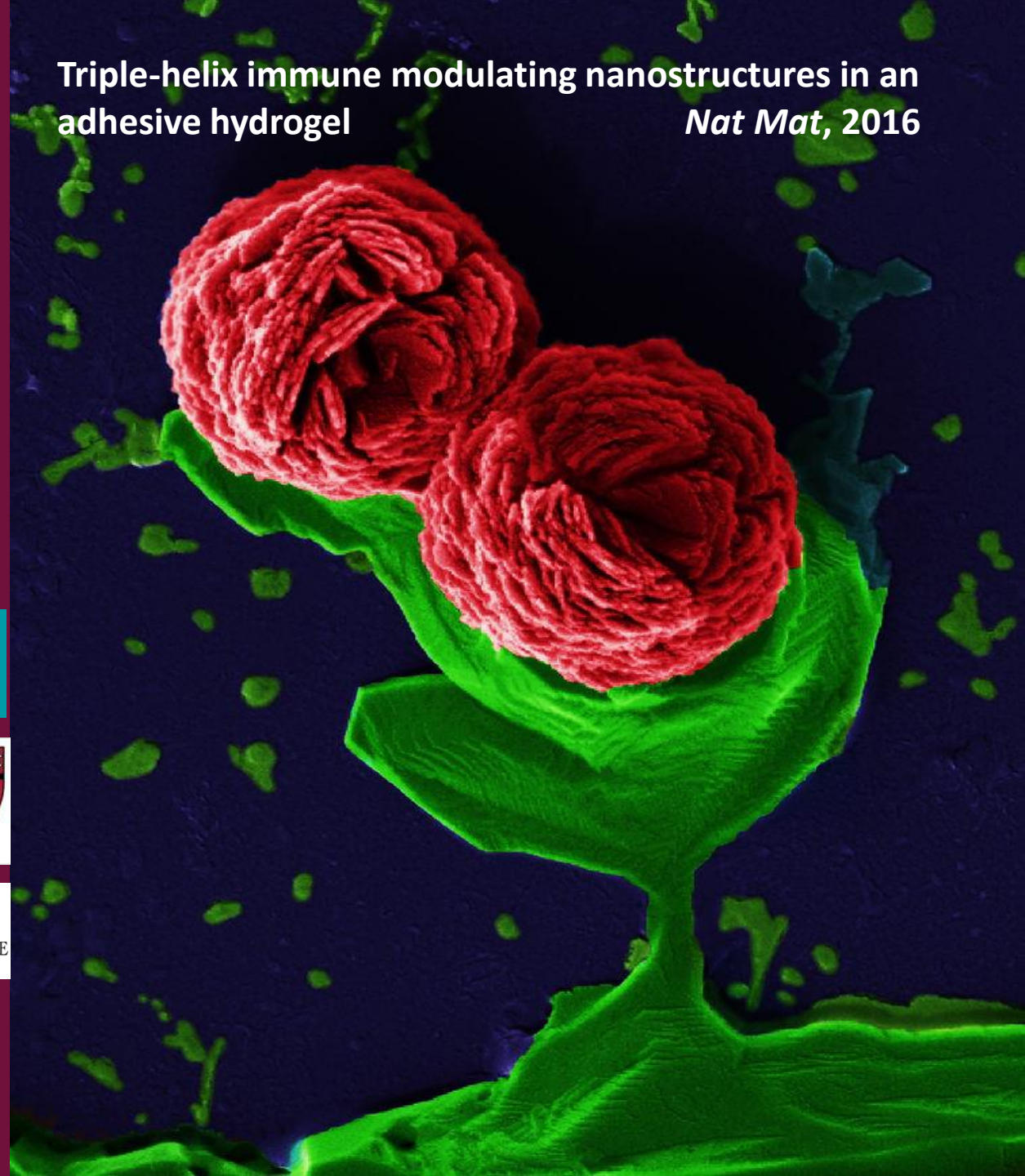
# Supercharging Immunotherapy Through Nanotechnology: Chemical Structure Matters


## Natalie Artzi, PhD

Head, Structural Nanomedicine
Gene and Cell Therapy Institute
Mass General Brigham
Harvard Medical School

Associate Institute Director
Wyss Institute for Biologically Inspired Engineering, Harvard University

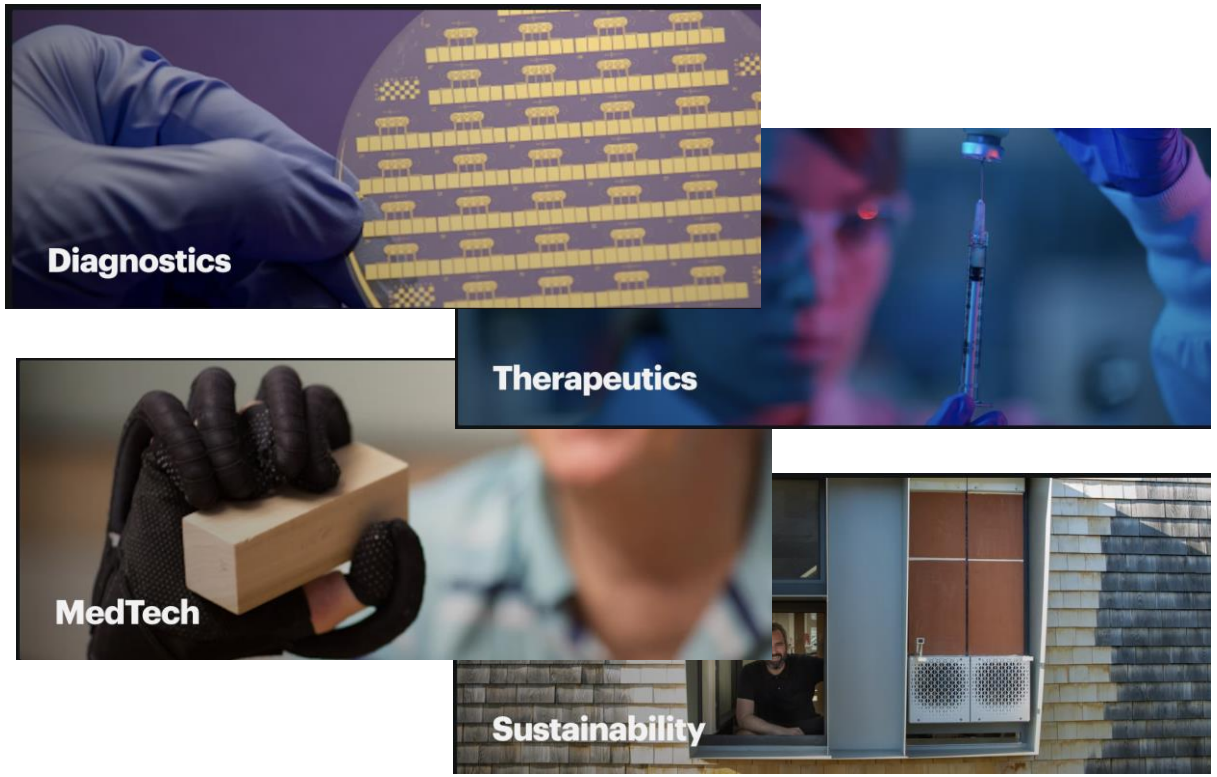
Triple-helix immune modulating nanostructures in an adhesive hydrogel

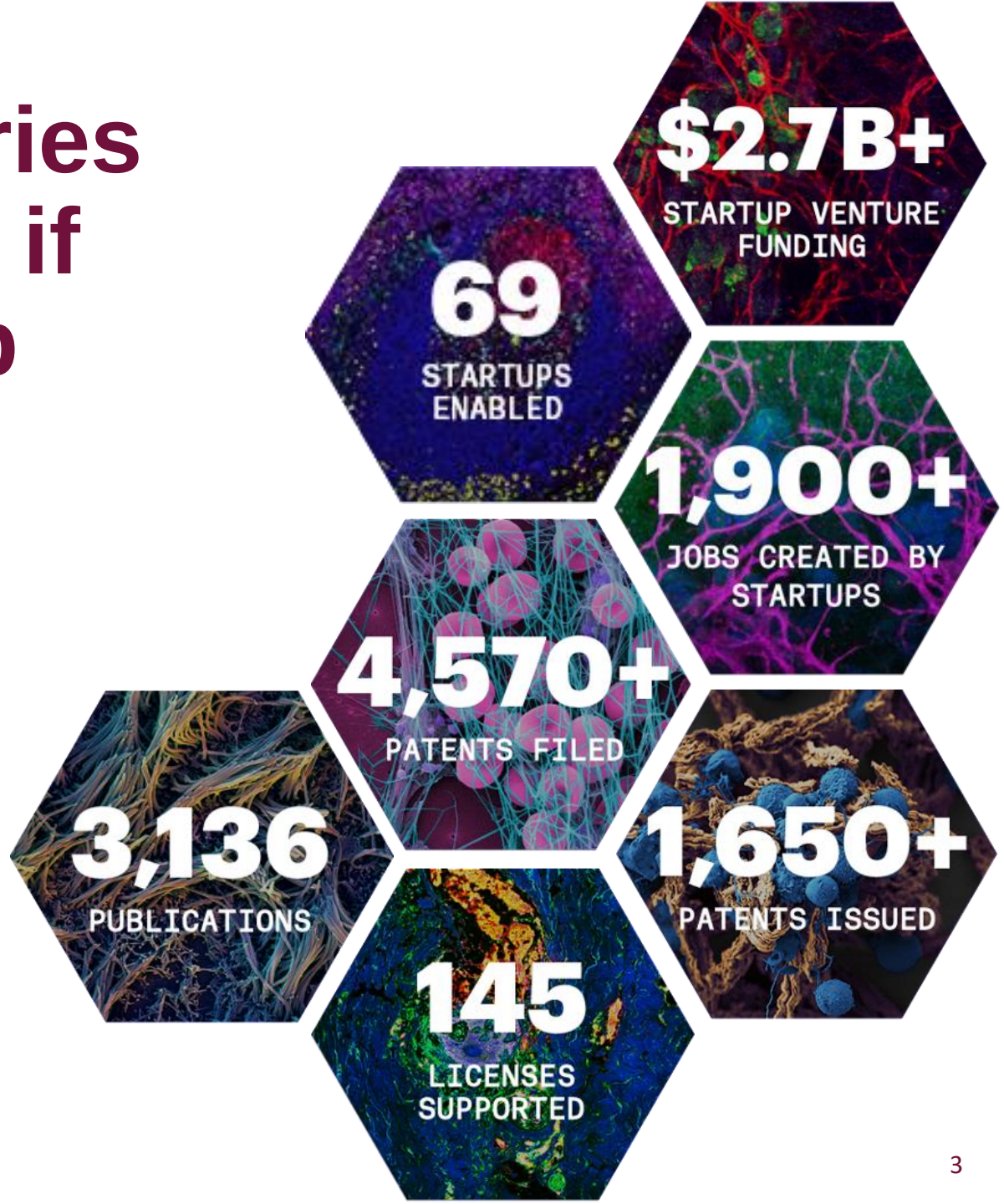
*Nat Mat*, 2016

# WYSS INSTITUTE FOR BIOLOGICALLY INSPIRED ENGINEERING

WYSS INSTITUTE

# Breakthrough discoveries can't change the world if they don't leave the lab



# Multidisciplinary Faculty

## *Focused on Solutions for Real World Challenges*

Natalie Artzi
Drug Delivery
(HMS/BWH/MIT)

Chris Chen
Tissue Engineering
(BU)

George Church
Genome Engineering
(HMS)

Jim Collins
Synthetic Biology &
Machine Learning (MIT)

Jennifer Lewis
Materials Science &
3D Printing (SEAS)

Samir Mitragotri
Chemical
Engineering (SEAS)

Dave Mooney
Tissue Engineering
(SEAS)

William Shih
Biophysics & Nanotechnology
(HMS/DFCI)

Pam Silver
Synthetic
Biology (HMS)

David Walt
Chemistry & Diagnostics
(HMS/BWH)

Peng Yin
Nanotechnology &
Computer Science (HMS)

Don Ingber
Cell Biology & Medicine
(HMS/ SEAS/BCH)

Joanna Aizenberg
Materials Nanoscience (SEAS)

Georg Duda
Orthopedics (Charite Hosp.)

Ellen Roche
Medical Devices (MIT)

David Weitz
Physics (SEAS)

Sangeeta Bhatia
Bioengineering (BWH/HMS/MIT)

Di Feng
Chronic Kidney Disease Modeling
(BIDMC/HMS)

Michael Springer
Clinical Diagnostics & Sustainable
Technologies (HMS)

Wesley Wong
Biophysics (BCH)

Elliot Chaikof
Vascular Surgery (BIDMC/HMS)

Mike Levin
Biology & Self Assembly (Tufts)

Conor Walsh
Robotics (SEAS)

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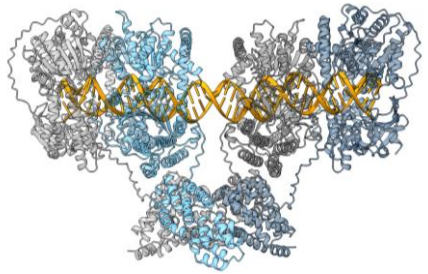
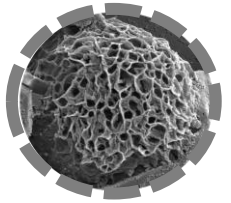
# TISSUE- AND CELL-RESPONSIVE MATERIALS

## Reengineer the immune system

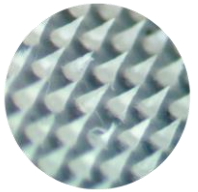
## Developing better drugs



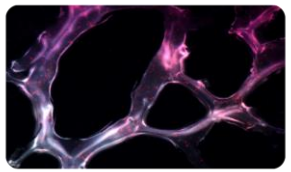
## Designing materials for tissue engineering and repair



NANOPARTICLES



MICRONEEDLES



HYDROGELS

Brigham and Women's Hospital
Founding Member, Mass General Brigham

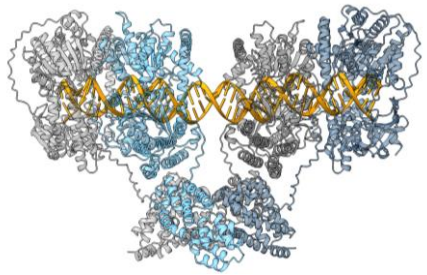
HARVARD MEDICAL SCHOOL

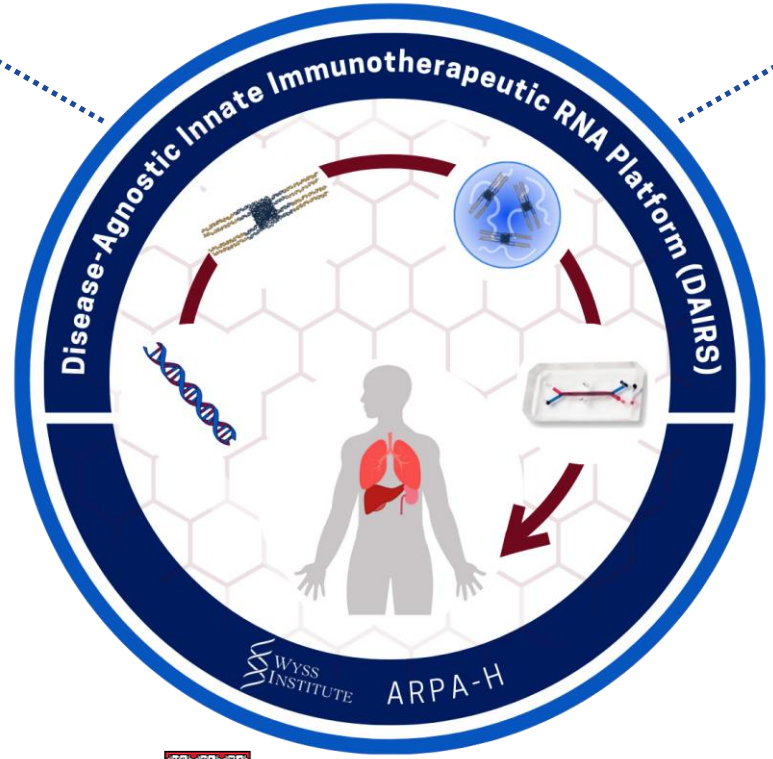
WYSS INSTITUTE

# TISSUE- AND CELL-RESPONSIVE MATERIALS

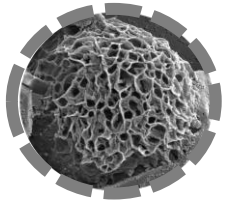
## Reengineer the immune system

## Developing better drugs






## Designing materials for tissue engineering and repair



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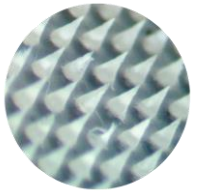

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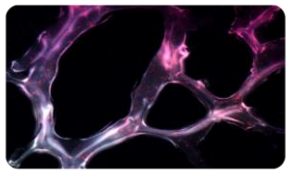

HYDROGELS

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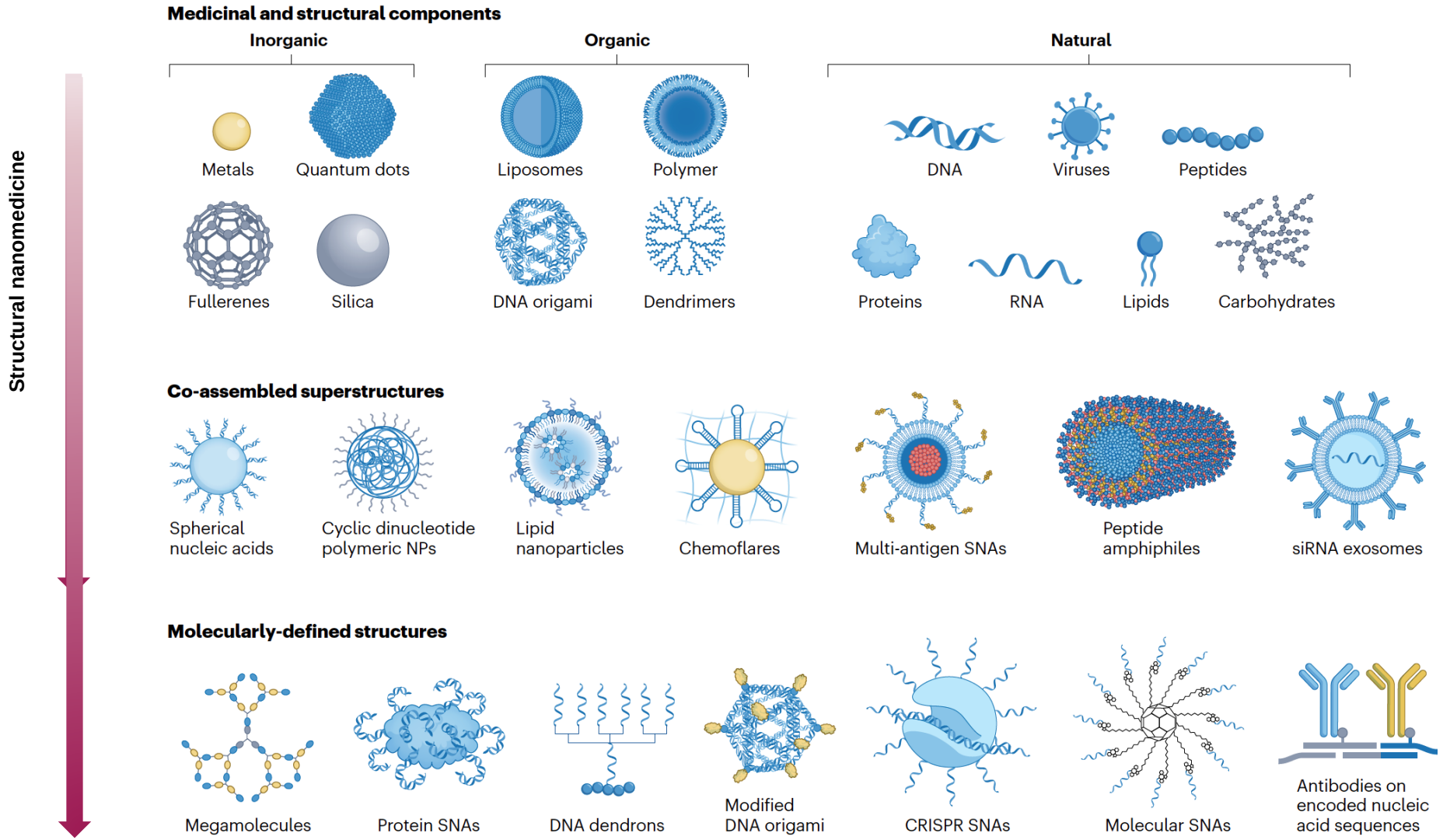
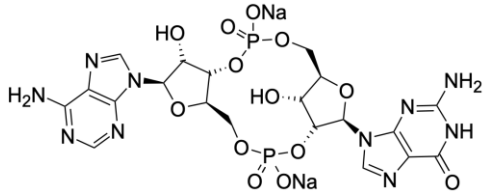
# STRUCTURAL NANOMEDICINE: FROM UNSTRUCTURED TO CO-ASSEMBLED TO MOLECULARLY DEFINED




Mirkin, Mrksich, and Artzi, The emerging era of structural nanomedicine, Nat Rev Bioeng. 2025.

# STABLE, CELL-RESPONSIVE STRUCTURES

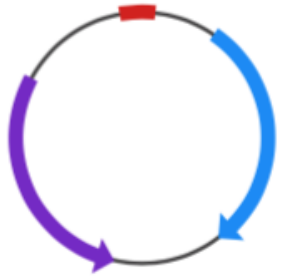
## Nucleic Acids Based Drugs



STING Agonist

RNAi

mRNA



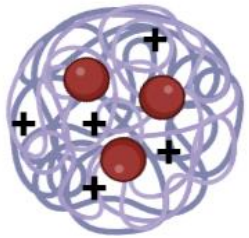
Plasmids

X **Rapid clearance** upon systemic administration

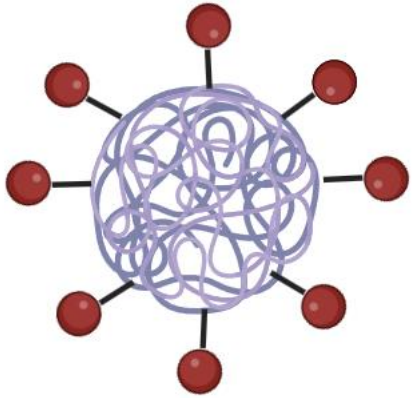
X **Negative charge** limits its ability to cross the cell membrane

X Susceptibility to **degradation** by nucleases

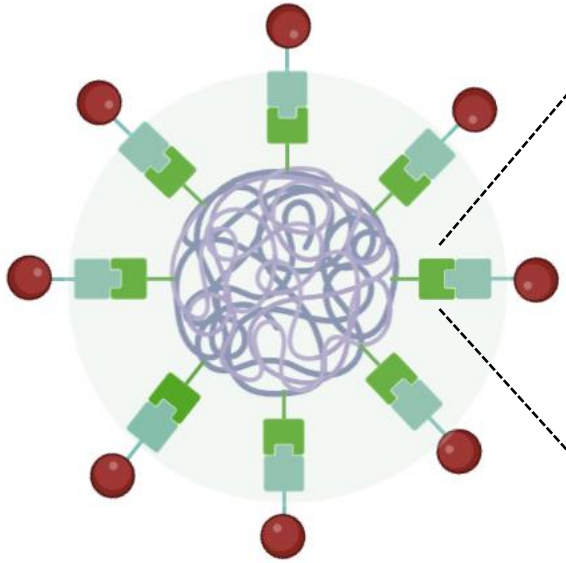
**Electrostatic**

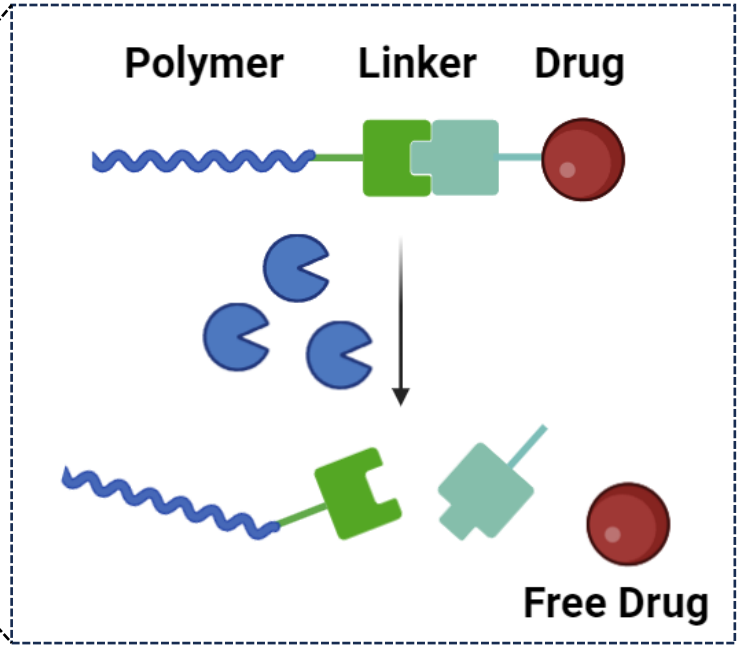


**Conjugated**



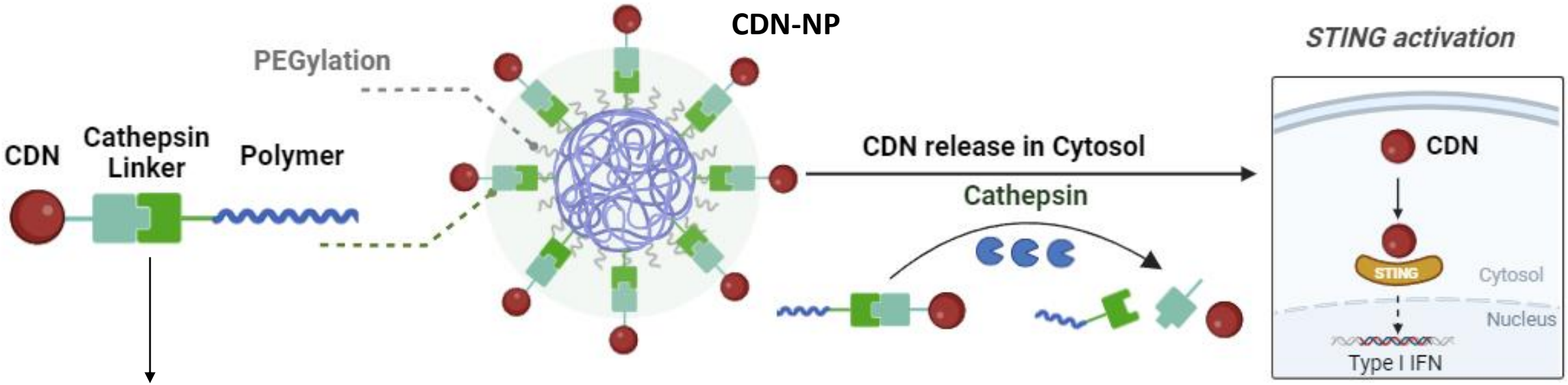
**Triggered release**

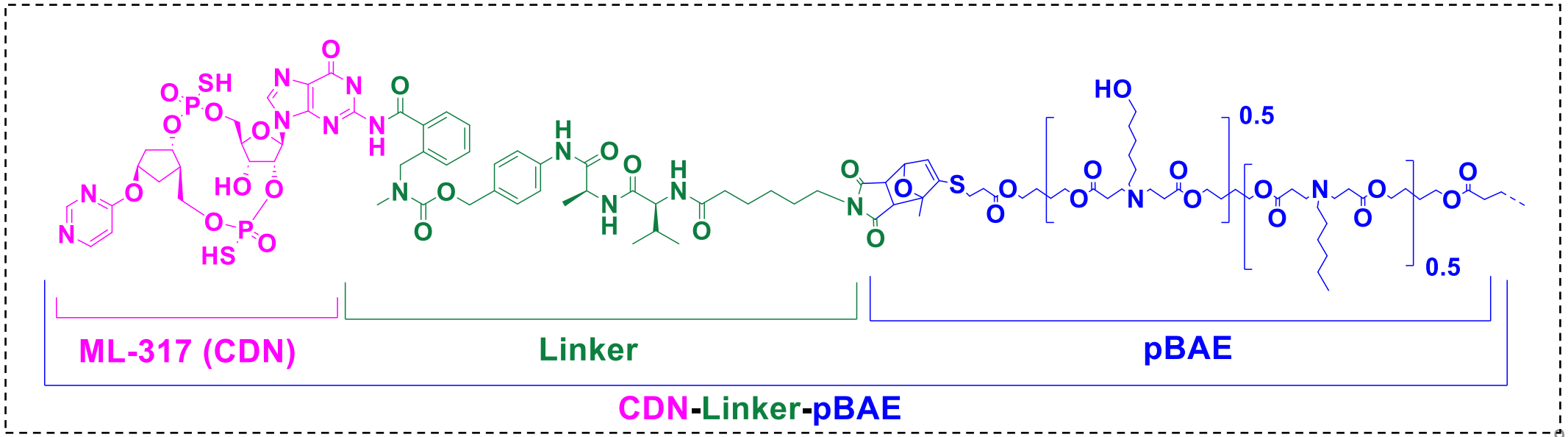





Artzi et al, *Nature Nanotechnology*, 2023

# CDN-POLYMERIC NANOPARTICLE FOR STING IMMUNOTHERAPY

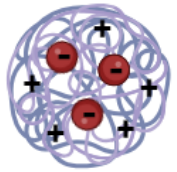


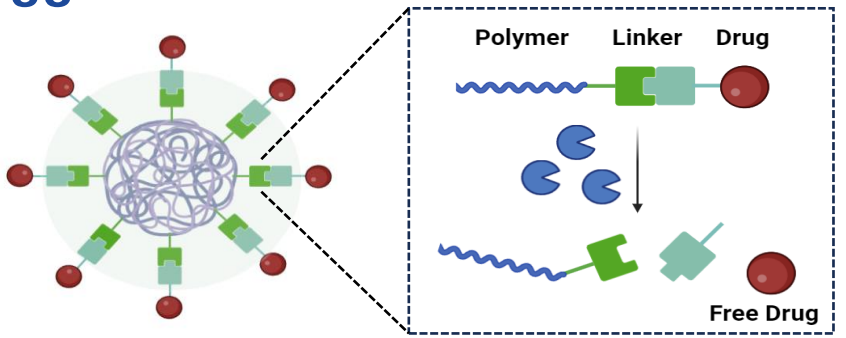

Dosta P. … Artzi N., *Nature Nanotechnology*, 2023.

# CELL-RESPONSIVE NANOSTRUCTURES ENHANCE STABILITY, POTENCY, AND EFFICACY

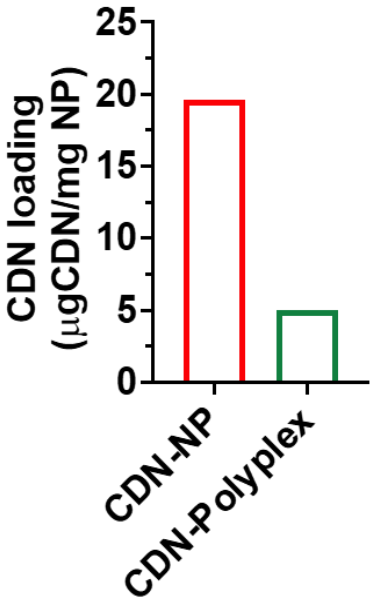
## Electrostatic

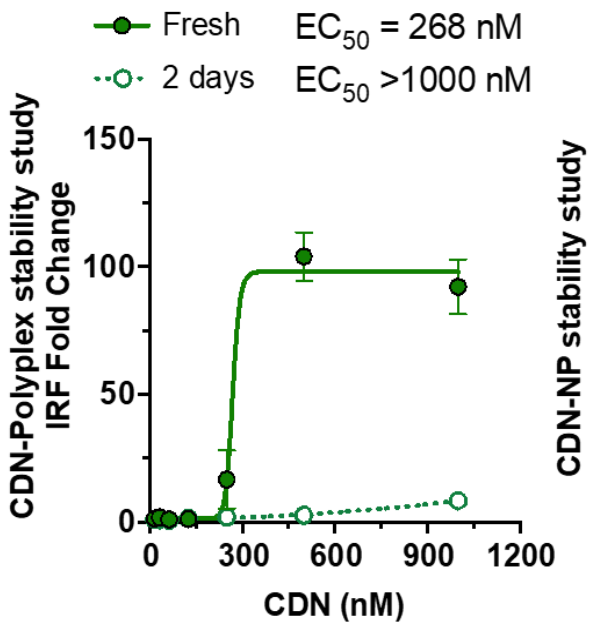


## Triggered release

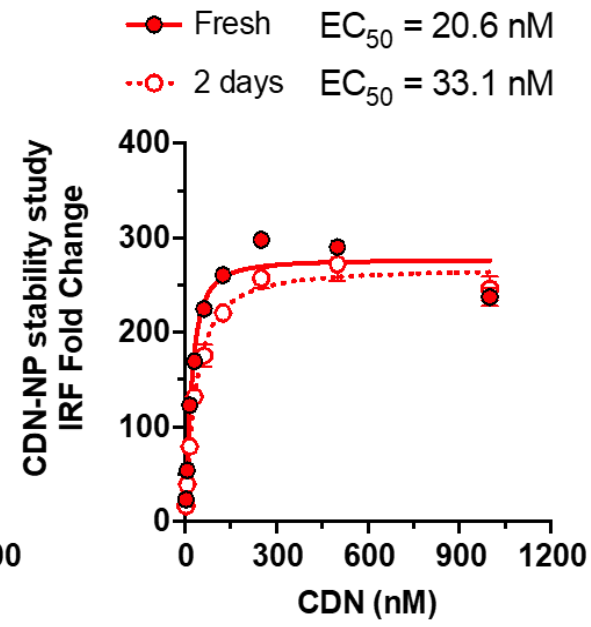


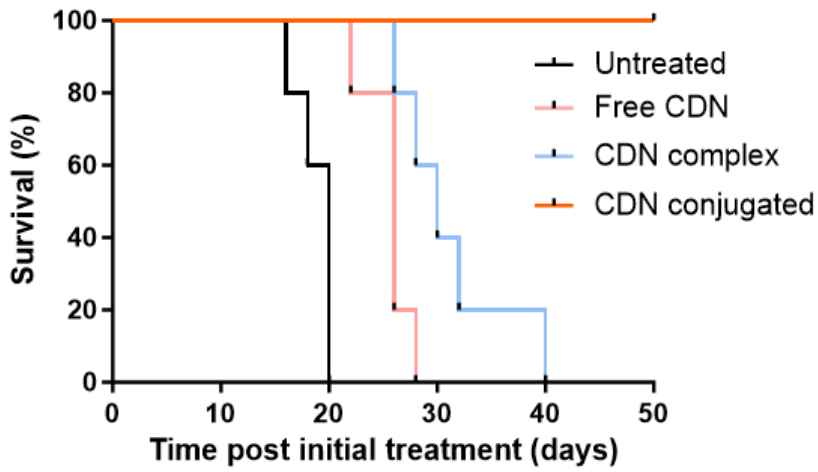

## CDN polyplex




## CDN-NP

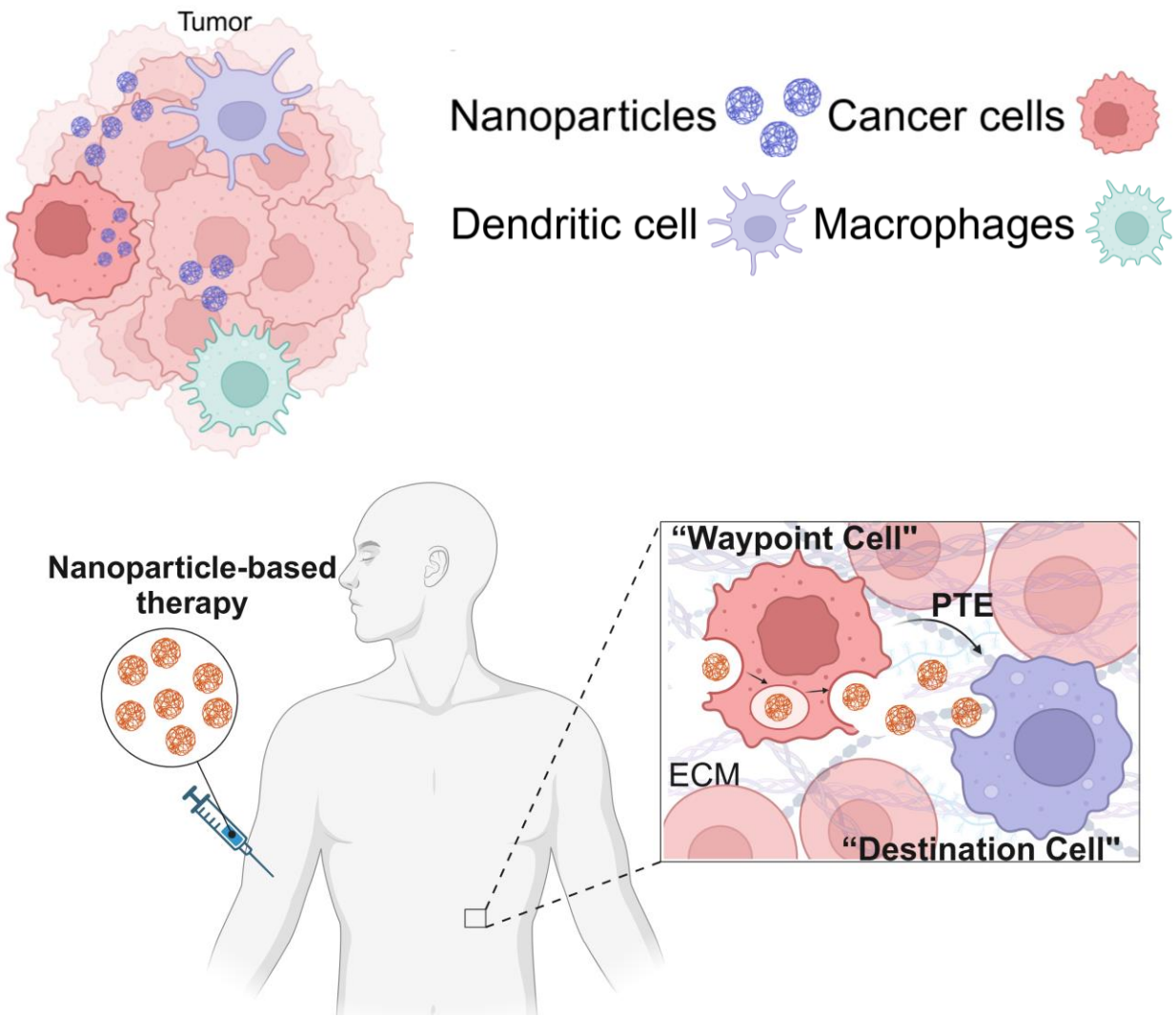


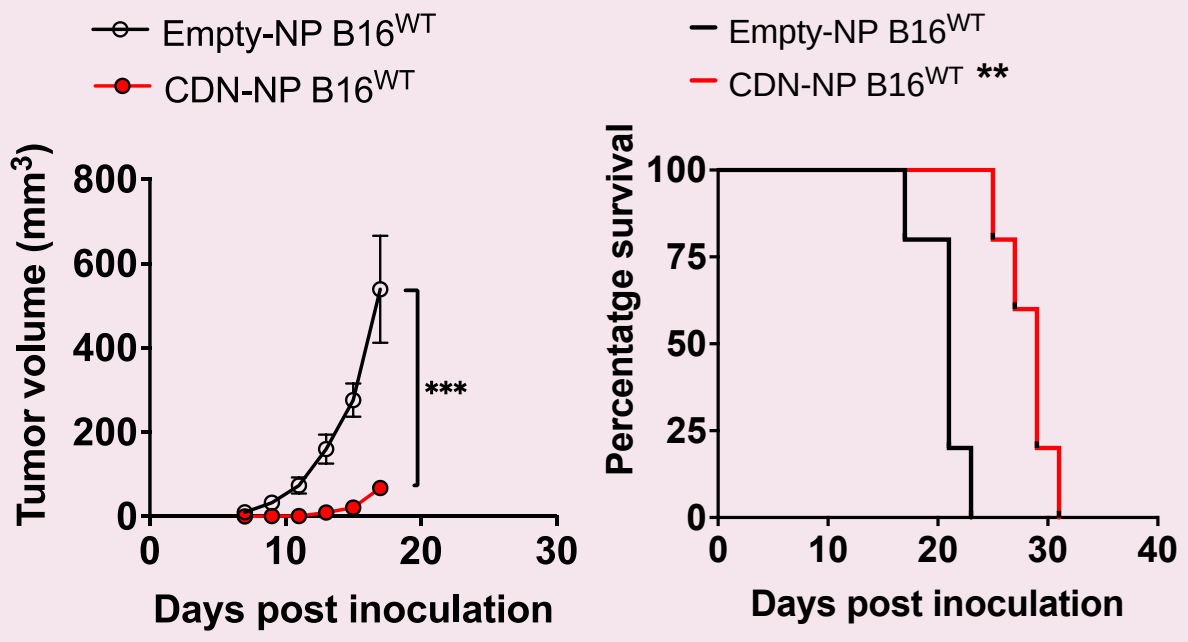






Artzi et al, Nature Nanotechnology, 2023

# THE PARACRINE TRANSFER EFFECT (PTE)

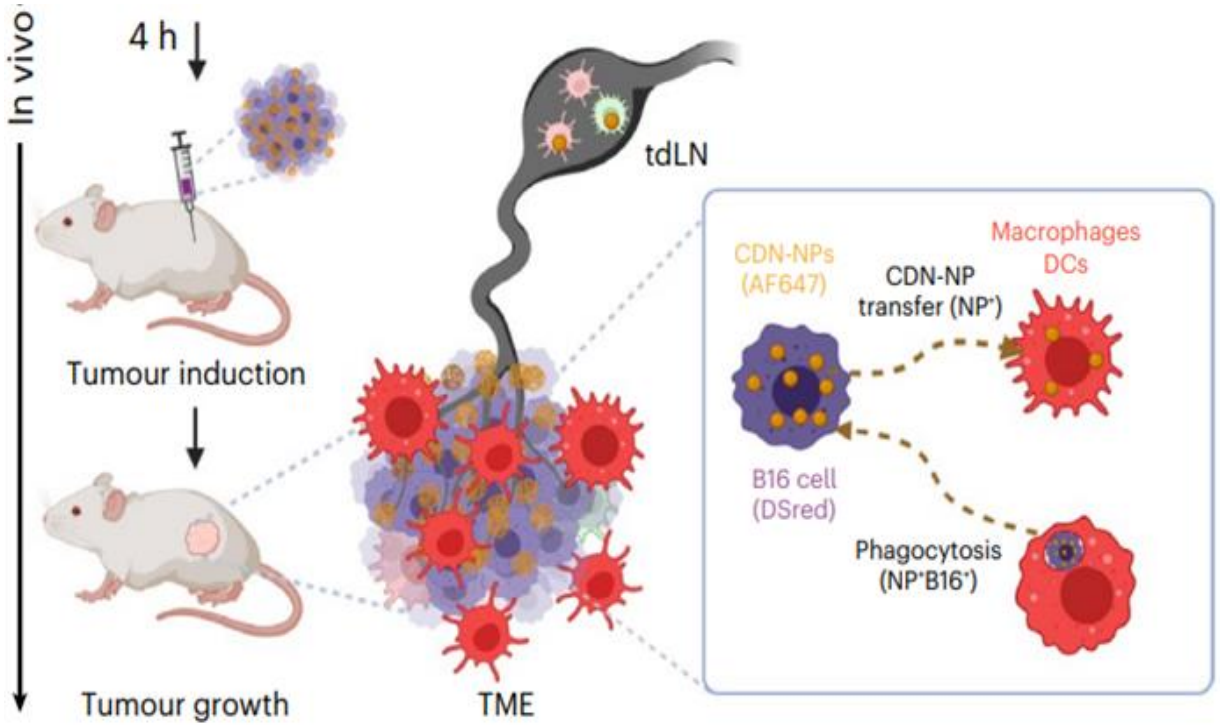


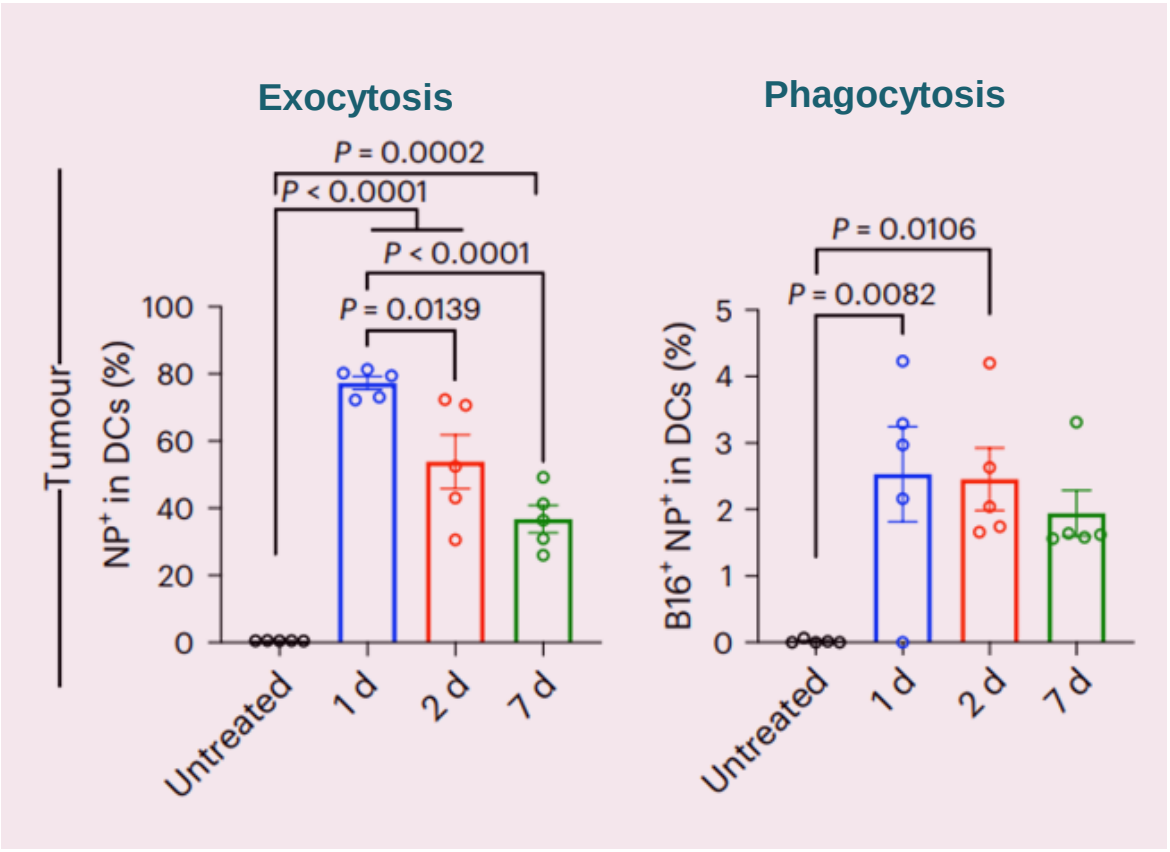





Paranandi KS, Amar-Lewis E et al 2025, ACS Nano
Dosta P, Cryer AM et al. 2023, Nat. Nantechnol.

# EXOCYTOSIS, RATHER THAN PHAGOCYTOSIS, DRIVES IMMUNE ACTIVATION

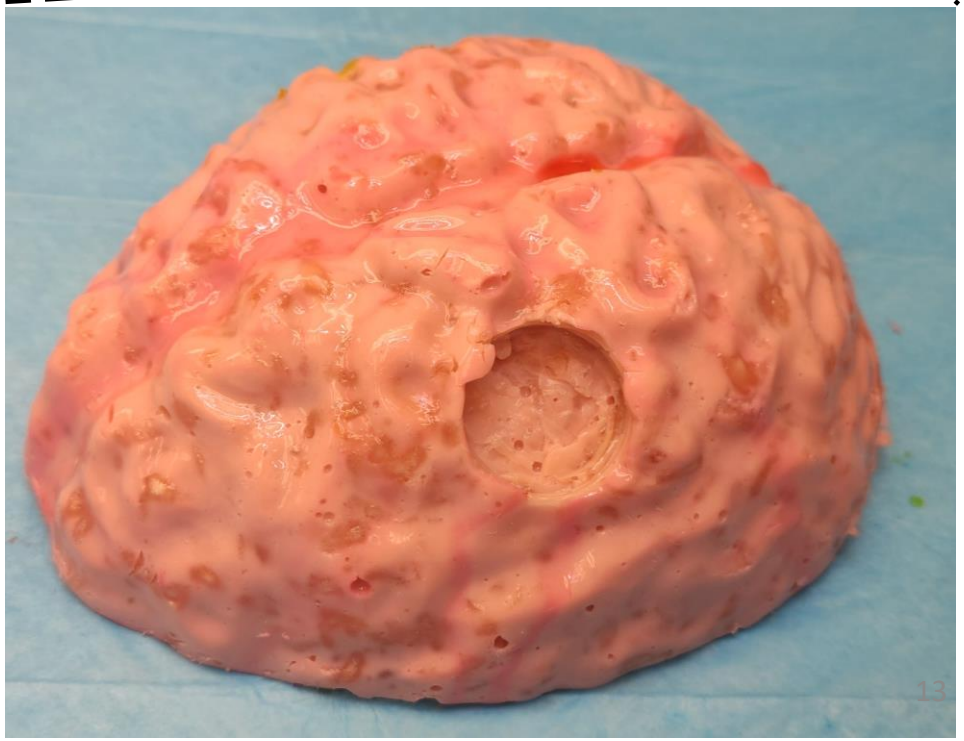


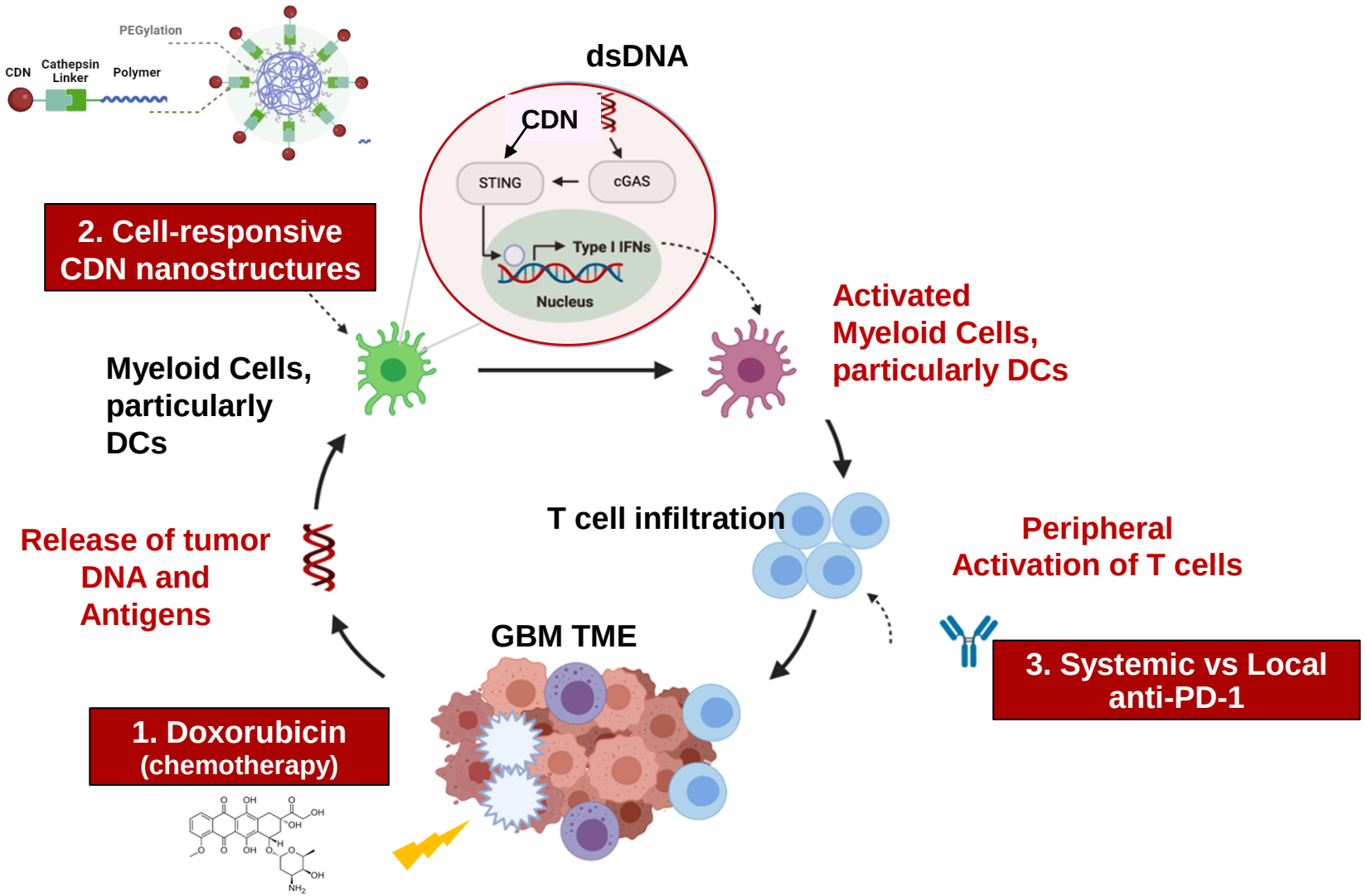
# NEXT-GENERATION LOCAL TREATMENT TO ELIMINATE BRAIN CANCER

| 2009 | 2011 | 2014 | 2015 | 2016 | 2016 | 2017 | 2021 | 2023 | 2025 |
|---|---|---|---|---|---|---|---|---|---|
| Tunable adhesion technology | Tissue specific material | Local release of chemo and antisense DNA in breast cancer | Local release of gold NP (siRNA, antibody) for triple negative breast cancer | Local release of microRNA for metastatic breast cancer | Triple therapy release for colon cancer | Tunable rheology of the material platform | Delivery of STING for melanoma | Delivery of conjugated STING+aPD-1 for melanoma, breast and colon cancers | Delivery of multiple APIs for brain cancer |

- ✓ **Easy to Administer**
- ✓ **Tunable Tissue Adhesion**
- ✓ **Controllable Delivery Kinetics**
- ✓ **Versatile Platform Delivery Technology**



# COMBINATION THERAPY REQUIRED TO STIMULATE MULTI-AXIS

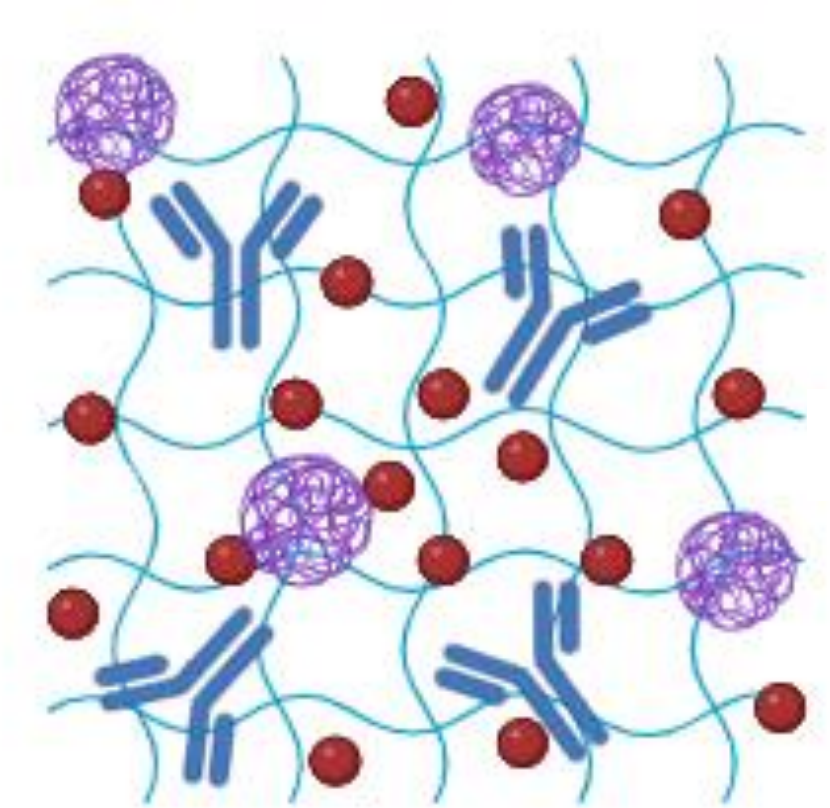



**Injectable adhesive hydrogel-drug complexes synchronize the release of chemoimmunotherapy to treat brain tumors in mice; bioRxiv**

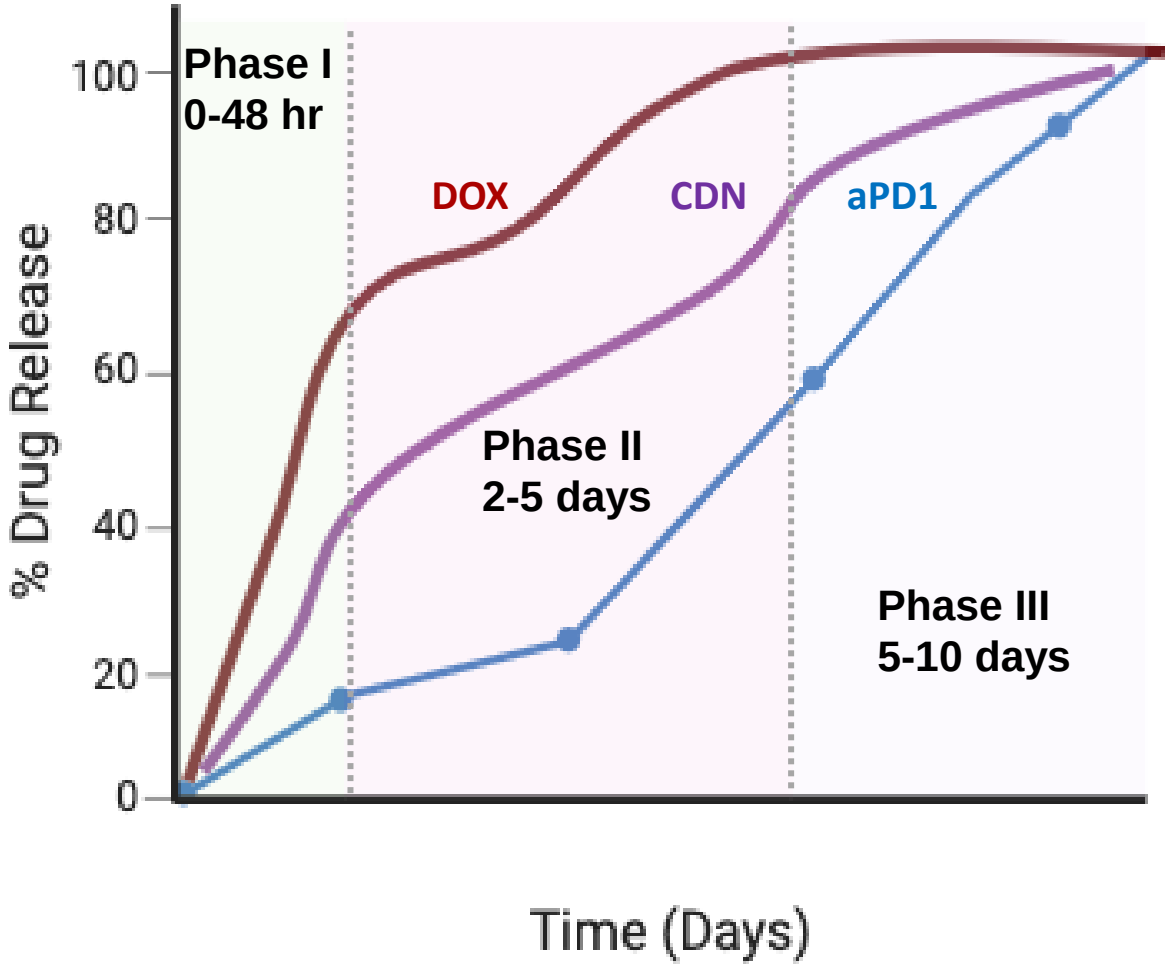
Dion M., …Brem H., Artzi N., **STM**, **Under Review**

# COMBINATION THERAPY REQUIRED TO STIMULATE MULTI-AXIS IMMUNE RESPONSES

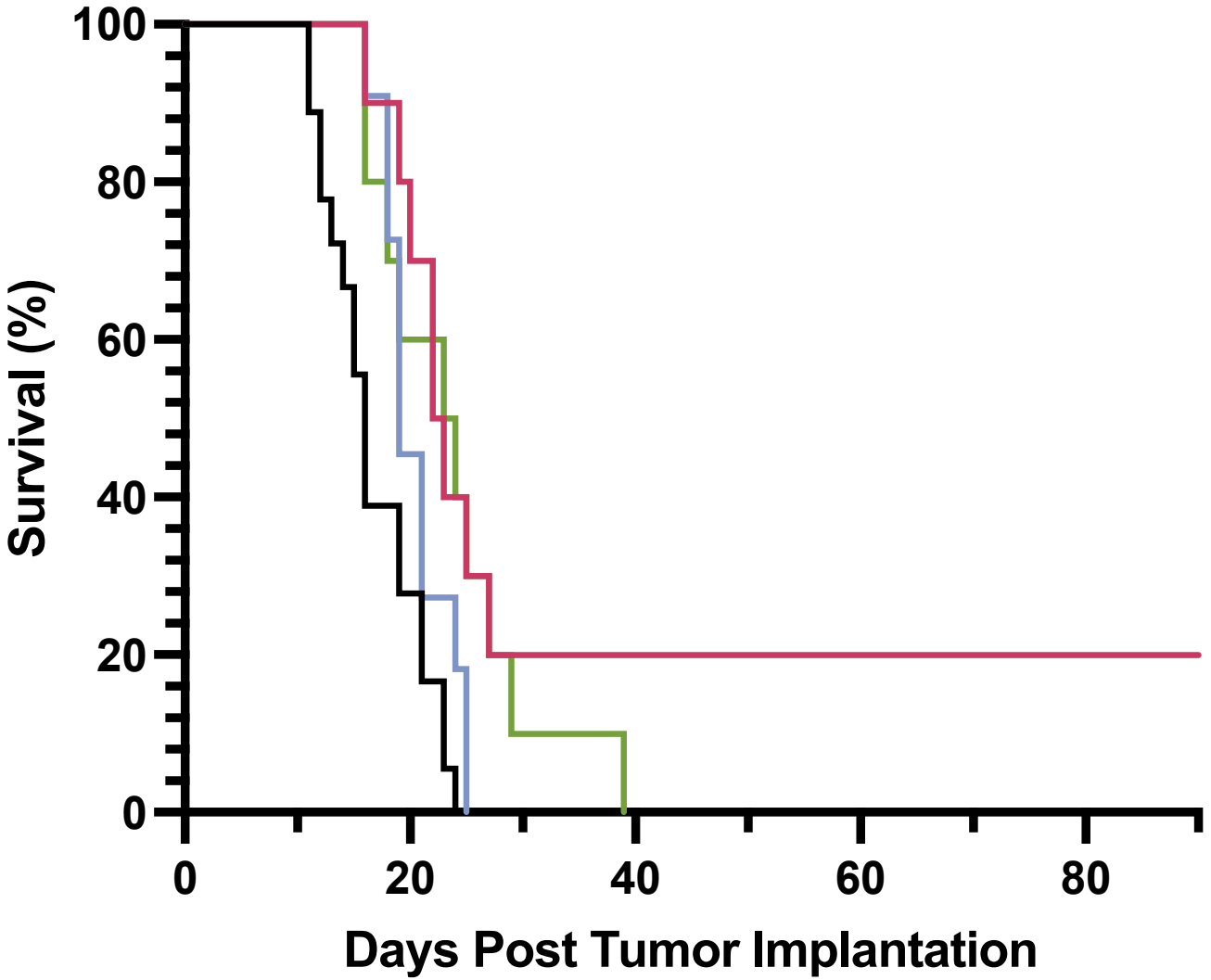
**Adhesive hydrogel**
***in situ* vaccine**



**Controlled Sustained drug release**



# HYDROGEL MONOTHERAPIES EXTEND SURVIVAL IN IMMUNOSUPPRESSIVE CT-2A MODEL



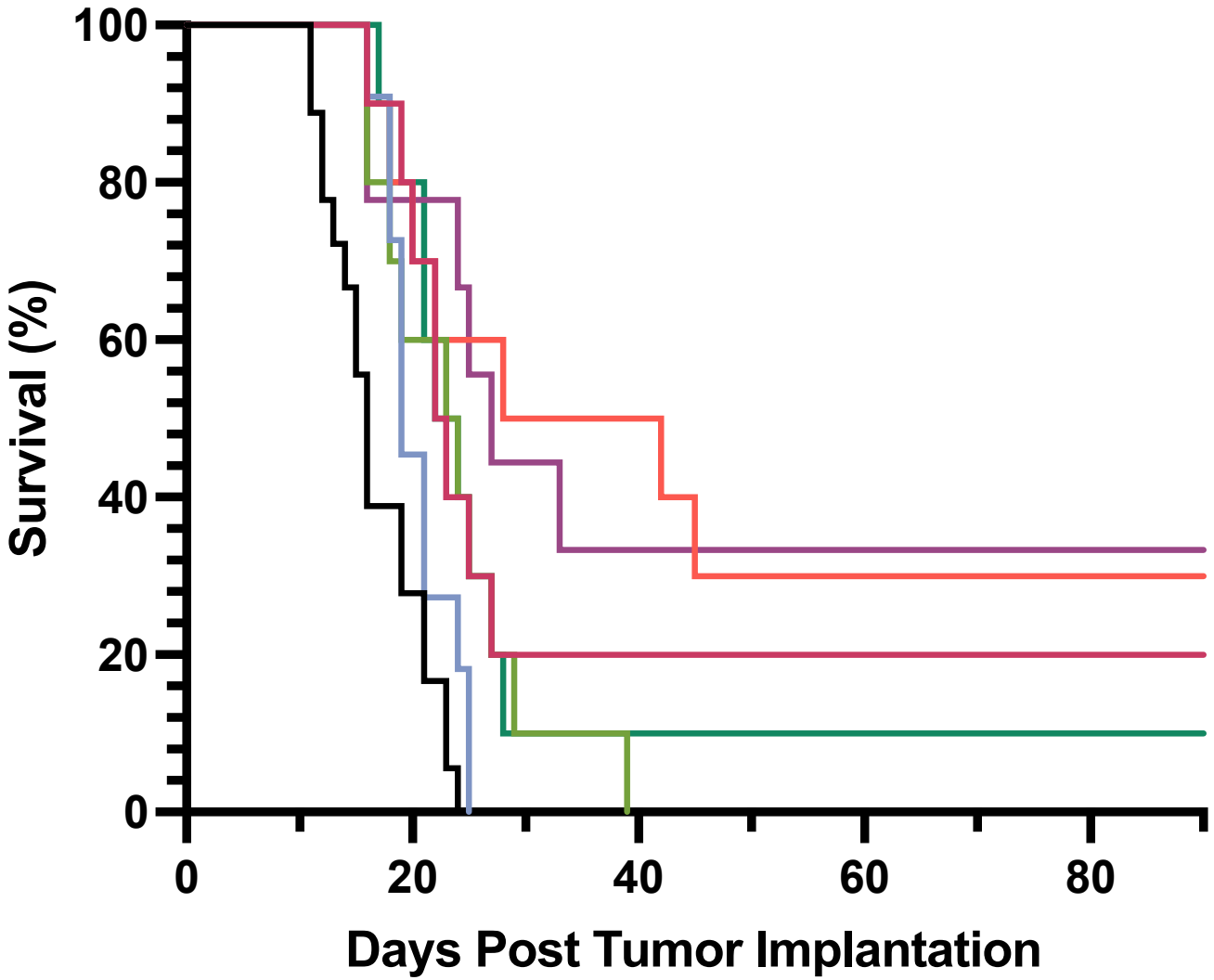

Control
Hydrogel DOX **
Hydrogel CDN-NPs *
Hydrogel anti-PD-1**

Log-Rank Mantel Cox Test

| | |
|---|---|
| * | <0.05 |
| ** | <0.01 |
| *** | <0.001 |
| **** | <0.0001 |

Significance in comparison to control

# COMBINATION THERAPIES INCREASES CURATIVE SURVIVAL, PARTICULARLY FOR COMBINATION IMMUNOTHERAPIES



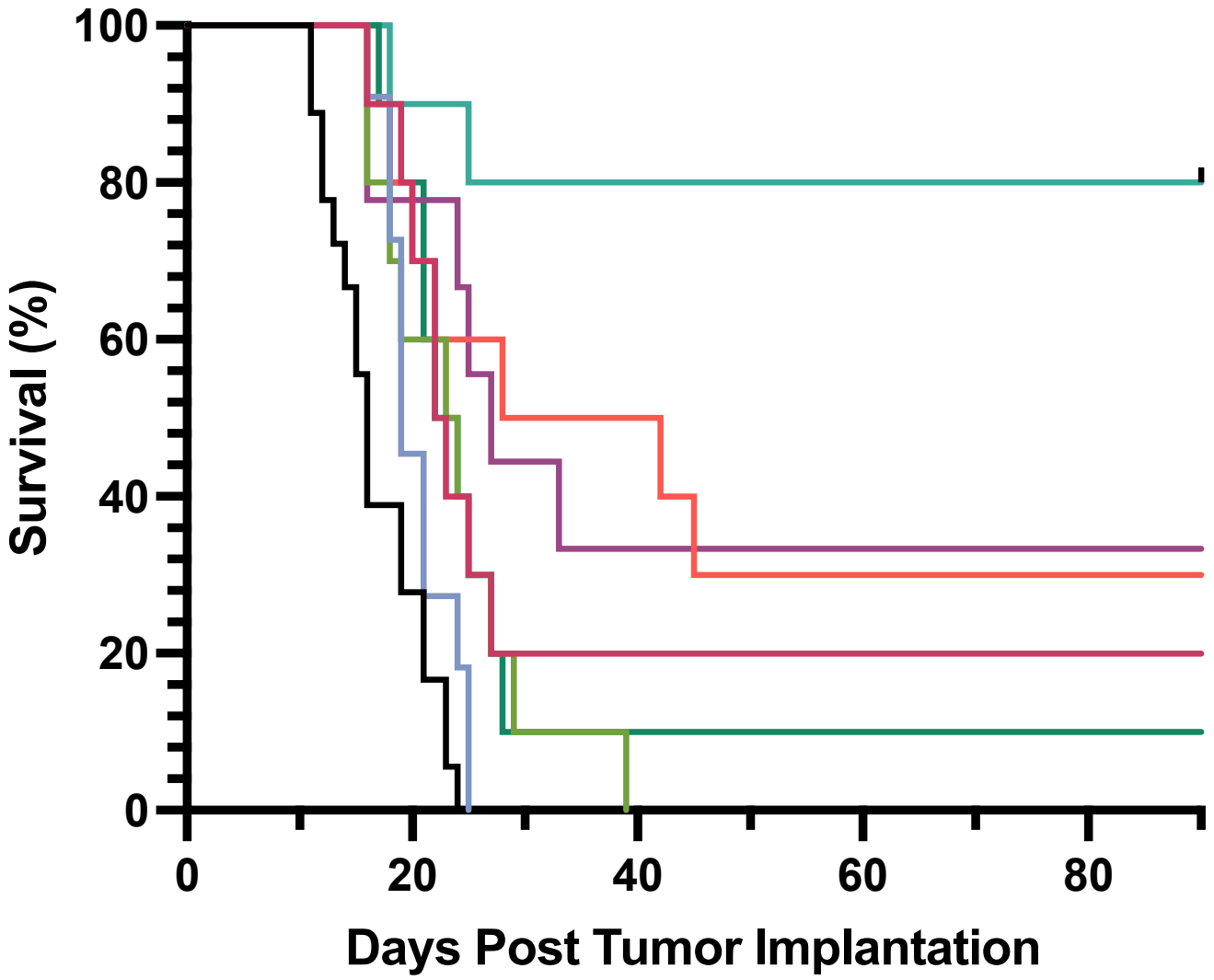

Control
Hydrogel DOX **
Hydrogel CDN-NPs *
Hydrogel anti-PD-1**
Hydrogel DOX/CDN-NPs ***
Hydrogel anti-PD-1/CDN-NPs***
Hydrogel DOX/anti-PD-1***

**
*
*

Significance in comparison to control unless otherwise indicated

Dion M., …Brem H., Artzi N., **STM**, **Under Review**

# DUAL HYDROGEL-MEDIATED COMBINATION THERAPIES INCREASE SURVIVAL IN IMMUNOSUPPRESSIVE CT2A MODEL

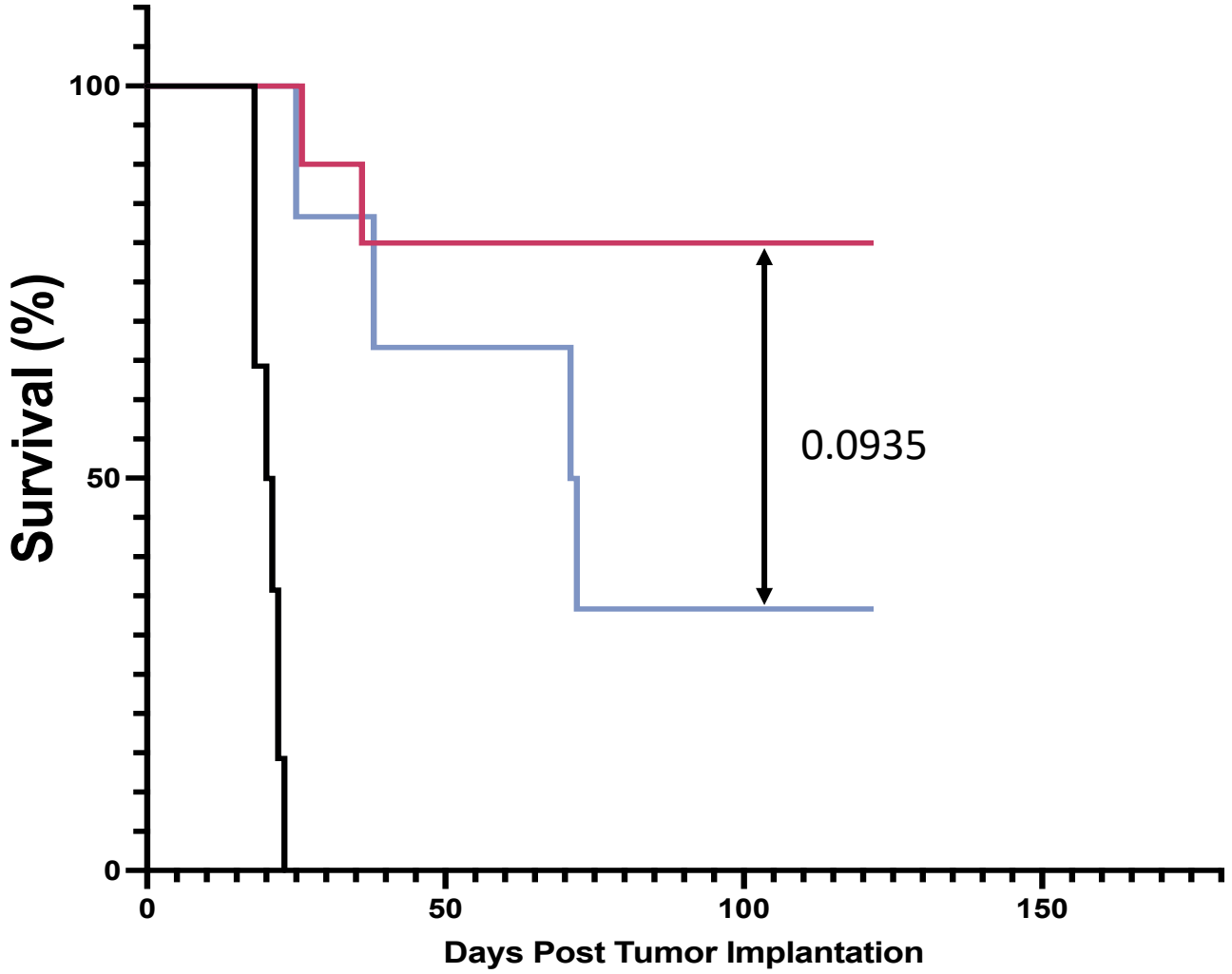


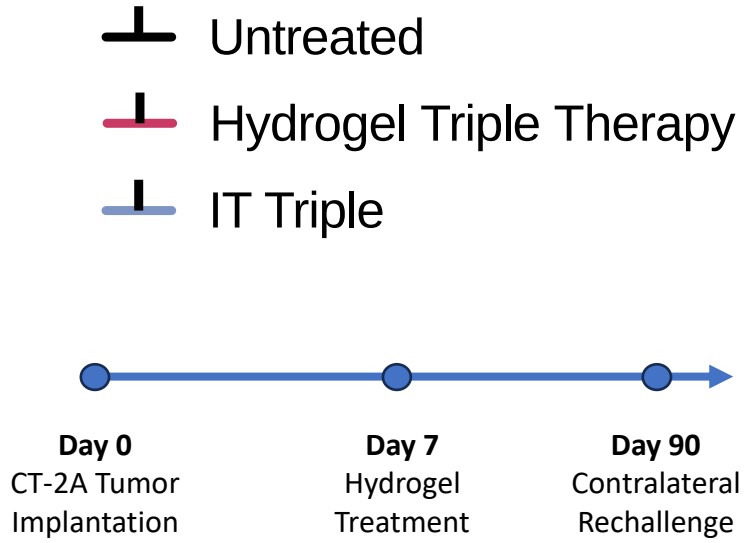

- Control ****
- Hydrogel DOX **
- Hydrogel CDN-NPs ***
- Hydrogel anti-PD-1 ***
- Hydrogel DOX/CDN-NPs *
- Hydrogel anti-PD-1/CDN-NPs *
- Hydrogel DOX/anti-PD-1 **
- Hydrogel DOX/CDN-NPs/anti-PD-1

N = 8-12 mice per treatment group

Dion M., …Brem H., Artzi N., **STM**, **Under Review**

# HYDROGEL-MEDIATED DELIVERY IMPROVES LONG-TERM SURVIVAL OF MICE TREATED WITH COMBINATION THERAPY RELATIVE TO INTRATUMORAL INJECTION

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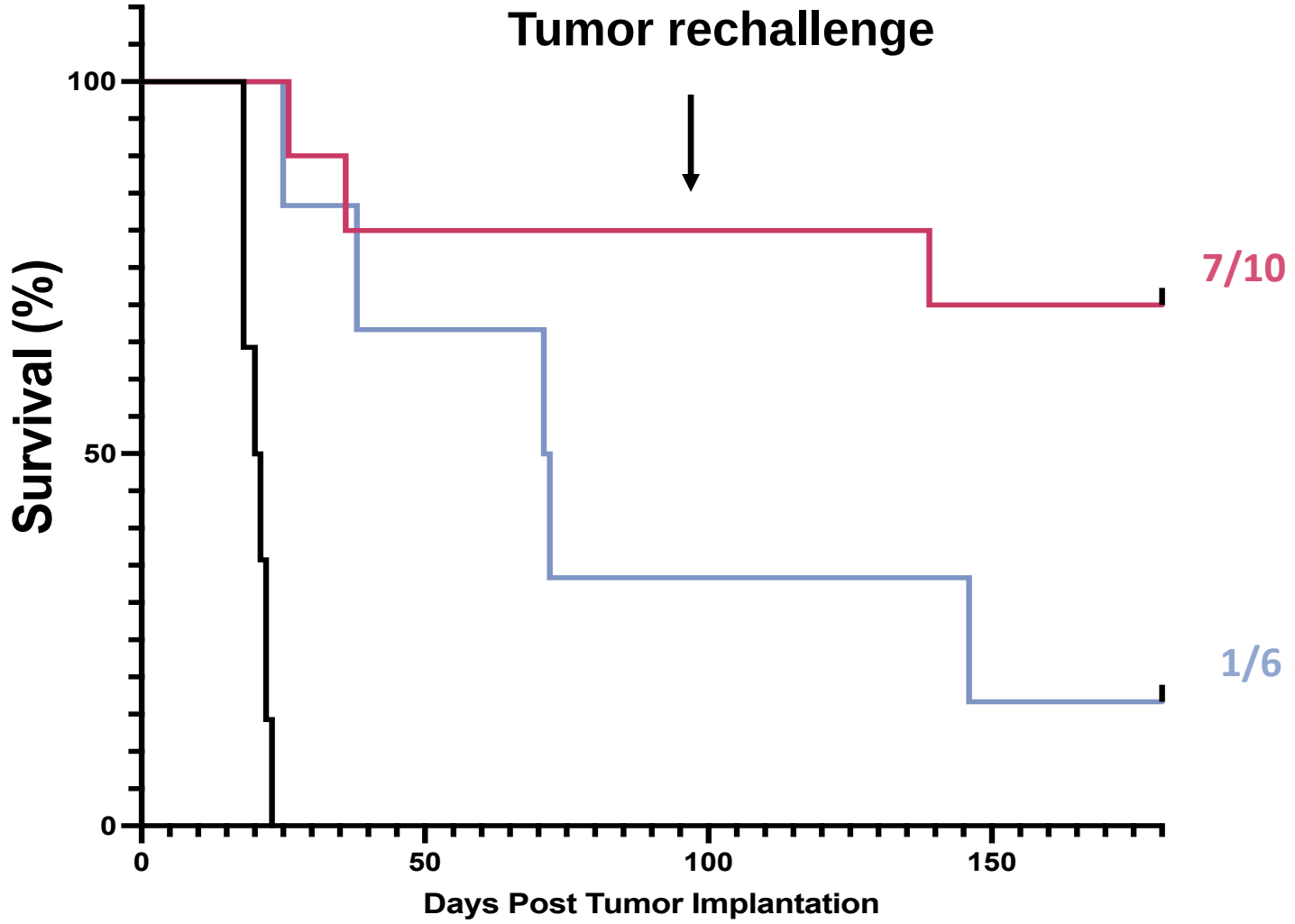
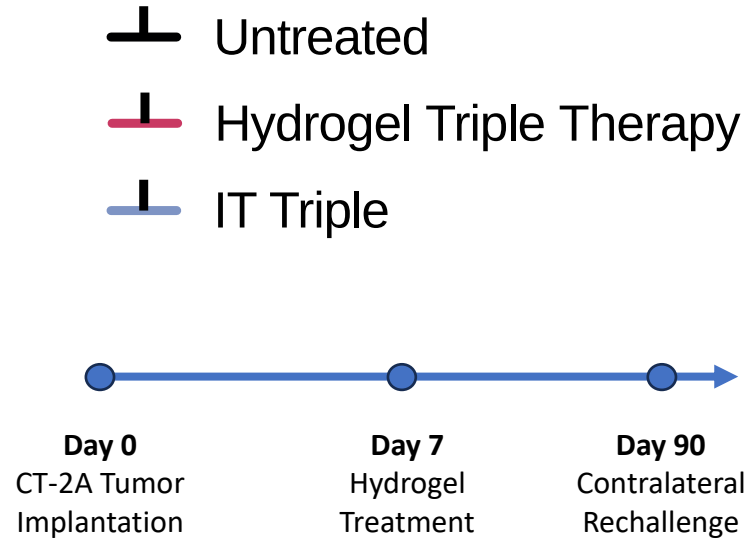
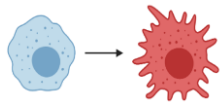


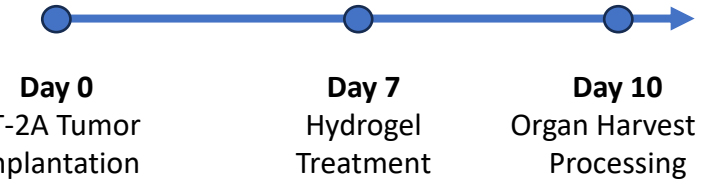



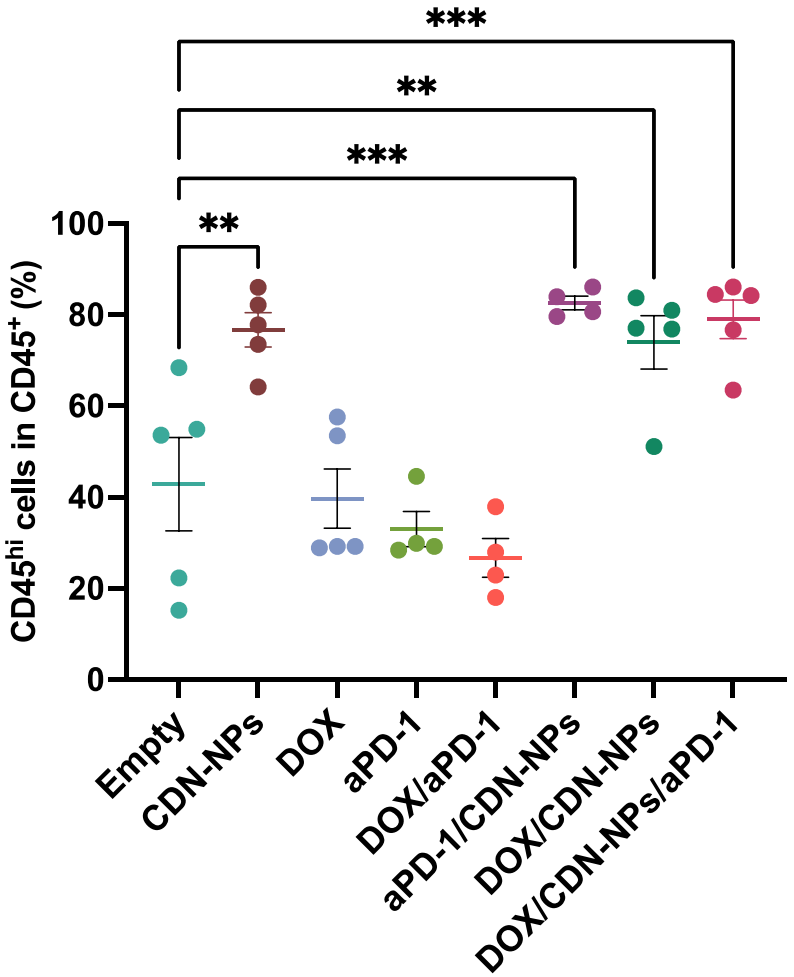

Dion M., …Brem H., Artzi N., **STM**, **Under Review**

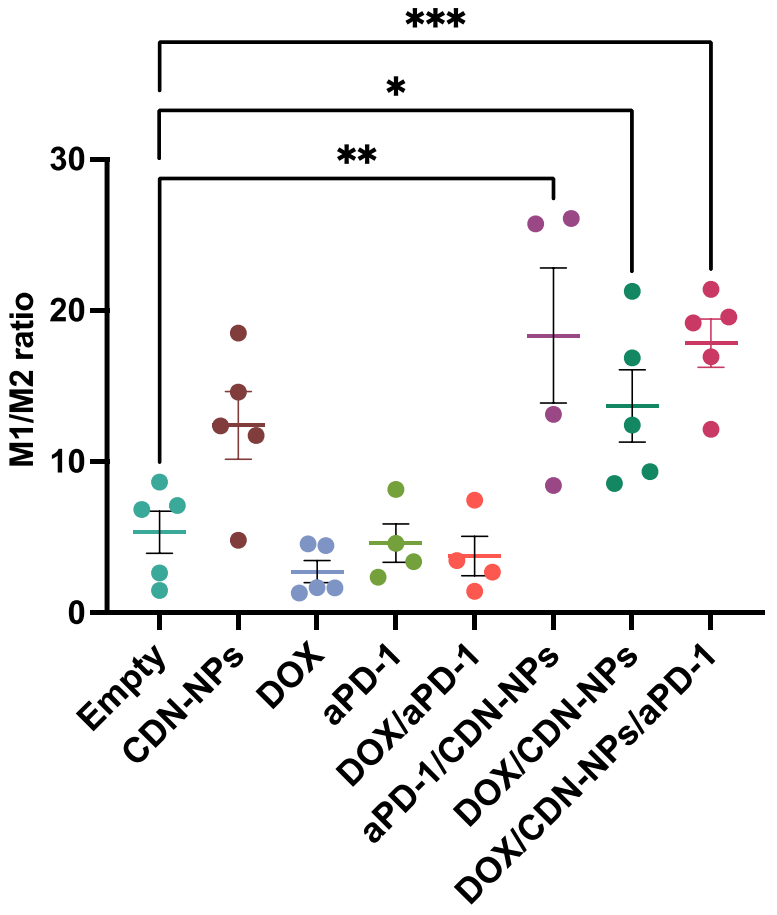
# HYDROGEL COMBINATION THERAPIES INDUCES IMMUNE CELL INFILTRATION AND ACTIVATION OF MYELOID CELLS



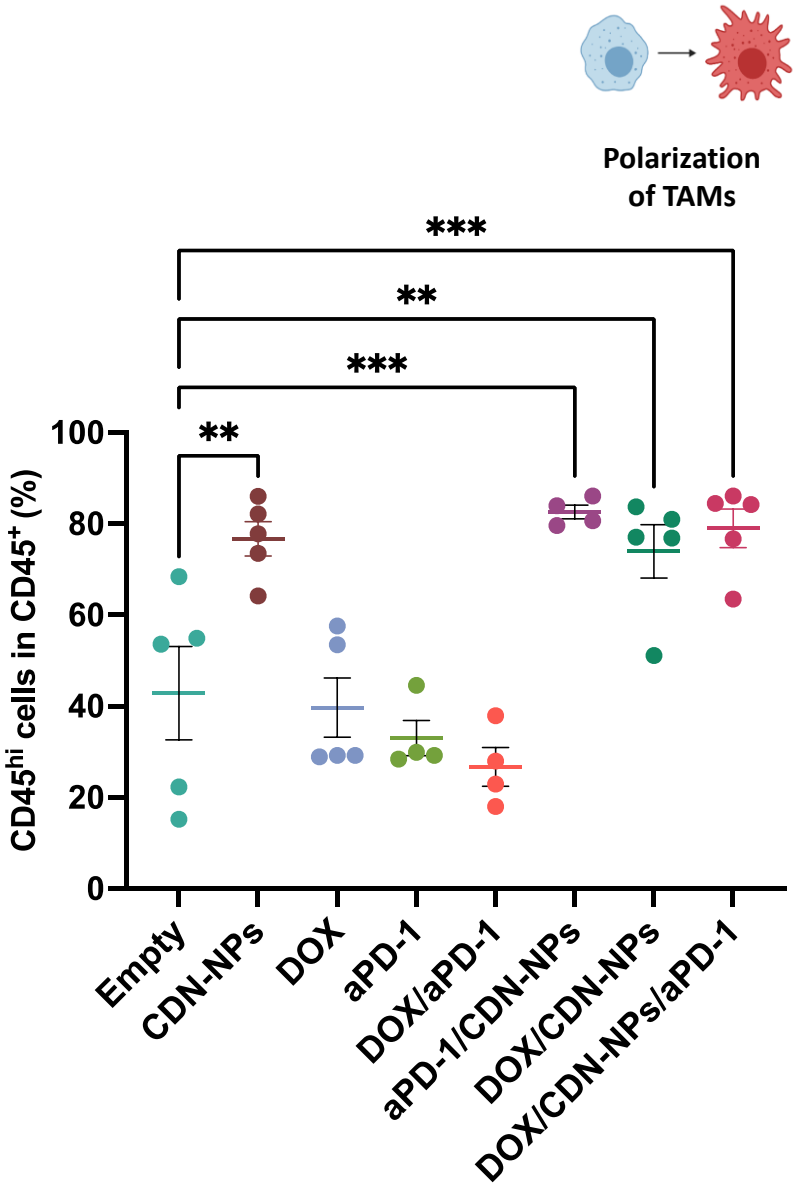
Polarization of TAMs

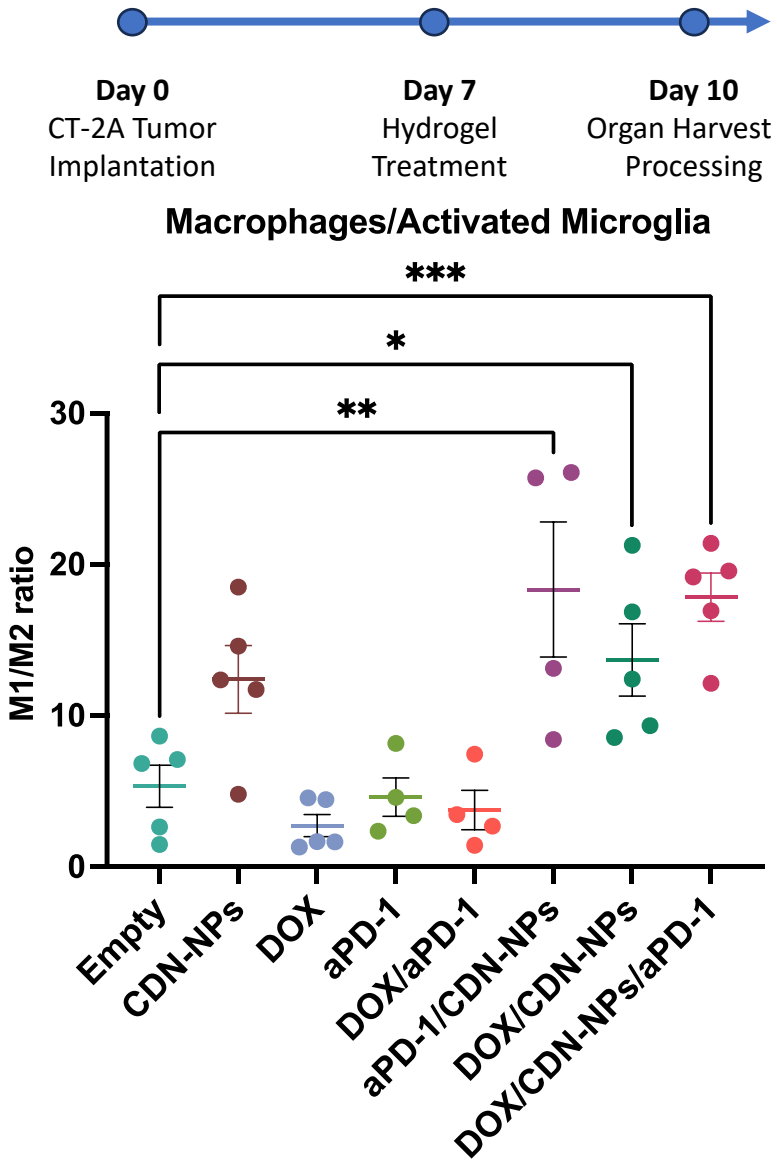


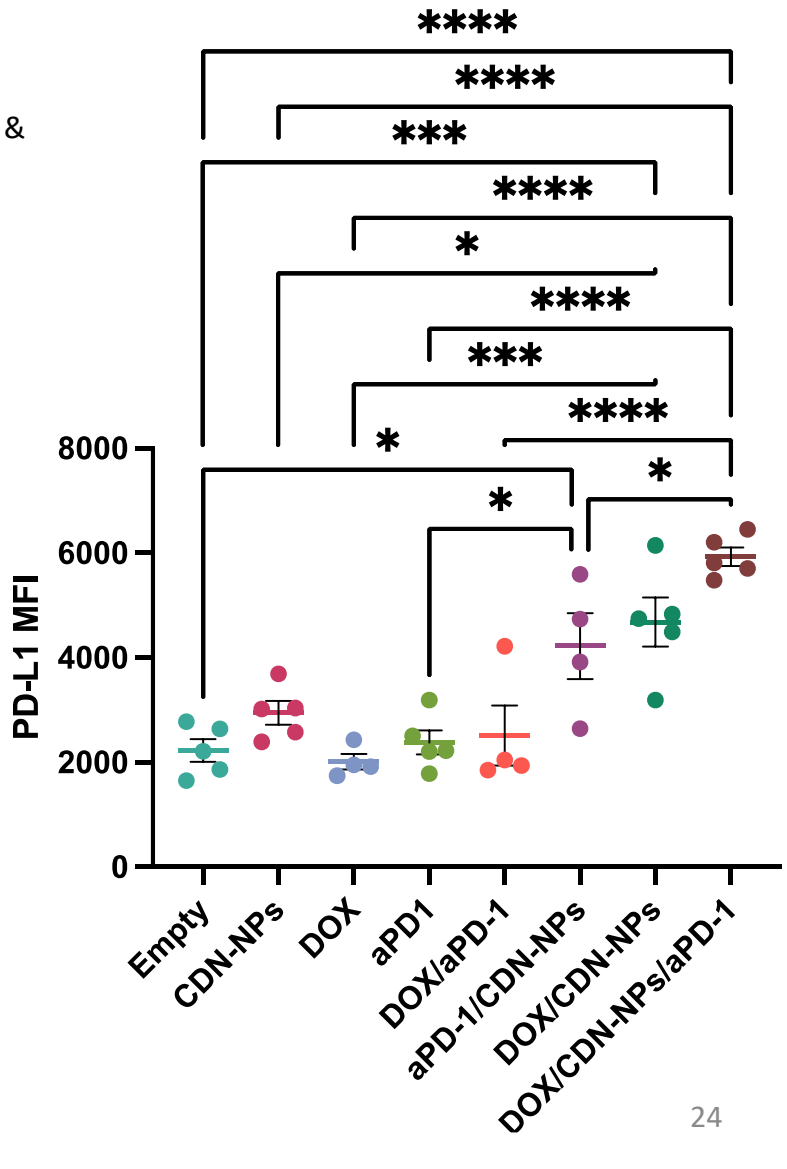



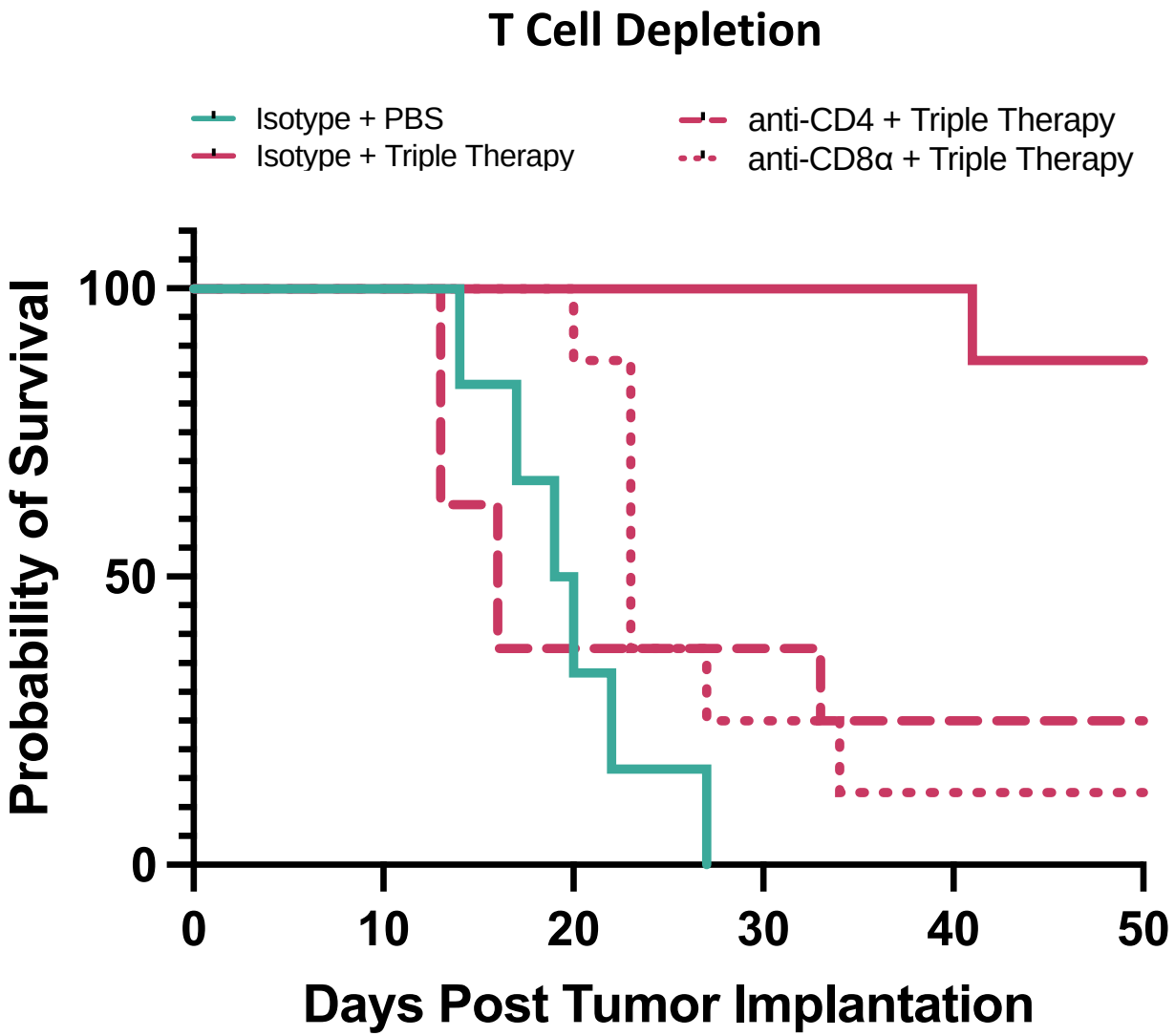
# HYDROGEL COMBINATION THERAPIES ACTIVATE MYELOID CELLS AND INDUCE INFLAMMATORY AND IMMUNOREGULATORY MARKER EXPRESSION

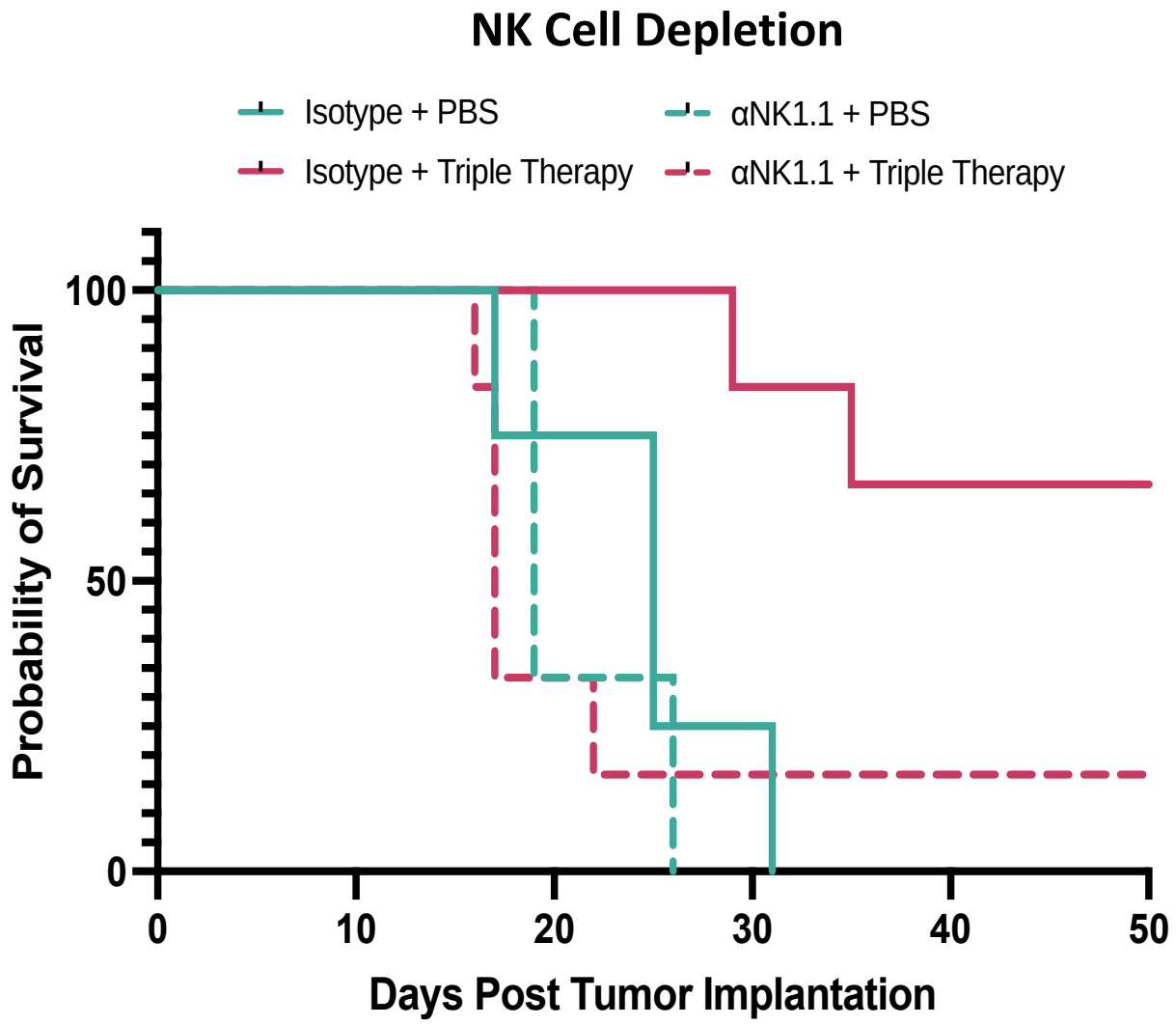


# NK AND CD8 T CELLS CONTRIBUTE TO TRIPLE THERAPY EFFICACY




Dion M., …Brem H., Artzi N., **STM**, **Under Review**

# MICRONEEDLES: A CHILD-FRIENDLY APPROACH FOR DRUG DELIVERY AND DIAGNOSIS

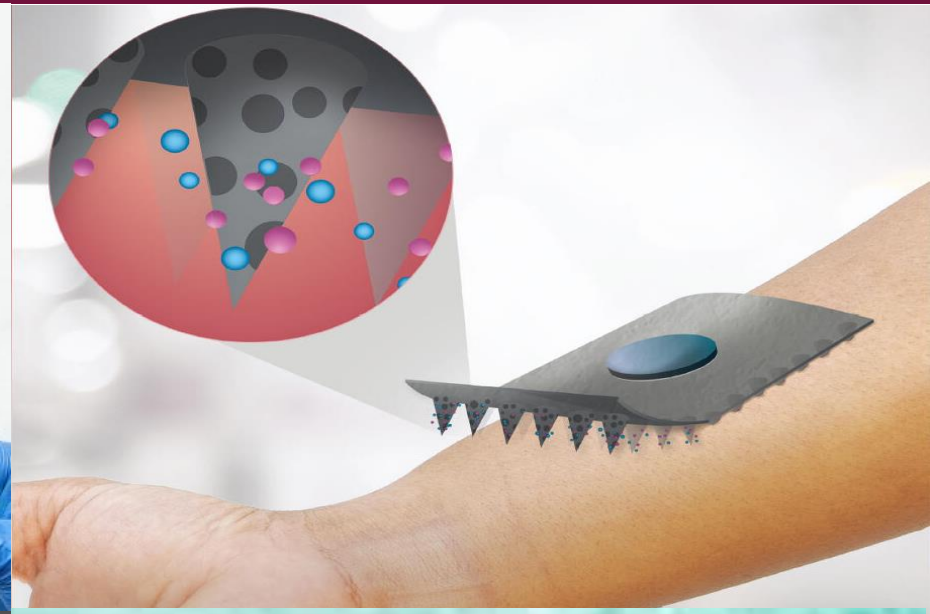
**~63% of children** suffer from needle fear

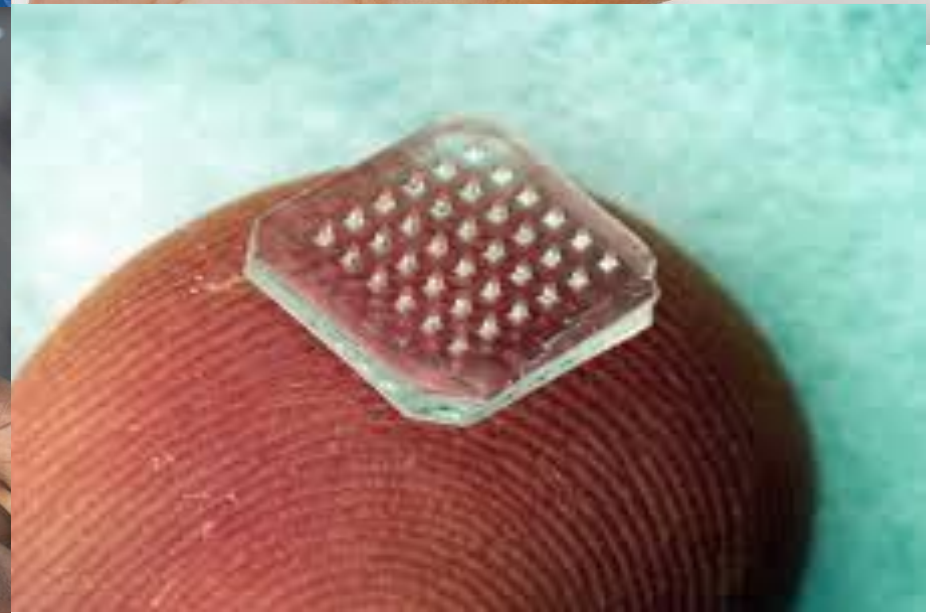
Microneedles are **painless** and **minimally invasive**

No need for trained personnel, **enabling at-home** or **school-based use**

**Improved compliance** and **reduced anxiety** in pediatric populations

**Proven efficacy** for vaccines and therapeutics in pediatric microneedle studies



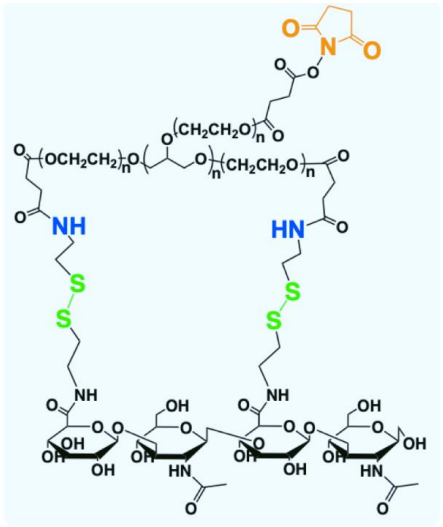


Adapted from BBC News

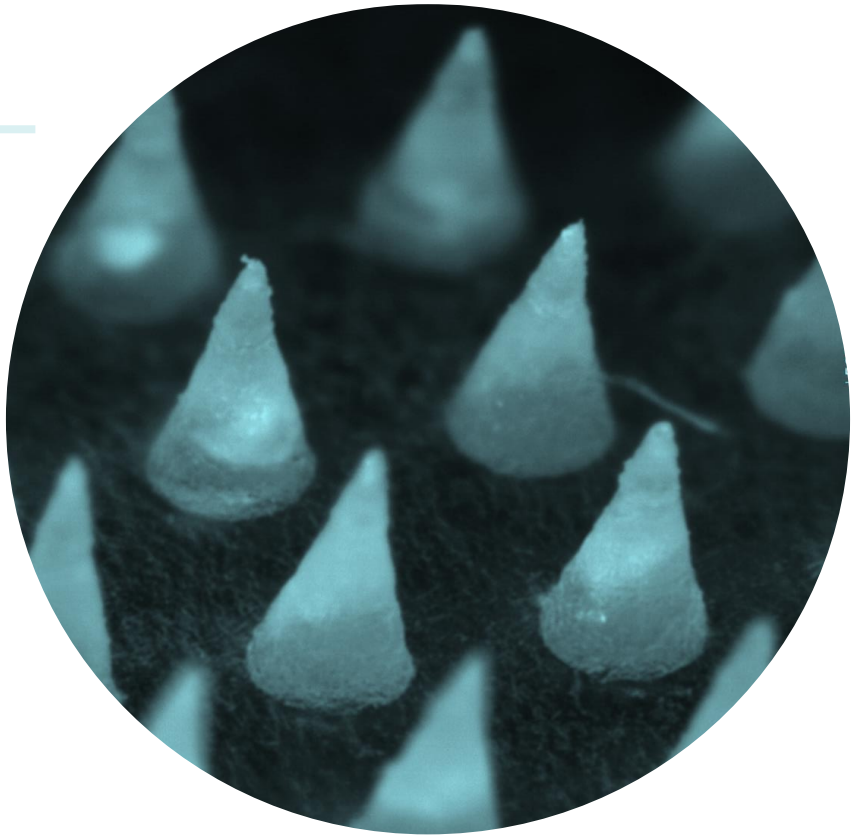
# FINE-TUNED PROPERTIES FOR ENHANCED DRUG DELIVERY/ISF SAMPLING

**Transdermal, painless drug delivery**

**Hyaluronic acid-based for biocompatibility**

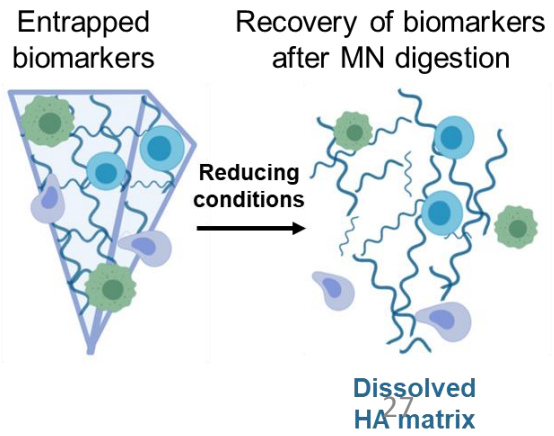


**Drug-agnostic platform**



**Translational efficacy: Skin cancer, skin transplant, alopecia areata**

**Hydrogel matrix allows superior sampling (cells and soluble biomarkers)**



# ALOPECIA AREATA: A DEVASTING AUTOIMMUNE SKIN DISEASE MANIFESTING WITH HAIR LOSS

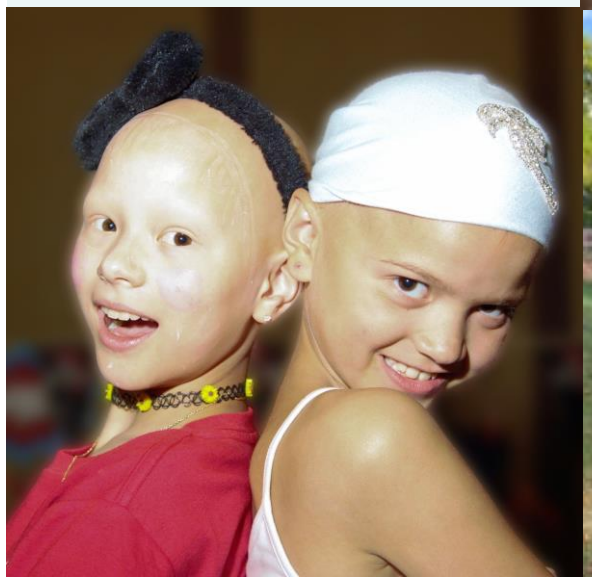
≈ 91%
of all AA patients

≈ 700K
patients USA

$54B (TAM)
15M global AA patients

- No FDA-approved treatments for focal AA
- Off-label approaches fail to sustain hair regrowth (corticosteroids, minoxidil)
- $T_{reg}$ imbalance triggers disease progression
- High patient demand and advocacy support

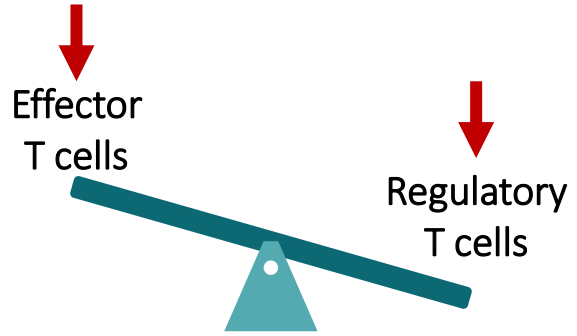
**No treatments available for pediatric populations**



# OUR APPROACH LEADS TO EQUILIBRIUM

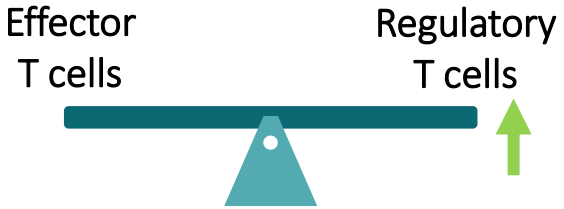
## Immunosuppression (JAK inhibitors) harms the regulatory immune system

### Immunosuppressants (JAK inhibitors)



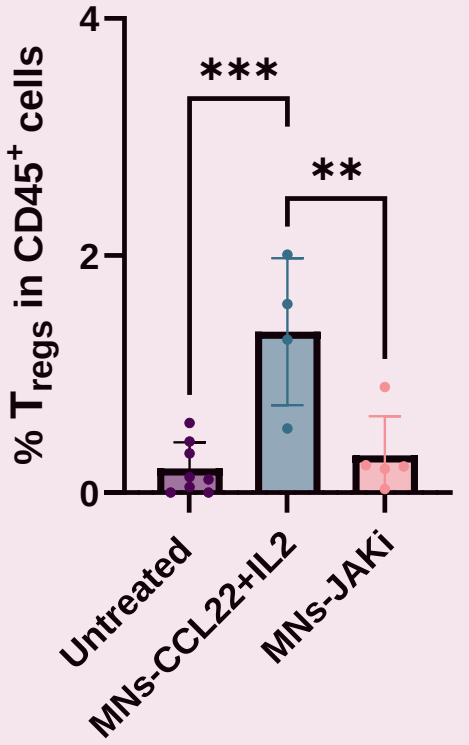

- Immunosuppressants (JAK inhibitors) suppress $T_{reg}$ expansion
- Non-specific immunosuppression leads to relapse and limits long-term efficacy

### Immunoregulation




- $T_{reg}$ expansion by delivering CCL22+IL-2 using our patch leading to immune equilibrium

$T_{reg}$ expansion (AA skin lesion)

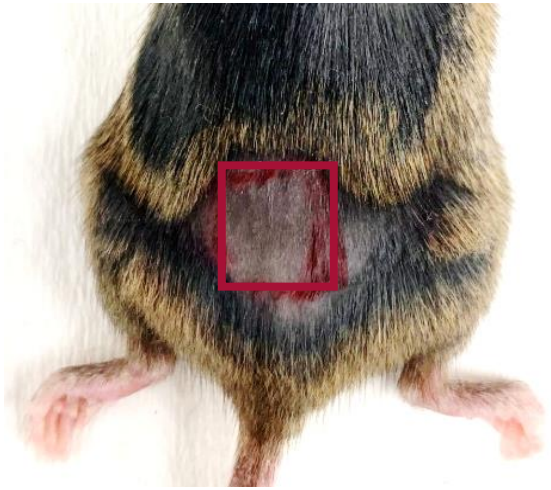



Microneedle-mediated Delivery of Immunomodulators Restores Immune Privilege in Hair Follicles and Reverses Immune-Mediated Alopecia. N. Puigmal*, N. Younis*, […] N. Artzi, J.R. Azzi (2024); Advanced Materials

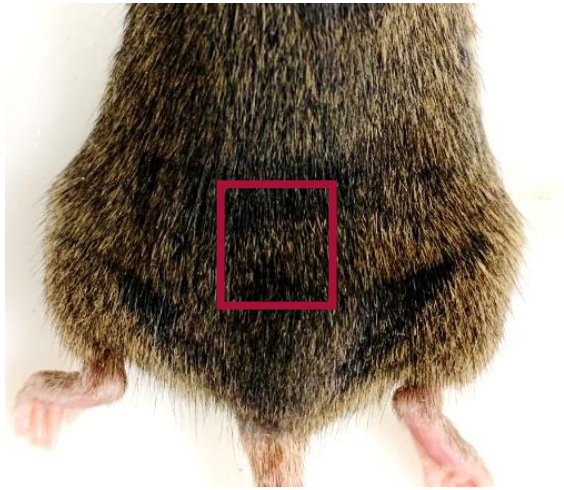
# RESTORING IMMUNE BALANCE

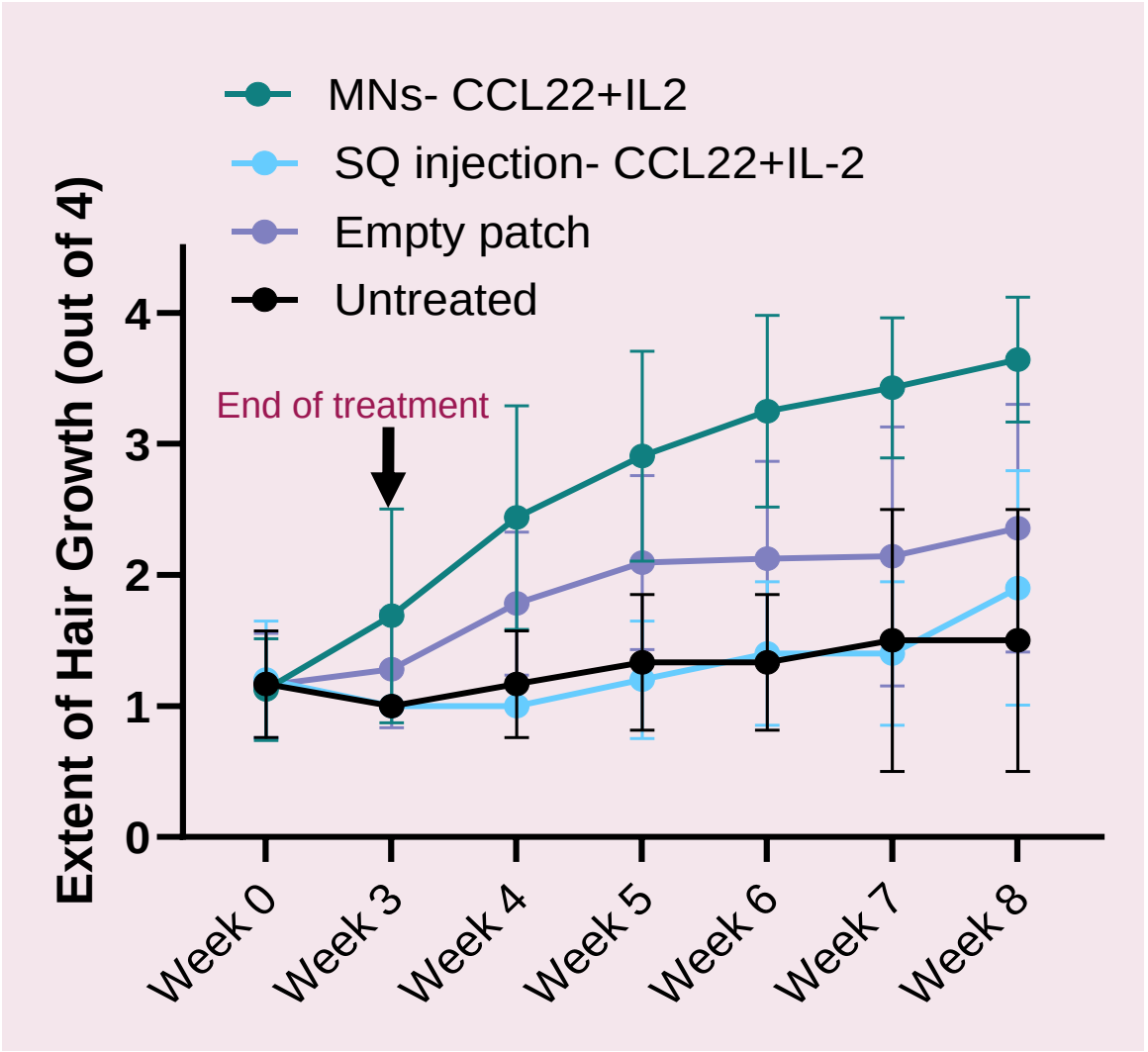
## Our patch restores the immune balance leading to hair regrowth beyond treatment discontinuation whereas hypodermic injection cannot

**Before treatment**



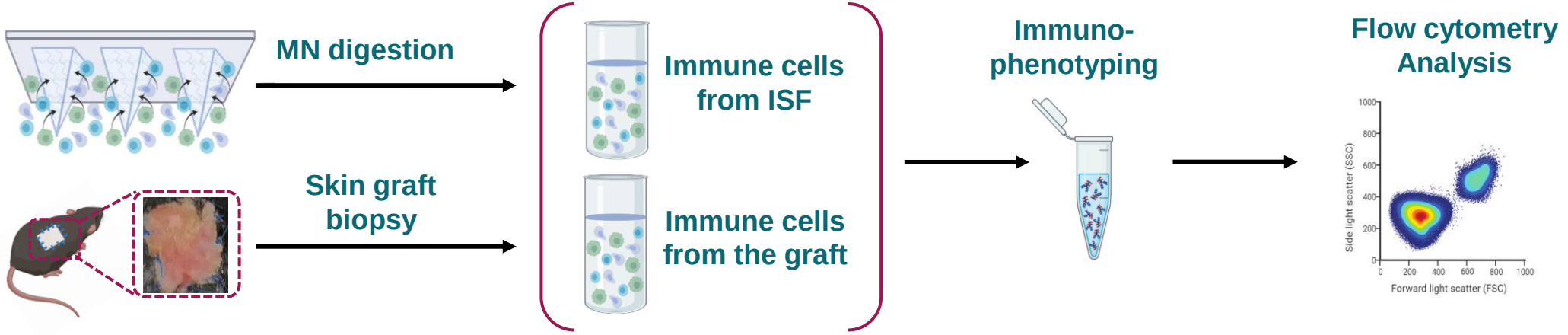
**After treatment (Week 6)**

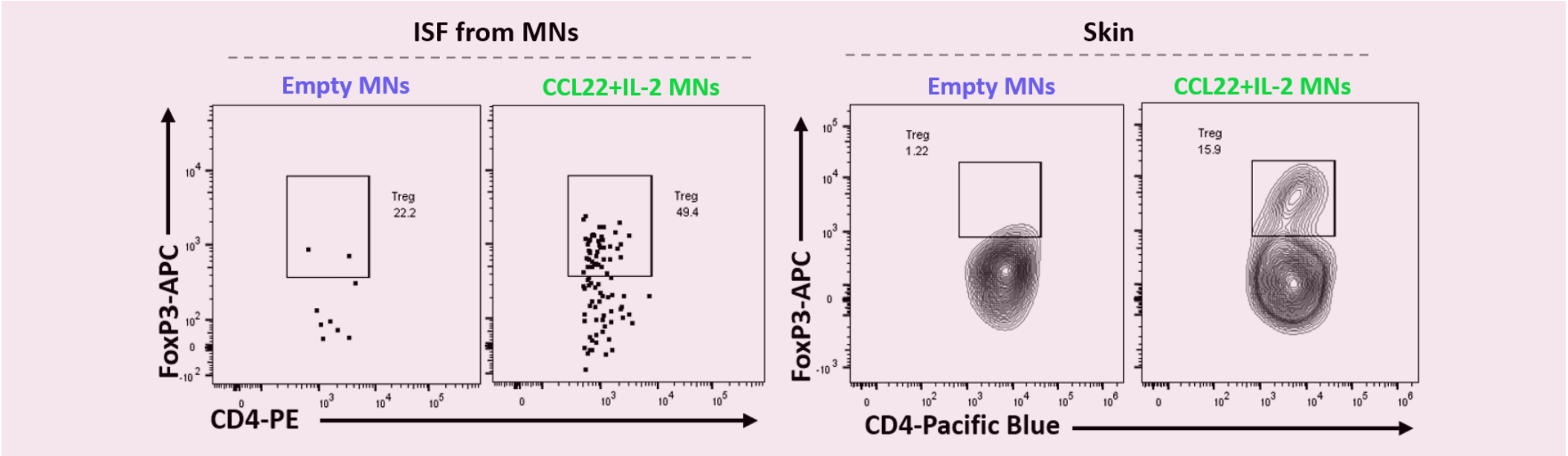





Microneedle-mediated Delivery of Immunomodulators Restores Immune Privilege in Hair Follicles and Reverses Immune-Mediated Alopecia.
N. Puigmal*, N. Younis*, […] N. Artzi, J.R. Azzi (2024); Advanced Materials

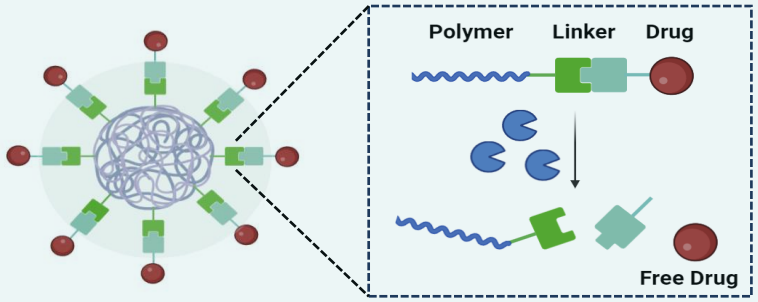
# MONITORING THE $T_{REG}$ HOMING PROCESS IN SITU UPON MN ADMINISTRATION



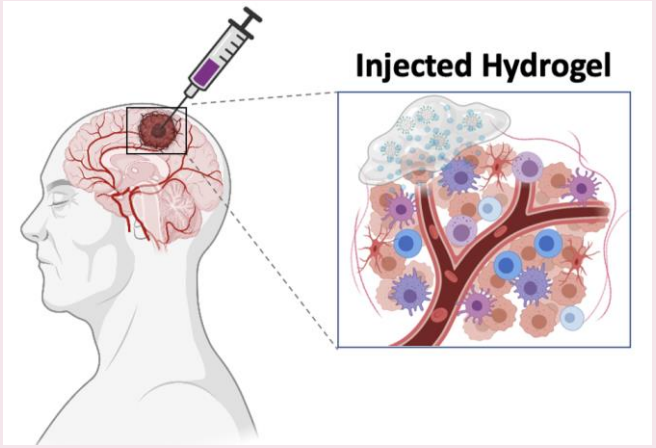




Puigmal N.,… Artzi, Natalie. Adv. Funct. Mater., 2021

# Biomaterials can be designed to respond to tissues and cells to maximize therapeutic efficacy



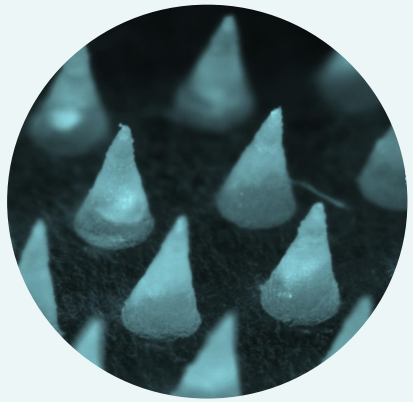

- **Chemically designing polymer-drug conjugates** can be used to engineer the therapeutic window of potent immunomodulatory drugs
- **Chemical structure** markedly influences NP pharmacokinetics and biological interactions, impacting immune responses
- The **PTE** can be a critical enabling tool in drug design




**SpideRx**

- **Chemically designed tissue-responsive adhesive materials** facilitate tissue adhesion and maximize drug retention
- **Sustained delivery** of chemoimmunotherapy is required for safe immune activation and memory formation

# Biomaterials can be designed to respond to tissues and cells to maximize therapeutic efficacy



**Lybra Bio**

- **MNs** allow **painless, non-invasive drug delivery and sampling** with high patient compliance.
- Delivery of immunotherapy through the skin can unleash **potent immune responses** without side effects (activation or regulation).
- Simultaneous drug delivery and sampling with MNs provides insight into the **mechanisms** driving therapeutic efficacy.

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