Seizing Life, episode 140 Post-Traumatic Epilepsy: What We Know and Where the Research is Going Guest: Elisa Zanier (Transcript)

Kelly Cervantes:	Hi, I'm Kelly Cervantes, and this is Seizing Life, a monthly podcast produced by CURE Epilepsy. This month on Seizing Life, we focus on the research being conducted around post-traumatic epilepsy or PTE. This past May, CURE Epilepsy co-hosted the International Conference on Post-Traumatic Epilepsy held in, Milan Italy. One of the co-chairs of this event, Dr. Elisa Zanier of the Mario Negri Institute, joins me today to discuss the conference, the current state of PTE research, and the path to understanding how and why PTE develops so we can create effective therapies to treat it.
Kelly Cervantes:	Dr. Zanier, thank you so much for joining us today. We've had a few episodes here at Seizing Life about post-traumatic epilepsies and TBI, traumatic brain injuries. But for anyone who is newer to the podcast, can you give us a brief explanation of what post-traumatic epilepsy is as well as traumatic brain injuries?
Dr. Elisa Zanier:	Sure. So thank you for giving me the opportunity to be here with you today first. So traumatic brain injury refers to any kind of injury to the head because of the biomechanical impact that leads to a neurological dysfunction and is a leading cause of morbidity and mortality worldwide. Just to give you some numbers, in the United States every year there are about two millions of new TBI patients.
Dr. Elisa Zanier:	Post-traumatic epilepsy is a long-term complication of traumatic brain injury, and that can develop over days, weeks, and months after the initial trauma. And this is also something that can happen even after what is defined mild traumatic brain injury. So what is important to note is that, however, what I just mentioned, there is this window of time between the trauma, the biomechanical impact, and the development of post-traumatic epilepsy that I should say is the occurrence of spontaneous recurrent seizures.
Dr. Elisa Zanier:	And so this is also a window of opportunity to interfere with the processes that are underpinning the mechanism leading to post-traumatic epilepsy, so offering, at least in principle, the opportunity to mitigate this risk in terms of PTE complication.
Kelly Cervantes:	It's such an interesting area to research because post-traumatic epilepsy in theory could be prevented because we know that it is caused by traumatic brain injury. So if someone has a traumatic brain injury and you have this window, is there a way that that person can be treated to prevent post-traumatic epilepsy from occurring?
Kelly Cervantes:	And so I think this area is so ripe for research. I want to talk about the Milan conference in a minute, but proceeding that, can you give us an understanding of the post-traumatic epilepsy research landscape? Who are the players? What has been studied up to this point?

Dr. Elisa Zanier:	Yeah, yeah. As you mentioned, here we have in principle a unique opportunity really to prevent a process. So not only to mitigate the injury, but to interfere its occurrence. However, we are not at that stage yet, unfortunately. But awareness towards the importance of studying PTE is increasing. And this is also thanks to multiple organization like NIH, NINDS, and the Department of Defense, but also smaller association like CURE, for example.
Kelly Cervantes:	In lay terms, can you help us to understand what is known about post-traumatic epilepsy and what we still need to discover?
Dr. Elisa Zanier:	So post-traumatic epilepsy, just to give you a number to start with, is responsible for about 20% of all the symptomatic cases of epilepsy. What we know is that there is a severity dependency in the risk of epilepsy later in life, which means that a mild traumatic brain injury has a lower risk than moderate to severe. I'm speaking like five to 10%, up to 20% of developing epilepsy. And this risk is even higher after penetrating traumatic brain injury and can reach up to 50% of the cases.
Dr. Elisa Zanier:	However, what we don't know is why between two patients that show the same initial injury severity we can see very distinct trajectories. So one may recover while the other will develop PTE later on. So what is really important is to understand which are the mechanisms underpinning these different trajectories. And here is where research also in the preclinical setting by developing model that are clinically meaningful can help us.
Kelly Cervantes:	We can see two people have the same brain injury. One goes on to develop post-traumatic epilepsy, the other doesn't. Is there any treatments or protocols? Because it seems to me someone gets a traumatic brain injury and let's just treat everyone just in case they might develop PTE. Are there any treatments that are available to someone who has had a TBI?
Dr. Elisa Zanier:	Yeah. So if the question relates to the possibility to prevent PTE onset, so post- traumatic epilepsy onset, or the progression of the disease, the answer is no. There are no treatment available able to interfere with the development of post-traumatic epilepsy after an initial traumatic brain injury. What we have are anti-seizures medications, and these are effective in planting seizures, clinically relevant seizures.
Dr. Elisa Zanier:	However, what is also known is that in terms of prophylactic treatment, there is lot to do yet. In fact, this month's new guidelines were published by the Neurocritical Care Society in order to provide a guide to clinicians on how to treat TBI patients that did not experience any early seizures in order to prevent seizure occurrence by anti-seizure medication.
Dr. Elisa Zanier:	And in fact, there is very little evidence that treating those patients with anti- seizure medication like phenytoin or levetiracetam may reduce the risk of delayed seizures, adverse events, or mortality. So if any and if the clinician will

	decide to use this medication as prophylactic treatment, the duration should be kept as short as possible.
Kelly Cervantes:	That's fascinating to know, because that's the first thing that pops into my mind is why not just treat everyone with TBI with anti-seizure medications, but it doesn't necessarily benefit the patient, and then you're also dealing with the side effects of those medications. The DOD, you mentioned, the Department of Defense, has invested considerably into researching post-traumatic epilepsy.
Kelly Cervantes:	Most specifically, CURE Epilepsy was the receiver of a five-year \$10 million grant to put together a research team, a team science approach to try and make some headway in post-traumatic epilepsy. What is the DOD's interest in post- traumatic?
Dr. Elisa Zanier:	So military service people are at high risk of traumatic brain injury because in the field they may experience a gunshot or a blast injury or any different types of injury. And because of what we just discussed on the link between traumatic brain injury and late post-traumatic epilepsy onset, it is with no surprise that this complication is of high relevance for military personnel.
Dr. Elisa Zanier:	So this, for sure, is one of the reason why the Department of Defense has an interest in PTE. But I should mention that more broadly, the Department of Defense has an interest in fostering research towards the understanding and the treatment of neurological condition that may arise after a trauma.
Brandon:	Hi, this is Brandon from CURE Epilepsy. Traumatic brain injury or TBI accounts for 20% of symptomatic epilepsy in the general population. CURE Epilepsy, in partnership with the Department of Defense, has implemented a research program focusing on post-traumatic epilepsy resulting from a traumatic brain injury. Go to cureepilepsy.org to learn what we're doing to fund research in the prevention and treatment of post-traumatic epilepsy. Now back to Seizing Life.
Kelly Cervantes:	I'm curious to hear how your institute, the Mario Negri Institute of Pharmacology, how did you get involved with CURE Epilepsy and our PTE research projects?
Dr. Elisa Zanier:	Yes. So this is a very unique experience, and they gave us in the end really the possibility to accelerate our research. Because originally our interest in PTE started here at the Mario Negri with no funding and was based on the fact that I have a primary interest in traumatic brain injury with a background in neurocritical care. And I was collaborating here with Annamaria Vezzani and Teresa Ravizza, which are epilepsy experts.
Dr. Elisa Zanier:	So we decided to join forces in order to deeply understand post-traumatic epilepsy, which is a combination of epilepsy after a traumatic brain injury. So it's a type of acquired epilepsy. And this was back in 2016. And it happened at that time, I was collaborating with Kevin Wang, which was one of the PI of The CURE

Initiative. I was discussing with him what we were doing here at the Mario Negri Institute.

- Dr. Elisa Zanier: And when I mentioned this model that we were fully characterizing with a high percentage of PTE onset by five months, which is a very key aspect of the model. So half of the animals develop post-traumatic epilepsy after the same injury and half do not. So he became very, very interesting because his interest was on the biomarker discovery.
- Dr. Elisa Zanier: We agreed that this could be a very convenient model in order to investigate which biomarker may really speak to injury evolution towards PTE. And in the end, this was how we joined the program because he decided we could be part of his team. And from that moment onwards, we were part of the CURE Epilepsy program.
- Kelly Cervantes: I love, love, love to hear about scientists working together and sharing their studies. Scientists and researchers have such a bad rap for working in silos, and it's always just so thrilling to me to hear when this kind of collaboration is occurring. Speaking of collaboration, there was a conference in Milan earlier this May that was in led by CURE Epilepsy to bring together experts in posttraumatic epilepsy from around the world. Can you tell us who was involved in this conference, as well as what the aims were, what the goals were?
- Dr. Elisa Zanier: Yes, sure. So these initiatives started during a dinner after a CURE meeting in Atlanta. And the original suggestion came from Ben Churn, which is program director at NIH. And he was really suggesting we should bring together people highly committed to understand PTE onset and progression and conduct maybe a relatively small meeting, but very concentrated in order to agree on fundamental steps that we need to follow in order to translate the pre-clinical evidence to clinical opportunities for patients.
- Dr. Elisa Zanier: And so we decided we should do this. And in that conversation, Laura Lubbers and I were involved, and so we decided to put together this application and organize a meeting to bring together people, so scientists, but also many representatives of the NIH, NINDS, and the DOD, and also patients in order to agree on what we need to do to accelerate the research to obtain new treatments for PTE patients.
- Kelly Cervantes: I think it is incredibly important and interesting that there was an invitation to patient one in particular to attend, and that was Captain Jack Somers, who is a good friend of CURE. He has been on our podcast before. Why is it important for you as a researcher to hear from patients?
- Dr. Elisa Zanier: I mean, this was very, very important. Is very important, because you need to have several angles and the discussion needs to have an active contribution for patients. Because in the end, we are not conducting research on PTE, but we are conducting research for post-traumatic epilepsy patients. And having Jack

	Somers here was really a unique possibility to keep this in mind for the whole duration of the meeting, and of course, also beyond this.
Dr. Elisa Zanier:	And also it's important to listen what really cares for patients. Because in the perspective of researchers, it may not be a given that what is important to you is what really may change the life of a patient experiencing post-traumatic epilepsy where lethal changes can make differences.
Kelly Cervantes:	When you're looking at computer reports or animal models, I can imagine that sometimes it dehumanizes the work a little bit. So I thought it was so great to hear that Jack, former Marine, has PTE himself, that he could be there to represent the community and be that patient voice that I think is often looked over in research.
Dr. Elisa Zanier:	And if I can add something, I think that something that was really important to me is that on a personal note, Jack really wanted to be part of this discussion, which is something that needs to be considered. So possibly decisions should never be taken without discussing this also with the patient community.
Kelly Cervantes:	Absolutely. So CURE has since launched the, and I'm going to make sure I get this correct here, it's the Post-Traumatic Astrocyte Biomarker Initiative. Did I pronounce Astrocyte correctly?
Dr. Elisa Zanier:	Yes.
Kelly Cervantes:	Great. Or the PABL. Can you tell us what that program entails?
Dr. Elisa Zanier:	Yeah, yeah, yeah, and this is the results of the original CURE Initiatives combined with a grant that I was coordinating and was supported by the Department of Defense back in 2018 as well. So the first research program was very broad in order to characterize new models and identify possible mechanisms underpinning evolution from TBI to PTE. And during these years, what emerged is that these astrocytes, which are cells in the brain that originally were classified as the glue of the brain, like with a really supportive function, but they do much more than this.
Dr. Elisa Zanier:	They also have immune properties, which means that they can modulate the inflammatory response, which we know has a key role in modulating disease progression after TBI and also epilepsy, emerged as key players. So the idea was why not writing a follow-on grants with this interest as the main focus of the project. And what we will do in this grant that is coordinated by Laura Lubbers with me as a co-PI, but also has other key partners, particularly Pavel Klein and David Mennon, will contribute with clinical work on two different cohorts of patients.
Dr. Elisa Zanier:	And again, Kevin Wang and Will Askins will be mainly involved to perform all the molecular analysis of what we will observe in terms of changes in the astrocyte

population after TBI speaking to PTE development. And this will also have a preclinical component with a TBI model that will be run here at the Mario Negri Institute in Milan. And we will also explore the possibility that we can image this cell population by advanced neuroimaging approaches. And to us, this is very interesting because ideally it can be directly transferred to the clinical setting.

- Kelly Cervantes: Which is amazing. And always the goal here is with all of this, the basic science that was originally done with that DOD grant to try and find a way to translate that so that it can have a direct impact on patients' lives. So it sounds like there are two main aims to this next astrocyte research.
- Kelly Cervantes: One is determining if the astrocytes are indeed a biomarker, and then additionally trying to figure out ways to disrupt whatever process is happening that then becomes post-traumatic epilepsy. Is this we need to find the biomarkers before we can do the treatment? Or are these two aims that can be concurrently researched and moved toward?
- Dr. Elisa Zanier: Yeah, no, in principle, these two aims can be concurrent. However, biomarkers are extremely important not really to select the treatment, but to monitor disease progression and to identify possibly patients that are at high risk for PTE development, which in other terms, gives us the possibility to enrich the population for patients that are really likely to experience this complication.
- Dr. Elisa Zanier: And this is a very important aspect in order to be able to make a clinical trial affordable, because since PTE onset is an important complication, but only, of course, luckily enough in a subgroup of patients if we do not know which are the patients that really have high risk. In order to understand whether our treatment towards PTE is effective or not, we need to treat many more patients.
- Dr. Elisa Zanier: So this is why in principle the two things can go in parallel. But ideally, if we can have a biomarker that can improve the way we select patients that are likely to have this complication is much better.
- Kelly Cervantes: That makes so much sense. I find this area of epilepsy research just so fascinating because it really feels like we can see differences treatments. I mean, preventing epilepsy is essentially a cure. We can see these things happening in our lifetime, and it is so exciting to see this progress being made. I wonder what are some of your other takeaways or the next steps coming out of the Milan conference?
- Dr. Elisa Zanier: Yes. So the indication from the research in the preclinical setting is that there are very promising potential treatment able to interfere with the onset and progression of PTE. However, we need to progress without missing any key steps in order to design affordable clinical trials that are effective in testing the best treatment possible.

Dr. Elisa Zanier:	So, one of the key messages that we should put in place a task force able to identify, screen, and select which are the most promising approaches, decide which are the key steps in the preclinical setting that still need to be finalized, and identify the best way to design an optimal clinical trial.
Kelly Cervantes:	Dr. Zanier, thank you so much for talking with us, for explaining all of this and giving us a wonderful landscape of where PTE research is headed. I thank you for the research that you are doing in your lab and with this amazing group of scientists. I applaud you, and I thank you.
Dr. Elisa Zanier:	Thank you, Kelly, for the opportunity to speak to you. Thank you.
Kelly Cervantes:	Thank you, Dr. Zanier, for discussing the International Conference on Post- Traumatic Epilepsy, and for sharing your work and insights on PTE. As mentioned in our discussion, CURE Epilepsy has been at the forefront of post- traumatic epilepsy research since its PTE initiative launched almost 10 years ago. We are continuing our commitment to the field with a new initiative focused on astrocytes. If you would like more information on CURE Epilepsy's PTE program, please visit the research initiative page at cureepilepsy.org. Thank you.
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