

Cover Story

Future of cartilage repair may involve cell-based, gene-based therapies

In this *Cover Story*, Henning Madry, MD, and other cartilage repair experts told *Orthopaedics Today Europe* the greatest promise in this field lies in techniques that use cells, tissue or a matrix.

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COVER STORY FROM OT EUROPE

Future of cartilage repair may involve cell-based, gene-based therapies

The new International Cartilage Repair Society registry will help determine the best results for each repair technique, lesion type and patient.

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About 20 years ago, the field of articular cartilage repair was a new and exciting area for researchers and clinicians with several promising treatments being developed and used. These included autologous chondrocyte implantation, microfracture, osteochondral transplant systems and mosaicplasty. As these techniques were used, evolved and gradually modified, it seemed patients — even high-level athletes — with chondral or osteochondral knee cartilage defects might be able to undergo treatment to lessen their pain and return them to normal activities and sports.

The International Cartilage Repair Society (ICRS), which was founded and held its first meeting in 1997, helped champion this area. It has provided a platform on which new basic science and clinical findings relevant to articular cartilage repair can be presented and has supported ongoing developments in the field.

Now, nearly 2 decades later, there is some concern the field may have stagnated. In August 2016, Stephen Lyman, PhD, at Hospital for Special Surgery Healthcare Research Institute, in New York City, and cartilage repair researchers and clinicians, wrote in the *Journal of Bone and Joint Surgery* that cartilage repair innovation has reached a standstill. One of the reasons, they said, is it has been 15 years since the U.S. Food and Drug Administration approved a cartilage repair technology or product.

They noted, however, the promise of this field lies in techniques that use cells, tissue or a matrix.

Field has matured, still growing

Experts involved this field spoke with *Orthopaedics Today Europe* on the state-of-the-science of articular cartilage repair and ways to advance the field, including stem cell technology and the new ICRS Global Cartilage Registry Project that launches this month at the ICRS World Congress in Sorrento, Italy.

“I think it is true, in the 1990s there was [clearly] a hype,” **Henning Madry, MD**, said.

He surmised much of the initial hype stemmed from a 1994 publication by Matts Brittberg, MD, PhD, and colleagues in the *New England Journal of Medicine*, which reported the results of autologous chondrocyte implantation (ACI). It was this study that first gave clinicians and their patients with cartilage lesions some hope, according to Madry, who is the chair of the Center of Experimental Orthopaedics and Osteoarthritis Research at Saarland University in Germany with a joint appointment in the Saarland University Department of Orthopaedic Surgery.



**Henning
Madry**

However, Madry told *Orthopaedics Today Europe* he tends to disagree with the article by Lyman and colleagues.

“Since [Brittberg’s study], I think the field has constantly grown, matured and evolved, especially from a basic science standpoint and I am more optimistic,” said Madry, who is studying gene therapy for cartilage defects and osteoarthritis (OA), and working with Dietrich Pape, MD, to determine the effect of axial malalignment on the onset and progression of early OA using high tibial osteotomy in a sheep model.

Long-term data published

Recently, some long-term studies have been published on the topic. One such study by Knutsen and colleagues compared results of microfracture (MFX) with ACI and followed patients treated 14 years to 15 years ago with these procedures.



Alberto Gobbi

Results like these must be scrutinized, but may prove helpful going forward, according to **Alberto Gobbi, MD**.

He told *Orthopaedics Today Europe*, “We should be careful when we read these studies. I understand it is long-term, but there are some flaws in the study project. The power analysis was low, many patients [were] lost to follow-up. We cannot just say that cartilage repair is today in sort of a standstill or a negative direction because, since the beginning of this, many other studies have been published and show different results.”

Gobbi said he, Elizaveta Kon, MD, and colleagues, published a study in 2009 that compared long-term results with matrix-induced ACI or MACI to MFX for chondral defects. It showed “absolutely better results in patients treated with MACI than patients treated with MFX, with a substantial difference after 3 years,” he said.

Yet, results from a similar study conducted by Daniël B.F. Saris, MD, PhD, of Utrecht, The Netherlands and colleagues were completely different, Gobbi noted.

These different outcomes, he said, emphasize the diverse results that can be expected from the long-term studies now available. Such findings also highlight why it is essential to use the proper procedure in patients who meet the indications for lesion type and location.

“It is important to consider that today we do not have a gold standard, but we understand much better what can do in particular lesions,” Gobbi said.

ACI today – cells matter

Leela C. Biant, FRCS(Tr&Orth), MS, of the Royal Infirmary of Edinburgh, told *Orthopaedics Today Europe*, “The science of ACI is absolutely proven. We have 20 years of great data. We have several randomized trials now over 10 years and the great majority of evidence is suggestive that cell therapy or ACI is effective. We know also who it is effective in and for, and we have an idea which defects will respond well and which will not do well.”

The ACI procedure, however, has been impacted by health care providers’ reluctance to pay for it and that has led to a regulatory and payment landscape that has hampered somewhat routine use of ACI worldwide, said Biant, who is chair of the ICRS registry committee.



Leela C. Biant

According to Biant, the need for the registry is great in a pioneering field like cartilage repair and it will ultimately benefit patients with the valuable and robust data it provides.

“We are at the cutting-edge of science and biological resurfacing and regeneration of joints, and we are at the pioneering end of new techniques. It is essential, from the clinician side and for the patient benefit, to have responsible innovation, and part of responsible innovation is to collect robust data on the techniques that are out there, as well as post-market surveillance on the older techniques [and] to be able to compare the results,” Biant said.

Real-time follow-up in registry

The web-based global ICRS registry, Biant said, will initially be launched in English but rapidly rollout in multiple languages. It has a core dataset that allows patients and surgeons to access their own data for free and see treatment and follow-up progress in real-time. Individual surgeons can also bolt on additional parameters of patient-related outcome measures or PROMS specifically for their patients.

“In the cartilage repair field, where a single center may not be doing huge volumes, if we pooled our data and our outcomes we would have a lot more useful scientific data, more rapidly,” Biant said. “Also, it benefits industry in that they have independent post-market surveillance of their technique or product.”

The EuroQual-5D will be included in the registry's core dataset, as well as the KOOS, which she said is a score cartilage repair surgeons determined was most responsive to the procedures they perform. Surgeons will also be able to add-on other scores they have collected over time for their patients, such as the WOMAC, Tegner or modified Cincinnati knee scores, according to Biant. The registry can also absorb pre-existing datasets with patients' consent.

"This is useful for continued follow-up of randomized controlled trials that have already been completed and have gone through 3 years or 5 years. We can continue to follow up those patients in the registry," Biant said.

Cell therapies, biomaterials

ICRS president **Norimasa Nakamura, MD, PhD**, who co-authored the study with Lyman into the state of cartilage repair and possible future regulatory and methodologic pathways, told *Orthopaedics Today Europe*, "this field might be at a standstill" in terms of cartilage repair products that can be actively marketed.

But, according to Nakamura, who is in the Department of Orthopedics at Osaka Health Science University in Osaka, Japan, "Fortunately, there are many promising seeds being developed through basic research, including stem cell therapy and biomaterials."

Nakamura said stem cell therapies, especially allogeneic stems cells, are an interesting new cartilage treatment approach. They are cost-effective, can readily undergo quality control and avoid patient donor site morbidity. In addition, because stem cell therapies have been researched more widely in Asia than in Europe or North America, the first such medical products of this kind may emerge from Asia, he said.



**Norimasa
Nakamura**

MSCs, bone marrow aspirate on scaffolds

Gobbi, whose group began in 2005 using mesenchymal stem cells (MSCs) in one-stage cartilage repair with Hylofast (Anika Therapeutics), a hyaluronic membrane, said his research and clinical experience indicate cell-based cartilage repair for small lesions will be used in the immediate future. His study of this treatment for ICRS grade IV femoral condyle or patellofemoral articulation lesions compared to MFX with 5-years follow-up is "a milestone because we understand we can achieve much better results with the membrane

or scaffold with MSCs than marrow stimulation with MFX," Gobbi said.

Bone marrow aspirate used with the same membrane, which can also be applied arthroscopically, is being compared with MFX in a 200-patient multicenter international study. The strict inclusion criteria, rehabilitation protocol and requirement for surgeons to be approved to participate in the study, will make it a complicated endeavor, Gobbi said.

"But, this is probably the only way to have a high-quality study," he added.

Biant called for caution in using stem cells combined with scaffolds and other variations of the ACI technique, for which there is good evidence in more than 10 years of clinical practice. "We do not have the

accumulated evidence of post-market surveillance for newer therapies and combinations,” she said.

Nakamura is focused on engineered cartilage repair constructs that are scaffold-free and derived from allogeneic MSCs. He anticipates a clinical trial into this approach will begin in 2017.

Madry has worked the last 20 years on gene therapy for cartilage repair in which gene transfer technology is used to deliver bioactive signals to a cartilage defect and heal it, an approach that may have a wider application in OA treatment. He said there is also promising work being done into matrices saturated with protein-based materials or a gene that are then applied to a cartilage defect.

“Or, you could have some intra-articular injective therapy similar to what has been studied for proteins,” Madry said. But, he noted, much of this work is still at the level of animal models.

Madry, who is ICRS World Congress co-program chair, said some companies that are testing promising new proteins and small molecules will be exhibiting at the meeting. This area should produce interesting new data in the next 5 years.

A new research question might identify the fate of the repair tissue generated by cartilage repair techniques and of the once-normal cartilage in the peri-lesional area, according to Madry. “Do you have OA there? Is this the starting point for OA development? That is another interesting field,” he said. – *by Susan M. Rapp*

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