Redesign

Annals of the Rheumatic Diseases redesign

L van de Putte

A new look for 2002

The observant reader of the *Annals* will notice that this first issue of the year 2002 looks different. The redesign of the journal is not just a manifestation of fashion, in a time where the only constant seems to be change. During the yearly and other meetings of editors of specialist journals published by the BMJ Publishing Group there has been a growing awareness that redesigning the journals is mandatory for the future. Although different editors may have varying opinions on the relative values of web versions and paper versions of their journals, it now becomes more and more clear that paper versions of these specialist journals will remain important for most of their readership, including that of the *Annals*. With this in mind it is important to make these journals as attractive as possible for the readership, to facilitate transfer of knowledge, and make the reading of the journal a true pleasure.

BMJ Publishing Group specialist journals editors increasingly found the current design dated and limited, and therefore called for a change. The main goal was and is that reading specialist journals, including the *Annals of the Rheumatic Diseases*, will be a better experience for the reader. What does that mean for the authors? Box 1 summarises differences between the old and new design.

Although the editorial team recognises that details of the redesign may have to be changed/improved in the forthcoming months, it is convinced that this change in design will please the reader and facilitate the goals of ARD—namely, bringing high quality science and education to the readership in the best possible way.

Box 1 Main differences

Papers
- New fonts
- "Two" column layout
- Authors' affiliations have moved
- New heading styles
- Tables boxed and shaded
- Flexible figure widths
- Summary boxes
- References—first author in bold

Leaders
- Three column layout
- Short, snappy title with "subtitle"
- Pull out quotes
- More illustrations

Reviews
- Very short summary paragraph
- Different page 1 layout, then as for papers

Ann Rheum Dis 2002;**61**:1

Authors' affiliations
L van de Putte, Editor

Osteoporosis

Steroids cause osteoporosis

S Paget

Excellent treatment options exist. So why don't we all prevent or treat it?

When doctors institute steroids for any illness and for any length of time, they take on a lifelong responsibility to that patient to both taper the drug as quickly as is possible and safe and prevent or treat the many well recognised steroid related side effects.[1] This is particularly true when steroid treatment lasts for more than one month and certainly for many months or years. Rheumatologists have a particular accountability because of the 1% of the population who are receiving long term steroids, most have rheumatological disorders.[2 3] Further, rheumatologists should have the best understanding of when the treatment course will be prolonged, the profound and negative physiological impact of steroids on bone, and the need to deal with this important issue in both men and women.[4 5]

A recent topic search for steroid-induced osteoporosis (SIO) yielded 79 000 articles since 1966 and 13 000 since 1998, most of which focused on the pathogenesis, clinical manifestations, and treatment of SIO. Despite the saturation publication on this topic for years, doctors do not seem to take heed: the majority of bone loss is rapid; most of the 50% of patients with atraumatic fractures develop them in the first year; SIO is the third most common cause of osteoporosis; vertebral and hip fractures are associated with profound short and long term morbidity and mortality; and, most importantly, SIO is both avoidable and treatable.[6 7] It is not a matter of *whether* clinically significant and quality of life altering bone loss will occur, but *when*. Similarly, it should not be a matter of *whether* treatment should be started, but *how soon*, and *which* therapeutic options should be instituted.

> "Steroid-induced osteoporosis is both avoidable and treatable"

These facts make the results of the paper by Gudbjornsson *et al* in this journal all the more disturbing (see page 32).[8] Over a two year period, they carefully studied a well defined population of 26 664 patients in northeast Iceland to determine their corticosteroid use and clinical information about their medical disorders and possible steroid related side effects. Owing to the centralisation of drug distribution and medical care and the use of questionnaires, one can assume excellent capture of drug data and clinical data. If anything, their data probably underreport the breadth of steroid related bone disorders. One hundred and ninety one patients, or 0.7% of

the population, were receiving chronic steroid treatment, defined conservatively as a time period of over three months of treatment. Although over a third of patients were receiving either calcium or vitamin D supplements, only 9% were taking bisphosphonates and 21% hormone replacement therapy. The take-home lesson from their excellent population and prevalence study in a well defined part of Iceland spells out a seemingly worldwide finding: a surprisingly large proportion of doctors who treat life or organ threatening inflammatory disorders do not appear automatically to connect the institution of steroids with the need for preventive, bone protecting treatment and monitoring for SIO.[9]

> "Many doctors do not connect the institution of steroids with the need for preventive treatment against osteoporosis"

All doctors who write an initial prescription for a thiazide diuretic for hypertension would reflexively monitor and replace potassium and, similarly, those starting a chemotherapeutic agent for cancer would check a white blood cell count. We are now trying to decrease the use of antibiotics to avoid worsening bacterial resistance. Yet, the majority of steroid treated patients who should be given calcium, vitamin D3, and anti-resorptive agents, such as bisphosphonates, oestrogen replacement therapy, and calcitonin, are not. What can account for such a medical conundrum?

Mixed messages about the safety of oestrogen replacement therapy, the slowness of incorporation of medical advances into practice, and the newness of data about the effectiveness of bisphosphonates in preventing or reversing SIO all have a role.[10 11] Also, despite a near educational blitz on this topic by pharmaceutical companies and doctors, it appears that doctors and patients are slow to learn in this setting of a bone disorder that may remain silent for many years after steroid institution. Clearly, also, many doctors who institute steroids believe that the course will be short. Then, when the regimen turns into a chronic phase, they either forget the drug's bone toxicity or are preoccupied by the disease that they are treating or the other more clinically apparent and disturbing steroid related side effects, such as infections, diabetes, or psychological and sleep problems.

Clearly, the answer is education and more rapid dissemination of information through journals and the internet. Neither the definition and measurement of bone loss with dual *x* ray absorptiometry nor the prophylaxis and treatment of SIO is perfect. However, the data strongly support their place in mainstream medicine in a manner similar to the measurement, treatment, and monitoring of hypertension, atherosclerosis, diabetes, asthma, and peptic ulcer disease. Reports like the one in this journal go a long way towards resetting the well meaning doctor's mind and putting SIO on their therapeutic radar screen. Hopefully, this group will look at this topic again in another two years and see whether their report, various excellent guidelines from national organisations, and the clinical use of new and exciting drugs, such as the bisphosphonates and the anabolic agent parathyroid hormone, will improve the focus and doctor's acceptance of, and action on, this important topic (table 1).[6 12 13]

Ann Rheum Dis 2002;**61**:1–3

Authors' affiliations
S Paget, Hospital for Special Surgery, 535 East 70th Street, New York, NY 10021, USA

Correspondence to Dr Paget; PagetS@HSS.edu

REFERENCES

1 **Saag KG**, Koehnke R, Caldwell JR, Brasington R, Burmeister LF, Zimmerman B, *et al.* Low-dose, long-term corticosteroid therapy in rheumatoid arthritis: an analysis of serious adverse events. Am J Med 1994;96:115–23.
2 **Walsh LJ**, Wong CA, Pringle M, Tattersfield AE. Use of oral corticosteroids in the community and the prevention of secondary osteoporosis: a cross sectional study. BMJ 1996;313:344–6
3 **Soucy E**, Bellamy N, Adachi JD, Pope JE, Flynn J, Sutton E, *et al.* A Canadian survey on the management of corticosteroid-induced osteoporosis by rheumatologists. J Rheumatol 2000;27:1506–12.
4 **Weinstein RS**. The pathogenesis of glucocorticoid-induced osteoporosis. Clin Exp Rheumatol 2000;18(suppl 21):S35–40.
5 **Goldring SR**, Gravallese EM. Mechanisms of bone loss in inflammatory arthritis: diagnosis and therapeutic implications. Arthritis Res 2000;2:33–7.
6 **American College of Rheumatology Ad Hoc Committee on Glucocorticoid-induced Osteoporosis**. Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis: 2001 update. Arthritis Rheum 2001;44:1496–503.
7 **Peat ID**, Healy S, Reid DM, Ralston SH. Steroid-induced osteoporosis: an opportunity for prevention. Ann Rheum Dis 1995;54:66–8.
8 **Gudbjornsson B**, Juliusson UI, Gudjonsson FV. The prevalence of long-term steroid therapy and the frequency of decision making to prevent steroid-induced osteoporosis in daily clinical praxis. Ann Rheum Dis 2002;61:32–6.
9 **Hougardy DM**, Peterson GM, Bleasel MD, Randall CT. Is enough attention being given to the adverse effects of corticosteroid therapy? J Clin Pharm Ther 2000;25:227–34.

Table 1 American College of Rheumatology recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis[6]

I Patient beginning treatment with glucocorticoid (prednisone equivalent of 5 mg or more/day with plans for treatment duration of greater than or equal to 3 months)
- Modify lifestyle risk factors for osteoporosis
  - Smoking cessation or avoidance
  - Reduction of alcohol consumption if excessive
- Instruct in weightbearing physical exercise
- Initiate calcium supplementation
- Initiate supplementation with vitamin D (plain or activated form)
- Prescribe bisphosphonate (use with caution in premenopausal women)

II Patient receiving long term glucocorticoid treatment (prednisone equivalent of greater than or equal to 5 mg/day):
- Modify lifestyle risk factors for osteoporosis
  - Smoking cessation or avoidance
  - Reduction of alcohol consumption if excessive
- Instruct in weightbearing physical exercise
- Initiate calcium supplementation
- Initiate supplementation with vitamin D (plain or activated)
- Prescribe treatment to replace gonadal sex hormones if deficient or otherwise clinically indicated
- Measure bone mineral density (BMD) at lumbar spine or hip, or both
- If BMD is not normal (that is, T score below −1), then:
  - Prescribe bisphosphonate (use with caution in premenopausal women)
  - Consider calcitonin as second line agent if patient has a contraindication to, or does not tolerate, bisphosphonate treatment
  - If BMD is normal, follow up and repeat BMD measurement either annually or biannually

10 **Saag KG**, Emkey R, Schnitzer TJ, Brown JP, Hawkins F, Goemaere S, *et al*. Alendronate for the prevention and treatment of glucocorticoid-induced osteoporosis. N Engl J Med 1998;339:292–9.
11 **Reid DM**,Hughes RA, Laan RFJM, Sacco-Gibson NA, Wenderoth DH, Adami S, *et al*. Efficacy and safety of daily residronate in the treatment of corticosteroid-induced osteoporosis in women and men: a randomized trial. J Bone Miner Res 2000;15:1006–1013.
12 **Mazzantini M**, Lane NE. Rheumatic diseases, glucocorticoid treatment and bone mass: recent developments. Clin Exp Rheumatol 2000;18(suppl 21):S2–4
13 **Lane NE**, Sanchez S, Modin GW, Genant HK, Pierini E, Arnaud CD. Parathyroid hormone treatment reverses glucocorticoid-induced osteoporosis: results of a randomized controlled trial. J Clin Invest 1998;102:1627–33.

Inflammatory arthritis

Mesenchymal precursor cells

M Corr, N J Zvaifler

What are mesenchymal precursor (stem) cells doing in rheumatoid arthritis joints?

Genes implicated in limb development and bone and joint formation,[1 2] particularly members of the segment polarity family that encode components of the hedgehog and wingless/Wnt signalling pathways, have recently been identified in inflamed synovial tissues,[3 4] prompting speculation about their role in the pathogenesis of rheumatoid arthritis (RA) (this issue, page 6). In the limb bud of the embryo these genes are associated with primitive mesenchymal cells, which can be identified by their expression of heterodimeric surface membrane molecules that bind members of the transforming growth factor β super family, including bone morphogenetic protein receptors (BMPR), endoglin, anaplastic lymphoma kinase 1, and transforming growth factor β receptors.[5 6] Postnatal bone marrow has similar mesenchymal progenitor cells (MPC) that provide the reticular stroma which supports haemopoiesis, and when appropriately stimulated MPC can give rise to bone, cartilage, fat, muscle, or fibrous tissues.[6 7] RA synovium also contains cells with phenotypic and functional characteristics of MPC.[8 9]

ORIGINS OF SYNOVIAL MPC

The primordial appendicular skeleton begins as a condensed rod of primitive MPC that develop into articular structures.[1] Among isolated normal rabbit and human synovial fibroblasts there is a minority population of cells that can be induced into osteogenic, chondrogenic, and adipogenic pathways, suggesting that a few undifferentiated MPC are normally present in synovial tissues.[10 11] Their numbers are greatly increased in RA synovial tissues; 5–10 times more BMPR+ cells are identified in the intimal lining,[12] and specific members of the Wnt family (5a and 13) are preferentially expressed in suspensions of whole synovium.[3] Such findings may reflect either an expansion of a local population of MPC or a migration of MPC from the marrow into the inflamed joint. Both scenarios assume that the disease process is already established. Inflammatory mediators might influence the growth of resident MPC, but which of the numerous factors present in the RA synovium stimulate or retard growth of MPC remains to be clarified. The alternative scenario is an extension of a conventional paradigm of RA pathogenesis—namely, inflammatory mediators, like tumour necrosis factor α, alter the endothelium of synovial blood vessels and facilitate entry of blood cells into the joint. The recent demonstration that MPC are normally present in the circulation of humans[13 14] supports this hypothesis. Thus through either expansion or ingress, mesenchymal progenitors might participate in perpetuation of synovial disease. But how could they play a part in the initiation of RA?

ROLE OF MPC IN THE INITIATION OF RA

A number of recent papers have speculated about the onset of RA: when and how it begins, and whether clinical synovitis is preceded by an asymptomatic innate immune reaction in the joint. Although difficult to confirm in humans, there is considerable support for this idea from animal models of arthritis (reviewed by Firestein and Zvaifler[15]). Injection of an arthritis prone strain of mice (DBA/1) with complete Freund's adjuvant results in increased numbers of activated cells in the juxtaarticular epiphysial bone marrow, increased inflammatory cytokines in the bone marrow, and enlargement of small vestigial channels (called cartilage canals) that traverse from the bone marrow into the joint through the "bare area".[16] These changes are seen many days before the appearance of arthritis. At the same time, large cells expressing BMPR are present in the marrow, within the cartilage canals, and in synovial tissues. These mesenchymal progenitors antedate the appearance of either neutrophils or lymphocytes.[16]

"What are the origins of RA? Do mesenchymal precursor cells have a role?"

MOLECULAR SIGNALS IN THE DEVELOPING LIMB

Limb bud formation begins at an early stage in embryogenesis at a time when fibroblast growth factor (FGF) in the lateral plate mesoderm indirectly signalling through Wnt molecules in the overlying ectoderm induces a condensation called the apical ectodermal ridge (AER; fig 1).[17] The AER interacts with primitive, undifferentiated mesenchymal cells in the underlying progress zone. The production of FGF proteins in the AER instructs the growth and differentiation of MPC to expand in a proximal-distal orientation to become limbs. A separate signalling region, called the zone of polarising activity, is responsible for development in a cranial (thumb) to caudal (little finger) orientation. Sonic hedgehog (Shh) protein, made in the zone of polarising activity, maintains FGF-4 production and together they activate HoxD gene expression and sustain cell division in the progress zone. Simultaneously, Shh induces the BMPs required for chondrogenesis and subsequent osteogenesis. Continued induction of Shh is controlled by reciprocal interactions with Wnt7a, FGF-4, and, possibly, retinoic acid (fig 1). Less is known about the downstream effector genes that interpret these signals.

EVIDENCE FOR EXPRESSION OF EMBRYONIC GENES AFTER BIRTH

If molecular programmes that regulate skeletal development are recapitulated in tissue regeneration and repair then they might be present in a diseased joint. Amphibians (*Axolotl* and *Xenopus*) can

completely replace amputated limbs. Gene expression is the same during regeneration as in the embryo.[18 19] For instance Msx genes, transcription factors expressed in the AER and progress zone that maintain embryonic tissues in an undifferentiated and proliferative state, are re-expressed within hours after either limb amputation or wound healing in adult *Axolotl*.[20] Fractured bone provides a good model for postnatal analysis of genes involved in repair of mammalian tissues. Molecular signals for osteogenesis (transcription factor cbfa-1, Indian hedgehog (Ihh), and osteocalcin), chondrocyte maturation (Ihh, transcription factor gli-1, and collagen type 2), and vascular invasion (matrix metalloproteinase (MMP)-9 and -13, and vascular endothelial growth factor) are the same in fetal development and adult repair.[21] However, there are two important differences. Firstly, the origin of the MPC that participate in the repair process is not known. They may derive from the bone marrow or periosteum, from MPC resident in the surrounding tissues, or within the bleeding that accompanies the fracture.[22] Secondly, both fracture healing and wound repair needs an initial inflammatory process.[23] This latter requirement may be more relevant to events in the rheumatoid synovium. The cells that accumulate at the site of injury elaborate cytokines and growth factors, activate clotting, and induce proteolytic digestion of fibrin, which are all essential for producing the scaffold and matrix that supports the subsequent tissue regrowth, scarring, and remodelling.[23] Inflammation appears to regulate the expression of certain critical developmental genes. For instance, Wnt genes are expressed in mouse skin within hours of wounding and Wnt4 production is greatly enhanced in cultured mouse fibroblasts by trauma and fibrinolytic fragments.[24] At the site of fractured bone Ihh and its receptors, Smoothened and Patched, are expressed rapidly.[25] Thus the presence of these same developmental genes in RA synovial tissues may reflect inflammation, regeneration, or tissue repair, or a combination of these. But do these gene products of MPC contribute to the pathogenesis of RA?

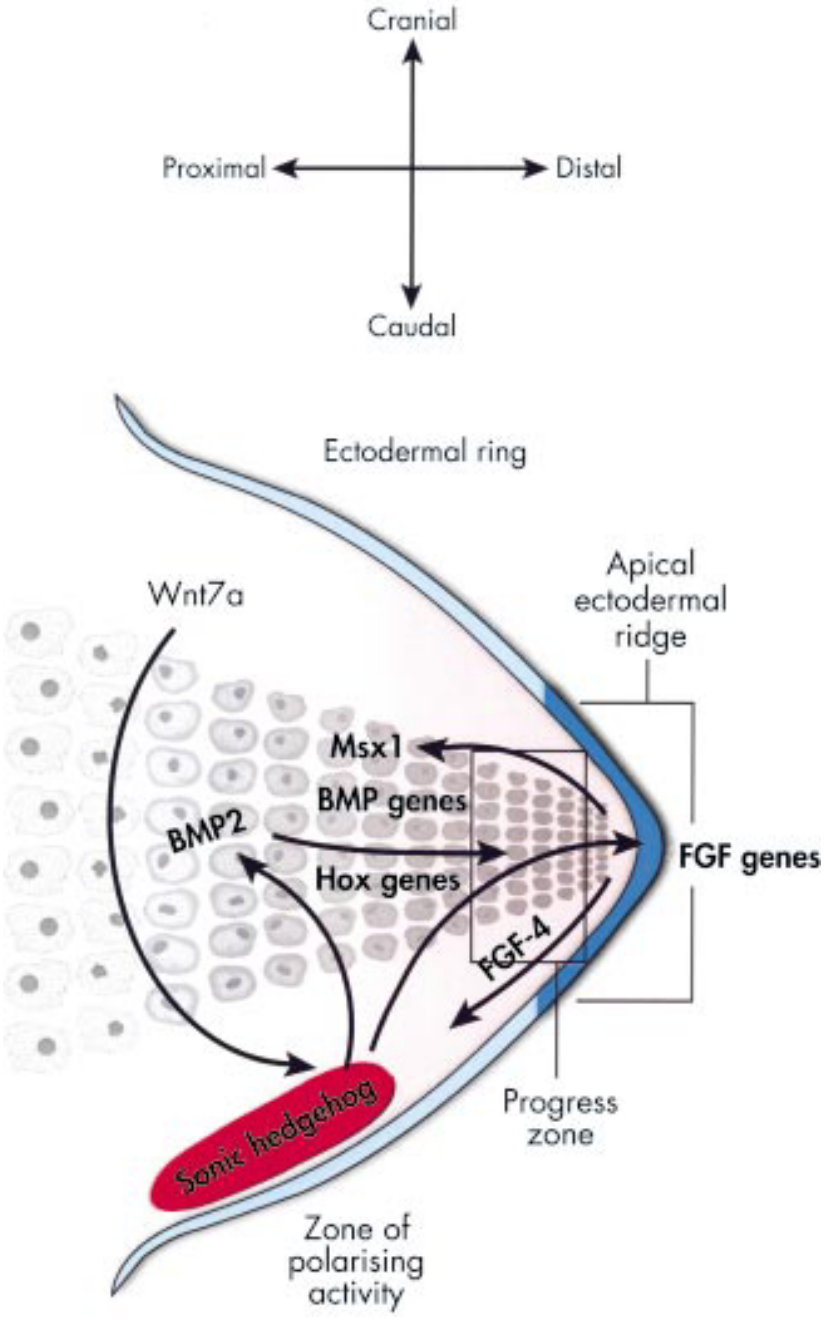

Figure 1 A schematic representation of the early events in limb development depicted in a proximal-distal and cranial-caudal orientation. Shown in colour are the locations of the relevant signalling regions: apical ectodermal ridge (AER), zone of polarising activity (ZPA), and the progress zone, where the most immature mesenchymal stem cells reside. Also displayed are the expression patterns of several relevant genes—namely, fibroblast growth factor (FGF), bone morphogenic protein (BMP), and homeobox (Hox).

RA—REGENERATION GONE AWRY?

The differential expression of proteins usually associated with embryonic limb patterning in the rheumatoid synovium might represent a physiological attempt to heal and restore inflamed or damaged tissue. However, a disruption of the regulated postnatal expression of these proteins can result in an abnormal phenotype, as suggested by certain hereditary syndromes. Pseudorheumatoid dysplasia is an autosomal recessive disorder associated with mutations in Wnt inducible protein 3.[26] This genetic deficiency is manifest by cartilage loss and destructive bone changes in children as they age, at times necessitating joint replacement surgery by the third decade of life. This syndrome suggests that limb patterning molecules function in normal homoeostasis of bone and joint structure and integrity. Perturbations of these molecules that maintain bone and cartilage could potentially lead to structural loss.

"Mesenchymal precursor cells may be attempting to restore the damaged joint in RA"

A recruitment or influx of MPC could gradually replace the fibroblasts of the

normal synovial lining. Rheumatoid synovial fibroblasts express embryonic morphogens that have roles in both limb bud mesenchyme and bone marrow stem cell development. The aggressive phenotype of invasive pannus, stimulated by intra-articular inflammatory cytokines, might be further accentuated by embryonic growth factors. The Wnt/frizzled signalling pathway is associated with transcriptional control of cell cycle proteins, adhesion molecules, and MMP-7 through β-catenin.[27–29] Moreover, Wnt5a has been reported to activate protein kinase C, thereby enhancing nuclear translocation of NFκB.[30] Transfection of synovial fibroblasts with a Wnt5a encoding construct results in enhanced interleukin (IL)6, IL8, and IL15 production.[3 4] Rheumatoid synoviocytes support osteoclast formation in vitro[31] and IL15 can stimulate the differentiation of osteoclast precursors.[32] In addition, frizzled signalling pathway might also influence the production of the osteoclast differentiation factor receptor activator of NFκB ligand (RANKL) by synovial fibroblasts.[4] Certainly, osteoclastic activity has a key role in the formation of erosions in RA.

In summary, the presence of an expanded number of MPC in the inflamed synovium in conjunction with the expression of morphogenic genes indicates previously unrecognised components in the pathogenesis of RA. The association between inflammation and wound repair suggests that these cells may be attempting to restore the damaged joint by a process akin to recapitulating the embryonic programme. Inflammatory messengers may be driving this process and enlarging the channels connecting the bone marrow with the synovial cavity. Growth of the pannus may result from a repopulation of the synovium with MPC that are stimulated to undergo differentiation. Cascading effects could then influence cell adhesion, cytokine secretion, osteoclast differentiation, and bone homoeostasis.

Ann Rheum Dis 2002;**61**:3–5

Authors' affiliations
M Corr, N J Zvaifler, Division of Rheumatology, Allergy and Immunology, Department of Medicine and The Sam and Rose Stein Institute for Research on Aging, University of California, San Diego, La Jolla, CA 92093–0664

Correspondence to: Professor Zvaifler; mzvaifler@popmail.ucsd.edu

REFERENCES

1 **Gilbert SF**. Development of the tetrapod limb. Chapter 18. *Developmental biology*. 5th ed. Sunderland: Sinauer Associates Inc, 1997.
2 **Hartmann C**, Tabin CJ. Wnt-14 plays a pivotal role in inducing synovial joint formation in the developing appendicular skeleton. Cell 2001;104:341–51.
3 **Sen M**, Lauterbach K, El-Gabalawy H, Firestein GS, Corr M, Carson DA. Expression and function of wingless and frizzled homologs in rheumatoid arthritis. Proc Natl Acad Sci USA 2000;97:2791–6.
4 **Sen M**, Chamorro M, Reifert J, Corr M, Carson DA. Blockade of Wnt-5A/frizzled 5 signaling inhibits rheumatoid synoviocyte activation. Arthritis Rheum 2001;44:772–81.
5 **Massague J**. TGFbeta signaling: receptors, transducers, and Mad proteins. Cell 1996;85:947–50.
6 **Pittenger MF**, Mackay AM, Beck SC, Jaiswal RK, Douglas R, Mosca JD, *et al*. Multilineage potential of adult human mesenchymal stem cells. Science 1999;284:143–7.
7 **Caplan AI**. Mesenchymal stem cells. J Orthop Res 1991;9:641–50.
8 **Zvaifler NJ**, Tsai V, Alsalameh S, von Kempis J, Firestein GS, Lotz M. Pannocytes: distinctive cells found in rheumatoid arthritis articular cartilage erosions. Am J Pathol 1997;150:1125–38.
9 **Imamura F**, Aono H, Hasunuma T, Sumida T, Tateishi H, Maruo S, *et al*. Monoclonal expansion of synoviocytes in rheumatoid arthritis. Arthritis Rheum 1998;41:1979–86.
10 **Nishimura K**, Solchaga LA, Caplan AI, Yoo JU, Goldberg VM, Johnstone B. Chondroprogenitor cells of synovial tissue. Arthritis Rheum 1999;42:2631–7.
11 **De Bari C**, Dell'Accio F, Tylzanowski P, Luyten FP. Multipotent mesenchymal stem cells from adult human synovial membrane. Arthritis Rheum 2001;44:1928–42
12 **Marinova-Mutafchieva L**, Taylor P, Funa K, Maini RN, Zvaifler NJ. Mesenchymal cells expressing bone morphogenetic protein receptors are present in the rheumatoid arthritis joint. Arthritis Rheum 2000;43:2046–55.
13 **Zvaifler NJ**, Marinova-Mutafchieva L, Adams G, Edwards CJ, Moss J, Burger JA, *et al*. Mesenchymal precursor cells in the blood of normal individuals. Arthritis Res 2000;2:477–88
14 **Kuznetsov SA**, Mankani MH, Gronthos S, Satomura K, Bianco P, Robey PG. Circulating skeletal stem cells. J Cell Biol 2001;153:1133–40.
15 **Firestein GS**, Zvaifler NJ. How important are T cells in chronic rheumatoid arthritis? : II. T cell independent mechanisms from beginning to end. Arthritis Rheum (in press).
16 **Marinova-Mutafchieva L**, Williams RO, Maini RN, Zvaifler NJ. Inflammation is preceded by TNF dependent infiltration of mesenchymal cells in experimental arthritis. Arthritis Rheum (in press).
17 **Kawakami Y**, Capdevila J, Buscher D, Itoh T, Rodriguez Esteban C, Izpisua Belmonte JC. WNT signals control FGF-dependent limb initiation and AER induction in the chick embryo. Cell 2001;104:891–900.
18 **Endo T**, Tamura K, Ide H. Analysis of gene expressions during Xenopus forelimb regeneration. Dev Biol 2000;220:296–306.
19 **Han MJ**, An JY, Kim WS. Expression patterns of Fgf-8 during development and limb regeneration of the axolotl. Dev Dyn 2001;220:40–8.
20 **Carlson MR**, Bryant SV, Gardiner DM. Expression of Msx-2 during development, regeneration, and wound healing in axolotl limbs. J Exp Zool 1998;282:715–23.
21 **Ferguson C**, Alpern E, Miclau T, Helms JA. Does adult fracture repair recapitulate embryonic skeletal formation? Mech Dev 1999;87:57–66.
22 **Bruder SP**, Fink DJ, Caplan AI. Mesenchymal stem cells in bone development, bone repair, and skeletal regeneration therapy. J Cell Biochem 1994;56:283–94.
23 **Mutsaers SE**, Bishop JE, McGrouther G, Laurent GJ. Mechanisms of tissue repair: from wound healing to fibrosis. Int J Biochem Cell Biol 1997;29:5–17.
24 **Labus MB**, Stirk CM, Thompson WD, Melvin WT. Expression of Wnt genes in early wound healing. Wound Repair Regen 1998;6:58–64.
25 **Ito H**, Akiyama H, Shigeno C, Iyama K, Matsuoka H, Nakamura T. Hedgehog signaling molecules in bone marrow cells at the initial stage of fracture repair. Biochem Biophys Res Commun 1999;262:443–51.
26 **Hurvitz JR**, Suwairi WM, Van Hul W, El-Shanti H, Superti-Furga A, Roudier J, *et al*. Mutations in the CCN gene family member WISP3 cause progressive pseudorheumatoid dysplasia. Nat Genet 1999;23:94–8.
27 **Behrens J**, von Kries JP, Kuhl M, Bruhn L, Wedlich D, Grosschedl R, *et al*. Functional interaction of beta-catenin with the transcription factor LEF-1. Nature 1996;382:638–42.
28 **Tetsu O**, McCormick F. Beta-catenin regulates expression of cyclin D1 in colon carcinoma cells. Nature 1999;398:422–6.
29 **Brabletz T**, Jung A, Dag S, Hlubek F, Kirchner T. Beta-catenin regulates the expression of the matrix metalloproteinase-7 in human colorectal cancer. Am J Pathol 1999;155:1033–8.
30 **Sheldahl LC**, Park M, Malbon CC, Moon RT. Protein kinase C is differentially stimulated by Wnt and frizzled homologs in a G-protein-dependent manner. Curr Biol 1999;9:695–8.
31 **Gravallese EM**, Harada Y, Wang JT, Gorn AH, Thornhill TS, Goldring SR. Identification of cell types responsible for bone resorption in rheumatoid arthritis and juvenile rheumatoid arthritis. Am J Pathol 1998;152:943–51.
32 **Ogata Y**, Kukita A, Kukita T, Komine M, Miyahara A, Miyazaki S, *et al*. A novel role of IL-15 in the development of osteoclasts: inability to replace its activity with IL-2. J Immunol 1999;162:2754–60.