AUSTRALIAN CELL THERAPY SOCIETY RESPONSE TO THE MBA CONSULTATION:

PUBLIC CONSULTATION ON CLEARER REGULATION OF MEDICAL PRACTITIONERS WHO PROVIDE COMPLEMENTARY AND UNCONVENTIONAL MEDICINE AND EMERGING TREATMENTS

20 JUNE 2019

The Australian Cell Therapy Society (ACTS) welcomes the opportunity to contribute to the Medical Board of Australia (MBA) proposed guidelines on complimentary, unconventional and emerging medicine. The Australian Cell Therapy Society would like to make the following 'general comments' and 'specific comments' on the Draft Guidelines, *Guidelines for registered medical practitioners - Complimentary and unconventional medicine and emerging treatments*.

General Comments

We have significant concerns with the following in the proposed guidelines:

1. The intermingling and merging of four completely different areas of medical practice – these being complementary, alternative medicine, stem cell treatments and emerging treatments. We fail to understand the rationale for lumping them together when the evidence-base, perceived risks and ethical concerns do not align.

2. ACTS members have raised particular concerns as to why after an exhaustive 3-year review with 2 public consultations by the TGA on stem cell treatments that has just been completed and implemented, that the MBA seeks further changes.

    a. The TGA extensively reviewed on how best to meet public and medical concerns on the safety and efficacy of autologous and allogenic stem cell treatments, without restricting the growing need for medical innovation which leads to improvements in patients' lives.

    b. The TGA substantially increased the regulations and implemented an adverse event register. Principally, all of the concerns raised in the Discussion paper appear to have already been met by the new TGA regulations on stem cells in which the MBA would have participated as a major stakeholder.

    c. Much of the background information provided in the Guidelines is outdated and flawed and does not relate to current clinical stem cell use after the TGA intervention eg: refers to an 8-year-old publication (2011) that contains no data on how the authors obtained their estimate on 40 doctors practicing in stem cells. A more recent 2016 informal review (based on Yahoo searches) estimated that there were only 19 clinics in Australia engaged in direct-to-consumer marketing of stem cell interventions [1]. With the TGA hospital use only intervention this number is likely to much less now. This is a small number in comparison to over 100,000 registered medical practitioners in Australia [2].

3. The proposed guidelines implement an unnecessary more complex two-tiered approach rather than the current Code of Conduct for all Doctors.

4. The proposed guidelines contain a combination of clear statements intermingled with vague ambiguous statements. This lack of clarity makes it difficult for doctors to meet these standards if they are unsure how to fulfil their obligations under the guidelines.

    a. For example, there is no clear definition of what is conventional medicine and emerging medicine – who decides what is conventional medicine, and when does emerging medicine become conventional medicine?

5. There are a number of 'conventional' surgeries and medicines that have less evidence-based peer-reviewed studies in the scientific literature than that of autologous cell therapies for diseases of the knee and hip (Attachment A). Although, the gold standard for evidence-based medicine is double-blinded randomised controlled trials (RCT) the majority of medical procedures (not drugs) are reviewed by comparison studies with an average of only 37 % of interventions supported by an RCT with an average of 76% of interventions supported by some form of compelling evidence [3].

Safety of Autologous Stem Cells

Too much media sensationalism is given to the generalised statements of "unproven and unnecessary stem cell procedures". It is imperative to separate media hype, opinion and commentary from scientific fact in order to progress innovation in medical practice. Evidence-based decisions should always be the primary consideration of regulatory decisions in this complex field.

- **There is no evidence of a pattern of harm, including international research and longevity studies over a period of 17 years, supporting the need for higher regulatory complexity for autologous cell therapies.**
- Given the breadth and scope of peer-reviewed clinical publications and clinical trials i.e. ~ 1000 clinical trials using stem cells being performed globally, and more than 10 stem cell-based products have been approved overseas [4], no pattern of harm has been demonstrated.

Efficacy of Autologous Stem Cells

Autologous cell-based interventions should be available for patient use when there is robust scientific evidence of safety and efficacy in the treatment of a disease. Autologous cell therapy tends to be investigator led (e.g. only 6% of autologous cell therapy clinical trials in the EU were company-led (2012)) [5]. Despite this lack of support by industry, there is a robust body of evidence for the safe and effective treatment of knee and hip disease with autologous cell-based therapies (**6,146 patients; 58 peer-reviewed publications over 17 years**).

Attachment A sets out a body of evidence in support of the use of bone marrow (BMC) and stromal vascular fraction (SVF) cell concentrate for the treatment of knee and hip disease over 17 and 9 years respectively. Of the 58 peer-reviewed publications, there are: 1 Level I study, 8 Level II studies and 7 level III studies which evidence over 36 publications for SVF-derived cells (2,438 patients); and 22 publications for bone-marrow derived cells (3,708 patients). Applying the NH&MRC guidelines on the interpretation of peer-reviewed data: "Levels of Evidence and Grade for Recommendations for Developers of Guidelines", at least a rating of **'C Satisfactory'** may be applied for the treatment of osteoarthritis.

The safety and efficacy of a procedure should be assessed in comparison to the standard conservative treatment of the disease. Autologous cell therapies compare favorably to orthopedic treatments with key advantages of low toxicity and a high safety margin:

1. An excess mortality rate of 0.12% has been observed for total knee and hip arthroplasty[6]. We can estimate from this that 1 Australian patient dies every 4 days from total knee and hip arthroplasty (76,357 primary total knee and hip replacements were performed in Australia (2014)) [7]. In contrast, 1 mortality has been reported in 6 years for the liposuction procedure

required for autologous cell therapy, and appropriate medical regulatory action was taken in response.

2. A high complication rate has been reported of 4.5% (1 in 22 patients) with total knee arthroplasty (TKA)[8]. Nearly 1/3 (31.6%) of joint replacement patients had more than one operation [9,10]. Few complications have been observed with autologous cell therapy in the treatment of joints.

3. Approximately 1 in 5 primary total knee arthroplasty patients are dissatisfied with the outcome [11,12].

4. Recovery period is minimal after cell concentrate therapy in comparison to knee and hip arthroplasty.

We need better treatment options for patients. There has been a failure to communicate the benefits of the autologous cell therapy.

SPECIFIC COMMENTS:

ACTS strongly recommend Option 1 - retain the status quo of providing general guidance about the board's expectations of medical practitioners who provide complimentary and unconventional medicine and emerging treatments by the board approved code of conduct.

SUMMARY:

The MBA refer to two incidences of inappropriate use of stem cells we note that in both these incidences that forceful disciplinary action occurred. The current sanctions from a medical board for inappropriate actions by a medical practitioner are already in place and working. In the course of 10 years of autologous stem cell therapy use, we question as to how many doctors have been disciplined in comparison to other streams of medicine, and the rationale for further increases in regulation?

ACTS strongly believe the recent substantial changes in the TGA regulations and the current Code of Conduct for Doctors in Australia addresses the concerns of the MBA. Regulation must be predictable, stable, comprehensive, consistently applied and transparent to allow best practice for patients, ongoing medical innovation and investment.

Thank you for the opportunity to provide feedback on regulations associated with cell therapies. We look forward to continued engagement with the MBA.

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Attachment A

Publication list of knee and hip joints treated by bone marrow-derived cells. Updated 6th July 2016. A total of 22 publications with 3,708 patients treated. With 4 Level II studies, and 2 level III studies.

Table 1 - Autologous Bone Marrow-Derived Cells

	Author	Patients	Disease	Follow-up	Cartilage Regeneration	Symptom Improvement
1	Centeno *et al* 2016 (1,590 BMC, 247 BMC + adipose graft, 535 MSC)[1]	2,372	Orthopaedic conditions:	9 years, average 2.2 years	Safety study: SAE; 0.55% possible and 0.17% definitely related (rate not greater than hyaluronic acid injections). No evidence that MSC of any type increased neoplasms .1.6% AE related to the procedure, 0.4% to the cells.	N/A
2	Soler et al 2016 (A-MSC)[2]	15	Knee OA	1 year **(Phase I-II)**	Safety study. Yes MRI	Yes
3	Gobbi 2015 (A-MSC and BMC & scaffold) [3]	37	patellofemoral chondral lesions	3 years **(Level II evidence)**	Yes- MRI and histological	Yes (both groups)
4	Yamasaki 2014 (A-MSC) [4]	12	High tibial osteotomy	16 months and 10 years **(Level II evidence)**	Safety study at 10 yr. At 16 month the arthroscopic and histological grading score was better in the cell-transplanted group than in the cell-free control	No
5	Vangsness 2014 allogeniec MSC [5]	55	Meniscus	1 yr **(Level II evidence)**	Yes - MRI	Yes
6	Centeneo 2014 (BMC) [6]	616	Knee OA	2 years	Safety study	Yes
7	Gobbi 2014 (BMC) [7]	25	Chondral defects	3 yr	Yes - MRI	Yes
8	Orzoco 2013 (A-MSC) [8]	12	Knee OA	1 yr	Yes-MRI	Yes
9	Saw 2011 (A - PBMC cultured) [9]	180 treated (5 - second look)	Cartilage defects and OA	2 yr **(Level II evidence)**	Yes – 2nd look	Yes
10	Kasemkjwattana 2011 (A-MSC) [10]	2	Femoral cartilage defect	30 months	Yes – 2nd look	Yes
11	Davatchi 2011 (A-MSC) [11]	4	Knee OA	1 yr	-	Yes
12	Nejadnik 2010 (A-MSC) [12]	72	MACI vs BMSC cartilage defect	2 yr **(Level III evidence)**	Yes – 2nd look	Yes – BMSC = MACI
13	Haleem 2010 (A-MSC) [13]	5	Femoral cartilage defect	1 yr	Yes- MRI	Yes
14	Centeno 2010 (A-MSC) [14]	227	Knee/back/hips	2 yr	Safety study	No difference in population cancer
15	Wakitani 2010 (A-MSC) [15]	41	Knee OA	**11 yr**	Safety study	No cancer no infections

16	Centeno 2008 (A-MSC) [16]	1	Knee cartilage defect	6 months	Yes - MRI	Yes
17	Centeno 2008 (A-MSC) [17]	1	Knee OA	6 months	Yes - MRI	Yes
18	Kuroda 2007 (A-MSC) [18]	1	Medial femoral cartilage defect	7 months	Yes – 2nd look	Yes – returned to sport
19	Centeno 2006 (BM) [19]	1	Hip OA	3 months	Yes - MRI	Yes
20	Wakitani 2007 (A-MSC) [20]	3	patellofemoral joint cartilage defect	1.5 yr	Yes - MRI & 2nd look	Yes
21	Wakitani 2004 (A-MSC) [21]	2	patellofemoral joint cartilage defect	5 yr	Yes – 2nd look	Yes
22	Wakitani 2002 (A-MSC) [22]	24	High tibial osteotomy	8 months **(Level III evidence)**	Yes – 2nd look	Yes

A-MSC - Autologous cultured mesenchymal cells, PBMC - peripheral blood monocytes, BMC - Autologous non-cultured bone marrow concentrate cells.

Publication list of knee and hip joints treated by autologous SVF updated 1st Feb 2019. A total of 36 SVF referred publications with 2,438 patients for Knee and Hip disease with 1 Level 1 study, 4 Level II studies and 5 Level III studies

Table 2- Adipose SVF Clinical Studies for Knee and Hip diseases

	Year/Author	No. Patients	Pathology	Study type	Cell type and source	Injection/implantation	Study Design	Follow-up	Cartilage Regeneration	Symptom Improvement
1	2019 Tran TDX *et al* [23]	33	Knee OA	**Level III Evidence** Non-randomised placebo controlled	SVF	1 injection	SVF + arthroscopic fracture vs arthroscopic fracture alone	2 yr	Significant improvement Lysholm score and cartilage were observed in the treatment group. More improvement in Kellgren-Lawrence grade 3 than 2 knees.	Yes. Improved VAS score and WOMAC index in the SVF-treated group compared to placebo group.
2	2019 Michalek *et al* [24]	29	Knee and hip OA in elderly	Case series	SVF	1 injection	SVF in > 80 years age	36 months	N/A	Yes. improves significantly the quality of life in elderly patients with medium to advanced grade osteoarthritis.
3	2018 Hong Z *et al* [25]	32	Knee OA	**Level II Evidence** Double-blind randomised	SVF	1 injection	SVF vs hyaluronic acid	1 yr	WORMS and MOCART measurements revealed a significant improvement of articular cartilage repair in SVF-treated knees compared with hyaluronic acid-treated knees	Yes. Significant improvement in SVF treated knee while the control knee with HA became worse from baseline measured by VAS, WOMAC, ROM
4	2018 Saikhov *et al* [26]	1	osteochondral lesion	Case study	SVF	1 injection	SVF + Fibrin	2 yr	MRI 1 and 2 years after the surgery showed the recovery of the damaged cartilage thickness.	Yes. Clinical score improvement
5	2017 Yubo *et al* [27]		Knee OA	**Level I Evidence** Meta-analysis	SVF/BMC		582 patients in 11 studies	2 yr	N/A	Yes. treatment shown to be safe and has great potential as an efficacious clinical therapy for patients with knee osteoarthritis
6	2017 Nugyen *et al* [28]	30	Knee OA	**Level III Evidence** Non-randomised placebo controlled	SVF + PRP	1 injection	SVF + PRP + arthroscopic fracture vs arthroscopic fracture alone	18 months	N/A	Yes. SVF treatment group significantly improved over placebo. Arthroscopy microfracture + SVF had better long-term outcomes than microfracture alone.
7	2017 Bansal *et al* [29]	10	Knee OA Grade 1 and 2 only	Case series	SVP + PRP	1 injection		1 yr	Cartilage thickness as determined by MRI improved by at least 0.2 mm in six patients, was unchanged in two patients and decreased by	Yes. WOMAC and 6MWD improved

									at least 0.2 mm in two patients.	
8	2017 Giddings *et al* [30]	2	Hip OA	Case series	SVF	1 injection	SVF + PRP	5 weeks	N/A	Yes. Womac score improved
9	2017 Pak *et al* [31]	1	Hip OA	Case study	SVF	1 injection	SVF + PRP +HA	20 weeks	MRI significant positive changes	Yes. Clinical improvement
10	2017 Tantuway *et al* [32]	101	Knee OA	Case series	SVF	1 injection	SVF + PRP	2 yrs	N/A	Yes. Average KOOS score improved from pre-operative 45.09 to post-operative 24 months average 80.27, which is a very significant improvement in all grades.
11	2017 Yokota *et al* [33]	13	Knee OA	Case series	SVF	1 injection	SVF	6 months	N/A	Yes. One month after injection of SVF, all the scores of JKOM, WOMAC, and VAS were significantly improved over baseline ($P < 0.01$). Ultimately, the scores were improved by an average of 35% over baseline for JKOM, 32% improvement in WOMAC, and 40% for pain (VAS).
12	2017 Yokota *et al* [33]	13	Knee OA	Case series	SVF	1 injection	SVF	6 months	N/A	Yes. One month after injection of SVF, all the scores of JKOM, WOMAC, and VAS were significantly improved over baseline ($P < 0.01$). Ultimately, the scores were improved by an average of 35% over baseline for JKOM, 32% improvement in WOMAC, and 40% for pain (VAS).
13	2017 Michalek *et al* [34]	1,128	Knee and hip OA	Multicentre case series	SVF	1 injection	SVF	17 months	Improvements in MRI in some cases	At least 75% Score improvement was noticed in 63% of patients and at least 50% Score improvement was documented in 91% of patients 12 months
14	2016 Koh *et al* [35]	80	Knee OA	**Level II Evidence** Prospective comparative	SVF	1 injection	SVF + Microfracture and fibrin glue vs microfracture	1 yr	Second-look arthroscopies showed good repair tissue quality, although no significant intergroup difference was observed.	Yes. Compared with MFX alone, MFX and ADSCs with fibrin glue provided radiologic and KOOS pain and symptom subscore improvements
15	2016 Pak *et al* [36]	3	Knee OA	Case series	SVF	1 injection	SVF + (PRP 4 x) + (HA 4x)	16 weeks	MRI data showed cartilage-like tissue regeneration	Yes. Clinical improvement
16	2016 Al-Salahat *et al* [37]	3	Meniscus	Case series	SVF	1 injection	SVF	16 weeks	Improved meniscus and cartilage-like tissue	Yes. Clinical improvement

17	2016 Kim *et al* [38]	20	Knee OA	Case series	SVF buttocks	1 injection with debridement	SVF + fibrin glue	2 yr	Cartilage lesions grades by MRI were significantly better than the preoperative values	N/A
18	2016 Fodor *et al* [39]	6	Knee OA	Case series	SVF	1 injection	SVF	1 yr	3 months MRI no changes	Yes. statistically significant improvement in WOMAC and VAS scores
19	2015 Gibbs *et al* [40]	4	Knee OA	Case series	SVF	1 injection	SVF + PRP	1 yr	N/A	Yes KOOS scores improved from preoperative
20	2015 Kim *et al* [41]	54	Knee OA	**Level III Evidence** Cohort study	SVF	1 injection	SVF + fibrin glue vs fibrin glue only	28 months	Second-look arthroscopy, there were better ICRS grades with SVF + fibrin	Yes. no difference was observed between the 2 groups
21	2015 Kim *et al* [42]	40	Knee OA	**Level III Evidence** Cohort study	SVF buttocks	1 injection with arthroscopic surgery	Group 1: SVF + PRP pair matched with Group 2: SVF + fibrin glue vs Group 3: arthroscopic	2 yr	Group 2 for knee OA resulted in better clinical and second-look arthroscopic outcomes than Group 1. Significant correlations between the number of administered and the postoperative clinical outcomes were found only in Group 1	Yes
22	2015 Koh *et al* [35]	80	Knee lesions (GIII/IV)	**Level II evidence** Comparative study	SVF buttocks	1 injection after debridement	> 3cm^2 defect + fibrin glue + microfracture (Group 1) vs microfracture alone (Group 2)	2 yr	MRI - Group 1: 65% complete lesion coverage. Significantly better signal intensity (80% normal signal intensity) vs Group 2: 45% coverage, 72% nsr)	KOOS pain and symptom subscores were significantly greater at follow-up in group 1 than in group 2
23	2015 Garza *et al* [43]	6	Knee OA	Case series	SVF	1 injection	SVF	3 months	Safety study	Yes
24	2015 Kim *et al* [41]	49	Cartilage lesions	Case series	SVF buttocks	1 injection after debridement	SVF + FG local adherent + knee brace (2 weeks)	28.6m 12.3m (second look)	patients with lesions >6.0 cm2 showed less favourable clinical outcomes after SVF implantation compared with lesions <6.0 cm2	Clinical improvement comparable for both Groups. Better ICRS scores at 2nd look for ADSC-FG group. Lower BMI and smaller size positively correlate with outcomes
25	2014 Bui *et al* [44]	21	Knee OA	Case series	SVF Abdominal	1 injection	SVF + PRP	6 months	Increased cartilage thickness on MRI	Function improvement in all patients at 8.5 m.
26	2014 Pak *et al* [45]	1	Meniscus	Case study	SVF abdominal	1 injection	SVF + PRP +HA + (PRP day 3, 7 14, 28 + HA day 14)	18 months	Yes- MRI	Yes
27	2014 Koh *et al* [46]	44	High tibial osteotomy (HTO)	**Level II evidence** Comparative study	SVF buttocks	1 injection after debridement	(i) HTO + PRP + (n = 23) (ii) HTO + SVF + PRP (n = 21)	2 yr	Better tissue healing at 2nd look for SVF +PRP	Better clinical improvement in PRP + SVF group
28	2014 Koh *et al* [47]	35	Knee OA	Case series	SVF buttocks	1 injection after debridement	SVF + local adherent technique	1 yr	24% lesions normal. 76% abnormal or severely abnormal repair tissue at	Clinical improvement; 94% patients excellent or good satisfaction

									2nd look	
29	2013 Koh *et al* [48]	30	Knee OA	Case series Elderly patients >65 years	SVF buttocks	1 injection	Arthroscopic lavage of joint + SVF + PRP	2 yr	2nd look arthroscopy within 24m improved or maintained cartilage status in 87% of patients. Further clinical improvement 24 versus 12m	Significant clinical improvement 14/16 (87.5%)
30	2013 Koh *et al* [49]	18	Knee OA	Case series	SVF - infrapatellar fat pad	1 injection after debridement	SVF + PRP	2 yr	Significant improvement of whole-organ MRI scores at final follow-up 60.0 to 48.3 points. Cartilage improved 28.3 to 21.7 points	Significant improvement of the clinical scores at final follow-up
31	2013 Pak *et al* [50]	91	Knee OA	Case series	SVF abdominal	1 injection	SVF + PRP + HA + (weekly PRP 4x)	30 months	Safety study	VAS improved 50–60% No major complications
32	2013 Pak *et al* [51]	3	Chondromalacia Patellae	Case series	SVF abdominal	1 injection	SVF + PRP + HA + (PRP day 3, 7, 14, 28 + dexamethasone day 14)	1 yr	Improvement in MRI	Pain improved: 50–70% at 1m 80–90% at 3m
33	2012 Koh *et al* [52]	Study :25 Control :25	Knee OA	**Level III evidence** Comparative Study	SVF infrapatellar fat pad	1 injection after debridement	(i) SVF + PRP + (weekly PRP 2x) (ii) Only PRP (control)	16 months	Safety study	Significant improvement in all clinical scores. Study versus control: n.s. at final follow-up, but study group had lower basal
34	2012 Pak *et al* [53]	2	Hip OA	Case report	SVF abdominal	1 injection	SVF + PRP +HA + (weekly PRP 4x)	12 months	Cartilage volume increased at MRI	Yes
35	2011 Pak *et al* [54]	4	Hip and Knee OA	Case report	SVF abdominal	1 injection	SVF + PRP +HA + (weekly PRP 4x)	3 months	Improvement in MRI	Yes
36	2010 Bright [55]	6	Knee and foot OA	Case series	SVF abdominal	1 injection	SVF	4 months	Safety study	Yes

Publication list of autologous SVF safety reviews and publications updated 1st Feb 2019. A total of 9 SVF referred publications with multiple routes and conditions

Table 3 - Adipose SVF and ASC Safety Reviews

1	2017 Toyserkani *et al* [56]		Route: Intra articular, Intra venous, intracranially, intramyocardial, Subcutaneous	Review safety	ASC and SVF	Route: Intra articular, Intra venous, intracranially, intramyocardial, Subcutaneous	Safety review, 36 studies			Autologous shown to be safe. Covered patients from North America, South America, Europe and Asia
2	2019 Mehranfar *et al* [57]	1,352	Knee OA	Review	SVP, PRP and ASC		11 SVF studies			Yes. Safe and clinical improvement
3	2019 Ha C-W *et al* [58]	1,352	Knee OA	Systemic Review	SVF and ASC		6 SVF studies			Yes. Safe and clinical improvement

4	2018 Lijima *et al* [59]	2,358	Knee OA	Systemic Review	ASC, SVF and multiple cell types		35 studies of which 4 are SVF			Minor adverse events (knee pain or swelling) were reported with a wide-ranging prevalence of 2-60%; however, no severe adverse events occurred
5	2017 Pak *et al* [60]	1,518	Range of orthopaedic conditions	Review safety	SVF		19 studies			Yes. All studies reviewed in this article presents potential benefits of autologous adipose SVF in various orthopedic applications without any serious side effects.
6	2016 Pak *et al* [35]	1,436	Cartilage defects	Review safety	SVF		12 studies			Yes. Clinical effectiveness and safe
7	2017 Berman *et al* [61]	1,524	Multiple conditions	Prospective safety	SVF	Multiple injections	59 studies via IV, intra-articular	5 yrs		Yes. No serious safety effects
8	2016 Siennicka *et al* [62]	145	Multiple conditions	Retrospective safety	SVF	Multiple injections	Route IV and intra-articular	2.5 yrs		Yes. No serious safety effects
9	2017 Comella *et al* [63]	676	Multiple conditions	Prospective safety	SVF	Multiple injections	5 clinical sites			Yes. No serious safety effects

Table 4 - Autologous Adipose ASC* Publications for Knee and Hip diseases

1	2017 Toyserkani *et al* [56]		Route: Intra articular, Intra venous, intracranially, intramyocardial, Subcutaneous	**Review**	ASC and SVF	Route: Intra articular, Intra venous, intracranially, intramyocardial, Subcutaneous	Safety review, 36 studies			Autologous shown to be safe. Covered patients from North America, South America, Europe and Asia
2	Pers *et al* (2016)[64]	18	primary femorotibial knee OA	Open Phase 1	ASC	1 injection	3 different doses of ASCs (2, 10, 50 x 10^6)	6 months	Safety study; 4 patients transient knee swelling	Improved pain and cartilage
3	Jo *et al* (2014) [65]	18	Knee OA	Case series	ASC abdominal	1 injection	Phase I: 3 doses of ASCs; the low-, mid-, and high-dose group with 3 patients each Phase II: 9 patients receiving the high dose of ASCs	6 months	Yes -arthroscopic (hyaline-like cartilage growth)	Yes

SVF - autologous stromal vascular fraction, HA - Hyaluronic acid, FG - fibrin glue, PRP - platelet rich plasma. *ASC - Adipose mesenchymal stem cells which have been grown and cultured from adipose tissue

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