

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

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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

2004 Personnel

LSU (Marino)

Electrophysiologist (Ph.D.)

Graduate Student

2 Technicians

Bioengineer (Ph.D.)

Orthopedic Specialists (Waddell)

Administrator

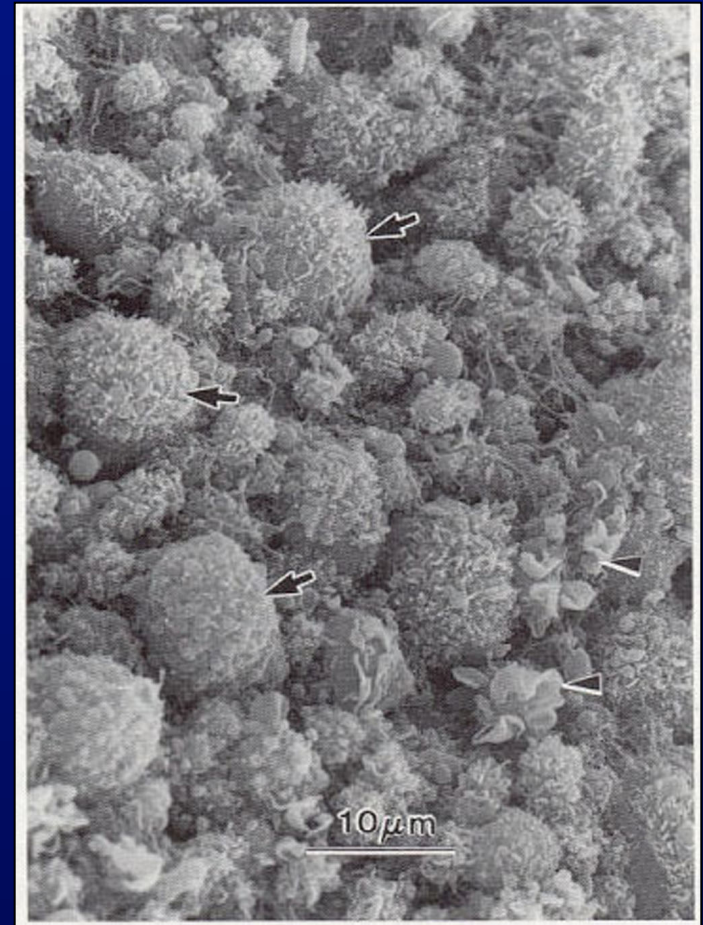
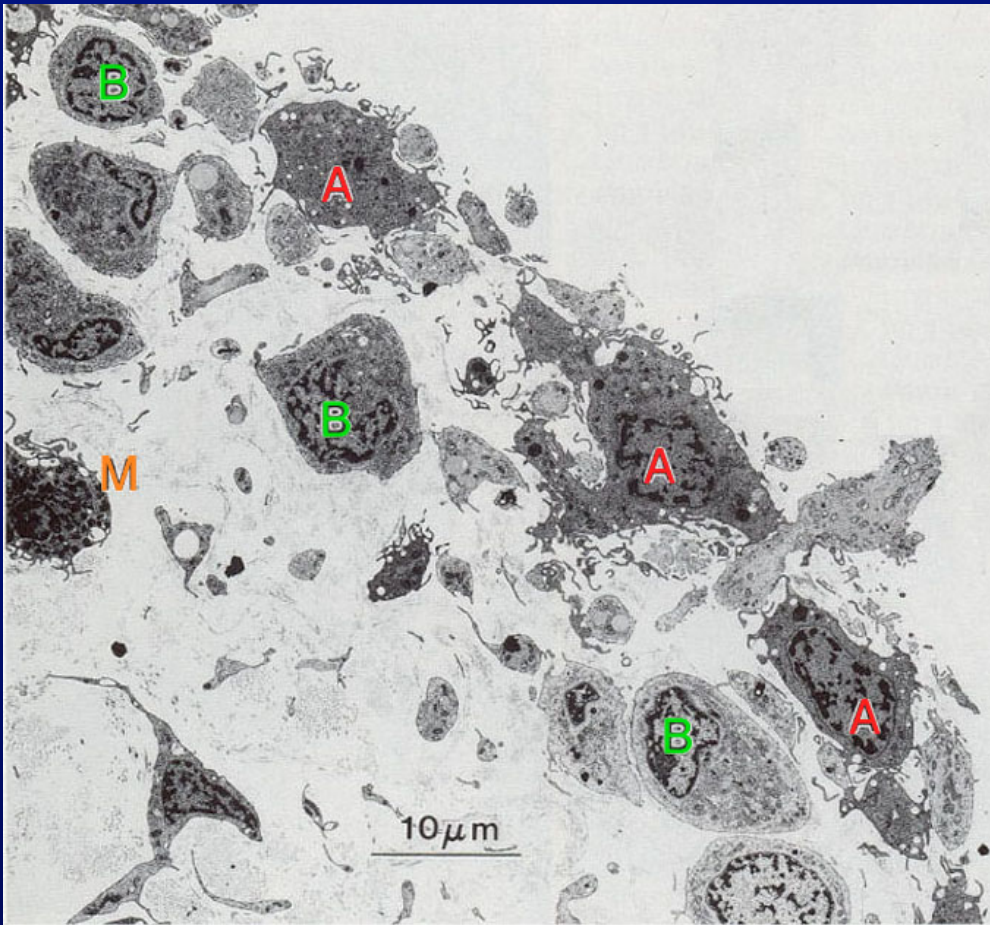
PA

Nurse

Research Assistant

Basic Assumptions

1 - Importance of Synovium



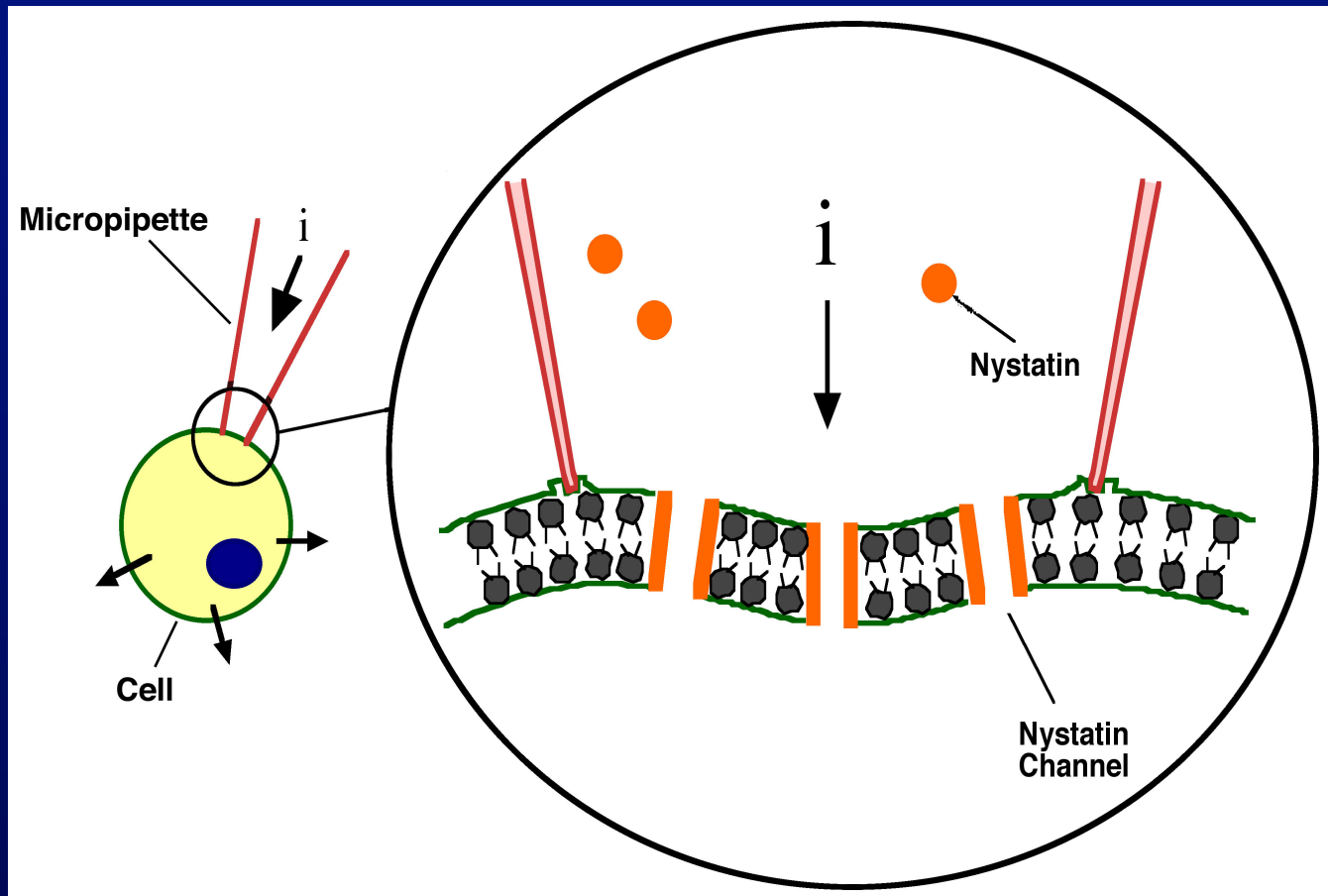
Type A: Macrophage

Type B: Secretory

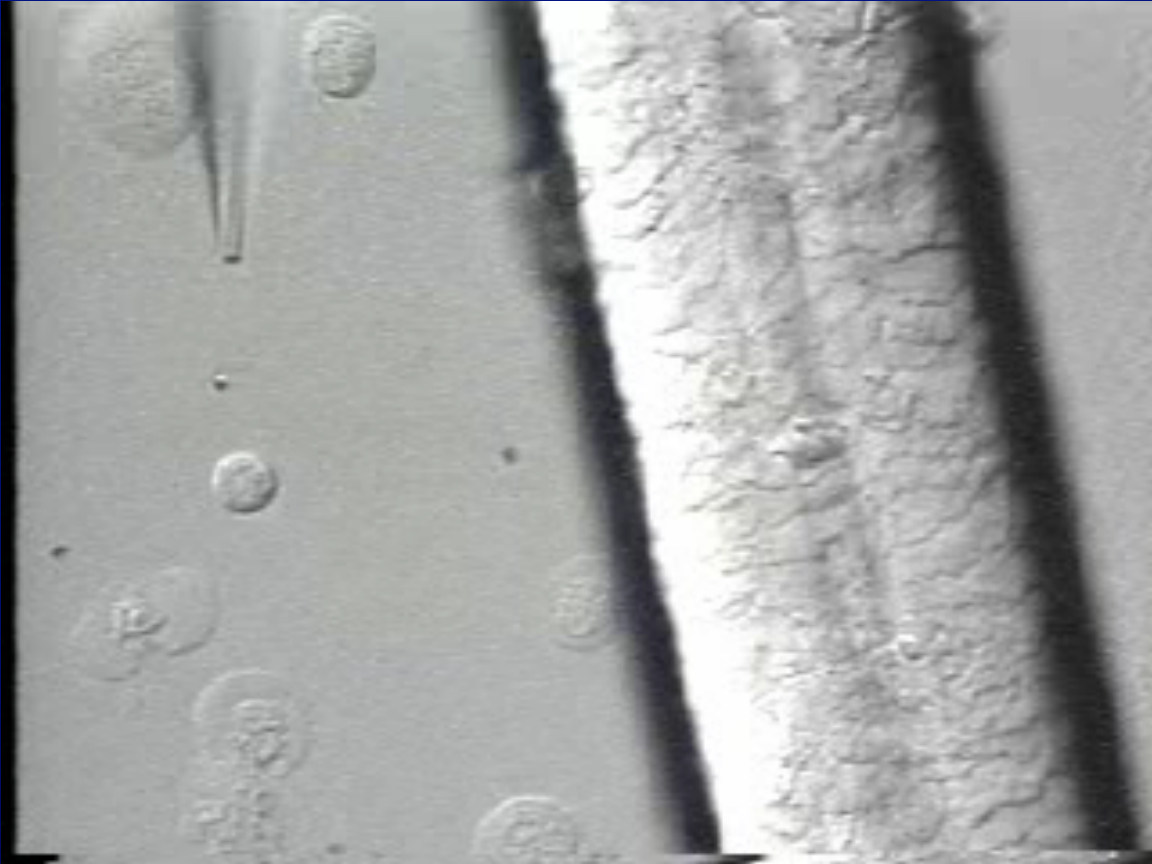
M: Mast cell

Basic Assumptions

2 - Importance of Electrophysiology



Nystatin Patch Clamp



Experimental Approach

Hypothesis

Cell Electrical Changes → Function

Methodology

Electrophysiology
& → Function
Enzyme Activity

Molecular Biology → Composition

Microscopy → Structure

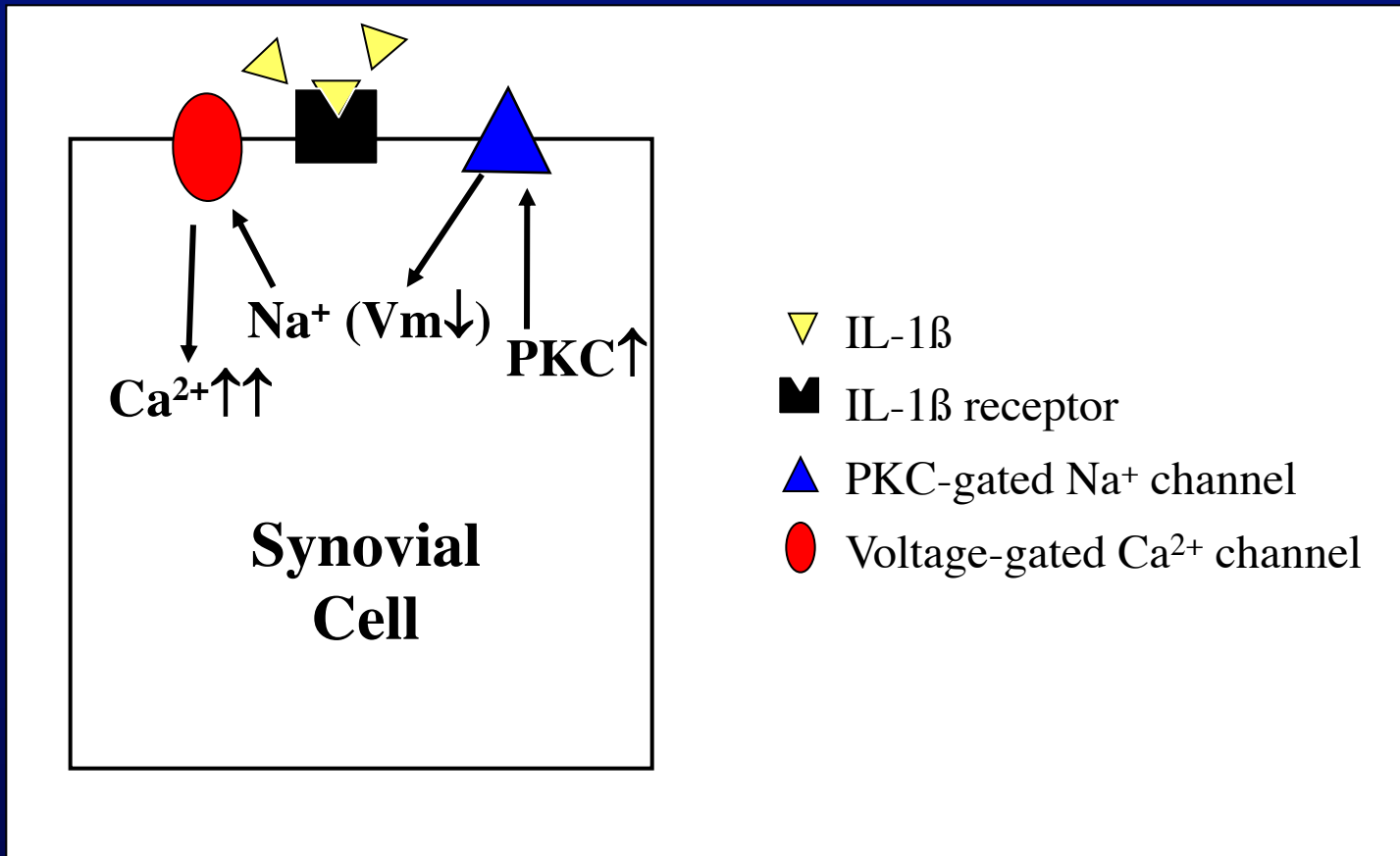
Objects of Study

HIG-82 Synovial Cells

Synovial Biopsies

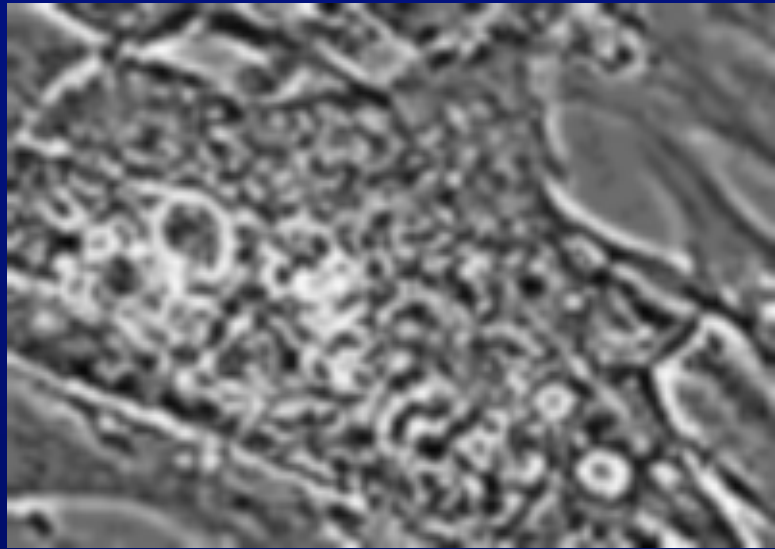
Important Discoveries

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

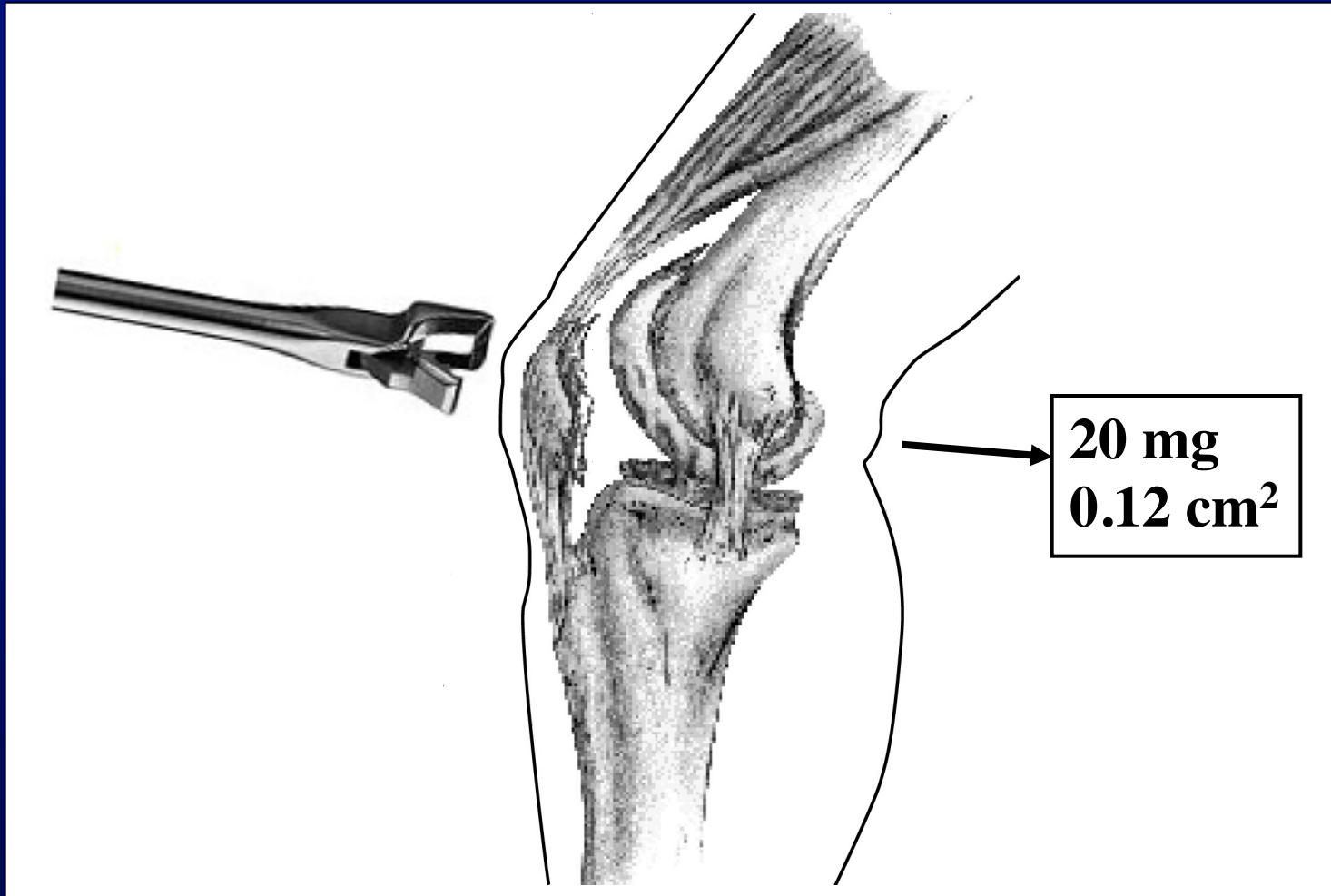


Gap Junctions



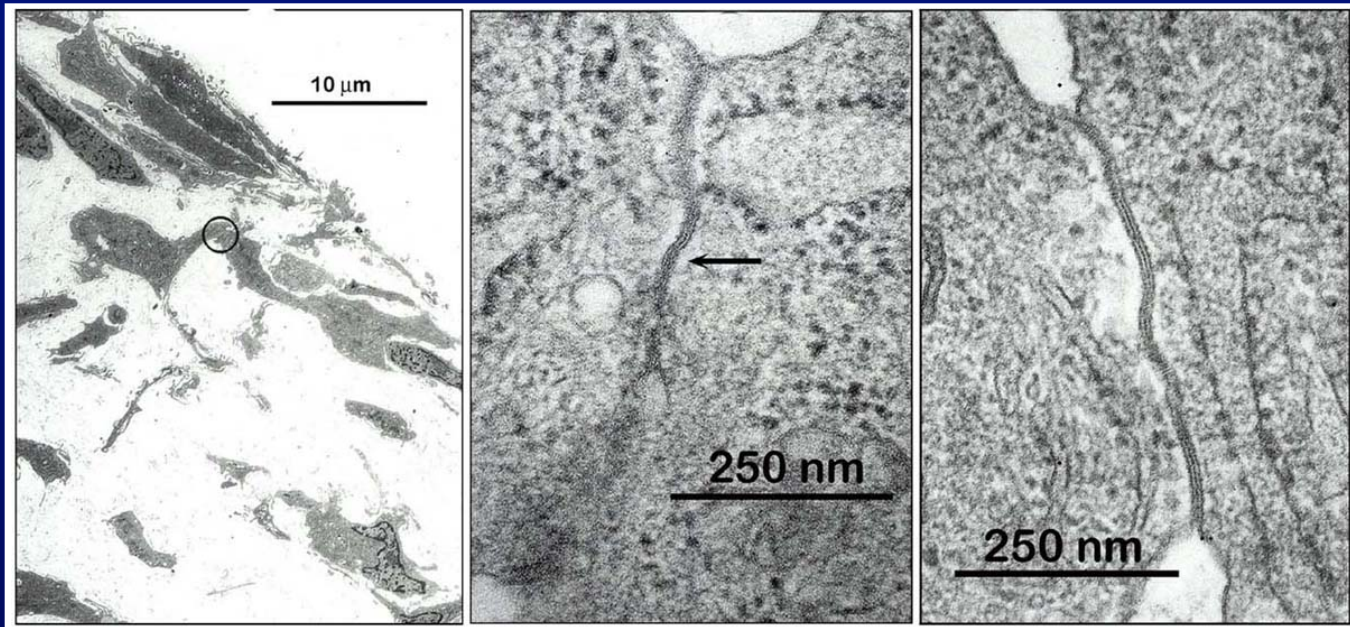


Surgical Biopsy Procedure

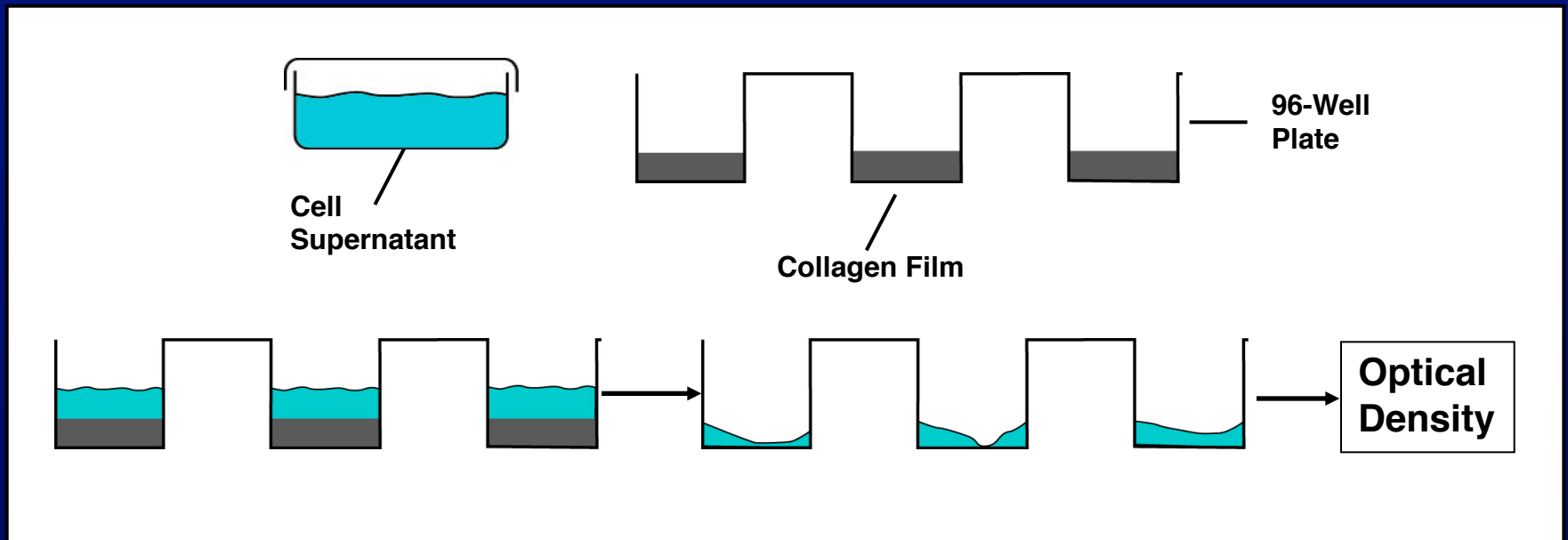


Important Discoveries

2. Gap Junctions Occur in Normal Human Synovium

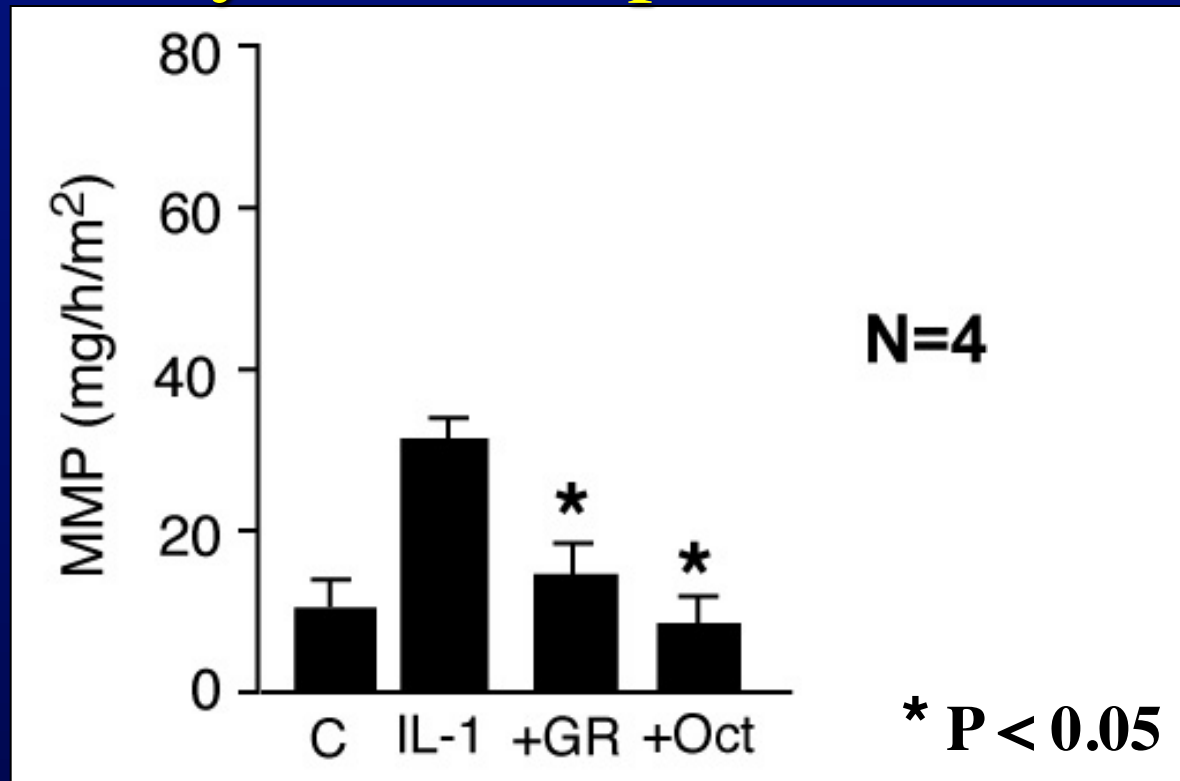


Metalloproteinase (MMP) Assay

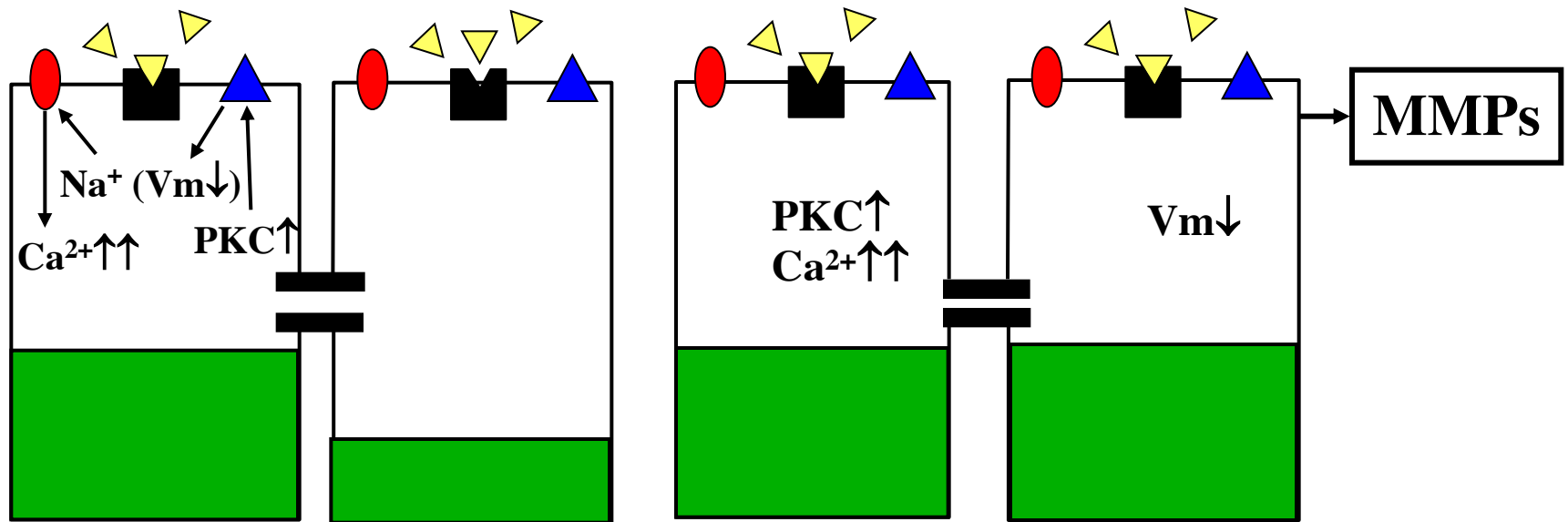


Important Discoveries

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



Modified Model



- ▼ IL-1 β
- IL-1 β receptor
- ▲ PKC-gated Na⁺ channel
- Relative Ca²⁺ concentration
- Voltage-gated Ca²⁺ channel
- = Gap-junction channel

Important Discoveries

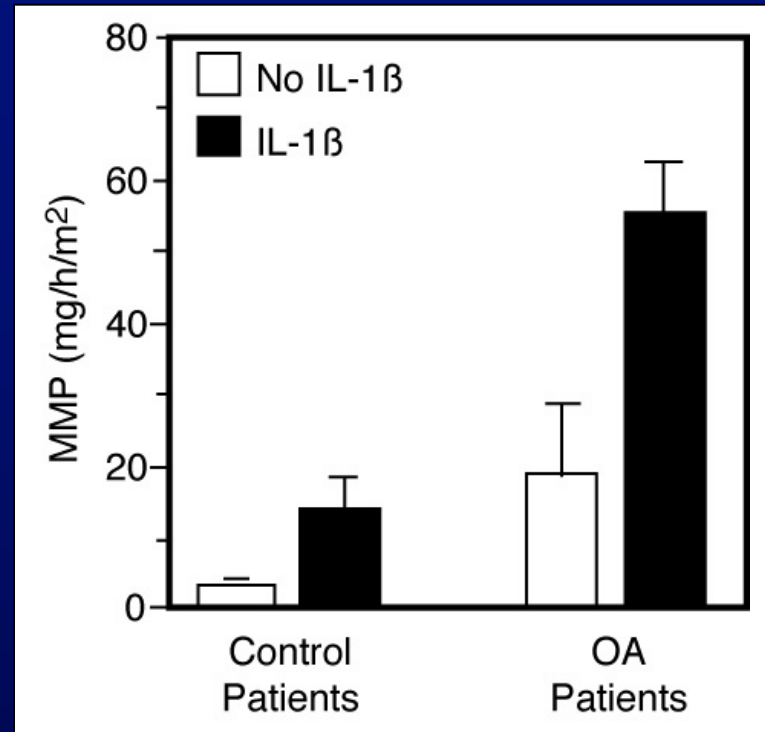
4. Relation Between Gap Junctions and Osteoarthritis

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

(Published this month in CORR)

Important Discoveries

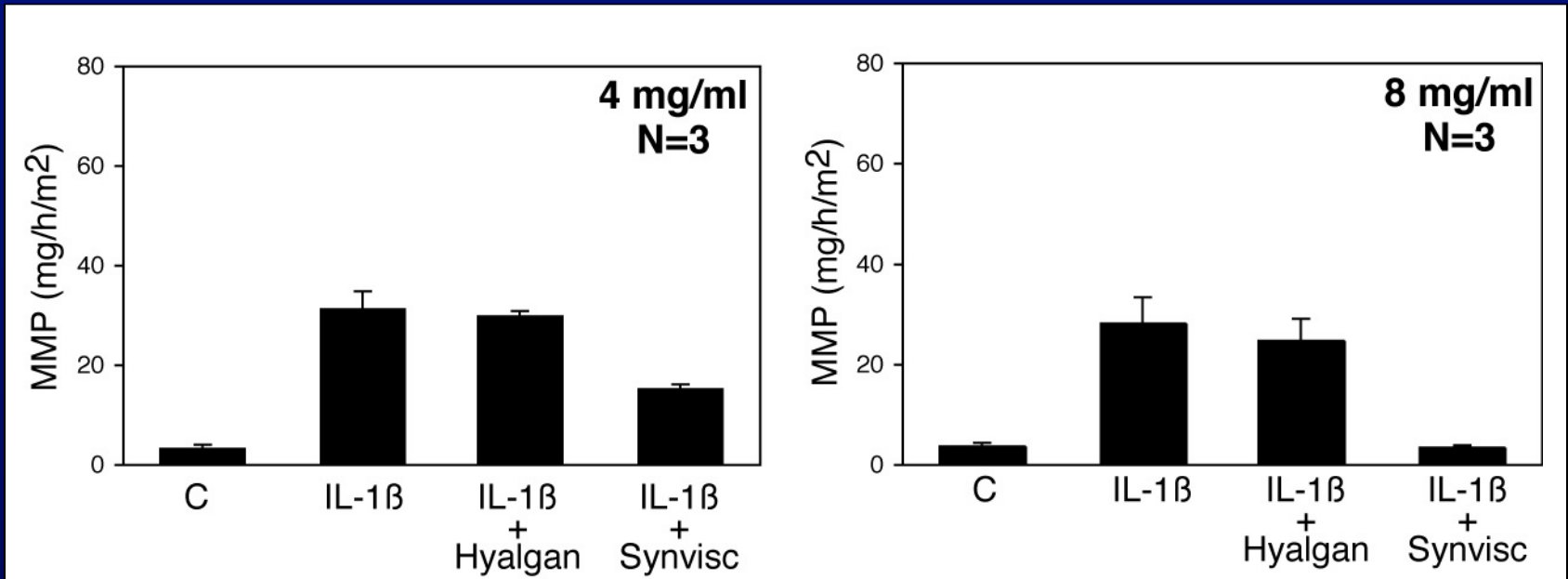
5. Synovial Cells Undergo a Phenotypic Change During the Development of Osteoarthritis



MMP Production by Synovial Tissue

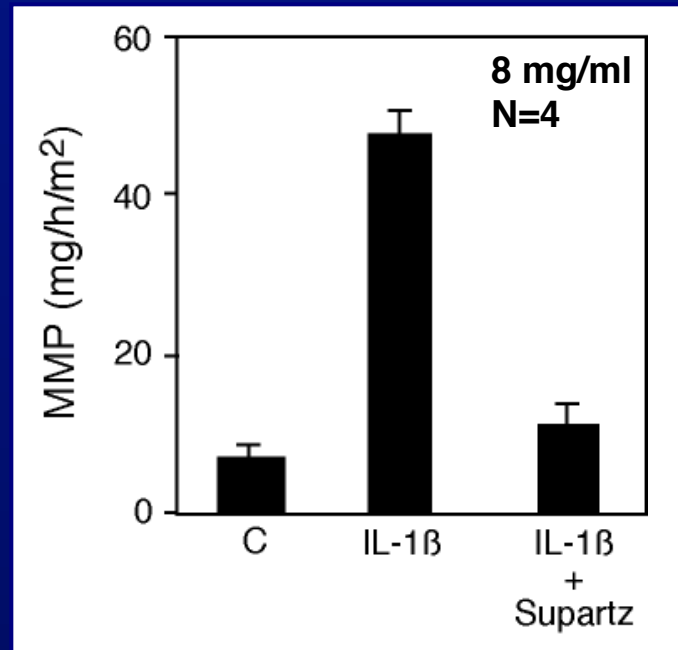
Important Discoveries

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

Supartz Antagonizes MMP Production



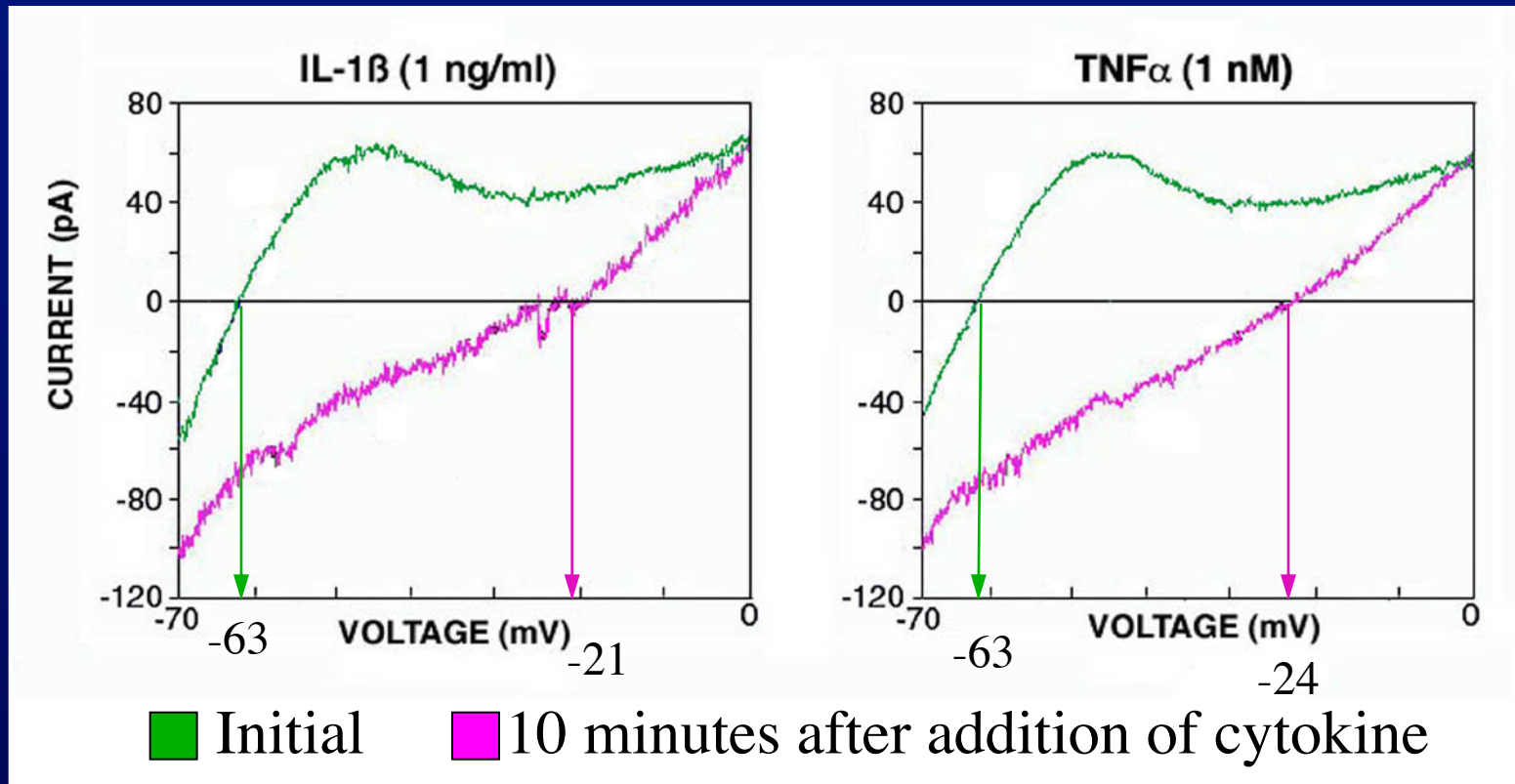
Effect of Supartz on IL-1 β Induced MMP Activity from Synovial Tissue of Osteoarthritis Patients

Present Status of Osteoarthritis Research

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

* Requesting 600K over 5 years from NIH, thus far, unsuccessfully

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

Na⁺





Ca⁺⁺



K⁺

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 reverse the disease