



32nd INTERNATIONAL PAK ORTHOCON 2018

Extending Standard Musculoskeletal Care to Less Privileged Areas



بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

Past Present & Future

پاکستان اک عشق اک جنوں



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Past Present & Future

Disclosure

Consultant for Lima
Consultant for Arthrex EMEA
Consultant for Lavander Medical
Consultant For Stryker
Consultant For Orthospace





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Past Present & Future





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Past Present & Future



Allah Ki Marzi Thi



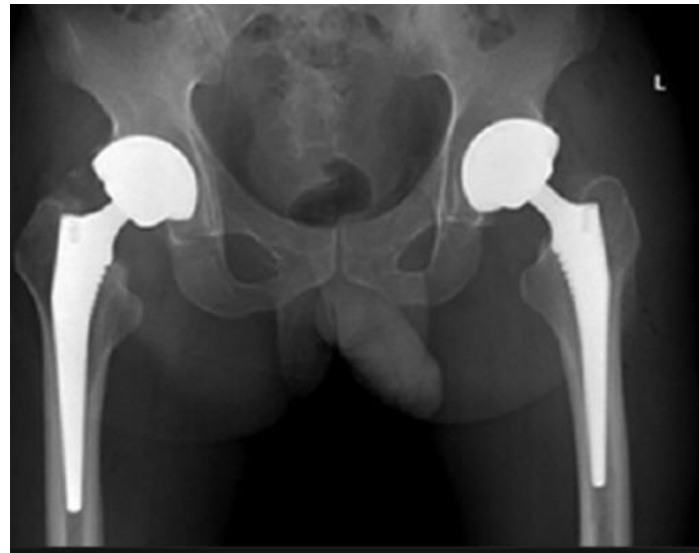


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Past Present & Future





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Past Present & Future





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Past Present & Future



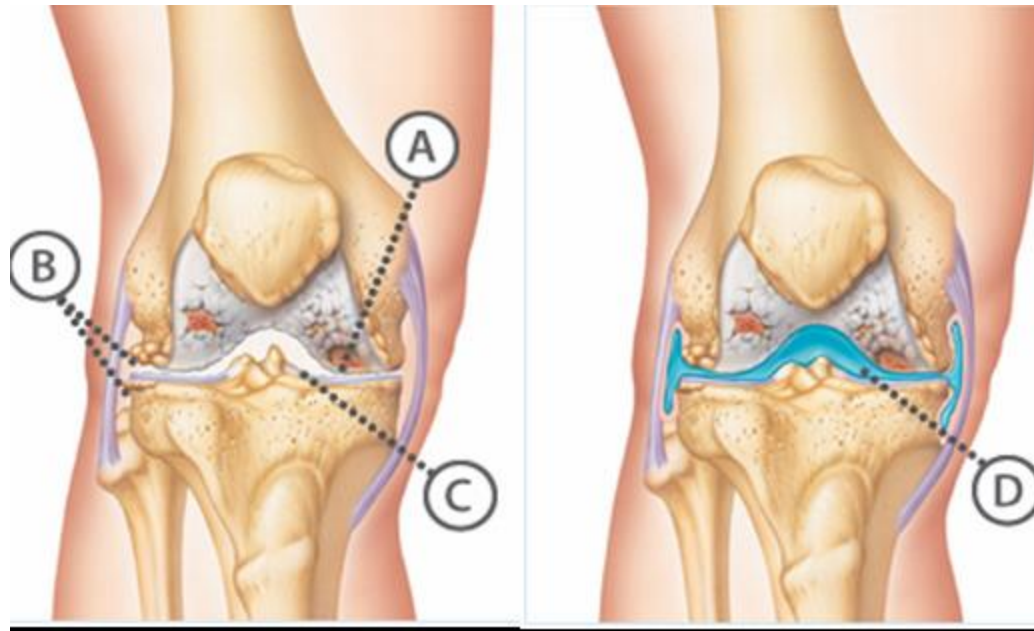


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Mechanical Cushion





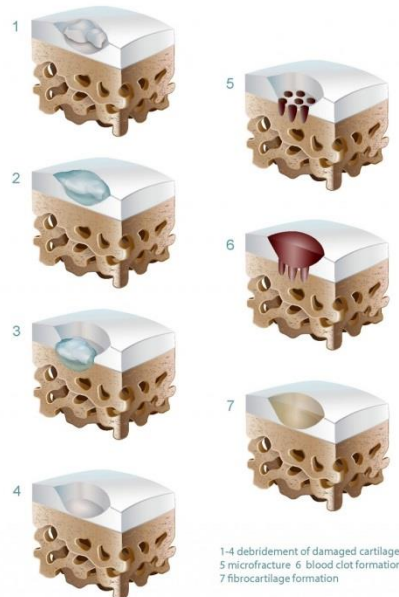
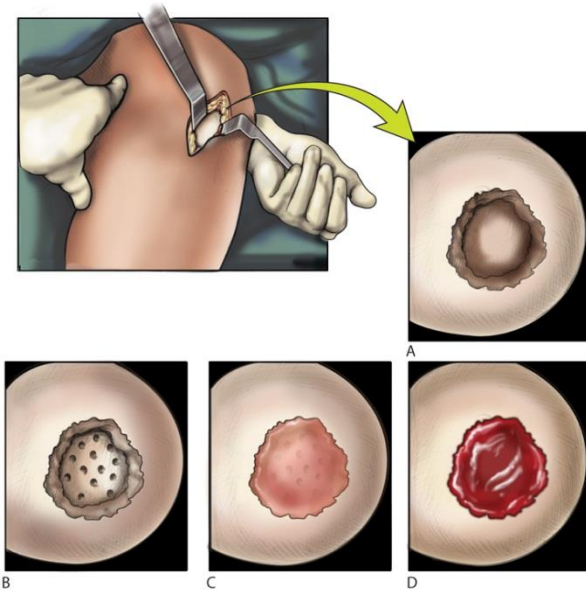
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Blood Stream Orthobiologics

Fig. 020 Debridement and microfracture





Blood Stream Orthobologics




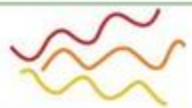



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Blood Stream Orthobologics

Grade	Form	Solubility	Absorption & digestibility	Application examples
Native collagen		Insoluble	None	Medical materials, collagen casings
Gelatin		Medium	Low	Gelatin desserts, confectionery
Collagen peptides		High	High	Dietary supplements, functional foods





Regenerative medicine

Orthobionics therapies are a specific type of regenerative medical treatment.

The **best news** is that it has gone from **science fiction** to a very **real** and very accessible form of treatment for a variety of orthopaedic injuries and joint degeneration.





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The Growing Field

Arthroscopic Management To Buy Time
Joint Replacement to restore movements
Real 3rd option “Orthobionics”



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Understanding Key

you gone learn today





Not a new Concept

The Quran states

“ ثُمَّ خَلَقْنَا النُّطْفَةَ عَلَقَةً فَخَلَقْنَا الْعَلَقَةَ مُضْغَةً فَخَلَقْنَا الْمُضْغَةَ عِظَامًا فَكَسَوْنَا الْعِظَامَ لَحْمًا ثُمَّ أَنْشَأْنَاهُ خَلْقًا آخَرَ ۚ فَتَبَارَكَ اللَّهُ أَحْسَنُ الْخَالِقِينَ

Then We made the sperm-drop into a clinging clot, and We made the clot into a lump [of flesh], and We made [from] the lump, bones, and We covered the bones with flesh; then We developed him into another creation. So blessed is Allah , the best of creators. (23:14)





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Not a new Concept

These verses clearly delineate the stages of Qur'anic embryology thus:

(references provide links to Lane's Lexicon of classical Arabic)

1. Dust/mud/clay (creation of Adam only)
2. Nutfah^[5] (drop of semen)
3. Alaqah^[6] (leech and certain creatures that cling and suck blood, or blood, thick blood or clotted blood)
4. Mudghah^[7] (bite-sized morsel of flesh, shaped and without shape)
5. 'Itham^[8] (bones, especially of the limbs)
6. 'Itham clothed^[9] with Lahm^[10] (flesh)
7. Another creation / child



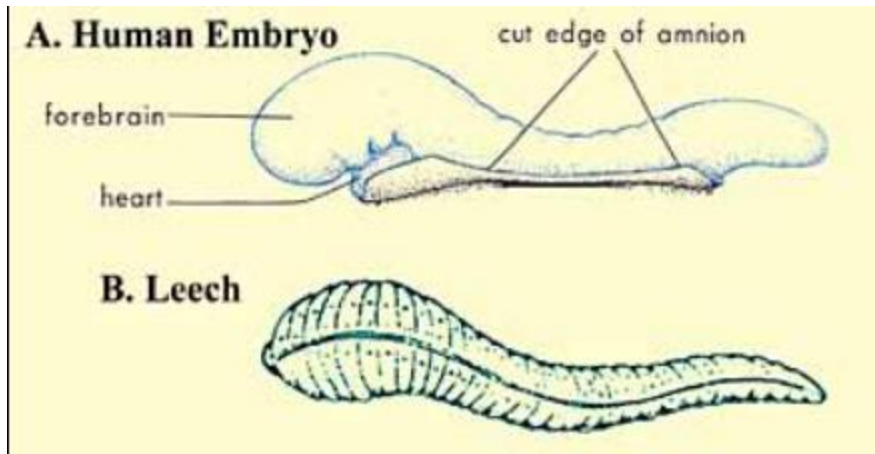


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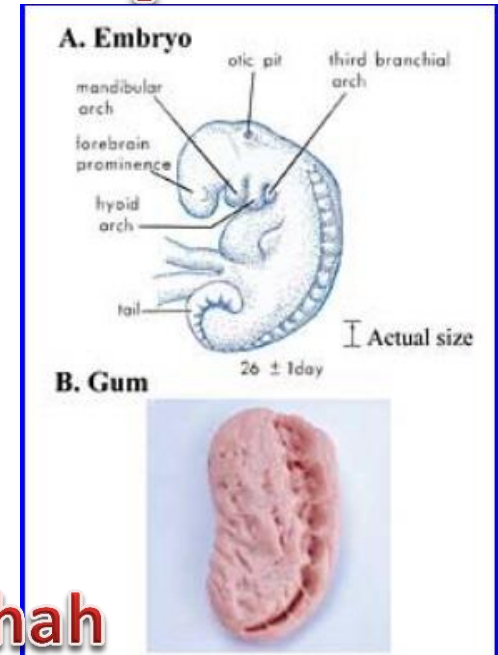
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Not a new Concept



Alaqah stage



Mudghah





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Not a new Concept

فَوَجَدَا عَبْدًا مِنْ عِبَادِنَا اتَيْنَاهُ رَحْمَةً مِنْ عِنْدِنَا وَعَلَّمْنَاهُ مِنْ لَدُنَّا عِلْمًا

DNA
ا ن د
A NE DE
←

In Surat al-Kahf, which refers to DNA and the year 1865 when the science of genetics began, DNA is repeated 7 times, as is RNA (the Arabic letters Ra-Nun-Alif). Like DNA, the RNA molecule is a molecule giving rise to genetic structure. For that reason, the appearance of DNA and RNA an equal number of times in this Surat is further proof that these molecules were referred to in the Qur'an hundreds of years ago. (Allah knows the truth.)





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Not a new Concept

3000 BC : As per Mahabharata, Adi Parva, chapter 114, shloka 17, the Kaurava were created by splitting the single embryo into 101 parts and growing each part in a separate kund or container. It is believed that Kaurva's birth mentioned here is first reported mention of what could be possible use of embryonic stem cell.



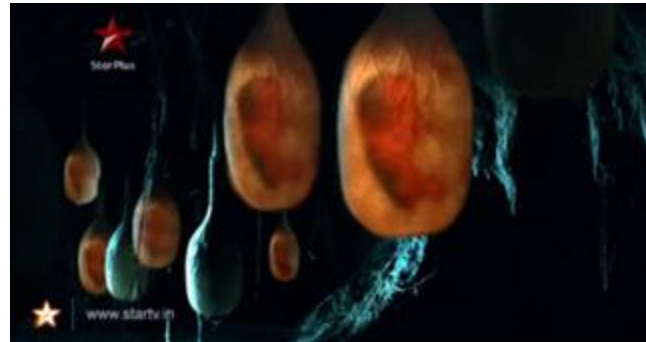


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Not a new Concept





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Not Long Ago...

- ❖ We looked for mechanical solutions to the biological problem.
- ❖ Over the years we realised that 'it is Biology Stupid'!
- ❖ Now we are increasingly looking for Biological solutions to biological problem!





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Evolution

First- generation biologics consisted of **viscosupplementation** for joint arthritis, in the form of HA. **PRP** emerged as the **second generation** of Orthobiologics, and the first Orthobiologics of the autologous form. In recent years, Bone Marrow Concentrate (**BMC**) has emerged as the **third generation** of Orthobiologics therapy.



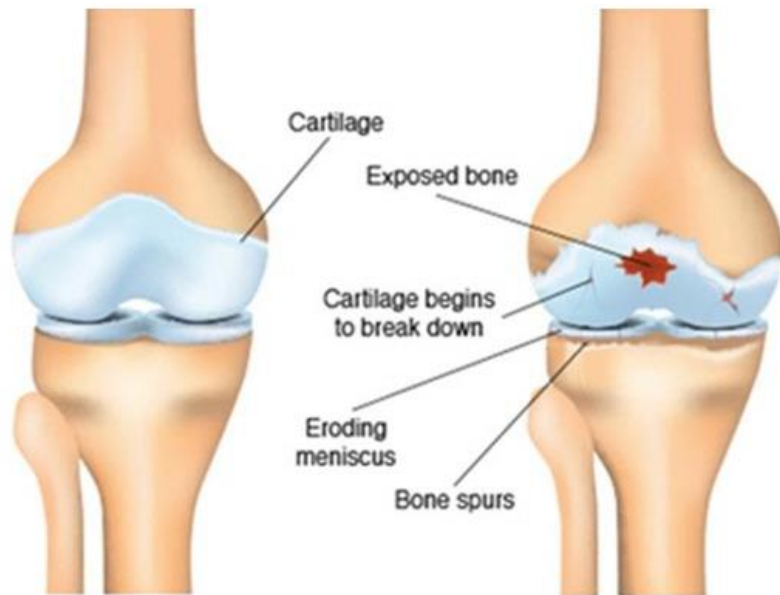


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Osteoarthritis (OA) – Knee



Healthy joint

Osteoarthritis

10 positive RCT Level I studies!!

>1,000 patients included

8 vs. HA; 3 vs. Placebo/NaCl

8 Reviews concluding

PRP superior to HA

PRP superior to placebo

PRP superior to corticosteroids

PRP superior to ozone





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PRP – Knee OA

Basic Science

Buul et al, AJSM, 2011

Andia et al, Op. Tech. Ortho, 2012

Smyth et al, Arthroscopy, 2013

Anitua et al, J Biomed Mat.Res, 2014

Braun et al, AJSM, 2014

Sundman et al, AJSM, 2014

Reviews

Filardo et al, KSSTA 2013

Koshbin et al, JARS 2013

Chang et al, ACRM 2013

Pourcho et al, Osteoarthritis 2014

Kanchanatawan et al, KSSTA 2015

Meheux et al, Arthroscopy 2015

Dai et al, Arthroscopy 2016

Shen et al, JCSN 2017

Level I Randomized Controlled Trials

Cerza et al, AJSM, 2012

PRP vs. HA

Sanchez et al, Arthroscopy, 2012

PRGF vs. HA

Paterson et al, BMC Musculoskelet Disord, 2013

PRP vs. HA

Patel et al, AJSM, 2013

PRP vs. Placebo

Vaquerizo et al, Jars, 2013

PRGF vs. HA

Görmeli et al, KSSTA, 2015

PRP vs. HA vs. Placebo

Paeissadat et al, Clin Med Insights,

PRP vs. HA



et al, AJSM, 2016

PRP vs. HA

mus et al, KSSTA, 2016

PRP vs. HA vs. Ozone

ift et al, AJSM, 2016

PRP vs. Placebo

Editorial Commentary: The Time Has Come to Try Intra-articular Platelet-Rich Plasma Injections for Your Patients With Symptomatic Knee Osteoarthritis

Timothy J. Hunt, M.D., Associate Editor



Arthroscopy: The Journal of Arthroscopic and Related Surgery, Vol 33, No 3 (March), 2017: pp 671-672



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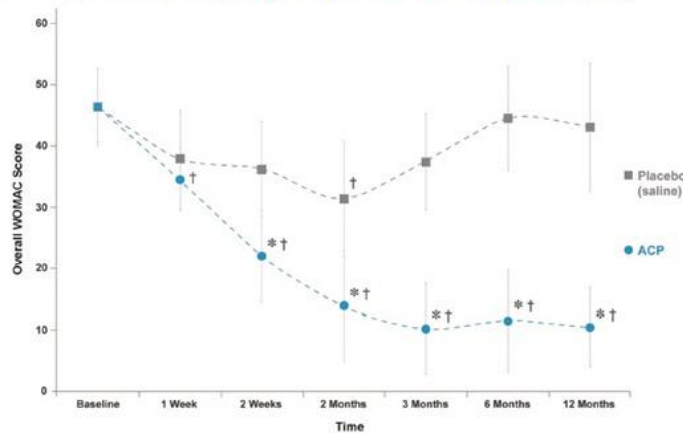
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OA Knee – ACP

PRP vs. Placebo (Smith, AJSM, 2016)



Results

From week 2 onwards, **PRP** was **significantly superior** to saline placebo up to 12 months

ACP group improved their WOMAC scores by 78% from baseline vs. 7% for the placebo group

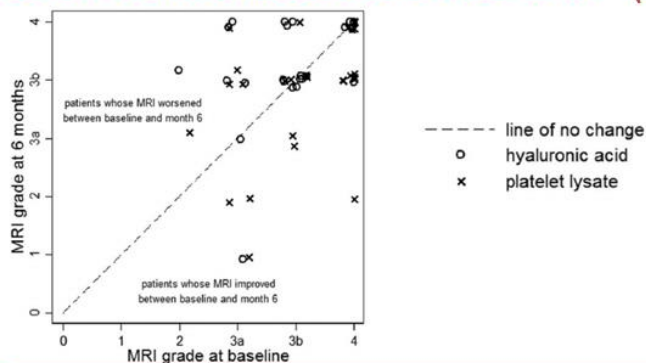
No adverse events

- RCT, double-blind, regulated by the FDA, level I
- 30 patients
- 3 injections, weekly interval
- OA grade II-III; WOMAC



What about cartilage regeneration?

„Treatment of knee osteoarthritis: platelet-derived growth factors vs. hyaluronic acid. A randomized controlled trial” (Lisi, Clin. Rehab., 2017)



Results

Intra-articular-activated PRP reduces articular damage (as evident at MRI) more than hyaluronic acid:

≥1 grade improvement (Shahriaree Classification System-modified):
48% PRP vs. 8% HA

It reduces pain, improves function and ameliorates quality of life for at least one year

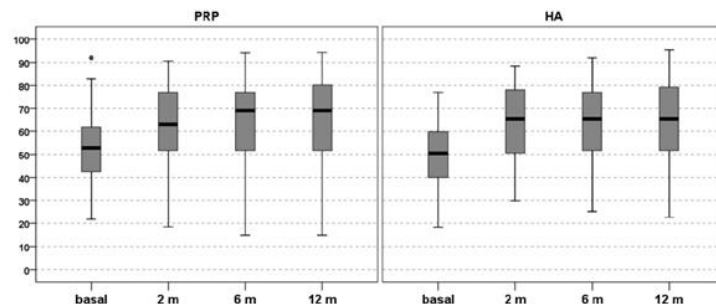
No side-effects

- RCT (assessors blinded)
- 50 patients
- 3 injections, 4-weekly interval
- Imaging (MRI) and scores (WOMAC, VAS...)



But there is the Filardo study...

...claiming „Platelet-Rich Plasma Intra-articular Knee Injections Show No Superiority Versus Viscosupplementation” (Filardo, AJSM, 2015)



No significant intergroup difference at any follow-up

...interesting to observe that the mean pain and swelling reaction observed after the injection was higher in the PRP group, thus supporting a possible detrimental effect of white cells

...leukocyte depletion might have led to better results

...deleterious effects of proteases and reactive oxygen released from white cells.

- RCT, level I
- 192 patients
- 3 injections, weekly interval, **leukocyte-rich PRP**
- OA grade 0-III, IKDC, KOOS, EQ-VAS



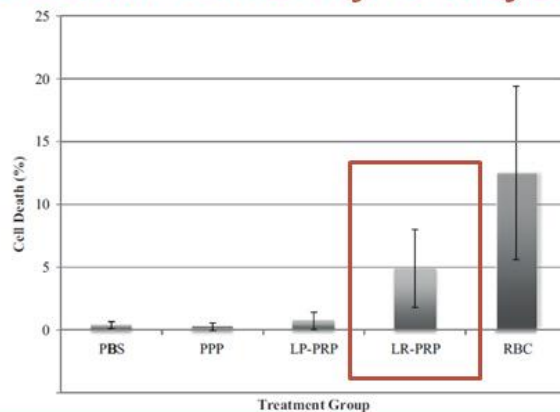
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Detrimental effect of leukocytes

...was indeed shown: „The Effect of Platelet-Rich Plasma Formulations and Blood Products on Human Synoviocytes” (Braun, AJSM, 2014)



Results

Treatment of synovial cells with **leukocyte-rich PRP** and **red blood cells** resulted in **significant cell death** and proinflammatory mediator production

“Clinicians should consider using **leukocyte-poor, red blood cells-free formulations of PRP** when administering intraarticularly”

- In-vitro comparison of a leukocyte-rich (LR) PRP preparation and a leukocyte-poor (LP) PRP





Review – Milant

“Responders to Platelet-Rich Plasma in Osteoarthritis: A Technical Analysis” (Milant, BMRI, 2017)

Review Article

Responders to Platelet-Rich Plasma in Osteoarthritis: A Technical Analysis

Christophe Milants,¹ Olivier Bruyère,^{2,3} and Jean-François Kaux^{1,3}

¹Physical Medicine, Rehabilitation and Sports Traumatology Department, SportS2, FIFA Medical Centre of Excellence, University and University Hospital of Liège, Liège, Belgium

²Department of Public Health, Epidemiology and Health Economics, University of Liège, Liège, Belgium

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Academic Editor: Giuseppe Filardo

- 19 RCTs analyzed

Very good responders: 7 studies

Bad responders: 4 studies

Use of leukocyte-rich PRP only found in
Bad responders group

**“...use of a single spinning technique, a
platelet concentration lower than 5 times
the baseline, and avoidance of
leukocytes should be preferred”**





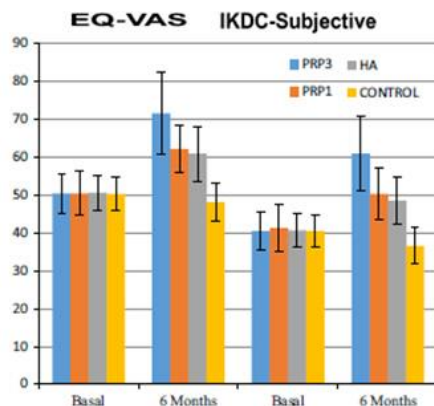
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Multiple Injections – LP-PRP for Knee OA

Görmeli et al., KSSTA, 2015



Results

Knee scores of patients treated with **three PRP injections** were significantly better than those patients of the other groups



- RCT, level I
- 162 patients, grade I-IV
- Single vs. 3 injections (weekly interval) vs. HA (3, weekly interval) vs. saline (3, weekly interval)





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Multiple Injections – PRP for Patellar Tendinopathy

Zayni, MLTJ, 2015

	At baseline			At 34 monthmean FU		
Clinical scores	VAS (SD)	Tegner score (SD)	VISA-P (SD)	VAS (SD)	Tegner score (SD)	VISA-P (SD)
Group a: 1 PRP Injection	7.1 (1.6)	4.1 (1.3)	36.7 (10.6)	3.6 (1.2)	5.9 (5.9)	65.7 (19.8)
Group b: 2 PRP injections	6.7 (1.7)	4.8 (0.94)	35.7 (9.4)	1.07 (1.5)	8.1 (1.7)	93.2 (14)
p value	ns	ns	ns	0.0005	0.0003	<0.0001

Results

PRP injection improved clinical outcomes in almost 77% of patients and allowed them to return to their pre-symptom activity level in 86% of cases.

Two consecutive ultrasound-guided intratendinous PRP injections showed a better improvement in their outcomes when compared to a single injection

- Randomized prospect. consec. series, level II
- 40 athletes
- Single vs. Two injections (2 weeks apart)
- VISA-P, VAS, Tegner





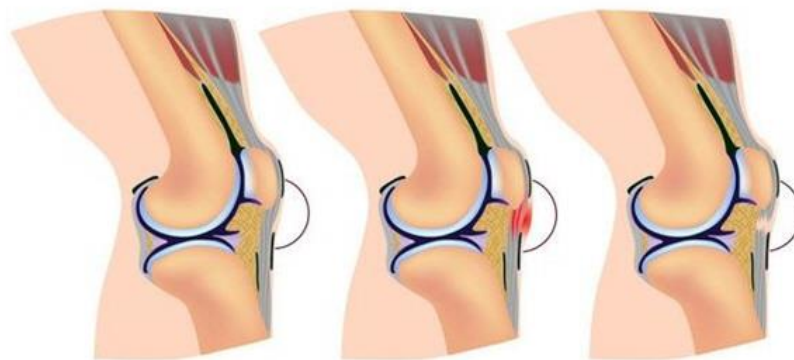
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Patellar Tendinopathy

Knee injury - Jumper's knee



Patellar tendon intact

Patellar tendon inflammation

Patellar tendon degeneration

2 positive RCT studies

1 vs. ESWT; 1 vs. Dry needling

2 positive series

Case series (level IV)

Randomized prospective series (level II)

2 Reviews concluding

PRP injection is an effective treatment for patellar tendinopathy





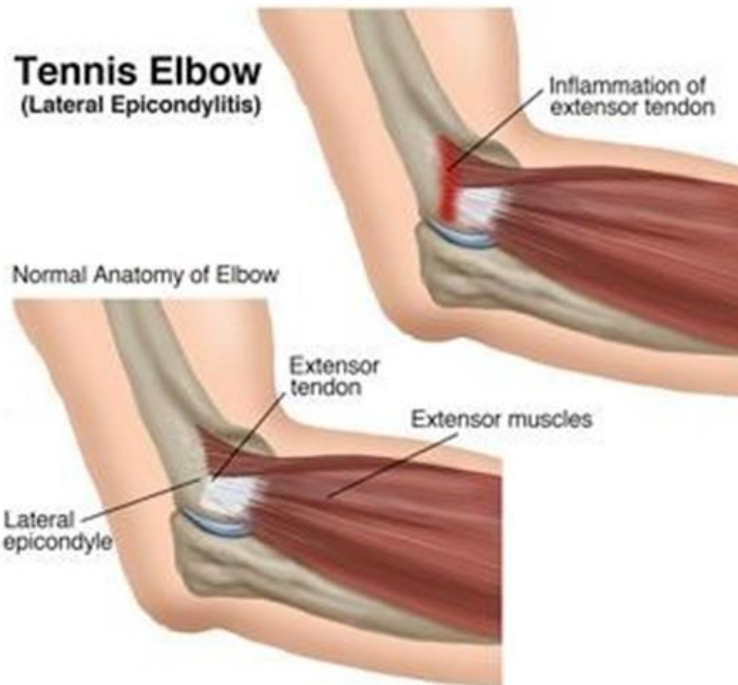
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Epicondylitis

Tennis Elbow (Lateral Epicondylitis)



7 positive RCT studies

4 vs. steroids; 2 vs. LA; 1 vs. blood

2 retrospective comparisons

4 Reviews concluding

PRP superior to steroids



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Plantar Fasciitis



4 positive RCT studies

4 vs. steroids

2 reviews concluding

PRP superior to steroids





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Muscle injuries



Hamid et al. AJSM 2014

RCT Level II

Grade 2 (partial tear) hamstring muscle injury

Single LR-PRP injection w/ rehab. vs. rehab.

PRP superior regarding pain reduction and mean time to return to play (27d vs. 43d)



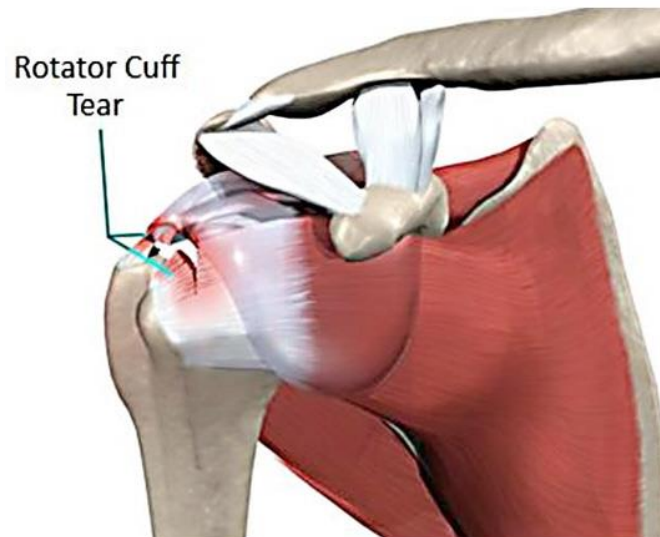


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Rotator cuff tears



Von Wehren et al. KSSTA 2015

Therapeutic study Level III

50 patients, partial rotator cuff tear

3 PRP injections (weekly) vs. 1 cortisone

VAS and shoulder scores (ASES, SST and CMS) statistically significant better after 3 months in PRP group, trend after 6 months

Werthel et al. 2014, Hak et al. 2014

PRP resulted in lower pain but no improvement regarding functional/structural outcome



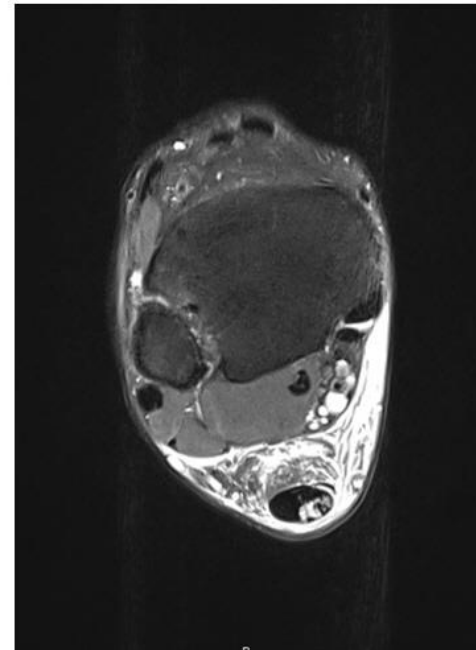
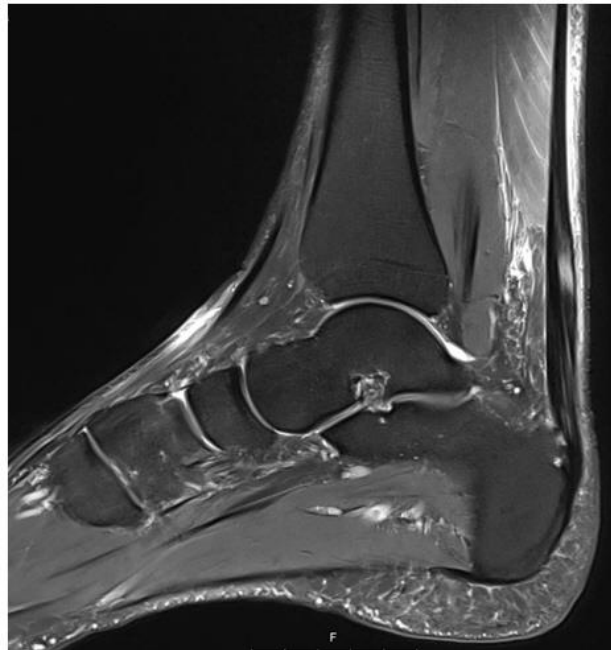


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Achilles tendon



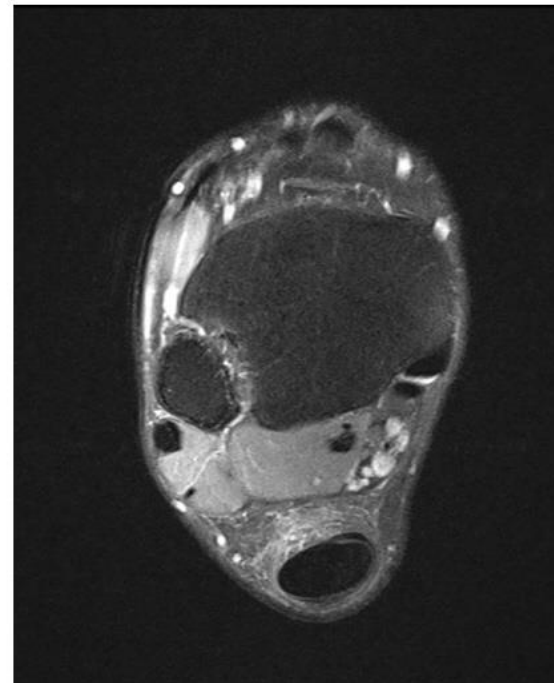


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10 Weeks after 1st ACP Injection



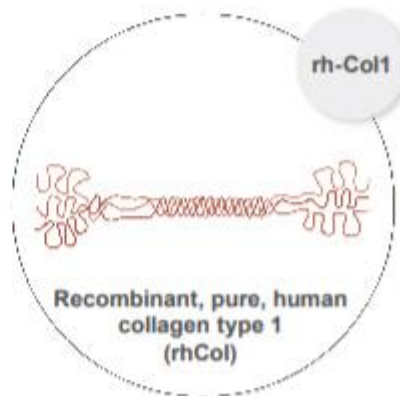
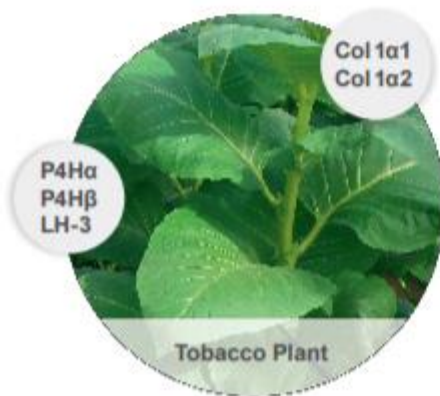


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Tendo-ACP



Vergenix STR – scaffold





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Tendo-ACP

Tissue-Extracted (Bovine/Porcine)⁹



- Partially denatured (crosslinked)
- Low cell-binding domains

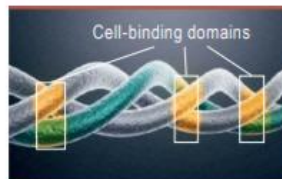


- Partially functional 3D matrix
- Thick fibers → low surface area



- Slow cell proliferation and slow tissue repair
- Foreign body response
- Edema
- Inflammation

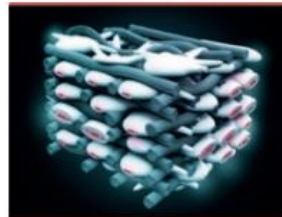
Plant-Derived⁹



- Perfect triple helix
- High cell-binding domains



- Fully functional 3D matrix
- Thin fibers → high surface area



- Fast cell proliferation and fast tissue repair





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Tendo-ACP



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WHAT ARE STEM CELLS?

- ❖ ... 'uncommitted' cells with the capacity for unlimited or prolonged self renewal and the ability to give rise to differentiated cells under appropriate conditions.





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WHAT ARE STEM CELLS?

What is a stem cell?

A single cell that can

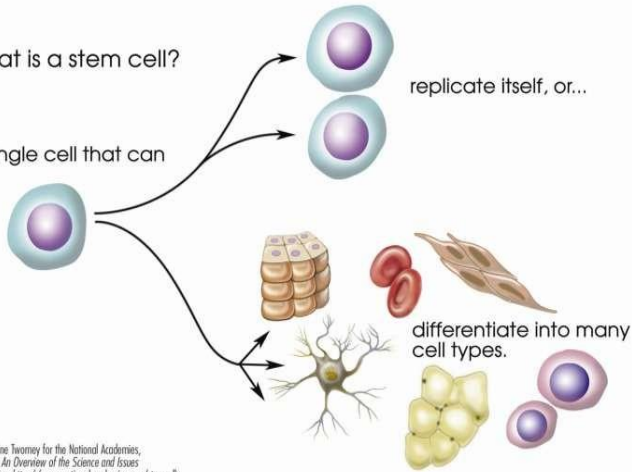
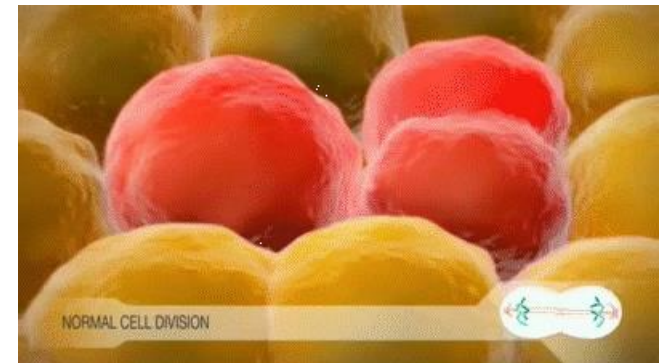


Image prepared by Catharina Twomey for the National Academies.
Understanding Stem Cells: An Overview of the Science and Issues
from the National Academies, <http://www.nationalacademies.org/stemcells>.
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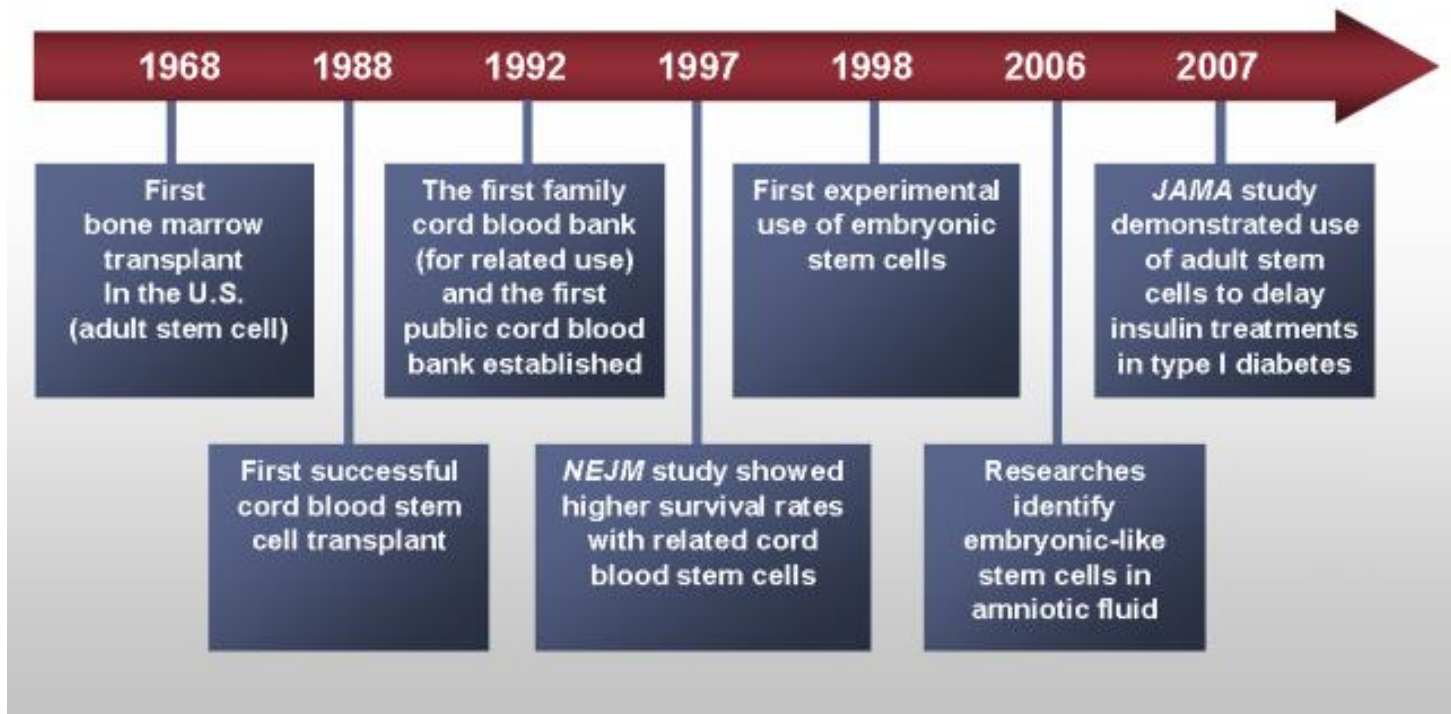


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STEM CELL TIMELINE





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Animal Cloning?

Dolly (sheep)	1 live birth out of 29 cloned embryos	3%
Cloned mice	31 live births out of 2468 cloned embryos	1%
Cloned pigs	5 live births out of 335 cloned embryos	1%
Cloned goats	3 live births out of 85 cloned embryos	3%
Cloned cattle	30 live births out of 496 cloned embryos	6%
Cloned cat	1 live birth out of 87 cloned embryos	1%
Cloned rabbits	6 live births out of 371 of cloned embryos	1%





Human Cloning?

On February 12, 2004, South Korean scientists, Dr. Woo Suk Hwang and Dr. Shin Young Moon of Seoul National University, reported the successful creation of 30 cloned human embryos developed to the blastocyst stage and then destroyed by stem cell extraction, yielding one embryonic stem cell line.





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Human Cloning?





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Frozen Embryos

Tens of thousands of frozen embryos are routinely destroyed when couples finish their treatment.

These surplus embryos can be used to produce stem cells.





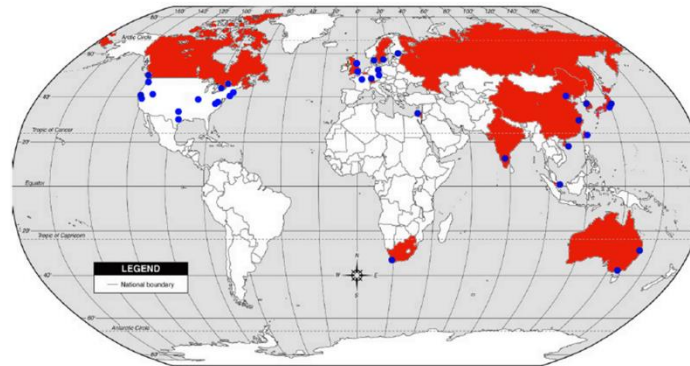
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Frozen Embryos

Regenerative medical research aims to develop these cells into new, healthy tissue to heal severe illnesses.



Countries with a permissive or flexible policy on embryonic stem cell research (in red)

- Denotes Genome Sequencing Center



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Source

The two most common sources of adult stem cells for clinical application in orthopaedics are bone marrow and adipose tissue.

Both bone marrow aspirate and lipoaspirate contain different cell fractions.





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BMAC MSCs & SVF

When bone marrow aspirate is centrifuged, bone marrow aspirate concentrate (BMAC) can be obtained from buffy-coat layer which contains mononuclear cells including very low percentage of Mesenchymal stem cells (MSCs)





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BMAC MSCs & SVF

When lipoaspirate is treated by enzymes and undergoes differential centrifugation, fat and mature adipocytes in the upper layer are separated. The bottom layer is stromal vascular fraction (SVF) that contains low percentage of MSCs.





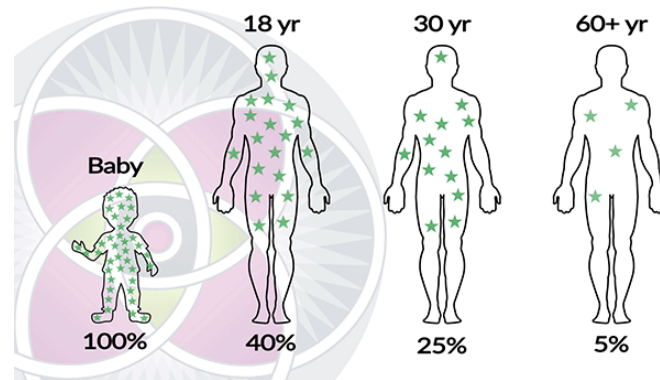
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BMAC MSCs & SVF

When BMAC and SVF are put into a monolayer culture on plastic dishes and passaged, cells that have characteristics of MSCs can be isolated.





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BMAC





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Stem Cell Therapies

Acute

Tendon injuries

- ✓ Achilles tendon
- ✓ Rotator cuff

Ligament injuries

- ✓ ACL
- ✓ Medial collateral ligament
- ✓ Ankle ligaments

Muscle tears

Intra / Post Op



Chronic

Osteoarthritis

- ✓ I, II, III

Tendinopathies

- ✓ Achilles tendon
- ✓ Tennis elbow
- ✓ Patella tendon
- ✓ Plantar fasciitis

Spine

- ✓ Facet Joints
- ✓ Sacroiliac Joint
- ✓ Epidural Injections





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Adipose-derived Mesenchymal Stem Cells (= Adipose-derived Regenerative Cells)

What?

Stromal vascular fraction (SVF) resuspended
in Platelet Rich Plasma (PRP)

**Made
of?**

Autologous blood and autologous adipose tissue

**What
for?**

Tissue regeneration



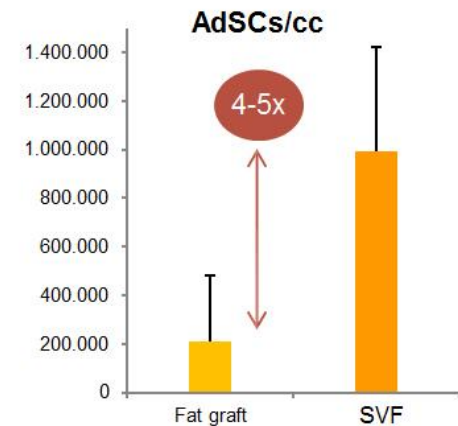
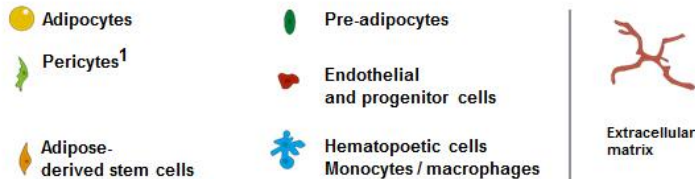
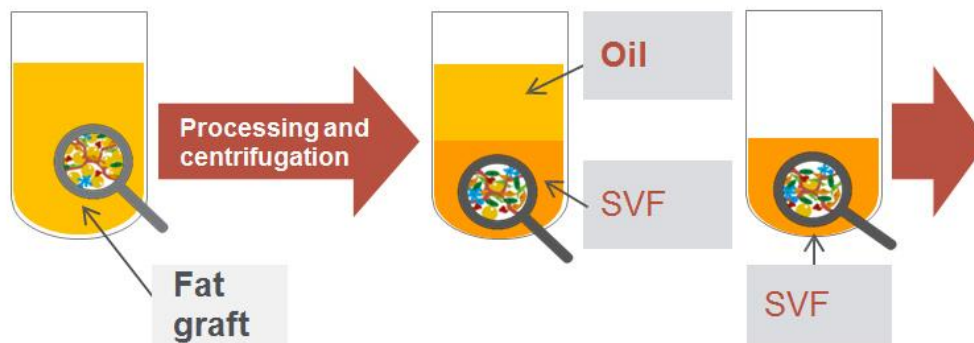


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SVF – AdSC concentration

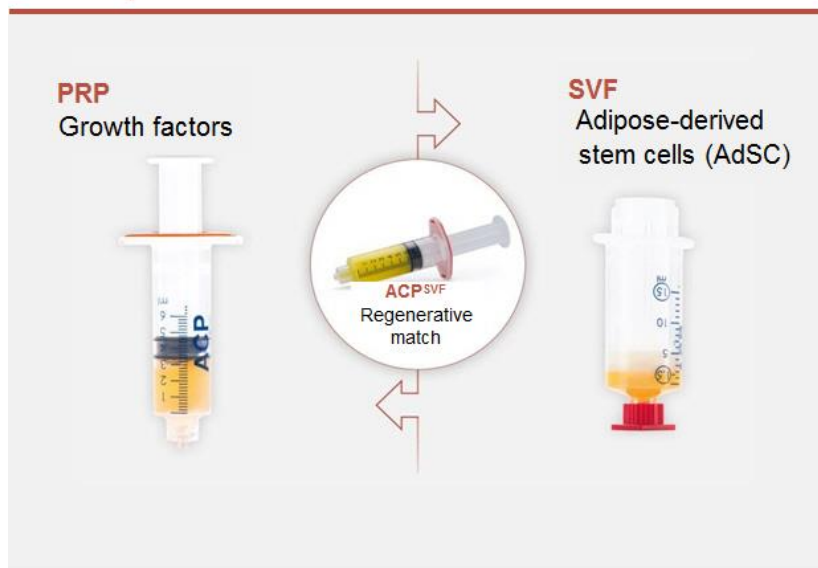


¹ Zhang J et al. Adipose Tissue-Derived Pericytes for Cartilage Tissue Engineering. Curr Stem Cell Res Ther 2017;12(6):513-521



ACP^{SVF} – the regenerative match

Principle of SVF



Benefits

- Source of growth factors
- Source of regenerative cells
- Growth and proliferation stimulating effect of PRP on AdSCs shown in vitro¹

Preparation



¹ Loibl et al, The effect of leukocyte-reduced platelet-rich plasma on the proliferation of autologous adipose-tissue derived mesenchymal stem cells. Clin Hemorheol Microcirc, 2016;61(4):599-614



ACP^{SVF} – Review

Indications

OA of knee and hip

Osteonecrosis of femoral head

Achilles tendinopathy

Proximal humeral fractures

Lateral epicondylitis

Pak et al. *Journal of Biomedical Science* (2017) 24:9
DOI 10.1186/s12929-017-0318-z

科技部 Ministry of Science and Technology

The work of Jaewoo Pak in *Journal of Biomedical Science* is based on the Ministry of Science and Technology, Korea.

Journal of Biomedical Science

REVIEW

Open Access



Current use of autologous adipose tissue-derived stromal vascular fraction cells for orthopedic applications

Jaewoo Pak^{1,2,3†}, Jung Hun Lee^{1,4†}, Kwang Seung Park⁴, Moonhee Park^{4,5}, Lin-Woo Kang^{6*} and Sang Hee Lee^{4*}

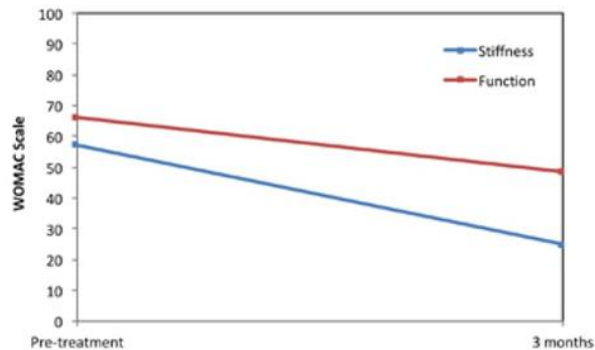
Results

“Great clinical potential to treat various orthopedic disorders”



ACP^{SVF} – OA

„Treatment of Osteoarthritis: Adipose Derived Stem Cell & PRP Therapy”
(Slynarski, Sportärztezeitung, 2017)



Results

stiffness and the function could be improved over a time period of 3 months

pain could be reduced by 50 percent and six weeks after the treatment it decreased even further

No adverse events

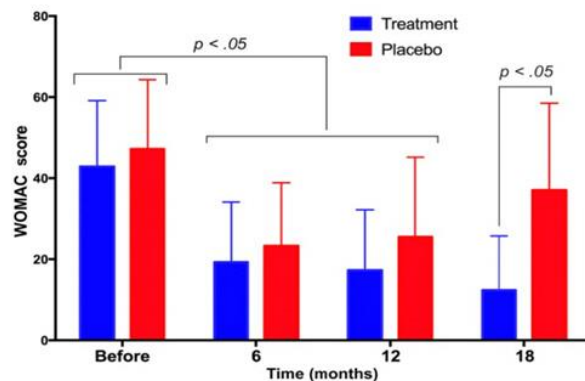
- Case series: 18 patients
- Single injection of ACP+SVF
- WOMAC, VAS



SVF – Indications

Early studies have shown promising results of SVF for OA^{1,2,3} and tendinopathies⁴

Example – OA



¹ Koh et al, Adipose-Derived Mesenchymal Stem Cells With Microfracture versus Microfracture alone: 2-Year Follow-up of a Prospective Randomized Trial. *Arthroscopy*, 2016;32(1):97-109

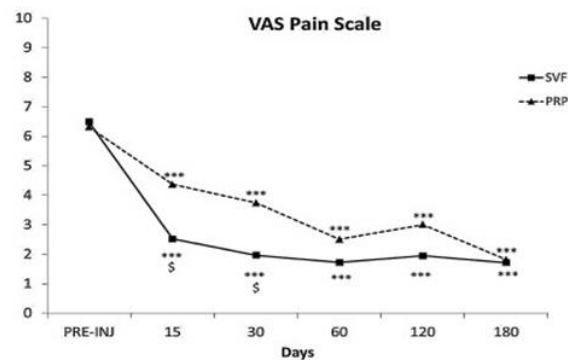
² Michalek et al, Autologous adipose tissue-derived stromal vascular fraction cells application in patients with osteoarthritis. *Cell Transplant*, 2015

³ Nguyen et al, Comparative Clinical Observation of Arthroscopic Microfracture in the Presence and Absence of a SVF Injection for Osteoarthritis. *Stem Cells Trans Med*, 2016;5:1-9

⁴ Usueili et al, Intratendinous adipose-derived stromal vascular fraction (SVF) injection provides a safe, efficacious treatment for Achilles tendinopathy: results of a randomized controlled clinical trial at a 6-month follow-up. *Knee Surg Sports Traumatol Arthrosc*. 2017 Mar 1. doi: 10.1007/s00167-017-4479-9.

SVF – Indications

Example – Achilles Tendinopathy



Knee Surg Sports Traumatol Arthrosc
DOI 10.1007/s00167-017-4479-9



ANKLE

Intratendinous adipose-derived stromal vascular fraction (SVF) injection provides a safe, efficacious treatment for Achilles tendinopathy: results of a randomized controlled clinical trial at a 6-month follow-up

Federico Giuseppe Uselli¹ · Miriam Grassi² · Camilla Maccario^{1,3} · Marco Viganò⁴ · Luciano Lanfranchi⁵ · Umberto Alfieri Montrasio² · Laura de Girolamo⁴

Received: 3 October 2016 / Accepted: 13 February 2017
© European Society of Sports Traumatology, Knee Surgery, Arthroscopy (ESSKA) 2017

Abstract Intratendinous SVF, ACRAS and VISA A scores significantly



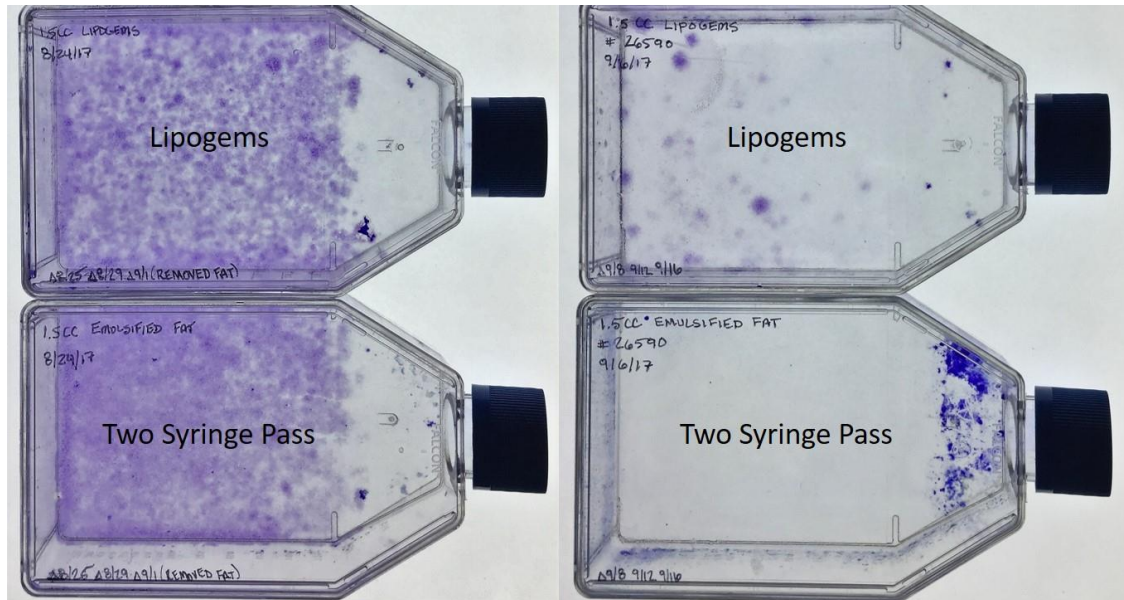


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Lipogem V Two syringe pass



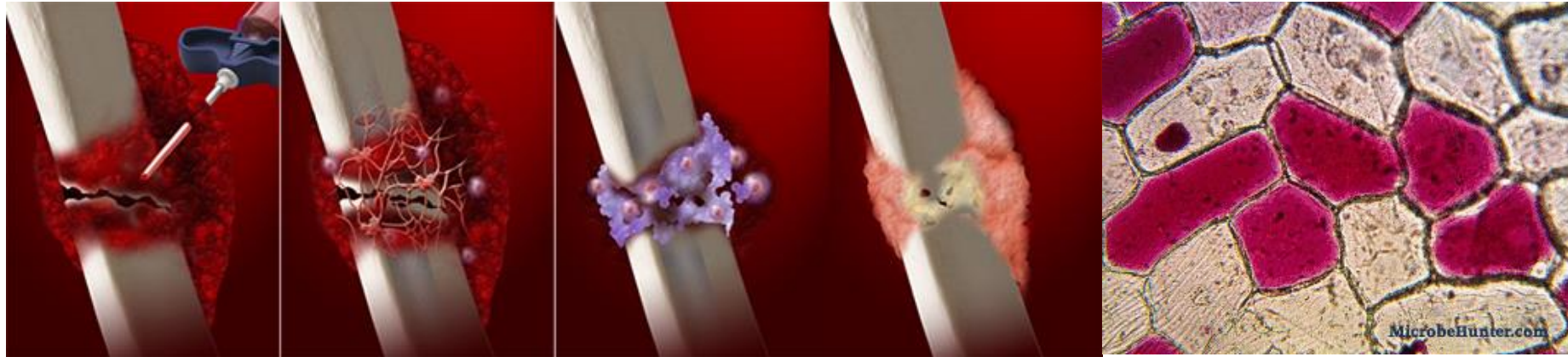


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Orthobilogs “The Holy Grail”



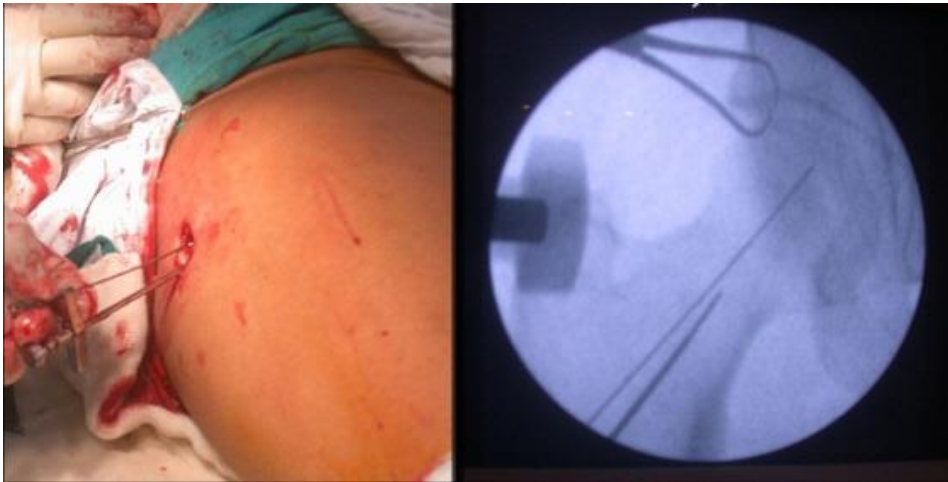


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Orthobilogs “The Holy Grail”



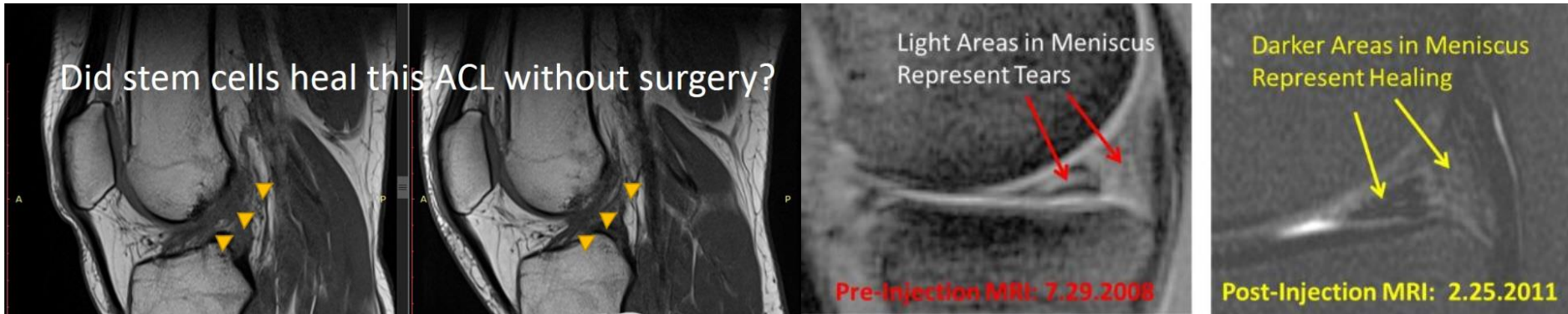


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Orthobilogics “The Holy Grail”





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Orthobilogics “The Holy Grail”





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Current Status

Best Evidence Is in Tendinopathy

PRP has reproducible results

Stem cell in **ON** is **encouraging**

Stem cell in **early OA** is a **reality**

Stem Cell in **ACL** has **inconclusive** results

Lipogems has so far very **little evidence**

ACP-SVF encouraging case series





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Future Directions and Conclusions

Biological treatments for orthopaedic injuries, a sector that was valued at **\$5 billion in 2015** and is expected to swell to **\$10.2 billion in 2025**, according to Million Insights data.





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Future Directions and Conclusions

Driving this growth over the **next seven years** will be the planet's **aging population**, **technological advancements**, **changing (more active) lifestyles**, and a **steady increase** in musculoskeletal-related conditions like **arthritis** and **osteoporosis**.





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TRAILER - ROAD AHEAD

- ❖ Promising
- ❖ Bumpy
- ❖ hope vs hype
- ❖ Use judgement & common sense
- ❖ Event Horizon: *Best way to predict future is to create it!*





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TRAILER - ROAD AHEAD





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THE FUTURE OF JOINTS IS NOT JOINT REPLACEMENT





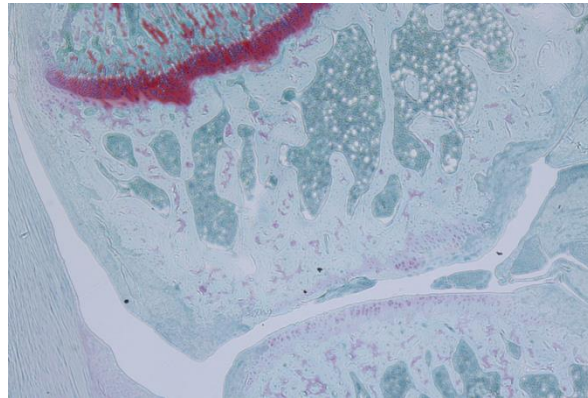
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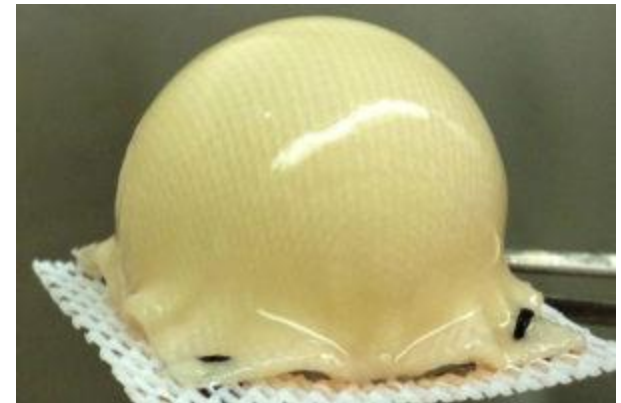
Future

THE FUTURE OF JOINTS IS NOT JOINT REPLACEMENT





The future of joints is not joint replacement



'Grow your own' hip replacements in a decade





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