Speaker 1 00:09

Hello and welcome back to Microbe Talk, the podcast by the Microbiology Society. I'm your host Lilly, the Communications and Media Officer, and today we're going to discuss an alternative to antimicrobials that you may never have heard of before. This alternative is different from traditional infection treatments in that it is a gas. This gas in question is called cold atmospheric plasma, and it is the focus of a recent paper published in the Journal of Medical Microbiology, investigating its ability to break down biofilms in infected wounds to help us understand what cold atmospheric plasma even is, what it can do, and how it could help tackle antimicrobial resistance in the future. Is co-author of the study Dr. Jason Brown from the University of Glasgow. So, Jason, thank you for joining me today. Would you like to start off by introducing yourself?

Speaker 2 01:01

Of course, yes. So my name is Dr. Jason Brown. I'm a lecturer at the University of Glasgow. I'm based in the School of Medicine, Dentistry, and Nursing, and I have my research group there. And some of the students within that group have worked together to to create this paper.

Speaker 1 01:17

So I think we should start at the very start. And would you mind explaining to us what exactly cold atmospheric plasma is for probably a lot of people that have never heard of it?

Speaker 2 01:29

Okay, so cold atmospheric plasma is a type of gas that has been electrically charged, and it ultimately results in this sort of mixture of reactive oxygen and nitrogen species, things like ozone, superoxide, hydrogen peroxide, and you know, going off the name, it's called cold atmospheric plasma for a reason. It can be applied at a biologically tolerable temperature, so it makes it quite an attractive type of therapy that can be used for, in this case, antimicrobial applications, but also in the wider field of biomedical science.

Speaker 1 02:05

It would be great to clarify how exactly it's being applied. I guess as well, because since it's a gas, how how how does it look? Does that make sense?

Speaker 2 02:14

Yeah, absolutely. So it's it is a technology, and there is commercially available cap devices now that you can purchase from certain certain companies, and and some of them are actually being used in clinical applications this in this modern day, and basically this these handheld devices in in in particular are kind of the size of a mobile phone, and they can be held by the clinician, and and at the end of of what would be the mobile phone sort of shape, it has jets which basically targets these chemical species, these reactive oxygen and nitrogen species towards a particular target, and the idea then is that there's this this production of this plasma that directs these species towards, in this case, a chronic wound, and all of these then reactive oxygen and nitrogen species can then work. They can do their job and basically target the microorganisms within within the bed of a chronic wound.

Speaker 1 03:19

Amazing. And where has CAP therapy kind of got its start, or before the study, what what was known about it that essentially led to this work being

Speaker 2 03:30

done? So for a number of years, CAP's been used sort of in hospitals. It's often used as a sterilization method, particularly like sterilizing sort of abiotic surfaces in in in hospitals. There's increasing evidence that it can be used within the context of cancer studies as well. There's evidence that these chemical species that are produced can actually drive cellular death and stress within within tumor cells in cancer. But then more recently, over the last 10 to 20 years, there's a lot of evidence that that cap can now be used because of its antimicrobial activity. There's you know long, long-standing evidence that it can be used in hospitals as sterilization of of abiotic surfaces or non-living surfaces, and we're starting to us as scientists and particularly physicists that are basically working with with these devices, they're starting to appreciate the mechanisms of the killing effect of the plasma, and therefore, as with any sort of scientific piece of evidence, the idea is: can you then apply that in humans? Is there a way that you can then bridge the gap between sterilization of an environment towards sterilization of an infection within a particular patient, and therefore CAP more recently is being explored within the context of wound care, particularly chronic or infected wounds. And and these these chemical species not only have they got antimicrobial activity but there's there's evidence that they can actually stimulate our immune system to repair any damage that's arisen from from those wounds.

Speaker 1 05:13

Yeah. So let's talk about the the study that's recently been published. What was the specific aim and and methodology that you and your team worked through.

Speaker 2 05:25

Sure. So it it actually stemmed from a piece of work that was published a few years ago from my research group, and this was a publication back. I think it was early 2023. It was published, and in that paper, what we found using this plasma device was that different microorganisms within biofilms will actually respond differently to the treatment. So the paper, which was called Staphylococcus aureus, which is a type of bacteria, certain strains of that bacteria can exhibit what we call heterogeneous tolerance. Basically, strains will react differently to the the plasma therapy, and basically, what we wanted to do in the the current study, which will will be published, is to try and break down this tolerance. Is there a way that we can find a way of basically improving the effectiveness of the plasma against these this otherwise tolerant strains of of the bacteria. So what we did was we we wanted to screen a range of different repurposed bioactive compounds. So basically, drugs that have been created for other uses. Is there a way that we can then repurpose them for applications against microorganisms, and what we did was we screened a range of different compounds from a library called the TokraScreen Library, and we identified an anti-cancer drug called KHS 101, which has a promising candidate to pair with the CAP therapy. And what we found was that the KHS, which I'm calling KHS for short, basically sensitized our biofilms to the cap therapy. And and one of the key things that arose from this was this idea of sensitization, because the KHS on its own didn't kill the biofilms, but it basically sensitized the biofilms to the subsequent cap therapy,

Speaker 1 07:24

right? So neither on their own were enough to break through, but in combination, first sensitized and then broke down the biofilms. Has that been done before?

Speaker 2 07:34

Yeah. So there's a lot of again. I keep saying this this term increased evidence, but a lot of work in recent years, as it's particularly concentrating on this idea of synergistic relationships between different drugs or compounds, or even in this case, technologies. So there is increasing evidence in the literature that you can basically have two different

compounds that maybe don't work together on their own, but if you bring them together, they can actually be effective against whatever you're testing against. But my understanding is this is one of one of the first studies that's looking at at breaking tolerance to to cap therapy.

Speaker 1 08:14

Has cap only been shown to work with bacteria or for other microbes as well so far,

Speaker 2 08:21

other microbes as well. So evidence in the literature has shown that it's effective against viruses. A big part of my research group is looking at bacteria as well as fungi as well. So from the original study, we we actually had three organisms, two bacteria and one fungi, and what we're able to show was that the cap was effective against the fungus, another bacteria called Pseudomonas aeruginosa. But for some reason, the Staphylococcus seemed to be tolerant to the cap, and that's what then led to this this follow-up study with the idea of trying to break that tolerance within this bacteria.

Speaker 1 09:01

What exactly is the mechanism by which these two work together, or perhaps they work via different ones that they break down biofilms? The

Speaker 2 09:13

short answer is we don't know, so there could be a an effect of of plasma on the the the cell surface of the bacteria, basically sort of sensitizing either the cell wall or the cell membrane of of the Staphylococcus bacteria, basically sort of basically welcoming in the reactive oxygen species or nitrogen species that is produced by the cap, or alternatively, it may just be a case of the KHS working against the extracellular matrix of the biofilm. So basically, in some way that we don't know yet, sort of basically breaking down the matrix and allowing this pathway for the the reactive oxygen and nitrogen. Species from the plasma to get into the biofilm and actually become exposed to the cells.

Speaker 1 10:07

Will this be a a step that you you move towards understanding?

Speaker 2 10:14

Yeah, this is work work that's ongoing. We're we're working to try and sort of add some sort of mechanism towards this sensitisation idea, and obviously different compounds will maybe have different mechanisms of action, and KHS is one of the compounds that we're trying to explore in terms of its its mode of action, and we're also trying to expand that to other compounds and also against other tolerant organisms.

Speaker 1 10:44

Do you think that this could go beyond wound infections and be applied through maybe other means to, yeah, other types of infections?

Speaker 2 10:58

Yep. So I mean that that would be the hope. So in terms of like delivery of the KHS, we we don't know how that could potentially be delivered within a patient. You know, is it a case of adding the KHS to some sort of gel and applying that gel onto the patient's you know chronic wound and then adding the plasma therapy? In terms of other infections, I've got other PhD students working in my group that are working on oral biofilms. So, is there a way that we can perhaps integrate KHS into things like mouthwashes or toothpastes to then potentially improve the effectiveness of you know other compounds, or just to have an effect on its own by increasing its concentration,

Speaker 1 11:42

is the plasma always applied by the handheld device that you mentioned before? Is there other ways that that can be applied as well?

Speaker 2 11:55

Yes, so there's generally two ways of applying of of applying plasma within this context of sort of biomedical applications, it's the sort of handheld device, or you can actually have plasma-activated water, whereby you basically create this cocktail of of these reactive oxygen nitrogen species within water, and then that water can be applied to. In in this case, could be applied to a chronic wound. It could be applied to surface sterilization. So yeah, there's generally two different methods of of achieving you know plasma's goal of of being antimicrobial.

Speaker 1 12:32

Do we know yet of any kind of potentially negative reasons, negative side effects of using plasma topically.

Speaker 2 12:45

So there is some side effects of plasma, or at least there still needs to be a lot of extra studies done into whether there may be side effects. So there is potential of excessive plasma use could maybe lead to formation of cancerous cells within your skin tissue, but obviously we don't know the mechanisms behind why that may be, and there's still a lot of researchers that are, as I mentioned earlier, working within the field of cancer studies. That maybe short bursts of plasma can actually be beneficial, but excessive use can be detrimental to the the in this case, the skin cells. So there is side effects, but there is side effects with most antimicrobial interventions at this moment in time because cap and plasma has not only antimicrobial activity, but it can also actually stimulate our immune system to to repair itself, which is often one of the cases of chronic wounds, the wounds tend to not heal because our immune system just isn't working as effectively as it should. The fact that it has this kind of dual action activity definitely offers it as a potential non-antibiotic intervention.

Speaker 1 14:00

Is is treating wound infection something that's particularly affected by antibiotic overuse?

Speaker 2 14:08

Yep. So it's very similar to lots of other types of infections. You know, there's lots of patients can come into a a clinic with a chronic wound that won't heal, and and lots of tests need to be done to try and identify the microorganism that's responsible, and that's very challenging because lots of of these infections are what we call polymicrobial. So there's lots of different microorganisms that are basically driving this infection. Therefore, it's really challenging to just pinpoint one organism that you could target with one antibiotic, and in most cases, what tends to happen is is the clinician will just give these broad spectrum antibiotics, which can obviously have detrimental effects on on lots of health associated microorganisms that you find throughout the body, and. Therefore, can be quite quite dangerous for the patient, and it can increase their risk of developing antimicrobial resistance. Obviously, IMR genes that are

constantly passed amongst different microorganisms within biofilms is it's an increasing issue, you know, globally, not only just in the UK, and you know, it's always important for us as microbiologists that work with sort of novel therapies. The idea is really: can you find alternatives to antibiotics? Is there a way that you can treat patients with various infections without the need to basically fire lots and lots of antibiotics against a particular microorganism or collection of microorganisms in a biofilm.

Speaker 1 15:45

Amazing. Yeah. As a final question, I wanted to ask: with the publication of this study, how do you feel about the progress of you know investigating CAP therapy and its potential for the future?

Speaker 2 16:00

Yeah. So obviously, very promising. You know, we we have been fortunate as as a research group to have, and obviously when this paper comes out, to have two really nice papers within the field over the last two and a half three years. You know, a lot of this work and and what was published previously made up a big part of what my first PhD student's thesis, and the good thing is, is that I can see lots of potential avenues moving forward for this work, and in particular, as as I've touched upon this idea of biofilm sensitization, you know, why how are we actually sensitizing tolerant cells to particular therapies, you know and and mechanistically is there a way that we can actually define what is a sensitized biofum cell? You know, is it something like different stresses that the cells encounter inside of itself? Is it something to do with the matrix that that it's producing to form the biofilm? So the good thing is, is that I can see lots and lots of of future work stemming from from not only this publication but the one I mentioned from a few years ago as well.

Speaker 1 17:15

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