



ORS Ask the Experts: Stem Cells in Orthopaedic Surgery

Dr. Jason Marvin: [00:00:00] My name is Jason Marvin. I am one of the members of the ORS Public Outreach Committee. And I'm joined today with a few of our colleagues on the committee, Dr. Dianne Little, Dr. Donna Pacicca, who is the Chair of the Committee, as well as some folks from ORS. This is actually the first installment of the Public Outreach Committee's "Expert Interview" series.

The goal of this series is for us to leverage basic science and clinical perspectives and expertise to address challenging and/or timely topics in orthopaedics research. Ultimately our goal is to provide information to the general public in an accessible manner. For this interview series, the focus of our topic will be stem cell therapies in orthopaedic surgery, and we're joined by three of our expert panelists.

The first being Dr. Rachel Frank, who is a board certified orthopaedic surgeon and sports medicine specialist who focuses on the surgical and nonsurgical management of knee, shoulder, and elbow injuries. Dr. Frank has specialized training and technical expertise in the areas of advanced knee and shoulder arthroscopy, ligament reconstruction, [00:01:00] cartilage/meniscus restoration surgery, shoulder instability surgery, biologic treatments for musculoskeletal pathology, and care specific to the female athlete.

Dr. Frank earned her undergraduate degree at the University of Illinois while playing four years of Division I soccer, and her medical degree at Northwestern University's Feinberg School of Medicine. She then completed her Orthopaedic Surgery Residency at the renowned Rush University Medical Center in Chicago, Illinois, as well as a sports medicine and shoulder fellowship at Rush University Medical Center, where she assisted in taking care of numerous sports teams in the local area including the USA Rugby Team and also DePaul University. Following her sports medicine fellowship, Dr. Frank completed a traveling fellowship throughout Canada and Europe, developing additional expertise in the areas of complex shoulder reconstruction, knee joint preservation surgery, advanced ligament repair and reconstruction, and techniques in orthobiologics.

Currently, Dr. Frank serves as an Associate Professor in Orthopaedic Surgery at the University of Colorado School of Medicine, is Director of the Joint Preservation Program at the University of Colorado, at the university of Colorado and his head orthopedic team physician for the Colorado [00:02:00] rapids professional soccer team. In her career, Dr. Frank has author or co-authored over 300 peer-reviewed journal articles , over 50 book chapters , and presents her research both nationally and internationally at orthopaedic conferences and meetings every year.

Her research has garnered dozens of prestigious national and international awards, including the prestigious AOSSM Bart Mann Award for the Advancement of Sports Medicine Research, as well as several competitive grants, including funding from the National Institutes of Health, the American Board of Orthopaedic Surgery, and Orthopaedic Research and Education Foundation.

Dr. Dianne Little: Thanks Jason. Dr. Farsh Guilak a Professor of Orthopaedic Surgery at Washington University School of Medicine, Director of Research for the St. Louis Shriners Hospitals for Children, and Co-Director of the Washington University Center for Regenerative Medicine. His laboratory pursues a multidisciplinary approach for developing new tissue engineering and stem cell-based therapies for musculoskeletal diseases, spearheading new approaches that combine genome engineering and synthetic biology to stem cells.

He's published nearly 400 articles in [00:03:00] peer-reviewed journals and has co-edited four books. He's the past editor-in-chief of the Journal of Biomechanics, and serves on numerous other journal editorial boards. He's won several national and international awards for his research, including five separate awards for mentoring. He has worked extensively in the translation of tissue engineering technologies as the founder of Cytex Therapeutics, a startup company focusing on developing new regenerative medicine therapies for musculoskeletal conditions. He was also recently elected as a member of the National Academy of Engineering.

Dr. Jason Marvin: Great. And our last speaker is Dr. Brian Saunders.

Dr. W. Brian Saunders received his Doctor of Veterinary Medicine degree from Texas A&M University and completed a rotating internship at the University of Tennessee. He then returned to Texas A&M to complete a PhD in vascular biology. He subsequently completed a small animal surgery residency at Texas A&M, is a Diplomate of the American College of Veterinary Surgeons a M M

Dr. Saunders is also a Diplomate of the American College of Veterinary Surgeons, and is also an ACVS founding fellow in Minimally Invasive Surgery. He is currently an Associate Professor of [00:04:00] Orthopedic Surgery at Texas A&M University where he's also the Director of the Canine Comparative Orthopedics and Cellular Therapeutics Lab and also holds the Linda and Dennis H. Clark '68 Chair in Clinical Research. Dr. Saunder's clinical interests include arthroscopic joint surgery, minimally invasive fracture repair, interlocking nailing, and joint replacement. Dr. Saunder's research interests include canine mesenchymal stem cells (MSCs), tissue engineering, and total joint replacement.

Question One: What is a stem cell?

Dr. Jason Marvin: So we're really excited to have all three of these great speakers representing different realms of science and medicine. For the format of the event, we'll be taking Q&A over the next 45 minutes. And to just kick it off, because this is geared towards a general audience, we wanted to pose this basic question of what are stem cells. Whoever wishes to start can just chime in.

Dr. Farshid Guilak: Well, I can start with the very classic definition of stem cells, which was derived from the field of hematopoiesis, which is the study of how blood forms in our body, which is where the original true stem cells were identified.

And [00:05:00] the definition of a stem cell is really simple. It has to meet two criteria. It's a cell, which is sort of the basic living unit of our body. It has to be able to self replicate, or basically divide and form a copy of itself. And the second part of the definition is that it has to be able to turn into another type of cell, or differentiate as we call it.

So that is the classic definition of a stem cell. However, in all of the therapeutic applications that are being used now, this definition has become more fluid and has changed. And we could, we can discuss that and argue whether any of the current therapies that are being used are truly stem cells or even the cells that we work with in the lab, whether they're stem cells because they meet that definition in the lab. But not necessarily in the body. So it's a simple and a complex definition at the same.

Dr. Rachel Frank: I would agree with that definition. I think the only thing I would add is that many, many people both professionally and in the public [00:06:00] think of stem cells as embryonic stem cells. And that's where this becomes a little bit of a hot topic.

In addition to that basic definition, when you up stem cells, there's more or less three main categories of cells that we think of. When we think of stem cells, we think of embryonic stem cells, we think of adult stem cells, and then we think of induced pluripotent stem cells.

And there's a lot of nuances with all of these definitions, but I think the most important thing was what was just said, and that the definition of a stem cell seems to be evolving and fluid and seems to mean different things to different people, especially when it comes to the therapeutic application of cells.

Doing research and performing clinical medicine is a little bit different when it comes to using these terms appropriately. And that creates a lot of confusion, but also a lot of excitement in terms of where the field is going.

Dr. W Brian Saunders: And the last comment I would make to sort of put a bow on this is I think there's oftentimes a misconception from the public. Certainly from our clients who bring veterinary patients to us pursuing [00:07:00] cell therapies that a stem cell and a population of stem cells are sort of this identical set of clones, meaning that every single cell in this preparation is about to be delivered to the patient is exactly the same. And when we isolate skeletal stem cells or MSCs from adult tissues, they really are a heterogeneous population of cells. Even if you take a single cell and allow it to grow a colony, there's a niche that develops within that colony. So not all the daughter progeny are the same. And so I think one of the exciting and challenging parts of this field is consistency of therapy, developing consistency in therapy. And how do we do that? How to identify the targets for its success and how do we develop a successful pipeline for treatment moving forward?

Question Two: Ethical controversies around the use of stem cells.

Dr. Dianne Little: As perhaps to follow up on some of those points a little more, could you elaborate more on some of the ethical controversies that are surrounded the use of [00:08:00] stem cells and then how as researchers and clinicians, we might be able to explain better to the patient, public, or the client how stem cells have their role despite these controversies.

Dr. Farshid Guilak: I can chime in again. As Dr. Frank pointed out, there are different types of stem cells. And I think really most of the controversy and ethical issues were brought up over this concept of the embryonic stem cell, where it was thought that you had to destroy an embryo to develop these cells.

There are now a number of approved lines by the NIH and the government that are being used continuously and require no other new embryos for this type of research to occur. But the majority of stem cells and stem cell research don't involve embryonic stem cells at this point. And none of the therapies, certainly none of the ones in the U.S. There are some that are being done in [00:09:00] medical tourism abroad. None of the ones in the U.S. would involve embryonic stem cells. There has been a lot of additional controversy in the U.S. in the application of stem cells as a therapy. And we'll probably talk about that in clinics in the U.S., the side effect of that has been that the word stem cell has become destigmatized.

And I think now, people are less likely to associate stem cells and stem cell therapies with embryonic stem cells, compared to 10 or 15 years ago when it was a real hot button item and a lot of confusion. Versus now there are somewhere between 600 and 700 clinics that purportedly offer stem cell therapies in the U.S.

And that level of controversy has really declined in my eye. I've seen much less of an issue and much less debate over stem cells in general, and partially due to a misunderstanding in multiple ways. But it's been a side effect of all of these stem [00:10:00] cell clinics opening up.

Dr. Rachel Frank:: Yeah, I couldn't agree more. I think so much of the controversy in the past was just due to that word embryo or embryonic. And while that still can be a buzzword and a hot topic and strike a positive or negative note depending on how you feel about that. When you hear the word embryonic stem cell, I think now more of the controversy is can you use the so-called cellular treatments appropriately, according to the FDA's definition of what's permissible and not permissible, at least here in the U.S..

Again, I think we'll get into that a little bit more later. But in the academic world, when I'm sure all of us are on the circuit lecturing, one of the first things I talk about is 351 and 361 pathways and what's permissible according to the FDA with regard to cellular treatment or biologics in general.

And there's so much vagueness to what is allowed and what's not allowed. And there's buzz terms: minimally manipulated, homologous use, etc. And I think that's now at least among many of us in academics where some of the controversy is. What truly is [00:11:00] a cellular treatment that is minimally manipulated or used for a homologous purpose?

And is that okay or not okay? That's further made controversial when we read a lot of the literature, much of which comes from outside the U.S., where there might be less stringent regulations on some of these cellular therapies. So you may have cellular products that are cultured or enzymatically enhanced or modified in some way that's not currently permissible in the U.S. outside of a clinical trial that's been approved. So I think the controversy now is what exactly are these so-called cellular therapy clinics or stem cell clinics saying they're delivering and what are they actually delivering to the patient? What's actually getting to the patient, be it a human or an animal or whatever it might be. For me, that's the controversial part of stem cells here.

Dr. W Brian Saunders: I can confirm for you that it's very interesting what you just said, because that's the exact challenge that we deal with in veterinary medicine. The real misconception is when someone believes their pet is [00:12:00] receiving stem cell therapy is what does that mean? And there's actually misconception about what the product is. Then the additional layer of that is has the product been shown to be efficacious for treating disease X, Y, or Z? We deal with the exact same thing in veterinary medicine, which is a misconception about what stem cell therapy is in the United States, at least under what's permitted currently.

Question Three: Is it true that stem cells can cure any disease?

Dr. Jason Marvin: Thank you all so much. This touches on many different key points about the evolving perception for the public of what these stem cells are. You have touched base on some of these applications and the context. How would you then describe, for example, a patient or an individual who comes to you and asks based on the extension of stem cell clinics and the evolving emergence of stem cells and their prevalence in the media. How would you address this question of is it true that stem cells secure any disease?

Dr. Rachel Frank:: I can start with that. I would say, at least here in Denver, but probably in many sports medicine heavy sites throughout the U.S., this is [00:13:00] a daily question that we get from patients. The short answer is no.

As a responsible clinician, you need to be upfront and honest with patients. As a clinician, even though I'm in an academic program, our model is a very private practice model. So, you don't want to turn away patients, or leave a sour taste in their mouth. But, you need to educate them appropriately and in a way that they can understand.

Patients don't typically come in and ask me, can they cure everything? But I have plenty of patients coming in saying that stem cell clinic down the road said if they inject my torn completely torn ACL as a 16 year old, then I can regrow my ACL and never need surgery. Or, for the 80 year old with bone-on-bone arthritis, if I get a few stem cell treatments in my hip or in my knee, I won't need a joint replacement and all of my pain will go away. What do you think about that? Those are the more common questions that I get, and those are actually some of the most difficult conversations because they take time. They take time to re-educate the patient on what they've been told or what they tell you they've been told and what my perspective is on that.

While the [00:14:00] field of biologic medicine and stem cells are incredibly exciting and the future, I think is the most exciting where we're at in 2022, the answer to both of those questions is quite frankly, no. Stem cells are not going to cure, regrow, or regenerate your ACL. They're not going to regenerate enough cartilage in a bone-on-bone, hip, or knee to make it so that you don't need a replacement. Those conversations ultimately end up difficult because such patients have been told by many people that this is going to cure their problem and you have to politely dispel that and then re-educate. Then when they say, well, what do they actually do? A lot of it is, I'm not really sure.

I don't really know exactly what these treatments will do in your knee or your hip or for your ACL. But here's what I can tell you is reproducible, predictable, reliable, and evidence-based. You can go through all the different treatments for that particular patient. But in sports medicine, this is a daily topic and it's only becoming more prevalent with patients hearing more and more about stem cells.

Dr. Farshid Guilak: I would completely agree with that. There's [00:15:00] really very little, if any, hard evidence that the way "current stem cell therapies", and I put those in quotes, are being used, can cure or treat any disease. Not to say that we aren't incredibly excited about the potential of using cells in different manners, to regrow and regenerate, deliver drugs, and reduce inflammation. But the way they're being used now, they're certainly not stem cells because if they were truly stem cells, they would violate FDA rules for minimal manipulation and implantation.

So they're not stem cells that are being implanted, and there's not good data that's evidence-based to show that they actually do anything or work. There's a huge placebo effect, oftentimes, for someone getting a procedure of removing cells from somewhere in their body and certainly just injecting anything into the body, particularly if you have a joint injection. Or this thought after paying several thousand dollars in cash for a therapy, [00:16:00] the placebo effect is

very strong. So until we have good, hard prospective studies that show that these therapies work, I don't think they really cure anything.

Dr. Rachel Frank: It's funny, it's exactly what you just said. So for the last four years, I've been trying to think of some sort of ethical study where we could have patients pay the price for "stem cells" that we offer here for stem cells. But for cellular treatment, because there are some therapies that are offered in my institution in the form of bone marrow or adipose. Two groups of patients, everyone pays the same amount, have a poke hole either in the iliac crest for bone marrow or in the abdomen or wherever you're taking fat from for adipose. Then, perform the procedure: harvest the cells from everyone, and then process them the way you would standardly process them.

Then have a foil-covered syringe and inject either saline or the end product of what might contain many growth factors and then maybe cells, and put that into the joint or area of [00:17:00] interest and see what the outcomes are. It's hard because I just don't know of a way to ethically have patients pay that cash pay price and not get the procedure.

If they turn out that they have a negative result, that just raises some eyebrows. We've thought of telling the patients, "you might not get this, but all money will be donated to research or donated to some charity" or something like that. So they feel good about it. But, if you have any ideas, I think that is the ultimate study in terms of just proving what many of us, if not all of us, probably think is what's happening. Do you have any comments on that? Dr. Saunders?

Dr. W Brian Saunders: I share the perspective of my two panel colleagues. There's a guidance document for veterinary cell-based products. This guidance document 218 states very clearly that minimally manipulated products can be used. The only thing that hasn't been uncovered a little bit as we unwrap this onion here is when a human patient or a veterinary client that has an animal that is pursuing stem cells believes that they are getting stem cells.

Currently, the product that's being administered is, [00:18:00] at least in veterinary medicine 99% of the time, something called a stromal vascular fraction preparation. What that is, is a sample of tissue. So, these cells exist in the bone marrow and they exist in many adult tissues. Adipose tissue or fat is a very common area of interest. So you can take a sample of fat and through enzymatic digestion, you can break that fat down and you can pull the nucleated cells from that fat tissue. You can separate the adipose from it. Then, what you have, is a minimally manipulated preparation of cells termed the stromal vascular fraction (SVF).

That includes endothelial cells, and pericytes, and smooth muscles muscle cells. Yes, it does have some MSCs in it. We did a study in dogs where we harvested tissues from a number of donor dogs. We looked at the yield of MSCs from various tissues and in fat tissue, only 5% of the nucleated cells were actually MSCs once we went through the process of characterizing them. You may have a [00:19:00] syringe with a million cells or 5 million cells of this stromal vascular fraction, but only a very small percentage of them are these mesenchymal stem cells or, or multipotent stromal cells. The MSCs that meet the criteria that were introduced at the beginning of this session.

To me, that's an ethical conflict when you're purporting to provide stem cell therapy yet only 3 to 5% of the cells in your injection system are meeting this criteria. Are we really administering stem cell therapy? No, we're administering stromal vascular fraction therapy.

The next question is, well, does it matter? Maybe not. If the SVF preparation palliates the patient's pain, that's great. But we (in veterinary medicine) don't also have strong evidence that that's the case either.

Question Four: Tell us about the stem cell research that your lab and/or clinical practice are working on.

Dr. Dianne Little: Great. Thank you. Moving on from that, perhaps you could elaborate a little bit about what specific research you're doing in the stem cell field, either in your lab or in your clinical practice, and perhaps, especially with regard to what we've just talked about on the clinical practice [00:20:00] side. Dr. Frank mentioned a little bit how potentially we could address the placebo effect, but what advantages does veterinary medicine have in that regard, if any.

Dr. W Brian Saunders: Dianne who did you want to start?

Dr. Dianne Little: Perhaps you.

Dr. W Brian Saunders: I'm a small animal surgeon and there's actually a large field of equine surgery and equine based cell therapies. So I'm not gonna speak to that. That's not my area of expertise, but the vast majority of pet owners that are pursuing stem cells are, for chronic management of multi-joint osteoarthritis. So the current paradigm is either intraarticular or intravenous injection of these products to treat patients and palliate patient's joint pain.

As I said, the level of evidence is really quite low. What we have found in animals, and I'm sure is the case in people, the case in animal studies is that

when you take a cell and a solution of saline or hyaluronic acid, and then you inject it into the joint. If it's not introduced on some sort of a matrix or a scaffold, it doesn't hang [00:21:00] around in the joint very long. It undergoes apoptosis; it doesn't engraft and stay around long term. Another misconception that people have is that when I get this therapy, that these cells are going to go into my joint and then graft and turn into chondrocytes and stay there for the rest of their life.

It turns out that that the vast majority of cells are rapidly eliminated from the treatment site. So you asked about what our group is doing. We're focused on two things. One is to objectively characterize veterinary stem cells, particularly canine stem cells. How do you isolate them, culture them? Then how can you use them to improve bone regeneration or cartilage repair? In that context, we really have switched as I'm sure many of my colleagues here have, from the concept of injecting cells in solution into a joint, to more of a tissue engineering approach where we are using cells as a component of developing a device to treat an early cartilage lesion.

Now we're talking about a tissue engineering scaffold, which contains complex matrix. It contains cells and it may [00:22:00] contain various growth factors. So that's the area that we're going and where we're headed in the future.

Dr. Dianne Little: Dr. Frank, do you want to comment next?

Dr. Rachel Frank:: Yeah, I think our practice is similar in terms of what we offer and what we're trying to do. So for us, it's two-fold. For me personally, very selfishly, I enjoy the research aspect of this. We try to characterize anything that comes out of a patient. Be it blood, bone marrow, adipose, and really get some tissue analysis in the lab to figure out exactly what we're putting in patients and what we think we're putting in patients. And those don't always match up. And then keep a registry of all of these patients, including again what we're putting in patients and then how their outcomes are. I think in our practice, we offer biologics as an option, either as a standalone treatment for some conditions or as a surgical augment.

The biggest concern, both from my perspective and the patient's perspective is the cost. These are all out-of-pocket costs unless the patient's enrolled in a trial [00:23:00] that is studying one of these biologic products. And then in that case, the cost is free. It's covered by the cost of the trial. But many of those trials can be difficult for a variety of reasons, including conflict of interest, who sponsors the trial, which product is being used, etc.

When I have this discussion about what I'm giving a patient when we agree to use a biologic, we kind of have that same conversation where we're putting autologous tissue back inside of your body. Whether it be to a tendon, a joint, cartilage procedure, etc. What I think I'm putting in at the end of the processing and spin process is 3 to 4 CC's.

Most of that we think is growth factors or contains growth factors. And we hope that the majority of those growth factors are favorable for the environment that we're injecting into from, with regard to catabolic and anabolic growth factors. We don't really have an ability just yet to maximize what exactly we want for a given pathology, but we hope we're going in that direction.

And then I [00:24:00] tell them, there may be some cells. We think that there are some cells in the lab. When we spin this down, there are some cells. But the goal is to get your body to start growing with its own cells. The goal is for these growth factors to attract your own cells to help with this area of cartilage repair or tendon healing or ligament reconstruction.

I think no matter what product it is, it's important to have that conversation. It's important to be very honest about what we don't know is actually potentially happening. What we think is happening, but we don't know is actually happening. Hopefully that answered the question a little bit. I feel like I keep coming back to the same themes, but hopefully that got there.

Dr. Dianne Little: Yes, thank you. And then Dr. Guilak.

Dr. Farshid Guilak: Yeah, those are great answers. I really want to re-emphasize what Dr. Saunders said is that one: it's just been a huge limitation in the field that if you just inject cells, this has been shown over and over and over again that within a day or two, 95 to 99% of them are gone. And after a week or two, they're undetectable. So the concept [00:25:00] is that we are either delivering growth factors or that those cells somehow impart a longer term memory. But what we've shown over and over is that there's not much of an effect of just a cellular injection. So we've been pursuing a couple of avenues to try to address that issue.

And one is the same that that Dr. Saunders described, which is to take these stem cells since they can turn into other cell types. They can form tissues outside the body. We can use this to tissue engineer replacement cartilage, bone, tendon, ligament, to put back in the body. At the same time, we've been very focused on taking those stem cells and for lack of a better word, making them super cells.

And we do this by using new techniques in genome engineering to basically rewire the DNA of those cells. So that they do all those things that we want them to, and we think stem cells should do, but maybe they're not doing it well enough. Just as an [00:26:00] example, we can take stem cells and amplify their ability to make anti-inflammatory molecules and pain-fighting molecules or growth factors by inserting the genes for those in specific places in the DNA. And one of the things we've done, for example, is to make cells that self-regulate. They detect inflammation through their normal sensors. And instead of having a bad inflammatory response, we've connected their gene circuit so that when they sense inflammation, they make drugs and they make anti-inflammatory drugs.

Because of that, we're able to now really beef up their ability to fight the cause of inflammatory diseases, such as joint inflammation. And for us, particularly things like rheumatoid arthritis, which are autoimmune diseases that are highly inflammatory. To keep the cells in place and to address that problem, we can then take those stem cells and make a little implant that either repairs the [00:27:00] cartilage, or just sits under your skin and does nothing until there's an inflammatory flare. Then it releases lots of drugs to combat the inflammation.

The other approach we've been making is to actually try to get cells that are injected to stay in place by taking the stem cells and differentiating them first into immune cells, like macrophages, which are actually really good at infiltrating and setting up shop in different tissues. And we've had some success with that where we can see the cells there now after a week or two. Still not really enough for a permanent cell transplant, unless you do irradiation in the bone marrow and basically repopulate the bone marrow. So, we still think that having an engineered tissue is probably one of the most stable ways to reintroduce stem cells, either therapeutically or structurally, like a cartilage replacement back into the body.

Question Five: Can you discuss the safety concerns about stem cell treatments?

Dr. Jason Marvin: Wonderful. Thank you all so much. So just hearing about all this work kind of segways to our next question, where as of recent, there [00:28:00] have been a lot of news reports about rejection quote-unquote of stem cells, as well as other adverse reactions. So previously y'all have talked about orthobiologics and these cellular injections. Aside from efficacy, could you also discuss perhaps some safety concerns about stem cell treatments that you're aware of? Either inpatient outcomes or those that you could foresee in terms of the process of translating these projects in the lab towards that of patient care. And perhaps we could have Dr. Frank start us off.

Dr. Rachel Frank: Yeah, sure. I think this is a great question. It's a really important question. And a really important topic. I've not really seen rejection so to speak from stem cells or what is referred to as stem cell therapy, locally more common at least again here in Colorado. What I see is complications like infection and we see complications such as re-injury or injury of other structures, particularly in the young athletic patient when they've been given a quote-unquote stem cell treatment. And it hasn't worked, they've [00:29:00] gone back or they think it's worked, they've gone they've been told it's worked, they've gone back to sport and then have on their non-magically healed ACL now completely trashed their meniscus or their articular cartilage at the age of 16. The infection situation with regard to the use of cells is troublesome.

What happens is these patients typically get a treatment somewhere in the community. Then they have a warm hot joint and they come into our office and they're infected and they need not only emergency or urgent surgery, but this can lead to significant complications for that patient's function. Burden, you know, just thinking globally burden to the healthcare system, etc., for something that probably never needed to have been done or was never indicated to be done.

With the type of cells that are typically applied in the sports medicine practice. You know, these are adult somewhat differentiated cells or they're thought to be in terms of when they're harvested from bone marrow, adipose, or even some of the off-the-shelf products. And so we don't necessarily see the rejection so to speak, or at least [00:30:00] that hasn't been part of my clinical practice that I've seen. But we see these other issues. For me, the most devastating issue, and just having been an athlete and having gone through a lot of surgeries myself, it's just devastating to see when someone is told and promised a result with a treatment pays cash for that treatment or their parents pay cash for this. And then they come in and they have a much worse injury than they initially had.

That's a complication that probably won't get reported anywhere because we could just chalk that up to, oh, they went back to sport and had a new injury. Their ACL was healed and they suddenly had a new injury after their healed ACL. And it's just so hard to have those conversations and turn what could have been a simple surgery into something more complex. But I would be curious to see what our other panelists have seen or witnessed or researched in this area.

Dr. Jason Marvin: And Dr. Guilak, would you like to share next?

Dr. Farshid Guilak: Sure. I think Dr. Frank and Saunders because they see patients have a better handle on this. But I've reviewed the literature and

infections are probably the number [00:31:00] one complication and adverse effect. But other than that, there has not been a large number of adverse effects. However, the ones that have occurred have been kind of horrific. And many of these have been due to medical tourism. There have been cases of embryonic stem cells injected into the body to treat all sorts of disease, such as spinal cord injury and so on. And those have led to tumor formation. There was a case of olfactory stem cells, which is basically stem cells from the nose that were used to treat again in the spine for spinal cord injury. That then differentiated into a mucus-forming organ nose in the spine of the patient. And of course had to have another surgery to come out.

And then a terrible case in a Florida clinic a few years ago where adipose stem cells were injected in bilaterally into both eyes of patients for macular degeneration and blinded both eyes in a series of patients. So there is this potential, even though it's [00:32:00] rare of really bad effects when stem cells or quote stem cells are not being used properly.

And I agree the rejection issue and most of these therapies are the patient's own cells. So the chance of immunologic rejection and the chances of infection, they're not zero, but they are very low for what we call autologous transplantation versus pulling cells off of a shelf for using embryonic stem cells and so on.

But that means we still really need to be careful and avoid these issues. And the ones that Dr. Frank just described of the unknown and unforeseen effects that can occur down the line. That are an adverse effect that may not be counted as.

Dr. Jason Marvin: And Dr. Saunders.

Dr. W Brian Saunders: So in veterinary medicine, the issues are very, very similar. The main issue that we deal with are joint infections. Animals, depending on the species can also have what I would refer to as a flare after any intraarticular injection. So whether it's a cell-based product or hyaluronic acid, or even just a big injection [00:33:00] of saline. Sometimes our veterinary patients will have inflammation and a temporary lameness associated with the delivery of a product.

And that's not just picking on stromal vascular fraction preparation. That can be any type of a joint injection. We're not in a place because of the current regulatory status which is not necessarily a bad thing that we can administer allogenic or culture-expanded cells in veterinary medicine. And if that was currently an ongoing treatment pathway, there would be additional issues you

would have to be concerned about regarding transmission of infectious diseases and exposure to potentially animal proteins that are used when we do culture expansion as the audience is probably aware. Many times a bovine serum is used to culture cells. There are ways to culture stem cells in what's called a serum-free manner even using blood products from an individual patient. So you can do platelet lysates and autologous culture with a patient's own serum. But most of the time we use some type of a bovine serum to expand the cells.

And [00:34:00] if that type of a treatment pathway ever develops where a pre-identified population of cells that's maybe screened to be very good for disease X is identified, used, and banked. And then in an allogenic way given to other patients, then that opens up the door for making sure that we have addressed the risk for disease transmission and reaction of the recipient. The patients to potential proteins that were used during the culture expansion.

Dr. Rachel Frank: If I may, I think one thing, especially for the audience, that's important to take home from all of this, whether they're clinicians, researchers, the public, etc. And it's one thing. One of my mentors, Aaron Rosenberg taught me very early on in residency. And that's that there's no free lunch and anything in medicine. I hope I'm not too much of a skeptic, but if it seems too good to be true, it probably is. And in a field like regenerative medicine and cellular therapies, it's so easy to just pop an injection in. It's so easy to take out some bone marrow or some adipose, [00:35:00] spin it down and pop it in and say, you've got stem cells, your tissue's going to regenerate. You're going to feel better.

It's the easy answer for a clinician to do in 2022. And it matches so many times what the patient wants. They want to hear that they want an easy, minimally invasive solution. They don't necessarily want surgery if they can avoid it. And they want kind of this magical cure, so to speak. I mean, we all want that. Any ailment. If I get a cold, I'd like a magical pill to make it go away in a day, you know, or in an hour. We all want those things. But with cellular treatments, the vast majority of what we think we know, we probably don't know how to measure or calculate in the human. And I'm assuming in the animal as well. So it becomes a risk benefit analysis and a single complication or a single infection. Or heaven forbid someone goes blind or loses a limb or becomes paralyzed in the spine. That single problem to me puts all of this into perspective and we have to be very, very careful with [00:36:00] how we move forward with clinical medicine.

I think in the lab, we should research everything we possibly can. But we have to be very careful with clinical application because of the potential for complications. And again, not every complication that we see clinically is going to be reported in a trial because it's a downstream effect and those are very difficult to report and those can be chalked up to something unattributable to the biologic treatment. When in fact it is likely attributable to the biologic treatment, but could never be proven. So for me, I'm super excited about the field of regenerative medicine and in particular cellular therapy for all the promise it has. But this question that you asked and all of our responses, I think should highlight to our listeners: it's a real potential problem.

And the risk benefit analysis right now, in many cases may favor more risk if we don't know exactly what we're putting into the patient.

Question Six: Addressing barriers and inequities to accessing these treatments.

Dr. Dianne Little: Thank you. So Dr. Frank has touched on this, but with regard to the risk benefit analysis and the fact that this is essentially a cash pay system by a patient [00:37:00] at the moment. For on the human side, what would it take to get insurance company buy-in to these therapies and what would be the next burden-of-proof if you'd like to be able to get those companies on board? And then on the veterinary medicine side, how do you see the field moving? You know, obviously the insurance is less of a role, but how do you see the field moving forward from essentially a cash pay benefit? And then as a follow on, obviously health inequities are widespread. Social, racial, across all, all, all, all barriers. How do you see these therapies reaching people that perhaps can't even access primary healthcare in an equitable way? Maybe Dr. Frank, do you want to address that first?

Dr. Rachel Frank:: Yeah, sure. I don't wanna hog all the air time here. That's a loaded three-part question. I think I'll start with the last part first in terms of disparities. This is a big problem. This is a cash pay business, so to speak. And I [00:38:00] hate even saying that as a clinician, I don't think of myself as a salesperson selling a treatment to a patient. I think of myself as a physician and surgeon offering the best care I can to a patient regardless of their insurance status, but when it comes to the field of regenerative medicine and in particular cellular treatments, because they are not currently covered by insurance, they are cash pay. And this is an area where profits sometimes take the center stage because there's a market for this. There's an aggressive market for this, and patients are willing to pay. But those are the patients who have the money. And so if you have a patient who does not have cash to spend on such a treatment,

even if we felt like the treatment was superior and would benefit their care, then you have a big disparity.

I think once we have data to support that a given treatment is superior or maybe, maybe not, but ideally we find a treatment that helps augment healing or [00:39:00] repair or regeneration. Then ideally we do get insurance approval and this becomes kind of a moot point, but until we get there and we're probably, I hate to say it, but we're probably a decade away or more from having the type of data that we would need to have codes to be able to have reimbursement from insurance companies. This will continue to be a cash based business and those without money will just not be able to participate unless they sacrifice that. That money that might be intended for bills for electricity, for water, or for food depending on their current social and socioeconomic status.

So this is a big problem and I don't think it's getting better in the near future as the healthcare. I mean, we're not really talking about the healthcare system, but as the healthcare system evolves in the U.S., I think this is going to continue to be a problem. I'd be curious, what our other panelists think about that, but I think this is a significant kind of unspoken about area or not spoken about enough with respect to biologic treatments. Because it is completely cash based. And so you're already focusing all of your, unless you're in a trial, you're focusing [00:40:00] all of your research into one socioeconomic group, more or less the group that can afford to pay for these cash based treatments.

And that, you know, that's not representative of our United States patient population as a whole. That's representative of one silo of patient.

Dr. Dianne Little: Dr. Saunders, perhaps?

Dr. W Brian Saunders: Well, you touched on it when introducing this question. Pet insurance does exist. And the percentage of pet owners that have half insurance is very regional.

In some areas it's below 5% and some areas it's upwards of 50%, but because of the lack of definitive efficacy that pet insurance to my knowledge does not cover any of the cell-based therapies that we've talked about today. So for me, before we talk about access, it really is documenting efficacy for a treatment. And if we can't document efficacy, it becomes a moot point moving forward. If we develop the strategies to produce an effective treatment for orthopedic injuries and animals or people then, you know, this has already been the pathway to addressing that I think has already [00:41:00] been addressed.

The only last thing I would comment on is that because most pet owners pay for their veterinary bills out of pocket with the exception of equine and insured race horses, which is a whole other field I'm not going to address, the use of a finite amount of resources that a pet owner might have on cell therapy actually can do more harm for the overall good of the pet. Because for example, if I have a pet that has an arthritic hip. A standard of care is a hip replacement, which we do a lot in animals. And hip replacement costs X amount of dollars out of pocket. And the pet owner has that to spend, but unfortunately they've used that money on three or four rounds of stem cell therapy that have actually have done nothing to help that patient.

Now that money that they would've spent on a lifelong effective treatment, they're not able to use for the gold standard treatment. So there's an additional area of, or avenue of frustration for using a finite amount of resources that different pet owners and different socioeconomic [00:42:00] statuses have on a therapy that may not be proven.

Dr. Dianne Little: Do you have anything to add?

Dr. Farshid Guilak: Yeah, not too much to add other than, you know, insurance companies. To pay for this, you have to show that in the future it's going to save them money, or that it's gonna be efficacious. And we're just lacking good clinical trials. And one of the biggest issues we have is that only a fraction of the clinical trials that are registered and performed are actually reported and published.

So in the broad stem cell field, the number is about 45% of clinical trials actually get reported. In the musculoskeletal orthopedic field, it's much, much worse. We don't have the exact numbers, but if you search on mesenchymal stem cell clinical trials, I'd say there's probably 250, 300 registered and maybe under 10 reported.

So it's a real issue because they're skewed to which trials are being reported. And until we have that data, then insurance companies can't make the decision. That it's worth their while to actually pay for these treatments. So I [00:43:00] agree with what both other panelists said that we're probably about 10 years away from having the real data that we need in either the vet market or the clinical market.

Dr. Rachel Frank: Well, and even to make that even more daunting of the trials that are reported. Less than 10% report on all of the steps that they used to harvest, process, and inject or apply their biologic. So even of the studies that

are published, even what seemingly is a good clinical trial, a level one or level two study with control groups, etc. They don't; not every author is. And in fact, under 10% of authors are reporting on the steps. So then the reproducibility of that said trial becomes so difficult for the next person or for someone in their office to try to replicate what those authors showed. And so I think even the data we have. And as an orthod, I would love to take pride in our gross body of research that's available. But in this particular field, we're not doing a very good job as a community of publishing what needs to be published. And [00:44:00] then of those studies that are published, writing down and documenting exactly what was done. So it's a whole challenge.

Question Seven: What are the primary obstacles that need to be overcome before widespread clinical use of stem cells becomes a reality.

Dr. Jason Marvin: Yeah, I really like this discussion because it leads us into a really good setup for our final question. So we've talked about these financial barriers to using stem cell treatments. I'm curious for each of the panelists, what would you foresee perhaps as the primary obstacle that needs to be overcome before we could have widespread clinical use of stem cells as a reality?

So whether that's going back to the research rigor and having more reproducible studies and reporting of these outcomes, or is it perhaps more of a regulatory landscape issue or clinical. You know, trials, etc. What do you put as your primary focus? And maybe let's start with Dr. Saunders.

Dr. W Brian Saunders: So in veterinary medicine, this is an easy question.

It's available funding to do non-biased studies. So in veterinary medicine, there are a handful of foundations that exist that are responsible for funding all of veterinary medical [00:45:00] health, not just orthopedics. And in order to do a trial like this with sufficient patient numbers that's powered properly with the right controls, the amount of money available to do these studies is not there. And so the biggest barrier to us is funds, available funds, to do non-compromised work. Now, there are companies that would be willing to sponsor study X, Y, or Z, but they're not gonna allow that data to be published unless it's a positive outcome.

And so there is, you know, there are challenges with the transparency of the data and has already been discussed. How many trials have been done that aren't published in veterinary medicine? It's a very similar experience. So one is just available dollars to do high-quality research.

Two is the veterinary centers that are available to do these kind of studies is a handful of programs compared to human medicine. And then moving beyond that, it would be really documenting efficacy for our one or two most pressing needs and developing a consistent cell pathway that was a production pipeline that was going to achieve clinical success in the majority of [00:46:00] patients that were gonna receive that cell therapeutic.

Dr. Jason Marvin: And Dr. Guilak?

Dr. Farshid Guilak: I think we need a lot of things. Certainly what Dr. Saunders just described. We need more basic science. And I just hate to say it, but we've tried injecting MSCs and adipose stem cells over and over and over again in their raw state or in the SVF forum. And if they worked, we would probably know it by now. And this is one of the problems with not reporting. These clinical trials, there's a huge positive bias. All the negative trials never get reported. So we need more basic science to really develop techniques that are going to work from the regulatory standpoint.

I feel very strongly. The FDA needs to crack down on clinics that are promising things that are not possible and are fiction. Not science fiction, they're just fiction because what they will do is set the field back a decade or two when they start to have adverse effects like blindness. And we look at the gene therapy field where one death set the field back for [00:47:00] decades, and this will happen in the stem cell field. And we'll have to try to recover from it, but if we can stop the incorrect use and incorrect marketing of the stem cell field, I think it's a n important step for the long-term efficacy and development of the field overall.

Dr. Jason Marvin: And Dr. Frank.

I would agree with everything just said. I think again, I hope we can overcome these obstacles as a combined field in medicine and orthopedics and combining, you know, human medicine and veterinary medicine, because the field is exciting. What we think these cells have the potential to do to augment our current techniques to help patients for whatever reason.

It's so exciting, but we need data. I think everything can be summed into that word: data. We need data that's unbiased and not necessarily promoted by one company or another company and to do good science, good basic science. And then hopefully [00:48:00] translational science. We need funding. And we need funding that comes from a non-biased source.

So I think my two co-panelists sum this up quite nicely until we have unbiased data, I think we're going to struggle to have an ability to use these treatments because we don't really know what treatments to use just yet for what clinical application, but if we can get funding to do unbiased research, then I think the future is incredibly exciting.

Wonderful. And that really hits the whole essence of this committee as well. I really appreciate all the time and the really thoughtful discussion that y'all provided today. So with that, on behalf of the committee, we like to really thank all three of our panelists again for a very wonderful discussion and for setting our very high bar for kicking off this event series.