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Strategies for Stronger Skin: Tissue Regeneration & Wound Healing

Dr. Greenberg:
What if our skin's natural immune response could be leveraged to improve tissue regeneration in wound healing? This isn't a question out of a sci-fi novel; this is what researchers at UCLA and Duke University actually set out to explore. And to their—and our—surprise, they found that to be a very real possibility.

Welcome to *DermConsult* on ReachMD. I'm Dr. Michael Greenberg, and joining me to discuss a biomaterial that can significantly reduce scar formation after wound healing are Drs. Philip Scumpia and Tatiana Segura. Dr. Philip Scumpia is a practicing dermatologist and an Assistant Professor of Dermatology at UCLA Health System. Dr. Scumpia, thanks for being here today.

Dr. Scumpia:
Thank you very much. It's a pleasure to be here as well.

Dr. Greenberg:
And Dr. Segura is a Professor of Biomedical Engineering, Neurology and Dermatology at Duke University. Dr. Segura, it's great to have you with us.

Dr. Segura:
Yes, thank you for having me.

Dr. Greenberg:
To start us off, Dr. Scumpia, can you please explain what you and your team knew about microporous annealed particle, or MAP, hydrogels before your research on scar formation? What was missing that you set out to explore?

Dr. Scumpia:
This started out as a collaboration that I became a part of when we were presenting data at a conference at UCLA. Don Griffin was presenting work out of Dr. Segura's lab, looking at different types of hydrogel, and I thought it would be interesting if they put it into wounds in mice. But he had a bit of a different idea. He wanted to make a new type of hydrogel, and it required the assistance of another professor of bioengineering, Dino Di Carlo, to make these hydrogel beads in almost like a computer chip, It's a microfluidic device. And then used the chemistry and the hydrogel technology that Dr. Segura has been working with to make these little beads. And these little beads come together in wounds and form a hydrogel scaffold within minutes. So we had a publication in 2015 where we used this, and we found they accelerated wound healing in mice. But when we looked at the pathology 21 days later, there was still a lot of hydrogel left, but it lost the kind of bead architecture we were used to because the hydrogels degrade using natural enzymes in the skin. So my question was, "Is there any way we can keep these beads longer in the skin?" And that's where Dr. Segura comes in with a novel idea she had from a different project to allow VEGF to last longer in the skin.

Dr. Greenberg:
Oh that's interesting. Dr. Segura, can you elaborate on that a little bit?

Dr. Segura:
Yeah, I think Phil did an excellent job explaining the origins of the hydrogel project. I would just add that in biomaterials research, it is difficult to have an injectable porous material, so most materials that have larger porous that allow fills to infiltrate are not injectable. They are more solid structures, imagine like a sponge, and so that really is what we were trying to do. We were trying to come up with an injectable, porous material that can flow and could actually be spread in a wound. And so Phil correctly points out that we did have a lot of gel left, and also we did have improved healing, but we also didn't have the tensile strength, so when you have a wound close, a

lot of times it forms a scar, and that tissue is not able to be stretched as normal tissue. If you can imagine a wound in your body, it feels different, it has a different mechanical property. So we were also trying to improve the way in which this wound heals, having a better mechanical structure. And so what we wanted to see is if we slowed down the degradation rate of these beads that Phil explained could we then preserve the microarchitecture – this open-pore structure, because it doesn't degrade and preserve the beads longer, thereby allowing for the tissue to grow, surrounding the structure. And so the way in which we did this is by using different chirality of peptides. And so in your body, we have a lot of different proteins, and all of these proteins have one type of architecture, and they're called "L". So all of our proteins are L. And so, if you present the opposite, the mirror image of that architecture, it's called "D," and your enzymes are not able to recognize the D peptides, or the D architecture because they have not evolved to do so. So all of our enzymes are also able to only recognize the one structure, the L. And so if we change just the amino acids surrounding the cleavage site, as Dr. Scumpia mentioned, enzymes the greatest material, and so we change the amino acids surrounding the cleavage site of this enzyme to D peptides as opposed to L peptides, not allowing the enzyme to recognize the structure as easily. So that was the hypothesis, that by changing the chirality of the peptides, we were gonna slow down the degradation rate of the structure in general.

Dr. Greenberg:
And staying with you for just another moment, Dr. Segura, did you have to modify the MAP gel, and if so, what results did you see on the wound?

Dr. Segura:
Well, the material wasn't changed completely. We kept the base material the same as Phil presented, which is beads crosslink to get into from our big scaffold. The structure of the material is still polyethylene glycol and is still crosslinked with a peptide. And so every component was the same, and we actually wanted every single thing to be the same except for the crosslinking peptides to slow down degradation. Can we actually get better tissue formation by having the gel last longer in the wound? And so we modified the peptide to degrade slower, and the way we did this is actually taking advantage of the fact that our body produces L amino acids. Every protein in our body produces L peptide. By changing the chirality or making that a mirror image to the D peptide, we actually could slow down degradation. So as Professor Scumpia mentioned, all hydrogels degrade by instamatic action, and enzymes recognize the L peptides, not D peptides. And so, if you change the peptide sequence to D, you actually could slow down degradation. And so once we implanted that into the wound, we actually did see a very different foreign body reaction, so when we implant the material into the body, we can get a range of responses, and these are all part of the foreign body response. Immune cells come in and start sensing the materials to see if they should react against it or not, and so as biomaterial scientists, we can actually design materials that are very stealth, or their immune diagnostic, the immune system of similar recognized them, or we can make materials that are very inflammatory or very reactive. And so we found that the T-gel, the MAP hydrogen that was cresting with D peptides, actually had a very different type of immune response. And I will let Phil fill in what that immune response was.

Dr. Greenberg:
Oh, yeah, thank you. Dr. Scumpia, would you like to elaborate on that?

Dr. Scumpia:
Yeah, so that was kind of the key advance that we found in 2015's manuscript, was basically our material, by making these individual beads anneal together in the tissue, it allowed cells to go into the hydrogel and into the tissue. It sort of acted like our body's own tissue, and it was, as Dr. Segura pointed out, immune stealth. So it was interesting when I looked at the pathology of the skin, because I'm a dermatopathologist as well, I saw something very interesting. Number one, the D amino acid hydrogel, the mirror image hydrogel, did not have any hydrogel in the tissue, whereas the L amino acid hydrogel, the normal one, did. So, there was a very large difference because number one, there was no hydrogel there anymore. But what was really exciting to me, looking at the pathology of the skin, we didn't see the typical appearance of scars in the tissue that had the D hydrogel implanted. In a scar, what we typically see is that the surface or the epidermis as we call it, which is a few cell layers thick, usually very flat, and then you have in the dermis, the layer of skin underneath that feeds the epidermis. You have parallel blood vessels, so the blood vessels go perpendicular to the skin, and they're all very interspersed and arranged in a scar. The collagen bundles of the dermis are basically all very flat, and you lose undulation of collagen fibers. We didn't see that in the skin samples treated with the hydrogel that had D peptides. It looked more like normal skin, and we saw hair follicles and sebaceous glands forming directly in the wound bed. Now there is a wound model called wound-induced hair neogenesis, where this happens spontaneously in very, very large wounds in mice. But in the small wound model that we used, I was used to only seeing scar as the end result. So, that's what was really exciting was in these small wounds that we were creating; we were able to see a completely new phenotype, where the hydrogel led to regenerated skin in a model where we don't typically see hair regeneration.

Dr. Greenberg:
Oh, thank you for that. And as a practicing dermatologist, Dr. Scumpia, how excited are you about this discovery, and what does this

mean for the future of dermatology?

Dr. Scumpia:
So number one, it brings in the fact that maybe human wounds can also be coaxed to regenerate. There's a lot of different types of wounds, some of them very difficult to heal. They turn into chronic wounds, and if we can ever eventually get these chronic wounds to heal, in patients with diabetes, with peripheral vascular disease, with venous insufficiency, if we ever do get them to heal, the problem is they're very prone to reinjury. And in addition, burn wounds, for instance, when they do heal, they lack function, so you can't regulate temperature like you would in normal wounds, in these healed wounds. So they lack structure, they lack function, they're prone to reinjury. So if we can do something very simple, like putting an immunomodulatory hydrogel in the wound, that would be a very exciting approach to induce tissue regeneration, rather than just accelerate scarring, which is what advanced biomaterials that are available now do. And it's kind of the best we can hope for now, is accelerate wound closure and basically the eventual scar formation because we can't regenerate the tissue.

Dr. Greenberg:
And turning to you, Dr. Segura, for the final word today. After observing the MAP hydrogel interacting with the immune system, what do you hope for in terms of research?

Dr. Segura:
Oh, I think that research is very exciting now. I think both Phil and I, as you can see, we have very complimentary expertise and we won't have seen the importance of this alone. And so I think that we each have a lot of exciting things that we want to do with this type of material. For me as a biomaterial scientist, this just opens the door to how to design materials that can actually communicate with the immune system directly, to lead to things like tissue repair and regeneration. That's what my lab has been primarily working on, this idea that we can actually use materials that don't deliver stem cells to actually use our own body's immune system and our own body's cells to promote regeneration, and so this is very much so what we've been trying to do for a very long time, so I'm just very excited to continue working on this type of materials.

Dr. Greenberg:
Well, I hope I have a chance to speak with you both again when that next phase of research is underway. But for now I want to thank my guests for joining me to talk about their discovery of a new MAP hydrogel. Dr. Scumpia and Dr. Segura, it was really great having you both on the program.

Dr. Scumpia:
Thank you very much for having us, and we appreciate your time.

Dr. Segura:
Yes, thank you very much.

Dr. Greenberg:
I'm Dr. Michael Greenberg. To access this episode and others in our series, visit reachmd.com/dermconsult, where you can Be Part of the Knowledge, and as always, we thank you for listening.