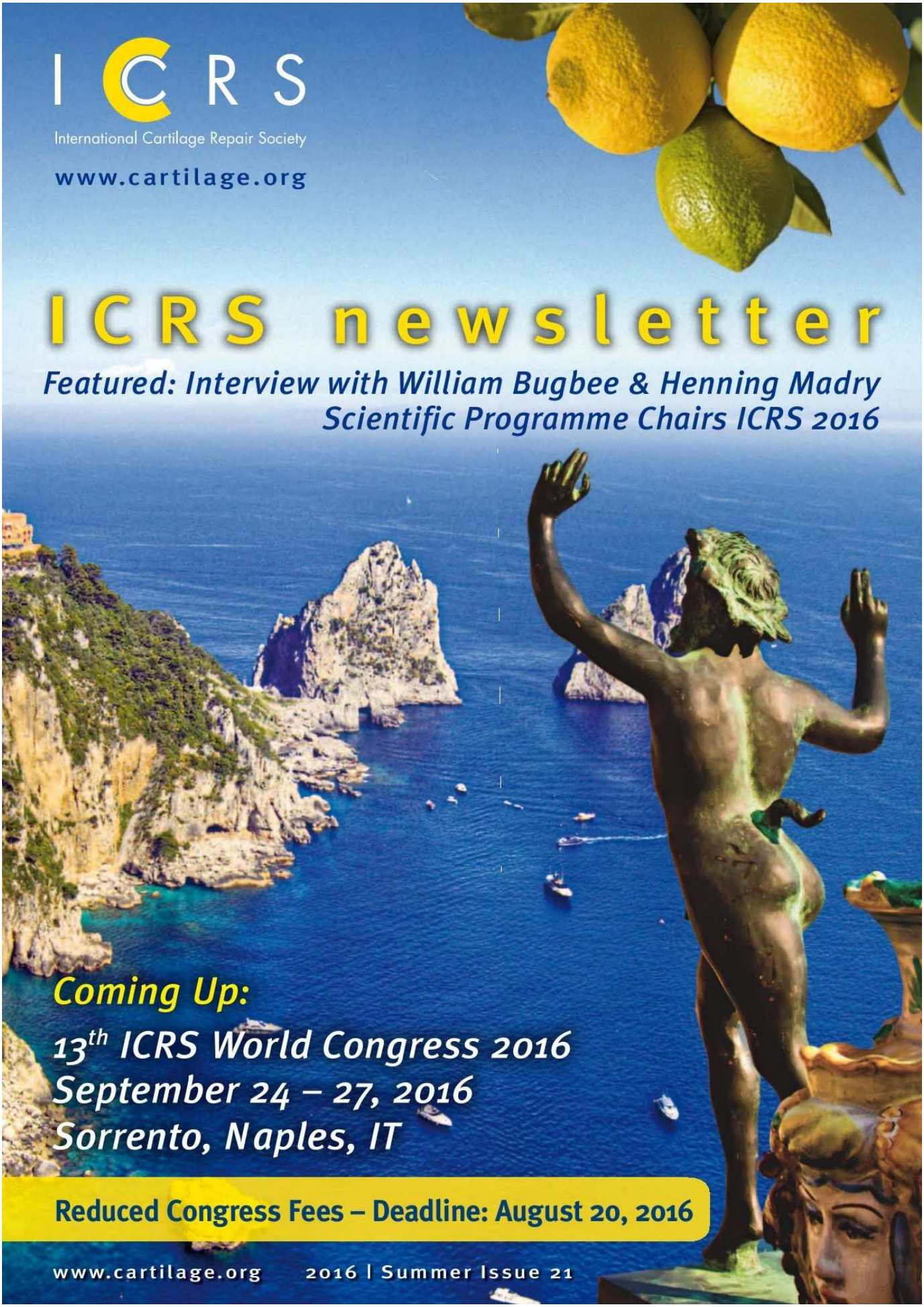
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Featured: Interview with William Bugbee & Henning Madry
Scientific Programme Chairs ICRS 2016
Coming Up:
13th ICRS World Congress 2016
September 24 – 27, 2016
Sorrento, Naples, IT
Reduced Congress Fees – Deadline: August 20, 2016
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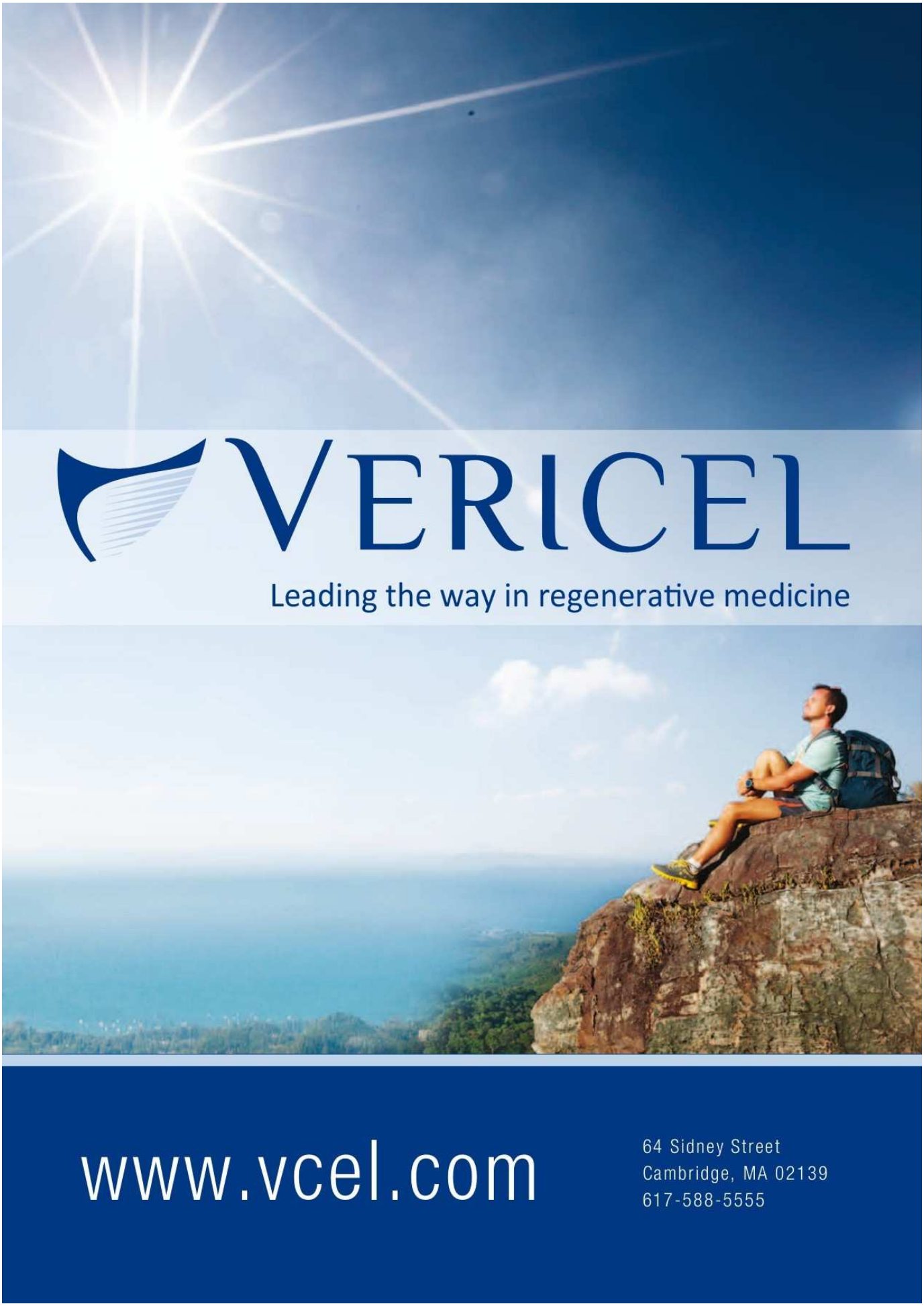
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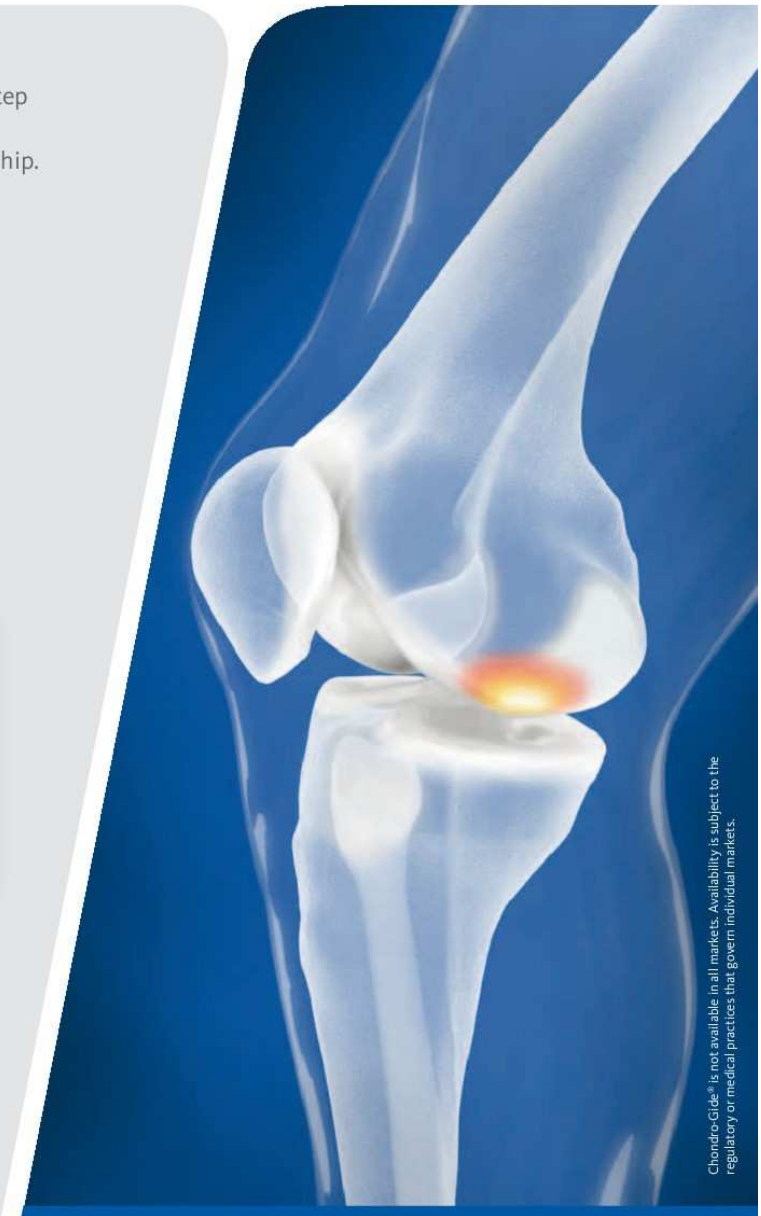

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CARTILAGE REGENERATION

Presidents' Voice

Norimasa Nakamura

Dear Colleagues, Partners and Friends

Time for paradigm shift?

With the advancement of science, the mechanisms of joint physiology and pathology have been revealed to show more diversity and complexity. Accordingly, it is clear that we need more tools to address these detailed problems based on scientific evidence. Therefore, it is reasonable to emphasize the importance of a multidisciplinary approach, from narrow to broad range. In this regard, our society is the unique embodiment of the international group that consists of scientists and clinicians from diverse specialty fields with the special focus on cartilage repair. At the same time, we should always be ready to introduce any latest scientific information into our society.

In this regard, what is our next stage? Here I would like to stress **the importance of increasing our spectrum.** In order to further grow and prosper, ICRS needs to open the focus and embrace the entire spectrum of the «cartilage disease,» that is osteoarthritis (OA). We should once revisit the simple question, "Why do we need cartilage repair?" We may easily say, "It is to prevent from OA." Yes, prevention of OA is one of our ultimate goals and thus, we should aim to make this goal, our principal mission. ICRS has been prioritizing research with clinical relevance and this makes us very unique and different from other societies, which are focusing on OA. Therefore, the shift of our direction does not mean the loss of our raison d›être. Now we want to be on the forefront of cartilage and early OA research internationally to move the field and the ICRS forward. In order to expand our research circle without losing the scientific quality, we should not hesitate to incorporate new research specialists along with new ideas and technologies to our society.

We recently held the ICRS Summit on April 2016 in Kyoto, Japan, in collaboration with Osteoarthritis Research Society International (OARSI) with the title "Wound healing" as a concept of Cartilage Repair: Is it time for a paradigm shift? This joint meeting aimed to promote insights into osteoarthritis and joint tissue regeneration through an interdisciplinary summit focused on the wound-healing paradigm. A short report of the event by one of the program chairs, Christian Lattermann, can be found in this Newsletter and the feedback we have had is that the meeting was a great success with the development of great networking among clinicians and scientists involved in this research field. I believe this meeting was a great embodiment of the concept as describe above. I am now convinced of the effectiveness of this collaborative approach and I do hope this unique joint project will continue and help the expansion of our spectrum under the leadership of each successive ICRS president.

Just following the Kyoto summit, we had the strategic planning meeting in Barcelona by the group members including the executive board in May. Coincidently, one of the most important issues we discussed was the expansion of our spectrums. The details of our discussions will be reported at the next world congress in Sorrento as well as in the next newsletter. I am confident that the direction, which ICRS is taking, is exactly along the right line. Let's work hard together to make our society better by further contributing to the promotion of QOL of the people all over the world!

During the summit meeting, we found more delegates than expected from Asia. Interestingly, most of them had not been familiar with ICRS until the Kyoto meeting, but they likely enjoyed the meeting with lots of discussion and exchange of ideas. Thus we have many new friends from Asia! The summit is a small-scaled meeting but this was the first meeting in Asia conducted by ICRS. It is clear that exploring the new venue for an ICRS meeting could contribute to increase our membership from the region.

At the last World Congress in Chicago, I delivered the strategy for my term 2015-16. Since then, one of the most important missions has been the further global expansion of our society. Along with this strategy, we have planning the ICRS World Series in Sao Paulo, Brazil, June 9-11, 2016. Thanks to the tremendous effort of the local team lead by Camila Kaleka Cohen, Moisés Cohen, Marco Demange and Luis Eduardo Tirico, we were ready to start this very special meeting with a wonderful programme. Also, on September 24 to 27, our 13th World Congress is waiting for all of us in beautiful Sorrento, Italy. Thanks to the great work by program committee chaired by Bill Bugbee and Henning Madry, we are developing a wonderful program full of cutting edge science. We have already received a record number of abstract submissions, which promises the great success of this meeting. Moreover, I am happy to say that the special local team led by Stefano Della Villa and Rosa Donato are preparing a very special setting of social events full of Southern Italian flavours. I am sure we will be able to share unforgettable moments with our friends and families. Stay tuned!

Finally, I would like to thank Gian Salzmann, the Chair of our Communications and Publication Committee and Stephan Seiler for editing this Newsletter, as well as to all the contributors.

I wish you all a wonderful summer season.
Norimasa Nakamura, ICRS President 2015– 2016

HyaloFast®

The one-step procedure for the treatment of chondral and osteochondral lesions

ICRS Office News

Welcome to our New Members (since December 2015)

New Junior Members

Ambra	Luiz	Boston	USA
Asnaghi	M. Adelaide	Basel	Switzerland
Browe	David	Dublin	Ireland
Buendia	Fredy	Quito	Ecuador
D'Ambrosi	Riccardo	Milano	Italy
Dijkstra	Koen	Utrecht	Netherlands
Fachim	Rafael	Sao Paulo	Brazil
Ferguson	Gabriel	Los Angeles	USA
Hagmeijer	Michella	Utrecht	Netherlands
Hamamoto	Shuichi	osaka	Japan
He	Yi	Herlev	Denmark
Hendriks	Jan	Enschede	Netherlands
Irgit	Kaan	Ulus Besiktas	Turkey
Kindler	Moritz	Duisburg	Germany
Kobayashi	Masato	Suita	Japan
Koizumi	Kota	Osaka	Japan
Kuiper	Nikki	Oswestry	UK
Lawyer	Tracye	Jackson	USA
Lei	Pengfei	Cambridge	USA
Levato	Riccardo	Utrecht	Netherlands
Liu	Qisong	Shenzhen	China
Ochoa	German	Cali	Colombia
Ozeki	Nobutake	Tokyo	Japan
Piuzzi	Nicolas	Buenos Aires	Argentina
Sasono	Bimo	Surabaya	Indonesia
Tingle	Casey	Thorofare	USA
Venturinelli	Fernando	Itapeva	Brazil
Vines	Jeremy	Birmingham	USA
Walters	Christy	Arlington	USA
Yahara	Yasuhito	Toyama	Japan
Yang	Ya-Ting	Taipei City	Taiwan

New Ordinary Members

Anz	Adam	Gulf Breeze	USA
Bernardina	Daniel Dalla	Colatina	Brazil
Blatz	Brice	San Jose	USA
Blunk	Torsten	Wuerzburg	Germany
Bozsik	Attila	Budapest	Hungary
Brunkhorst	Joey	Ankeny	USA
Carreira	Dominic	Fort Lauderdale	USA
Carrillo Gamboa	Jose Luis	Queretaro	Mexico
Carrington	Richard	Potters Bar	UK
Cochran	Barbara	Freeland	USA
Cunniffe	Gráinne	Dublin	Ireland
Danin	Michal Alexander	Brasilia	Brazil
Di Bella	Claudia	Fitzroy	Australia
Doan	Thien	Gainesville	USA
Donnermeyer	Dennis	Portsmouth	USA
Enginsu	Müjdat	Bursa	Turkey
Fang	Hsu-Wei	Taipei	Taiwan
Farndon	Mark	Harrogate	UK
Ferreira	Eron	Santarem	Brazil
Freitag	Julien	Box Hill North	Australia
Gao	Kai	Shanghai	China
Gladkov	Roman	Saint-Petersburg	Russian
Grant	John	Ann Arbor	USA
Greller	Michael	Freehold	USA
Halbrecht	Joanne	Boulder	USA
Haqqi	Tariq	Rootstwon	USA
Hruzova	Dagmar	Brno	Czech Republic
Hurt	James	Clinton	USA
Ioan	Dunca	Kraainem	Belgium
Jacobs	Cale	Lexington	USA
Kupczik	Fabiano	Curitiba	Brazil
Lim	Aaron	Penang	Malaysia
Liu	Hwa-Chang	Taipei	Taiwan
Mugrabi	Selim	Sisli istanbul	Turkey
Mukai	Shogo	Kyoto	Japan
Murakami	Tomohiko	Takatsuki-City	Japan
Ohel	Kitty	Or Akiva	Israel
Pinto	Flavio Henrique	Fortaleza	Brazil
Pires	Marcos Paulo	Sao Paulo	Brazil
Pires	Gustavo	Fortaleza	Brazil
Rajaratnam	Samuel	Polegate	UK
Roche	N. D'Arcy	San Mateo	USA
Sachdev	Ranjan	Bethlehem	USA
Shindo	Masaaki	Asahikawa	Japan
Somers	Jan	Leper	Belgium
Spagnoli	Anna	Chicago	USA
Suzuki	Tomoyuki	Sapporo	Japan
Tiberiu	Bataga	Targu-Mures	Romania
Toh	Wei Seong	Singapore	Singapore
Walther	Markus	München	Germany
Whyte	Graeme	New York	USA
Winkler	Leonardo	Caxias do Sul	Brazil
Zappala	Giorgio	Bergamo	Italy

New ICRS Patient Information Website is now Online

www.cartilage.org/patient

During past years, the ICRS has developed an extensive new patient information platform. On this new website, patients can find useful, updated information on specific cartilage-related conditions and possible treatments options, written by world-renowned ICRS experts, helpful patient information to read and download, and other useful resources such as a new "Doctor Finder" as well as a "Cartilage Industrial Devices Finder". To allow patients to find and contact clinical ICRS Members in specific regions and for specific conditions, all members are required to fill in a short online form in the member's area.

This website would not have been possible without the substantial support of the Swiss "Mäxi Foundation". The ICRS would like to express a deep gratitude for this very generous contribution to the International Cartilage Repair Society and the respective patient community, making it possible to provide updated information about cartilage damage and cartilage repair technologies free of charge to all interested persons.

Try it out and recommend this site to your patients for all cartilage related questions. We would welcome any feedback on this new section to lei.ji@cartilage.org

ICRS World Congress Sorrento

Interview with William Bugbee, La Jolla, Califonia

Interviewed by Michael Angeline, Lake Geneva, Wisconsin

Dr. William Bugbee is an attending physician at Scripps Clinic, La Jolla and Professor, Department of Orthopaedics, University of California, San Diego. He received his medical degree from the University of California, San Diego (UCSD) and his undergraduate degree in biology at the University of California, Los Angeles. Dr. Bugbee completed his internship in surgery and residency in orthopaedic surgery at the UCSD Medical Center and completed his fellowship in Adult Lower Extremity Reconstruction at the Anderson Orthopaedic Research Institute in Alexandria, Virginia. Prior to joining Scripps Clinic, Dr. Bugbee was the chief of arthritis surgery and joint reconstruction and the director of the Cartilage Transplantation program at UCSD. His clinical interests are in arthritis surgery of the hip, knee and ankle, osteochondral allograft transplantation and cartilage restoration. His research interests include biologic response to implants, innovation in knee replacement technique and design, Osteochondral transplantation, cartilage tissue engineering and biologic joint repair.

Dr. Bugbee was recently awarded the 2015 Kappa Delta Elizabeth Winston Lanier Award for his work on Osteochondral Allograft (OCA) Transplantation in Cartilage Repair. He is an active member of ICRS and Chair of the Scientific Programme Committee for the upcoming 13th World ICRS Congress to be held in Sorrento, Naples IT.

MA: How did you become interested in OCA transplantation?
WB: It started when I was a medical student in the early 80's when I witnessed my first allograft transplantation performed by Drs. Richard Convery and Marvin Meyers. I was amazed at what they did. The patient was a young man in his early twenties from Alaska that had osteonecrosis of the femoral head. They performed a femoral head allograft and I was fascinated with the concept. As you can imagine, at that time no one would do an arthroplasty in someone so young, so he had no other real options. That was my first experience with allografts. Subsequent to that, I became a resident at UCSD and was able to see and perform quite a few allograft transplantations during my residency. Finally, I returned to UCSD as a member of the faculty in 1997 and became the director of the Allograft Transplantation program at UCSD after the retirement of the early pioneers Drs. Convery and Meyers.

MA: How has your training in adult reconstruction/arthroplasty influenced your outlook on cartilage restoration?
WB: That is a great question because the first thing I tell my patients and colleagues is that I am trained as an arthroplasty surgeon and that I consider myself a specialist in arthritis. Now, people are more and more understanding of the arthritis cascade and the biology of a joint with a focal cartilage injury. My interest is in what is the biological fate of that joint. I think of it in bigger terms and to me the problem is related to more complex lesions with multiple tissues deficiencies rather than a focus on a small cartilage injury, which really is not the typical clinical problem. I think that I have a unique perspective in dealing frequently with patients that have premature arthritis in my daily practice, particularly young people.

MA: What have been your biggest research challenges while investigating OCA transplantation as a treatment method for articular cartilage injury?
WB: Aside from funding (of course!), I think that we have really done a good job in looking at the basic science, but every time you pose a question and try to answer it ten more questions are created. We spent a lot of time, for example, looking at cell viability as that was the holy grail so to speak, and now it turns out that the behavior of the subchondral is perhaps more important. As a result, we have shifted our focus on understanding bone biology and transition from being only a cartilage scientist to a bone scientist as well. The challenge on the basic science side is to understand the biological response to a transplant of multiple tissues. On the clinical side, the biggest challenge has been to accumulate a large enough patient database to ask specific questions. We have over one thousand patients in our database and now we can perform specific studies utilizing logistic regression in an effort to analyze factors that may influence outcome. This helps patients understand when allografting is a great operation, a good operation or a salvage with modest expectations. This type of research could not be done before using Level 4 case series data with twenty patients, for example. We need enough patient data to perform statistical analyses of multiple variables.

MA: You recently published your experience with OCA transplantation in the femoral trochlea, which demonstrated excellent clinical outcomes. How does your approach differ when dealing with trochlear or patellar based lesions?
WB: That is an interesting idea because I have always thought that allografts were the best way to treat patellar and trochlear lesions simply because

you can restore normal cartilage. An allograft gives you mechanically sound mature cartilage from day 1, and cell based treatments or microfracture in that harsh mechanical environment have never fared well. It turns out that most of my colleagues have not thought in the same terms. They thought allografts were not good simply because the anatomic complexities made it technically challenging, but us and others have been doing this and there is instrumentation that can help to create an anatomically correct graft. I think allografts are uniquely suited to the patellofemoral joint and now there are more people that are agreeing with this.

MA: Who were your mentors in your early career and why?

WB: As far as my mentors I have to name 4 people. Dr. Wayne Akeson, the Chairman of Orthopaedics at UCSD, was a brilliant man and a pioneer in biology of orthopaedic tissues. He was always encouraging and I will never forget his statement when I presented my paper at our small University research meeting. He said "it looks like you have a whole career of work ahead of you", and that was so true. The pioneers of allograft surgery have also been mentors. I have to tip my hat to Dr. Allan Gross as he is a legend in the field and really pioneered the use of grafts for post-traumatic arthritis. Dr. Marvin Meyers, who started the first allograft program in the US back in the early 70s, and his colleague Dr. Richard Convery were both influential in developing the allograft program in San Diego during the early 80s. I was fortunate enough to be in San Diego as a medical student and resident during this time. Finally, as any clinician scientist knows, collaboration is critical and I have been fortunate to be mentored by two "legends". David Amiel, head of the cartilage biochemistry laboratory, was my first scientific and career mentor at UCSD and he made all the difference to me. Robert Sah, director of the cartilage tissue engineering lab at UCSD, is another great mentor with whom I still work closely.

MA: What research projects are you currently involved in?

WB: I have spent the last couple of years focusing on the clinical data as we have enough patients to ask specific questions, which is reflected in our clinical publications. Now, we are going back into the lab and looking at the behavior of bone and osteochondral tissue engineering. There are certain questions that need to be answered as to how do you make the allograft bone heal better, which is also in the context of our understanding that a cartilage injury is really an injury to the subchondral bone as well. With this, the question then becomes how do you manage biology of the subchondral bone as I think this is a theme that everyone agrees is important. We are looking at ways to improve the allograft and improve the behavior of the bone. Also, in conjunction with Dr. Darryl D'Lima here at Scripps, we have a large 12-million-dollar stem cell grant that was awarded by the California Institute of Regenerative Medicine. Our charge here is to develop a stem cell based repair strategy not just for cartilage but also for other regenerative issues within synovial joints. This will be our focus over the next five years.

MA: What does the future hold for OCA transplantation and is there a role for biological treatment options?

WB: If you talk to people that are in the arthroplasty field, total joint replacement will never go away, as the demographics of osteoarthritis are too overwhelming. However the concept of early intervention is becoming more and more important. So I think we are leveraging our understanding of cartilage repair with the fields of arthritis and rheumatology, as both fields understand the biology of synovial joints. A game changing treatment will be some type of disease modification and it may not be a surgical issue but possibly an stand alone intervention or an adjunct to surgery. This is why I believe there is such popularity with PRP and stem cell injections since there is such a big hole in our treatment algorithm with nothing proven to fill it.

MA: How did you first become involved with ICRS?

WB: I submitted a paper to one of the early ICRS meetings and it was accepted. After presenting the paper, I found that I really enjoyed the society, the people and the collaborative nature of clinicians and scientists being together. Since then, it has become one of my favorite venues so I have made it a point to go to every meeting every year. To this day, I feel that it is one of my favorite organizations and have been happy to see the growth of the organization.

MA: As the Scientific Programme Chair for the 13th ICRS World Congress 2016 what can we expect?

WB: Of course it is in Italy, so you can expect a beautiful venue with wonderful hospitality. On the scientific side, my co-programme chair Dr. Henning Madry and I have made it a point to ensure scientists and clinicians are in the same room talking. We are also this year emphasizing discussion in an effort to help provide ample time for questions to be answered and have everyone involved. We hope that this collaborative spirit will make for a great meeting. So please everyone submit your research and bring your questions.

ICRS World Congress Sorrento

Interview with Henning Madry, Homburg, Germany

Interviewed by Michael Angeline, Lake Geneva, Wisconsin

Dr. Madry is the Chair of Experimental Orthopaedics and Osteoarthritis Research at Saarland University in Germany, with a joint appointment at the Department of Orthopaedic Surgery. He received his MD in 1996 from Humboldt University in Berlin and performed his resident training at the Department of Trauma Surgery, Charité, Berlin from 1996-98. His postdoctoral research fellowship was at the Department of Orthopaedic Surgery, Massachusetts General Hospital, Harvard Medical School, Boston with Stephen B. Trippel from 1998-2000 and also at the Department of Chemical Engineering at the Massachusetts Institute of Technology with GordanaVunjak-Novakovic and Bob Langer. Dr. Madry's research program aims at translating novel molecular, cell biology and tissue engineering approaches into clinical applications in Orthopaedic surgery with a focus on osteochondral regeneration. Dr. Madry is an active member of the ICRS and Chair of the Scientific Programme Committee for the upcoming 13th World ICRS Congress to be held in Sorrento, Naples IT.

MA: What are your main responsibilities as Chair of Experimental Orthopaedics and Osteoarthritis Research at the Saarland University?

HM: I am directing a research program, which aims to bridge the gap between the basic science and the clinics. We have at the moment 29 members in our lab, many of them medical students, and a good mix between PhDs and MDs. We work on projects reaching from the basic science of early osteoarthritis and cartilage defects to gene-based treatments for cartilage repair. We think it is important to ask clinically relevant questions, and we do have an excellent interaction with our clinical colleagues. Research questions, for example, focus on the subchondral bone in articular cartilage degeneration and repair, improvement of cartilage repair techniques such as marrow stimulation and cell based therapies. On the other hand, we develop molecular therapies using either direct or ex vivo gene transfer strategies for cartilage defects and osteoarthritis. Basically, we try to look in many different angles at the osteochondral unit.

MA: How did you first become interested in translational research?

HM: Probably at the age of 16 I became interested in research. While early on in school, I was quite interested in chemistry and biology, and did quite some experiments in our basement. Then, I wanted to be a medical doctor but I always felt it was important to have that combined with a lot of basic science insight. So actually, I did some electives besides my medical studies in scientific institutes and was finally writing a MD thesis focusing on no viral gene therapy approaches for kidney diseases. Since I then started my residency in orthopedic and trauma surgery, and I thought it was very interesting doing research that originates from clinical questions. As you know that the residency takes a lot of time leaving little space for basic science, I decided to do a postdoc in the USA to exclusively focus on basic science. I personally think that translational research is very interesting and also a lot of fun.

MA: How did your postdoctoral training at the Massachusetts General Hospital and within the Department of Chemical Engineering at the Massachusetts Institute of Technology influence your outlook on cartilage regeneration?

HM: I did my postdoctoral training with Stephen Trippel at MGH and he is a very important person to me because he has taught me a lot of insights into the mystery of cartilage, making it a very fascinating tissue to work with. I think that it was a very important time for me to be there at Mass General Hospital. In the lab of Steve, I laid the basis for our animal work on no viral gene transfer for cartilage repair. There, I also had the great opportunity to do a bit of clinical work with Dr. Henry Mankin. While being there, I did a second postdoc in the lab of Gordana Vunjak-Novakovic and Bob Langer at MIT. They taught me very different aspects of cartilage, including the principles of tissue engineering applied to articular cartilage, and the use of bioreactors. This was really great work because it was like opening a new door into a field where you can actively try to regrow cartilage tissue as a three-dimensional structure. These were very influential people in my scientific development I would say, besides my thesis advisor Detlev Ganten.

MA: What research projects are you currently involved in?

HM: We are part of a large research consortium funded by the German government looking at the influence of axial malalignment on the development and progression of early osteoarthritis. For this, we are using a sheep model of high tibial osteotomies that Dietrich Pape from Luxembourg and I have developed. Now we are able of introducing precisely defined degrees of malalignment in the sheep knee. This is a large project, and currently ongoing.

Besides this, we have, as a lab, a heavy focus on gene therapy approaches for cartilage repair and osteoarthritis. For this, I am actually very fortunate working

together with my wife Magali Cucchiarini, as she is an expert in the potent recombinant adeno-associated viral (AAV) vector technology for cartilage repair. She did a lot of basic science in vitro studies using these AAV vectors, for example in human MSCs and chondrocytes, and we apply them together with the non-viral approaches for both the repair of focal cartilage defects and osteoarthritis.

We are also part of the great international research consortium "Acute Cartilage Injuries", which is funded by the AO Foundation. We work together with experts like Farshid Guilak from St. Louis, Robert Mauck and George Dodge from Philadelphia, and Mauro Alini and Martin Stoddart from Davos to name just a few. We use different solid and hydrogel scaffold-based approaches in combination with gene therapy approaches for the repair of full thickness lesions. Personally, I think this is a great team and is is very satisfying to work with these different groups.

MA: What do you see as the biggest difficulty for the clinical implementation of gene transfer protocols in the treatment of osteoarthritis?
HM: I think the biggest difficulty here is the shortage of sustained funding programs funding for the clinical studies that are required, and probably also regulatory issues. Besides, early transdisciplinary communication is critical for the development of clinically relevant products. For this I love the ICRS because this close cooperation in ICRS between basic scientists and clinicians is precisely what is needed today. There are actually some very interesting phase II clinical studies going on in Asia where a gene based approach using ex vivo transduced chondrocytes is used as a treatment for OA. I think these studies will continue and I think they are very promising. It will be interesting to determine using quantitative structural analysis whether these cells will be able to allow for a sustained restoration of the damaged cartilaginous surface. Such gene based technology will probably never replace the classical surgical and nonsurgical treatment options, but may be of additional value.

MA: What does the future hold for the development of tissue engineered articular cartilage?
HM: I think what we will probably see is more approaches where scaffolds used for cell delivery are bio-instructive or where growth factors or other biological signals will be attached to such matrices. Along this line, there may even be approaches where such a scaffold will be implanted without additional cells, and such a bio-instructive scaffold has the same capabilities as tissue engineered cartilage or autologous chondrocytes combined with a scaffold. I think for many aspects it seems to be important to provide a one-step procedure rather than a two-step procedure. This is probably going to be the next generation of treatment.

MA: As the Scientific Programme Chair for the 13th ICRS World Congress 2016 what can we expect?
HM: The goal of Bill and I is to put basic science back on the stage with a clinical flavor. We have a lot of talks on interesting subjects where you see a clinical problem being viewed not only from the clinical standpoint but also from the basic science standpoint. This is how we designed both Opening Sessions on September 24. If you look at these very first sessions, you will see that that we have a cartilage session, and a concurrent meniscus session, and in both we have tried to combine clinical and basic science talks from great speakers that should give the audience a nice overview picture of the entire subject both from clinical and basic science point of views. So it's like a fusion of these two viewpoints into a single session, so even if some sessions seem to have only clinical topics, they will always include basic research. Actually, we and our Program Committee tried to reflect the idea of the very first ICRS meeting in Fribourg, Switzerland in 1997 that I was lucky to have the chance to attend. Here you had basic scientists and clinicians sitting together in one room trying to find answers to the question of cartilage repair. This to me is still the biggest challenge and the noblest work to do.

ICRS World Congress Sorrento

13th ICRS World Congress 2016
September 24 – 27, 2016, Sorrento, Naples, IT

By Bianca d'Angelo, Mp Congressi and Jane Hayward, O.A.S.I. Bioresearch Foundation on behalf of the ICRS local team

The Home Team Welcome's you to Sorrento

Gardens of Villa Rufolo

The Amalfi Coast

The Amalfi Coast is one of the 50 Italian sites on the UNESCO World Heritage List. It is a unique setting, a perfect example of Mediterranean landscape with great cultural and natural value. From the days of ancient Rome, the Amalfi Coast has enchanted its visitors with its fairy tale panorama.

Amalfi cathedral

The small towns and villages that make up the coastline are individual and unique, each with its own traditions. The thing that characterizes the area is the Romanesque architecture of its monuments such as the Cathedral in Amalfi and it's 'Cloisters of Paradise' which displays a strong Eastern influence, or Ravello with its stunning Cathedral and the superb Villa Rufolo.

The charming town of Vietri sul Mare is considered the birthplace of ceramic tiles, all you need to do to see some stunning examples is look to the roof of the beautiful church of San Giovanni Battista and the façade of the Arch of the Annunciation and the Rosary.

Amalfi, the most famous of these towns, was founded in the 4th century AD and gives its name to the coastline. As an Ancient Maritime Republic Amalfi wielded a strong monopoly on trade in the Tyrrhenian sea exporting Italian products such as wood, iron, weapons, wine and fruit to the markets in the East and in return importing to Italy such wonders as spices, perfumes, pearls, jewelry, textiles and carpets.

Sorrento

Sorrento is perched on a plain above the Tyrrhenian sea overlooking the Bay of Naples, to the north the view encompasses Vesuvius, Naples and the island of Ischia.
It has a delightful old town and lively port with ferries departing for Capri, Naples and Amalfi and is in easy reach of the Amalfi Coast, Pompeii and Herculaneum.

There are colorful shops, relaxed cafes and restaurants to while away the time while soaking up the marvelous atmosphere and watching the world go by. Not to be missed in Sorrento are a look at the Basilica of Saint Antonino, the Cathedral, Marina Grande and the Correale Museum and many more.

Pompeii

Pompeii was buried under a blanket of ash and lapilli approximately six meters deep when, in the 79th century AD, Mount Vesuvius erupted.

ICRS World Congress Sorrento

Excavations of the city started in 1748 and since then have unearthed a vast archaeological site which has been part of the UNESCO heritage list since 1997. Pompeii has become one of the most important examples of Roman civilization giving historians the opportunity to expand their knowledge of the habits, trading traditions and ordinary daily life of the time. It is one of the most visited archaeological sites in the world with around 2.5 million visitors a year.

Herculaneum
Herculaneum is famous the world over for the archaeological excavations of this Roman city which, according to legend was founded by Hercules. Located on a volcanic plateau overlooking the sea, Herculaneum, like other Vesuvian cites such as Pompeii, Oplontis and Stabiae was covered by the eruption of Vesuvius in 79 AD, which buried the city under 23 meters of mud, ash and lapilli. The city was unearthed by chance during the excavations conducted by the Borboni. It has been a UNESCO World Heritage site since 1997. The site offers visitors the opportunity to observe urban structure and housing distribution of the time, a magnificent spa complex, gymnasium and a monumental Basilica. The fact that many artifacts have been preserved in a perfect state allows historians and visitors to reconstruct the daily life of the times.

And lastly.....
Let us not forget the wonderful opportunity to taste pizza in its home town of Naples, mozzarella that's nothing like the mozzarella you get elsewhere. And please don't leave this stunning area of Italy without trying a small glass of ice cold Lemoncello..... pure delight!

Registry Update

By Leela C Biant
University of Edingburgh

The ICRS is delighted to announce that its' ambitious Global Cartilage Registry Project is on course for delivery and entry of patients in September 2016. The ICRS agreed start-up funding, and our Industry Partners have recognised the value of such a registry and have also agreed significant support for the project. The web-based registry will be free of charge for surgeons and patients to use, and participation by all encouraged. It can accommodate any patient with an articular cartilage defect, whether or not the defect is addressed surgically. It will be rolled out in multiple languages, five in the first wave and additional languages added rapidly based on demand. Surgeons and patients have access to their own data and progress. The registry records a common core dataset, with the ability for the surgeon to also collect additional data points or scores specifically for her or his patients. This would enable continued collection of scores that any surgeon has already been collecting by preference, and also the inclusion of patients who have had surgery some time ago.

The ICRS Registry can absorb smaller hospital-or regional databases for pooling of data and continued follow-up of patients at no cost to the hospital. The ICRS Registry is also an ideal vehicle for continued follow-up of patients following short- to medium-term trials.

Secure data storage, encryption of anonymised data, safe back-up, consent issues, national and international data transfer and servers and patient self-registration have all been discussed with the selected Registry provider. This specification is available in detail to any member who wishes to see it. A 'hospital pack' containing the required descriptions of legal and ethical protocols of the registry will be provided to any member for local IRB or Ethics Committees purposes. Benefits to patients of such a registry include feedback on their progress and engagement in patient education through links to the ICRS patient information area. Advantages to surgeons include a free mechanism of patient data capture, ability to monitor cases performed and their progress for appraisal and revalidation, and anonymised data they may need to support applications to healthcare providers. The partnership with Industry is mutually beneficial. Large corporations and smaller biotech companies all have much to gain from the ICRS Registry. Industry partners may support the registry in a pyramidal manner that allows graded access to anonymised datasets proportional to their level of support. This includes data involving their own product, comparator cohorts of microfracture or demographic information of where cartilage surgery occurs.

The ICRS would like to invite our Industry Partners to contact us to further discuss their involvement in the ICRS Registry. With their support, the ICRS can sustain an objective, safe, functional registry. The Registry Committee looks forward to introducing the ICRS Registry to members at the Congress in Sorrento.

ICRS World Congress Sorrento
Best Rated Abstracts

■ Stem-cell-based tissue engineered constructs (TEC) combined with collagen sheets for cartilage repair

H. Fujie1, K. Oya2, S. Yarimitsu1, M. Ikeya1, S. Yoshida1, M. Yamazaki1, T. Ogura3, N. Nakamura4; 1Hino/JP, 2Musashino/JP, 3Toride/JP, 4Suita/JP

Purpose

We have been developing a novel biomaterial for cartilage repair using a mesenchymal stem cell (MSC)-derived tissue engineered construct (TEC). Although a partial chondro-defect was successfully repaired with a normal TEC, handling of the TEC during implantation was slightly unstable due to its fragile property. To solve the problem, MSCs were cultured on a collagen sheet (CS) to produce a novel TEC/CS composite in the present study. We assessed the histological and frictional properties of the TEC/CS composite.

Methods and Materials

Synovium-derived MSCs were cultured on the upper part of an animal-derived CS in the DMEM (Fig.1). TEC/CS composites consisting of the extracellular matrix combined with the CS were produced. Implantation of the TEC/CS composite or TEC alone into a cylindrically-shaped partial defect of 5 mm in diameter and 2 mm in depth in rabbit femoral cartilage was performed. Fourteen weeks after implantation, repaired cartilage-like tissues were subjected to histological observation using safranin-O staining. Those tissues were also subjected to a reciprocating friction test against a stainless-steel ball of 3 mm in diameter in saline solution at 37°C at the speed of 5 mm/s with the pressure of 2.25 MPa.

Results

Histological observation indicated that the layer structure is well organized in the TEC/CS group as compared with in the TEC and Defect groups (Fig.2). The coefficient of friction of the TEC/CS group was similar to that of the TEC group at both 0 m and 10 m of friction distance. However, the friction coefficient was more stable with smaller variation in the TEC/CS group as compared with those in the TEC and Defect groups.

Conclusion

We found that cartilage-like tissues repaired with the TEC/CS composite exhibited well organized layer structure, and low and stable frictional property. It is suggested that the MSC-derived TEC/CS composite is useful biomaterial for cartilage repair.

■ Customized collagen scaffold combined with intra-articular delivery of gefitinib for meniscal regeneration

Z. Pan; Hangzhou/CN

Purpose

Meniscal injury is one of the most common injuries of the knee joint that is still a major challenge in today's clinical practice.The propose of our study is to investigate customized collagen scaffold with EGFR-specific small-molecule inhibitor for meniscal defect regeneration and osteoarthritis prevention.

Methods and Materials

The function of gifitinib in meniscal cells differentiation was evaluated in vitro and in vivo. After confirming the gefitinib effect, intra-articular delivery of gefitinib together with implantation of anatomically correct, multi-layer collagen scaffold were carried out to substitute for lost meniscal tissue to prevent cartilage degeneration, improve function.

Results

The anatomical, mechanical match scaffold was fabricated and gefitinib was used for promoting the fibrocartilage formation. In vitro, it was demonstrated for the first time that inhibition of EGFR signaling significantly increased Col 1 and 2 expressions in meniscal fibrochondrocytes. Our initial data also suggest that anabolic genes of fibrochrondrocyte differentiation, including Col 1, Col 2, aggrean and Sox 9 mRNA expression were significantly stimulated, whereas catabiosis genes, MMP13 and ADAMTS-5 expression, were down-regulated when treated with EGFR inhibited by gefitinib. In vivo, implantation of scaffold promoted holistic regeneration of meniscus and the characteristics of the regenerated meniscus, including gross morphology, cell shape, ECM accumulation and collagen microstructure were almost similar to native meniscus.

Conclusion

In summary, our study developed an anatomic match collagen scaffold which not only enhanced meniscal regeneration, but also protected articular cartilage from degeneration, as well as suppressed OA occurrence. This study also highlights the importance of using "small molecule drug" to create a conductive healing environment for endogenous cells, and proposes the concept of not utilizing exogenous seed cells for tissue engineering-based therapies. The results provide valuable insight for future meniscal tissue engineering studies and clinical practice.

ICRS World Congress Sorrento
Best Rated Abstracts

■ Reoperation Rates Following Arthroscopic Meniscus Repair versus Partial Meniscectomy

R.M. Frank, S. Rosas, T.Y. Law, B. Erickson, B. Nwachukwu, N. Verma, B.R. Bach, Jr., B.J. Cole, F. McCormick; Chicago/US

Purpose

Reoperation after meniscus repair and partial menisectomy is not uncommon. This study aimed to quantify the rate of return to the OR following meniscus repair surgery and compare it with a cohort of patients undergoing partial meniscectomy at a minimum 4-year follow-up.

Methods and Materials

Consecutive patients who underwent arthroscopic meniscus repair (CPT codes 29882 and 29883) and meniscectomy (CPT codes 29880 and 29881) for the years 2007 through 2011 were identified using the PearlDiver Patient Record Database (PearlDiver Inc., Warsaw, IN). All patients were tracked for subsequent meniscal procedures. Subgroup analysis was performed by sex and age. Statistical analysis was both descriptive and quantitative utilizing linear regression and Student t tests with significance set as $p<0.05$.

Results

A total of 8,219 patients undergoing isolated meniscus repair (5,041 males; 3,103 females) and 194,773 patients undergoing partial meniscectomy (111,329 males; 83,444 females) were identified. At all time points, mean cumulative reoperation rates after meniscus repair were significantly higher than those following partial meniscectomy: (90-day, 7.49%, 4.28%; 1-year, 17.13%, 6.68%; 2-years, 20.50%, 7.94%; 4-years, 22.1%, 8.57%)($P<0.05$ for all). The most common procedure performed following meniscus repair was meniscectomy (59.22%) followed by revision meniscus repair (14.09%). The most common procedure performed following partial meniscectomy was revision partial meniscectomy (66.97%) followed by meniscus repair (23.0%). Male meniscus repair patients had a higher reoperation rate across all age groups at 2 years (odds ratio 1.146 95%CI 1.015-1.294). Younger patients (10-29 years) had a significantly higher reoperation rate compared to older patients (30+ years) at 1 year, 2 years, and 4 years ($P<0.05$ for all).

Conclusion

Within a large United States private payer database, the reoperation rate following meniscus repair is significantly higher than following partial meniscectomy. The most common procedure following either procedure is partial meniscectomy.

■ Interleukin 1β alters TGFβ signaling in human MSC through SMAD2/3 linker modification

G.G.H. Van Den Akker, H.M. Van Beuningen, E.N. Blaney Davidson, P. Van Der Kraan; Nijmegen/NL

Purpose

Although cartilage repair using Mesenchymal Stem Cells (MSC) is a promising strategy for the treatment of cartilage damage, inflammation inhibits chondrogenic differentiation of MSC. TGFβ signaling is required for MSC chondrogenic differentiation and signals through SMAD2/3 transcription factors. TGFβ receptors activate SMADs through C-terminal phosphorylation and SMAD function can be modulated by phosphorylation of the linker region (Fig.1A). We hypothesize that inflammatory mediators alter TGFβ signaling through direct modulation of SMADs.

Methods and Materials

Human MSC were cultured in Lonza medium and stimulated with TGFβ1 and/or IL1β. Signaling activity was determined using immunoblotting (SMAD2 phospho-isoforms) and qPCR (target genes; PAI1). Pharmacological inhibition of TAK1 was achieved with 5Z-7-Oxozeaenol.

Results

A detailed time course experiment revealed that IL1β delayed rather than suppressed TGFβ induced pSMAD2-C (Fig.1B, left panel). In addition TGFβ stimulation led to phosphorylation of the SMAD2 linker region and this was again delayed by co-stimulation with IL1β (Fig.1B, right panel). This delay was confirmed by downstream PAI1 expression. IL1β alone induced pSMAD2-L without inducing pSMAD2-C (Fig1.C, right panel). The kinetics of IL1β induced pSMAD2-L differed from TGFβ, TGFβ being dominant upon co-stimulation (Fig.1B). To determine the biological effect of IL1β induced pSMAD2-L, we evaluated nuclear translocation of pSMAD2-C. IL1β co-stimulation led to accumulation of pSMAD2-L in the cytoplasm and decreased pSMAD2-C in the nucleus.

Multiple kinases are known to mediate phosphorylation of the SMAD2/3 linker region. Pharmacological inhibition of multiple candidates led to the identification of TAK1 as crucial for IL1β induced pSMAD2-L.

Conclusion

SMAD2/3 signaling is important for MSC chondrogenic differentiation and this is inhibited by inflammation. We show that IL1β induces phosphorylation of the SMAD2/3 linker region. Linker modified SMAD2 accumulates in the cytoplasm and thus delays TGFβ signaling. Importantly, we identify TAK1 as crucial mediator of SMAD2/3 linker modification. Therefore, TAK1 represents a promising target to enhance cartilage repair using MSC.

Società Italiana di Chirurgia del Ginocchio, Artroscopia, Sport, Cartilagine e Tecnologie Ortopediche

6° NATIONAL CONGRESS

Palazzo dei Congressi - Florence, 28-30 September 2016

SIGASCOT 2016

Presidents of the Congress: **Massimo Innocenti - Stefano Zaffagnini**
Presidents of the Scientific Program: **Luigi Pederzini - Pietro Randelli**

Wednesday, 28 September

Highlight Lectures
- Thirty years of knee surgery
- Myths and truths in ACL reconstruction: the truth in the scientific literature
- Partial ACL reconstructions
- ACL reconstruction in the professional footballer: 360° management

Live Surgery
- Ankle

Symposia
- Current management of Achilles tendon rupture
- Multiligament knee injuries
- Stem cells and sports traumatology
- Meniscus surgery in 2016: everything I should know
- The biceps tendon: from the long head to the distal head in athletes
- Rotatory instability associated with anterior cruciate injury

Combined Symposium ICRS-SIGASCOT
- What's new in scaffolds for the regeneration of osteocartilaginous tissue

Instructional Course Lectures
- How to treat acromioclavicular and stern/clavicular dislocations
- Fundamental steps in arthroscopic ACL reconstruction
- How to write a scientific paper

Free Paper Sessions and Keynote Lectures
- All-inside posterior cruciate ligament reconstruction
- Innovations in the treatment of cartilage lesions
- Kinespring: how to reduce overload

Industrial exhibition visit - Sponsored lunch time workshops - Espresso corners

Opening Ceremony

Thursday, 29 September

Highlight Lectures
- Meniscus transplant - State of the art
- Treatment of cartilage lesions: my way
- Tibial osteotomies of the knee: indications, technique and results
- How to perform a biplanar subtraction osteotomy of the femur
- Knee replacement surgery in extensive joint resections

Presidential Lecture

Live Surgery
- ACL
- Elbow arthroscopy and radial head replacement

Symposia
- Mini-invasive knee replacement surgery. Uni-, bi-uni, patellofemoral, total and PCL - retaining
- The adolescent athlete: ACL lesions and osteochondritis
- Anatomical and mechanical alignment and correct soft-tissue balancing in prosthetic knee surgery
- Tissue sparing and fast track in TKR
- Surgery for patellar instability

Combined Symposium SICSeG-SIGASCOT
- Shoulder instability in athletes (anterior, posterior, multidirectional, acute and chronic)

Instructional Course Lectures
- Anterior knee pain: instructive clinical cases
- Managing groin pain in athletes
- Elbow arthroscopy from basic to advanced

Free Paper Sessions and Keynote Lectures
- Difficult knee arthroplasty: choice of prosthesis, technique and complications

Best Paper Session – X Factor

Clinical Case Discussion Session
- TKR revision surgery: clinical cases discussion with tips and tricks

Industrial exhibition visit - Sponsored lunch time workshops - Espresso corners

SIGASCOT General Assembly

Friday, 30 September

Highlight Lectures
- Athlete's hip
- Athlete's ankle
- Athlete's Shoulder
- How to treat elbow instability
- How to treat elbow stiffness
- How to repair the biceps tendon at the elbow
- Knee tumours: a systematic approach
- Why an Italian can be a baseball champion
- What will be the future role of navigation in total knee replacement surgery

Live Surgery
- Total knee replacement

European Consensus Conference about Meniscal Lesion Treatment

Symposia
- Hip arthroscopy: the state of the art
- Ankle instability: when to opt for arthroscopy / open surgery
- Current treatment of rotator cuff injuries: an international perspective
- Treatment of tendinopathies
- Hyaluronic acid vs PRP in early knee osteoarthritis

Instructional Course Lectures
- Primary-implant total knee replacements: state of the art

Course for physiotherapists

Clinical Case Discussion Sessions
- Difficult knee prostheses: clinical cases discussion with tips and tricks
- Sport traumatology

Free Paper Sessions and Keynote Lectures
- Patellofemoral joint replacement
- State of the art in shoulder arthroscopy
- New techniques in knee replacement surgery: the efficiency system

Special Resident Session

Award Winner

INTERNATIONAL INVITED FACULTY

Annunziato Amendola (Durham - USA)
Michael J. Axe (Newark - USA)
Gregory I. Bain (Bedford Park - AUS)
Roland Becker (Brandenburg - D)
Philippe Beaufils (Paris - F)
Mats Brittberg (Kungsbacka - S)
Charles A. Bush-Joseph (Chicago - USA)
David Dejour (Lyon - F)
Pieter D'Hooghe (Leuven - B)
Freddie Fu (Pittsburgh - USA)
Thorsten Gehrke (Hamburg - D)
Andreas Gomoll (Boston - USA)
Feng Hua (Beijing - ROC)
John Karlsson (Göteborg - S)
Gino M.M.J. Kerkhoffs (Amsterdam - NL)
Koen Carl Lagae (Anversa - B)
Anthony Miniaci (Cleveland - USA)
Norimasa Nakamura (Osaka - J)
Philippe Neyret (Lyon - F)
Mitsuo Ochi (Hiroshima - J)
Marc Safran (Redwood City - USA)
Romain Seil (Luxembourg - L)
Daniel Slullitel (Rosario - RA)
Lynn Snyder-Mackler (Newark - USA)
Carsten Tibesku (Straubing - D)
Niek van Dijk (Amsterdam - NL)
Gijs Van Hellemondt (Nijmegen - NL)
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Upcoming ICRS Events

Sicot/ICRS Combined Cartilage Symposium Rome, Italy – September 9, 2016

By Stephen P. Abelow

As Chairman of Arthroscopy and Sports Medicine of SICOT (Societe International of Chirurgie et de Trau-matology), I am delighted to have collaboration with the ICRS (Inter-national Cartilage Repair Society) to have a special, two-part Cartilage.

Symposium (3 hours total) featuring the World Experts in Cartilage Repair and Regeneration at he 37th SICOT World Congress to be held in Rome, Italy, September 8-10, 2016. The 13th ICRS World Congress will be in Sorrento, Italy September 23-27, 2016.

On behalf of the executive committee of ICRS (Nakamura Norimasa, MD –President; Kenneth Zaslav, MD- President Elect; Elizaveta Kon, MD- General Secretary and Stefan Seiler- CEO) and SICOT (Keith Luk, MD- President, Shanmuganathan Rajasekaran, MD- President Elect; Jochen Eulert, MD-General Secretary), we have invited the Premier Orthopaedic Surgeons and Scientists in the world involved in cartilage repair, regeneration, and stem cells to participate in this special educational symposia, I would like to invite and encourage all Orthopaedic Surgeons and Researchers to attend both of these important World Congresses. I would also like to personally thank Dr. Fabio Valerio Siarretta for his assistance in this wonderful educational symposium.

SICOTs mission is to promote the advancement of the science and art of orthopaedics and traumatology on an international level. SICOT represents over 110 coun-tries. ICRS mission is to promote world collaboration in advancing science and education in cartilage repair and regeneration. ICRS represent over 60 countries and 1300 members.

The SICOT/ICRS Cartilage Symposium will feature as keynote speakers Drs. Giancarlo Pudu (who will teach us about ostotomies about the knee) and Lars Peterson (who will teach us about Autologous Chhondrocyte Implantation). The remainder of our International Cartilage Faculty includes Drs. Rodkey, Stone, Abelow (USA); Dr. R Verdonk (Belgium), Drs. Pedro and Marta Guillen (Spain) and Drs. Kon, Gobi, Zaffagnini and Sciarretta (Italy) and will discuss ALL current and future technologies available for cartilage repair and regeneration.

As an added highlight, on the morning of September 9, all faculty will be involved in an Instructional Course Lecture entitled "My Favorite ACL Technique." A live demonstration of Wireless Video Arthroscopy (with hands on experience) is also planned as well as a symposium on "What's New in Sports Medicine...What's Hot and What's Not"

I hope to see you all in Rome and Sorrento this September.

ICRS Focus Meeting – Subchondral Bone Tel Aviv, Israel – September 26 – 27, 2017

By Nogah Shabshin, Tel Aviv

Bone Marrow Edema is a confusing term. It describes different conditions that have a similar imaging appearance. Although this condition is very common, there is no consensus about the terminology and causes of pathology. Although treatment options have been suggested, guidelines have not yet been agreed upon. This meeting will focus on all aspects of bone marrow edema syndromes and the relationship with the subchondral bone unit. After aiming for consensus in terminology on the discussed on the second day of the meeting. The meeting will be held in Tel Aviv, on the Mediterranean Sea shore, close to old Jaffa, and colorful markets and surrounded by great restaurants and bars. Tel-Aviv, also called the white city, is a protected site by UNESCO due to the unique historical architecture style. The weather in January is around 18oC.

Upcoming ICRS Events

ICRS Heritage Summit 2017
June 30 – July 1, 2017

By Ken Zaslav, President Elect ICRS 2016-2017

We are pleased to announce a special Presidential Summit in the summer of 2017. This meeting, to be chaired by myself and Past President & Editor in Chief of our Journal "Cartilage" Mats Brittberg, will be held at Gothia Towers in Gothenburg, Sweden. It will be a little different than past summits, which have concentrated on a single topic in depth and instead, will be a "Heritage Summit" celebrating the 20th anniversary of the founding of the ICRS in 1997 and the 30th anniversary of the first ACT - Articular Cartilage Transplant by Lars Petersen in 1987.

We hope many of you will plan to attend and help us celebrate the remarkable past 20 years in our specialty. A single session meeting, similar to how we started this association's scientific sessions with all participants involved in all lectures, and plenty of time for comments, questions and answers will run from noon on June 29 – July 1. Our founding and past Presidents will also be honored.

Academically the first afternoon session will concentrate on a historical perspective of the major milestones in Cartilage Repair and transplantation, reconsidering the history and long term results of osteotomy, marrow stimulation, cellular, scaffold and allograft treatments. The second day will concentrate on future technologies for the treatment of articular cartilage injury and early arthritis including newer scaffolds, bio-fabrication or bio-printing, pharmacologic options and enhanced chondrocyte and stem cell therapies. The final morning will concentrate on an inclusive discussion concerning the future of the society in the next two decades and its role in promoting research and therapies for Regenerative medicine and the treatment of early Arthritis and Articular Cartilage Injury.

We hope all ICRS members and our industry partners will consider joining us for this important milestone meeting for this society during a beautiful time in Sweden on the banks of the Gota Alv river with the midnight sun shining light on our past, present and potential exciting future.

ICRS Focus Meeting – Osteoarthritis in Athletes
Sept. 28-29, 2017

By Gian Salzmann

The ICRS will offer a Focus Meeting in September 2017 (September 28th and 29th) in beautiful Zurich, Switzerland. It is in the center of Europe and thus easy to reach for everybody. In September Zurich is presenting itself very nicely with warm temperatures of the lake and still summer-like days. The focus of that meeting will be „Osteoarthritis in the Athlete". A topic that everybody is and will be confronted with more and more in the future. As our population is being increasingly demanding and involved in more sporting activity than ever the rate of trauma and therefore degeneration is logically increasing. "I have mild pain. You have mild arthritis. I want to do sports like ever before." That would be a typical communication between physician and surgeon. The treating doctor as to be optimally equipped with knowledge and instruments to treat this collective of patients. During the meeting we will look at all major joints that are typically affected: hip, knee and ankle. Mostly clinical topics (conservative and operative) will be added by some basic scientists that will give insight what is coming from the bench. Virginia Kraus from Duke University will give a highlight lecture on Osteoarthritis. Tim Spalding will report on when we can still approach from a biological standpoint and when it is too late to save the joint. Michael Leunig will report on current surgical trends at the hip joint.

The french patellofemoral group will be represented by Elvire Servien. Nick van Dijk will speak about his current understanding of OD treatment. Floris Lafeber will inform us about functionality, technique und foremost outcome of joint distraction. Only to name a few of internationally well known physicians that already agreed to contribute. It will be a fully packed 2-day meeting covering all major topics when OA in the Athlete is regarded. We consider that the audience will be excited by the speaker line-up and topics. Furthermore it is a good chance to enjoy Zurich during one of the best times of the year. More information including final program to be announced soon.

Report from Past Events

ICRS Allograft Summit in Brussels, Belgium – January 29, 2016

By Andreas Gomoll & Peter Verdonk

On January 29th and 30th, 2016, over 26 faculty and 150 participants came together in Brussels to discuss the current state and future directions of allograft tissue transplantation for the treatment of musculoskeletal disorders. A wide range of topics were discussed, all focused on discussing current clinical practice, identifying causes of limited availability, and map out a path to improve access to allograft tissue in Europe and worldwide.

The use of allograft tissue in Orthopaedic surgery has a long history spanning over 40 years. Currently, more than 1 million units of allograft tissue are used in the US per year, the majority in the form of bone grafts for procedures such as spinal fusion, fracture fixation and ligament reconstruction. Approximately half of all ACL reconstructions in the US are performed with the use of allografts, including tibialis, achilles and patellar tendons. Lastly, but of critical interest to our society, fresh osteochondral and frozen meniscal allografts are used to reconstruct articular and meniscal damage in more than 4000 patients per year. Whereas allograft tissue is readily available in the US, access remains limited in many parts of the world. The use of allograft tissue decreases donor site morbidity, and allows the management of conditions that otherwise have no treatment alternatives, such as the completely meniscectomized knee. While not without limitations, allografts have improved the lives of countless patients worldwide. Its use, however, remains limited by supply, as well as political and regulatory hurdles.

Organized by congress-chairmen Andreas Gomoll (USA) and Peter Verdonk (Belgium), the ICRS Allograft Summit was dedicated to finding solutions to these very limitations. It brought together leaders from EU and local regulatory agencies, industry and physicians to create a forum for the exchange of ideas, discuss regulatory hurdles and strategies to educate the public and health care providers about the possibilities and limitations of musculoskeletal allograft transplantation.

Over the course of two days, state of the art techniques in allograft reconstruction, as well as potential alternatives to human allograft tissue, were presented by an international panel of physicians. Basic scientists provided insights into biologic mechanisms of graft integration and function. Our partners in industry were able to share the evolution of allograft tissue use in the US, address potential concerns by discussing the strict procedures in place to ensure safety, and present their strategies to improve access in Europe.

We are optimistic that the connections and collaborations initiated at the ICRS Allograft Summit will evolve into a strong collaboration of all involved interest groups to make these crucial treatment options available to patients worldwide in a safe and efficient manner.

George Bentley & Norimasi Nakamura in Brussels

Report from Past Events

ICRS Summit Kyoto, Japan 2016
Breaking down the Barriers!

By Christian Lattermann

The 3rd ICRS Summit meeting took place on April 10/11 in Kyoto, Japan. Hosted by our president, Norimasa Nakamura, MD, PhD the "Kyoto Summit" pushed the envelope on collaborative thinking and expanding our horizon in the understanding of early cartilage injury and healing.

The Kyoto Summit originated from the previous "Zermatt Summit" and sought to bring together faculty from the ICRS and the Osteoarthritis Research Society International (OARSI) in order to align our mutual interests and thought processes with the goal to advance research and understanding of cartilage injury and early osteoarthritis.

The organizers of this meeting, Drs. Virginia B. Kraus, Susan Chubinskaya, Christian Lattermann and Norimasa Nakamura, asked the faculty to focus on wound healing as an approach to cartilage healing and early OA.

This approach was pursued from the most diverse angles allowing faculty and participants to discuss and think out of the box. In two days of intense talks and discussions the paradigm of cartilage healing was scrutinized from various angles. The role of inflammation was addressed from a clinical perspective as well as regarding involvement of synovium, macrophages and the anabolic and catabolic environment of synovial fluid. Compromised wound healing in the skin was compared to ineffective cartilage repair and similarities and differences with regards to cell senescence and differences in cartilage collagen turnover between different joints was discussed. The overall concept of isolated chondral defects in the light of progressive early OA was challenged and conceptualized to be more of a continuum of disease rather than a single

pathology. An ensuing discussion over stem cell potency, PRP and appropriateness of use in wound repair and specifically cartilage repair may open a pathway to better use of this technology in the future. Furthermore, the audience learned that there may be a significant genetic variability in the human ability to endogenously repair articular cartilage. This line of thought may open a pathway towards personalized treatment approaches in the future. In a final wrap up discussion on day two a fruitful and important discussion surfaced about the still existing difficulties to translate research into the clinical setting. Despite significant advancement in the description and standardization of animal models there is still a substantial gap in the translation of animal model data to clinical application. Particularly the recognition of whole

joint organ effects of early cartilage damage and specific therapies are often neglected in targeted models. It appears that while the focus on repair of cartilage tissue is currently a mainstay of our profession the focus has to shift and include other factors affecting the healing joint environment. Factors such as inflammation, genetics, insufficient, failed or erroneous intrinsic cartilage healing, synovial repair response as well as the contributions of the extracellular matrix likely play a larger role in cartilage repair than previously thought.

Dr. Nakamura and his team not only nurtured the scientific but also the culinary and spiritual needs of the faculty. It may have been the inspiring "cherry blossom" atmosphere in the City of Emperors or the serenity of the UNESCO World Heritage Kiyomizu-dera temple and its extraordinary Moon-Garden that were masterfully introduced and presented to the participants during two unforgettable dinners.

With 175 registered participants the Kyoto Summit was the largest summit meeting to date. This clearly underlines the need for interdisciplinary and provocative research summits of this nature. The Kyoto Summit pushed the bar ever higher for these meetings in the future and may be the beginning of a fruitful and rich collaboration between various disciplines of soft tissue research to come together with a common goal in mind: to understand, prevent and successfully treat cartilage damage and early OA. Let's continue to break down more silos and open up our horizon!

2nd ICRS World Series Brazil: Treating Cartilage Defects in South America, June 9-11, São Paulo, Brazil,

By Camila Kaleka, Luis Tirico, Marco Demange, Moises Cohen

The second ICRS World Series Brazil was held in São Paulo, one of the most important cities in Latin America. The course took place from June 9th to June 11th with presentations and clinical case discussions and a cadaver lab on the third day for 18 clinicians. The event brought together 19 faculties and more than 200 physicians, physiotherapists, scientists and industry experts focusing on the treatment of cartilage defects in South America. The intention of the meeting was to discuss basic science and indications for the treatment of cartilage lesions that are available in South America with emphasis in new technologies and associated procedures in cartilage repair.

We have started the first day of the meeting discussing basic science, imaging and cartilage markers in cartilage defects learning that while a specific cartilage marker to evaluate cartilage degradation are yet to be determined, novel imaging techniques are possible to evaluate functional and metabolic state of cartilage structure. This was followed by a large discussion of surgical techniques and rehabilitation following microfracture, autologous osteochondral transplantation and enhanced microfracture with collagen membranes. The importance of alignment of the limb when evaluating cartilage lesions on the tibiofemoral and patellofemoral joint was largely emphasize followed by a clinical case discussion of simple and complex chondral and osteochondral lesions. The last module of the first day considered surgical techniques of meniscal repair and the possibility of meniscal transplants, substitutes and future trends that are still not available in South America.

The second day of the course started with a discussion of osteochondral allograft transplantation basic science, surgical techniques and rehabilitation followed by a clinical case discussion of what to do when fresh allografts are or are not available for repair. That was followed by a module of cell therapy talking about autologous chondrocyte implantation, stem cells, juvenile cartilage fragments and its particular rehabilitation and protocol for return to sports. As many of this techniques are still under regulatory discussion here in Brazil, a clinical case discussion was held considering cartilage repair when cell therapy is available or not. After an invigorating lunch break the importance of injectable therapy as PRP, Hyaluronic Acid and BMAC was announced as a possible minimally invasive procedure that still needs to show is role in the paradigm of cartilage repair. Last, but not least, the second day of the course ended highlighting the importance of subchondral bone along with procedures that are currently used for initial degenerative joint diseases, as subchondroplasty and partial arthroplasties.

The third day took place in the wet lab at University of São Paulo, there were 8 faculties, 24 clinicians and technical exhibits. Cartilage repair procedures such as enhanced microfracture, autologous osteochondral transplantation, subchondroplasty and AMIC were performed along with associated techniques as meniscal repair, tibial tubercle osteotomy and valgus tibial osteotomy. The participants were able to have the tips and pearls of many experienced faculty surgeons and were delighted with the organization of the course and the opportunity to have an ICRS event in their home country again after many years. We hope to have another course in the close future, according the ICRS interests and we thank the ICRS Board for the opportunity to organize the 2nd World series in Brazil.

events

Event Calendar

2016

05 08.2016
Basic Orthopaedic Procedural Skills
Royal College of Physicians and Surgeons of Glasgow
Glasgow, United Kingdom
www.rcpsg.ac.uk/events/basic-ortho.aspx

15 – 17.09.2016
AGA-Congress 2016
Basel, Switzerland
www.aga-kongress.info

24 – 27.09.2016
ICRS 2016 – 13th World Congress, Naples – Italy
Hilton Sorrento Palace
www.cartilage.org/13th-icrs-world-congress/

28 – 30.09.2016
6° National Congress SIGASCOT
Palazzo dei Congressi
Florence, Italy
www.sigascot2016.it

05 – 07.10.2016
EUROSPINE 2016
CityCube Berlin, Messedamm
Berlin, Germany
www.eurospine2016.eu

07 – 08.10.2016
Knee & Ankle Current Concept
Hotel Park Inn by Radisson, Cracow, Poland
www.ortopedia2016.pl

20 – 22.10.2016
4th World Congress on Controversies, Debates & Consensus in Bone, Muscle and Joint Diseases (BMJD)
Hilton Barcelona, Barcelona, Spain
www.congressmed.com/bmjd/

2017

26 – 27.01.2017
ICRS Focus Meeting – Subchondral Bone
Tel Aviv, Israel
www.cartilage.org

04 – 08.06.2017
11th Biennial ISAKOS Congress
Shanghai, China
www.isakos.com/2017Congress

29.06 – 01.07.2017
ICRS Heritage Summit 2017
Gothia Towers, Gothenburg, Sweden
www.cartilage.org

07 – 09.09.2017
AGA-Congress 2017
München, Germany
www.aga-kongress.info

28 – 29.09.2017
ICRS Focus Meeting – Osteoarthritis in Athletes
Zurich, Switzerland
FIFA Auditorium Sonnenberg
www.cartilage.org

This listing is not complete and does not constitute a recommendation or endorsement by ICRS. Further investigation by interested parties is always necessary. For further information, visit the ICRS online event calendar at our website.

News from Industry

Mergers, Acquisitions and Clinical Trials: Update on Industry Partners

By Leanna Caron & Peter Bak

The last year saw quite a bit of activity among industry partners. In an effort to ensure clarity around these events, the following summary was prepared.

Aesculap Biologics, LLC was established in January 2012 as a company focused on biological approaches to the repair and regeneration of diseased or damaged tissues.

AlloSource launched a new product ProChondrix® Cartilage Restoration Matrix. This is a cellular 3D fresh cartilage matrix, described as a sheet of cartilage which helps support a structure for cellular migration and adhesion while preserving growth factors. Very similar to Cartiform, the presence of native growth factors help maintain healthy cartilage and facilitate chondrocyte functionality and the viable chondrocytes are present and can aid in cartilage repair by generating extracellular matrix proteins that help promote chondrogenesis.

Anika Therapeutics, Inc. HYALOFAST is a biodegradable scaffold. HYALOFAST plus autologous Bone Marrow Aspirate Concentrate (BMAC) in a one-step, minimally invasive arthroscopic procedure showed it was able to successfully regenerate a hyaline-like repair tissue. HYALOFAST is CE Marked in Europe and is available commercially in 18 countries. A pivotal HYALOFAST Phase III clinical study is planned as a prospective, randomized trial. In this multicenter study where the evaluators will be blinded, the goal is to establish the superiority of a hyaluronan-based scaffold (HYALOFAST) with autologous bone marrow aspirate concentrate (BMAC) in the treatment of articular knee cartilage defect lesions. The study will enroll approximately 200 patients at up to 30 sites in the U.S. and Europe."

Arthrex offers BioCartilage®: Cartilage Extracellular Matrix for smaller, contained lesions. This scaffold is placed over a microfractured defect providing a tissue network that can potentially signal autologous cellular interactions and improve the degree and quality of tissue healing within a properly prepared articular cartilage defect. This method augments a traditional microfracture procedure. This is an FDA 361 HCT/P product, considered to be a minimally manipulated allograft product used for homologous purposes.

CartiHeal Ltd is the developer of a cell-free, off-the-shelf cartilage and bone regeneration device, Agili-C(TM). It is a bi-phasic implant consisting of composite coral and hyaluronic acid. It has been successfully implanted in nearly 200 patients throughout Europe with encouraging early results both clinically and with MRI analysis. Agili-C(TM) is CE-marked for the treatment of cartilage and osteochondral defects in degenerative and non-degenerative lesions. The company recently announced the culmination of a $15M financing round which will be used to promote ongoing manufacturing scale-up, plan for initial European commercialization in 2017 and expansion of clinical studies to new therapeutic areas. This product would require an IDE/PMA in the US.

Finceramica has established International partnerships and scientific cooperation programs such as the one with the Rizzoli Orthopaedic Institute, which have made it possible to develop biomedical products. MaioRegen is a new therapeutic concept using nanotechnology. The scaffold is made of biomimetic nanostructured materials. A prospective study showed early clinical benefit, but a longer maturation process with MRI bony findings. There is currently a 10 center RCT vs Microfracture underway.

Geistlich provides Chondro-Gide® Bilayer Collagen Matrix. The unique bilayer structure of the matrix offers a protective environment for cell differentiation and the formation of new cartilage, which is the principle intent of the AMIC® (Autologous Matrix-Induced Chondrogenesis) procedure. AMIC is described as a single-step, cost efficient and effective technique for augmenting the use of microfracture surgery in larger cartilage lesions. Bio-Gide, the US approved collagen matrix, is approved for dental applications only, but is used in an off-label indication with autologous chondrocyte implantation.

Histogenics, the developer of the Neocart implant, a preformed 3-D disk of the patient's own neocartilage, has characteristics similar to that of maturing native articular cartilage. The company announced in February 2016 it had enrolled 123 of the 245 patients required to complete enrollment of its ongoing NeoCart Phase 3 clinical trial. This trial is being conducted under a Special Protocol Assessment (SPA) with the United States Food and Drug Administration (FDA). Recently, the FDA approved changes to the Phase 3 clinical trial inclusion/exclusion criteria to help broaden and improve the recruitment efforts. The Trial is expected to complete enrollment by the end of the second quarter of 2017 and enter the market in 2020.

Osiris Therapeutics, Inc., a cellular and regenerative medicine company, entered into a partnership with Arthrex, Inc. (October 2014) granting Arthrex exclusive commercial distribution rights to Cartiform. The two companies will both contribute to the design and future development programs related to Cartiform. Cartiform is a cryopreserved perforated osteochondral Allograft, with the purpose of augmenting a microfracture proce-

18th EFORT Congress 2017

www.efort.org/vienna2017

EFORT – JOINT EFFORTS

Abstract submission
15 Sept. – 13 Nov. 2016

18th EFORT Congress

Vienna, Austria: 31 May–02 June 2017

#EFORT2017

Congress Highlights – Main Theme: Sports Activities & Orthopaedic Practice

General Orthopaedics
- e-Health Applications In Orthopaedic Research
- Computer Models In Orthopaedic Biomechanics Research

Trauma
- Hip Trauma And Sport
- Return To Sport After Knee Trauma

Paediatrics
- Sport Activities After Deformity Corrections
- Better To Do Sports In Childhood Than Playing The Games On The Computer

Lower Limb
- The Painful Total Hip Arthroplasty
- Sports Activities After THA
- Sport Expectations After Knee Surgery
- Functional Outcomes After UKA And TKA

Upper Limb
- Shoulder Instability Management
- Sports & Elbow
- Less Frequent Shoulder Sport Injuries
- Lesions Of The Ulna Carpus And The DRUJ After Sports
- Boxer's Fracture And Pulley Lesions - How To Treat?

Spine
- Cervical Spine And Sports

Musculoskeletal Tumours
- Advances In The Treatment Of Soft-Tissue Sarcomas

Musculoskeletal Infections
- Treatment Of Chronic Bone Infection

Key dates

Abstract submission & registration open: 15 September 2016
Abstract submission closes: 13 November 2016 23:59 CET
Early registration deadline: 27 February 2017

dure. It is composed of viable chondrocytes, chondrogenic growth factors and extracellular matrix proteins.

Smith & Nephew acquired BST-CarGel, a first-line cartilage repair product. Through this transition, Smith & Nephew will acquire ownership of all the products and intellectual property assets related to BST-CarGel from Piramal Healthcare (Canada). BST CarGel is approved for use in Australia, Canada and the European Union. BST-Cargel is a biopolymer-based solution that is mixed with the patients' blood and implanted into the defect following a microfracture procedure. Once implanted, it acts as an internal scaffold to help stabilize the blood clot by incorporating a thrombogenic and adhesive polymer. BST-CarGel was the first microfracture augmentation product and the principle behind this product has led to the development of other augmentation products. This product would require an IDE/PMA in the US.

NOVOCART 3D Autologous Chondrocyte Transplantation System is a biologic-device combination product composed of ex vivo expanded autologous chondrocytes seeded on a bioresorbable biphasic collagen scaffold. In Europe, NOVOCART 3D is conducting a phase III trial to be approved as Advanced Therapy Medicinal Product and within the United States, a second Phase 3 clinical study is underway with a potential completion date of 2022. Novocart is 351 HCT/P which requires clinical evidence in-order to achieve FDA marketing approval.

TiGenix: ChondroCelect was the first cell-based product to receive the approval by the European Marketing Authorization 2009. Effective June 1 2014, the company has entered into a distribution agreement with Sobi (Swedish Orphan Biovitrum AB) for the exclusive marketing and distribution rights with ChondroCelect in Europe

On April 13, 2016, the US Food and Drug Administration – FDA has originally scheduled a public hearing, which has since been postponed due to the overwhelming feed-back FDA received from providers and industry. The goal was to obtain input relating to the regulation of human cells, tissues, or cellular or tissue-based products (HCT/Ps), specifically on the four recently issued draft guidances:

1. Same Surgical Procedure Exception under § 1271.15(b): Questions and Answers Regarding the Scope of the Exception; Draft Guidance for Industry (Same Surgical Procedure Exception Draft Guidance);

2. Minimal Manipulation of Human Cells, Tissues, and Cellular and Tissue-Based Products; Draft Guidance for Industry and Food and Drug Administration Staff (Minimal Manipulation Draft Guidance);

3. Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) from Adipose Tissue: Regulatory Considerations; Draft Guidance for Industry (Adipose Tissue Draft Guidance);

4. Homologous Use of Human Cells, Tissues, and Cellular and Tissue-Based Products; Draft Guidance for Industry and Food and Drug Administration Staff (Homologous Use Draft Guidance).

The purpose of this public hearing is to solicity opinion and comments on the draft guidances and the definition of the term "homologous use of minimal manipulation of allograft materials and the use of stem-cell therapies." Based upon the outcome of this meeting, products that are currently categorized as 361 HCT/P potentially could be re-categorized to 351 HCT/P which would require clinical evidence in-order to achieve premarketing approval.

Zimmer, June 2015, completed the acquisition of Biomet in a cash and equity transaction currently valued at approximately $14.0 billion. Zimmer Biologics currently has two cartilage products in its portfolio. DeNovo® NT Graft is a particulated juvenile cartilage implant used for the repair of articular cartilage damage while Chondrofix is an osteochondral allograft for full thickness osteochondral lesions.

Vericel, formerly Aastrom, completed the acquisition of Sanofi's Cell Therapy and Regenerative Medicine Business. The two cell-based orthopedic products included in the acquisition were Carticel® (autologous cultured chondrocytes), a first-generation autologous chondrocyte implant (ACI) product marketed in the United States, and MACI® (matrix-applied characterized autologous cultured chondrocytes), a third-generation ACI product approved in the European Union for the treatment of focal chondral defects in the knee. In January 2016, Vericel announced that it had submitted a Biologics License Application (BLA) to the U.S. Food and Drug Administration for MACI™ The MACI product ATMP approval is currently suspended in Europe.

News from Industry

■ Vericel Announces FDA Acceptance for Filing of BLA for MACI for the Treatment of Symptomatic Cartilage Defects in the Knee

CAMBRIDGE, Mass., March 7, 2016 (GLOBE NEWSWIRE) — Vericel Corporation (NASDAQ: VCEL), a leading developer of patient-specific expanded cellular therapies for the treatment of severe diseases and conditions, today announced that the U.S. Food and Drug Administration has accepted for filing its recently submitted Biologics License Application (BLA) for MACI™ (matrix applied characterized autologous cultured chondrocytes), the company's investigational autologous cellular product intended for the treatment of symptomatic cartilage defects of the knee in adult patients. The FDA provided a PDUFA (Prescription Drug User Fee Act) goal date of January 3, 2017. In addition, the FDA communicated that it is not currently planning to hold an advisory committee meeting to discuss the application. "The FDA's acceptance of the MACI BLA for review re of providing a new treatment option for the repair of symptomatic cartilage defects of the knee in adult patients," said David Recker, MD, chief medical officer of Vericel. "We look forward to continuing to work closely with the FDA during the BLA review process for MACI in the United States."

About MACI

MACI (matrix applied characterized autologous cultured chondrocytes) is a third-generation autologous chondrocyte implant (ACI) product intended for the treatment of symptomatic cartilage defects of the knee in adult patients. MACI is an autologous implant consisting of autologous cultured chondrocytes seeded onto a resorbable Type I/III collagen membrane. Autologous cultured chondrocytes are human-derived cells which are obtained from the patient's own cartilage for the manufacture of MACI. MACI is an investigational product that was studied in the pivotal Phase 3 clinical trial SUMMIT ("Superiority of MACI Implant to Microfracture Treatment") and the three-year SUMMIT Extension trial. SUMMIT was a two year, prospective, multicenter, randomized, open-label, parallel-group clinical trial designed to evaluate the safety and efficacy of MACI to reduce pain and improve function compared with arthroscopic microfracture in the treatment of patients (n = 144) with symptomatic Outerbridge Grade III or IV focal cartilage defects. The SUMMIT Extension trial evaluated the safety of both treatments for an additional three years.

About Vericel Corporation Vericel Corporation is a leader in developing patient-specific expanded cellular therapies for use in the treatment of patients with severe diseases and conditions. The company markets two autologous cell therapy products in the U.S.: Carticel® (autologous cultured chondrocytes), an autologous chondrocyte implant for the treatment of cartilage defects in the knee, and Epicel® (cultured epidermal autografts), a permanent skin replacement for the treatment of patients with deep-dermal or full-thickness burns comprising greater than or equal to 30% of total body surface area. Vericel is also developing MACI™, a third-generation autologous chondrocyte implant for the treatment of cartilage defects in the knee, and ixmyelocel-T, a patient-specific multicellular therapy for the treatment of advanced heart failure due to ischemic dilated cardiomyopathy. For more information, please visit the company's website at www.vcel.com.

This document contains forward-looking statements, including, without limitation, statements concerning anticipated progress, objectives and expectations regarding the commercial potential of our products, intended product development, clinical activity timing and regulatory pathway and timing, and objectives and expectations regarding our company described herein, all of which involve certain risks and uncertainties. These statements are often, but are not always, made through the use of words or phrases such as „anticipates," „intends," „estimates," „plans," „expects," „we believe," „we intend," and similar words or phrases, or future or conditional verbs such as „will," „would," „should," „potential," "can continue," „could," „may," or similar expressions. Actual results may differ significantly from the expectations contained in the forward-looking statements. Among the factors that may result in differences are the inherent uncertainties associated with competitive developments, integration of the acquired business, clinical trial and product development activities, regulatory approval requirements, the availability and allocation of resources among different potential uses, estimating the commercial potential of our products and product candidates and growth in revenues and improvement in costs, market demand for our products, and our ability to supply or meet customer demand for our products. These and other significant factors are discussed in greater detail in Vericel's Annual Report on Form 10-K for the year ended December 31, 2014, filed with the Securities and Exchange Commission („SEC") on March 25, 2015, Quarterly Reports on Form 10-Q and other filings with the SEC. These forward-looking statements reflect management's current views and Vericel does not undertake to update any of these forward- looking statements to reflect a change in its views or events or circumstances that occur after the date of this release except as required by law.

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Anika Therapeutics HYALOFAST™: a one-step technique for Cartilage Repair with no age limitation

Injury of the cartilage tissue represents a major challenge for orthopedic surgeons especially in elderly population. In fact numerous studies have described changes in articular cartilage that are relatively consistent and inevitable consequences of aging. The evidence that articular cartilage chondrocytes synthesize smaller, more irregular aggrecans with increasing age, suggests that older articular cartilage is less able to repair and restore itself. (1, 2)

A new trend in the use of cartilage regeneration treatments is represented by one-step procedures involving scaffolds and mesenchymal stem cells (MSCs), due to the easy availability and versatility of autologous bone marrow mesenchymal stem cells and their chondrogenic potential. After the first use of these techniques for cartilage resurfacing in the knee and ankle joint of young patients, an increasing attention is being gained by the treatment of cartilage defects in the still active middle-aged population where common techniques such as microfractures typically result in high failure rates. (3, 4)

Hyalofast™ a non – woven pad, made of HYAFF®11, a derivative of hyaluronic acid, a key component of the healthy cartilage extracellular matrix, in combination with bone marrow aspirate concentrate (BMAC) has been successfully applied in young patients with cartilage lesions of the knee and the ankle showing durable clinical results up to medium-term follow-up. (5-7)

Thanks to its composition and physical conformation, Hyalofast is easy to be used both in miniarthrotomy and arthroscopic procedures, allowing the least surgical invasiveness. Given its soft texture, Hyalofast™ conforms, covers and fills both regular and irregular lesions. Due to its uniform single layer structure, it can be applied in any orientation or stacked.

Noteworthy is the recent prospective assessment of Hyalofast with BMAC in patients over 45 years (mean age 50.0 + 4.1 years) comparing them with a control group of patients with an age ⟵ 45 years (mean 36.6 + 5.0) for the treatment of large ICRS grade 4 cartilage defects in the knee at medium-term follow up. (8)

At 4 years final follow-up, all clinical scores (KOOS, Tegner, IKDC subjective) significantly improved (P ⟵ 0.001) in both groups. MRI showed complete filling in 80 % of patients in the study group and 71 % in the control group with no signs of hypertrophy. Integration with adjacent cartilage was complete in more than 90% of the patients in both groups, with restoration of the cartilage layer over the subchondral bone. No documented deterioration was detected in either group at final follow-up. In addition, a subgroup analysis showed that results were affected by lesion size and number, but not by concomitant surgical procedures.

Hence, the use of Hyalofast combined with bone marrow concentrate represents a safe, simple, and effective one-step technique in large full thickness knee cartilage defects in a broader patient population including the challenging active middle-aged population (⟶ 45 years). The clinical results in the ⟶45 years population had no significant impairment compared to younger patients and confirmed to be durable at medium-term follow-up.

For further information, please contact Anika Therapeutics, http://www.anikatherapeutics.com or at ICRS World Congress in Sorrento

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News from other Societies

ORS 2016 – Orlando, Florida Basic Science Report

By Karin Payne

The 2016 Annual Meeting of the Orthopaedic Research Society was held from March 5-8, 2016 at Disney's Coronado Springs Resort in Orlando, Florida. It provided a forum for clinicians and scientists from around the world to share and discuss their latest research in all areas of musculoskeletal research through spotlight sessions, workshops, and over 2,200 scientific podium and poster presentations. Topics related to articular cartilage repair included stem cell therapies, gene therapy, novel scaffold materials for cartilage tissue engineering, biology of cartilage development, as well as the importance of the 3-dimensional microenvironment for optimal design of cartilage repair therapies.

Research on stem cells and progenitor cells for cartilage repair continues to focus on mesenchymal stem cells (MSCs) derived from bone marrow, adipose tissue, or various tissues surrounding the human knee. Other sources such as those from perinatal tissue are also being investigated and showing promise for chondrogenic differentiation. In addition to MSCs, this year also included presentations on the potential of induced pluripotent stem cells for cartilage repair. These adult derived pluripotent stem cells can undergo chondrogenesis and also have the ability to resist inflammatory cytokines. As a result, they offer a novel cell source for cartilage repair. Overall, it remains clear that research on cell therapies is continuing at a rapid pace and the identification of the ideal chondroprogenitor cell is still ongoing.

In addition to chondroprogenitor cells, growth factors are also an integral part of cartilage repair strategies. While direct delivery of proteins continues to be studied, there is a renewed interest in the use of gene therapy to deliver biological factors. This was presented by numerous groups in a session dedicated to the topic of joint repair and gene therapy and in many poster presentations. Of interest was novel technology being developed for the delivery of adeno-associated virus or RNA into cartilage. Research into the development of lipid nanoparticles and nanopieces that "sandwich" RNA between nanotubes are some examples of the work presented this year.

New advances in biomaterials for articular cartilage repair were also presented. There was a focus on biologically-inspired biomaterials where pore size, as well as biochemical and biomechanical niche cues are incorporated. Most still included the incorporation of stem cells, while others focused on acellular scaffolds that contain stem cell attracting factors that would enhance the migration of endogenous stem cells into the defect area. Decellularized cartilage ECM was also shown to be a potential scaffold for cartilage repair.

In developing different approaches to repair cartilage, it continues to be important to be able to analyze the tissue formed. An example of one of the novel techniques presented was the use of a multi-color protein labeling system which can track and quantify the temporal dynamics of the extracellular matrix being produced by chondrocytes or MSCs at the single-cell level. This could provide important information for cartilage tissue engineering.

On the last day of the conference, there was an interesting workshop on 3-dimensional human tissue models to study musculoskeletal physiology and pathophysiology. This reinforced the need to move studies from 2D to 3D, which better incorporates the complexity of the native tissue, where multiple cell types interact with each other and with the extracellular matrix. The presentations focused on the use of organs on a chip as the potential future of personalized medicine, the use of genome editing of stem cells to create custom designed cells for 3D tissue systems and the development of a 3D tissue culture platform that models osteochondral tissue. There was also mention of how 3D printing could eventually be used to model the total joint; where one could incorporate osteoarthritic tissue, bone tissue and fat tissue, to name a few.

Overall, the basic science research presented at the ORS 2016 Annual Meeting indicated that there has been much progress in all areas of cartilage research and there are new technologies being developed, all of which offer exciting new opportunities for the future of cartilage repair.

Basic Science Study – Giuseppe Filardo, Rizzoli Orthopaedic Institute, Italy

Review on: **"Chondrocytes Cocultured with Stromal Vascular Fraction of Adipose Tissue Present More Intense Chondrogenic Characteristics Than with Adipose Stem Cells."***By Wu L, Prins HJ, Leijten J, Helder MN, Evseenko D, Moroni L, van Blitterswijk CA, Lin Y, Karperien M.*

The authors explored the possibility to replace part of the chondrocytes in autologous chondrocyte implantation procedures by other cell sources, in order to avoid the present obligatory, costly, and time-consuming cell expansion phase. While previous studies mainly focused on bone marrow-derived mesenchymal stem cells, they investigated another attractive source for cartilage tissue engineering: adipose stem cells (ASC), which are abundant in adipose tissue, and more easily accessible than bone marrow. Moreover, with the aim to simplify the procedure, beside the expanded plastic-adherent ASC subpopulation they also investigated the minimally processed stromal vascular fraction (SVF) cell population. From the perspective of clinical practice, SVF cells have great advantages over ASC, since it is possible to harvest them during the operative procedure itself by processing in the operation theatre and putting them back into the patient without laboratory expansion. Because adipose tissue is an abundant source of stem cells, cell numbers required for reimplantation can easily be obtained.

The first experimental step involved the comparisons of surface marker profiles and chondrogenic potential of SVF and ASC. In general, ASC contained a more homogenous cell population, which was CD31, CD34, and CD45 negative, but positive for MSC markers like CD105 and CD166, while SVF represented a heterogeneous cell population containing not only cells with typical MSC characteristics, but also $CD31^+$ endothelial progenitors, a minority of slightly positive $CD45^+$ hematopoietic cells and CD34+ stem cells. The evaluation of the chondrogenic differentiation potential in pellet culture showed that ASC formed better aggregates and a matrix containing more GAGs than SVF. The second step showed instead that chondrocytes cocultured with SVF produced more GAG and a tendency for more collagen than with ASC. Interestingly, while the initial seeding ratio of 1:4 didn't significantly change in ASC cocultures, it changed to almost 60% chondrocytes and 40% SVF after 4 weeks, which could be explained both by an increased cell death of SVF cell fractions in combination with a larger stimulatory effect on chondrocyte proliferation.

Finally the authors evaluated the ectopic cartilage formation of SVF and ASC mixed with chondrocytes in vivo, with cell mixtures incorporated in an alginate gel and subcutaneously implanted in immunotolerant mice. Eight weeks after implantation, SVF+chondrocyte group produced more ECM, with the presence of more collagen type 2, GAG, and fewer cells in engineered cartilage, thus suggesting that the SVF mixed with chondrocyte produced more cartilage matrix than ASC in vivo.

This study showed that SVF is a better cell source than ASC in facilitating cartilage formation in coculture with chondrocytes, probably thanks to a nonmesenchymal cells enhancement of the trophic MSCs effects, at least in this coculture model. Although speculative, the niche or local microenvironment may be crucial for keeping the adipose stem cell›s function as a trophic mediator. It is possible that endothelial cells may better preserve some of the adipose stem cell›s characteristics which are lost during in vitro expansion, such as their ability to express trophic mediators. Moreover, hematopoietic cells such as monocytes and lymphocytes, which are abundant in SVF but absent after in vitro expansion, may also regulate the trophic property of MSCs. However, the exact mechanism remain unknown. Nonetheless, these data demonstrated that chondrocytes form better cartilage tissue when cocultured or coimplanted with SVF of adipose tissue than with ASC.

These results support the clinical potential of a one-step therapy for cartilage repair, in which SVF from adipose tissue and chondrocytes from the nonweight bearing joint surface are isolated, mixed, and implanted back into the patient during the same surgical procedure.

From Bench to Bedside – Clinical Applications of engineered Nasal Cartilage Grafts

By Andrea Barbero, Marcus Mumme and Ivan Martin
University Hospital Basel, Switzerland

The idea

In the past years one of the focal research areas of the Tissue Engineering group at the University Hospital Basel in Switzerland has been dedicated to generate the scientific and pre-clinical basis towards the therapeutic use of nasal chondrocytes (NC), in the form of engineered cartilage grafts, for different clinical indications. In a recent ICRS newsletter (2014, Winter Issue 18, section ICRS Journal Club) Dr. Dobrila Nesic (University Bern, Switzerland) has reviewed two of our recent studies in this field. But why did we decide to use nasal chondrocytes as a cell source for cartilage repair? About 15 years ago (2001 - 2002), Dr. Anthony Hollander (at that time at the University of Bristol, UK) observed that bovine NC could deposit larger amounts of GAG and type II collagen than articular chondrocytes (AC) and contacted us to test whether also human cells would follow the same trend. Indeed, harvesting of nasal cartilage (tissue characterized as hyaline cartilage, like articular cartilage) would be minimally invasive, could be performed as an outpatient procedure under local anaesthesia and would lead to minimal donor site morbidity, due to the fact that the donor site is easily accessible and not subjected to high levels of physical forces. The study demonstrated that both bovine and adult human NC have enhanced and more reproducible cartilage forming capacity as compared to AC (Kafienah et al., 2002), thus advocating their potential use as a robustly chondrogenic cell source.

The beginning

The intriguing finding was followed up in Basel in collaboration with plastic surgeons, who demonstrated that the mechanical properties of nasal tissue engineered cartilage (N-TEC) were compatible with reliable fixation at the recipient site (e.g., suturing) and could further positively develop upon ectopic implantation (Farhadi et al, 2006). Encouraged by these results, we then decided to test whether autologous N-TEC could be safely introduced for the clinical reconstruction of the alar lobule of the nose after tumor excision. Typically, for this procedure native cartilage tissue harvested from ears or ribs of the patient is used, which involves a second site of operation and is associated with additional morbidity. For the prospective phase I clinical trial (Clinical-trials.gov NCT 01242618, Swissmedic TpP-I-2010-002), five patients with two-layer defects from non-melanoma skin cancer in the alar lobule were enrolled. The N-TEC grafts were GMP-manufactured in Basel using cells isolated from a 6 mm biopsy of nasal septum cartilage, expanded for 2 weeks and cultured for additional 2 weeks in Chondrogide™ collagen sponges, generously provided by the company Geistlich (Fig. 1). It is important to remark that at this stage the graft does not consist in cells seeded on a scaffold (corresponding to a MACI-like construct), but rather in a cartilage tissue, with abundant extracellular matrix deposited. After tumour excision, the grafts transferred to the operating room were shaped to fit the defect and implanted under a flap, as in the standard reconstruction using native cartilage. At least one year after implantation, when reconstruction is typically stabilized, all patients were satisfied with the aesthetic and functional outcome and no adverse reactions were recorded. The procedure resulted in recovery of sensibility and structural stability of the reconstructed area, with adequate respiratory function, no donor site morbidity and full satisfaction of the involved plastic surgeons (Dr. Dirk Schaefer and Dr. Martin Haug) (Fulco et al, 2014).

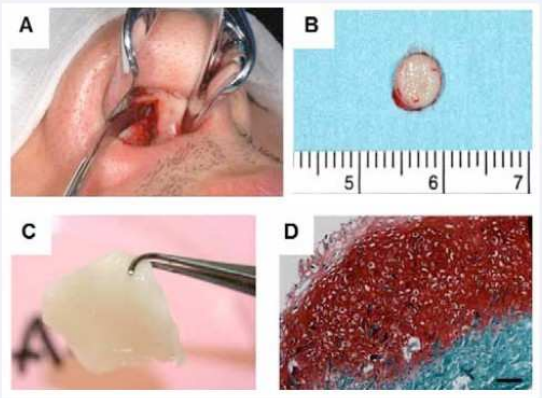
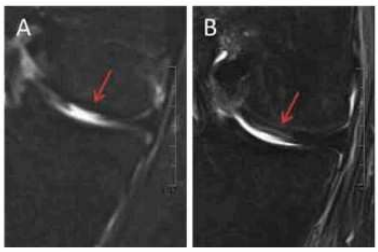


Fig.1. (A) Collection of a nasal cartilage biopsy from a patient, this procedure is performed under local anaesthesia and results in minimal donor site morbidity. (B) Biopsy of nasal cartilage septum. (C-D) Tissue engineered cartilage graft: macroscopic (C) and histological appearance (Safranin-O staining specific for sulfated glycosaminoglycans (D).

In the meantime, orthopaedic/trauma surgeons in Basel, under the guidance of Dr. Marcel Jakob, were thrilled by the possibility to use N-TEC for the repair of articular cartilage defects. We were initially afraid to use nasal chondrocytes to treat knee cartilage defects, in particular since eminent cartilage development biologists, including Dr. Charlie Archer from Cardiff, correctly warned us to consider the different embryologic origins of nasal vs articular chondrocytes (i.e., neuroectodermal vs mesodermal derivation). Several additional investigations were then carried out to assess the potential compatibility of NC with a joint environment. We first verified that NC are able to respond to physical forces resembling joint loading similarly to AC and, in collaboration with the group of Dr. Mauro Alini in Davos, we demonstrated that NC exposed to surface motion up-regulate molecules typically involved in joint lubrication (Candrian et al., 2008). After showing that N-TEC grafts efficiently recover from exposure to inflammatory cytokines typically present at a cartilage injury site (Scotti et al., 2012), we then addressed the fate and molecular compatibility of NC in experimental cartilage defects. Those studies, carried out in goat models in collaboration with Dr. Pierre Mainil-Varlet (at that time at the University of Bern) and Dr. Brigitte von Rechenberg (Uni-



C

	Pre-surgery	12 month post-surgery
MOCART		31.9 (5 – 55)
dGEMRIC (rel ΔR1)		1.40 (0.78 – 2.17)
IKDC	49.4	77.5
KOOS Pain	78.2	92.2
KOOS Symptoms	73.5	85.0
KOOS ADL	78.1	95.9
KOOS Sport/Rec	45.7	76.0
KOOS QOL	44.6	57.5

Fig. 2: MRI before (A) and 4 months after transplantation (B), displaying the maintenance of the graft or repair tissue at the defect site (red arrows). C Improvement of the IKDC and KOOS scores after 12 months of surgery (from n = 5 patients).

versity of Zürich) demonstrated the ability of NC to modify their biological positional memory, defined by their Hox gene expression, and to adopt their otherwise constitutive molecular identity to the environment of the implantation site. Possibly as a result of such plasticity, NC could directly contribute to the repair of the articular cartilage defects and resulted in superior outcome than AC, used as control (Pelttari et al., 2014).

Where are we now

Due to these encouraging results and the efficient continued interactions with the orthopedics and plastic surgery units in Basel, we resolved to test the safety and feasibility of implanting N-TEC grafts for the clinical treatment of traumatic articular cartilage injuries in the knee. So far 17 patients have been enrolled in this study (Clinical-trials.gov NCT01605201, Swissmedic TpP-I-2012-001) and 5 have reached the 12-month follow-up time. The early clinical observations indicate not only safety and feasibility of the procedure, but also promising results for efficacy of the treatment, as indicated by stability of the graft, dGEMRIC quantitative assessments, and improvement in clinical scores after 12 months (Fig. 2).

In order to extend efficacy data to larger patient numbers within a controlled, randomized study, we are preparing to initiate a multicenter phase II clinical trial (total of 108 patients), thanks to funding recently received by the European Union through the Horizon 2020 program (Project BIO-CHIP, http://biochip-h2020.eu). The study will involve 4 clinical centers (Dr. Marcel Jakob in Basel, Dr. Philippe Niemeyer in Freiburg, Germany, Dr. Giuseppe Peretti in Milan, Italy, and Dr. Alan Ivkovic in Zagreb, Croatia) to test the efficacy of treatment of traumatic cartilage lesions in the knee with N-TEC vs NC delivered from the same scaffold but without extensive pre-culture. This trial will formally test the hypothesis that maturation of the implanted cartilage graft will improve the clinical efficacy, leading to an increase of at least 10 points in the main primary outcome (i.e., the pain and functionality self-assessed score KOOS).

The pipeline

The organization of the trial, expected to start during summer 2016, is requiring extensive efforts not only in the harmonization of procedures but also in the acceptance of the same protocols by different ethical committees and national regulatory authorities. In parallel, a few lines of future investigations are being explored. For example, in the context of the European funded consortium BIO-COMET (http://www.biocomet.eu), we are advancing towards the manufacture of N-TEC in closed and automated bioreactor systems and testing their applicability in the setting of osteochondral lesions, using sheep as pre-clinical model. Moreover, we are planning to evaluate the use of N-TEC for the treatment of "kissing lesions" in a sheep model. The data generated from these animal studies would represent important steps towards the treatment of more challenging indications, with features typically associated with osteoarthritic degeneration.

Would NC and N-TEC find applications beyond reconstruction of the nose or of articular cartilage? In cooperation with the Spine Surgery unit in Basel, led by Dr. Stefan Schaeren, we have recently started a pioneering program to test the use of NC to revert degeneration of the nucleus pulposus of intervertebral discs. The scientific basis is still related to the extraordinary regenerative capacity and environmental plasticity of the very special cells residing in human septal cartilage, recently defined as the "pacemaker" for the growth of various skeletal structures (Hall et al., 2013).

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ICRS Journal Club

Bioreactors

By Prof. Martin J. Stoddart,
Albert-Ludwigs University Freiburg, Germany

Bioreactors offer exciting possibilities to partially recreate in vivo environments in vitro. Many publications describe experiments using custom built devices that are able to apply various combinations of perfusion, tension, uniaxial compression, multiaxial compression, and hydrostatic pressure. These can provide valuable data regarding initiation of chondrogenesis, maintenance of the chondrocyte phenotype and maturation of the developing tissue. Often, it can provide data that cannot be obtained under static conditions. I love bioreactors, I also hate them. When they work the data obtained can be amazing, but they break down. Sometimes a lot.

When the bioreactor works as planned, the problem later becomes, how can we compare the data obtained from different custom devices? This can start with the publications abstract and title. When searching for papers there are an increasing number of mechanobiology studies. Stating in the abstract «we applied cyclical load to chondrogenic samples for 1 hour a day» is not going to attract much attention as it is too vague. «We applied shear superimposed over uniaxial compression» is much more likely to attract the readers you want to attract. It is imperative that when describing novel devices in publications as much detail as possible should be provided on how it works and what exactly it does. This should also have then been validated before studies started. For example, if applying compression to a cartilage plug, does the frame remain rigid under load or does it flex? This will change the actual load applied when the apparent load is the same. Does each sample have a load cell or is one load cell being used to approximate the load from other samples? If each sample has a slightly different height does the machine compensate and if so how? A number of these questions can only be answered by performing repeated validation experiments prior to the actual study. This ensures the bioreactor behaves as you believe, providing much more confidence in the data obtained.

Tips on developing your own bioreactor:
Make sure you recognise the limits of the bioreactor, it is always an approximation and to some extent an artefact. When designing a new bioreactor, make sure the engineer and the biologist are speaking from day 1. On one occasion the engineer building a new device thought «sterile culture room» meant that the whole room was sterile. The first prototype was completely unusable.

Show the engineer exactly where the bioreactor needs to go, especially if it will be in an incubator with high humidity. Cell culture incubators have conditions that are extremely detrimental to many materials and components.

Clarify which parts need to be sterilized and reused, and which parts not. Which parts need to come into contact with culture medium? Explain what goes into the culture medium as it plays a major role in which materials can be used.

Detail the kind of experiments you want to do, which frequencies, which loads?

As bioreactors become more complex, they require more complex software and more crucially they break down more often. When considering what you want, you need to consider what support you will have to keep the machine running smoothly.

One-step surgery with minced cartilage to treat osteochondral defects. How does it work?

By S. Clockaerts, AZ Groeninge, Kortrijk, Belgium

Introduction

The established dogma that cartilage has no capacities for self–repair, may partly be due to the lack of chondrocyte outgrowth or migration from articular cartilage tissue in a cartilage defect . Autologous Chondrocyte Implantation is a cell based cartilage repair strategy that overcomes this problem through the direct delivery of culture-expanded chondrocytes. However, practical and financial issues remain regarding cell culture preparation and the challenges of a two-stage procedure.

The use of minced cartilage might be an alternative. The idea is to fragmentate cartilage mechanically before implantation in the defect, thereby increasing tissue surface area and thus outgrowth or migration of chondrocytes[ii].

Techniques

Two main concepts have been described: the use of freshly harvested autologous chips that are placed in the defect and held by a scaffold (Cartilage Autograft Implantation System (CAIS; DePuy/Mitek, Raynham, MA)), and the use of Particulated Juvenile Allograft Cartilage (PJAC; DeNovo Natural Tissue ISTO, St. Louis, MO)[iii] that is fixed with fibrin glue.

1) With CAIS, cartilage is harvested from a low weight bearing area such as the lateral ridge of the trochlea. The amount of cartilage needed is similar to ACI (± 200 mg). The cartilage is minced into peaces of 1-2 mm, dispersed on a biodegradable scaffold (polycaprolactone – polyglycolic acid – polydioxanone mesh) and secured with fibrin glue. The cartilage defect is approached through a small arthrotomy, debrided and the edges are smoothened. The scaffold is then positioned in the defect and fixed with bioabsorbable staples[iv].

CAIS was already described in 1983 by Albrecht et al in a rabbit model with a hyaline like repair in the treatment group compared to no cartilage formation in the untreated group[v]. It was then left dormant until in vitro and in vivo studies on this topic were published between 2006 and 2013. These papers confirmed the potential of CAIS and the hyaline like repair with outcomes comparable or even better than Autologous Chondrocyte Implantation [3] [vi] [vii] [viii] [ix] [x]. Recently, an animal study on minipigs demonstrated improved fibrocartilage formation when adding autologous cartilage chips to autologous bone graft in the defect[xi]. These studies confirm the concept of chondrocyte outgrowth enhancement by mincing the cartilage.
The first clinical trial on CAIS was performed by Cole et al in 2011 based on a study group of 29 patients. Although MRI results at 24 months were similar for the microfracturing group and the CAIS group, they noted more intralesional osteophytes in the microfracturing group. IKDC and KOOS were significantly higher in the CAIS group[4].

2) Juvenile allograft fragments (PJAC) can be placed in the prepared defect through a small arthrotomy or arthroscopically[xii], and fixed in situ with fibrin glue. Alternative is to copy the shape of the defect in a sterile foil, add fibrin glue and add the particulated juvenile cartilage fragments. When the fibrin glue is solid, the created construct can then be placed into the defect[xiii].
Good results were reported in clinical follow up studies with PJAC so far [xiv] [xv] [xvi] [xvii].
As with other cartilage repair techniques, some technical issues remain to be resolved. The main issues are discussed here.

CAIS or PJAC?

Bonasia et al compared juvenile fragments with adult and mixed adult/juvenile both fragments in vitro and in vivo [4] [xviii], and found that mixed juvenile/adult fragments gave better results than adult fragments alone. Young chondrocytes have better gene profiles for cartilage repair, and have increased metabolic activity, cell density and proliferation rate than the adult chondrocytes [xix]. PJAC also has the advantage of no donor site morbidity and is a solution for larger cartilage defects where large amounts of chondrocytes are needed.

Although the superior in vitro results with juvenile cartilage could indicate that PJAC is a more appropriate technique, good results have also been noted with CAIS. This might be explained by a process of 'transitory rejuvenation', in which migrating adult chondrocytes undergo mitogenic activation and seem to shift toward a motile and proliferative phenotype [5] [9] [xx] [xxi]

Fragment size and fixation method?

A study by Bonasia et al in 2015 showed that the more fragmented grafts (fragments smaller than 1 mm, 'cartilage paste') lead to a more optimal extracellular matrix production [20]. However, the cartilage paste needs to be uploaded on a scaffold to provide stability. This requires more preparation and is technically more demanding, which can be seen as a disadvantage for some surgeons. The alternative is the use of larger cartilage fragments that can easily be fixed with fibrin glue, but these fragments would lead to a less optimal matrix production. In addition, although it has been stated that the chondrocytes are able to migrate into the fibrin glue and form new cartilage, this concept has recently been contradicted by Andjelkov et al, who showed that there is no migration of the chondrocytes in the fibrin glue in vitro. It is, however, possible that in the in vivo situation, fibrinolysis by endogenous fac-

tors occurs and thus allows the migration of the chondrocytes in the fibrin glue[xxii].

Adding growth factors

The addition of growth factors such as Granulocyte - Colony Stimulating Factor to enhance chondrocyte characteristics might be an option to improve chondrocyte characteristics in minced cartilage. Further research on this topic is needed[19].

In conclusion, the use of particulated cartilage seems to be a very promising technique with good first clinical outcomes reported. Underlying mechanisms of action need to be elucidated and further clinical studies should be performed to confirm its efficacy and to compare this technique with ACI. Surgical indication (defect size, shape, containment) and the influence of patient factors should be investigated.

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Case report

Chondral Fracture

By Michael Iosifidis & Ioannes Melas

It is presented a case of delayed treatment of a chondral fracture in the knee of a preadolescent footballer by re-fixation of the avulsed fragment using a biodegradable implant.

A boy aged 12 years and 3 months was referred to our unit due to persistent pain and mechanical symptoms in his left knee after a sports (football) injury around 4 months prior to presentation. On physical examination, the patient had mild effusion and painful limitation of the range of motion of his left knee joint.

A magnetic resonance imaging (MRI) scan of the affected knee revealed a large chondral fracture involving the anterior surface of the lateral femoral condyle with the avulsed fragment freely floating in the suprapatellar pouch [Figure 1].

Following initial evaluation, the patient underwent arthroscopy of his left knee. An articular cartilage defect measuring 2 x 1 cm was located in the anterior lateral femoral condyle [Figure 2], whereas a corresponding chondral loose body was identified and retrieved from the lateral gutter [Figure 3]. The tissue covering the surface area of the defect was removed, exposing the subchondral bone, where microfractures were performed in order to promote healing by means of marrow stimulation. Through lateral arthrotomy the avulsed cartilaginous fragment was subsequently reduced and fixed in its original position, filling the defect, by the use of a biodegradable interference screw 5 mm diameter and 15 mm length (ConMed Linvatec, Largo, FL, USA) [Figure 4]. The patient has had an uneventful postoperative course and made a complete recovery, resuming his sports activities in full and without any complications.
An MRI scan performed at his 1 year follow up visit showed evidence of healing of the chondral fracture [Figure 5].

The current case adds to a rather small body of literature reporting on the reduction and fixation of isolated fractures of the articular cartilage in the skeletally immature knee [1-5]. Nonetheless, this case is unique in that the outcome was successful, although there was an interval of about 4 months between the time of injury and that of surgery. The chondral fragment ("lose body") proved to be the best graft option for the young boy even after several months from the injury.

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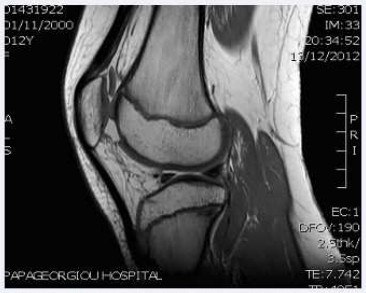

Figure 1. Preoperative MRI image showing a defect in the articular cartilage of the anterior lateral femoral condyle, as well as a corresponding chondral loose body floating in the suprapatellar pouch.

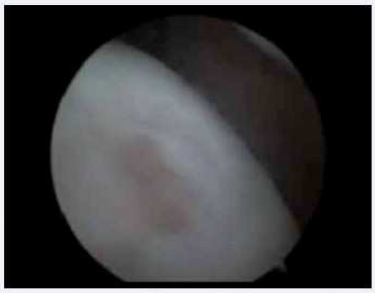

Figure 2. Arthroscopic image of the chondral defect located in the anterior surface of the lateral femoral condyle.

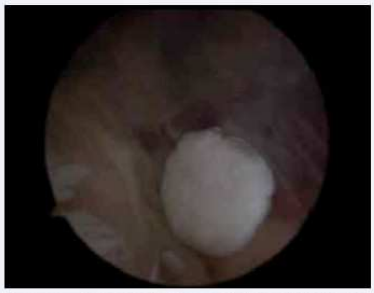

Figure 3. Arthroscopic image of the cartilaginous loose body (avulsed fragment) found in the lateral gutter.

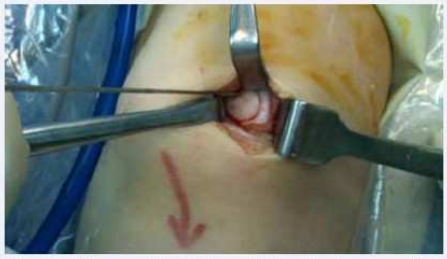

Figure 4. Intraoperative photograph showing temporary fixation of the reduced chondral fragment in its original position using a K-wire.

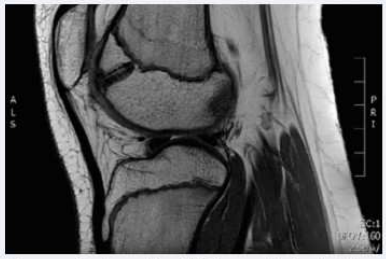

Figure 5. Postoperative MRI image obtained at the 1 year follow up visit showing healing of the chondral fracture.

3D printing

By Marcy Zenobi-Wong and Michael Müller
www.cartilage.ethz.ch

3D printing of plastics and metals has begun to revolutionize diverse industries ranging from automotive to preoperative surgery planning. In medical and health applications, additive manufacturing of dental implants and hearing aids has become standard practice. Bioprinting, however, which uses inks containing living cells to produce cellular grafts, is a nascent technology with much promise but no clinical products to date. Excitement for bioprinting is shared by many in the ICRS community who look for novel treatments for conditions with no good surgical options: i.e.large osteochondral lesions in highly-contoured, hard-to-access sites. The workflow to generate computer models from medical imaging data is fairly well-established and available through companies like Materialise. The workflow begins with the production of a 3D model from DICOM data and uses software to slice the model and produce printer 'driving directions' (G code). For bioprinting, however, the lack of materials or bioinks with sufficient mechanical and biological for use in osteochondral grafts remains a huge challenge for the field.

Our laboratory at ETH begin its bioprinting journey in 2012 with the purchase of the BioFactory from the Swiss company regenHu. At that time there were no bioinks on the market and the company used Nivea hand cream for their demonstrations and training sessions. Since those early years, the field has learned much about how rheology can predict which materials will print well. Critical for a good extrusion bioink is shear thinning behavior, a property which describes the drop in viscosity of a polymeric solution with increasing shear rate. Ideally, such a material also has a yield point rather than zero shear viscosity and will therefore never flow unless sufficient force is applied. The material's shear recovery behavior, which describes how fast the material regains its initial properties after shear, helps determine the accuracy of the extruded material after deposition.

Another critical step was the discovery of a few tricks which rendered materials, which could not be printed due to their low viscosity, at once printable. For instance, low viscosity materials could be effectively locked into position by mixing them with thermoresponsive polymers. After crosslinking, the transient material could be eluted simply by lowering the temperature. Another finding was the addition of viscosity enhancers such as nanofibers to low viscous solutions, giving them desirable rheological properties such as yield behavior and shear thinning. Recently, we have developed cartilage bioinks which are printable, biocompatible and use unmodified, generally recognized as safe materials, thus easing translation of cartilage printed grafts to the market. As an outlook, we are working towards more functional biomimetic bioinks. We and others are exploring the addition of extracellular matrix components such as BioCartilage, growth factors and morphogens into the inks, thereby incorporating more of the complexity of the matrisome.

The extrusion of the bioink takes place additively, i.e. in a line-by-line and layer-by-layer manner. 3D bioprinting can have very good fidelity to the model, however, the process has several potential limitations including alterations of the cell phenotype by shear forces and introduction of material defects into the structure from the printing process. The effect of all of these parameters on the final function of the graft must be quantified before clinical use can even be considered. Recently, we have introduced guidelines for bioprinting which we hope will help the field to standardize the evaluation of inks and printing processes (Kesti et al, 2016, BioNanomaterials).

Cartilage is a tissue whose function is defined by its shape, surface contours, zonal organization, and gradient of material properties. Intuitively, 3d printing of models generated from CT and MRI data has the capacity to fabricate anatomically accurate grafts for treating complex cartilage lesions. Indeed, given sufficient progress on the side of polymer chemists, material scientists and biologists, the chance is good that cartilage will be one of the first successful bioprinted products to reach the market. The tissue's avascularity, single cell type and structural nature are all significant advantages compared to more complex metabolically active tissues and organs whose shapes have little or no relationship to their function.

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2500 print copies & 7000 electronic distribution
Newsletter release in July and December
All ICRS Members receive a complimentary copy of the ICRS Newsletter

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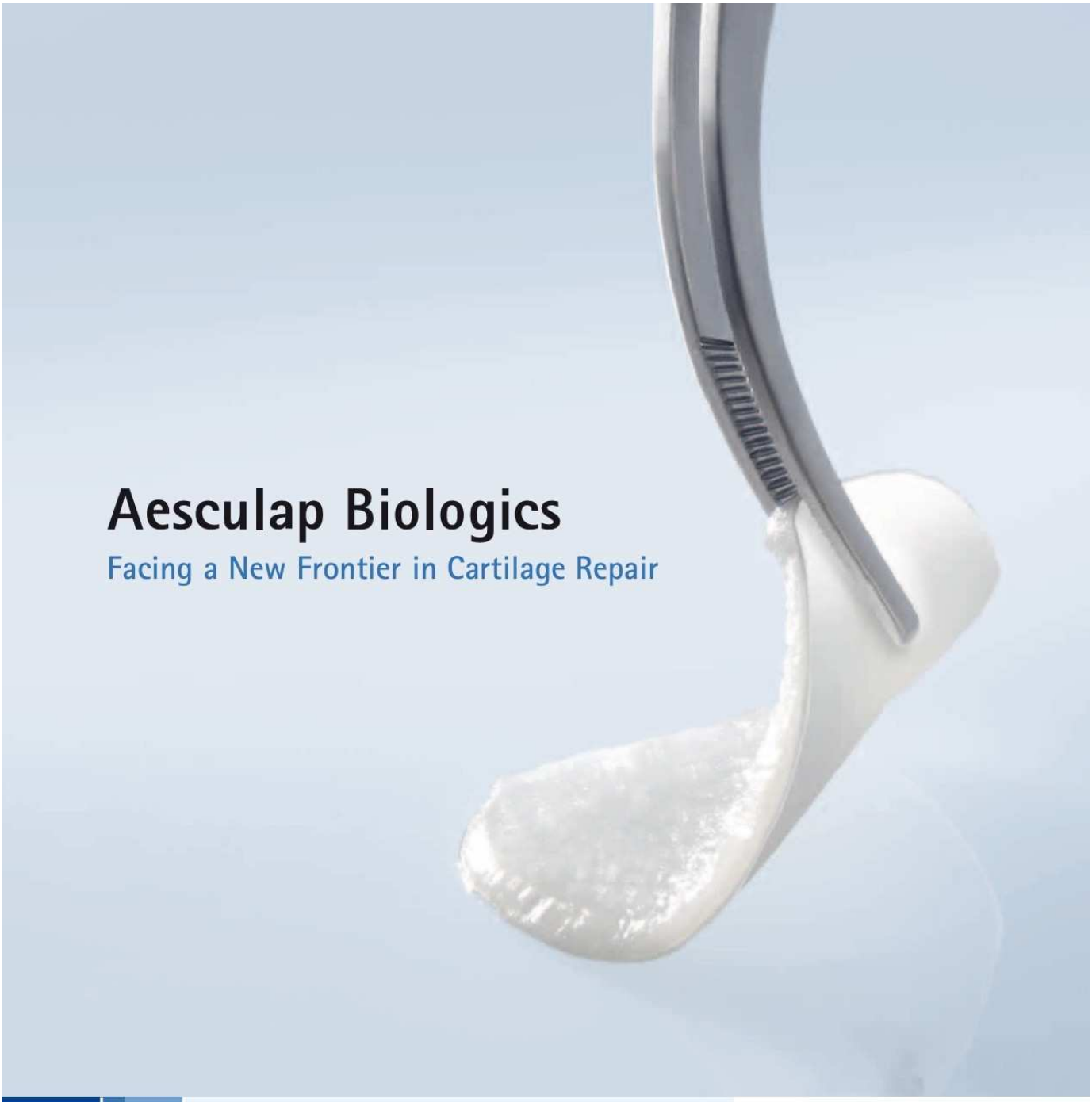

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