

Dr. Justin Arner:

Welcome everyone. I'm Dr. Justin Arner from the University of Pittsburgh Medical Center in Pittsburgh, Pennsylvania. Today I have the pleasure of speaking with Dr. James Voos, Professor and Chair of the Department of Orthopedic Surgery at University Hospitals and Case Western Reserve in Cleveland, Ohio. Dr. Voos is the senior author of the paper titled "Biologics, Stem Cells, Growth Factors, Platelet Rich Plasma, Heme Arthroscopy and Scaffolds May Enhance ACL Surgical Treatment," which is in press in the Arthroscopy journal. Welcome Dr. Voos, and thanks so much for joining us.

Dr. James Voos:

Yeah, thanks Dr. Arner. Really appreciate it.

Dr. Justin Arner:

Yeah, this is great. Certainly, we have so much to learn about this topic, and you're such an expert, and everything that you have going on at your institution is really exciting. So, I'm excited to learn from you, and get the word out a little bit. So first I wanted to congratulate you on putting together such a comprehensive, and excellent review of this topic for the readers, and I wanted to ask you, what was your impetus of undertaking this project, and why did you decide to write this up?

Dr. James Voos:

There were a few things that really piqued our interest, and really stemmed the desire to see what's out there, and push the science forward. One is the demand from our patients. We have all of our patients coming in, whether it's with knee arthritis, or an ACL injury, and certainly the request from our patients is out there, and being at an academic institution, we want to be able to provide the most scientifically rigorous information, and treatments to our patients. So, that was number one, is let's go out and find what is truly the most scientific way, or the most evidence-based way to take care of our patients.

The second was a really serendipitous part, of being at our institution. Case Western is actually the origin of the mesenchymal stem cell, Arnold Kaplan, Dr. Kaplan actually coined the term MSC here several years ago, and is one of our investigators on the paper here with us. So, we have an obligation at an institution where the MSC originated, to really look at what's the next phase of science, and how to move things forward.

Dr. Justin Arner:

That's awesome. I wasn't aware of that, so that's a great history. So tell us about... That's a good segue. Tell us about MSCs. Like you mentioned, we have all these patients come in, and they always say, "What about stem cells?" With their knee arthritis, or like you mentioned, a lot of different types of pathologies. Tell us about MSCs, and kind of the history of getting away from the term stem cells. What MSC mean, where they come from, and kind of your preferred choice. I know that's a big question, but how they fit, in especially the United States, with FDA regulations, et cetera.

Dr. James Voos:

And as we know with the mesenchymal stem cell, there's multiple sources, and the most common being the iliac crest, or of any bony origin, as well as adipose tissue, the fat pad in the knee, the synovium, and I think the iliac crest, and our fat harvesting have been the most common, and from my end, we have utilized our iliac crest primarily. But if we back up to the term mesenchymal stem cell, even our most expert regenerative medicine scientists, and Dr. Kaplan himself, at a recent grand rounds, I think we've

all agreed the term MSC is probably the wrong term to utilize, and it's more of a pluripotent progenitor cell is probably more of our term that defines the cell better, although less exciting of a term. I think it's more accurate, knowing that these cells are probably a little more committed than a true stem cell is.

But nonetheless, it's still the same cell, and our goal is to figure out how to make these cells work the best. And I talk with a lot of our residents, and fellows about the three Es when it comes to stem cells, or in any biologic. And one is, it needs to be efficacious. So you have to be confident of what you're putting in your patient, or treating your patient with works, so that you can at least be able to describe what the outcome is going to be. So, that's number one. The second is, is it executable? Meaning is the system you're going to utilize, is the way you're going to deliver those stem cells, something that you can integrate, or do in your practice? There's some different systems and different ways to use stem cells out there that seem excellent, but they may not be appropriate, or reasonable for your practice.

And then finally, is the expense. Here, as we all know, these are not covered by insurance, and being comfortable with the cost of the implants and being... Or the cost of the biologic, and being a steward of your patients, making sure that you're economically, making sure whatever you're going to recommend is worth it. So, we want it to be efficacious, want it to be executable, and we want it to have the appropriate expense.

Dr. Justin Arner:

Yeah, all certainly so important to... We see people all the time, I'm sure the same in your practice, have spent \$10,000 or more for certain treatments, and they're not really sure what they're getting, and we owe it to ourselves, and them, certainly, all great points. So, you mentioned some of the bone marrow harvest. Tell us a little bit about how you typically are doing this. Have you jumped to performing some of these in clinic for folks with knee arthritis? Tell us what you found to be the most reasonable financially, and for patient satisfaction, and comfort, and those kinds of things?

Dr. James Voos:

Yeah, that's a great question, and this was one I was really struggling with, as to how to integrate this into my practice. And so, we took a multi-phased approach, and the first was to talk with your friends, and colleagues, and mentors, and see what they've used, what's worked, and hasn't worked, to get a sense of some of those who have had the learning curve before you. So, that was number one, which is a bit of expert opinion.

The second was we've used a lot of our academy resources, the Arthroscopy Association or the AAOS, the AOSFM, all of those resources to see what's out there. And in particular, looking at technique guides. I felt as though I understood the literature, but wanted to figure out which type of techniques work. So, that was number two, was looking at all of the technique guides, and the expert publications.

The third, when we actually started performing these, I started out doing them in the ambulatory surgery center, where we do it under some conscious sedation, or at least under local, where we have the ability to place the patient under MAC, or some level of conscious sedation. That allowed me to make sure it was comfortable for the patients, that I had the system down, that I could have the technique down, where I could do this more comfortably.

As we've worked through that, as you can select the appropriate patients, have moved to be able to perform this in the office setting, or in a procedure room, setting in our office under local anesthesia, and certainly it's all about patient selection, and you talk with the patients about the discomfort they may feel, and some still elect to do it in the surgery center. Obviously, that adds a little element of cost to the patients, when you're doing it in a facility. But I took that gradual approach, expert opinion, reading as much as we could about the technique, doing it under anesthesia, and then ultimately

moving it to doing it under local. And surprisingly, as we've become more streamlined with the technique, and really discussing the type of discomfort with the patient, the majority of patients have tolerated this really well in the office setting.

Dr. Justin Arner:

Yeah, that's great to know. I was curious to how to incorporate this into our own practice, because a lot of the listeners, as we talked about before we started, a lot of us are younger career physicians, and certainly this is something that patients want, like you mentioned, it's not going anywhere. So, can you tell us a little bit about what you tell the patients regarding the discomfort, and then are you doing the ASIS or PSIS typically in the office? Or just give us a little rundown of your setup, and how you discuss it with patients.

Dr. James Voos:

Yeah, we've had the good fortune in our lab, which we'll talk about a little bit further, has been a well established stem cell lab for quite some time. So, we were able to look at both, whether we took the cells, harvested the cells from the posterior crest, or the anterior crest, and we were able to identify the same number, and quality of cells. So, in the office, I'll actually do it in the anterior crest, and I think the patients have felt more comfortable being on their back. It's a little bit more natural of a position that we as physicians are all used to utilizing.

In the operative suite, when folks are asleep, we'll often do it prone, and it's a little bit more from my end as an educational aspect, to show people both ways to do it. So, we've had just as good of results doing it supine in the office, with the anterior crest, has been my preferred, and it's nice that we've been able to validate that with our cell counts, as we've done our clinical trials.

Dr. Justin Arner:

Yeah, certainly doing it the right way, with the real science. Now, you mentioned about your stem cell trials, and I know from Pittsburgh, we've sent you, and Dr. Bradley specifically has sent you patients, because really you have some exciting trials going on that are pretty unique, especially in the United States. Can you tell us a little bit about your research trials, and any of the hypotheses, or preliminary findings that you had? And just let us know what's going on in Cleveland at university hospitals that you're engaging in?

Dr. James Voos:

Yeah, this is what we're most excited about, and where I encourage our physicians in training to really think about academic medicine, because this is a great way to... These type of research studies are very stimulating, and you're never... It never surprises me how you come in contact with those that you may do research with.

And our dean of our medical school, and head of the cancer center, Dr. Gerson, has been utilizing stem cells in his lab for cancer treatments for years, and years, and years, and has FDA approval to grow stem cells, which as we know, the federal government requires you have FDA approval to more than minimally manipulate the cells. So he and I encountered each other at a hospital event, and started conversing, and he said, "We should really use these in the musculoskeletal setting." So, we got both of our teams together, and it took a little over two years, and quite a bit of financial resources to ultimately go through all the FDA regulation, and receive IND approval.

So, we now, on clinicaltrials.gov, have an active trial for patients 18 to 60, with mild to moderate arthritis of their knee. We will in the office, or in the ambulatory suite, harvest your stem cells. We'll

identify those cells in the lab, and grow them into the hundreds of thousands. That takes about two weeks to get through the multiple passages, and then we'll do some sterility, and quality control. And then in the office setting, two weeks later, we'll do an injection into the knee. So, this first trial is for knee arthritis. We've done six patients, of which five of the six have eclipsed their six month mark. Most important, we've had no adverse events. So, no major adverse events from that standpoint. And when we look at our early outcomes of pain, and improved ambulation, overall improved activity scales, those have all improved in our patients.

We have noted the first couple days after surgery, the knees are a little sore, and it's, as you can imagine, from the high cellular content of what we're injecting in the knee, you probably get a little local inflammatory response. So, this first study is a safety and efficacy study of 16 patients, and we're a little over a third of the way through those 16. Once we get through that, we look to expanding it even further.

The second study is focusing more down on our ACL injuries, where now that we have the ability to identify, and multiply these cells, as a secondary aspect, we can measure their cytokine profile. So, when we get the cells at time zero, all those cells are in this PRP, and biologic milieu of cytokines that, that's what we're normally injecting at time zero, in the current stem cell setting. It's a couple stem cells, and all of their associated cytokines.

So, we've analyzed those cytokine profiles, and realized as you expand the cells, each of those passages, multiplying them, the cytokine profiles change. They may make more growth factors, and less inflammatory factors. So, the next part of the study is evaluating how those cytokines change as you multiply the cells. And then on top of that, we have added orthopedic adjuvants to those cells. So, PRP, steroid, HA, to show that we can alter those cytokine profiles through each passage. And we just presented that at the ICRS meeting in Berlin this summer, showing, again, that we can further manipulate the cells in terms of dialing in what type of cytokines to produce.

And then the final is knowing that we can utilize these cells now, now in young athletes with an acute ACL, and an acute heme arthrosis, we're aspirating that heme arthrosis, and assessing the cytokine profile. We're also identifying the stem cells from that heme arthrosis, that again, we can multiply, and the end goal, and when we're talking about this in sports terms, is to utilize our ACL repair enthusiasm, and scaffolds that are available, to now implant these expanded stem cells onto these ACL scaffolds.

And we've had a great track record at our institution with that. In fact, Rob Gillespie, and [inaudible 00:13:54] recently published in AJSM, the use of these stem cells in a rotator cuff scaffold that we're really looking forward to translating into our ACL study. So, a few different clinical trials going, one for arthritis, one for cytokines, the other for ACL repair. So, it's an exciting time. Certainly, as you know, Dr. Arner, as each study comes with its results, that generates as many questions as it does conclusions. So, we've got a lot of work to do.

Dr. Justin Arner:

Yeah, certainly congratulations. I can't imagine the number of meetings, and paperwork, and things that took to put those together, because certainly this is a difficult... And appropriately so, regarding the FDA, and all these stem cells. So, we're certainly excited. This is a machine that's starting to get going, and we're excited. I'm sure we'll see a lot of excellent, and exciting data from your institution. So, thanks for sharing all that. You mentioned the rotator cuff portion. Tell us, besides the knee arthritis, how are you using biologics in your practice? Are you injecting some BMAC after your ACLs? Or how are you using it currently, clinically?

Dr. James Voos:

So the majority of the time, I use biologics in my practice, it's still in the arthritis setting. That's where I've had the most success, and where I can most predictably tell the patient there's some potential for pain relief, and improved function. So, it's usually in that mild to moderate arthritis, most of the time in our knees, but in the shoulders as well. And it's worked very well in our professional athletes, of which we've used the PRP formulas in season, and our stem cell formulations out outside of the season, or on the edges, in the off season, are when there's bi-weeks, time for folks to recover.

So I've still been pretty conservative in terms of using it primarily in that setting, in the knee arthritis setting. We will use some of the PRP, or less cellular components and some of our soft tissue, hamstring injury, things of that standpoint. With our ACLs, I still have been quite conservative, in terms of what we're injecting around the graft. So, at time zero with ACLs, I have not been utilizing, with an ACL reconstruction, have not been utilizing any biologics. We have, after some discussion with a few of the patients during the remodeling phase of the ACL, at three and six months, have utilized PRP, or BMAC during those intervals, and for the statement of opinion, to fertilize the graft, for lack of a better term. But I've been a little cautious about doing it at time zero, to avoid inciting too much of an inflammatory response.

Dr. Justin Arner:

Yeah, an exciting time for sure. Tell us a little bit about the scaffolds. We talked a lot about the biologics, but there's a great discussion of different scaffolds in your paper. Do you use scaffolds much in your practice currently? You did mention the rotator cuff portion, or how do you see this in the future? Do you think we will be repairing ACLs with scaffolds? And what's your outlook on this exciting technology?

Dr. James Voos:

Well, this is one of the most exciting reasons to have us talking today, and I know your group, Dr. Arner, has been very busy with this, as well as others across the country. When we think about ACL surgery, it's one of the reasons many of us went into sports medicine, it's the surgery that everybody loves doing, but it's still one of the only procedures in sports, where we steal from you, We borrow, or we cause some morbidity, harvesting your patella tendon, or your quad tendon, or your hamstring.

And it's my goal, and I think the goal of many scientific teams, is to, if we can perform ACL surgery, whether it's repair, regeneration, use of scaffolds, and not have to cause that morbidity of a harvest, I think we've really changed the procedure. Obviously, ACL reconstruction utilizing autograph is very predictable, and a well, well-established procedure, but I think it can be better.

And so, that's really been my drive in practice, and in my mission, is can I contribute to the literature, by getting us closer to doing ACL surgery without the graft? So, I do think scaffolds are the answer. And I do think, this is all hypothesis, that if we can get to the ACL sooner, and have opportunity to repair, and augment the ACL with the scaffold, and that's where the combination of the scaffold, the cells, and the growth factors all will come into play, and I think that's where we're all working towards that formula, that's really the clinical goal that I'm trying to get to.

So, currently we are using a collagen based scaffold, and Case Western has proprietary collagen scaffold textile we're using as part of our ACL studies that we're currently doing pig studies on. But, there are many different hydrogels, and PLA, and other collagen based scaffolds out there. I think if you're going to utilize these, you want to find one that you're comfortable with its preparations, what is it made of, where does it come from, how fast that it dissolves, what's its cost? But, I definitely believe that's where we're headed, is to find the appropriate scaffolds that we can populate with those cells, and repairing the remnant of the ACL.

Dr. Justin Arner:

An exciting time, and certainly so many factors, and appreciate all of your guidance, and your base of scientists. So, a lot to get together. So, we're certainly indebted. You mentioned your last E, with expense. All this is so exciting, but tell us a little bit about, in your practice currently, or how you'd advise people getting involved in biologic treatments, regarding cost. You're working with your hospital systems, and then also in the future, based on your discussions with the FDA, and all of your trials, do you think there's a time that insurance companies may start paying for this? It's always been a little surprising to myself, and have conversations regarding hyaluronic acid being covered, but not something like PRP. So, give us a little bit of your thoughts regarding cost, and the future of that.

Dr. James Voos:

I think the onus really is on us as academic physicians, and clinical orthopedic surgeons to do the research to prove the efficacy of these treatments. Because ultimately, certainly if we can show improvement of quality of life, maybe we're using less implants, and more scaffolds, or cells. Ultimately, to have this covered by insurers, I think is what serves the patients the best, and serves science the best. So, I think that's our biggest challenge here now, is to put some true science, and rigor to the use of stem cells, or whatever biologic, to ultimately have them covered by insurance.

I think there's such wide variation there now. It's understandable why it's hard to cover when it hasn't been as well of a defined treatment modality. As you start in your practice, I do think it's really first and foremost a conversation with your patients to get a sense of what your patients are willing to pay, or what it's worth to them, and then ultimately, what you feel comfortable charging a patient. And we're in an academic medical center, so we work with our hospital system to find an appropriate price. And as we know, the PRPs, and those type are much less expensive than our stem cell, or BMAC type of preparation. So, if you're going to start it in your practice, maybe you start with that, which is a little more cost effective, and then get a sense of what you're comfortable with, and then maybe build that menu of things to offer your patients.

We, in pushing the science forward, have really been very aggressive about applying for grants, as well as we've had tremendous support from several of our donors, and philanthropy in Cleveland that have really taken great interest in this, including the owners of our professional football team, who have funded our initial clinical trials, and that's allowed us to grow, and expand these cells, and recruit patients at a much more rapid rate, when the trial is free to the patients. So, we've been really able to accelerate our data with that great support from philanthropy, as well as from grant. That's really helped us move things forward, and ultimately the ability to do that allows us to put forth the product that if there is a cost to it, we can tell the patient that it's been studied in a rigorous fashion, and it's worth the cost.

Dr. Justin Arner:

Yeah, that's definitely doing the right way, rather than starting on the other end, which unfortunately we sometimes do get excited about a technique before the science comes about. So, definitely makes us feel better, regarding education of the patient. So to wrap this up, where do you see biologics in the future? You mentioned some of your thoughts about ACL surgery in the future. Tell us a little bit about how you think biologics will fit into our practice in 10, 20, 30 years, or whatever, regarding rotator cuff surgery, and other treatments. It's such an exciting time, and you look back at some of my mentors, and what was popular, and the most common surgeries, and how things have changed so much, it's exciting to think what's upcoming. So what are your thoughts about that?

Dr. James Voos:

I think this is a great time for orthopedic surgeons, and particularly those coming out of training. And when you think back to the major milestones, whether it was the AO, and internal fixation, and then the advent of arthroscopy, and our different techniques of doing surgery, I think our understanding of the biologics really is the next frontier, and we're really on the steep part of that curve, as we're all climbing quickly, with our knowledge base.

So, it's a great time to jump in, and as you're starting an academic career, to really... This is an opportunity to get in, again, on the ground floor as this is really becoming a true specialty, and be able to contribute. So, I do think the ability to utilize, and harness someone's own reparative capacity really is the future, and more and more, the ability to manipulate the cells, and we may find it's not only the cells are not the cells at all, maybe it's the growth factors that the cells produce.

So, I think there's a couple different angles here, whether it's the cells, whether it's the growth factors, it's probably all of the above, but I do think that's where we're headed, more and more, to utilize the patient's own healing capacity. The scaffolds are going to continue to develop, and become more refined, and more user-friendly, as we understand more about the cells. And I think as the use of stem cells in this way become more responsible, and understood, I hope the FDA sees this in a positive light, as the opportunity to really expand this, and have it be of wider use.

Dr. Justin Arner:

Yeah, we're certainly excited to see what your institution, with your leadership, is going to put out, and we'll be excited to see that. So, thank you so much for sharing your time, and expertise, and knowledge with us, and hope you stay warm, and I look forward to seeing you at the Brown Steelers game. Hopefully it's a little above zero degrees, which it's been, I think, in Pittsburgh, and Cleveland lately.

Dr. James Voos:

See if we can survive one more game in the cold here. I really appreciate it. Thanks Dr. Arner, this is a fantastic series you do here with the podcast, so thank you for allowing me to be a part of it. Really appreciate it.

Dr. Justin Arner:

Yeah, thanks so much for your time. Dr. Voos' article titled Biologic Stem Cells, Growth Factors, Platelet Rich Plasma, Heme Arthrosis, and Scaffold May Enhance ACL Surgical Treatment, is in press in the Arthroscopy Journal, and is available online at arthroscopyjournal.org. Thanks so much for joining us.

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