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UNIVERSIDAD CATÓLICA
DE MURCIA

FESTIVIDAD DE SAN ANTONIO DE PADUA

Ceremonia de Investidura como Doctor Honoris Causa del

Dr. D. Stephen P. Abelow

Director de la Clínica de Traumatología del Deporte de Lake Tahoe
(Nevada, USA)

Templo del Monasterio de Los Jerónimos
Murcia, 12 de junio de 2015

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ÍNDICE

LAUDATIO DEL PROFESOR DR. PEDRO GUILLÉN GARCÍA EN LA INVESTIDURA COMO DOCTOR HONORIS CAUSA DEL DOCTOR D. STEPHEN ABELOW

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Templo del Monasterio de Los Jerónimos
Murcia, 12 de junio de 2015

Excelentísimo Presidente de la Universidad Católica San Antonio de Murcia,

Su Eminencia Reverendísima Cardenal Antonio Cañizares Llovera, Arzobispo de Valencia.

Excelentísima y Magnífica Rectora de esta Universidad,

Excelentísimo y Reverendísimo Señor Obispo de la Diócesis de Cartagena,

Excelentísimas e Ilustrísimas Autoridades Académicas, Eclesiásticas, Civiles y Militares.

Claustro de profesores, personal de administración y servicios, alumnos e invitados a este solemne acto académico.

Hoy es un día grande y gozoso para la UCAM y además especialmente festivo, pues con sus mejores galas recibe como Doctor Honoris Causa al eminente cirujano ortopédico D. Stephen Abelow de Nevada (USA). Agradezco a nuestro Presidente, el Excmo. Sr. D. José Luis Mendoza y a nuestra Magnífica Rectora, Dña. Josefina García, primero que aceptaran la candidatura que desde la Cátedra de Traumatología del Deporte hicimos, y segundo por la deferencia de invitarme para que haga su Laudatio.

Me cabe el honor de contarles la vida profesional del Doctor Honoris Causa, de uno de los más brillantes cirujanos ortopédicos de USA en el campo de la Traumatología del Deporte, y que tiene la gran particularidad de haber estudiado en España, en la Universidad Complutense de Madrid. Posteriormente vuelve a su país para realizar la especialidad de Cirugía Ortopédica y Traumatología. Siempre ha sido un enamorado de España y de sus costumbres.

Gracias Presidente y Rectora.

A continuación comentaré de forma breve la vida profesional de D. Stephen Abelow.

Querido Profesor y amigo D. Stephen Abelow, es un gran honor para mí hacer el Laudatio de tu Investidura como Doctor Honoris Causa de la Universidad Católica San Antonio de Murcia.

"Por sus méritos" es lo que significa la expresión latina DOCTOR HONORIS CAUSA. Se concede a modo honorífico y es el título de máximo prestigio de una universidad, en reconocimiento a los méritos personales y profesionales.

Nació en Brooklyn, New York, USA, en mayo de 1946 cuando ardía en llamas Europa con ocasión de la Segunda Guerra Mundial. Casado y con tres hijos, y su esposa María, nos acompaña.

Estudios realizados:

- Escuela Superior (High School): Oceanside High School 1960-1964, Oceanside, Long Island, NY.
- Universitario (College): Boston University 1964-1968 (Bachelor of Arts) Boston, Massacusetts.
- Universidad de Madrid, Facultad de Medicina: 1969-1971 (Años preclínico).
- Medical Doctor Degree (M.D.) Mayo de 1974. Hahnemann Medical College Philadelphia, Pennsylvania (número 3 en USA en estos años).
- Internship: Hahnemann Medical College Hospital, Philadelphia, 1975, General Surgery.
- Orthopaedic Surgery Residency: Tufts New England Medical Center, Boston 1978.
- Diplomated American Board of Orthopaedic Surgery, Julio de 1984.

Tras realizar su especialidad en Cirugía Ortopédica y Traumatología (COT), visita los mejores centros médicos de Patología del Aparato Locomotor de USA (Boston University, Hahnemann Medical College Philadelphia, Tufts New England Medical Center, Boston) teniendo como profesor al Dr.

Steadman y finalmente ejerció su especialidad en el "Lake Tahoe Sports Medicine Center" South Lake Tahoe, California, USA, siendo el Director Médico. Allí atendió a los más destacados deportistas americanos de la nieve y llegó a ser consultor en Traumatología del Deporte.

Hacía veinte años que dejó España y cuando ya era un prestigioso cirujano ortopédico, nos encontramos en San Francisco con ocasión de un congreso médico sobre el uso del laser en ortopedia. ¡Se le había olvidado el español! Pronto surgió su admiración por España y desde entonces, nos visita tres-cuatro veces al año, informándonos de los últimos avances en cirugía ortopédica en su país. Es consultor extranjero en COT de Clínica CEMTRO.

Excelente cirujano, excelente compañero, excelente persona y excelente degustador de todo lo español. Embajador en USA y resto del mundo de nuestros logros médicos. Su estado de alerta en medicina y su pasión por la investigación, hacen del Dr. Abelow uno de los más prestigiosos conferenciantes en el mundo de la ortopedia.

Tras estos breves comentarios sobre su formación humana y profesional, remarcamos los siguientes méritos médicos:

- Es Presidente de Medicina Deportiva y Artroscopia de la SICOT (Sociedad Internacional de Cirugía Ortopédica y Traumatología).

- Tesorero del Fundación SICOT

- Profesor Clínico de Ortopedia Deportiva y Traumatología de la Clínica CEMTRO.

- Profesor Honorífico de Medicina y Traumatología Deportiva de la Universidad Católica San Antonio de Murcia.

- Director Médico del Lake Tahoe Sports Medicine Center, South Lake Tahoe, California.

- Miembro del ICRS (International Cartilage Repair Society).

- Miembro del American College of Utilization Review Physicians.

- Certirfied American Board of Quality Assurance & Utilization Review: 1986. Recertified November 1999, 2002, 2005.

- Certified, American Board of Independent Medical Examiners: 1997. Recertified October 2003.

Publicaciones/Presentaciones

- Matrix autologous chondrocyte implantation of the patella from ACI to MACI to ICC in the patellofemoral joint. Springer Verlag, 2014.

- Osteochondral lesions of the talar dome: New horizons in cartilage replacement in AANA advanced arthroscopy, the foot and ankle. 2010.

- Increasing the dose of autologous chondrocytes improves articular cartilage repair: Histological and molecular study in the sheep animal model (co-author). Cartilage 2014.

- Arthroscopic delivery of matrix-induced autologousj chondrocyte implant: International experience and technique recommendation (co-author). Cartilage 2012.

- Arthroscopic technique for matrix-induced autologous chondrocyte implantation for the treatment of large chondral defects in the knee and ankle, operative, techniques in orthopedic, articular cartilage surgery. Elsevier. October 2006.

- The future of management of articular cartilage injuries: Gene therapy and cartilage repair (co-author), in Journal of Sports Physical Therapy, fall 2006.

- Use of lasers in arthroscopic surgery in advanced arthroscopy. Springer-Verlag, 1999.

- Laser-assisted capsular shift for multidirectional instability of the shoulder. Techniques of Sports Medicina, Octobrer, 1997.

- Overview of current laser use in orthopedics in the United States: And arthroscopic laser surgery clinical applications. Springer-Verlag. 1995.

- Use of lasers in Meniscal surgery. In Current Techniques & Arthroscopy, J. Serge Parsien, Editor, 1996.

- Use of lasers in orthopedic surgeon surgery. Orthopedics, Mayo 1993.

- Orthopedic grand rounds: Use of lasers in orthopedic surgery. A) Universiry of California Davis, Sacramento Medical Center, 1991. B) New England Baptist Hospital-Boston, MA, December 1991. C) Tufts New England Medical Center-Boston, MA, April 1992.

- Holmium laser. American Academy of Orthopaedic Surgeons Instructional Course, Richmond, VA, October 1992.

- CO2 laser. American Academy of Orthopaedic Surgeons Instructional Course, Richmond, VA, October 1992.

- Use of lasers in arthroscopic surgery: Current concepts, Sympoisum, Arthroscopy Association of North America, Boston,MA, April 1992. Complications and cost analysis of laser surgery, Arthroscopy Association of North America, Desert Springs, CA, April 1993.

- Future of lasers in orthopedic surgery. International Society of Laser Medicine & Surgery, Anaheim, CA, December 1991.

- Use of Holmium laser in knee arthroscopy. International Society of Laser Medicina & Surgery, Anaheim, CA, December 1991.

- Laser-assisted endoscopic carpal tunnel release. Instructional Course, orthopaedic Laser Society of North America, October 1991, December 1991, March 1992.

- Faculty, San Diego Shoulder Arthroscopy (James C. Esch),M.D., San Diego, CA, 1987-2010. Laboratory Director, 1998-2003.

- Faculty, Endoscopic Anterior Cruciate Ligament Reconstruction, Laguna Hills, CA, July 1990, July 1992, November 1993.

- Faculty, Endoscopic Carpal Tunnel Release, Laguna Hills, CA, May 1991, October 1991.

- Faculty, Shoulder Arthroscopy, Laguna Hills, CA, September 1989, May 1991, June 1992, march 1993, November 1994, November 1995, October 1996, November 1997, October 1998, October 1999, October 2000-2006, Decembre 2007, October 2008-14.

- Faculty Orthopaedic Laser Society of North America Instructional Course, October 1991, December 1991, March 1992.

- Ski Doc. Column, Starting Gate (weekly sports medicine article in the professional ski racing newspaper), 1986-1999.

- Faculty, Shoulder Controversy / Shoulder Arthroscopy, September 2014, Laguna Hills, CA.

- Faculty, Shoulder Arthroscopy, AANA Motor Skills Workshop, 1992-2005

- Faculty, Elbow Arthroscopy, AANA Motoer Skills Workshop, November 1996-2000.

- Faculty, Ankle Arthroscopy, AANA Motor Skills Workshop, November 1998-2007.

- Associate Master Instructor, The Masters Experience/Shoulder, AANA Orthopedic Learning Center, Rosemont,IL, 1994, 1995, 1996 (2) 1997 (2), 1998, 1999(2) 2000, 2001, 2002 (Master Instructor 2), 2003, 2004.

- Master Instructor, The Masters Experience/Knee, AANA Orthopedic Learning Center, Rosemont, IL, September 2000.

- Master Instructor, The Masters Experience/Shoulder, AANA Orthopedic Learning Center, Rosemon, IL, June 1998, July 2002.

- Associate Master Instructor, The Masters Experience/Ankle, AANA Orthopedic Learning Center, Rosemont, IL, October 1996-2009.

- Use of lasers in arthroscopic shoulder surgery. Shoulder Arthroscopy, San Diego, CA, June 1994.

- Use of lasers in shoulder arthroscopy. California Orthopedic Association Annual Meeting, Squaw Valley, CA, May 1994.

- Use of 1.44 >MD:YAG laser in small joint arthroscopy. Philadelphia, PA, January 1994.

- Complications of laser surgery. American Society of Laser Medicine & Surgery, San Diego, CA, April 1995.

- Lasers for shoulder instability. Shoulder Arthroscopy. 1995 San Diego, CA, June 1995-1996.

- Laser controversies. Instructional Course Lecture, Arthroscopy Association of North America Annual Meeting, San Diego, CA, April 1997.

- Laser controversy. Instructional Course Lecture, Arthroscopy Association of North America.

- Use of lasers for multidirectional instability. Shoulder Arthroscopy in 1997, San Diego, CA, June 1977.

- Thermal modification of capsular tissue for shoulder instability. Shoulder Arthroscopy 1998, San Diego, CA, June 1998.

- Use of laser in shoulder arthroscopy. SICOT Sidney, Australia, April 1999.

- Thermal modification of capsular tissue for shoulder instability. 1999 Instructional Course, ISAKOS, Washington DC, May 30, 1999.

- Co-chairman, Lake Tahoe Knee & Shoulder Sports Medicine Update, December 1996-2000 (500 participants, international faculty of 50).

- Thermal controversies in shoulder arthroscopy. Instructional Course Lecture, AANA Annual Meeting, Miami, FL, April 2000.

- Use of thermal energy in the ankle. Instructional Course Lecture, AANA Annual Meeting, Miami, FL, April 2000.

- Complications in anterior cruciate ligament surgery: How to avoid them. International Knee Symposium, Madrid,Spain, January 2002.

- Fracture lateral process of talus in snowboarders. International Ankle Congress, Madrid, Spain, November 2002.

- Thermal modification for chronic ankle instability. International Ankle Congress. Madrid, Spain, November 2001.

- How I do my ACL-my favorite technique. International Knee Symposium, Madrid, Spain, January 2003.

- ACL reconstruction in children with open physes (skeletally immature). Congress of Pediatrics Sports Training, Murcia, Spain, March 2003.

- Ski an snowboard injuries in the immature athlete. Congress of Pediatrics Sports Training, Murcia, Spain, March 2003.

- Moderator. Current concepts and use of laser, RF and other wavelengths in orthopedic surgery. SICOT International Meeting, San Diego, CA, August 2002.

- Use of RapidLoc Meniscal repair system. International Knee Symposium. Madrid. Sapin, January 2002.

- Treatment of cartilage lesions in the athlete´s knee. Keynote Address, European Federation of Orthopaedic Sports Traumatology (EFOST), March 2004.

- Matrix autologous chondrocyte implantation for large chondral defects of the knee and ankle. American Orthopaedic Society for Sports Medicine Annual Meeting, Keystone, CO, July 2005.

- Matrix autologous chondrocyte implantation for large chondral defecfts of the knee and ankle. Current treatment of cartilage defects in the athlete´s knee. American Orthopaedic Society for Sports Medicine Course, Rosemont, IL, August 2005.

- Matrix autologous chondrocyte implantation for large chondral defects of the knee and ankle. AANA, Vancouver, British Columbia, Canadá, May 2005.

- Knee lab instructor, American Orthopaedic Society for Sports Medicine, Rosemon, IL, August 2005.

- Moderator. Meniscus Symposium, SICOT Triennial Meeting, Istambul, Turkey, September 2005.

- Arthroscopic technique for shoulder instability repair, what´s new in orthopedic surgery. Madrid, Spain, November 2005.

- Current treatment of chondral defects of the knee. International knee Symposium, Madrid, Spain, January 2006.

- Avoiding complications and pitfalls of anterior cruciate ligament surgery. International Knee Sympoisum. Madrid. Spain. January 2006.

- Second and third generation treatment of chorndral injuries, the Swedish experience, Spanish experience, Italian experience and American experience. Instructional Course lecture. Moderator. American Orthopaedic Society of Sports Medicine. Hershey, PA, July 2006.

- Membrane/matrix autologous chondrocyte implantation for large chondral defects of the knee and ankle. Instructional Course Lecture, American Orthopaedic Society of Sports Medicine, Hershey, PA, July 2006.

- Current treatment of cartilage lesions. Curso de Verano. University Rey Juan Carlos, Aranjuez, Spain, July 2006.

- Treatment of anterior cruciate ligament injuries. SICOT International Symposium. Buenos Aires, Argentina, August 2006.

- Meniscus repair techniques. SICOT Internation Symposium, Buenos Aires, Argentina, August 2006.

- Collagen meniscus implantation. SICOT Internation Symposium, Buenos Aires, Argentina, August 2006.

- Allograft meniscal implantation. SICOT Internation Symposium, Buenos Aires, Argentina, August 2006.

- Membrane/matrix-induced autologous chondrocyte implantation for large chondral defects of the knee. Arthroscopy Association of North America, Masters Experience, Cartilage, Rosemont, IL, September 2006.

- Membrane/matrix-induced autologous chondrocyte implantation for large chondral defects of the ankle. Arthroscopy Association of North Americ, , Masters Experience, Cartilage, Rosemont, IL, October 2006, September 2007, September 2008, September 2009.

- Anterior cruciate ligament reconstruction, 3o years´ experience and current concepts, "Visiting Professor, Northwestern University, October 2006.

- Current and future treatment of cartilage defects of the knee and ankle. Wavering Lecturer, Northwestern University School fo Medicine, Chicago, IL, October 2006.

- Current treatment of chondral injuries of the knee and ankle. Internationel Tissue Engineering Symposium, Madrid, Spain, November 2006.

- Artroscopic technique for multidirectional shoulder instability, what´s new in orthopedic surgery. Madrid, Spain, November 2006.

- Treatment of chondral defects of the knee. International Knee Symposium, Madrid, Spain, January 2007.

- ACL reconstruction. International Knee Symposium, Madrid. Spain, January 2007.

- Meniscal allograft transplantation. International Knee Symposium. Madrid, Spain, January 2007.

- Regenerative cartilage techniques in the shoulder- Arthroscopy Association of North America Annual Meeting, Instructional Course Lecture. Non-prosthetic Treatment of Shoulder Arthritis. San Francisco, CA, April 2007.

- New arthroscopic treatments and instrumentarion for autologous chondrocyte implantation, podium presentation, Arthroscopy Association of North America Annual Meeting, San Francisco, CA, April 2007.

- Wireless arthrosocopy, presentation at Arthroscopy Association of North America Annual Meeting, San Francisco, CA, April 2007.

- Matrix-induced autologous chondrocyte implantation in the knee, arthroscopic techniques. ISAKOS Annual Meeting, Florence, Italy, May 2007, Osaka, Japan, April 2009.

- Associate Master Instructor, Knee & Shoulder Arthroscopy Association of North America, Master Experience, AANA Learning Center, Rosemont, IL, December 2009.

- New advences in the treatment of cartilage, lesions in the knee and ankle osteochondral transfer. ACI, MACI, AANA Masters Experience, Senior Residents and Fellows, Rosemont, IL, December 2009.

- Arthroscopic membrane/matrix autologous chondrocyte implantation (MACI), emerging cartilage technologies in Europe. St. Joseph´s Hospital, Stockton, CA, October 2009.

- Arthroscopic membrane/matrix autologous chondrocyte implantation for treatment of large osteochondral defects of the knee. SICOT, Gothenburg, Sweden, 2010.

- Athroscopic membrane/matrix autologous chondrocyte implantation for treatment of large osteochondral defects of the knee. International Cartilage Repair Society, Miami, FL, May 2000.

- Arthroscopic membrane/matrix autologous chondrocyte implantation for treatment of large osteochondra defects of the knee. International Cartilage Repair Society, Sitges, Spain, September, 2010.

- Reconstruction of anterior cruciate ligament with autologous fibroblast or mesenchymal cells seeded on a type 1/3 collagen membrane. Western Orthopaedic Association, Honolulu. HI July 2011.

- Arthroscopic membrane/matrix autologous chondrocyte implantation for the treatment of large osteochondral defects of the knee. SICOT International Meeting, Prague, Czechoslovakia, September 2011.

- ACL and allograft state of the art in the USA 2011. International Knee Symposium, Madrid Spain, January 2011.

- ACL and meniscus state of the art in the USA 2012. Clinica CEMTRO, 11th International Practical & Theoretical Course of the knee, January 2012.

- Cartilage regeneration. 12th International Cartilage Symposium, Madrid, Spain, Clinica CEMTRO, November 2012.

- New treatment for articular cartilage regeneration. Internatioanl Cartilage Regeneration Symposium, Clinica CEMTRO, Madrid, Spain, Novmeber 2013.

- Orthobiologics in the shoulder, PRP. November 16, 2012, 11th International Orthopaedic Advances Symposium, November 2012. Madrid, Spain.

- Osteochondral allograft. SICOT Orthopaedic World Conference, November 2012. Dubai.

- Cartillage update. SICOT Orthopaedic World Conference, November 2012. Dubai.

- Orthobiologics of the shoulder and PRP. SICOT International World Conference. Dubai 2012.

- Osteochondral allograft. SICOT Orthopaedic World Conference October 2013. Hyderabad. India.

- Cartilage regeneration. SICOT/SBOT International Meeting, Rio de Janeiro. Brazil. November 2014.

- Cartilage regeneration. International Surgical Research Association, Rio de Janeiro, Brazil, November 2014.

- ACL, my favorite technique. SICOT/SBOT International Congress, Rio de Janeiro. Brazil. November 2013.

- Autologous chondrocyte implantation/arthroscopic technique. VuMedi, February 14, 2012.

- PRP/PRGF farct of fiction, Shoulder Controversy. Napa, CA 2011.

- Moderator, Cartilage Debate, ISAKOS, Toronto, Canada 2013.

- New advances in cartilage treatment. BrazilianOrthopaedic Trauma Society (SBOT), Rio de Janeiro, Brazil, November 2014.

- Faculty, International Knee Symposium, Clinica CEMTRO, January 2015.

Community Functions:

- Board of Directors, Barton Memorial Hospital, South Lake Tahoe, CA, 1987-1997.

- Board of Directors, South Lake Tahoe Rotary, 1990-1991

- Board of Directors, Tahoe Human Services, 1985-1992

- Honorary Board of Directors, Tahoe Human Services, 1993-present

- Member, South Lake Tahoe Rotary, 1986 to 2015 (present)

Employment History: (Vida Laboral)

- Owner, Lake Tahoe Sports Medicine Center, continuously employed 1979 to present.

- Partner, Lake Tahoe Orthopedic Institute, January 1998 to Mayo 2002 (retired).

- Owner, Elite Evaluations Medical Group, 1988 to present.

- Clinical Professor, Orthopaedic Sports Traumatology, Clinica CEMTRO, Madrid, Spain (working on third and fourth generation cartilage implantation techniques) Mayo 2002 to present.

- Professor, Orthopaedic Surgery & Sports Traumatology, HON, Universidad Católica San Antonio, Murcia, Spain. Clínica CEMTRO Madrid Spain 2003.

- Chairman, Arthroscopy & Sports Medicine, Internationl Society of Orthopedic Surgery & Traumatology (SICOT), 2011-present.

- Treasurer, SICOT Foundation, 2011-present.

Su preparación en el campo de la Cirugía Ortopédica es tan extensa y conocida que las más importantes sociedades de la especialidad le encargan que dicte cursos prácticos de enseñanza sobre patología del hombro, rodilla, tobillo y sobre la aplicación de los cultivos de condrocitos autólogos en las lesiones condrales.

También ha dirigido un Máster Instructor para la AANA en Artroscopia de rodilla y hombro y como Instructor Asociado Master para la artroscopia de tobillo. Dicta cursos a los doctores en formación sobre Artroscopia en las grandes Sociedades Médicas como AOSS, AANA, SICOT, ISAKOS, ICRS y en congresos de cualquier país le solicitan para cursos prácticos de artroscopia y traumatología deportiva.

Es importante señalar que en los últimos años dedica gran parte de su tiempo a la investigación sobre el cultivo celular de condrocitos, parcela de la que es un consumado especialista.

Tras leer su extensa vida académica, su amplia actividad asistencial, su gran capacidad como docente y por último su viraje a la investigación entenderán que nos encontramos ante uno de los más destacados de la cirugía ortopédica.

Como pueden comprobar su Currículum Vitae está repleto de méritos para merecer la gran distinción de Doctor Honoris Causa de la UCAM.

El tema que va a exponer es:

"Aportación de los Cultivos Celulares (Condrocitos) a las articulaciones dañadas"

Por todo lo expuesto y en reconocimiento a sus méritos, solicito se proceda a investir al Doctor Stephen Abelow, del grado de "Doctor Honoris Causa" por la Universidad Católica San Antonio de Murcia.

"His de causis, peto gradum, Doctoris Honoris Causa Domino Stephen Abelow"

Discurso de Investidura como Doctor Honoris Causa de la Universidad Católica San Antonio de Murcia

"Aportación de los Cultivos Celulares (Condrocitos) en las Lesiones de las Articulaciones Dañadas

REGENERACIÓN DEL CARTÍLAGO. Desde ACI a MACI y desde ICC a IPC"

Stephen P. Abelow, M.D., F.A.C.S

Murcia, 12 de junio de 2015

Saludos y Palabras de Agradecimiento.

- Excelentísimo Presidente de la Universidad Católica San Antonio de Murcia, D. José Luis Mendoza.

- Su Eminencia Reverendísima Cardenal Antonio Cañizares Llovera, Arzobispo de Valencia.

- Excelentísima y Magnífica Rectora de esta Universidad, Dña. Josefina García.

- Excelentísimo y Reverendísimo Señor Obispo de la Diócesis de Cartagena.

- Excelentísimas e Ilustrísimas Autoridades Académicas, Eclesiásticas, Civiles y Militares.

- Claustro de profesores, personal de administración y servicios, alumnos e invitados a este solemne acto académico.

Ser nombrado Doctor Honoris Causa por la Universidad Católica San Antonio de Murcia es un sueño que nunca imaginé, y que ha sido posible por la benevolencia de todos los miembros de la UCAM.

Es un gran honor para mí recibir tan alta distinción y agradezco profundamente al departamento de la Cátedra de Traumatología del Deporte, en nombre de su director, el Prof. Pedro Guillén, que propuso mi investidura. Querido amigo Pedro Guillén, muy agradecido por tu amistad y generosidad.

Aportación de los Cultivos Celulares (Condrocitos) en las Lesiones de las Articulaciones Dañadas

REGENERACIÓN DEL CARTÍLAGO. Desde ACI a MACI y desde ICC a IPC"

Stephen P. Abelow, M.D., F.A.C.S

El cartílago articular es un tejido conectivo que cubre las superficies articulares y tiene importantes propiedades biológicas y biomecánicas. Con un coeficiente de fricción de 0,002, el cartílago articular es 1.000 veces más resbaladizo que el hielo al contacto con el propio hielo.[1] Permite la fricción mínima entre fuerzas conjuntas opuestas que con el movimiento distribuye el peso sobre las articulaciones en zonas amplias y minimiza las tensiones máximas sobre el hueso subcondral.[2]

El 95% del contenido del colágeno en el cartílago articular es colágeno de tipo II, que proporciona el marco cartilaginoso y la fuerza extensible. El colágeno de tipo II tiene una vida media de aproximadamente 25 años y es en consecuencia muy estable.[1]

El cartílago articular carece de vasos sanguíneos (avascular), de nervios (aneural) y de vasos linfáticos (alinfático) por lo tanto tiene una capacidad limitada de reparación o regeneración intrínseca. Esto se complica por el hecho de que los condrocitos (las células básicas de cartílago adulto que sintetizan la matriz extracelular) están rodeados por una matriz extracelular espesa y no son capaces de migrar de la matriz no lesionada a una zona lesionada (Figura 1). Los condrocitos producen un colágeno de tipo II.

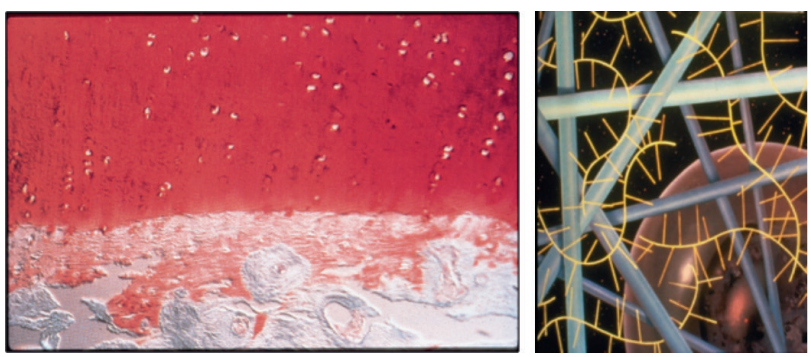

Figura 1

Buckwalter y Mankin señalaron que las lesiones del cartílago que no comprometen el hueso subcondral visten una difícil recuperación. Lesiones de grosor total que violan el hueso subcondral pueden formar un tejido fibrocartilaginoso (o hueso endocondral).[3]

El objetivo de cualquier procedimiento de restauración del cartílago es restaurar la superficie articular haciendo coincidir las propiedades histológicas, bioquímicas y biomecánicas del cartílago hialino normal, mejorar los síntomas y la función y prevenir o retrasar la progresión de la lesión condral focal en el estadio terminal de la artritis.

El propósito de mejorar la cura de las lesiones del cartílago a través de la implantación de condrocitos antólogos y de la ingeniería de tejidos constituye nuestra meta actual.

MODALIDADES DE TRATAMIENTO PARA EL CARTÍLAGO

Lavado articular: se ha utilizado con la idea de enjuagar la articulación para eliminar residuos y enzimas catabólicos. No hay regeneración de cartílago hialino. Se han reportado resultados variables a corto plazo pero no se han registrado mejoras a largo plazo estadísticamente significativas.

Desbridamiento: se ha utilizado para eliminar los síntomas mecánicos de un colgajo condral suelto, cuerpos libres, cartílago degenerativo, osteofitos, o para sinovectomía. No se ha intentado reparar o remplazar el cartílago articular dañado. Esto es en gran parte un procedimiento paliativo y cualquier alivio positivo inicial de los síntomas a menudo disminuye con el tiempo.

Técnicas de estimulación de la médula como artroplastia de abrasión, perforación o micro-fractura se elaboraron para permitir el acceso a la zona lesionada a las células madres mesenquimales y a otros elementos bioactívos curativos, con el fin de estimular una respuesta de sanación en el cartílago. El problema de estas técnicas es que proporcionan un relleno fibrocartilaginoso sobre el defecto del cartílago. El tejido fibrocartilaginoso regenerado tiene menos Col II, más Col I y menos agrecano del cartílago hialino normal.[4] Una revisión sistemática a Nivel II, de 15 estudios de Nivel I y II de Goyal et al. en 2013, observó resultados clínicos positivos durante el seguimiento a corto plazo para tratamiento de lesiones pequeñas en pacientes con bajas

demandas postoperatorias. Los pacientes más jóvenes mostraron mejores resultados clínicos. Señalaron que "Después de 5 años desde la operación se podría esperar un fracaso del tratamiento tras una micro fractura, independientemente del tamaño de la lesión."[5]

Autoinjerto Osteocondral (OAT/ Mosaicoplastia) es la trasferencia de un tapón osteocondral de hueso y cartílago de un área de baja tensión a una superficie de cartílago dañado. Estos se han utilizado con éxito en defectos de cartílago de tamaño tanto moderado como en grande (1.5-3cm de diámetro). Las preocupaciones mayores que se plantean con la practica Oat/Mosaicoplastia son que "desnuden a un santo para vestir otro," una morbilidad de la zona donante, malangualación, malrotación, y autoinjerto que sean demasiado sobresalientes o demasiado avellanados. Si se utilizan varios tampones de hueso podría haber espacios muertos entre los injertos circulares. También se pueden encontrar diferentes espesores y propiedades mecánicas entre el donador y el cartílago articular receptor (ej. El cartílago articular de la rodilla tiene entre 3-6 mm de espesor mientras el cartílago articular del astrágalo 8,9 mm). La transferencia osteocondral autóloga parece proporcionar resultados de buenos a excelentes en varios casos. (Fig 4)

Figura 4

Los aloinjertos ostocondrales se han realizado con éxito para defectos más extensos del cartílago. Es un procedimiento a fase única y se puede utilizar para pérdidas óseas profundas. Los aloinjertos deben cosecharse dentro de las 24 horas después de la muerte del donante si son 100% viables y se pueden almacenar a 40C durante un máximo de 28 días. Los aloinjertos no se deben congelar puesto que la congelación del aloinjertos condrales conduce a la muerte de los condrocitos y no es apropiado para la preservación del injerto. La viabilidad celular disminuye después de 5 días. La correspondencia entre el tejido y la supresión inmunológica son innecesarias. Bugbee et. al. reportó una sobrevivencia del 86% a los diez años del seguimiento (92 pacientes; estudio de Cohorte de Nivel III).[6] Según el Dr. Bugbee se deben considerar 1-3 mm de subsistencia y el 28% 4-5 mm de subsistencia.[7]

Las indicaciones para las técnicas quirúrgicas de sustitución del cartílago son lesiones sintomáticas profundas caracterizadas por la Sociedad Internacional de Reparación del Cartílago (ICRS) Grado 3 (más del 50% de profundidad de cartílago y en dirección descendente, pero no a través del hueso condral) y Grado 4 : hueso subcondral expuesto (con lesiones que se extienden a través de la placa ósea subcondral o más profundamente en el hueso trabecular). No debería haber ninguna alineación incorrecta o inestabilidad y ninguna artrosis significativa. (Fig. 2,3)

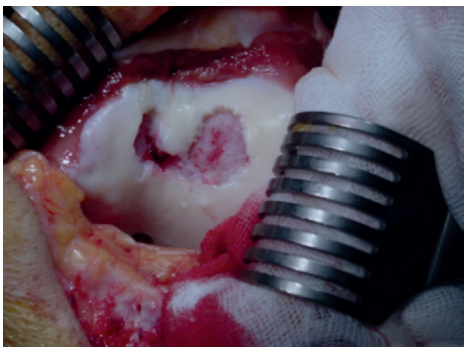

Figura 2

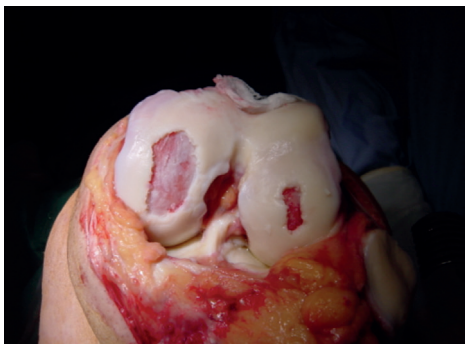

figura 3

IMPLANTES DE CONDROCIDOS AUTÓLOGOS

El implante de condrocitos autólogos (ACI) es la implantación de condrocitos autólogos in vitro en cultivo utilizando una cubierta de tejido perióstico después de la expansión de los condrocitos aislados.

El implante de condrocitos autólogos (ACI) fue señalado por primera vez por Brittberg y sus compañeros de trabajo en Gotemburgo, Suecia, en 1994,[8] de ellos han sido utilizados con éxito en la articulación de la rodilla y el tobillo. Este procedimiento ha dado un 80-90% de buenos a excelentes resultados en los casos de lesiones aisladas del cartílago articular y osteocondritis disecante en los cóndilos femorales de la rodilla.

El ACI es un proceso de dos etapas. Los condrocitos del cartílago articular se cosechan por técnicas artroscópicas o abiertas. Se cultivan los condrocitos in vitro durante 3-5 semanas, se expanden y se reimplantan por artrotomía. Un injerto de periostio debe ser cosechado y suturado sobre el defecto condral de una manera "hermética" (2.3 mm de distancia). Los condrocitos autólogos cultivados se inyectan entonces en el defecto bajo del parche perióstico y se cierra la incision artrotómica. A menudo, esto requiere la realización de una gran incisión artrotómica para permitir la sutura adecuada del injerto del periostio. Las complicaciones incluyen la hipertrofia del injerto, la delaminación del defecto, y la adherencia intra-articular[9,10] (FIG. 5)

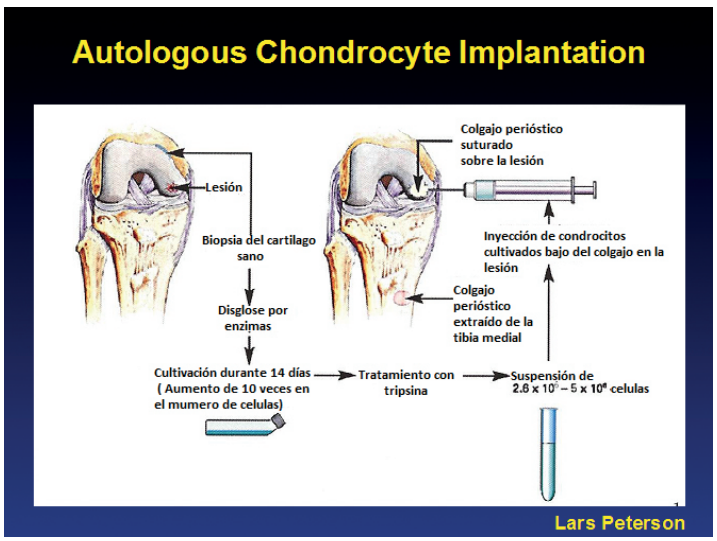

Figura 5

Desde 1996 a 2001 se realizaron 152 casos de ACI. El tamaño promedio del defecto fue de 6,1 cm (0,25 cm-13,5). Hubo 146 rodillas y 6 tobillos (cóndilo femoral medial 64). Edad media: 30 años (12-54 años). Resultados (retrospectiva nivel 5) de 3 a 8 años de seguimiento: 82% buena a excelente, 13% razonable; 5% deficiente. Hubo un caso significativo de delaminación perióstica en un jugador de fútbol de élite.

IMPLANTES DE CONDROCIDOS AUTÓLOGOS CUBIERTOS DE COLÁGENO(CACI)

La recolección y la sutura de un parche de periostio en la implantación de condrocitos autólogos son técnicamente exigentes y requieren un tiempo excesivo. Problemas como la calidad perióstica del parche, hipertrofia perióstica sintomática, y delaminación han llevado al desarrollo de membranas biocompatibles y bioabsorbibles para cubrir el defecto condral. Una membrana bicapa I/III de colágeno porcino absorbible (Condro-Gide, biomaterial Geistlich, Wolhuser Suiza) se ha utilizado en lugar de un parche de periostio. La membrana se degrada por división enzimática (colágenas) y los resultantes fragmentos de colágeno se desnaturalizan a gelatina a 37 grados C. (Figs 6,7)

Figura 6

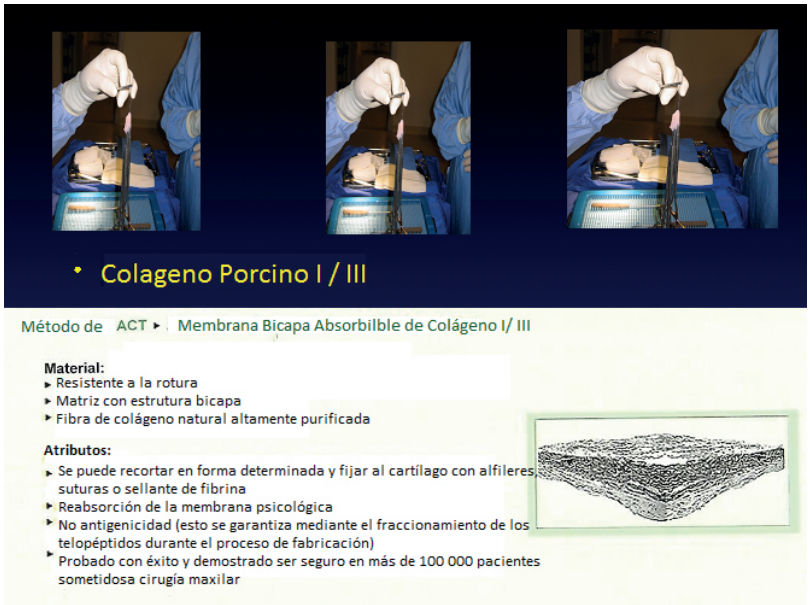

Figura 7

¿Es un necesario un parche perióstico? En un estudio prospectivo Steinwachs observó 63 pacientes con una membrana de colágeno (Condro-Gide) ACI.[11] 88% reportó resultados de buenos a excelentes tres años después de la cirugía. No hubo ningún caso de hipertrofia de la membrana. En otro estudio, 100 pacientes fueron sometidos a ACI con un parche de periostio con un reporte de 78% de buenos a excelentes resultados.[12]

IMPLANTES DE CONTROCIDOS AUTÓLOGOS INDUCIDOS POR MEMBRANA-MATRIX (MACI)

El MACI es un proceso de implantación de condrocitos de tercera generación. Es una nueva biotecnología que permite la impregnación de condrocitos autólogos cultivados en una membrana de colágeno porcino I / III altamente purificado (Vericell, Cambridge, MA). El implante MACI se puede fijar al defecto condral con cola de fibrina (con poca o ninguna sutura necesaria), con sutura, con pernos o con tachuelas bioabsorbibles. El procedimiento se puede realizar por artroscopia o por mini-artrotomía y no se necesita ningún injerto perióstico. (Fig. 8)

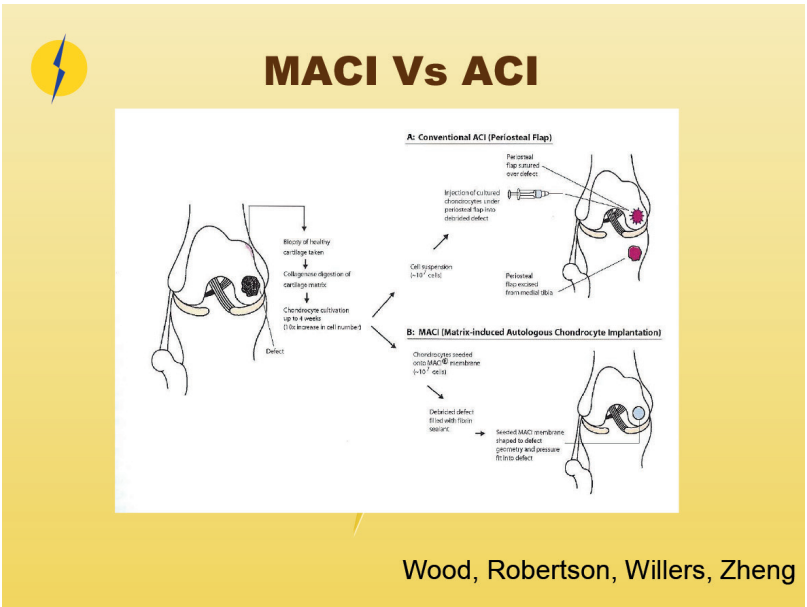

Figura 8

TÉCNICA DE MACI ABIERTO

Inicialmente se cosechan los condrocitos artroscópicamente de una zona sin carga de peso de la rodilla ipsilateral (200-300 mg de cartílago sano). (Fig. 13)

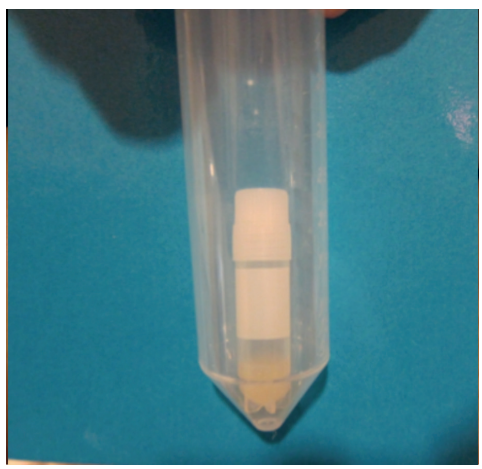

Figura 13

A continuación se cultivan los condrocitos, se expanden in vitro (durante 3-5 semanas) y luego se impregnan en una membrana absorbible tridimensional a dos capas, de colágeno porcino I/III. La estructura bicapa tiene un lado suave no poroso, actúa como una barrera natural y se sitúa frente a la articulación. Los condrocitos se siembran en el lado poroso de la matriz. La membrana es resistente a la rotura y puede ser fácilmente adaptada y recortada en la forma deseada. La membrana no es auto-adherente y puede ser "enrollada" y manejada con instrumentación artroscópica estándar que permite la implantación artroscópica de la membrana.[13,14,15] La membrana no es antigénica (los telopéptidos se parten durante el proceso de fabricación) y es bioabsorbible. Puede ser fijada al defecto del cartílago con pegamento de fibrina, alfileres o sutura (Fig. 7,8)

Utilizando técnicas de mini-Artrotomía o Artrotomías el defecto del cartílago se desbrida y curetea con una cureta de anillo afilado para eliminar la capa de cartílago fibroso calcificado sin penetrar en el hueso subcondral. (Hay que evitar el sangrado del hueso subcondral) (Fig 9).

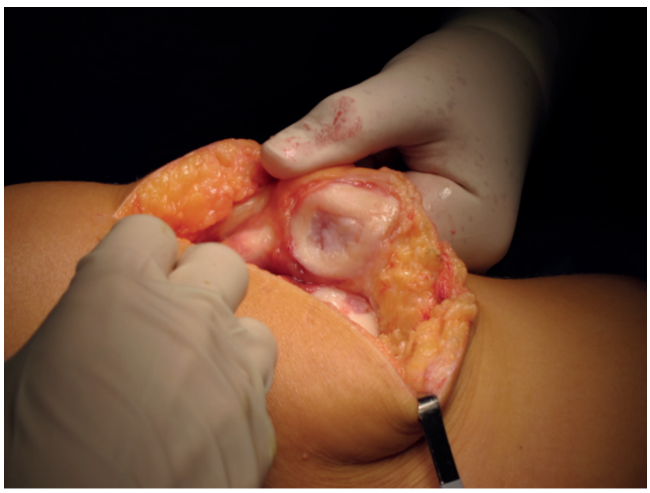

Figura 9

Se crea así una llanta de cartílago estable con paredes verticales afiladas de cartílago sano. (Nota: todo el cartílago "dañado" debe ser desbridado y traído a una frontera saludable estable). (Figuras 9, 10,11,12). Los osteofitos

intralesionales, en sus casos deben ser eliminados. El defecto condral se mide basado en una plantilla. (Figuras14,15)

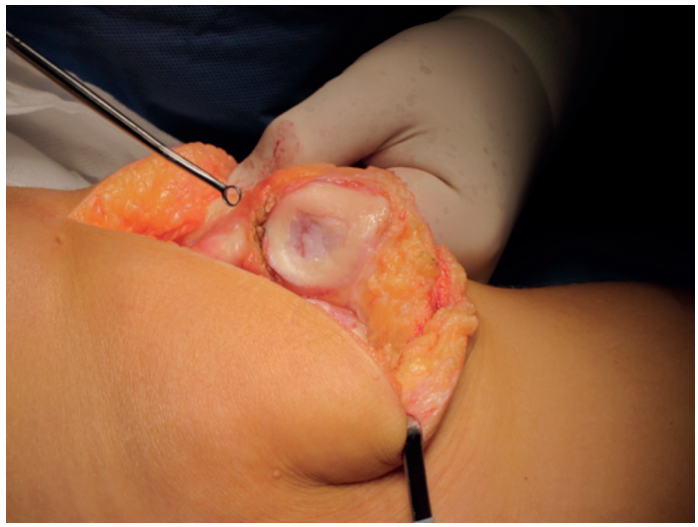

Figura 10

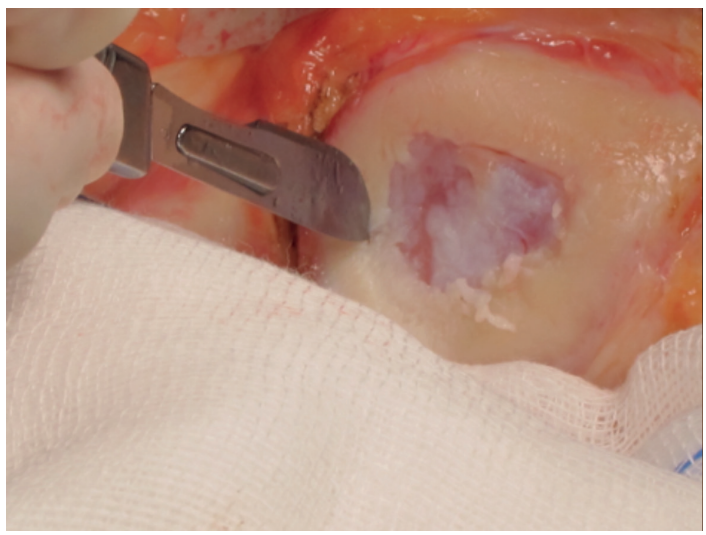

Figura 11

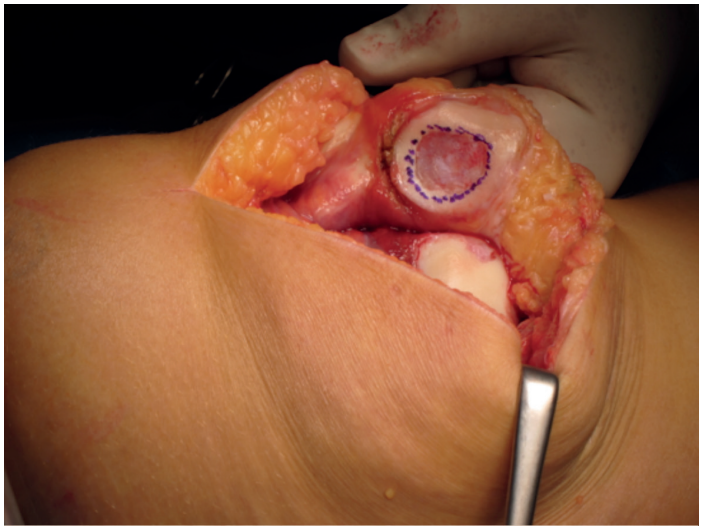

Figura 12

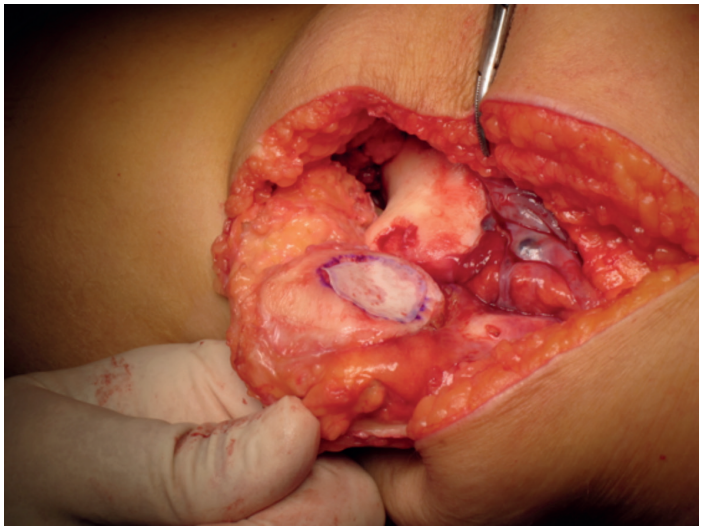

Figura 14

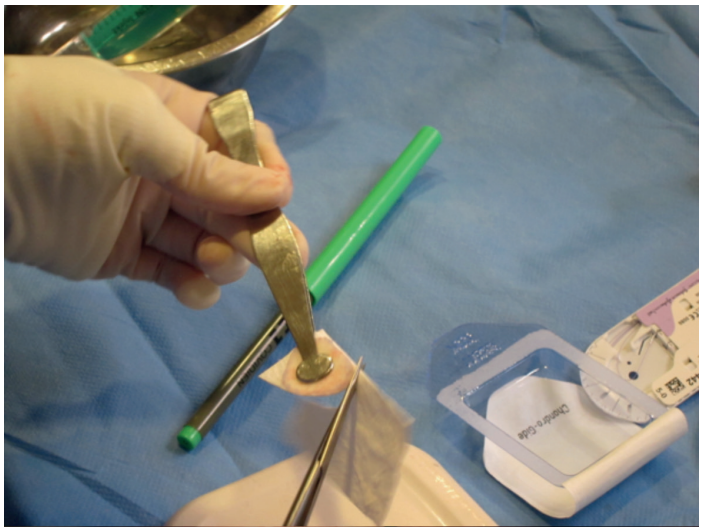

Figura 15

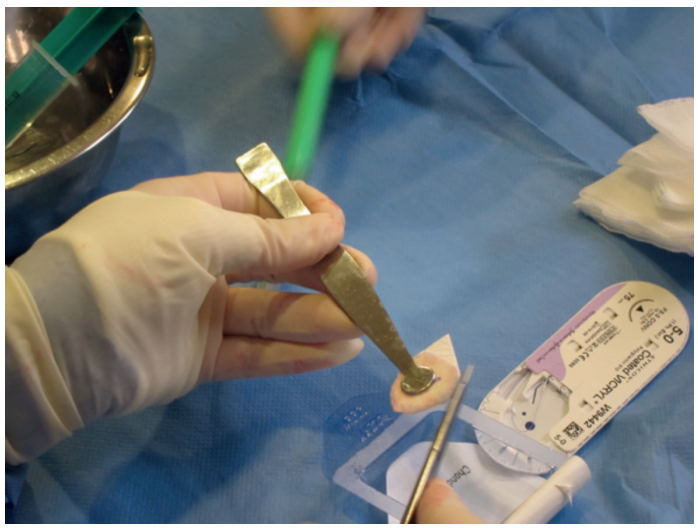

Figura 16

La membrana MACI se corta a la forma adecuada con un bisturí o unas tijeras. (Figs 15,16) La membrana se fija entonces con pegamento de fibrina (Tisucol, Baxter, España). Se utiliza sutura para la rótula (fig. 18)

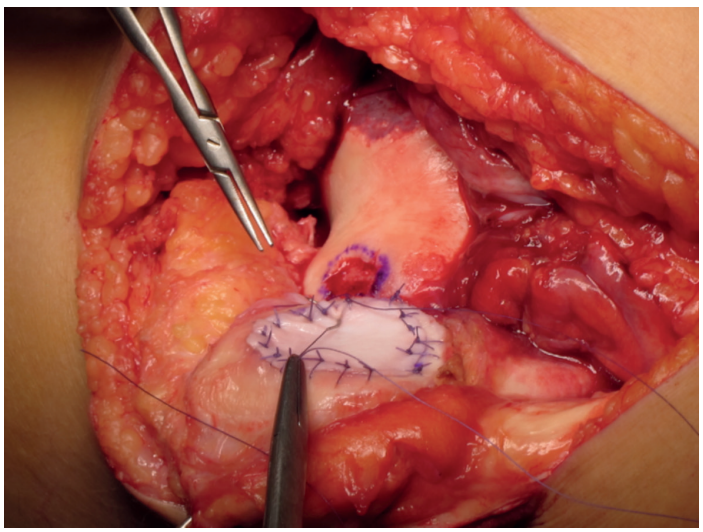

Figura 18

Después de la operación se pone un vendaje suave al paciente y se coloca en movimiento pasivo continuo (cuando esté disponible) durante 8 semanas. Se mantiene el paciente en actividad con carga de peso parcial durante 8 semanas. Para lesiones centrales más grandes se mantienen carga de peso parcial durante 12 semanas

TECNICA ARTROSCÓPICA MACI [13,14,15]

Después de una biopsia previa y del cultivo de los condrocitos, se realiza una artroscopia estándar a través de una cánula artroscópica especialmente diseñada y se desbrida el defecto del cartílago utilizando una cureta con anillo afilado para eliminar la capa de cartílago calcificado. Se crea un borde estable con paredes verticales afiladas de cartílago sano. Usando una regla flexible, una sonda estándar y una pinza artroscópica especialmente diseñada, se calcula el tamaño de la lesión. Se crea una plantilla (utilizando envases de un paquete de sutura o drenaje de goma) y se coloca en el defecto de cartílago para la prueba de tamaño.

Se visualiza el área del defecto del cartílago utilizando un microscopio (aire ambiente, sin insuflación). En la Clínica CEMTRO se ha desarrollado una instrumentación que permite perforar la membrana MACI en su centro y luego colocarla en el centro del defecto del cartílago. A continuación se empuja la membrana dentro de la cánula con un insertador articulado ranurado y se mantiene fijo por el "pincho" artroscópico. El pegamento de fibrina se coloca entonces debajo de la membrana MACI, y la membrana se alisa utilizando un tamper articulado con forma de "T". Se retira el exceso de pegamento, y las membranas contornean el defecto del cartílago mientras que la cola de fibrina se ajusta. Anclajes de sutura mini o pasadores absorbibles pueden ser utilizados si se requiere una fijación más segura para la estabilidad. Se produce un rango de movimientos de la articulación para asegurar la estabilidad del injerto. (Fig. 19,20)

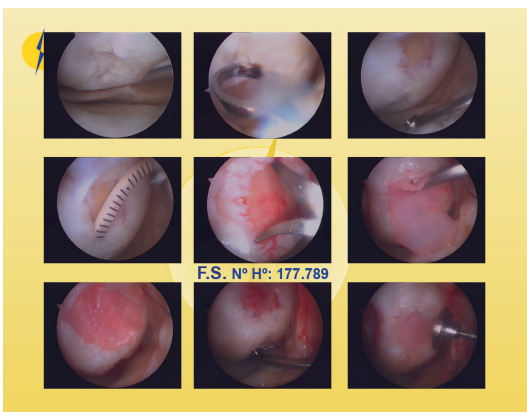

Figura 19

Figura 20

ICC
(Figuras 9-18)

La membrana MACI, como se suministra actualmente, es de 3x5 cm y se siembra con 1 millón de condrocitos por cm^2 para un total de 15 millones de condrocitos. (Anteriormente el tamaño de la membrana era 4x5 cm^2 con un total de 20 millones de condrocitos.)

Si se tuviera que tratar una lesión 3x2 cm^2 de la rótula con la técnica tradicional MACI, se utilizarían 6 millones de condrocitos y 9 millones de condrocitos serían "literalmente" desechados. La misma lesión tratada con ACI tradicional tendría potencialmente 12 millones de células en el sitio de la lesión del cartílago, que es el doble de la cantidad de condrocitos entregados en la misma lesión de tamaño tratado con MACI. Dado que un lado de la membrana no es poroso, las membranas MACI, realmente, no pueden ser apiladas una sobre otra. (Fig. 24)

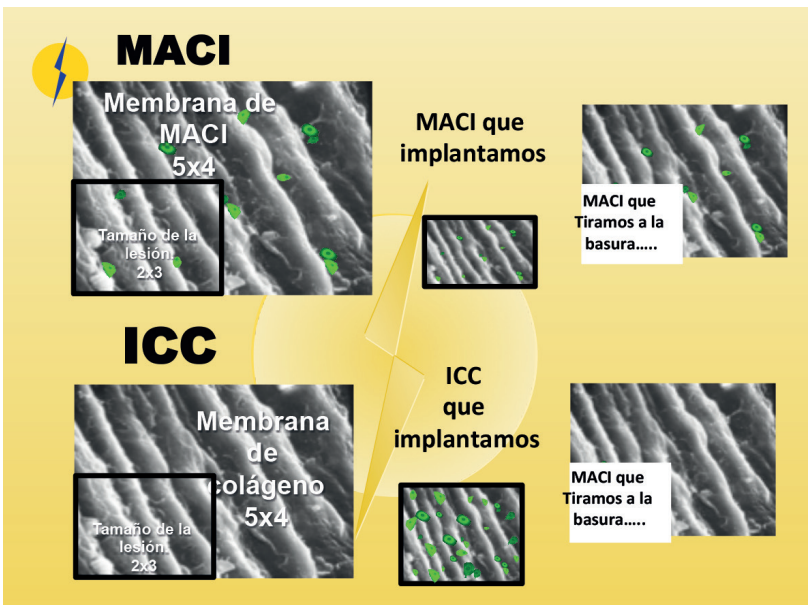

Figura 24

En la Clínica CEMTRO de la Universidad Católica San Antonio de Murcia (UCAM) se investigó el concepto de "densidad celular" en relación con los condrocitos. En un reciente artículo sobre el cartílago, Foldger, Gomol, Lind y sus colegas afirman que "En ausencia de evaluaciones sistemáticas de los efectos de la densidad de las células y el resultado clínico, muchos médicos siguen utilizando uno o dos millones de condrocitos por cm^2, que, a pesar de la falta de pruebas y del hecho de que la mayoría de los estudios in vitro apuntan hacia beneficios de altas intensidades, se ha asociado con resultados clínicos favorables y casi se aproxima a las densidades encontradas en cartílago articular nativo en adultos.[18]

En un intento para determinar el número ideal de células por centímetro cuadrado y que sean óptimas (célula mesenquimal o de condrocitos) en la Clínica CEMTRO se estudiaron 15 hembras de ovejas merinas con lesiones del cartílago articular tratados con condrocitos autólogos o células mesenquimales sembradas sobre membrana de colágeno porcino I/III. Los grupos experimentales fueron 5.000.000 de condrocitos por cm^2; 1 millón de condrocitos por cm^2; 5 millones de células mesenquimales por cm^2; y microfractura. Se analizaron todas las muestras para histología celular, el colágeno de tipo I, colágeno tipo II y agrecano. La expresión de agrecanos se observó en todas las muestras. El perfil de expresión de Col II (marcador de cartílago hialino) mostró que el grupo de control fue mayor de 5 millones de condrocitos, que era mayor que 1 millón de condrocitos, a su vez mayor que 5 millones de células mesenquimales, que era más que la microfractura. El perfil de expresión de Col I era en microfractura mayor que 5 millones de células mesenquimales mayores de 1 millón de condrocitos mayores de 5 millones de condrocitos. Los resultados fueron estadísticamente significativos. La histología mostró 5.000.000 y 1.000.000 condrocitos para tener una mayor estructura de cartílago hialino que cualquiera de la micro-fractura o implantación de 5 millones de células mesenquimales. El aumento de la densidad de condrocitos mejoró la calidad del tejido regenerado[4] (Fig 21,22,23)

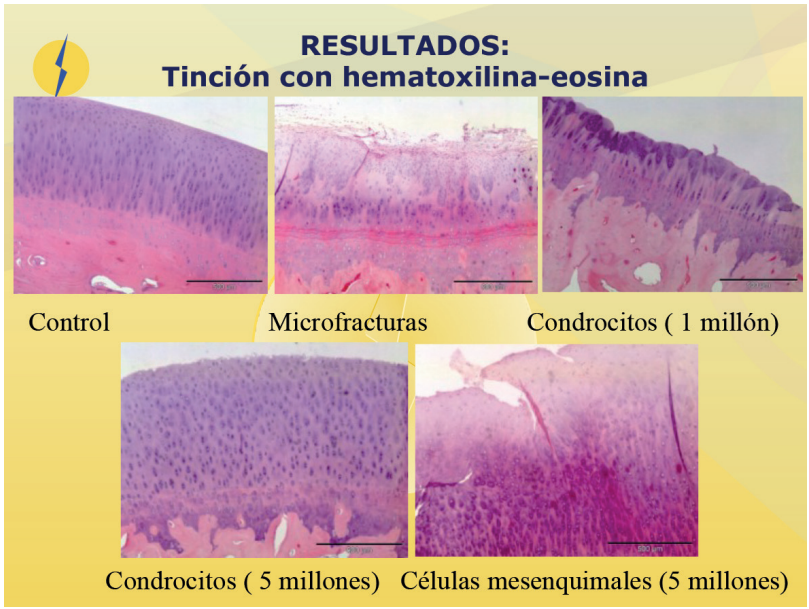

Figura 21

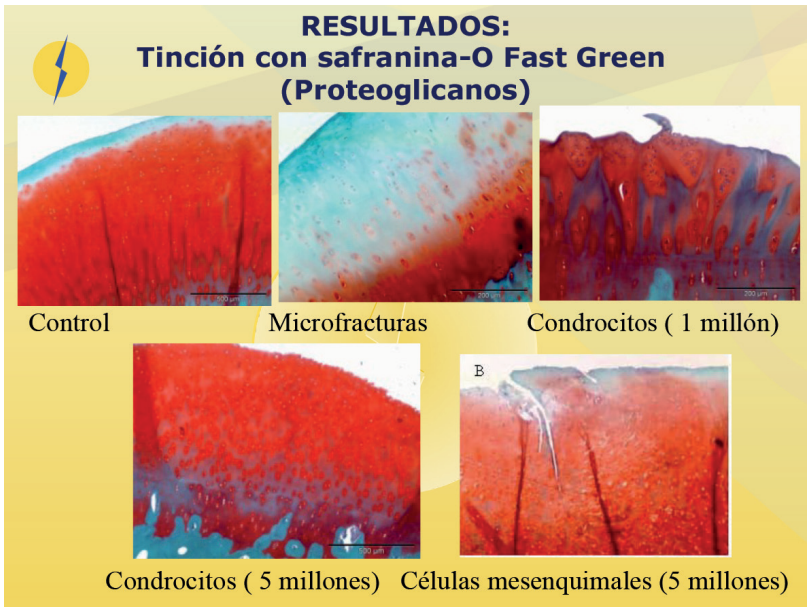

Figura 22

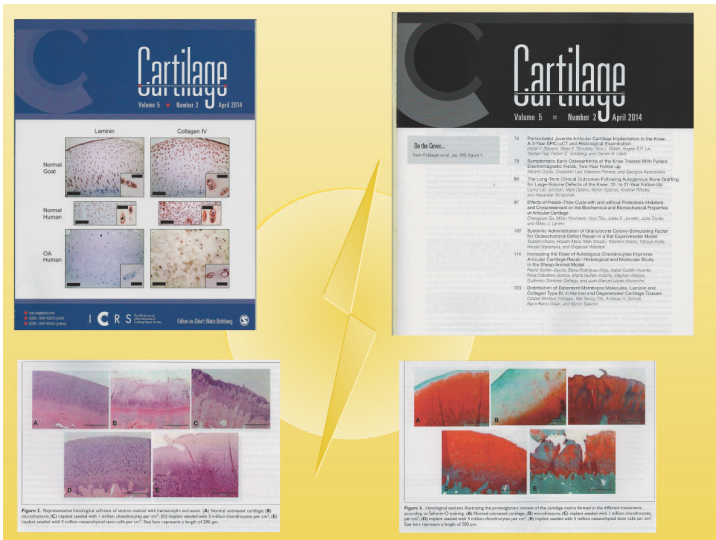

Figura 23

Basándose en el hecho de que 5 millones de condrocitos mostraron un tejido de cartílago regenerativo mejor que 1 millón de condrocitos y 5 millones de MSC, la Clinica CEMTRO ha desarrollado una modificación del procedimiento MACI aumentando el número de células por cm^2 sembradas sobre la membrana de colágeno. (Instant CEMTROCELL-CPI, Madrid, España). (Fig.24)

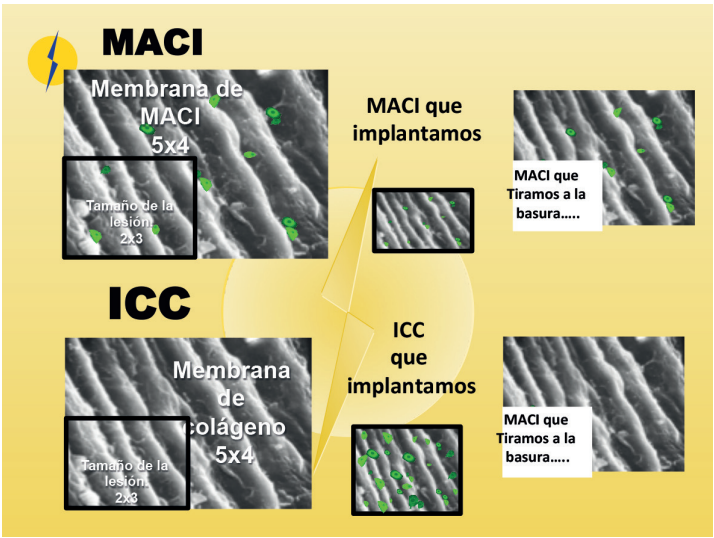

Figura 24

Después de la biopsia por artroscopia, del aislamiento de condrocitos, y del cultivo celular a 20 millones de células, la suspensión celular se transfirió a la sala de operaciones. La lesión se midió de acuerdo a la plantilla. (Fig. 14) La membrana de Chondro-Gide se cortó al tamaño de la lesión (Fig. 15,16) y la totalidad de la suspensión de células se sembró en ella. (Fig 17) Las células se sembraron en la membrana de colágeno porcino I/ III de acuerdo con el método de Steinwachs.[11] Los condrocitos cultivados se colocan en la membrana de colágeno y después de un período de 10 minutos de tiempo para permitir la absorción de los condrocitos, la membrana se implanta en el defecto del cartílago articular. (Por ejemplo, una lesión de 2x3 cm^2 cartílago recibiría más de 3 millones de condrocitos por cm^2 (Figura 17)

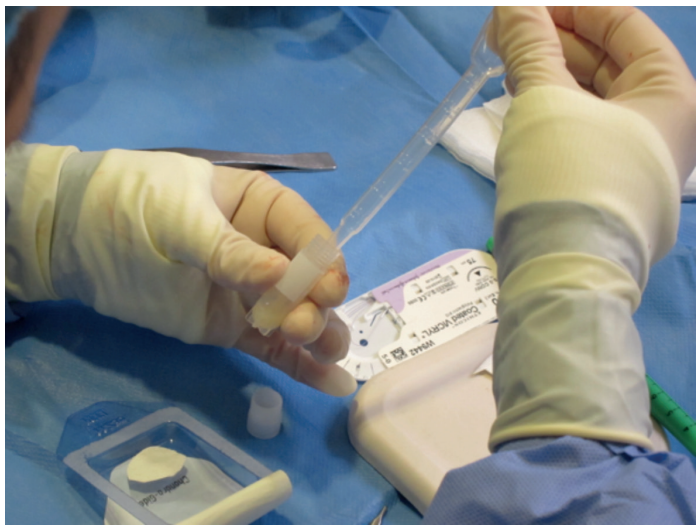

Figura 17

Los estudios histológicos y genéticos de la CPI han demostrado, hasta ahora, una proliferación de matriz de colágeno, una población de condrocitos maduros viables, y la población inmadura de condrocitos con ausencia de expresión de la proteína S-100, la ausencia de mitosis atípicas (ausencia de expresión de P52), y una capacidad proliferativa.

Cartilago Nativo, Cartilago Regenerado, y MACI: Un Estudio Comparativo[16]

En un intento de definir la adecuación de los condrocitos cultivados se estudió la distribución de células en el tejido, la morfología celular, el colágeno tipo II y X, y la presencia FGFR3 (factor de crecimiento Fibroblástico Receptor 3) en el cartílago nativo, cartílago regenerado y MACI). (En la acondroplasia hay una mutación heterocigota del gen que codifica el factor de crecimiento fibroblástico 3).

El cartílago sano tenía 117,6 +/- 6,2 células / mm^2 en comparación con el cartílago regenerado, que tenía 57,3 +/- 2,7 células / mm^2. (Figura 27). Un análisis comparativo por Western Blot electroforesis demostró la presencia de colágeno normal de tipo II en el cartílago nativo y MACI y poco cartílago de tipo II en el tejido regenerado. (Figura 28) En cuanto a colágeno tipo X, los resultados inversos estaban presentes. Había abundante colágeno tipo X en el cartílago regenerado y sólo un mínimo de colágeno tipo X en el cartílago nativo y MACI cartílago. (Figura 29)

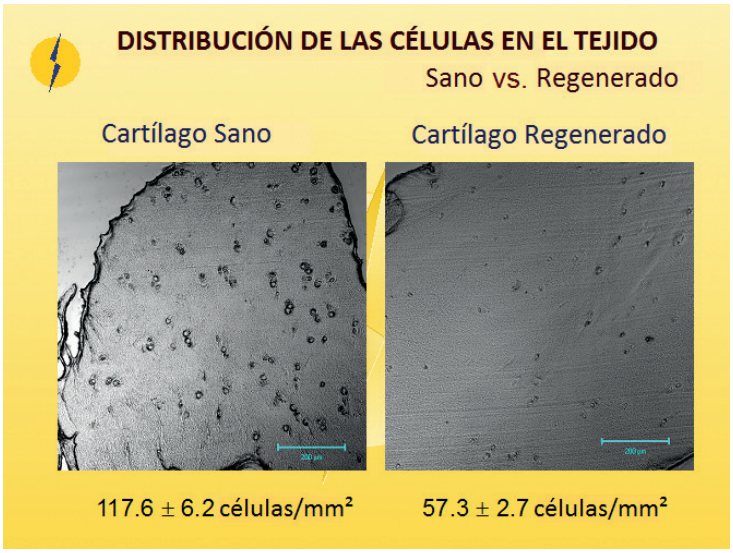

Figura 27

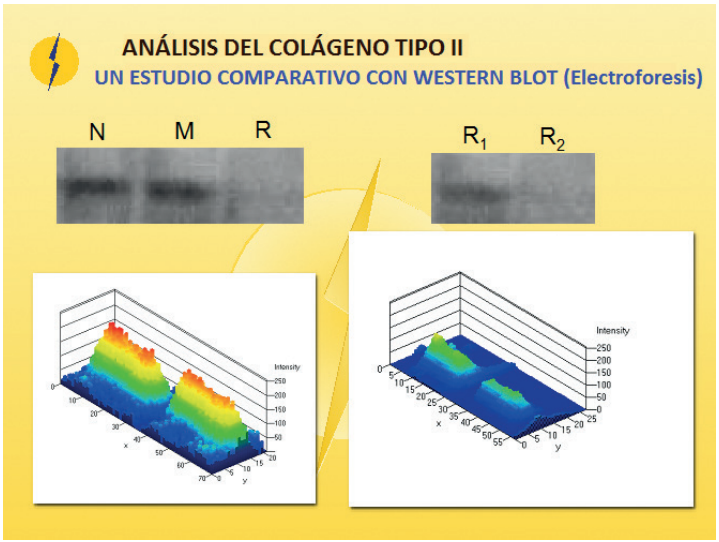

Figura 28

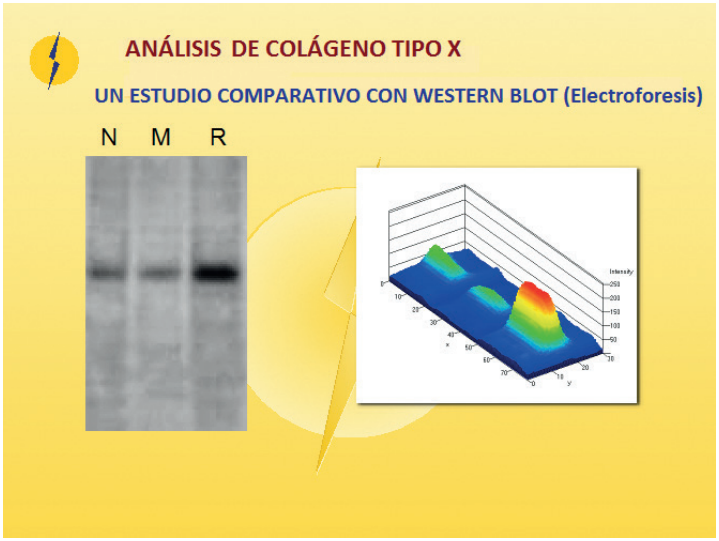

Figura 29

Un análisis de la presencia de receptor del factor de crecimiento fibroblástico 3 demostró cantidades normales de RFCF3 en los condrocitos del cartílago nativos sanos y en los condrocitos del cartílago MACI. Condrocitos regenerados mostraron sólo una pequeña cantidad de RFCF3 (30%). (Fig 30,31).

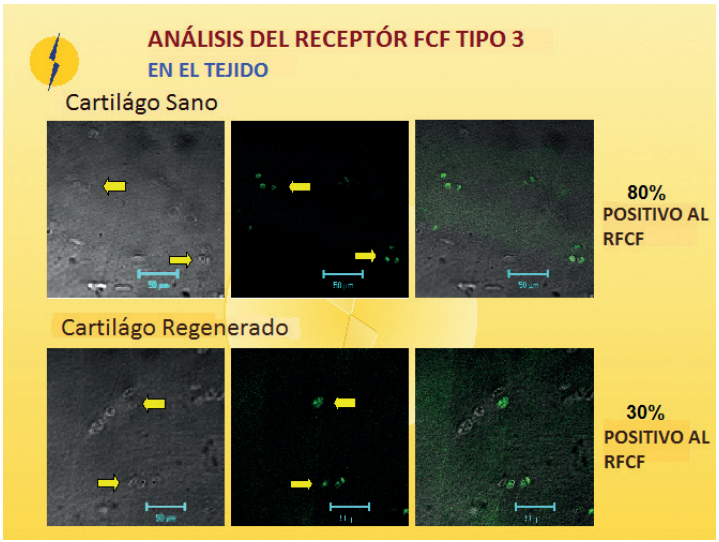

Figura 30

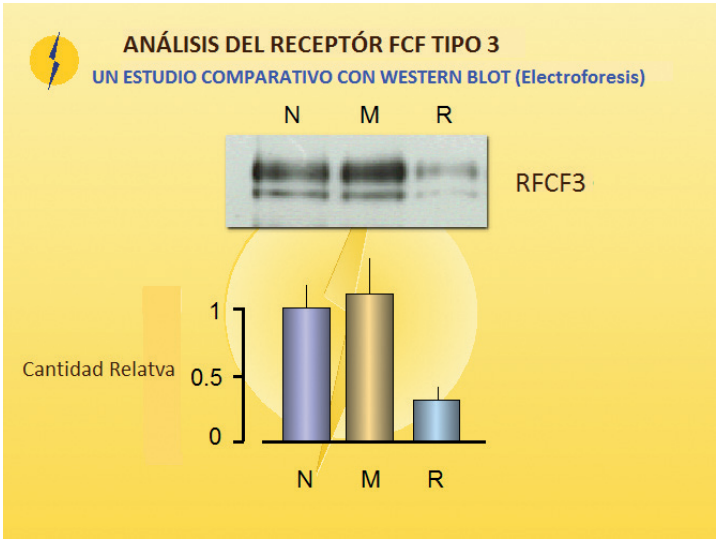

Figura 31

Este estudio mostró que el cartílago regenerado en comparación con el cartílago normal y con cartílago MACI tenía el 50% del número de células. Los condrocitos MACI en comparación con condrocitos normales presenta cantidades idénticas de receptor FCF3, niveles de colágeno tipo II, y niveles de colágeno tipo X. Los condrocitos del cartílago regeneradas producen menos colágeno de tipo II y más colágeno tipo X de los condrocitos normales o MACI. Los condrocitos del cartílago regenerados mostraron una falta de receptores de RFCF3 en comparación con los condrocitos normales o MACI (sólo 30% de las células tenían este receptor).

La relevancia clínica de este estudio es que de acuerdo con el doctor Arnold Caplan en el Congreso Mundial de la Sociedad Internacional de Reparación (Chicago, Il., EE.UU. mayo de 2015) la proporción de RFCR3 a RFCF 1 podría ser un importante factor determinante en la progresión de células progenitoras de condrocitos en la producción de cartílago articular en lugar de osificación endocondral.

¿CÓMO SE PUEDE POTENCIAR LA CAPACIDAD DE LOS CONDROCITOS CULTIVADOS?

En un intento de potenciar los condrocitos cultivados se han utilizado muchos factores de crecimiento, otros polipéptidos y proteínas de cadena. La experimentación con la adición de una molécula de dinucleótido (diadenosina tetrafosfato -ap $_4$D$_2$) al medio de cultivo mostró mejoras significativas en las características de crecimiento de los condrocitos cultivados. (Fig. 32) La diadenosina de tetrafosfato es una molécula que se encuentra en el líquido sinovial humano. (Fig. 33) El Ap$_4$D$_2$ favoreció la proliferación de condrocitos en casi un 30%. (Fig 35) El Ap$_4$D$_2$ favoreció la producción de matriz extracelular a casi el doble. (Fig. 34) El tejido tratado mostró más colágeno tipo II y menos colágeno de tipo X que el tejido no tratado. La adición de Ap$_4$D$_2$ redujo el número de receptores de RFCF3 en la membrana de condrocitos.

La experimentación con animales está actualmente en curso.

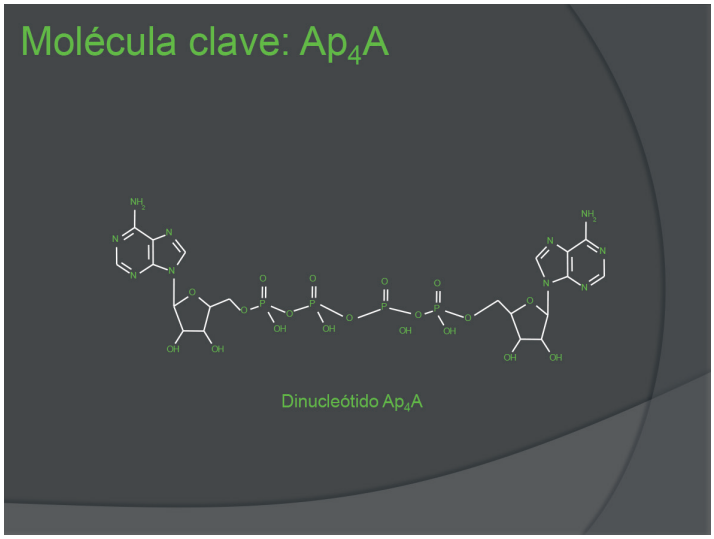

Figura 32

Figura 33

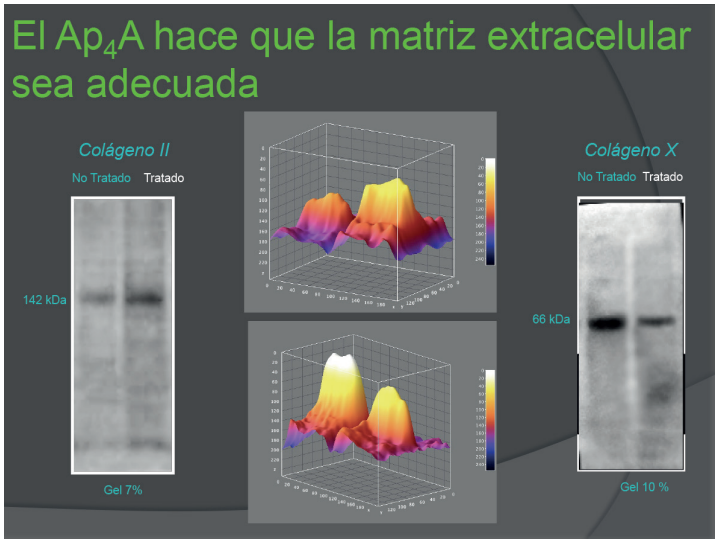

Figura 34

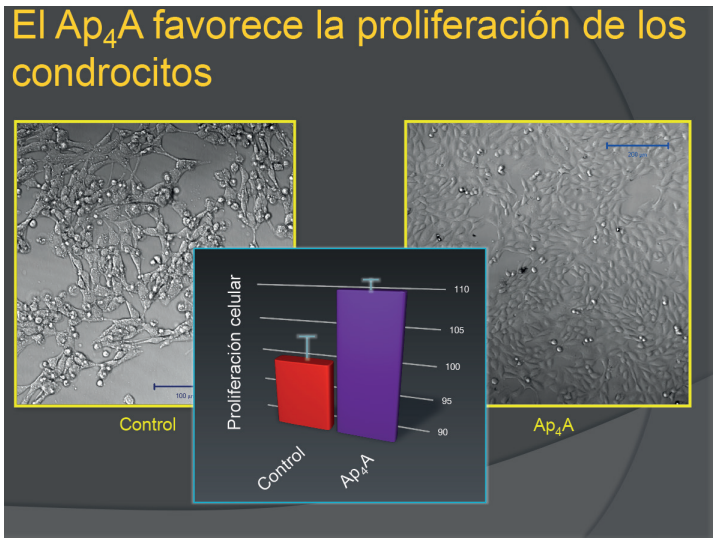

Figura 35

CELULAS MADRES PLURIPOTENTES INDUCIDAS (iPSC)

Las células madre pluripotentes inducidas (IPSC) son células madre de tipo "embrionario " que se desarrollan a partir de las células propias de una persona como la piel, la sangre, las MSC, etc.) (Fig 36,37) y re-inician o re-programan de estas células de diferenciarse en otros tipos de tejidos incluyendo condrocitos. Estas células madre embrionarias ", como" se desarrollan a través de la transducción de genes utilizando factors transcripción ESC-específica.[17]

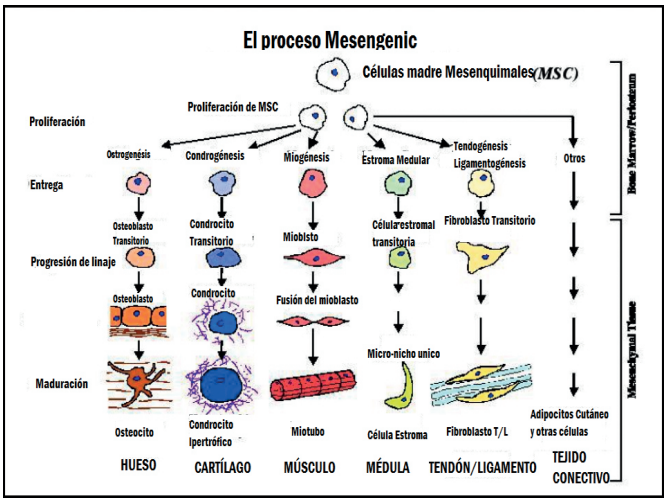

Figura 36

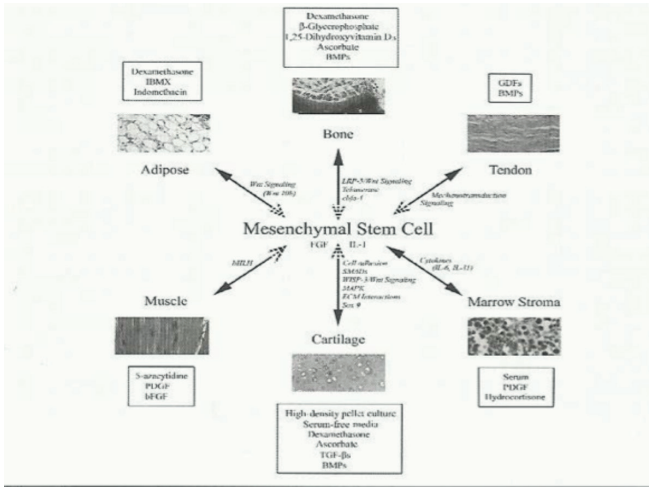

Figura 37

Yamanaka introdujo el concepto de células madre pluripotentes inducidas en 2006. Shinya Yamanaka y John Gurdon fueron ganadores del Premio Nobel de Medicina en 2012. (Fig. 38)

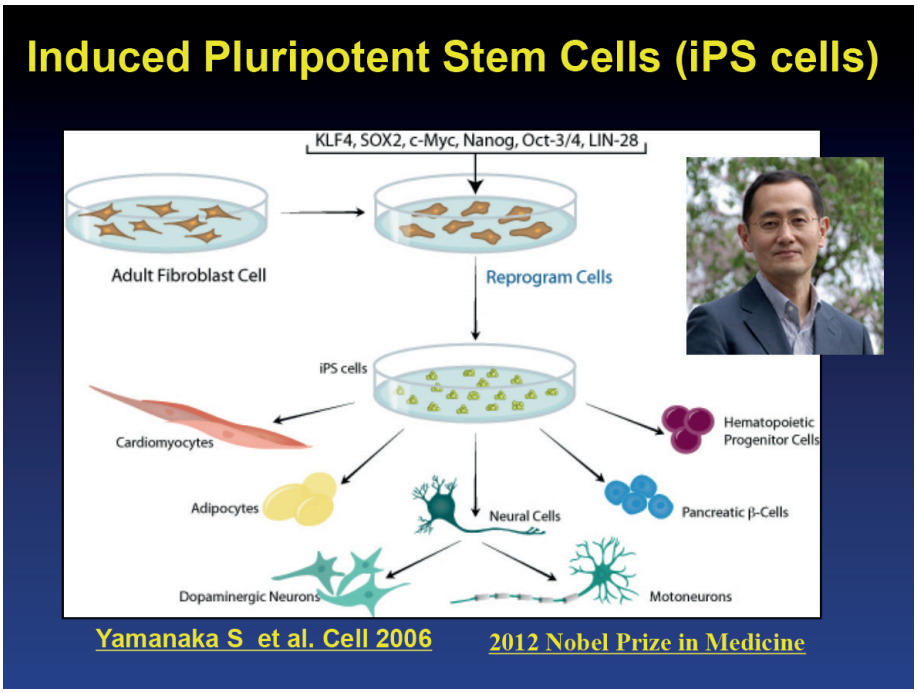

Figura 38

Estos iPSCs son células pluripotentes, como los CES y son autólogas en origen. El CMPI sería teóricamente capaz de auto-renovación indefinida. No debe haber preocupaciones éticas. Estos CMPI se podrían utilizar en múltiples aplicaciones de tejido, incluyendo la regeneración del cartílago.

Las preocupaciones de seguridad más relevantes con iPSCs serían que su naturaleza indiferenciada y tendencia a crecer sin restricciones podrían conducir al desarrollo de la formación de tumores o teratoma.

Un estudio realizado por la Universidad de Connecticut Stem Cell laboratorio en comparación condrocitos normales, condrocitos artrósicos, fibroblastos dérmicos (de la piel) y mononucleocitos de sangre de cordón en la formación de CMPi cartílago.

Su estudio demostró que iPSCs derivados de cualquiera de los condrocitos articulares normales o artrósicos poseen un mayor potencial de formación de condrocitos en comparación con las células iPS a partir de la piel o de la médula mononucleocitos sanguíneos. Sus datos mostraron que el tejido de origen afectado el potencial destino de CMPI para diferenciarse en condrocitos. Informaron que las CMPI derivadas de condrocitos articulares artrósicas muestran inducción similar de marcadores condrogénicas primeros en comparación con iPSCs de condrocitos normales

La Clinica Centro (Madrid, España) / UCAM (Murcia, España) colabora con el Instituto Salk de San Diego, California, EEUU y han comenzado ya a cultivar células madre mesenquimales transformadas o reprogamadas en condrocitos añadiendo TGF – beta.[19] (Figs. 39 a 44)

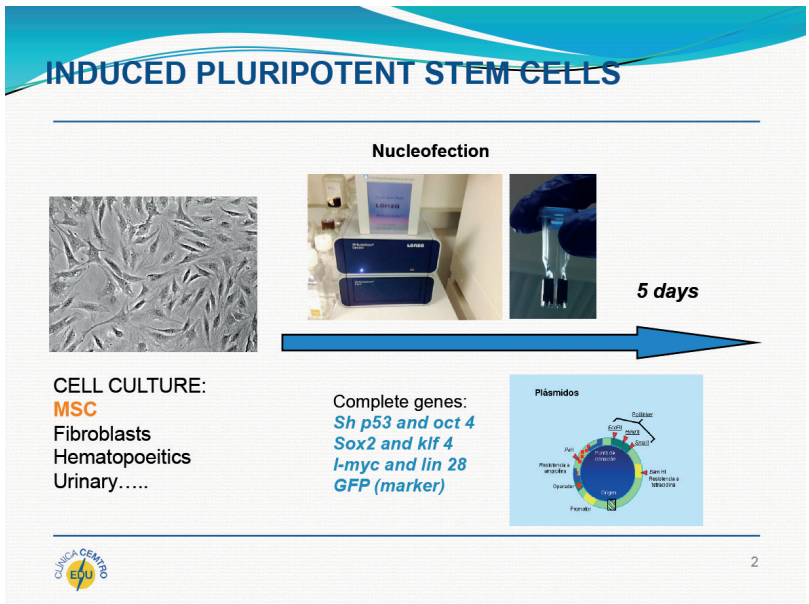

Figura 39

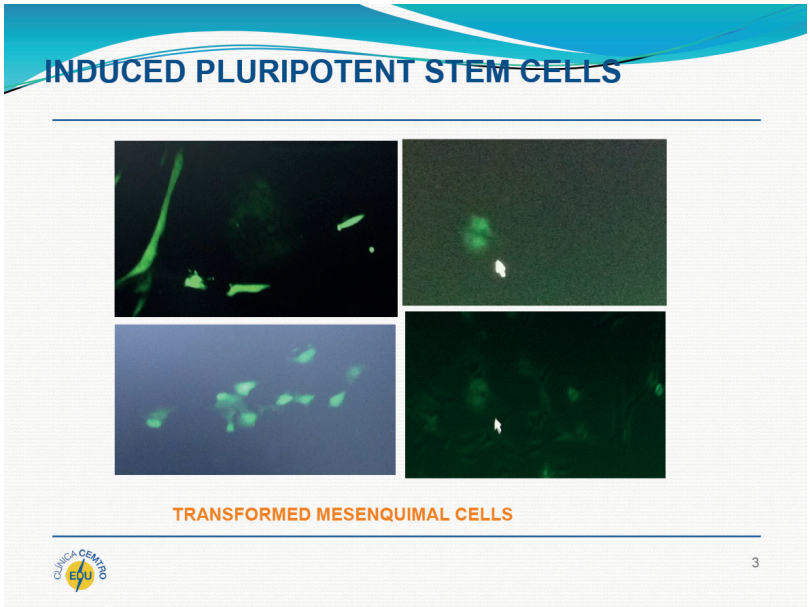

Figura 40

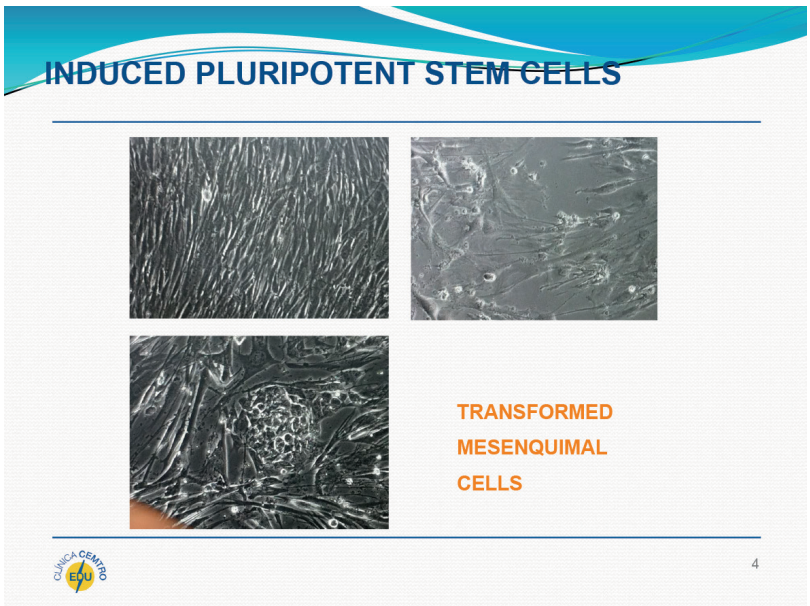

Figura 41

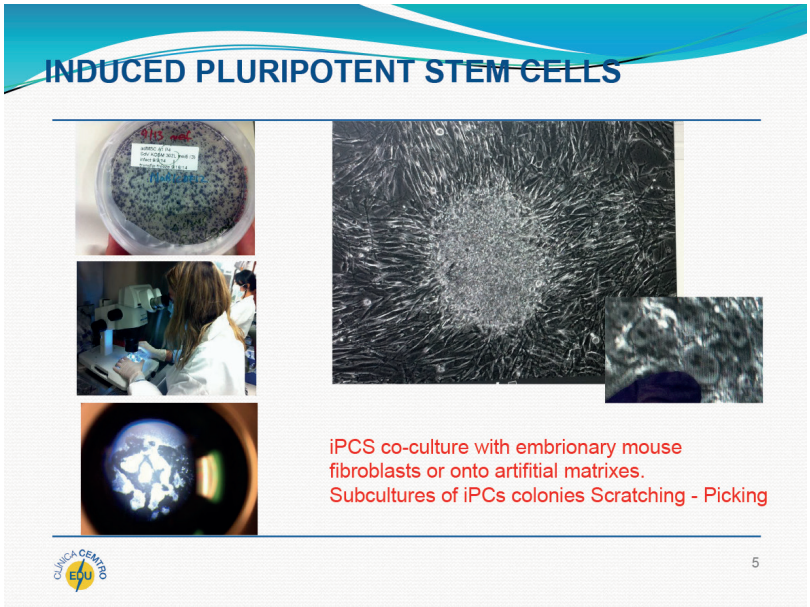

Figura 42

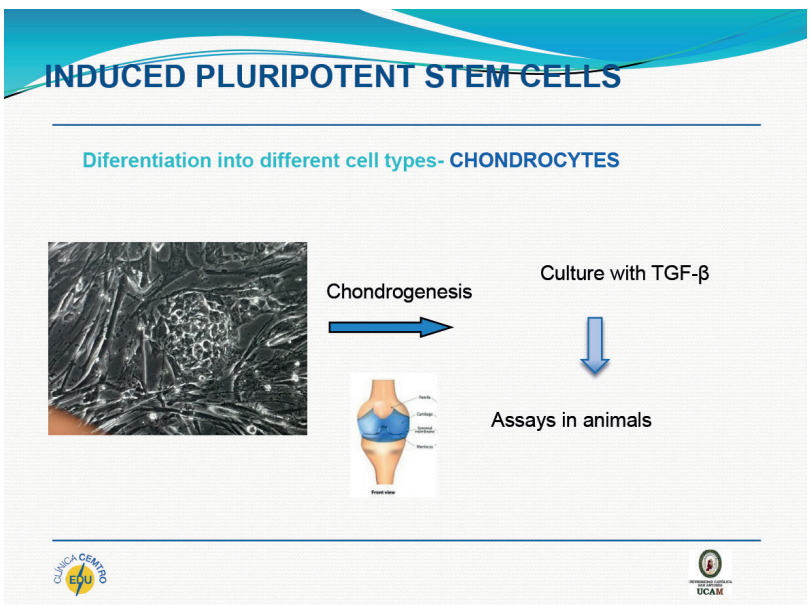

Figura 43

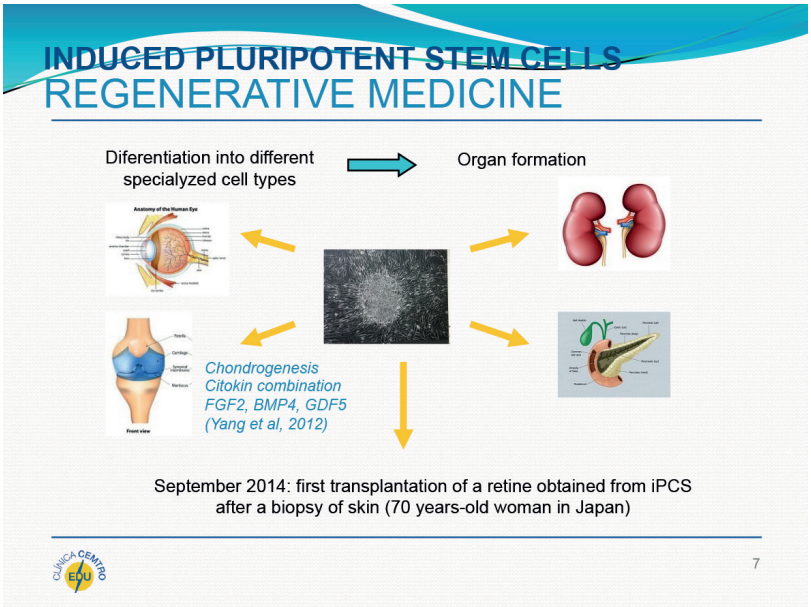

Figura 44

He dicho,

Gracias.

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English version

LAUDATIO OF PROFESSOR DR. PEDRO GUILLEN GARCIA IN THE INVESTITURE AS DOCTOR HONORIS CAUSA OF THE DOCTOR MR. STEPHEN ABELOW.

LAUDATIO BY PROF. DR. PEDRO GUILLÉN GARCÍA IN THE INVESTITURE AS DOCTOR HONORIS CAUSA OF DR. STEPHEN ABELOW

Temple of the Jerónimos Monastery
Murcia, 12 June, 2015

His Excellency, President of the Catholic University of San Antonio de Murcia,

His most Reverend Eminence Cardinal Antonio Cañizares Llovera, Archbishop of Valencia.

Her Excellency and Magnificent Rector of this University,

His Excellency and most Reverend Lord Bishop of the Diocese of Cartagena,

The Excellent and Illustrious Academic, Ecclesiastic, Civil and Military authorities.

Faculty, staff administration and services, students and guests to this solemn academic act.

Today is a great and joyful day for the UCAM and also especially festive, with all their finery, receive as Doctor Honoris Causa the eminent orthopedic surgeon Mr. Stephen Abelow of Nevada (USA). I am grateful to our President, the Hon. Mr. D. José Luis Mendoza and to our Magnificent Rector, Ms. Josefina Garcia, for accepting the nomination from the Chair of Sports Traumatology, and secondly for the courtesy of inviting me to make his Laudatio.

I have the honour of telling you about the professional life of the Doctor Honoris Causa, one of the USA's most brilliant orthopedic surgeons in the field of Sports Traumatology, and who has the great distinction of having studied in Spain, at the Complutense University of Madrid. Subsequently, he returned to his country to practice the specialty of orthopaedic surgery and traumatology. He has always been a lover of Spain and its customs.

Thank you President and Rector.

In the following, I will comment briefly on the professional life of Mr. Stephen Abelow.

Dear professor and friend, Mr. Stephen Abelow, it is a great honour for me to make the Laudatio of your investiture as Doctor Honoris Causa of the Catholic University, San Antonio of Murcia.

"For his merits." This is the meaning of the Latin expression DOCTOR HONORIS CAUSA. It is granted in honorific mode in recognition of personal and professional merits and is the university title of the highest prestige.

Born in Brooklyn, New York, USA, in the May of 1946, when Europe was burning in the flames of World War II. Married with three children - today he is accompanied by his wife, Maria.

Education:

- Escuela Superior (High School): Oceanside High School 1960-1964, Oceanside, Long Island, NY.

- Universitario (College): Boston University 1964-1968 (Bachelor of Arts) Boston, Massachusetts.

- Universidad of Madrid, Faculty of Medicine: 1969-1971 (Preclinical years).

- Medical Doctor Degree (M.D.) May 1974. Hahnemann Medical College Philadelphia, Pennsylvania (number 3 in the USA in these years).

- Internship: Hahnemann Medical College Hospital, Philadelphia, 1975, General Surgery.

- Orthopaedic Surgery Residency: Tufts New England Medical Center, Boston 1978.

- Diplomated American Board of Orthopaedic Surgery, July 1984.

After his specialty in orthopedic surgery and traumatology (COT), he visited the best medical centers of locomotive pathology of the of USA (Boston University, Hahnemann Medical College Philadelphia, Tufts New England Medical Center, Boston) with Professor Dr. Steadman and finally practiced his specialty in the "Lake Tahoe Sports Medicine Center" South Lake, Tahoe, California, USA, as the Medical Director. There he attended the most outstanding American snow sports athletes and became a consultant in Sports Traumatology.

Twenty years ago he left Spain when he was already a prestigious orthopedic surgeon; we then reencountered him in San Francisco, on the occasion of a medical Conference on the use of lasers in orthopedics. By then had forgotten his Spanish! But his admiration for Spain soon became manifest and since then, we visit three-four times a year, has been informing us of the latest advances in orthopedic surgery in his country. He is a foreign consultant for COT and the CEMTRO clinic.

He is an excellent surgeon, excellent companion, excellent person and an excellent taster of everything Spanish. And is Ambassador in the USA and the rest of the world for our medical achievements. For his alertness in medicine and his passion for research, Dr. Abelow is one of the most prestigious lecturers in the world of Orthopedics.

After these brief comments on his human and professional training, we emphasize the following medical merits:

- Is President of Sports Medicine and Arthroscopy of the SICOT (International Society of Orthopaedic Surgery and Traumatology).
- Treasurer of the SICOT Foundation
- Clinical Professor of Sports Orthopedics and Traumatology of the CEMTRO Clinic.
- Honorary Professor of Sports Traumatology and Medicine of the San Antonio Catholic University of Murcia.

- Medical Director of the Lake Tahoe Sports Medicine Center, South Lake, Tahoe, California.

- Member ICRS (International Cartilage Repair Society).

- Member of the American College of Utilization Review Physicians.

- Certified American Board of Quality Assurance & Utilization Review: 1986. Recertified November 1999, 2002, 2005.

- Certified, American Board of Independent Medical Examiners: 1997. Recertified October 2003.

Publications/Presentations

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- Faculty, San Diego Shoulder Arthroscopy (James C. Esch), M.D., San Diego, CA, 1987-2010. Laboratory Director, 1998-2003.

- Faculty, Endoscopic Anterior Cruciate Ligament Reconstruction, Laguna Hills, CA, July 1990, July 1992, November 1993.

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- Faculty, Shoulder Arthroscopy, Laguna Hills, CA, September 1989, May 1991, June 1992, march 1993, November 1994, November 1995, October 1996, November 1997, October 1998, October 1999, October 2000-2006, December 2007, October 2008-14.

- Faculty Orthopaedic Laser Society of North America Instructional Course, October 1991, December 1991, March 1992.

- Ski Doc. Column, Starting Gate (weekly sports medicine article in the professional ski racing newspaper), 1986-1999.

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- Faculty, Shoulder Arthroscopy, AANA Motor Skills Workshop, 1992-2005.

- Faculty, Elbow Arthroscopy, AANA Motor Skills Workshop, November 1996-2000.

- Faculty, Ankle Arthroscopy, AANA Motor Skills Workshop, November 1998-2007.

- Associate Master Instructor, The Masters Experience/Shoulder, AANA Orthopedic Learning Center, Rosemont, IL, 1994, 1995, 1996 (2) 1997 (2), 1998, 1999(2) 2000, 2001, 2002 (Master Instructor 2), 2003, 2004.

- Master Instructor, The Masters Experience/Knee, AANA Orthopedic Learning Center, Rosemont, IL, September 2000.

- Master Instructor, The Masters Experience/Shoulder, AANA Orthopedic Learning Center, Rosemont, IL, June 1998, July 2002.

- Associate Master Instructor, The Masters Experience/Ankle, AANA Orthopedic Learning Center, Rosemont, IL, October 1996-2009.

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- Co-chairman, Lake Tahoe Knee & Shoulder Sports Medicine Update, December 1996-2000 (500 participants, international faculty of 50)

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- Treatment of cartilage lesions in the athlete´s knee. Keynote Address, European Federation of Orthopaedic Sports Traumatology (EFOST), March 2004.

- Matrix autologous chondrocyte implantation for large chondral defects of the knee and ankle. American Orthopaedic Society for Sports Medicine Annual Meeting, Keystone, CO, July 2005.

- Matrix autologous chondrocyte implantation for large chondral defects of the knee and ankle. Current treatment of cartilage defects in the athlete´s knee. American Orthopaedic Society for Sports Medicine Course, Rosemont, IL, August 2005.

- Matrix autologous chondrocyte implantation for large chondral defects of the knee and ankle. AANA, Vancouver, British Columbia, Canadá, May 2005.

- Knee lab instructor, American Orthopaedic Society for Sports Medicine, Rosemont, IL, August 2005.

- Moderator. Meniscus Symposium, SICOT Triennial Meeting, Istanbul, Turkey, September 2005.

- Arthroscopic technique for shoulder instability repair, what´s new in orthopedic surgery. Madrid, Spain, November 2005.

- Current treatment of chondral defects of the knee. International knee Symposium, Madrid, Spain, January 2006.

- Avoiding complications and pitfalls of anterior cruciate ligament surgery. International Knee Symposium. Madrid. Spain. January 2006.

- Second and third generation treatment of chorndral injuries, the Swedish experience, Spanish experience, Italian experience and American experience. Instructional Course lecture. Moderator. American Orthopaedic Society of Sports Medicine. Hershey, PA, July 2006.

- Membrane/matrix autologous chondrocyte implantation for large chondral defects of the knee and ankle. Instructional Course Lecture, American Orthopaedic Society of Sports Medicine, Hershey, PA, July 2006.

- Current treatment of cartilage lesions. Summer Course. University Rey Juan Carlos, Aranjuez, Spain, July 2006.

- Treatment of anterior cruciate ligament injuries. SICOT International Symposium. Buenos Aires, Argentina, August 2006.

- Meniscus repair techniques. SICOT International Symposium, Buenos Aires, Argentina, August 2006.

- Collagen meniscus implantation. SICOT International Symposium, Buenos Aires, Argentina, August 2006.

- Allograft meniscal implantation. SICOT International Symposium, Buenos Aires, Argentina, August 2006.

- Membrane/matrix-induced autologous chondrocyte implantation for large chondral defects of the knee. Arthroscopy Association of North America, Masters Experience, Cartilage, Rosemont, IL, September 2006.

- Membrane/matrix-induced autologous chondrocyte implantation for large chondral defects of the ankle. Arthroscopy Association of North America, Masters Experience, Cartilage, Rosemont, IL, October 2006, September 2007, September 2008, September 2009.

- Anterior cruciate ligament reconstruction, 3o years´ experience and current concepts, "Visiting Professor, Northwestern University, October 2006.

- Current and future treatment of cartilage defects of the knee and ankle. Wavering Lecturer, Northwestern University School fo Medicine, Chicago, IL, October 2006.

- Current treatment of chondral injuries of the knee and ankle. International Tissue Engineering Symposium, Madrid, Spain, November 2006.

- Artroscopic technique for multidirectional shoulder instability, what´s new in orthopedic surgery. Madrid, Spain, November 2006.

- Treatment of chondral defects of the knee. International Knee Symposium, Madrid, Spain, January 2007.

- ACL reconstruction. International Knee Symposium, Madrid. Spain, January 2007.

- Meniscal allograft transplantation. International Knee Symposium. Madrid, Spain, January 2007.

- Regenerative cartilage techniques in the shoulder- Arthroscopy Association of North America Annual Meeting, Instructional Course Lecture. Non-prosthetic Treatment of Shoulder Arthritis. San Francisco, CA, April 2007.

- New arthroscopic treatments and instrumentation for autologous chondrocyte implantation, podium presentation, Arthroscopy Association of North America Annual Meeting, San Francisco, CA, April 2007.

- Wireless arthrosocopy, presentation at Arthroscopy Association of North America Annual Meeting, San Francisco, CA, April 2007.

- Matrix-induced autologous chondrocyte implantation in the knee, arthroscopic techniques. ISAKOS Annual Meeting, Florence, Italy, May 2007, Osaka, Japan, April 2009.

- Associate Master Instructor, Knee & Shoulder Arthroscopy Association of North America, Master Experience, AANA Learning Center, Rosemont, IL, December 2009.

- New advances in the treatment of cartilage, lesions in the knee and ankle osteochondral transfer. ACI, MACI, AANA Masters Experience, Senior Residents and Fellows, Rosemont, IL, December 2009.

- Arthroscopic membrane/matrix autologous chondrocyte implantation (MACI), emerging cartilage technologies in Europe. St. Joseph´s Hospital, Stockton, CA, October 2009.

- Arthroscopic membrane/matrix autologous chondrocyte implantation for treatment of large osteochondral defects of the knee. SICOT, Gothenburg, Sweden, 2010.

- Athroscopic membrane/matrix autologous chondrocyte implantation for treatment of large osteochondral defects of the knee. International Cartilage Repair Society, Miami, FL, May, 2000.

- Arthroscopic membrane/matrix autologous chondrocyte implantation for treatment of large osteochondra defects of the knee. International Cartilage Repair Society, Sitges, Spain, September, 2010.

- Reconstruction of anterior cruciate ligament with autologous fibroblast or mesenchymal cells seeded on a type 1/3 collagen membrane. Western Orthopaedic Association, Honolulu. HI July 2011.

- Arthroscopic membrane/matrix autologous chondrocyte implantation for the treatment of large osteochondral defects of the knee. SICOT International Meeting, Prague, Czech Republic, September, 2011.

- ACL and allograft state of the art in the USA 2011. International Knee Symposium, Madrid Spain, January 2011.

- ACL and meniscus state of the art in the USA 2012. Clinica CEMTRO, 11th International Practical & Theoretical Course of the knee, January 2012.

- Cartilage regeneration. 12th International Cartilage Symposium, Madrid, Spain, CEMTRO Clinic, November 2012.

- New treatment for articular cartilage regeneration. International Cartilage Regeneration Symposium, CEMTRO Clinic, Madrid, Spain, November 2013.

- Orthobiologics in the shoulder, PRP. November 16, 2012, 11th International Orthopaedic Advances Symposium, November 2012. Madrid, Spain.

- Osteochondral allograft. SICOT Orthopaedic World Conference, November 2012. Dubai.

- Cartillage update. SICOT Orthopaedic World Conference, November 2012. Dubai.

- Orthobiologics of the shoulder and PRP. SICOT International World Conference. Dubai 2012.

- Osteochondral allograft. SICOT Orthopaedic World Conference October 2013. Hyderabad. India.

- Cartilage regeneration. SICOT/SBOT International Meeting, Rio de Janeiro. Brazil. November, 2014.

- Cartilage regeneration. International Surgical Research Association, Rio de Janeiro, Brazil, November 2014.

- ACL, my favorite technique. SICOT/SBOT International Congress, Rio de Janeiro. Brazil. November, 2013.

- Autologous chondrocyte implantation/arthroscopic technique. VuMedi, February, 14, 2012.

- PRP/PRGF farct or fiction, Shoulder Controversy. Napa, CA 2011.

- Moderator, Cartilage Debate, ISAKOS, Toronto, Canada 2013.

- New advances in cartilage treatment. Brazilian Orthopaedic Trauma Society (SBOT), Rio de Janeiro, Brazil, November 2014.

- Faculty, International Knee Symposium, CEMTRO Clinic, January 2015.

Community Functions:

- Board of Directors, Barton Memorial Hospital, South Lake Tahoe, CA, 1987-1997.

- Board of Directors, South Lake Tahoe Rotary, 1990-1991.

- Board of Directors, Tahoe Human Services, 1985-1992.

- Honorary Board of Directors, Tahoe Human Services, 1993-present.

- Member, South Lake Tahoe Rotary, 1986 to 2015 (present).

Employment History:

- Owner, Lake Tahoe Sports Medicine Center, continuously employed 1979 to present.

- Partner, Lake Tahoe Orthopedic Institute, January 1998 to Mayo 2002 (retired).

- Owner, Elite Evaluations Medical Group, 1988 to present.

- Clinical Professor, Orthopaedic Sports Traumatology, CEMTRO Clinic, Madrid, Spain (working on third and fourth generation cartilage implantation techniques) May 2002 to present.

- Professor, Orthopaedic Surgery & Sports Traumatology, HON, Universidad Católica San Antonio, Murcia, Spain. CEMTRO Clinic Madrid Spain 2003.

- Chairman, Arthroscopy & Sports Medicine, International Society of Orthopedic Surgery & Traumatology (SICOT), 2011-present

- Treasurer, SICOT Foundation, 2011-present.

His preparation in the field of Orthopedic Surgery is so extensive and renowned that major societies of the specialty request him to make practical courses of education on pathology of the shoulder, knee and ankle, and on the application of autologous chondrocytes crops in chondral lesions.

He has also directed a Master Instructor for the AANA in Arthroscopic of the knee and shoulder and as Associate Master Instructor for ankle Arthroscopy. Teaches doctors in training in Arthroscopy in the major medical societies such as AOSS, AANA, SICOT, ISAKOS ICRS and at conferences

of any country that request workshops for Arthroscopy and Sports Traumatology.

It is important to note that in recent years he dedicated much of his time to research on cell culture of chondrocytes, an area in which he is a consummate specialist.

After reading his extensive academic life, his broad health care activity, his great ability as a teacher and finally his turn to research, means that before us we have one of the most prominent figures in the world of orthopedic surgery.

As you can see, his Curriculum Vitae are filled with the merits that deserve the great distinction of Doctor Honoris Causa of the UCAM.

The issue to be expounded:

"Contribution of the Cell Culture (chondrocytes) to damaged joints"

For all these reasons, and in recognition of his merits, I request to proceed to invest to the Doctor Stephen Abelow, the degree of "Doctor Honoris Causa" by the Universidad Católica San Antonio de Murcia.

"His de causis, peto gradum, Doctoris Honoris Causa Domino Stephen Abelow"

Discurso de Investidura como Doctor Honoris Causa de la Universidad Católica San Antonio de Murcia

"Aportación de los Cultivos Celulares (Condrocitos) en las Lesiones de las Articulaciones Dañadas"

"CARTILAGE REGENERATION FROM ACI to MACI to ICC to IPC"

Stephen P. Abelow, M.D., F.A.C.S

Murcia, 12 de junio de 2015

Saludos y Palabras de Agradecimiento.

- Excelentísimo Presidente de la Universidad Católica San Antonio de Murcia, D. José Luis Mendoza.

- Su Eminencia Reverendísima Cardenal Antonio Cañizares Llovera, Arzobispo de Valencia.

- Excelentísima y Magnífica Rectora de esta Universidad, Dña. Josefina García.

- Excelentísimo y Reverendísimo Señor Obispo de la Diócesis de Cartagena.

- Excelentísimas e Ilustrísimas Autoridades Académicas, Eclesiásticas, Civiles y Militares.

- Claustro de profesores, personal de administración y servicios, alumnos e invitados a este solemne acto académico.

Ser nombrado Doctor Honoris Causa por la Universidad Católica San Antonio de Murcia es un sueño que nunca imaginé, y que ha sido posible por la benevolencia de todos los miembros de la UCAM.

Es un gran honor para mí recibir tan alta distinción y agradezco profundamente al departamento de la Cátedra de Traumatología del Deporte, en nombre de su director, el Prof. Pedro Guillén, que propuso mi investidura. Querido amigo Pedro Guillén, muy agradecido por tu amistad y generosidad.

Aportación de los Cultivos Celulares (Condrocitos) en las Lesiones de las Articulaciones Dañadas

CARTILAGE REGENERATION FROM ACI to MACI to ICC to IPC

Stephen P. Abelow, M.D., F.A.C.S

Articular cartilage is a connective tissue that covers joint surfaces. It has important biological and biomechanical properties. With a coefficient of friction of 0.002, articular cartilage is 1000 more times slippery than ice-on-ice.[1] It allows minimal friction between opposing joint forces with movement and articular cartilage distributes loads on the joints over wide areas and minimizes peak stresses on subchondral bone.[2]

95% of the collagen content of articular cartilage is Type II collagen. This provides the cartilaginous framework and tensile strength. The Type II collagen has a half-life of approximately 25 years and is thusly very stable.[1]

Articular cartilage has no blood vessels (avascular), no nerves (aneural) and no lymphatics (alymphatic) and thusly has a limited capacity for intrinsic repair or regeneration. This is complicated by the fact that the chondrocytes (the basic cell of adult cartilage which synthesizes extracellular matrix) is surrounded in a thick extracellular matrix and the chondrocytes are unable to migrate from the uninjured matrix to a zone of injury. (Fig 1) Chondrocytes produce a Type II collagen.

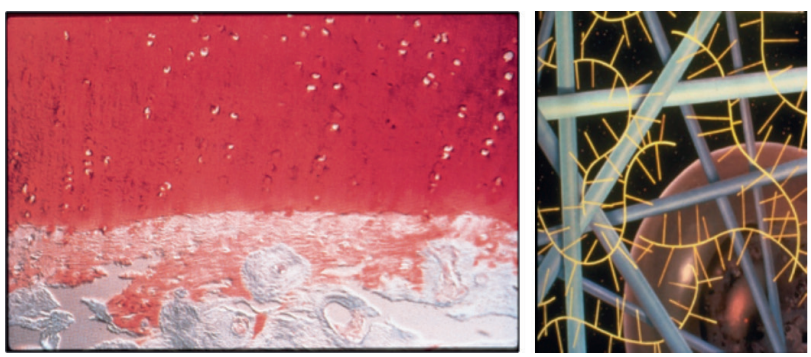


Figure 1

Buckwalter and Mankin reported that cartilage lesions that do not compromise the subchondral bone have difficulty healing. Full thickness injuries that violate the subchondral bone can form a fibrocartilaginous tissue (or endochondral bone).[3]

The goal of any cartilage restoration procedure is to restore the articular surface by matching the histological, biochemical and biomechanical properties of normal hyaline cartilage, improve patients symptoms and function, and prevent or slow the progression of focal chondral injury to end-stage arthritis.

The goal of improving the healing of cartilage lesions by means of autologous chondrocyte implantation and tissue engineering is the current goal,

TREATMENT MODALITIES FOR CARTILAGE

Joint lavage has been utilized with the idea of rinsing the joint of debris and catabolic enzymes. There is no regeneration of hyaline cartilage. Variable short-term results have been reported but no statistically significant long-term improvements have been reported.

Debridement has been utilized to remove mechanical symptoms from a loose chondral flap, loose bodies, degenerative cartilage, osteophytes, or for synovectomy. No attempt to repair or replace damaged articular cartilage is made. This is largely a palliative procedure and any initial good symptom relief often declines with time.

Marrow stimulating techniques such as abrasion arthroplasty, drilling, or microfracture were conceived to allow mesenchymal stem cells and other healing bioactive elements access to a damaged area in order to stimulate a healing response in the cartilage. The problem with these techniques is that they provide a fibrocartilaginous fill of the cartilage defect. This fibrocartilage-regenerated tissue has less Col II, more Col I and less aggrecan than normal hyaline cartilage.[4] A Level II, systematic review of 15 Level I and II

studies by Goyal, et. al. in 2013 reported good clinical outcomes at short-term follow-up for the treatment of small lesions and patients with low postoperative demands. Younger patients showed better clinical outcomes. They reported "Beyond 5 years postoperatively, treatment failure after microfracture could be expected regardless of lesion size."[5]

Osteochondral autograft (OATS/ Mosaicplasty) is the transference of an osteochondral plug of bone and cartilage from an area of low stress to an area of damaged cartilage. These have been used successfully in moderate to large sized cartilage defects (1.5-3cm. diameter). Concerns with Oats/Mosaicplasty procedures are that they "Rob Peter to pay Paul," donor site morbidity, malangulation, malrotation, and autografts that are either too proud or too countersunk. If several bone plugs are used, there can be dead spaces between the circular grafts. There can be different thickness and mechanical properties of the donor and recipient articular cartilage. (e.g. Knee joint cartilage 3-6mm thick; Talar joint cartilage 0.89mm thick). The short-term result of autologous osteochondral transfer seems to be good to excellent in many cases. (Fig 4)

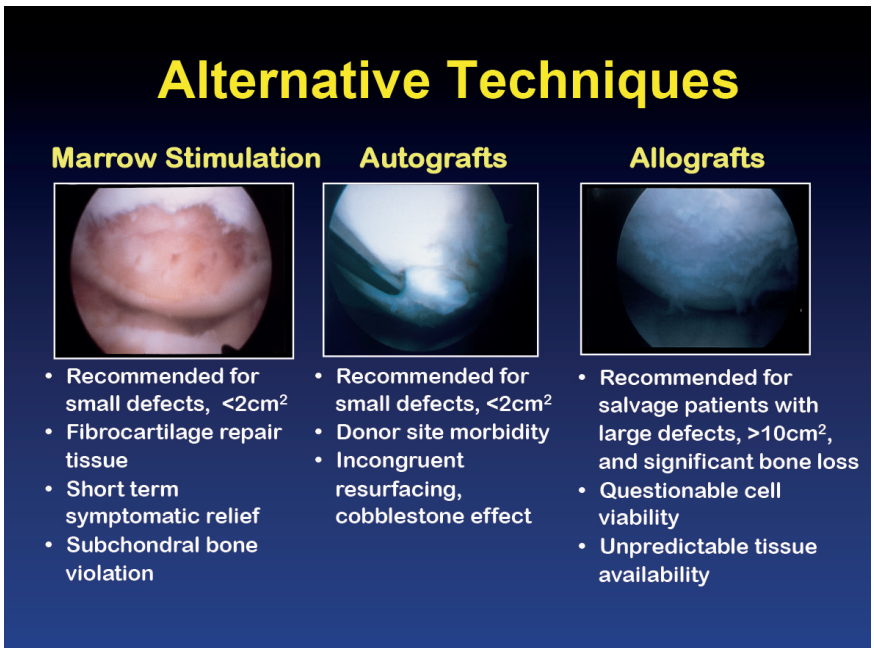


Figure 4

For larger cartilage defects *osteochondral allografts* have been successfully performed. This is one stage procedure and can be utilized for deep bone loss. The allografts should be harvested within 24 hours of donor death when they are 100% viable and can be stored at 40C for up to 28 days. The allografts should not be frozen. Freezing of chondral allografts leads to chondrocyte death and is not appropriate for graft preservation. Cell viability does decline after 5 days. Tissue matching and immunologic suppression is unnecessary. Bugbee et. al. reported an 86% survivorship at ten years follow-up (92 patients; Cohort Level III study).[6] According to Dr. Bugbee one should expect 1-3 mm of subsidence and 28% get 4-5 mm of subsidence.[7]

The indications for cartilage replacement surgical techniques are symptomatic deep lesions characterized by the International Cartilage Repair Society (ICRS) Grade 3: deep greater than 50% cartilage depth and down to but not through the chondral bone and Grade 4: subchondral bone exposed (with lesions extending through the subchondral bone plate or deeper into the trabecular bone). There should be no uncorrected malalignment or instability and no significant osteoarthritis. (Fig. 2,3)

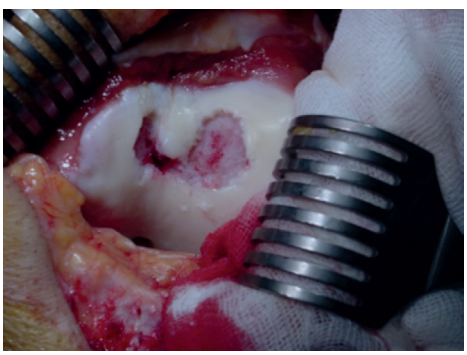


Figure 2

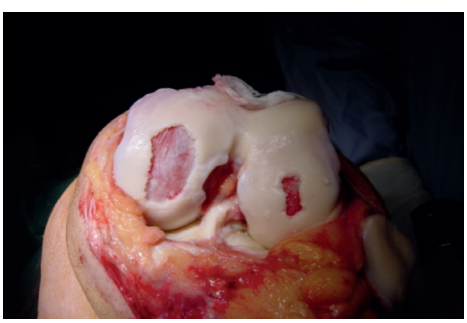


Figure 3

AUTOLOGOUS CHONDROCYTE IMPLANTATION

Autologous chondrocyte implantation (ACI) is the implantation of *in vitro* cultured autologous chondrocytes using a periosteal tissue cover after expansion of the isolated chondrocytes.

Autologous chondrocyte implantation (ACI) was first reported by Brittberg and coworkers in Gothenburg, Sweden in 1994,[8] has been successfully utilized in the knee and ankle joint. This procedure has yielded 80-90% good to excellent results in cases of isolated articular cartilage injuries and osteochondritis dissecans on the femoral condyles of the knee.

ACI is a two-stage process. Articular cartilage chondrocytes are harvested by either arthroscopic or open techniques. The chondrocytes are cultured in vitro for 3 to 5 weeks, expanded and reimplanted by arthrotomy. A periosteal graft must be harvested and sutured in place over the chondral defect in a "water tight" manner (2-3 mm apart). The cultured autologous chondrocytes are then injected onto the defect under the periosteal patch and the arthrotomy incision is closed. This often requires a wide arthrotomy incision to be made to allow for proper suturing of the periosteal graft. Complications include graft hypertrophy, delamination of defect, and intraarticular adhesions.[9,10] (FIG. 5)

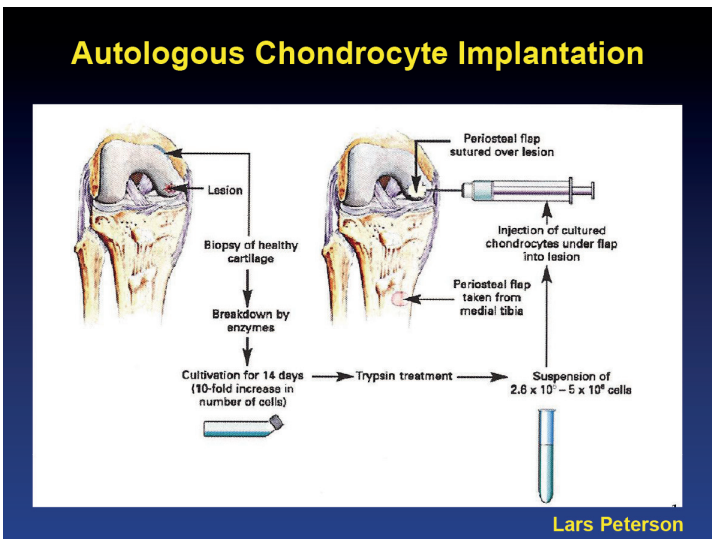


Figure 5

152 cases of ACI were performed from 1996 thru 2001. Average size of the defect was 6.1cm (0.25cm-13.5). There were 146 knees and 6 ankles (medial femoral condyle 64). Average age was 30 years (12-54 years). Results (retrospective Level 5) 3 to 8 years follow-up: 82% good to excellent 13% fair; 5% poor. There was one significant case of periosteal delamination in an elite level football player.

COLLAGE COVERED AUTOLOGOUS CHONDROCYTE IMPLANTATION (CACI)

Harvesting and suturing of a periosteal patch in autologous chondrocyte implantation is technically demanding and time consuming. Problems such as periosteal patch quality, symptomatic periosteal hypertrophy, and delamination have led to the development of biocompatible and bioabsorbable membranes to cover the chondral defect. A bilayer absorbable porcine collagen I/III membrane (Chondro-Guide, Geistlich Biomaterial, Wolhuser Switzerland) has been used instead of a periosteal patch. The membrane is degraded by enzymatic division (collagenase) and the resultant collagen-fragments denature at 37 degrees C. to gelatin. (Figs 6,7)

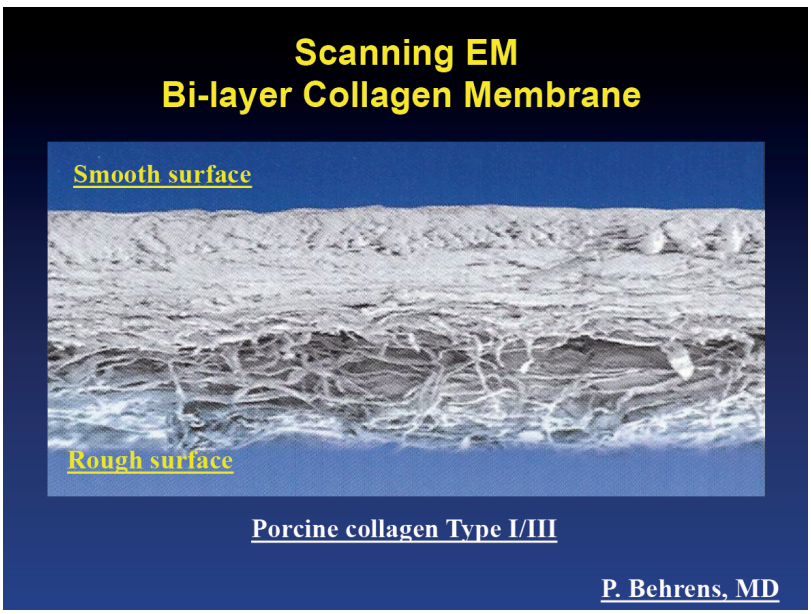


Figure 6

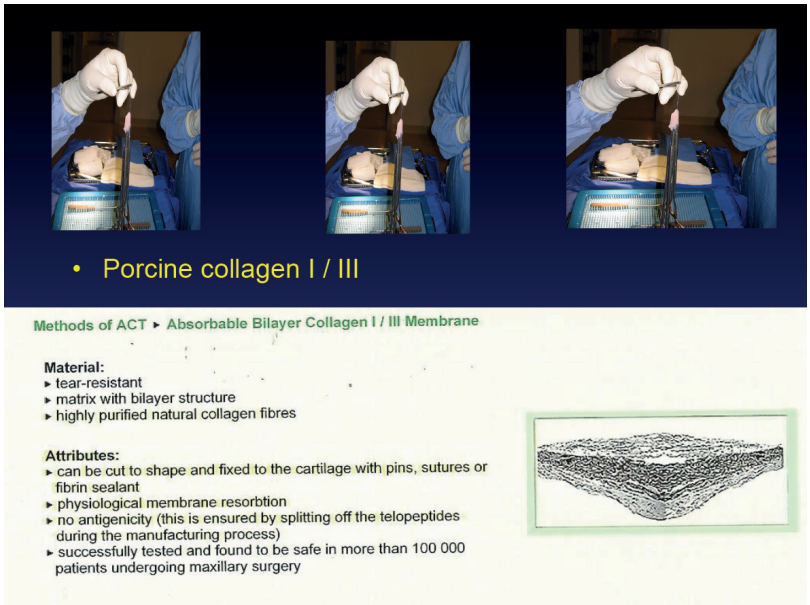


Figure 7

Is a periosteal patch necessary? Steinwachs in a prospective study reported on 63 patients with a collagen membrane (Chondro-Gide) ACI.[11] 88% reported good to excellent results three years after surgery. There was no case of membrane hypertrophy. In another study, 100 patients underwent ACI with a periosteal patch with 78% reported good to excellent results.[12]

MATRIX/MEMBRANE-INDUCED AUTOLOGOUS CHONDROCYTE IMPLANTATION (MACI)

MACI is a third generation chondrocyte implantation process. MACI is a new biotechnology allowing the impregnation of autologous cultured chondrocytes onto a highly purified porcine collagen I/III membrane (Vericell, Cambridge, MA). The MACI implant can be fixed to the chondral defect by fibrin glue (with little or no suture necessary), suture, or bioabsorbable pins or tacks. The procedure can be performed arthroscopically or by mini-arthrotomy. No periosteal graft is needed. (Fig. 8)

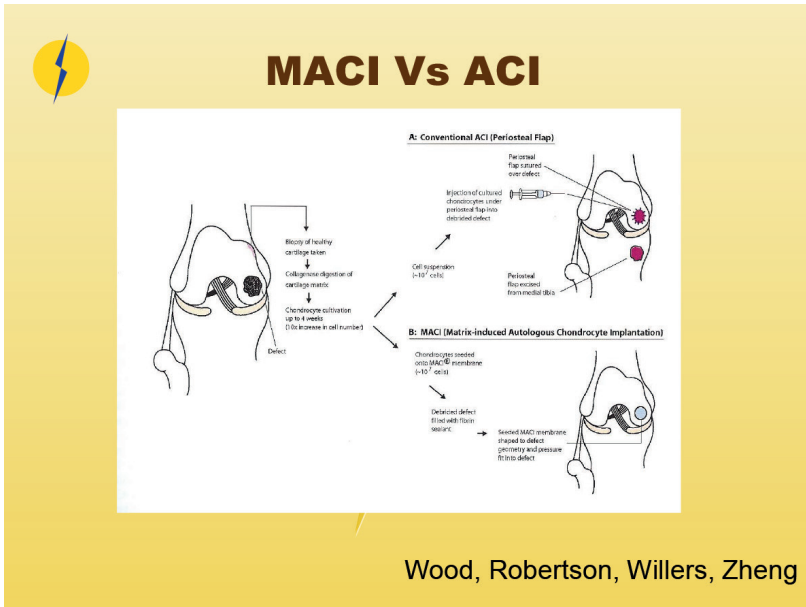


Figure 8

OPEN MACI TECHNIQUE

Initially chondrocytes are harvested arthroscopically from a non weight-bearing area of the ipsilateral knee (200-300 mg of healthy cartilage). (Fig. 13)

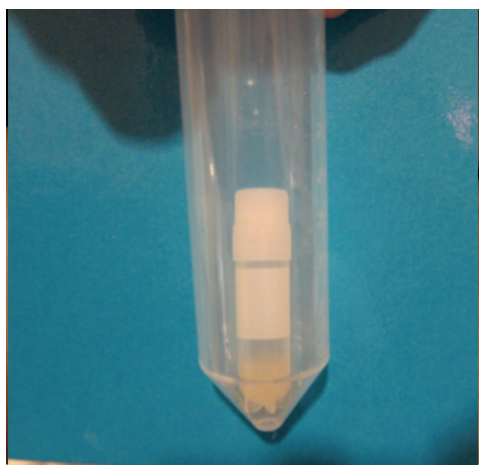


Figure 13: Chondrocytes in cell culture

The chondrocytes are then cultured, expanded *in vitro* (in 3-5 weeks) and then impregnated on an absorbable three-dimensional bilayered, purified porcine collagen I/III membrane. The bilayer structure has a smooth side that is non-porous acting as a natural barrier and faces the joint. Chondrocytes are seeded on the porous side of the matrix. The membrane is tear resistant and can be easily templated, trimmed, and cut to shape. The membrane is not self-adherent and can be "rolled-up" and handled with standard arthroscopic instrumentation allowing for arthroscopic implantation of the membrane.[13,14,15] The membrane is non-antigenic (telopeptides are split during the manufacturing process) and is bioabsorbable. The bioabsorbable membrane can be fixed to the cartilage defect with fibrin glue, pins or suture. (Fig. 7,8)

Utilizing mini-arthrotomy or arthrotomy techniques the cartilage defect is debrided and curetted with a sharp ring curette to remove the calcified fibrous cartilage layer without penetrating the subchondral bone. (Avoid bleeding of the subchondral bone!) (Fig 9)

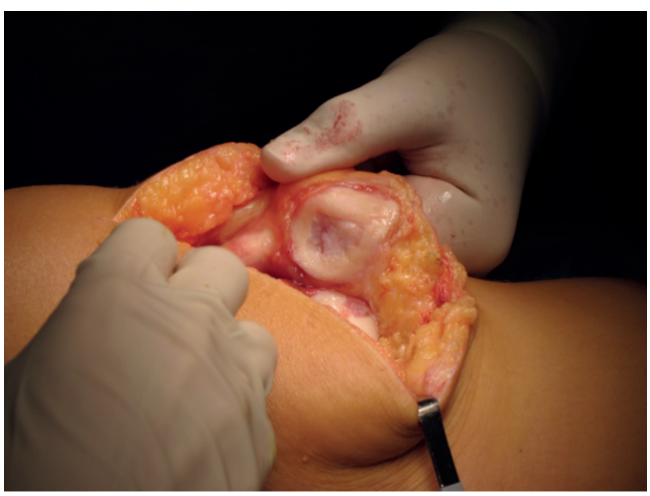


Figure 9: Chondral defect of the patella

A stable cartilage rim with sharp vertical walls of healthy cartilage is created. (Note: all "damaged" cartilage should be debrided back to a healthy stable border). (Figs 9,10,11,12) Intralesional osteophytes, if any should be

removed. The chondral defect is measured and templated. (Figs 14,15) The MACI membrane is cut to the proper shape with a scalpel or scissors. (Figs 15,16)

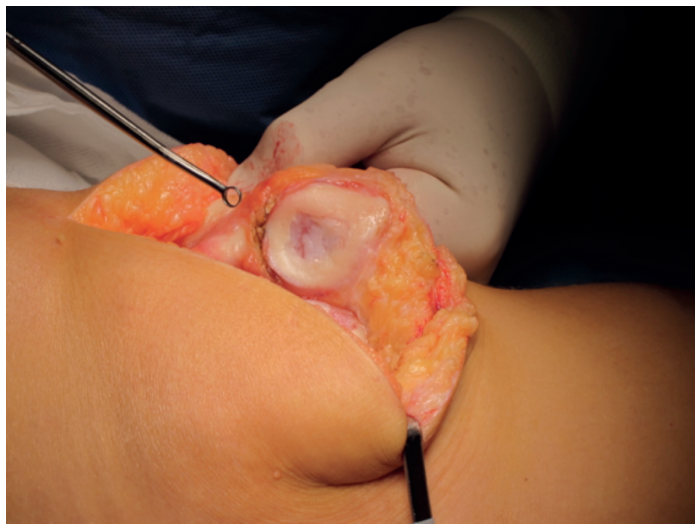


Figure 10: Chondral defect of patella curetted

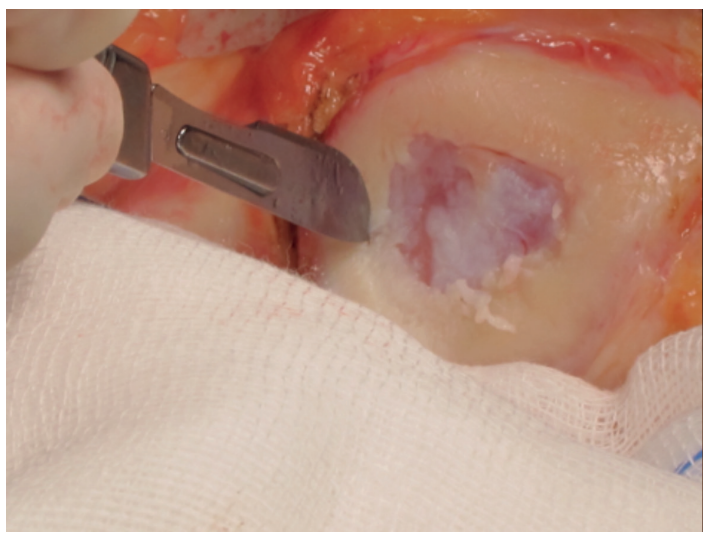


Figure 11: Create a stable rim with stable walls

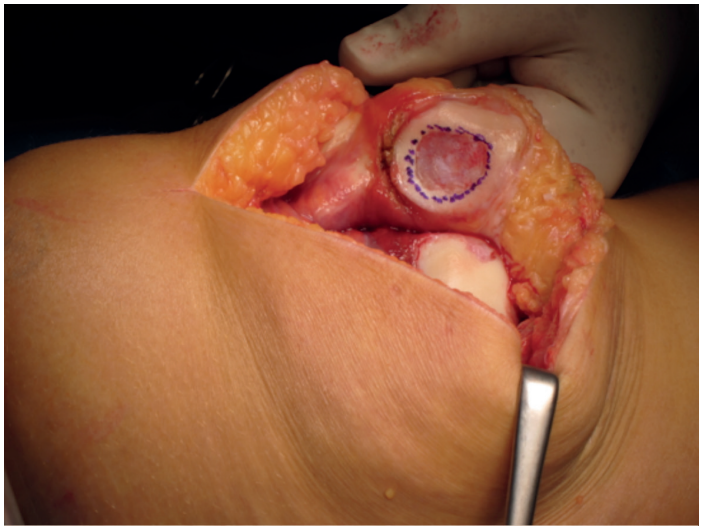


Figure 12: Cartilage lesion patella with stable vertical wall

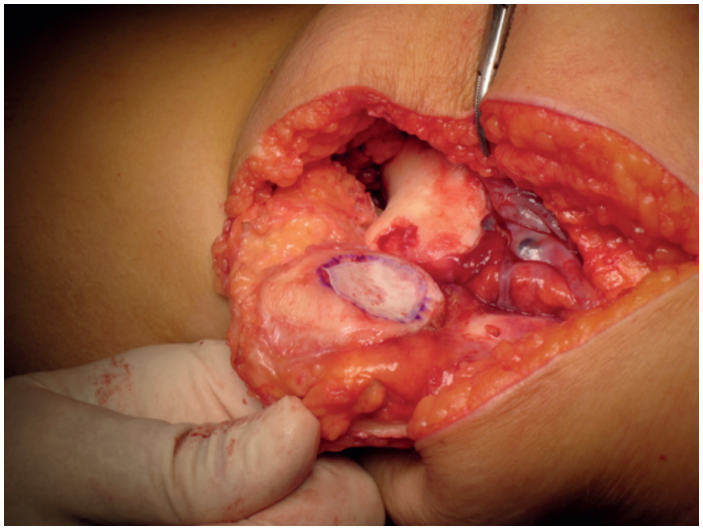


Figure 14: Lesion of patella templated

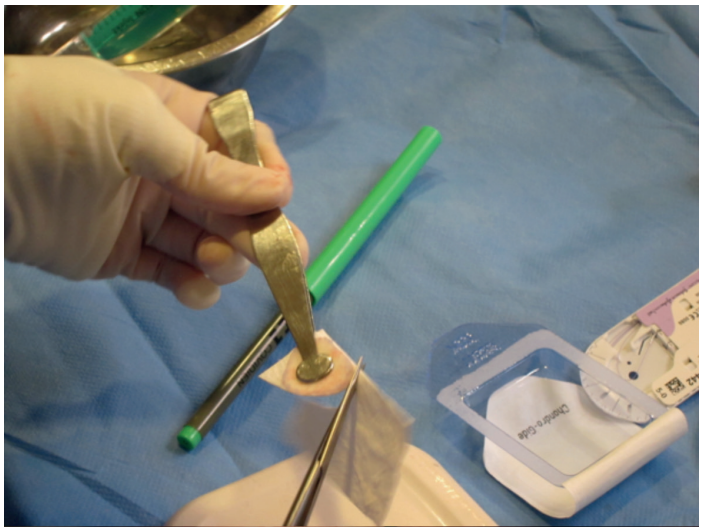


Figure 15: Chondro-Gide membrane cut to size of lesion

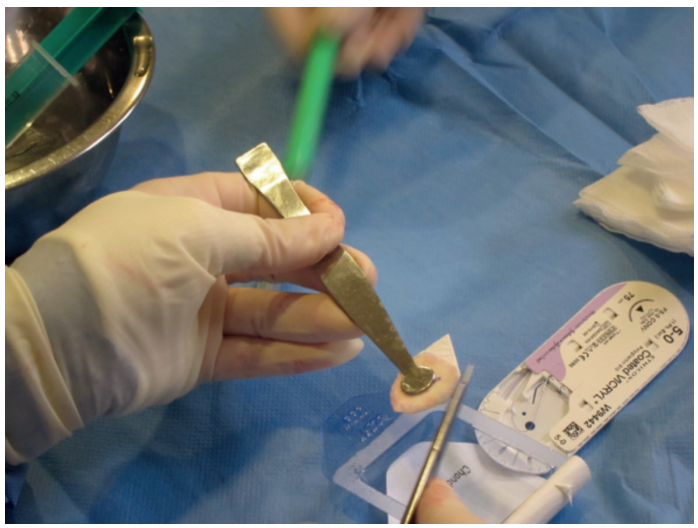


Figure 16: Trimming the Chondro-Gide membrane

The membrane is then fixed with fibrin glue (Tisucol, Baxter, Spain). Suture is used for the patella (fig. 18)

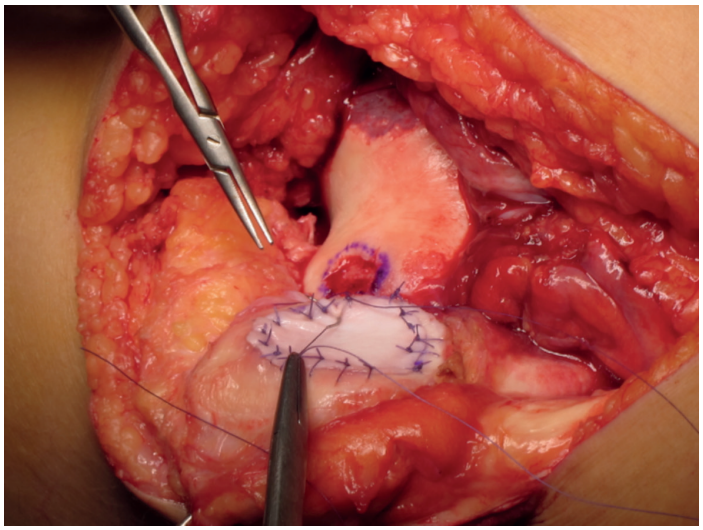


Figure 18: ICC membrane sutured in place

Postoperatively the patient is placed in a soft dressing and placed on continuous passive motion (when available) for 8 weeks. The patient is kept to partial weight bearing activity for 8 weeks. Larger and more central lesions are kept partial weight bearing for 12 weeks.

ARTHROSCOPIC MACI TECHNIQUE[13,14,15]

After previous biopsy and culturing of chondrocytes, a standard arthroscopy is performed thru a specially designed arthroscopic cannula and the cartilage defect is curetted using sharp ring curettes to remove the calcified cartilage layer. A stable rim with sharp vertical walls of healthy cartilage is created. Using a flexible ruler, a standard probe and a specially designed arthroscopic caliper, the size of the lesion is calculated. A template is created (using packaging from a suture pack or rubber drain) and placed in the cartilage defect to test for size.

Utilizing a "dry scope" the area of the cartilage defect is visualized (ambient air, no insufflation). Instrumentation has been developed at the Clinica CEMTRO that allows the MACI membrane to be pierced in its center and then placed in the center of the cartilage defect. The membrane is then pushed down the cannula with a slotted articulated inserter and held in place by the arthroscopic "skewer". Fibrin glue is then placed under the MACI membrane, and the membrane is smoothed out using an articulated "T" smoother/tamper. The excess glue is removed, and the membrane contours to the cartilage defect while the fibrin glue is setting. Mini suture anchors or absorbable "pins' can be used if a more secure fixation is required for stability. The joint is taken through a range of motion to insure the graft is stable. (Fig. 19,20)

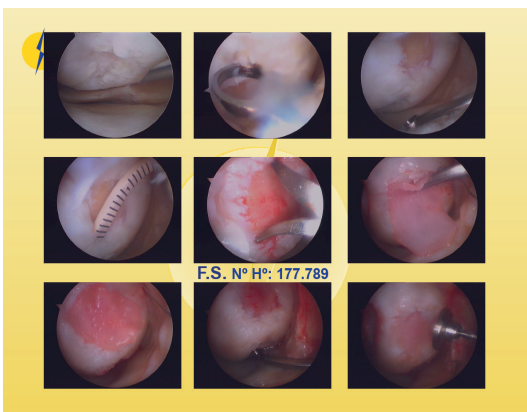


Figure 19

Figure 20

ICC
(Figures 9-18)

The MACI membrane as currently supplied is now 3x5 cm and is seeded with 1 million chondrocytes per cm^2 for a total of 15 million chondrocytes. (Previously the membrane size was 4x5cm^2 with a total of 20 million chondrocytes.)

If one were to treat a 3x2 cm^2 lesion of the patella with the traditional MACI technique, 6 million chondrocytes would be utilized and 9 million chondrocytes would "literally" be thrown away. The same lesion treated with traditional ACI would potentially have 12 million cells at the site of the cartilage lesion, which is double the amount of chondrocytes delivered to the same sized lesion treated with MACI. Since one side of the membrane is not porous, the MACI membranes really cannot be stacked upon one another. (Fig. 24)

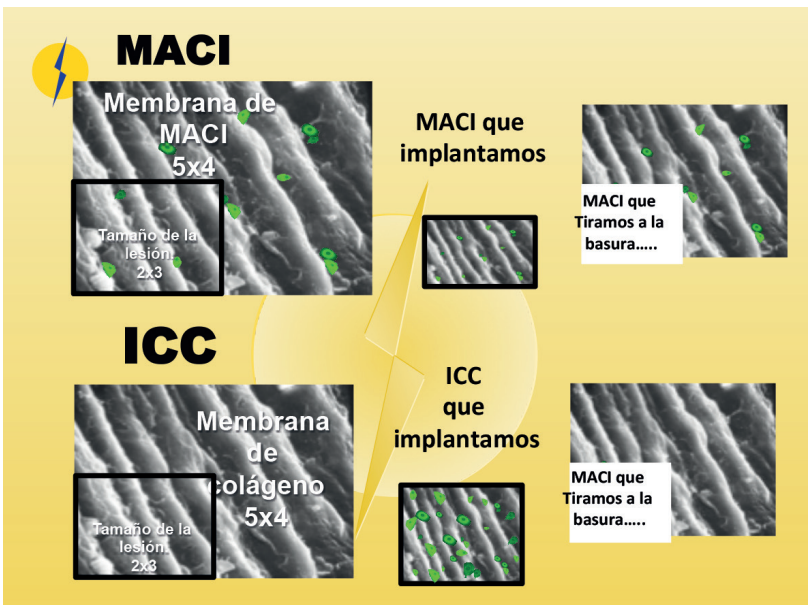


Figure 24

At Clinica CEMTRO/ Universidad Catholic San Antonio de Murcia (UCAM) the concept of "Cell Density" concerning chondrocytes was investigated. In a recent article in Cartilage, Foldger, Gomol, Lind and colleagues reported "In the absence of systematic evaluations of the effects of cell density and clinical outcome, many clinicians continue to use one or two million chondrocytes per cm^2, which, despite its lack of evidence and the fact that most in vitro studies point toward benefits of high intensities, has been associated with favorable clinical outcomes and nearly approximates the densities found in native adult articular cartilage."[18]

In attempt to determine which type of cell (mesenchymal cell or chondrocyte) and the number of cells per square centimeter that are "optimal", at Clinica CEMTRO we studied 15 female merino sheep with articular cartilage lesions treated with autologous chondrocytes or mesenchymal cells seeded onto a porcine collagen I/III membrane. Experimental groups were 5 million chondrocytes per cm^2; 1 million chondrocytes per cm^2; 5 million mesenchymal cells per cm2; and microfracture. All samples were analyzed for cellular histology, type I collagen, type II collagen and aggrecan. The expression of aggrecans was seen in all samples. The expression profile of Col II (marker of hyaline cartilage) showed the control group was greater than 5 million chondrocytes, which was greater than 1 million chondrocytes, which was greater than 5 million mesenchymal cells, which was greater than microfracture. The expression profile of Col I was microfracture greater than 5 million mesenchymal cells greater than 1 million chondrocytes greater than 5 million chondrocytes. The results were statistically significant. The histology showed 5 million and 1 million chondrocytes to have a more hyaline-like cartilage structure than either the microfracture or implantation of 5 million mesenchymal cells. Increasing the density of chondrocytes improved the quality of the regenerated tissue.[4] (Fig 21,22,23)

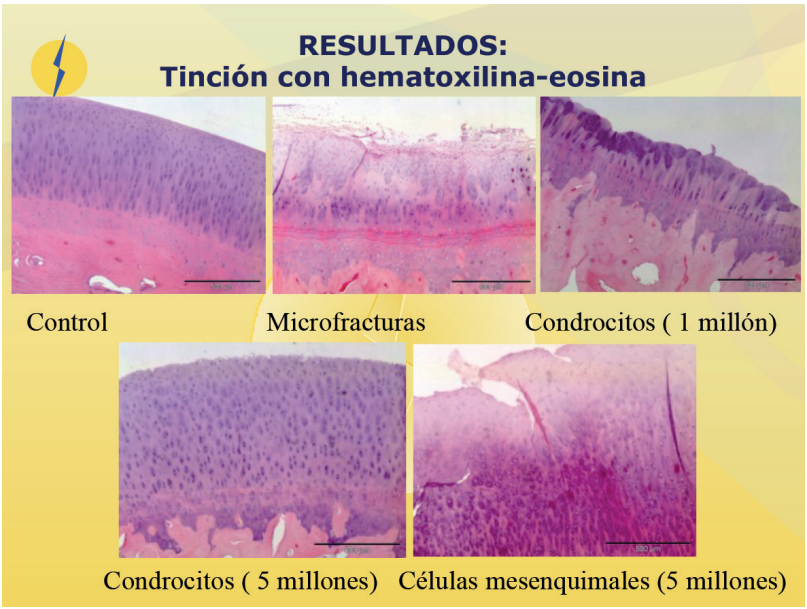


Figure 21

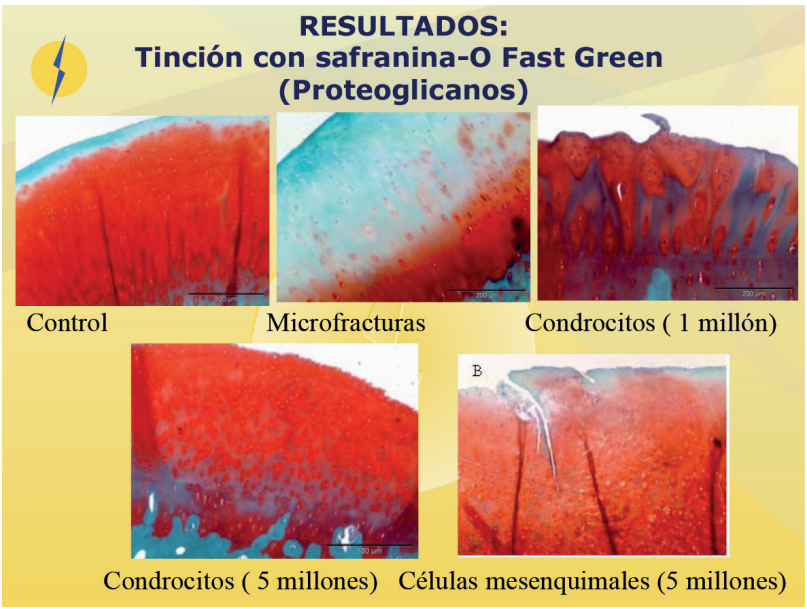


Figure 22

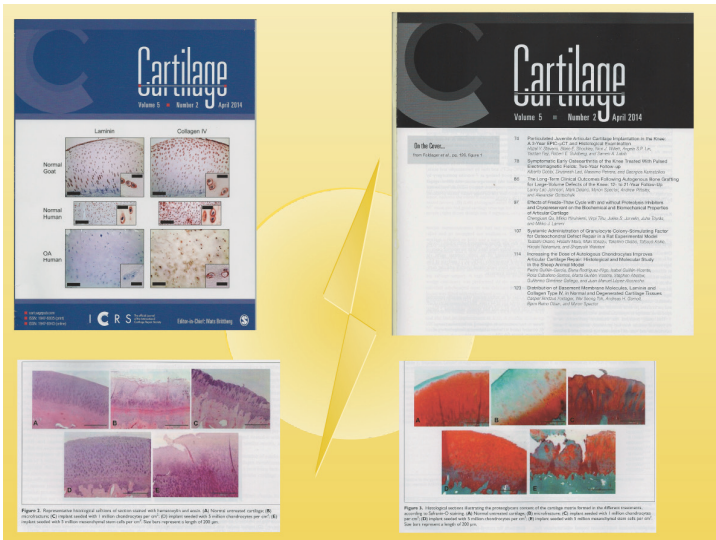


Figure 23

Based upon the fact that 5 million chondrocytes demonstrated a better regenerative cartilage tissue than 1 million chondrocytes or 5 million MSC, Clinica CEMTRO has developed a modification of the MACI procedure increasing the number of cells per cm^2 seeded on the collagen membrane. (Instant CEMTROCELL-ICC, Madrid, Spain). (Fig.24)

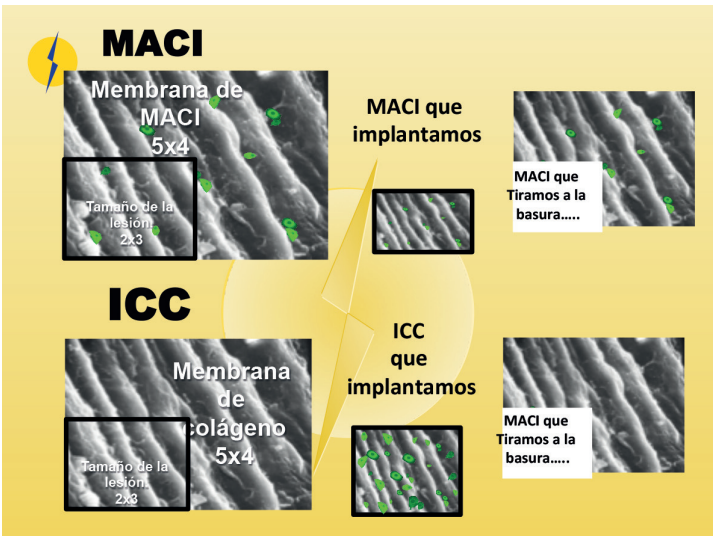


Figure 24

After biopsy by arthroscopy, isolation of chondrocytes, and cell culture to 20 million cells, the cell suspension is transferred to the operating room. The lesion is templated. (Fig. 14) The Chondro-Gide membrane is cut to the size of the lesion (Fig. 15,16) and all of the cell suspension is seeded on it. (Fig 17) The cells are seeded on the porcine collagen I/III membrane according to the method of Steinwachs.[11] the cultured chondrocytes are placed on the collagen membrane and after a 10-minute period of time to allow for the absorption of chondrocytes, the membrane is implanted on the articular cartilage defect. (e.g. a 2x3 cm^2 cartilage lesion would receive more than 3 million chondrocytes per cm^2 (Fig 17)

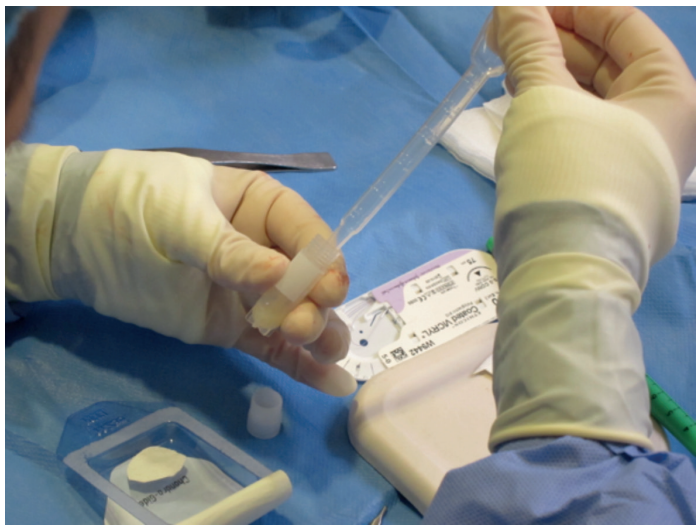


Figure 17: ICC cultured chondrocytes placed on Chondro-Gide membrane

Histological and genetic studies of ICC to date have shown a proliferation of collagen matrix, a population of viable mature chondrocytes, and immature population of chondrocytes with absence of expression of protein S-100, absence of atypical mitosis (absence of expression of P52), and a proliferative capacity.

Native Cartilage, Regenerated Cartilage, and MACI: A Comparative Study[16]

In an attempt to define the adequacy of the cultured chondrocytes we studied the cell distribution in tissue, cell morphology, collagen type II and X, and FGFR3 presence (Fibroblastic Growth Factor Receptor 3) in native cartilage, regenerated cartilage and MACI). (In achondroplasia there is a heterozygous mutation of the gene encoding fibroblastic growth factor 3).

Healthy cartilage had 117.6 +/- 6.2 cells/mm^2 compared to regenerated cartilage, which had 57.3 +/- 2.7 cells/mm^2. (Fig 27) A comparative analysis by Western Blot Electrophoresis demonstrated normal collagen type II in native and MACI cartilage and little type II cartilage in the regenerated tissue. (Fig 28) Looking at collagen type X, the reverse findings were present. There was abundant collagen type X in the regenerated cartilage and only minimal collagen type X in native cartilage and MACI cartilage. (Fig 29)

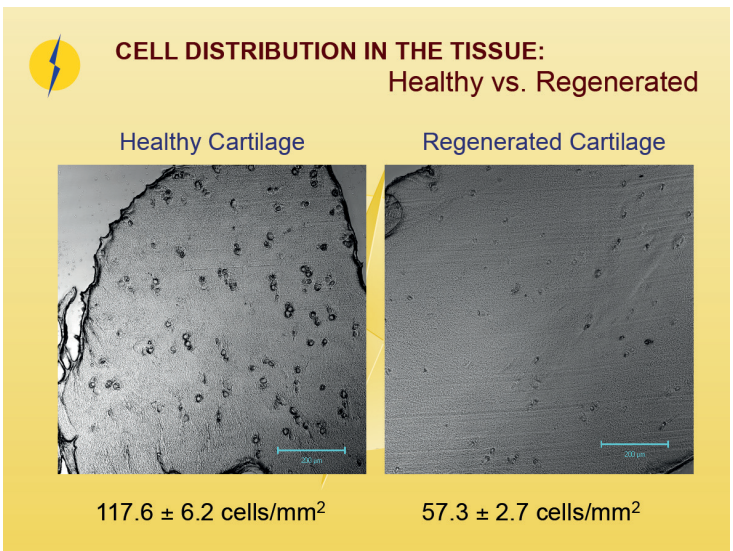


Figure 27

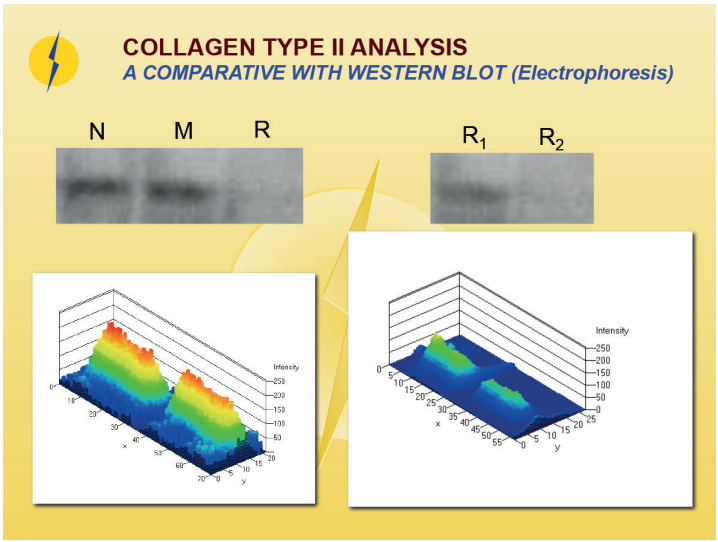


Figure 28

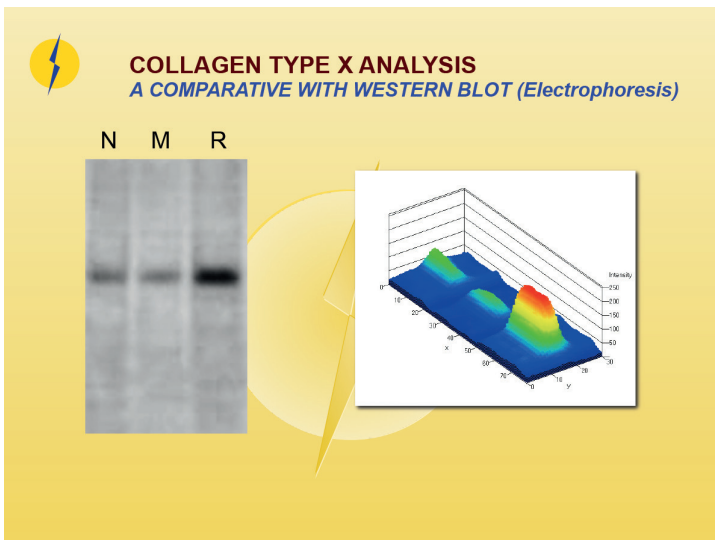


Figure 29

Analysis of the presence of fibroblastic growth factor receptor 3 demonstrated normal amounts of FGFR3 in healthy native cartilage chondrocytes and MACI cartilage chondrocytes. Regenerated chondrocytes showed only a small amount of FGFR3 (30%) (Fig 30,31)

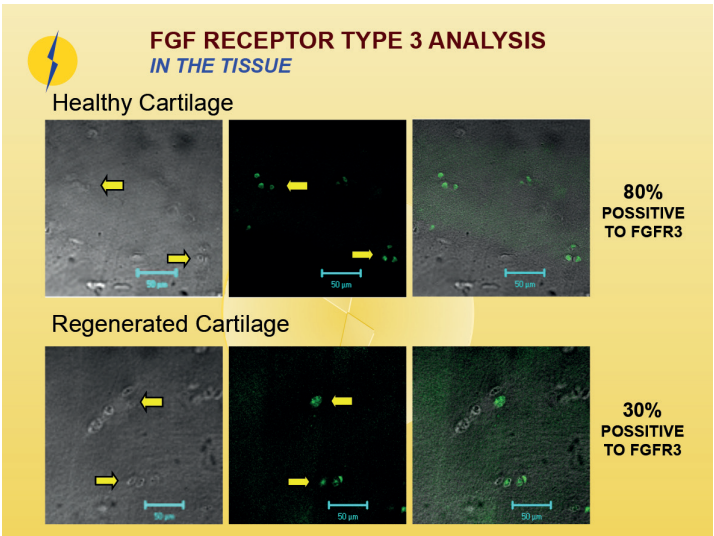


Figure 30

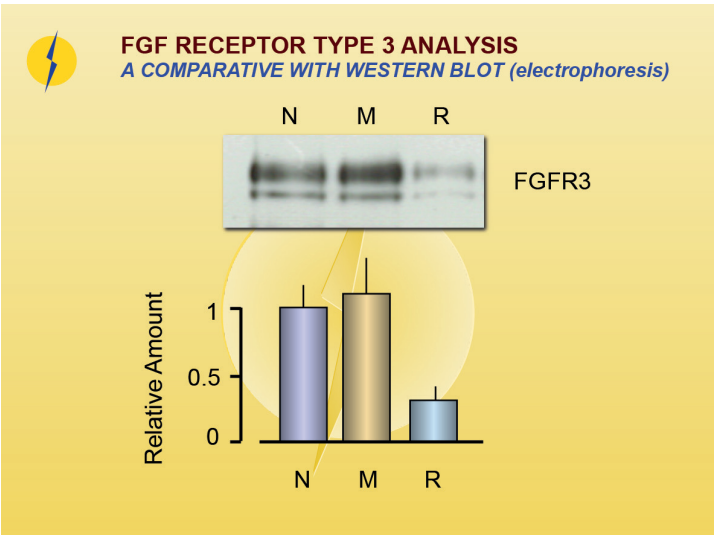


Figure 31

This study showed that regenerated cartilage compared to normal cartilage and MACI cartilage had 50% the number of cells. MACI chondrocytes compared to normal cartilage chondrocytes presents identical FGFR3 receptor amount, collagen type II levels, and collagen type X levels. Regenerated cartilage chondrocytes produce less collagen type II and more collagen type X than normal or MACI chondrocytes. Regenerated cartilage chondrocytes showed a lack of FGFR3 receptors compared to normal or MACI chondrocytes (only 30% of the cells had this receptor.

The clinical relevance of this study is that according to Arnold Caplan, PhD at the International Repair Society World Congress (Chicago, Il., USA May, 2015) the ratio of FGRF3 to FGRF 1 may be an important determining factor in the progession of chondrocyte progenitor cells into producing articular cartilage rather than enchondral ossification.

HOW CAN WE POTENTIATE THE CAPACITY OF THE CULTURED CHONDROCYTES?

In an attempt to potentiate the cultured chondrocytes many growth factors and other polypeptides and long-chain proteins have been utilized. Experimentation with the addition of a dinucleotide molecule (diadenosine tetraphosphate –Ap_4D_2) to the culture medium showed significant improvements in the growth characteristics of the cultured chondrocytes. (Fig. 32) Diadenosine tetraphosphate is a molecule that is found in human synovial fluid. (Fig. 33) The Ap_4D_2 favored the proliferation of chondrocytes by almost 30%. (Fig 35) The Ap_4D_2 favored the production of extracellular matrix by almost double.(Fig. 34) Treated tissue demonstrated more collagen type II and less collagen type X than the untreated tissue. The addition of Ap_4D_2 reduced the number of FGFR3 receptors in the chondrocyte membrane.

Animal experimentation is currently underway.

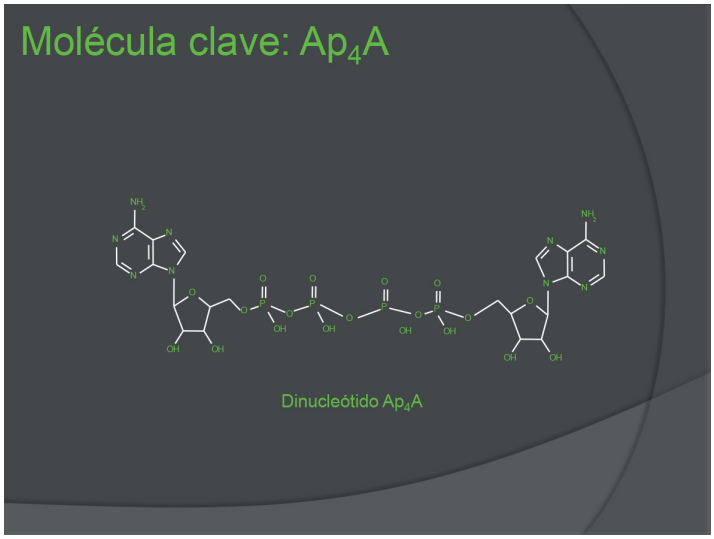


Figure 32

Figure 33

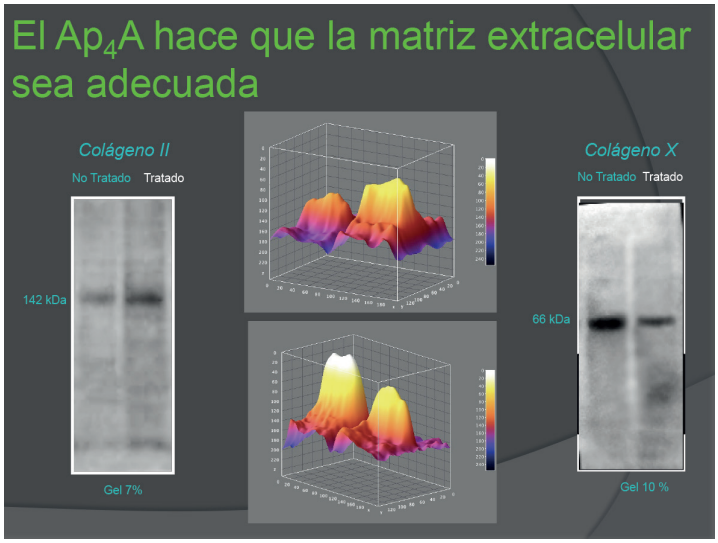


Figure 34

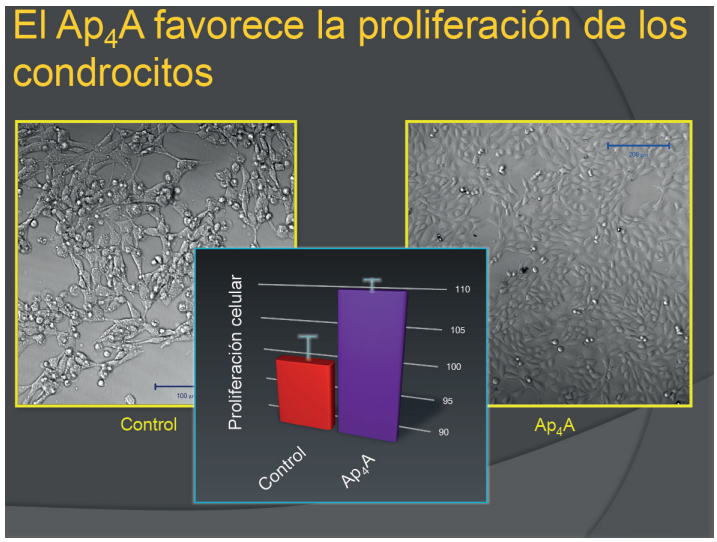


Figure 35

INDUCED PLURIPOTENT STEM CELLS (iPSC)

Induced Pluripotent Stem Cells (iPSC) are "embryonic-like" stem cells that are developed from a persons own cells such as skin, blood, MSCs, etc.)(Fig 36,37) and Re-engineer or Re-program these cells to differentiate into other tissue types including chondrocytes. These "embryonic-like" stem cells are developed by means of gene transduction using ESC-specific transcription factors.[17]

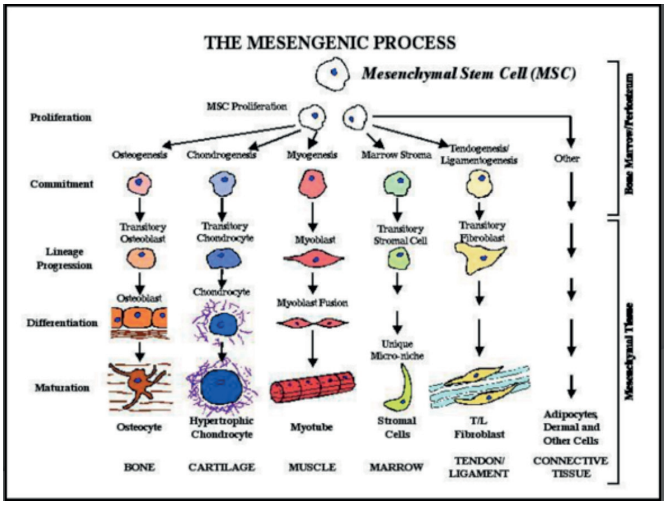


Figure 36

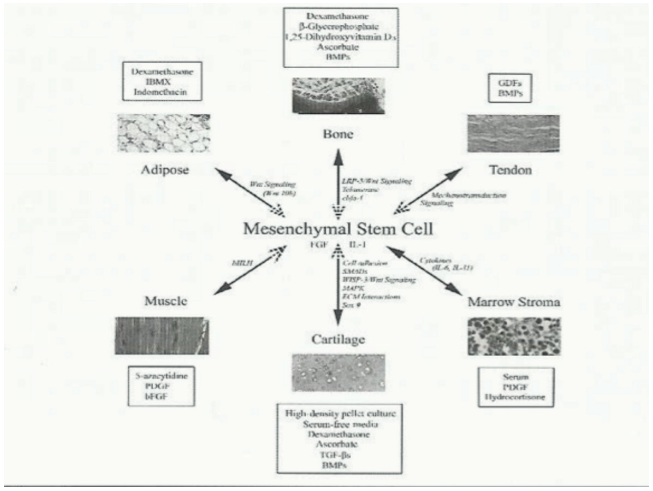


Figure 37

Yamanaka introduced the concept of Induced Pluripotent Stem Cells in 2006. Shinya Yamanaka and John Gurdon were Nobel Prize Winners in Medicine in 2012.(Fig. 38)

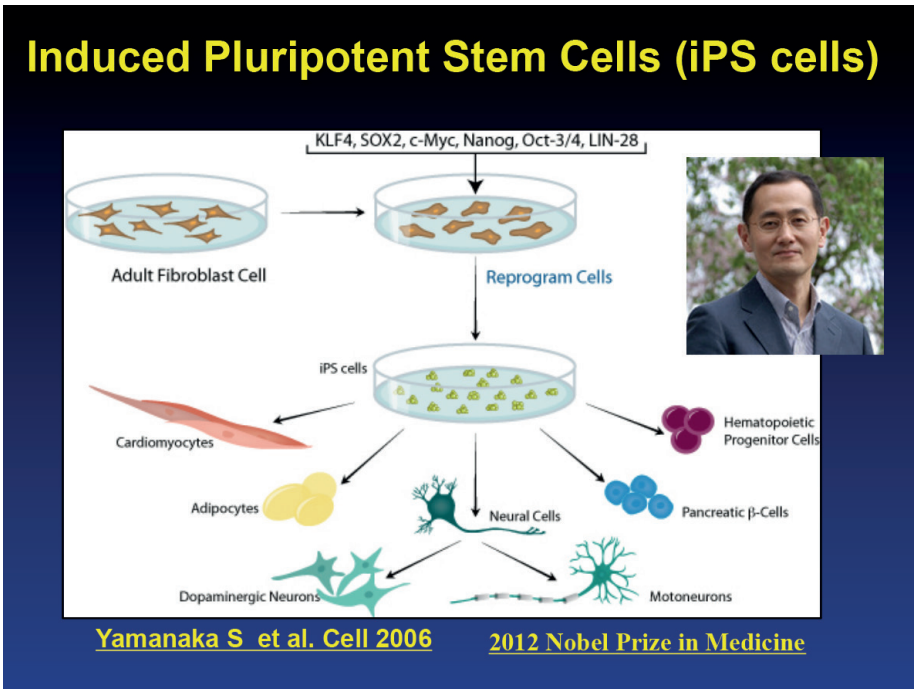


Figure 38

These iPSCs are pluripotent cells like ESCs and are autologous in origin. The iPSCs would theoretically be capable of indefinite self-renewal. There should be no ethical concerns. These iPSCs could be used in multiple tissue applications including cartilage regeneration.

Safety concerns with iPSCs would be that their undifferentiated nature and tendency to grow without restraint could lead to the development of tumor or teratoma formation.

A study performed by the University of Connecticut Stem Cell Laboratory compared normal chondrocytes, osteoarthritic chondrocytes, dermal fibroblasts (skin) and cord blood mononucleocytes in forming cartilage iPSCs.

Their study demonstrated that iPSCs derived from either normal or osteoarthritic articular chondrocytes possess a greater chondrocyte-forming potential compared to the iPSCs from skin or cord blood mononucleocytes. Their data showed that the tissue of origin affected the fate potential of iPSCs for differentiating into chondrocytes. They reported that the iPSCs derived from osteoarthritic articular chondrocytes displayed similar induction of early chondrogenic markers compared to iPSCs from normal chondrocytes.

Clinica CEMTRO (Madrid, Spain) / UCAM (Murcia, Spain) are in collaboration with the Salk Institute of San Diego, California, USA and have already started to culture mesenchymal stem cells transformed/ reprogrammed into chondrocytes with the addition of TGF-beta.[19] (Figs. 39-44)

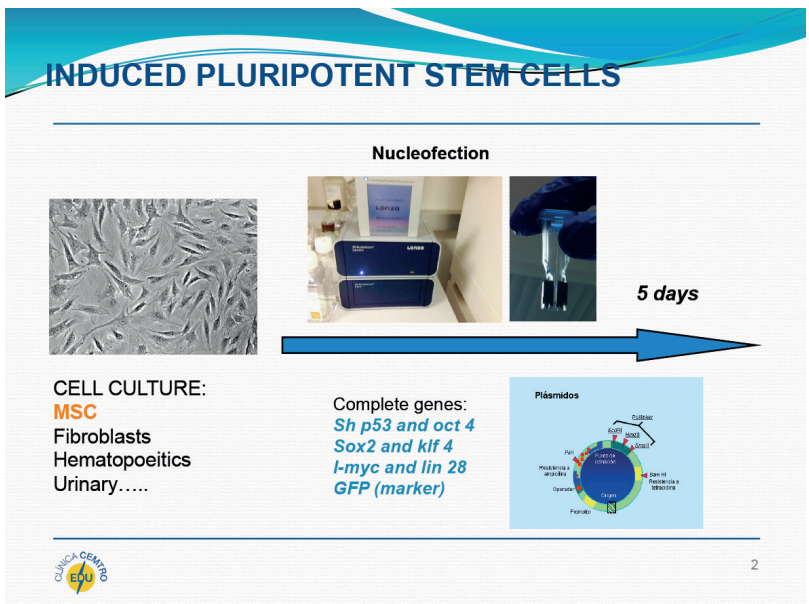
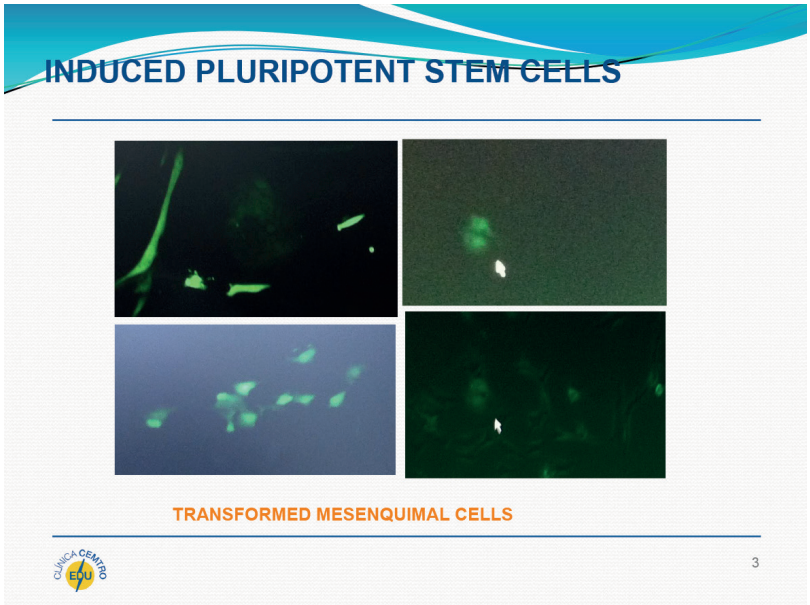


Figure 39



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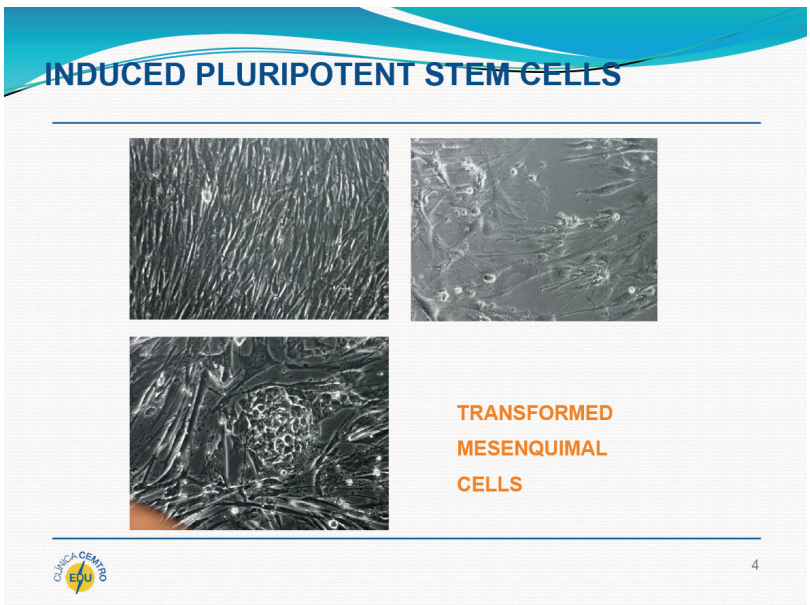
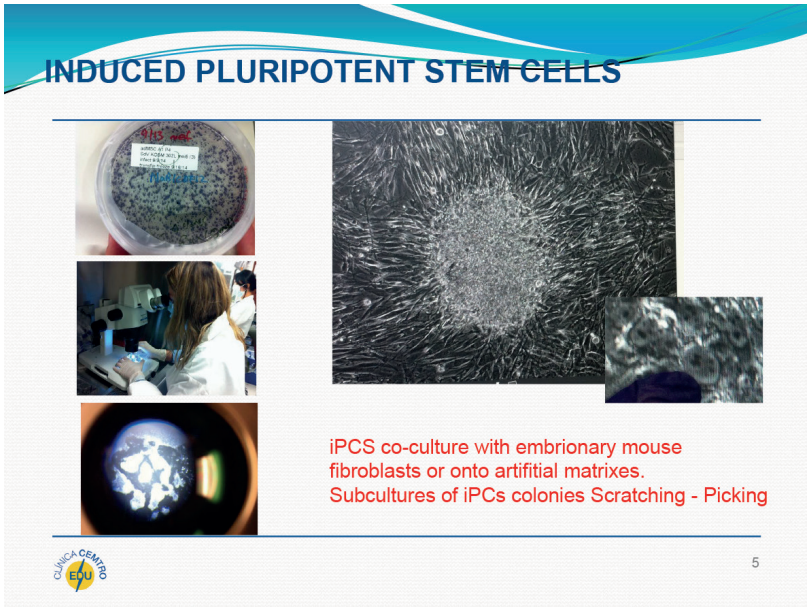


Figure 41



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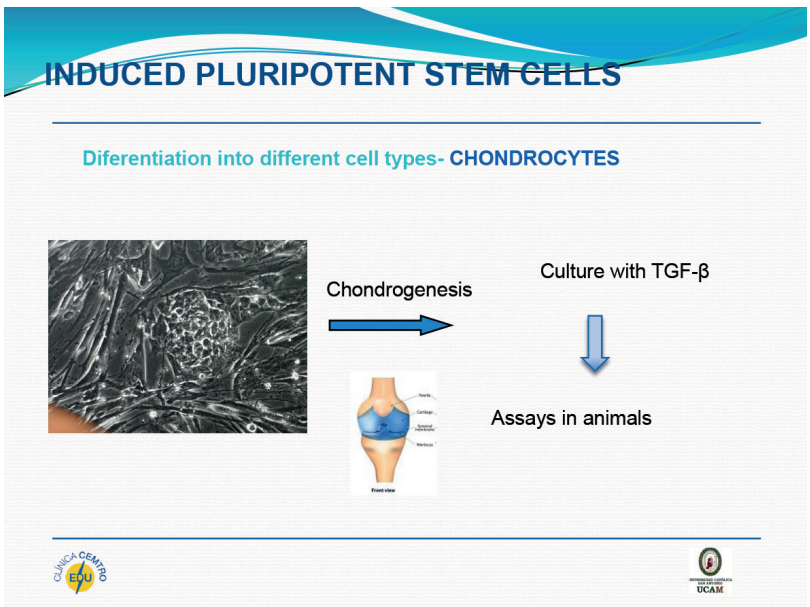

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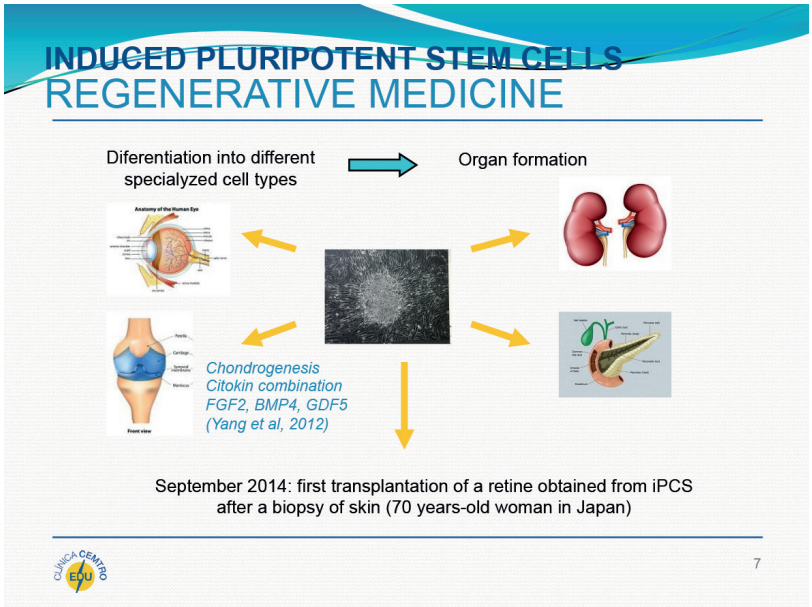

Figure 44

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