

Biology for MX

MSE – 212

Prof. Maartje M.C. Bastings

Programmable Biomaterials Laboratory

**Course 9: Nanomaterials to reverse
Rheumatoid Arthritis**



BLOCK 1: Introduction and engineering with cellular components

Lecture 1.	Intro to biology and cells	(February 21)
Lecture 2.	Proteins and protein based materials	(February 28)
Lecture 3.	DNA and DNA-based materials	(March 6)
<i>Exercise 1.</i>	<i>Proteins, peptides and DNA</i>	<i>(March 13)</i>

BLOCK 2: Inter- and intracellular action

Lecture 4.	ECM, adhesion and artificial matrices	(March 20)
Lecture 5.	Virus, antibodies and immune engineering	(March 27)
Lecture 6.	Bacteria	(April 10)
<i>Exercise 2.</i>	<i>Nanoparticles and Scaffolds</i>	<i>(April 17)</i>

BLOCK 3: Physics of biological processes

Lecture 7.	Receptors and targeting	(April 24)
Lecture 8.	Endocytosis	(May 1)
Lecture 9.	Signaling and communication	(May 8)
<i>Exercise 3.</i>	<i>Engineering functionality</i>	<i>(May 15)</i>
Lecture 10.	Revision and conclusion	(May 22)
<i>Open office.</i>	<i>Questions, discussion, exam prep</i>	<i>(May 29, with TAs)</i>

Viruses



If you do not publish your data, you might as well not do the experiment...

How to write,

Scientific storytelling,

Methods and Materials,

Graphics,

Data analysis,

Clear conclusion...

Practice, practice, practice



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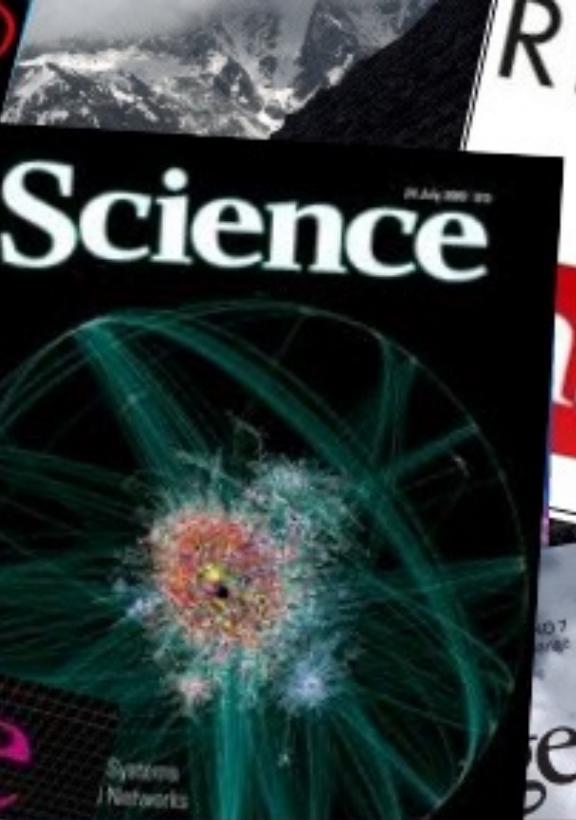
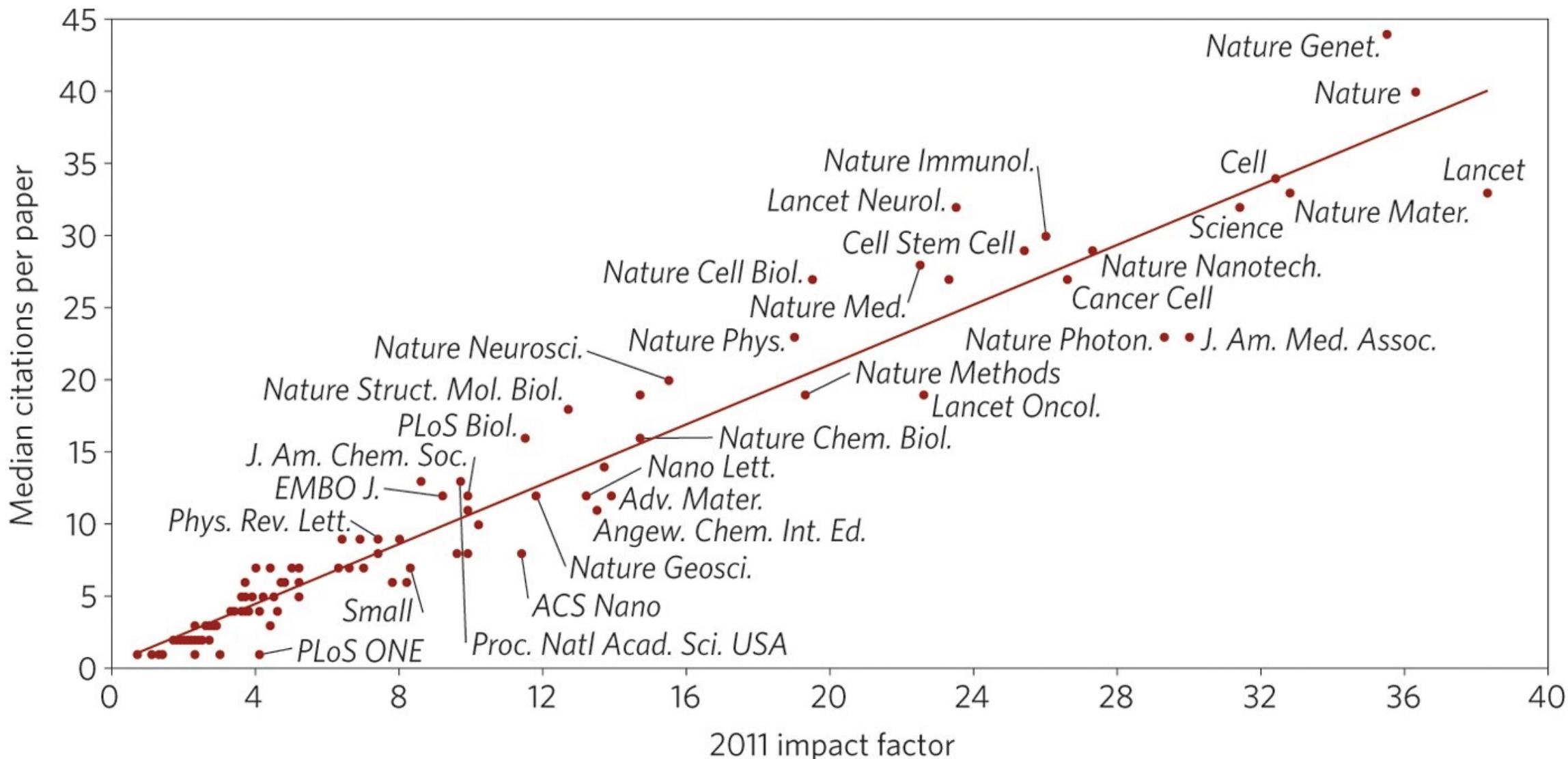


Image from Google



A DNA origami device spatially controls CD95 signalling to induce immune tolerance in rheumatoid arthritis

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 Check for updates

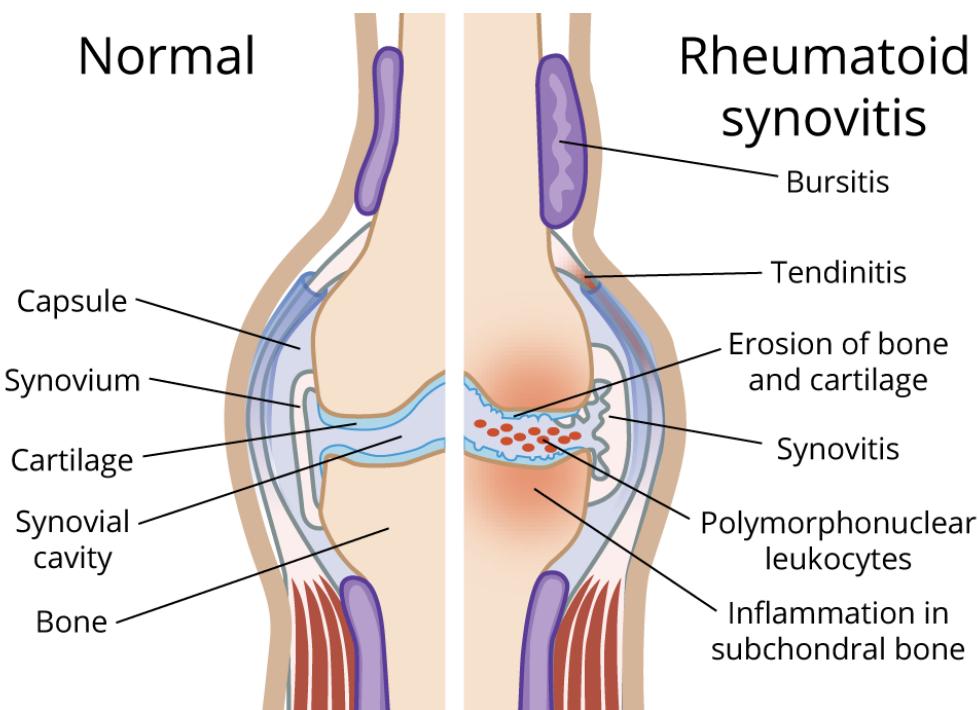
Ling Li  ^{1,9}, Jue Yin  ^{2,9}, Wen Ma  ^{3,9}, Longguang Tang  ^{4,9}, Jianhua Zou  ^{5,6,7}, Linzi Yang  ², Ting Du ¹, Yi Zhao  ³, Lianhui Wang  ², Zhen Yang  ³✉, Chunhai Fan  ⁸, Jie Chao  ²✉ & Xiaoyuan Chen  ^{5,6,7}✉

DNA origami is capable of spatially organizing molecules into sophisticated geometric patterns with nanometric precision. Here we describe a reconfigurable, two-dimensional DNA origami with geometrically patterned CD95 ligands that regulates immune cell signalling to alleviate rheumatoid arthritis. In response to pH changes, the device reversibly transforms from a closed to an open configuration, displaying a hexagonal pattern of CD95 ligands with ~10 nm intermolecular spacing, precisely mirroring the spatial arrangement of CD95 receptor clusters on the surface of immune cells. In a collagen-induced arthritis mouse model, DNA origami elicits robust and selective activation of CD95 death-inducing signalling in activated immune cells located in inflamed synovial tissues. Such localized immune tolerance ameliorates joint damage with no noticeable side effects. This device allows for the precise spatial control of cellular signalling, expanding our understanding of ligand–receptor interactions and is a promising platform for the development of pharmacological interventions targeting these interactions.

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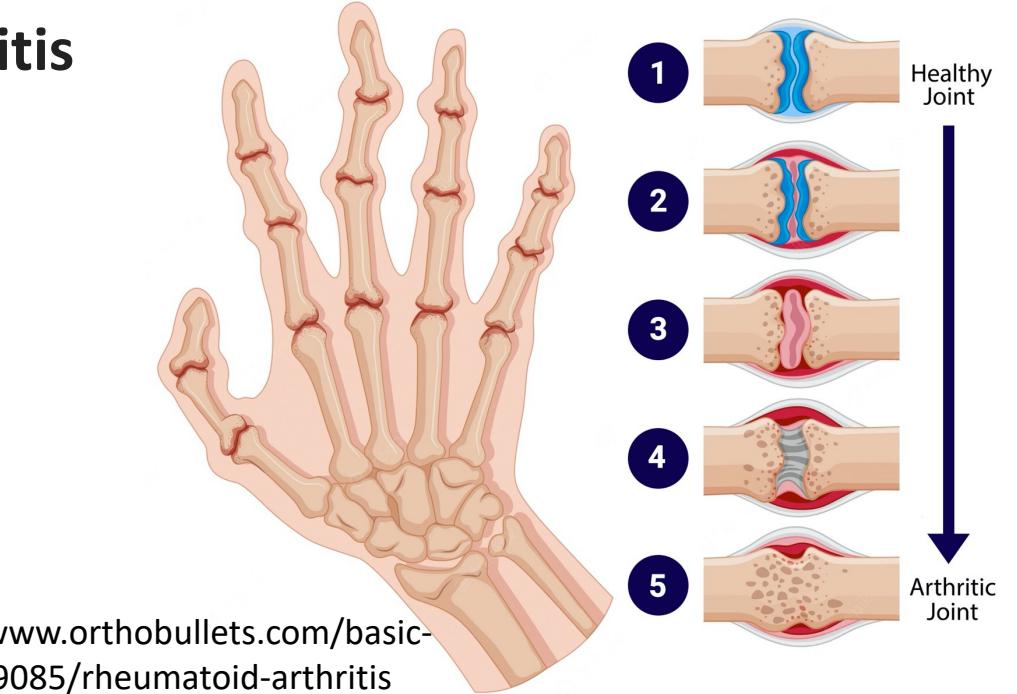
Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a systemic autoimmune disease that affects polyarticular joints. The inflammatory process is characterized by infiltration of various inflammatory/immune cells (including T cells, B cells and macrophages) into the synovial hyperplasia, leading to progressive destruction of joints and bone.



Recklies AD, Poole AR, Banerjee S, et al: American Academy of Orthopaedic Surgeons, 2000, pp 489-530.

<https://www.orthobullets.com/basic-science/9085/rheumatoid-arthritis>



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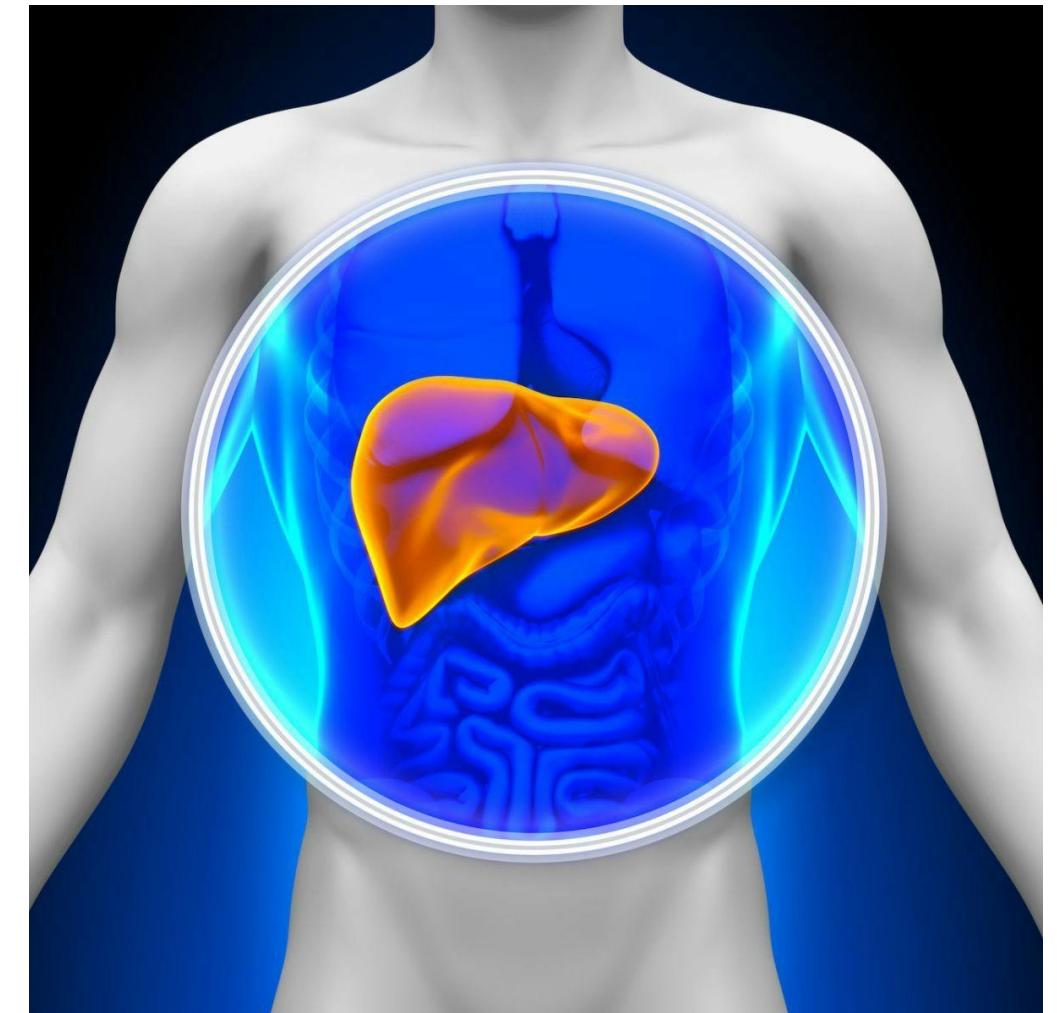
Rheumatoid Arthritis

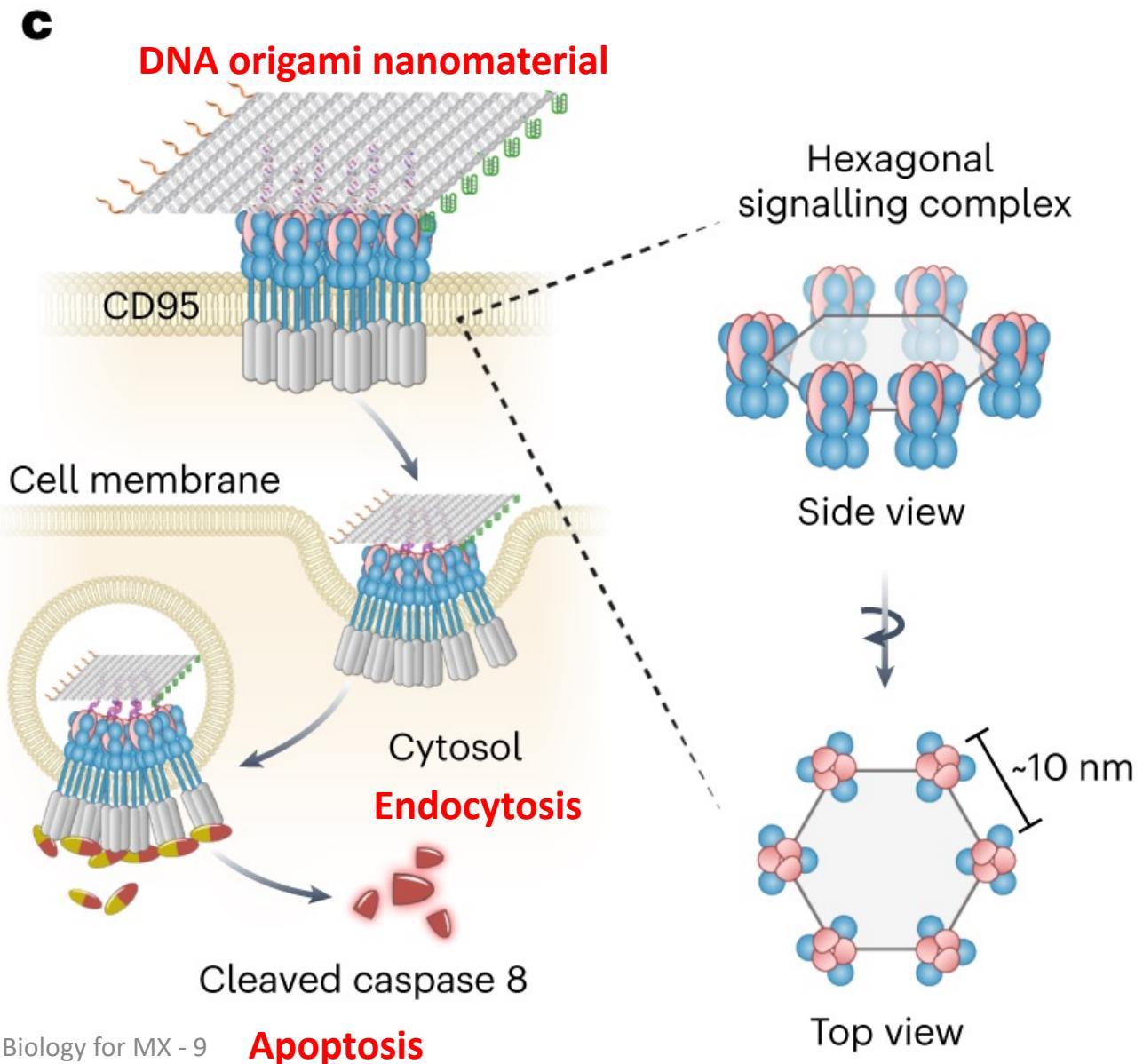
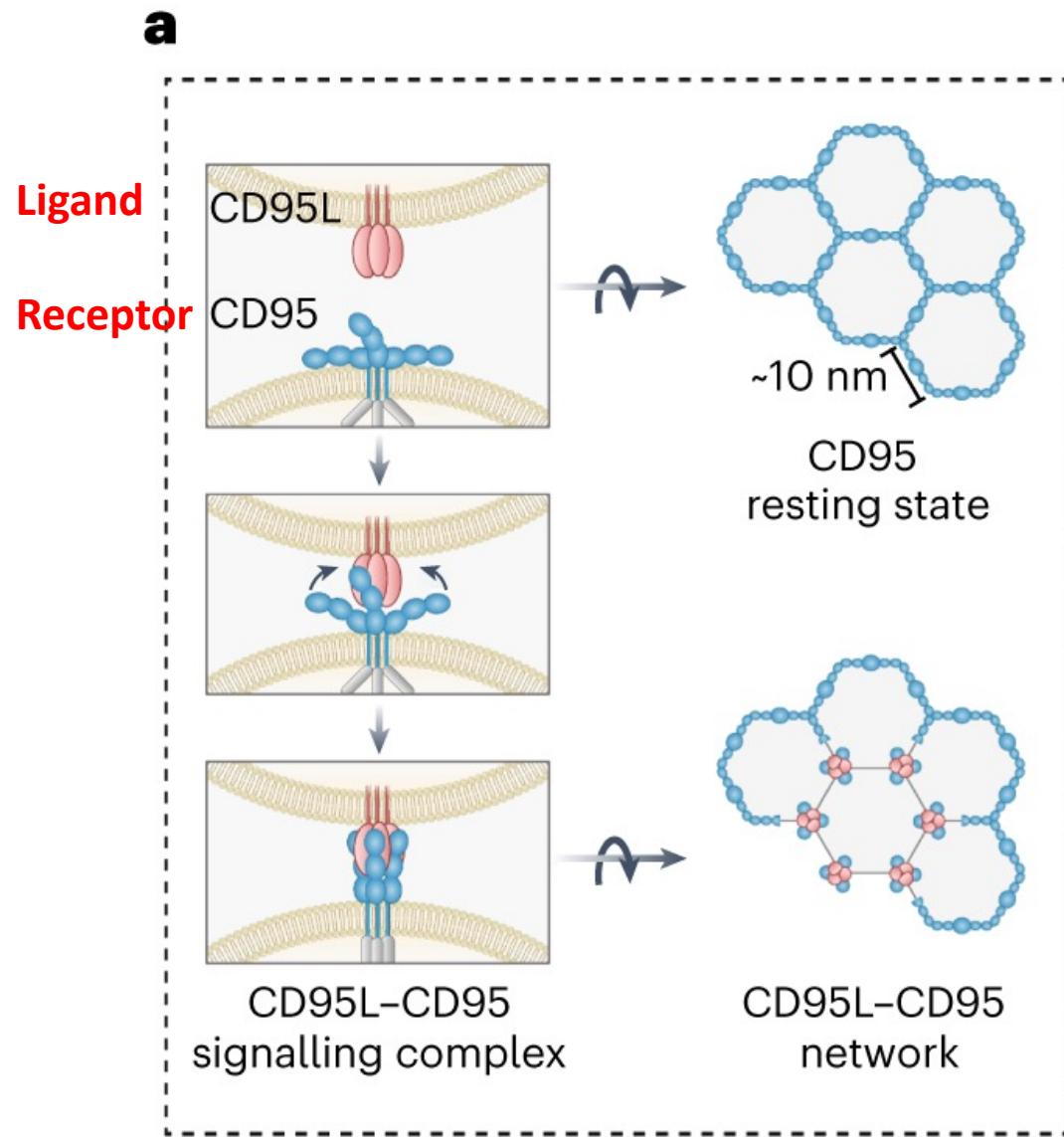
Current Treatment Problem: liver toxicity

Because of chronic medication

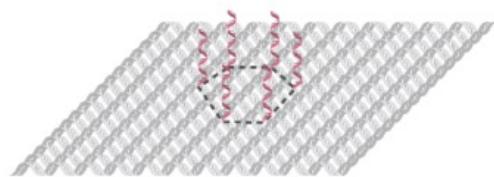
RA rarely affects the liver by itself but liver damage has been a common adverse effect in RA patients over long-term or on irregular medication intake.

Liver damage occurs in RA patients, mostly during NSAIDs and methotrexate (MTX) therapy

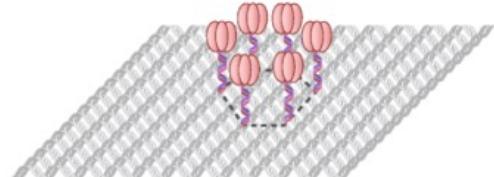
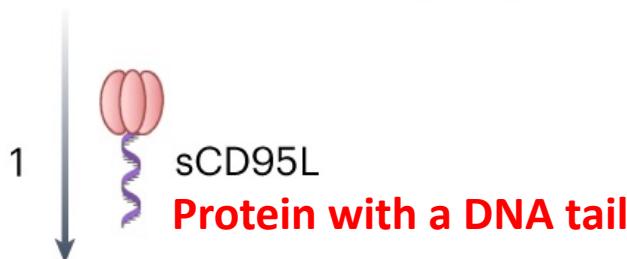
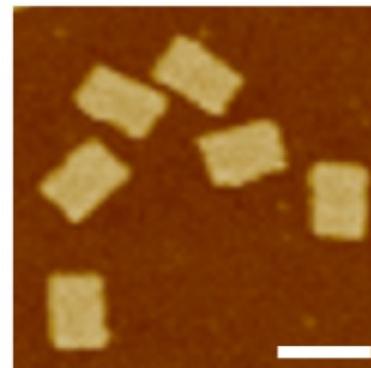
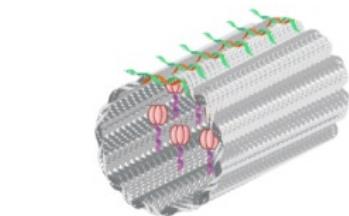
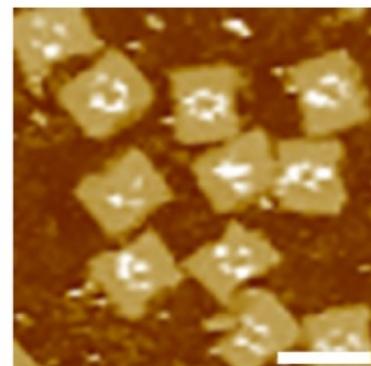
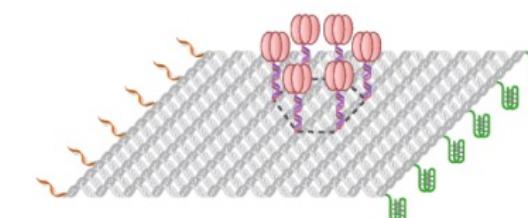
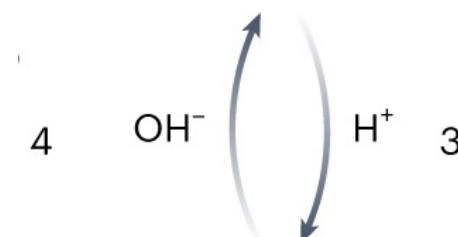
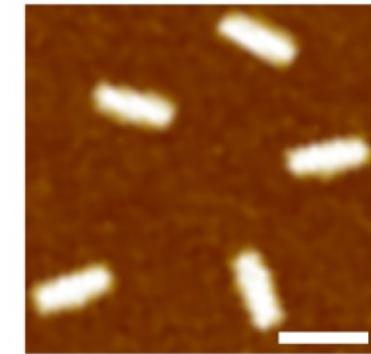
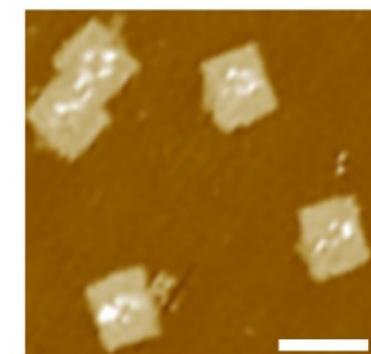




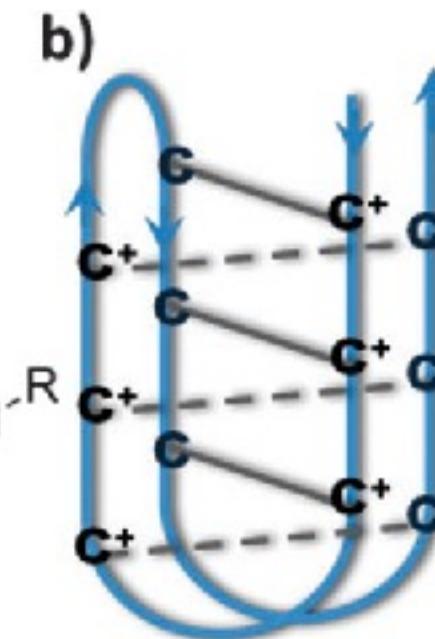
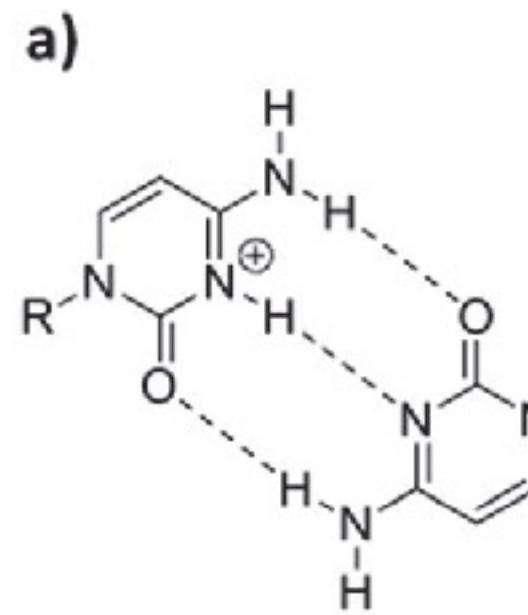
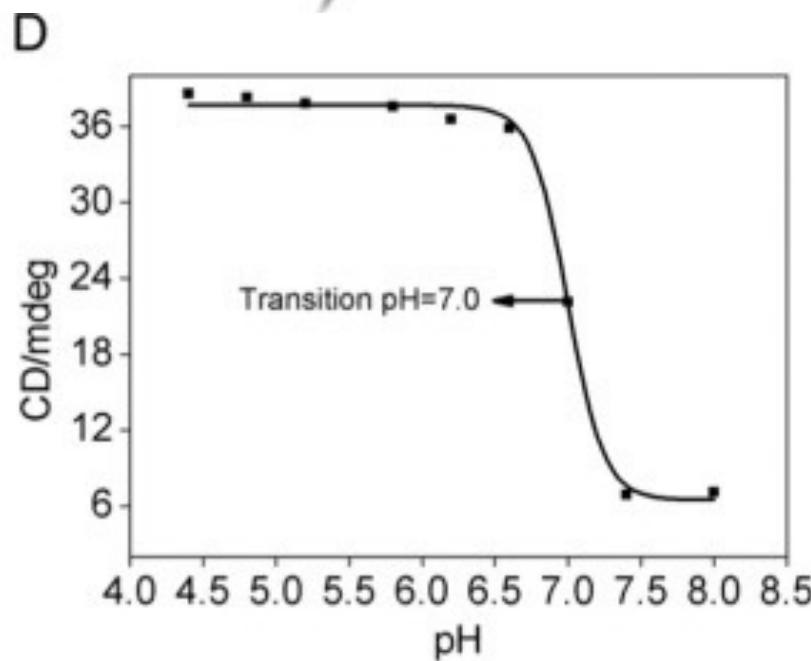
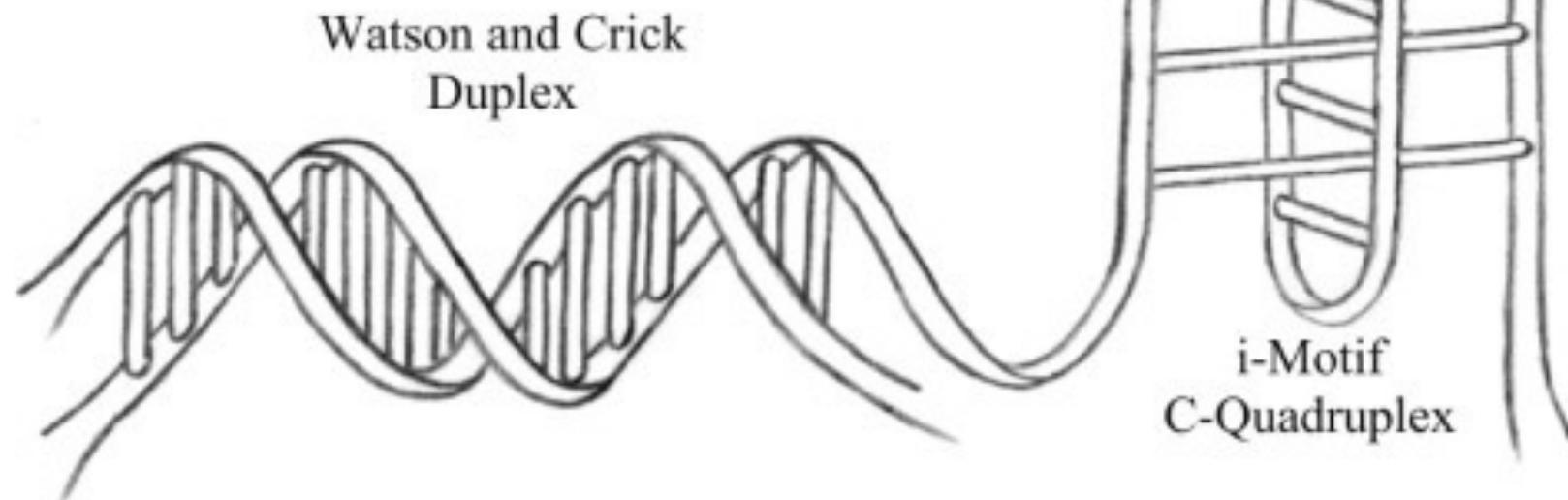
A designer DNA origami for spatial control of CD95

b

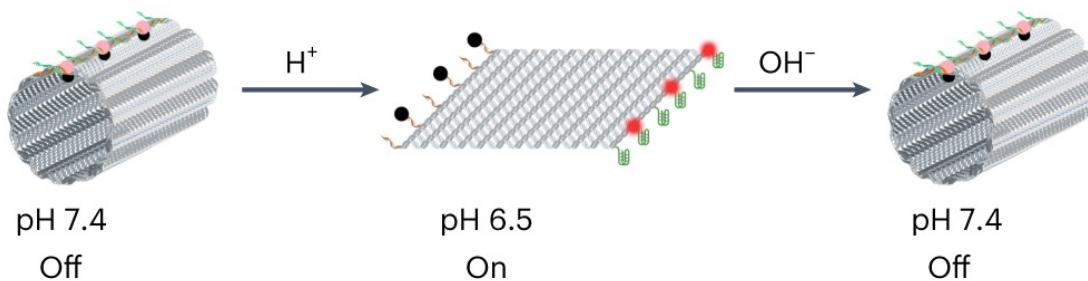
Origami nanosheet

CD95L-loaded
origami nanosheetOrigami nanodevice
(closing state)Origami nanodevice
(opening state)**i-motif**
Fastener

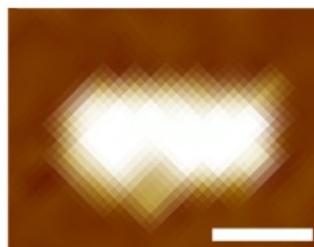
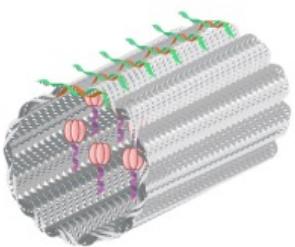
I-Motif DNA



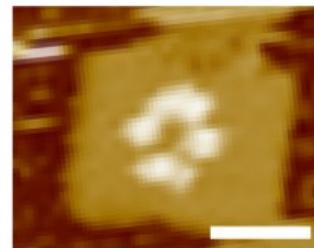
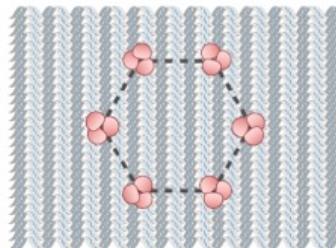
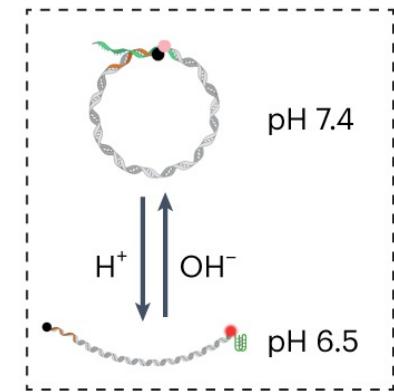
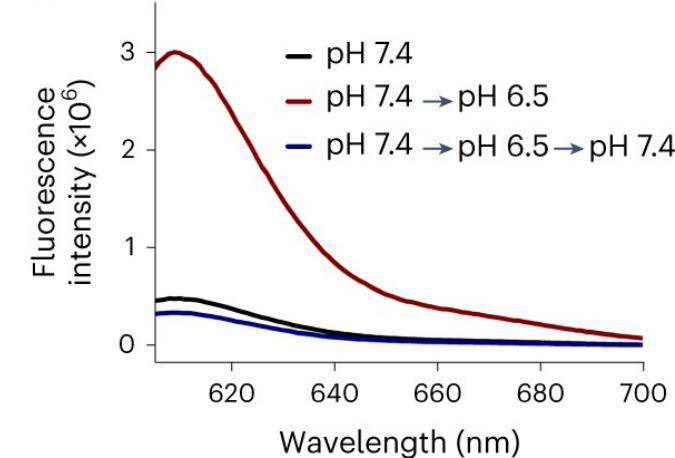
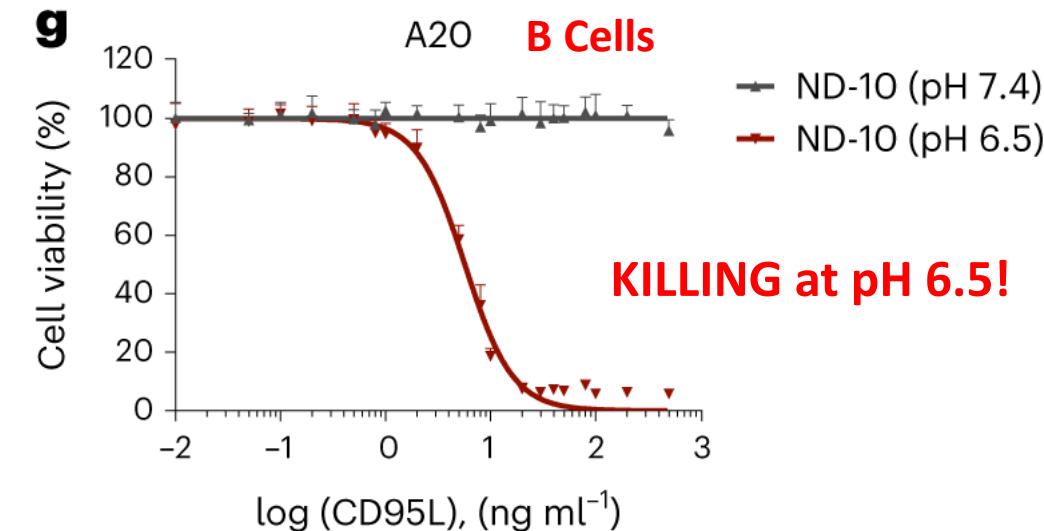
I-Motif DNA

a

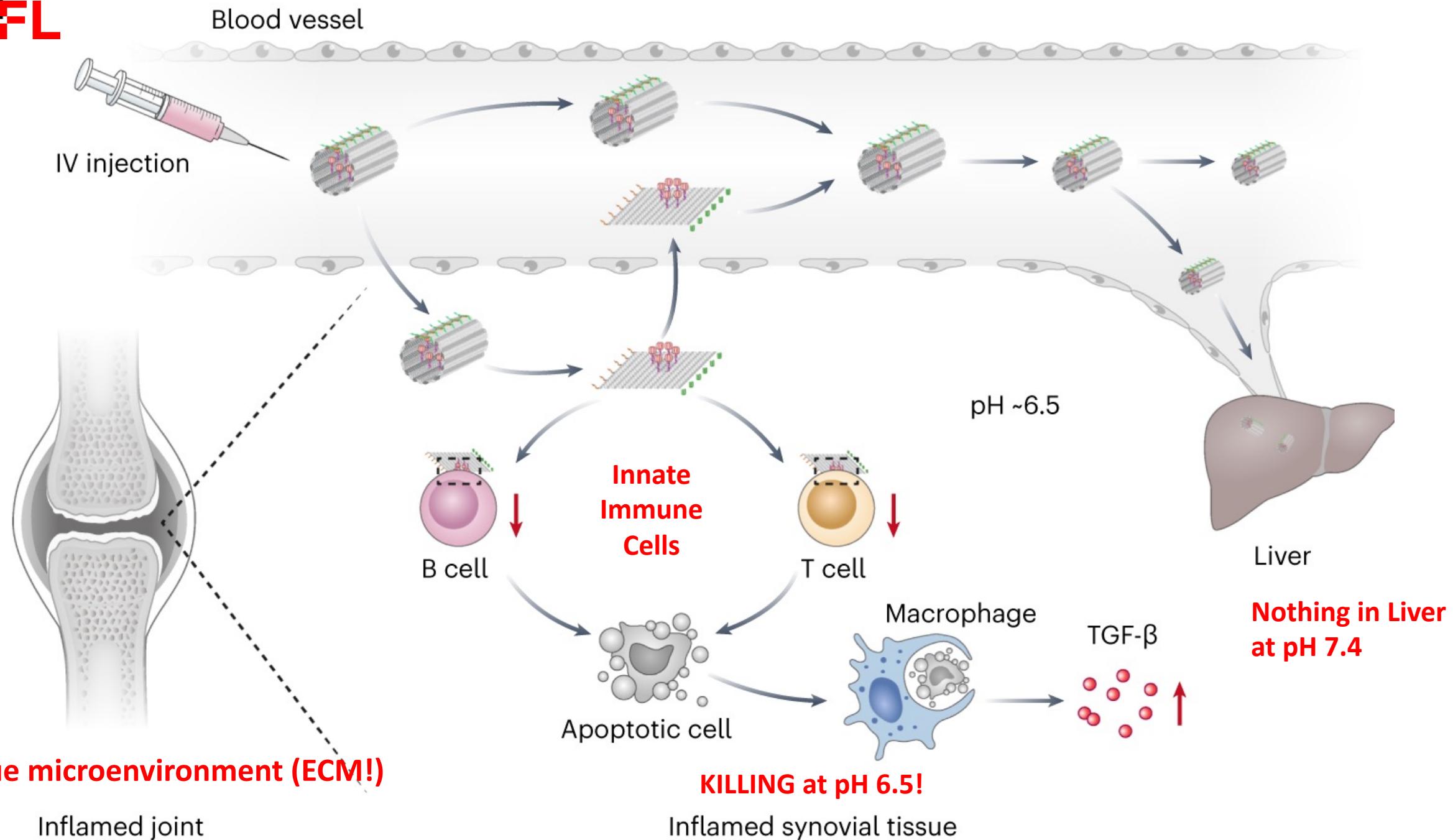
ND-10



NS-10

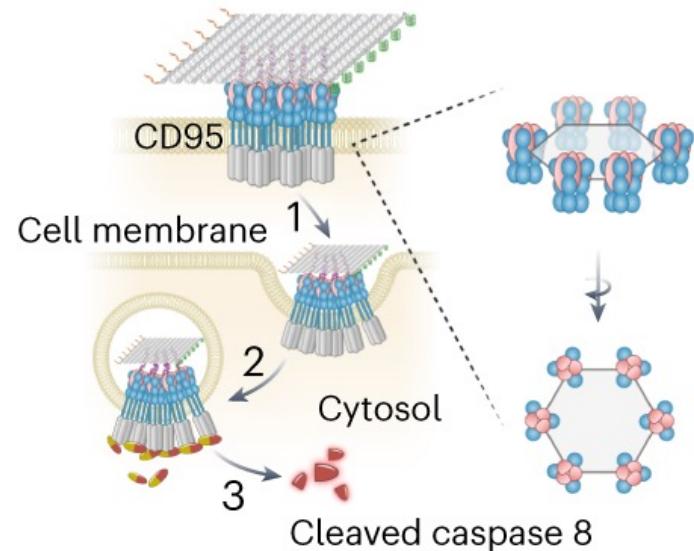
**b****g**

Biol



Spatial arrangement of the CD95L array directs the activation of CD95 signalling in A20 cells.

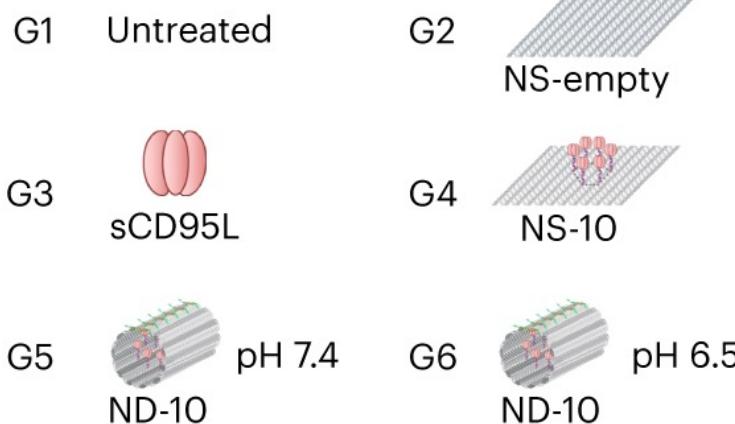
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Analysis:

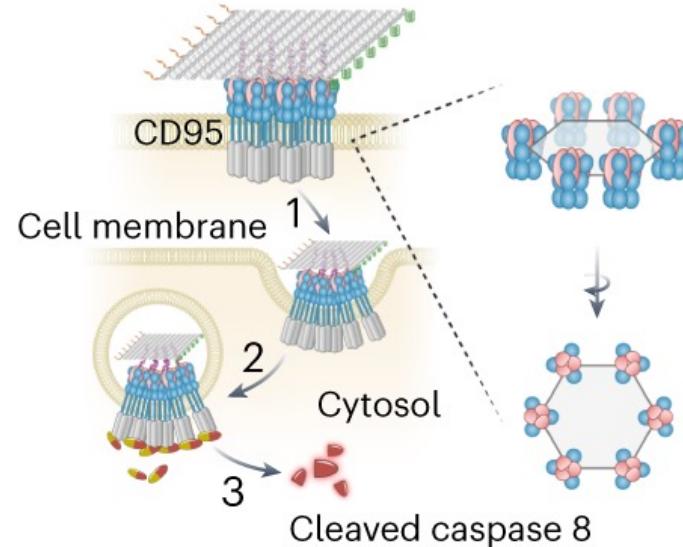
- 1) Clustering of CD95 (= metric of binding)
- 2) Production of caspase 8 (= metric of functional effect)

Important to test all the controls!

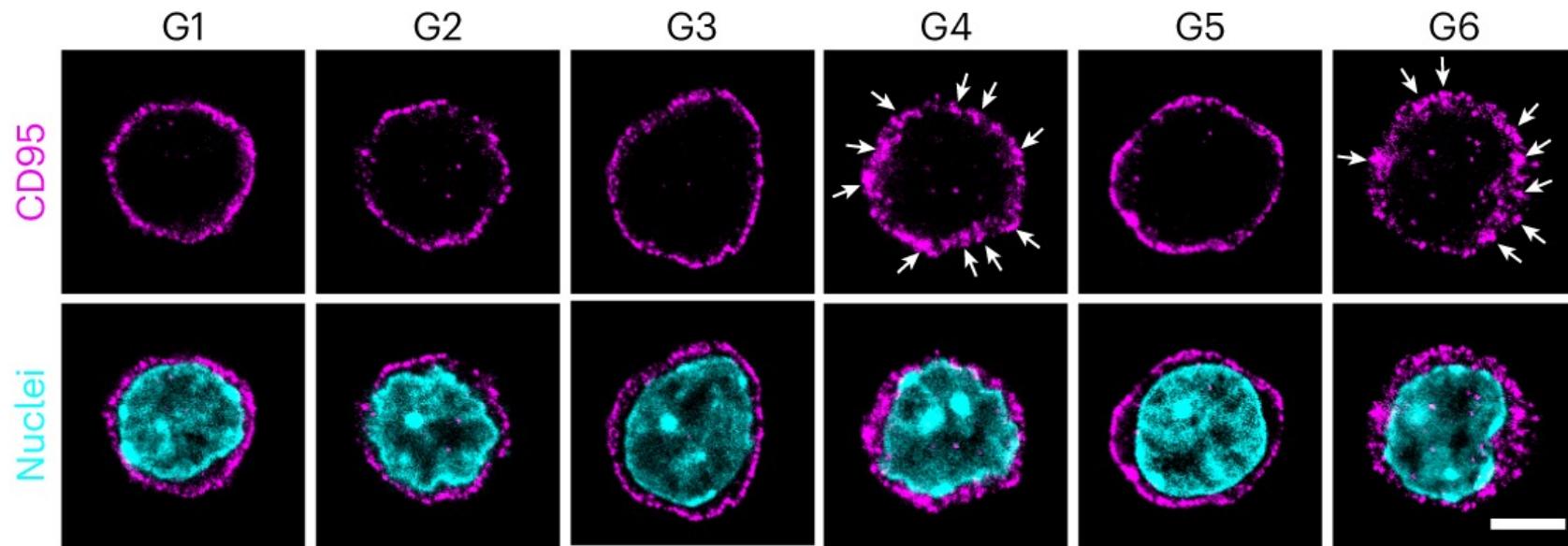


Spatial arrangement of the CD95L array directs the activation of CD95 signalling in A20 cells.

a



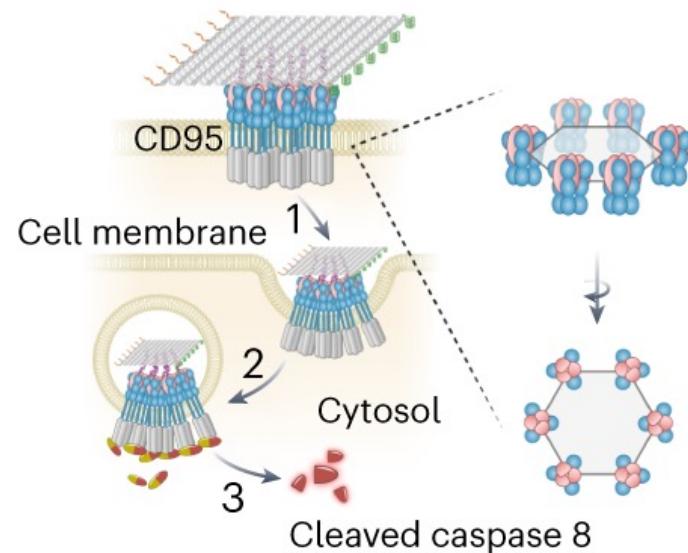
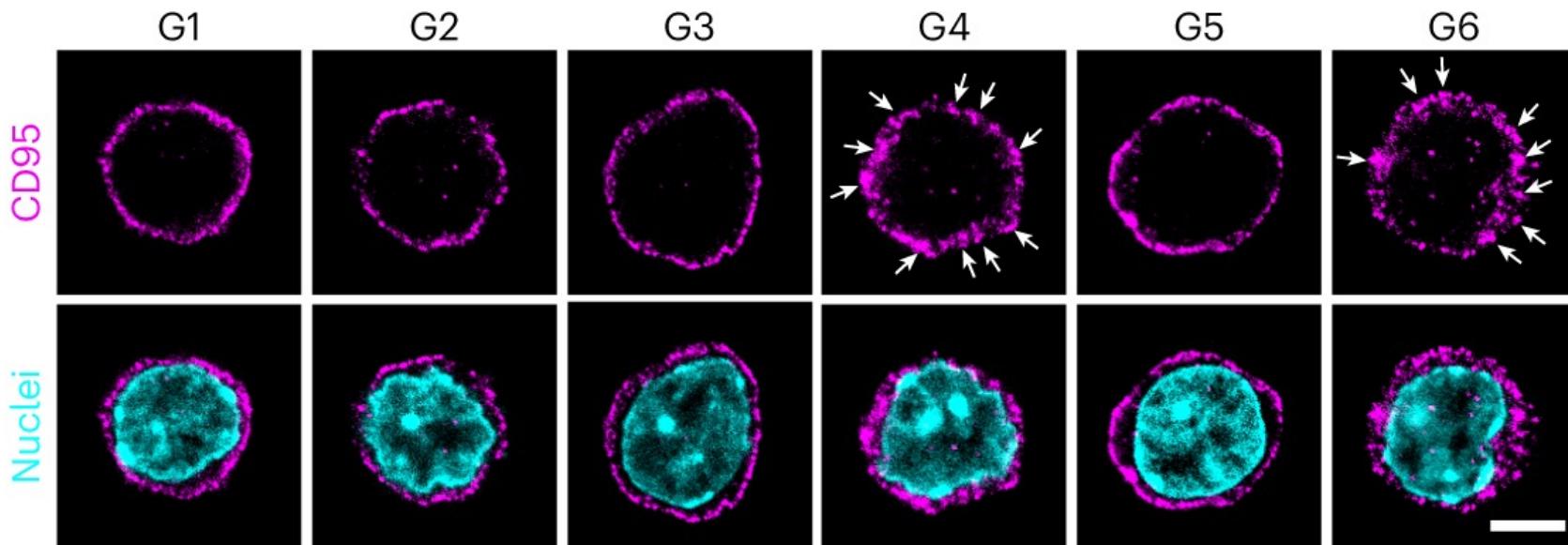
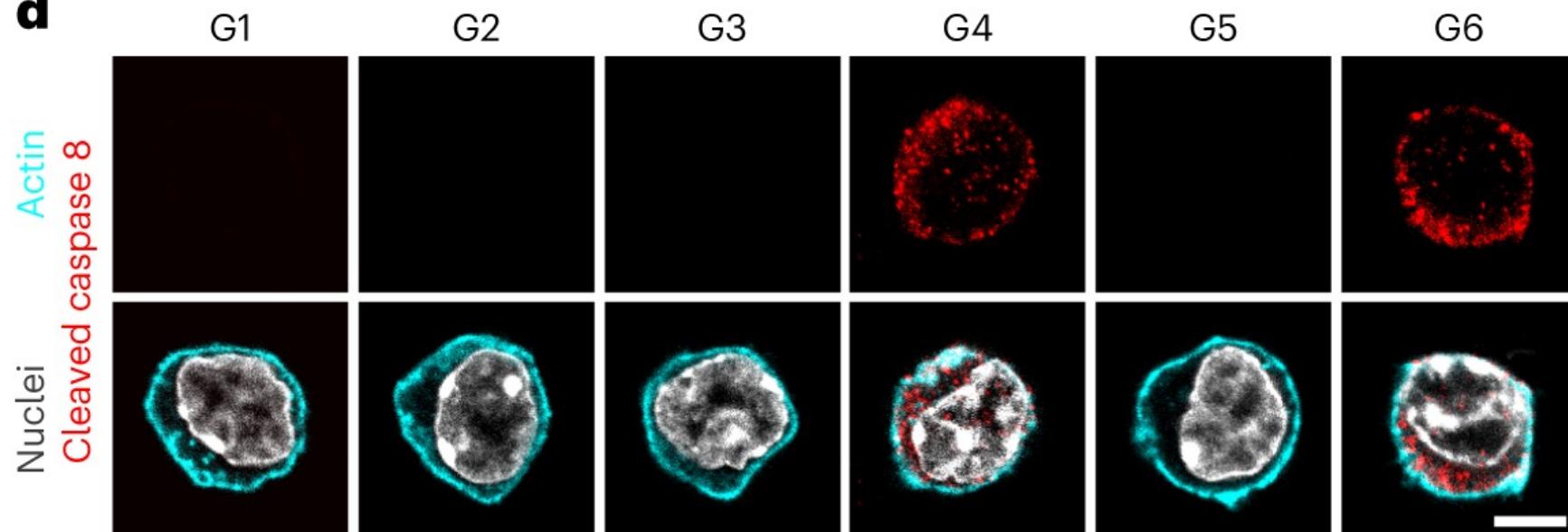
b



G1	Untreated	G2	NS-empty
G3	sCD95L	G4	NS-10
G5	ND-10 pH 7.4	G6	ND-10 pH 6.5

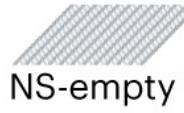
Imaged with a fluorescent microscope using an antibody—fluor dye to see the CD95 and a small molecule to color the nucleus blue

Spatial arrangement of the CD95L array directs the activation of CD95 signalling in A20 cells.

a**b****d**

G1 Untreated

G2



G3



G4



G5 pH 7.4

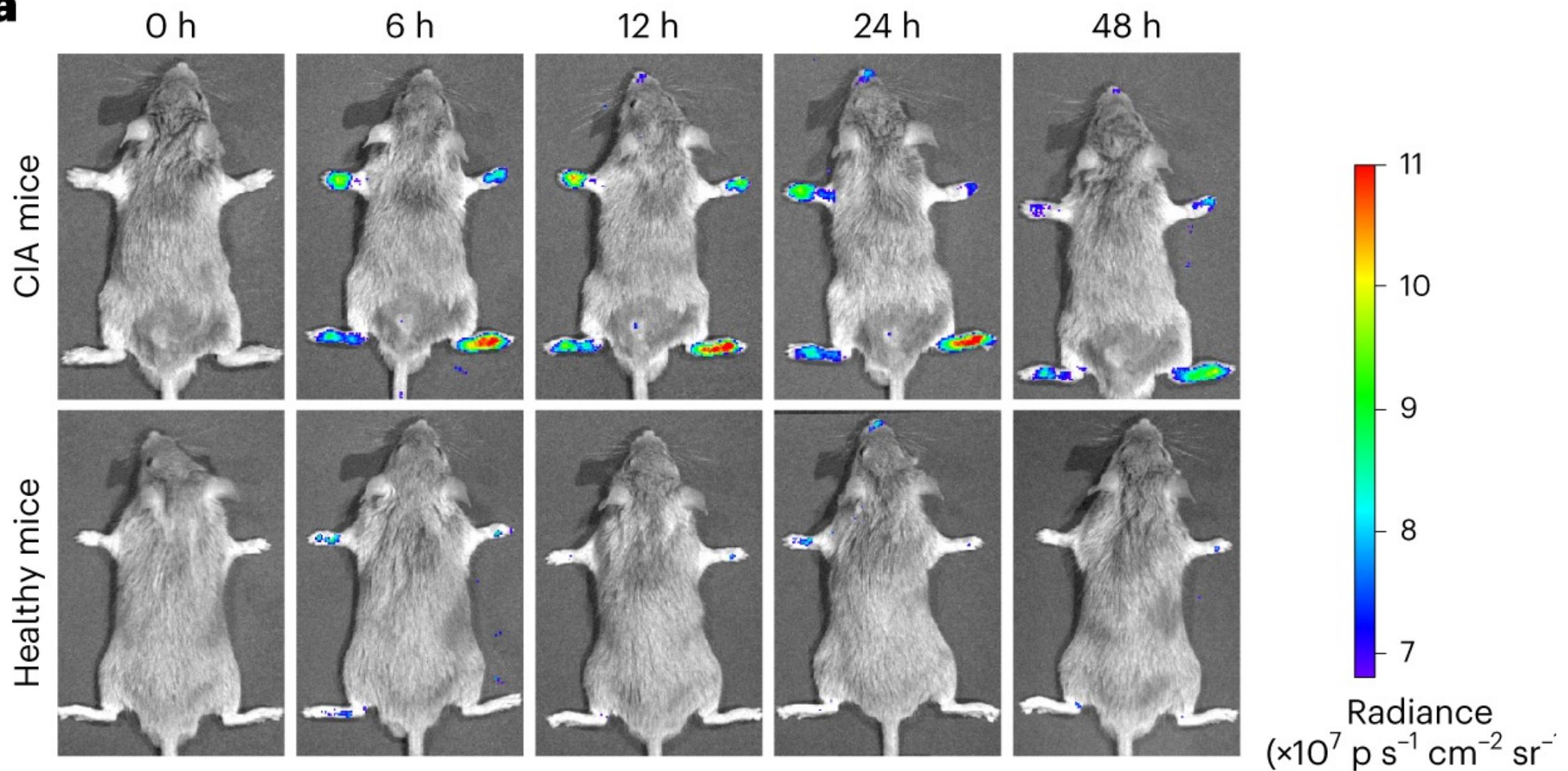


G6



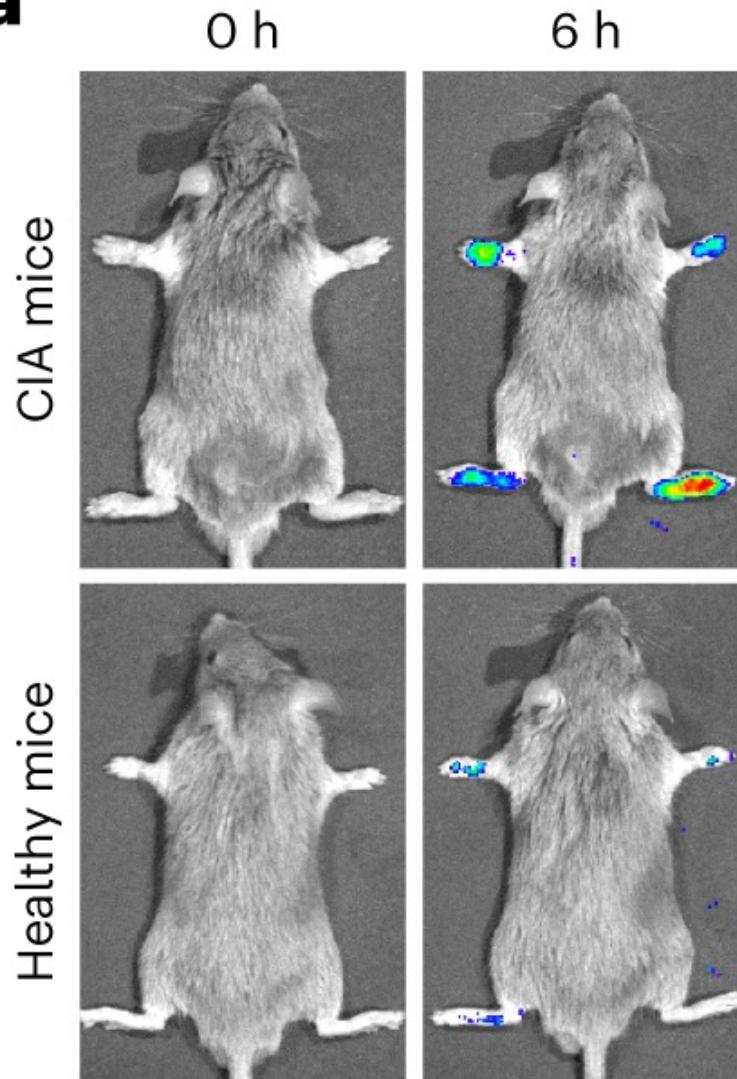
In vivo distribution and biosafety of the designer DNA origami in mice.

a



In vivo distribution and biosafety of the designer DNA origami in mice.

a

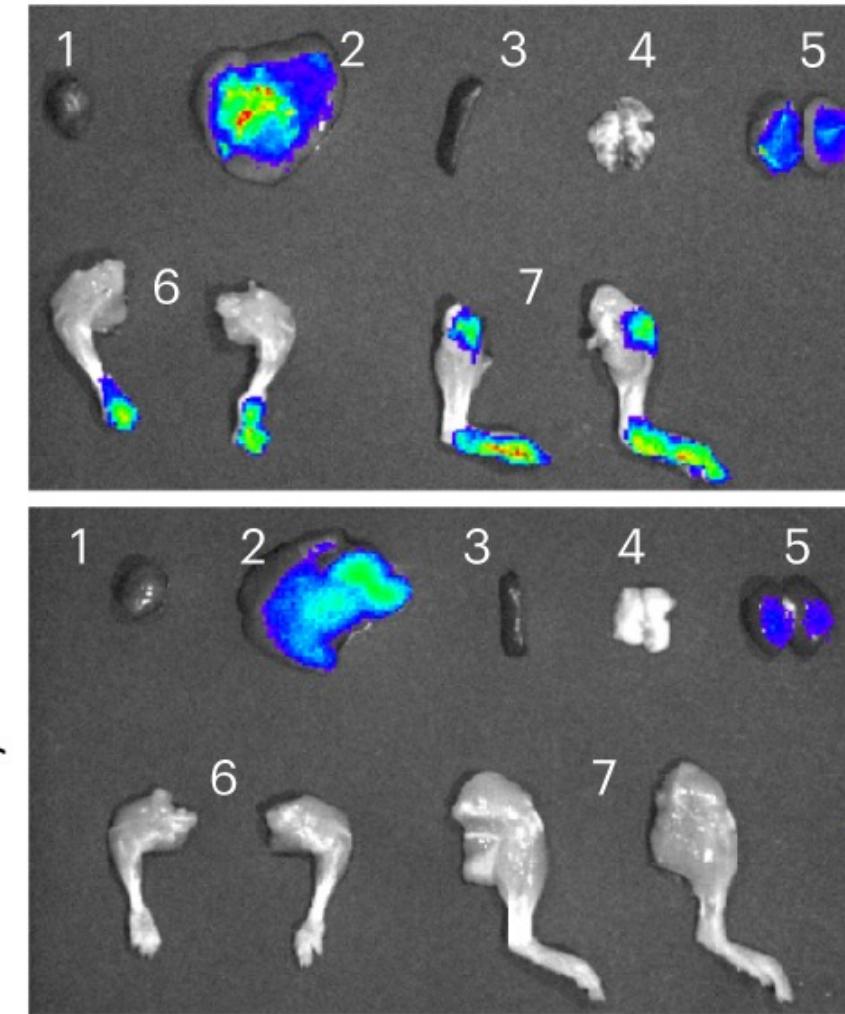


CIA mice

0 h

6 h

Healthy mice



CIA mice

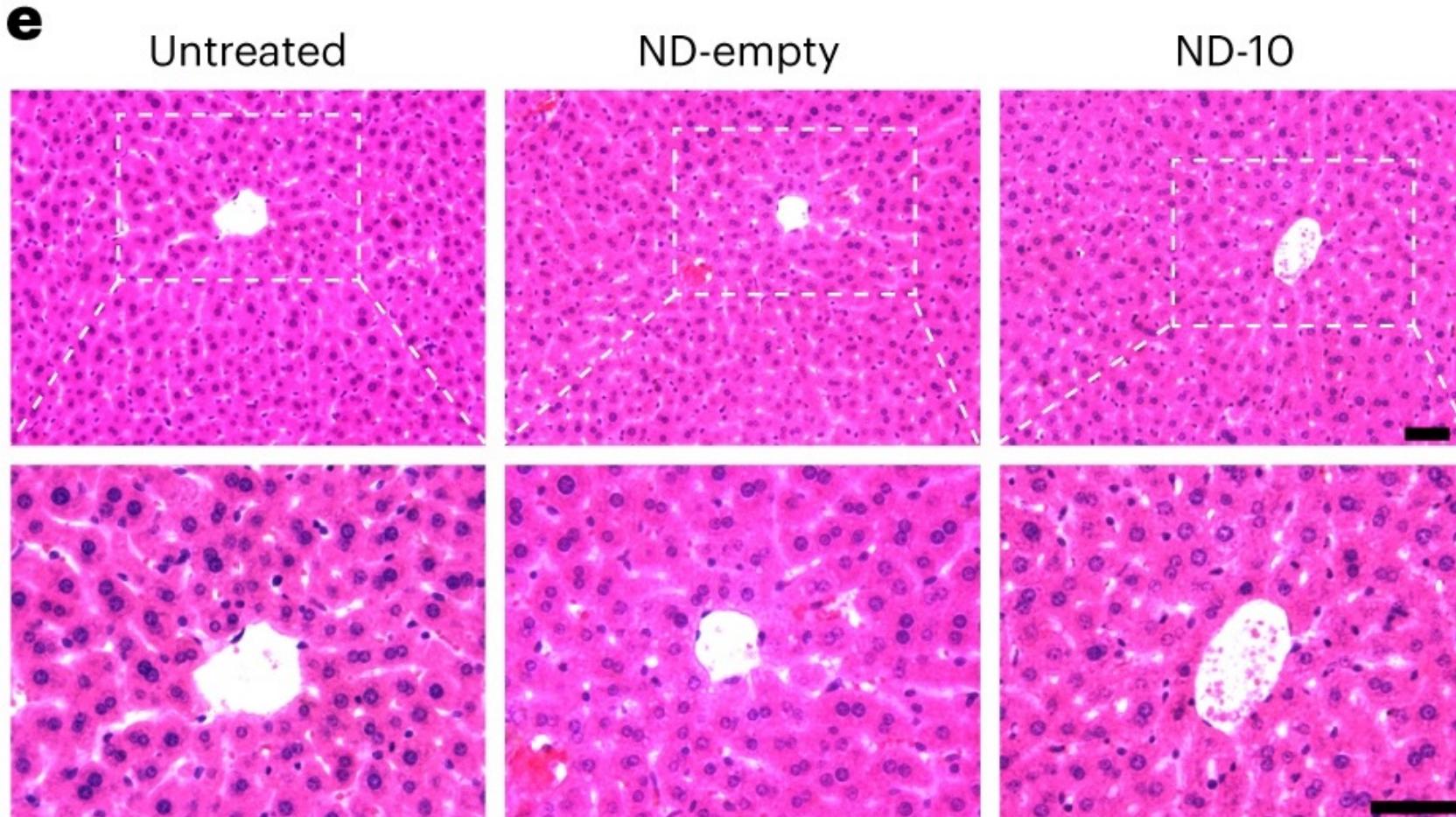
Healthy mice

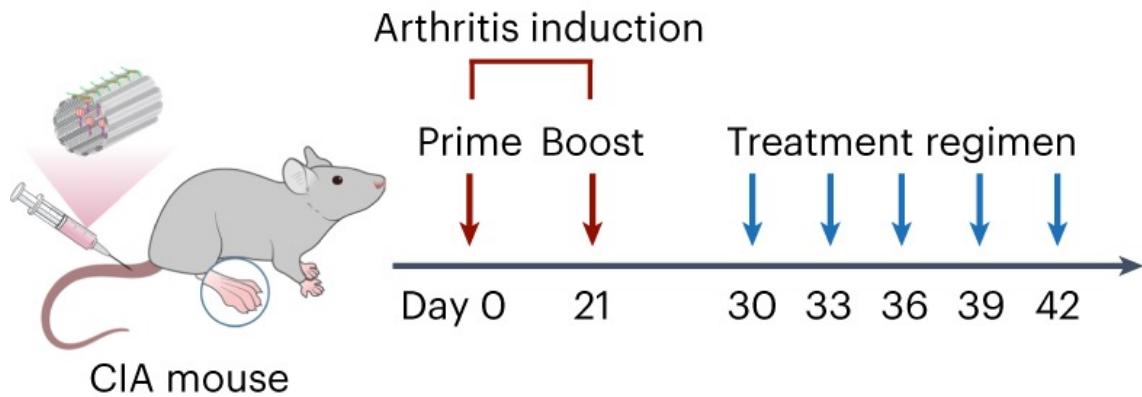
1.0
0.8
0.6
0.4
0.2
Radiance
($\times 10^{10} \text{ p s}^{-1} \text{ cm}^{-2} \text{ sr}^{-1}$)

Histological examination (H&E staining) of liver sections

obtained from healthy mice following the indicated treatments;

scale bar, 50 μ m.





Healthy mice

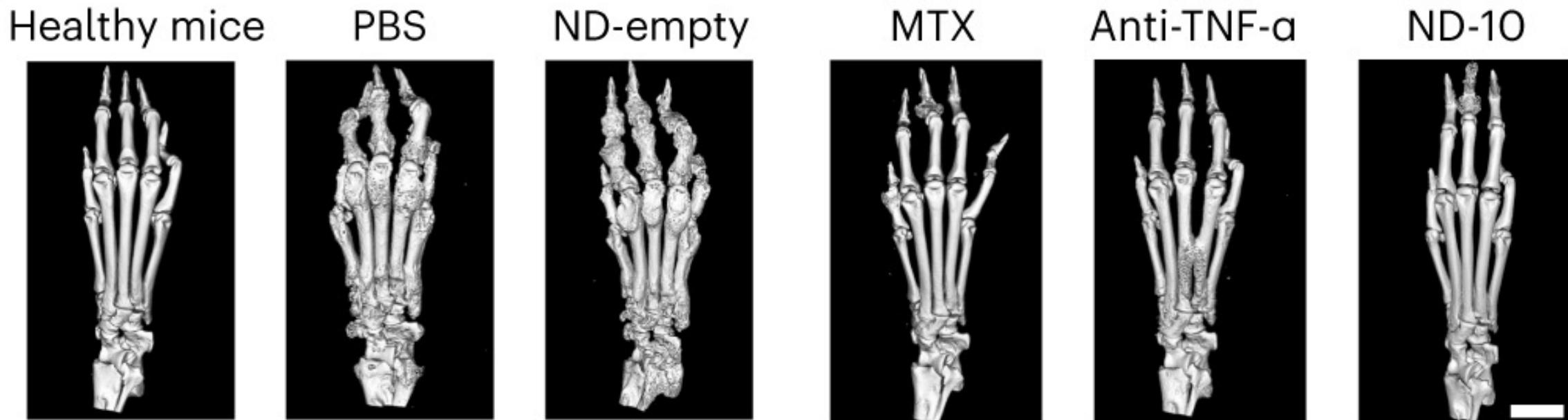
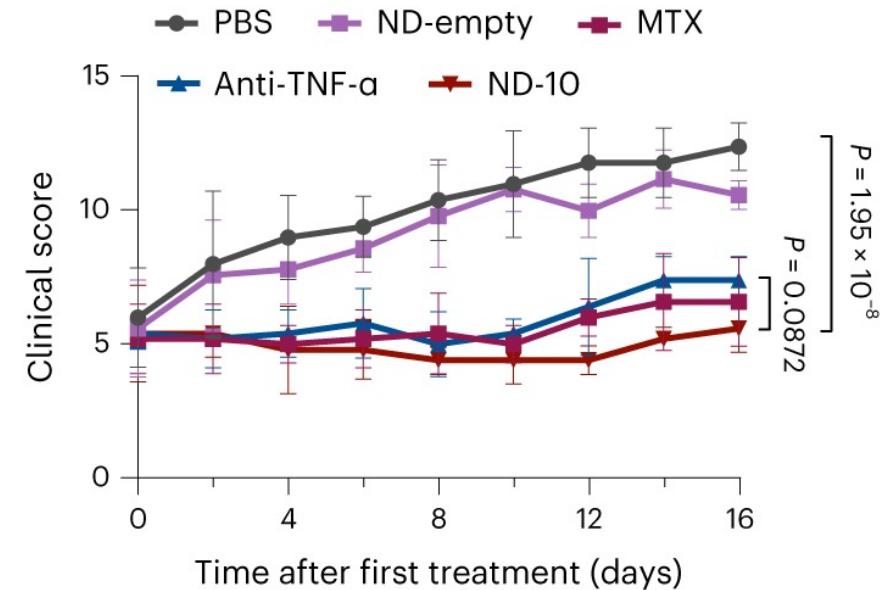
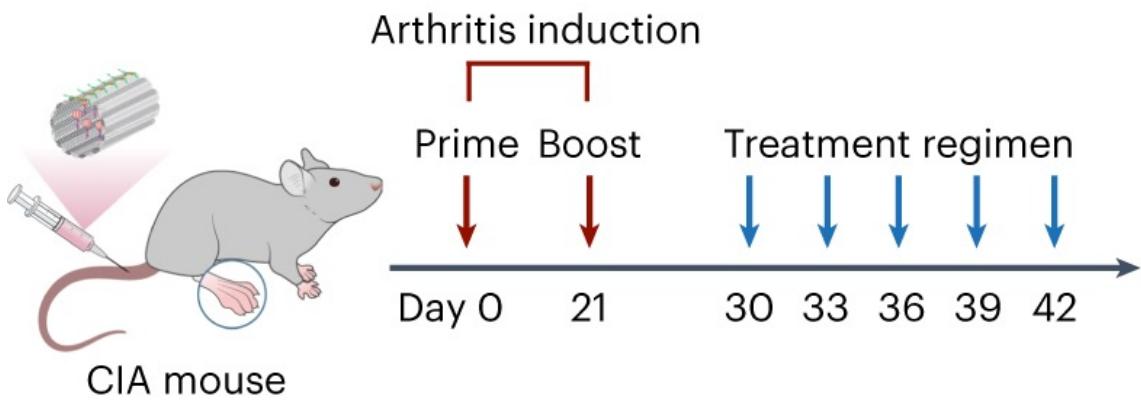


PBS



Does it work?

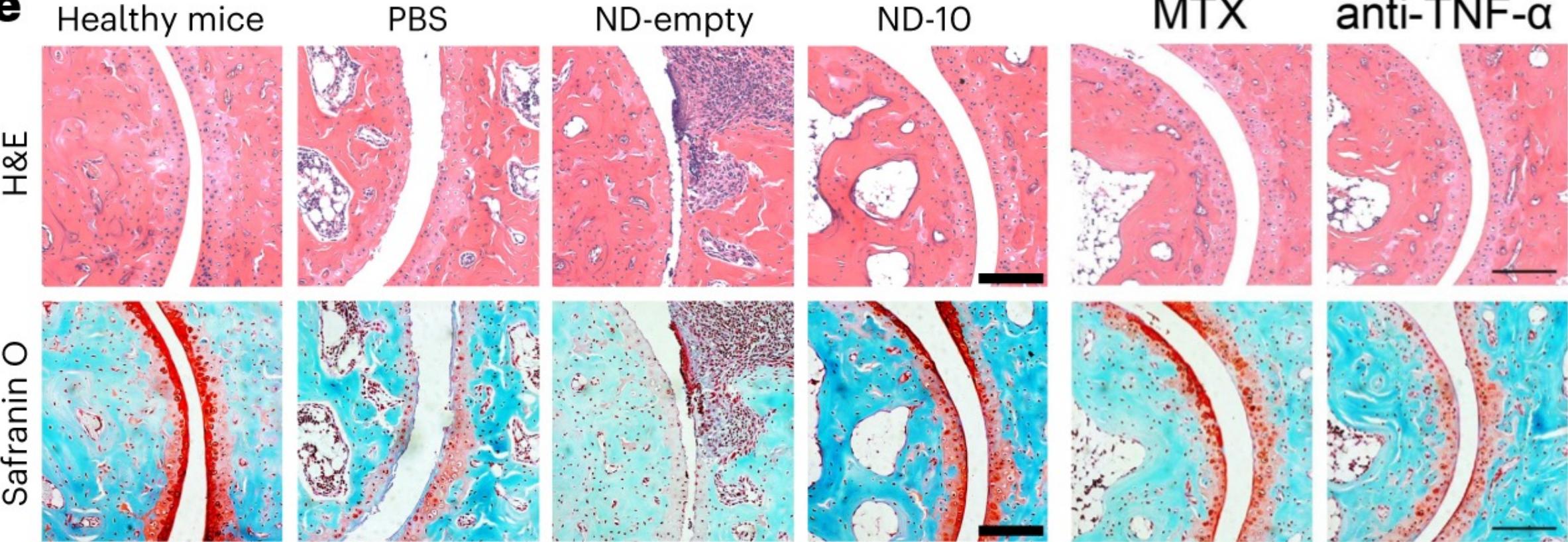
DNA origami very similar to current drugs!



Histology of the joint

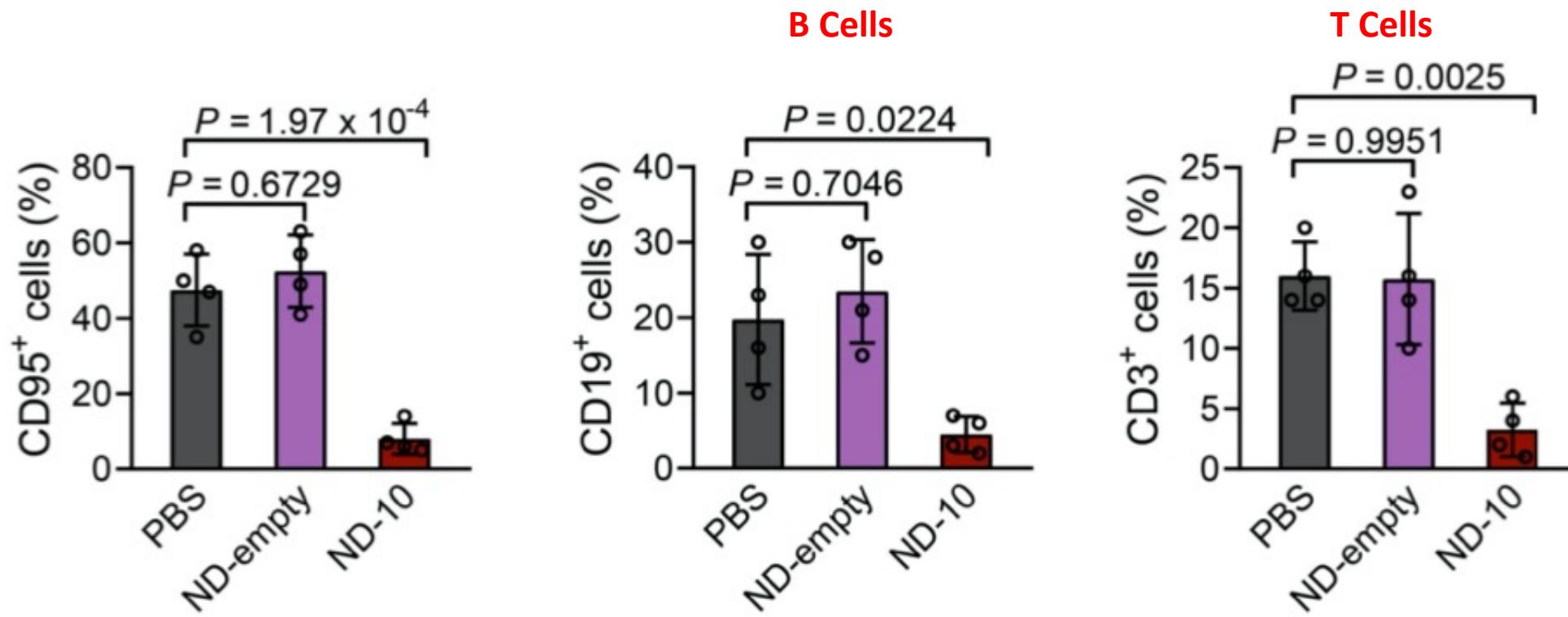
Haematoxylin and eosin (H&E) staining of joints showed serious bone destruction

e



Safranin O is used for the detection of cartilage (= red)

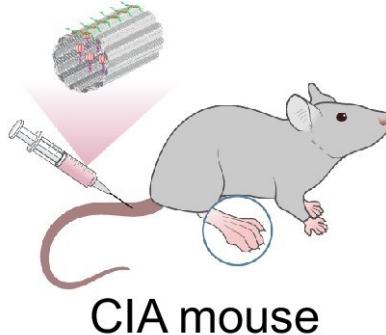
Does it work?



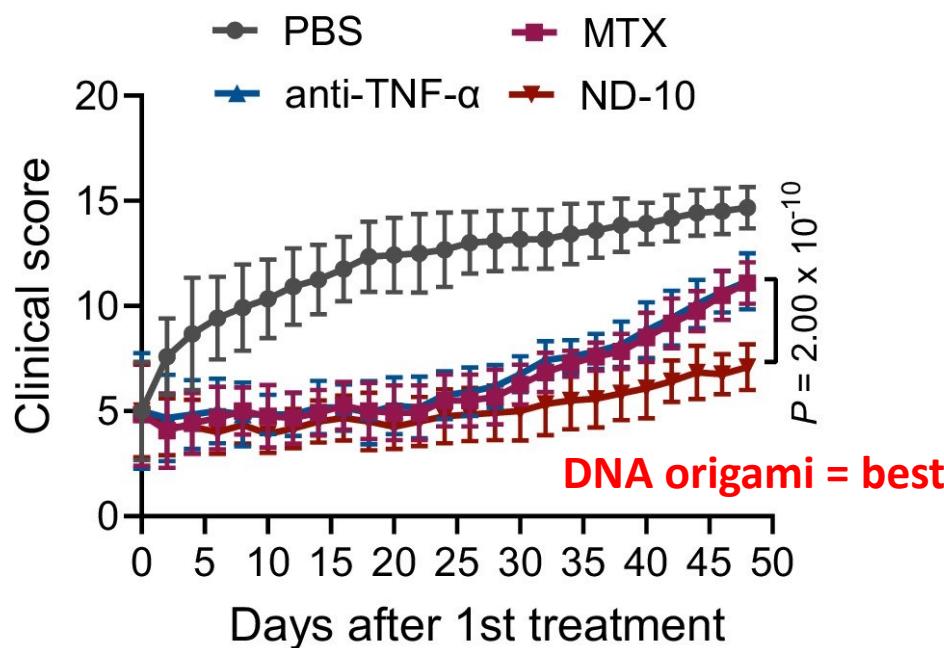
Supplementary Figure 40. The quantification of CD95⁺ cells, B cells (CD19⁺), and T cells (CD3⁺) in the synovial tissues of the mice after indicated treatments by immunohistochemical analysis. $n = 4$ biologically independent samples. Data are presented as means \pm s.d.

Long term therapeutic effect?

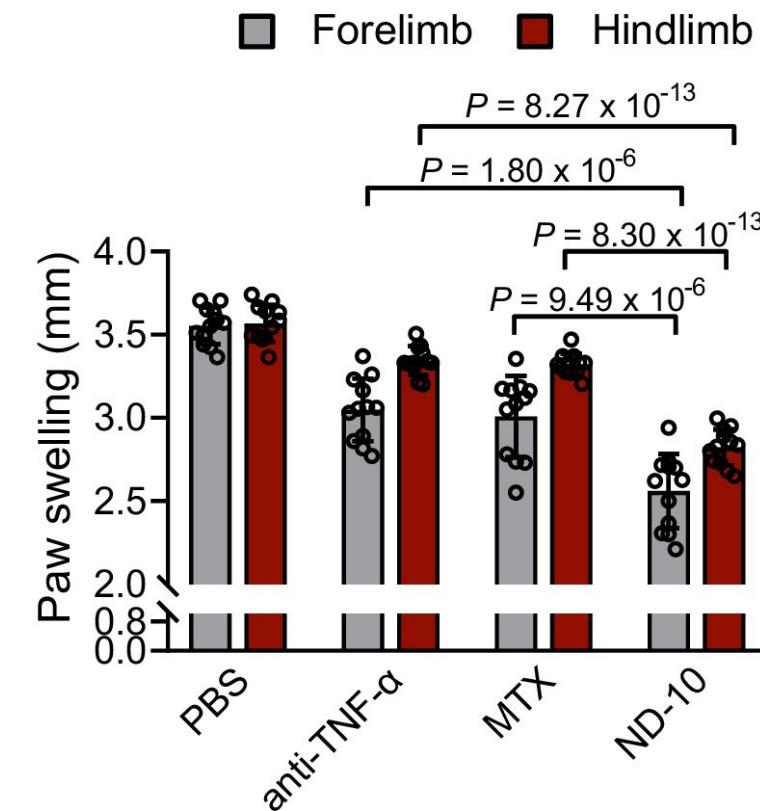
a



b



c



- 1) Nanomaterials can be designed with unique precision using DNA
- 2) Need to study the target to retro-engineer the best particle organization
- 3) Challenges might come from other places than the disease (e.g. liver here)
- 4) in biology, many different cells are present at once, need to consider them all
- 5) A disease microenvironment creates a unique space that can be used to advantage
- 6) Dosing and repetition of treatment go together with stability and distribution
- 7) For a new material to make it to a therapy, many years of animal models and patient models are required
- 8) Mice are nice, but very small and won't complain when you need to inject every 3 days...
- 9) What does this work tell us? Therapeutic targets are within reach, but, robustness needs optimization
- 10) Example for other biological targets, and stimuli responsive interactions

Cells, Organs, Biodistribution, Immune system, Ligand-receptor, targeting, DNA origami, protein engineering, extracellular matrix, endocytosis