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"Musculoskeletal Applications of Biological Therapies: Platelet Rich Plasma Mesenchymal Stem Cells"

Presented by: Dr Diana Robinson - MBBS FACSP Sport and Exercise Physician

Will commence LIVE from Sydney, Australia at 7pm AEDT

Be sure to convert to your own time zone at www.worldhealthwebinars.com.au

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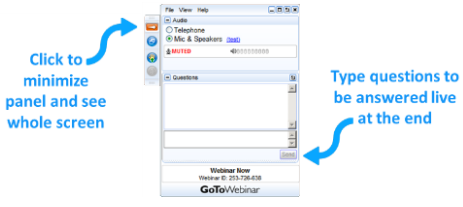
Andrew Ellis

BSc (Ex. Sci), M. Phty

- World Health Webinars CEO
- World Health Webinars (Australia/NZ) Host



Dr Diana Robinson

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Sport and Exercise Physician

- Specialist Sport and Exercise Physician at Sydney Sportsmed Specialists
- Fellowship of the Australasian College of Sports Physicians (ACSP) in 1995, being one of the first formally trained sports physicians in Australia.
- Represents the ACSP on the Enhanced Medical Education Advisory Board, which advises the Department of Health and Ageing on Medical Specialist Training issues.
- Medical Director for "So You Think You Can Dance" dance competition televised on Channel 10, since its inception.
- Australian Team Doctor for the Manchester 2002 Commonwealth Games, Medical Director for the Men's and Women's Triathlon and Athletics doctor at the Sydney 2000 Olympic Games, Medical director of the Uncle Toby's Surf Life Saving Ironman Series and the Devondale Women's Series for many years, and the medical director of the Triathlon Grand Prix and Formula One professional races.

Musculoskeletal Applications of Biological Therapies

Platelet Rich Plasma
Mesenchymal Stem Cells

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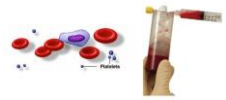
Platelet Rich Plasma

- **Aim**
  - To stimulate biologic factors
  - Manipulate growth factors and cytokines
  - Promote healing



- Autologous
- Affects the recruitment, proliferation and differentiation of cells involved in tissue regeneration
- Available since 1970's – aesthetic and maxillofacial medicine, cardiothoracic, dermatology, ophthalmology

Platelet Rich Plasma

- **Platelets**
  - Small non-nucleated bodies in peripheral blood
  - Contain a number of proteins, cytokines, bioactive factors
  - These initiate and regulate basic wound healing
  - 150,000 – 300,000µ/L
- **Plasma – fluid portion of blood, clotting factors, proteins, ions**
- **PRP is associated with enhancement of healing**
  - 1,000,000/µL platelets in 5ml
  - 2-8 x concentration cf whole blood
- **3-5 fold increase in GF concentration in PRP**

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Current Clinical Applications

- **Literature – safe and effective**
  - Animal studies, case reports, small case series
  - Musculoskeletal medicine – issues with many papers
    - Small series
    - Uncontrolled
    - No standardised preparation of PRP – hard to compare
- **Chronic Tendinopathies**
- **Osteoarthritis**
- **Intra-operative augmentation**
- **Acute injuries eg muscle tears, ligamentous injuries?**

Tendinopathies

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- **CEO tendinosis: refractory**
  - Post-injection – eccentric strengthening, functional progression, with a gradual return over 6-8 weeks
  - Painless full ROM with no localised tenderness
- **Mishra et al 2006 15 PRP, 5 controls.**
  - PRP group, 60% improvement 8 weeks, 81% 6 months, 93% at 12 months
- **Peerboms et al, 2010 PRP (51) vs CSI (49)**
  - Double blinded RCT, with eccentric exercises
  - Significant improvement in VAS and functional scores at 1 yr in PRP group cf corticosteroid injection

My protocol; 3 injections 4-6 weeks apart followed by eccentric rehab and graduated functional rehab

Tendinopathies

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- **Achilles Tendonosis**
  - Mucoid degeneration, lipomatous infiltration, cell death, loss of fibrillary pattern
  - Refractory disease – failed conservative treatment
  - Aim to stimulate angiogenic infiltration and remodelling by tenocytes
  - Research less convincing than "tennis elbow"
  - May reflect load bearing requirement
- **Plantar Fasciitis**
  - Evidence to suggest is a useful agent

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PRP Therapy - Osteoarthritis

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- **Eur J Orthop Surg Traumatol. 2012 Jul 7**
  Platelet-rich plasma (PRP) injections as an effective treatment for early osteoarthritis: Jang SJ, Kim JD, Cha SS.:
- **Am J Sports Med. 2013 Feb;41(2):356-64**
  Treatment with platelet-rich plasma is more effective than placebo for knee osteoarthritis: a prospective, double-blind, randomized trial. Patel S, Dhillon MS, Aggarwal S, Marwaha N, Jain A;
- **E.Kon et al (2010)**
  Platelet Rich Plasma: Intra articular knee injection produced favourable results on degenerative cartilage lesions.
- **G. Filardo,Kon et al. (2011)**
  Platelet Rich Plasma intra articular knee injections for the treatment of degenerative cartilage lesions and osteoarthritis.- "Median duration for clinical improvement was 9 months"
- **Wang-Saeguma, Cugat et al (2010)**
  Infiltration of plasma rich in growth factors for osteoarthritis of the knee short term effects on function and quality of life.- 312 patients, 6 month F/U

Acute Injuries

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- **Acute Ligamentous Injuries**
  - Unpublished study, 11 pts, MCL injury injected within 72 hours, 11 controls.
  - Return to play time shortened by 27% cf controls
- **Cugat – unpublished data 14 pts 2005**
  - Soccer, basketball players
  - Return to play interval diminished
  - Grade 1-2 > 50% reduction in RTP
- **Concerns – may induce fibrotic healing response**
  - Due to Increased TGF-β
  - ? re-injury

Clinical Process

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- **Venesection 30-60mls**
- **Centrifugation - 3-6mls PRP**
- **Local Anaesthetic**
  - Changes pH
  - ?decrease effectiveness
- **Ultrasound Guidance**
  - Control depth of needle, into area of disease
- **Post-injection – ice locally**
  - No NSAIDS for 1 week prior
  - Nil NSAIDS for 2-3 weeks after
  - Standard rehab for strength and functional progressions

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Stem Cell Publications by Year

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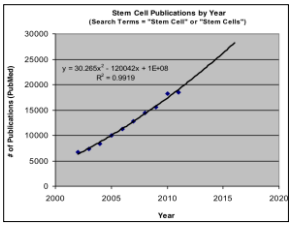
- 3,000+ papers on Mesenchymal Stem Cells (MSC) in 2011 alone
- Mostly Research papers



Stem Cells

World Health Webinars

- Haemopoietic stem cells in cancer treatment
- Human HSC system uses differentiation to produce 100 billion blood cells each day
- Exploited this capability to repopulate blood after Chemotherapy and Radiotherapy
- Led to the perception that differentiation potential is key to other stem cell therapies
- Mesenchymal stem cells muscle, fat, blood, marrow

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Mammalian Traits

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Adipose Tissue - Fat

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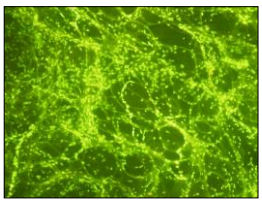

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Perivascular 'stem' cells – the guardians of inflammation

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inflammation

www.moleculartherapy.org vol. 20 no. 1, 14–20 jan. 2012
http://en.wikipedia.org/wiki/Wound_healing

Animal Model Studies

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cells at the injury site - repair

cells by remote delivery - repair

secretions by remote delivery - repair

Revised understanding of mechanism

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Cells from the SVF of Adipose Tissue

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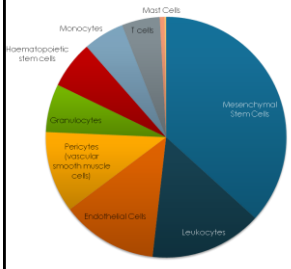

- MSCs
  - Pluripotent
  - Secrete other substances
- Endothelial progenitor cells
  - May induce angiogenesis
- Immune Regulatory Monocytes/Macrophages
  - Anti-inflammatory effect
- T-Regulatory cells
  - Immune suppressive
- Adipocytes
  - Anti-inflammatory effect from e.g. Leptin

Non-expanded adipose stromal vascular fraction for multiple sclerosis. NH Riordan, T Ichim, WP Min, H Wang, F Solano, F Laram M Alfaro, JP Rodriguez, RJ Harman, A Patel, MP Murphy, RR Lee, B Minev, *Journal of Translational Medicine 2009, 7:29*

Clinical potential of MSC: Secretory signaling

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MSC

trophic factors → **chondrocytes**
- ➜ proliferation
- ➜ cartilage matrix formation

anti-inflammatory cytokines → **immune cells**
- ➜ Down-regulation of inflammation
- ➜ decrease in pain

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MSC as secretion factories

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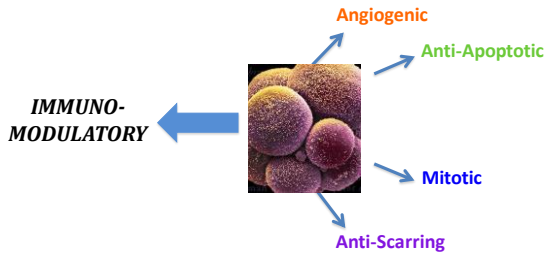

Major focus of stem cell research

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Can Cell Therapy influence this balance?

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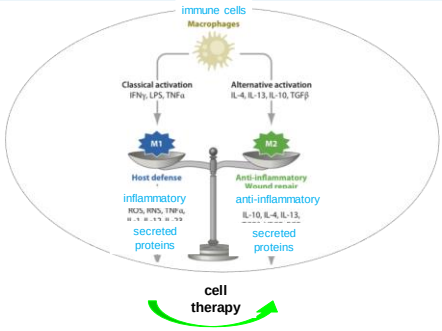

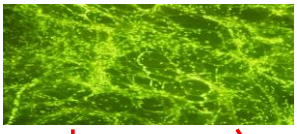

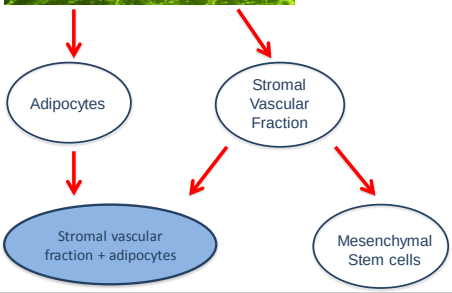

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Cells are happier with their mates

You get a potent therapeutic effect from fresh, mixed cell populations

Human 27-plex cytokine panel

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Pro-inflammatory	Anti-inflammatory	Chemokines	Growth Factors	Dual Roles
IFN-γ	IL-1Ra	Eotaxin	bFGF	IL-2
IL-1β	IL-4	IP-10	G-CSF	IL-6
IL-5	IL-10	MCP-1	GM-CSF	
IL-8	IL-13	MIP-1α	IL-7	
IL-9		MIP-1β	PDGF-bb	
IL-12		RANTES	VEGF	
IL-15				
IL-17				
TNF-α				

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Canine Study – adipose derived MSC

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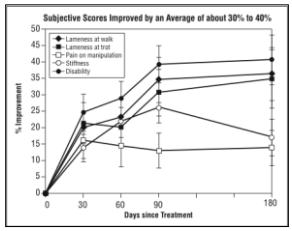
- LL Black, J Gaynor et al 2007
- Autologous adipose derived MSC in canine OA elbows
- N=14
  - Lameness improved
  - Pain decreased
  - Range of motion increased
  - All significant differences



Veterinary Therapeutics • Vol. 9, No. 3, Fall 2008

Canine Study – adipose derived MSC

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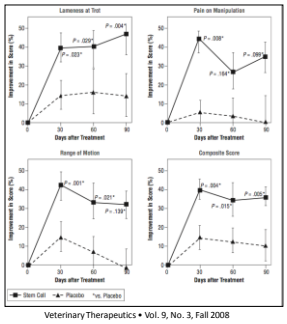

Veterinary Therapeutics • Vol. 9, No. 3, Fall 2008

Cartilage regeneration demonstrated in many animal models

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Stem Cell Therapy in a Caprine Model of Osteoarthritis

J. Mary Murphy,[1] David J. Fink,[1] Ernst B. Hunziker,[2] and Frank P. Barry[1]

Enhanced early chondrogenesis in articular defects following arthroscopic mesenchymal stem cell implantation in an equine model

Markus M. Wilke[1], Daryl V. Nydam[2], Alan J. Nixon[1,*]

Article first published online: 2 APR 2007

DOI: 10.1002/jor.20382

Journal of Orthopaedic Research

Volume 25, Issue 7, pages 913–925, July 2007

STEM CELLS
TRANSLATIONAL AND CLINICAL RESEARCH

Injectable Mesenchymal Stem Cell Therapy for Large Cartilage Defects—A Porcine Model

KEVIN B.L. LEE, JAMES H.P. HUI, IM CHIM SONG, LENNY ARDANY, ENG HIN LEE

The Department of Orthopaedic Surgery, National University of Singapore, and the Department of Experimental Surgery, Singapore General Hospital, Singapore, Republic of Singapore

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Bringing Cell Therapy to the Clinic

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Research → Clinical use

Adipose tissue

- Rich source of MSCs – 500 to 1000 x bone marrow
- Easily accessible via mini-liposuction procedure
- Autologous
- Harvest to treatment in 75mins

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Bone Marrow Derived – Japan Study

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Author	Patients	Disease	Follow-up	Cartilage Regeneration	Symptom Improvement
Wakitani 2002	24	HTO vs HTO and cells	3.5 years	Yes – 2nd look	Yes
Wakitani 2004	2	PFJ cartilage defect	5 years	Yes – 2nd look	Yes
Wakitani 2007	3	PFJ cartilage defect	2 years	Yes – MRI	Yes
Koruda 2007	1	Medial femoral cartilage defect	1 year	Yes – 2nd look	Yes Returned to sport
Wakitani 2010	41	Knee Osteoarthritis	11 years	Safety Study	No Cancer No infections

Bone Marrow Derived – USA Study

World Health Webinars

Author	Patients	Disease	Follow-up	Cartilage Regeneration	Symptom Improvement
Centeno 2006	1	Hip Osteoarthritis	3 months	Yes – MRI	Yes
Centeno 2008	1	Knee Osteoarthritis	6 months	Yes – MRI	Yes
Centeno 2008	1	Knee Cartilage defect	6 months	Yes - MRI	Yes
Centeno 2010	227	Knee, Back, Hips	2 years	Safety study	No Cancer No infections

Case Study - Pain Physician, May 2008

World Health Webinars

Increased Knee Cartilage in Degenerative Joint Disease using Percutaneously Implanted Autologous Mesenchymal Stem Cells. Case Report (2008; 343-353)

Christopher Centeno MD, Dan Busse MD, John Kisiday PhD, Cristin Keohan, Michael Freeman PhD, David Karli MD

Results at 24 weeks

- *"significant cartilage and meniscus growth on MRI"*
- *" increased range of motion and decreased modified VAS pain scores"*

Conclusions

- *" significant cartilage growth, decreased pain and increased joint mobility"*
- *" significant future implications for minimally invasive treatment of osteoarthritis and meniscal injury"*

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Safety Studies

- **Wakitani (2011)**
  - 41 patients. Knee OA. 11 year follow-up
  - No cancer, no infections
- **Lalu (2010)**
  - Systematic review of Mesenchymal Stem Cell treatment. 24 studies, 652 patients
  - *"MSC administration appears to be safe based on the available evidence"*
- **Centeno (2010)**
  - 227 patients. Knee, Back and Hips. 2 year follow-up
  - No tumors, no joint infections

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Regulatory Framework

- **TGA Act 1989**
- **HiQCell therapy is a Biological – specified in TG Order (exclusion)**
- **TGA – low risk category**
  - Autologous
  - Tissue and cells minimally processed
  - Under supervision of Physician
  - Single indication treatment
- **Protocol must be followed to ensure compliance with TGA regulations**

Patient Selection

- Grade 2-3 OA. ? Early Grade 4
- Chondral defects
- No major malalignment
- Not obese
- No mechanical issues eg: instability, locking
- No significant osteophytes
- ? Co-morbidities

Stem Cell Treatment - Protocol

- **Patient consultation**
  - VAS / KOOS score/HOOS/ Oxford Shoulder Score
- **Patient education**
  - Procedure / risks and benefits / expectations / costs
- **Patient investigations**
  - Xray / MRI / MRSA swabs / HIV / Hep B & C
- **Patient review**
  - Hospital forms (Hurstville Medica Centre)
  - Consent

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Stem Cell - Quality Assurance

- Hospital setting
- Microbiological reporting
- Pre-op IV antibiotics
- Laboratory testing of each cell suspension
  - Microscopy and culture
  - Cell count and viability
  - Independent audit
- Patient SAFETY as priority

Post Procedure Management

- Post Op
  - Liposuction site discomfort
  - ADLs – first 2 weeks
  - Activity modification – first 6 weeks
  - Normal activities – post 12 weeks
  - ? valgising / varising brace
- MRI pre-procedure and 6 months
- VAS score ADLs (2, 6, 12, 26 wks)
- KOOS pre Rx and 6 months

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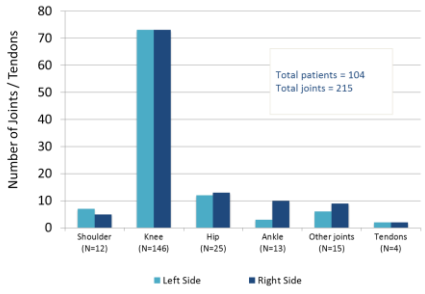
Results To Date - Overview

- 222 patients / 451 joints and tendons treated – various musculoskeletal conditions.
- Post treatment reviews for up to 18 months
- Key findings to date:
  - Consistent significant decreased pain
  - large treatment effect (effect size)
  - significantly over estimated placebo effect
  - Similar effect as observed in canine evaluations

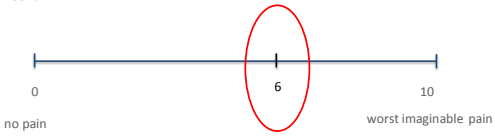
Joints treated – with follow up



VAS: Visual Analogue Scale

Example Only

Q: What was the level of pain from your joint on average over the past week?



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Preliminary Outcomes

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HiQCell Responders*			
Time Point	Joints with Follow-up (N)	Joints Responded (%)	Decrease in Pain (%)
2 weeks	161	49%	66%
3 Months	149	66%	72%
6 Months	101	73%	79%

*30% or more reduction in pain score from pre-treatment score

At 6 months post treatment, 73% of 101 joints responded, with an average reduction in pain of 79%

Preliminary Outcomes

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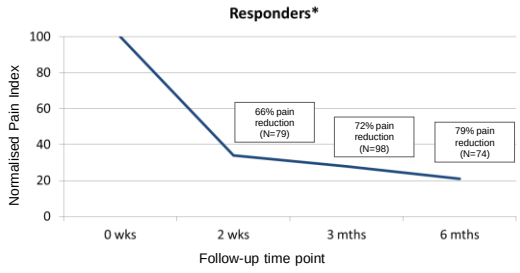

*30% or more reduction in pain score from pre-treatment score

Treatment effect – by OA Grade

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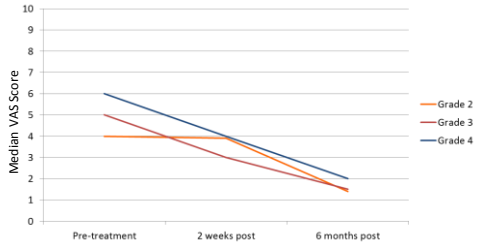

All grades of OA may benefit from HiQCell Treatment

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Overall Treatment Effects

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Benefits

- Pain reduction
- Improved range of motion
- Reduced stiffness
- Improved function

Fast

- After 10 – 14 days significant pain reduction & increased mobility

Intermediate

- Continued pain reduction with increased quality of life

Long Term

- Possible stabilisation of disease
- ?cartilage regeneration/meniscal healing

- **HiQCell® treatment consistently leads to significantly decreased pain**
- **Further follow up will determine disease stability long term**
- **Promising early indications of cartilage regeneration**
- **Goal is to achieve delayed joint replacement**

Next Step

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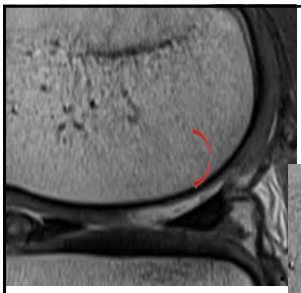
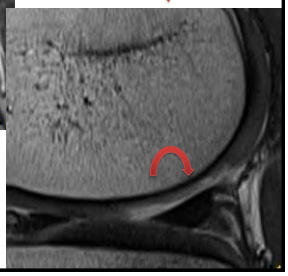
- **Cryopreservation**
  - Freezing of 2 aliquots of cells for later use
- **More TGA regulation**
  - Single indication
  - Oversight process by medical practitioner
  - Stored Cryosite
- **Viability**
- **Infection control**
- **Now available commercially**



5 months post injection; complete coverage of defect with 30 – 50% cartilage thickness



43 year old male;
left knee lateral femoral condyle chondral defect

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January 2012 T2 Image: 26yr old male

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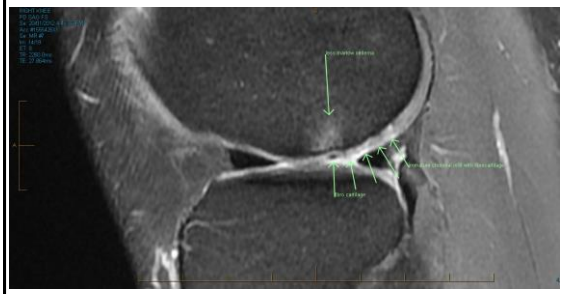

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Conclusion

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Further information:

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Web: www.sportsdoc.com.au

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Live Q & A

With Dr Diana Robinson

1/200 chance to win an iPad

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Live Q & A

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Thank you

From Dr Diana Robinson
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