

# Developing polymeric microneedles for the treatment of rheumatoid arthritis

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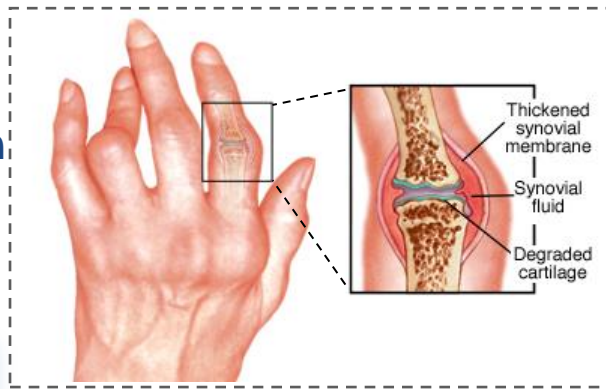
Xun Sun

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Chengdu, China



# ►► Current treatments for Rheumatoid arthritis (RA)

- Affecting approximately **1%** of the adult population
- Characterized by chronic synovitis and cellular infiltration
- Leading to **bone erosion** and **cartilage destruction**



- 10 to 20 years, or even lifelong medication

## ● DMARDs



Methotrexate



Hydroxychloroquine



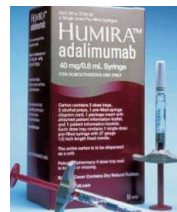
Dexamethasone



Prednisolone

## ● Steroids

## ● Biological Agents



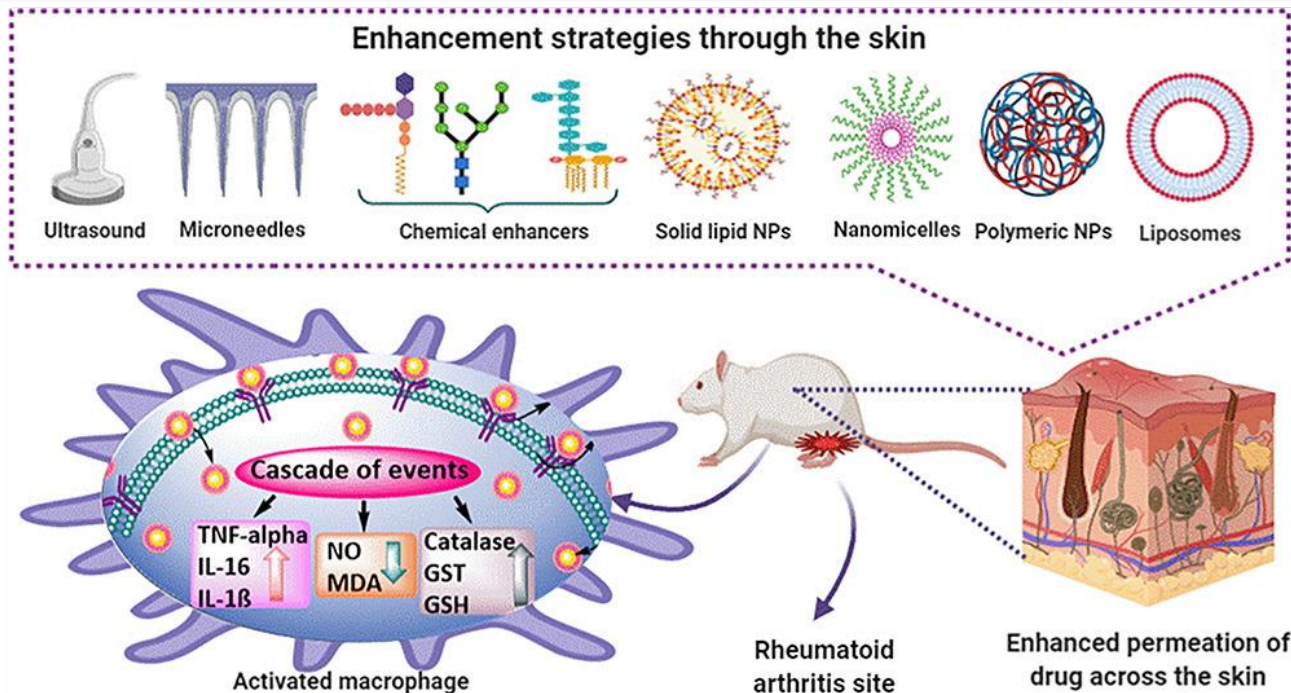
TNF- $\alpha$ , IL-6, CD20



# ►► Transdermal administration for RA

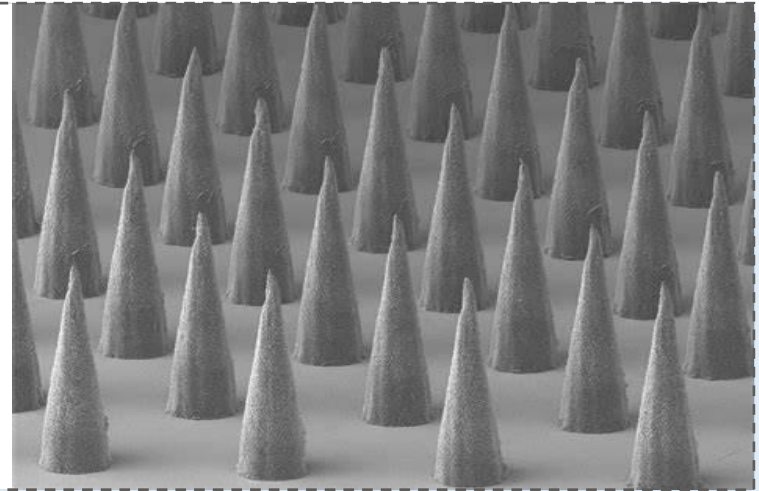
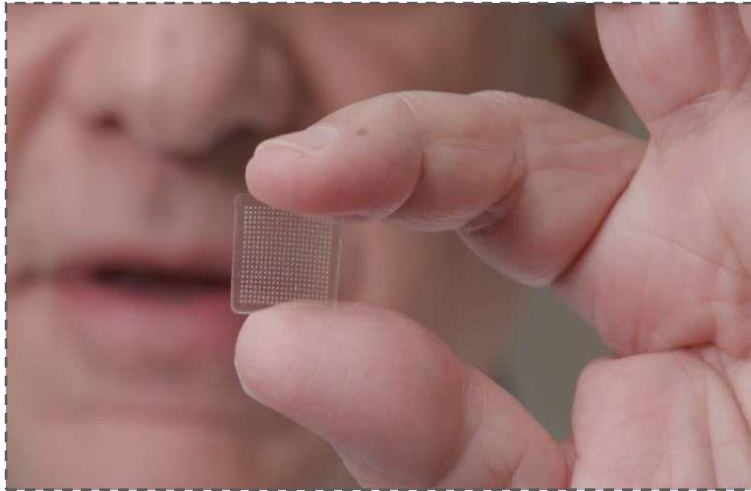


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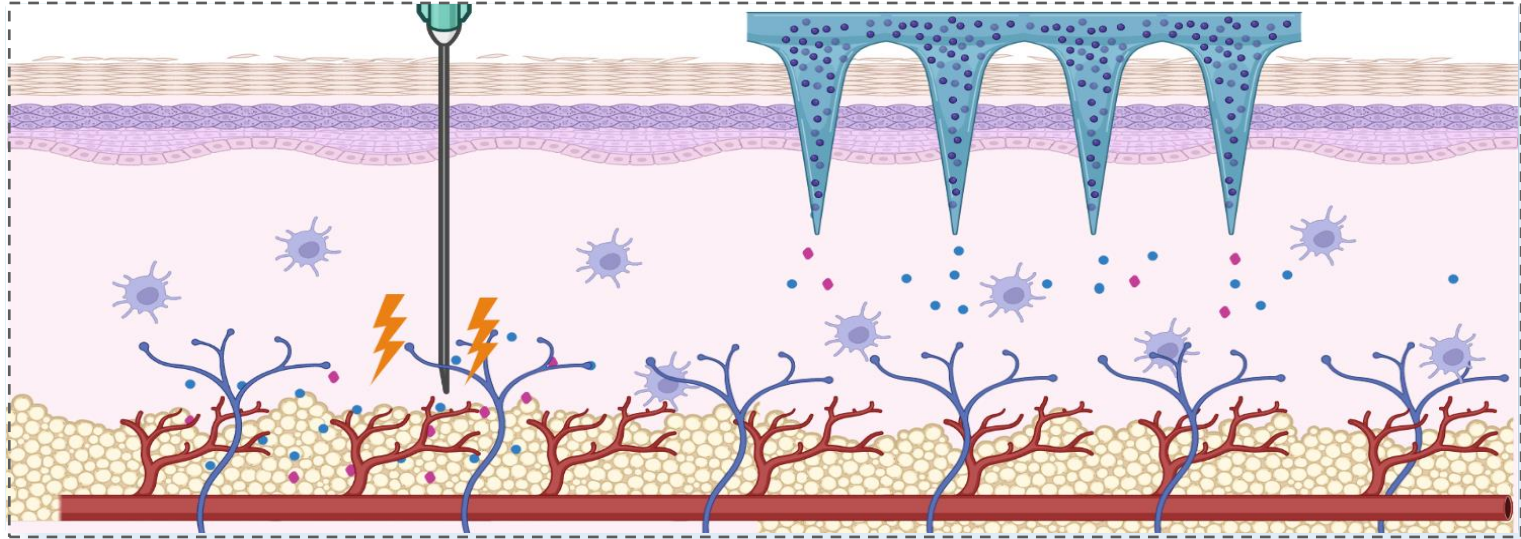
- Bypass of first-pass effect
- Avoidance of gastrointestinal harsh environment
- Improved patient compliance
- Reduction of dosing frequency

**Microneedles (MN) are micro size needles which are used in set of arrays**





# ►► Advantages of MN

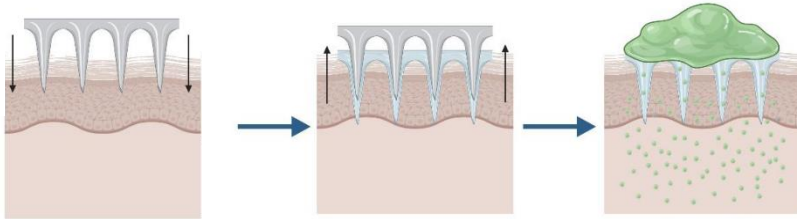


The needles (normally  $200\text{ }\mu\text{m}$ - $1\text{ mm}$ ) can be fabricated to be long enough to **penetrate the stratum corneum**, but short enough to **not come into contact with nerve endings**

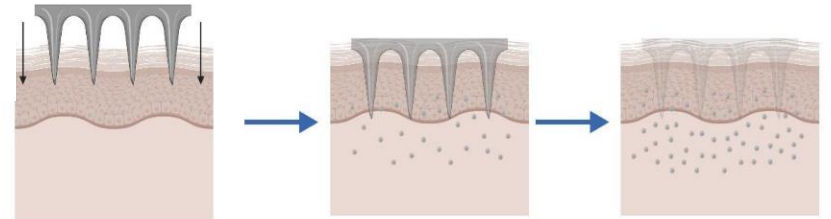
# ►► Categories of MN



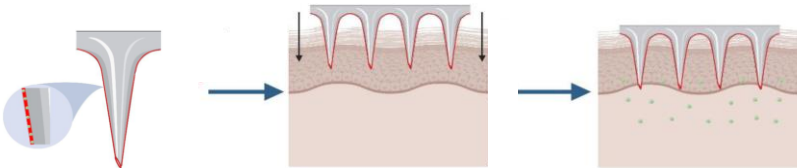
**Solid MN**



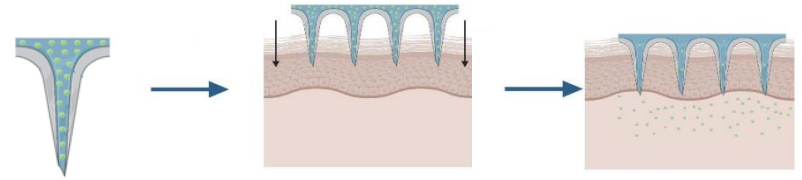
**Polymer MN**



**Coated MN**



**Hollow MN**

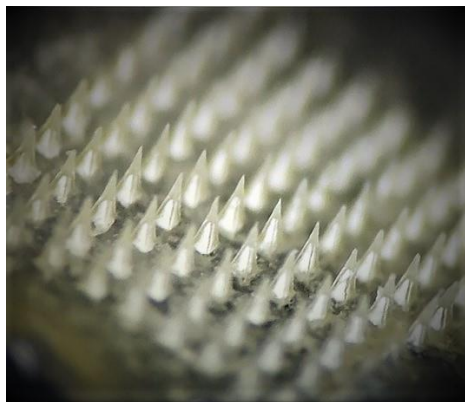


# ►► Polymer MN prepared in our lab

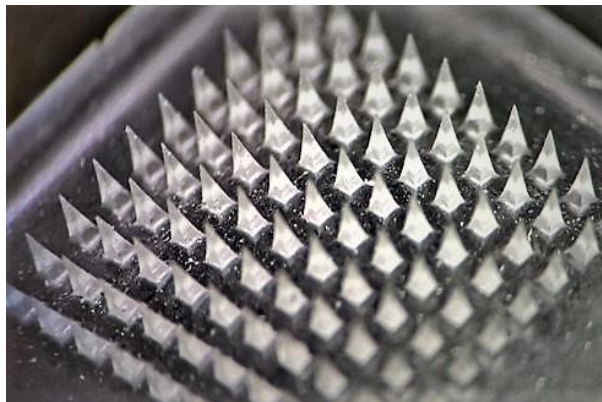


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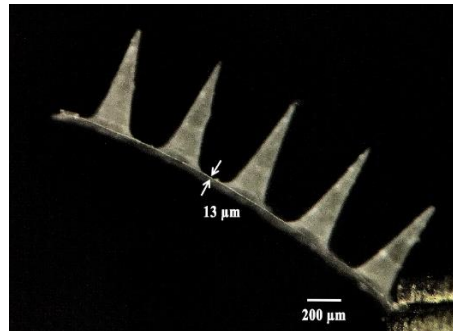
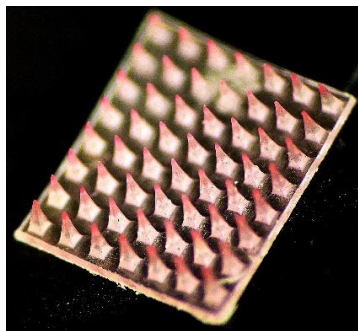
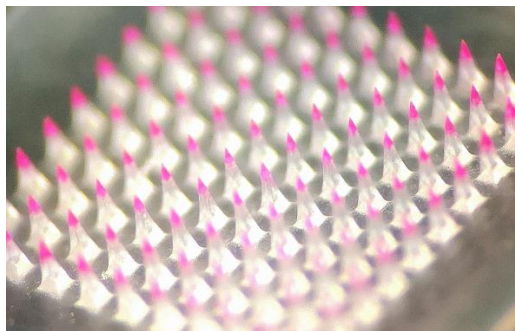
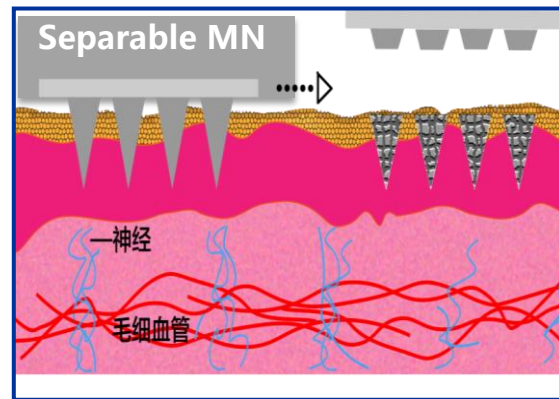
## Powder MN



## Vaccine MN



## Tip separable MN



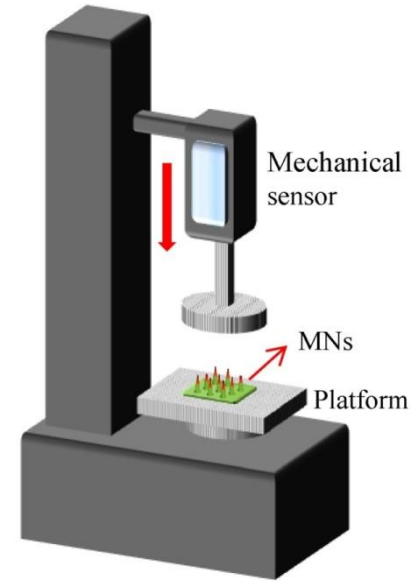
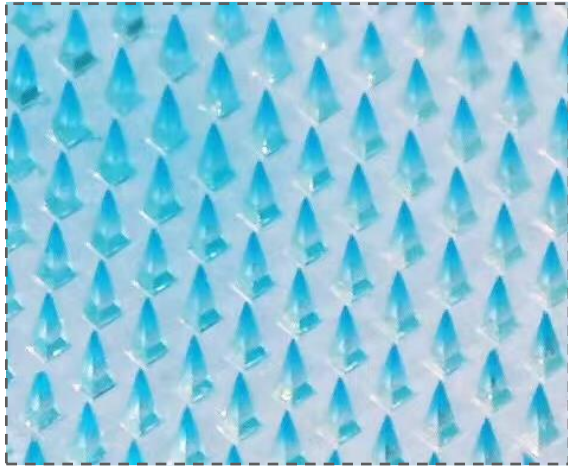
## Tip loaded MN

## Flexible and wearable MN

Precise characterisation of mechanical  
strength of individual MN with  
**micromanipulation**



# ►► Mechanical property of polymeric MN



The **mechanical property of microneedles** is crucial for their skin penetration

Available strategies only provide **average rupture force**

# ►► Micromanipulation



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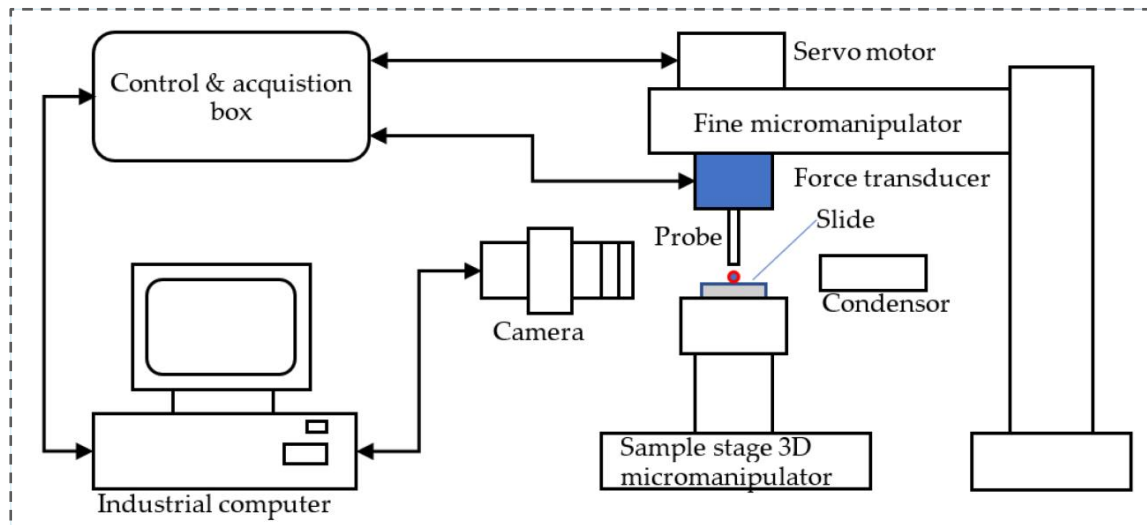
UNIVERSITY OF  
BIRMINGHAM



**Prof. Zhibing Zhang**

University of Birmingham, UK

Fellow of the Royal Academy of Engineering



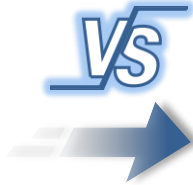
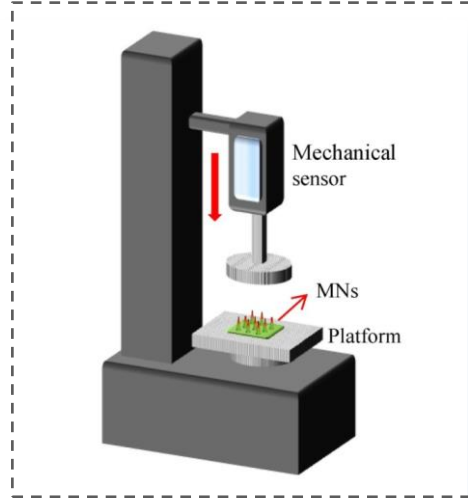
**Micromanipulation** was developed in Pro. Zhang's lab for mechanical property characterisation of micro- and nano-scale particles

# ►► Advantages of micromanipulation

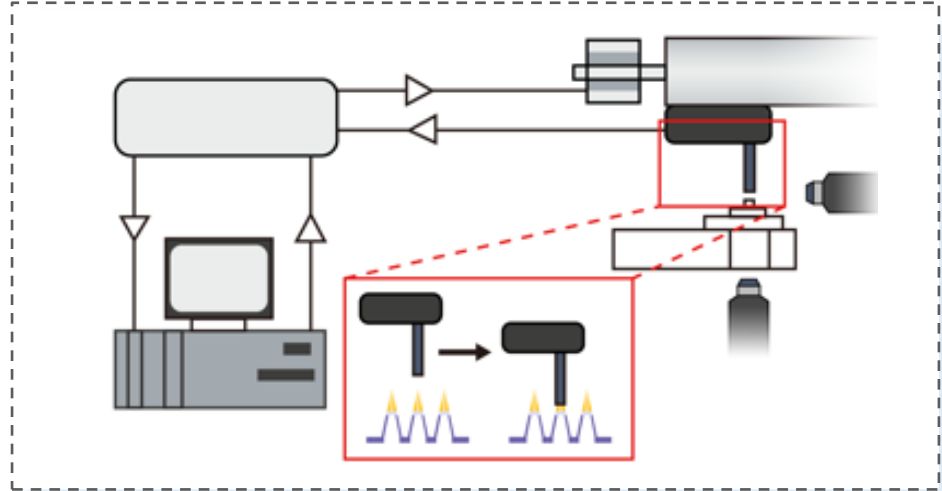


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## Available strategies



## Micromanipulation

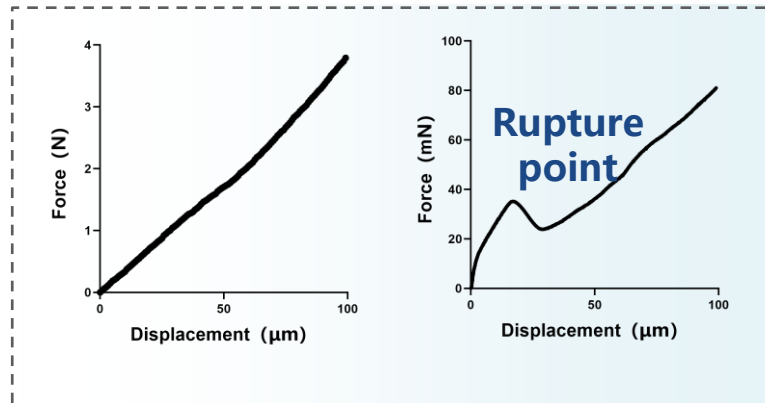


- Detection limit was increased by **1000** times
- Accuracy was increased by **100** times
- **Multidimensional** characterization

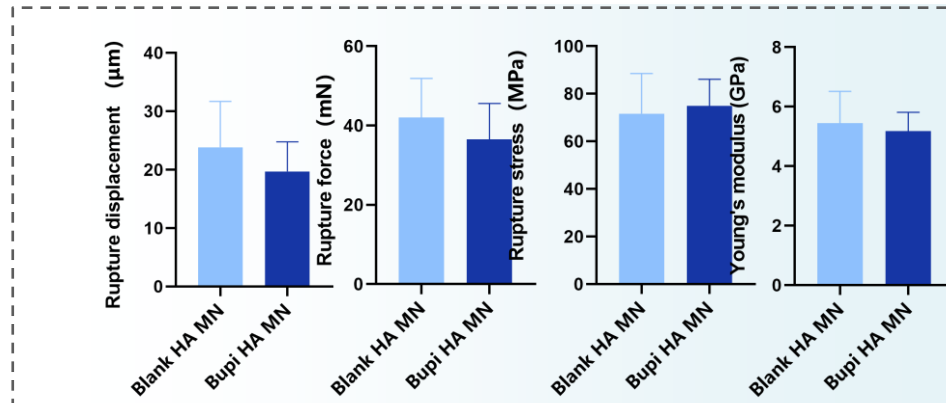
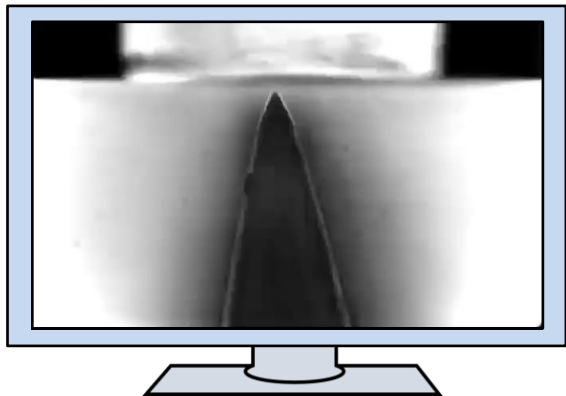
# ►► Advantages of micromanipulation



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► High precision



► Multiple dimensions

- ✓ Rupture displacement
- ✓ Rupture force
- ✓ Rupture stress
- ✓ Young's modulus

# ►► Characterization of the fracture behavior with micromanipulation

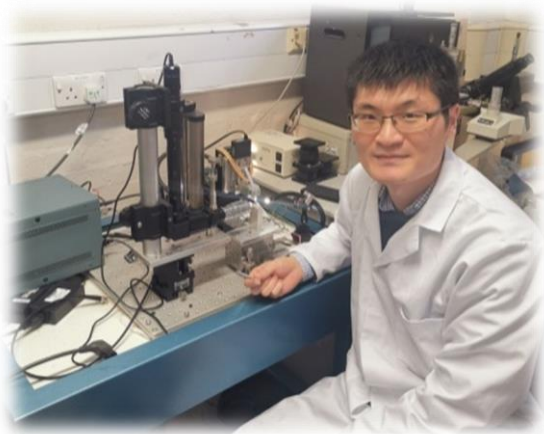
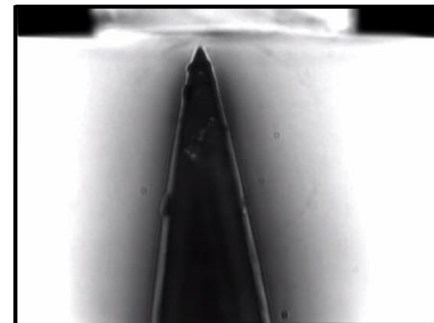


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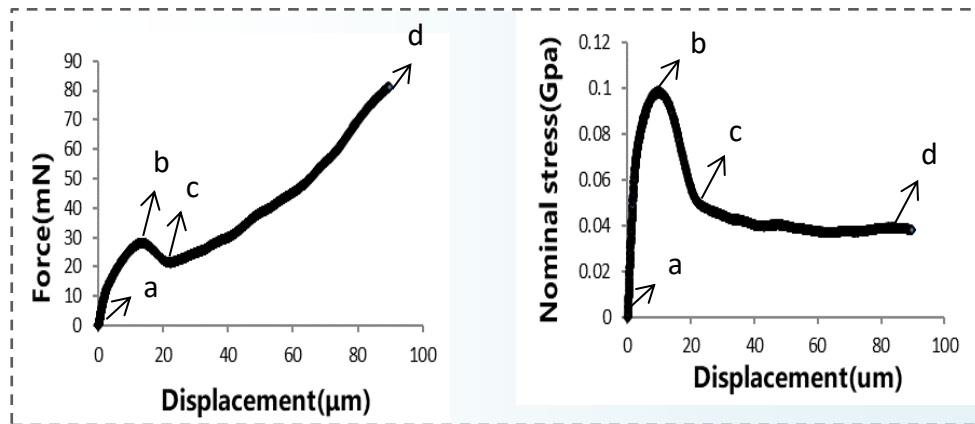


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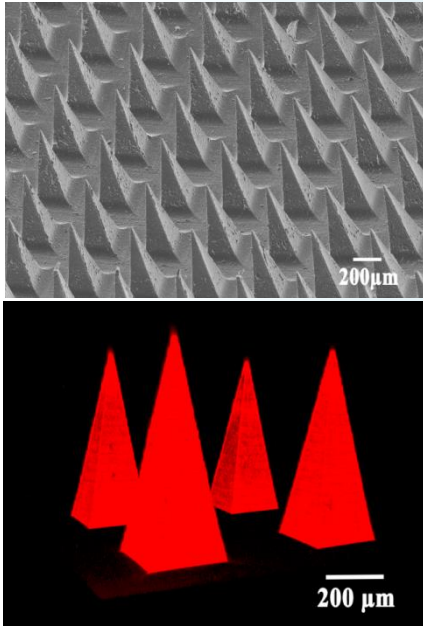


**Dr. Guangsheng Du**  
Sichuan University

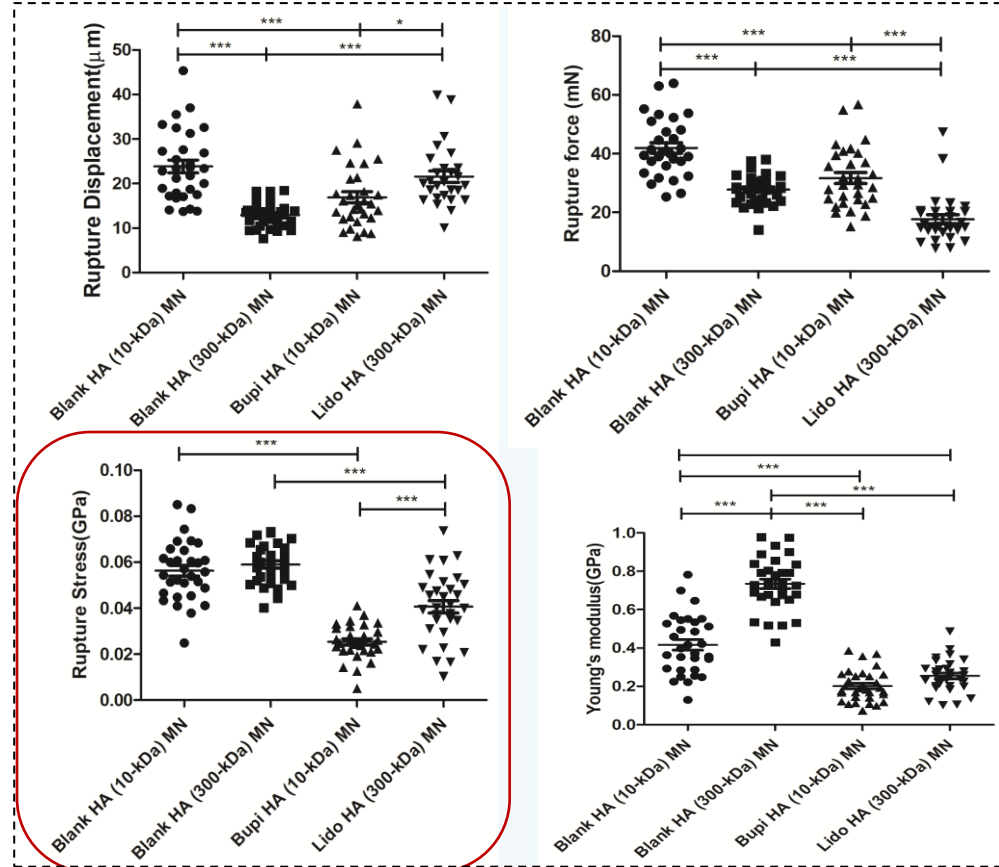




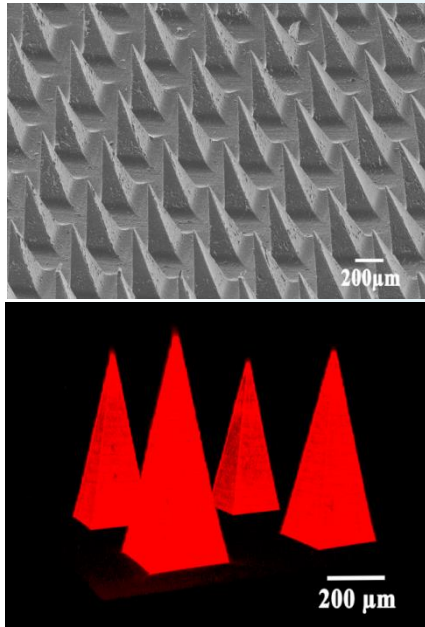
# ►► Precise characterisation of mechanical strength of individual microneedles



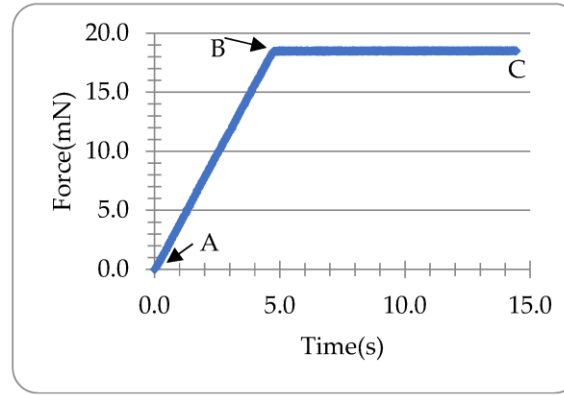
**Rupture stress** is more suitable to characterize the mechanical strength of MN



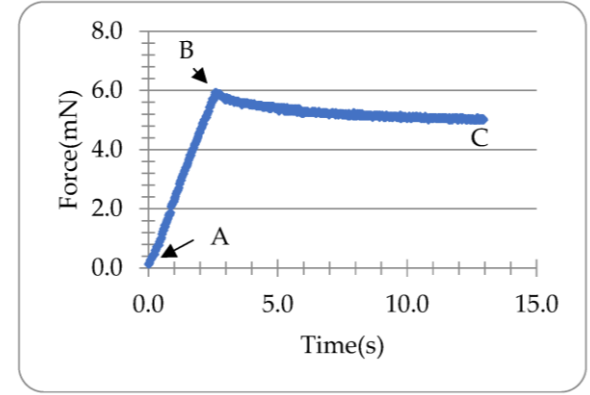
# ►► Precise characterisation of mechanical strength of individual microneedles



Glass plate test



MN test



$G_0$ (MPa)	$G_\infty$ (MPa)	$E_0$ (MPa)	$E_\infty$ (MPa)
171.1	114.4	513.3	343.2

- Polymer MN have relatively higher viscoelasticity

Polymer MN deliver melittin for the  
treatment of rheumatoid arthritis (RA)

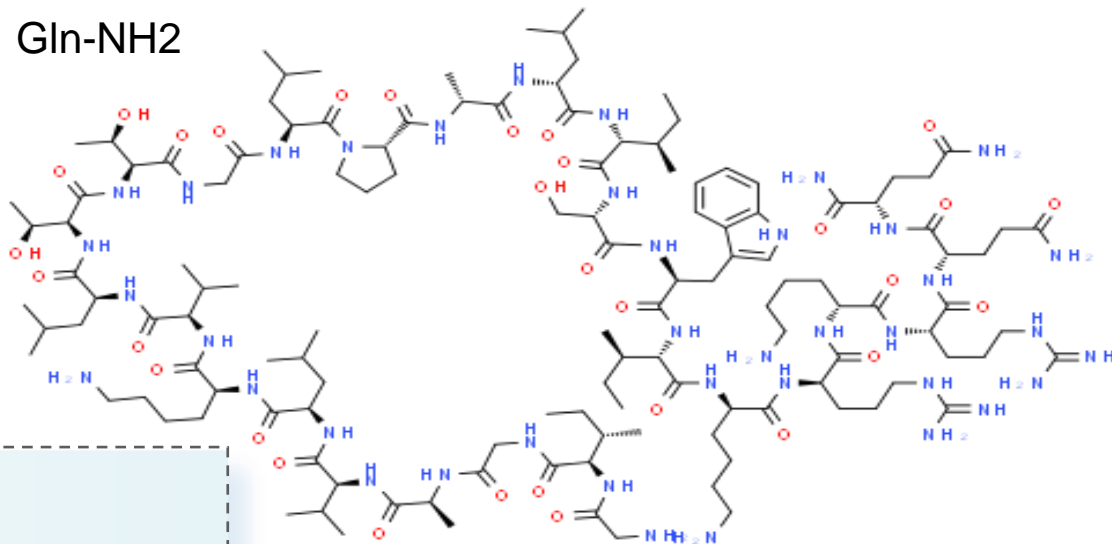
# ►► Bee acupuncture therapy in the treatment of RA



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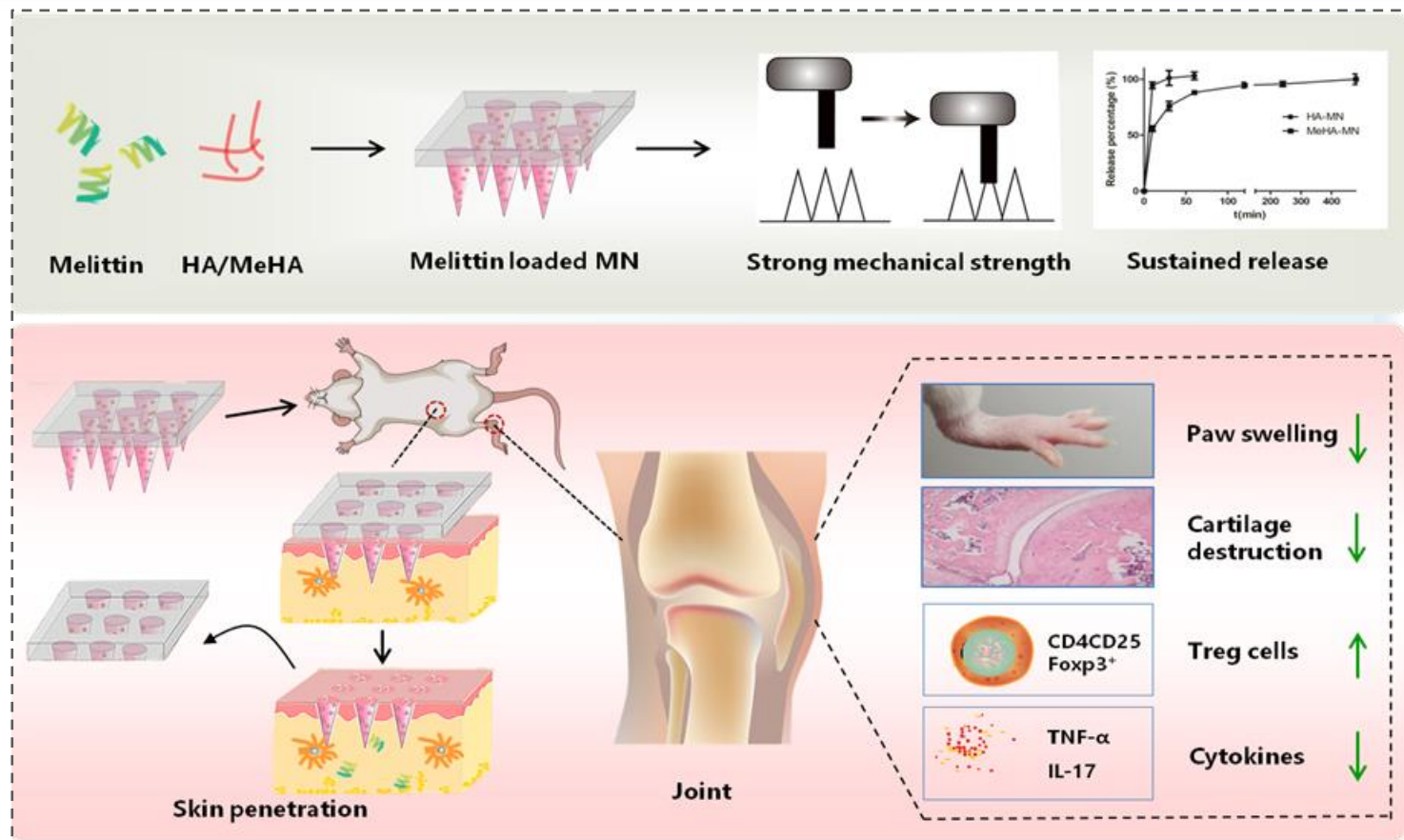
- **Melittin:** H-Gly-Ile-Gly-Ala-Val-Leu-Lys-Val-Leu-Thr-Thr-Gly-Leu-Pro-Ala-Leu-Ile-Ser-Trp-Ile-Lys-Arg-Lys-Arg-Gln-Gln-NH<sub>2</sub>



## Merits and demerits:

- Good therapeutic effect
- Professional operation is required
- Painful and poor compliance

# ►► Treatment of RA by MN loaded with melittin

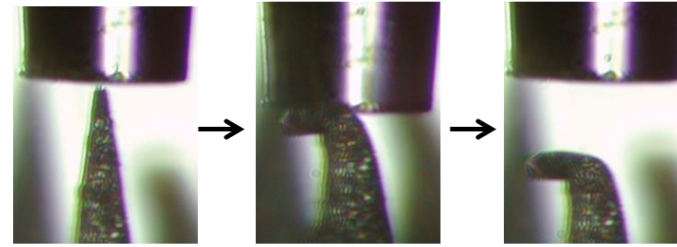
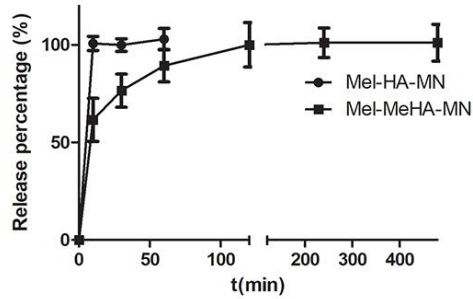




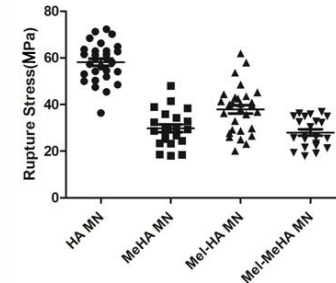
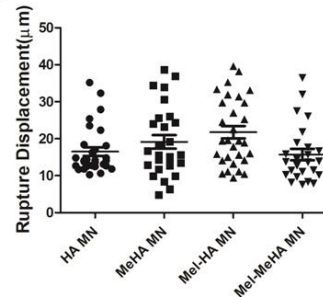
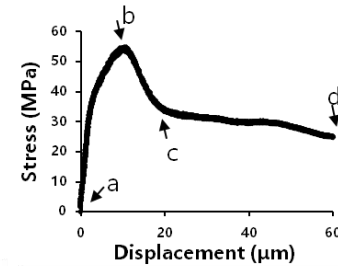
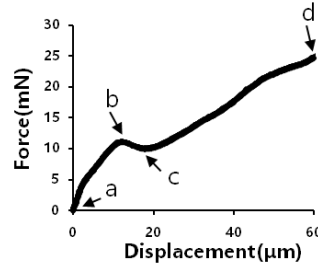
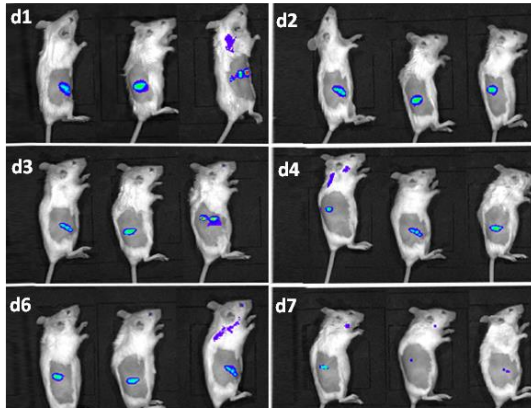
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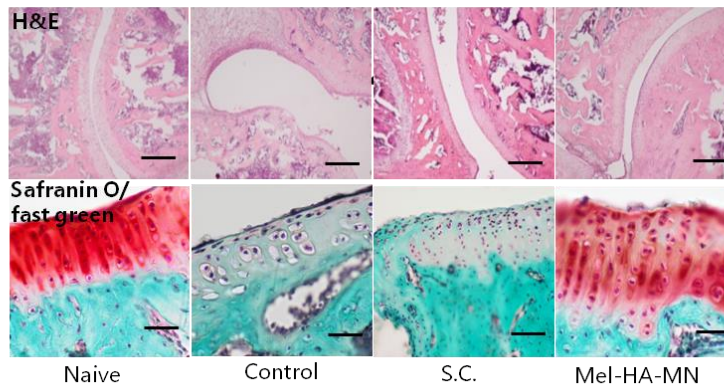
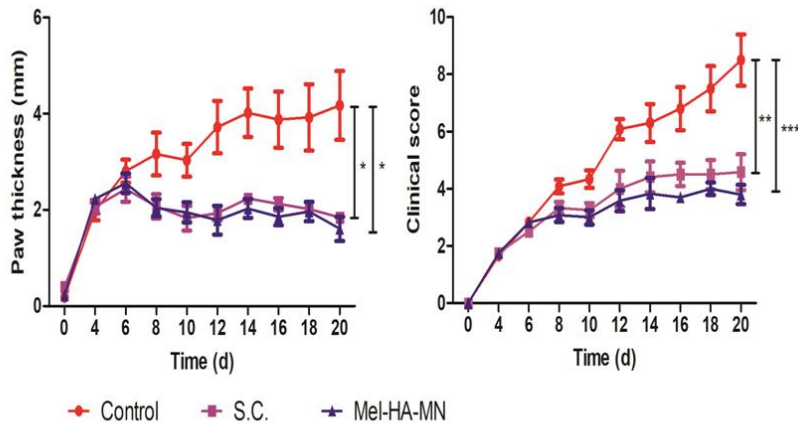
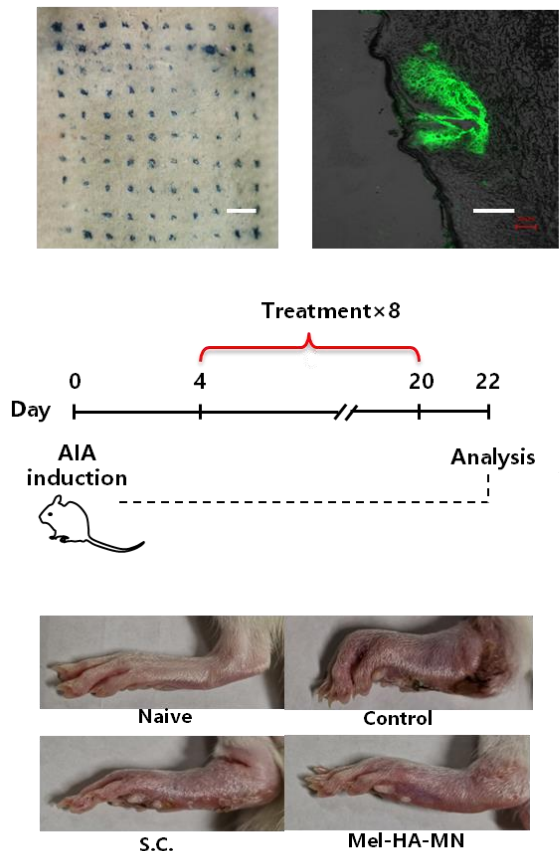
# ►► MN release and mechanical strength characterization



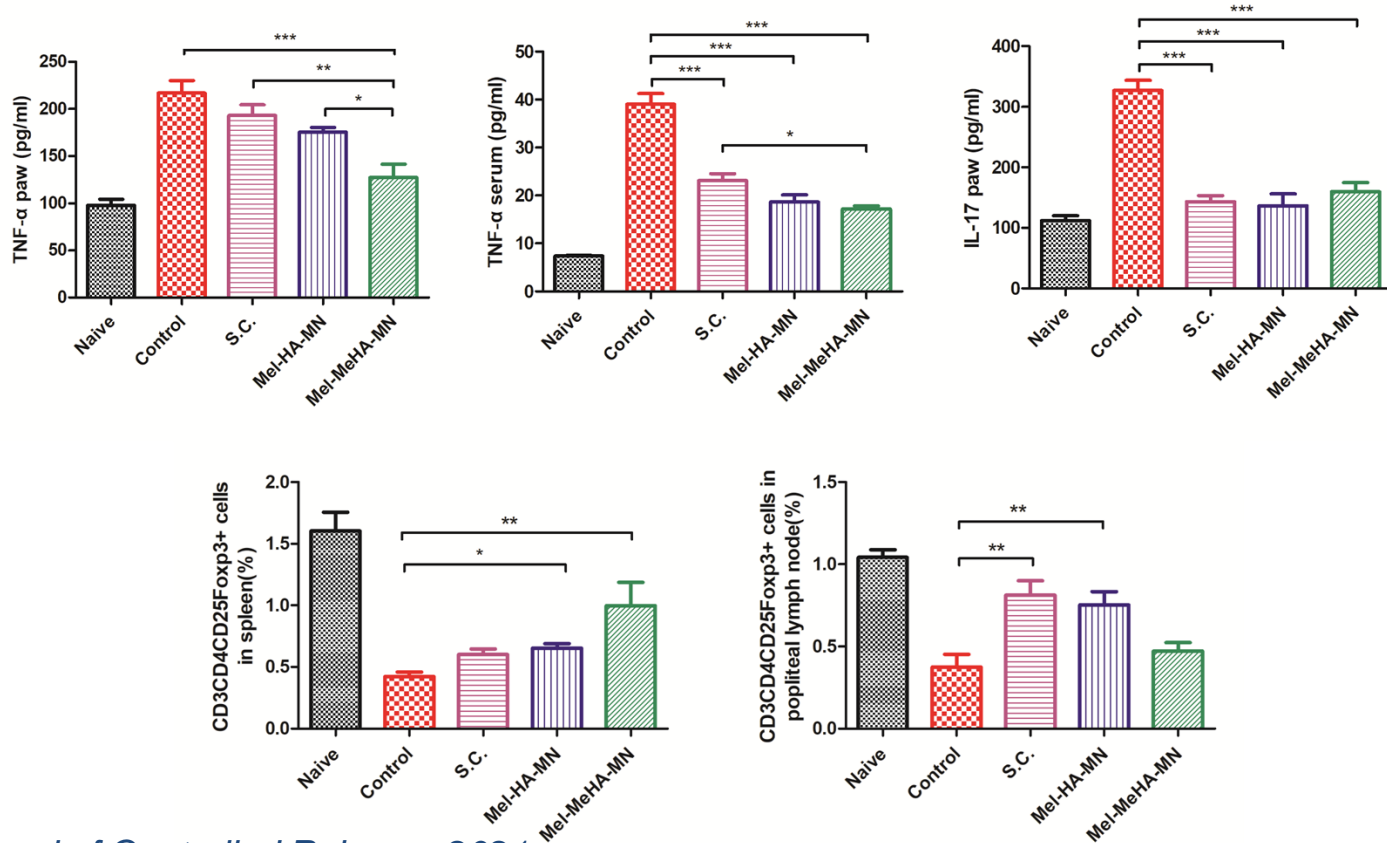
Before compression      Rupture of microneedle      After compression



# ▶▶ Therapeutic effect of AIA model in rats



# ►► Decreased inflammatory factors and increased proportions of Treg

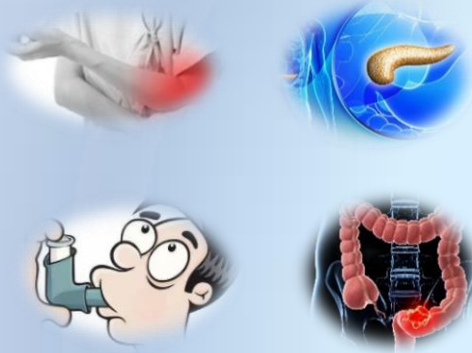


# War and peace of immune system

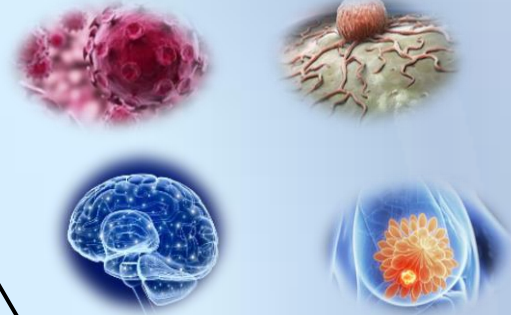


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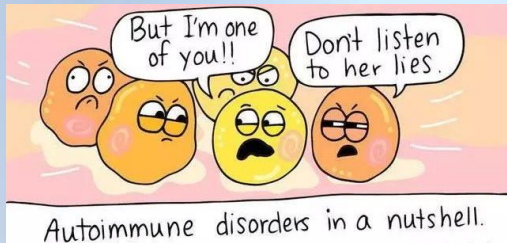
## Allergies and autoimmunity



## Influenza and cancer



## Immune regulation

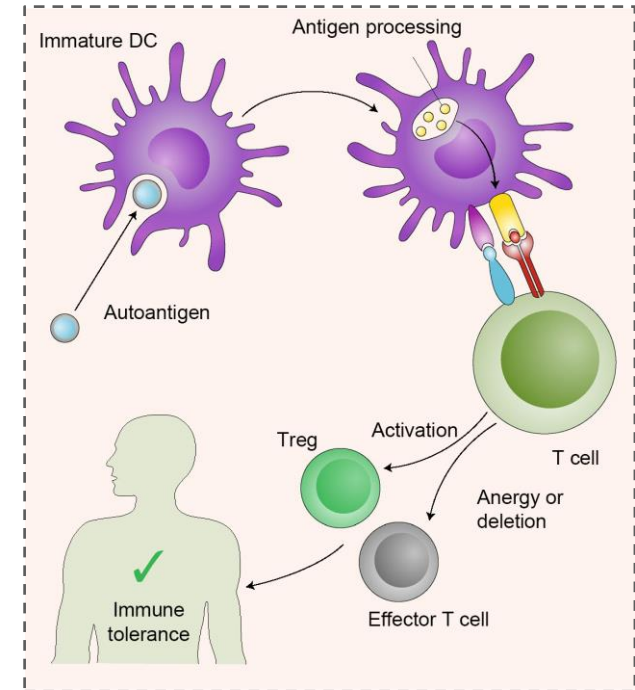
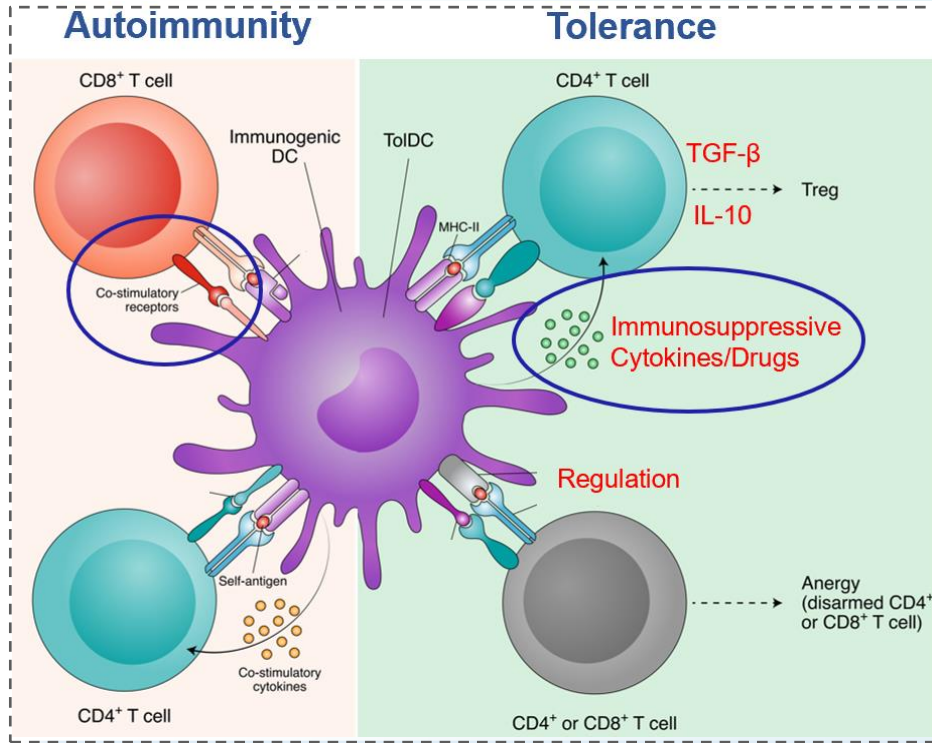


## Immune activation

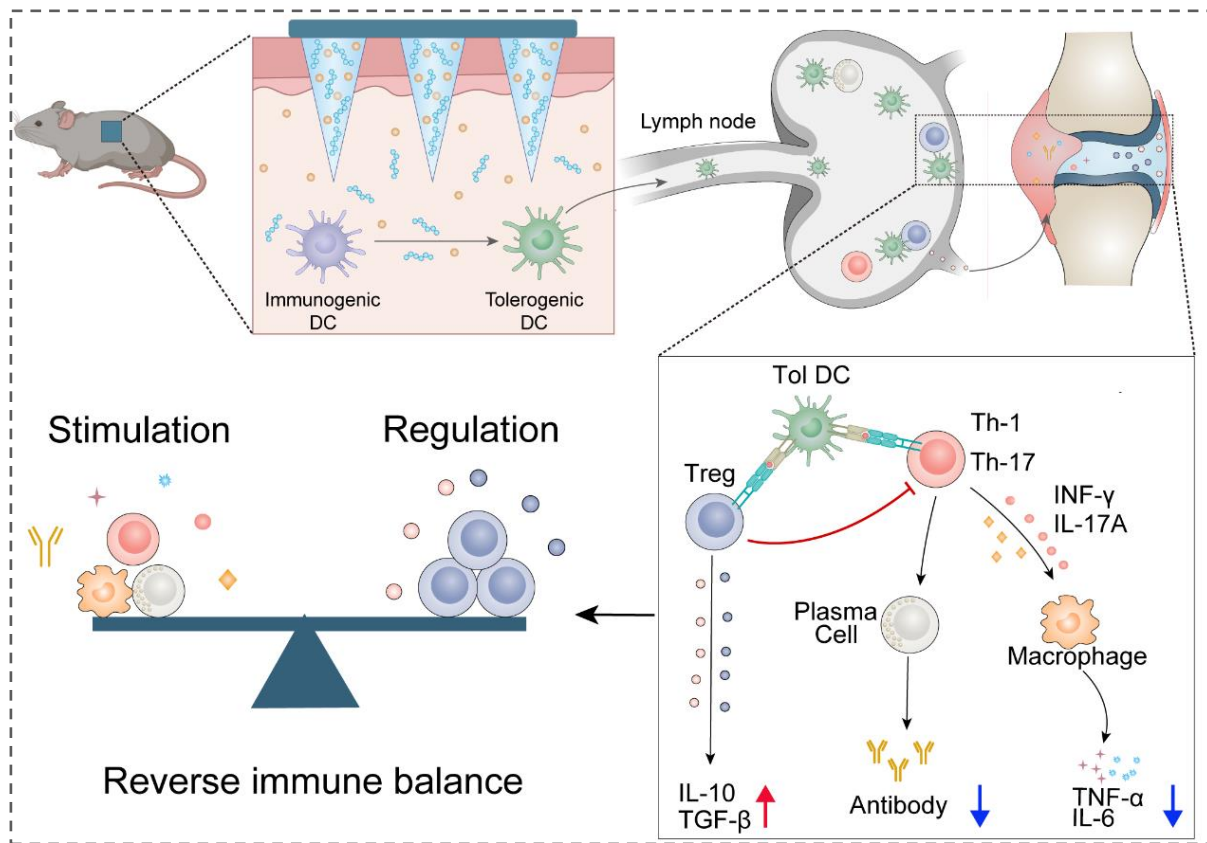




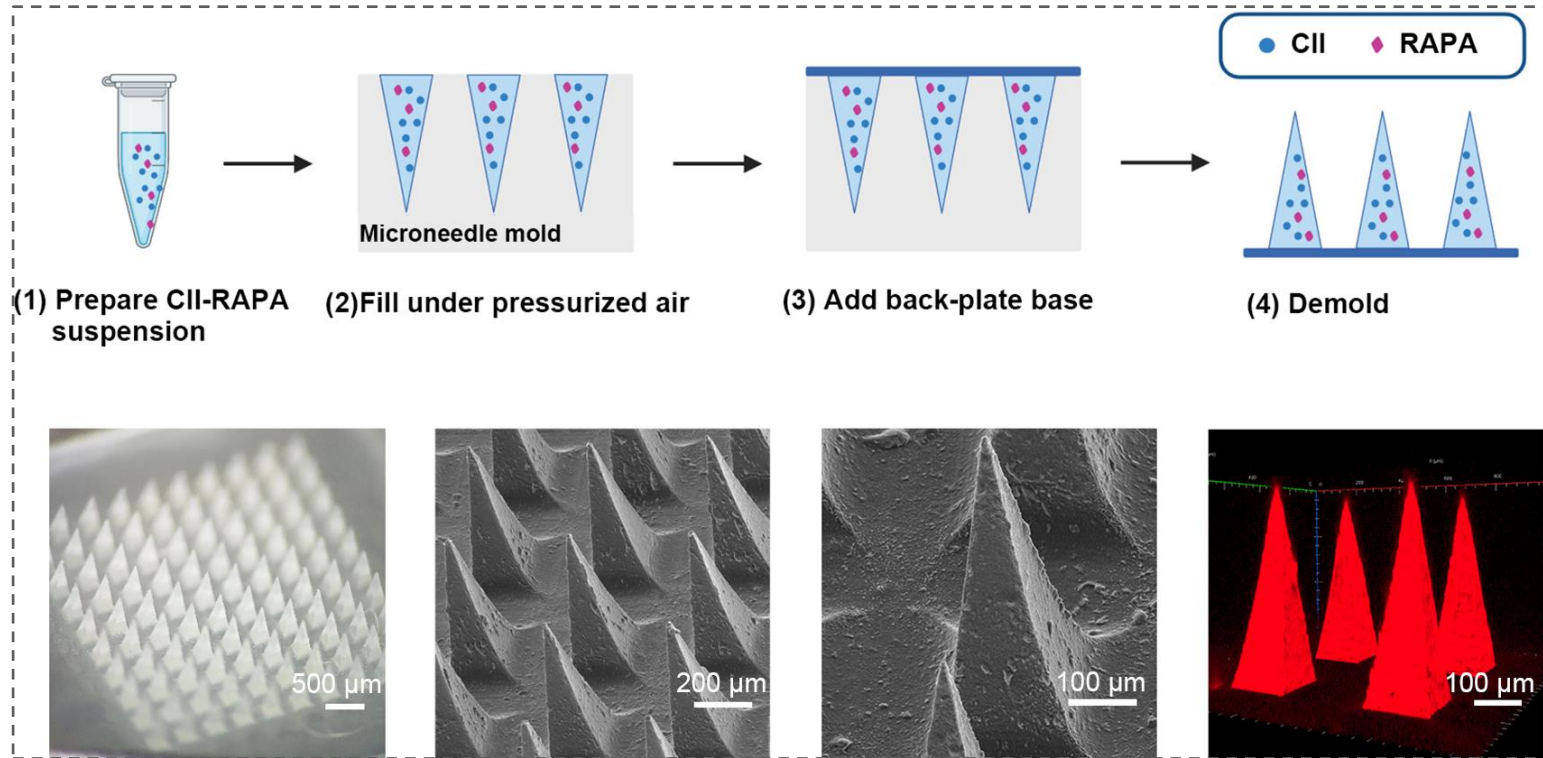
# ►► Tolerance induction is the ultimate goal for RA treatment



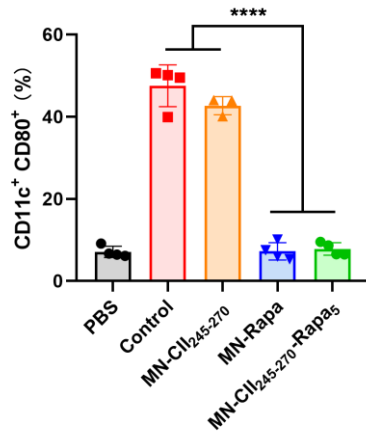
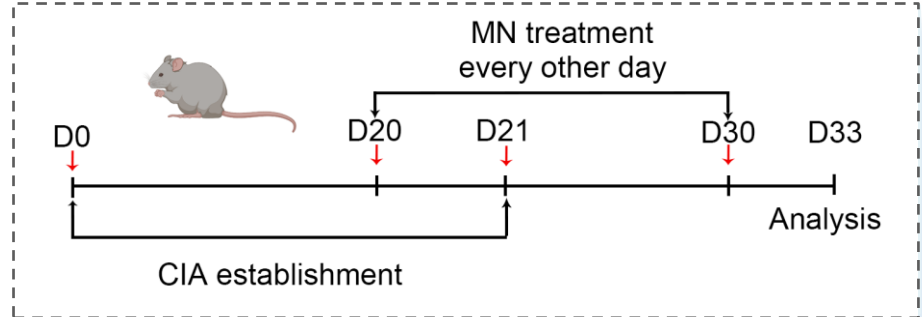
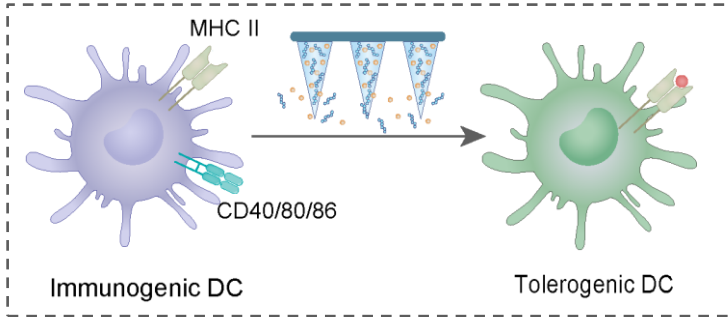
## ►► Induction of immune tolerance by MN for RA treatment



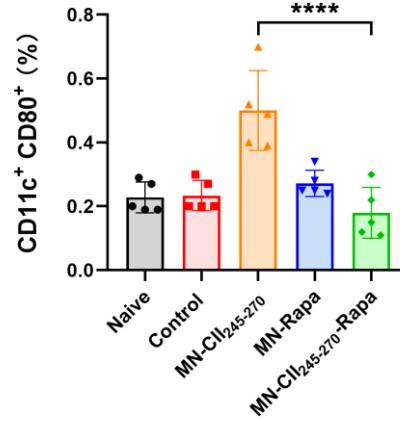
# ►► Preparation and characterization of MN



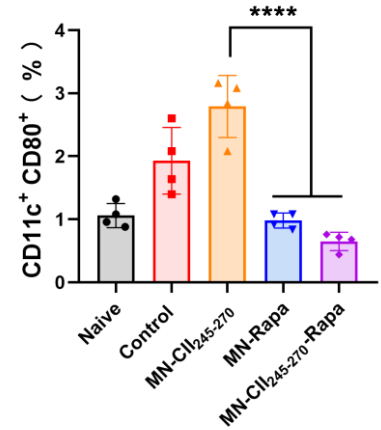
## ►► CII peptide and Rapa co-loaded MN induced tolDCs



● In vitro TolDC

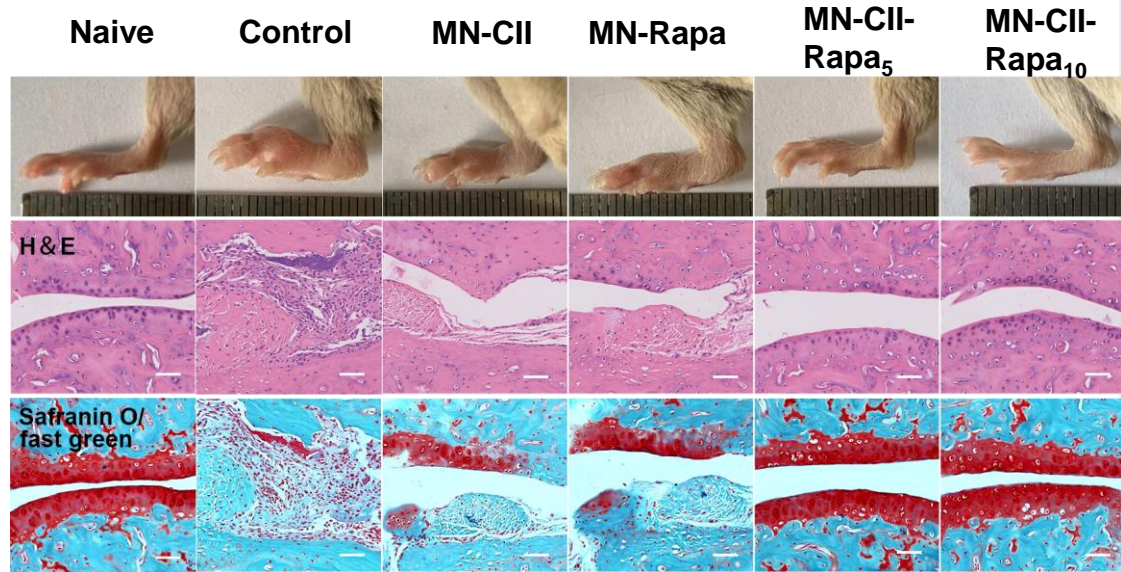
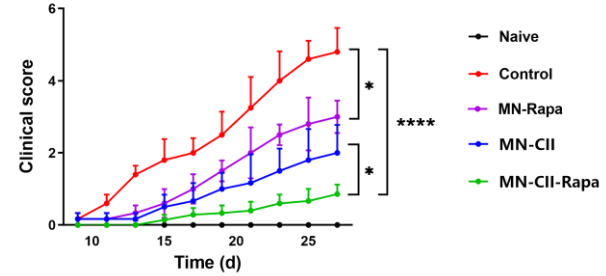
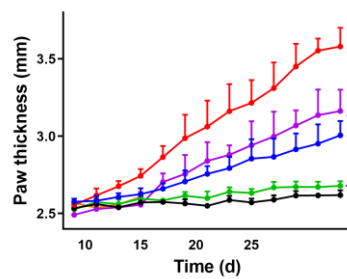
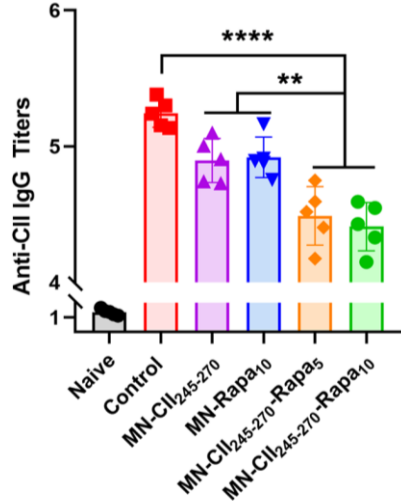
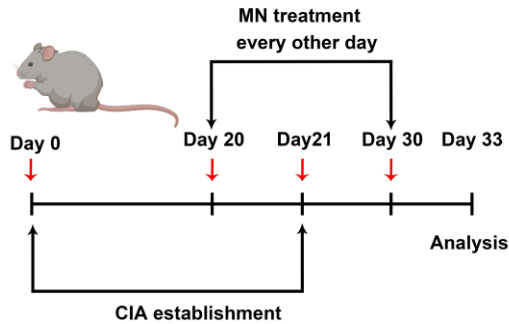


● TolDC in skin



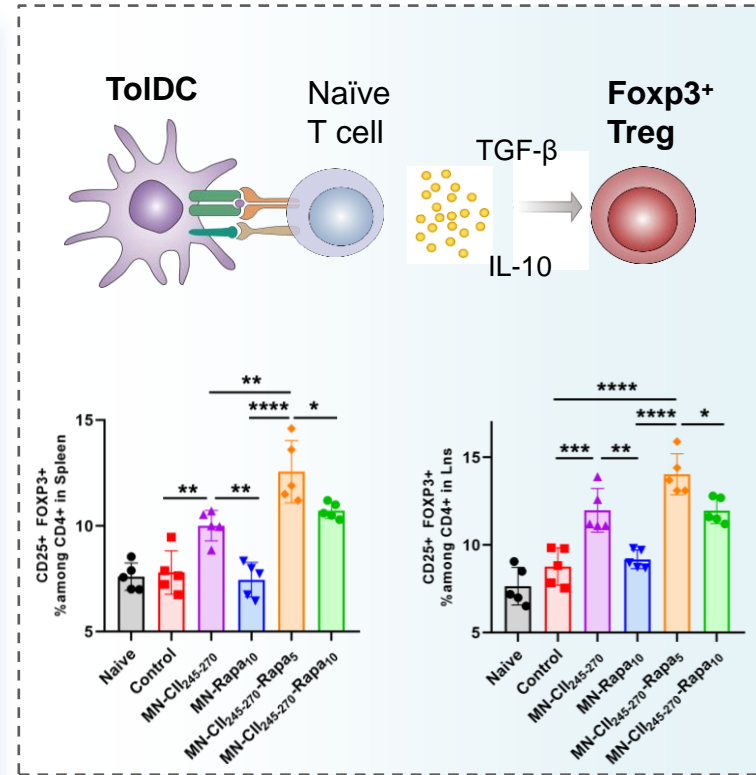
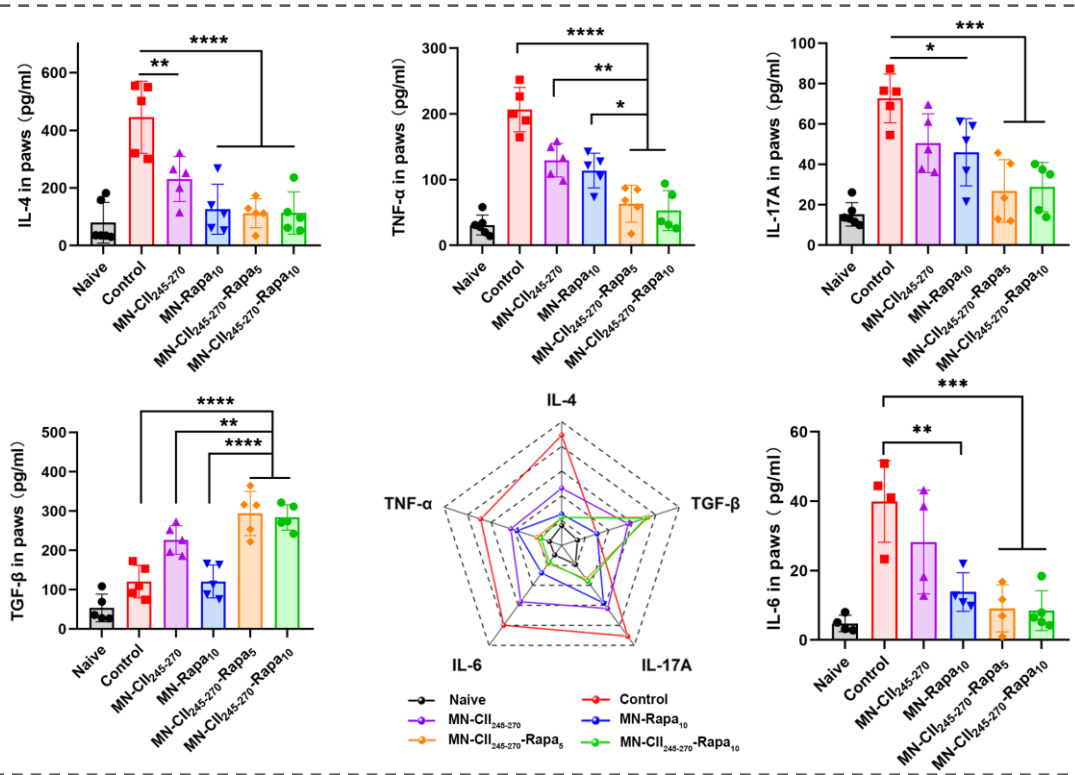
● TolDC in LN

# ►► Therapeutic effect of MN in CIA mouse model





# ►► MN reversed restored the immune balance

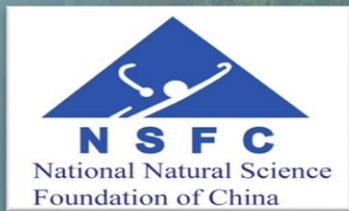


## ▶▶ Conclusion

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- ▶ The micromanipulation can accurately characterize the fracture behavior and mechanical strength of a single MN.
- ▶ Polypeptide drugs delivered by polymer MN with sustained release properties can effectively treat RA.
- ▶ The transdermal delivery of auto-antigen peptides and rapamycin can efficiently induce tolerogenic dendritic cells in the administration site, and further activated systemic Treg cell differentiation and restored the immune disorders in RA.

# Acknowledgements



National Natural Science  
Foundation of China



Newton Advanced Fellowship





# Welcome to West China College of Pharmacy, Sichuan University!







Thanks for your attention !