really know why. Um, but yeah, bats do have this crazy immune system. We think it's linked to the evolution of flight. Uh, so bats are the only flying mammal. Um, and flight is a really metabolically expensive form of locomotion. So if you have a human running at full speed, they raise their basal metabolic rate, maybe two to three times, um, a rodent running might raise their basal metabolic rate seven times. Um, but a bat flying raises its metabolic rate 40 times. Um, so this is really metabolically expensive. Uh, and with metabolism, we produce these what are called oxidative free radicals, uh, and that can result in what's called the oxidative stress. So these oxidative free radicals can, uh, can damage DNA. And we have cellular pathways for mitigating this damage, but at a certain point, the damage caused by metabolism can outrun this ability to mitigate the damage.

Guth: Um, and that's what we know as aging. Um, so eventually, you know, your tissues and your body can't keep up with this rate of DNA damage and, uh, things start to break

down. Um, so bats, when you think for having such a high rate of metabolism, uh, wouldn't live as long as they're gonna, you know, you'd expect to have a really high rate of DNA damage. Um, and we see this with rodents, rodents have a higher metabolism than many other mammals, and they don't live as long. Um, but bats live for a really long time. Um, so the longest lived bat is the brand that, and it lives up to 40 years in the wild. And so what we think is happening is that bats have evolved these really efficient cellular pathways to mitigate the damage that they're causing to their DNA by flying. Um, and that these cellular pathways to mitigate DNA damage have also helped them sustain the damage that's caused by, um, viral infection, because a viral infection can also cause a similar amount of, um, damage that you see from metabolism, uh, because there's a lot of inflammation, so that are able to sustain a really high level of inflammation.

Guth: Um, because oftentimes like when we have a viral infection, our symptoms and the damage that's caused for our body is often a result of our own immune response. So for example, with COVID-19, um, you might've heard that patients that have a bad outcome have this cytokine storm, um, that causes a lot of inflammation and cytokines are just these, these signaling molecules that activate the immune system. And yeah, it causes this really massive inflammatory response and bats and humans. We don't have the ability to sustain that inflammation, but we think that that's are, are essentially primed to sustain that inflammation because they've been doing that for, to sustain the inflammation that's caused by flight.

Saintsing: I got a couple questions for that. So the biological clocks that you make, I guess wouldn't be applicable to other animals, right. Because bats have unique rates of aging. And so you kind of have to like really like tune it to bats.

Guth: Yeah, yeah, exactly. Um, and I mean, biological clocks, these epigenetic clocks, people are making based on DNA. Methylation are very species specific regardless, but yeah, definitely. Um, we would not be able to look at compare, um, the DNA methylation levels of bats with humans per se, and apply the same epigenetic clock.

Saintsing: Right. And then, so with the cytokine storm, I guess I always just thought that like part of the problem was that you, you have so much acute inflammation, right. So, but the bats have inflammation. It's just that they keep it under control or like what, what do you mean? They're like primed for it? And they like sustain high levels of it.

Guth: The papers I've read have generally said that they they're able to keep inflammation or negative inflammation at a minimum. Um, and then they're able to use inflammation when they need it, um, when it's useful. Whereas, um, and people are humans, you know, often will have it just like this massive inflammatory response that's completely unrestricted and uncontrolled, whereas bats have a better ability to control it. So for example, to get more into molecular details, I guess, that I'm not qualified to talk about, but, um, they have bats have this, uh, a constituent of interferon alpha, which is a specific, it's a type of cytokine. Um, it's a signaling molecule that activates the immune system. Um, but it's really, really powerful. Um, so, in bats, it's, constituently expressed,

so it's already there. It's ready to go. And when a virus comes in, it's able to activate a massive immune cascade.

Guth: Um, but then the bats are able somehow able to manage that level of inflammation. Whereas, uh, I think so we don't have, constituently expressed interferons. Um, we do have interference in our immune system, but they're, they're activated, they're not already there because if they were just already there, we would have way too much inflammation and it would be how we'd have really negative outcomes. I have read that they use interferons in some cases in cancer treatments and it's a really, really brutal treatment. Um, and they use it in very small doses, cause it is such a powerful, it does elicit such a powerful response. And again, like bats are capable of withstanding that, but the human body is not.

Saintsing: Okay. I see what you said. So basically the, the bats have all have like the signaling, um, information that we have. And so they, their immune system knows what's going on, but they have some capacity to just like, not go crazy with their response essentially. No, they just don't swell up. Like we would and all of that. And they don't have like really high fevers, I guess, that we would have.

Guth: They, um, yeah. Another weird thing about that is they actually are able to withstand really high temperatures. Um,

Saintsing: I guess that makes sense because like they fly, so they like heat while they fly.

Guth: So the flying actually kind of almost creates this fever response. Um, and there was a hypothesis, um, in the literature. I don't know if people are still considering this, but they, people were saying that maybe that's one way of controlling these viral infections is that flying is like fever and that's how they keep replication down. Um, but the, the evolution of flight hypothesis seems to be more, um, more popular.

Saintsing: It sounds like you're doing really interesting, cool stuff. What was it like being in a Madagascar for eight months?

Guth: Yeah. And I really enjoyed it. We have a really great team of local researchers and then there is a few other American techs with me. It's definitely very different than Berkeley, but it was really cool. I really loved being in the field. Um, I had never done field work before this, um, are really held in animal at all. It was really cool. Yeah. It's good to be able to do everything and to collect data on the ground.

Saintsing: Did you, like you stayed at a remote field station kind of, um, away from any bigger cities or any or something like that?

Guth: Um, so I actually lived in the capital and the biggest city and things like one between one and 2 million people. Um, and I lived at the hospital, um, cause they have a lab there. Uh, so we would go into the field and collect biological samples and then bring our samples back to the lab. Um, and the idea was to, uh, start doing DNA and RNA

extractions in the lab, in the capital, um, and, but we had to leave because of coronavirus. So I was kinda in the middle of working on that.

Saintsing: Oh, so you, you had the, the idea was to collect all of the samples and then start the, and start like extracting RNA and DNA after you had collected all of your samples.

Guth: The idea was to, can I do it simultaneously. Um, but it took a while to figure out what extraction kits to use and, and kind of get all the resources in country. Yeah. I'll probably go back next January in between teaching to try to do some lab work.

Saintsing: So do you think you'll be able to get it done in what a month or something like that?

Guth: Um, maybe I don't know. We'll find out. Yeah. I'm not really sure. There, there is a really great team of local researchers there. Uh, so we may, they may also get involved in the lab work, but yeah, we'll see, figure things out.

Saintsing: A lot of, uh, figuring things out. I guess you came in with a plan, but it's been a lot of like adapting to different circumstances, right?

Guth: Yeah. Yeah. And that's, I mean, Madagascar is all about that. It's like you think, you know, what's going to happen and then, you know, you spend three days trying to get to your field site because the roads have been washed out, but

Saintsing: I guess kind of like field science or even science in general. Right?

Guth: Yeah, exactly.

Saintsing: Yeah. So did you always know that you were going to be a scientist? Did you always want to study science growing up?

Guth: I did not know. Um, I didn't know that research could be a career. It was really a field until I was a sophomore or junior in college. Um, I did a research experience for undergraduates internship, the REU internship, um, after my junior year. And they kind of trained you on what grad school was and how to apply. And that's why I decided to go to grad school. Um, cause I was really interested in science, but I thought if you studied science, you had to become a high school biology teacher. And that was the only option.

Saintsing: Yeah. And the REU experiences, I guess, really good because it really motivated you to pursue the research as a career.

Guth: Yeah, that was definitely a life changing, internship and experience. Um, I realized that I just really loved research and collecting data. Um, I had a really hands off advisor. Um, and so I just kind of got to, like, he told me the title of the project and um, some data I collect and I just kind of ran with it for the summer. Um, and you're also living very closely with, you know, 14 other interns from all over the world, all doing different projects. Um, and you just spend the summer, you know, all doing your research projects

and hanging out and learning about different, um, disciplines. I actually did. I was in a, it was a, um, an engineering program. Um, so I was kind of the one out. It was an environmental engineering. Uh, so it was all geared towards environmental science, which was, um, I was a joint biology and environmental science major. So that was a part of my work. But, uh, definitely I was like a little bit out of, um, a little bit out of my wheelhouse, but, uh, I just really enjoyed getting to know everybody and their different fields. And then also leading, um, or playing such a big role in this project that my advisor was doing.

Saintsing: It looks like we're running out of time on the interview. Do you, uh, have, uh, have anything you'd like to leave the audience with?

Guth: So, you know, these days everyone is obviously really focused on, um, COVID-19 it's having a huge impact on the world and, um, there's a lot of people building epidemiological models to make predictions about what's going to happen and you know, what our requirements for, uh, PPE and what's going to be when the peak of the epidemic is going to happen. Um, and how many, what distribution of vaccines we would need. Um, and there's a lot of different models coming out. Um, and I've my lab. And I have noticed that, um, the models that get the most attention are often the models that have the sexy web interface that are easy to interact with. Um, so there was a model, uh, that came out of a group in Washington. I think that, um, has been kind of flooding social media. Um, that's essentially, it's just a statistical model fitting.

Guth: Um, that predicts how many cases we'll see in different areas based on, uh, the epidemic curves we've seen in completely different parts of the world. Um, and I think I would just caution people to, when you see models like this, not take it at face value and try to look under the hood and see what the, what the methods are, how are they building the model? You know, is it statistic is a statistical model? Is it a mechanistic model? If it's a mechanistic model, how are they estimating the transmission rate? Because there's a really, really wide estimate, um, or range for, uh, estimates of transmission rate. And that has a huge impact on the predictions because it can be, uh, uh, it can be confusing to kind of weed through all these models that are coming out and figure out what predictions will actually be. So, yeah, I think just being careful about reposting models that you see published and, you know, not just taking that at face value, thinking a little bit more critically about what the information you're seeing is built on.

Saintsing: Yeah. Okay. Um, that's like a really good point. And you know, even not just in, uh, times of COVID-19, but also in understanding science in general, right. It's really important. Today I've been speaking with Sarah Guth from the Department of Integrative Biology. Thank you so much for being on the show, Sarah.

Guth: Yeah, thanks for having me.

Saintsing: So great to have you.