

Is Osteoarthritis an Acquired Channelopathy? A Novel Basic-Science Approach

Andrew A. Marino, Ph.D.

Oleg Kolomytkin, Ph.D., D.Sc.

David D. Waddell, M.D.

Summary

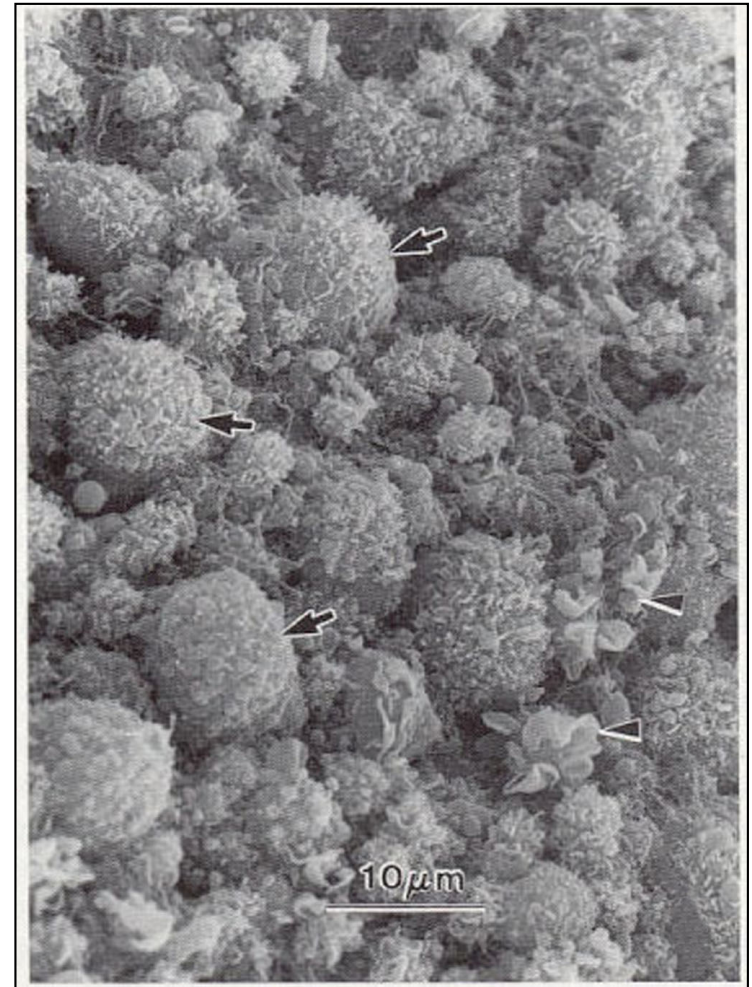
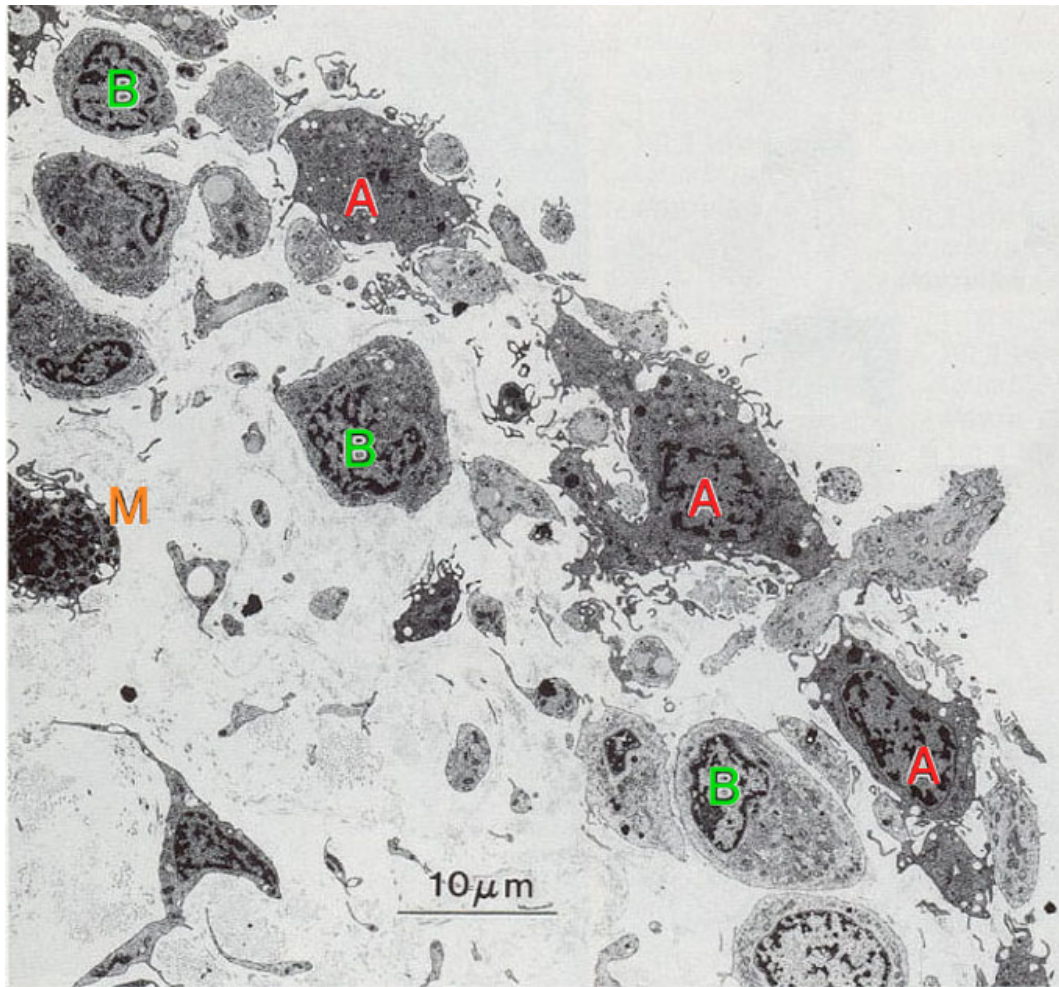
- Background of Work
- Basic Assumptions
- Important Discoveries
- Plans for Osteoarthritis Studies

Background

- 1996 Marino & LSU Co-workers
- 2000 Waddell and OSR Co-workers
- 2002 Genzyme Biosurgical Contract Support

Basic Assumptions

1 - Importance of Synovium



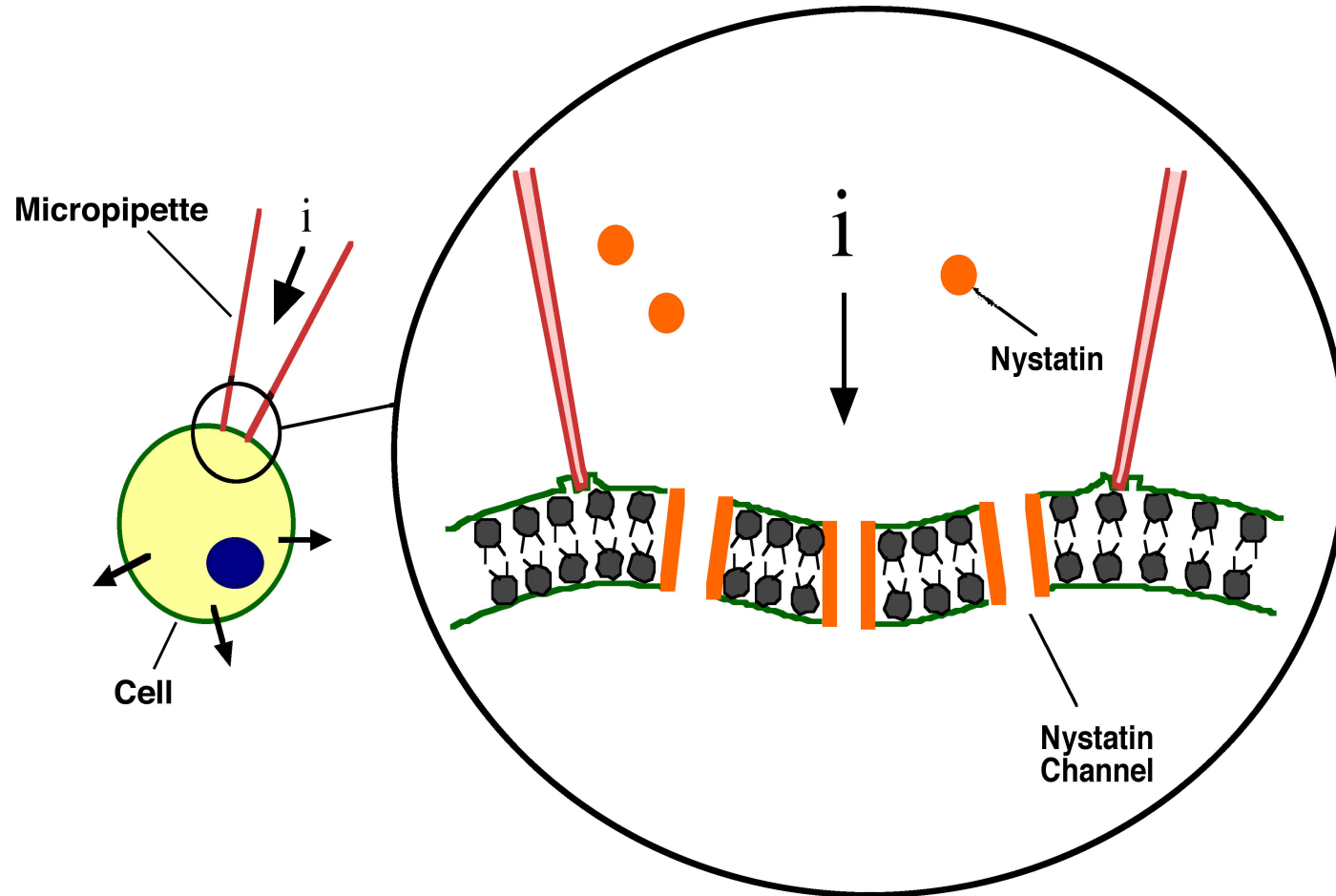
Type A: Macrophage

Type B: Secretory

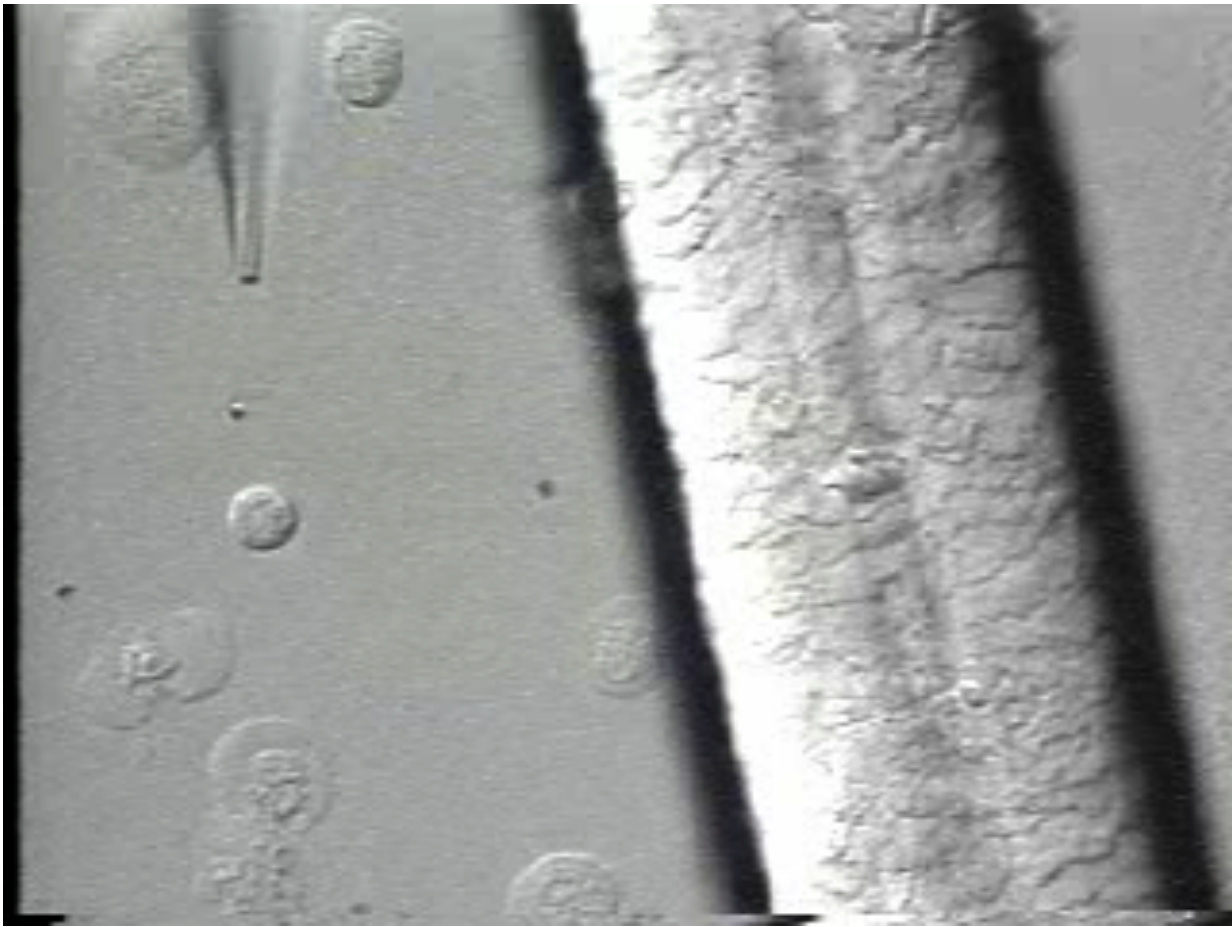
M: Mast cell

Basic Assumptions

2 - Importance of Electrophysiology



Nystatin Patch Clamp



Experimental Approach

Hypothesis

Cell Electrical Changes → Function

Methodology

Electrophysiology

& Enzyme Activity → Function

Molecular Biology → Composition

Microscopy → Structure

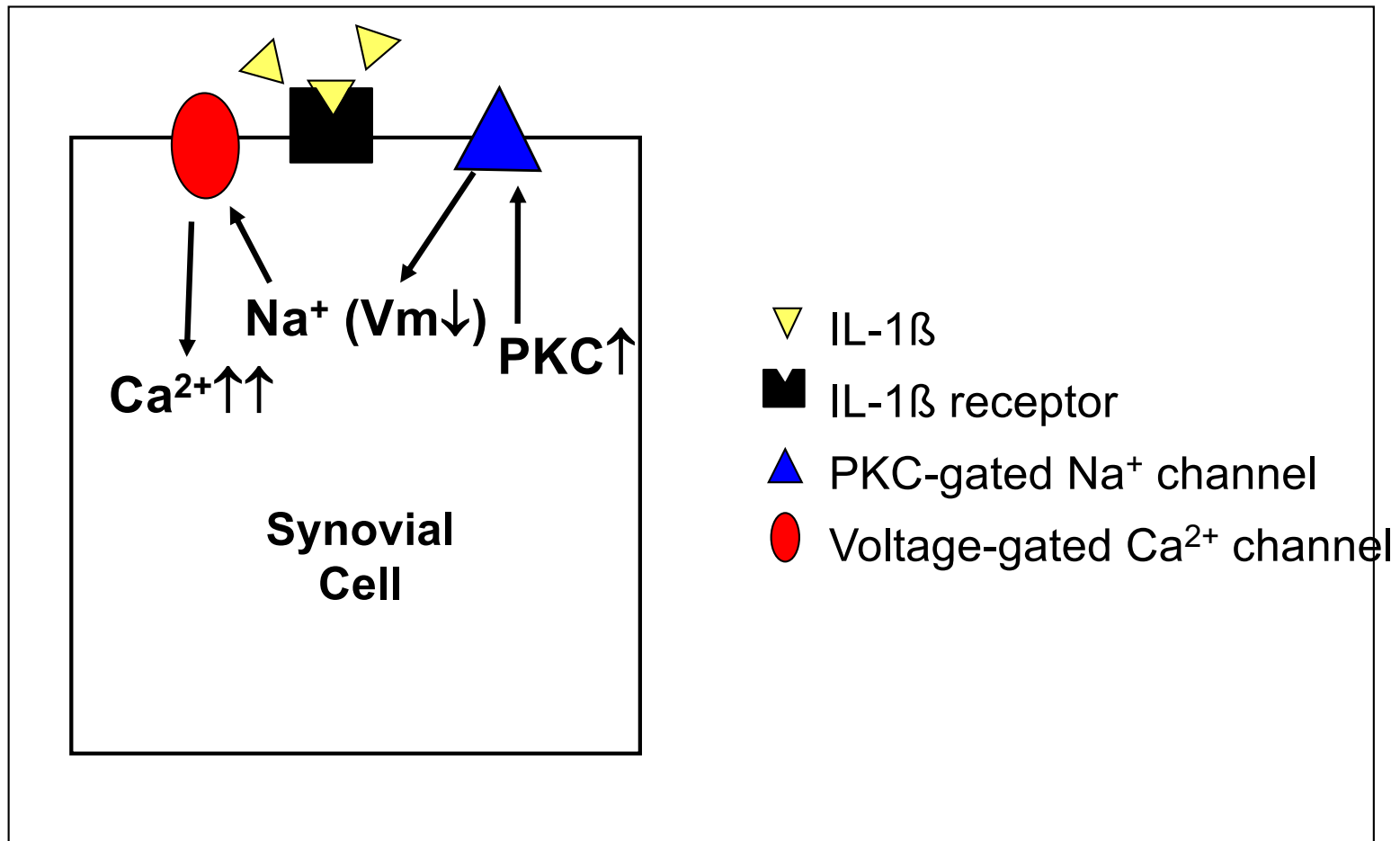
Objects of Study

HIG-82 Synovial Cells

Synovial Biopsies

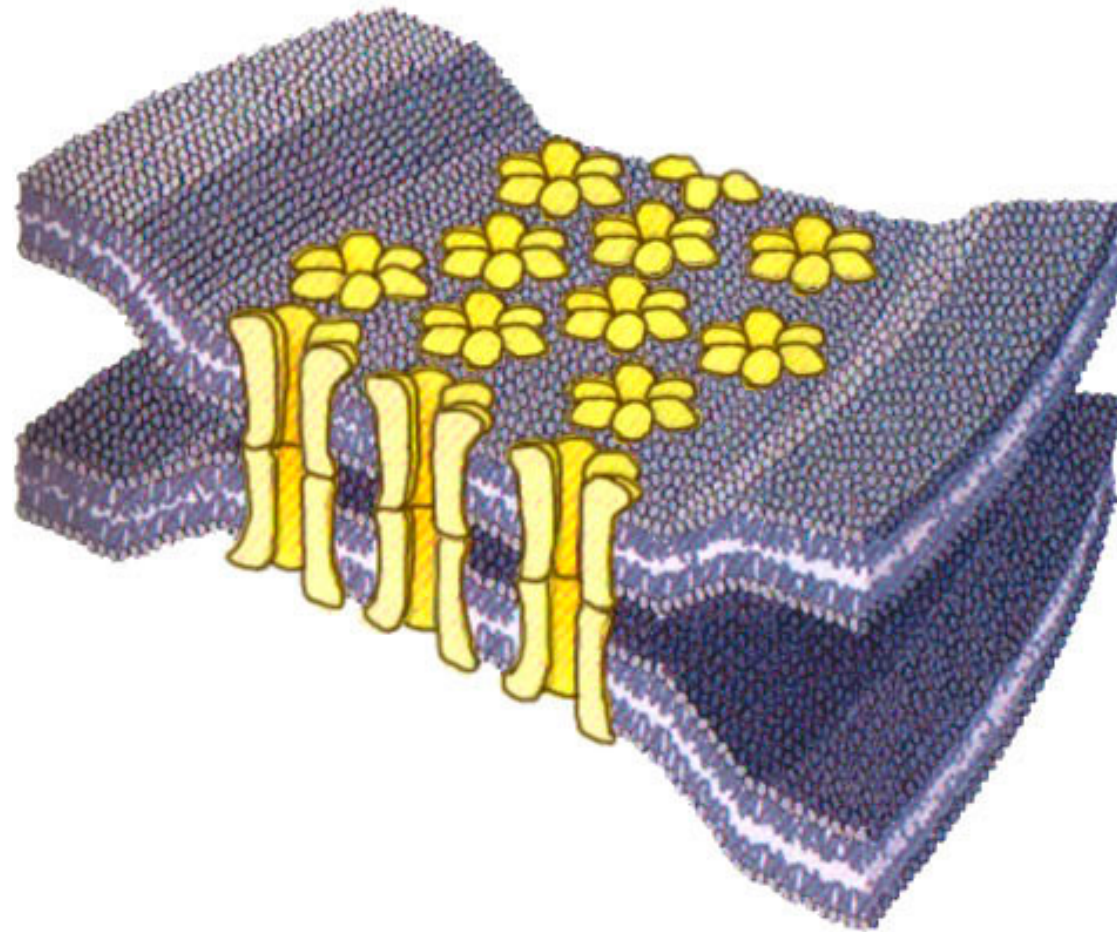
Important Discoveries

1. Signal Transduction in Synovial Cells Early Events (15 minutes)

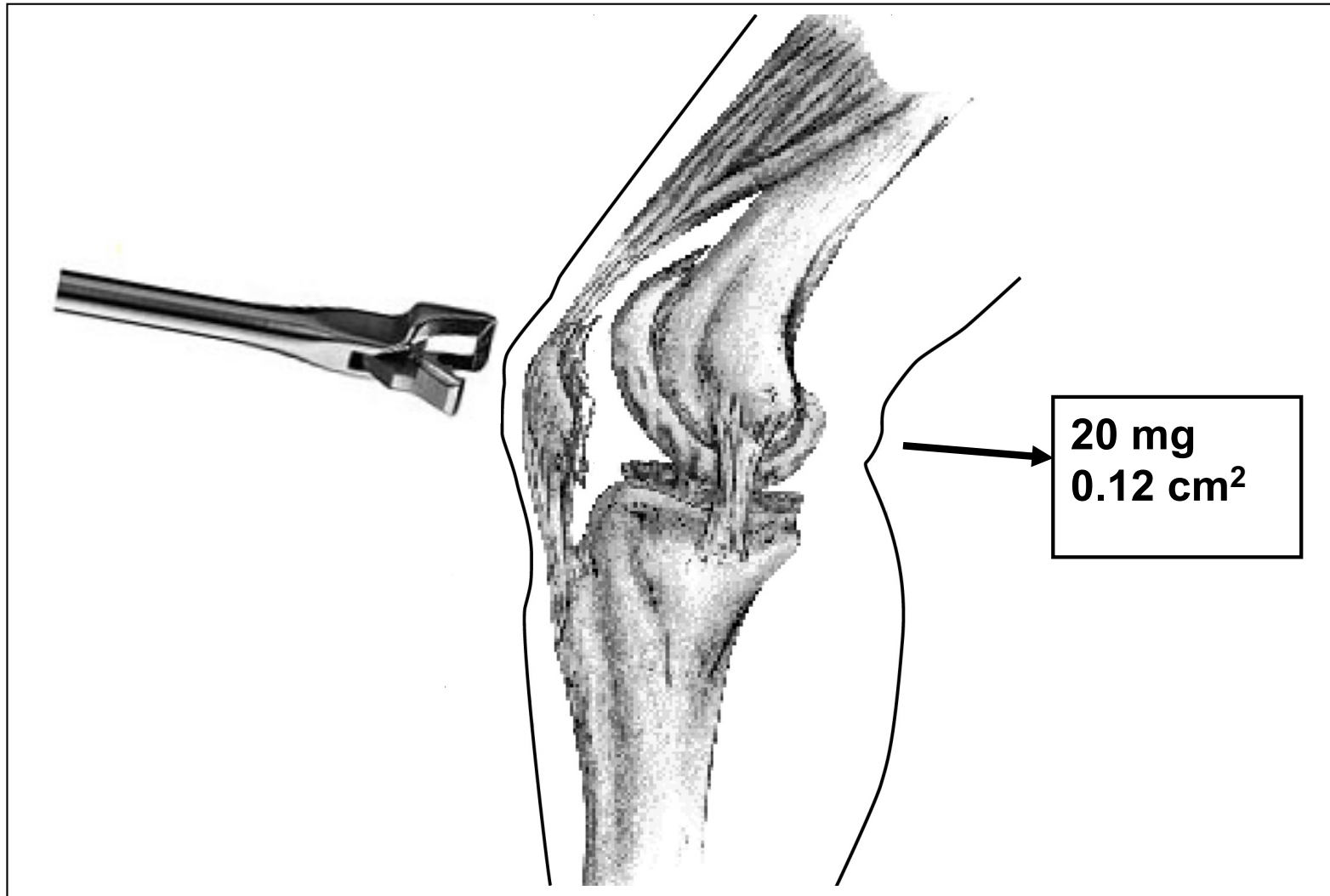


Important Discovery

Gap Junctions

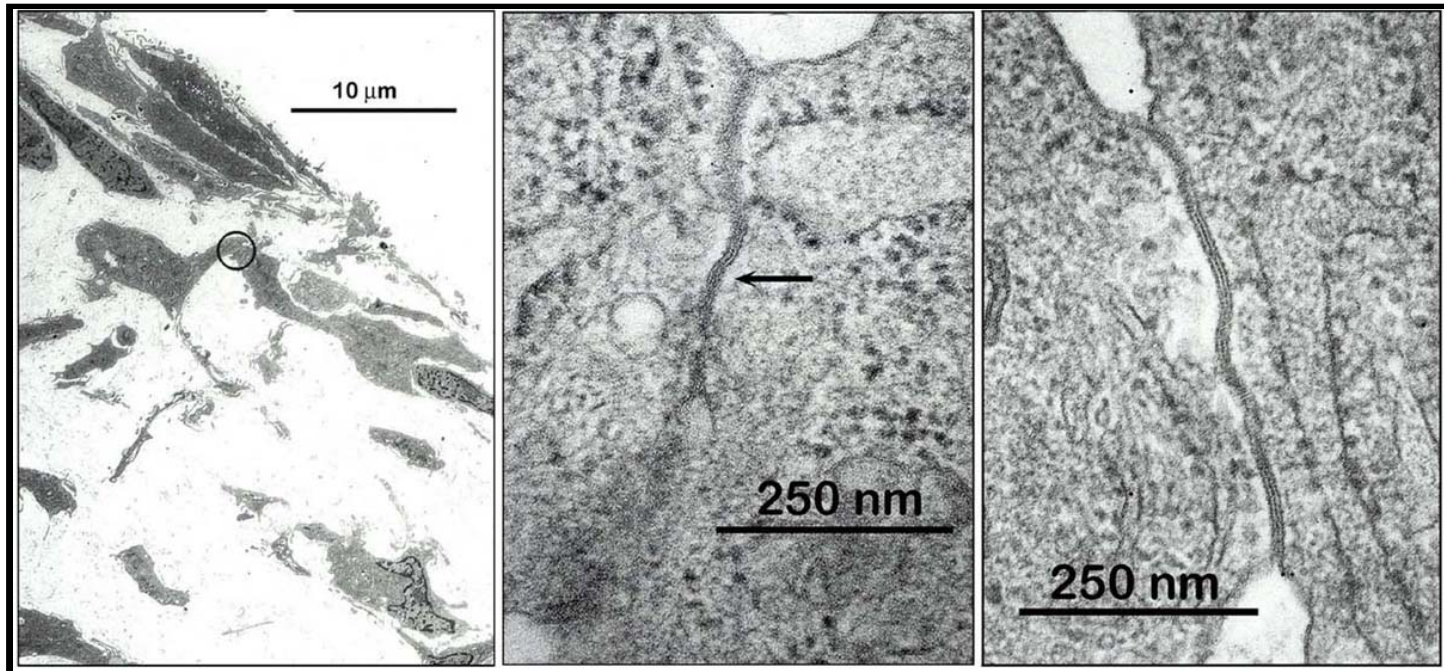


Surgical Biopsy Procedure

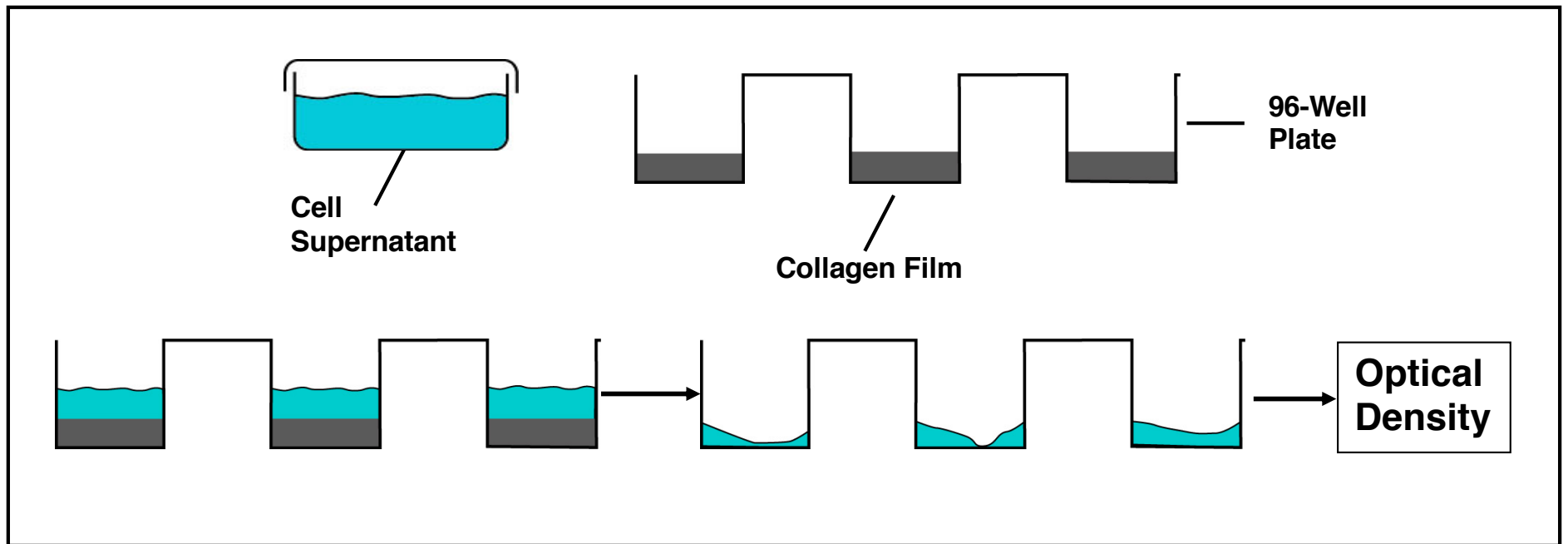


Important Discoveries

2. Gap Junctions Occur in Normal Human Synovium

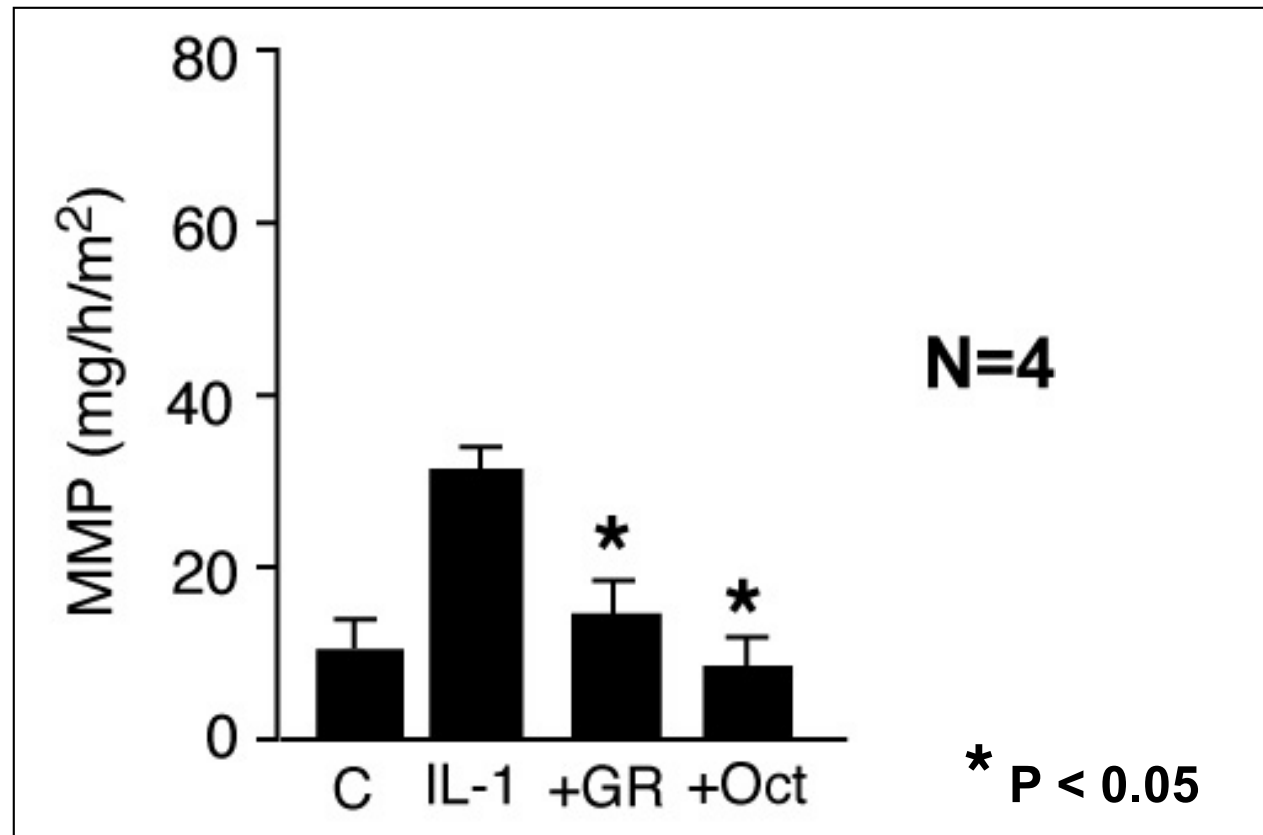


Metalloproteinase (MMP) Assay

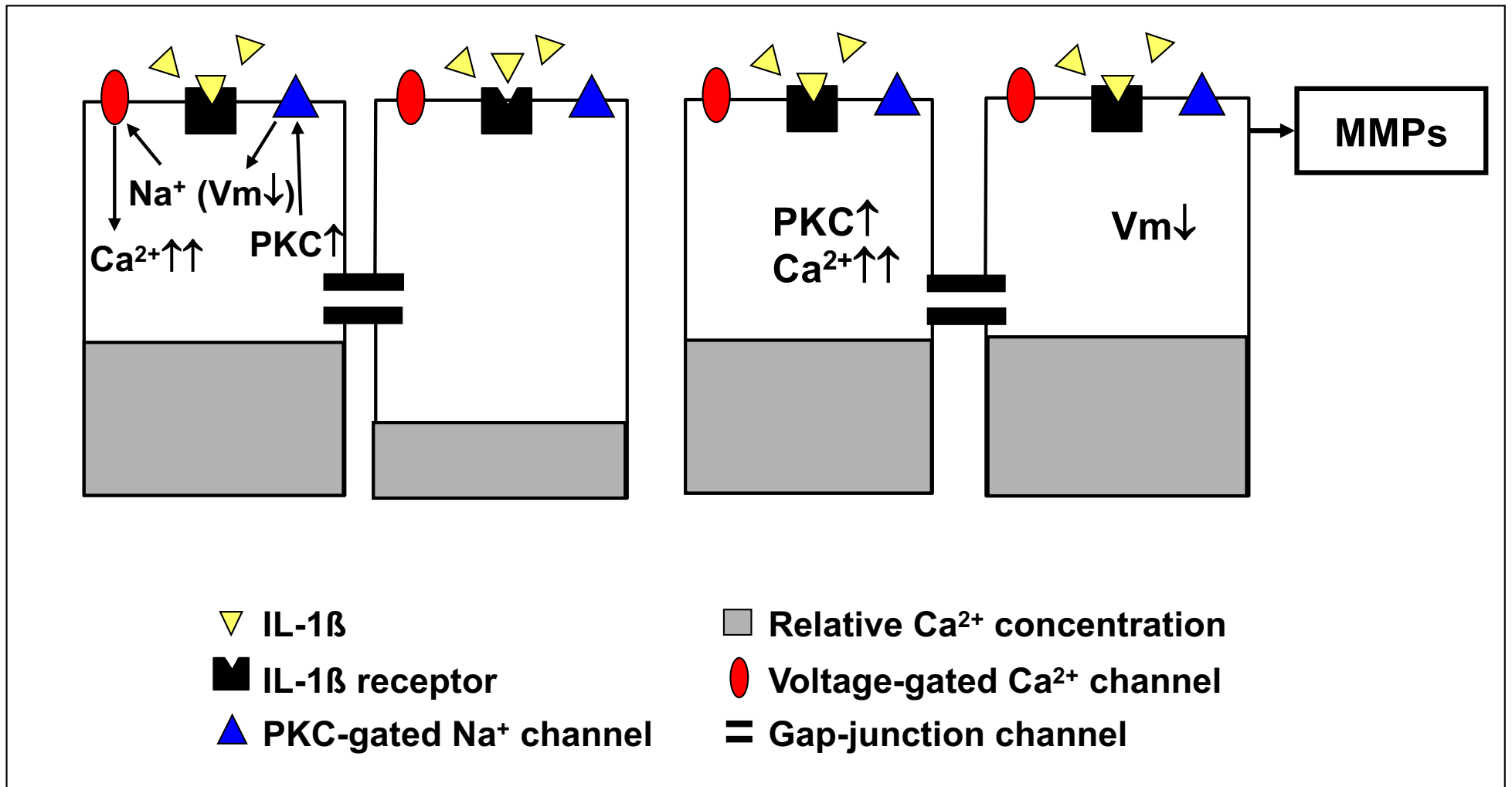


Important Discoveries

3. Gap Junctions are Essential for Synovial-Cell Secretory Response by Synovial Explants



Modified Model



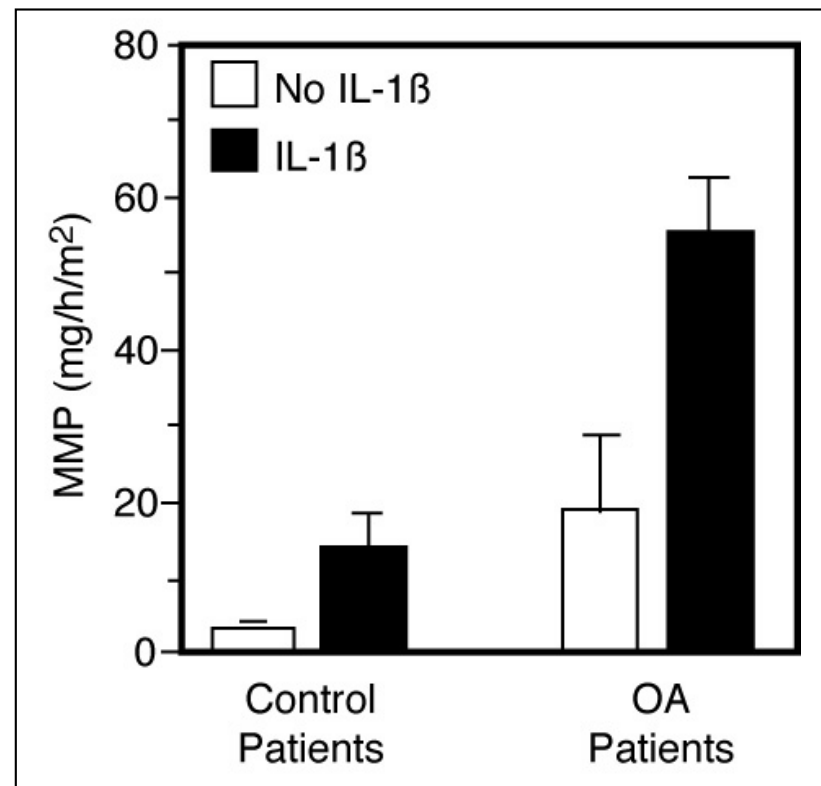
Important Discoveries

4. Relation Between Gap Junctions and Osteoarthritis

- Larger number of gap junctions in OA
- More gap-junction protein in OA (connexin 43)
- Larger gap junctions in OA

Important Discoveries

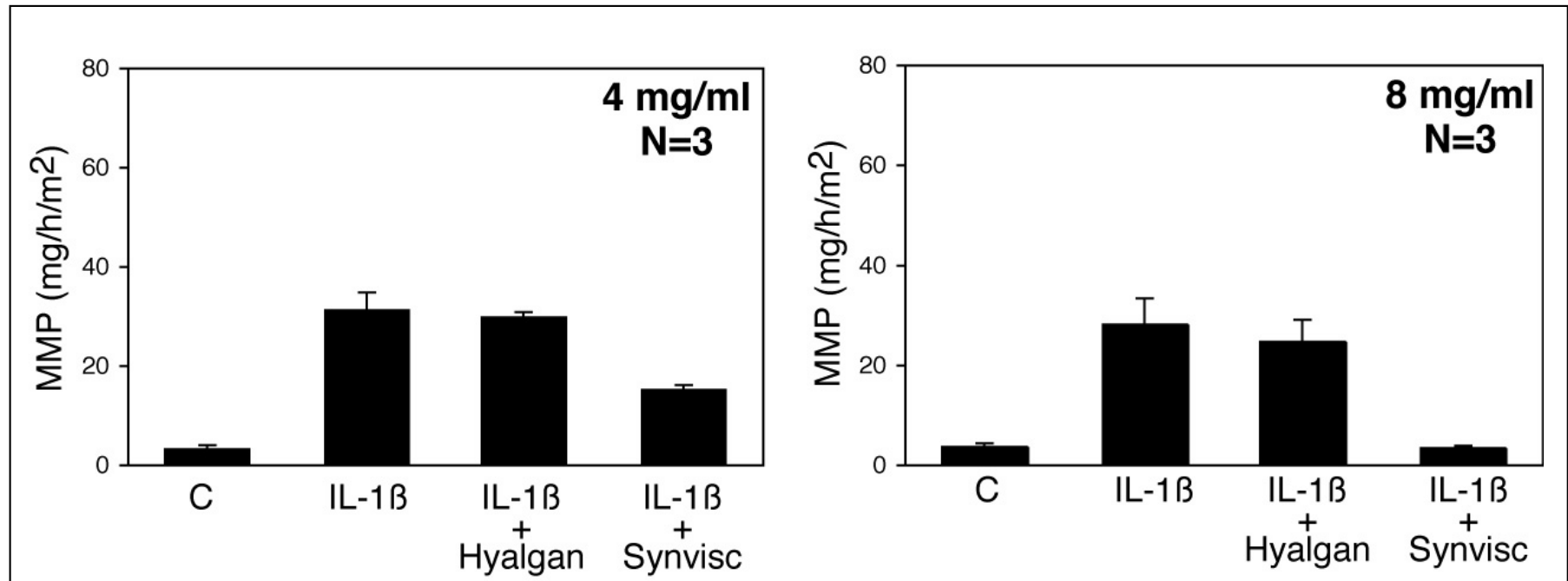
5. Synovial Cells Undergo a Phenotypic Change During the Development of Osteoarthritis



MMP Production by Synovial Tissue

Important Discoveries

6. Hyaluronan Antagonizes MMP Production: The Effect is Concentration- and Size- Dependent



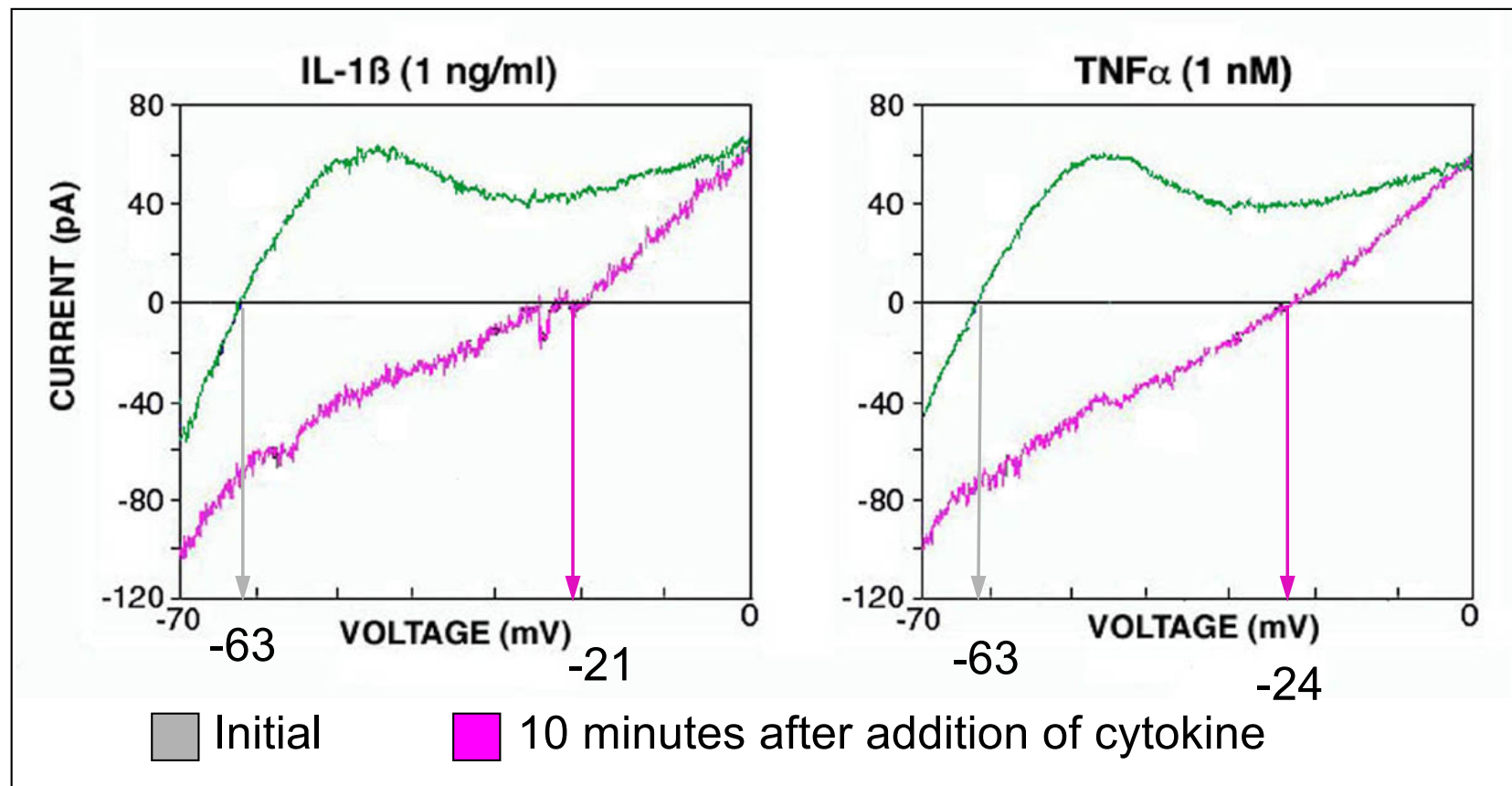
Effect of Hyalgan and Synvisc on IL-1 β Induced MMP Activity from Synovial Tissue of Osteoarthritis Patients

Present Status of Osteoarthritis Research

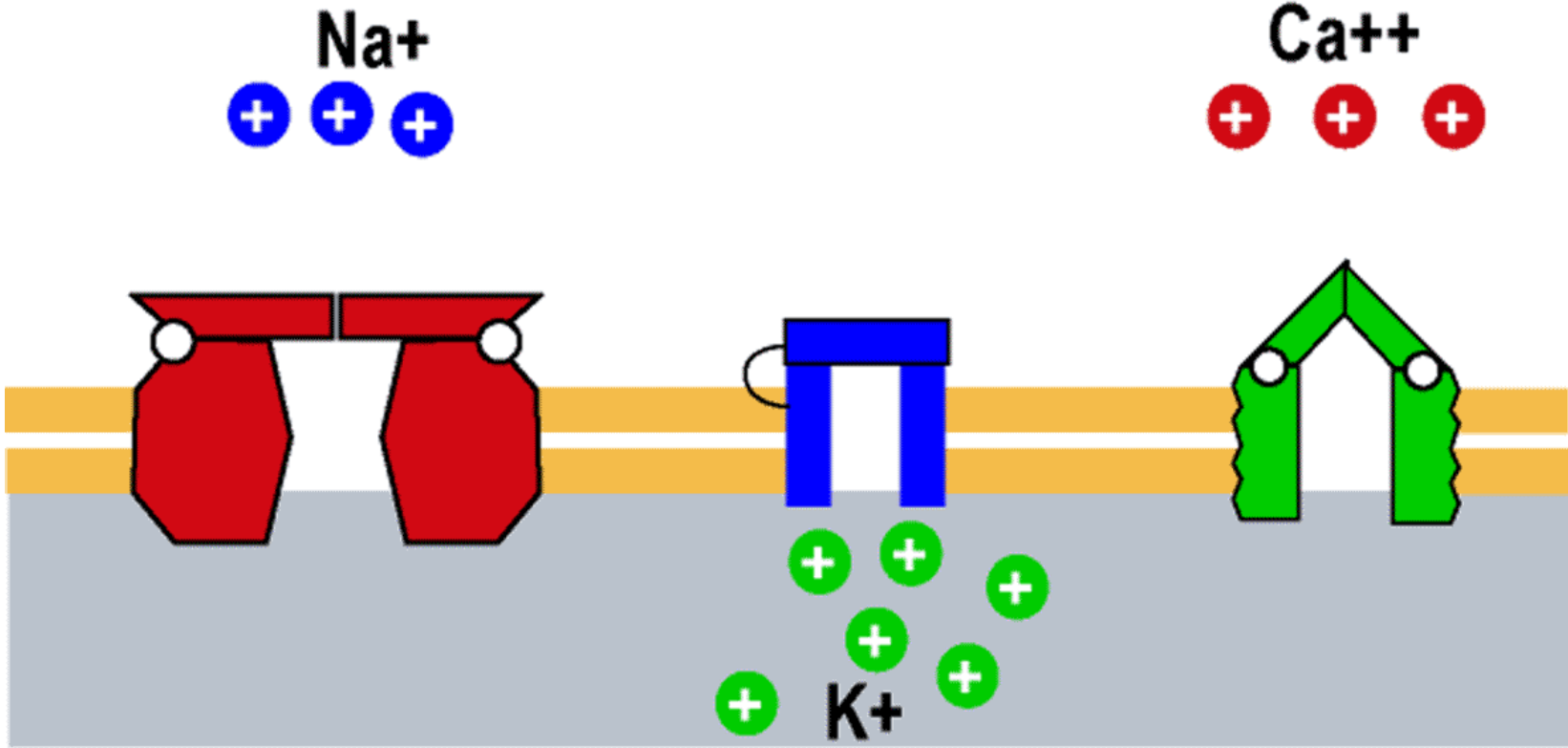
<u>Work</u>	<u>Support</u>	Intellectual <u>Property Rights</u>
Gap junctions	LSU	LSU
Hyaluronan Gap junctions	Genzyme	OSR
Membrane channels	?*	OSR/LSU

* Requesting 600K over 5 years from NIH

Profound Electrical Changes Occur in Synovial Cells Within Minutes of Exposure to Inflammatory Cytokines

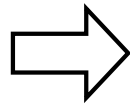


Effect of Cytokines on Current-Voltage Curves in HIG-82 Synovial Cells



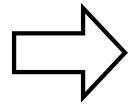
Proposed Membrane-Channel Research

Basic
Idea



Pathological changes in specific synovial- membrane ion channels mediate progression of OA

Proposal



- 1) Identify the channels functionally by comparing OA and normal synovial cells
- 2) Design agents to activate/inhibit the altered function to arrest or release the disease