Melanie Cole (Host): Welcome to the podcast series from the specialists at Penn Medicine. I'm Melanie Cole and today, we're discussing taste receptors with Dr. Noam Cohen. He's a Ralph Butler Endowed Professor for Medical Research at Penn Medicine. Dr. Cohen, it's a pleasure to have you with us today. As we get into this really interesting topic, can you provide a little background on your role and an overview about what we're talking about today? What have we learned about taste receptors that we didn't know say 20 years ago?

Noam Cohen, MD, PhD (Guest): Sure Melanie. So, 20 years ago, taste receptors were thought to only be found on the tongue where they help us identify things that either taste good or taste bad. In the last 10 years though, it's been identified that these receptors have been repurposed throughout the body. And pretty much we're finding them expressed anywhere that our body comes in contact with microrganisms.

So, they're found in your GI tract, they're found in your GU tract, they're found in your respiratory tract. And that's where I got interested in them as an otolaryngologist who focuses in rhinology. I got interested in their role and what they could be doing up in the nose. And so, there are multiple modalities of taste, as you all know, there's bitter, there's sweet, there's sour, there's something called umami, which is protein. So bitter and sour are tastes of aversions. And typically when we taste something like that, we spit it out. The fact that we enjoy alcohol, that's an acquired taste, but in general, if you give something that is bitter to a baby, they will spit it out.

And what we started identifying is that these bitter receptors that we thought were there to detect things like toxins, like plants that we don't want to eat, actually are identifying molecules that bacteria secrete to communicate with each other, something called quorum sensing molecules. And so, we found these receptors in close proximity to where bacteria in the nose would be. Basically in the cilia, bathing the mucus. And so, as bacteria get into your nose and they start to multiply, they secrete these factors that lo and behold, they taste bitter. That's why when food spoils, it tastes bitter, but these receptors in the nose would detect those molecules and stimulate an innate defense system. Basically an ability for the lining of the nose to send out anti-microbial factors that would then reduce the bacterial load in the nose, so you don't get infected.

Host: That was an excellent explanation, Dr. Cohen. So then, since they have so many functions that many people don't realize, do they have disease implications when the taste receptors are located in the nose?

Dr. Cohen: Yeah. So just like the receptors in the tongue, there is tremendous genetic variability in people's ability to taste molecules that taste bitter. And some of you may have heard of a term called a supertaster or a non-taster, and that's in the context of a specific bitter molecule, where certain individuals don't taste it at all and other individuals taste it and it's repulsively bitter. And that is genetically determined. And in the Caucasian population it follows a near classic Mendelian genetics. So about 25% of Caucasians taste this molecule in exceedingly small concentrations and find it very, very bitter, about 25% of the population doesn't taste it at all, and 50% are somewhere in the middle.

And it turns out that that receptor that has been identified for a hundred years as either functioning or nonfunctioning is the receptor that we found in the nose that detects gram negative organisms. And so, in the clinical context, what we were able to identify is that patients that are able to detect this molecule on their tongue, they have a lower incidence of sinusitis because the receptor is working better in their nose to detect the bacteria and stimulating these innate defenses.

And I haven't gotten into that yet, but individuals that don't detect that molecule on their tongue, don't detect the bacterial molecules in their nose. They don't release these anti-microbial factors and the bacteria multiply and result in sinusitis. And so, our early studies demonstrated that this case correlation, of ability to detect PPC, this bitter molecule, correlated to the disease state in sinusitis. Now, the molecule that is regulated in the nose. So when you put something bitter on your tongue, you say, oh, I taste something bitter, in the nose, you don't say, oh, there's something bitter in my nose. Your epithelium starts making the molecule nitric oxide and nitric oxide has two functions in the nose.

It increases mucociliary clearance. And it also diffuses out into the airway where it can kill bacteria. So if you have a functional receptor and you detect a bacteria, you start making a lot of nitric oxide, and you kill the bacteria before it really has a chance to set up an infection. If you don't have a functional receptor and you don't taste that molecule and you don't detect the bacteria, the bacteria multiplying gives you a sinusitis.

Host: Wow. That's absolutely fascinating. So, how can you use these as targets for therapy? What kinds of therapies would these have broad reaching implications for?

Dr. Cohen: Right. So, we have been focusing really on one bitter receptor, but there are 25 bitter receptors in our gene pool and they detect a whole myriad of

bitter molecules. And so, the idea that we had, and we've shown that all 25 of these receptors are found in the nasal epithelium, they're all up in the nose.

Some of them regulate the release of this nitric oxide. Some of them release another component of antibacterial defense called anti-microbial peptides. And we thought that if we could trick these receptors to be stimulated and release one of these two factors, we could use that as a way to treat sinus infections without using conventional antibiotics. And so, the idea is to squirt a bitter molecule up the nose and see if that would activate these receptors to either make nitric oxide or antimicrobial peptides. And if you can do that, then you can basically reduce the bacterial load in the nose. Now, the problem is, the genetics. As I mentioned, with this one receptor 25% of the population doesn't respond at all.

But if we take all of the bitter taste receptors, all 25 of them together, we should be able to find molecules that stimulate other receptors, or we could make a mixture of different bitter molecules that activate different receptors. Or we could find a molecule that activates multiple bitter receptors.

And as we were trying to think about these three different ideas, the most common bitter molecule that people think about is quinine. It's in tonic water, it's in your gin and tonic. And so, we started doing experiments with quinine and, lo and behold, we found that when we put quinine on our nasal cells in the lab, those cells generate a lot of nitric oxide.

And the reason why we liked quinine was it's already out there. People are ingesting it all the time. It's safe. It's already been used in several studies in the airway, so the FDA has already approved it. But the reason why we really liked quinine is it was highly promiscuous and it activated multiple bitter taste receptors.

So you didn't have to really worry about whether one receptor wasn't working because of the genetics. If it activated nine receptors, one of those receptors would be activated. And so, sure enough, if we were to take our cells and treat them with quinine at the same time as bacteria, we can reduce the amount of bacteria that live on those cells.

And so, we took this idea to the FDA as a topical treatment for sinus infections and that was approved. We got our I&D approved. Then we partnered up with a pharmaceutical company who helped us with the clinical trials. And we're just about ready to launch our trial in post sinus surgery infections. And then the pandemic hit.

So the trial was on hold, but we do have a lot of safety data that it is safe to put quinine in your nose. It's basically tonic water, a little bit more concentrated, and that it does generate that nitric oxide. So we're still waiting on starting that trial, which we're trying to get off the ground now.

And if this works, this would be an alternative to treating sinusitis with antibiotics. And so, one of the things that we worry about, especially in otolaryngology, we treat a lot of ear infections, we treat a lot of sinus infections, is we need to reduce the amount of antibiotics that we're prescribing.

And if this works, this would at least give us an alternative to treating sinus infections without using standard systemic antibiotics.

Host: What a huge advancement for stewardship as far as antibiotics are concerned. And, and as you're telling us about your research that you and your team are conducting, tell us about what your findings have led to. And what you're discussing right now is this the nasal spray that you're developing?

Dr. Cohen: Yeah. So it would be a nasal spray, that has a bitter molecule in it and some preservatives and basically it would be twice a day or three times a day treatment that we have to work out once we get the clinical trials up and running. But in the lab, it looks like a twice a day treatment is safe over 14 days. It didn't kill any of the cells that we had growing in the incubator. And it was able to continuously produce that nitric oxide over a two-week period. So from the basic science standpoint, it looks like this is as a proof of concept, it's there and now we just have to take it to the next step and actually run the trials.

Host: And when is that going to happen?

Dr. Cohen: Hopefully in the next year to year and a half. We ended up actually diverting all of our nasal spray during the pandemic. And we repurposed this as a COVID prophylaxis. Cause there is evidence from the first SARS epidemic in 2005, that nitric oxide has anti coronavirus properties. And so, the FDA allowed us to do that. And so, we burned through all of our sample. The problem is that when we did our trial here to see if we could prevent COVID, we were at the nadir of the infection. No one was getting infected. But we do have safety data now and over 200 people when there were no adverse events.

So we know that it's safe, we just don't know if it's effective against COVID nor against bacteria yet. So we're hoping to be able to get everything lined up again, and probably start by fourth quarter of this year for our trial again.

Host: Well, I hope you'll join us again to update us as this trial goes on. It's so interesting. So, Dr. Cohen, as we get ready to wrap up here, it's becoming clear that those T2 are bitter. And the sweet taste receptors that you've been discussing are part of this pathogen detection network in the airway, which I'm sure, as I discovered in my research that many people didn't realize and this emerging and exciting field of extra oral taste receptors that you've been discussing has so much potential to reveal insights into pathogen interactions and human disease in such a variety of ways. Where do you see this going in the future? Where would you like to see this going? What would you like other providers to know?

Dr. Cohen: Well, one of the projects that we recently ran was to look whether this system is replicated in the middle ear. So as I mentioned in ENT, we deal with a lot of sinus infections, but we also deal with a lot of ear infections. And so, lo and behold, we were able to show that these receptors are found in middle ear mucosa.

And so, this could be a potentially a topical treatment through an ear tube for middle ear infections. Thinking more globally outside of otolaryngology, these receptors are found in the gut, they're found in the GU system. You know, they could be playing a role in urinary tract infections, so I think that figuring out how to harness these taste receptors in a therapeutic realm will truly help us treat different infections of different body parts with topicals, if you can get to it.

Host: I'm sure they will. And thank you so much, Dr. Cohen, for joining us today. What a fascinating interview this was. To refer your patients to rhinology at Penn Medicine, please call our 24/7 provider only line at 877-937-7366 PENN. Or you can submit your referral via our secure online referral form by visiting our website at pennmedicine.org/refer your patient. That concludes this episode from the specialists at Penn Medicine. Please remember to subscribe, rate and review this podcast and all the other Penn Medicine podcasts. I'm Melanie Cole.