本教材製作參考相關書籍作為資料來源，僅以非營利教學使用，無任何非法營利之行為。
相關圖片請尊重病人隱私與智慧財產權。

臨床醫師執行醫學研究之經驗分享

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Professor & Chairman
Department of Orthopaedics
Chung Shan Medical University (Hospital)

From Bedsides to Benches

從床邊到實驗桌

從臨床到研究

從臨床到基礎

From Beds to Benches

從床上到實驗桌

從睡覺到痛苦

Reasons Why We Write

1. Gain intellectual stimulation
2. Share ideas
3. Report research
4. Express an opinion
5. Generate discussion
6. Advance one's discipline
7. Assert "ownership" of a topic
8. Attain promotion/tenure
9. Report a case
10. Enhance one's personal reputation
11. Achieve some small measure of immortality by publishing our ideas
12. Earn income

Reasons Given for not Writing

1. Not enough time
2. Nothing to write about
3. No one to work with in writing
4. Lack of secretarial support
5. Lack of knowledge as to how to research information
6. No mentor for writing activities
7. No motivation
8. No self-confidence
9. Don’t know how to start
10. “I hate writing”

研究寫作失敗最常見的原因

1. 沒有搞清楚要研究什麼？寫什麼？
2. 為誰而研究？為誰而寫？
3. 為什麼要研究？為什麼要寫？

- *研究寫作之初沒有花點時間思考這些問題。*
- *不需要面對空白螢幕或白紙搜索枯腸。*
- *在散步、搭車、坐馬桶...的同時都是思考的好時機。*


近幾年之研究內容與主要研究成果
1. 惡性腫瘤有關的基礎研究
2. 結合基礎和臨床，膝關節炎（退化）有關
3. 臨床的文章
Take Home Messages

近幾年之研究內容與主要研究成果（第一或通訊作者）

1. 惡性腫瘤、主要是骨癌有關的基礎研究成果，包含**paclitaxel**、**silibinin**和**NAT**、**MMPs**、**u-PA**、**PAI**…有關的研究
2. 結合基礎和臨床，跟膝關節炎有關的（**MMPs**、**u-PA**、**PAI**、**uPAR**…）研究成果
3. 臨床的文章


近幾年之研究內容與主要研究成果
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Take Home Messages

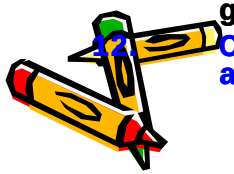
惡性腫瘤有關的基礎研究，共9篇
（第一或通訊作者，全部SCI）

1. Hsieh YS, Chu SC, Yang SF, Chen PN, Liu YC, Lu KH*. Silibinin suppresses human osteosarcoma MG-63 cell invasion by inhibiting the ERK-dependent c-Jun/AP-1 induction of MMP-2. *Carcinogenesis* 2007;28:977-87. (SCI)
2. Lu KH, Lue KH, Chou MC, Chung JG*. Paclitaxel induces G2/M arrest and apoptosis via caspase-3 activation in osteogenic sarcoma (U-2 OS) cells. *J Orthopaed Res* 2005;23:988-94. (SCI)
3. Lu KH, Lue KH, Hsia TC, Chou MC, Lin KL, Chung JG*. Oral administration of paclitaxel affects the distribution and metabolism of 2-aminofluorene in various tissues of Sprague-Dawley rats. *Phytomedicine* 2005;12:577-87. (SCI).
4. Lu KH, Lue KH, Liao HH, Chung JG*. Induction of caspase-3-dependent apoptosis in human leukemia HL-60 cells by paclitaxel. *Clin Chim Acta* 2005;357:65-73. (SCI)
5. Lu KH, Wang DY, Lue KH, Hsiao YM, Chou MC, Chen YS, Chung JG*. PCR and flow cytometric analysis of paclitaxel-inhibited arylamine N-acetyltransferase activity and gene expression in human osteogenic sarcoma cells (U-2 OS). *Anticancer Res* 2004;24:83-90. (SCI)
6. Lu KH, Cheng KC, Hsia TC, Lin KL, Wu CL, Chou MC, Chung JG*. Paclitaxel affects the amounts of the N-acetylation of 2-aminofluorene and DNA-2-aminofluorene adduct formation in Sprague-Dawley rats. *In Vivo* 2003;17:137-44. (SCI)
7. Lu KH, Lin KL, Yang CC, Hsia TC, Hsiao YM, Chou MC, Ho HC, Chung JG*. Paclitaxel affects gene expression and activity of arylamine N-acetyltransferase and DNA-2-aminofluorene adduct formation in human leukemia HL-60 cells. *Food Chem Toxicol* 2002;40:705-13. (SCI)
8. Lu KH, Lin KL, Hsia TC, Hung CF, Chou MC, Hsiao YM, Chung JG*. Tamoxifen affects gene expression and activity of arylamine N-acetyltransferase and DNA-2-aminofluorene adduct formation in human leukemia HL-60 cells. *Res Commun Mol Path* 2001;109:319-31. (SCI in 2000 and 2001)
9. Hung CF, Lu KH*. Vitamin C inhibited DNA adduct formation and arylamine N-acetyltransferase activity and gene expression in rat glial tumor cells. *Neurochem Res* 2001;26:1107-12. (SCI)


近幾年之研究內容與主要研究成果
1. 惡性腫瘤有關的基礎研究
2. 結合基礎和臨床，膝關節炎（退化）有關
3. 臨床的文章
Take Home Messages

結合基礎和臨床，膝關節炎（退化）有關，共12篇（第一或通訊作者，全部SCI）

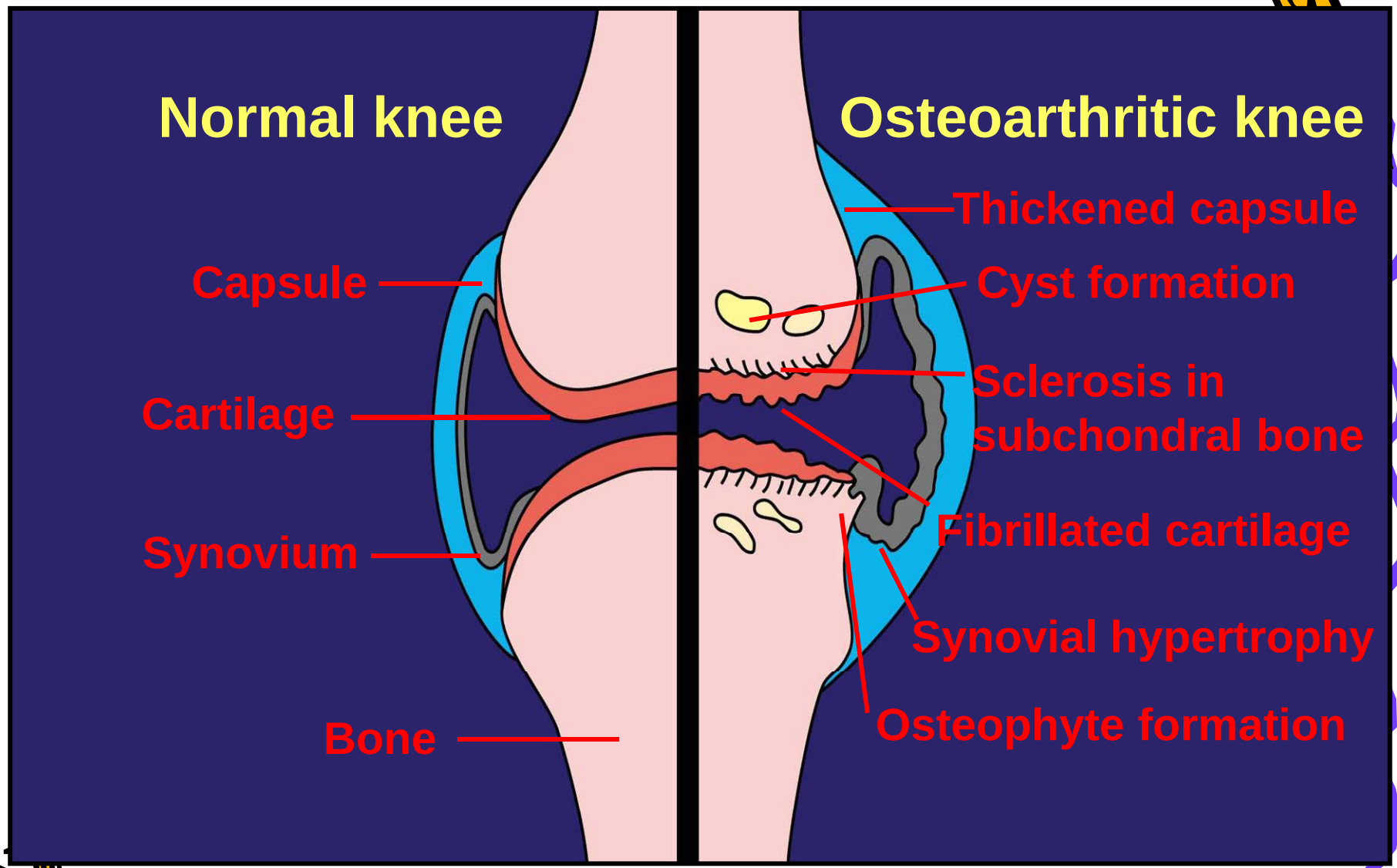
1. Hsieh YS, Yang SF, Lue KH, Chu SC, Lu KH*. Effects of different molecular weight hyaluronan products on the expression of urokinase plasminogen activator and inhibitor and gelatinases during the early stage of osteoarthritis. *J Orthopaed Res* 2008;26:475-84. (SCI)
2. Yang SF, Hsieh YS, Lue KH, Chu SC, Chang IC, Lu KH*. Effects of nonsteroidal antiinflammatory drugs on the expression of urokinase plasminogen activator and inhibitor and gelatinases in the early osteoarthritic knee of humans. *Clin Biochem* 2008;41:109-16. (SCI)
3. Chu SC, Yang SF, Lue KH, Hsieh YS, Li TJ, Lu KH*. Naproxen, meloxicam and methylprednisolone inhibit urokinase plasminogen activator and inhibitor and gelatinases expression during the early stage of osteoarthritis. *Clin Chim Acta* 2008;387:90-6. (SCI)
4. Hsieh YS, Yang SF, Lue KH, Chu SC, Lu KH*. Upregulation of urokinase-type plasminogen activator and inhibitor and gelatinases expression via three MAPKs and PI3K pathways during the early development of osteoarthritis. *J Rheumatol* 2007;34:785-93. (SCI)
5. Chu SC, Yang SF, Lue KH, Hsieh YS, Lee CY, Chou MC, Lu KH*. Glucosamine sulphate suppresses the expressions of urokinase plasminogen activator and inhibitor and gelatinases during the early stage of osteoarthritis. *Clin Chim Acta* 2006;372:167-72. (SCI)
6. Hsieh YS, Yang SF, Lue KH, Lu KH*. Clinical correlation with the PA/plasmin system in septic arthritis of the knee. *Clin Orthop* 2006;447:172-8. (SCI)
7. Chu SC, Yang SF, Lue KH, Hsieh YS, Hsiao TY, Lu KH*. Urokinase-type plasminogen activator, receptor and inhibitor correlating with gelatinase-B (MMP-9) contribute to inflammation in gouty arthritis of the knee. *J Rheumatol* 2006;33:311-7. (SCI)
8. Chu SC, Yang SF, Lue KH, Hsieh YS, Wu CL, Lu KH*. Regulation of gelatinases expression by cytokines, endotoxins and pharmacological agents in the human osteoarthritic knee. *Connective Tissue Res* 2004;45:142-50. (SCI)
9. Chu SC, Yang SF, Lue KH, Hsieh YS, Lin ZI, Lu KH*. Clinical significance of gelatinases in septic arthritis of native and replaced knee. *Clin Orthop* 2004;427:179-83. (SCI)
10. Hsieh YS, Yang SF, Chu SC, Chen PN, Chou MC, Hsu MC, Lu KH*. Expression changes of gelatinases in human osteoarthritic knees and arthroscopic débridement. *Arthroscopy* 2004;20:482-8. (SCI)
11. Lu KH, Yang SF, Chu SC, Chen PN, Chou MC, Hsiao TY, Hsieh YS*. The significance of altered expressions of gelatinases in the synovium of patient with arthritic effusions. *Clin Rheumatol* 2004;23:21-6. (SCI)
12. Chu SC, Yang SF, Lue KH, Hsiao TY, Hsieh YS, Lu KH*. The clinical significance of gelatinase B in gouty arthritis of the knee. *Clin Chim Acta* 2004;339:77-83. (SCI)



Arthritis

- Osteoarthritis (OA)
  - primary
  - secondary
- Rheumatoid arthritis (RA)
  - adult
  - juvenile
- Arthritis due to infection (bacteria, TB)
- Metabolic disease affecting joints (gout)
- Ankylosing spondylitis
- Neuropathic joint disease (Charcot's joint)
- Nonspecific monarthritis
- Special forms
  - hemophilic arthritis
  - psoriatic arthritis
  - psychogenic rheumatism

Normal vs OA Joint



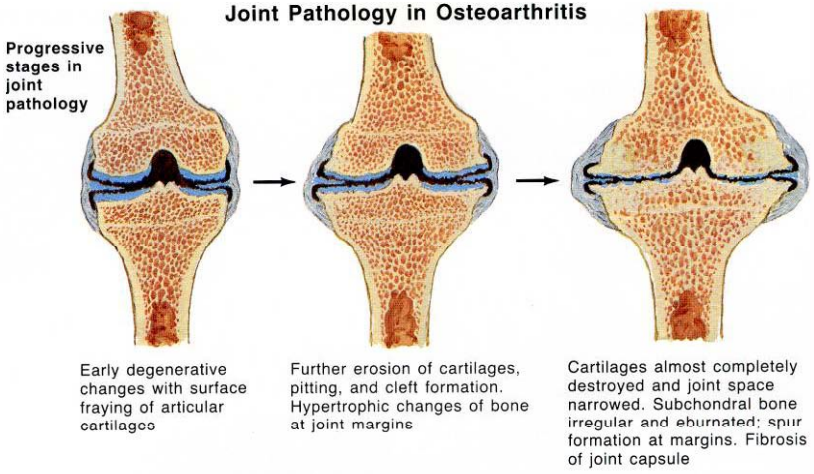
Osteoarthritis (OA)

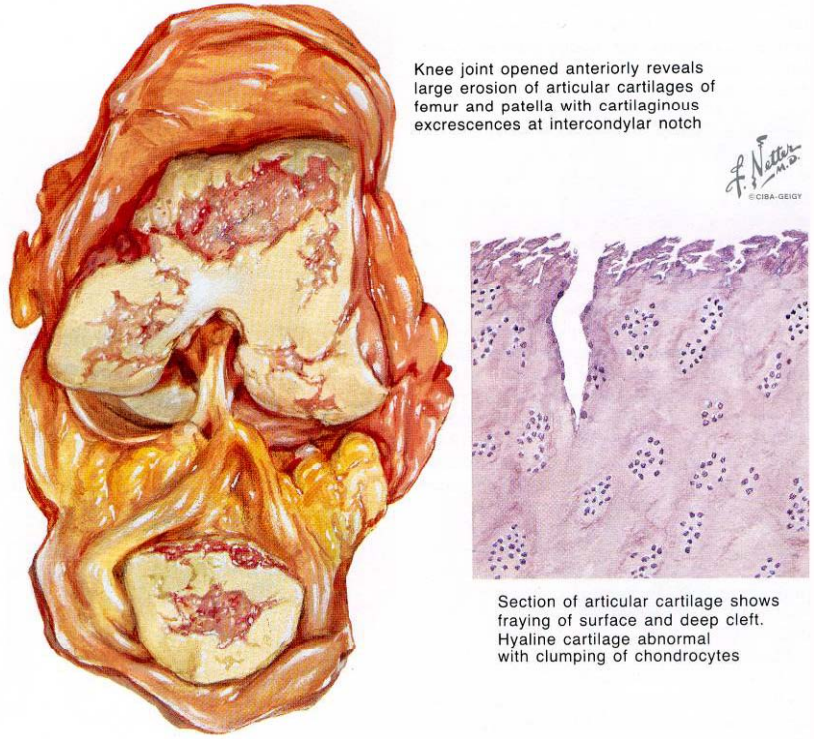
- ***Primary osteoarthritis***
  - *polyarticular degenerative arthritis of unknown origin*
  - *rarely occurs before the age of 35 years*
  - *especially in weight-bearing joints, more common in obese patients over the age of 50 years*
- ***Secondary osteoarthritis***
  - *monarticular*
  - *mechanical derangement, pyogenic infection, congenital anomaly, physeal separation, ligamentous instability, and fracture into a joint are among the common causes*
- **The prognosis is better for the primary type, polyarticular degenerative arthritis, than for the secondary type**
- **The progression of primary osteoarthritis is usually slower and less relentless**
- **An association of osteoarthritis of the hip with occupations requiring heavy lifting and elite sporting activity, no such relationship between osteoarthritis of the knee and activity levels**

Figure 25-8 In osteoarthritis of knee varus or valgus deformities concentrate stress of weight-bearing in either medial or lateral part of joint, and degenerative changes in that part are accelerated.

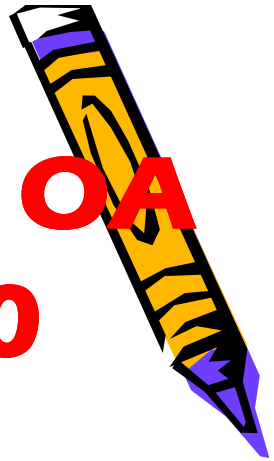
OA of the Knee

- Result of mechanical and biological events that destabilize the normal processes of degradation and synthesis of articular cartilage chondrocytes, extracellular matrix, and subchondral bone
- Include increased water content, decreased proteoglycan content, and altered collagen matrix, all leading to the deterioration of articular cartilage
- Radiographs
  - nonuniform joint space narrowing
  - cortical sclerosis on the weight-bearing bony surfaces
  - subchondral cyst
  - marginal osteophytes
  - loose bodies and subluxation
- Treatment
  - conservative
  - surgical





Goals of ACR Guidelines for OA of the Hip and Knee 2000



- Control of pain
- Improvement in function and health-related quality of life
- *Delay progression of the disease*
- Avoidance, if possible, of toxic effects of therapy

Arthritis & Rheum 2000; 43: 1905-1915.

2000 ACR Guidelines for Hip and Knee OA

Nonpharmacologic therapy:

- Patient education
- Self-management program
- Personalized social support through telephone contact
- Weight loss (if overweight)
- Aerobic exercise program
- Physical therapy range-of-motion exercises
- Muscle-strengthening exercises
- Assistive devices for ambulation
- Patellar taping
- Appropriate footwear
- Lateral-wedge insoles (for genu varum)
- Bracing
- Occupational therapy
- Joint protection and energy conservation
- Assistive devices for activities of daily living

Pharmacologic therapy:

Oral

- Acetaminophen
- Coxibs
- Ns-NSAIDs + misoprostol or PPI
- Nonacetylated salicylate
- Other pure analgesics
  - Tramadol
  - Opioids

Intra-articular

- Glucocorticoids
- Hyaluronan

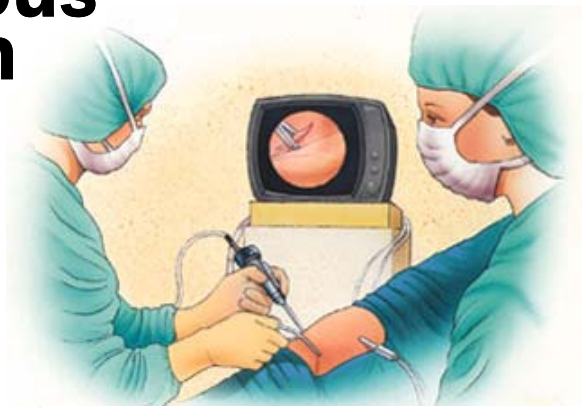
Topical

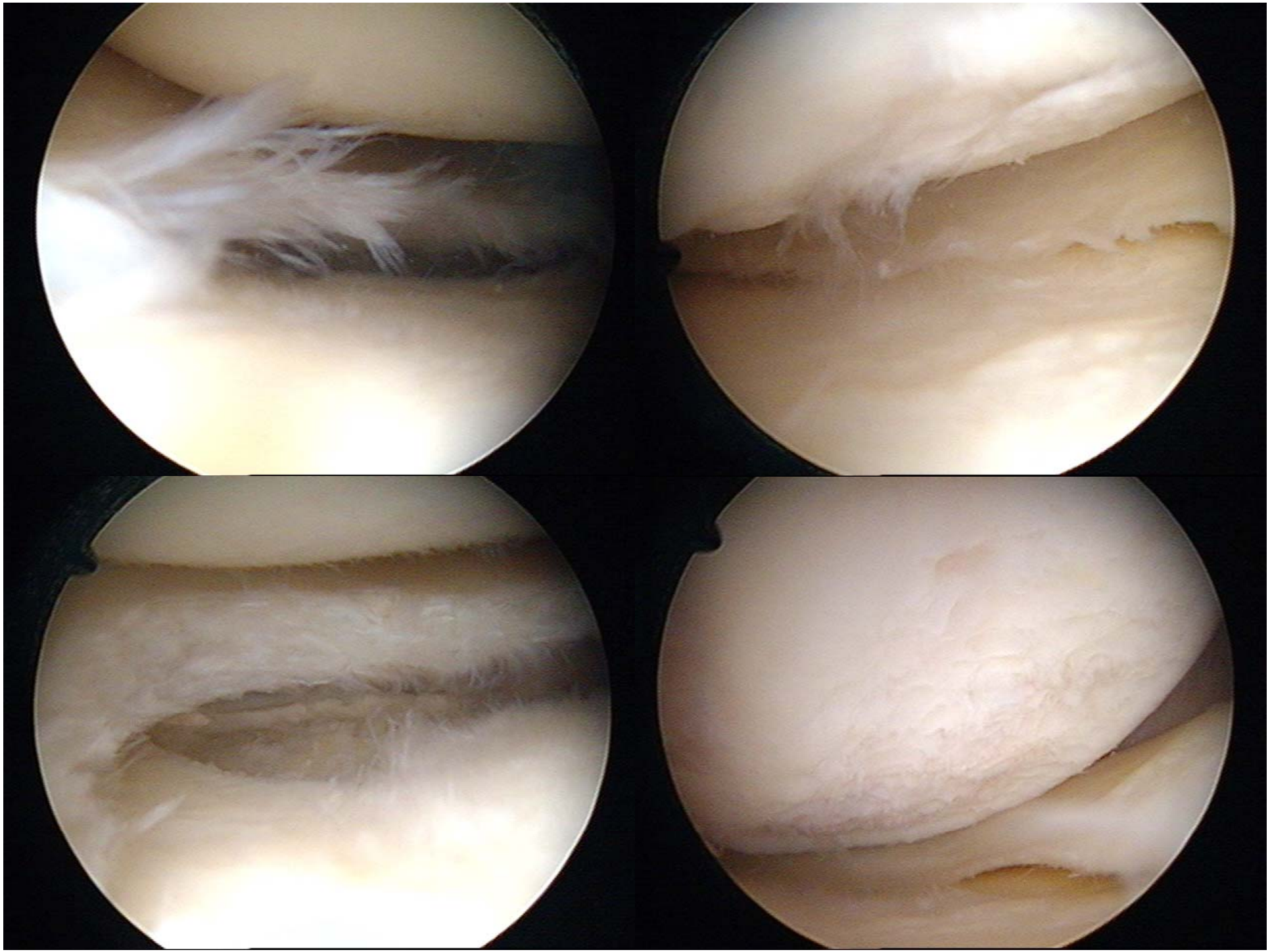
- Capsaicin
- Methylsalicylate

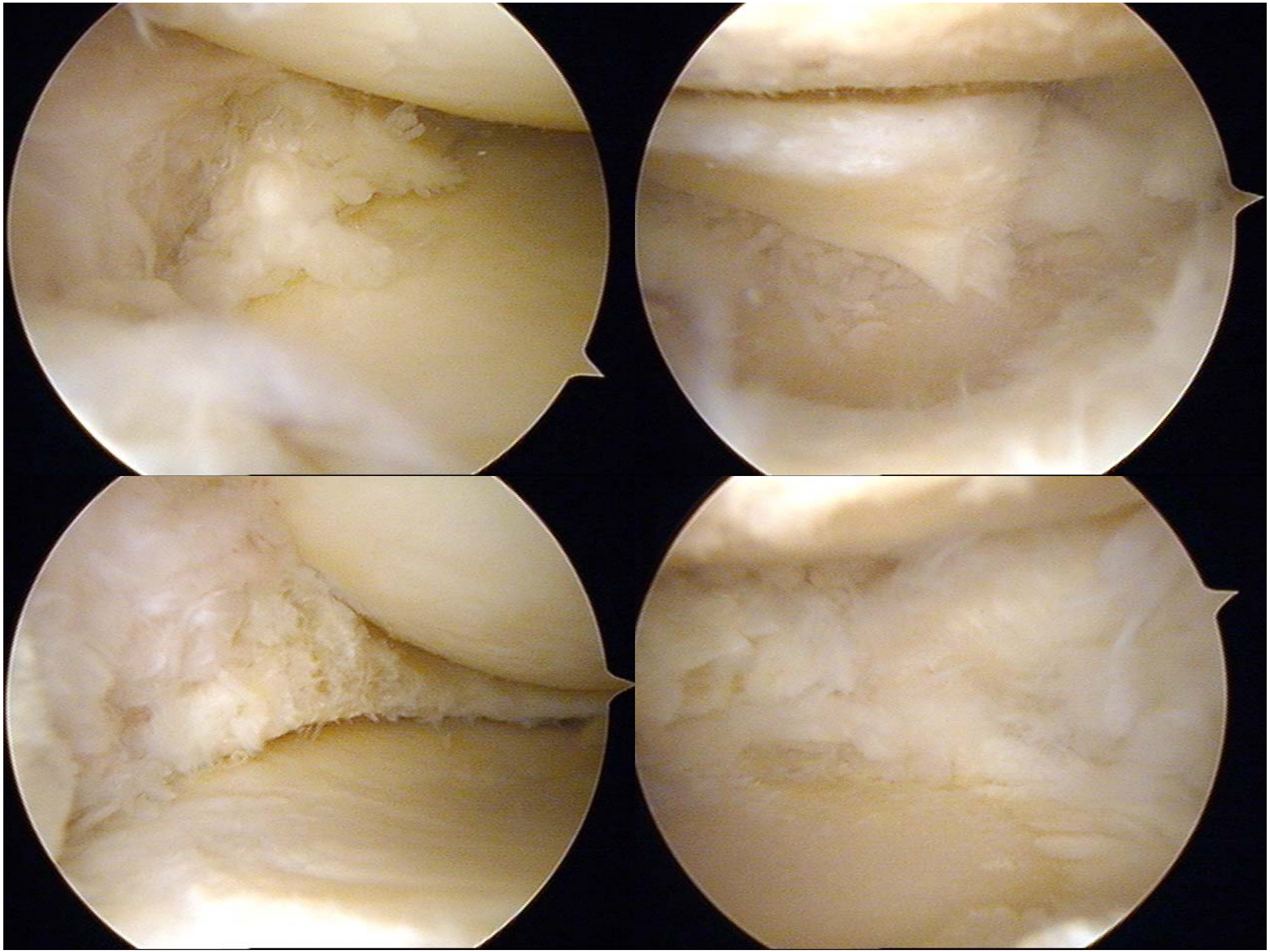
Arthritis & Rheum 2000; 43: 1905-1915

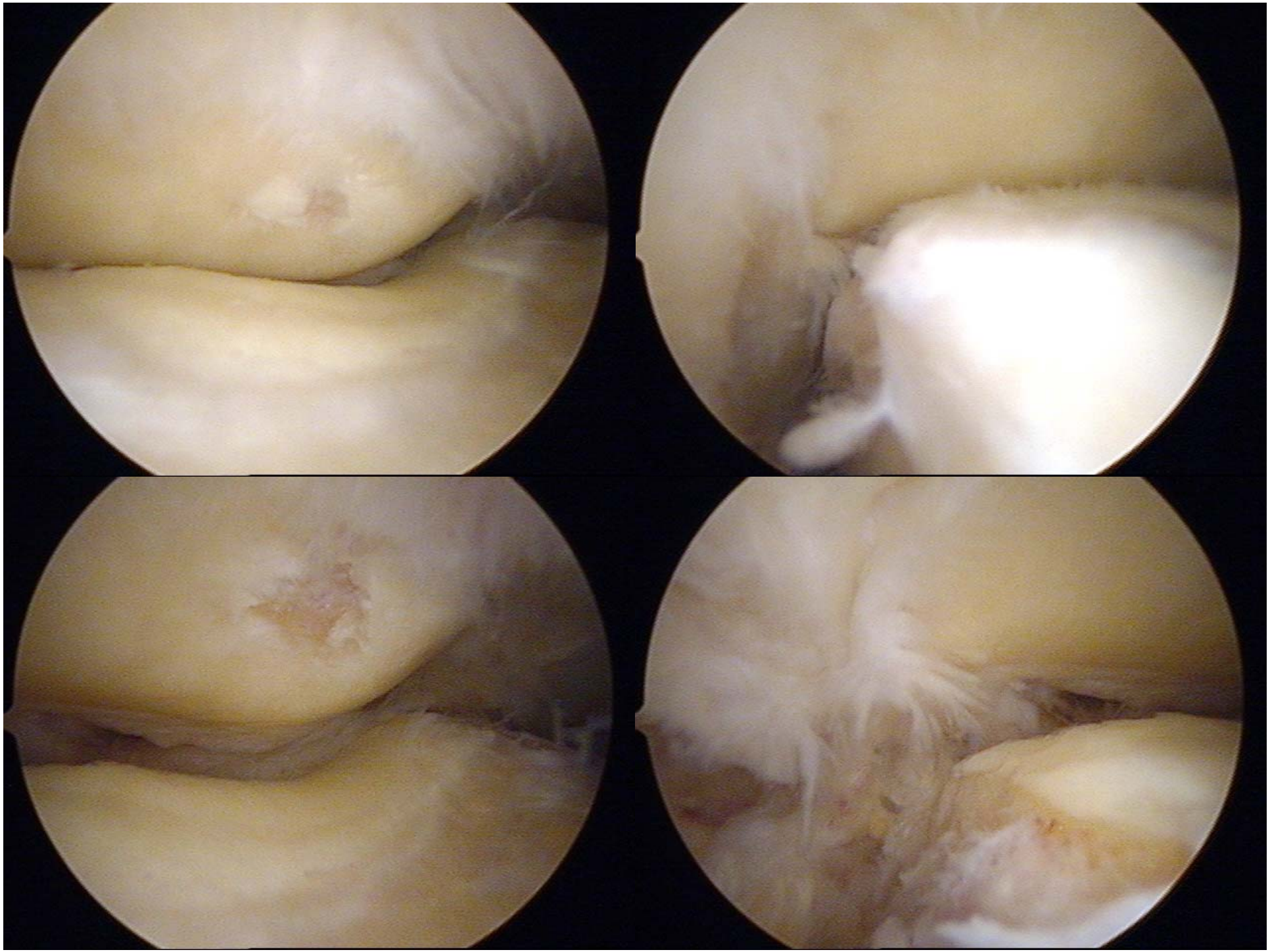
Surgical Treatment of Knee OA

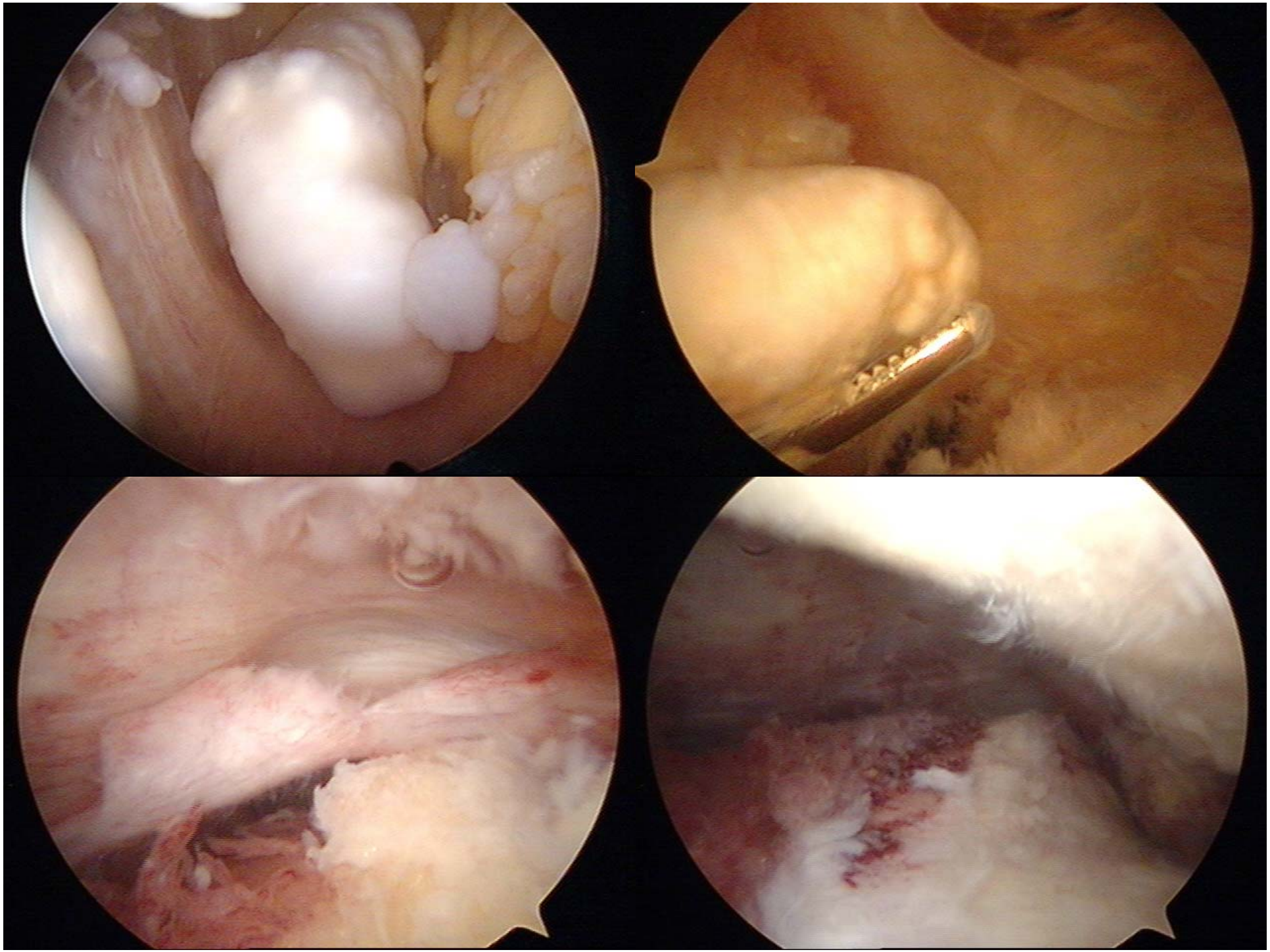
- Arthroscopic joint débridement
- Osteochondral and autologous chondrocyte transplantation
- Ostectomy
  - patellectomy
- Osteotomy
  - HTO, supracondylar femoral osteotomy , tibial tubercle elevation or transfer
- Arthrodesis
- Arthroplasty
  - unicompartmental or total knee arthroplasty



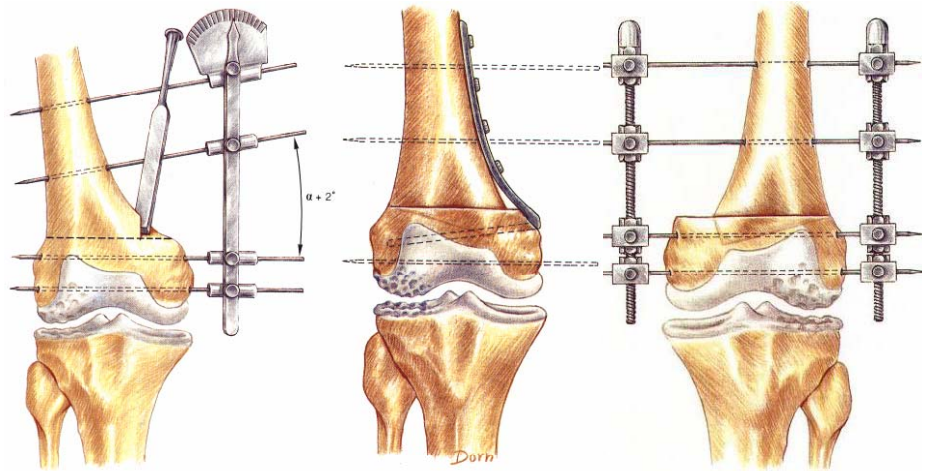








Distal Femoral Osteotomy



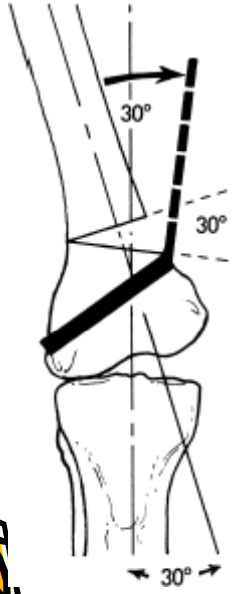


Figure 25-23 Coventry technique of lower femoral osteotomy. Angle to be corrected is measured on preoperative roentgenogram, and nail of blade plate is driven into femoral metaphysis so that plate will accomplish desired correction when attached to osteotomized femoral shaft. Wedge with apical angle equal to amount of correction is removed with osteotomy.

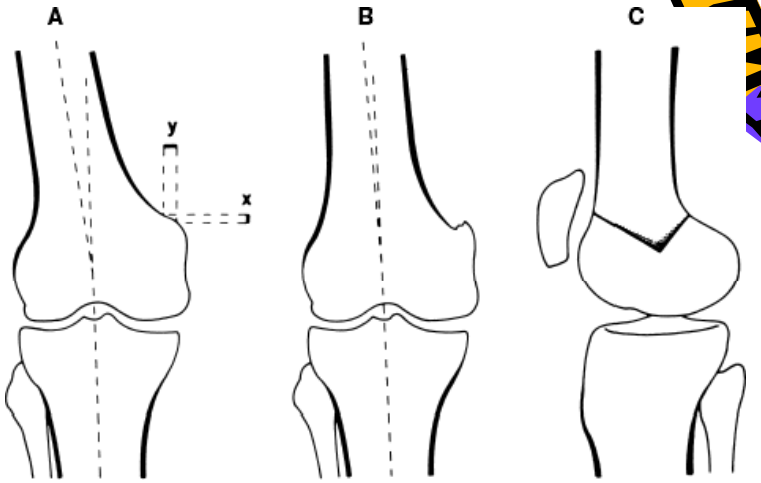


Figure 25-24 Supracondylar V osteotomy for correction of valgus deformity. A, Because of shape of medial femur, minor shortening of cortex of proximal fragment (*x*) produces sufficient narrowing (*y*) to allow cancellous penetration on medial side with no lateral openings or translation (B). C, No wedges are taken, and minimal bone removal is required.

High Tibial Osteotomy

Dome-shaped

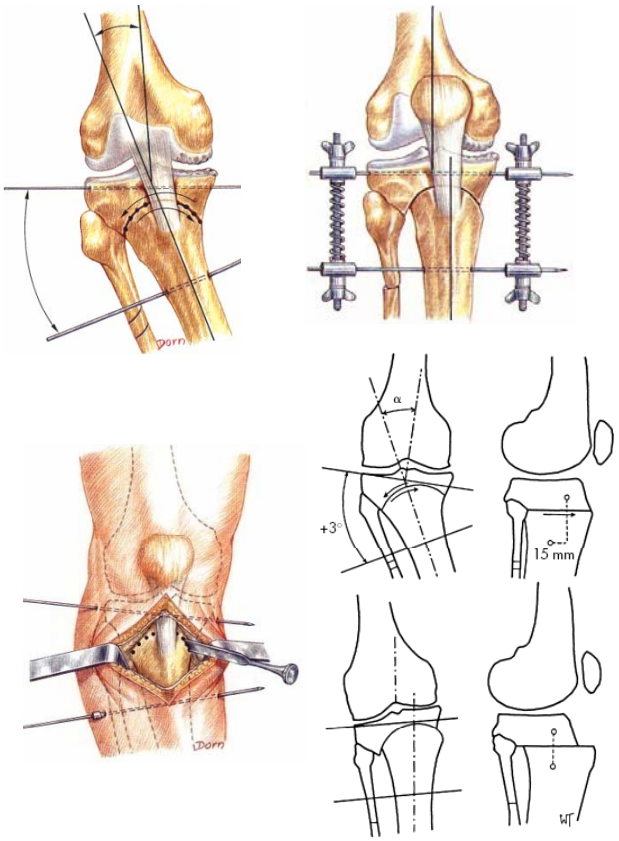
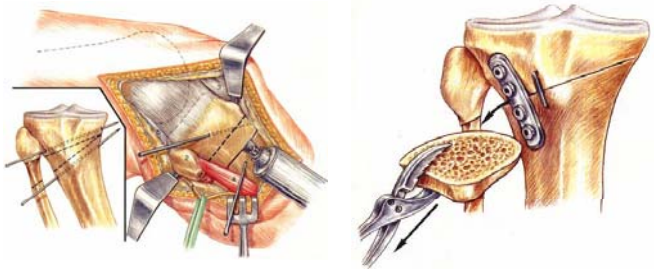


Figure 25-18 Barrel-vault osteotomy of Maquet uses special jigs to properly orient dome osteotomy. Distal tibia can be translated if needed.

Wedge-shaped



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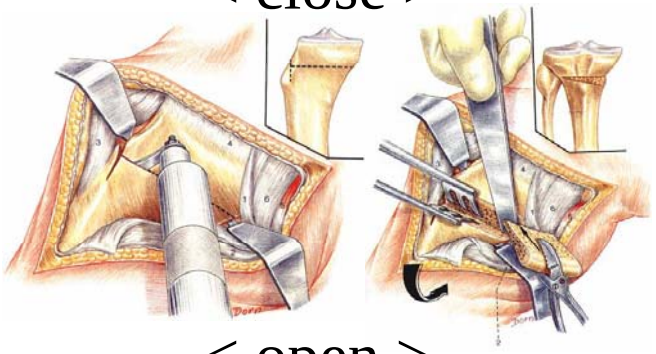

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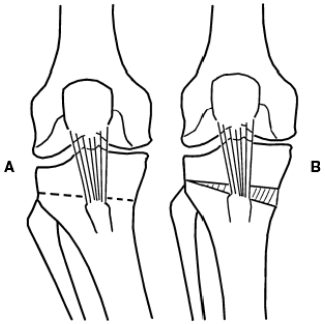
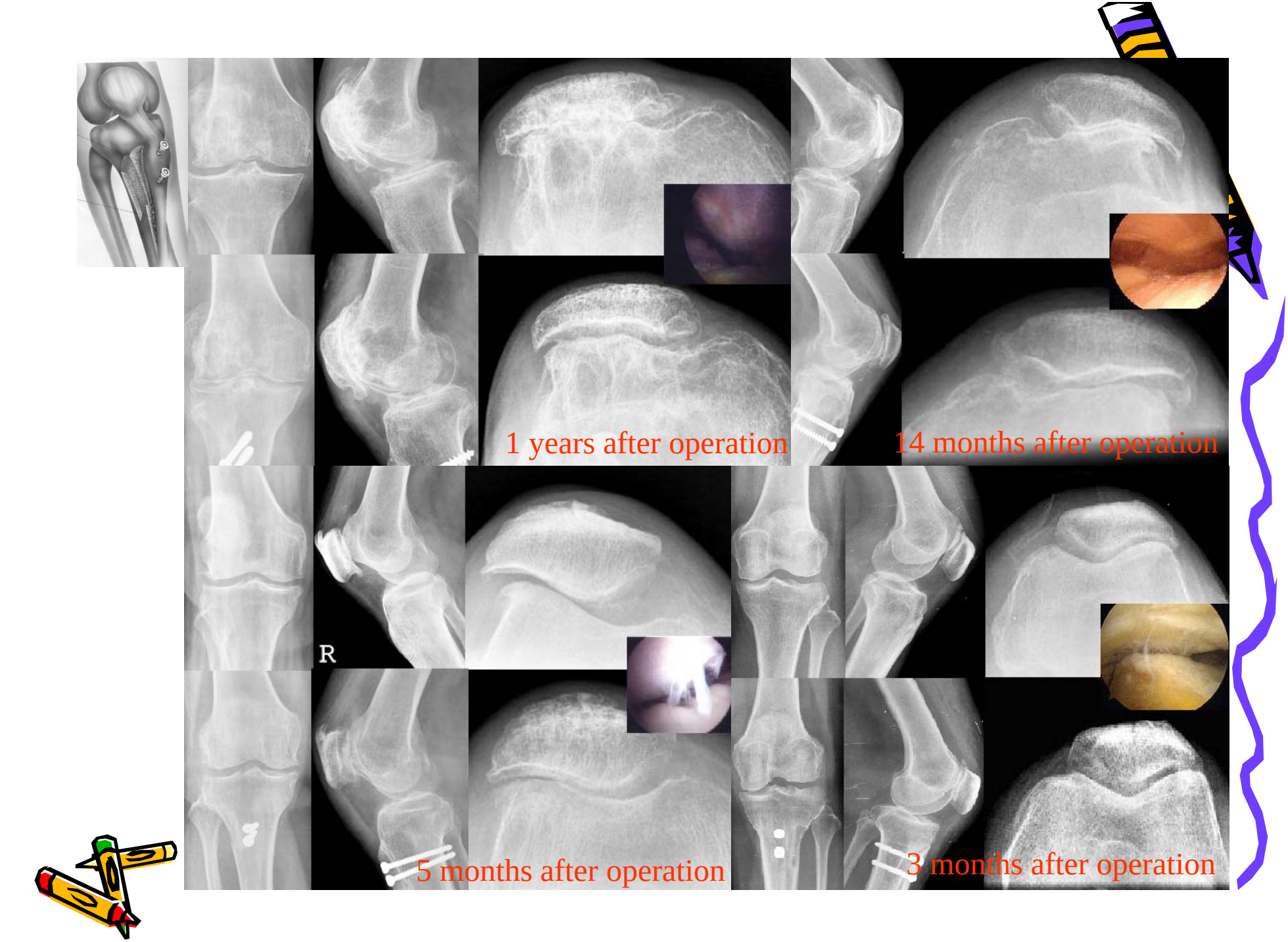
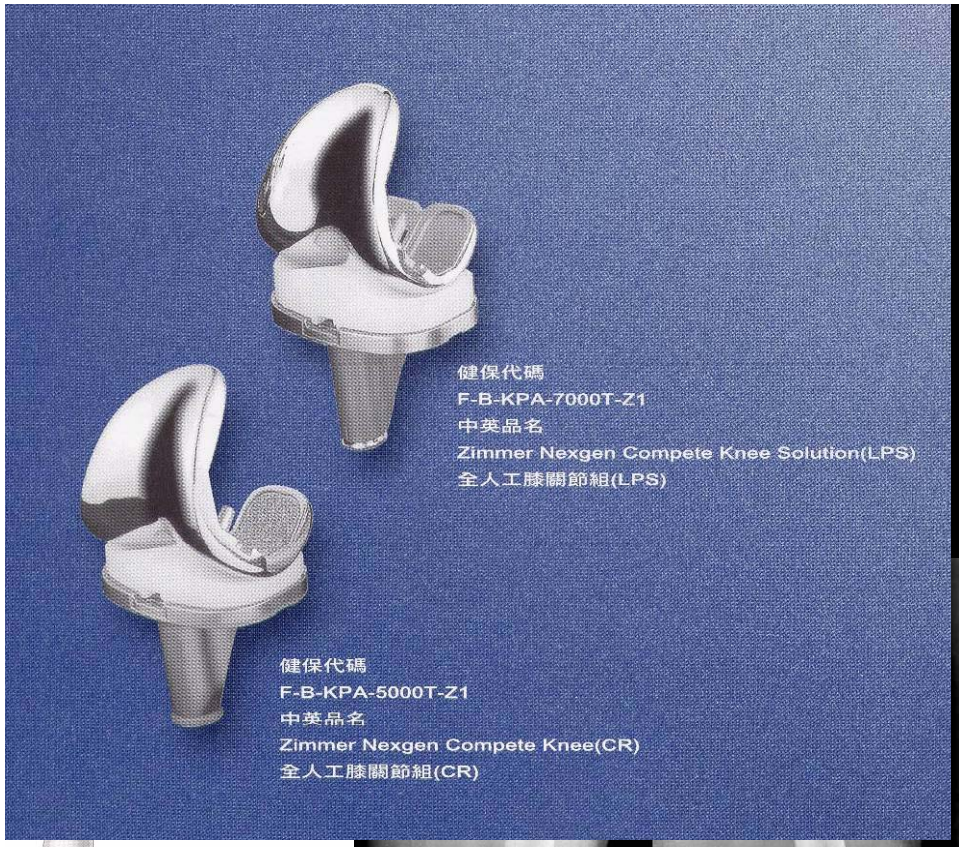
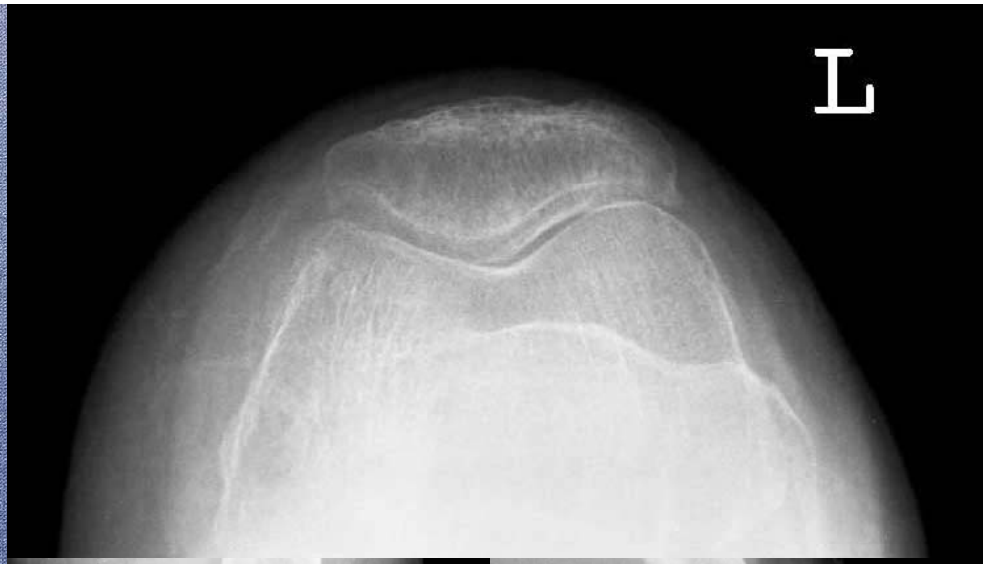


Figure 25-19 Medial opening wedge tibial osteotomy. A, Osteotomy proximal to tibial tubercle begins 3.5 cm distal to medial joint line and is directed toward proximal tip of fibula, leaving lateral part of cortex intact. B, Osteotomy is pried open, and wedge-shaped bicortical iliac bone grafts are inserted. Osteotomy is fixed with plate and screws.


1 years after operation
14 months after operation
R
5 months after operation
3 months after operation


健保代碼
F-B-KPA-7000T-Z1
中英品名
Zimmer Nexgen Compete Knee Solution(LPS)
全人工膝關節組(LPS)
健保代碼
F-B-KPA-5000T-Z1
中英品名
Zimmer Nexgen Compete Knee(CR)
全人工膝關節組(CR)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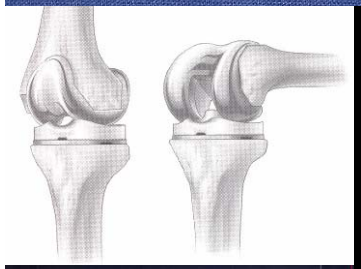


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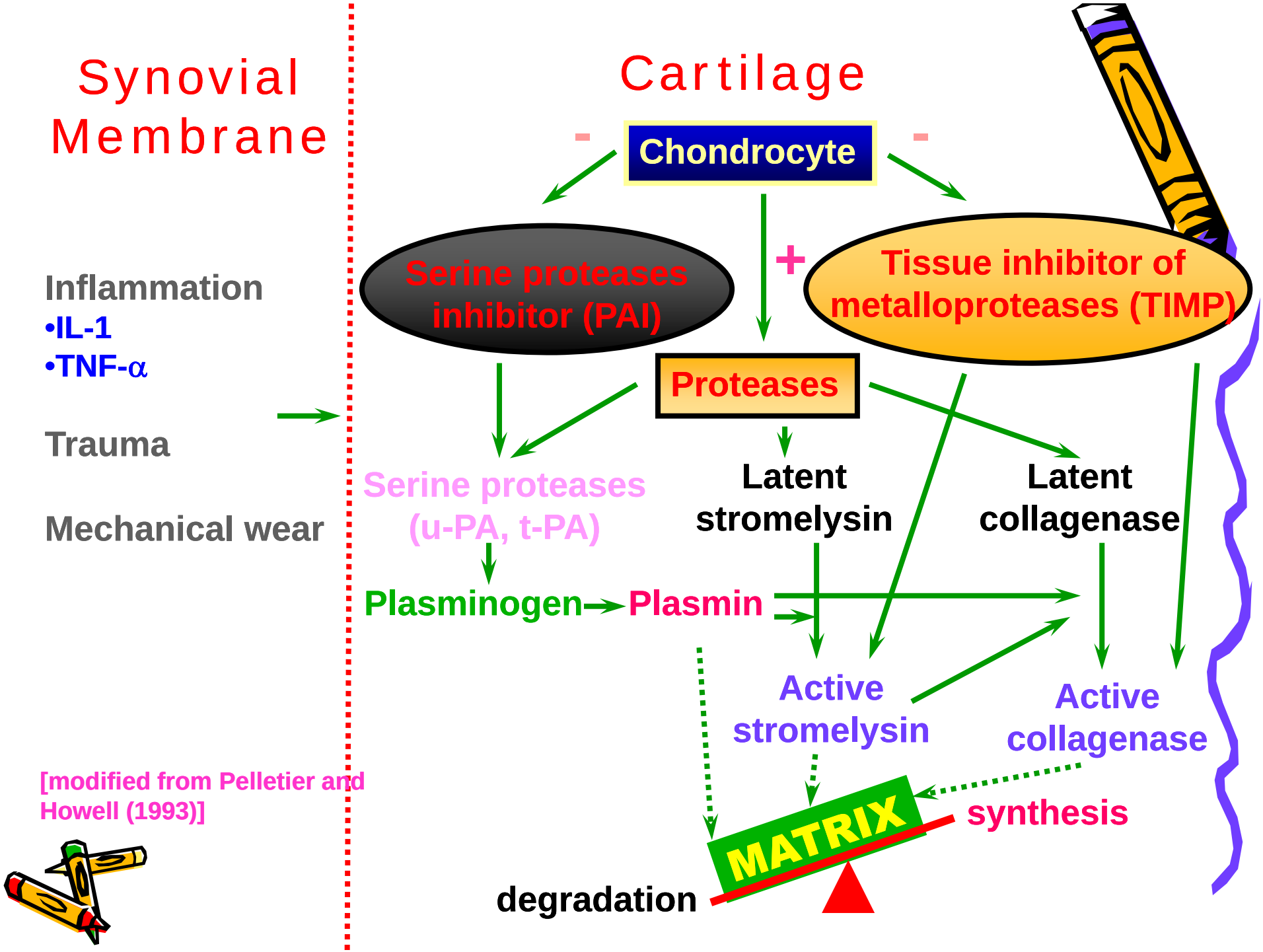
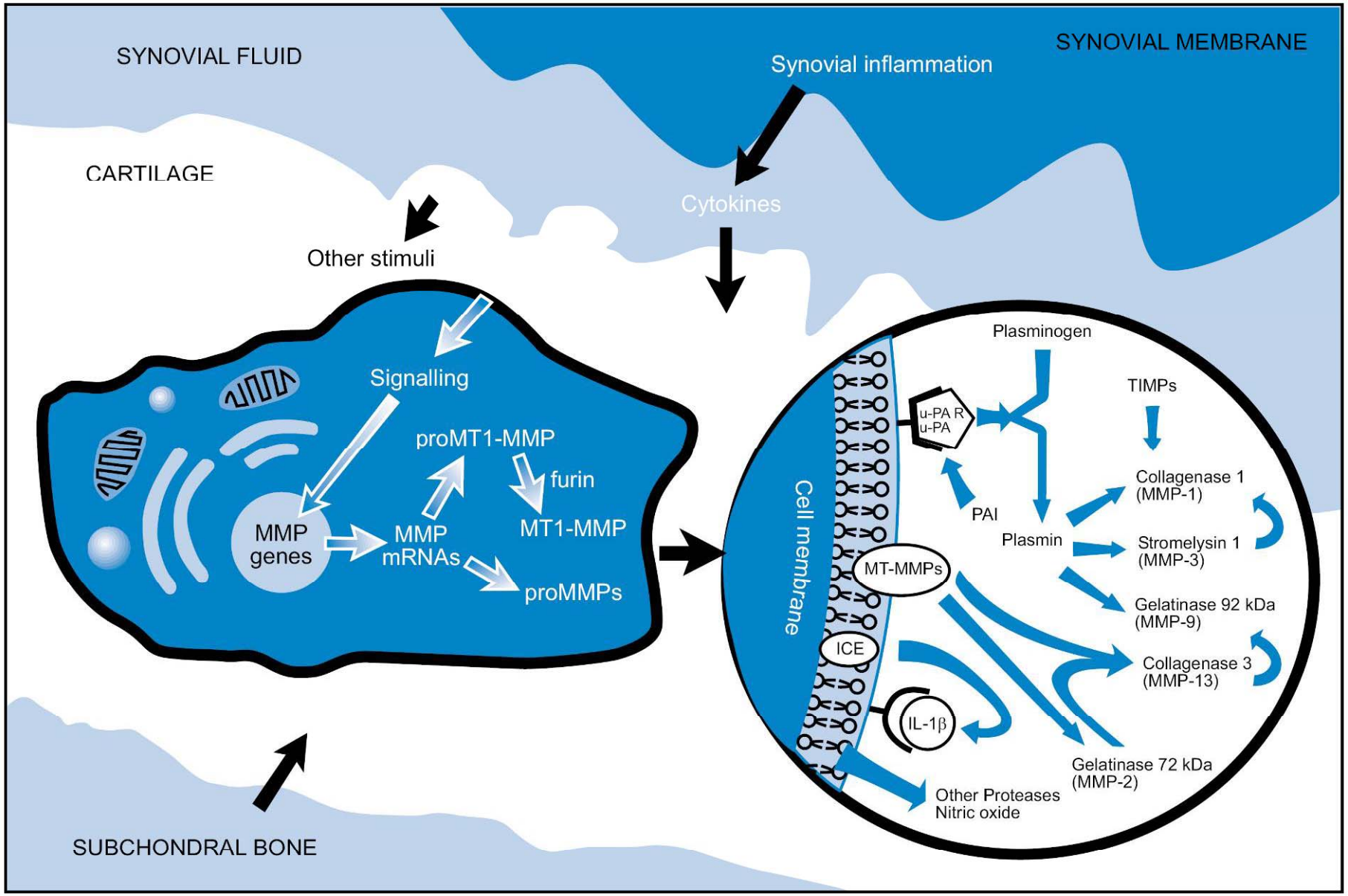

Synovial Membrane
Cartilage
Chondrocyte
-
-
+
Serine proteases inhibitor (PAI)
Tissue inhibitor of metalloproteases (TIMP)
Proteases
Inflammation
•IL-1
•TNF-α
Trauma
Mechanical wear
Serine proteases (u-PA, t-PA)
Latent stromelysin
Latent collagenase
Plasminogen
Plasmin
Active stromelysin
Active collagenase
MATRIX
synthesis
degradation
[modified from Pelletier and Howell (1993)]

Matrix Metalloproteinases

a gene family of neutral Zn^{2+} metalloproteinase

- **Collagenases**
  - **tissue collagenase (MMP-1), neutrophil collagenase (MMP-8), collagenase 3 (MMP-13) and collagenase 4 (MMP-18)**
- **Gelatinases**
  - **gelatinases A (MMP-2) and gelatinase B (MMP-9)**
- **Stromelysins**
  - **stromelysins 1 (MMP-3), stromelysin 2 (MMP-10) and stromelysin 3 (MMP-11)**
- **Matrilysins**
  - **matrilysin 1 (MMP-7) and matrilysin 2 (endometase, MMP-26)**
- **Membrane-type MMPs (MT-MMPs)**
  - **MT1-MMP (MMP-14), MT2-MMP (MMP-15), MT3-MMP (MMP-16), MT4-MMP (MMP-17), MT5-MMP (MMP-24), MT6-MMP (leukolysin, MMP-25)**
- **Other MMPs**
  - **metalloelastase (MMP-12), MMP-19, enamelysin (MMP-20), and MMP-23**


SYNOVIAL FLUID
SYNOVIAL MEMBRANE
Synovial inflammation
CARTILAGE
Cytokines
Other stimuli
Signalling
proMT1-MMP
furin
MT1-MMP
MMP genes
MMP mRNAs
proMMPs
Plasminogen
TIMPs
u-PA R
u-PA
Collagenase 1 (MMP-1)
PAI
Plasmin
Stromelysin 1 (MMP-3)
MT-MMPs
Gelatinase 92 kDa (MMP-9)
Cell membrane
ICE
Collagenase 3 (MMP-13)
IL-1β
Gelatinase 72 kDa (MMP-2)
Other Proteases
Nitric oxide
SUBCHONDRAL BONE

Clin Rheumatol (2004) 23: 21–26
DOI 10.1007/s10067-003-0774-6

ORIGINAL ARTICLE

Ko-Hsiu Lu · Shun-Fa Yang · Shu-Chen Chu
Pei-Ni Chen · Ming-Chih Chou · Tang-Yan Hsiao
Yih-Shou Hsieh

The significance of altered gelatinase expression in the synovium of patient with arthritic effusions

First author

Lu KH, et al. *Clin Rheumatol* 2004;23:21-6.

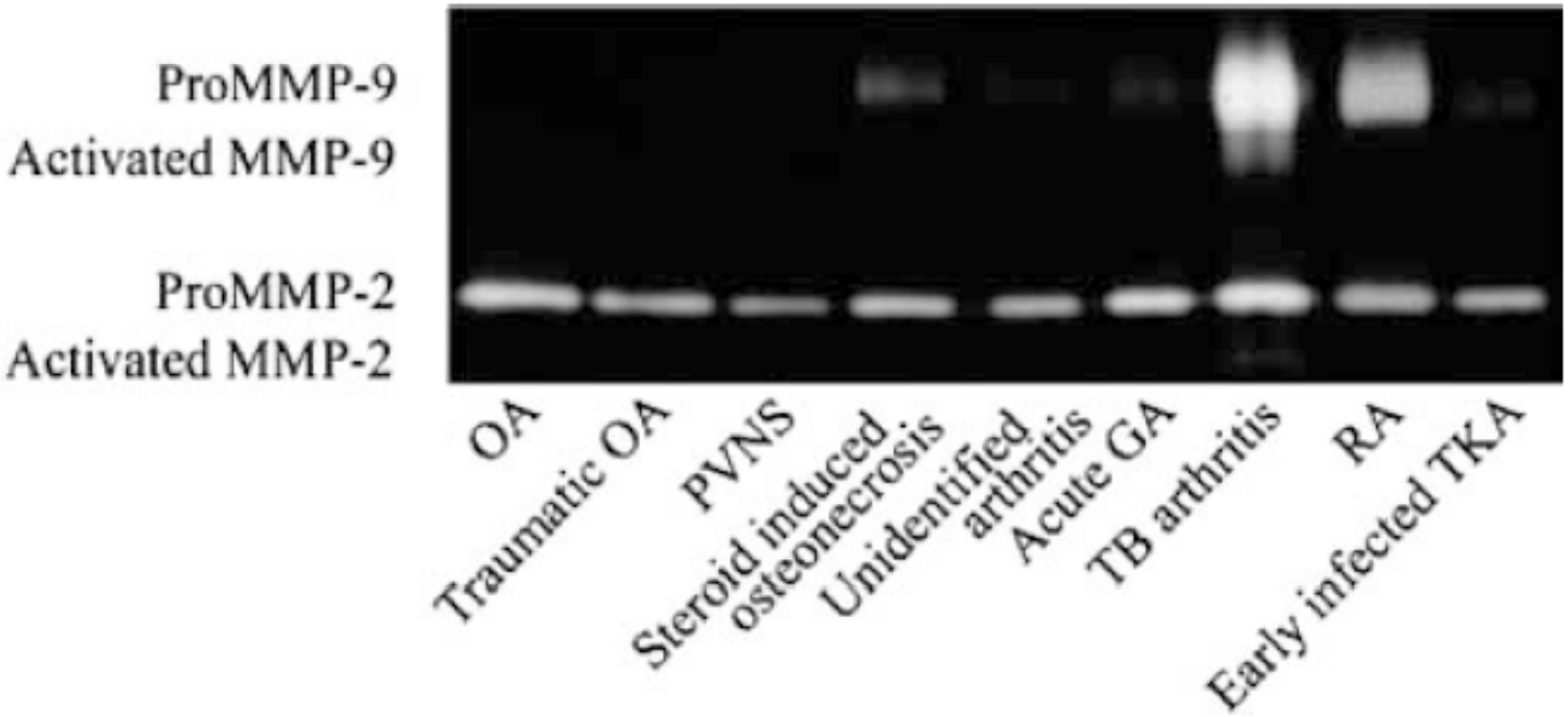


Fig. 1 Gelatinase activity in knee joint effusions of patients with various forms of arthritis (series I) was quantified by gelatin zymography. The proMMP-2 was produced in all effusions in equivalent amounts. The active form of MMP-2 appeared mainly in TB arthritis. Significantly more proMMP-9 appeared in effusions of the inflammatory group than in the non-inflammatory and hemorrhagic group

Lu KH, et al. *Clin Rheumatol* 2004;23:21-6.

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Clinica Chimica Acta 339 (2004) 77–83

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The clinical significance of gelatinase B in gouty arthritis of the knee

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Chu SC, et al. *Clin Chim Acta* 2004;339:77-83.

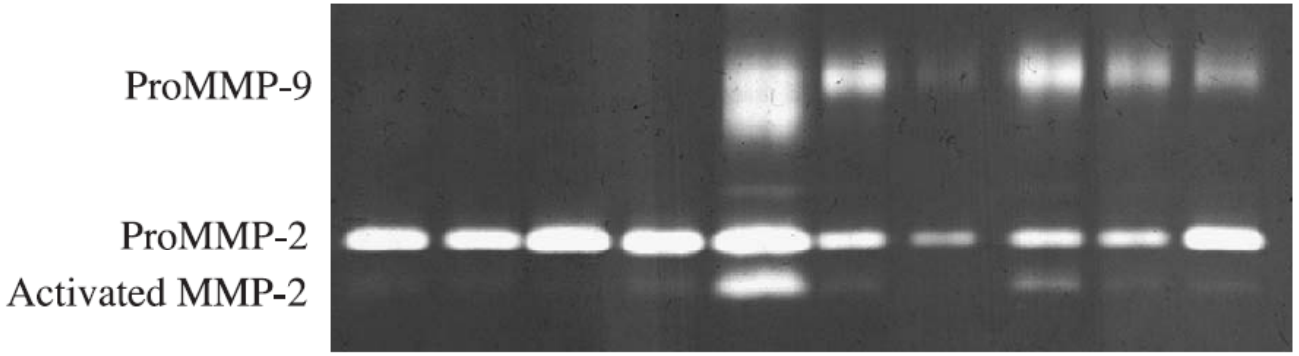

Fig.1. Gelatinase activities in knee joint effusions of patients with gouty arthritis were quantified by gelatin zymography. The proMMP-2 was produced in all effusions in equivalent amounts. The active form of MMP-2 and proMMP-9 appeared in some effusions and varied in amount.

Chu SC, et al. *Clin Chim Acta* 2004;339:77-83.

J Rheumatol 2006;33:311–7

Urokinase-type Plasminogen Activator, Receptor, and Inhibitor Correlating with Gelatinase-B (MMP-9) Contribute to Inflammation in Gouty Arthritis of the Knee

SHU-CHEN CHU, SHUN-FA YANG, KO-HUANG LUE, YIH-SHOU HSIEH, TANG-YAN HSIAO, and KO-HSIU LU

Corresponding author

Chu SC, et al. *J Rheumatol* 2006;33:311-7.

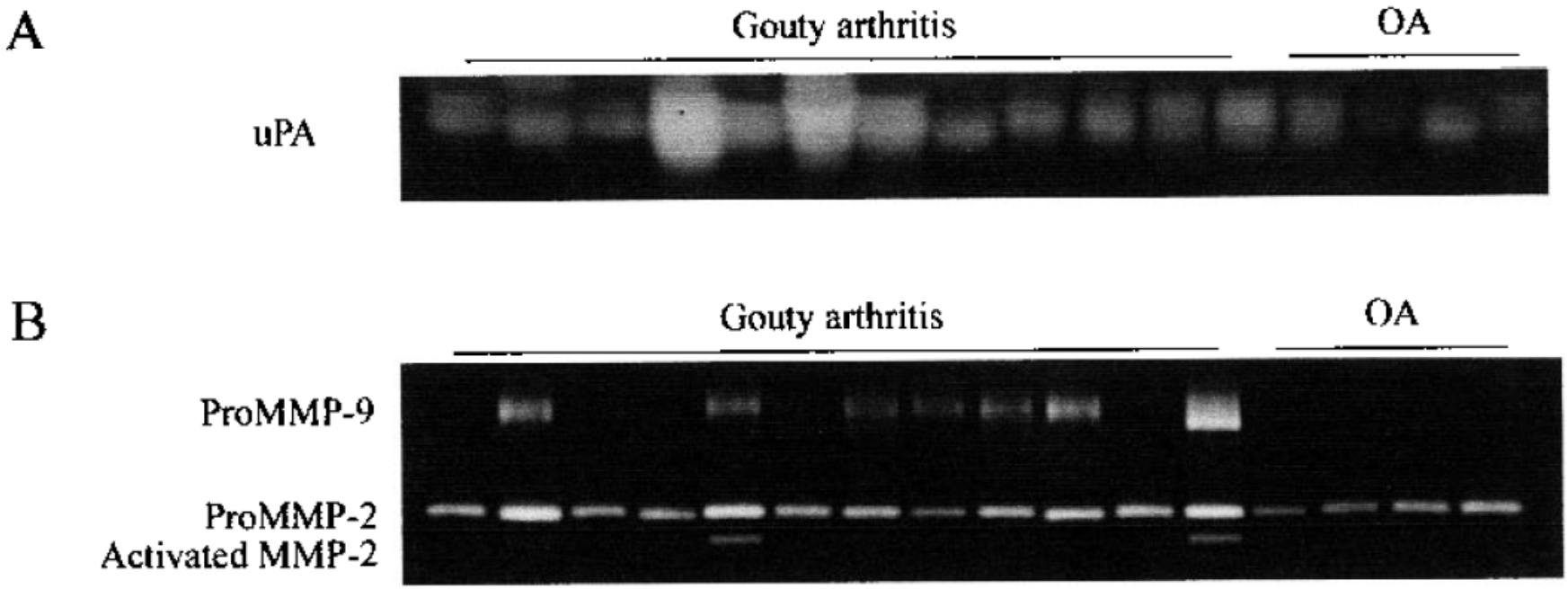

Figure 1. A. uPA levels in knee joint SF of patients with gouty arthritis and OA were determined by casein zymography. B. Gelatinase levels in knee joint SF of patients with gouty arthritis and OA were quantified by gelatin zymography. Pro-MMP-2 was produced in all SF in equivalent amounts. The active forms of MMP-2 and pro-MMP-9 appeared in some gouty arthritis SF in various amounts.

Chu SC, et al. *J Rheumatol* 2006;33:311-7.

CLINICAL ORTHOPAEDICS AND RELATED RESEARCH
Number 427, pp. 179–183

Clinical Significance of Gelatinases in Septic Arthritis of Native and Replaced Knees

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Corresponding author

Chu SC, et al. *Clin Orthop* 2004;427:179-83.

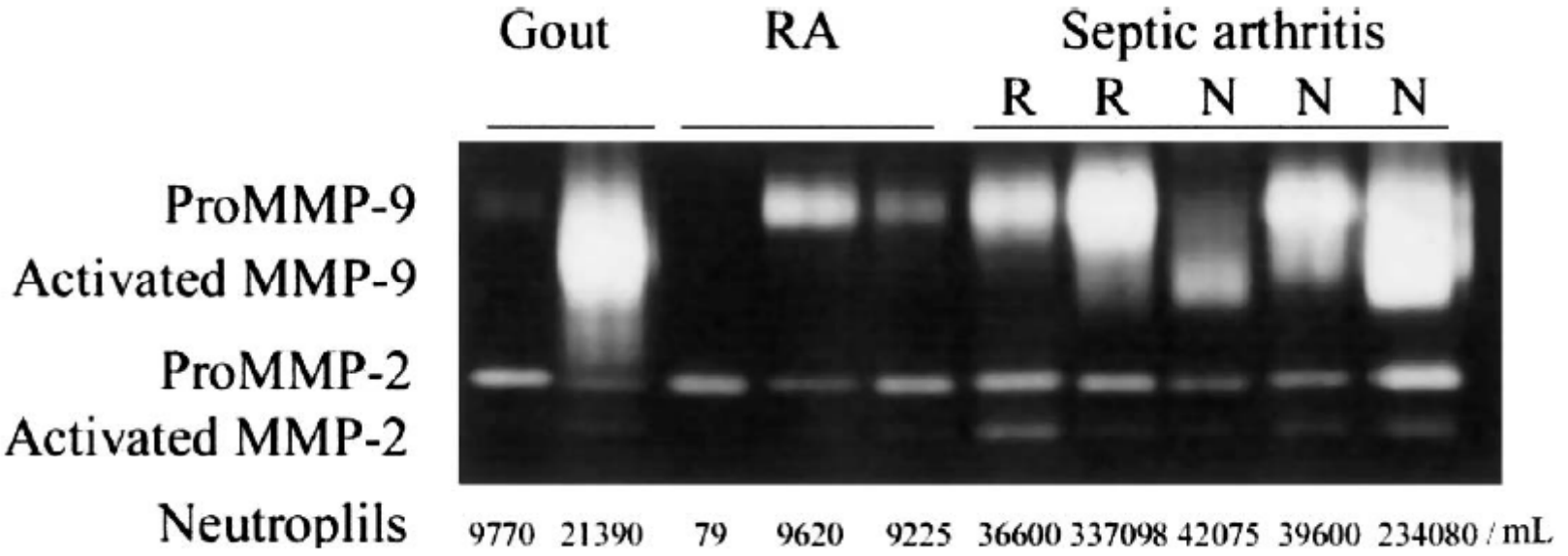

Fig 1. Gelatinase levels in effusions of patients with gouty arthritis, RA, and septic arthritis were quantified by gelatin zymography. The proMMP-2 was produced in all effusions in equivalent amounts. Activated MMP-2 and MMP-9 appeared in some effusions and varied in amount. R = replaced knee; N = native knee

Chu SC, et al. *Clin Orthop* 2004;427:179-83.

CLINICAL ORTHOPAEDICS AND RELATED RESEARCH
Number 447, pp. 172–178

Clinical Correlation with the PA/Plasmin System in Septic Arthritis of the Knee

Yih-Shou Hsieh, PhD; Shun-Fa Yang, PhD*; Ko-Huang Lue, MD†; and Ko-Hsiu Lu, MD, PhD†‡*

Corresponding author

Hsieh YS, et al. *Clin Orthop* 2006;447:172-8.

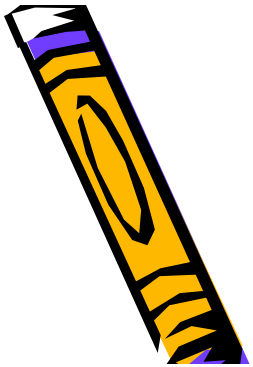

TABLE 2. Levels of MMP-2, MMP-9, u-PA, and PAI-1 in 135 Effusions

Arthritis	ProMMP-2 (percent)	Activated MMP-2 (percent)*	ProMMP-9 (percent)	Activated MMP-9 (percent)†	u-PA (pg/μL)	PAI-1 (pg/μL)	u-PA/PAI-1
Osteoarthritis	61.55 ± 15.14 (26.85–83.69)	ND	ND	ND	0.82 ± 0.39	4.13 ± 1.67	0.21 ± 0.11
Gouty arthritis	56.39 ± 14.50 (20.51–86.42)	1.91 ± 4.31 (0–25.51)	22.93 ± 32.34 (0–98.64)	ND	2.62 ± 2.94	5.57 ± 4.34	1.01 ± 4.46
Rheumatoid arthritis	47.23 ± 15.81 (24.02–26.38)	7.30 ± 9.42 (0–33.76)	47.73 ± 43.39 (0–99.69)	7.81 ± 19.97 (0–70.97)	5.39 ± 3.51§,‖	11.22 ± 6.49§,‖	0.57 ± 0.36
Septic arthritis	63.97 ± 12.13 (8.59–84.09)	8.44 ± 8.76 (0–39.78)	71.27 ± 23.93 (23.18–99.99)	15.83 ± 33.84 (0–99.99)	8.07 ± 4.33§,‖,¶	18.45 ± 8.02§,‖,¶	0.54 ± 0.49
F value					28.871‡	44.970‡	0.458

Results are shown as the mean and standard deviation (range); ND = not detectable; MMP = matrix metalloproteinase; u-PA = urokinase-type PA; PAI-1 = PA inhibitor type-1; *$p < 0.001$ versus corresponding values in u-PA and PAI-1 of all tested effusions (Pearson correlation); †$p = 0.005$ versus corresponding values in u-PA of all tested effusions (Pearson correlation); ‡$p < 0.001$ analysis of variance with Scheffe posteriori comparison; §Significantly different at $p < 0.05$ compared with osteoarthritis; ‖Significantly different at $p < 0.05$ compared with gouty arthritis; ¶Significantly different at $p < 0.05$ compared with rheumatoid arthritis

Hsieh YS, et al. *Clin Orthop* 2006;447:172-8.

Expression Changes of Gelatinases in Human Osteoarthritic Knees and Arthroscopic Debridement

Yih-Shou Hsieh, Ph.D., Shun-Fa Yang, M.S., Shu-Chen Chu, Ph.D., Pei-Ni Chen, M.S., Ming-Chih Chou, M.D., Ming-Cheng Hsu, M.D., and Ko-Hsiu Lu, M.D., Ph.D.

Corresponding author

Arthroscopy: The Journal of Arthroscopic and Related Surgery, Vol 20, No 5 (May-June), 2004: pp 482-488

Hsieh YS, et al. *Arthroscopy* 2004;20:482-8.

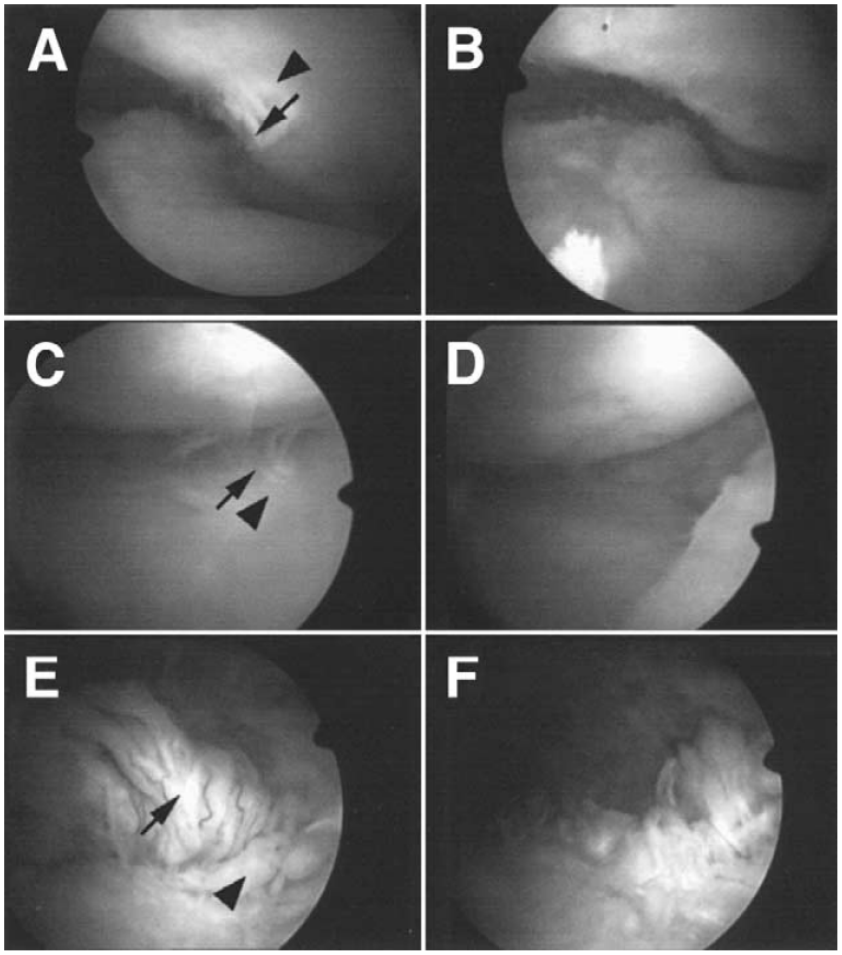

FIGURE 1. Arthroscopic debridement for excising and smoothing the pathologic lesions of osteoarthritis. (A) Intraoperative view of the lesional (arrow) and paralesional (arrowhead) areas of chondral ulcer and fibrillation. (B) Arthroscopic chondral shaving and osteophyte excision. (C) Intraoperative view of the lesional (arrow) and paralesional (arrowhead) areas of meniscal degenerative tear. (D) Arthroscopic partial meniscectomy and chondral shaving. (E) Intraoperative view of the lesional (arrow) and paralesional (arrowhead) areas of hypertrophic villi. (F) Arthroscopic limited synovectomy.

Hsieh YS, et al. *Arthroscopy* 2004;20:482-8.

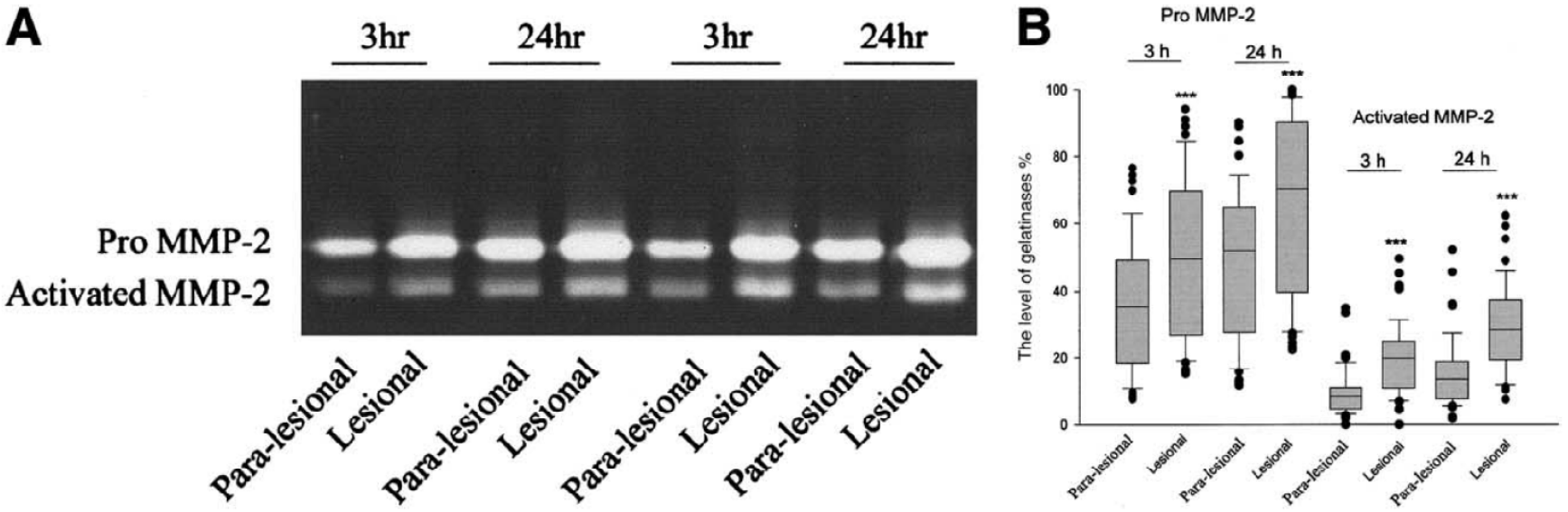

FIGURE 2. Gelatinase levels in a series of chondral cultures of patients with knee osteoarthritis at various times (3 and 24 hours) were quantified by gelatin zymography. (A) Latent and activated forms of MMP-2 appeared in serial chondral cultures. (B) The levels in lesional cultures were significantly higher than those in paralesional ones and increased in a time-dependent manner ($P < .001$).

Hsieh YS, et al. *Arthroscopy* 2004;20:482-8.

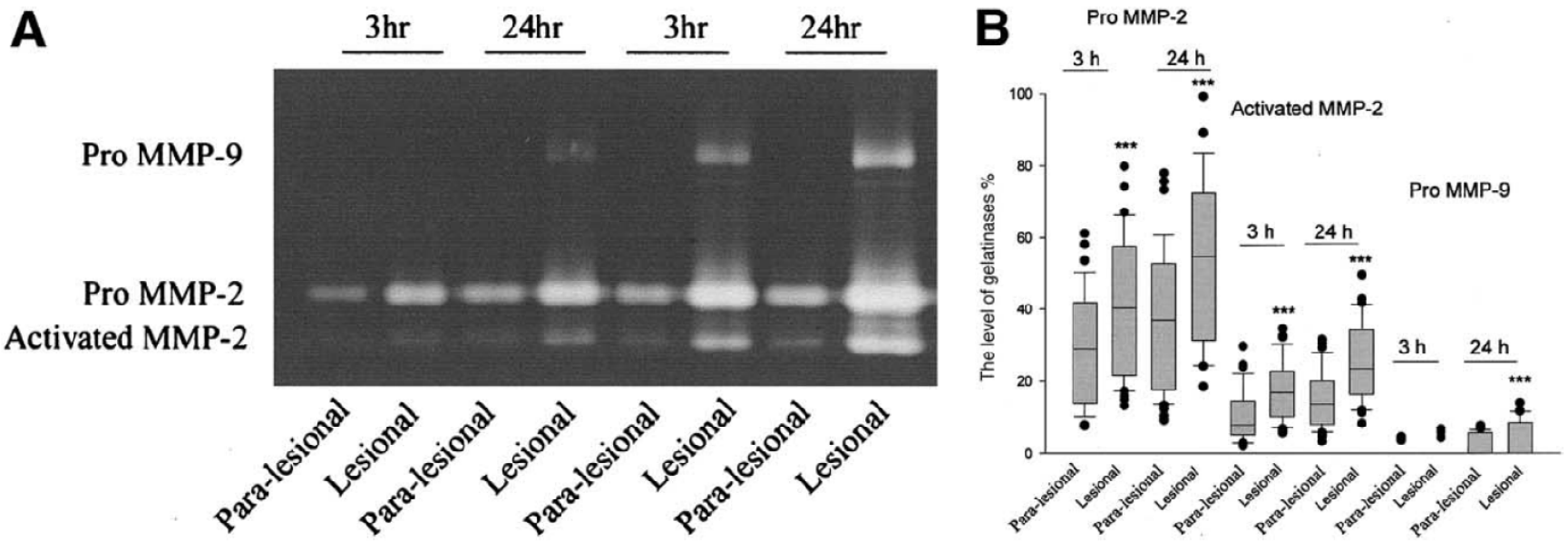

FIGURE 3. Gelatinase levels in a series of meniscal cultures of patients with knee osteoarthritis at various times (3 and 24 hours) were quantified by gelatin zymography. (A) Latent and activated forms of MMP-2 and proMMP-9 appeared in serial meniscal cultures. (B) The levels of the latent & activated forms of MMP-2 in lesional cultures were significantly higher than those in paralesional ones and increased in a time-dependent manner ($P < .001$). The level of proMMP-9 in lesional cultures was significantly higher than that in paralesional ones after 24 hours of incubation ($P < .001$). Nevertheless, no significant differences were found between lesional and paralesional cultures after 3 hours incubation ($P = .109$).

Hsieh YS, et al. *Arthroscopy* 2004;20:482-8.

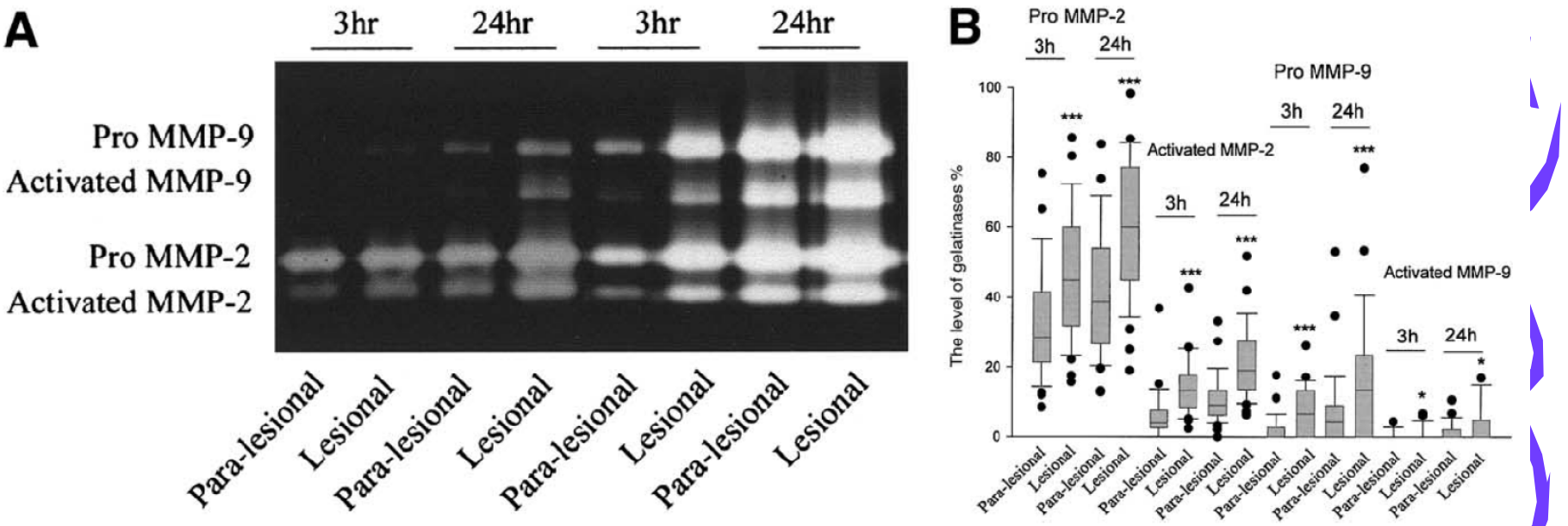

FIGURE 4. Gelatinase levels in a series of synovial cultures of patients with knee osteoarthritis at various times (3 and 24 hours) were quantified by gelatin zymography. (A) Latent and activated forms of MMP-2 and -9 appeared in serial synovial cultures. (B) The levels in lesional cultures were significantly higher than those in paralesional ones and increased in a time-dependent manner (proMMP-2 and -9 and activated MMP-2, $P < .001$; activated MMP-9, $P < .05$).

Hsieh YS, et al. *Arthroscopy* 2004;20:482-8.

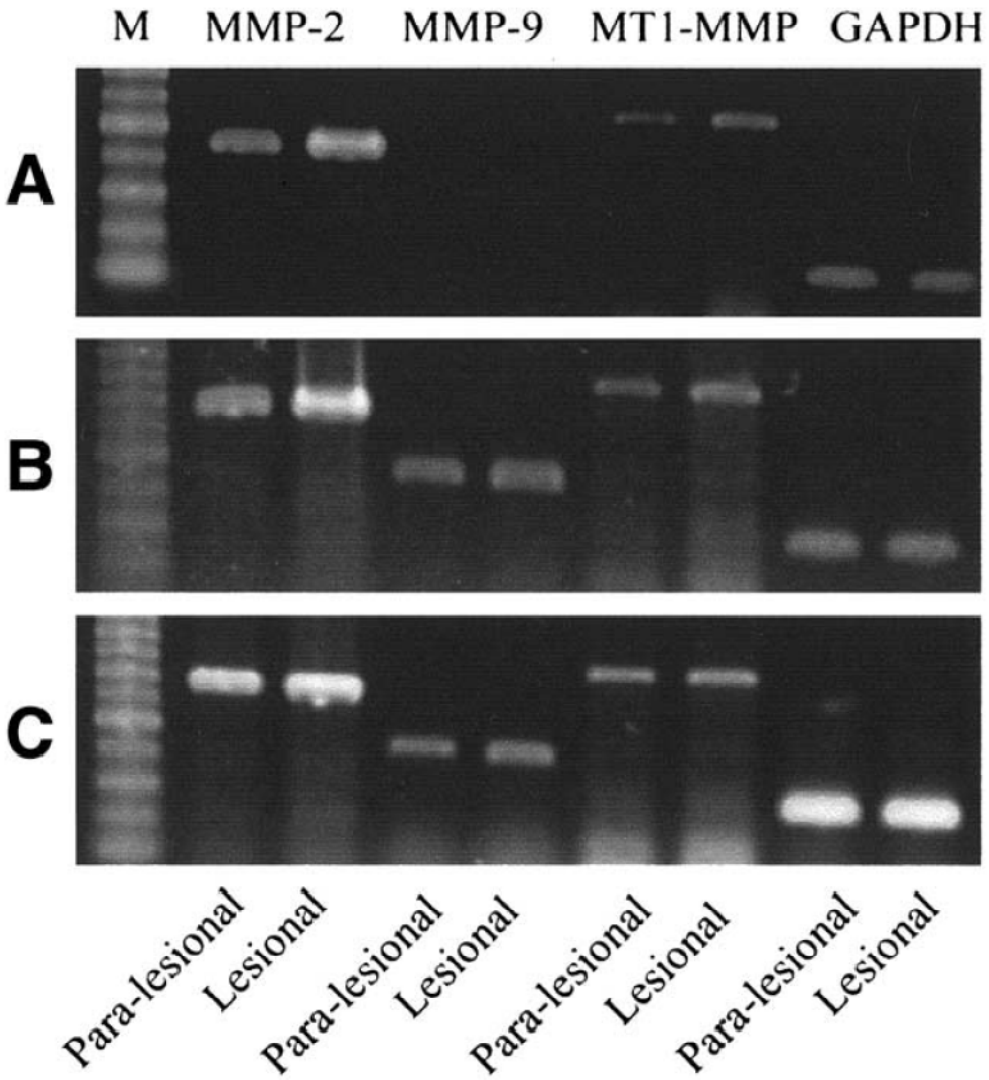

FIGURE 5. MMP-2 and -9 and MT1-MMP mRNA levels in serial (A) chondral, (B) meniscal, and (C) synovial cultures after 24 hours of incubation were examined. All increased in lesional cultures.

Hsieh YS, et al. *Arthroscopy* 2004;20:482-8.

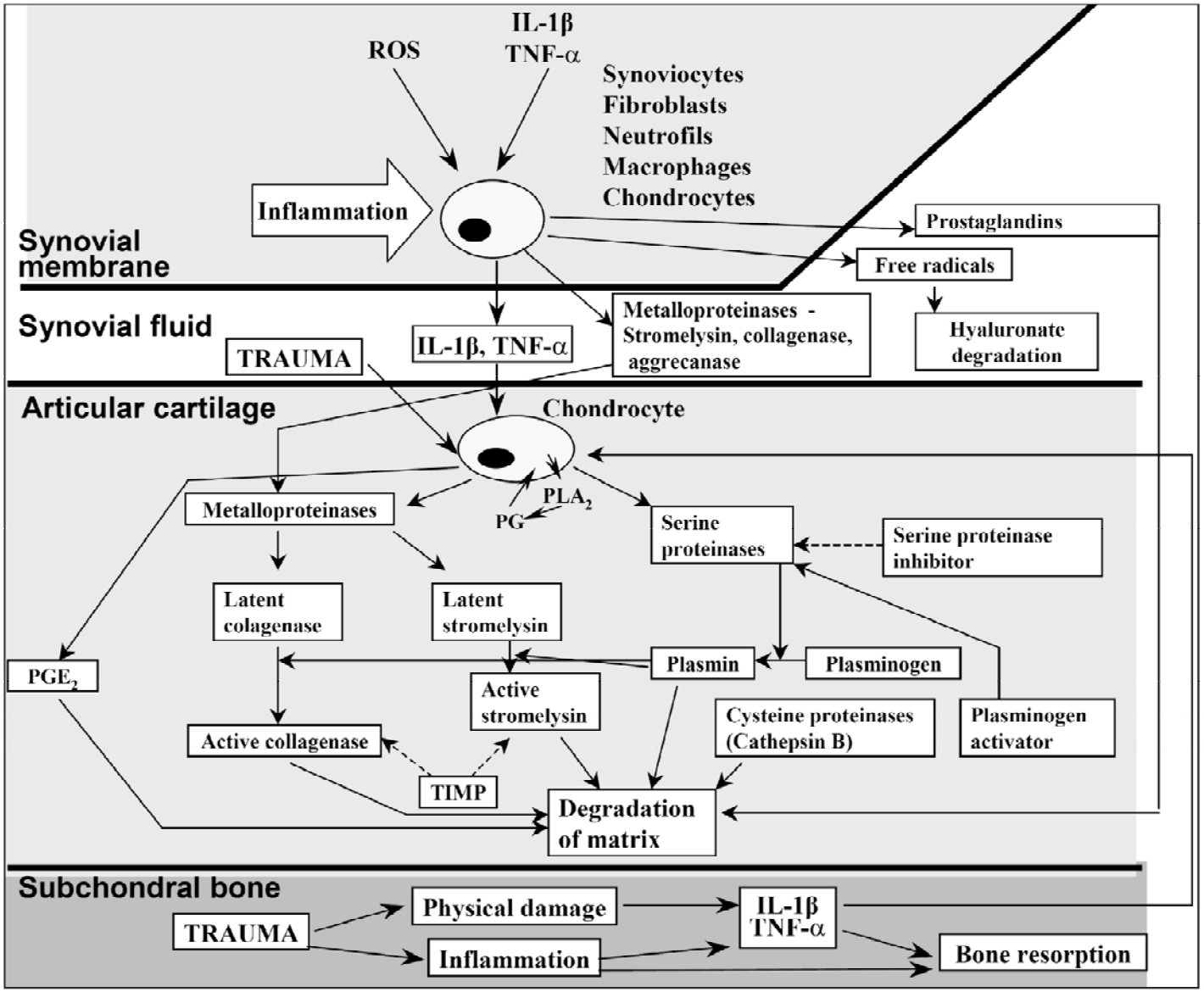

Fig. 1. The current concept of osteoarthritic cascade of events (ROS – reactive oxygen species, TIMP – tissue inhibitors of metalloproteinases).

Connective Tissue Research, 45: 142–150, 2004

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Regulation of Gelatinases Expression by Cytokines, Endotoxin, and Pharmacological Agents in the Human Osteoarthritic Knee

Shu-Chen Chu,[1] Shun-Fa Yang,[2] Ko-Huang Lue,[3] Yih-Shou Hsieh,[2] Chih-Lung Wu,[5] and Ko-Hsiu Lu[4,5]

Corresponding author

Chu SC, et al. *Connective Tissue Res* 2004;45:142-50.

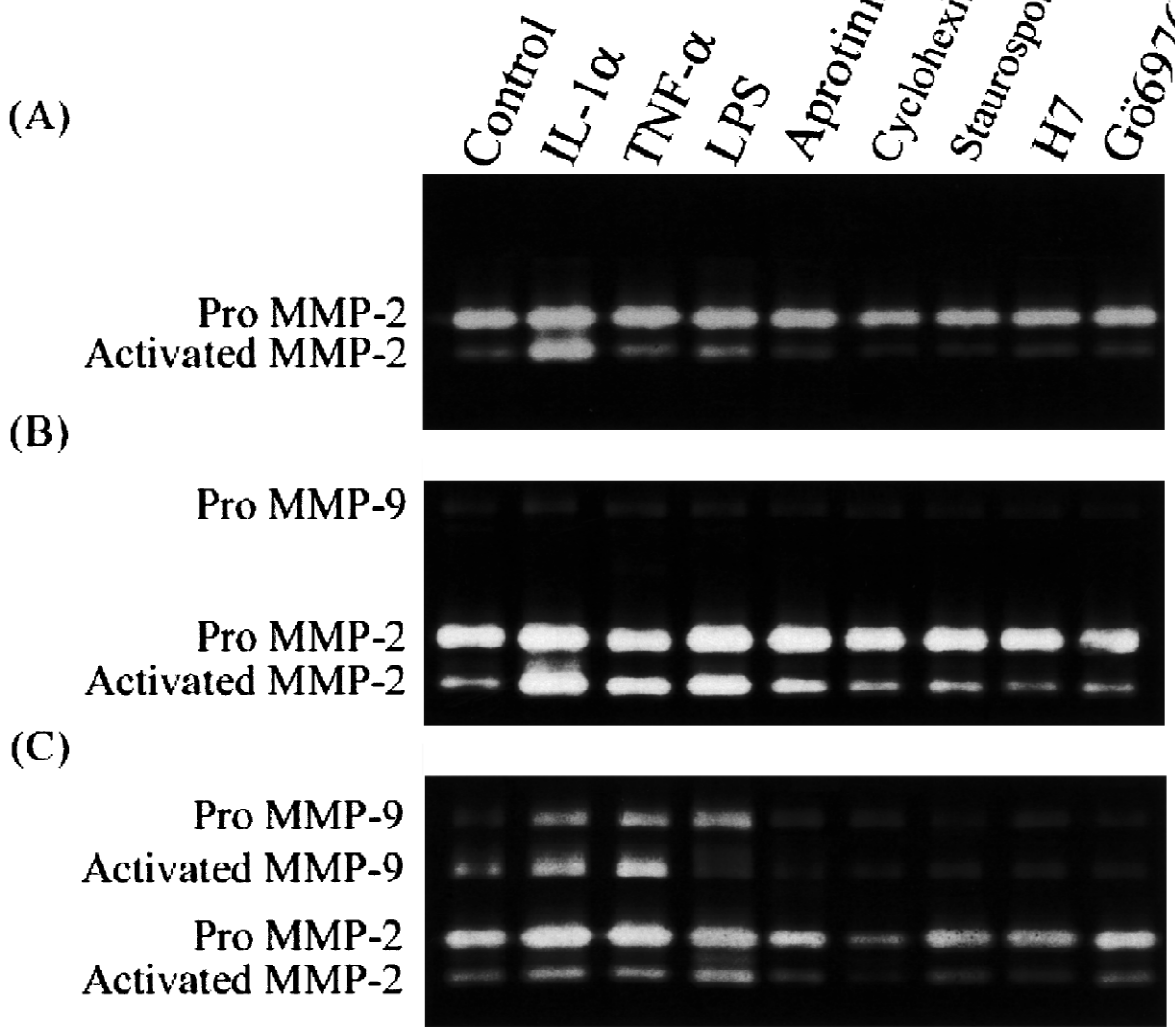
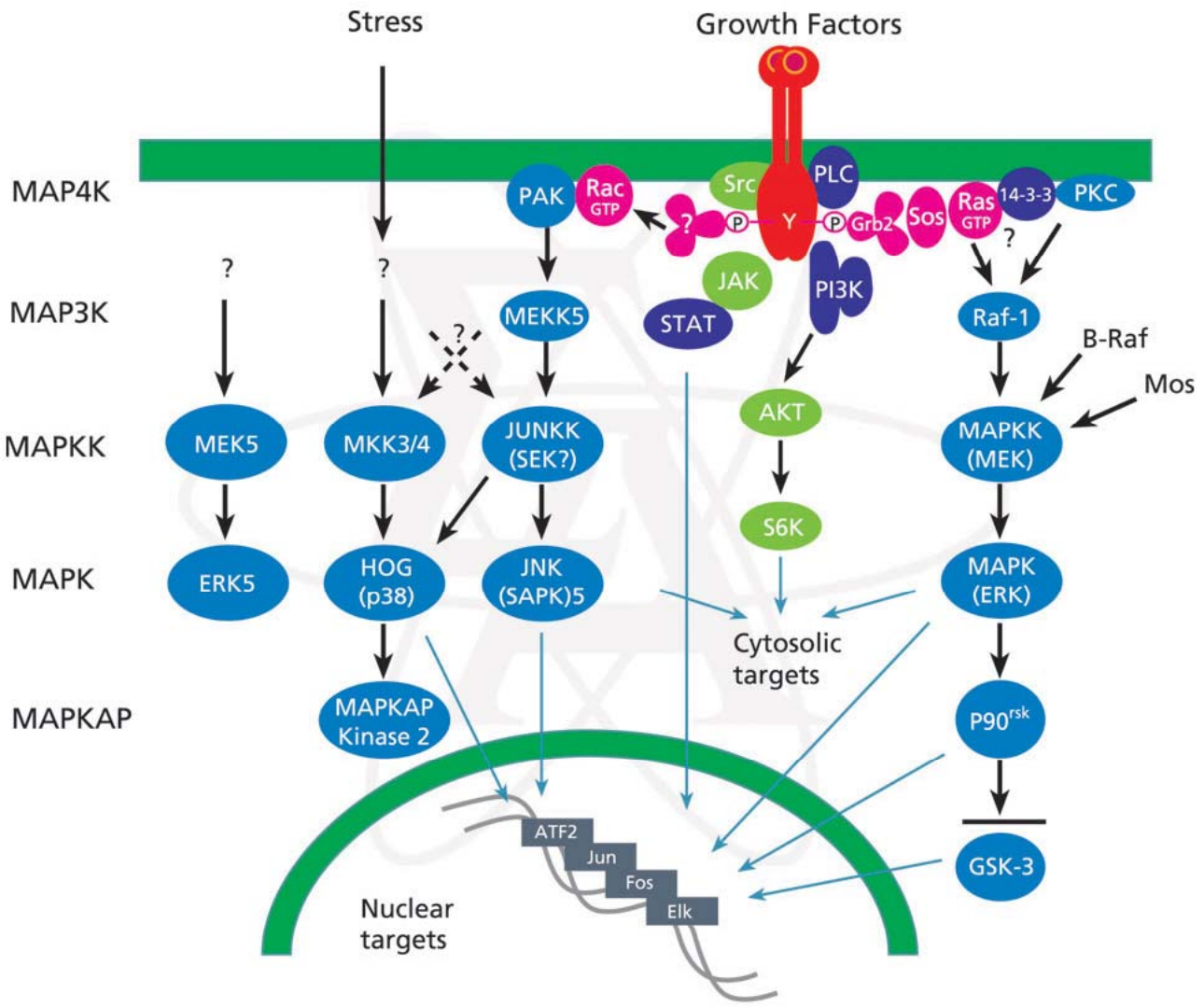


Figure 1. Gelatinase levels in osteoarthritic chondral (A), meniscal (B), and synovial (C) cultures co-treated with or without catabolic cytokines (10 ng/ml IL-1α and 10 ng/ml TNF-α), 1 μg/ml LPS, and pharmacological agents (100 μg/ml aprotinin, 10 μM cycloheximide, 5 nM staurosporine, 10 μM H7, and 2 μM Gö6976) on 24 hr were quantified by gelatin zymography.

Chu SC, et al. *Connective Tissue Res* 2004;45:142-50.

The Mitogen-activated Protein Kinase (MAPK) Cascades

SIGMA-ALDRICH



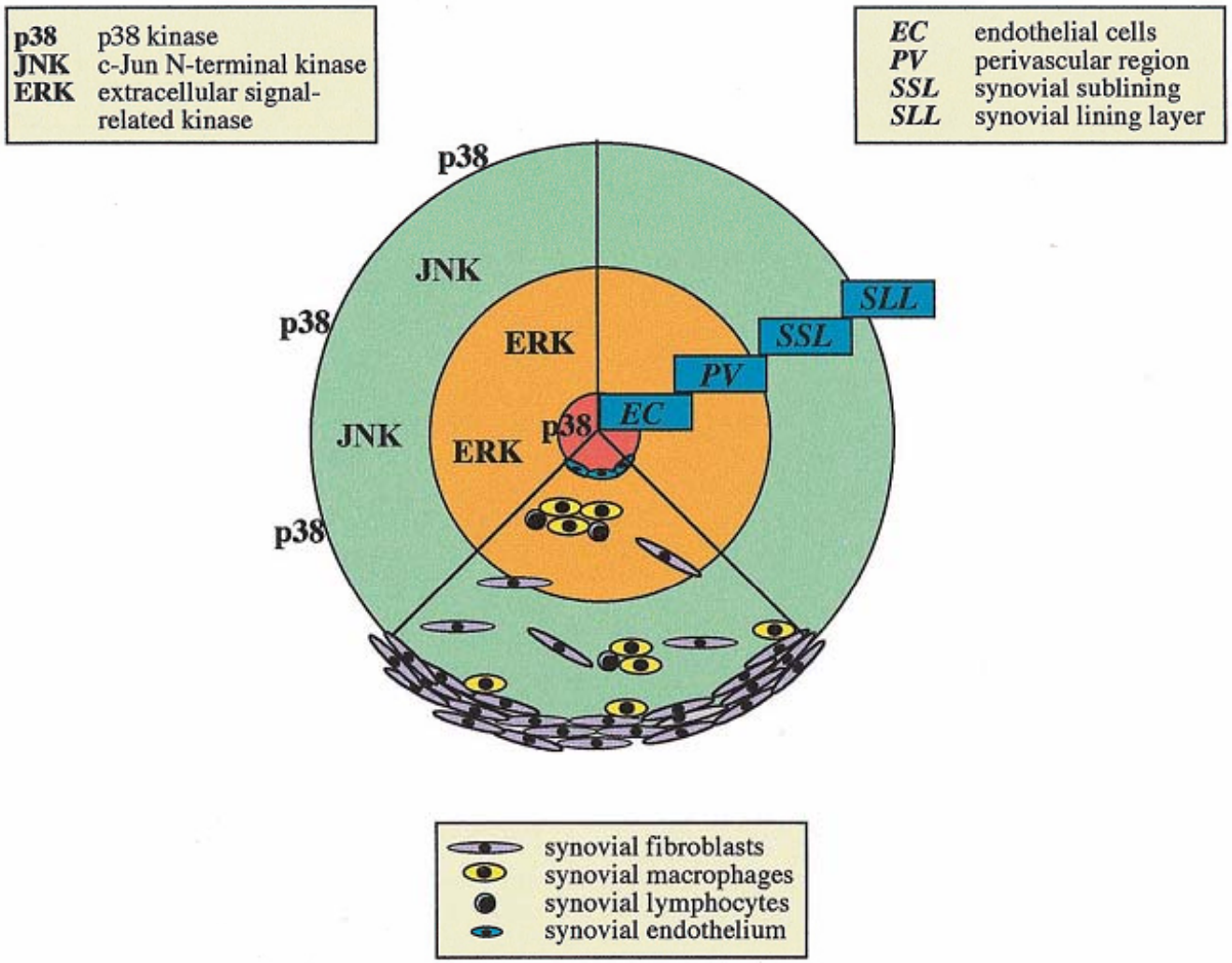


Figure 7. Differential localization of activation of stress- or mitogen-activated protein kinases in RA synovial membrane. The right upper sector shows the subcompartments of the synovial membrane. Endothelial cells cover a synovial microvessel in the center, and are in turn surrounded by a perivascular region, the synovial sublining, and finally the synovial lining layer. The left upper sector shows the predominant localizations of p38 MAPK, JNK, and ERK activation. The lower sector illustrates the histomorphologic structures and cell types of the synovial membrane.

The Journal of Rheumatology 2007; 34:4

Upregulation of Urokinase-type Plasminogen Activator and Inhibitor and Gelatinase Expression via 3 Mitogen-Activated Protein Kinases and PI3K Pathways During the Early Development of Osteoarthritis

YIH-SHOU HSIEH, SHUN-FA YANG, KO-HUANG LUE, SHU-CHEN CHU, TZUNG-JE LI, and KO-HSIU LU

Corresponding author

Hsieh YS, et al. *J Rheumatol* 2007;34:785-93.

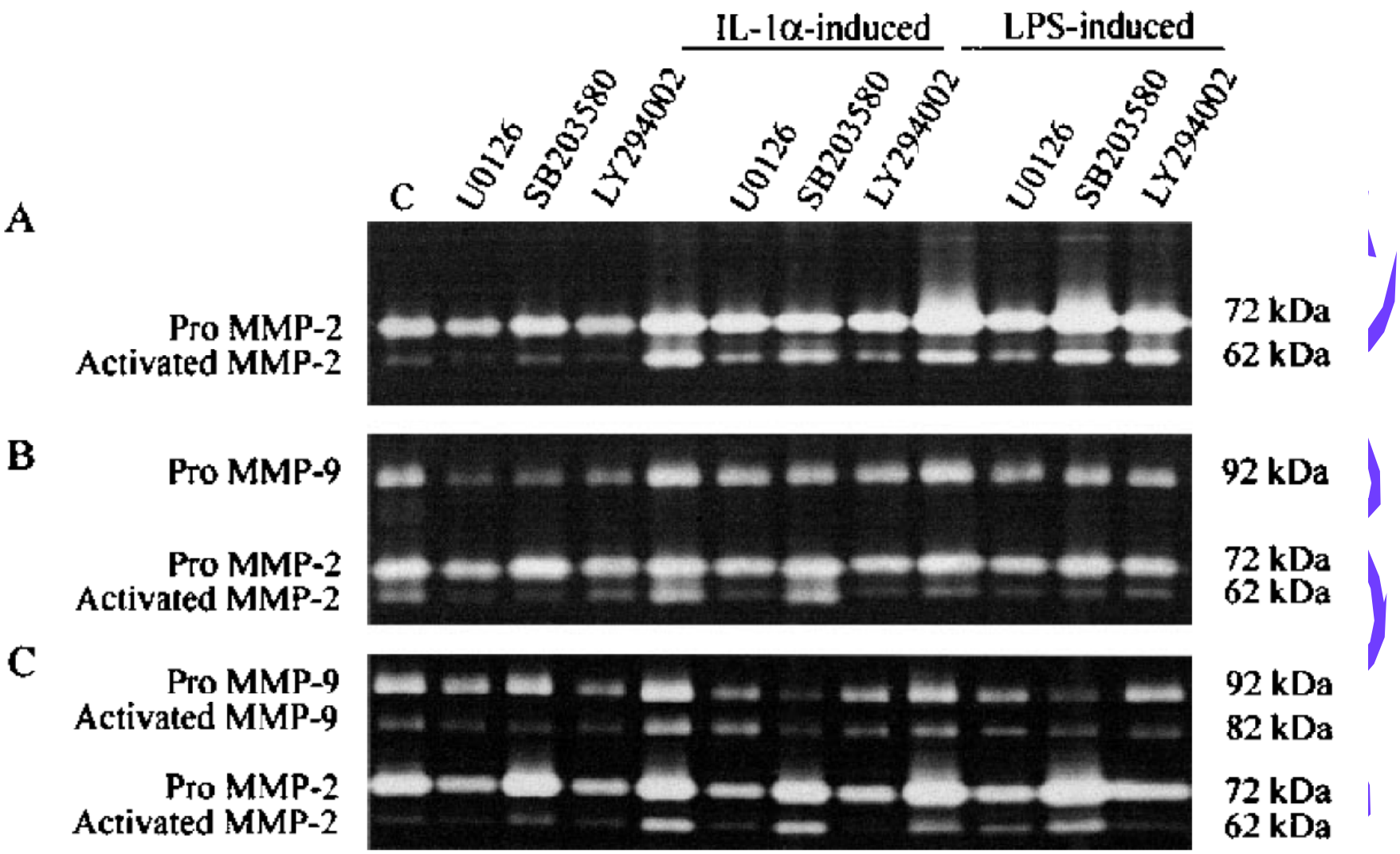


Figure 1. Gelatinolytic activity in osteoarthritic (A) chondral, (B) meniscal, and (C) synovial cultures co-treated with or without various inhibitors for 24 h were assessed by gelatin zymography.

Hsieh YS, et al. *J Rheumatol* 2007;34:785-93.

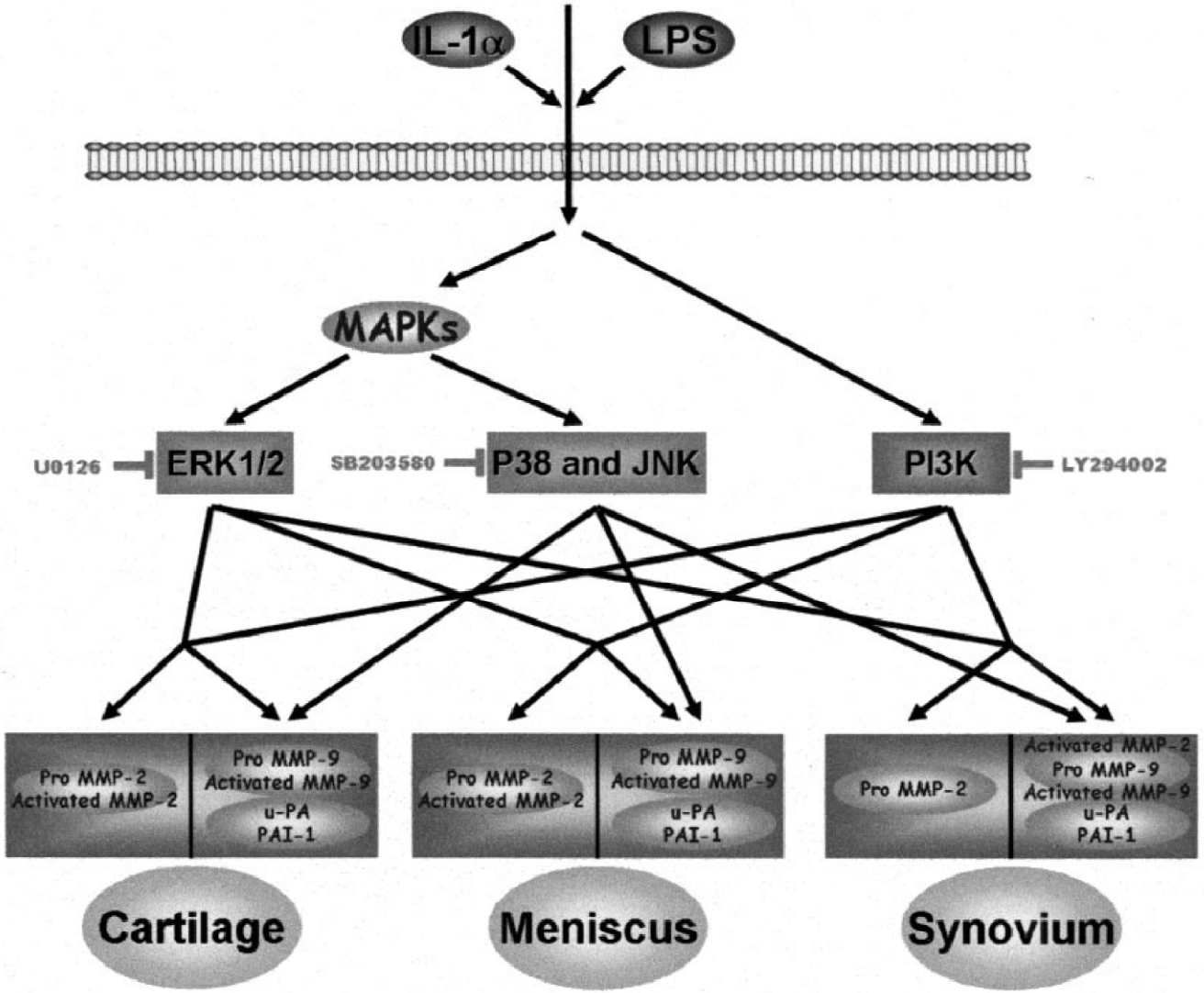
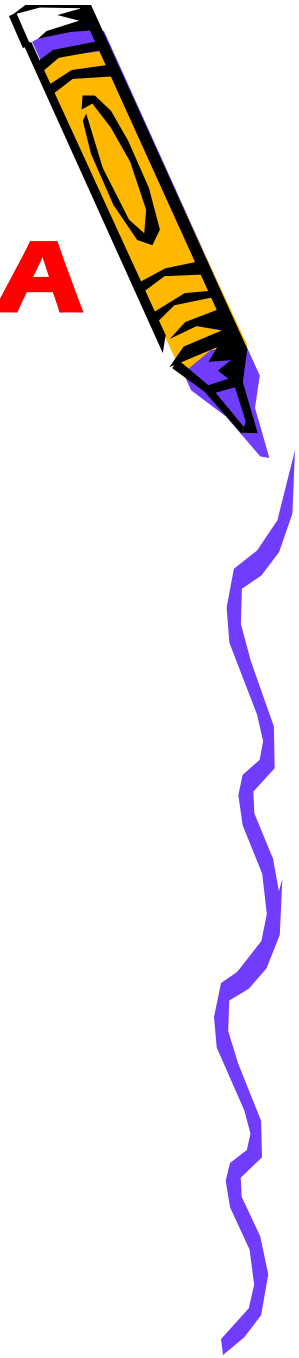


Figure 6. Three MAPK and PI3K signaling pathways involved in u-PA, PAI-1, MMP-2, and MMP-9 expression during the early development of OA. JNK and p38 inhibitor SB203580 could not decrease the levels of latent and activated forms of MMP-2 in chondral and meniscal cultures and proMMP-2 in synovial cultures, whereas SB203580 did suppress the level of activated MMP-2 in synovial cultures. IL-1α- and LPS-induced groups showed similar changes.

Hsieh YS, et al. *J Rheumatol* 2007;34:785-93.

Therapies Under Investigation for Use in OA



- Pharmacologic agents
  - nutritional agents
    - glucosamine
    - chondroitin sulfate
    - antioxidants
  - disease-modifying OA drugs
  - MMP inhibitors
  - growth factors
- Devices
  - acupuncture
  - magnets
  - pulsed electromagnetic fields
- Lasers

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Glucosamine sulfate suppresses the expressions of urokinase plasminogen activator and inhibitor and gelatinases during the early stage of osteoarthritis

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Corresponding author

Chu SC, et al. *Clin Chim Acta* 2006;372:167-72.

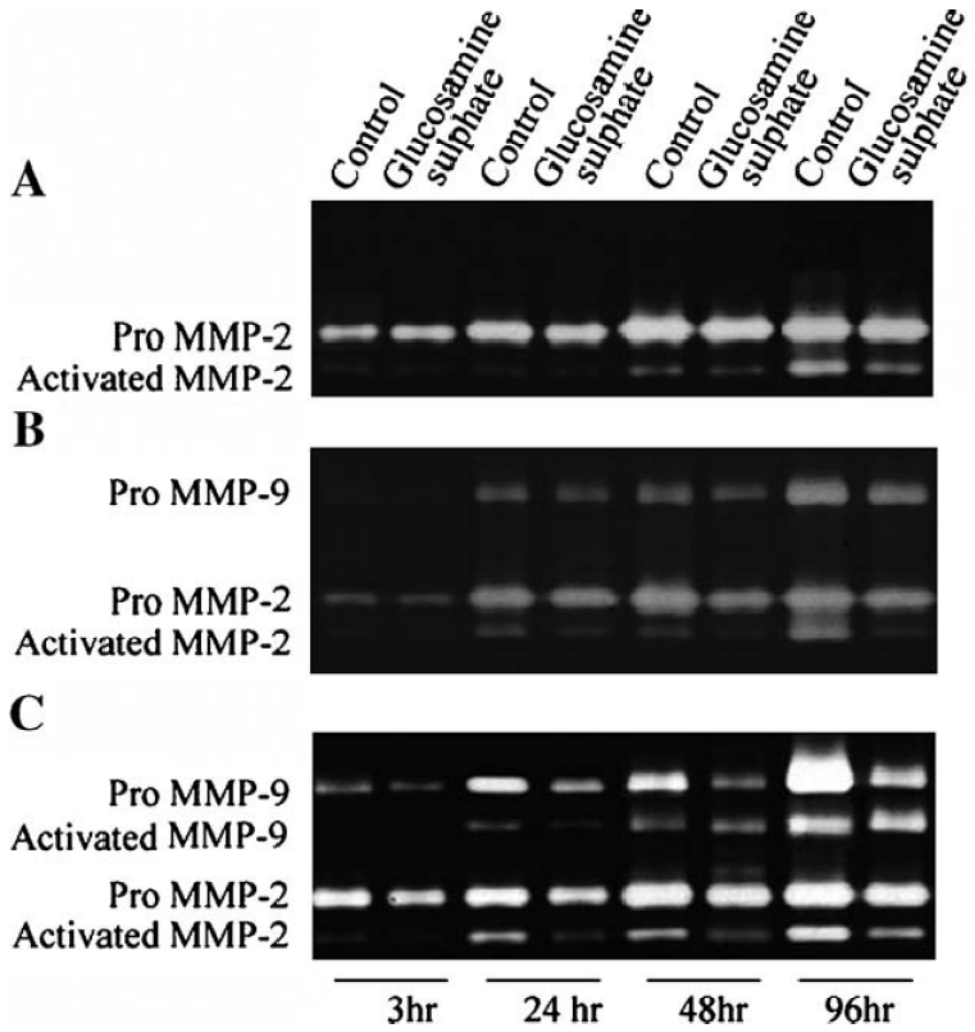

Fig. 1. MMP-2 and MMP-9 levels in conditioned media from human osteoarthritic chondral (A), meniscal (B) and synovial (C) cultures treated with or without glucosamine sulfate at 3, 24, 48 and 96 h were assayed by gelatin zymography.

Chu SC, et al. *Clin Chim Acta* 2006;372:167-72.

Pharmacologic Therapy for OA

- Oral
  - acetaminophen (cost, efficacy, safety)
  - coxibs
  - nonselective nonsteroidal anti-inflammatory + misoprostol or proton pump inhibitor (in patients at increased risk for upper G-I adverse events)
  - nonacetylated salicylate
  - other pure analgesics
    - tramadol
    - opioids
- Intra-articular
  - glucocorticoids
  - hyaluronan
- Topical
  - capsaicin
  - methylsalicylate

Arthritis & Rheum 2000; 43: 1905-1915.

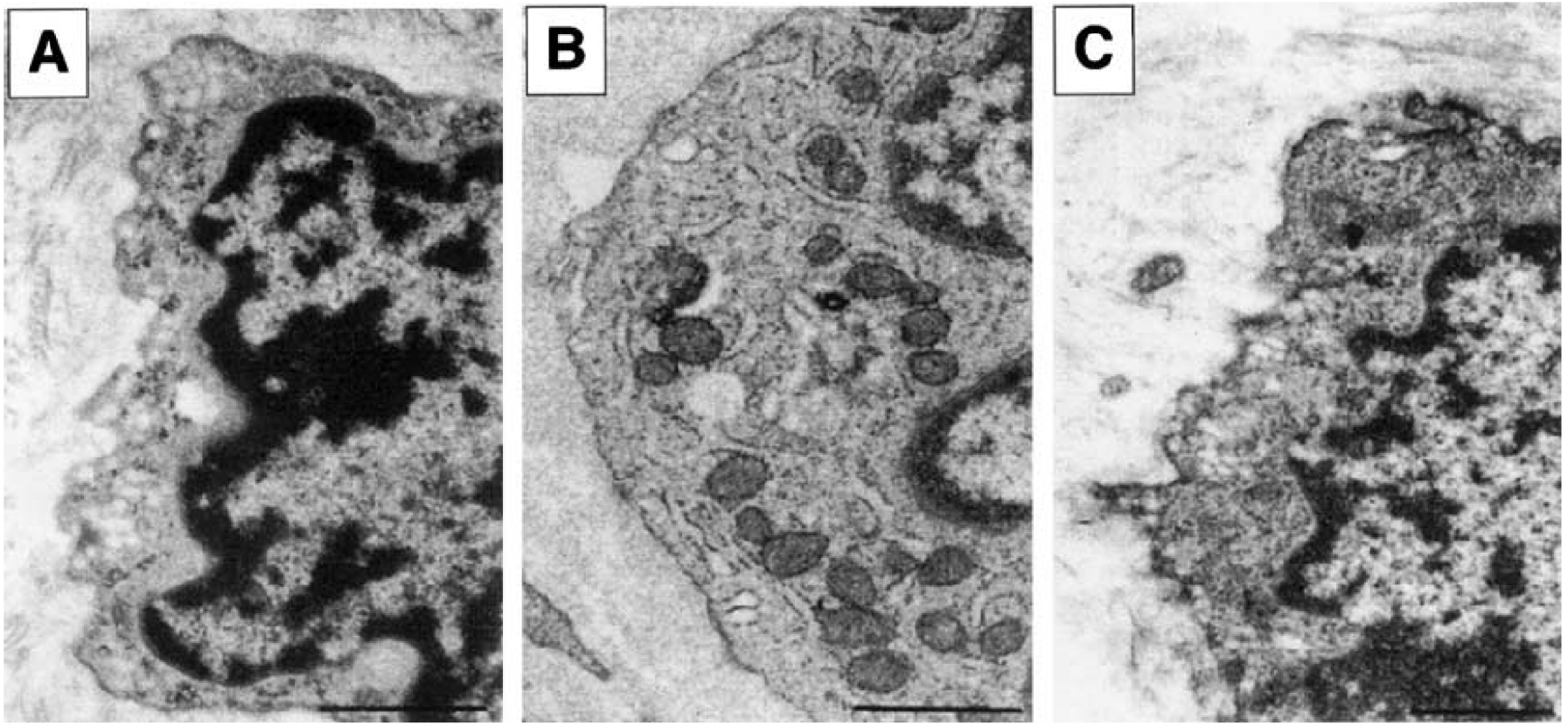

Fig 8. Ultrathin sections of synovial biopsy specimens taken at arthroscopy, stained with uranyl acetate and lead citrate for transmission electron microscopy. (A) In normal subjects, the plasma membrane of type B synoviocytes is decorated almost completely by pinocytic vesicles. (B) These disappeared in biopsy specimens derived from OA joints. (C) They become evident again 6 months after HA therapy. Scale: bar shown = 1 μm. Modified from Pasquali Ronchetti et al (179).

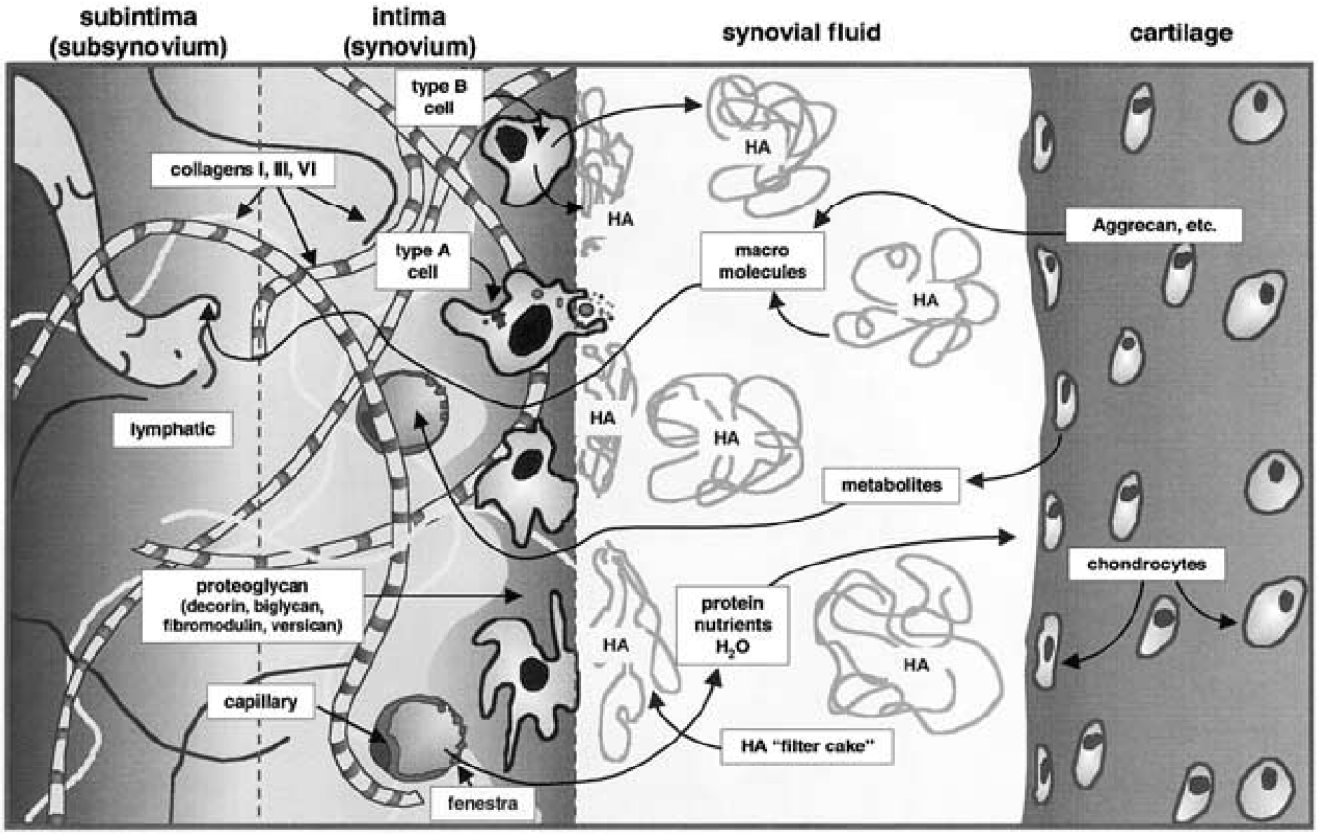

Fig 6. Diagrammatic representation of the synovial compartments showing the major matrix components in the intima and subintima which could influence passage of HA molecules from the synovial cavity into the circulation via the lymphatics. Nutrient and metabolite exchange between cartilage and the synovium is facilitated by HA, but large MW plasma proteins are normally excluded from SF. The extracellular space surrounding the synovial lining cells is rich in HA and proteoglycans. The type B synovial fibroblasts are the major source of HA while the type A cells are specialized macrophages.

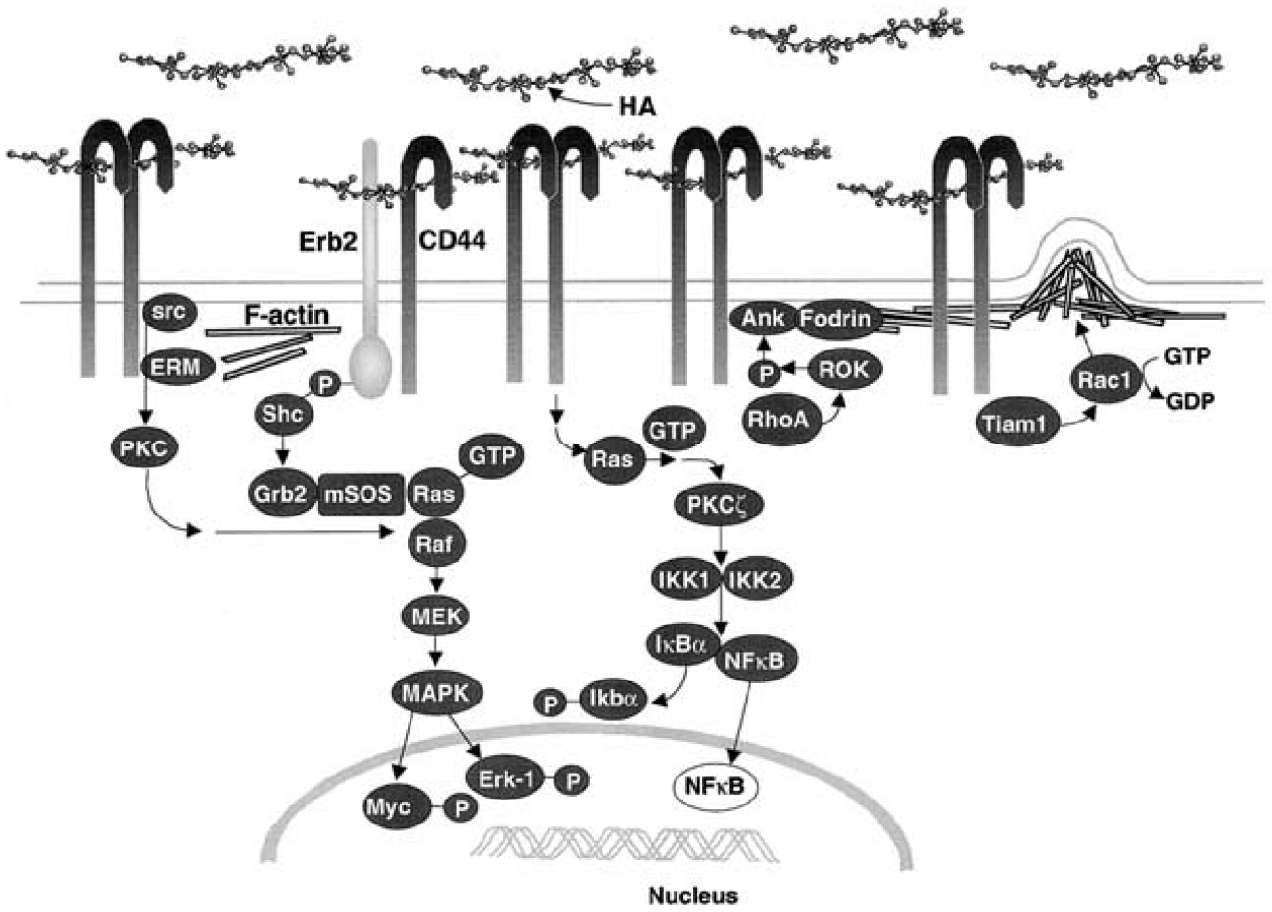

Fig 2. Diagrammatic representation of the CD44 cell surface receptors showing their possible intracellular signaling pathways, which can be activated by HA. The 4 signaling cascades involving CD44 have been identified. Pathway (A) requires activation of the src-related tyrosine kinases, (B) heterodimerization of CD44 — erb B2 may activate a MAP kinase (MAPK) cascade, (C) the nuclear transcription factor $\kappa\beta$ (NF-$\kappa\beta$) may be activated through HA interaction with CD44 and a protein kinase C (PKCζ) dependent cascade, and (D) activation of GTPases by HA-CD44 interaction can lead to reorganization of the actin cytoskeleton. Modified from Lee and Spicer (71).

Effects of Different Molecular Weight Hyaluronan Products on the Expression of Urokinase Plasminogen Activator and Inhibitor and Gelatinases during the Early Stage of Osteoarthritis

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J Orthop Res 26:475–484, 2008

Hsieh YS, et al. *J Orthopaed Res* 2008;26:475-84.

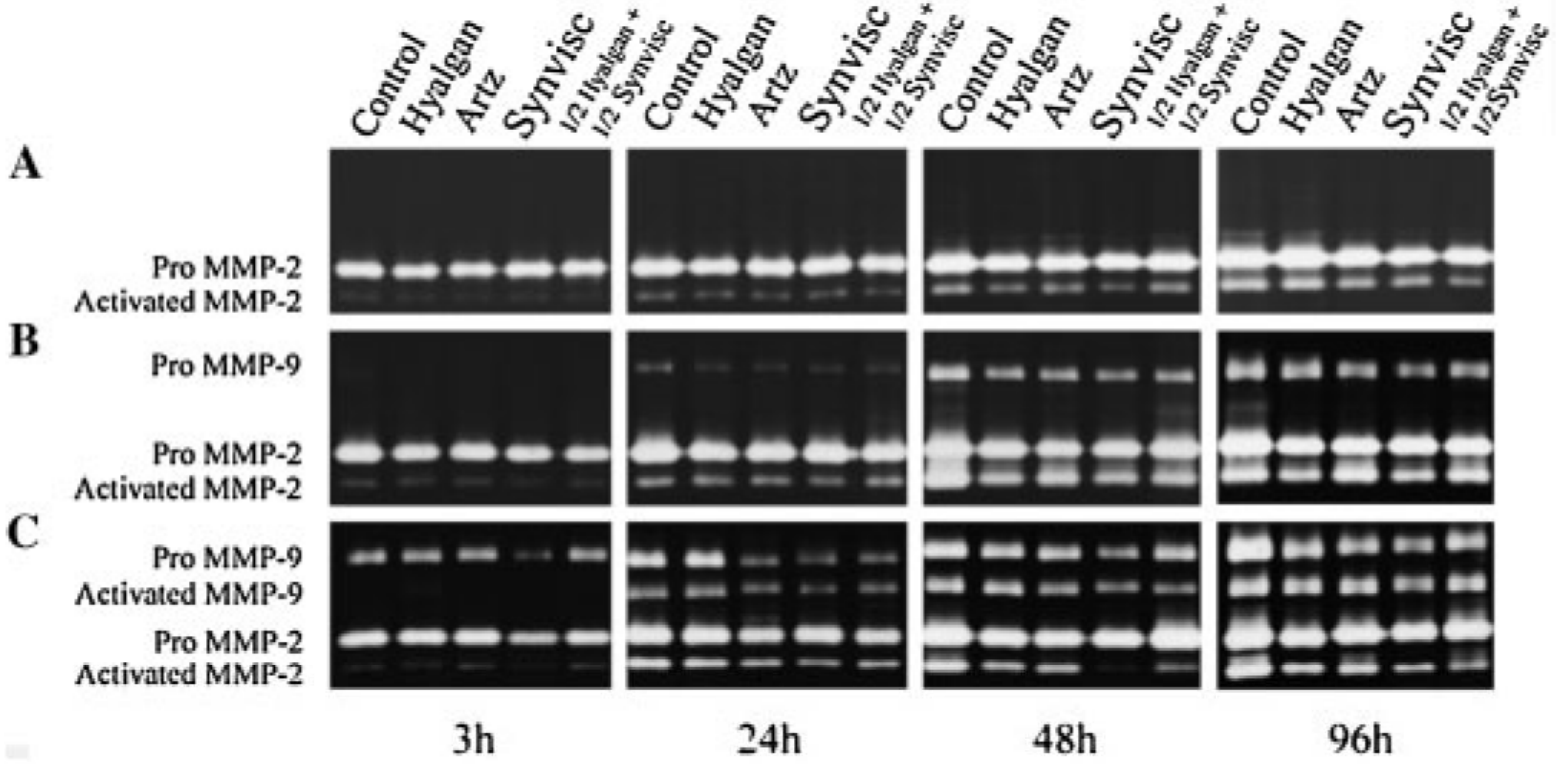

Figure 1. MMP-2 and MMP-9 levels in conditioned media from (A) chondral, (B) meniscal, and (C) synovial cultures co-treated with or without different MW HA products and HA of $\frac{1}{2}$ Hyalgan + $\frac{1}{2}$ Synvisc at 3, 24, 48, and 96 h were assayed by gelatin zymography.

Hsieh YS, et al. *J Orthopaed Res* 2008;26:475-84.

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Naproxen, meloxicam and methylprednisolone inhibit urokinase plasminogen activator and inhibitor and gelatinases expression during the early stage of osteoarthritis

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Chu SC, et al. *Clin Chim Acta* 2008;387:90-6.

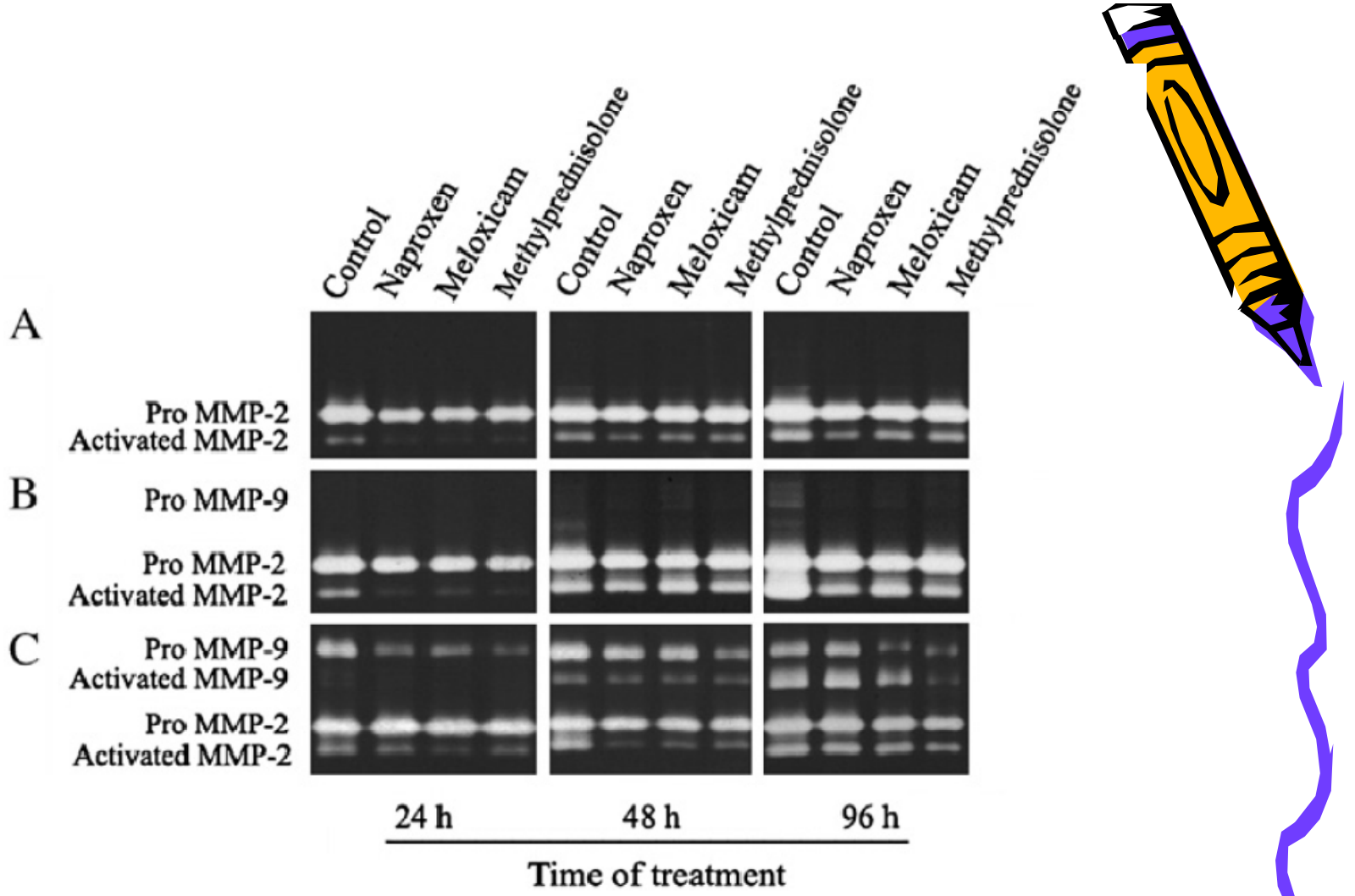

Fig. 1. MMP-2 and MMP-9 levels in conditioned media from (A) chondral, (B) meniscal, and (C) synovial cultures co-treated with or without naproxen, meloxicam and methylprednisolone at 24, 48 and 96 h were assayed by gelatin zymography.

Chu SC, et al. *Clin Chim Acta* 2008;387:90-6.

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CLINICAL BIOCHEMISTRY

Effects of nonsteroidal anti-inflammatory drugs on the expression of urokinase plasminogen activator and inhibitor and gelatinases in the early osteoarthritic knee of humans

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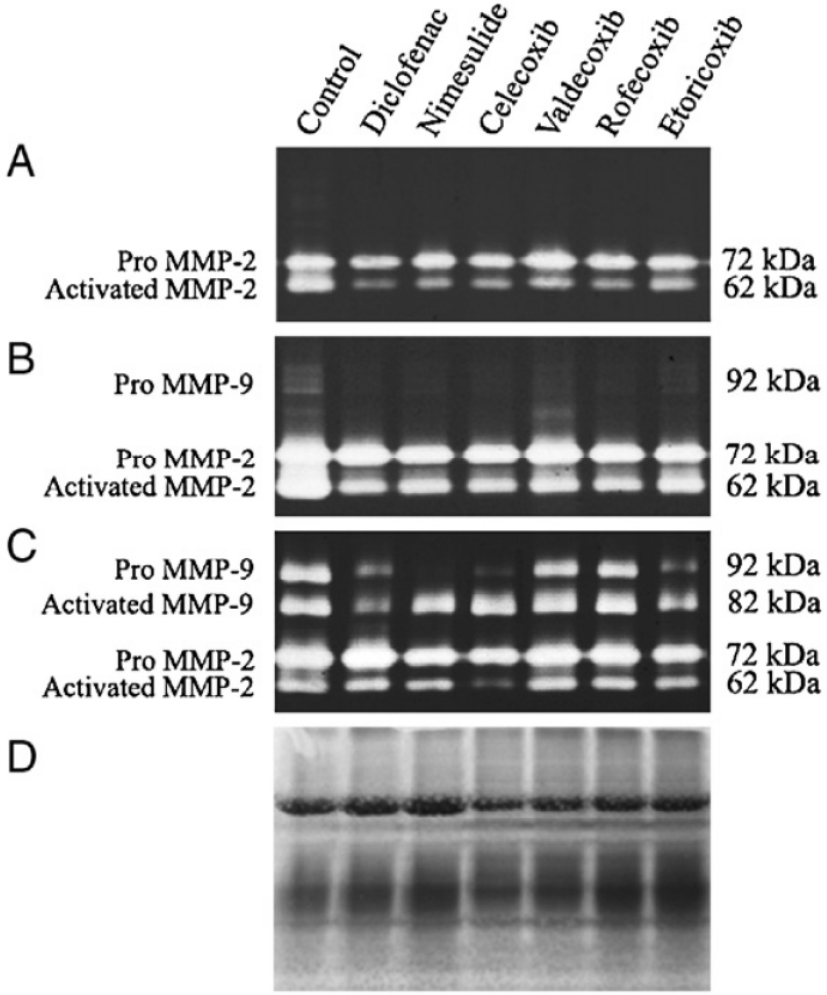


Fig. 2. Levels of MMP-2 and MMP-9 in conditioned media from (A) chondral, (B) meniscal and (C) synovial cultures co-treated with or without different NSAIDs at 48 h were assayed by gelatin zymography. (D) A loading control corresponded to the above media of synovial cultures was assayed by silver staining to ensure that each lane contains the same amount of protein.

Yang SF, et al. *Clin Biochem* 2008;41:109-16.


近幾年之研究內容與主要研究成果
1. 惡性腫瘤有關的基礎研究
2. 結合基礎和臨床，膝關節炎（退化）有關
3. 臨床的文章
Take Home Messages

臨床的16篇文章（13篇[1-13]為SCI）（單一或通訊作者）

1. Chou CW, Lu KH*, Lee HS, Lin RC, Lue KH. Synvisc has better pain-relief and cost effectiveness than Artz in treating early osteoarthritic knees. *J Formos Med Assoc* 2009; (in press) (SCI)
2. Lin RC, Lu KH*, Lue KH. Adjuvant arthroscopy for ankle tuberculosis. *Foot Ankle Int* 2009;30:74-9.
3. Liu YC, Lue KH, Lu KH*. Conservative treatment for a symptomatic solitary ganglion cyst of the anterior meniscus invading into the infrapatellar fat pad. *Knee Surg Sports Traumatol Arthrosc* 2007;15:220-4.
4. Lu KH*.Arthroscopic meniscal repair and needle aspiration for meniscal tear with meniscal cyst. *Arthroscopy* 2006;22:1367.e1-4.
5. Li TJ, Lue KH, Lin ZI, Lu KH*. Arthroscopic treatment for gouty tophi mimicking an intra-articular synovial tumor of the knee. *Arthroscopy* 2006;22:910.e1-3.
6. Lin RC, Lue KH, Lin ZI, Lu KH*. Primary synovial chondromatosis mimicking medial meniscal tear in a young man. *Arthroscopy* 2006;22:803.e1-3.
7. Hsu MC, Lue KH, Lin ZI, Lu KH*. Stress fracture at the junction of the middle and distal third of the ulnar diaphysis in a spinner bowler: a case report and a review of the literature. *Knee Surg Sports Traumatol Arthrosc* 2005;13:499-504.
8. Lu KH*. Subcutaneous pigmented villonodular synovitis caused by portal contamination during knee arthroscopy and open synovectomy. *Arthroscopy* 2004;20:e9-e13.
9. Lu KH*. Arthroscopic excision of juxta-articular giant-cell tumor arising from the patellar tendon sheath. *Arthroscopy* 2004;20:e35-e38.
10. Lu KH*. Arthroscopically assisted replacement of the dynamic hip screw for unrecognized joint penetration of lag screw through a new portal. *Arthroscopy* 2004;20:201-205.
11. Lu KH*. Unusual solitary ganglion cysts of the anterior segment of the lateral meniscus. *Arthroscopy* 2003;19:E16.
12. Lu KH*. Unusual solid ganglia of the anterior cruciate ligament mimicking lateral meniscal tears. *Arthroscopy* 2003;19:E14.
13. Lu KH*. An unusual case of meniscal hematoma mimicking a medial meniscal cyst. *Arthroscopy* 2002;18:E22.
14. Ng HN, Hsiao YM, Lu KH*. Cyclops lesions unusually caused by complete rupture of the anterior or posterior cruciate ligament without reconstruction. *J Orthop Surg Taiwan* 2009;26:22-6.
15. Wu CL, Lu KH*. Surgical treatment for fixed equinovarus in patients who recover from a prolonged vegetative state: A report of two cases. *J Orthop Surg Taiwan* 2008;25:189-93.
16. Liu YC, Hsu MC, Lin ZI, Lu KH*. Unusual and complicated areas of juxta-articular osteoid osteoma—two cases report. *J Orthop Surg Taiwan* 2006;23:51-6.

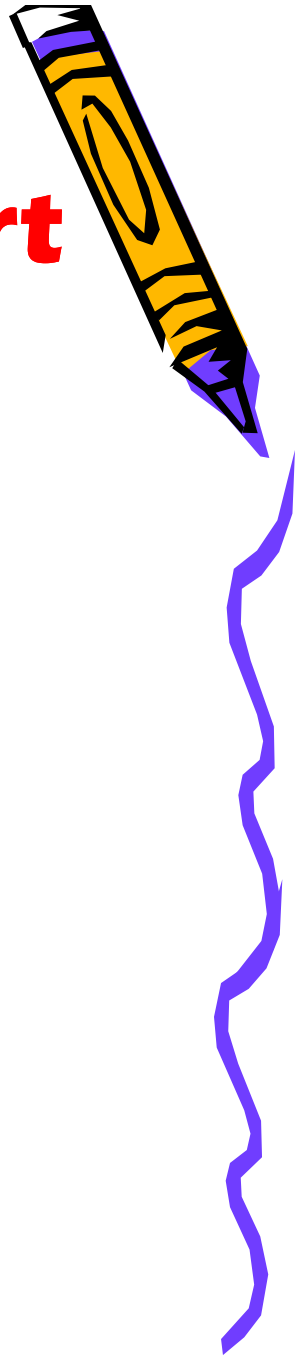
個案報告Case Report

1. 獨一無二的個案，或過去尚未被討論過的症狀或疾病
2. 從未被探討過的病因
3. 過去未曾嘗試過或預期的治療方法，或未曾發現的藥物副作用等
4. 深具教育意義
5. 近來學界的趨勢是越來越龐大的統計樣本
6. 「個案報告」已經供過於求
7. 必須慎選願意採用「個案報告」的期刊
8. 找出一個具有顯著臨床（教育）意義的主旨message，言之有物（最好是新發表）
9. 不是稀少的個案rare case，特別是地區性的疾病 local disease

Case Report 的摘要

1. 所研究病例的一般相關特性
   - 如果可能的話，用一個句子來陳述
2. 所研究病例的問題特性和問題解答
   - 簡述研究對象、問題、處理方法和結果
3. 問題的重要性及其所延伸的進一步研究方向和理論
   - 可能的話，用一至二個句子來陳述

Format for the Case Report



- Introduction
- Case description
- Discussion (literature review)
- Conclusion
- References


近幾年之研究內容與主要研究成果
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2. 結合基礎和臨床，膝關節炎（退化）有關
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有一個研究：「一場演講……

- 只聽到了所說的一半
  - 聽進了所聽到的一半
    - ✓了解了所聽進的一半
      - ➢相信了所了解的一半
        - » 記得了所相信的一半

$$\left(\frac{1}{2}\right)^5$$

聽一小時，記得內容不到兩分鐘

Take Home Messages

1. *A naturalist's life would be a happy one if he had only to observe and never to write.* 如果僅只需要觀察而不必寫作，那麼自然科學家的生活將是何等快樂。 — Charles Darwin
2. *Without publication, science is dead.* 沒有著作發表，就沒有科學。— Gerard Piel
3. *Writing is easy. All you do is stare a blank sheet of paper until drops of blood form on your forehead.* 寫作是容易的。你所要做的就是凝視著一張空白紙，直到前額形成血滴。 — Gene Fowler
4. *A bad beginning makes a bad ending.* 不善始者不善終。 — Euripides
5. *The fool collects facts; the wise man selects them.* 愚蠢的人收集諸事，聰明的人挑選它們。— John Wesley Powell
6. *The great tragedy of science—the slaying of a beautiful hypothesis by an ugly fact.* 科學的最大悲劇就是一個完美的假設被醜陋的事所扼殺了。 —T. H. Huxley
7. *I've always been in the right place and time. Of course, I steered myself there.* 我總是在對的地點和時間。當然，我是自我操控到那裡的。— Bob Hope


誌 謝
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林巧雯博士生、劉育銓碩士、‥‥‥‥‥‥
• 醫學研究所
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楊嘉欣博士生、‥‥‥‥‥‥


Thank You
for Your Attention
Q & A