# Nanoparticle Interactions with Extracellular Matrix Modulate Immune Responses


**Alexandra Stubelius**

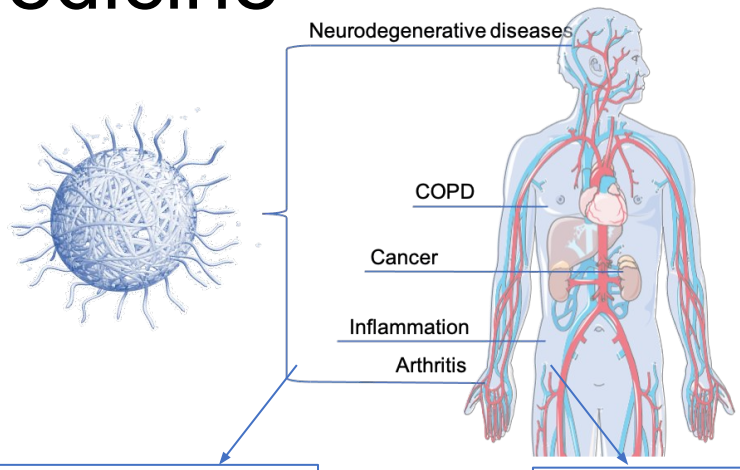
Department of Life Sciences
Chalmers University of Technology
Sweden



CONTROLLED RELEASE SOCIETY
CRS 2023 ANNUAL MEETING & EXPOSITION
JULY 24-28, 2023 Paris Hotel » Las Vegas, NV, USA
THE FUTURE OF DELIVERY SCIENCE

# Immunomodulating Nanomedicine lab-
## Materials for Precision Medicine

- Organic and Nanoparticle synthesis and characterization
- Cell, tissue, and animal models
- Patient material
- Flow cytometry, histology, spectroscopy
- Proteomics




**Increase Drug Delivery Specificity to Reduce Side Effects**

Design Inflammation-Specific Nanocarriers controlled by the microenvironment

**Design Materials To Modulate Key Immune-cell Checkpoints**

Targeting Glycans As Novel Immunomodulatory Mechanisms

**Define How Immune-cells, Nanoparticles and Tissues Interact**

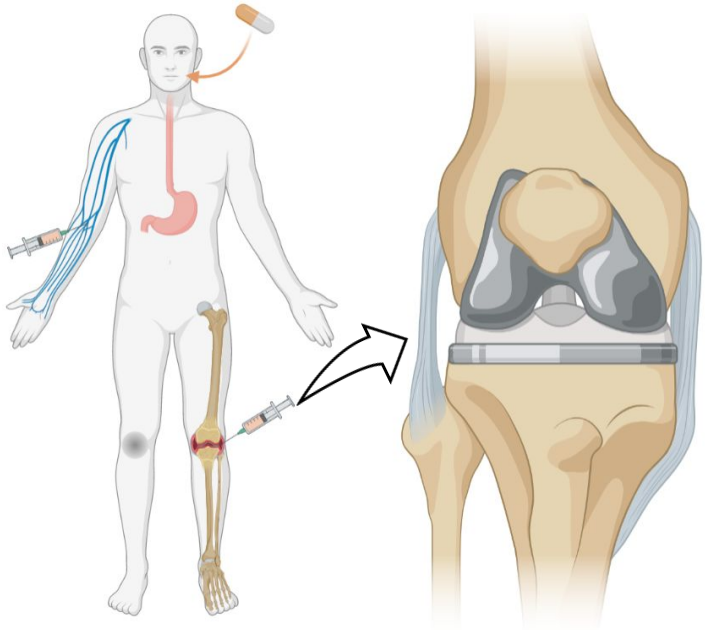
**To Develop Increasingly Specific Immunomodulatory Materials**

# **Osteoarthritis (OA)-** Degenerative Joint Disease Without Treatment

Incidence is on the rise:

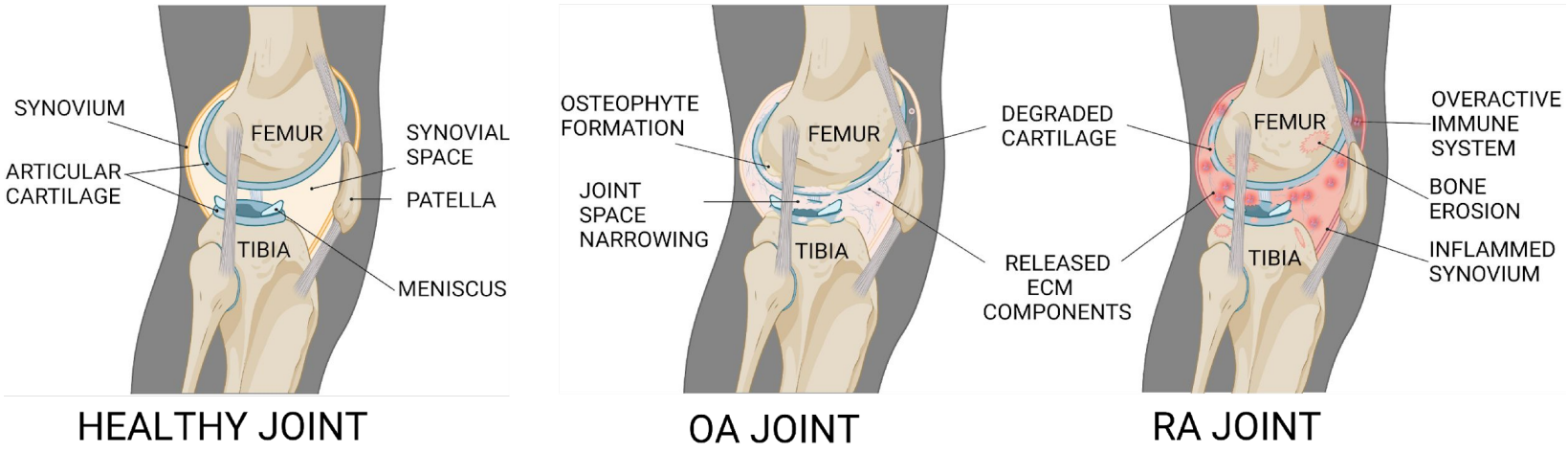
1 in 5


Insufficient treatments



# Challenges for drug delivery to joints

1. Synovial space: high clearance rate
2. Cartilage: extremely dense meshwork forms a barrier to drugs

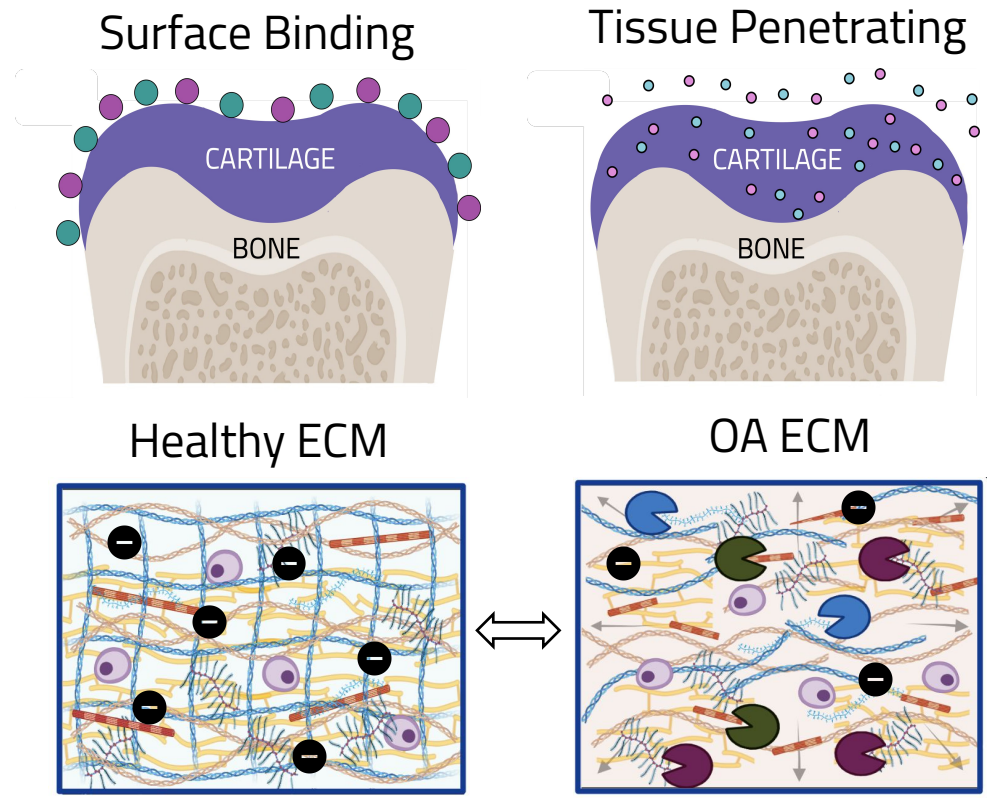



Macromol Biosci. 2022 DOI: 10.1002/mabi.202200037

# Nanomedicine for Intra-articular Targeting

Small carriers (NPs) can pass through the barrier

Environment utilized for therapeutic strategies



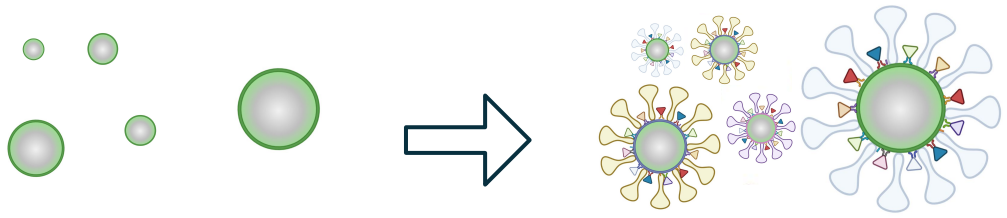
# Challenges for Nanomedicines Include Understanding Material-Biology Interactions

CHALMERS

THERAPEUTIC ADMINISTRATION

PHYSIOLOGICAL RESPONSE

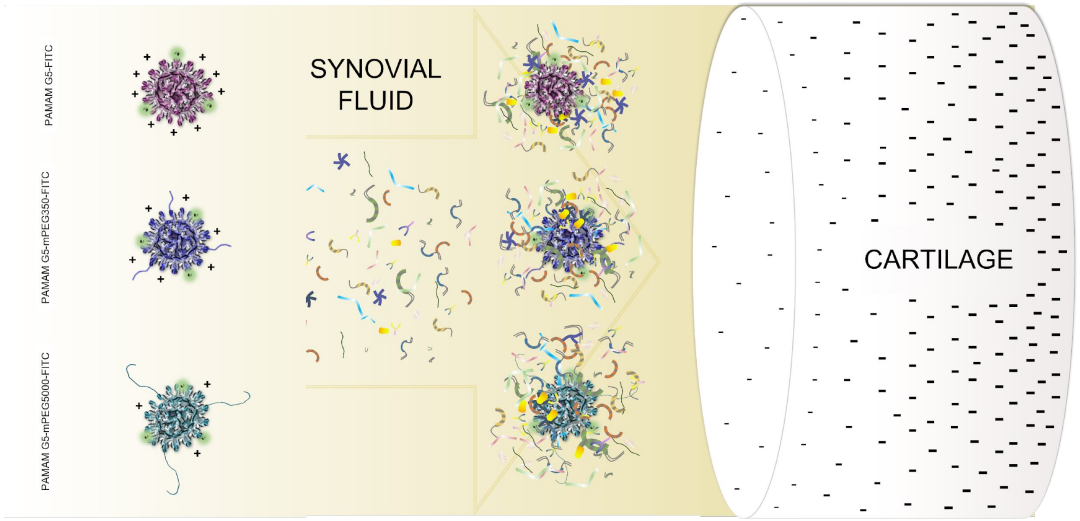
THERAPEUTIC OUTCOME

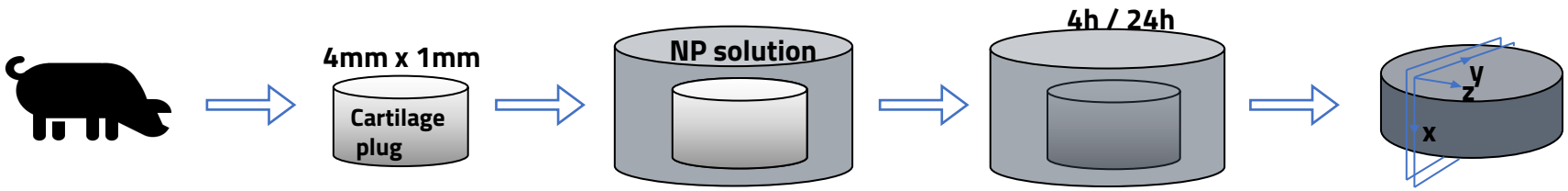


SYNTHETIC IDENTITY

BIOLOGICAL IDENTITY

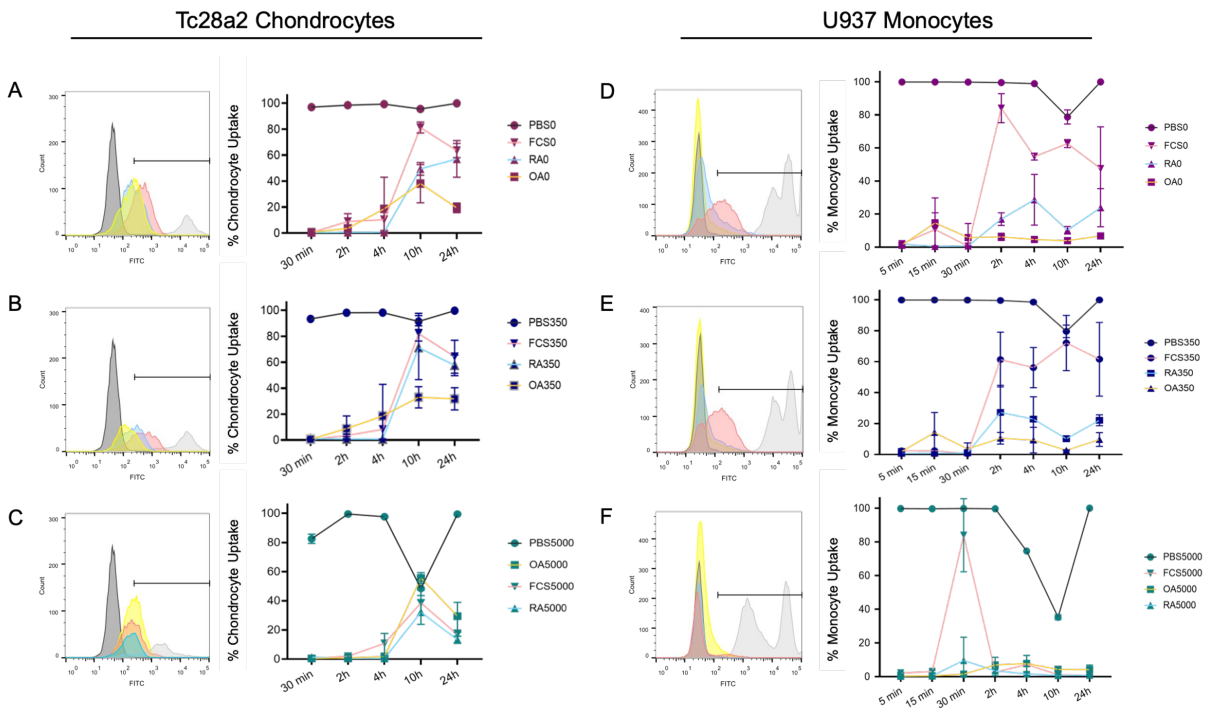
# Define How the Biological Identity of NPs Affect Cell and Tissue Interactions

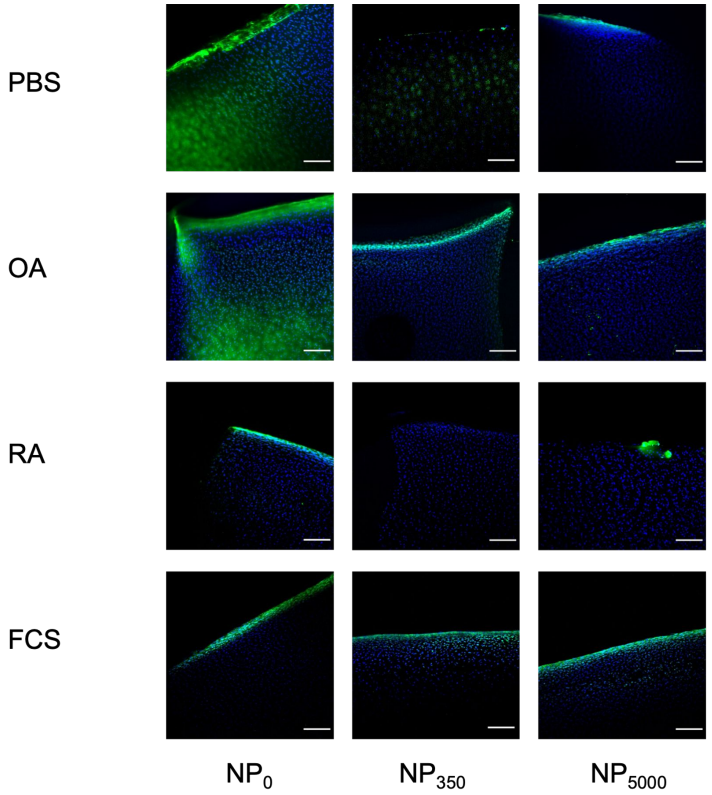



Osteoarthritis Cartilage DOI: 10.1016/j.joca.2022.07.002

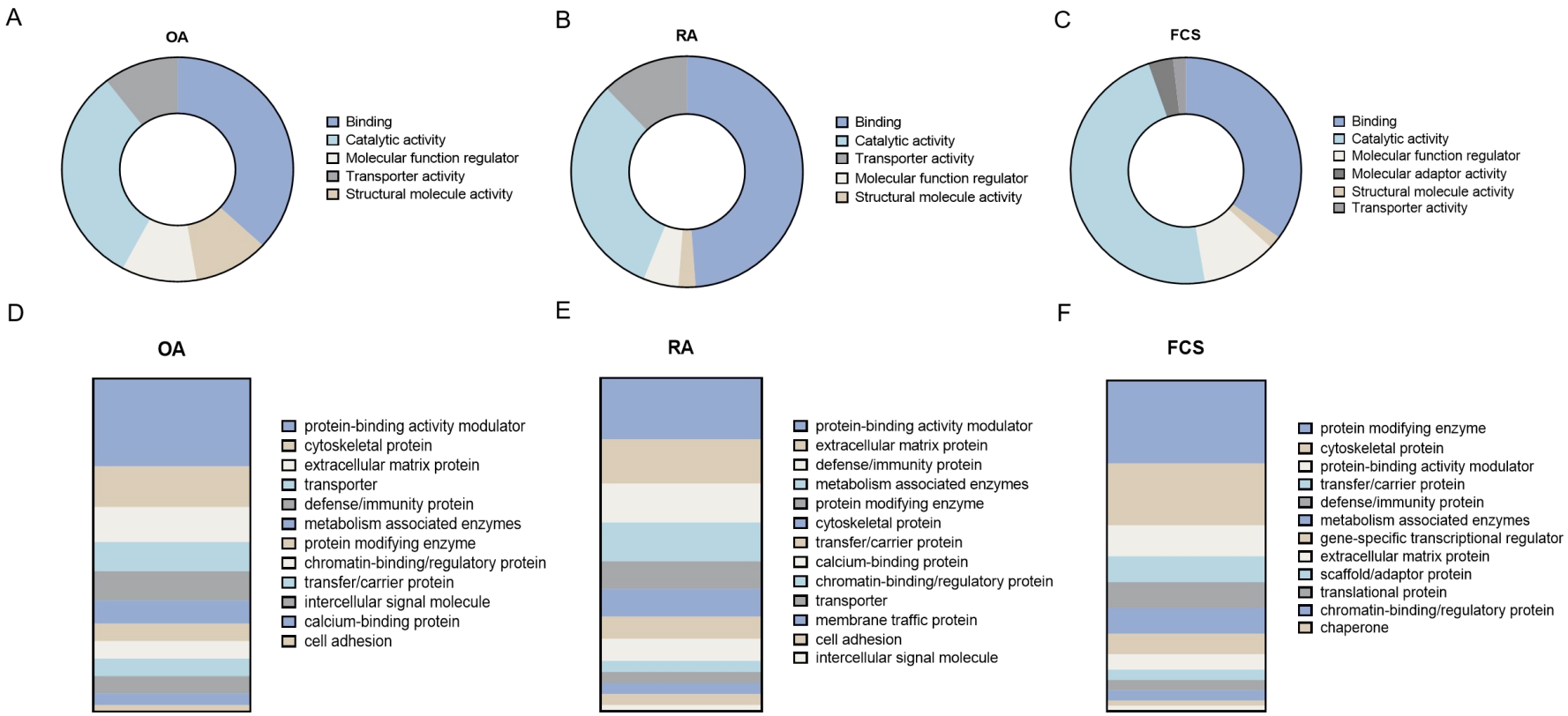
# The Biological Identity of NPs Affect Cell and Tissue Uptake



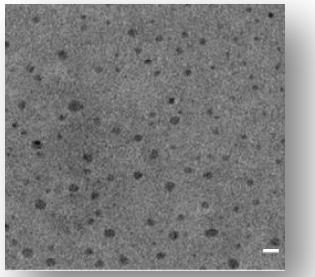
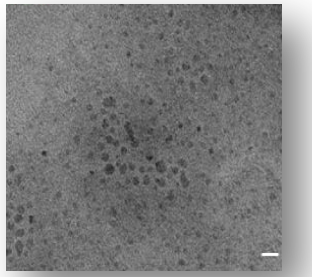
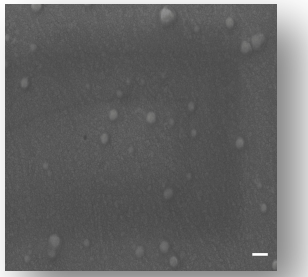
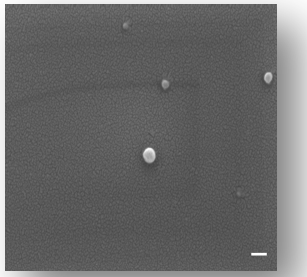

Osteoarthritis Cartilage DOI: 10.1016/j.joca.2022.07.002

# Proteomic Analysis Revealed Several Catalytic Enzymes



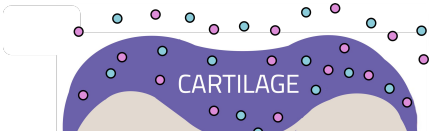

Osteoarthritis Cartilage DOI: 10.1016/j.joca.2022.07.002

# Cartilage Targeting NP Characteristics

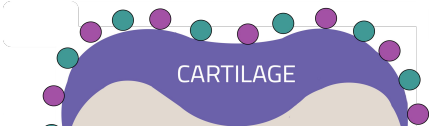
| | PAMAM-FITC (NP0) | PAMAM-PEG-FITC (NP5000) | PLGA-PEI-PEG-FITC 1:10 (PLGA-$PEI_H$) | PLGA-PEI-PEG-FITC 1:30 (PLGA-$PEI_L$) |
|---|---|---|---|---|
| |  |  |  |  |
| SIZE ($d_h$) (nm) | 6.0 ± 0.8 | 8.6 ± 3.1 | 270 | 265 |
| ZETA POTENTIAL (mV) | +16.5 | +6.4 | +22.2 | +3.8 |

Scale bar = 100nm

Tissue Penetrating




Surface Binding

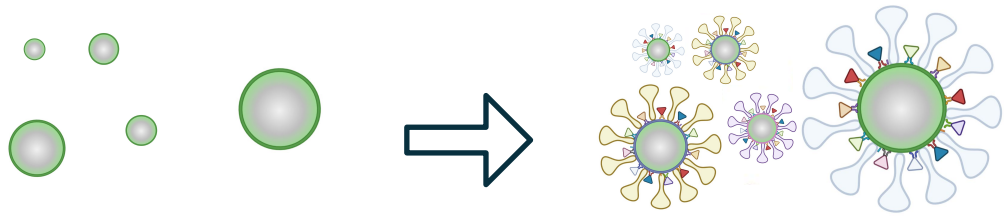


# Study Aim

Understand how NPs and cartilage ECM interact to determine:

I. The effects on structural components

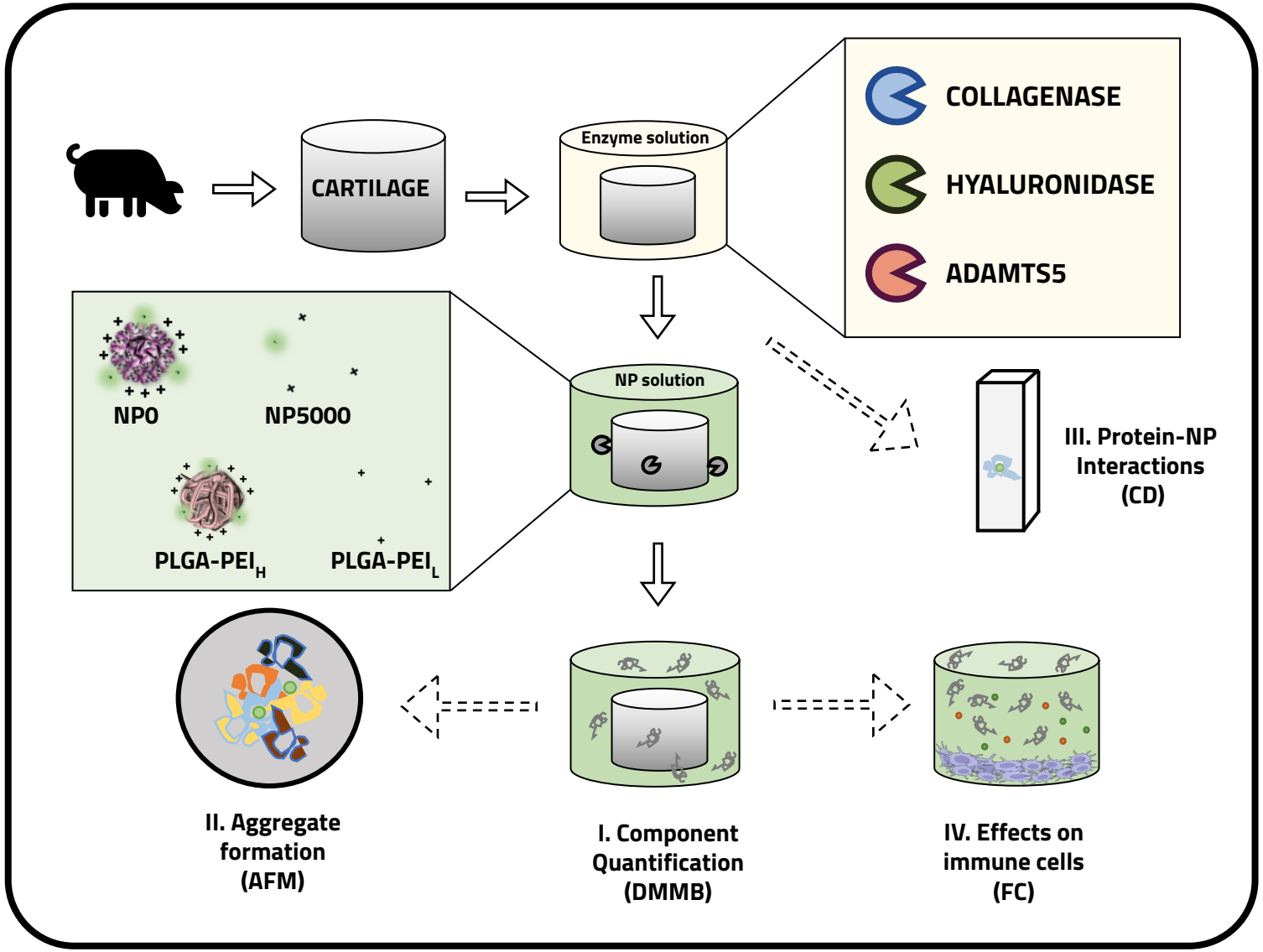
II. Subsequent immune engagement



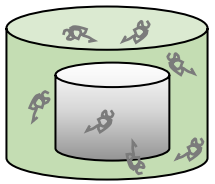
SYNTHETIC IDENTITY

BIOLOGICAL IDENTITY

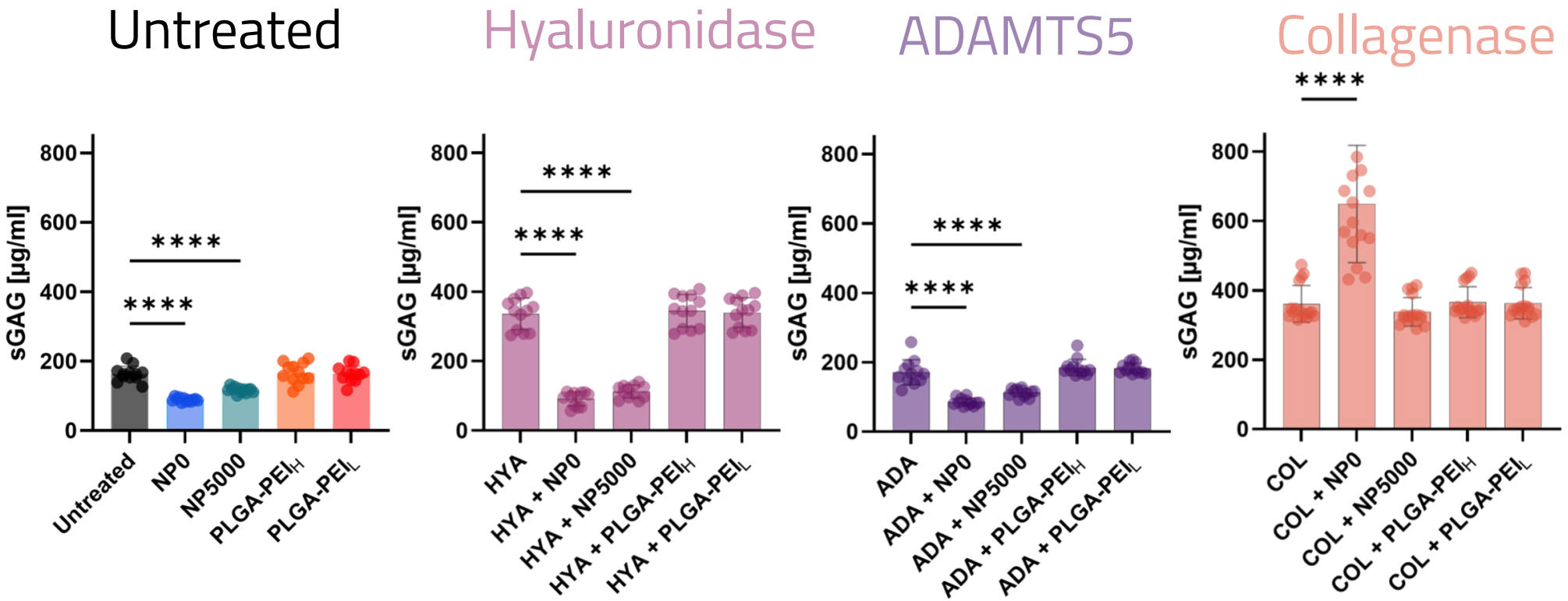
# Study Design



# GAG-Release is Influenced by NPs

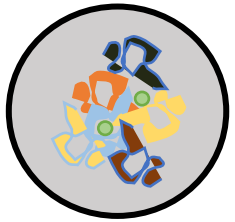


I. Component Quantification (DMMB)

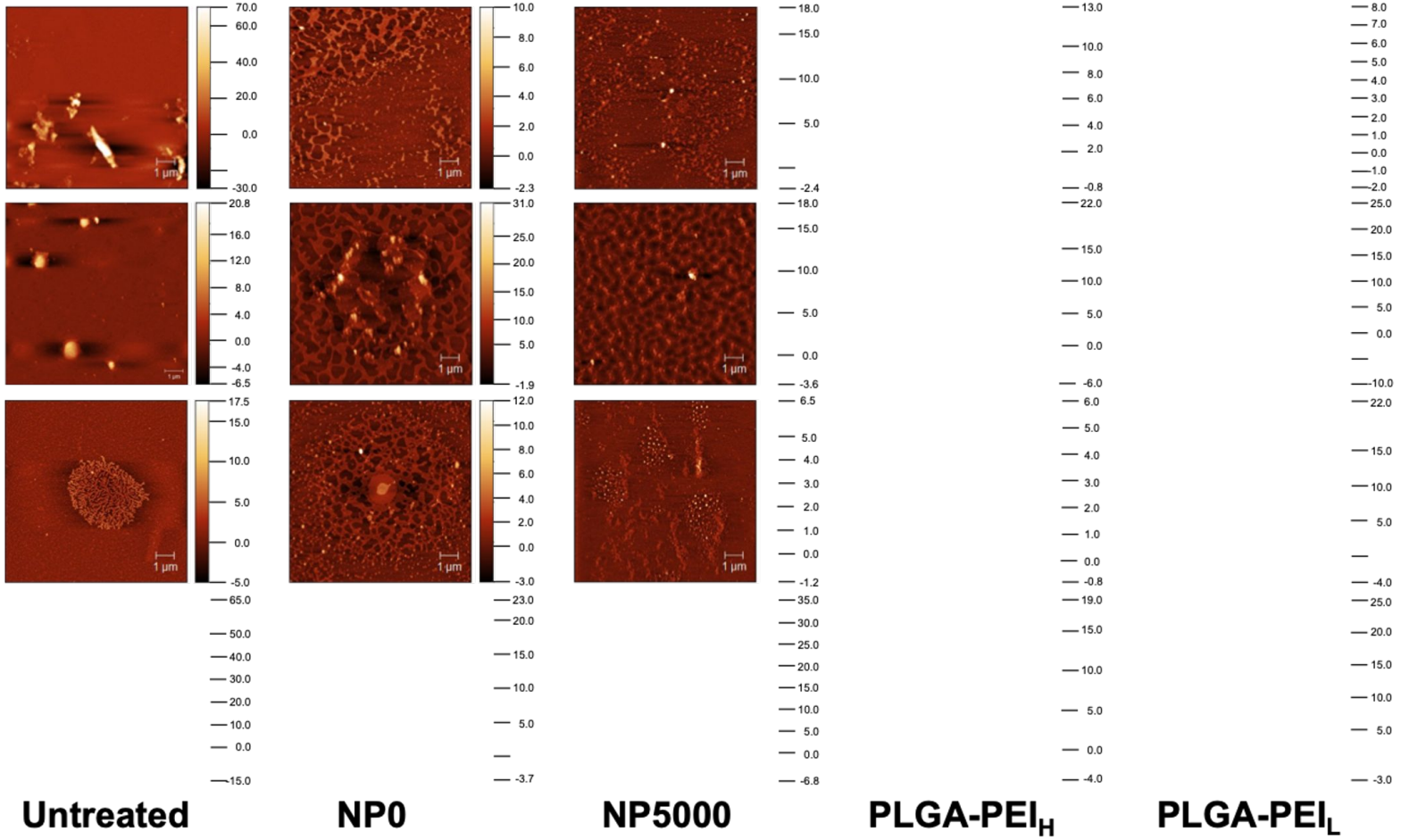



Data represents ANOVA analysis, where * = p ≤ 0.05, ** = p ≤ 0.01, *** = p ≤ 0.001, **** = p ≤ 0.0001

# Aggregates Depend on NP Properties

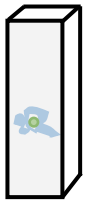


II. Aggregate formation (AFM)



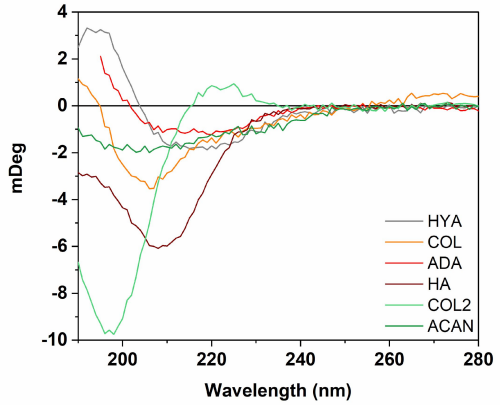

Scale bar = 1 µm

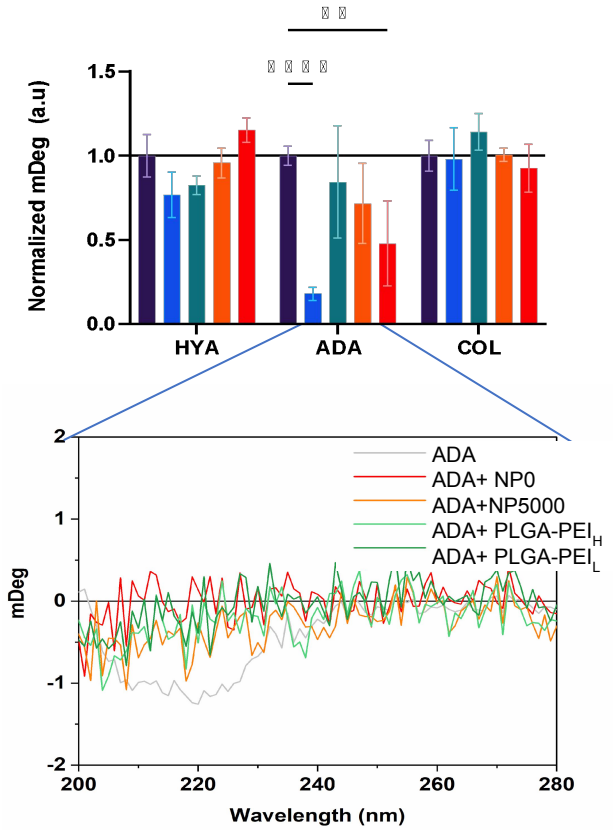
# Circular Dichroism Reveal Distinct NP-Interactions

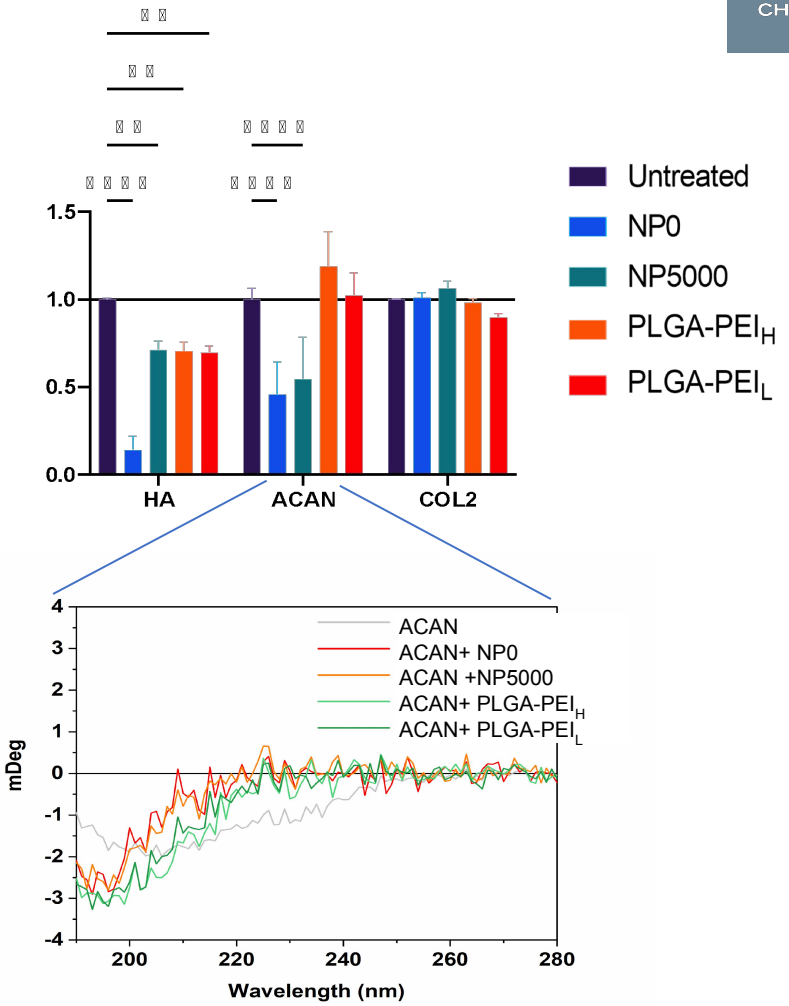


**III. Protein-NP Interactions (CD)**

## Baseline Secondary Structures

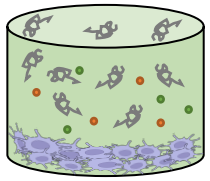


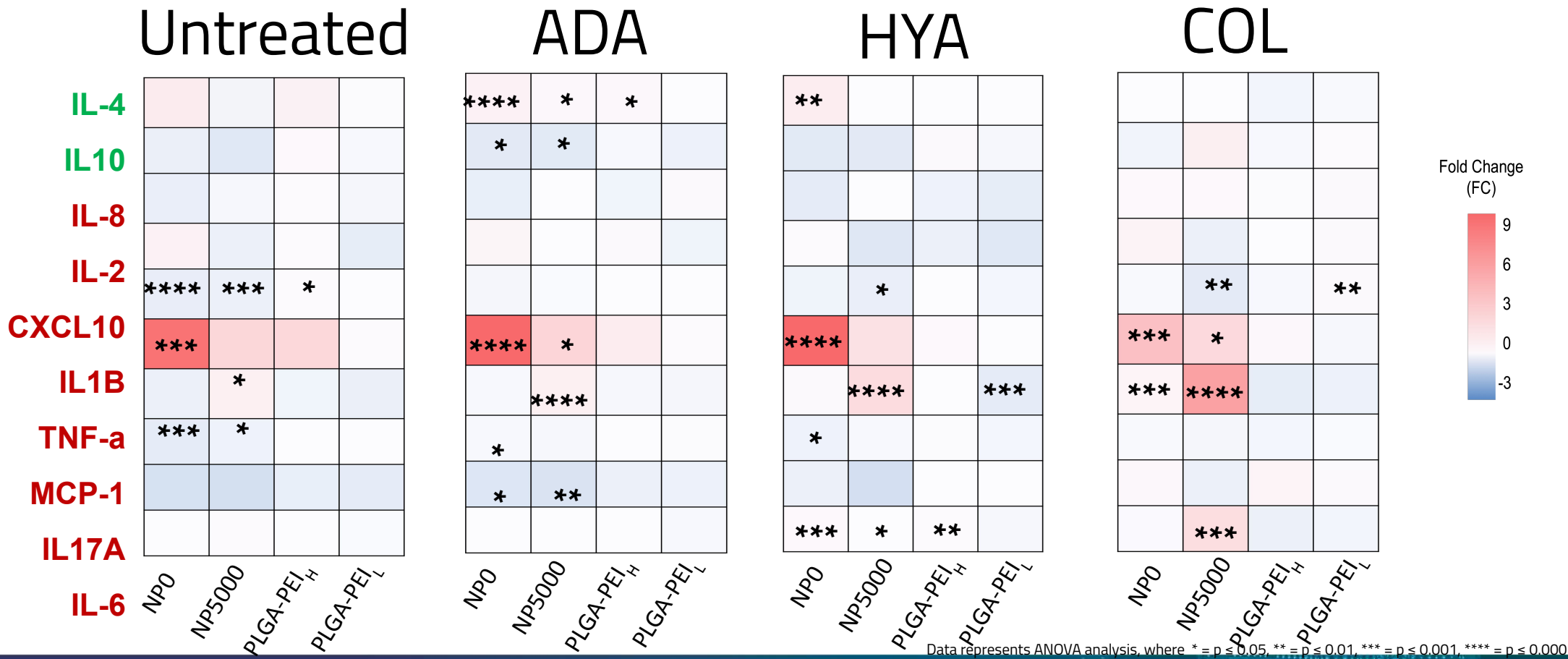




Data represents ANOVA analysis, where * = p ≤ 0.05, ** = p ≤ 0.01, *** = p ≤ 0.001, **** = p ≤ 0.0001

# Macrophages Produce Cytokines in Response to Aggregates



IV. Effects on immune cells



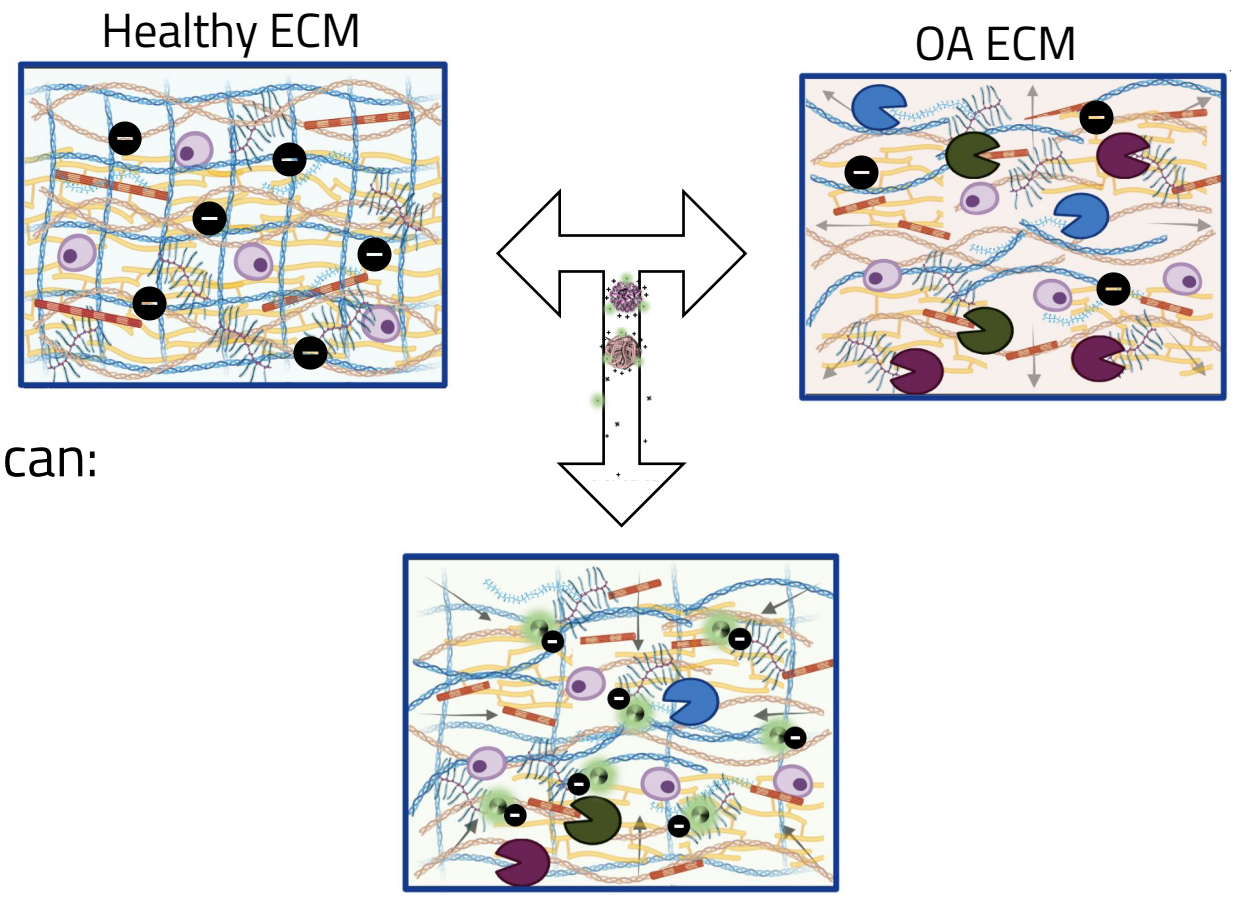

Data represents ANOVA analysis, where * = p ≤ 0.05, ** = p ≤ 0.01, *** = p ≤ 0.001, **** = p ≤ 0.0001

# Conclusions

By altering the structures of ECM proteins, electrostatic interactions between cationic nanoparticles and anionic ECM components can:

I. Stabilize cartilage integrity

II. Induce distinct immune responses



**Immunomodulating Nanomedicine Lab-**

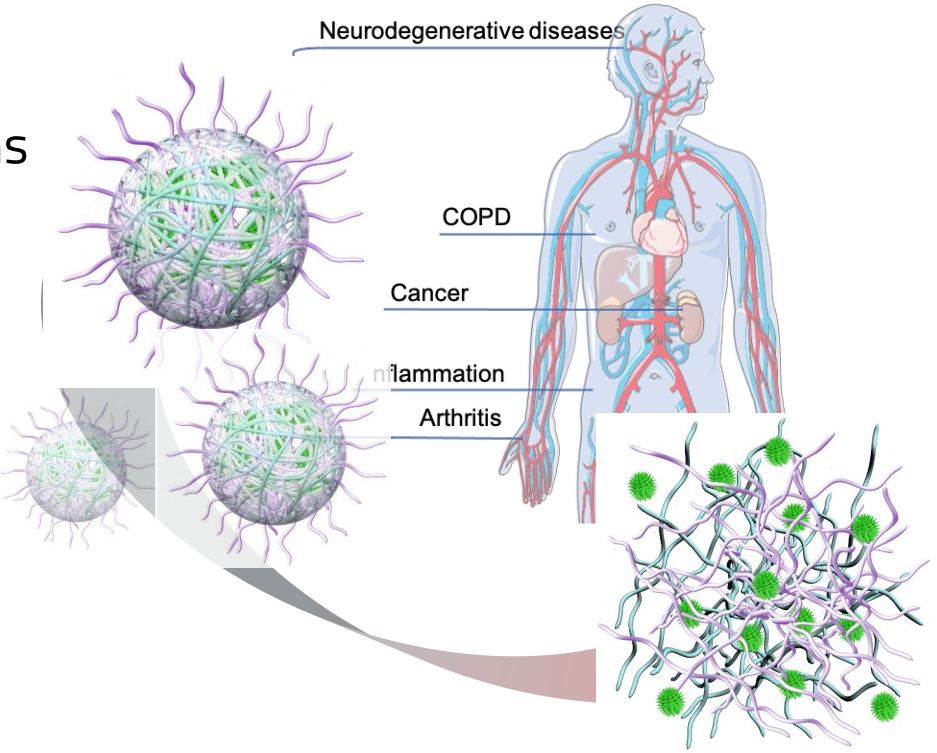
# Future Challenges

- Time dependency to understand the duration of the interactions
- Drug loading for NP therapeutic efficacy

- Define microenvironmental cues
- Identify targets

Control the microenvironment

- Responsive materials
- High affinity materials



## Immunomodulating Nanomedicine lab-

# Acknowledgements


Hasselbladstiftelsen Hasselblad Foundation

IngaBritt och Arne Lundbergs Forskningsstiftelse

Kungl. Vetenskaps- och Vitterhets-Samhället i Göteborg (KVVS)
*The Royal Society of Arts and Sciences in Gothenburg*

Stiftelsen Konung Gustaf V:s 80-årsfond

Stiftelsen Sigurd och Elsa Goljes Minne

Stiftelsen Apotekare Hedbergs
Fond för Medicinsk Forskning

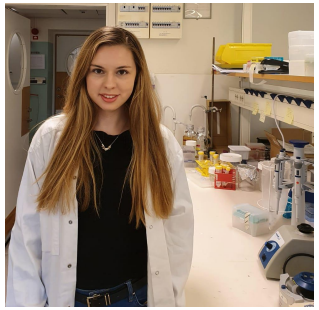
KUNGL. VETENSKAPS-AKADEMIEN
THE ROYAL SWEDISH ACADEMY OF SCIENCES

Jeanssons Stiftelser

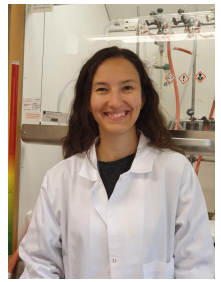
Vetenskapsrådet

CHALMERS
UNIVERSITY OF TECHNOLOGY

Excellence Initiative
NANO

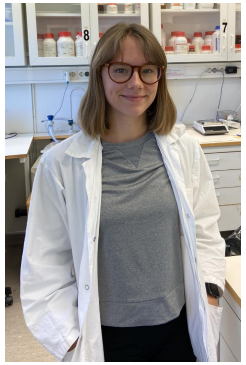



**Ula, Nano/Biomaterial Biologist, PhD Student**



**Gizem, Organic Chemist Postdoc**

**Elin, Biotech Engineer, Project Assistant**



**Loise, Molecular Biologist, PhD Student**

Graduate and undergraduate students:

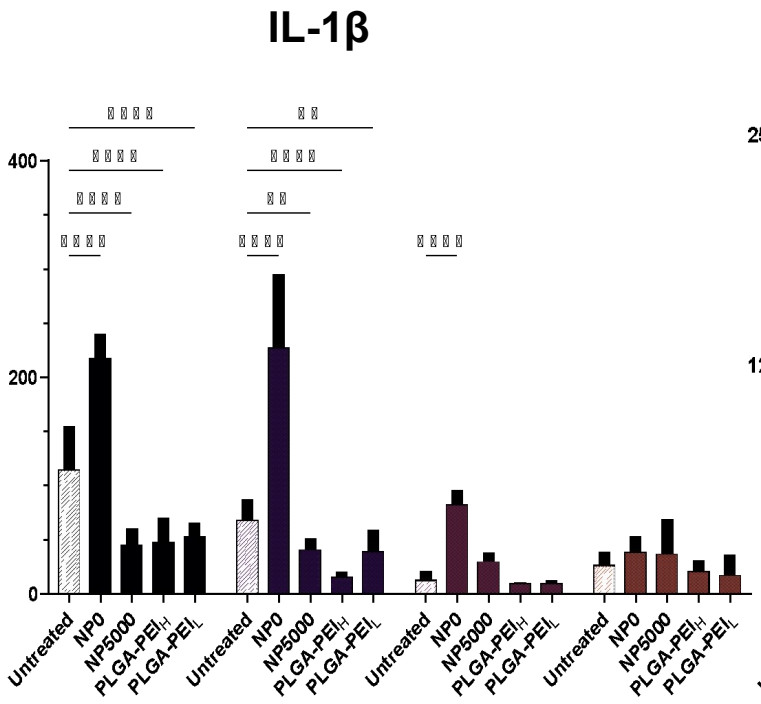
Joan and Yoliti (Pharmacy: Spain, Sweden),
Aline (Biotech: Sweden)
Sandra (Biomaterials: Austria)
Alex (Physics: Sweden)

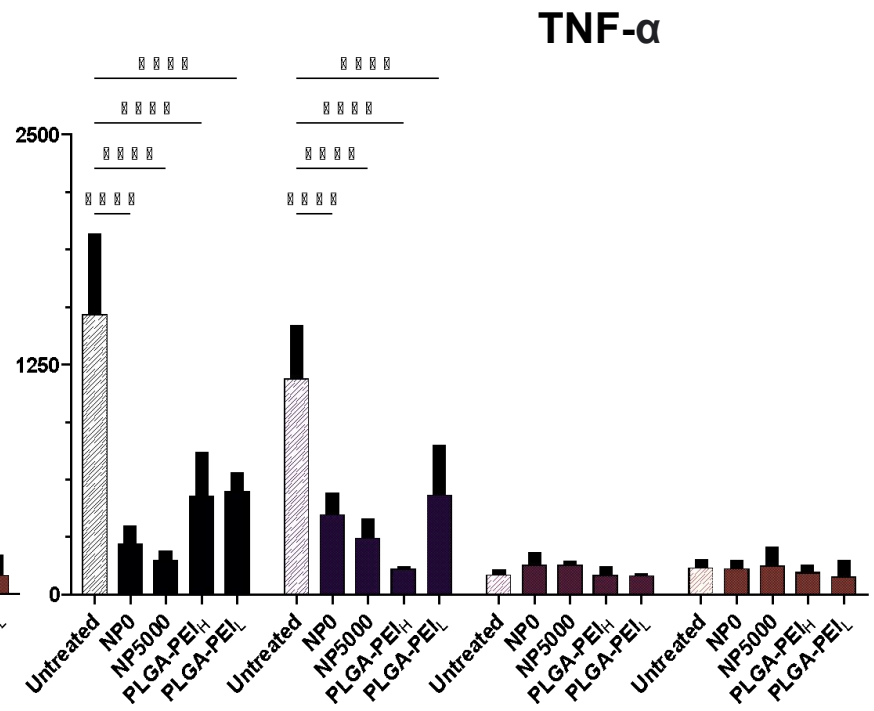

CHALMERS

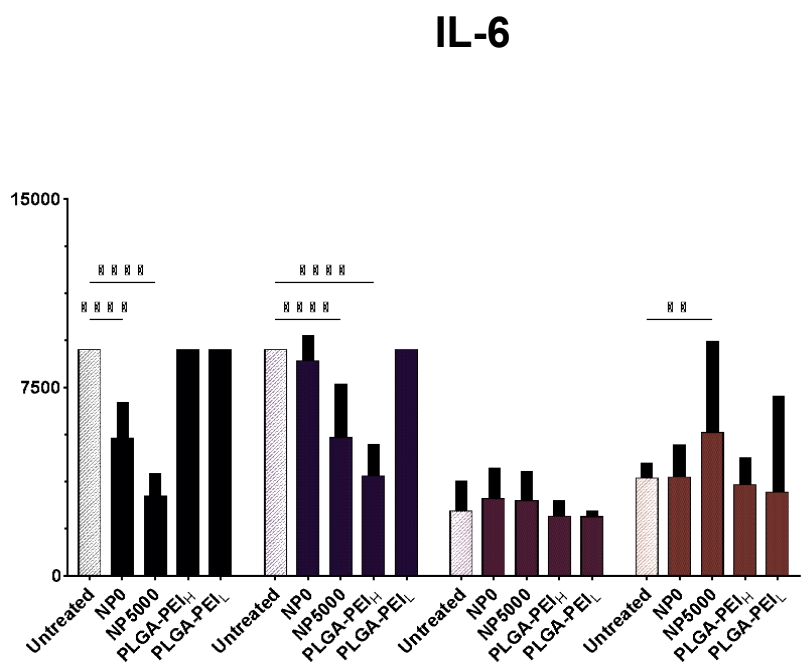
CHALMERS

# *Supplementary Information*

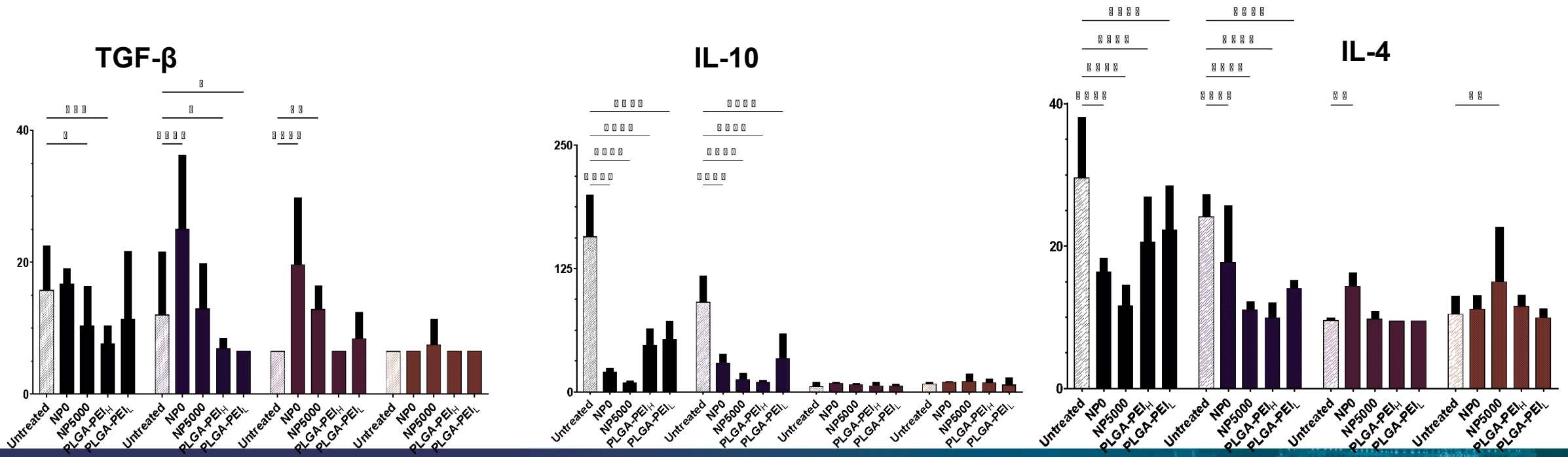
# Macrophage Cytokine Production to Aggregates



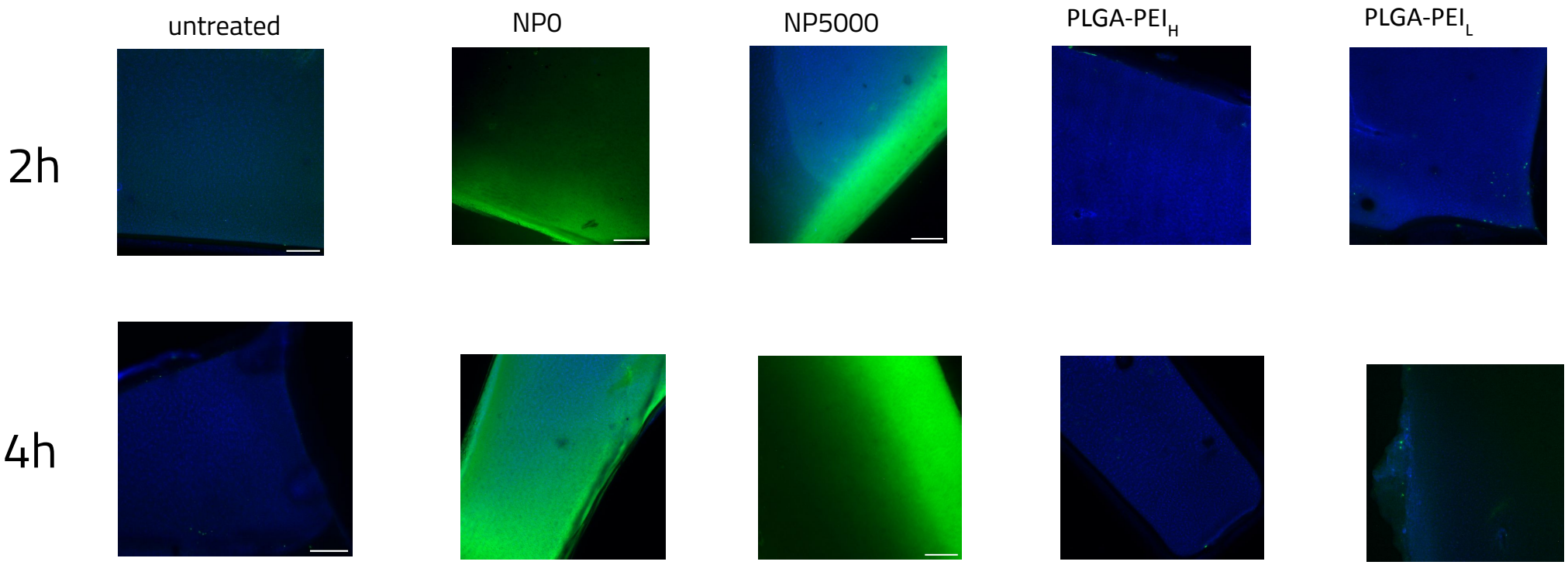



# Macrophage Cytokine Production to Aggregates



# Cartilage Uptake Into Cartilage Explants






untreated