

Dr. Travis Dekker:

Welcome to the Arthroscopy Association's Arthroscopy Journal Podcast. I'm Dr. Travis Dekker from Eglin Air Force Base and today I'll be talking to Dr. Nicholas DePhillipo, who currently serves as a research associate at the University of Pennsylvania and the chief operating officer of Mechano-Therapeutics, a startup biotech company that specializes in improving drug delivery for musculoskeletal tissue applications. Nick is a dear friend and colleague of mine as he now inspires me and has inspired me for greater than five years as he takes his practical knowledge as an athletic trainer, first assist and practice manager and has applied it to his doctorate and research as he continues to lead the way in both bench side and clinical research of the knee.

Dr. Travis Dekker:

No one is more knowledgeable than Nick when it comes to meniscal pathology and the importance of recognizing and addressing even subtle tears. Today, we'll be discussing Nick's article entitled, Preventative and Disease Modifying Investigations for Osteoarthritis Management are Significantly Underrepresented in the Clinical Trial Pipeline: A 2020 Review. This article was published more recently in August of 2021 and although I helped co-author this paper, Nick truly spearheaded this effort and came away with some key findings that I think the readership would be extremely interested in, as we look into the future in advancement of knee osteoarthritis research. Welcome to the podcast, Nick.

Dr. Nick DePhillipo:

Travis, thanks so much for having me, for the very kind intro. It's an honor to be on the podcast.

Dr. Travis Dekker:

Nick, to begin with, typically the podcast has had excellent discussions with leading surgeon scientists in the field. However, the spectrum of the readership of the journal and the listeners of the podcast come from all different backgrounds, as the journal has promoted cutting edge techniques, technology and advancements in the field for decades. Can you give the listeners a little bit of a background on yourself, the research you're passionate about and really what gave you the idea for this paper?

Dr. Nick DePhillipo:

Absolutely. In that regard, I would say, I'm definitely a small fish in a big pond and have been extremely fortunate to be part of some of the best clinical and research teams that have been contributing to orthopedics, so it's always a team effort. But as you mentioned, I'm an athletic trainer by trade. I went to Rowan University for undergrad and then University of Hawaii for my master's degree in exercise physiology. I ended up pursuing a PhD in sports medicine in Norway, under the mentorship of Dr. Lars Engebretsen. And I recently completed my master's in business association degree. As an athletic trainer, I really worked in almost every setting, covering high school, collegiate, professional, Olympic sports, similar to yourself. But my real passion for orthopedics came about when doing a fellowship at the Steadman Clinic in Vail, where I met my mentor and the man who has inspired really both of us in our careers, Dr. Rob LaPrade.

Dr. Nick DePhillipo:

I worked for Dr. LaPrade in clinic surgery and research for five years at both Steadman and then at Twin Cities Orthopedics in Minnesota. And I've had an amazing opportunity to work alongside Rob and Lars, who are as you know, two amazing surgeon scientists. And I've learned so much in a very condensed time and developed passionate research interest in meniscal preservation, posttraumatic osteoarthritis,

optimization of ACL injuries and the management of complex knee injuries in both on field and off field care. As far as this paper, we all know that osteoarthritis is a complex problem with limited therapeutics available to patients. The idea for doing this study really came from my own curiosity about existing osteoarthritis drugs that are in development but also from listening in clinic to so many patients who ask about the potential disease modifying therapies that are in active clinical trials today, that can help them not necessarily currently in their clinic visit, but hopefully in the near future. We set out to answer that question and help provide content text to both patients and clinicians about the therapies that are in clinical trials currently to treat osteoarthritis.

Dr. Travis Dekker:

Awesome. Nick and impressive background and there's been a lot of mentors that have inspired both of us along the way. And as we dive into your paper and looking at the specifics of the manuscript, you found some very interesting trends about that active running trials. I feel like we hear all the time about this disease prevention methods and biologic interventions, as they're a true hot topic. However, your results demonstrated that yes, this does continue to be a topic, but maybe it's not the main one when it comes to looking at active osteoarthritis research. Can you break down your principal findings from your extensive research that you did on this study?

Dr. Nick DePhillipo:

Sure, Travis. We looked at almost 4,000 clinical trials when we started and we ended up including 310 that were currently active. And what we found was that the majority or overwhelming majority, 89%, were focused on symptomatic resolution for existing osteoarthritis and a large focus was on joint arthroplasty, which is obviously important and it's needed for the appropriate patient population. But this was a little disheartening from a sports medicine perspective because obviously joint replacement is not a suitable option for young patients with posttraumatic osteoarthritis. And we found that only 6% of trials were focused on quote unquote disease modifying therapies and then even less, 5%, were focused on prevention of arthritis in high risk patient populations. As you mentioned, cellular biologics remains a hot topic and a promising area for modifying symptomatic OA. But interestingly, in our study there was a significantly higher number of trials, it was actually more than double that looked at biologics for disease modifying therapies compared to development of traditional pharmaceutical drugs, which may be an ongoing trend in the future of osteoarthritis research and something we can talk about later on as well.

Dr. Travis Dekker:

Nick, that's really interesting and it's the type of patient that I see almost every day in my clinic with these young, active duty patients that definitely are too young to pursue any type of arthroplasty intervention. It'd end their career early and there's no perfect solution. And so the proverbial statement of the young patient with an old knee, clinical scenario, it remains problematic. And it seems like the research does a good job at pointing out the gaps in the available treatment options currently for these younger patients. Can you discuss other interesting trends that you're able to uncover regarding the development of osteoarthritis therapies?

Dr. Nick DePhillipo:

The two other biggest trends that we saw were the concentration of clinical trials in medical devices compared to pharmaceuticals and that over 60% of trials were targeting the knee joint specifically. I think that tells us a few things. First, as far as the knee joint predominance, this makes sense because it aligns well with previous epidemiological studies that report that knee osteoarthritis accounts for the

large majority, over 85% of the total burden of osteoarthritis worldwide. This is encouraging to all patients with knee problems. However, when you have this over exposure, obviously that means that we're limited in other areas, so shoulder, hip, ankle and even spine. Now looking at the focus of development in medical devices, this can be explained by, I think, two things, financing and then regulatory approved. Obviously it costs significantly less time and money to bring a medical device to market than a pharmaceutical drug.

Dr. Nick DePhillipo:

For example, a class one medical device typically requires just registration with the FDA and no proof of safety or clinical efficacy. Class two devices typically require pre-market otherwise notification, otherwise known as a 510(k) application with limited clinical evidence. And then class three devices do require pre-market approval with level one or level two clinical trial research. However, the majority, over 75% of class one devices and even a small amount of class two devices, qualify for exempt status. Which means there is no requirement to show proof of safety or efficacy or to conduct a single clinical trial. And obviously this can be problematic. And as we've seen in historical cases, the incentives of low cost and less regulation, do not always serve our industry well and can result in underdeveloped and poorly designed products. I think that's those two things were stuck out in my mind as big trends.

Dr. Travis Dekker:

Nick, common interest for many of the readership remains the biologic aspect and looking at the biologics and pharmaceutical drugs in the current clinical trial pipeline. What does the time horizon look like in regards to the phases of drug development for osteoarthritis therapies?

Dr. Nick DePhillipo:

That's a very good and I think very important question to look at, Travis. What we found was that the majority of osteoarthritis research, over 40% was in phase two, just little under 30% was in phase three. And currently there are very few in phase four and even less in early phase zero or one for osteoarthritis therapy. This means we are going to actually realize some of these successes, hopefully they are successful, soon in the near future, but these products have to make it past the biggest challenge yet, which is phase three clinical trials. And regardless of the medical specialty, phase three is sort of the gauntlet of doom. 80% of all drugs fail in phase three clinical trials due to efficacy and safety concerns. Osteoarthritis research is no different. We saw this with the drug sprifermin, which is a recombinant human version of fibroblast growth factor 18. And this showed great promise through phase two clinical trials but has since then stalled. Getting past phase three trials remains an enormous hurdle for upcoming therapies in the osteoarthritis drug development pipeline.

Dr. Travis Dekker:

I love that, the gauntlet of doom. That's awesome. As we look to future research of this prevalent disease, you've identified possible sources of funding and support that may be underutilized at this time. Can you comment on the discoveries you made about how the majority of osteoarthritis research is currently being funded?

Dr. Nick DePhillipo:

Yeah. Another great and tough question. From publicly available records, so this data that we're talking about is from clinicaltrials.gov database. And what we saw was that the majority of funding for osteoarthritis clinical trials is coming from government sources, such as the NIH and DoD, as well as the

sector, but there remains a lack of funding from the biopharma industry. Now, I don't think it's fair that this review can capture the full picture of financing osteoarthritis research and drug development, but it is important to discuss what we do know. We know that it takes on average 10 years and \$1 billion to develop a single drug and bring it to market. And one of the primary reasons it costs so much are the massive expenses associated with performing clinical trial research. It costs, if you look at the averages, on average \$36,500 per patient per phase and there are thousands of patients that need to be enrolled in usually three to four phases of clinical trials, as you know, so the expense of clinical trials is one of the main reasons why biopharma industry remains underfunded.

Dr. Nick DePhillipo:

And then not to mention, there's risk, there's financial risk associated with developing new drugs. And we know that only five to 10% of drugs have a rate of approval. That's a very, very low probability of success and compounded with the fact that the basic science, the pathogenesis of osteoarthritis is very complex, unclear and varies among patients, makes this not a great investment opportunity. And that's just the harsh reality. This uncertainty is another reason why financing disease modifying and curative therapies is so difficult and can explain in part again, why the amount of funding from industry for osteoarthritis treatment was low in our study. Also, I think it's important to note that the healthcare related cost of treating patients with osteoarthritis, account for nearly 1% of the GDP in the United States, which is an enormous cost to stakeholders and taxpayers, which are all of us. That is why increased government funding for developing disease modifying and even preventative therapies is essential to reduce the cost burden of treating osteoarthritis patients in the United States.

Dr. Travis Dekker:

Whether it is the media or even the push from our own industry to evaluate therapeutic biologic interventions in a world of a lack of standardization and consistency orthobiologics did remain a hot topic of discussion when it comes to osteoarthritis. At this time, can you discuss from your findings, how orthobiologics are really being evaluated and critiqued when it comes to symptomatic osteoarthritis?

Dr. Nick DePhillipo:

Absolutely. You said it Travis, first and foremost, there is still a lack of standardization when it comes to reporting the use of biologics for orthopedic applications. But what we are seeing from clinical trials are that these cellular products, both autologous and allogenic, are very appealing because of their point of care availability and known anti-inflammatory properties. Cellular biologics may be more popular than traditional pharmaceuticals, as I was talking about earlier for at least disease modifying approaches because of their proposed advantages for reversing or even halting osteochondral structural damage that occurs after a traumatic injury. We know that the presence of blood in the joint and the resultant inflammatory process that occurs after a traumatic joint injury can be devastating to chondrocyte regeneration and survival. And there are numerous inflammatory cytokines and other degenerative cellular byproducts that can lead to early chondrocyte death, chondrocyte loss over time and ultimately progression of osteoarthritis. Being able to target symptom resolution by neutralizing inflammatory cytokines, while also promoting chondrocyte repair, that's what makes cellular biologics a promising area and such an exciting area for future clinical therapy in osteoarthritis.

Dr. Travis Dekker:

Nick, I really do appreciate your taking time out of your schedule to sit down with me, tackle an interesting topic as it applies to all of our practices, both in operative and non-operative interventions

for osteoarthritis. Do you have any parting words on the future of osteoarthritis research and how it may alter the landscape of our practice?

Dr. Nick DePhillipo:

Thanks again, for having me, Travis. I'm obviously a fan of the podcast and work that you do with interviewing some of the best of the best in orthopedics is amazing and it's an honor and privilege to be on the podcast. I think a lot of focus will continue to remain on biologics for the aforementioned reasons but I can see also the use of exosomes becoming increasingly promising as well as targeted drug delivery methods, which as we know, drug delivery remains a constant challenge, considering the harsh environment of musculoskeletal joints. But ultimately I think that innovative technologies that continue to seamlessly personalize and optimize patient treatment, that's what's going to alter the landscape of our practices.

Dr. Nick DePhillipo:

I don't know exactly what that is, but what this research study has really taught me is that the future of osteoarthritis, just like so many other complex diseases, ultimately depends on collaboration. And obviously we need continued collaboration among clinicians and scientists like ourselves but also with government funding agencies and industry to help not only discover new ways to better treat patients with osteoarthritis, but to have the appropriate financing for commercialization to then take these treatments from the lab and into the marketplace where they can make an impactful difference in people's lives.

Dr. Travis Dekker:

Dr. DePhillipo's Arthroscopy article entitled, Preventative and Disease Modifying Investigations for Osteoarthritis Management was published in August of 2021. Nick, thanks so much for joining us and this article can be currently accessed at www.arthroscopyjournal.org. Thank you all for joining us and have a great evening.

Dr. Travis Dekker:

The views expressed in this podcast do not necessarily represent the views of the Arthroscopy Association or the Arthroscopy Journal and are not meant to be treatment recommendations for individual patient.

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