Development of New Intra-articular Therapy for Osteoarthritis

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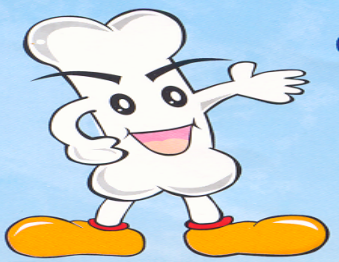
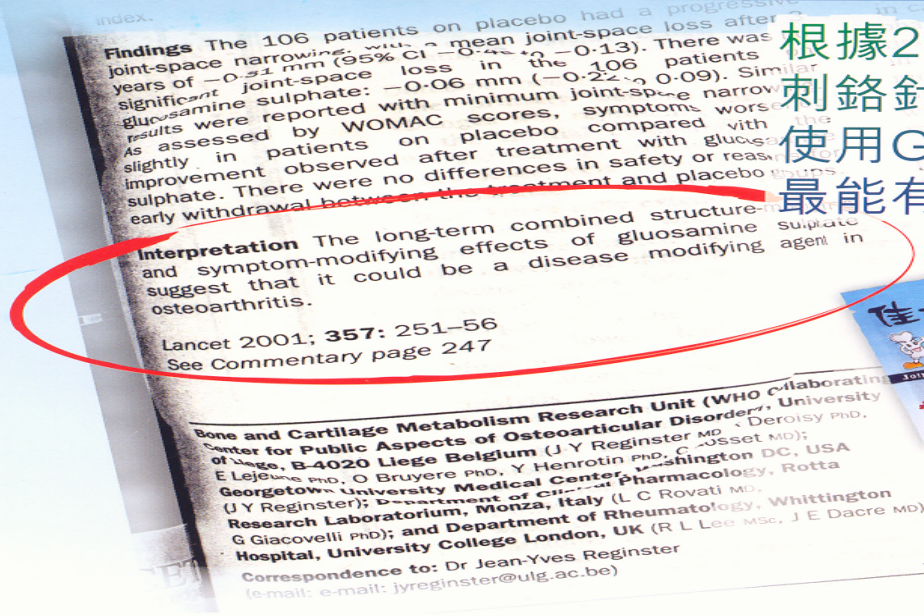
佳古立™ 自創沖泡式 舒適包

JointGood® Sachet





Findings The 106 patients on placebo had a progressive joint-space narrowing; with a mean joint-space loss after years of −0·31 mm (95% CI −0·49 to −0·13). There was significant joint-space loss in the 106 patients glucosamine sulphate: −0·06 mm (−0·22 to 0·09). Similar results were reported with minimum joint-space narrowing. As assessed by WOMAC scores, symptoms worsened slightly in patients on placebo compared with improvement observed after treatment with glucosamine sulphate. There were no differences in safety or reasons for early withdrawal between the treatment and placebo groups.

Interpretation The long-term combined structure- and symptom-modifying effects of glucosamine sulphate suggest that it could be a disease modifying agent in osteoarthritis.

Lancet 2001; **357:** 251–56
See Commentary page 247

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根據2001年元月份權威醫學雜誌
刺鉻針(Lancet)的報導，
使用Glucosamine 1500毫克每天一次，
最能有效緩解關節炎的發炎疼痛症狀...

適合對象

- 各種關節炎患者
- 骨質疏鬆症
- 骨折及骨外科手術之恢復治療

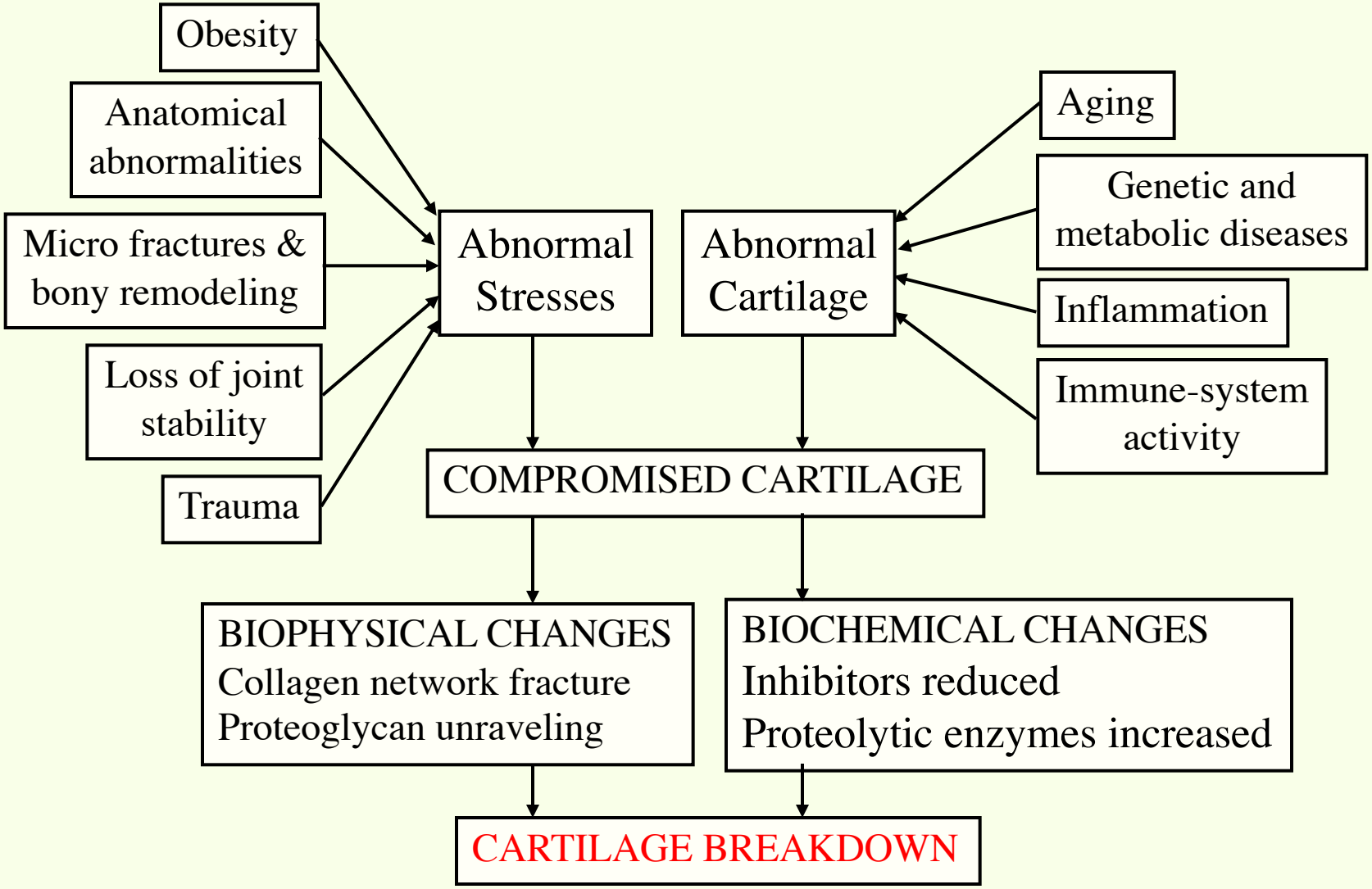
（每包）主成份	葡萄糖胺	1500毫克
	軟骨素	300毫克
	膠原蛋白	200毫克
	維他命C	100毫克
	薑黃素	200微毫克
服用方式	每日一包，以開水沖泡（80℃以下）飯後服用；一個療程三個月	
包裝	30包/盒	
貯存	室溫下保存	

經銷商
向天貿易有限公司
地址：台北市南京東路二段174號4樓
電話：02-2542-8220

製造廠
KUNTA PHARMACEUTICAL CO.,LTD
No.12, 2nd RD. TZE-LI, NAN TOU City, NAN TOU County

推薦者		日期		特惠價：NT$1280／盒

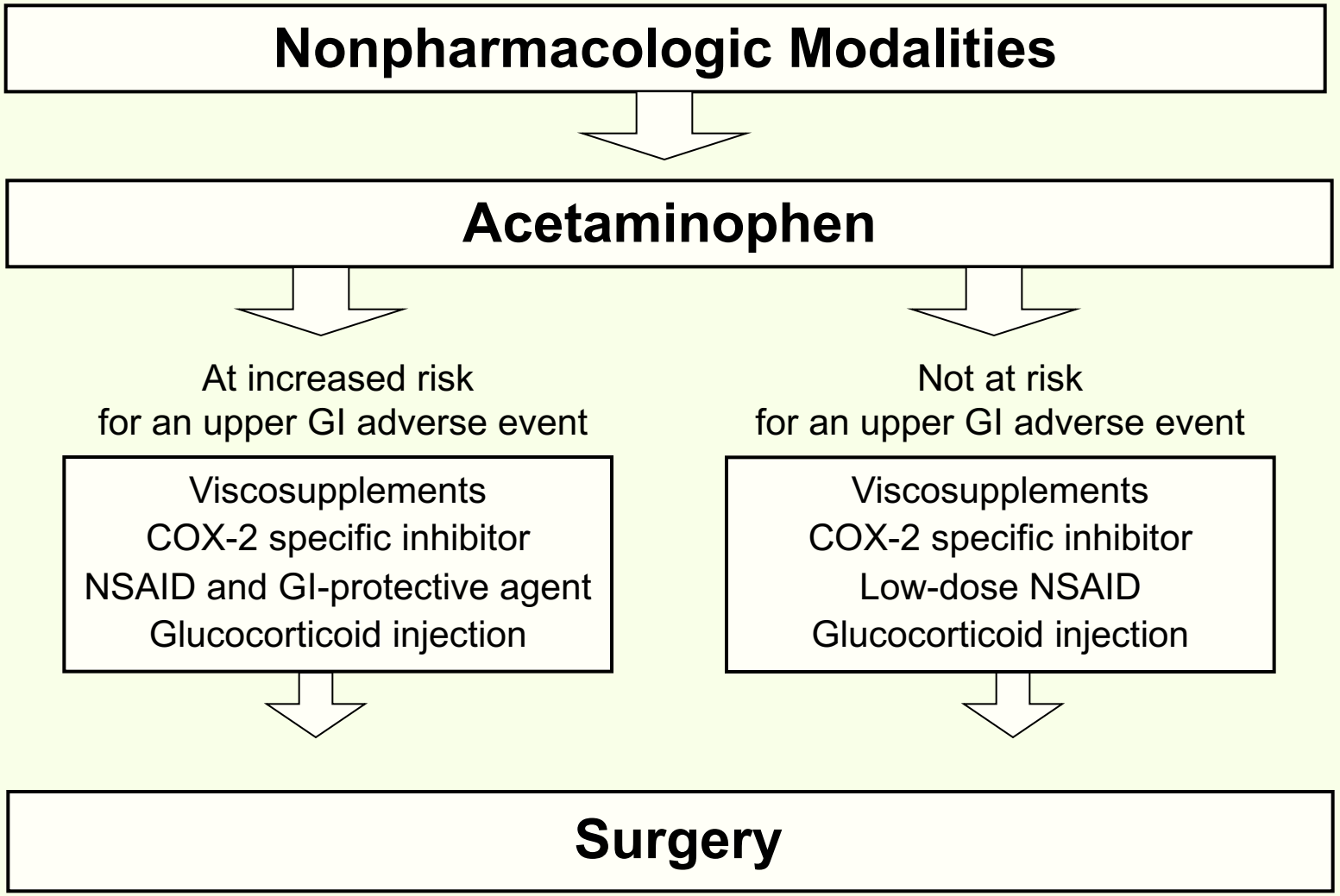
Factors Involved in Osteoarthritis



Osteoarthritis Treatment

- OA is often a locally manifest disease
- Local therapy for local disease
- Avoids systemic adverse events (COX II side effects)
- Lower doses of therapeutic agents achievable.

American College of Rheumatology 2000 Guidelines



Osteoarthritis Local Therapies

- Intra-articular steroids
- Hyaluronan agents
- Transdermal non-steroidal agents
- New agents?

Orthopedic Specialists of La.: Synvisc Experience Nov. 1, 1997 – Sept. 9, 2004

3524 Knees

10,572 Injections

Osteoarthritis Radiographic Grade

- OA Grade 1 1%
- OA Grade 2 7%
- OA Grade 3 13%
- OA Grade 4 79%

Gap Junctions and Osteoarthritis

- Journal of Physiology 1997
- Journal of Physiology 2001
- Clinical Orthopedics and Related Research 2004

Marino, Kolomytkin and Waddell

LSU Health Sciences Center

Shreveport, Louisiana

Electron Microscopy
Number of Gap Junctions

PATIENT No.	DIAGNOSIS	No. GAP JUNCTIONS per 100 CELLS	MEAN ± SD
1	Normal	1.43	
2	"	0.40	
3	"	1.11	
4	"	0.00	
5	"	0.62	0.71 ± 0.57
1	Osteoarthritis	3.72	
2	"	1.26	
3	"	3.61	
4	"	3.65	
5	"	7.52	
6	"	6.35	* 4.35 ± 2.24

* $P < 0.05$

Summary

- Background of work
- *In vitro* study
- Animal study
- Clinical study
- Future plans

Present Support

Genzyme Biosurgical (HA studies)
OSR
Department of Orthopaedic Surgery (LSU)
*Center for Excellence in Arthritis (LSU)

*Ended in 2004

Personnel

LSU (Marino)	OSL (Waddell)
Electrophysiologist (Ph.D.)	Administrator
Graduate Student	PA
2 Technicians	Nurse
Bioengineer (Ph.D.)	Research Assistant

Approach to Osteoarthritis

- Emphasis on synovium
- Importance of electrophysiology
- Focus on signal transduction

Experimental Approach

Hypothesis

Cell Electrical Changes → Function

Methodology

Electrophysiology & Enzyme Activity → Function

Molecular Biology → Composition

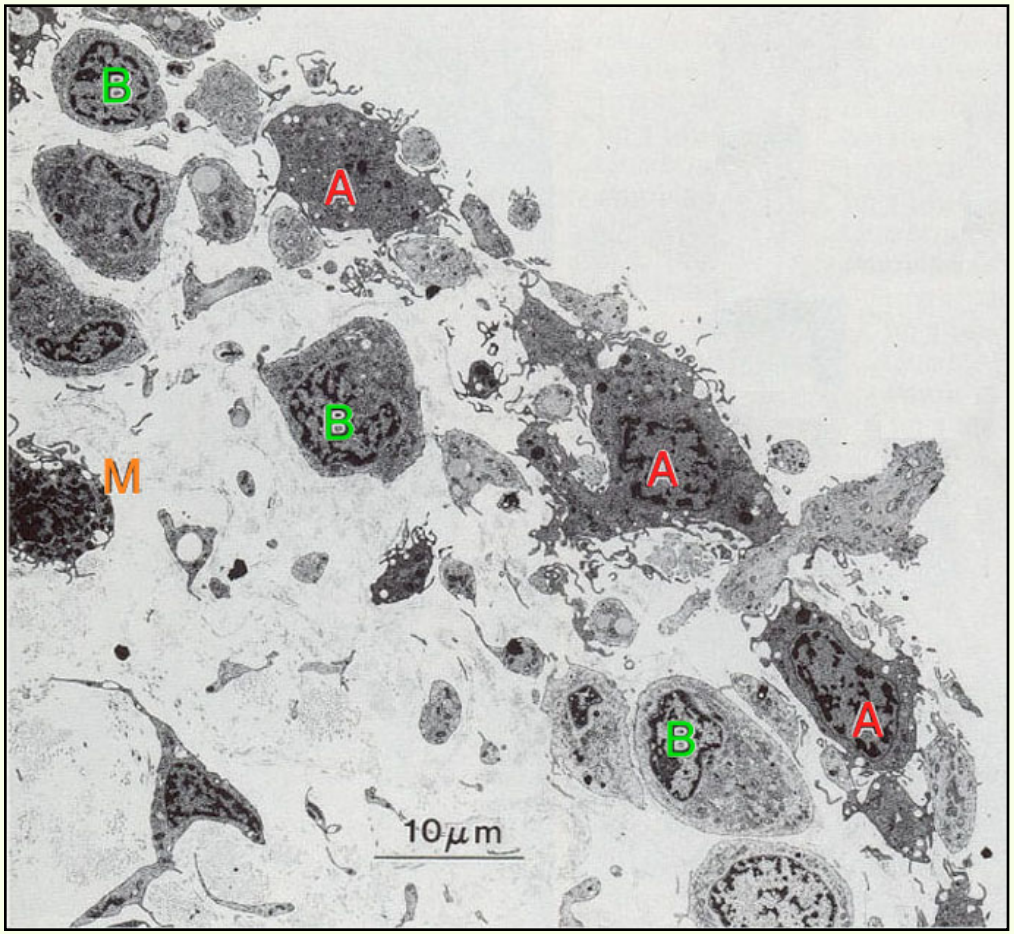
Microscopy → Structure

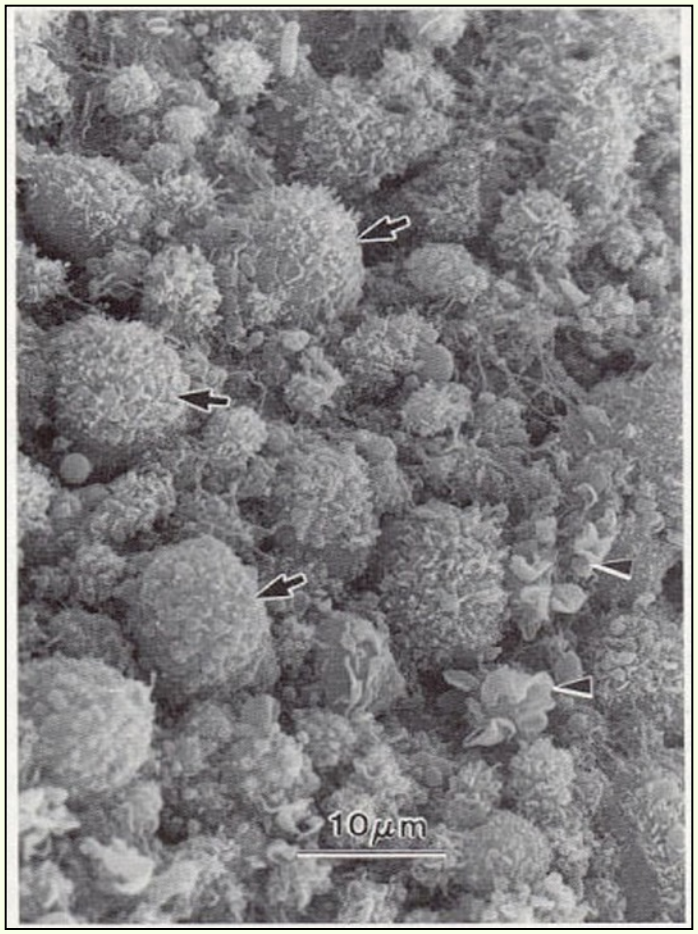
Objects of Study

HIG-82 Synovial Cells

Synovial Biopsies

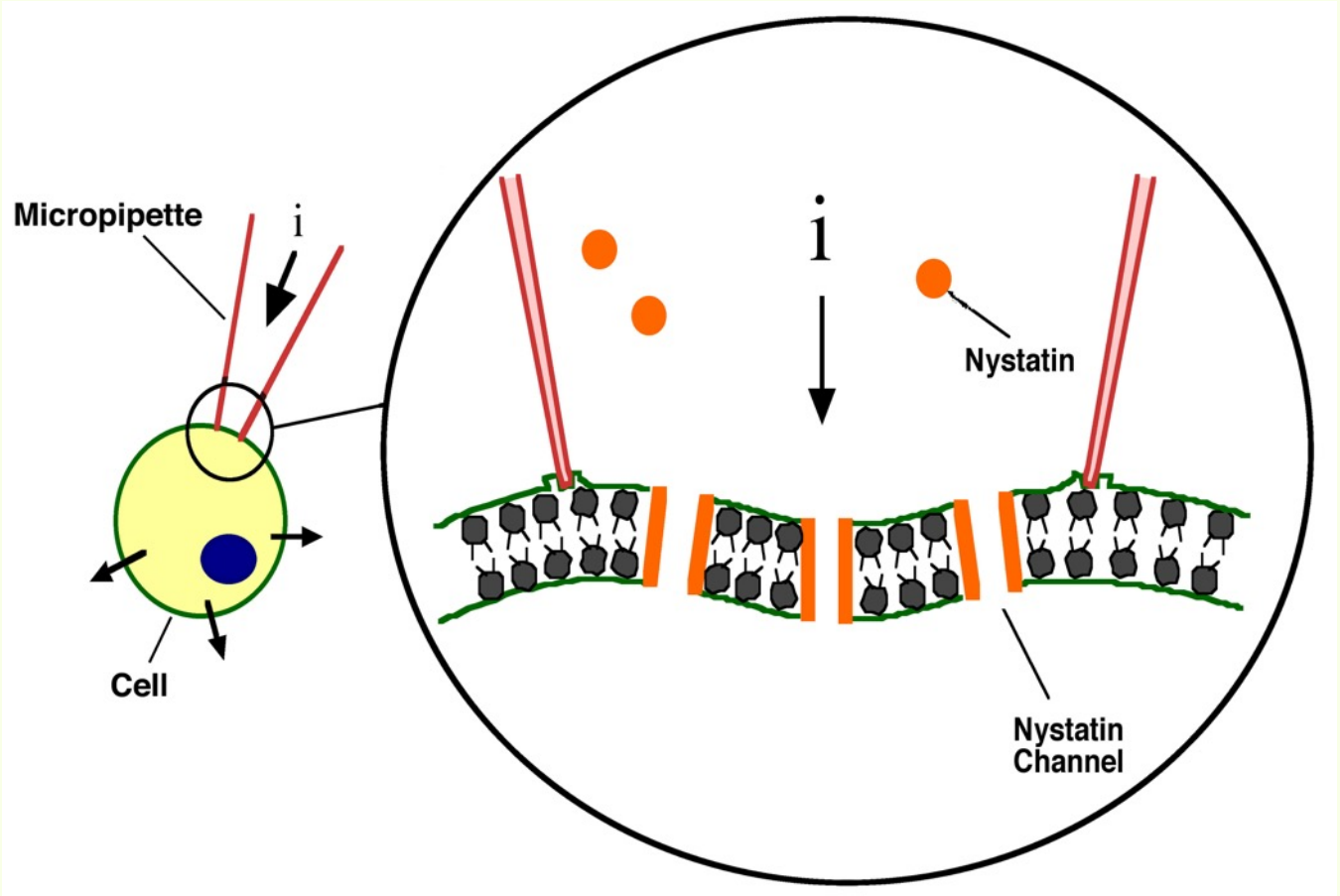
Importance of Synovium



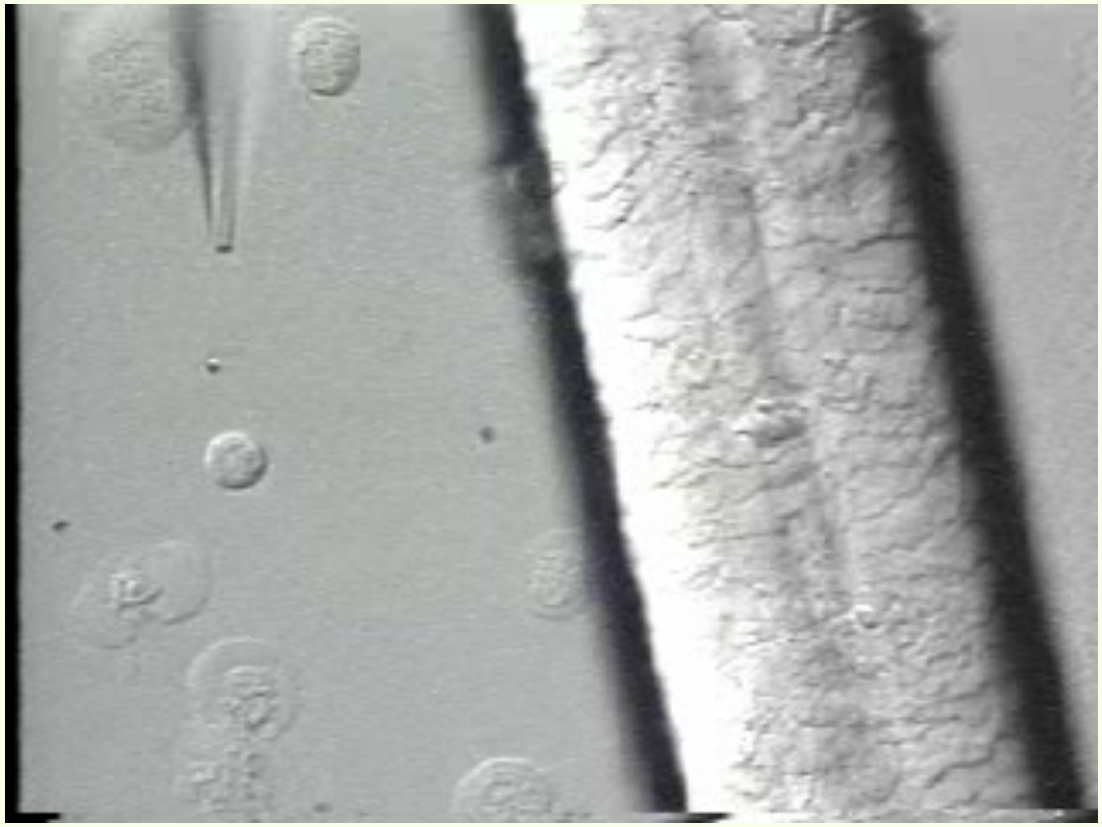


Type A: Macrophage Type B: Secretory M: Mast cell

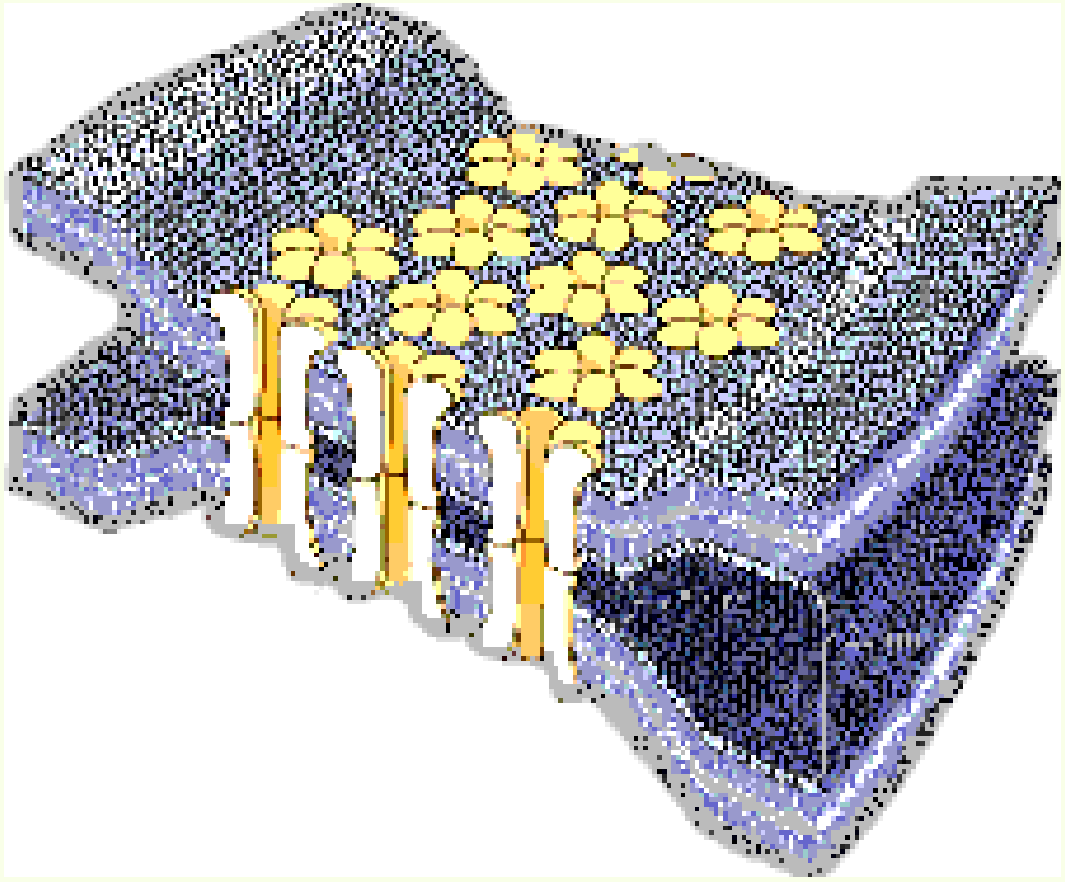
Electrophysiology Methods



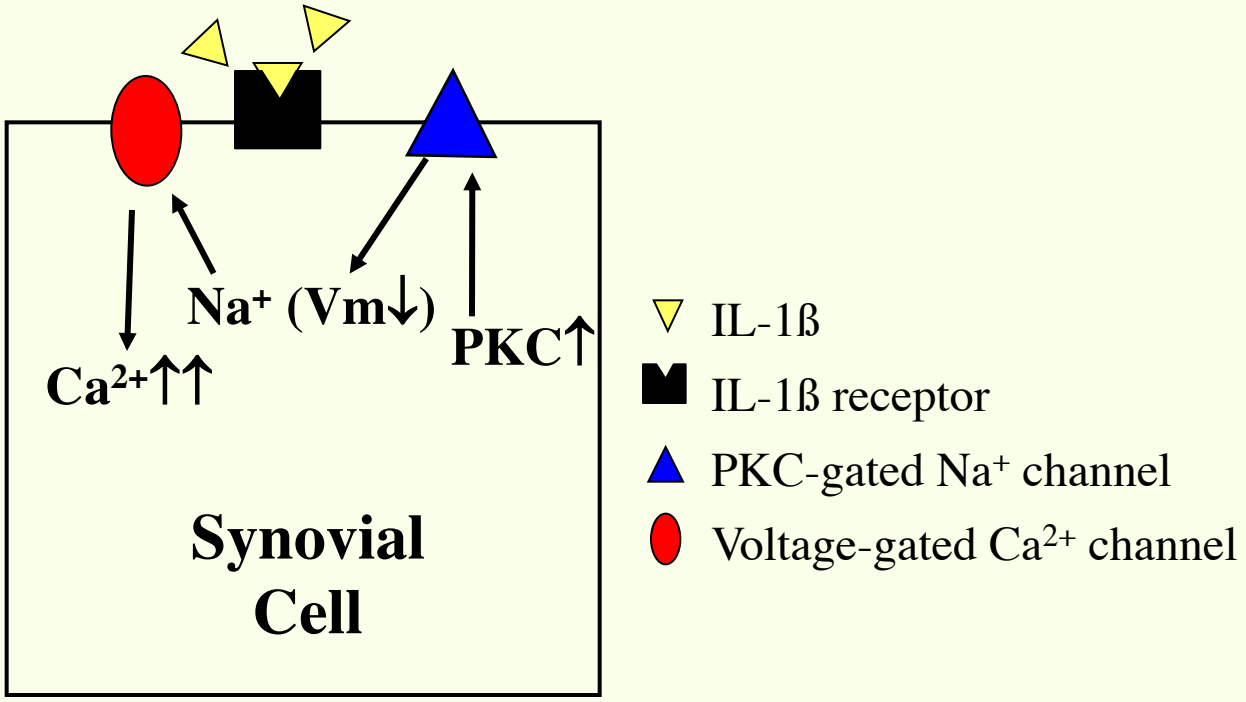
Nystatin Patch Clamp



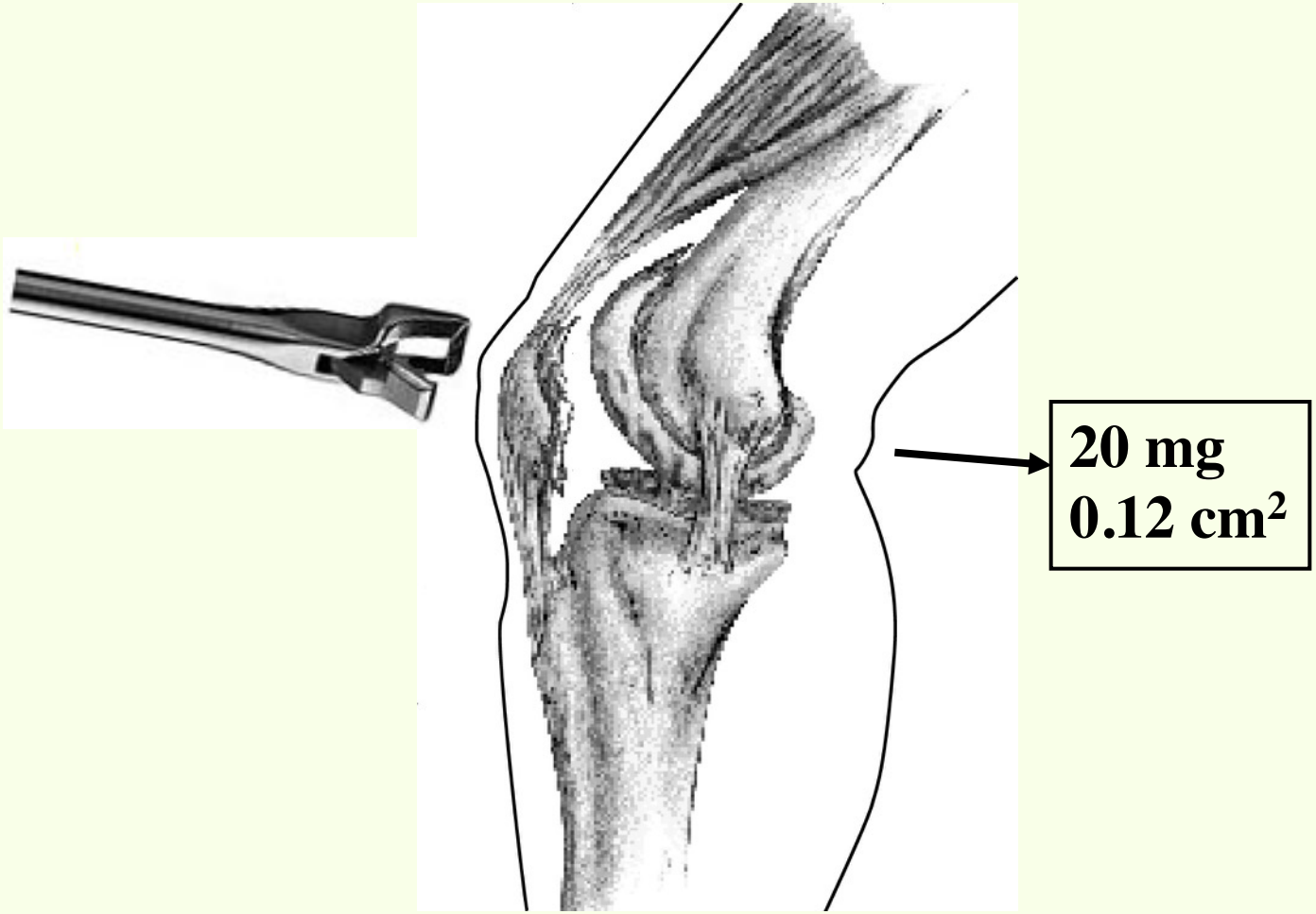
Important Discovery
Gap Junctions



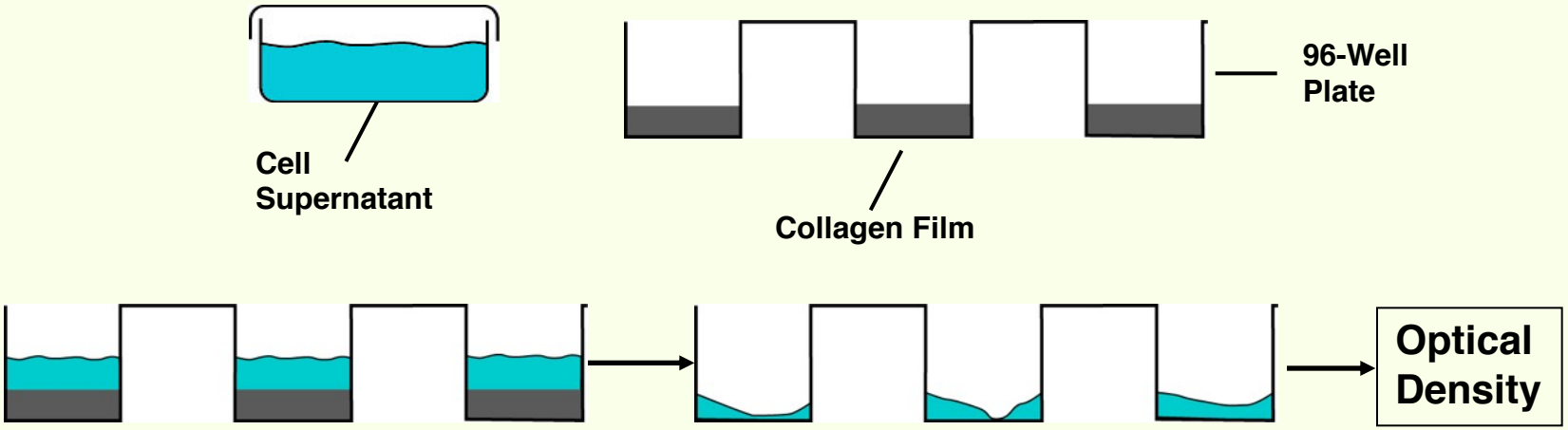
Important Discovery
Signal Transduction in Synovial Cells
Early Events (15 minutes)



Surgical Biopsy Procedure

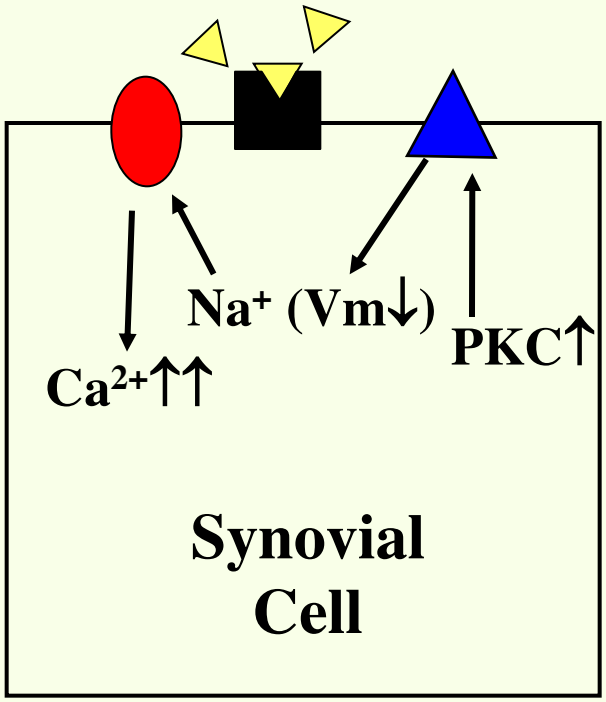


Metalloproteinase (MMP) Assay



Important Discovery
Signal Transduction in Synovial Cells

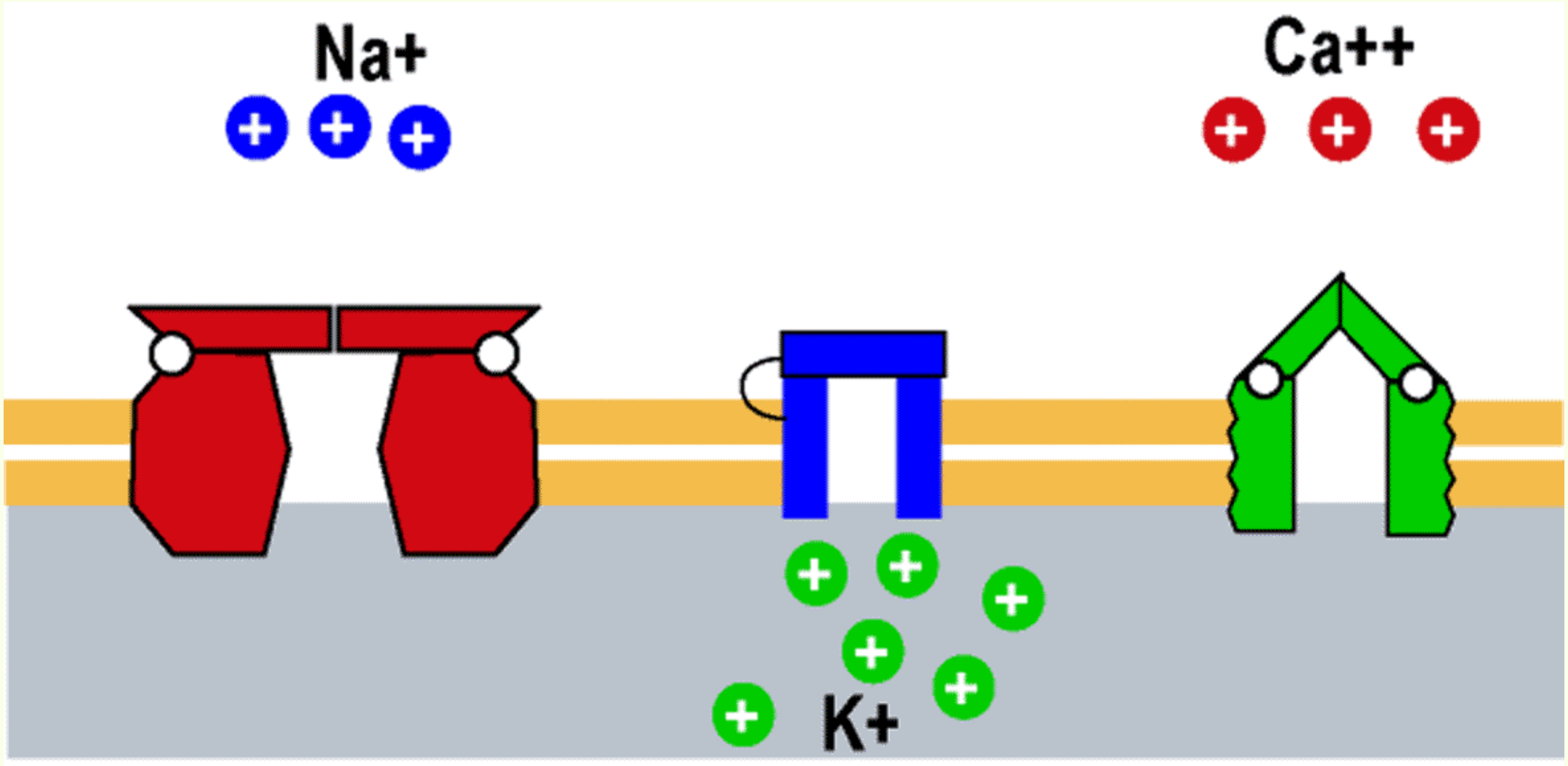
Early Events
(15 minutes)



IL-1ß
IL-1ß receptor
PKC-gated Na^+ channel
Voltage-gated Ca^{2+} channel

Late Events
(2-48 hrs)

MMPs → OA


Na+
Ca++
K+

Proposed Membrane-Channel Research

Basic Idea ⇨ Pathological changes in specific ion channels mediate progression of OA

Proposal ⇨

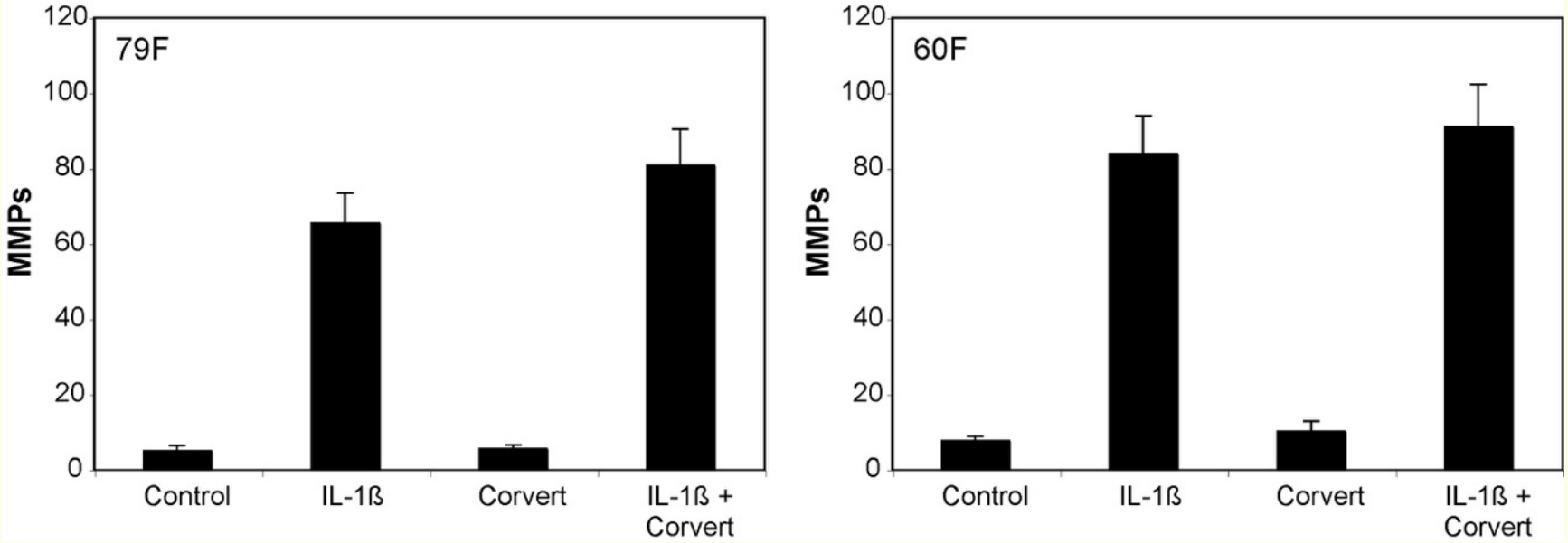
1) Identify the channels functionally by comparing OA and normal synovial cells

2) Design chemical agents to block the altered channels

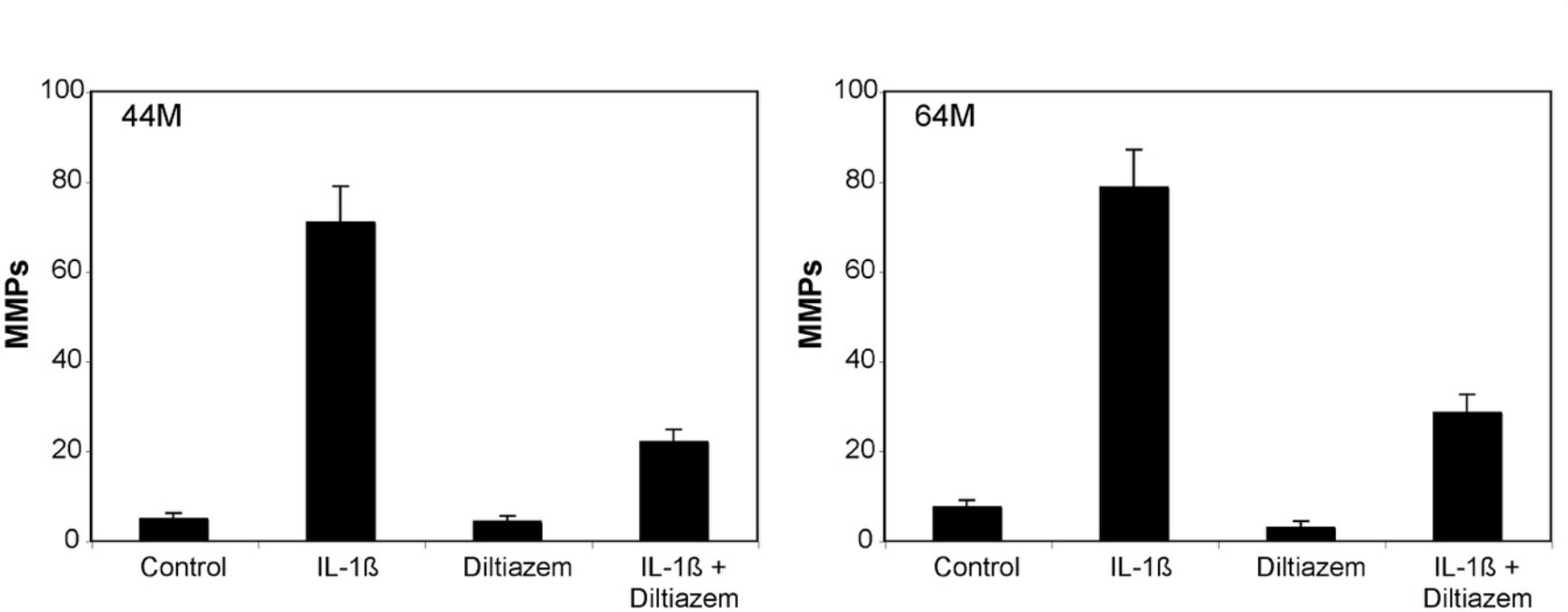
Dr. Waddell:

“What if we injected the blockers that are already on the market for heart problems.”

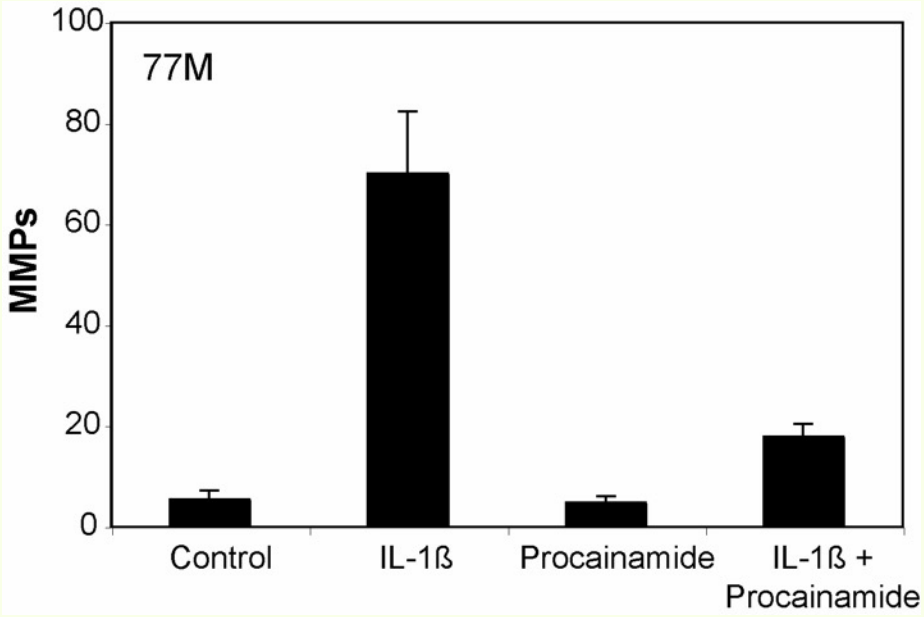
Effect of Potassium-Channel Blocker Corvert (13 μg/mL) on MMP Production



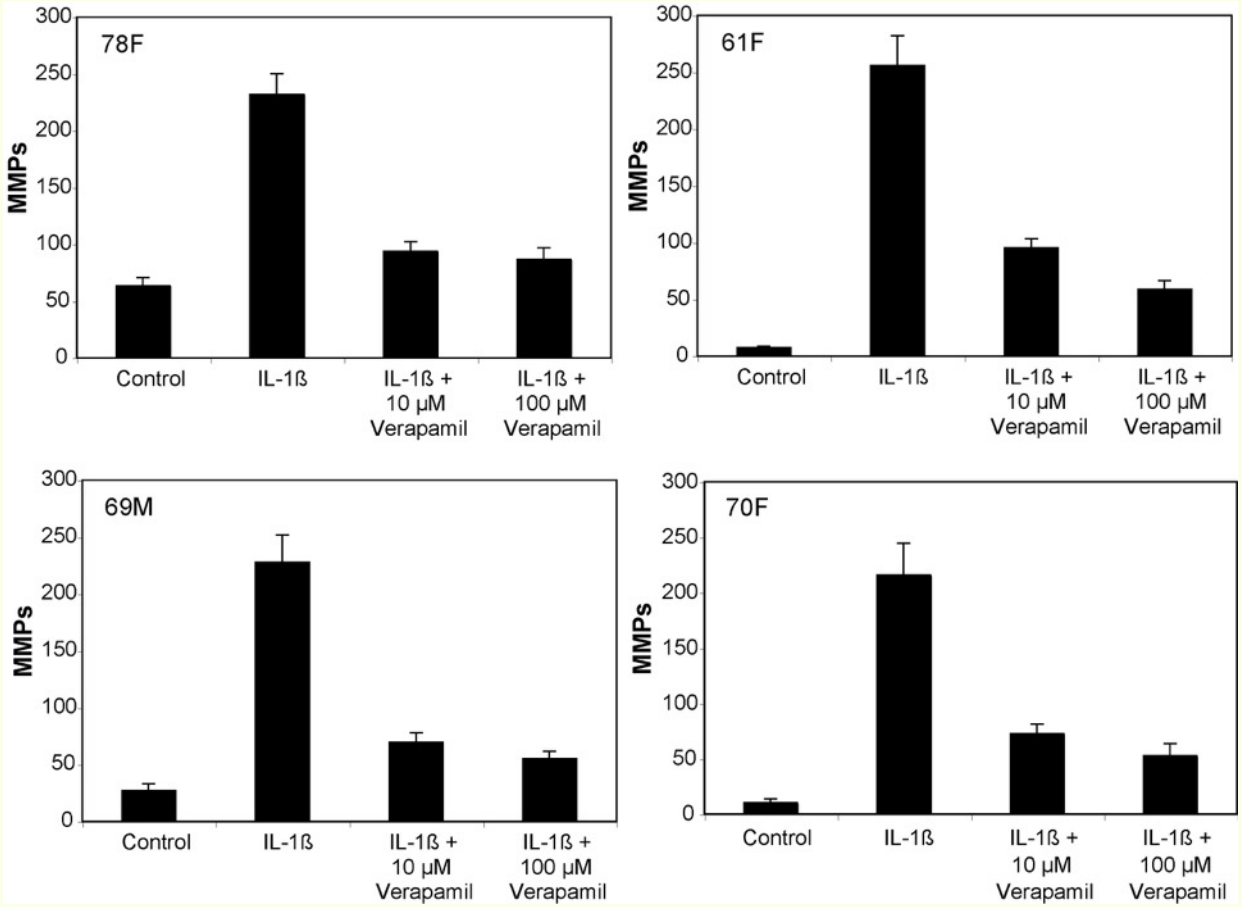
Effect of Calcium-Channel Blocker Diltiazem (3 μg/mL) on MMP Production



Effect of Sodium-Channel Blocker Procainamide (10 μg/mL) on MMP Production



Effect of Calcium-Channel Blocker Verapamil on MMP Production

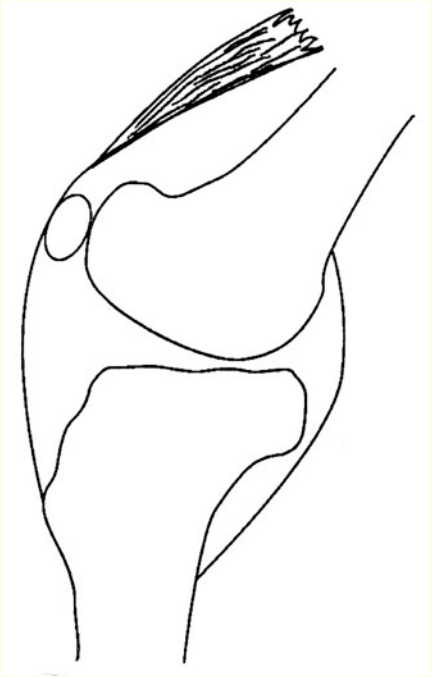


Mouse Verapamil Study

Animals:	BALB/c ♂, 6 months old
Dose:	0.4-2.5 μg/10 μL (≤100 μM)
Injection Site:	Knee (intra-articular)
Recovery Times:	4 hrs, 24 hrs, 4 days
Endpoint:	Inflammation

Zeuner, Arthritis Rheum. 46: 2219, 2002

Histological Evaluation



- Mid-saggital plane used for evaluation
- Inflammation scale 0-3
- Scoring by blinded observer (pathologist)

Mouse Study Results

	INFLAMMATION SCALE (Untreated)			
	0	**1**	**2**	**3**
	7	1	0	0

	INFLAMMATION SCALE (4 Hours)			
	0	**1**	**2**	**3**
Control	0	1	3	0
Verapamil	0	5	1	0

	INFLAMMATION SCALE (1 Day)			
	0	**1**	**2**	**3**
Control	1	0	3	0
Verapamil	3	2	0	1

	INFLAMMATION SCALE (4 Days)			
	0	**1**	**2**	**3**
Control	1	2	1	0
Verapamil	3	0	1	0

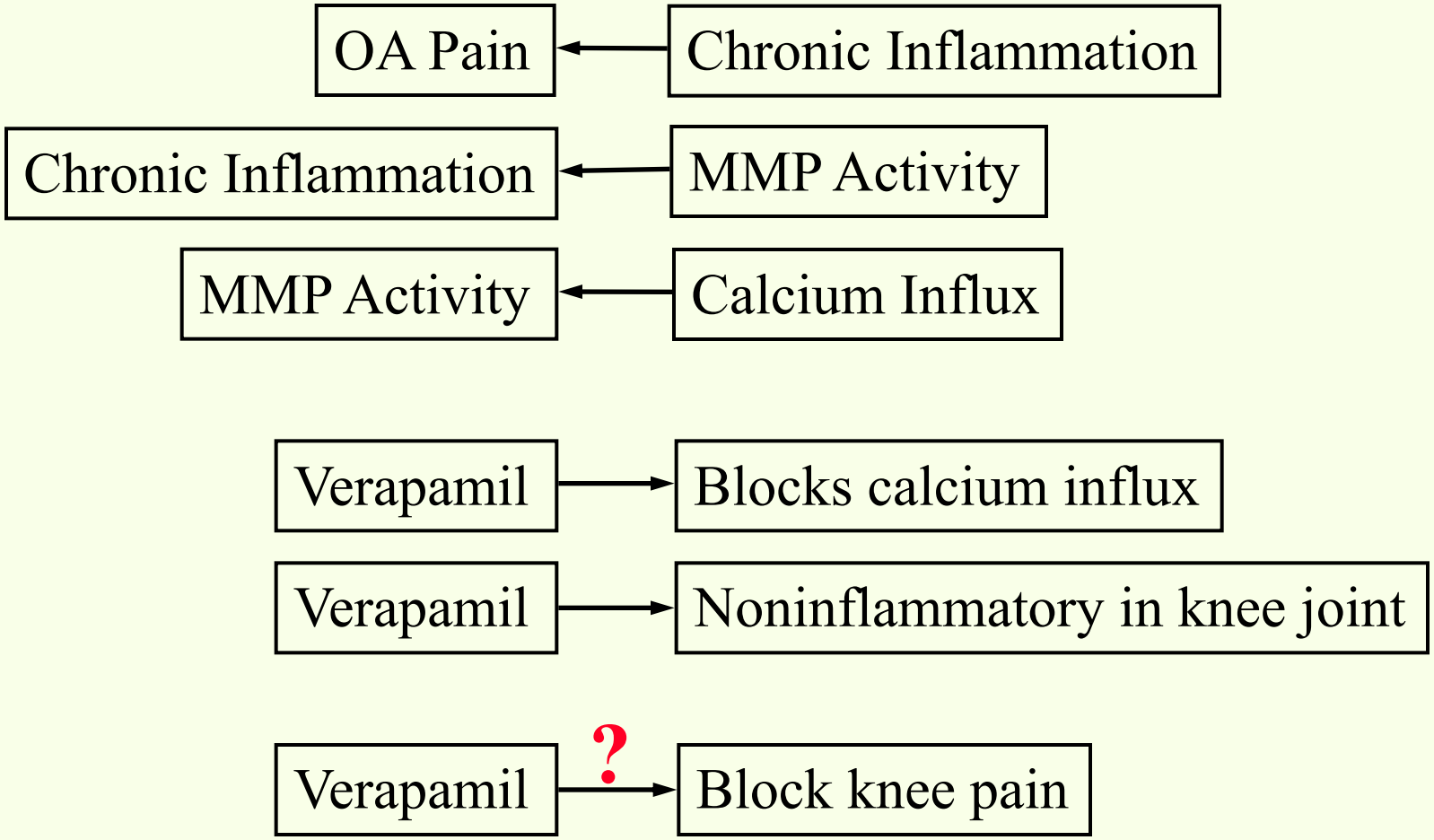
Untreated	
Control	0.25±0.5

4 Hours	
Control	1.75±0.5
Verapamil	1.25±0.5

1 Day	
Control	1. 5±1.0
Verapamil	1.0±1.41

4 Days	
Control	1.0±0.82
Verapamil	0.5±1.0

Summary

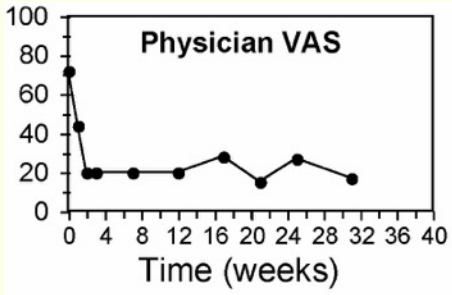

OA Pain
Chronic Inflammation
Chronic Inflammation
MMP Activity
MMP Activity
Calcium Influx
Verapamil
Blocks calcium influx
Verapamil
Noninflammatory in knee joint
Verapamil
?
Block knee pain

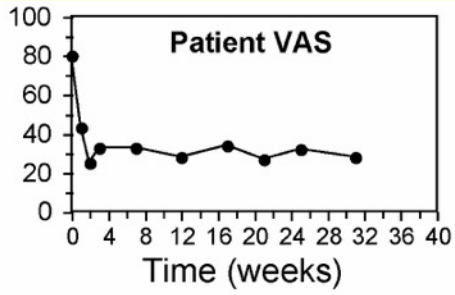
Open Study Evaluating Verapamil in Osteoarthritis of the Knee

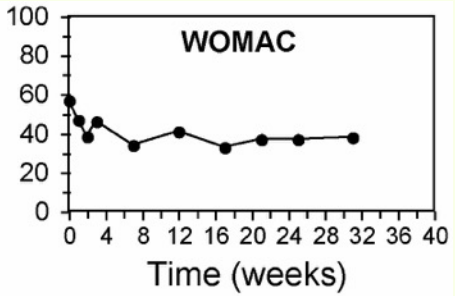
IRB	LSUHSC-S
Study Design	Open study (no contemporaneous control)
Principal Investigator	David Waddell, M.D.
Other Investigators	None
Study Location	OSL
Dose	0.2 mg & 0.5 mg
Inclusion Criteria	OA-IV
Study Hypothesis	Symptomatic treatment of OA pain
Study Endpoints	WOMAC Physician VAS Patient VAS
Duration of Study	6 months
Follow-up Schedule	1, 2, 3, 4, 5, 16, 20, 24 weeks

Verapamil Study No. 1 (0.2 mg)

Pt. No. 1
57F







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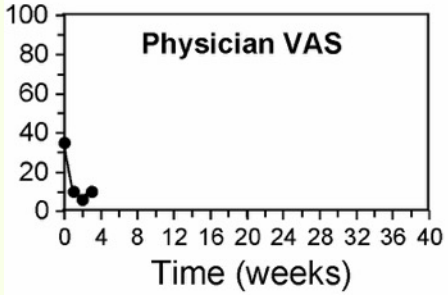
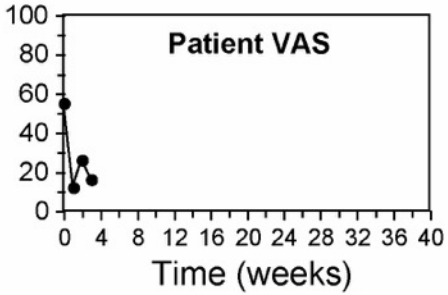
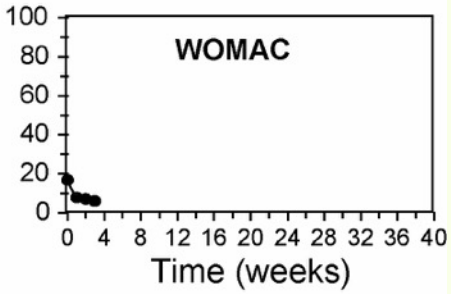
41M







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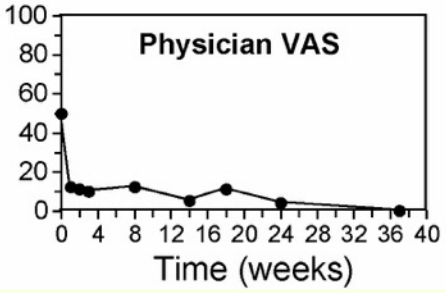
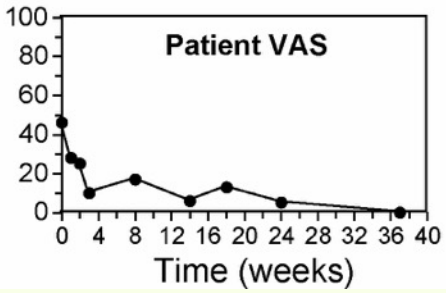
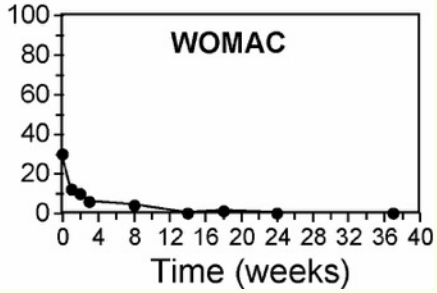
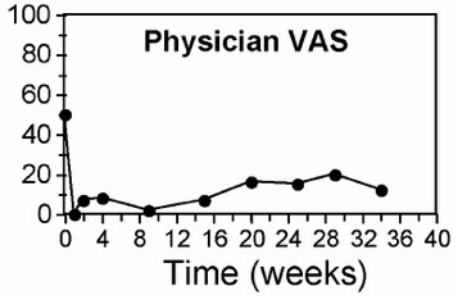


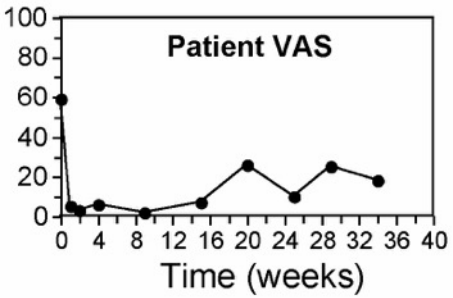


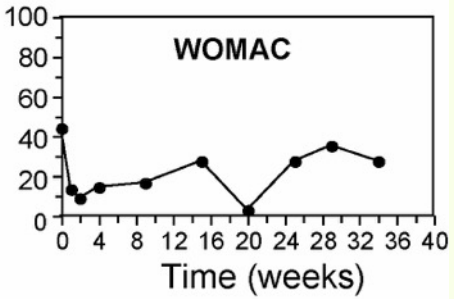


Verapamil Study No. 1 (0.2 mg)

Pt. No. 4
56F







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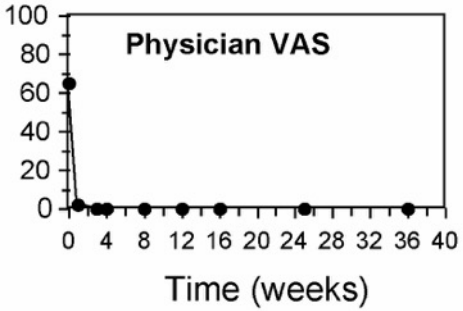

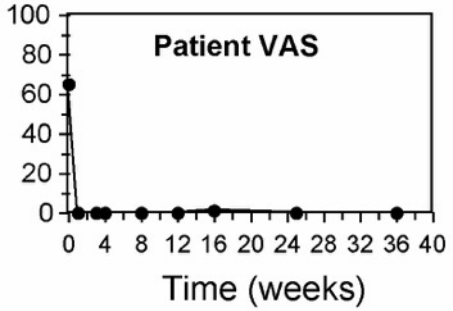

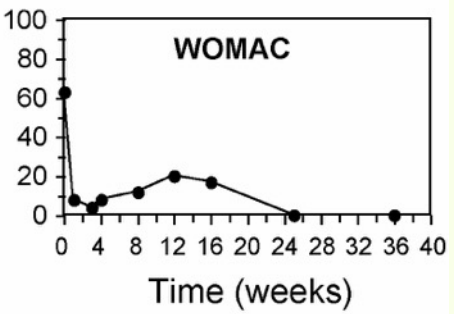

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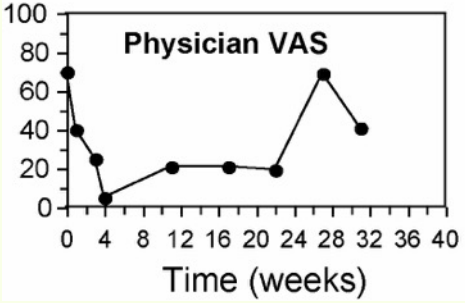
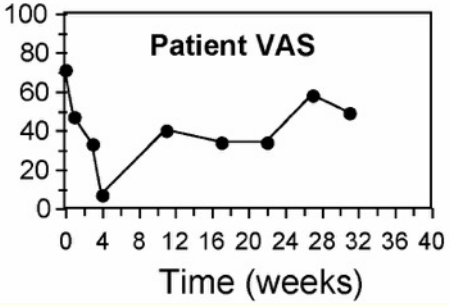
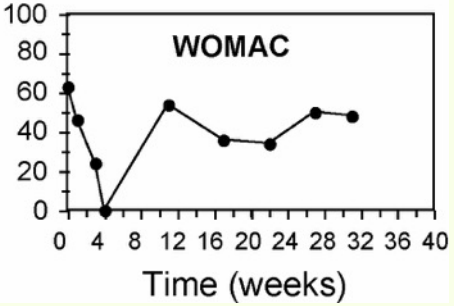
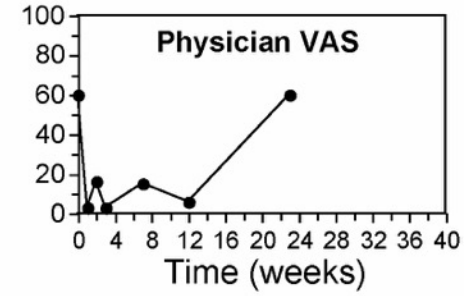


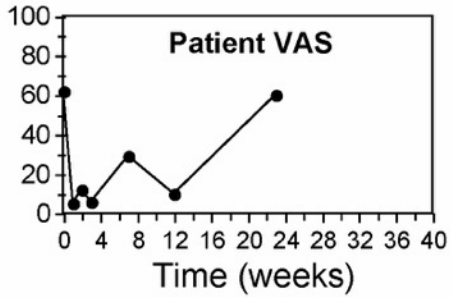


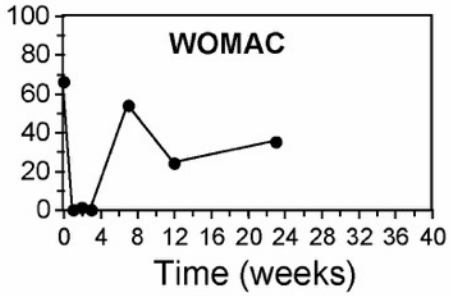


Verapamil Study No. 1 (0.2 mg)

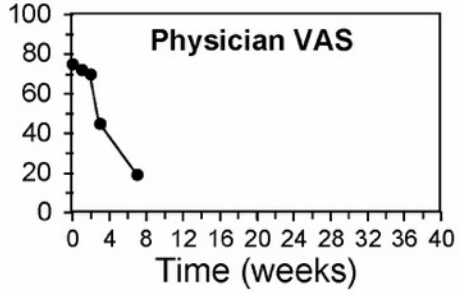
Pt. No. 7
51M

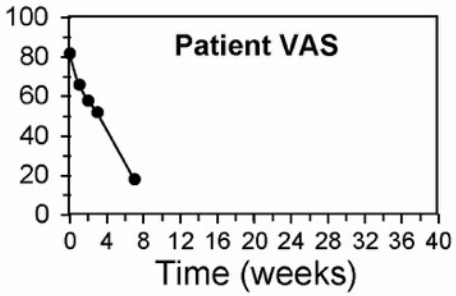


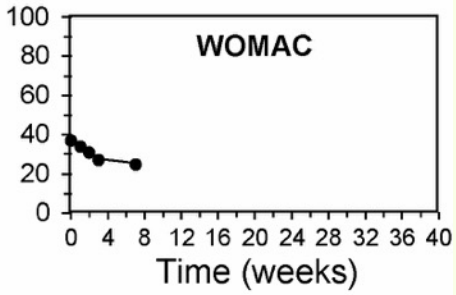




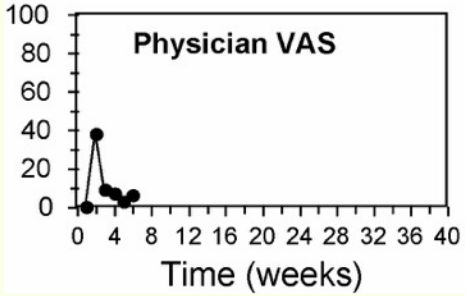
Pt. No. 8:
54M

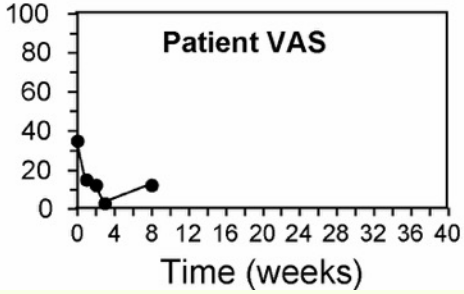


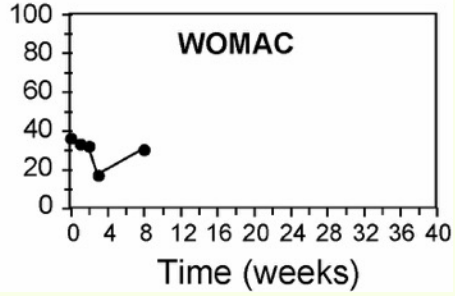




Pt. No. 9:
41F

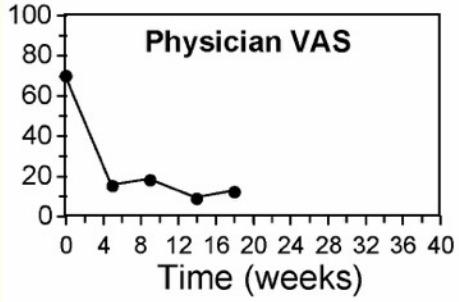


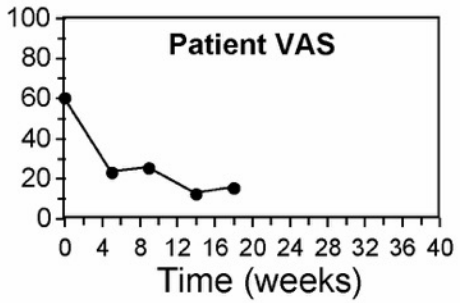


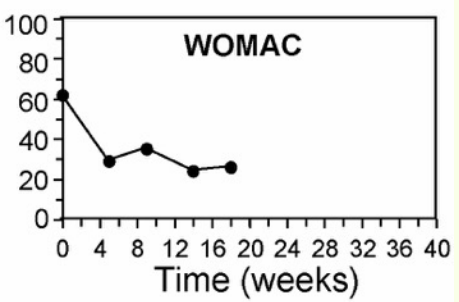


Verapamil Study No. 1 (0.2 mg)

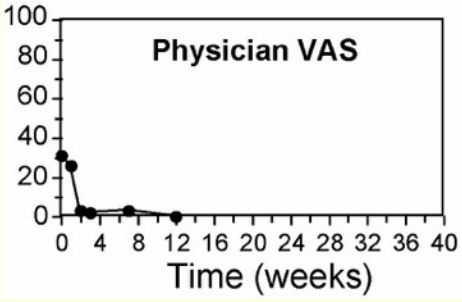
Pt. No. 10: 56F

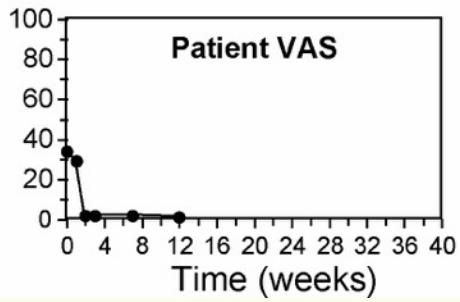


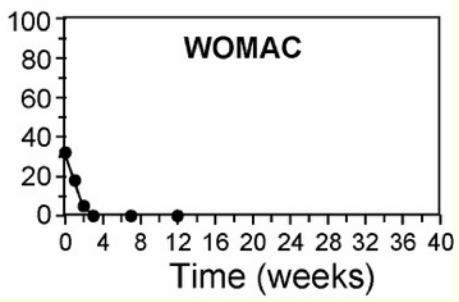




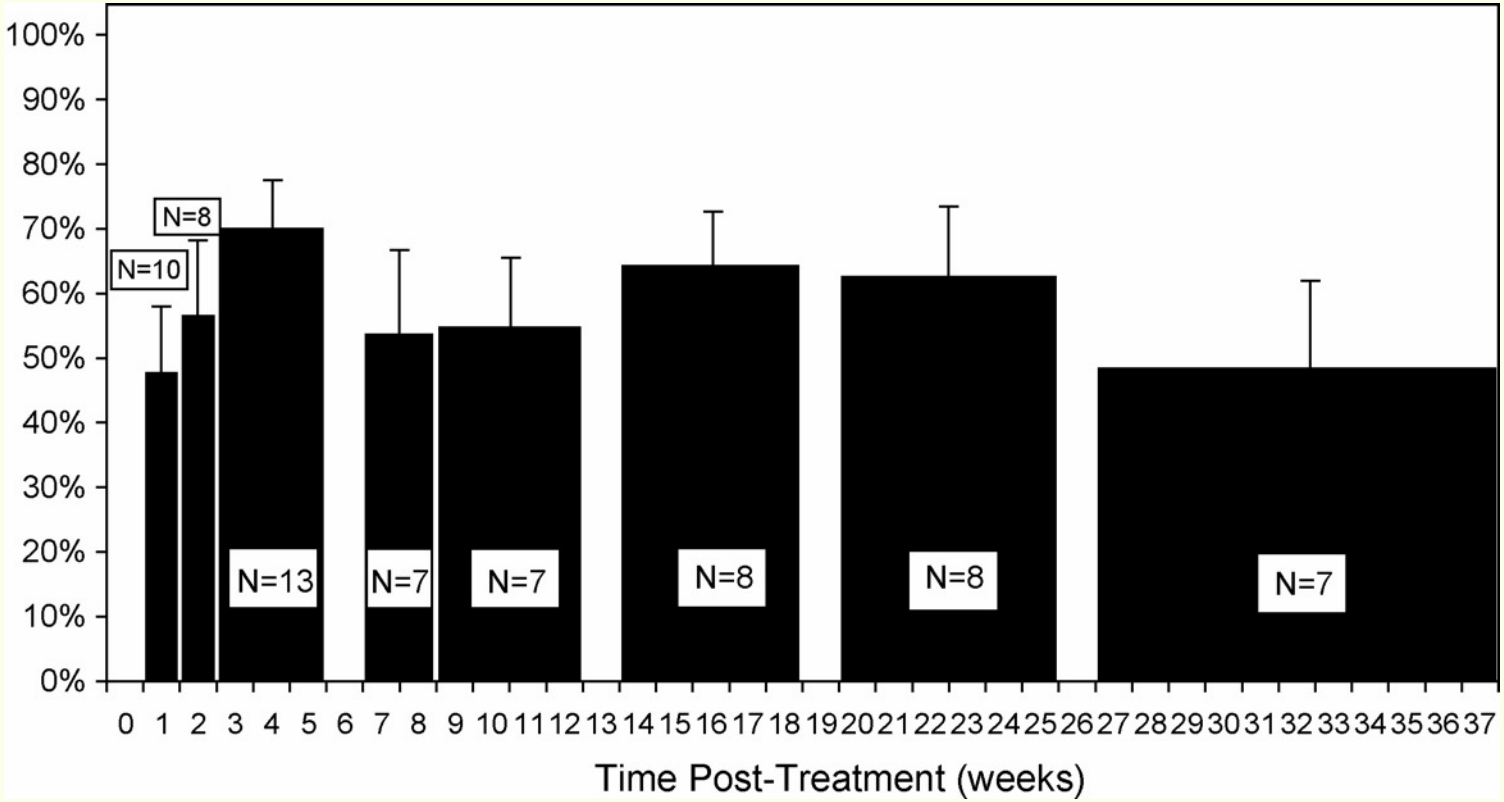
Pt. No. 11: 55M





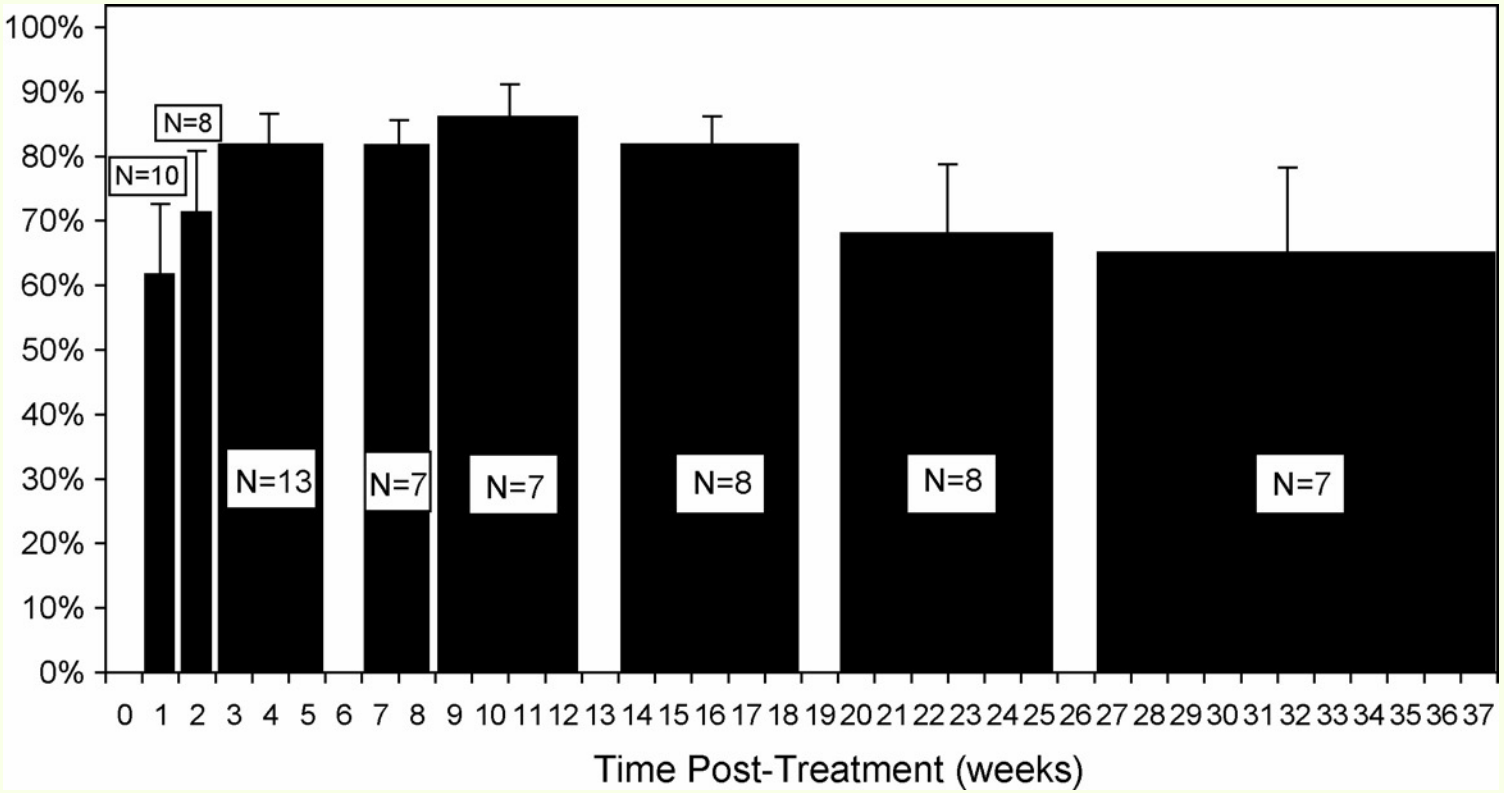


Verapamil Study No. 1 (0.2 mg)
% Decrease in WOMAC



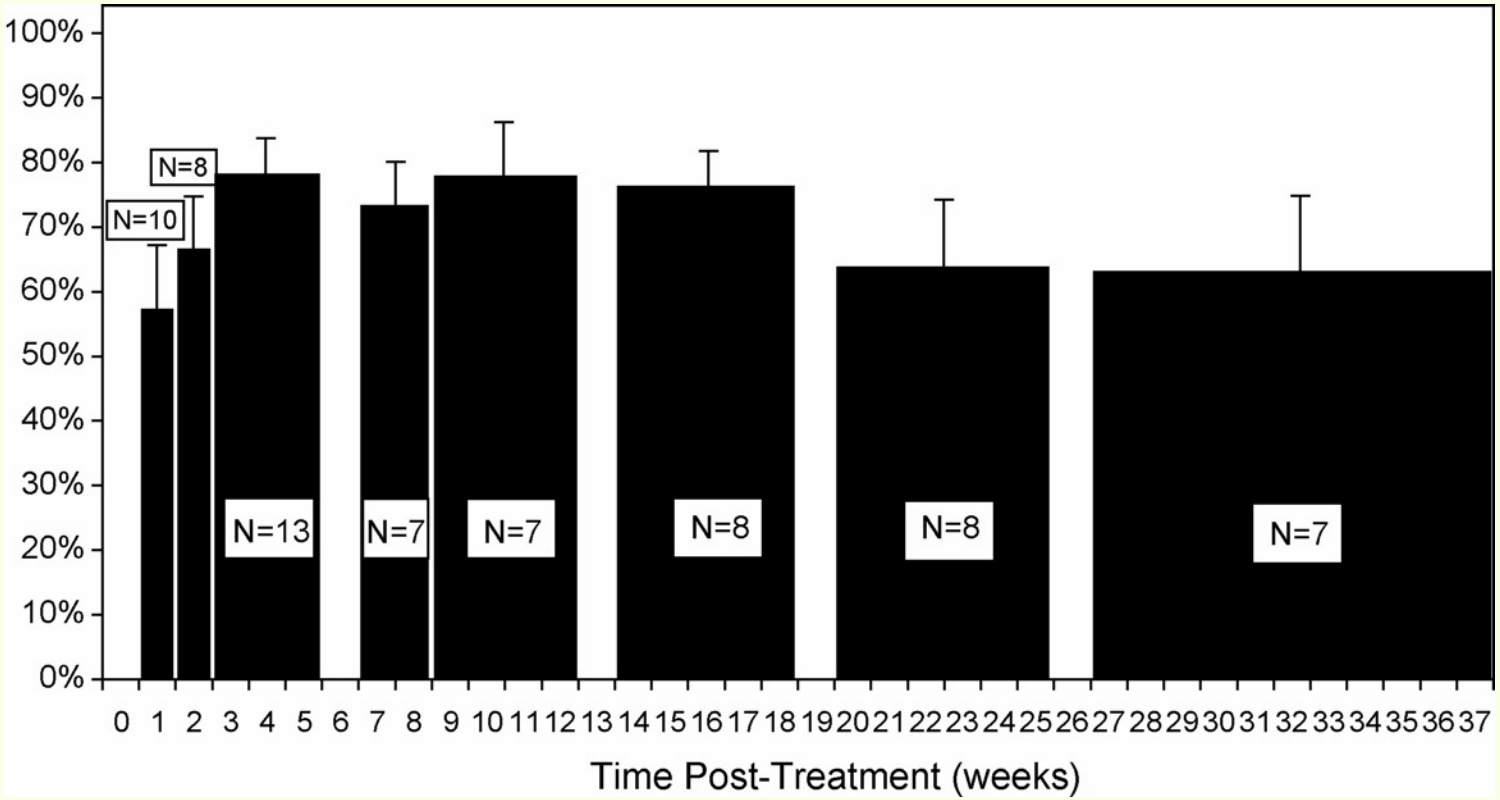
$$\%\text{Decrease} = \frac{\text{score at } t = 0 \ - \ \text{score at } t}{\text{score at } t = 0} \text{x} 100$$

Verapamil Study No. 1 (0.2 mg)
% Decrease in Physician VAS



$$\%\text{Decrease} = \frac{\text{score at t} = 0 \ - \ \text{score at t}}{\text{score at t} = 0} \text{x} 100$$

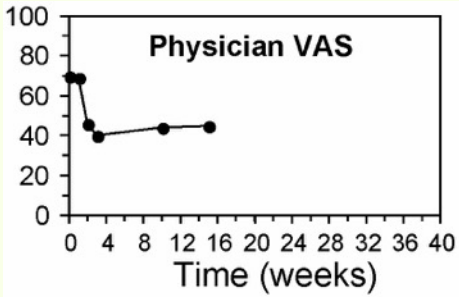
Verapamil Study No. 1 (0.2 mg)
% Decrease in Patient VAS

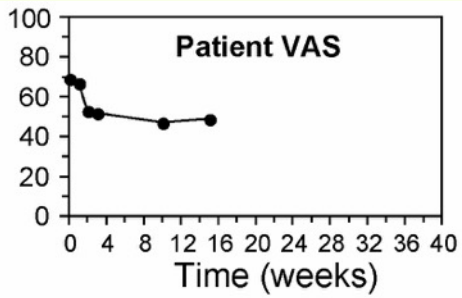


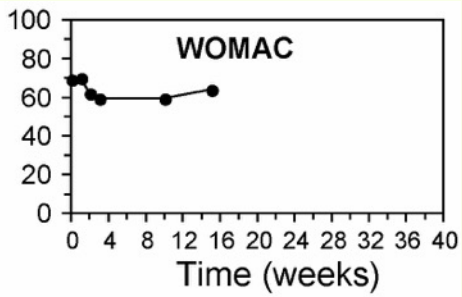
$$\%\text{Decrease} = \frac{\text{score at t} = 0 \ - \ \text{score at t}}{\text{score at t} = 0} \text{x}100$$

Verapamil Study No. 2 (0.5 mg)

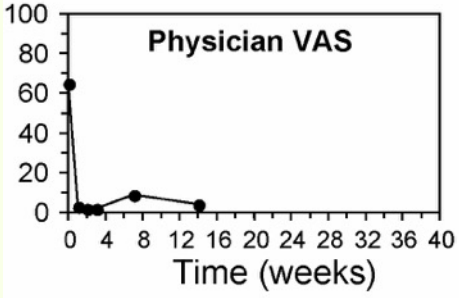
Pt. No. 1
49F

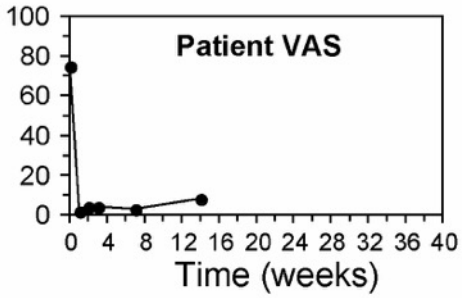


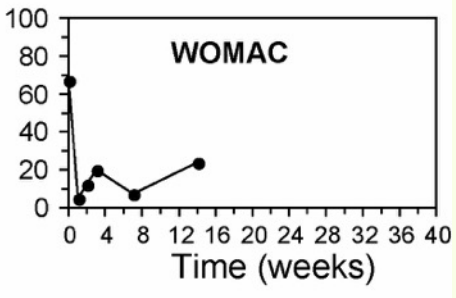




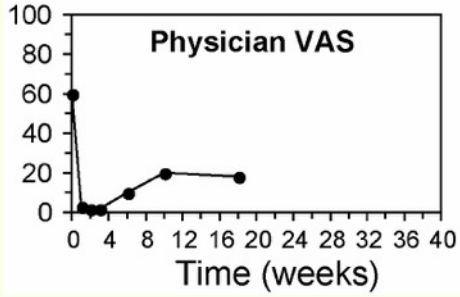
Pt. No. 2
64F

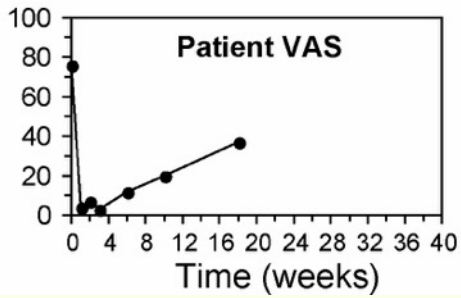


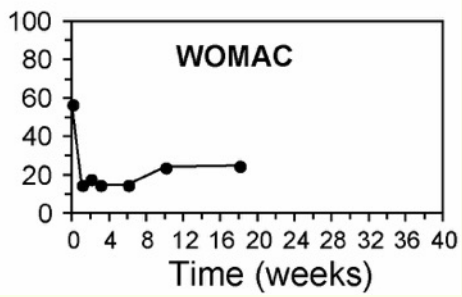




Pt. No. 3
75F

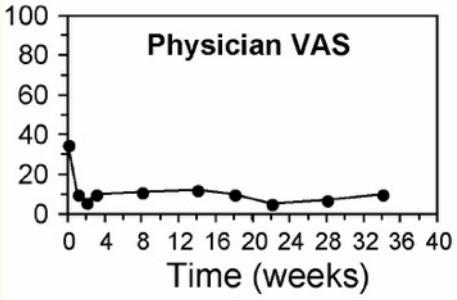


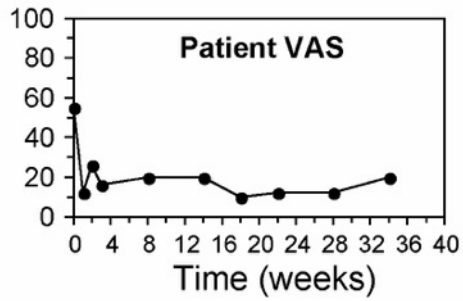


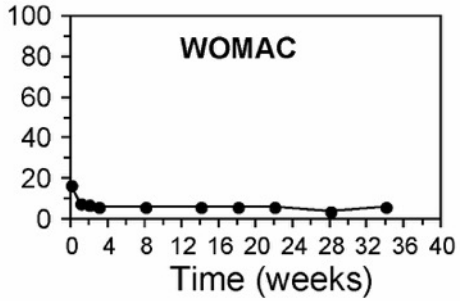


Verapamil Study No. 2 (0.5 mg)

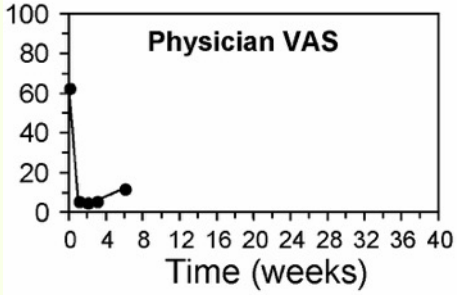
Pt. No. 4-1
42M

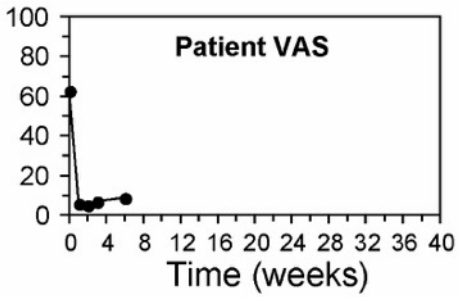


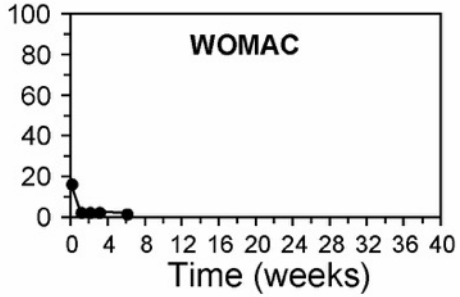




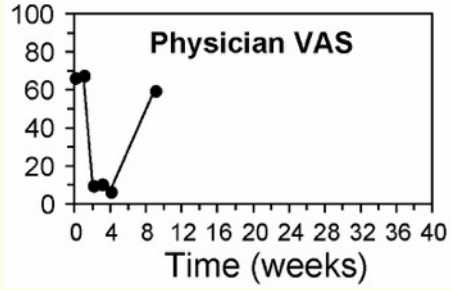
Pt. No. 4-2
42M

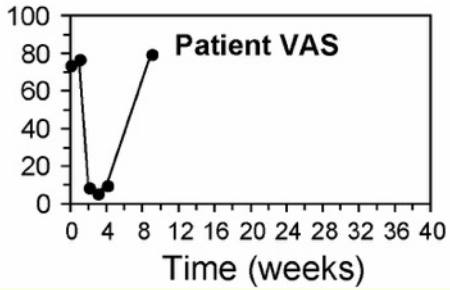


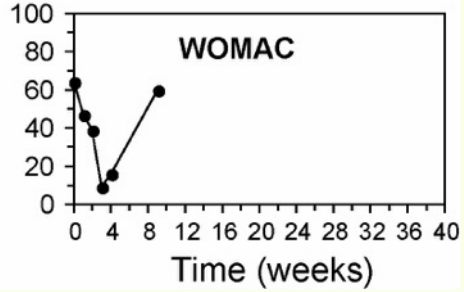




Pt. No. 5
68M

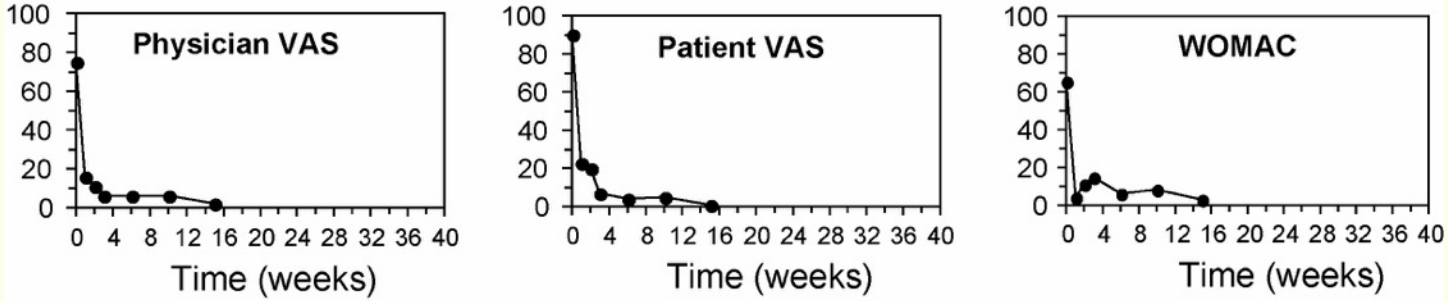




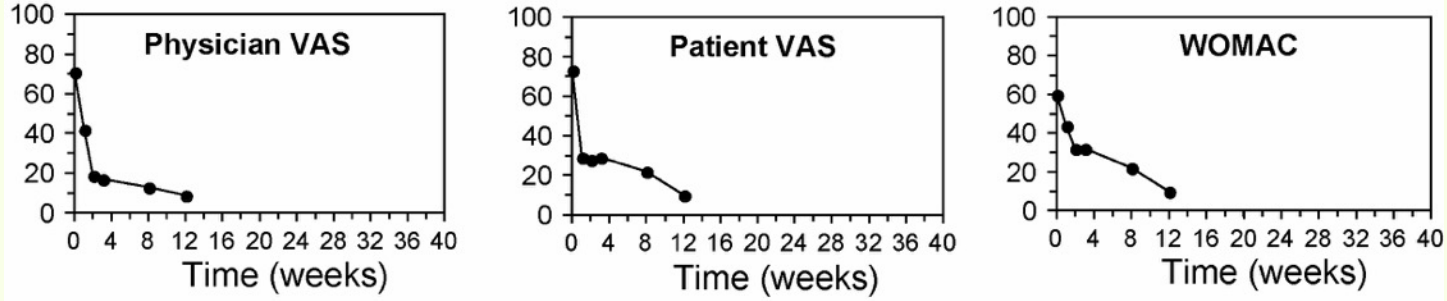


Verapamil Study No. 2 (0.5 mg)

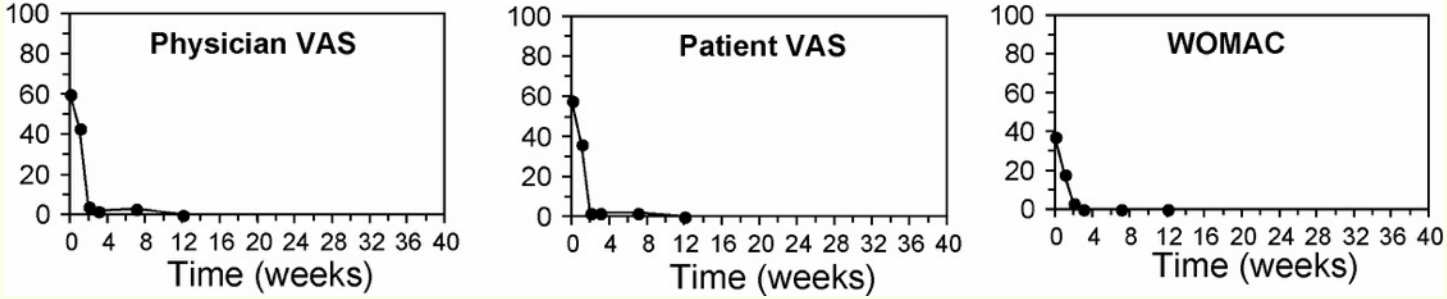
Pt. No. 6
67F



Pt. No. 7
70F

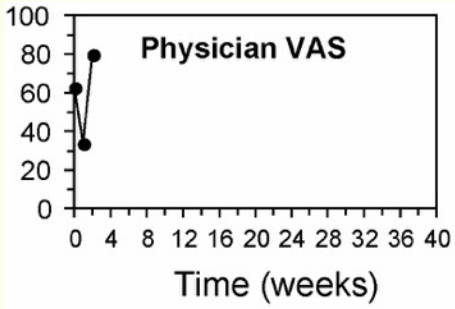


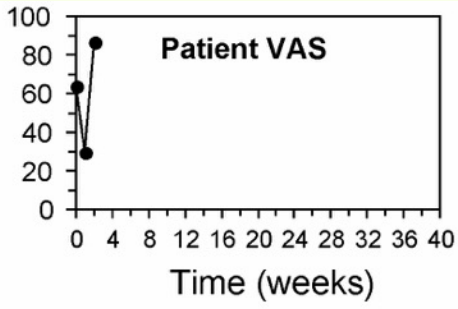
Pt. No. 8
55M

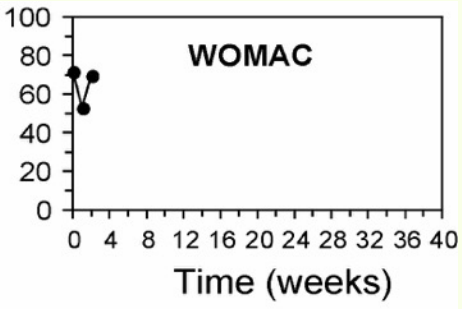


Verapamil Study No. 2 (0.5 mg)

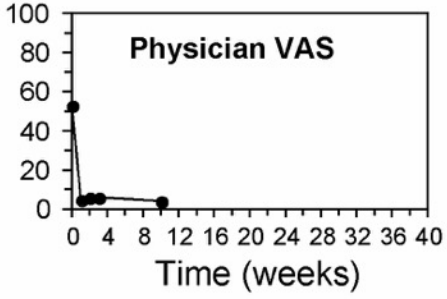
Pt. No. 9
41M

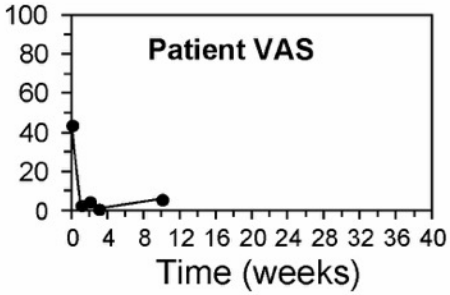


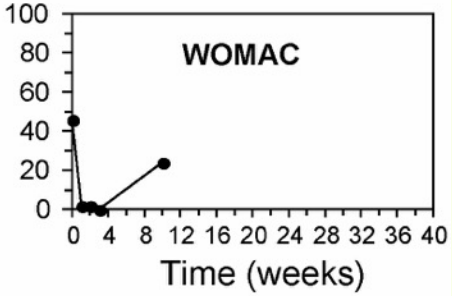




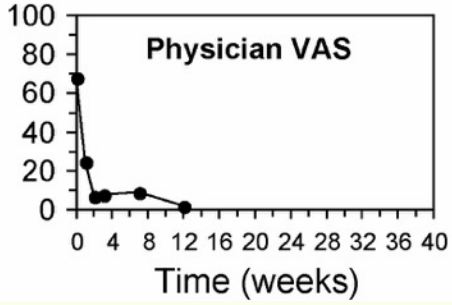
Pt. No. 10
64F

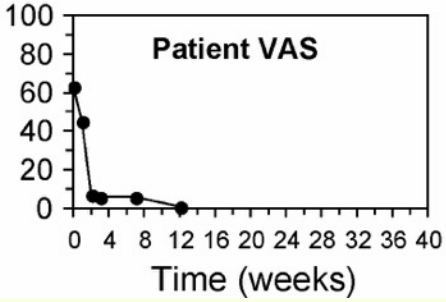


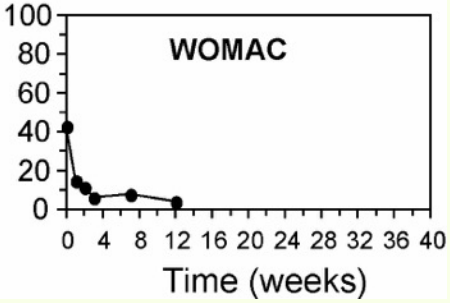




Pt. No. 11
67F

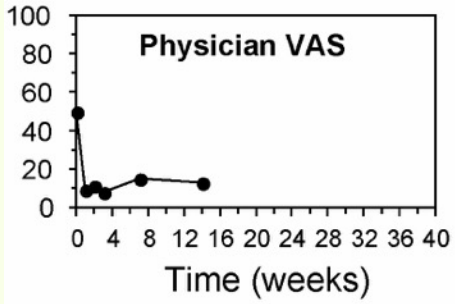


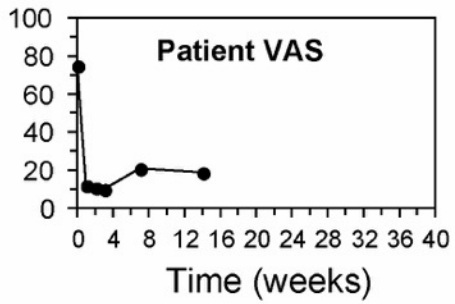


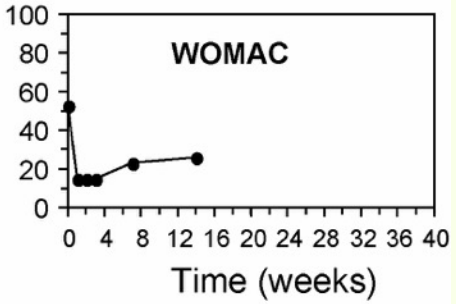


Verapamil Study No. 2 (0.5 mg)

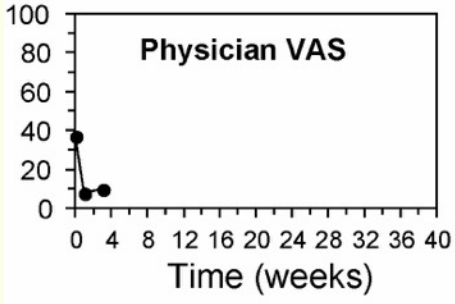
Pt. No. 12
75F

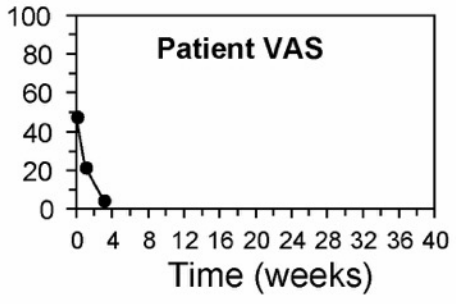


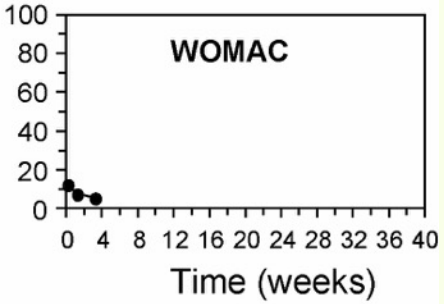




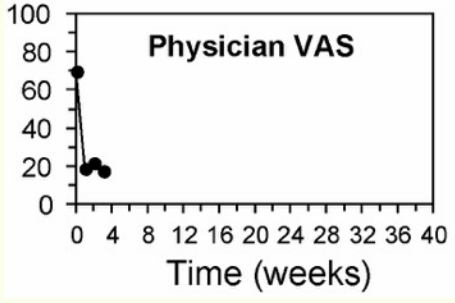
Pt. No. 13
42M

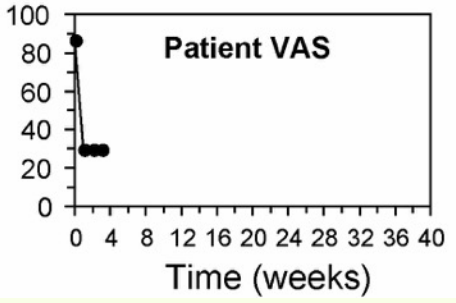


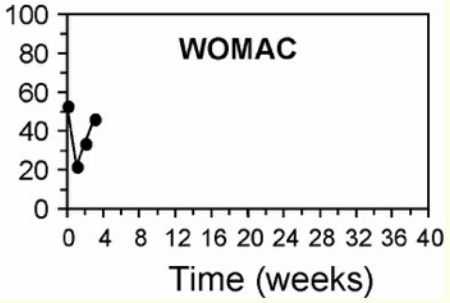




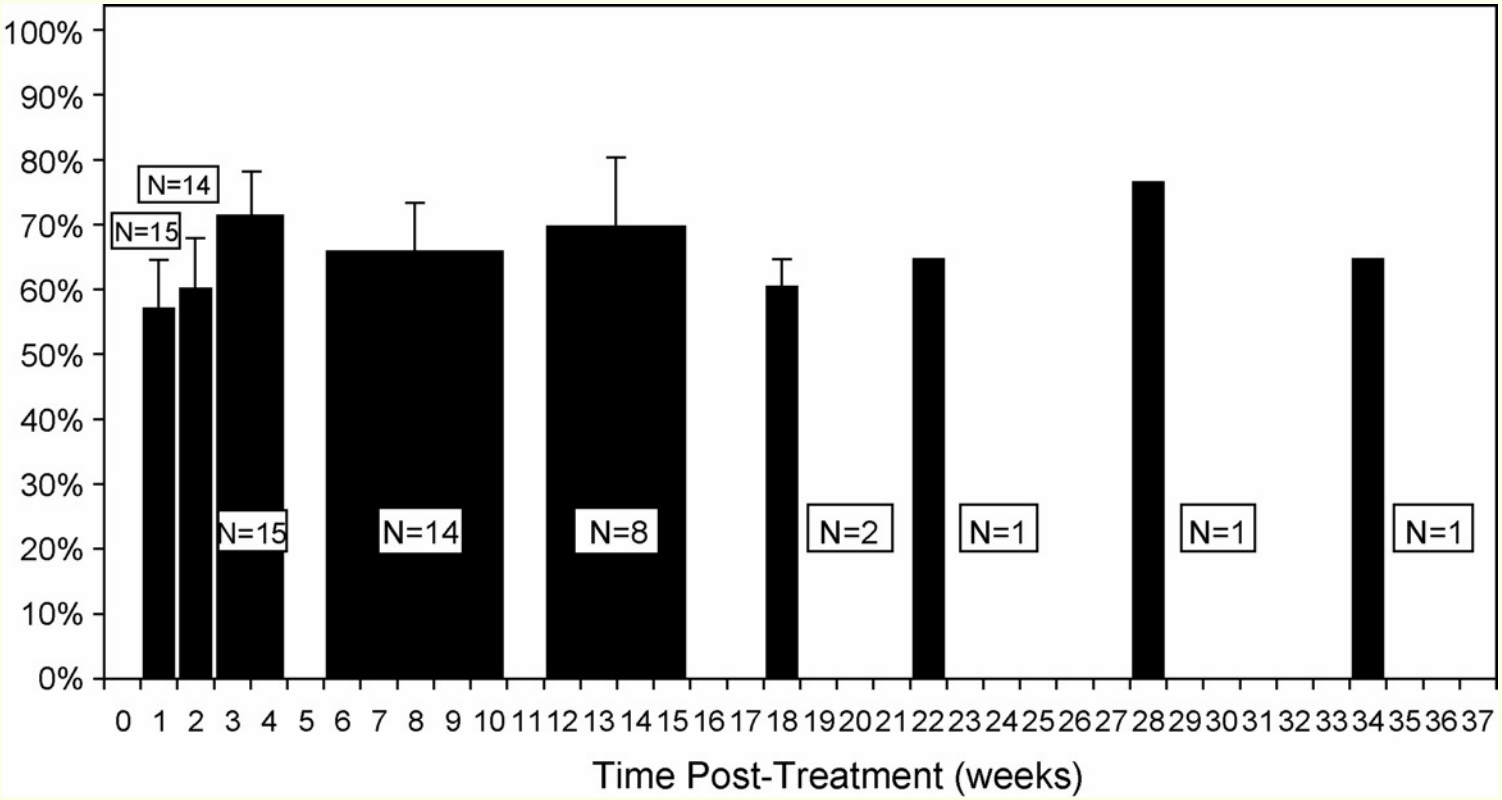
Pt. No. 14
55F





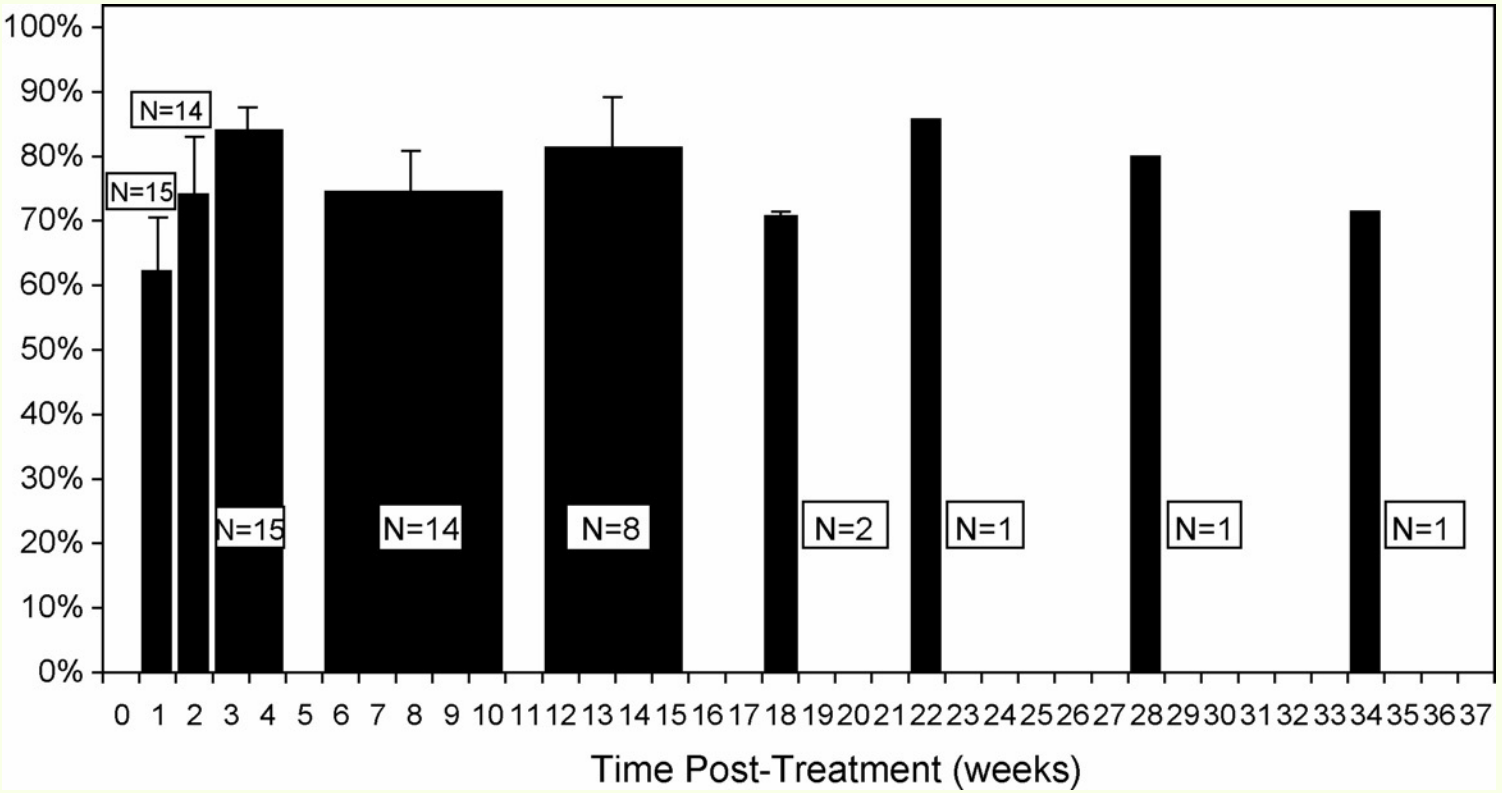


Verapamil Study No. 2 (0.5 mg)
% Decrease in WOMAC



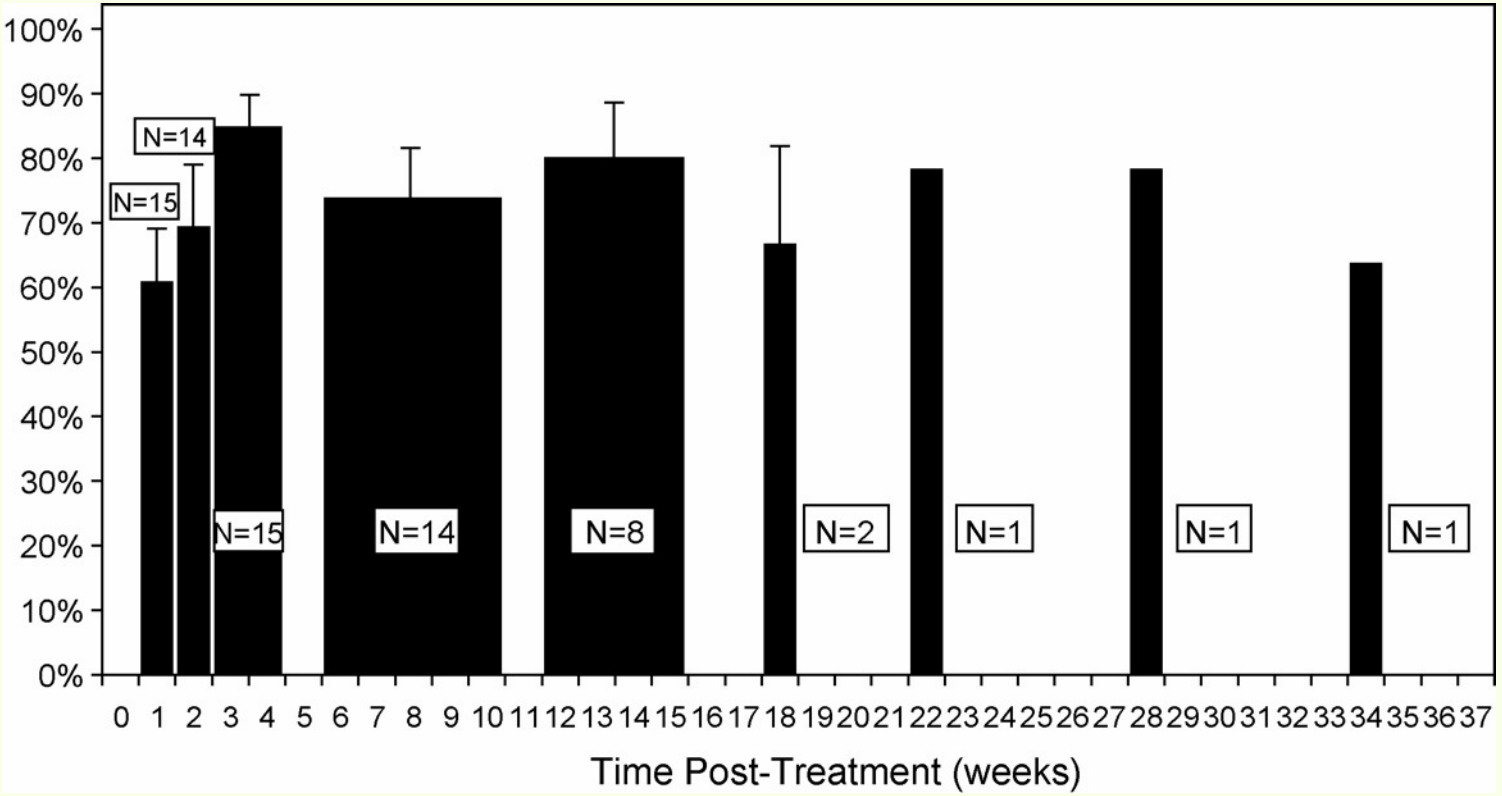
$$\%\text{Decrease} = \frac{\text{score at } t = 0 \ - \ \text{score at } t}{\text{score at } t = 0} \text{x} 100$$

Verapamil Study No. 2 (0.5 mg) % Decrease in Physician VAS



$$\%\text{Decrease} = \frac{\text{score at t} = 0 \ - \ \text{score at t}}{\text{score at t} = 0} \text{x} 100$$

Verapamil Study No. 2 (0.5 mg)
% Decrease in Patient VAS



$$\%\text{Decrease} = \frac{\text{score at } t = 0 \ - \ \text{score at } t}{\text{score at } t = 0} \text{x} 100$$

Single Injection Verapamil Pilot Study for the Treatment of Osteoarthritis

- 25 patients
- Experienced physician injection
- ALL data points included in slides
- Initially planned as pilot study to see if there was sufficient clinical efficacy to warrant more expansive study.
- Very positive results noted on 3 efficacy tools.

Important Clinical Fact:

- Clinical pilot study that showed efficacy of Verapamil in knees which were mostly Kellgren-Lawrence Grade IV.
- Most hyaluronans are tested in patients with Kellgren-Lawrence Grade II and III disease.

What is the Market Looking For?

- A single injection therapy for osteoarthritis has many benefits.
- Physicians and patients prefer simplified therapies.
- One injection q 3-6 months

Single Injection Verapamil for Osteoarthritis

- Single injection local therapy for a local disease.
- No adverse events noted in the 25-patient pilot study. No blood pressure changes.
- Basic science infers possible disease modifying capability with MMP inhibition.

Single Injection of Verapamil for the Treatment of Osteoarthritis

- Local therapy for local symptoms
- Local therapy avoids systemic adverse events.
- Verapamil is technically easier to inject than ANY hyaluronan.

Patient Testimonial

- Previously had 3 courses of Synvisc.
- Received single injection of 0.5 mg Verapamil
- Injection of Verapamil more comfortable than Synvisc.
- More relief with Verapamil than any course of Synvisc.

U.S. Patents Pending

- U.S. Patent Application No. 11/138,738 COMPOSITIONS FOR TREATING OSTEOARTHRITIS
- U.S. Patent Application No. 11/138,744 METHODS FOR TREATING OSTEOARTHRITIS

Future Plans:

Current pilot study shows strong positive evidence that a single injection of Verapamil is therapeutic in the treatment of osteoarthritis.

Single Injection Verapamil for the Treatment of Osteoarthritis

- Recommend IND multiple site study for efficacy.
- Verapamil already has a proven safety record in humans.