Susan Manfull, ...: 00:00:07 Untangling Pandas and Pans is a podcast about two little known medical disorders characterized by the sudden and dramatic onset of symptoms such as obsessions and compulsions, vocal or motor ticks, and restricted eating behaviors, and a whole host of other symptoms following a strep or other bacterial or viral infection. I have [00:00:30] the privilege of interviewing some of the top researchers and clinicians in this rapidly growing area, known by various names such as immune mediated neuropsychiatric disorders, infection associated neuro immune disorders, and autoimmune encephalitis, or simply Pandas and Pans. My name is Dr. Susan Manfull. I am a social psychologist, the executive director of the Alex Manfull Fund, and the mother of Alex Manfull, who died at 26 years [00:01:00] old. Due to Pandas a disorder, my husband and I knew next to nothing about, certainly not that our daughter could die from it.

Bill Manfull: 00:01:18 This is episode eight of Untangling Pandas and Pans recorded November 23rd, 2024.

Susan Manfull, ...: 00:01:27 More than 2000 years ago, the Greek physician [00:01:30] and philosopher Hippocrates famously said, all disease begins in the gut. Today. Some researchers are taking a closer look at this proclamation. Today we are thrilled to talk with Dr. Pawel Kiela, a leading expert in autoimmune and autoinflammatory disorders. We talk about his research on the gut brain connection, particularly how the gut microbiome and microglia [00:02:00] may play pivotal roles in the pathogenesis of neuro immune psychiatric disorders, such as Pandas and Pans. All right, let's get started. We have a very special guest, Dr. Pawel Kiela. He has a doctorate degree in veterinarian medicine, and he has a PhD in developmental physiology. The DVM degree is from the Warsaw University of Life Science in Poland, [00:02:30] and a PhD is from the same university and Lund University in Sweden. He is now a Panda endowed professor in autoimmune disease at the University of Arizona College of Medicine in the Department of Pediatrics.

00:02:49 Drilling down a little further, he is in the Steele Children's Research Center. The Steele Children's Research Center is a very interesting [00:03:00] place. It is a integrated program of basic research and clinical research, clinical care and teaching to address a spectrum of neuropsychiatric disorders such as Pans, Pandas, and Sydenham's chorea. And I should mention before we go any further, I I said that Dr. Kiela is a panda endowed professor that is unrelated [00:03:30] to Pandas as we're, um, accustomed to using that, that acronym. panda, in this case, stands for, uh, people acting now discover Answers. And it is a relatively small group of philanthropists who fund medical research to create healthier futures for children. So, Dr. Kiela, that's [00:04:00] a long description of what it is that you do, but

there's even more to what it is that you do, and I think that you're probably in a better position to talk about some of the centers of excellence in which you are a, uh, lead scientist. So can you elaborate on, on, uh, the Centers of Excellence under the Seal Children's Research Center?

Dr. Pawel Kiela: 00:04:27 Yes, of course. First of all, thank you, Susan, for having me on [00:04:30] your podcast. I, um, I'm really honored to be a part of it. Um, yes. So within the, the Steele, uh, children's Research Center, we have, uh, centers of Excellence, which are focused on, uh, addressing some of the specific disorders, uh, afflicting, uh, children. And I'm, I'm a member of two of them. Um, I'm a lead scientist, uh, in the CPAE Center of Excellence where CPAE stands for Children's Post-Infectious Autoimmune Encephalopathy, [00:05:00] uh, a term that we coined as a, as an umbrella term that covers Pans and Pandas and related, um, neuro inflammatory and behavioral, um, conditions in children. And I'm also a member of, uh, of recently created, uh, Daniel Cracchiolo Institute for Pediatric Autoimmune Disease Research within our center. So the, the, the, it may seem like there may be some overlap between the two, uh, in terms of the autoimmune component, and that's, that's [00:05:30] where I thrive.

Susan Manfull, ...: 00:05:31 And you are also an associate director of a relatively new

Dr. Pawel Kiela: 00:05:35 Yes. I'm the Associate Director of the Steele, uh, Children's Research Center for Basic research, uh, and an associate director of the Pediatric Gastroenterology Fellowship program, where I assist our fellows in developing and conducting research projects as part of the fulfillment of their, uh, fellowship, um, curriculum.

Susan Manfull, ...: 00:05:56 Well, Dr. Kiela, I don't know when you find time to sleep <laugh>,

Dr. Pawel Kiela: 00:06:00 [00:06:00] That's, I, I don't <laugh>

Susan Manfull, ...: 00:06:03 <laugh>. All right. Now, I know that, uh, your research, if I recall correctly, has a, uh, particular focus on Crohn's disease and ulcers of colitis, but there are many other subjects that you are interested in. Could you just give an overview of that now as well?

Dr. Pawel Kiela: 00:06:25 Yes. So my, um, my primary research is within [00:06:30] the physiology and pathophysiology of the gut. Um, and that includes studying, uh, chronic inflammatory disorders like Crohn's disease and ulcerative colitis, trying to understand the role of interaction between gut microbiota, bacteria that reside within our guts with the epithelial cells that line and separate, uh, our organism from the countless bacteria within the, the lumen of our gut. [00:07:00] Uh, and trying to understand how, uh,

bacteria shape immune, both innate and adaptive immune responses, not just within the gut, um, but also beyond. And, uh, for a long time we've had a program also where we studied, um, the link between, uh, gut inflammation and bone, um, formation. And, and that also at some point, uh, [00:07:30] led us to become really interested in the role of gut microbiota in shaping systemic immune responses and also, um, neuroinflammatory responses in Pans and Pandas.

Susan Manfull, ...: 00:07:43 So how did you make that leap to Pandas and pens?

Dr. Pawel Kiela: 00:07:50 So when we created the, uh, center for Pediatric or Autoimmune Encephalopathy, um, tasks with getting some [00:08:00] preliminary data to see if microbiome of mucosal surfaces, and there was both nasal throat and gut in some way correlated with, um, the symptoms of, of Pandas, um, in our patients. And it was a, it was a sort of a leap of faith, uh, simply based on an assumption that microbiome, uh, is a potent [00:08:30] modulator of immune responses. And we wanted to see if there's a correlation whether this can be exploited as a, a diagnostic tool or perhaps help explain some of the, uh, pathogenesis associated with neuroinflammation. Uh, and at at that time, there was already quite significant amount of information published that indeed gut microbiota can play a role in, in, in shaping neuroinflammatory responses and neurodegenerative responses. And, [00:09:00] um, so it wasn't, it wasn't, it was not a completely insane idea, but we were operating in, in largely in, in, in vacuum thinking that, that that could be the case.

Susan Manfull, ...: 00:09:12 What year about was that?

Dr. Pawel Kiela: 00:09:15 I think it was about 2018, 2019 when we started working on this.

Susan Manfull, ...: 00:09:20 Okay. Alright. So I mentioned that the Steele Children's Center has several arms, the basic science, the clinical research, [00:09:30] uh, clinical care and teaching. Was it, uh, in the clinic, were the clinicians already seeing patients that they were diagnosing as Pans and Pandas or, um, is, is that what drove the question into your research clinical observations?

Dr. Pawel Kiela: 00:09:52 As you said, the mission of our department and the Steele center is to combine clinical care with [00:10:00] research, and that is one of the strengths of, of our department, which is the only pediatric hospital that has an associated research, uh, arm and research center. And we always try to, when we plan development of any clinic, we always try to merge and blend research, teaching and, and clinical care together, uh, to continue, you know, along that [00:10:30] path of the combined strength of these three arms and, and, and that every center that we create, uh, has a common mission, which is to, to heal, to, to

teach and to, to do research. Uh, so when, um, when the CPAE Center was created, we already knew that we, we want research to be a, a, a critical part of that, that center. And, uh, and at that, and at that point, I was, uh, [00:11:00] I, I joined that, um, that center of excellence to see if we can do some meaningful translational research using mouse models and, uh, cells and, uh, as well as human samples to see if we can get some better understanding of the pathophysiology of the disease and maybe come up with better objective tools for diagnostic screening.

Susan Manfull, ...: 00:11:25 You, you really have the perfect background to move into that with your [00:11:30] autoimmune and autoinflammatory, uh, research that had already taken place. You're in the pediatrics department and you have a clinic there seeing a pediatric population. So I, that's a really, uh, fortuitous combination, I think to have the research and the clinic right there. Lots of, as we said at our recent symposium dialogue, I imagine between [00:12:00] the two groups.

Dr. Pawel Kiela: 00:12:01 Absolutely. Uh, I think we can deliver the best care by combining, you know, efforts and close collaboration between clinicians and scientists, and that that is really our long-term goal.

Susan Manfull, ...: 00:12:13 Okay. So I, I do have some questions about that, but let me just back up a moment and ask you, um, what took you to Arizona? I, I don't know if you came from Poland or Sweden, but what took you to Arizona?

Dr. Pawel Kiela: 00:12:27 So after I graduated, uh, with my PhD, [00:12:30] I, I took a postdoctoral fellowship position in the Department of Pediatrics, uh, where I, uh, I had an opportunity to continue in, um, working in a much more mechanistic and molecular way on the developmental aspects of, of cat physiology. Uh, and that was in 1996. And I, I fell in love with Tucson and, uh, the, I found the, the, the mentoring of, of, uh, [00:13:00] my, uh, department head and my still father like figure almost, uh, Dr. Han, uh, a huge asset. And the research environment at the University of Arizona was, was extremely helpful in, in growing, you know, my career and, and, and moving along the ranks. And I think I, I was really, really lucky. Uh, the combination of, of great mentorship access to, to, to resources, uh, collegial and [00:13:30] collaborative atmosphere here helped me really to, to get where I am today.

Susan Manfull, ...: 00:13:35 Well, and I had the, my husband and I had the pleasure of meeting you and touring the Steele Children's Research Center in December of 2018. And that was right after our daughter Alex Manful, um, died. And as most listeners know, and I know, you know, [00:14:00] she died from complications having to do with, um, with her diagnosis of Pan Pandas. So there I met, uh, Dr.

Danes, who is a, uh, pediatrician with special interest in allergy and immunology, uh, Dr. Rice, Sidney Rice, who's a developmental pia, uh, pediatrician. And Faye Ham, your mentor, who [00:14:30] is a pediatric gastroenterologist, uh, with a strong interest in, in nutrition. I hope I, um, summarized their backgrounds accurately. And we met, because you took my husband and me on a tour of your lab, we were very impressed with your, uh, large and, uh, very sophisticated lab at, while we were touring [00:15:00] it.

00:15:00 You told me about some research that you were doing, having to do with the microbiome in, um, three pairs of twins. And we found that a, uh, captivating story almost in an area that we were just learning about as I think, you know, our daughter was diagnosed with Pandas, but it was not long after she was formally diagnosed [00:15:30] that she passed away. So we were hungry for more information, and we were fortunate to be able to, um, visit your lab and the, the center in gen in, in general, shortly after she died, died. And we're, we've been very, I remain grateful for that, that visit. So I'm wondering if we can, um, begin by having you tell me about that study that you were doing at the time [00:16:00] and that we, the Alex Manfull Fund eventually, uh, contributed to.

Dr. Pawel Kiela: 00:16:07 Yes. So, uh, we, we started with, uh, an assumption that, uh, microbiome in, uh, patients with Pandas may be different than, uh, from their healthy, um, age and, uh, gender matched, um, controls, uh, in some cases siblings. [00:16:30] And, and, and we did that because, uh, microbiome, uh, or a collection of microbes that, uh, live on our mucosal surfaces and, and, and within the gut, uh, as I, as I mentioned, are very potent modulators of, of immune response, uh, in, in many different physiological and pathophysiological states. So we wanted to see whether, uh, nasal microbiome, throat microbiome, or gut microbiome changes in these children. [00:17:00] And we found that, uh, it was, it was pretty surprising to see about that neither nasal and throat microbiome, which theoretically, you know, these are the sites that where the infection originates were not that different. Um, but gut microbiome, uh, the entire microbial community of the gut, uh, looking at fecal samples was, was very different between healthy controls and, and, and, and Pandas patients.

00:17:27 And it, it could be especially visible [00:17:30] among siblings, uh, that were discordant for Pandas. So children that shared the shame, same environment, household environment, presumably shared the same exposure to the same pathogen, shared the same diet, uh, and yet the gut microbiome was different. But there was really, um, eye-opening to us, and, and, and, and we realized that it, it, it may be very difficult to, to try to say that [00:18:00] different gut microbiome is the precipitating factor in, in, in the

disease onset, because this disease, as you know, uh, has a very rapid onset and, uh, and catching patients prior to the onset to see if microbiome was already different, is practically impossible. Um, especially that many of, of the hands and Pandas patients as, as you well know, they're not properly diagnosed frequently [00:18:30] for months, uh, from the initial onset of symptoms. So, uh, but at the same time, um, we reason that changes in the gut microbiome, perhaps precipitated by eating disorder, that, that often these children develop, uh, could contribute to the establishment of, of chronic and relapsing nature of this disorder and can still contribute, [00:19:00] uh, to, um, changes in immune reactivity and, and, and maybe also to neuroinflammation.

00:19:06 And that was really the start of our work.

Susan Manfull, ...: 00:19:09 So your findings are, are particularly interesting because you were working with twins, um, you know, one identical, uh, set of twins and two fraternal. Yes. Why would the microbiomes be so different? Um, you said diet, but they're in the same family. You mentioned eating disorders. [00:19:30] Any other reasons why you'd see those? The differences in the microbiome, but also the, the stark difference in terms of one person having Pandas and the other, um, being quote unquote healthy,

Dr. Pawel Kiela: 00:19:47 Right? So to start with each individual, even within the same household, they do have their own sort of fingerprint or, you know, microbial signature within the gut. So we are [00:20:00] very different in, in that respect, but, uh, probably not to the point that that, that those differences would, uh, would show us dramatic as we saw, uh, in, in these twins discordant for, for Candace. So I think that the reasons for, for that difference is, is pretty complicated. And I don't know if we can assign any any one reason to that certainly changes in, in diet. And, and, and we know that these children [00:20:30] do have changes in, uh, in eating habits, uh, very severe dietary restrictions refuse to eat certain foods, and, um, and in, in somewhat similar to, to children with autism can, can be very, very picky in, in what they eat. So that that diet being one of the strongest modulator of, of gut microbial composition, uh, most likely contributes to, to those changes. Another possibility is [00:21:00] that, uh, that a childhood developed, um, more severe reaction to, let's say streptococcal infection was given antibiotics and the other child was not. And, uh, the recovery from antibiotics may have been different because of a combination of eating disorder, uh, maybe the length of antibiotic treatment and so forth. So even though we made sure that our, uh, patients [00:21:30] were not taking antibiotics for at least four weeks prior to sampling, we still saw those residual differences in microbial composition in the gut.

	00:21:41	Uh, which again, is, is, is likely the result of a combination of factors, dietary changes, and, um, and perhaps poor recovery from antibiotics.
Susan Manfull, ...:	00:21:57	Interesting. And [00:22:00] refresh my memory, please. At what point did you, uh, examine the microbiome? Uh, at what point into the disorder did you work with these patients? Another holla, how long ago was the onset
Dr. Pawel Kiela:	00:22:19	Within a year of diagnosis.
Susan Manfull, ...:	00:22:22	Okay. It really would be wonderful to do a longitudinal study.
Dr. Pawel Kiela:	00:22:27	Yes. And this is, this is what we are, uh, [00:22:30] doing right now with, uh, Juliette Madan at, at Dartmouth, uh, looking at, uh, collection of stool micro, uh, stool samples, uh, in, in, uh, regular intervals to, to see whether we can capture, maybe change in gut microbial composition at the time of, let's say, weaning from antibiotics and at the onset of relapse, because these, these children are probably, you know, in analytical, uh, aspect, [00:23:00] they serve as their ideal control. It's for themselves, it's just looking at the gut microbiome remission and, uh, and how it changes before the onset of a relapse.
Susan Manfull, ...:	00:23:13	Have you started that study?
Dr. Pawel Kiela:	00:23:14	Yes, we are actively collecting samples. It, uh, it'll take time, but, uh, we are, we're beginning to accumulate, uh, samples from these patients.
Susan Manfull, ...:	00:23:25	And what are the ages of the patients?
Dr. Pawel Kiela:	00:23:28	Um,
Susan Manfull, ...:	00:23:29	Is [00:23:30] it just children or are you including young adults?
Dr. Pawel Kiela:	00:23:34	Adolescents, uh, the oldest patient and I, I would have to open up the, um, the file where we have this information. I think the oldest right now is about 14 years.
Susan Manfull, ...:	00:23:47	Okay.
Dr. Pawel Kiela:	00:23:49	Of course, this, this may change as as, as we recruit more patients.
Susan Manfull, ...:	00:23:53	That's great. All right. Well, backing up to your original study there, I [00:24:00] am wondering if you have any ideas that you could share with us about why you didn't see differences in the, the nasal and throat samples and you did in the fecal samples?

Dr. Pawel Kiela: 00:24:15 I think it's actually a more difficult question to answer than when you actually do see differences. Uh, I, it's, um, I, I can't, I can't really explain it why we don't see the differences.

Susan Manfull, ...: 00:24:30 [00:24:30] Well, do you think the fecal samples are a more sensitive measure of, um, what's going on in

Dr. Pawel Kiela: 00:24:38 The microbiome? I think fecal fecal samples reflect, uh, more because diet perhaps does not affect, uh, the throat and nasal composition as significantly as it does to, to the gut microbiome composition.

Susan Manfull, ...: 00:24:55 Okay. In the study with Dr. Madan, are you collecting [00:25:00] nasal, um, are you collecting just fecal samples or are you also collecting nasal and throat samples? Just outta curiosity?

Dr. Pawel Kiela: 00:25:07 I think we are focused on fecal samples a here in Tucson. We are, we continue to collect both, uh, throat and nasal spots.

Susan Manfull, ...: 00:25:18 And will that research have any implications for, um, uh, using, um, what do we call it, fecal matter, uh,

Dr. Pawel Kiela: 00:25:27 Uh, transplant, uh, fecal microbiome transplant? [00:25:30] Uh, potentially, uh, I mean, it's, it's, it's a technique that is, is gaining traction right now. We have, I believe, two FDA approved products, uh, to, uh, to be used for, uh, recurrent clostridium difficile infection, which is a, uh, uh, often hospital acquired, uh, infection. And, uh, fecal microbiome transplant is the best, uh, treatment for that. Um, we have some preclinical and clinical trial data [00:26:00] from patients with autism, uh, showing that fecal microbiome transplant can to, to, to a certain degree, um, improve the symptoms. We also know that in autism, uh, fecal microbiome and changes in fecal, uh, in in gut microbial metabolic, uh, activity, uh, contributes to, um, microbial metabolized that can promote aggression and anxiety in children with autism. Uh, so translating some [00:26:30] of these findings to, to Pans and Pandas, uh, may at some point lead to a clinical trial with fecal microbiome transplant, especially that we, we see that in, um, in mouse models that when we transplant microbiome from Pandas patients to, to mice, uh, we definitely see, um, higher inflammatory response, systemic inflammatory response in this mice.

00:26:58 And we are also currently [00:27:00] looking at, um, how fecal microbiome from Pandas patients, as compared to healthy controls, affects, um, the brain function and, uh, expression of genes associated with inflammatory response in, in different regions of the brain. So hopefully we'll have some of the results to share with you in the next couple of months in if indeed we, we, we, we have convincing evidence that changes

[00:27:30] in the gut microbiome in, in, in patients with Pandas re, uh, result in a more pro-inflammatory type of microbiome in the gut, uh, approaches that would help to fix it or replace it with a more healthy community could potentially contribute to, to, uh, to much better outcomes, uh, in treatment. Of course, fecal microbiome transplant is not an easy thing to do. And, uh, and it, and it can be a dangerous thing to do. It's not just the cost. [00:28:00] Um, but it's the fact that it's, it's very difficult for scientists and clinicians in the field of, of gut microbiome is very difficult to define a healthy microbiome and what it is.

Susan Manfull, ...: 00:28:14 Oh, that's interesting.

Dr. Pawel Kiela: 00:28:15 So, so the source of the fecal microbiome transplant, uh, is extremely important in making sure that we are not transplanting inadvertently something else. And I'm not necessarily talking about pathogens, [00:28:30] although that that is also a critical element of, of choosing what we transplant. Um, but also as a community, uh, gut microbiota can do a lot of different things, sometimes unanticipated things. So case reports have been, have, have shown that you, you, you can transplant, uh, let's say acne with microbiome, you can transplant, uh, depression [00:29:00] or susceptibility to depression with, with microbiome. So again, the definition of what a healthy microbiome is, is difficult. And identifying a microbiome that would be curative for any given patient, uh, is also quite challenging. But the field is getting there and, and, and, and, and, and hopefully, you know, in, within my lifetime, this will become a standard approach to a lot [00:29:30] of different disorders.

Susan Manfull, ...: 00:29:33 That's really fascinating. I know our daughter was very interested in fecal transplant treatments, but didn't live long enough to explore them. When you mentioned, um, a few minutes ago about transplanting in, in mice, I think you said you were transplanting microbiome.

Dr. Pawel Kiela: 00:29:55 Yes. So, so we take bacteria from, uh, the twins discordant [00:30:00] for the disease

Susan Manfull, ...: 00:30:01 Okay.

Dr. Pawel Kiela: 00:30:01 And transplant them into germ-free mice, so mice that are devoid of any bacteria or viruses or fungi, uh, within their body anywhere. So they serve as this empty reservoir that we can repopulate with bacteria from either other mice or from, from human, from from patients.

Susan Manfull, ...: 00:30:20 Okay. Uh,

Dr. Pawel Kiela: 00:30:22 And then we can study the outcomes, um, of that drug.

Susan Manfull, ...: 00:30:25 And you found, I, I think you said, um, correct me if I'm wrong, that you [00:30:30] found an increased, uh, increased inflammatory response Yes. In those mice. And what, and what was that measured by? What as evidenced by,

Dr. Pawel Kiela: 00:30:41 So we looked at, um, production of cytokines by, um, by immune cells in locally in the gut and in meic lymph nodes, but also systemically in the, in the spleen.

Susan Manfull, ...: 00:30:56 I guess my next question is what were some [00:31:00] of the, um, main findings in the, in the twin study? And one of them, I believe had to do with the number, with the increase in cytokines when the microbiome was transferred, or am I mistaken? And, and I'm referring to the mice study?

Dr. Pawel Kiela: 00:31:16 Uh, no, no, no, no, you're right. I mean, the, the, the main findings, uh, was that, uh, twins discordant for Pandas had very different micro microbial composition in the gut. And the transplant of bacteria from, [00:31:30] uh, from these, uh, discordant twins to mice resulted in very different immune response where mice transplanted with microbiome from Pandas had more aggressive immune response.

Susan Manfull, ...: 00:31:43 So I have here in my notes, um, in, uh, related to 20 or more cytokines that were increased if the microbiome was transferred.

Dr. Pawel Kiela: 00:31:53 Correct.

Susan Manfull, ...: 00:31:53 Um, and IL 17 was, was, yeah. So there's a lot of, [00:32:00] uh, research right now on IL 17. That's

Dr. Pawel Kiela: 00:32:05 Correct. Because it's one of the pro-inflammatory cytokines, uh, that is capable of disrupting blood brain barrier that allows the influx of, um, autoreactive antibodies to the brain parenchyma, but potentially other compounds from circulation, including perhaps compounds of microbial origin, uh, that can [00:32:30] contribute, uh, or promote neuroinflammatory responses. And this is, this is also something that we actively investigated because we did, um, untargeted metabolomics of both fecal samples and serum samples from patients with Pandas and healthy controls. And it's a method that allows us to look at several thousands of, of different metabolites, um, both of microbial origin as well as of human origin, [00:33:00] dietary origin, uh, and, and look which ones are different. Um, and, and we found pretty substantial differences in metabolic composition, both in, in the fecal samples, but perhaps even more so in, in serum of patients with Pandas. And, uh, this was

fascinating because about half of those metabolites that were differentially abundant in patients [00:33:30] with Pandas, uh, can also be found in a database of microbial metabolites.

00:33:37 Um, that doesn't necessarily mean that every one of those compounds is exclusively produced by bacteria because there's, there's a considerable overlap. Some metabolites are produced by the host or humans in this case, and by and by bacteria. Um, but, but the fact that such a large proportion [00:34:00] of, of differentially abundant metabolites could be potentially attributed to changing the, to, to changes in the gut microbial composition and metabolic activity may actually be, uh, very relevant to, to the pathogenesis of the disease, especially, you know, in the context when blood barrier function is compromised. And, uh, and potentially many of these compounds which normally would not be able to penetrate into the, [00:34:30] the brain parenchyma, now they can.

Susan Manfull, ...: 00:34:34 Okay.

Dr. Pawel Kiela: 00:34:34 And that's, that's what prompted us really to look at, uh, uh, what happens if we expose human microglia, uh, to serum from patients with Pandas or healthy controls? Uh, would we be able to see activation of these microglia, uh, which, um, which could contribute to neuroinflammation.

Susan Manfull, ...: 00:34:59 Okay. [00:35:00] Put a pin in that thought for a moment. I've got <laugh> I have a couple more questions on, on this. Um, and, and so just, just to put this in a, in a larger perspective that i, l 17 is a, is a cytokine that's investigated in, in other areas beyond Pandas and Pans. Um, one is Crohn's disease, if I recall correctly, which is, is that right or am I mixing up

Dr. Pawel Kiela: 00:35:27 Something? Yes. So interleukin 17 is a, is a very important, [00:35:30] uh, mediator of inflammation in, in IBD, including Crohn's disease. Um, um,

Susan Manfull, ...: 00:35:37 You studied initially,

Dr. Pawel Kiela: 00:35:38 Correct? Yes. Although clinically it's not, it's not the most useful target because ah, if they're looking 17 as one of those, as, as there's a lot of them in, in, in, in, in biology, double-edged sorts.

Susan Manfull, ...: 00:35:53 Yes.

Dr. Pawel Kiela: 00:35:53 Uh, where

Susan Manfull, ...: 00:35:54 Can you elaborate,

Dr. Pawel Kiela: 00:35:55 You know, small, small amount in the right place is protective. Too much of it for too long and in [00:36:00] the wrong place is detrimental. And, uh, and targeting IL 17 in, in inflammatory bowel disease turned out to be, um, in some cases detrimental and, and at best and not clinically, uh, viable or, um, you know, um, it, it didn't have any, any positive outcomes

Susan Manfull, ...: 00:36:23 In Pandas. It is, uh, an educated guess that, [00:36:30] uh, IL 17 modulators might be useful in a subset of these patients. Correct?

Dr. Pawel Kiela: 00:36:39 Yes. Yes. We, we talked about it at the, at our last meeting in, in Portsmouth. Yes. We, there's certainly a, a lot of interest from clinicians in, in, in targeting IL 17, um, uh, for the treatment of pants and Pandas. And it's, it's definitely an area worth exploring, especially that there are products [00:37:00] on the market, uh, that can be used, uh, off-label to, to test it in clinical

Susan Manfull, ...: 00:37:06 Trials. Yeah. So it's a really exciting time. Alright. And one more question with regard to your, um, your twin study. It, um, in, in your, uh, you presented the study at our first symposium, um, and there were a lot of oohs and ahs in the audience when you identified [00:37:30] some of the bacteria, some of the differences in the number of bacteria that were present in Pandas versus not Pandas patients. Uh, can you elaborate on that a little bit?

Dr. Pawel Kiela: 00:37:44 Yes.

Susan Manfull, ...: 00:37:44 Maybe even backing up, like the normal microbiome is the normal healthy one is very diverse,

Dr. Pawel Kiela: 00:37:52 Correct? Correct, correct. So, loss of diversity is a very common feature of, uh, any chronic inflammatory disorders. [00:38:00] And, and we know that it's, it's, it's part of the problem. Um, I, I often, um, I often compare the diversity of microbiome to diversity of your retirement portfolio, <laugh>. Um, you know, that, that the more diverse your portfolio, if the market takes a hit, uh, your portfolio will be less affected or will recover easier. Uh, whereas ct, if you invest in two or three different stocks and the market, um, [00:38:30] goes down, you know, you could be very severely affected and have a difficult time recovering your, uh, your retirement fund. It's, it's, it's, it's quite similar with, with gut microbiome is the, the more, the more diverse the, the ecology of the gut, the more resilient it is in the face of, uh, uh, an an environmental insult, be it a, an infection, be it antibiotic treatment [00:39:00] or anything.

Susan Manfull, ...: 00:39:02 However, we can fix our, uh, stock portfolio by purchasing, uh, stocks in different areas. It doesn't translate quite as well in, um,

yet it seems to me in, um, buying supplements for the microbiome, or am I wrong?

Dr. Pawel Kiela: 00:39:23 No, no. You're, uh, you're right. I mean, it is a very active area of investigation. Unfortunately, it's somewhat polluted [00:39:30] by, uh, by, um, companies that try to market, uh, to people directly, often without, uh, good scientific support for, for some of the products. Um, the, the field in of probiotics prebiotics, uh, is, is really quickly evolving. And we are beginning to understand that, um, not only the traditional probiotics, which are usually, [00:40:00] uh, um, you know, like milk fermentation products associated, like the BAI and other pro uh, bacteria do not really do as much good, uh, to, to human health as, as the, you know, manufacturers would want us to, uh, to think. And, but we also realize that, um, prebiotics, uh, which are often [00:40:30] soluble and insoluble fibers that, uh, that, um, that we are also, um, bombarded in the ads, um, about their health benefits. They, they may actually be, their effectiveness may be different depending on an individual.

00:40:50 And, um, so it, uh, I guess what I'm trying to say is that there's no, um, one solution [00:41:00] that fits everybody. And, uh, and it it is a lot more complex than we, than we all wish. Uh, it was, but, but certainly there's a lot of research also in developing new generation probiotics, which are bacteria derived from the gut, uh, of healthy patients, uh, well characterized for their beneficial effects in preclinical and clinical studies and, and, and, and using them in combination. Um, that, [00:41:30] um, so these would be bacteria that are more of colonizing the human gut and staying there for a extended period of time, if not permanently. Uh, and of course, we have the emerging field of fecal microbiome transplant that can help the increase the diversity of gut bacteria.

Susan Manfull, ...: 00:41:52 So one of your findings was that akkermansia, uh, bacteria by the [00:42:00] name of Akkermansia

Dr. Pawel Kiela: 00:42:02 Ac Akkermansia Muciniphila.

Susan Manfull, ...: 00:42:04 So there was a significant difference, a, a significantly lower amount of this bacteria found in the gut microbiome of those with Pandas. And so our audience in that first, uh, symposium thought a ask you, um, can we go out and buy that, that bacteria? Can you tell us why that's not gonna work [00:42:30] right now?

Dr. Pawel Kiela: 00:42:31 I'm not, I'm not saying that it won't work. I, we just don't have enough, uh, data, uh, to support this. Um, and, and it's, it's also a, a bit of a, a, a risky adventure to do it, even though you can go on Amazon and purchase amania phi, uh, probiotic supplement. And the reason I'm saying is, um, yes, we, we see a decline, um, in, uh, in the abundance of akkermansia Muciniphila species and

strains, [00:43:00] which is especially dramatic in when we compare twins discordant for the disorder. Um, the reason why I say that it's, uh, it, it may be a little dangerous, is that the scientific literature on the role of akkermansia Muciniphila is still evolving in their contrary information about, uh, benefits versus risks of akkermansia supplementation and, and their role in the disease process. Um, [00:43:30] one of the, uh, studies that was somewhat related to, to dupan and Pandas was a study with patients with multiple sclerosis that showed that these patients actually have higher levels of, of this bacteria in their guts.

00:43:45 And, and the initial conclusion of the authors was that it, since it's higher, it probably contributes to the disease. Um, but, um, but then a follow up paper from another group showed that it actually may be a, uh, [00:44:00] a, a, a response that that is aimed at counteracting the disease process, trying to actually reduce inflammatory response, um, you know, aimed at the, the central nervous system. Um, because in a, in a, in a mouse model of, um, of multiple sclerosis, they showed that supplementation with akkermansia was able to at least partially attenuate the disease. Now, [00:44:30] follow up studies, uh, often related to intestinal inflammation, show that you can see both beneficial and detrimental effects of akkermansia, which may be dependent on the, uh, strain of this one bacterium that you're supplementing, uh, where some of them, uh, show beneficial effects and some detrimental. Uh, [00:45:00] and since there's more than one strain of amania Muciniphila in the gut, it may be really important to know which one we are trying to supplement.

00:45:10 Um, the, the other issue with, uh, um, over the counter supplementation with Akkermansia is that this bacterium is, uh, is an obligate ope. What it means is that it lives only in [00:45:30] strictly anaerobic conditions where the, without any exposure to oxygen and even very short exposure to a small amount of oxygen kills them. And because it's not a bacterium that creates spores that would allow them to survive, uh, normal environment in which we live, I would, I would love to see some evidence that the probiotic that is being produced by these companies and sold over the counter [00:46:00] contains actually viable bacteria. Uh, I mean, it, it's hard to imagine for me that, uh, that, um, that during the manufacturing process, these bacteria are not exposed to, uh, to oxygen. And, um, and if they do, um, they're most likely dead. Having interest said that, having said that, uh, I cannot possibly exclude a possibility that even dead [00:46:30] bacteria, uh, could serve some sort of protective, uh, immunomodulatory effect in the gut. But, um, but the, uh, there's really no good, uh, clinical or preclinical data, uh, to show that yet.

Susan Manfull, ...: 00:46:49 And this just underscores again, how complicated these disorders are. And nothing can be fully understood in a vacuum. [00:47:00] It's all can, it has to be seen in context.

Dr. Pawel Kiela: 00:47:03 Yeah, absolutely.

Susan Manfull, ...: 00:47:08 All right. Well, still just wrapping up that very important study, um, your preliminary data or I, in that study, I, the thought emerged at least maybe you can elaborate on this part, um, that the [00:47:30] Pandas systemic microbiome is associated with the activation of microglia. So that is our transition into your recent research that you presented at our symposium. Can you talk a little bit about what led you to think that and, um, what exactly micro, um, uh, microglia are?

Dr. Pawel Kiela: 00:48:00 [00:48:00] Right. Um, so microglia, uh, are what, um, immunologists considered to be brain resident macrophages. So they're part of the innate immune system, uh, innate meaning that they don't develop memory. They're part of the ancient, uh, um, um, conserved immune, uh, response mechanism. Um, but these cells have evolved really to play a [00:48:30] lot of, uh, functions in the central nervous system where they, uh, under normal circumstances, they, they contribute to, um, to synaptic, uh, trimming to, uh, to, uh, healing from any, uh, type of injury, uh, cleaning up debris. So they, they do have a lot of positive function, but when, when [00:49:00] exposed to stimuli that normally they are not exposed to, they can become pathogenic and they can promote, uh, tissue damage, inflammatory response, and chronic neuroinflammation and activation of microglia is, is, is very common feature of most, if not all, neuroinflammatory and neurodegenerative diseases.

00:49:30 [00:49:30] And, uh, why we became interested in, in, in these cells is it's, it's, it's because of the metabolomic analysis that I, that I mentioned earlier that we did in the serum of Pandas patients, which identified a lot of compounds changing in the circulation, uh, that, uh, that could be of microbial origin, could be of host origin, um, but, uh, compounds that potentially in the [00:50:00] context of impaired blood brain barrier can actually, uh, penetrate into the gap, par into the brain parenchyma and activate microglia to push them out of their normal, uh, homeostatic, if you will, or health, uh, healthy state into a pathogenic state of activity. And, um, so we wanted to work with, um, human microglia [00:50:30] to make this, um, more relevant to human disease. And, uh, and that's why collaboration with, uh, Arab Blackman from, um, from Albert Einstein, uh, college of Medicine was so helpful because he's a, he's a true expert in modeling, uh, human disease using pluripotent stem cells, but which can be forced to differentiate into different specific types of cells, including microglia. Uh, so we, we learn

[00:51:00] how to, how to use these reproducible pluripotent stem cells and, um, and push them to differentiate into hematopoietic stem cells initially, and then to, to microglia. And then we expose these cells to, to Sierra from patients from Pandas or healthy controls. And we looked at their activation status, uh,

Susan Manfull, ...: 00:51:25 And what did you find?

Dr. Pawel Kiela: 00:51:26 It was really striking that, uh, that [00:51:30] serum from, uh, patients with Pandas, uh, was consistently much more, um, much more prone in, into, into, to, to pushing microglia towards inflammatory state. Um, and what we also found, uh, was that some of the changes that we observed, particularly, uh, expression of the typical markers of activation of microglia, [00:52:00] which are associated with, uh, inflammatory state, uh, was dependent on, um, endotoxin, uh, or the, uh, or, um, the receptor for endotoxin tolike receptor four, uh, and that we, if, if we scavenge endotoxin from serum, uh, in this case, we use, uh, uh, uh, an antibiotic that can bind to endotoxin, uh, prevent [00:52:30] it from binding to TLR four, it's polyx and B, or using antibodies that bind to the receptor for this endotoxin or tolike receptor four, TLR four, we were able to attenuate this, this response and expression of activation markers, uh, on microglia and to, to us, it, it also added an additional line of evidence, or at least a strong suggestion, that patients with [00:53:00] Pandas, in addition to changes in the gut microbiome, may also have a, a defect in gut permeability or a leaky gut, if you will, that allows end the toxin, which comes largely from, um, from gram-negative bacteria in the gut to translocate to the circulation, and then, um, activate downstream inflammatory, uh, signaling pathways.

00:53:30 [00:53:30] Importantly, endotoxin, uh, is also a very potent, uh, substance that, uh, breaks down the integrity of the blood brainin barrier. So perhaps a combination of, uh, inflammatory mediators such as interleukin 17 and, and the presence of endotoxin in the blood, uh, contribute to the breakdown of the blood, uh, brain barrier. And then, um, and then endotoxin [00:54:00] can continue to, uh, to activate microglia towards more pro-inflammatory stage and then promote neuroinflammation and all the behavioral changes that we see in those, uh, children. Um, so I, I think it, it's going to be in the near future, it's going to be really important to find to, to have to create this integrative approach to Pans and Pandas, uh, where, you know, scientists and clinicians can work together on, on, [00:54:30] on identifying the entire pathway, you know, that, that we don't, don't work in silos, but rather collaborate and, and, and, and try to create this, this, this integrated picture of what happens holistically in the body of patients with Pandas.

	00:54:52	Uh, you know, working on the autoimmune aspect and finding auto, auto antibodies, uh, towards, um, [00:55:00] basal ganglia is not done in, in a vacuum that it's, it's, it is done in the context of damaged blood brainin barrier, uh, the role of microbial compounds, uh, and, uh, the role of gut microbiome in altering, uh, intestinal barrier function that allows the, these compounds to cross the otherwise impenetrable [00:55:30] intestinal barrier. And then the next stage cr, you know, for these compounds to cross the otherwise impenetrable blood brain barrier and then lead to, uh, downstream inflammatory, uh, responses in in the brain parent. I think it's going to be really, really important that, that we all work together and we try to holistically approach all of those findings.
Susan Manfull, ...:	00:56:00	[00:56:00] That's fascinating. Can we just drill down a little bit for those of us who, um, don't use this language all the time, can you more or less explain what an endotoxin is? Can you, um, provide a, a definition now for it for us?
Dr. Pawel Kiela:	00:56:20	Yes. So, um, endotoxin, uh, is a, is a lipopolysaccharide, uh, that, uh, is a, a compound, [00:56:30] uh, that is, um, part of a bacterial wall. Uh, majority of endotoxin producing bacteria are in the gut. Uh, they reside there permanently, uh, but endotoxin does not, uh, get across the intestinal barrier unless it is disrupted by some insult,
Susan Manfull, ...:	00:56:57	Like,
Dr. Pawel Kiela:	00:56:58	Um, [00:57:00] like in intestinal inflammation.
Susan Manfull, ...:	00:57:03	Okay. Alright.
Dr. Pawel Kiela:	00:57:05	And when, and so if changes in gut microbiota in these patients lead to even a low grade, uh, inflammation in the gut and increased permeability or leakiness, uh, some of these microbial products that are normally sequestered to the lumen of the gut and expelled Mm-Hmm. <affirmative>, uh, with PCs with poop, uh, [00:57:30] may get across into the circulation and, uh, lipopolysaccharide maybe one of them.
Susan Manfull, ...:	00:57:41	And what is that?
Dr. Pawel Kiela:	00:57:42	That's endotoxin.
Susan Manfull, ...:	00:57:44	Oh, that's the endotoxin, right? That's
Dr. Pawel Kiela:	00:57:45	The endotoxin. Okay. And, uh,
Susan Manfull, ...:	00:57:46	All right.

Dr. Pawel Kiela: 00:57:47 So lipopolysaccharide, uh, works on a lot of immune cells, but also on epithelial cells. It practically affects the function of every cell in the body that expresses, uh, uh, a receptor for, [00:58:00] for endotoxin. Uh, and that receptor is called toll-like receptor four or TLR four. And, uh, that's what I was referring to, that if we block the function of this receptor to block the ability of endotoxin to bind to it, we can, uh, partially, uh, restore, um, the expression of activation markers on, on, on, um, [00:58:30] microglia. But it's not, it's not all of the story, uh, because we, we see a lot of other changes in microglia, pro-inflammatory changes that are not dependent on endotoxin. So there's clearly multiple signals within the, you know, the soluble fraction of, of proteins or other type of metabolites in circulation of Pandas patients that can affect microglia and push them into this more pro-inflammatory state. [00:59:00] And, uh, one of our goals is to identify what they are,

Susan Manfull, ...: 00:59:04 What the other factors are correct that push microglia into the inflammatory state. All right. Um, so it's, um, frequently, uh, observed in, um, uh, children and adolescents and young adults who have, um, I sick with just saying Pandas who have, uh, Pandas, [00:59:30] um, that if they become sick a few days later, they may have a flare. Could this be related to the endotoxin, uh, uh, uh, a bacteria that gets into the system and the endotoxin in the, in the gut, or am I just being a real lay person

Dr. Pawel Kiela: 00:59:55 Here? Um,

Susan Manfull, ...: 00:59:56 Is there any kind of connection with that observation that is, [01:00:00] is pretty common

Dr. Pawel Kiela: 01:00:03 At this point? I don't know if we can, uh, point to endotoxin as the only one, uh, you know, component of, of, of the relapse. Uh, like I said, that it is, it is probably much more complex than that, although in, in a way, your question is correct in that our hypothesis is that changes in the gut microbiota [01:00:30] that children with Pandas develop as a consequence of the disease, or perhaps treatment contributes to establishment of the chronic and relapsing nature of the disorder. And again, the, you know, the gut microbiome and, and, uh, intestinal barrier function may not be the initiating factor, but they may be the sort of the second, um, hit [01:01:00] that helps establish the chronicity and, and relapsing nature of, of pants and Pandas. And, and maybe we can intercept that and we by, by targeting gut microbiota and, uh, gut barrier function, um, to prevent relapses because we, we don't know how to prevent the disease, right?

Susan Manfull, ...: 01:01:25 Mm-Hmm.

Dr. Pawel Kiela: 01:01:25 <affirmative>, so it's mm-hmm. Acute onset, and we don't really know at this point [01:01:30] what makes one individual more likely to, to develop it and, and, and not, and, and the other individuals do not. We don't know the answer to that. But once the disease is diagnosed, can we come up with ideas of how to maintain remission and prevent relapse? And maybe in that context, uh, the role of the gut and gut brain axis in, in Pandas may be [01:02:00] a very attractive

Susan Manfull, ...: 01:02:01 Target. So I, I'm, I'm not sure how to articulate this question, but how, knowing that there is an, um, can be acute changes as the disease, uh, ebbs and flows and the individual can, can have changes in behavior and, uh, neuropsychiatric symptoms, [01:02:30] uh, very quickly changing the endotoxin and the TRL4 contribution in getting into getting out of the lumen. Is that correct? Yeah. And, and then, um, uh, causing the blood brain barrier to be more permeable, is that something that happens quickly?

Dr. Pawel Kiela: 01:02:57 Um, it, it can, um, [01:03:00] now I don't, I don't know in the context of pants and Pandas if, uh, if that happens quickly, but in the context of, uh, intestinal injury and inflammation, it can happen very quickly. Um, now, because we know that usually pants and Pans and Pandas are precipitated by a respiratory infection, um, I'm, I'm not sure to what extent acute changes in [01:03:30] the gut function can contribute, you know, to the original symptoms. Mm-Hmm. <affirmative>, it, it's, it's not impossible that they do. Um, but, but again, because of the, the nature of the onset of this disease, it's, uh, it could be difficult to study if, certainly if we had access to patients who just presented with a disorder, patients [01:04:00] that were not, that did not go to multiple doctors that ignored the symptoms or, uh, decided to treat it as a psychiatry condition. Um, but rather, you know, patients that can be immediately diagnosed, that we can also study their intestinal permeability, gut microbiota at this point and so forth. I think we would gain a much better knowledge of the early events associated with, with the disease development. [01:04:30] Uh, and, and, and hopefully as the medical field becomes more cognizant of, of the problem, um, we, we may be able to, to go earlier and, and find out more about, you know, the early events associated with the symptom development.

Susan Manfull, ...: 01:04:53 Uh, I wonder if a worthy substitute to, um, what you've just said, which as you've also said, would [01:05:00] be difficult to see that patient, um, very quickly after the onset of the initial symptoms. I wonder if in the patients that are being seen, if they're exposed to, um, strap, for example, if they come in and have, um, their microbiome, um, for lack of better words, analyzed [01:05:30] at that time to see how it changes it. And it

would be particularly interesting if that did precipitate a flare, like what happened in the microbiome.

Dr. Pawel Kiela: 01:05:41 Right. So, so, you know, the best substitute for early detection and early sampling is, is longitudinal sampling in, in patients with chronic pants and Pandas, uh, right. And I think we talked about it earlier, that, that that can help us, uh, to, to establish [01:06:00] a baseline in, in microbiome and gut permeability, uh, during remission and, and perhaps capture the events leading up to a flare,

Susan Manfull, ...: 01:06:12 For example, if they've been sick.

Dr. Pawel Kiela: 01:06:14 Right.

Susan Manfull, ...: 01:06:14 Which, yeah. Um, just for the record, Alex was sick five days before she had a flare, and I would venture to say that she had never had anything remotely similar happen to her. [01:06:30] She did not have flares in, in such an extreme case, but she was sick five days before that. Um, this is all in incredibly interesting, I just thought, I, I would share with you, uh, in, as you know, we donated Alex's brain, um, and it eventually, uh, uh, is resting at Georgetown University Medical Center in the pond. Brain bank, uh, pond [01:07:00] stands for Pandas Pans and other neuro immune disorders. And she, her brain had, um, two, um, auto, um, autopsies or this final anatomic diagnoses. And she, her brain was diagnosed, they observed, uh, mild gliosis of the cardiac nucleus and the thalamus and the, [01:07:30] um, the gliosis that was found in the caudate nucleus, uh, is, uh, again, I dunno how to pronounce the word, um, uh, it's per Kyle Peral Mm-Hmm. <affirmative>, um, parenchymal astrogliosis of the caudate nucleus and observing, I mean, reading that, I'm wondering if some [01:08:00] of your research in the future might involve, um, brain tissue.

Dr. Pawel Kiela: 01:08:06 So we are certainly looking at the brain tissue in mice, as I mentioned. We, uh, we want to know what, how bacterial community from panda's patients contributes to changes in, in the expression of genes in the different regions of the brain. And we Mm-Hmm, <affirmative>, we plan to, uh, we are, we are doing it right now actually, uh, [01:08:30] to use a technique called spatial transcriptomics, uh, which allows us to look at, uh, large, uh, gene expression panels and looking at gene expressions at the level of single cell within the, uh, known architecture of the brain so that we, we can, we can, we can define which types of cells and in which regions of the brain, uh, develop, uh, changes [01:09:00] in gene expression that we can then perhaps, um, attribute to, uh, an ongoing inflammatory process. Mm-Hmm. <affirmative>. So if, if this is successful, then, then perhaps working with, um, brain, human brain, um,

from Georgetown repository would be, uh, would be the next step, uh, where we [01:09:30] could, um, utilize perhaps even a section of, of Alex's brain, um, particularly from the, the region of basal ganglia and, uh, a new spatial transcriptomics, and compare that to gene expression profile in the brain of maybe a victim of accident.

01:09:51 Um, I, I don't think Georgetown has brains from sort of healthy controls. Um, they

Susan Manfull, ...: 01:09:59 Do.

Dr. Pawel Kiela: 01:10:00 [01:10:00] They do, they do. Okay.

Susan Manfull, ...: 01:10:02 Mm-Hmm. <affirmative>,

Dr. Pawel Kiela: 01:10:03 Uh, so that would be, that would be very helpful. And, uh, we can get a glimpse not just at morphological differences between human brain with Pandas, um, but, but also molecular differences, uh, that could help us maybe define really what's going on there. Mm-Hmm. <affirmative> at molecular and single cell level, it's [01:10:30] a, it's, it's, uh, it's still a very costly technique. Um, the, I believe that, uh, the, the work that we are doing right now in mice will cost us, uh, upwards of $20,000. And I would imagine that comparing, uh, human brains would be, um, quite similar to that. Um, but it may be a very important, uh, experiment to do and could, could yield potentially a lot of useful information.

Susan Manfull, ...: 01:11:00 [01:11:00] So she had perivascular astrogliosis in the thalamus, um, and I know this is astrogliosis opposed to micro gliosis, and there's, so there's what, five different types of glial cells, something like that, right?

Dr. Pawel Kiela: 01:11:19 Yeah. Yeah.

Susan Manfull, ...: 01:11:20 What, um, is the, are the astroglia cells, um, [01:11:30] informative with regard to, or, or as informative as microglia with regard to neuroinflammatory disorders?

Dr. Pawel Kiela: 01:11:38 Uh, absolutely. Astrocytes are also critical components, uh, in inflammatory response. Um, but what, what you're describing are histological findings.

Susan Manfull, ...: 01:11:49 Mm-Hmm. <affirmative>,

Dr. Pawel Kiela: 01:11:50 Um, and, uh, histological findings are, are, are, are very important for diagnostic purposes, but they, we, you, [01:12:00] you miss functional changes, uh, that may be equally important

as increasing numbers of astrocytes in a particular location. I see. So, uh, microglia may be in an activated state, and yet you won't really see that on, on an h and e or hematoxylin and eosin stain slide, which is the typical way that, uh, pathologists look [01:12:30] at, uh, tissue sections.

Susan Manfull, ...: 01:12:35 Okay. Well, um, I can talk to you later, uh, about that, but I was, I was just curious. Um, so the microglia, uh, has, has certainly, or the views of microglia have certainly changed in recent years. You and I talked about this book, the Angel in the Assassin by Donna Jackson, uh, [01:13:00] Nakazawa, and it, that, which is basically about the history of, uh, microglia, um, use in science, I think we could say, and particularly relying on, uh, Beth Stevens, who is a neuroscientist in, uh, in the Boston area. Um, and I'll just, just to put it in perspective for how much things have changed for our listener, I'll, um, read you an excerpt from the book, which says, until recently, [01:13:30] microglia were thought to be merely the brain's housekeepers. Later in the book, it refers to the microglia as the garbage man, or something like that. It helpfully removing damaged cells. But a recent, uh, groundbreaking discovery revealed them to be capable of terrifying Jekyll and Hyde behavior when triggered. And anything that stirs up the immune system in the body can activate microglia. [01:14:00] They can morph into destroyers, sparking a wide range of problems from memory loss and anxiety to depression and Alzheimer's. And in our conversation, possibly Pandas and Pans under the right circumstances. However, microglia can be coaxed back into being angelic healers able to repair the brain in ways that can help alleviate symptoms and hold the promise to prevent disease.

Dr. Pawel Kiela: 01:14:29 That [01:14:30] that is a wonderful quote. And it really encapsulates not just the changes in the, in the scientific view of microglia, but changes in, in our view of the brain as a whole, which we used to think of as an immune privileged organ, uh, where, uh, it's, it's always under every circumstance protected, uh, from the outside influenza of, um, inflammation and immune [01:15:00] cells and, uh, uh, antibodies and all of that. And the, the view of the brain and the immunity or immunology of the brain has, has really gone a long way since, since those textbook, uh, assumptions. Um, and, uh, you know, more and more frequently we realized that perhaps many, if not most of the psychiatric disorders or what we [01:15:30] considered psychiatric disorders have neuroinflammation as the, you know, as a, as a fundamental, um, base or, or, or cause of, of, of symptoms. Um, how many of them are induced by infection, viral, bacterial? We don't know. But, uh, I would, I would imagine that Pans and Pandas are just part of a large sort [01:16:00] of syndromic, uh, response, uh, where, where the brain is, um, attacked as a bystander in, in response to, to

		infection. We see more and more cases in clinics, and I, I'm sure when you speak with Juliette, she will, uh, she will speak to that as well, uh, in, in patients with Covid,
	01:16:26	Um, that, that also are suggestive [01:16:30] of, uh, of post-viral, uh, neuroinflammatory responses. Uh, it, it's an evolving field, and it's a, it's a fascinating field to, to, to follow. And, um, I'm a little scared as a GI scientist to venture into this area, but I hope I can find ways to, to contribute something meaningful to it.
Susan Manfull, ...:	01:16:54	Well, I'd venture to say you already have, and I think that that's a, a great way to, to conclude [01:17:00] our, our talk. Um, I, I don't think it's an exaggeration on my part to say that our conversation has been really riveting to me and cast a lot of light on some of the things that, or some of the connections that I was unable to make without this conversation. So, Dr. Kiela, I thank you very much for, for talking with me today.
Dr. Pawel Kiela:	01:17:26	Thank you, Susan. It's, it's been an privilege and honor and, uh, and I [01:17:30] appreciate, uh, the organizing of your symposiums, which, which has helped our group tremendously in, in creating networks of, of, of collaborators and helping each other in the field, but, but also for your initial support and the seed ground that helped us look at, uh, some of the auto, uh, auto antibodies in, um, in Pandas. And you've been a, a champion and it's, it's, it's really a privilege to be working with you.
Susan Manfull, ...:	01:18:00	[01:18:00] Thank you. I would say the privilege is, is mine. And, um, and again, we're just very grateful for what, for what you're doing, so thank
Dr. Pawel Kiela:	01:18:10	You. Now it's time to start publishing our work.
Susan Manfull, ...:	01:18:13	This is true, <laugh>. All right. Thanks so much, Pawel.
Dr. Pawel Kiela:	01:18:17	Thank you, Susan.
Bill Manfull:	01:18:20	This concludes episode eight of Untangling Pandas and Pans. Thank you for listening. [01:18:30] For more information about Pandas and Pans and the Alex Manfull Fund, please visit the alex Manfull fund.org. The content in this podcast is not a substitute for professional medical advice, diagnosis, or treatment. Always seek the advice of your physician or other qualified healthcare provider with any questions you may have [01:19:00] regarding a medical condition.