

Developing polymeric microneedles for the treatment of rheumatoid arthritis

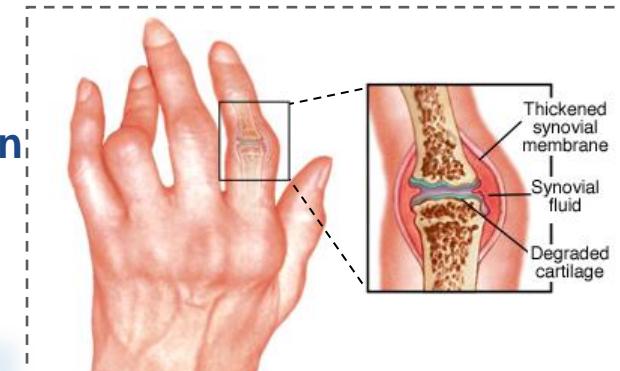
Xun Sun

West China School of Pharmacy, Sichuan University
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

● Steroids



Dexamethasone

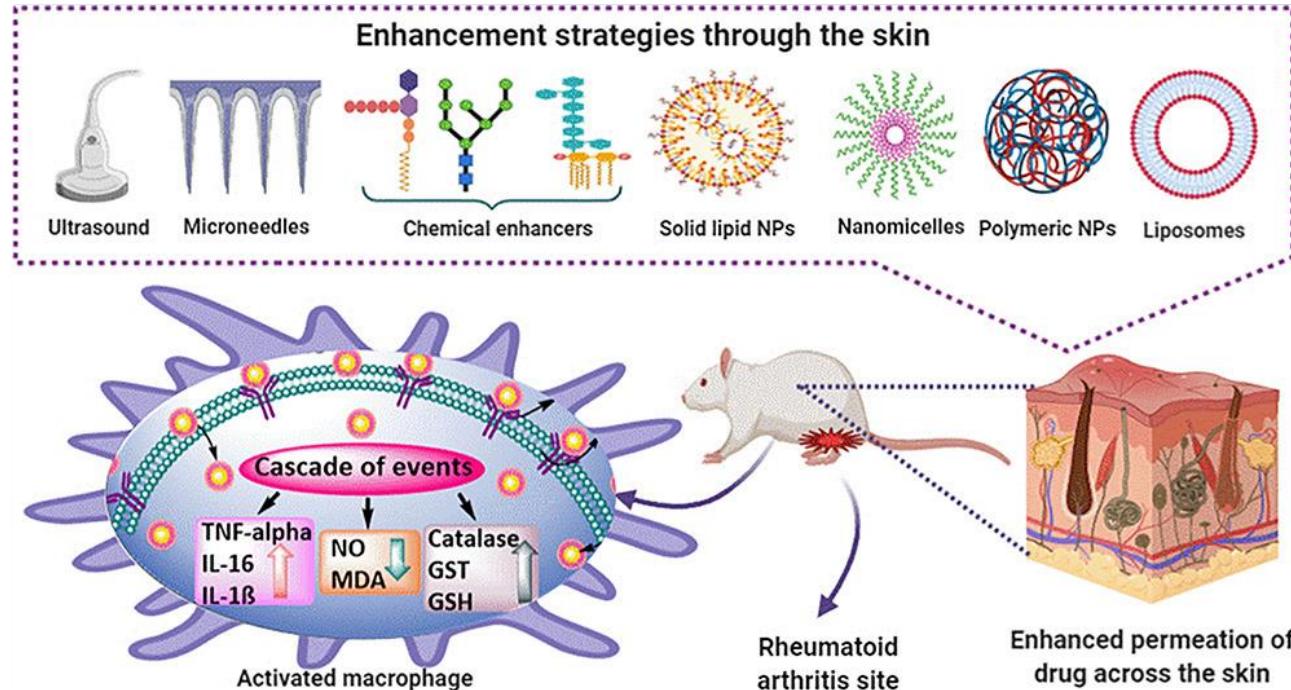
Prednisolone

● Biological Agents



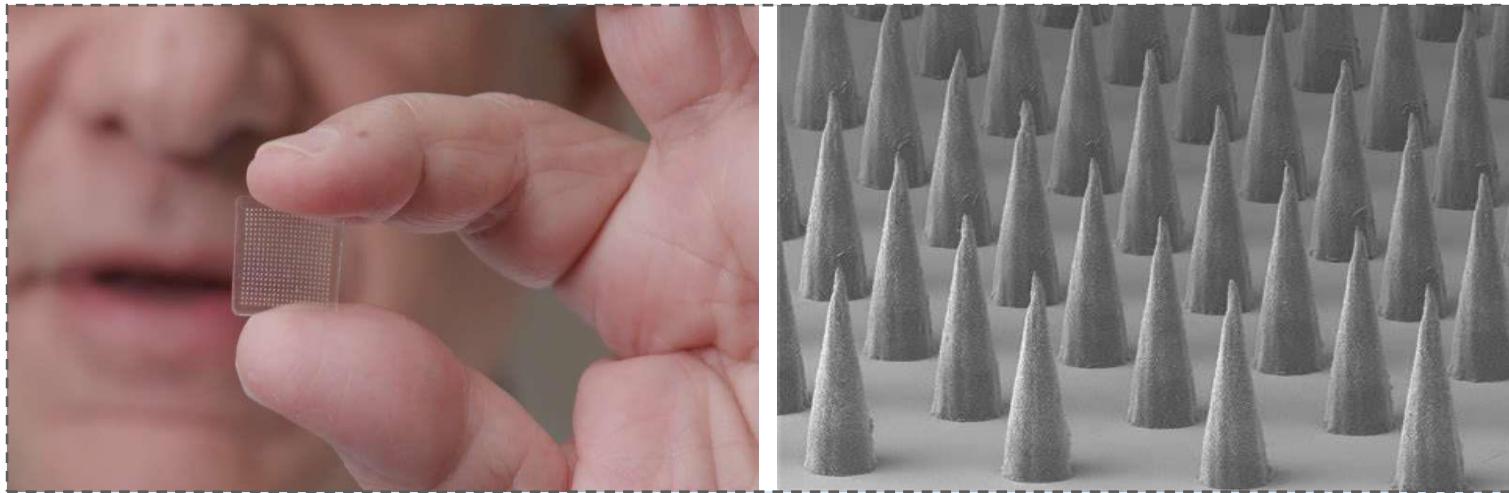
TNF- α , IL-6, CD20

► Transdermal administration for RA



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

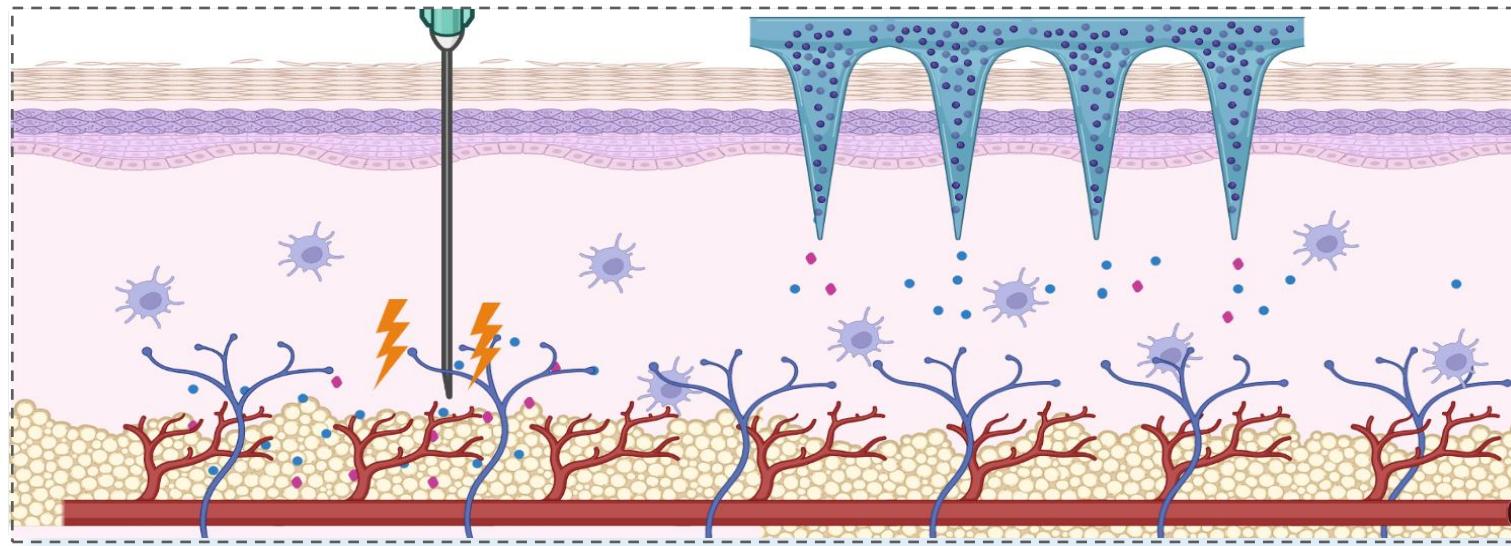
Microneedles (MN) are micro size needles which are used in set of arrays



►► Advantages of MN



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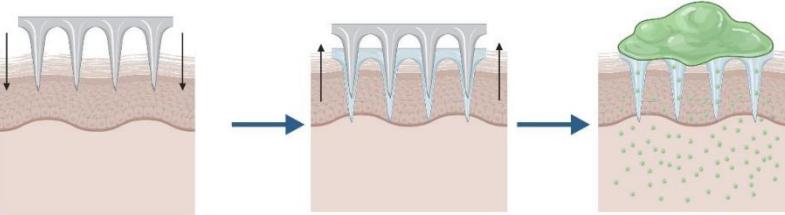


The needles(normally $200 \mu\text{m}$ - 1mm) can be fabricated to be long enough to penetrate the stratum corneum, but short enough to not come into contact with nerve endings

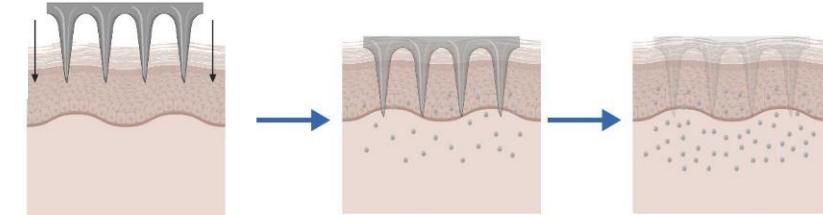
►► Categories of MN



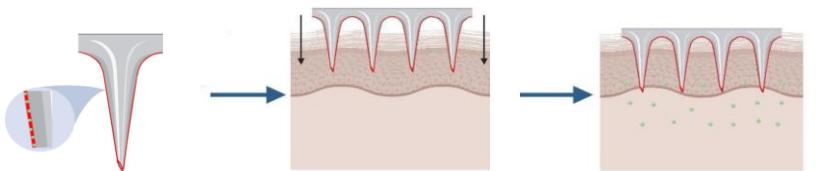
Solid MN



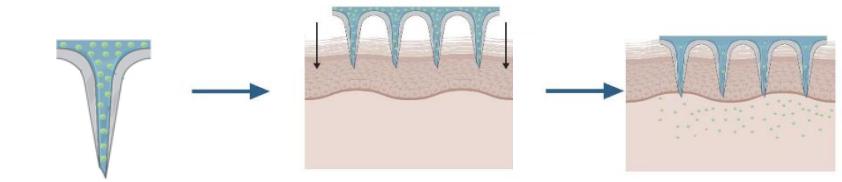
Polymer MN



Coated MN

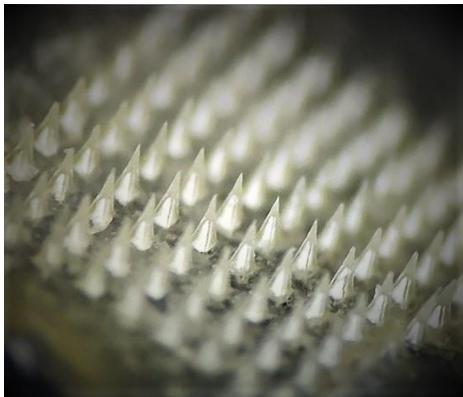


Hollow MN

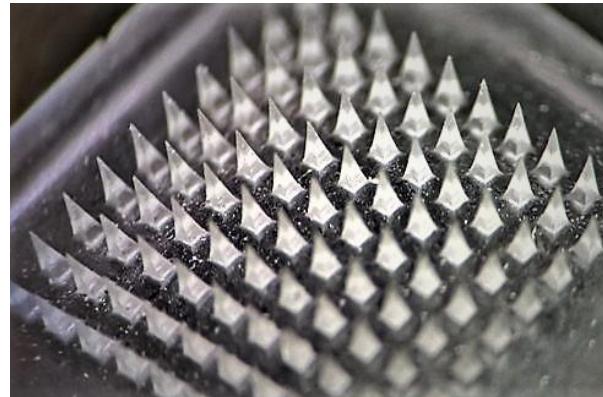


►► Polymer MN prepared in our lab

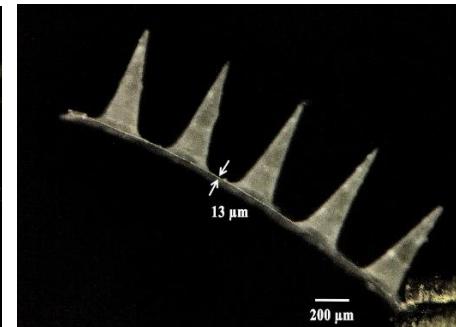
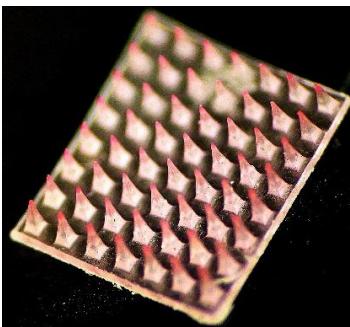
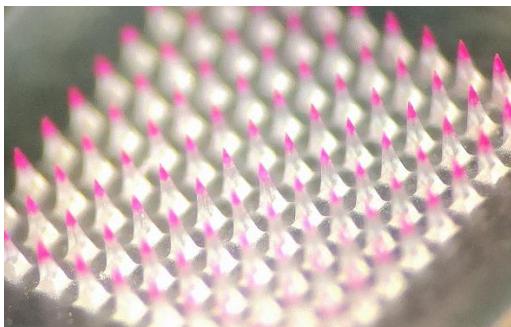
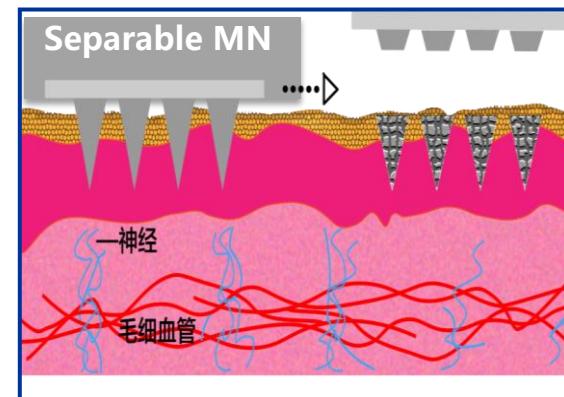
Powder MN



Vaccine MN



Tip separable MN

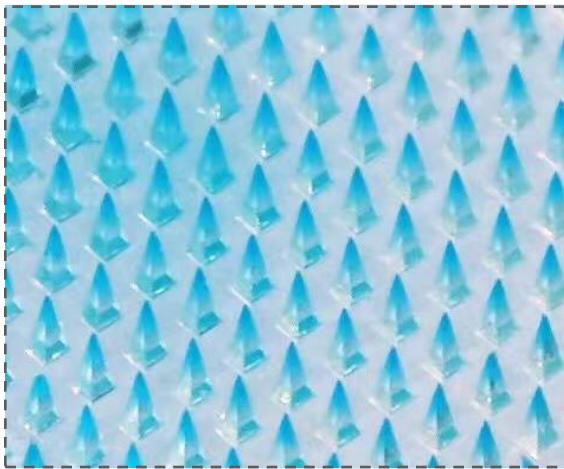


Tip loaded MN

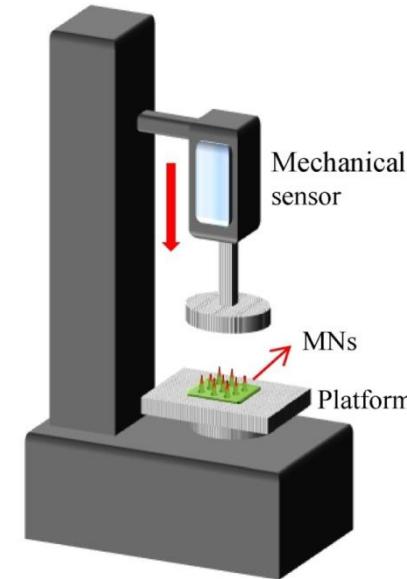
Flexible and wearable MN

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



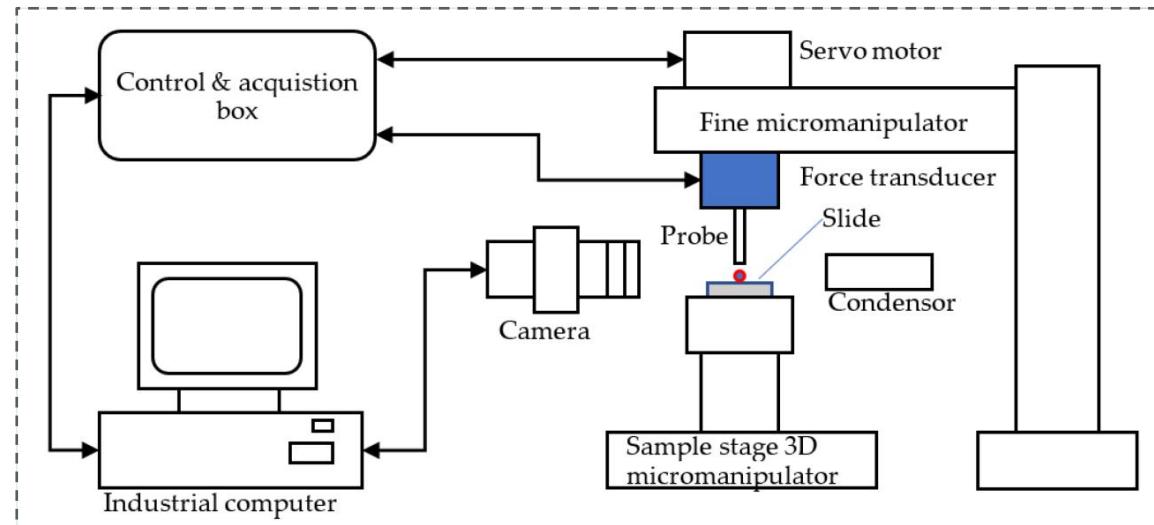
Available strategies only provide average rupture force



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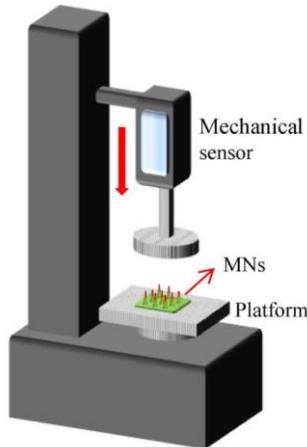
Prof. Zhibing Zhang
University of Birmingham, UK
Fellow of the Royal Academy of Engineering



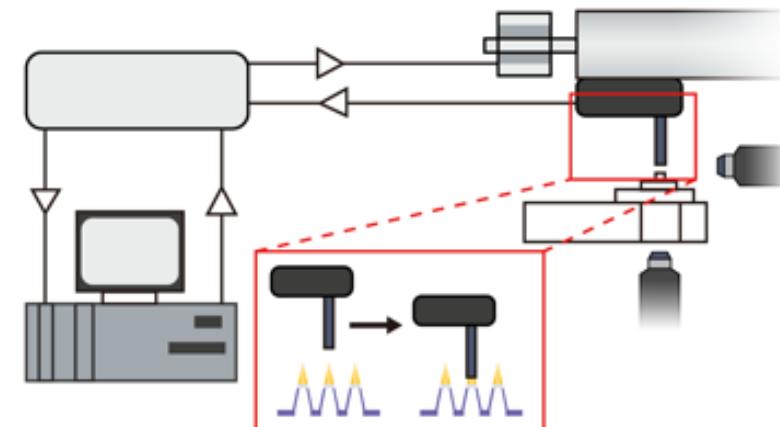
Micromanipulation was developed in Pro. Zhang's lab for mechanical property characterisation of micro- and nano-scale particles

►► Advantages of micromanipulation

Available strategies

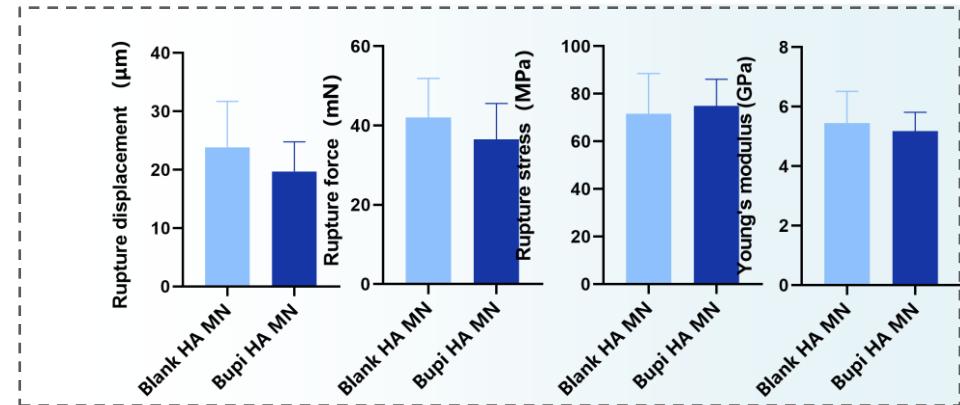
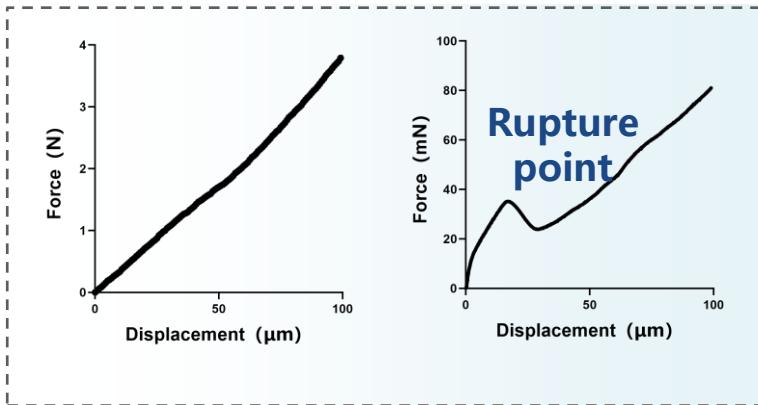


Micromanipulation

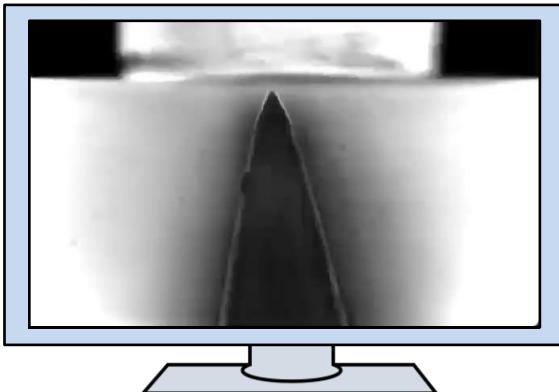


- Detection limit was increased by **1000** times
- Accuracy was increased by **100** times
- **Multidimensional** characterization

►► Advantages of micromanipulation



► High precision



► Multiple dimensions

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

►► Characterization of the fracture behavior with micromanipulation

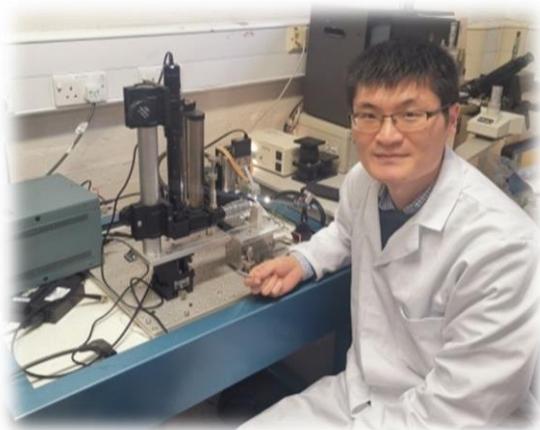
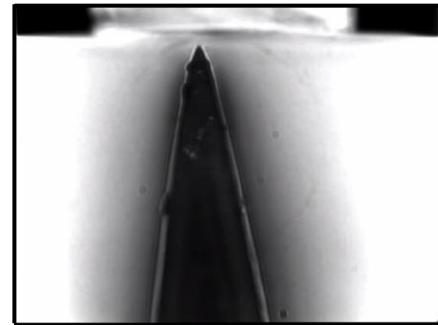


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Foundation of China

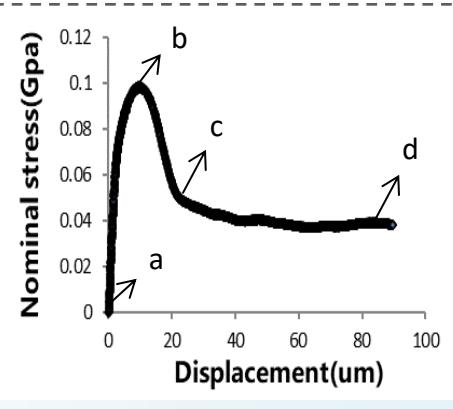
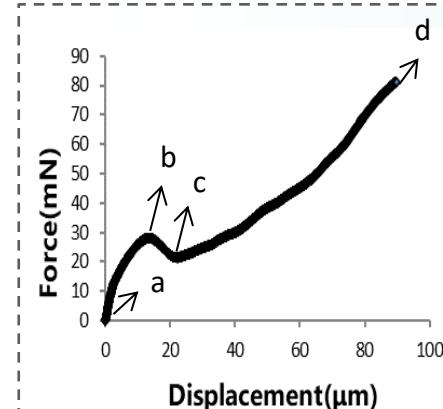


THE ROYAL SOCIETY

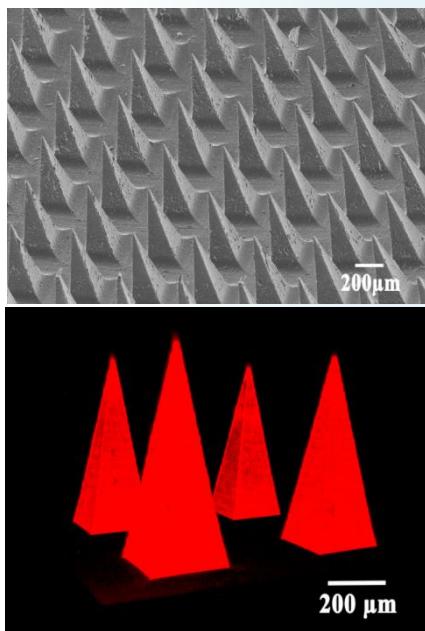
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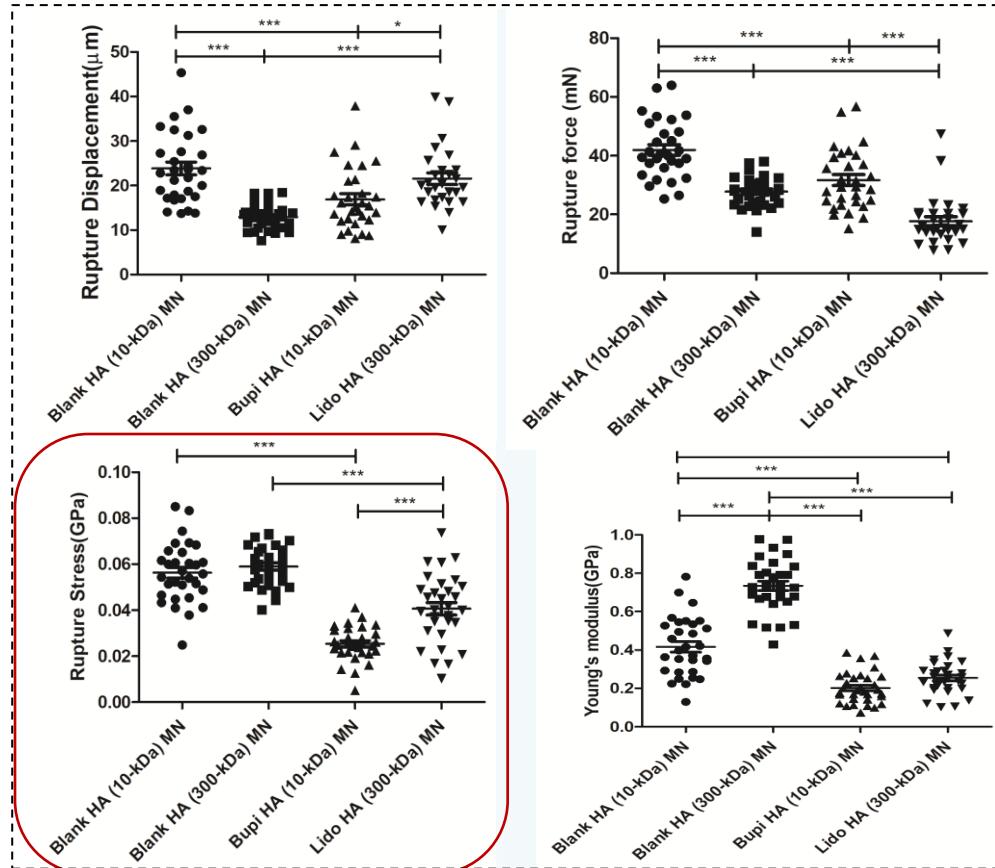
Dr. Guangsheng Du
Sichuan University



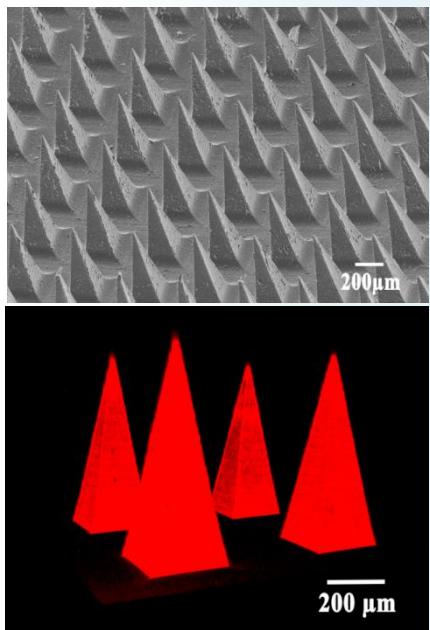
▶▶ Precise characterisation of mechanical strength of individual microneedles



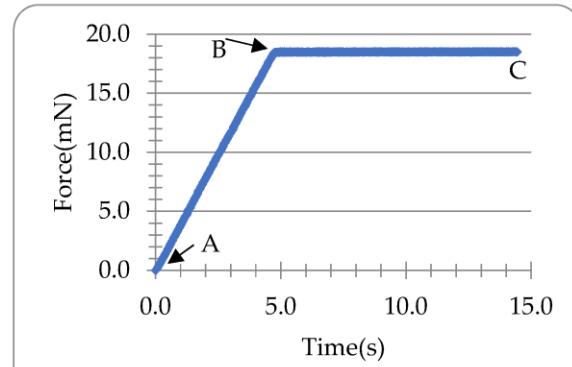
Rupture stress is more suitable to characterize the mechanical strength of MN



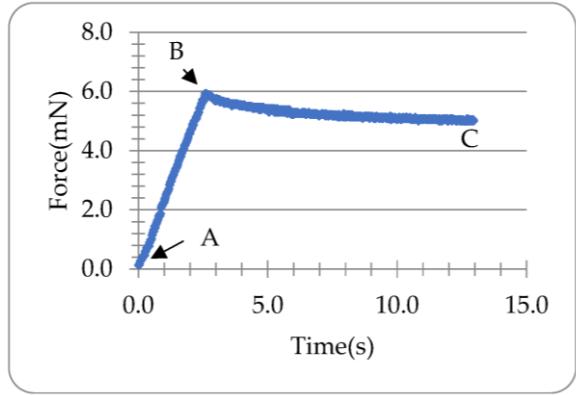
►► Precise characterisation of mechanical strength of individual microneedles



Glass plate test



MN test



G_0 (MPa)	G_∞ (MPa)	E_0 (MPa)	E_∞ (MPa)
171.1	114.4	513.3	343.2

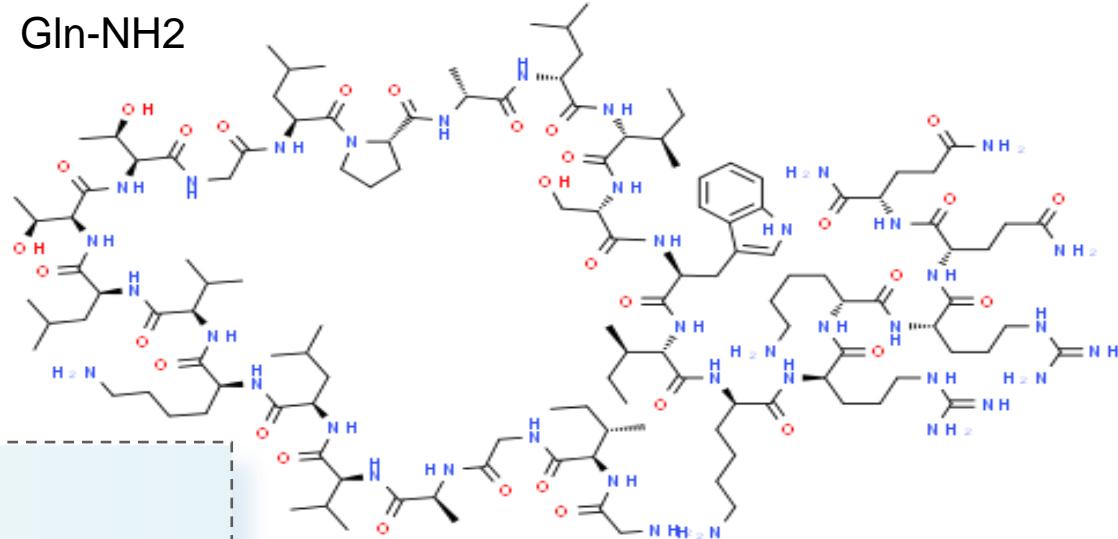
- Polymer MN have relatively higher viscoelasticity

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

►► Bee acupuncture therapy in the treatment of RA



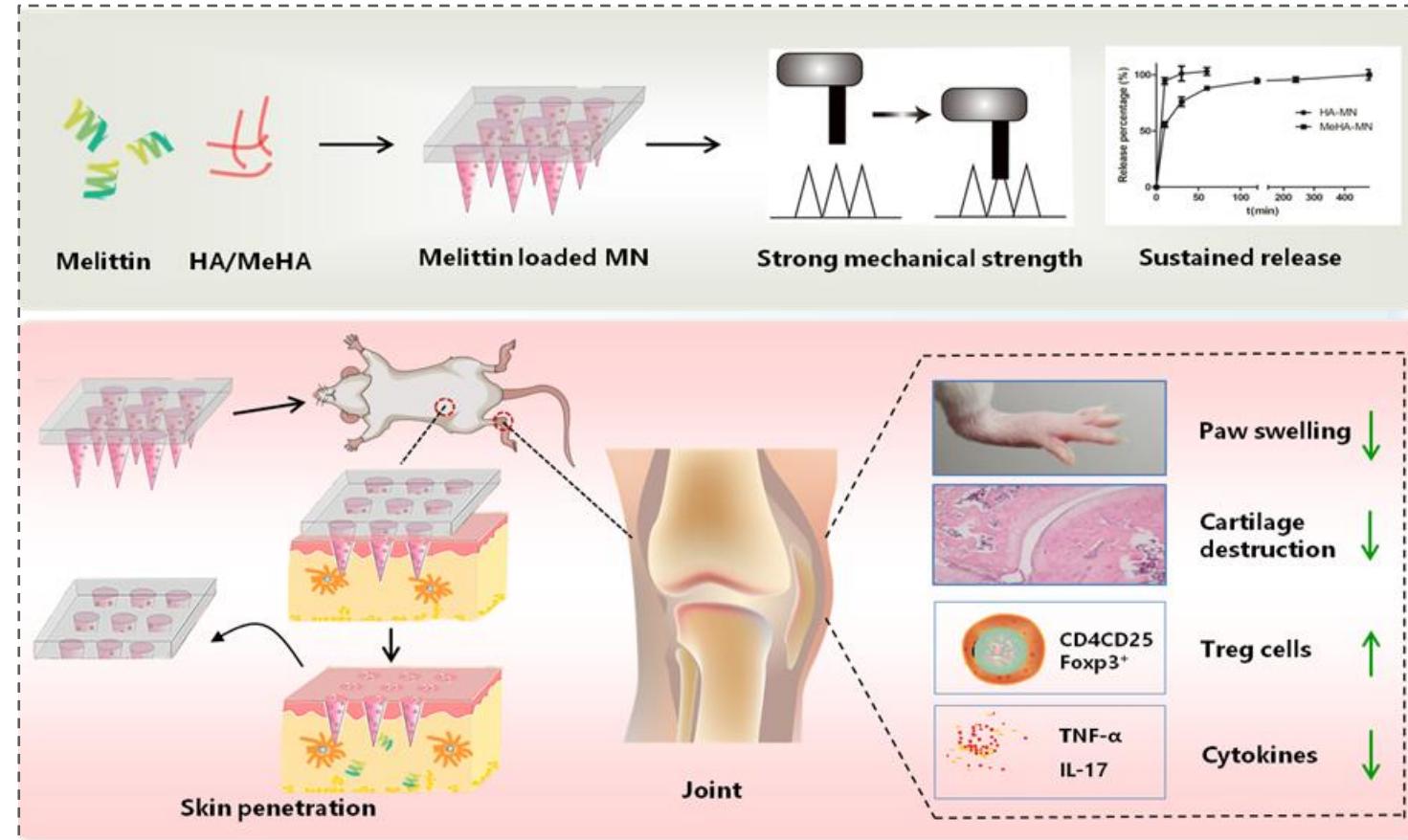
- **Melittin:** H-Gly-Ile-Gly-Ala-Val-Leu-Lys-Val-Leu-Thr-Thr-Gly-Leu-Pro-Ala-Leu-Ile-Ser-Trp-Ile-Lys-Arg-Lys-Arg-Gln-Gln-NH2



Merits and demerits:

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

► Treatment of RA by MN loaded with melittin

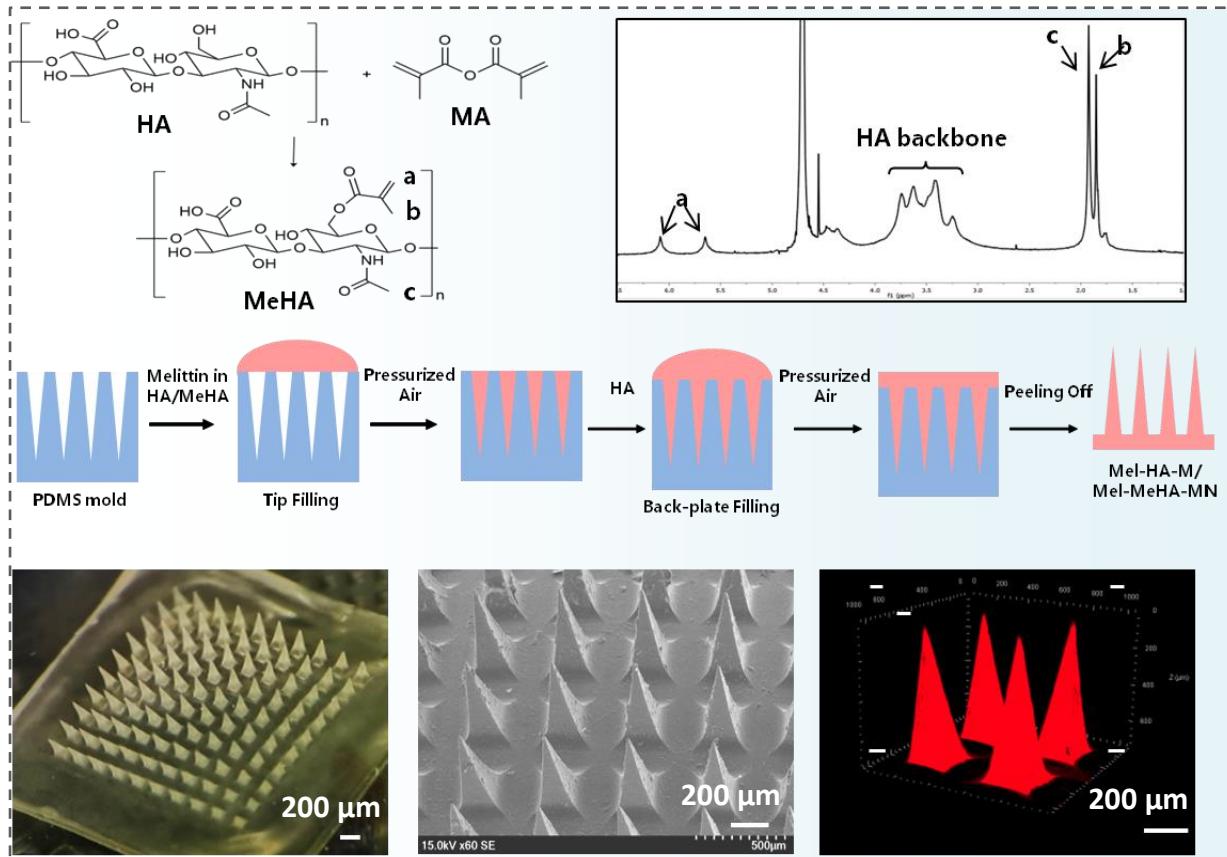




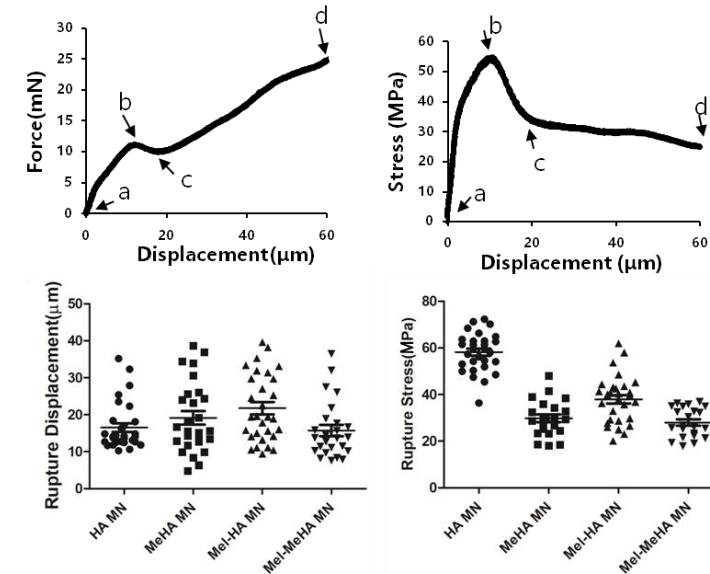
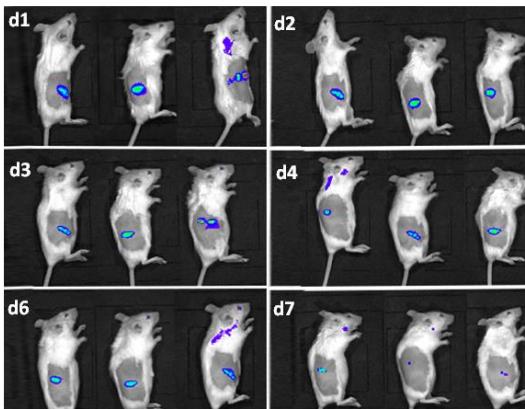
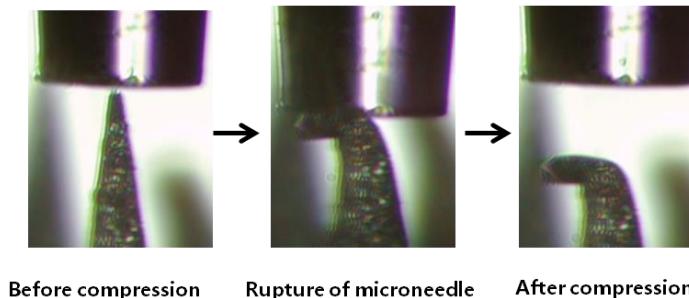
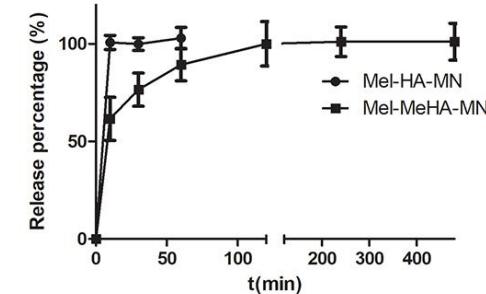
Preparation and characterization of polymer MI



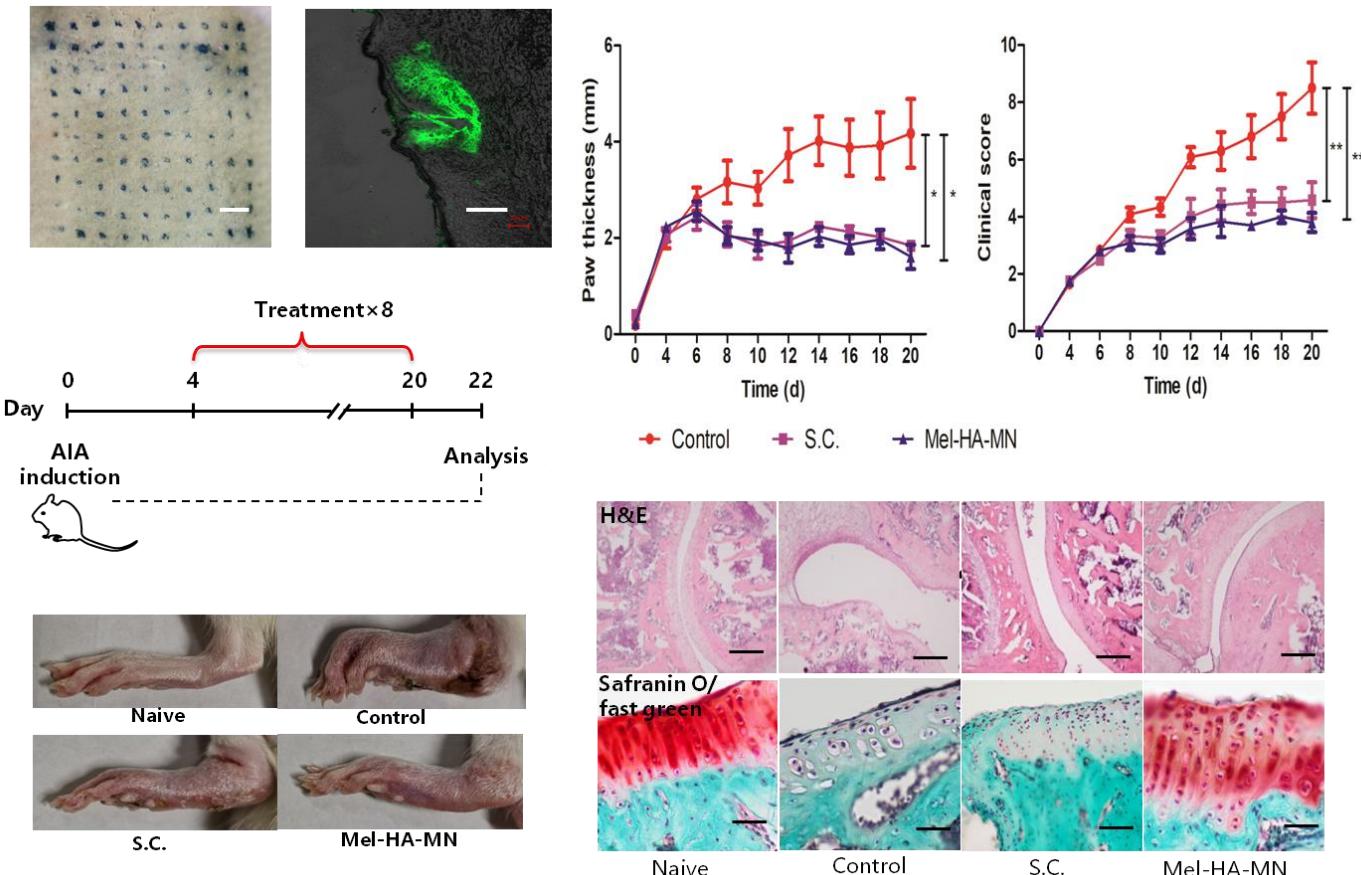
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►► MN release and mechanical strength characterization

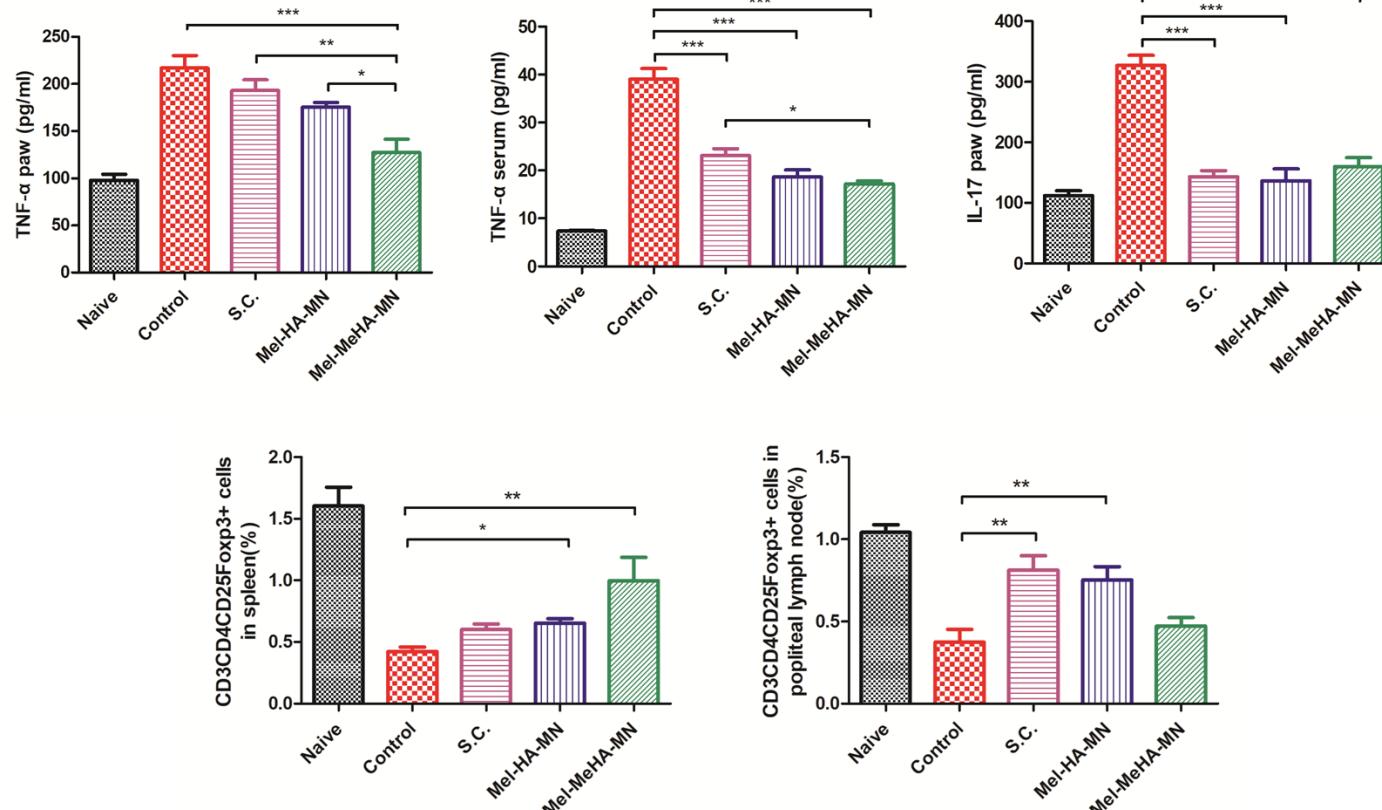


►► Therapeutic effect of AIA model in rats





Decreased inflammatory factors and increased proportions of Treg

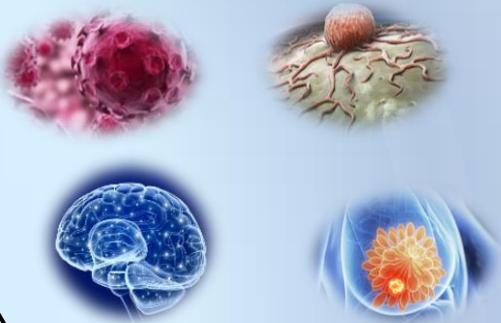


►► War and peace of immune system

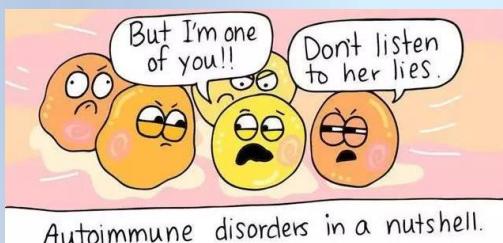
Allergies and autoimmunity



Influenza and cancer



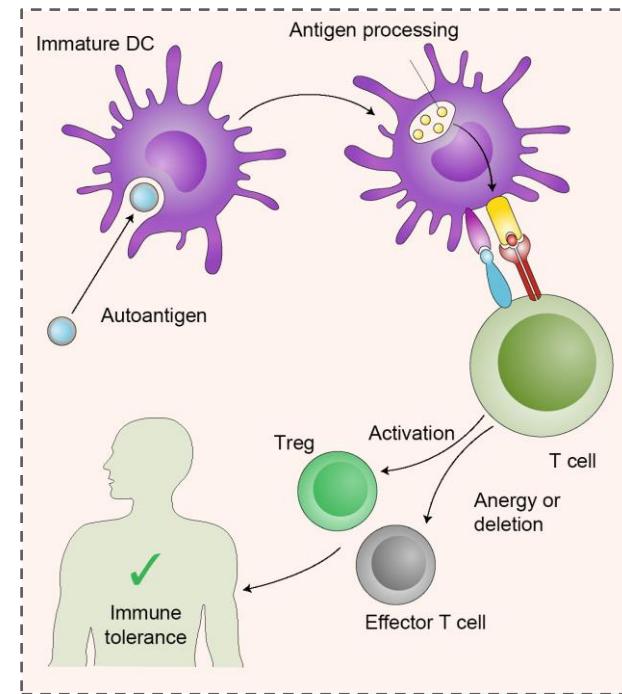
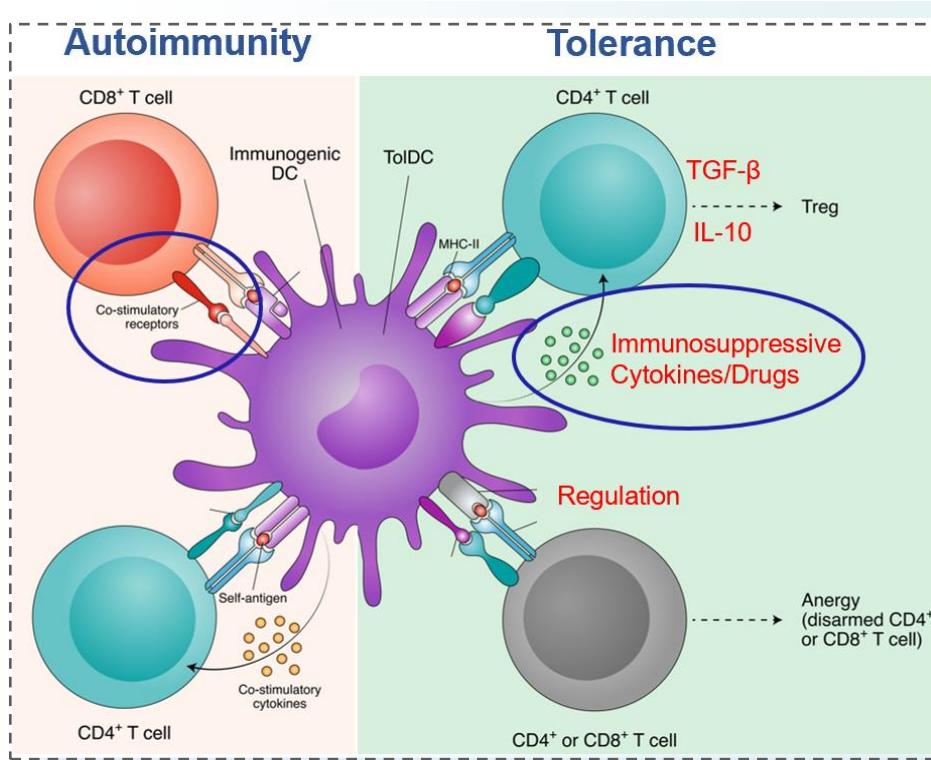
Immune regulation



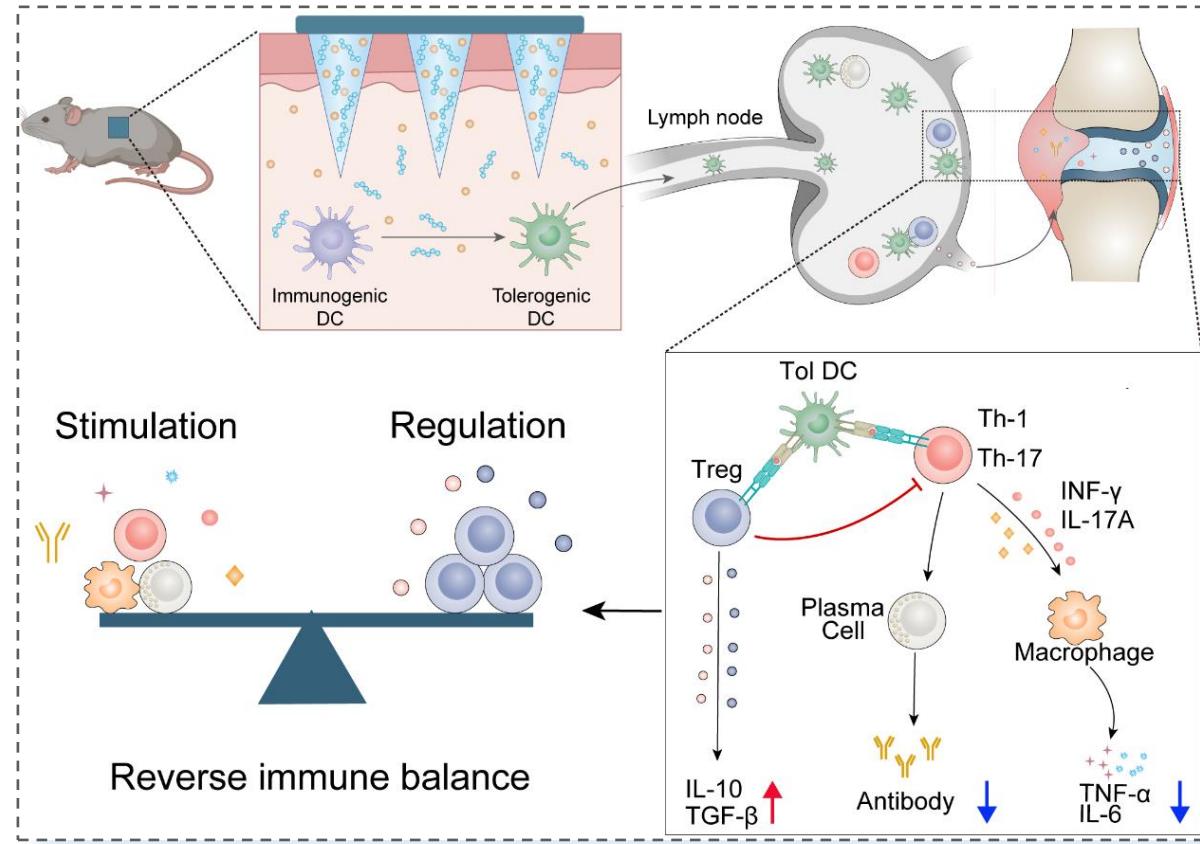
Immune activation



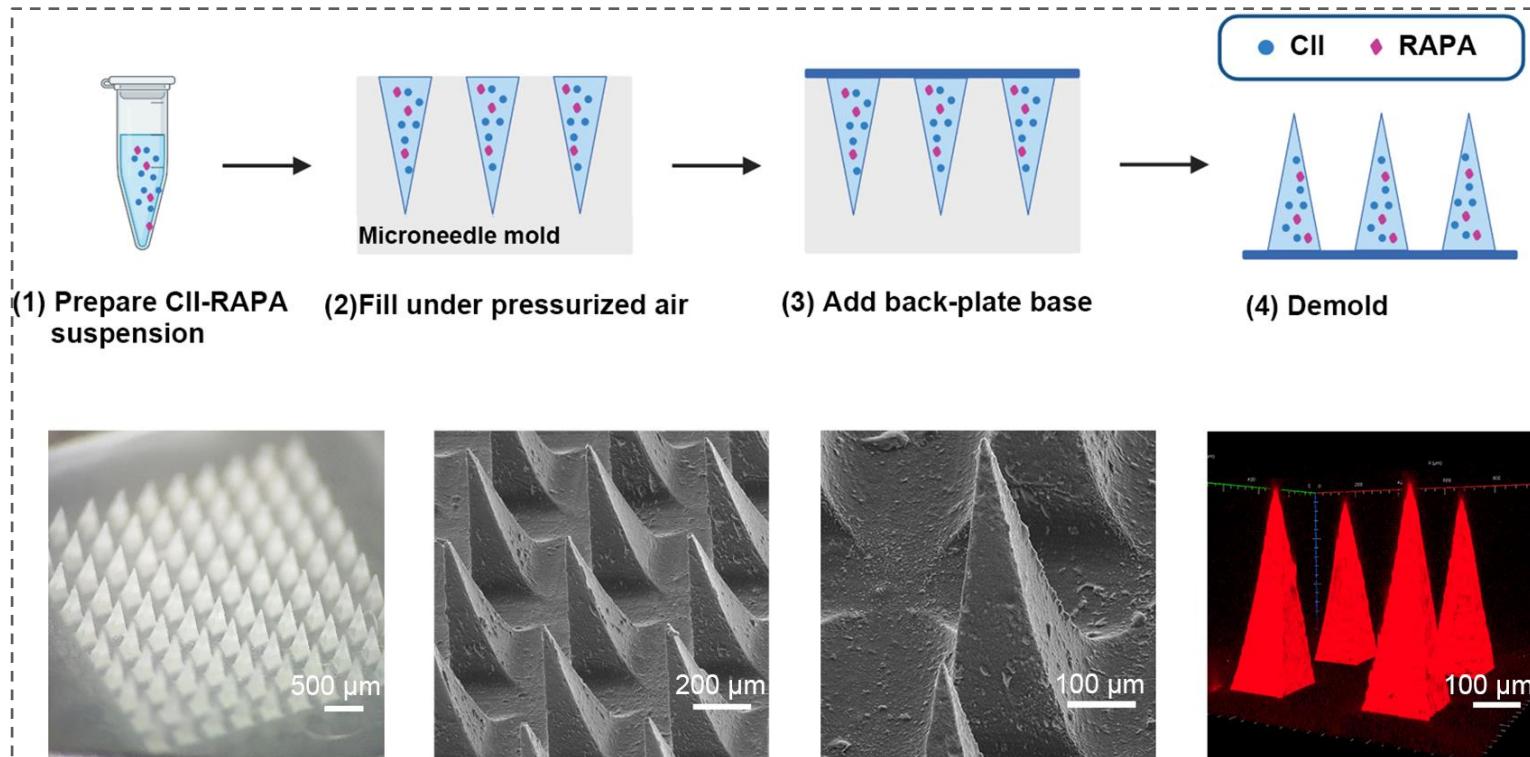
►► Tolerance induction is the ultimate goal for RA treatment



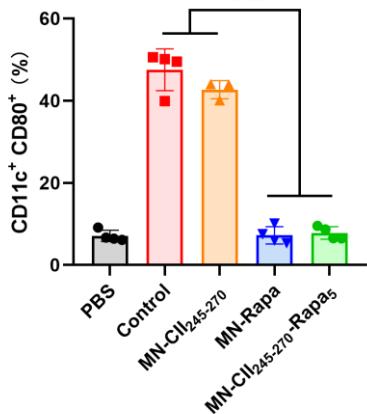
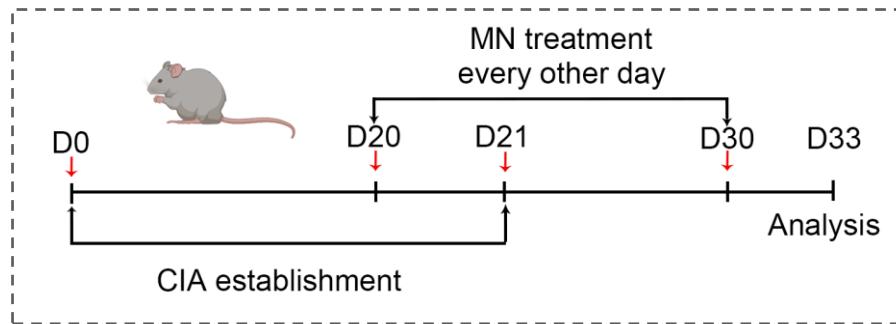
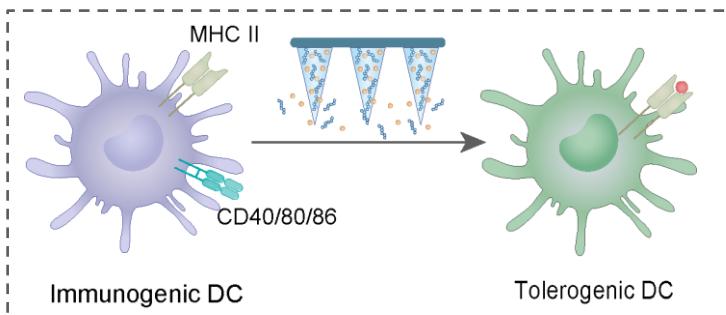
►► Induction of immune tolerance by MN for RA treatment



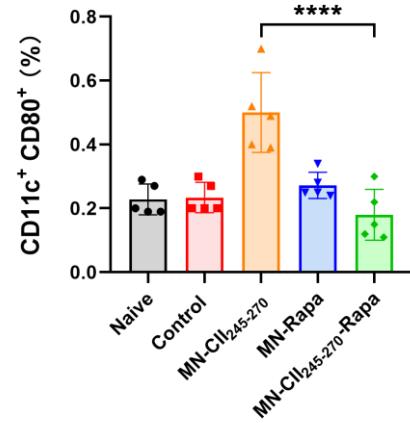
▶▶ Preparation and characterization of MN



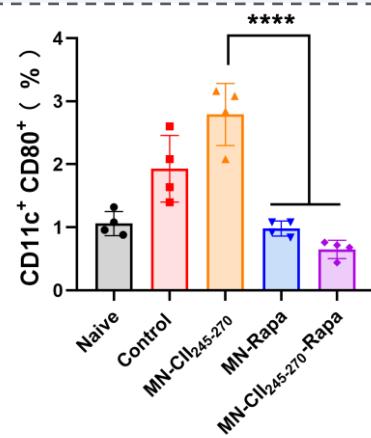
►► CII peptide and Rapa co-loaded MN induced tolDCs



● In vitro TolDC

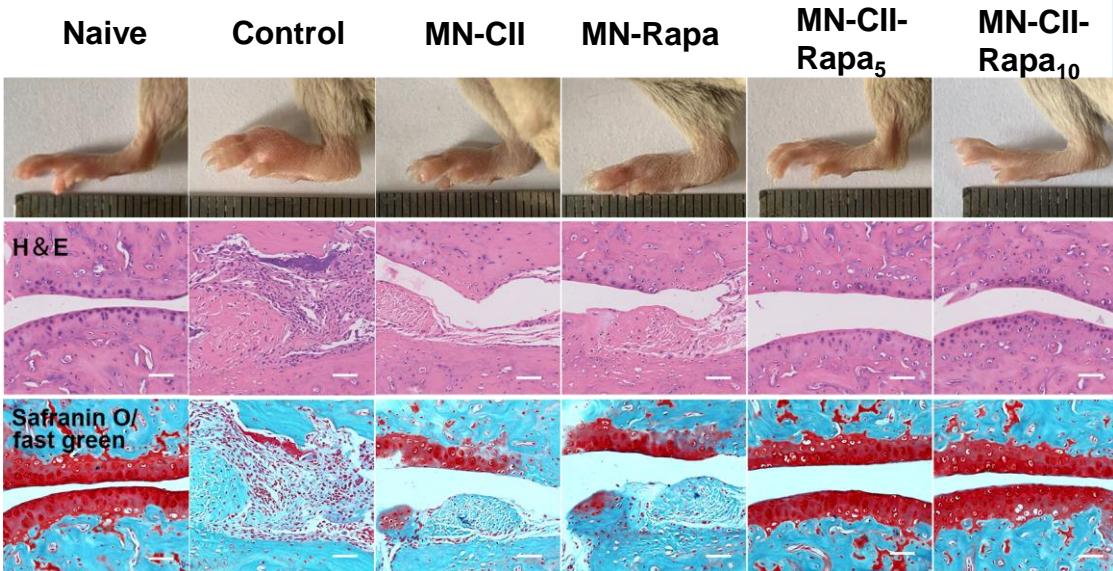
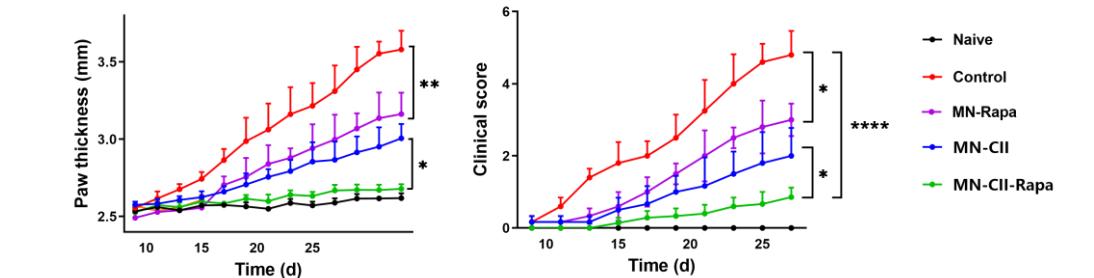
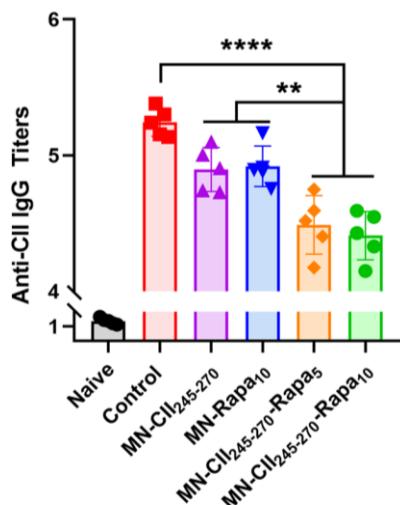
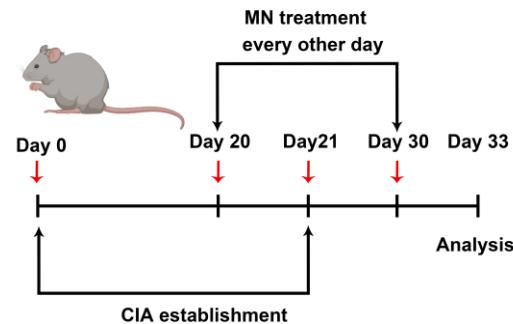


● TolDC in skin



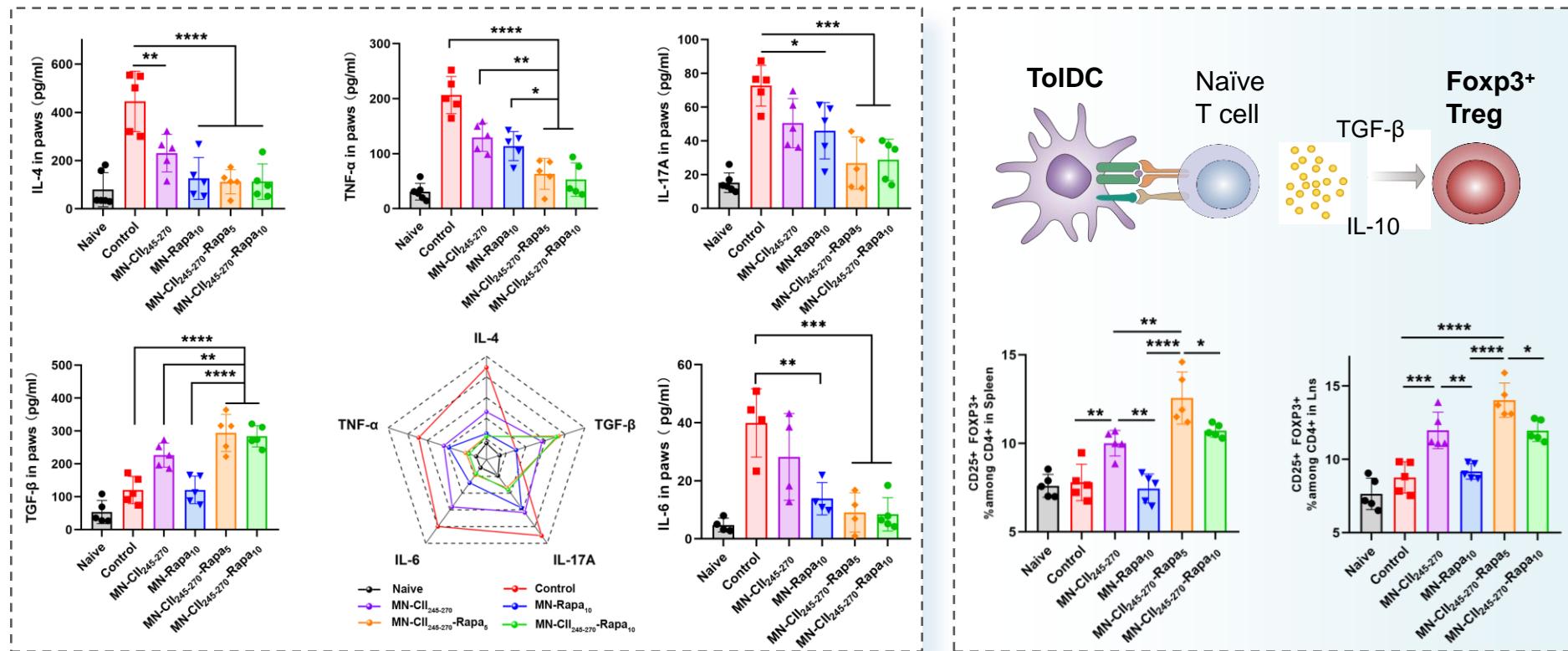
● TolDC in LN

► Therapeutic effect of MN in CIA mouse model





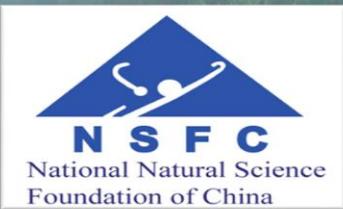
MN reversed restored the immune balance



► Conclusion

- ▶ 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!



An aerial photograph of a university campus. The image shows traditional Chinese architecture with grey tiled roofs and red-painted wooden structures. A large, ornate building with a red roof and a traditional Chinese lantern is visible on the left. The campus is lush with green trees and several large, yellow autumn trees. A paved walkway leads through the campus, and a modern sports field with a green running track and white lines is visible in the top right corner. The overall scene is a blend of traditional and modern elements.

Thanks for your attention !