When Science Finds a Way

Season 4, Episode 3
What happens when fungi find their way into our brains?

Show notes

Episode description:

It might sound like something out of TV shows like The Last of Us, but brain-invading fungi are a real-world problem. Alisha Wainwright speaks to Drs. Rachael Dangarembizi and Rebecca Drummond, an immunologist and a neuroscientist collaborating across continents to tackle Cryptococcal Meningitis – the leading cause of fungal death worldwide. Dr Kyla Murphy also talks about the new tests and treatments saving lives from the disease, and Alisha shares the story of her own mother's brush with a dangerous fungal infection.

Mentioned in this episode and further reading:

- Will climate change lead to more fungal infections? An explainer by Wellcome (wellcome.org/insights/articles/will-climate-change-lead-more-fungal-infections)
- Wellcome Fungal Adaptation Call Awardees (wellcome.org/research-funding/funding-portfolio/funded-grants?f%5B0%5D=funding_scheme_grants_awarded%3ABiology%20of%20fungal%20adaptation)
- Global incidence and mortality of severe fungal disease, David W Denning, The Lancet Infectious Diseases (thelancet.com/journals/laninf/article/PIIS1473-3099(23)00692-8/fulltext)
- The WHO fungal priority pathogens list as a gamechanger, Matthew C. Fisher & David W. Denning, Nature Reviews Microbiology (nature.com/articles/s41579-023-00861-x#citeas)
- How fungi shape our world...and how the climate is shaping our fungi – The Naked Scientist Podcast in partnership with Wellcome (thenakedscientists.com/podcasts/naked-scientists-podcast/how-fungi-shape-our-world)

Transcript

Music starts 00:00

[00:00:00] **Rebecca Drummond :** We don't really understand a lot about this, uh, kingdom, right? We, we think there's millions of different species, but a lot of those are unidentified or, or uncharacterized. So a lot to learn actually about this one kingdom of life.

[00:00:12] **Alisha Wainwright:** Fungi are an incredibly diverse kingdom. They come in all shapes, sizes, and colors.

They live in the soil, in the air, and inside our bodies. And as we learn more about them, scientists are exploring their incredible potential for good to transform agriculture, tackle plastic pollution, and usher in medical breakthroughs. But fungi have another side. What happens when fungi finds its way into our brains?

This question sounds like the stuff of sci-fi, and yes, we are looking at you The Last of Us, but for the millions of people around the world whose immune systems are compromised by HIV, by cancer treatment, by organ transplants, this is a very real concern and it's exactly what we're exploring today.

Cryptococcal meningitis. And the incredible science, which is being done to plug the gaps in our understanding,

[00:01:07] **Racheal Dangarembizi:** I think we will be able to generate answers to the questions we've always had much faster than we would have 50 years ago.

[00:01:15] **Alisha Wainwright:** There are about 180,000 cryptococcal infections worldwide every year.

It's one of the leading causes of fungal death worldwide, if untreated. It's fatal. Today I'm joined by two scientists tackling this disease from very different angles. Dr Racheal Dangarembizi is a neuroscientist at the University of Cape Town where she runs a lab dedicated to understanding how this infection damages the brain.

[00:01:42] **Racheal Dangarembizi:** We are able to look at thousands of gene. In, in each cell, right? And that just, you know, unlocks a rich data set that answers so many questions

[00:01:53] **Alisha Wainwright:** And Dr. Rebecca Drummond, a professor of fungal immunology at the University of Birmingham, is studying how the immune system fights and sometimes worsens the infection.

[00:02:04] **Rebecca Drummond :** I like to look at how immune cells flood into the brain in response to that infection. What do they do with the fungus when it gets there?

[00:02:11] **Alisha Wainwright:** How are these different disciplines working together to better understand this huge threat? I'm Alisha Wainwright and this is When Science Finds a Way, a podcast about the science changing the world.

Okay, let's get into it.

Rachel, Rebecca, thank you so much for joining me today.

[00:02:31] **Racheal Dangarembizi:** Well, thank you for having us. Really exciting to be here.

[00:02:34] **Rebecca Drummond :** Yeah. Looking forward to our conversation.

[00:02:36] **Alisha Wainwright:** So a lot of people have just come to, uh. Be more aware of fungi, particularly because of some pop culture editions like the TV show, The Last Of Us.

Uh, the premise of the show is sort of set where fungi is one of the main, uh, antagonists of the show, and it's brought a lot of conversation around fungi to people who've never talked about it before, previously. So I've, of course, I'm curious, have you guys seen the show? And if you have seen the show.

What do you make of it?

[00:03:07] **Rebecca Drummond :** Yeah, so I, I have seen the show and I'm, I'm a really big fan and part of the reason I'm a fan is because of the significant new awareness that it's brought into our field and the research that we do. I think a lot of people hadn't appreciated that fungal infections are something that can kill you.

I think there's really been a lot of people understand fungal infections to be things like athletes' foot and, and thrush and, you know, stuff that is quite annoying or embarrassing, but not something you would necessarily have to worry about. And actually knowing that there's these infections out there that could kill you, um.

It's really been quite important to kind of bring that into the mindset because without that awareness, we can't, you know, do our research effectively. We don't get the funding. We, we can't convince, uh, you know, policymakers or our clinicians to start thinking more about this.

[00:03:47] **Alisha Wainwright:** So, let's zoom out from the show for just a second.

Rebecca, I wanna ask, what exactly is fungi?

[00:03:54] **Rebecca Drummond :** So you have all these different kingdoms of life, right? So you've got animals, plants, bacteria, and then you have fungi. So people have always thought of fungi as being grouped with plants or, or bacteria or something like that, but they're their own, uh, unique kingdom.

Their closest relations actually us. So a lot of their biochemistry of their cells is very similar to ours. And so we would kind of talk about animals and fungi is eukaryotes. This means that the way we organize our DNA is quite similar and it's very different to for, say, um, bacteria, for example.

And it's a really big, diverse kingdom of life. So, you know, you have ranging all the way down from tiny, little microscopic, microscopic, uh, yeast cells up to really large, you know, mushroom forming, uh, fungi. And some of those can be absolutely enormous. Some of the largest living things on earth we think are actually fungal, uh, colonies.

Um, and we don't really understand. A lot's about this, uh, kingdom, right? We, we think there's millions of different species, but a lot of those are unidentified or, or uncharacterized. So a lot to learn actually about this one kingdom of life.

[00:04:52] **Alisha Wainwright:** But what is the present state of research in the field and how much do we know about fungi?

[00:04:57] **Rebecca Drummond :** So I think we have a good understanding of some of the, uh, fungal pathogens. So we know a lot about the microbiology of them. We understand, you know, how to identify them. We know what their genes are. We know we've got good databases for that. Where I think the, uh, information starts to fall down is how those fungi actually affect our bodies and how our immune response actually starts to fight those, how the fungus then adapts to that attack.

Because if you don't understand that, it's quite difficult to identify, uh, ways we can develop treatments, you know, to try and prevent, right, the fungus from, you know, hiding from the immune system, for example. So that is very, uh, poorly understood in the context of, uh, fungal infection research.

[00:05:36] **Alisha Wainwright:** Before we dive into cryptococcal meningitis and more depth, maybe we can explain a bit about your different perspectives on fungi.

Rachel, you are a neuroscientist, and Rebecca, you are an immunologist, so where do your interests overlap and where do they not?

[00:05:55] **Racheal Dangarembizi:** Um, so as Rebecca said earlier, what we don't understand about fungi is how they interact with the human hosting infection. And I would like to add another layer to that, that we least understand how fungi interact with the brain, especially because it is a very different organ from other organs in the body.

And for diseases like cryptococcal meningitis, I think the interaction of the fungus with the brain is the least understood of all. And so I live in an area or a region with high infectious disease burden, and therefore very high cases of these, you know, infections spilling into the brain. And my interests are from a neurobiological perspective.

What is happening to the brain? What are the mechanisms underlying damage and how can we prevent that besides just killing the fungus, which is the current approach for therapy.

[00:06:49] **Rebecca Drummond :** Yeah, and so I, I'm an immunologist who's been interested in understanding, um, how the immune response is different in different organs in the body.

So. You know, I started out by working in the kidney and the guts and so on, and then I started to work on a, uh, an immunodeficiency called CARD9 deficiency which where you get spontaneous fungal infections forming in the brain. Um, so it's very, very rare, um, disease. So I spent a few years working on this, and this is what kind of really opened up to, as Rachel said, how little we know actually about brain immunity generally, but especially, uh, fungal infections. And what surprised me actually when I was doing that research is how little was known about cryptococcal meningitis specifically because I thought I could learn quite a lot from the cryptococcal meningitis field and apply it to the research I was doing

these very rare patients, but actually there was very little known. And I think that's how Rachel and I kind of seeked out and found each other of this kind of shared interest on understanding the brain very specifically. But we come at it from different angles. So I like to look at how immune cells, you know, flood into the brain and responds to that infection.

What do they do with the, uh, fungus when it gets there? But I kind of ignore the neurons and all that, and Rachel kind of takes over, um, at that point.

[00:07:58] **Alisha Wainwright:** Um, that's so I love that you're both approaching. The same enemy, if you will, from different perspectives because it is such a complicated infection. I mean, basically if you have cryptococcal meningitis, your success rate if untreated is not very high, correct?

[00:08:20] **Racheal Dangarembizi:** That's correct.

[00:08:21] **Alisha Wainwright:** And can you just, uh, define what is cryptococcal meningitis? How do we catch it, and why is it so dangerous?

[00:08:29] **Racheal Dangarembizi:** Cryptococcal Meningitis is a fungal infection of the brain that is caused by a fungus that is known as Cryptococcus, which is actually an environmental organism, which is commonly found in soil, um, or in bird droppings or rotting wood.

So it's pretty ubiquitous. Most of us are exposed to it quite early in life. Maybe by the time we are like two years old, we have already been exposed to it.

[00:08:54] **Alisha Wainwright:** Oh, wow.

[00:08:55] **Racheal Dangarembizi:** So, infection by cryptococcus occurs by inhalation of the spores which are the small little fungal, um, uh, particles that one breaths in through, um, either dust particles and then when they get into the lungs, they can cause a primary infection in the lung.

So in people who have a strong immune system, they're able to clear that quite easily. But for people that are immunocompromised, they fail to clear that primary infection. And what then happens is that it is then disseminated to other organs in the body with a preference for the brain. So when the fungus gets into the brain, it causes inflammation of the brain.

And that is what is called, um meningitis, basically inflammation of the membranes that protect the brain, which are called meninges.

[00:09:52] **Alisha Wainwright:** And, and, uh, that's dangerous because inflammation of the brain is obviously not a good thing.

[00:09:58] **Racheal Dangarembizi:** Yes. So it is dangerous because once it crosses into the brain, it's not just inflammation that it causes, it also causes quite a lot of injury of brain tissue.

As you know, brain tissue is actually quite special because the cells in the brain, the main cells, which are called the neurons, they're not, they're, they're non renewing. They don't divide like other cells in other organs. So the ones you are born with are the ones that you keep for life. So if there's any kind of damage, you don't replace them.

That is why the neurological damage that is associated with cryptococcal is irreversible and fatal, even with treatment.

[00:10:38] **Alisha Wainwright:** So why are we globally becoming more at risk of fungal infections like cryptococcal meningitis, and why is it particularly affecting Sub-Saharan Africa?

[00:10:50] **Racheal Dangarembizi:** I think what has happened over the last a hundred years is the emergence of diseases that suppress the immune system.

And an example is, uh, HIV and AIDs. And that has led to a greater or a significant population of start here immunosuppressed and vulnerable to opportunistic infection, um, including fungal infections.

[00:11:14] **Alisha Wainwright:** When, when there's neuron damage, uh, would you call that brain damage from cryptococcal meningitis? What effects does that have on a person?

Is it just loss of memory, motor function? What's happening to a person if they're losing those neurons that they can't replace?

[00:11:32] **Racheal Dangarembizi:** So the brain directs almost every aspect of bodily function from motor function to sensation, to cognition and memory. And so depending on where the damage is, you will see quite a lot of deficits.

But, uh, patients with Cryptococcal Meningitis typically present with issues with motor function, they, uh, sometimes can go into a coma, especially if the brain stem is affected. They have increasing pressures within the brain, or what's called intracranial pressures as a result of fluid buildup. So what the fungus does is that it basically disrupts all of the different processes happening within the brain, not just damaging the neurons, but disrupting metabolism, for example, disrupting fluid flow within the brain, et cetera.

So you end up with all of these complications, everything comes to a stop. People can no longer see. People can no longer hear. So blindness is a problem, hearing and deafness is an issue. So it just depends on which part of the brain has been damaged, basically. And that's one of the things that we're also pursuing.

[00:12:45] **Alisha Wainwright:** So Rebecca, Rachel mentioned the overlap with the HIV burden. Are there other populations at risk of fungal infections?

[00:12:56] **Rebecca Drummond :** Yeah. So, uh, a lot of these fungal infections affect people who have any kind of disruption to the, uh, immune system. So in the case of cryptococcal meningitis, this could also additionally be, uh, people who've had organ transplants because in order to make sure that we don't reject that organ transplant, we tend to put people on immunosuppressive drugs.

So that dampens all the immune system down, and it's good because it prevents you from getting organ rejection, but it also opens you up to getting, uh, infections potentially. Um, and we do see cryptococcal meningitis appearing in those patients as well as a number of other, um, fungal infections. And then there's various other, uh, types of drugs that can cause this, uh, chronic antibiotic use this is less with an, uh, cryptococcal meningitis, but with other fungal infections, for example. These damage the immune system in a way that then kind of creates holes, if you like, that the fungus can then get through. Mm. Because I, you know, as mammals, we are actually really quite resistant against fungal infections.

Our immune systems are really very good at protecting us. Um, the reason we're starting to see more fungal infections in recent years is because we now have a much larger population of people who have immune system problems, and that's partly caused by the HIV pandemic, but it's also caused by all of these other new drugs that we use.

Um. To give you another example, um, some of these new drugs are coming through to treat cancers again, they suppress the immune system in such a way that then you can start to see more fungal infections in those patients. So these drugs are helpful because they help cure people of their cancer, but they also cause these infections.

And this is something that we're trying to understand in a lot more detail about how is the immune system damaged, you know, by these different treatments 'cause we don't wanna stop those treatments, but we want to be able to protect those people, um, who are at much higher risk of getting these fungal infections.

[00:14:31] **Alisha Wainwright:** And I have a totally anecdotal story about my mom. So a few years ago, uh, she's an avid gardener to this day, loves to garden, but at the time, she, uh, put her hand, uh, in some soil that she had cut her finger from, uh, some sort of Rose Bush or something, put her hand in some soil, and, um, noticed that it had some white stuff in the soil, but she didn't think much of it.

A month goes by and all of a sudden her entire body is covered in these crazy, almost like laceration looking sores. And they could not figure out what was wrong with her until they discovered that she had gotten, I had to write it down because the word does not come to me easily. Uh, Sporotrichosis, which is er Rose Gardner's Disease, and she had to take a very intense treatment.

It's like over six months.

[00:15:26] **Rebecca Drummond :** I actually worked on a, a fungal infection like that. So it really opened you up to, um, how vulnerable we could be, right, with maybe without even knowing it, because, uh, I think it also highlights how easily exposed we are to fungi. Fungi are everywhere, right? They're in the soil.

Uh, we breathe in the spores, so it's not possible to take patients who are immune compromised and, um, isolate them the way we would from like a vital infection, right? It's just not possible because. Fungi are, are part of life. You know, they're really important to life actually. And we're exposed all the time.

And I think that's why it's so essential to say, to do this research, to try and better understand how we can tackle it once it does take hold. Um, 'cause they're, you know, they're here to stay.

[00:16:05] **Racheal Dangarembizi:** I was just gonna end that, um. Just the length of time that you need to treat an, uh, fungal infections with antifungal drugs and how that impacts, especially people in low resource settings, for example, because um, fungi are really difficult to treat, and if somebody has to undergo treatment for eight months, that's, you know, there's a cost attached to that. And in low and middle income countries where, you know, people don't really have access to free healthcare and they have to pay for treatment out of pocket, that then means that most people stop halfway and do not finish the full course of treatment.

And then there's persistence and recurrence of infection. So just to bring back the point that fungi are really difficult to treat. Simply because they are quite close to us. As Rebecca said earlier on the are eukaryotes, were quite similar to them. So we, we have to find ways of killing them that do not also damage us, you know, because of our similarity.

[00:17:07] **Alisha Wainwright:** So, these infections sound like they're hard to treat, but because of the way the symptoms present, they could be general, like maybe a, just a headache. It might seem like just a headache. Does that also make it hard to diagnose?

[00:17:23] **Racheal Dangarembizi:** Okay, so I don't think that crypto is really difficult to diagnose as a result of the symptoms being different.

I think it's, uh, is that people show up in hospitals, especially here in Africa, quite late and with serious complications that make it really difficult to know what it is exactly they are, they're suffering from. Diagnosis of Cryptococcus, um, a cryptococcal meningitis is actually quite easy. There are lateral flow assays or even almost like dipstick type of tests that you can use for testing in urine or blood or CSF.

And it's a very quick test and very, very specific. Um, but it has to be done in good time. They are confirmation tests that one has to do, maybe perhaps do microbiology, but those are just confirmation. The actual test is very easy to do. But the challenge in, uh, low and middle income countries is that people will go to their primary healthcare facility and they are not tested at all for any fungal disease because you know, people, they don't know anything about fungal diseases. Somebody just shows up with a headache and they're gonna be given painkillers and they go back and then they say for two weeks or three weeks with a persistent headache, when they come back again, more, more serious than they were the first time, then they are referred.

It's only at the referral hospital that people will start investigating, and I think that's where the system is kind of not helping the burden of, of fungal diseases. If we had better health systems where these diseases are picked up quite early um, then, you know, we wouldn't have as much mortality as we have.

[00:19:10] **Alisha Wainwright:** Even with the enormous strides that have been made. There are still lots of challenges in the way of successful treatment, which is why research has started asking a different question entirely. What if we didn't wait for meningitis to develop at all? You might remember Rachel mentioning the lateral flow test.

It turns out that the test isn't just a diagnostic tool for those who already have symptoms. It's become the foundation of a whole new prevention focused approach. I spoke to Dr. Kyla Murphy, a clinical trials doctor based in Cape Town, who works closely with Rachel about a trial called Effect, which is exploring treating people before meningitis ever takes hold.

[00:19:54] **Kyla Murphy:** Over the last 10 to 15 years or so, our focus in Cryptococcal research has really shifted from initially trials looking at identifying the best, most effective and most, uh, tolerable to the patients regimens of antifungal therapy for the treatment of meningitis. And now we are moving towards uh, you know, the one step earlier, which is patients who have the cryptococcal infection but don't have meningitis and trying to prevent them from developing the meningitis and subsequently from from dying. You know, with the fact that this infection is inhaled, starts in the lung, spreads to the blood, and then to the central nervous system, we have the opportunity to detect the infection when it starts, um, spreading.

And so this, uh, test was developed called the Cryptococcal Antigen Lateral Flow assay. Which is able to pick this up in the blood. It's an incredibly sensitive and specific test. So it's basically, you know, like the ideal screening test if it's done when it needs to be done, it is almost universally correct in its results.

And if that cryptococcal antigen test and the blood is positive, um, regardless of whether the person is exhibiting any symptoms of meningitis, we recommend a lumbar puncture where we can then test the same cryptococcal antigen on the cerebral spinal fluid that surrounds the brain. And if that is positive, then that's indicative of Meningitis and, and you know, it could be really early if the person is not yet symptomatic and we think that it would make sense that if you find it that early and treated it that early, that the results of complications are much lower. Um, but also we have the potential to treat it before it even gets there.

So if a patient's CSF is negative for the cryptococcal antigen test, then they don't yet have meningitis, but they have what we call antigenemia, so antigen in the blood and we can treat those patients with antifungal therapy. What we are working on now in the Effect trial is to see whether Flucytosine being this sort of seeming silver bullet or very kind of critical drug in, in most cryptococcal regimens. If adding Flucytosine to the Fluconazole for people with early cryptococcal infection who don't yet have meningitis, might improve their outcomes as well, because there's still a small proportion of people, even after treatment with Fluconazole who go on to develop cryptococcal meningitis and die.

So the Fluconazole alone is not a hundred percent effective.

[00:22:23] **Alisha Wainwright:** Okay. That's, um, that's a lot to unpack from Dr. Murphy. I found it so interesting that because of the high mortality research is pivoting more towards prevention. Is the process she described with the lateral flow one that's available for other fungal diseases, or is this something that's really novel that's leading the way?

[00:22:46] **Rebecca Drummond :** There are some sort of broad tests for fungal infections, right? So it's something like a Beta-D-Glucan. So that's basically looks for carbohydrate that you find in the cell wall of fungi, but you wouldn't find in our bodies. So people have used this test in says like spinal fluid or blood to look for the presence of fungi in, in places where it shouldn't be, right?

You don't want fungi in your blood, for example. Um, so there's these kinds of broad tests, but they're not specific. They're just looking at whether or not you have a fungal signature, and it can be useful in people are heavily infected, or particularly if you are infected with some kind of pathogen that's well known or understood.

Um, I think the problem becomes for these sort of newer fungal pathogens that are emerging, um, these are really poorly understood. There's really not very many tests, um, available out them that's gonna give you that specificity, um, to tell you exactly, you know, what you're actually infected with.

[00:23:39] **Alisha Wainwright:** Hmm. And Rachel, is this early detection process already implemented across South Africa? I mean, you mentioned earlier the problems with access. Do they also apply in this instance too?

[00:23:51] **Racheal Dangarembizi:** So this early detection actually came as a result of a challenge that we were getting when antiretroviral therapy was introduced.

What was happening was that people would come and would, would be recruited to antiretroviral therapy, and then, um, as a result of, of restoration of the immune system, they would end up with what's called paradoxical IRIS or an inflammatory form of cryptococcal meningitis that is actually quite fatal. So what was happening was that someone would have an underlying cryptococcal infection that was not really causing any symptoms because the immune system is really down.

But if you put them on antiretroviral therapy and you reawaken the immune system, then the immune system will detect the presence of that underlying infection and it will just. Sort of creates a storm of inflammatory mediators and that then would cause death.

[00:24:51] **Alisha Wainwright:** Can you explain the treatment that you're, uh, uh, talking about

[00:24:56] **Racheal Dangarembizi:** antiretroviral therapy?

So it's the therapy that we use for treating HIV that is the go-to now for HIV. Which reverses the immune suppression by replenishing the immune cells that are usually depleted by the virus. Right?

[00:25:12] **Alisha Wainwright:** And then once you have your great immune system, then it's like, wait, what is this? And then it has a giant, uh, inflammatory response, that makes sense

[00:25:19] **Racheal Dangarembizi:** And that ends up being damaging to the, to the host that was causing death.

So then it became a requirement or a policy that everybody who's going to be recruited onto antiretroviral therapy has got to be tested for cryptococcal meningitis at least, just to see if they've got the antigen at all and underlying infection. And if they do, then we do what's called preemptive uh antifungal therapy, um, and they're treated first for that underlying fungal infection before they can then be given the antiretroviral drugs. So that opened up an opportunity for us to get people with early infection that is probably non-symptomatic, and, and that has actually opened up a window for us to research the disease quite early on um before symptoms show up. And, um, and that has saved also a lot of lives, right? Because in most cases, people would discover quite late with really serious symptoms that they've got the disease.

[00:26:23] **Alisha Wainwright:** So there is real momentum behind prevention. But there's another thread running through everything Rachel, Rebecca, and Kyla have touched on today and it's worth pulling on because even the best prevention strategy has limits.

There will always be cases that make it through, and when they do, we still don't fully understand what is actually happening inside the brain or why some people fare so much worse than others. So what do we actually know about the fundamental pathology of this infection and what are the missing pieces?

Let's hear from Kyla again.

[00:27:03] **Kyla Murphy:** Since we still see a significant mortality associated with crypto, but also morbidity so patients who survive, but with, you know, long-term, um, health consequences, disability. We are definitely not all the way there and we can try and prevent as many cases of meningitis as possible through crypto antigen screening and preemptive treatment.

But there will still always be those cases that make it through. And one of the things that we are hoping to achieve is to better understand the host pathogen interaction with cryptococcus. So how our own immune reaction to the infection might actually be one of the drivers of disease. Um, I often compare it now to COVID, which a lot of people understand that, you know, a lot of the symptoms one would experience and the, you know, really bad respiratory symptoms are not directly necessarily a, a, an effect of the organism, but actually of your body's own immune response to that organism. And so there is certainly an interest in immune therapies that could be used in combination with antifungal therapies to try and stem that overactive immune response reduce the symptoms, particularly that result in a lot of the brain injury.

Some immune therapies have been trialed before, like using steroids, which was found not to help and in fact to make things worse. So it'll be a fine balance of kind of figuring out what is the main driver of this inflammatory response in these patients and what could we potentially target with a clinical trial to, uh, reduce that response.

And so together with, uh, the crypto lab at UCT, we are collecting specimens from our patients from the effect trial, so patients with cryptococcal antigenemia who don't have meningitis, as well as similar patients who have meningitis both without symptoms and with symptoms to see at what point the various biomarkers change and whether there's some kind of key biomarkers that we could use to predict maybe even without a lumbar puncture, and create a slightly more tailored therapeutic option for patients that isn't as binary as yes meningitis or no meningitis, um, but rather treats the kind of symptoms and risk profile of the patient.

[00:29:23] **Alisha Wainwright:** That's so exciting.

Um, so Kyla mentioned your crypto lab. Rachel, can you expand a bit more on what you're trying to achieve there?

[00:29:32] **Racheal Dangarembizi:** So what we've observed from our, you know from our data is that patients with cryptococcal meningitis present with this massive inflammation that we are not sure where it comes from and at what point it develops.

So the work we are doing in conjunction with the Effect trial, for example, is trying to go as early as we can during the course of the disease and then follow up with. The disease to see at what point, what point is the inflection point, so to speak, where you know, it's tips towards the inflammatory side and we can be able to see which biomarkers are being generated at that point that can help to be pointers or signatures of disease that will use for future cases. Um, we are also looking in the brain to see the mechanisms of that inflammation, which cells are, you know, hyper inflammatory and why are they hyper inflammatory? Um, we are looking at other secondary causes of inflammation that are outside of just the immune system being disturbed, for example.

And so we are trying to get to the bottom of this development of inflammation when it develops, how it develops, what causes it so that we can be able to then find therapies for that. And that is really exciting that we can do it in preclinical models using, you know, mice and, and other models. And we can also translate that directly into, you know, patients with cryptococcal meningitis that we see in the hospital.

[00:31:00] **Alisha Wainwright:** I think it's so fascinating, kind of what we touched on earlier about how if you can just test people who don't have symptoms, but they do have the antigen, you can sort of catch it way earlier than you ever could before and then sort of monitor. So it's just this almost wide open door of opportunity of access that you wouldn't, would've not had previous.

And all of this is built on decades of research to be able to even get this test. It's just, um, it almost feels like a little bit of a snowball. I'm wondering if you feel the same way, Rachel.

[00:31:34] **Racheal Dangarembizi:** Yeah, that's correct. Um, and just to add that, you know, we are also at that point where there are so many other cutting edge techniques that we can pair up with this research. So, for example, we are able to look at thousands of genes in, in each cell, right? And that just, you know, unlocks a reach dataset that answers so many questions. And so it's, I feel like it's quite exciting and I'm very hopeful genuinely for the fields that we are now going to unlock answers faster than we could, than we could long back.

[00:32:07] **Rebecca Drummond :** Yeah, I, I think I would add to that actually, that there's a field of neuroimmunology, right? So trying to understand the immune response in the brain. And this is largely being, you know, looked at a lot in things like neurodegeneration. There's been lots of technological advances done in that sort of space, but we can use those technological advances and apply them to infection.

And that really opens up, say this idea to get this kinda big picture that Rachel was describing and to better understand exactly what is going on in that brain during an infection. Um. And we can look at individual cells, but we can also look at where those cells are sitting in the brain. And that's really important for looking at different neurons and how they might be damaged, different regions of the brain and how they might get damaged during infection.

It wasn't previously possible to really look at that level of detail. And now we can, and that's something that Rachel and I think are really quite excited to start applying that in our own research.

[00:32:56] **Alisha Wainwright:** I'm just curious, how are you guys working together?

[00:32:59] **Rebecca Drummond :** So your, your, your brain has its own immune system if you like.

Actually, most of your organs do they have immune cells that, you know live there. And one of their roles actually is to act almost as guards, right? So they're checking for anything that's not supposed to be there. And so they can alarm to other immune cells in your blood, for example, that they need help. So one of the things that I've been quite interested in is how does that happen in different organs, right? And, and the brain being a good example of this, um, but it, it becomes quite difficult to, um, put that into context because actually it matters where those cells are sitting in an organ, particularly something like a brain, right? So your brain's covered in this, uh, membrane layer called the meninges.

Um, and that gets very inflamed during, uh, you know, during crypto meningitis. But understanding the kind of, uh, communication, if you like, between that layer and the deep layers of the brain that can be quite difficult to understand. And that's where a neuroscientist perspective is really quite important for me.

And that's where, you know, having discussions with Rachel has really kind of made me think differently about my own data and the way I think of things. I think when you're a, an immunologist, you, you're very, um, baised right? Everything that's happening is because of the immune system. But actually when you speak to the neuroscientists, you're like, well, you know, the brain, you know, is quite important for doing this thing, and actually you have this big effect on the whole body, as Rachel was describing. So actually some of what we're seeing might not be localized. It might be more systemic. And those are kind of perspectives that kind of force you to kind of, uh think of it on a little bit more and that challenges the way that we would interpret our data.

And I think that gives us a better, uh, picture at the end. Um, that's probably going to be more translational to what is actually going on in people, um, as well.

[00:34:39] **Alisha Wainwright:** And Rebecca, I also wanted to pick up on Dr. Murphy's comparison to COVID. It's not something that came to to mind, but now that she's pointed it out, does that comparison track for you?

[00:34:51] **Rebecca Drummond :** I really liked how she started to saying that the, the immune response is, is so important because that then tells you about what types of inflammatory, uh, complications that you might get, um, from this disease. I think she also made a lot of good points that it's not simple, right? So we know particularly immune cells in your brain can become infected with the virus and how that then you know, affects your ability to fight the fungal infection. We really don't know. Um, so there's a lot of big open, uh, questions there and it's why it's so important to understand the immune response and inflammation and how they develop, why they develop in some people, but not in others. That's another, you know, I think open question there because as, as, as Kyla was saying, if you can do that, you can then give more tailored therapy, uh, to people and that will make it less likely that we introduce therapies that actually might harm people rather than help them.

And I think another way of kind of correlating it, and not just COVID-19, but is cancer. So immune-based therapies have revolutionized cancer, right? Immune, immune checkpoint blockade. If anyone, if you know anyone unfortunately who's had cancer, chances are they

might have been given these immune checkpoint blockade type therapies and they work by blocking, um, certain aspects of the immune response to make sure you get a better, uh, reaction against the tumors or against the cancer.

But that hasn't really been applied in the context of infection. So we're quite a bit behind there. And part of that is because of a, a poor understanding of immune responses to certain types of infections, particularly in a localized way. So in cryptococcal meningitis looking within the brain, for example. So there's a big opportunity there if you compare it to other types of diseases where immune-based therapies are actually used as standard in a lot of cases.

[00:36:26] **Alisha Wainwright:** How hopeful do you feel about the future of the research of fungal infections, and is the research going in the right direction?

[00:36:34] **Rebecca Drummond :** I, I, I'm very hopeful because the field is growing, which is good. Um, because the more people we get in, the more people we get working on this and interested in this, the chances are our will we make bigger, um, advances.

So it's great to see people actually who maybe not traditionally come from, uh, you know, classic like microbiology backgrounds coming into this field and applying fresh perspectives to it. So Rachel is, uh, is a great example of that. I'm also pleased to see that there's a lot more clinical trials and efforts to try and get more clinical trials, particularly in the context of cryptococcal meningitis.

So that's, I've made quite big strides in terms of the antifungal drug therapy. We've made quite big advances in that, but there's still a lot to be done, particularly in the context of inflammation and the immune response, um, as well.

[00:37:15] **Racheal Dangarembizi:** I think I touched on this earlier, I'm quite hopeful, especially because as Rebecca said, there's much more awareness now and there's growing awareness still.

And um, what makes me even more excited is that this has gone to the level of policy. So, for example, the WHO in 2022, for the first time in human history put down a list of 19 pathogens of a fungal origin that should be prioritized for research. And that was quite a, you know, a game changer in the field of fungal research 'cause now we know what to focus on. And that had a lot of funders actually changed their mind about funding, uh, fungal research. But outside of that, the evolution of science itself makes me really excited that now we have got better tools and better platforms, even with Bioimaging that can help us to study fungi at, you know, at unprecedented resolutions.

Um, and even in real time, right? So we are able to answer much more deeper biological questions about fungi and faster, and I think we will be able to generate, you know, answers or solutions to, to the questions we've always had much faster than we would have 50 years ago.

[00:38:31] **Alisha Wainwright:** I love how you both have described offering new perspectives or working with other fields can offer new perspectives In your field of research, would you like to see more collaboration across different disciplines in science when it comes to studying fungi?

And is that something that maybe other areas of science can take into consideration?

[00:38:54] **Rebecca Drummond :** Yeah, I, I think interdisciplinary research really is the future, right? We, you should be doing a lot more of it, and it really does, uh, make a very big difference actually to what you can achieve. When you're running a research lab, you can't do everything. It's, it's not possible to have every single technology set up. Some of these assays or experiments that we could do can take years to set up and get them working properly. For example, I, I wouldn't want to try and set up some of these sort of behavioral or neurological, um, assays that Rachel does in my lab.

'cause it would take us a really long time to do that. So it's better just to collaborate and then we can share, um, our models and tools and things that we're developing in our data. And that means we get to an answer much faster. And, you know, with, in the current, uh, you know, climate actually, um, is, it is actually you can do international, uh, collaborations quite easily.

Um. So, yeah, I, I think we should do a lot more of it and, uh, I think it'll make a very big difference to the types of advances that we'll be able to get to, uh, in the future.

[00:39:48] **Racheal Dangarembizi:** I also believe in multidisciplinary teams in trying to address this because there are quite a number of different aspects, you know, that one has to look at.

So not just, you know, the immunology or the neuroscience, but there's so many other things. The physical principles. For example, we've had to get a physicist and a mathematician to come and help us answer some of the questions that are related, for example, to fluid disruption within the brain. So trying to be everything is just not possible and one has to sort of build a multidisciplinary team, which is what I've tried to do and now with the introduction of all of these multiomics and big data, et cetera, et cetera, as a PI, you end up feeling very limited and you have to get the people with the right kind of skills to be able to come and contribute to that. So I think, as Rebecca said, collaboration is really the future of science, and that's the way to go.

[00:40:39] **Alisha Wainwright:** Thank you both so much for your time today.

[00:40:42] **Racheal Dangarembizi:** Thank you so much for having us.

[00:40:44] **Rebecca Drummond :** Yeah, it's been great. Thank you.

[00:40:48] **Alisha Wainwright:** That's all for this episode. Thanks to Dr. Rachael Dangarembizi, Dr. Rebecca Drummond and Dr. Kyla Murphy for that incredible insight into this huge challenge facing the world. What stayed with me from this conversation is that sometimes the most important scientific progress isn't the dramatic breakthrough.

It's the painstaking work of going back to basics, understanding exactly what this infection does to the brain and why is what will unlock the next steps when it comes to treatments. And what gives me real optimism is who's doing the work. A neuroscientist and an immunologist. Working across continents, each bringing a unique perspective to the table and moving faster because of it.

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