

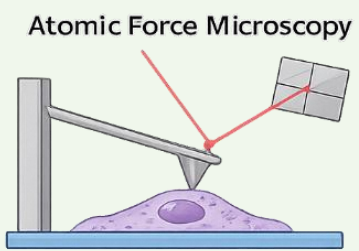
# Remote control of mechanosensitive ion channels with magnetic nanoconjugates

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## Background

- Mechanobiology studies how cells convert physical forces into biochemical signals through mechanoreceptors.
- Precise control of mechanical stimulation remains challenging:

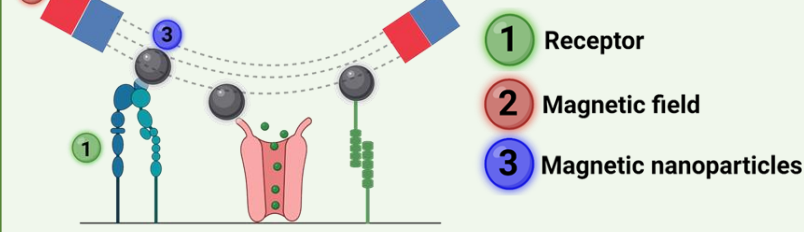


### Limitation

- One cell at a time
- Low penetration
- Invasive
- Remote control

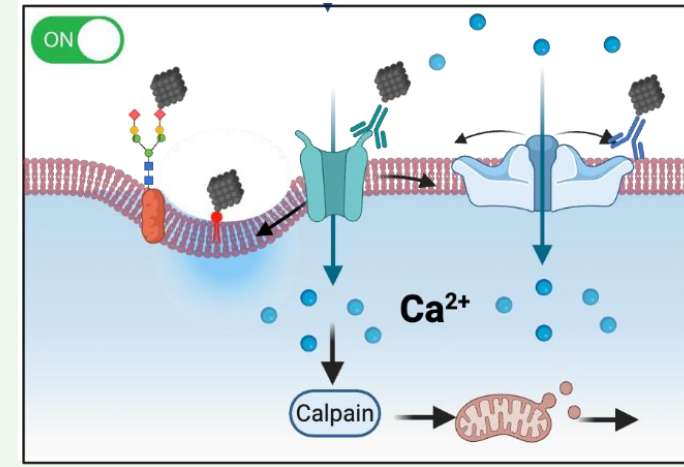
- Magnetic nanoparticles (MNPs)** enable remote, non-invasive and tunable force application to a high numbers of cells simultaneously.

### Magnetogenetics



## Objective

The goal is to activate mechanosensitive ion channels such as **Piezo1** and **TRPV4** using magnetic nanoparticles that generate controllable forces when exposed to an external **magnetic field**.



### Mechanical stretching

↓

Ion channel opening

↓

Elevated Ca<sup>2+</sup> levels

↓

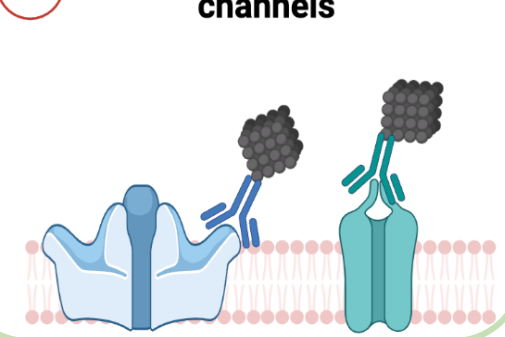
Cellular response

## Experimental strategies

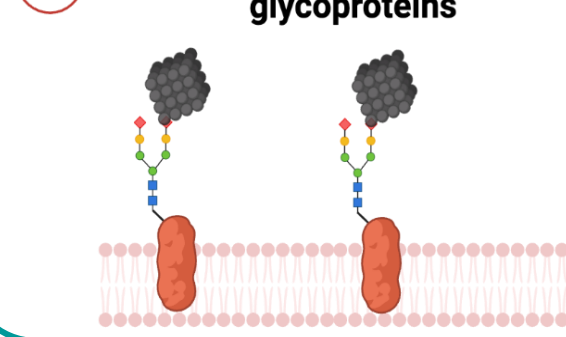
We propose two MNPs-based strategies to activate mechanosensitive ion channels

### STRATEGIES

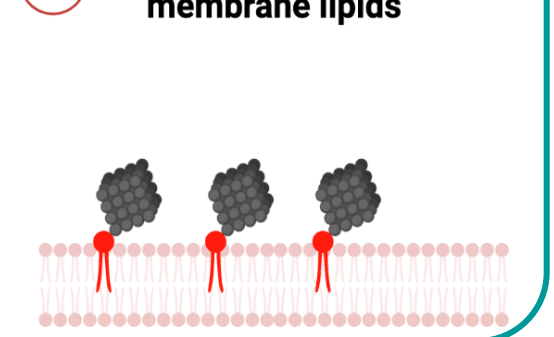
#### 1 Direct targeting of MS ion channels



#### 2a MNP attachment to cell membrane glycoproteins

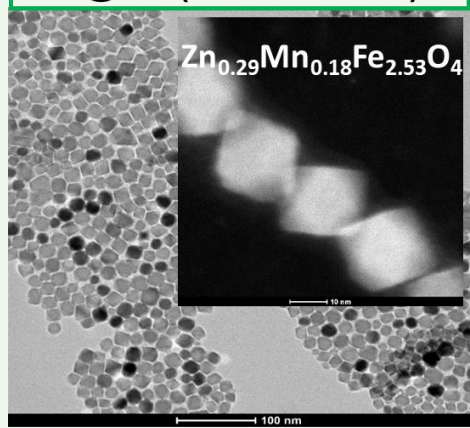


#### 2b MNP attachment to cell membrane lipids

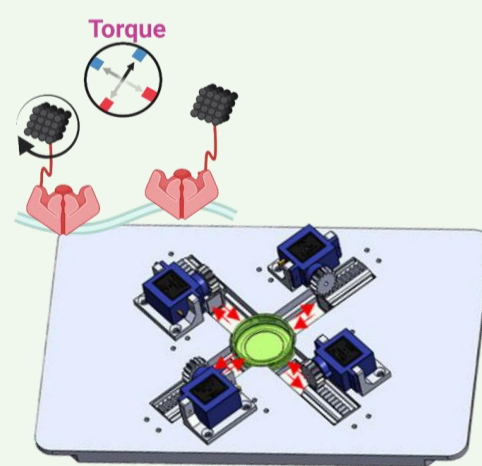
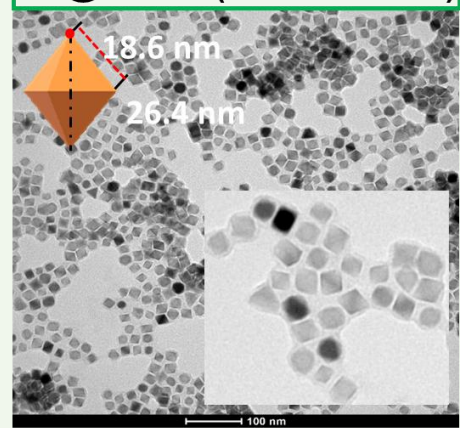


## Results

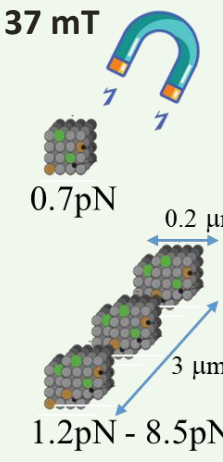
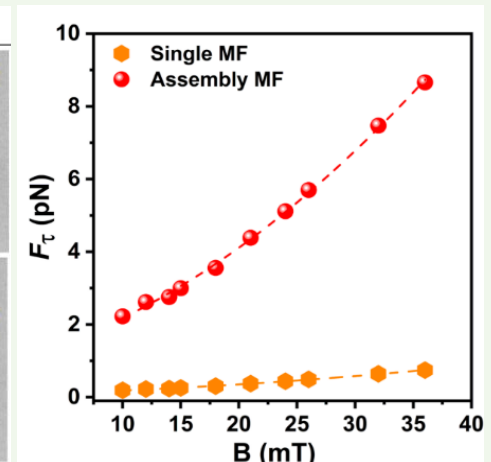
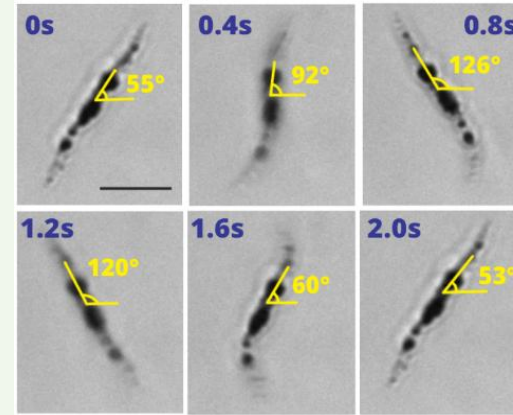
### MF@OA (18.6 ± 1.9 nm)



### MF@PMAO (18.0 ± 1.6 nm)



### Magnetic field ON



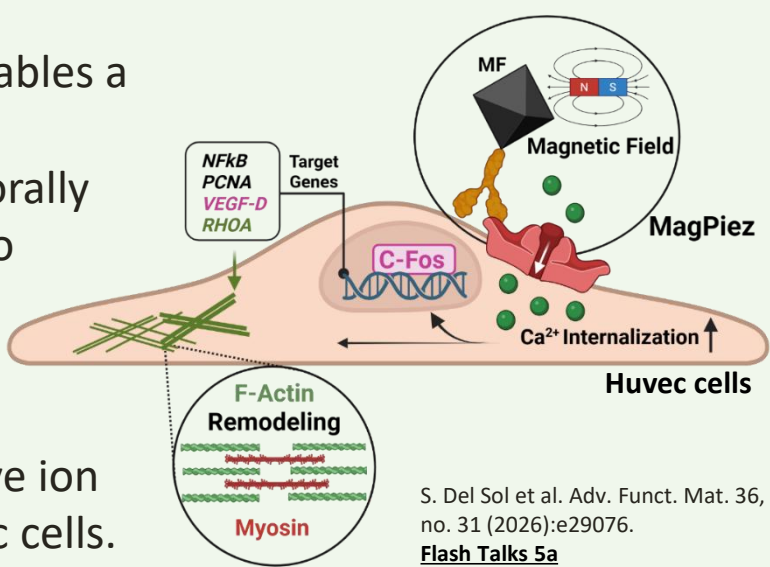
Mixed ferrite (MF) synthesis by one-step thermal decomposition. Transference into water by polymer coating.

Custom-made magnetic field applicator suitable for in situ fluorescence imaging.

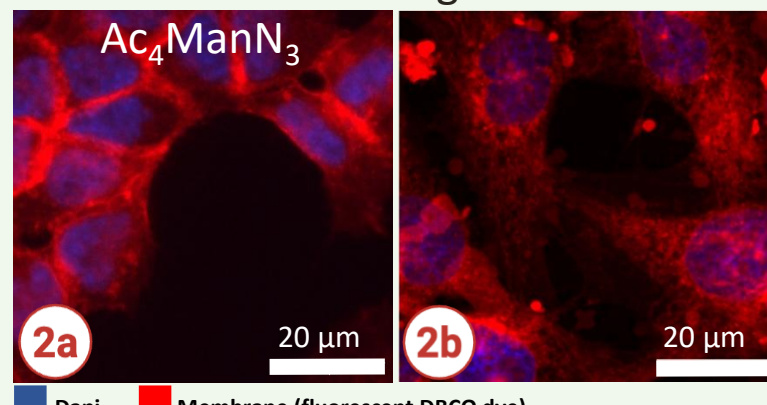
Force generated by an assembly of MNPs when subjected to a dynamic magnetic field (10–37 mT).

**1 Direct force on the channel:** MNPs are functionalized with antibodies that specifically bind the extracellular domains of the ion channels, allowing force to be delivered directly.

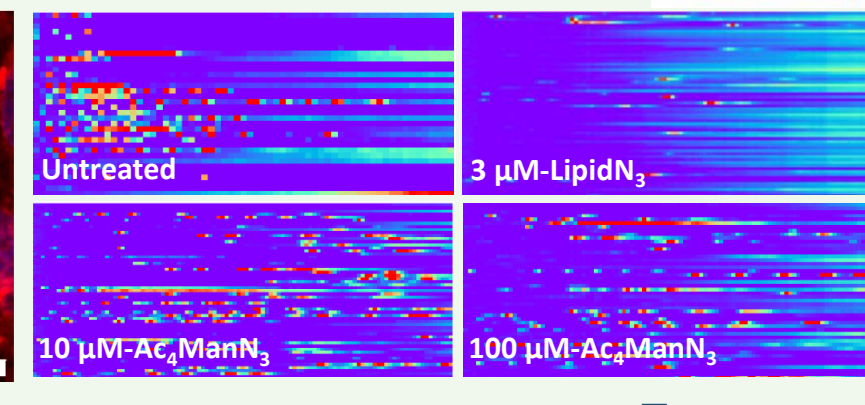
**MagPiez** tool enables a remote, precise, and spatiotemporally controlled way to modulate endogenous **Piezo1** mechanosensitive ion channel in Huvec cells.



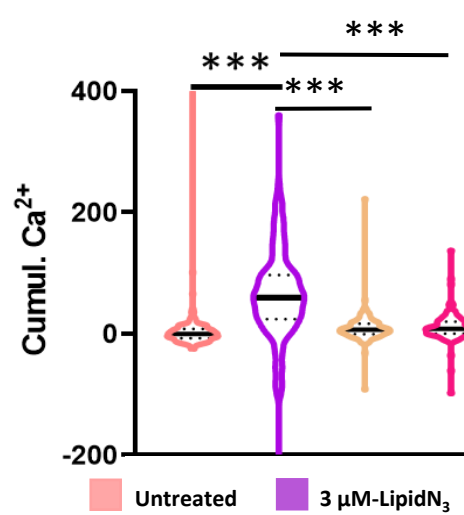
### Membrane labeling of A431 cells



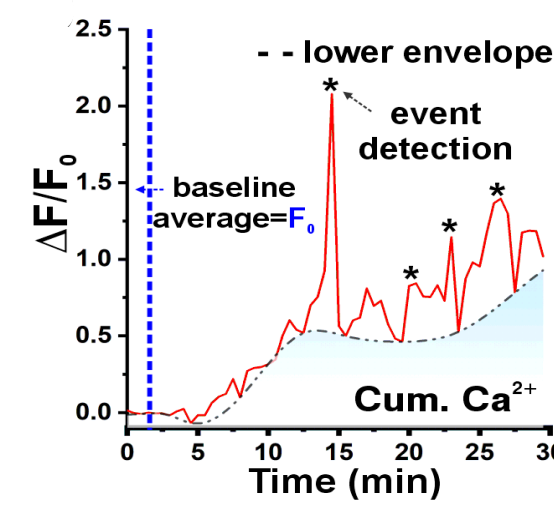
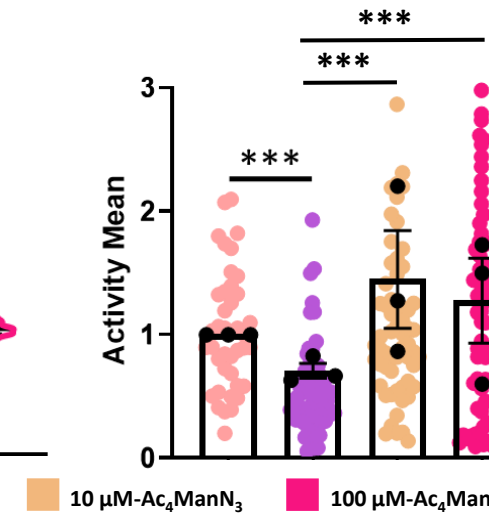
### Ca<sup>2+</sup> influx



### Calcium accumulation

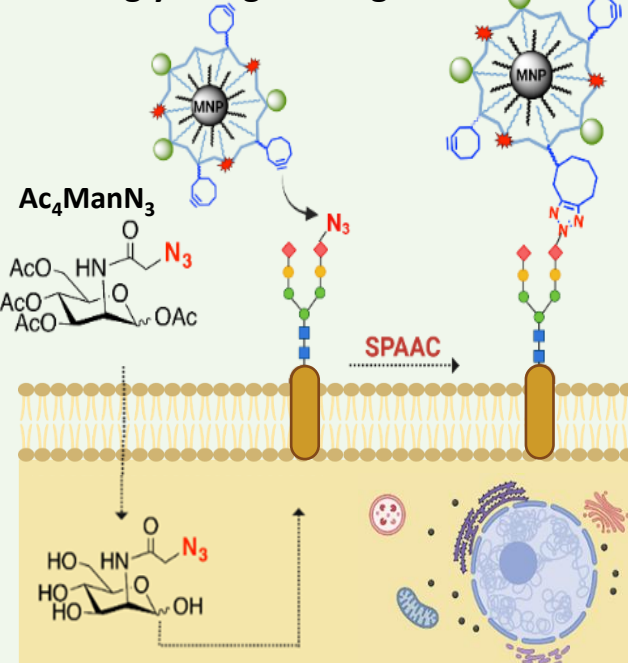


### Intensity of events

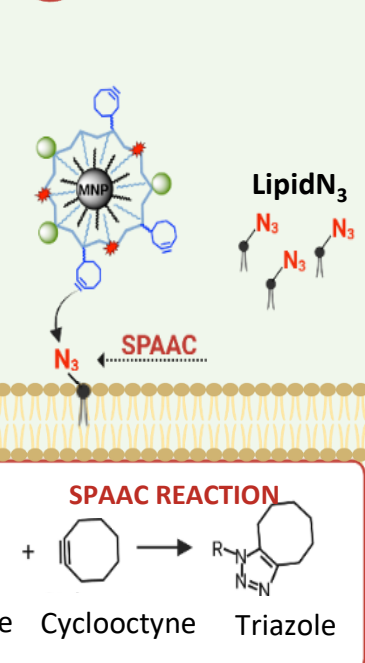


**2 Force through the membrane:** MNPs are attached to the cell membrane using covalent bioorthogonal chemistry, creating localized membrane tension or curvature that can indirectly activate the ion channels.

### 2a Metabolic glycoengineering



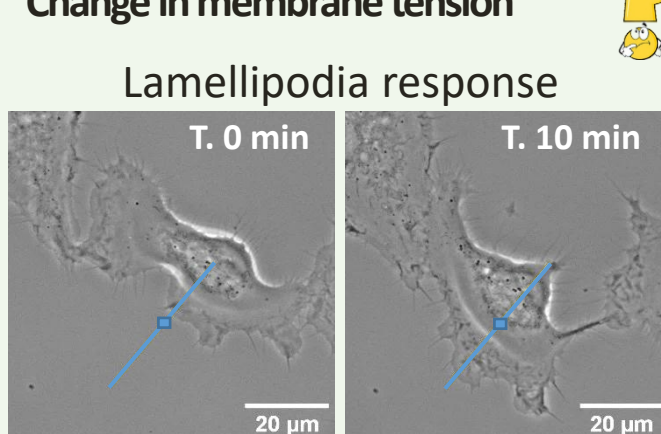
### 2b Lipid insertion



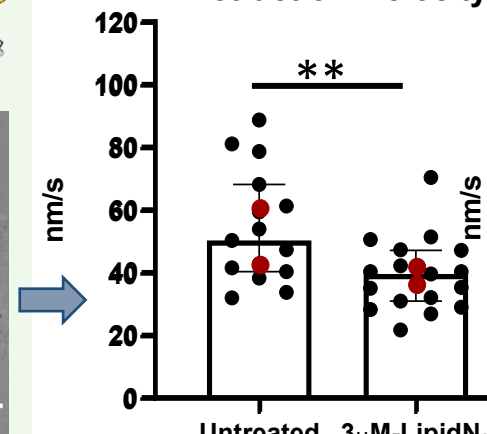
### Bioorthogonal chemistry

Lipid-N3 ↓ Activity, ↑ Calcium accumulation

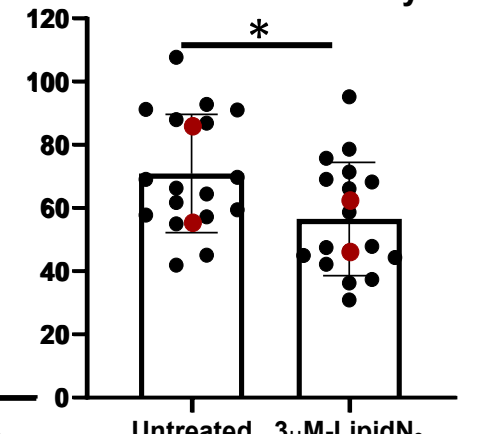
### Change in membrane tension



### Retraction velocity



### Extension velocity



## Conclusions

- Piezo1 can be activated remotely with MNPs, using strategy 1.
- Preliminary results using strategy 2 indicate an alteration of membrane tension after LipidN3 treatment.
- Future work: test strategy 1 for TRPV4 activation and analyze further the effects of cell membrane modification in strategy 2.