Clin Orthop Relat Res (2014) 472:2564–2568 / DOI 10.1007/s11999-014-3789-1

Clinical Orthopaedics and Related Research®
A Publication of The Association of Bone and Joint Surgeons®

Published online: 15 July 2014

Editor's Spotlight/Take 5

Editor's Spotlight/Take 5: *CORR*® ORS Richard A. Brand Award for Outstanding Orthopaedic Research: Engineering Flexor Tendon Repair With Lubricant, Cells, and Cytokines in a Canine Model

Seth S. Leopold MD

It is with great pleasure that we present the inaugural *CORR*® ORS Richard A. Brand Award for Outstanding Orthopaedic Research to Dr. Peter C. Amadio and colleagues for their exciting project that employed a cellular-engineering approach to address a common clinical problem: Finding the right balance between repair strength and tendon gliding after flexor-tendon repair. Although this was an applied-science project in an animal model, nonexperts and clinicians alike can readily approach, understand, and enjoy this thought-provoking work. In fact, clinicians *should* familiarize themselves with this project, as the direction these authors are pursuing seems likely to survive the jump from the laboratory to the operating room..

But before going further, a few words about the award itself. Our mission at *CORR*® is "Disseminating orthopaedic knowledge." The vision of the Orthopaedic Research Society (ORS) is to "transform the future through unique global multidisciplinary collaborations, focusing on the increasingly complex challenges of orthopaedic patient treatment." [1]. Our publication and the ORS therefore should be natural partners. Together, with the support of our journal's parent society, the Association of Bone and Joint Surgeons®, this partnership created a research award associated with (what is now) the largest prize in our specialty – USD 25,000. We were delighted with the many excellent submissions we received, and we are thrilled to honor this paper with the award.

Richard A. Brand, the man for whom this award is named, was the Editor-in-Chief of our journal from 2002 through 2012. Prior to his work at *CORR*®, Dr. Brand edited the *Journal of Biomechanics*, and so it is especially fitting that the first paper to be honored with an award in his name should involve clinically relevant, applied-science research with an engineering angle, exactly the kind of work for which Dr. Brand was justifiably well known.

Flexor tendon injuries are common, morbid, and difficult to treat. Effective repairs should be strong, but not so

Note from the Editor-In-Chief: In "Editor's Spotlight," *one of our editors provides brief commentary on a paper we believe is especially important and worthy of general interest. Following the explanation of our choice, we present* "Take Five," *in which the editor goes behind the discovery with a one-on-one interview with an author of the article featured in* "Editor's Spotlight."

The authors certify that they, or any members of their immediate family, have no commercial associations (eg, consultancies, stock ownership, equity interest, patent/licensing arrangements, etc) that might pose a conflict of interest in connection with the submitted article.

All ICMJE Conflict of Interest Forms for authors and *Clinical Orthopaedics and Related Research*® editors and board members are on file with the publication and can be viewed on request.

The opinions expressed are those of the writers, and do not reflect the opinion or policy of *CORR*® or the Association of Bone and Joint Surgeons®.

This comment refers to the article available at: DOI: 10.1007/s11999-014-3690-y.

S. S. Leopold MD (✉)
Clinical Orthopaedics and Related Research, 1600 Spruce Street, Philadelphia, PA 19013, USA
e-mail: sleopold@clinOrthop.org

Editor's Spotlight/Take 5

sticky or bulky that they impair the tendon's ability to glide. The ideal adjunctive treatment would improve gliding (and decrease work of flexion), but not result in more-frequent reruptures, as occurred in some earlier, related work from this same group [2].

By adding cells and cytokines to an effective lubricant, the investigators appear to be on their way towards solving an important problem. In this randomized large-animal study, the authors combined a surface treatment designed to decrease adhesions (carbodimide-derivatized gelatin, hyaluronan, and lubricin, or cd-HA-lubricin) with cellular therapy that sought to increase tendon healing (bone-marrow stromal cells supplemented with growth differentiation factor 5, or GDF-5). The evaluation was thorough, and included both histology and mechanical testing to confirm repair strength, as well as several approaches to assess friction, work of flexion, and adhesions. The adjunctive treatment resulted in fairly substantial reductions in terms of work of flexion (an effect size of about 60% after 6 weeks of healing), and mitigated – but did not eliminate – the load-to-failure issue associated with lubricin treatments observed in their earlier work [2].

This approach currently is limited by preparation time, as it takes 2 to 3 weeks to harvest and make the bone marrow stromal cell patches they used. The experiment also only followed animals out to 42 days, so further work with longer surveillance periods is in order. And, certainly, it seems likely that future efforts will need to focus further on strength of the healed repair, which remain something of an unsolved problem with this approach.

But even with those caveats, this approach seems promising, and perhaps close to clinical applicability. Please join me as I go "behind the discovery" with Dr. Peter Amadio of the Mayo Clinic, senior author of this exciting work, in the Take 5 interview that follows.

We also invite basic scientists, translational researchers, and clinician scientists to submit their best work for consideration in next year's *CORR*® ORS Richard A. Brand Award for Outstanding Orthopaedic Research. Please visit www.abjs.org and click on the Awards link for more details.

Take Five Interview with Peter C. Amadio MD, senior author of "*CORR*® ORS Richard A. Brand Award for Outstanding Orthopaedic Research: Engineering Flexor Tendon Repair With Lubricant, Cells, and Cytokines in a Canine Model"

Seth S. Leopold MD: *Congratulations on this excellent work, and on winning the first CORR® ORS Richard A. Brand Award for Outstanding Orthopaedic Research. Please share with our readers a bit about how your group came to take such a creative approach to solving this resistant problem?*

Peter C. Amadio MD: Thank you, Seth. It was a great honor to receive this award. It was truly a team effort, and I must begin by thanking my collaborators, many of whom are long-term partners, going back 20 or 25 years.

The approach that we describe here is the result of an evolution, starting with a clinical problem, poor function after flexor tendon repair in the fingers, and gradually nibbling away at it. Whenever possible, we have cycled back to use what we have learned in patients, because their problems are the reason we embarked on this journey. I am also grateful to the NIH and especially the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), which has funded nearly all the experimental work during the past nearly two decades.

We started looking at something relatively simple – stronger tendon repairs, and modifications to tendon rehabilitation protocols. We were able to translate those back into patients relatively easily. But while clinical results improved, we still saw many patients with adhesions.

Editor's Spotlight/Take 5

Peter C. Amadio MD

Through a fortuitous encounter at an ORS meeting, I became aware of the work Gregory Jay was doing with lubricin, which is the main lubricant in cartilage. During the past decade, we have partnered to study the effect of lubricin on tendon lubrication in vitro, and on adhesion formation in our animal model. What we found was truly exciting – the adhesions nearly completely disappeared. But the lubricin also seemed to slow the tendon healing, so the repaired tendons, while adhesion free or nearly so, were more likely to rupture.

That is when we came up with the idea of adding stem cells and growth factors, to give the healing a compensatory boost while continuing to take advantage of the lubricant we had developed. That is the work we submitted for the Brand award.

Dr. Leopold: *What do you see as the next steps in – and, if you can, the timeframe of – the transition of your discovery from laboratory science to clinical practice? Presumably, some work still needs to be done to increase the load to failure of the healing tendons, which seems still somehow to be diminished by the surface treatment.*

Dr. Amadio: We are working on a number of separate but complementary projects. One, as you suggest, is to continue to refine our approach, using different cytokines or perhaps a cocktail of them such as platelet-rich plasma, to test different sources of stem cells in order to determine if some are better than others at getting tendons to heal. We are also looking at mixing the cells and cytokines in a patch that might have some adhesive power of its own. The second approach is translating this into a related application, tendon grafting. When a flexor tendon cannot be repaired and must be replaced, current options are limited mostly to tendon sources that do not look or behave anything like an intrasynovial finger tendon. In that case, we would use a decellularized allograft of perhaps a flexor profundus tendon as the scaffold, and then add our cells, growth factors, and lubricant to regenerate a living tendon with host cells. There, we have the added complexity of customizing three different environments – the tendon-bone interface, the gliding part of the tendon, and the tendon graft-host tendon interface. That is also being funded by NIAMS, and some of the early animal work is pretty exciting. The third approach is determining the best use of our lubricated and augmented tendon repair. It is probably not needed for a sharp laceration and a limited soft tissue injury. What we are thinking is that it might have its best use when the

Editor's Spotlight/Take 5

tendon repair is complicated, and the usual early active motion rehabilitation cannot be used, such as in patients with polytrauma, or in severe injuries, such as replantation. The final, and perhaps most difficult challenge, is to get these tissue engineering solutions to market. The regulatory environment is at least as complex as the biological one we have been studying. We are currently looking for partners to help us with that.

Dr. Leopold: *While perhaps no other kind of tendon injury has to balance strength and smoothness quite as well as the zone-II flexor-tendon laceration, strength and smoothness are important – at least to some degree – to many tendon repairs, such as in the rotator cuff. How do you see elements of your work influencing the care of patients with tendon injuries elsewhere in the body?*

Dr. Amadio: That is a great question. Yes, we are looking to use these concepts in rotator cuff repair and reconstruction as well. The tendon there is flat instead of round, but it is also intrasynovial, and the principles are similar.

Dr. Leopold: *Your work involves many partners – experts from several scientific disciplines, funding through NIH/NIAMS, and some corporate collaboration. I imagine that each of those collaborations has been important in your success. How do you mentor your trainees on the topic of navigating systems and partnerships in the solution of big problems?*

Dr. Amadio: Yes, as I mentioned at the start of this interview, this is team science. No one person has the combination of clinical, biological, and engineering expertise needed to be successful in this field. It is essential to emphasize to trainees how important it is to develop true partnerships in research. Leading by example is important. I work at Mayo Clinic, where team-based care and team-based research go back more than a century, so the culture helps a lot. There are a couple quotes from the Mayo brothers that summarize it well. One is that the brothers never used the word "I" alone. It was always "my brother and I" or some other expression to emphasize that nothing was done in isolation. Another well-known quote is "The best interest of the patient is the only interest to be considered, and in order that the sick may have the benefit of advancing knowledge, a union of forces is necessary." But I think that the most important mentoring I do is to develop a sense of scientific discipline and especially scientific equipoise. Many trainees want to know what result I want from a particular experiment. I emphasize to them that what I want is a scientifically valid and reproducible result. To me, if you have a good research question, a good study design, good methods, and good recordkeeping, whatever result you get is going to be interesting. Different results will lead to different sets of new questions of course, but in the long run, science is really about the process. The other important mentoring advice in my opinion is to ground your work in real life – if you are trying to solve real clinical problems, the questions you ask are going to be interesting, and every result is either a step closer to a new therapy or a blind alley that others can now avoid. Either way, you have done something worthwhile.

Dr. Leopold: *Speaking of partnerships, we are especially proud to have partnered with the Orthopaedic Research Society in the creation of this award, which now is the largest research award in orthopaedic surgery. Can you comment briefly on the importance of the ORS and of this award to your program?*

Dr. Amadio: In my opinion, the ORS is the essential forum for musculoskeletal translational research. It gathers together a broad mix of scientists and clinicians; the collaboration I formed there, that led to this award, is just one example among many. That serendipitous event led to 10 years of NIH funding and to this award. As to the importance of the award, the

Editor's Spotlight/Take 5

recognition is great and hopefully the receipt of this award will capture the attention and imagination of someone out there, someone who will become a future collaborator, maybe the person or people who will help us get some of these novel therapies approved for clinical use.

Acknowledgements The author thanks Clare M. Rimnac PhD and Montri D. Wongworawat MD for their thoughtful suggestions, which improved this commentary.

References

1. Orthopaedic Research Society. Our purpose, mission, and core values. Available at: http://www.ors.org/mission/. Accessed May 29, 2014.
2. Zhao C, Sun Y-L, Kirk RL, Thoreson AR, Jay GD, Moran SL, An KN, Amadio PC. Effects of a lubricin-containing compound on the results of flexor tendon repair in a canine model in vivo. *J Bone Joint Surg Am.* 2010;92:1453–1461.