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Contents

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EDITORIAL

What is the purpose of launching *World Journal of Rheumatology*?

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Abstract

The first issue of *World Journal of Rheumatology* (*WJR*), whose preparatory work was initiated on December 16, 2010, will be published on December 31, 2011. The *WJR* Editorial Board has now been established and consists of 116 distinguished experts from 29 countries. Our purpose of launching *WJR* is to publish peer-reviewed, high-quality articles *via* an open-access online publishing model, thereby acting as a platform for communication between peers and the wider public, and maximizing the benefits to editorial board members, authors and readers.

Key words: Rheumatology; Journal; Open-access; Peer-reviewed

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INTRODUCTION

I am very pleased to announce that the first issue of *World Journal of Rheumatology* (*World J Rheumatol*, *WJR*, online ISSN 2220-3214, DOI: 10.5499), on which preparation was initiated on December 16, 2010, is officially published on December 31, 2011. The *WJR* Editorial Board has now been established and consists of 116 distinguished experts from 29 countries. It is my great honor to have the world reknowned rheumatologist Jörg HW Distler, MD, Assistant Professor, as the first Editor in Chief of *WJR* (Figure 1). What is the purpose of launching *WJR*? And what is the scope and how are the columns designed?

The role of academic journals is to exhibit the scientific levels of a country, a university, a center, a department, and even a scientist, and build an important bridge for communication between scientists and the public. As we all know, the significance of the publication of scientific articles lies not only in disseminating and communicating innovative scientific achievements and academic views, as well as promoting the application of scientific achievements, but also in formally recognizing the "priority" and "copyright" of innovative achievements published, as well as evaluating research performance and academic levels. To realize these desired attributes of a journal and create a well-recognized journal, the following four types of personal benefits should be maximized.

MAXIMIZATION OF PERSONAL BENEFITS

The maximization of personal benefits refers to the pursuit of the maximum personal benefits in a well-considered optimal manner without violation of the laws, ethical rules and the benefits of others.

Maximization of the benefits of editorial board members

The primary task of editorial board members is to give a peer review of an unpublished scientific article *via* online office system to evaluate its innovativeness, scientific and practical values and determine whether it should be published or not. During peer review, editorial board members can also obtain cutting-edge information in that field first hand. As leaders in their field, they have priority to be invited to write articles and publish commentary articles. We will put peer reviewers' names and affiliations along with the article they reviewed in the journal to acknowledge their contribution.

Maximization of the benefits of authors

Since *WJR* is an open-access journal, readers around the world can immediately download and read, free of charge, high-quality, peer-reviewed articles from *WJR* official website, thereby realizing the goals and significance of the communication between authors and peers as well as public readers.

Maximization of the benefits of readers

Readers can read or use, free of charge, high-quality peer-reviewed articles without any limits, and cite the arguments, viewpoints, concepts, theories, methods, results, conclusion or facts and data of pertinent literature so as to validate the innovativeness, scientific and practical values of their own research achievements, thus ensuring that their articles have novel arguments or viewpoints, solid evidence and correct conclusion[1].

Maximization of the benefits of employees

It is an iron law that a first-class journal is unable to exist without first-class editors, and only first-class editors can create a first-class academic journal[2,3]. We insist on strengthening our team cultivation and construction so that every employee, in an open, fair and transparent environment, could contribute their wisdom to edit and publish high-quality articles, thereby realizing the maximization of the personal benefits of editorial board members, authors and readers, and yielding the greatest social and economic benefits.

CONTENTS OF PEER REVIEW

In order to guarantee the quality of articles published in the journal, *WJR* usually invites three experts to comment on the submitted papers. The contents of peer review include: (1) whether the contents of the manuscript are of great importance and novelty; (2) whether the experiment is complete and described clearly; (3) whether the discussion and conclusion are justified; (4) whether the citations of references are necessary and reasonable; and (5) whether the presentation and use of tables and figures are correct and complete.

SCOPE

The aim of *WJR* is to report rapidly new theories, methods and techniques for prevention, diagnosis, treatment, rehabilitation and nursing in the field of rheumatology. *WJR* covers topics concerning osteoarthritis, metabolic bone disease, connective tissue diseases, antiphospholipid antibody-associated diseases, spondyloarthropathies, acute inflammatory arthritis, fibromyalgia, polymyalgia rheumatica, vasculitis syndromes, periarticular rheumatic disease, pediatric rheumatic disease, miscellaneous rheumatic diseases, and rheumatology-related therapy, pain management, rehabilitation, traditional medicine, and integrated Chinese and Western medicine. The journal also publishes original articles and reviews that report the results of rheumatology-related applied and basic research in fields such as immunology, physiopathology, cell biology, pharmacology, medical genetics, and pharmacology of Chinese herbs.

COLUMNS

The columns in the issues of *WJR* will include: (1) Editorial: To introduce and comment on the substantial advance and its importance in the fast-developing areas; (2) Frontier: To review the most representative achievements and comment on the current research status in the important fields, and propose directions for the future research; (3) Topic Highlight: This column consists of three formats, including (A) 10 invited review articles on a hot topic; (B) a commentary on common issues of this hot topic; and (C) a commentary on the 10 individual articles; (4) Observation: To update the development of old and new questions, highlight unsolved problems, and provide strategies on how to solve the questions; (5) Guidelines for Clinical Practice: To provide guidelines for clinical diagnosis and treatment; (6) Review: To systemically review the most representative progress and unsolved problems in the major scientific disciplines, comment on the current research status, and make suggestions on the future work; (7) Original Articles: To originally report the innovative and valuable findings in rheumatology; (8) Brief Articles: To briefly report the novel and innovative findings in rheumatology; (9) Case Report: To report a rare or typical case; (10) Letters to the Editor: To discuss and make reply to the contributions published in *WJR*, or to introduce and comment on a controversial issue of general interest; (11) Book Reviews: To introduce and comment on quality monographs of rheumatology; and (12) Guidelines: To introduce consensuses and guidelines reached by international and national academic authorities worldwide on

the research in rheumatology.

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REVIEW

Synovial mesenchymal stem cells *in vivo*: Potential key players for joint regeneration

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Abstract

Unlike bone marrow (BM) mesenchymal stem cells (MSCs), whose *in vivo* identity has been actively explored in recent years, the biology of MSCs in the synovium remains poorly understood. Synovial MSCs may be of great importance to rheumatology and orthopedics because of the direct proximity and accessibility of the synovium to cartilage, ligament, and meniscus. Their excellent chondrogenic capabilities and suggested transit through the synovial fluid, giving unhindered access to the joint surface, further support a pivotal role for synovial MSCs in homeostatic joint repair. This review highlights several unresolved issues pertaining to synovial MSC isolation, topography, and their relationship with pericytes, synovial fibroblasts, and synovial fluid MSCs. Critically reviewing published data on synovial MSCs, we also draw from our experience of exploring the *in vivo* biology of MSCs in the BM to highlight key differences. Extending our knowledge of synovial MSCs *in vivo* could lead to novel therapeutic strategies for arthritic diseases.

Key words: Mesenchymal stem cells; Synovium; Fibroblasts; Synovial fluid; Arthritis

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INTRODUCTION

Only a decade has passed since their original discovery[1], but synovial mesenchymal stem cells (MSCs) have already become primary candidates for joint regeneration strategies for osteoarthritis and traumatic joint injuries[2]. Their existence has been inferred from experiments where the synovium was digested and culture-expanded, with daughter cells being able to differentiate into bone, cartilage, fat, and muscle lineages[1]. Numerous original articles have demonstrated that culture-expanded synovial MSCs could represent an optimal MSC source for cartilage and meniscus regeneration[3-6]. In contrast, the nature of parental culture-initiating MSCs resident *in vivo* is much less understood. Given that the substantial regenerative capacity of synovial tissue following synovectomy[7], this points towards their immense *in vivo* potential for joint repair.

From this perspective, we first consider the biology of synovial MSCs in comparison to synovial fibroblasts (SFs). This is particularly relevant, because SFs are often

considered as malevolent, destructive cells in arthritis[8,9], whereas synovial MSCs are believed to be beneficial, regenerative cells. Even in healthy individuals, the relationship between synovial MSCs and SFs remains unclear, and whether the regenerative and destructive potentials represent different faces of the same coin, remains to be determined. Secondly, we describe currently available data on the biology of synovial MSCs *in vivo* in the context of bone marrow (BM) MSCs, which we reviewed recently[10]. A comparative analysis of these two types of MSCs is likely to shed more light on tissue-specificity and heterogeneity of MSCs *in vivo*.

RELEVANT SYNOVIAL ANATOMY

The normal synovium has a membrane and a sub-membrane fibro-fatty tissue, surrounded by a joint capsule. The synovial membrane is composed of type A (monocytic) and type B (fibroblastic), or synovial intimal, fibroblasts cells and is normally 1-2 cells thick. Normally, the synovial membrane plays a key role in joint lubrication, but can undergo substantial hyperplasia during chronic inflammatory processes[8]. The sub-synovium accumulates many myeloid and lymphoid lineage cells during chronic inflammation, which is associated with extensive tissue remodeling, new blood vessel formation, and related increase in proliferation of SFs. As arthritis develops, SFs change their gene expression, leading to further attraction and accumulation of inflammatory cells in the subsynovium[9,11]. In rheumatoid arthritis (RA) and other settings of chronic inflammation, increased proliferation of SFs may lead to the formation of an invasive stromal tissue, termed pannus. The combined hyperplasia of both components of the synovium leads to villus formation. Currently, the location of synovial MSCs, whether from one or both of these synovial compartments, and their contribution to pannus formation remain unclear.

SFs AND SYNOVIAL MSCs

Similar to synovial MSCs, SFs are isolated by plastic adherence and cultured in serum-rich medium[1,12,13]. Surface markers, initially described to be specific for synovial MSCs[14,15], were later shown to cross-react with synovial and other types of fibroblasts[9,16-20]. The synovial MSCs, however, can be distinguished from SFs by their higher proliferative capacity and faster growth rates. MSCs are highly proliferative cells, capable of over 20 population doublings (PDs)[21]. According to Smith and Hayflick[22], the majority of fibroblasts have "a maximum doubling potential of about eight PDs"[22]. Based on these considerations, MSCs have been historically defined as cells initiating rapidly growing, highly proliferative clonal cultures[1,16,23-26]. MSC clones can be isolated either by plating synovial cells in limiting dilution conditions[1,16,23,24] or at a very low seeding density[3,5,27]. Under the latter conditions, MSCs are believed to "overgrow" SFs because of their faster proliferation rates. Indeed, clonal synovial cultures

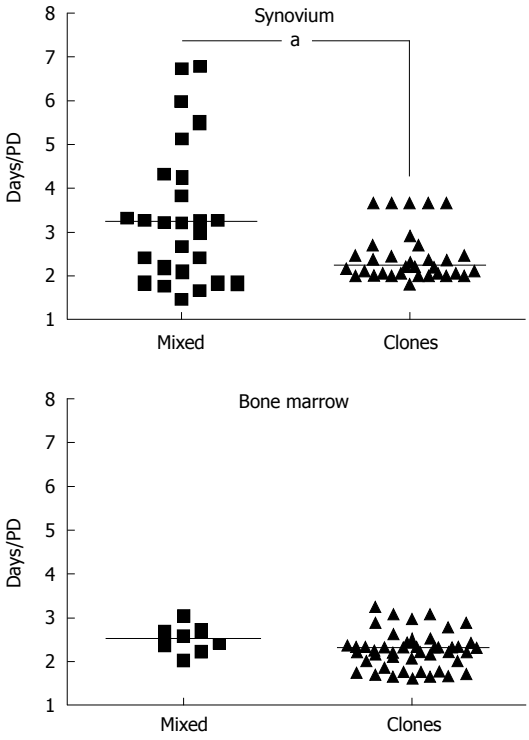

Figure 1 Growth rates of mesenchymal stem cells derived from human synovium and bone marrow. Faster growth rates of clonal synovial mesenchymal stem cell (MSC) cultures compared to standard polyclonal cultures (mixed with synovial fibroblasts; n = 26 donors, $^{a}P < 0.05$). Bone marrow MSCs are used as the control (n = 9 donors, P = 0.06). Median values are shown as horizontal bars. PD: Population doubling.

grown in our laboratory[18] demonstrate faster growth rates compared to mixed synovial cultures. The same trend was observed for BM-derived controls[28] (Figure 1).

Regardless of the cultivation conditions, senescent cells eventually accumulate in clonal synovial MSC cultures[26], suggesting that current *in vitro* cultivation conditions do not support indefinite "self-renewal" of synovial MSCs. In the BM, the fastest growing clonal MSCs are truly tripotential, whereas relatively slower-growing clones are bi- or unipotential[29-31]. Although fast- and slow-growing clonal MSCs can be also grown from the synovium, no link with their multipotentiality could be established[26]. Thus, it appears that in the BM, high and rapid proliferative capacity is linked with robust tripotentiality, whereas in the synovium, it might not be. From a practical perspective, this may explain why it has proving difficult to find a marker for synovial MSCs based solely on *in vitro* expansion/differentiation experiments.

SYNOVIAL MSC ISOLATION BASED ON SURFACE MARKERS

In high-density expansion conditions, synovial MSCs may be "contaminated" with SFs. Several investigations attempted to purify synovial MSCs prospectively (Table 1). Unlike studies with BM MSCs[32-35], the expansion and differentiation capacities of unsorted control preparations are not

Table 1 Synovial mesenchymal stem cell isolation studies based on pre-defined phenotypes

Candidate phenotype	Control standard culture: "without separation"		Control negative fraction: "opposite phenotype"	
	Expansion capacity	Differentiation capacity	Expansion capacity	Differentiation capacity
$CD9^+CD90^+CD166^+$[14]	NR	Similar	NR	NR
SP (bovine)[98]	NR	NR	NR	Chondro: similar
SP (bovine)[99]	NR	NR	Significantly lower	Chondro: inferior Osteo: similar Myo: absent
$CD105^+$[100]	NR	Chondro: present	NR	Chondro: present
$CD45^-CD31^-$[18]	NR	NR	Absent	NR

First described for muscle and hemopoietic stem cells[101,102]. Chondro: Chondrogenesis; Osteo: Osteogenesis; Myo: Myogenesis; NR: Not reported; SP: Side population, this cell population is defined functionally and cytometrically by the ability of cells to expel fluorescent dyes.

commonly reported, making the evaluation of functional improvement following isolation somewhat difficult. Furthermore, sorting is sometimes performed from passage 0 cells, rather than from primary tissue digests, making cell adherence, and not sorting, the primary selection step.

In our recent studies, we optimized the cell sorting methodology for digested human synovium[18,36] and demonstrated an exclusive presence of clonogenic synovial MSCs in the $CD45^-CD31^-$ (non-hematopoietic, non-endothelial) fraction[18]. Our most recent data show that highly-proliferative clonogenic MSCs (capable of over 20PDs) represent no more than 1% of synovial $CD45^-CD31^-$ cells[18]. These data suggest that molecules with expression levels markedly above 1% are unlikely to be selective for synovial MSCs. These ineffectual markers include CD73, CD44, and CD90 (expressed on approximately 90% of freshly-isolated synovial cells)[18,37], and should be better categorized as markers of SFs and not MSCs. CD44 expression on SFs has been previously documented[17,38].

We, and others, have previously shown that CD271 is very selective for *in vivo* BM MSCs[32,33,39]. CD271 has been also proposed to be MSC-specific in adipose tissue[40-43]. The CD271-positive population represents approximately 10% of the $CD45^-CD31$ fraction[36], making CD271 a fairly promising candidate for synovial MSC isolation. Indeed, CD271-positive cells isolated from mixed synovial cultures were found to be highly chondrogenic[44]. The CD73-positive subpopulation was less chondrogenic and the CD106-positive cells were most undifferentiated[44]. This agrees with studies from adipose tissue that have been unable to define a singular specific marker that is enriched in all cells with MSC activity[45,46]. In the latter study, adipose-derived MSCs were identified in both CD34-positive and CD271-positive fractions[46]. In the BM, all clonogenic MSCs reside in the $CD34^-CD271^+$ fraction[10]. In the synovium and adipose tissue, this fraction does not appear to be highly selective for MSCs, suggesting that a theory of the "common phenotype" of MSCs in different tissues is unlikely to hold true. The recent study by Kurth *et al*[47] also indicated that synovial MSCs may be more phenotypically heterogeneous than BM MSCs.

In addition to synovial MSCs, the $CD45^-CD31^-$ synovial fraction is likely to contain more committed mature cells, myofibroblasts, and adipocytes. MSC differentiation towards these lineages is affected by inflammation[48]; therefore, studies on normal synovial tissue are needed to find markers for the isolation of these separate cell types alongside the MSCs.

CAN SYNOVIAL MSCs BE IDENTIFIED AND ISOLATED BASED ON INTRACELLULAR MARKERS?

Surface markers may indeed be useful tools for stem cell isolation, but they rarely shed light on the stem cell nature of their target cells. CD34 is useful for hemopoietic stem cell isolation, but it is also expressed on endothelial cells and on adipose tissue MSCs[42,43], where its precise function remains unknown. Receptors and downstream intracellular molecules directly involved in specific stem cell maintenance and differentiation pathways may represent much more valuable tools. Molecules involved in BMP signaling (BMPR1A and pSMAD1/5) were the first to be used for the identification of MSCs in the synovium[49,50]. Similarly, lineage-specific transcription factors and downstream molecules activated by BMPs (Sox9, aggrecan and others) have been proposed to mark synovial chondroprogenitors[51]. Finally, Cadherin-11-expressing mesenchymal cells have been shown to orchestrate synovial tissue architecture[52]. Although these studies offer new opportunities for molecular analysis of marker-positive cells, the necessity to fix the cells for intracellular flow cytometry precludes downstream live cell experimentation. Furthermore, these mesenchymal lineage-related pathways may be equally active in SFs, in addition to MSCs, as shown earlier by their continuous activation in the inflamed synovium[53,54]. Therefore, their MSC-selectivity, even in the normal synovium, remains to be proven.

SYNOVIAL MSC ISOLATION BASED ON DISTINCT TOPOGRAPHICAL NICHES

Most recently, the idea of a perivascular location of MSCs in diverse human tissues has become predominant[55-57]. This does make sense, because MSCs have been found in the majority of solid tissues where blood vessels may be the only common anatomical structure[56,58]. Furthermore, such a concept is very plausible, given that early embryonic limb development is characterized by epithelial-mesenchymal transition, where the mesenchyme acts as a "space filler" before the development of a vascular system[59]. Based on this "pericyte" concept, it has

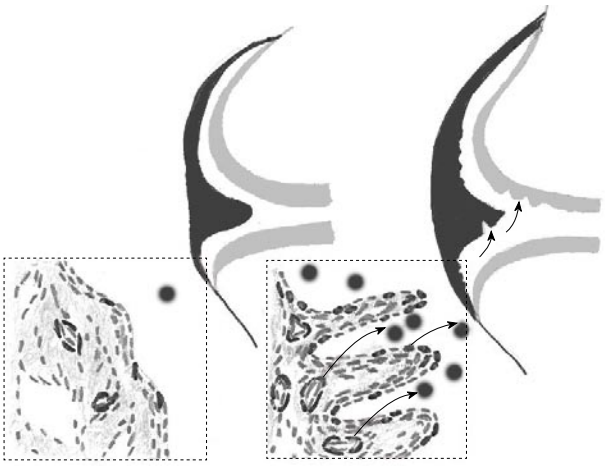

Figure 2 Schematic of the potential involvement of synovial mesenchymal stem cells in cartilage and meniscal repair following injury. Left: Normal joint, only few mesenchymal stem cells (MSCs) escape into the fluid; Right: Cartilage/meniscal injury leads to MSC to egress into fluid and to traffic along chemotactic gradients emanating from injury-induced signaling centers. Proposed topographical niches of synovial MSCs are shown in the inserts and include synovial lining and perivascular distribution in sublining regions.

been suggested that MSC frequency directly correlates with blood vessel density in solid tissues[60], including the synovium[61].

Although many studies suggest that MSCs are perivascular and are possibly derived from pericytes, it should be noted that articular cartilage, an avascular tissue, has been reported to contain MSC-like cells[62-64], which argues against an exclusive perivascular location of MSCs. In the BM, MSC activity is associated with adventitial reticular cells, which are specialized pericytes of venous sinusoids[65], and also with cells lining bone surfaces[28,66]. Most recently, Feng *et al*[67] showed the existence of a non-pericyte stem cell population in a rodent incisor growth model. These non-perycitic MSCs were capable of migration toward areas of tissue damage and differentiation into odontoblasts. Similarly, lineage-tracing experiments in a mouse model of joint surface injury have proven the presence of slow-cycling MSCs in the synovium that were distinct from pericytes and differentiated to chondrocytes in response to injury[47].

One study proposed the presence of MSCs in synovial tissue projections, i.e. the exterior areas of the tissue exposed to synovial fluid[68]. Although these observations need to be confirmed by direct isolation of candidate Stro-1+ cells, this correlates well with our findings relating to synovial fluid MSCs[16,23], which most likely originated in the synovium[23,69]. Both "synovial projection" and "pericyte" topographies allow easy egress of synovial MSCs into the fluid, without the need of extensive migration through several layers of cells and the extracellular matrix (Figure 2).

POTENTIAL SYNOVIAL MSC MIGRATION INTO THE FLUID

With the exception of joint cartilage, the synovium lines the entire joint surface, including intra-articular ligaments. As stated above, synovial fluid MSCs are most likely to originate from the synovium[23,69]; however, their superficial cartilage origin in healthy young individuals cannot be excluded[62]. Biophysical factors, trauma, and local injury-induced signaling centers[70] could potentially induce MSC egress into the fluid (Figure 2). This indicates a mechanism whereby synovial MSCs can gain access to cartilage and meniscal areas that are remote from the synovium, and explain how synovial MSCs can continuously effect homeostatic repair of microdamage in these tissues. Although synovial fluid MSCs are rare[16,23], their proliferative capacity is huge (normally a million-fold), which is likely to be sufficient for repairing small lesions in cartilage, considering its low cellularity[71]. Notably, physiological cartilage repair in humans[72] and animal models[73] has been documented, and the role of synovial fluid MSCs in these repair processes cannot be excluded. Most recently, a proof-of-concept study in rabbits demonstrated the regeneration of the entire articular surface of the synovial joint without cell transplantation, mediated by endogenous host cells, potentially derived from the synovium[74]. Further augmentation of MSC concentration in the fluid by injecting more MSCs facilitated good meniscal and cartilage repair *in vivo*[6,69,75]. The synovial fluid microenvironment can affect the migratory[76], proliferative[23], and differentiative potential of MSCs[77-80], which could further enhance their repair capabilities.

There is conflicting evidence for the presence of circulating BM MSCs[10,81,82]; however, in studies that suggest MSC circulation, very few colony-forming cells have been found[83]. RA SFs may be able to circulate in the SCID mouse model and contribute to the diffuse pattern of joint disease evident in RA[84]. Whether healthy SFs or synovial MSCs possess similar transmigration capacities, remains to be investigated. Even if rare MSC circulate, their tissue of origin remains to be determined.

UNRESOLVED CONTROVERSIES

It must be acknowledged that there are several unresolved controversies pertaining to the identification of synovial MSCs *in vivo*. The *in vitro* proliferative index of clonal synovial MSCs may be different from what actually happens *in vivo*. As mentioned above, the addition of synovial fluid to synovial MSCs can enhance their proliferation[23], indicating that *in vivo* factors may have a major effect on MSC divisions. SFs can be easily converted into pluripotent iPS cells *in vitro*[85], which involves the activation of a telomerase gene[86,87]. Synovial MSCs have low telomerase activity[26]. However, if a telomerase gene is activated in susceptible SFs *in vivo*, they may theoretically acquire an increased proliferative capacity, i.e. they may emerge as *de novo* MSCs. On the other hand, the *in vivo* inflammatory milieu can inhibit synovial MSC proliferation[18], as well as their differentiation and immunomodulatory capabilities[18,88]. This highlights the dynamic, rather than static, nature of the SF/MSC equilibrium in the synovium and may explain, at least in part, the massive pannus tissue

formation in RA.

Finally, the *in vitro* conditions that are used to derive clonal synovial MSCs, by their very nature, artificially induce cellular senescence. Therefore, massively expanded clonal MSCs, when used for therapeutic implantation, may be near the end of their natural lifespans. This suggests that, for therapeutic applications, methodologies based on extensive synovial MSC proliferation should be avoided. In contrast, minimally expanded synovial MSCs may provide a better solution for joint tissue regeneration approaches.

CONCLUSION

In contrast to the BM MSC field, where there is a consensus on the MSC identity[10,89-91], data on synovial MSC topography and phenotype are scarce. Synovial MSCs and SF are intricately inter-related; in fact, one cannot exclude the possibility that mature SFs are direct descendants of ancestral MSCs and that SFs have a limited lifespan *in vitro* because of previous extensive proliferation of ancestral MSCs *in vivo*. An ideal marker for synovial MSCs would possibly be linked to their superior proliferative potential, showing notably lower levels of expression on SFs. Conversely, the majority SFs are likely to express higher levels of senescence-associated transcripts and shorter telomeres, which were initially proposed for BM MSCs and their progeny[31,92,93]. Furthermore, definitive markers may exist that identify SFs with increased reprogramming potential. Future studies analogous to those performed with BM MSCs[94-96] may discover such markers. Direct implantation of freshly isolated synovial MSCs based on these new markers, without culture-expansion and associated senescence, may ultimately be required to establish the *in vivo* phenotype of synovial MSCs.

A better understanding of the biology of synovial MSCs *in vivo* would not only lead to novel cell-based regenerative medicine approaches[2,97], but would also permit the development of cell-free interventions based on increased understanding of synovial MSC migration[74,76] and their metabolic responses to injury[47,70]. Therefore, the preliminary data on synovial MSCs, as outlined here, should serve as a platform for the pursuit of novel therapeutic strategies for joint degeneration. Novel methodologies, including lineage tracing, knockdown analysis, and laser-dissection microscopy of gene-marked cells in animal models, are likely to provide a much-needed breakthrough in this area.

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Excellence in Rheumatology
Madrid, Spain

February 16-17, 2012
3rd National Conference - Metabolic Bone Disorders 2012
London, United Kingdom

February 24-25, 2012
III Simposio de Enfermedades Sistémicas Autoinmunes
Las Palmas de Gran Canaria, Spain

March 3, 2012
Symposium on Rheumatic Diseases: Hot Topics in Rheumatology (Cedars-Sinai)
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Canadian Rheumatology Association Annual Meeting
Victoria, Canada

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OARSI 2012 - World Congress on Osteoarthritis
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Rheumatology 2012
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8th International Congress of Autoimmunity 2012
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Acknowledgments

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Chinese journal article (list all authors and include the PMID where applicable)

2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

In press

3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

No volume or issue

9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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Write as mean ± SD or mean ± SE.

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Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

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