Session: Nanomedicine and Nanoscale Delivery III

Urease-Powered Nanomotor for Bladder Cancer Immunotherapy

Seok Cheon Endowed Chair Prof. Sei Kwang Hahn

Biomedical Nanomaterials Lab

Department of Materials Science and Engineering, POSTECH

CONTROLLED RELEASE SOCIETY
CRS 2024 Annual Meeting AND Exposition
JULY 8-12, 2024 • BOLOGNA, ITALY

INTEGRATING
Delivery Science
ACROSS DISCIPLINES

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Nature Communications, In Revision (2024)
Bioactive Materials, 9, 54-62 (2022)
Biomaterials, 279, 121201 (2021)
Nature Reviews Materials, 5, 149-165 (2020)
ACS Nano, 14(6), 6683-6692 (2020)
ACS Applied Materials & Interfaces, 10, 2338-2346 (2018)

1. Introduction

1-1. Bladder Cancer

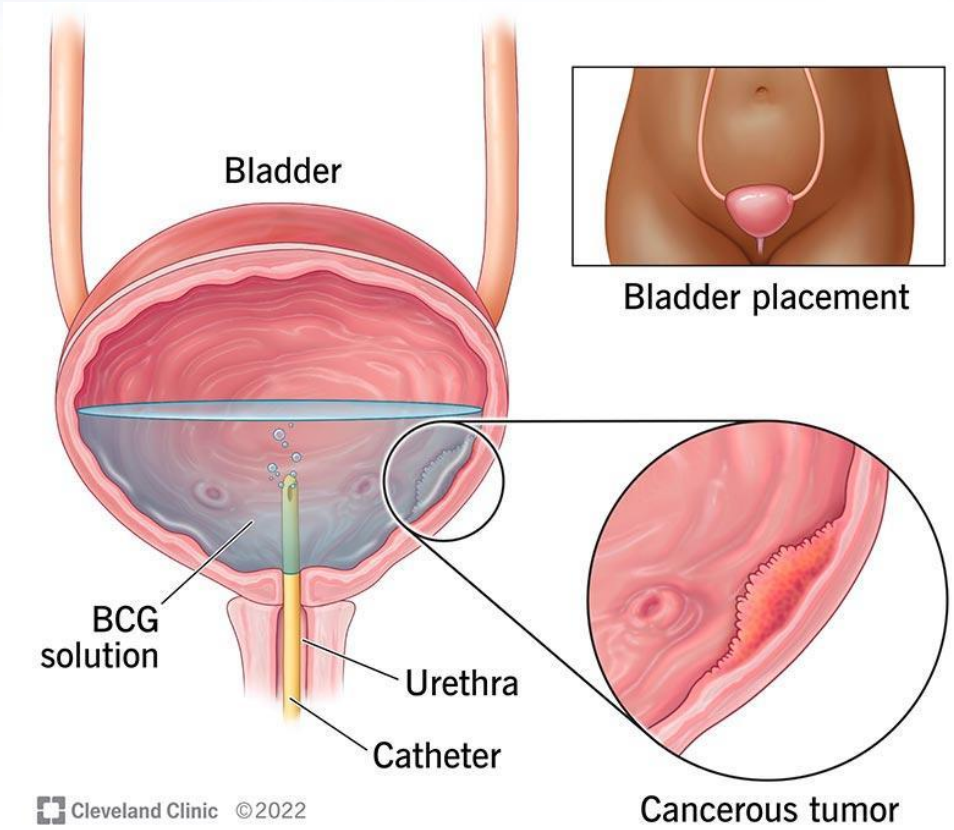
1-2. STING Agonist Immunotherapy

1-3. Micronanomotors

Bladder Cancer

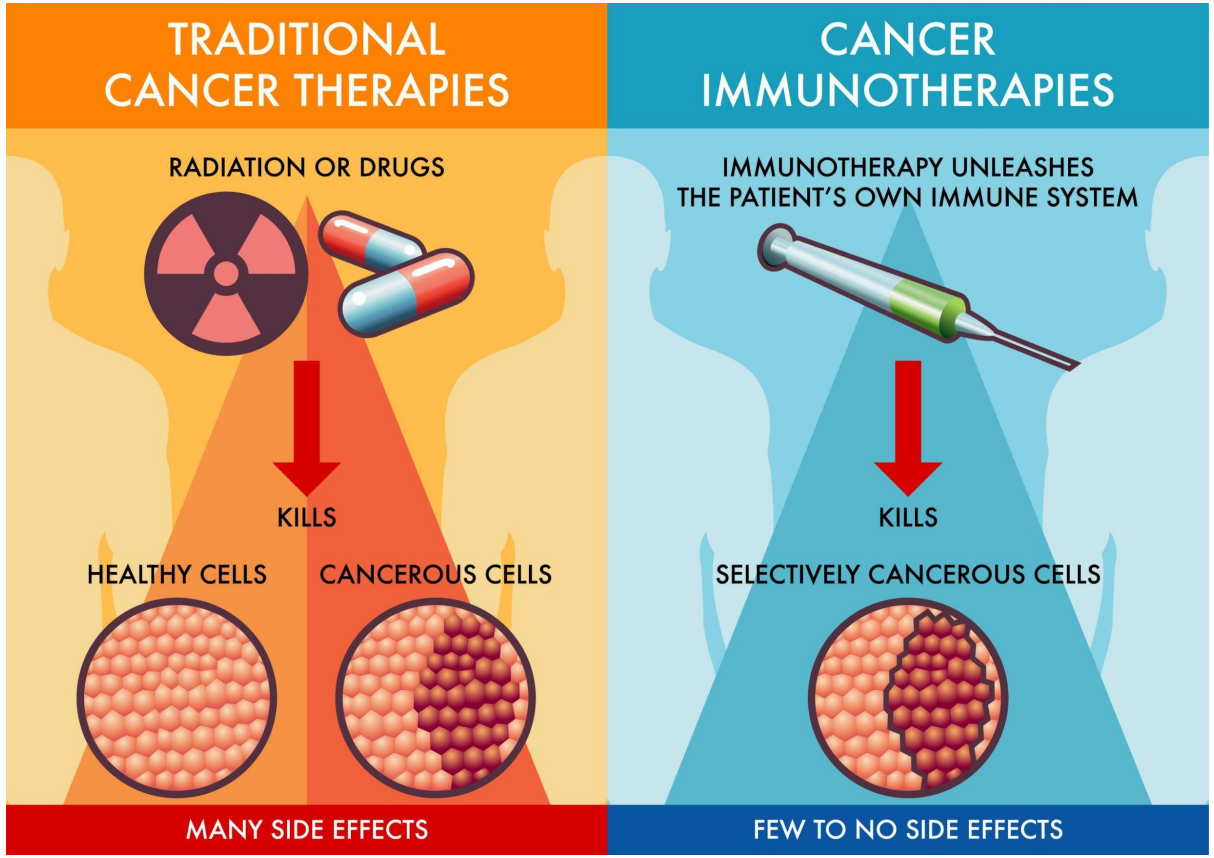
❖ Bladder cancer and intravesical immunotherapy

- Non-muscle invasive papillary carcinomas over 75%
- Muscle invasive urothelial cancers



Bacillus Calmette-Guerin (BCG) Treatment

- Long-lasting effect, low metastasis rate and low recurrence rate

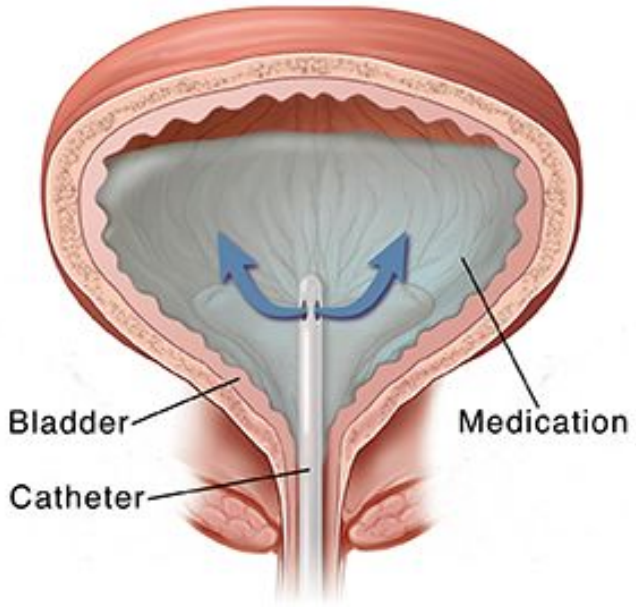


Nature Reviews Cancer 2021, 21, 104–121

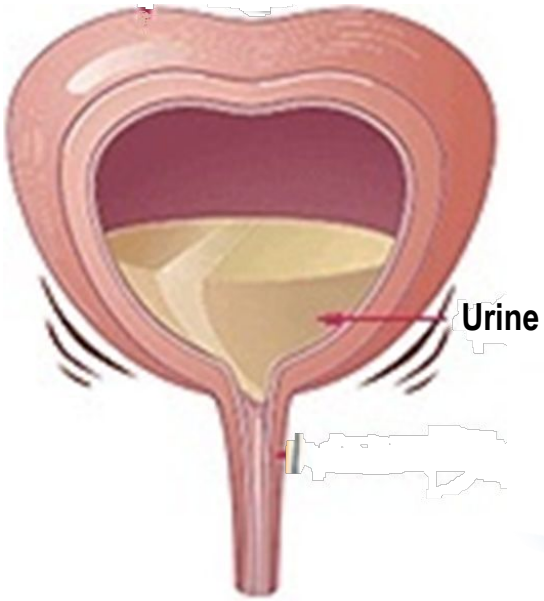
Conventional Intravesical Therapy

❖ Limitations of conventional intravesical cancer therapy

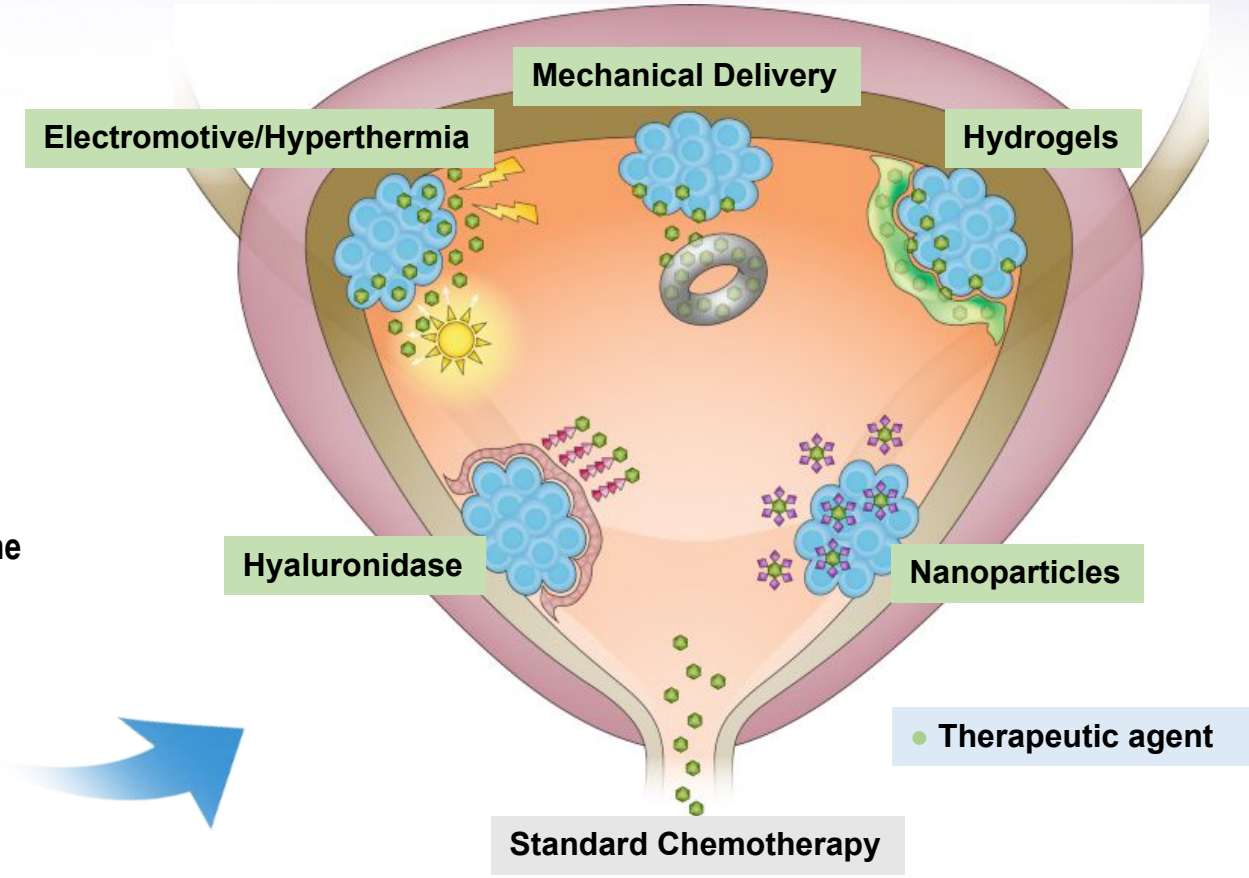
- Clearance from the bladder by repeated urination
- Penetration inhibition by GAG layer



Intravesical instillation



Urination

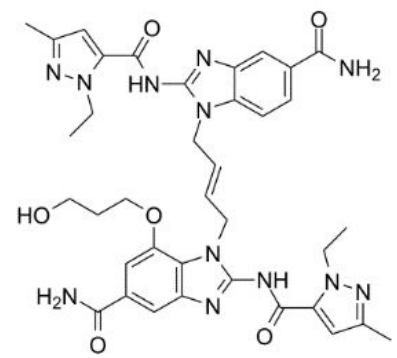


Nature Reviews Urology 16, 599-612 (2019)

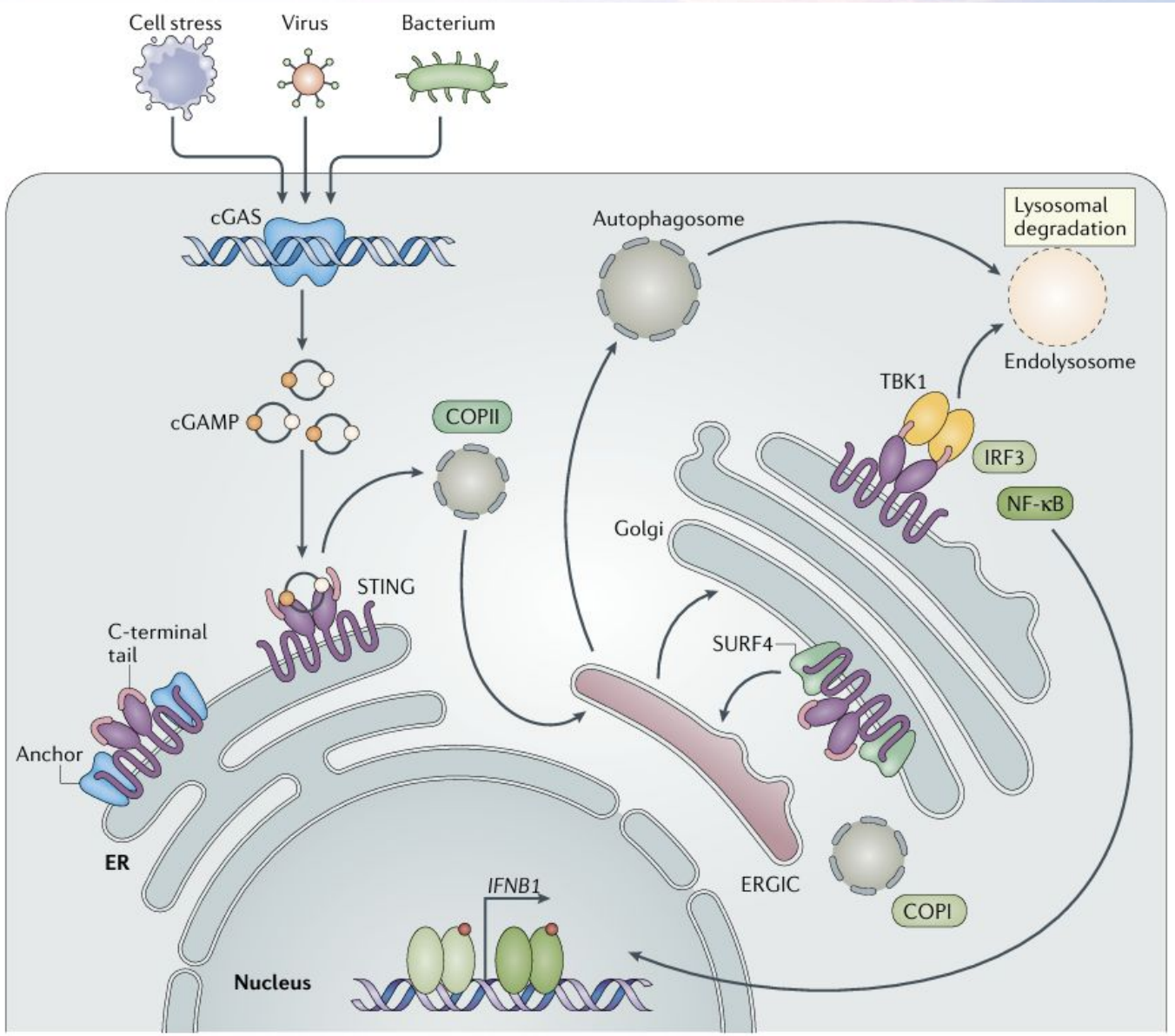
STING Agonist

❖ STING pathway in dendritic cell

- STimulator of INterferon Genes (STING) mediates innate and adaptive immune system.
- Aberrant cytoplasmic exposure of double strand DNAs is recognized by cyclic GMP-AMP synthase to trigger STING pathway for cancer immunotherapy.



STING Agonist



Nature Reviews Immunology 21, 548-569 (2021)

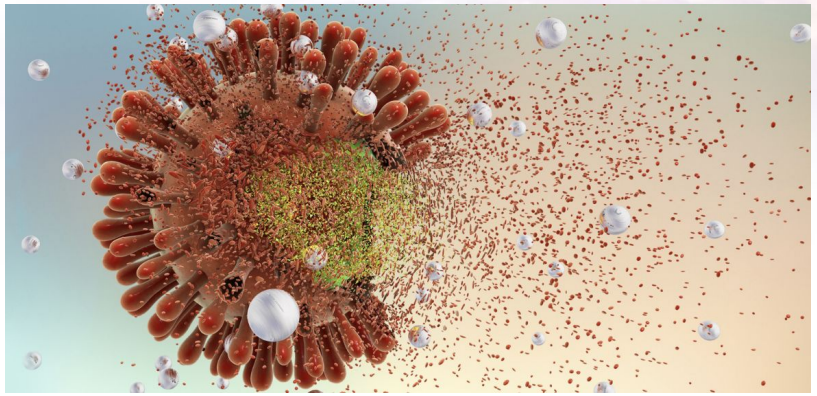
Multifunctional Nanomaterials for Smart Healthcare

NATURE REVIEWS | MATERIALS

Multifunctional materials for implantable and wearable photonic healthcare devices

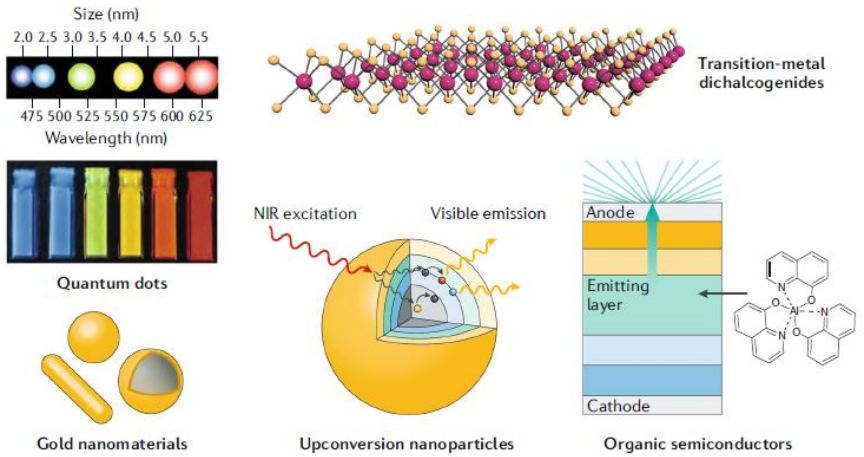
Geon-Hui Lee[1,2,9], Hanul Moon[2,3,9], Hyemin Kim[4,9], Gae Hwang Lee[2,5], Woosung Kwon[6], Seunghyup Yoo[3], David Myung[2,7], Seok Hyun Yun[8], Zhenan Bao[2]* and Sei Kwang Hahn[1,2,4]**

[Nature Reviews Materials 2020, IF = 84.5, Citation 460]

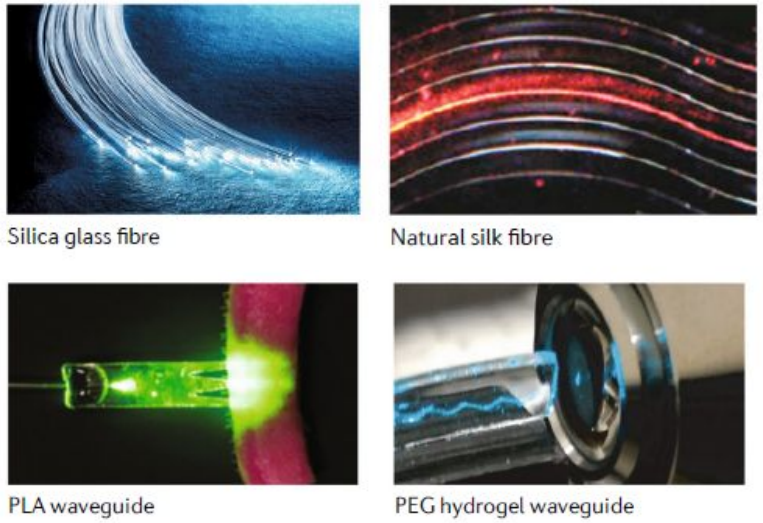


nature reviews materials

Light-responsive materials



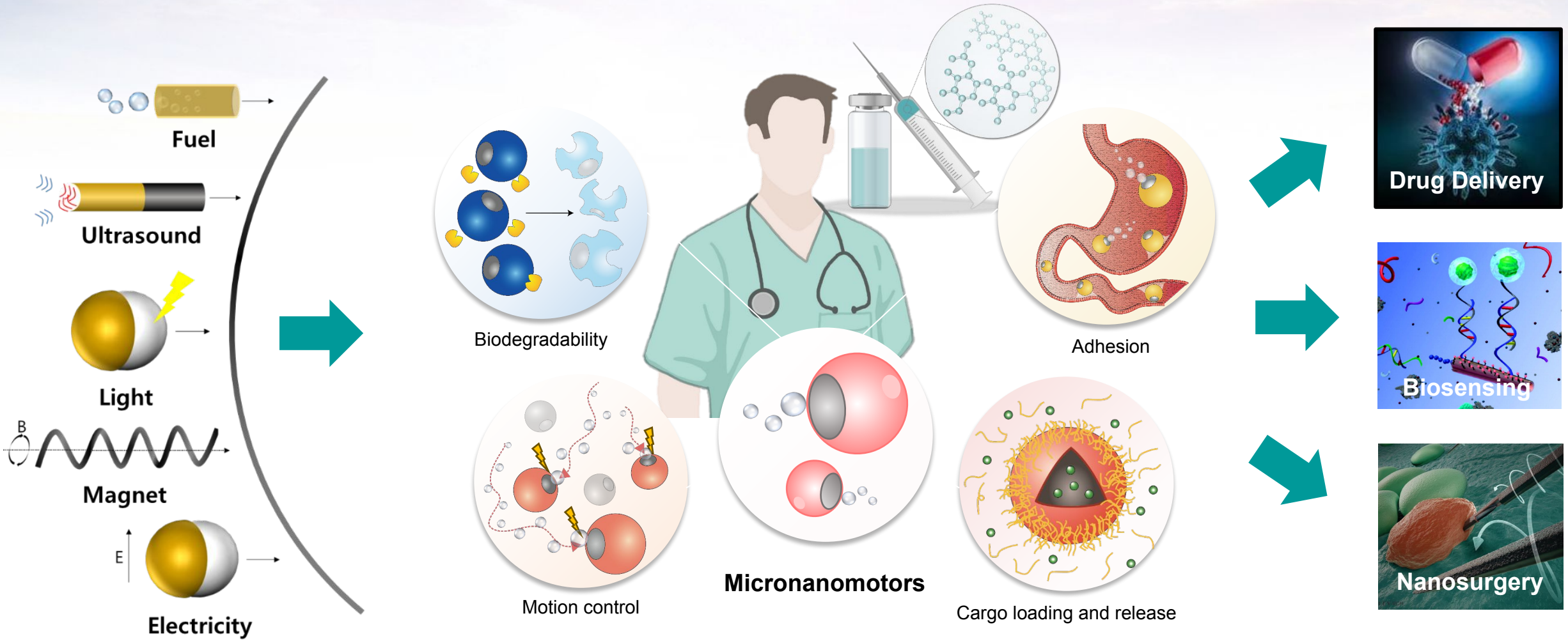
Light-delivering materials



Hahn et al. Nat. Rev. Mater. 5, 149 (2020) and Adv. Mater. 30, 1701460 (2018)

Micro/Nanomotors (MNMs)

❖ Propulsion mechanisms, characteristics, and applications of micronanomotors



Adv. Mater., *25*, 6581, 2013 / Adv. Mater., *28*, 832, 2016

II. Results and Discussion

II-1. Synthesis of Urase-Powered Nanomotors

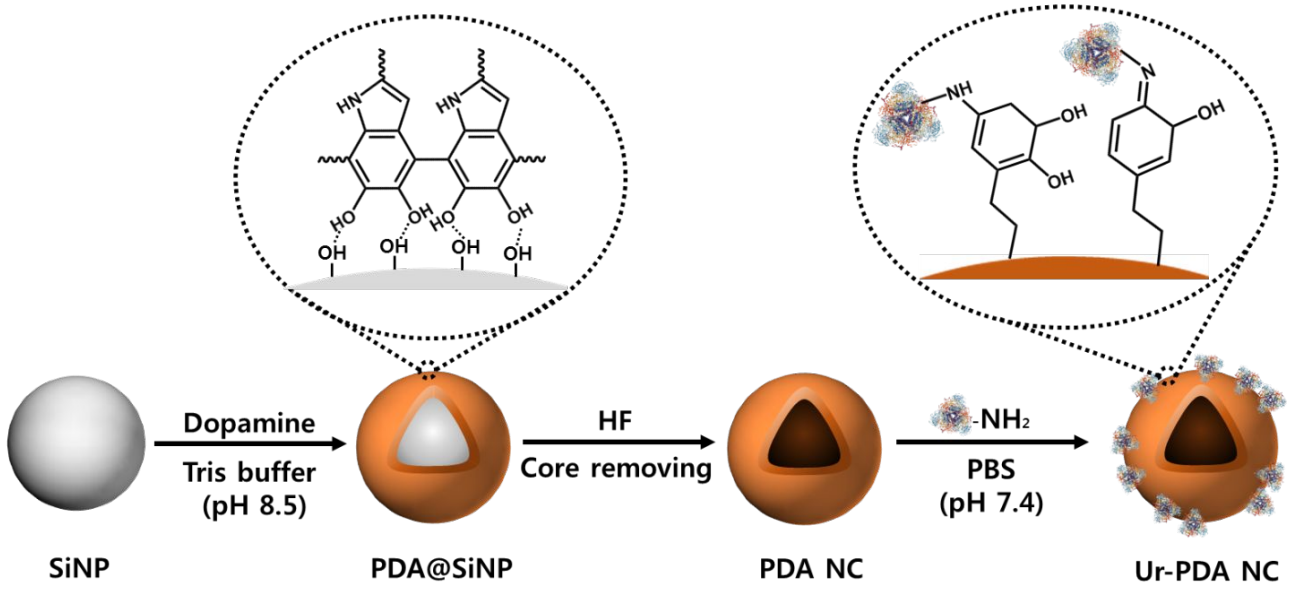
II-2. Characteristics of Urase-Powered Nanomotors

II-3. Bladder Cancer Immunotherapy

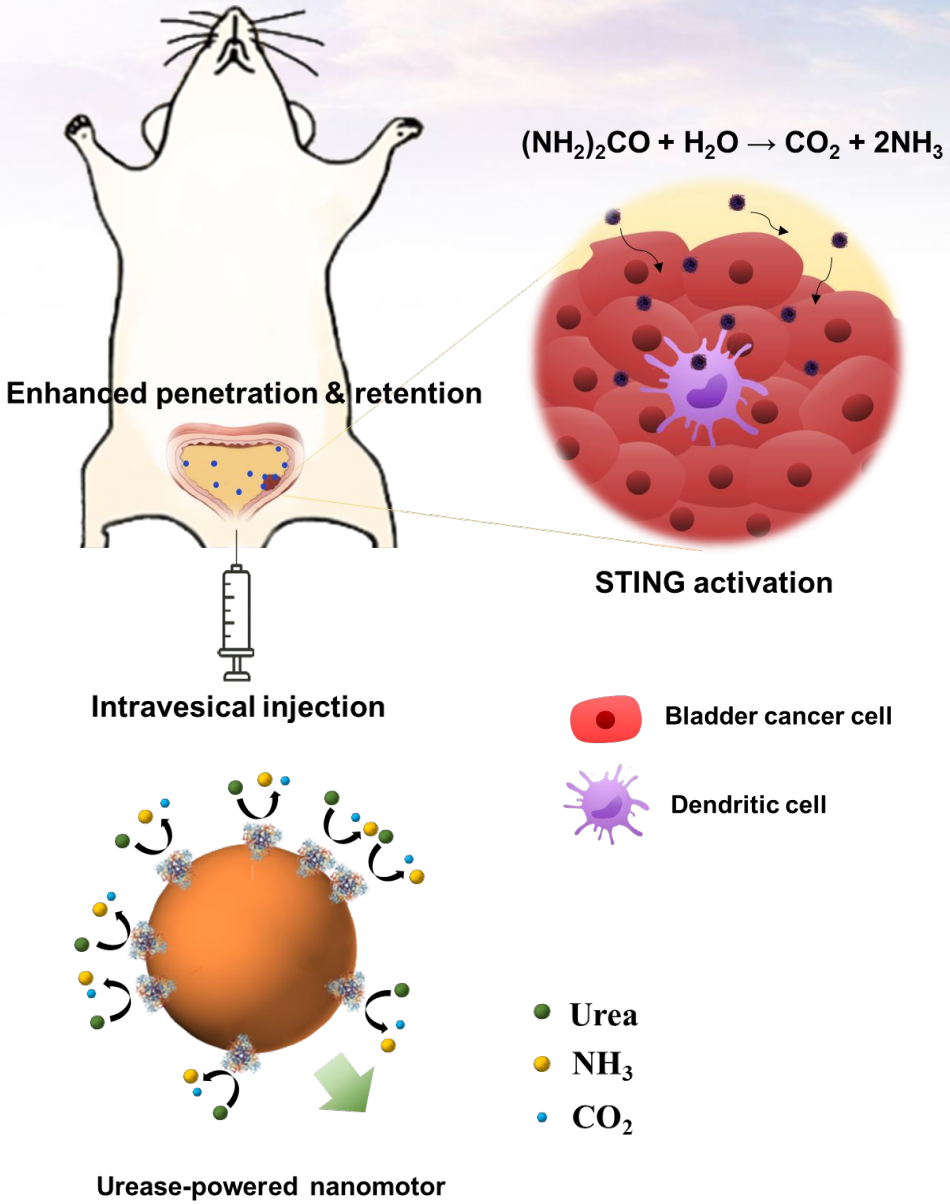
Enzyme-Powered Nanomotor for Bladder Disease Therapy

❖ Synthesis of urease-powered nanomotor

- Coating of PDA onto the silica nanoparticle (SiNP)
- Core removing to form PDA nanocapsule (PDA NC)
- Immobilization of urease onto the PDA NC

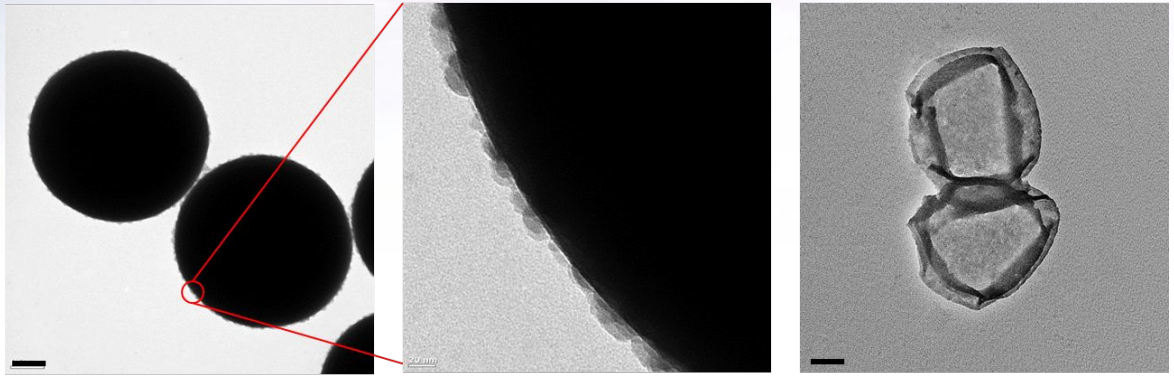


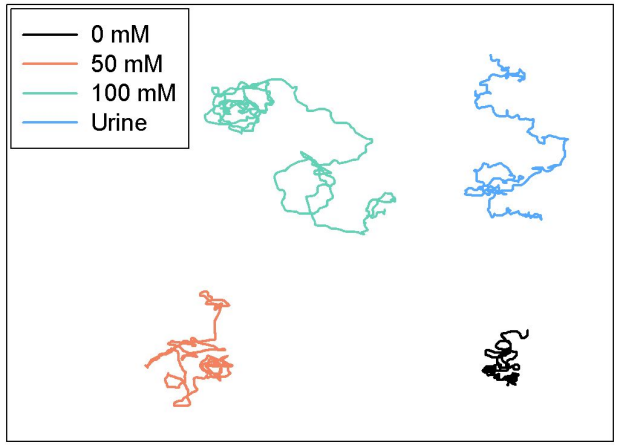
Hahn et al. ACS Nano, 14, 6683-6692 (2020)

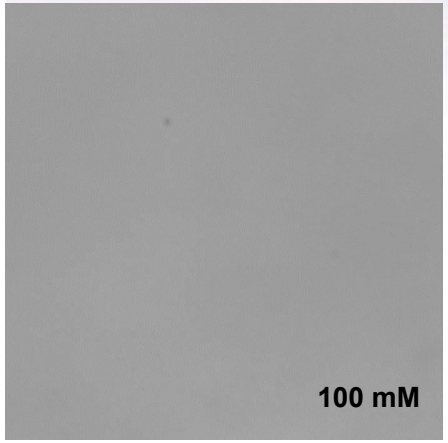


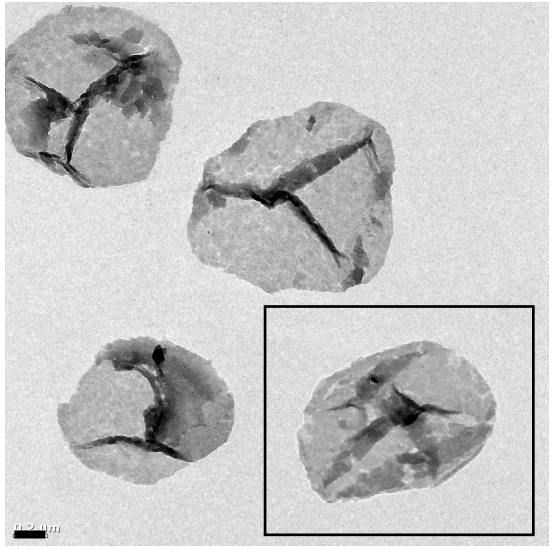
Enzyme-Powered Nanomotor for Bladder Disease Therapy

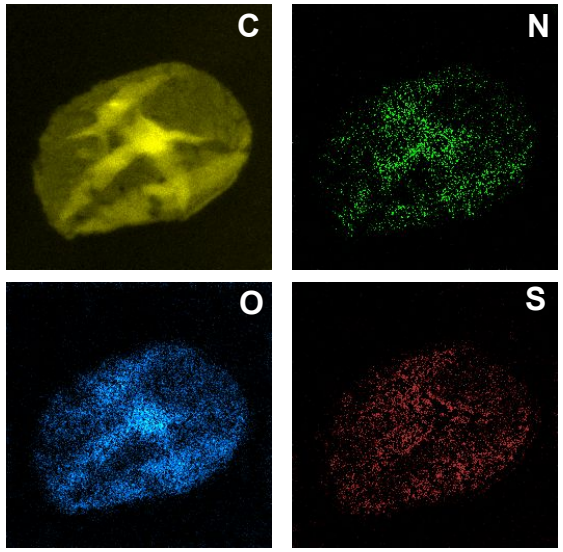
❖ Characteristics of urease-powered nanomotor



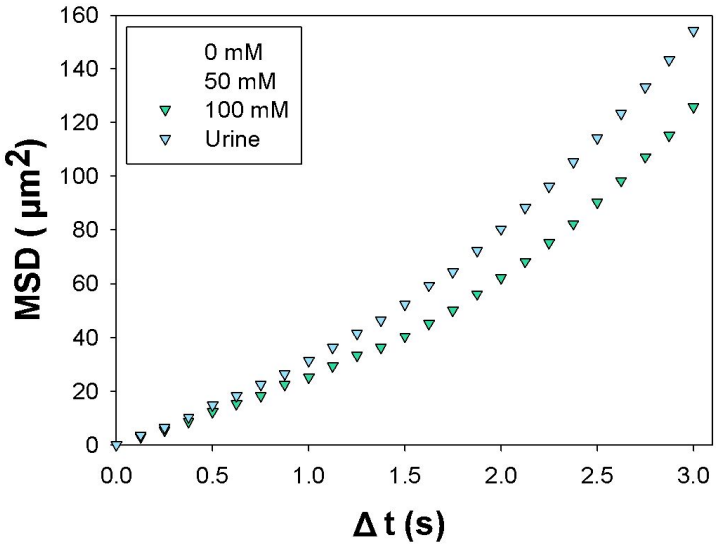








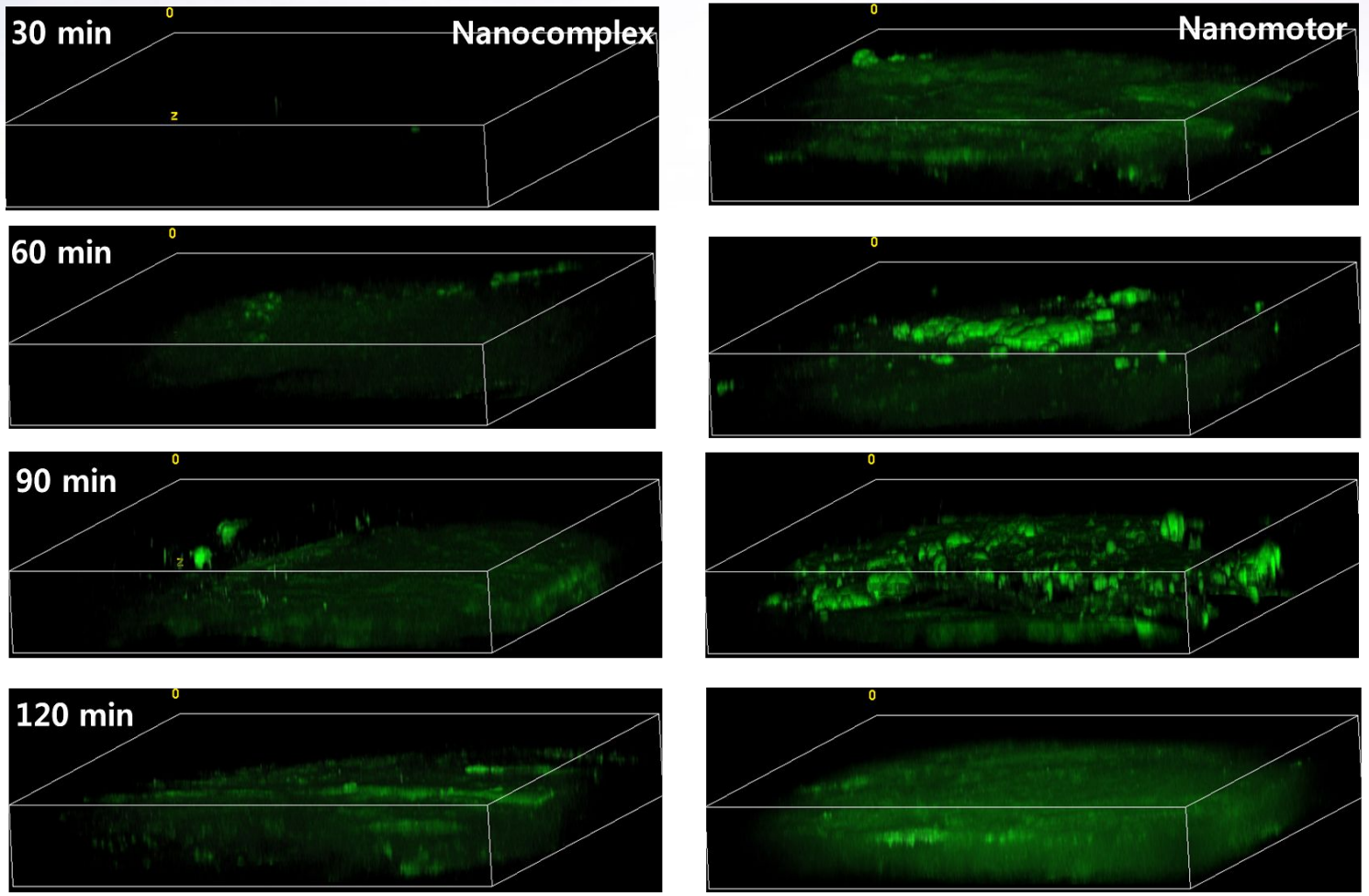
Scale bar : 200 nm

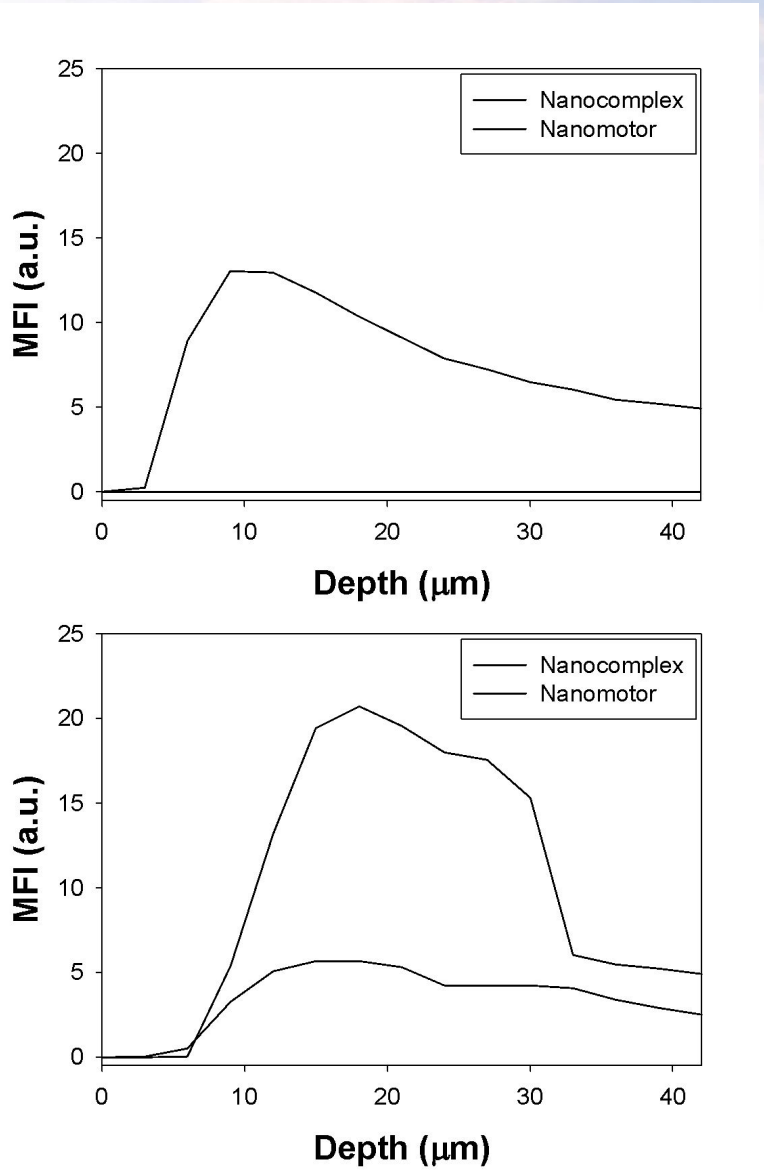


Hahn et al. ACS Nano, 14, 6683-6692 (2020)

Enzyme-Powered Nanomotor for Bladder Disease Therapy

❖ *Ex vivo* bladder penetration



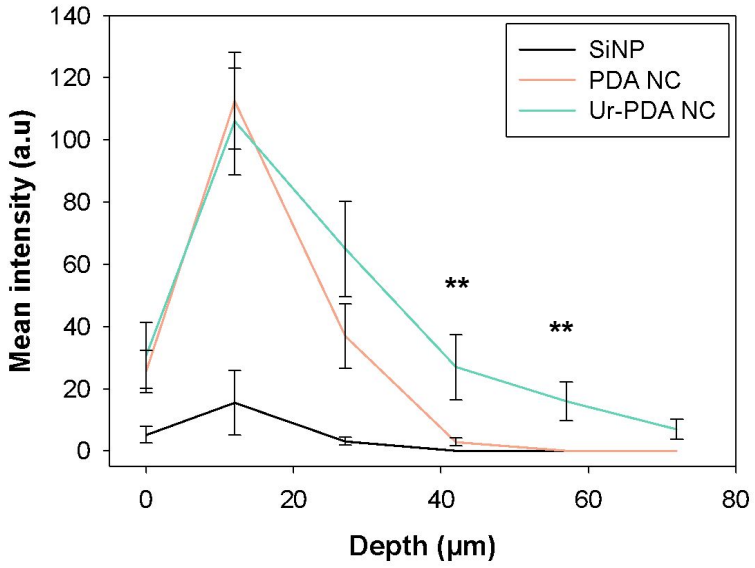


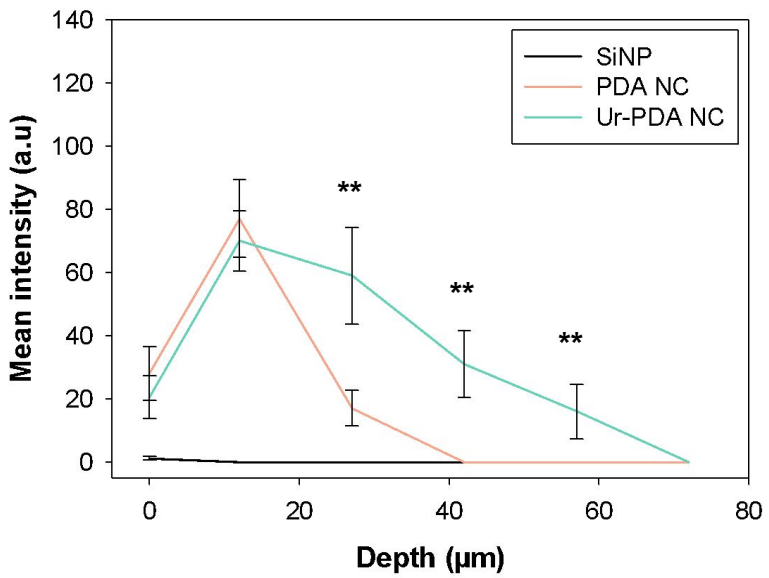
Hahn et al. ACS Nano, 14, 6683-6692 (2020)

Enzyme-Powered Nanomotor for Bladder Disease Therapy

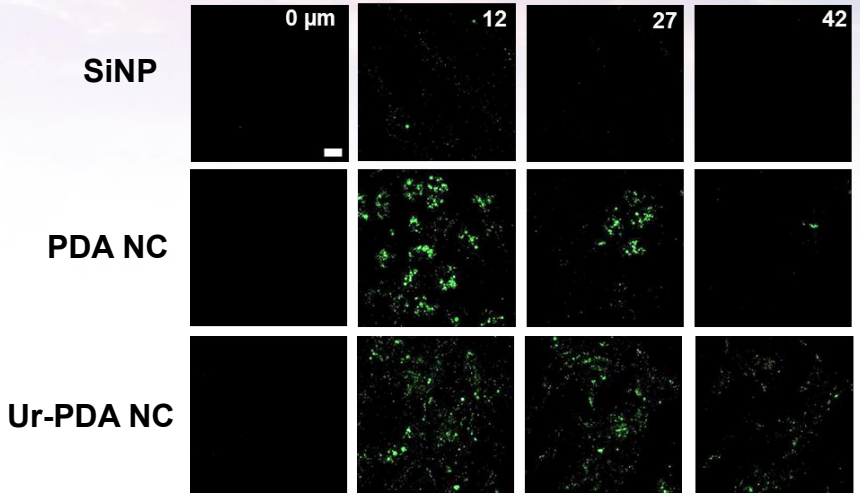
❖ Penetration and Retention of Nanomotor

- FITC-labelled Samples (SiNP, PDA NC and nanomotor)
- Two-photon images of bladder after intravesical injection

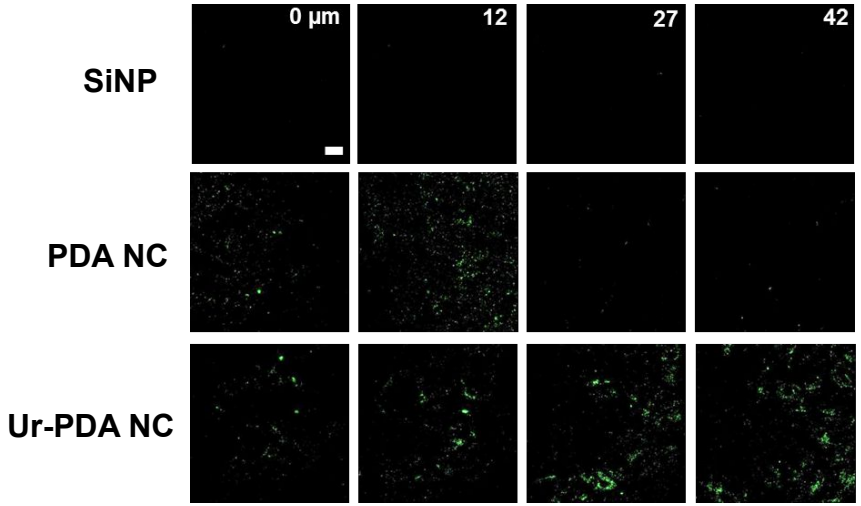




[Two-photon image by depth 1 h post-injection]



12 h post injection



Scale bar : 300 μm

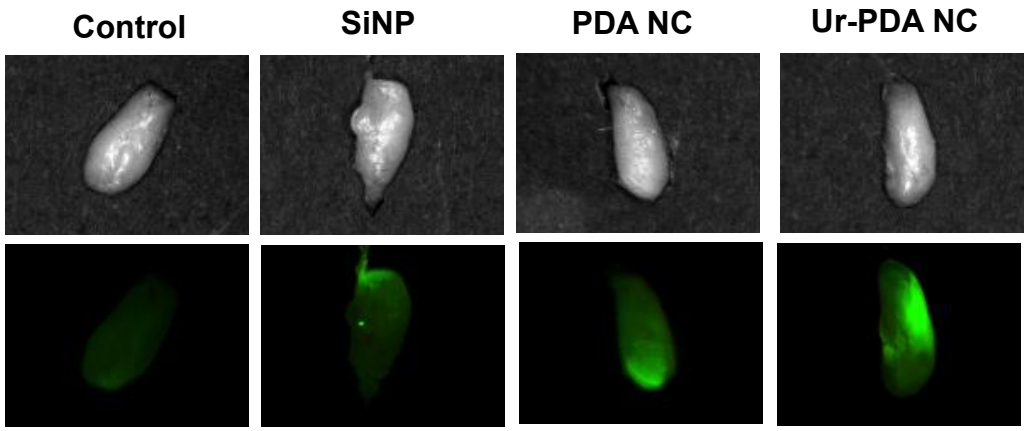
Hahn et al. ACS Nano, 14, 6683-6692 (2020)

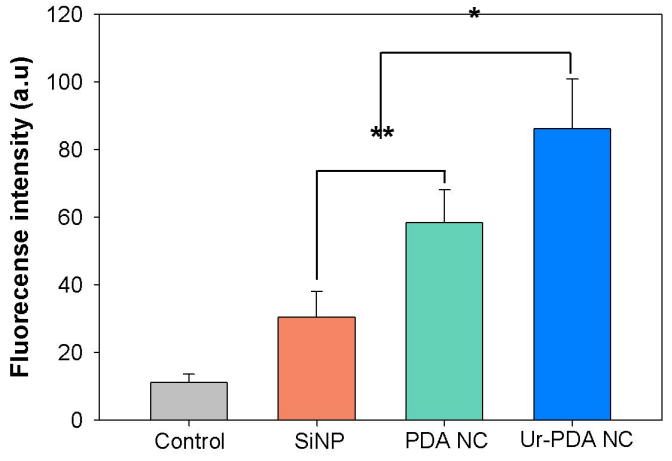
Enzyme-Powered Nanomotor for Bladder Disease Therapy

❖ Retention of nanomotors

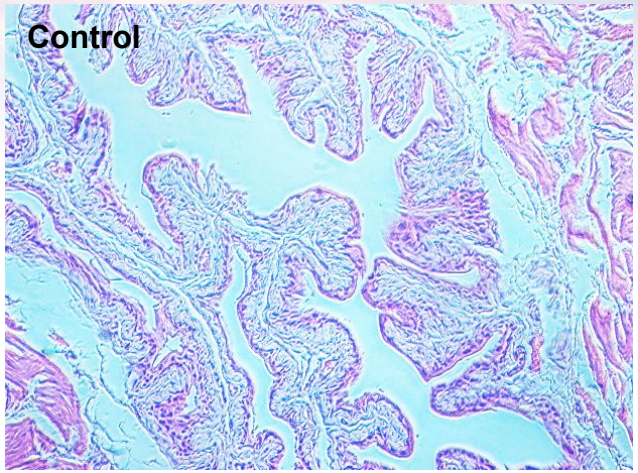
- No difference between control and nanomotors injection group
- No necrosis of bladder after 12 h-post injection of nanomotors

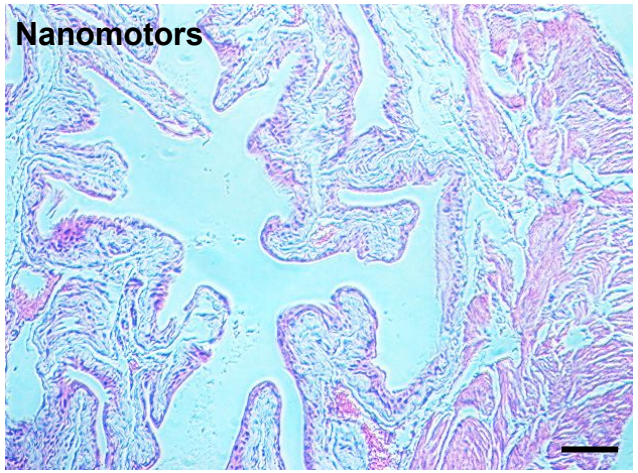
[*Ex vivo* bioimaging]





[Histology]





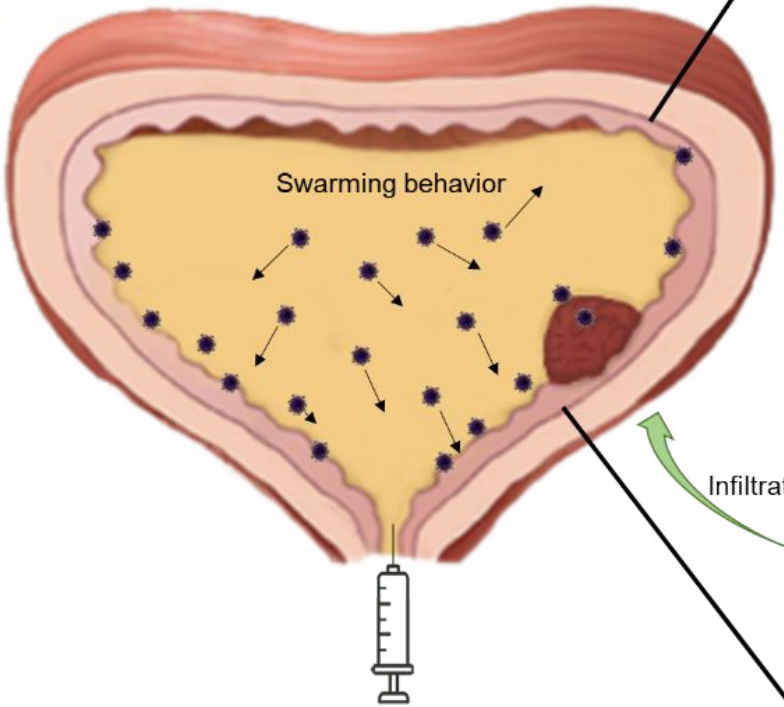
(Scale bar : 100 μm)

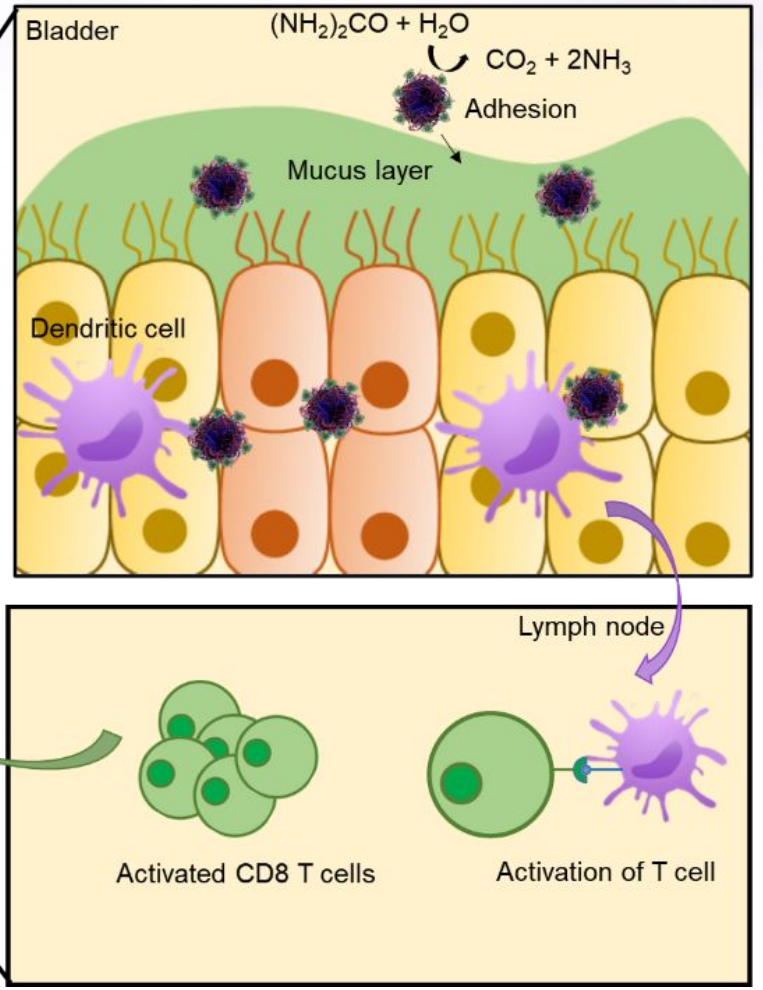
Hahn et al. ACS Nano, 14, 6683-6692 (2020)

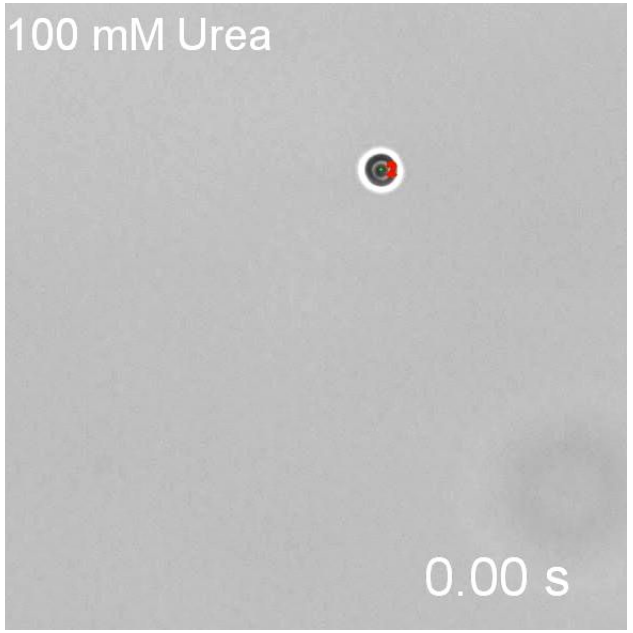
Urease-Powered Nanomotor for Bladder Cancer Therapy

❖ Schematic illustration for the mechanism of bladder cancer treatment

1. Fast and efficient adhesion to the bladder
2. Penetration through the mucus layer





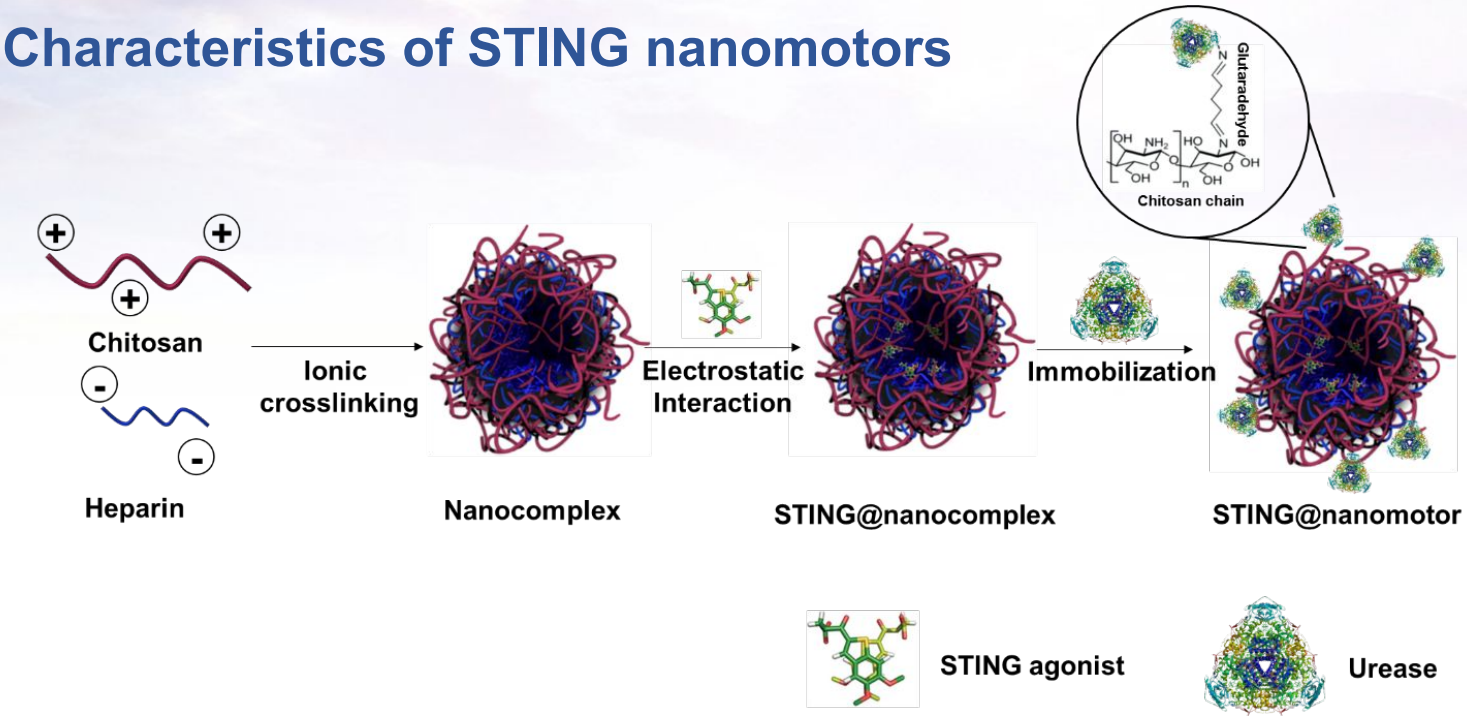


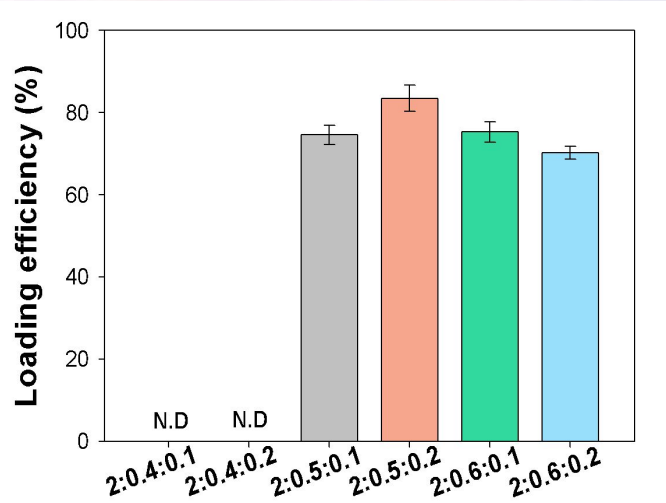
- Chitosan-heparin nanocomplex
- STING agonist encapsulation
- Urease immobilization with GA

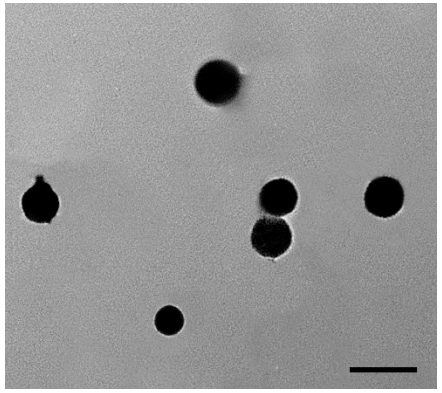
Hahn et al. Nature Communications, In Revision (2024)

Synthesis of STING Nanomotors

❖ Characteristics of STING nanomotors







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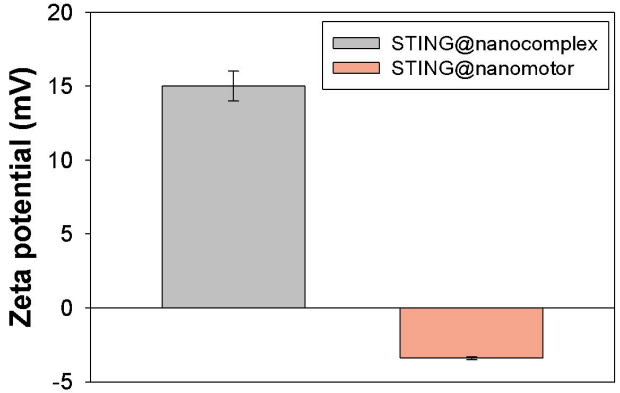
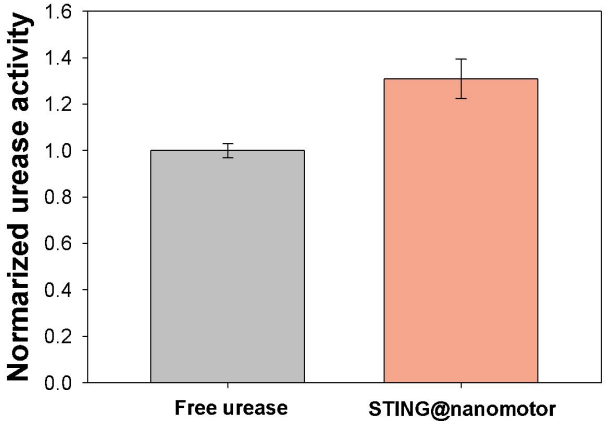
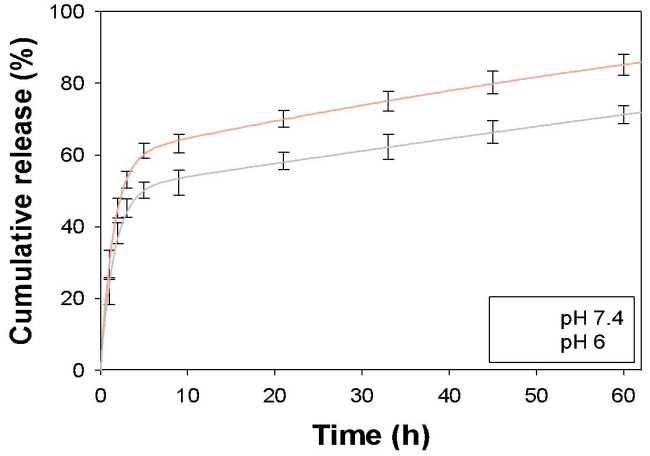


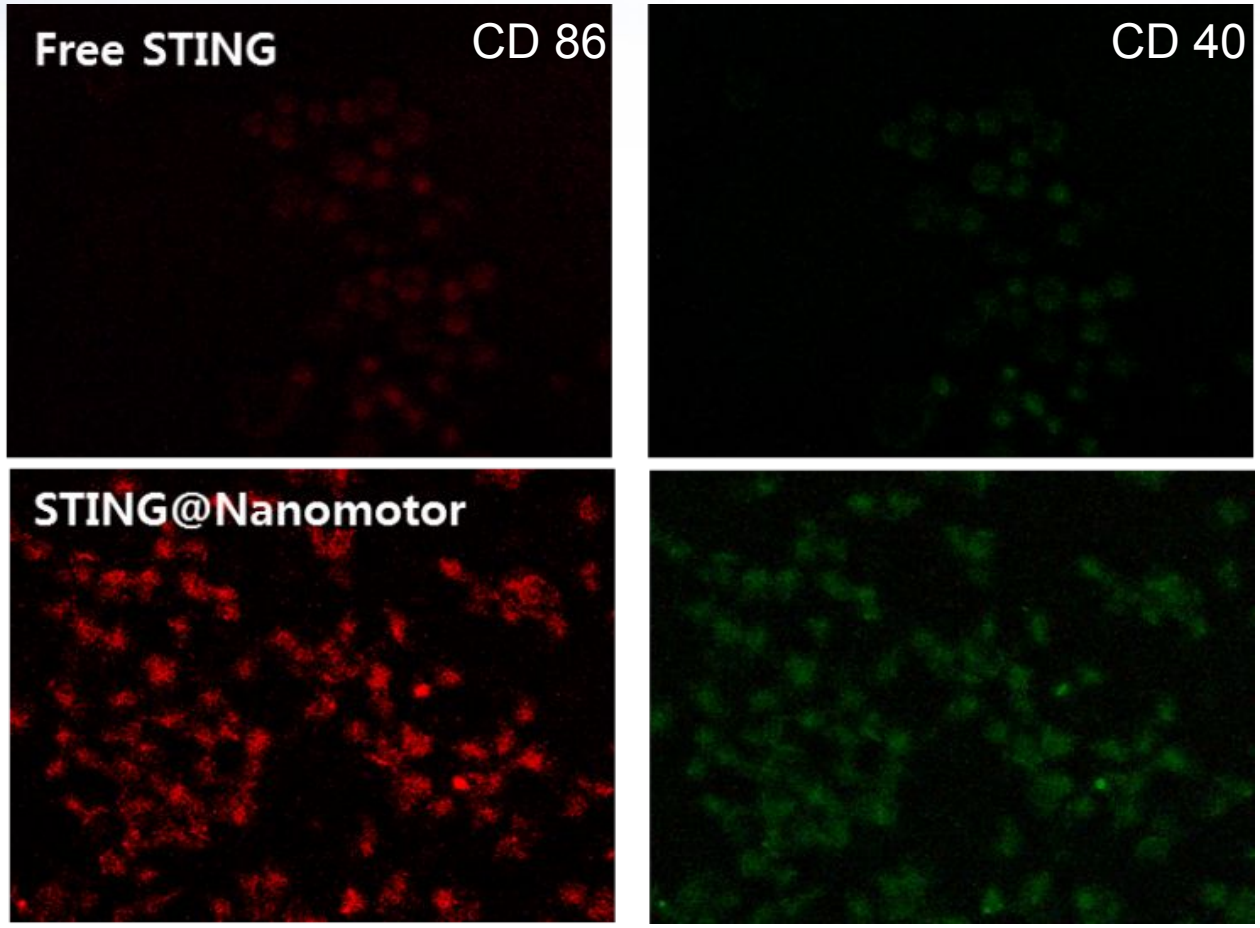


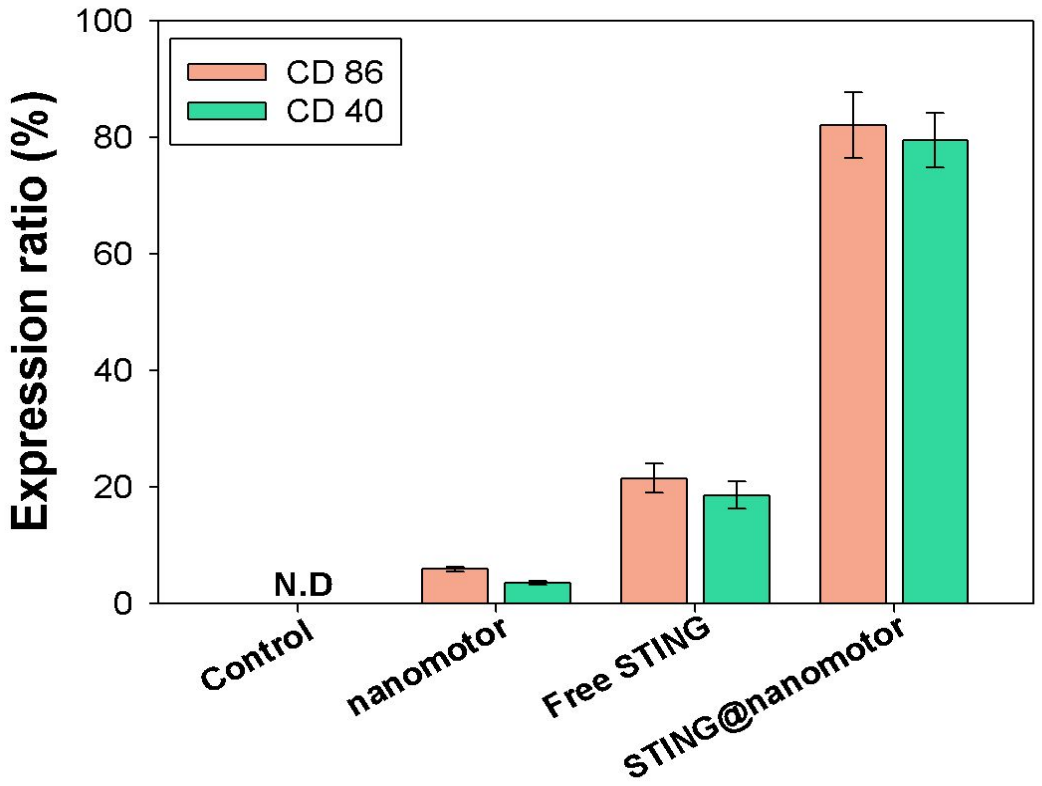


In Vitro Cell Activation Test

❖ Immunostaining of proteins on the dendritic cell

- **Enhanced expression ratio of CD 86 and CD 40 in STING@nanomotor.**



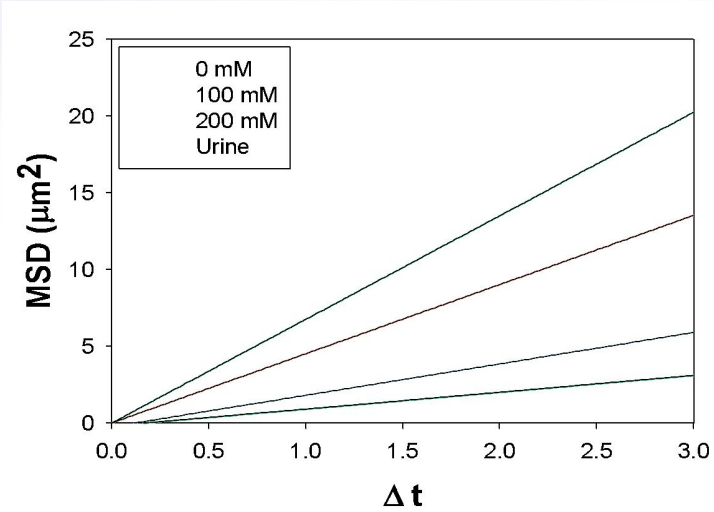


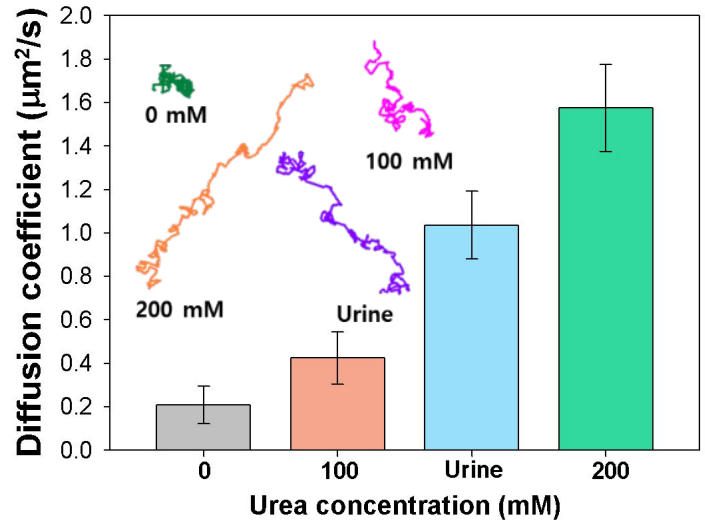
Hahn et al. Nature Communications, In Revision (2024)

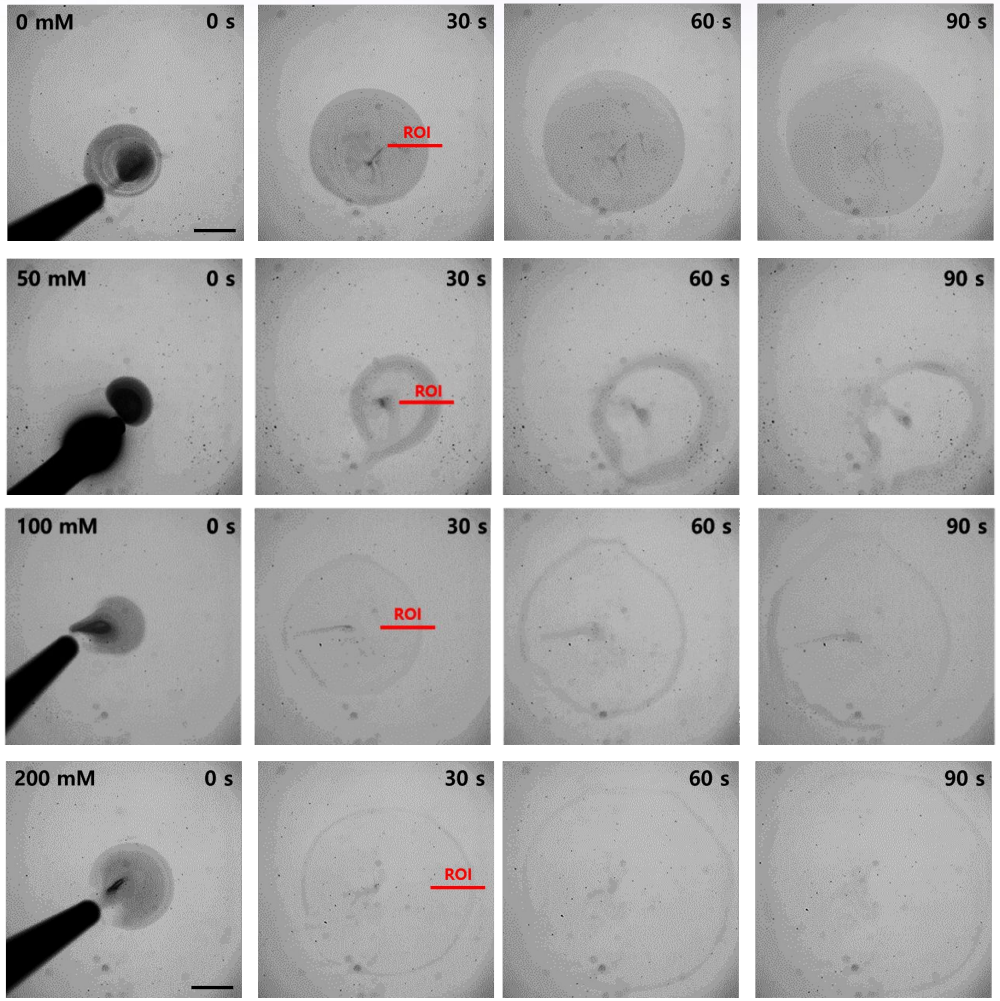
Motion Analysis

❖ Motion analysis of nanomotor depending on urea

- **Enhanced individual and collective motion of STING@nanomotor in the presence of urea**



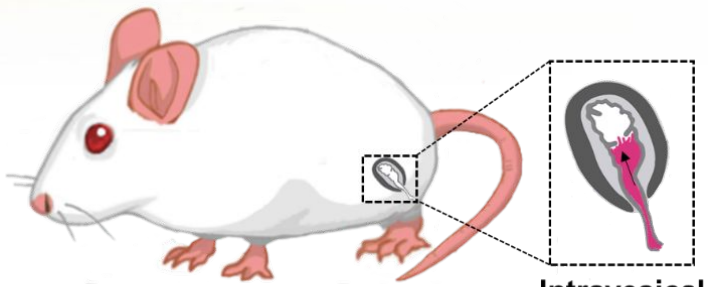




Retention Test in Bladder

❖ *In vivo* retention test depending on self-propulsion effect

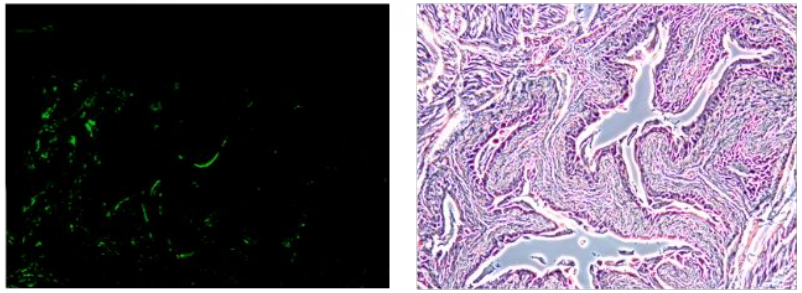
- **Prolonged retention of nanomotor in bladder after several urination**



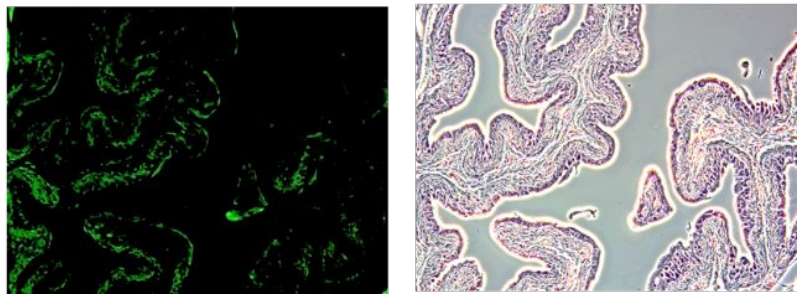
Intravesical injection

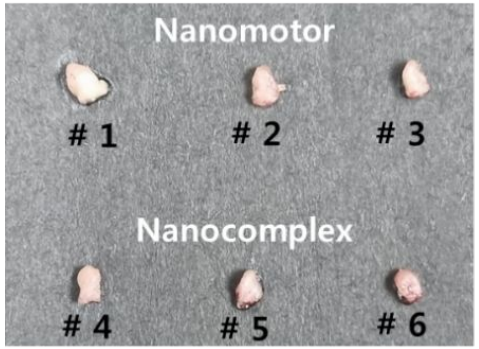
Sectioned bladder
Whole bladder
(IVIS imaging)

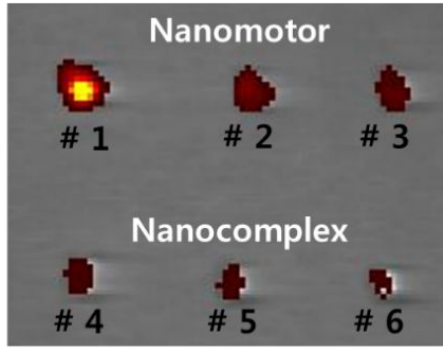
Nanocomplex

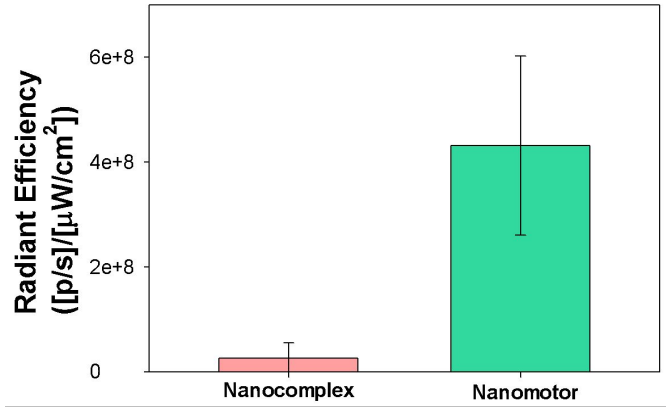


Nanomotor







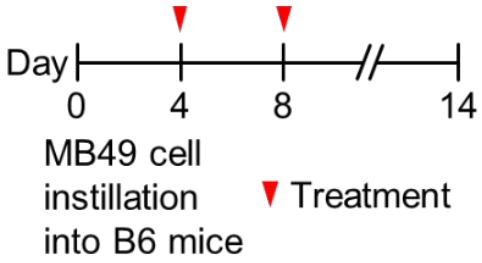


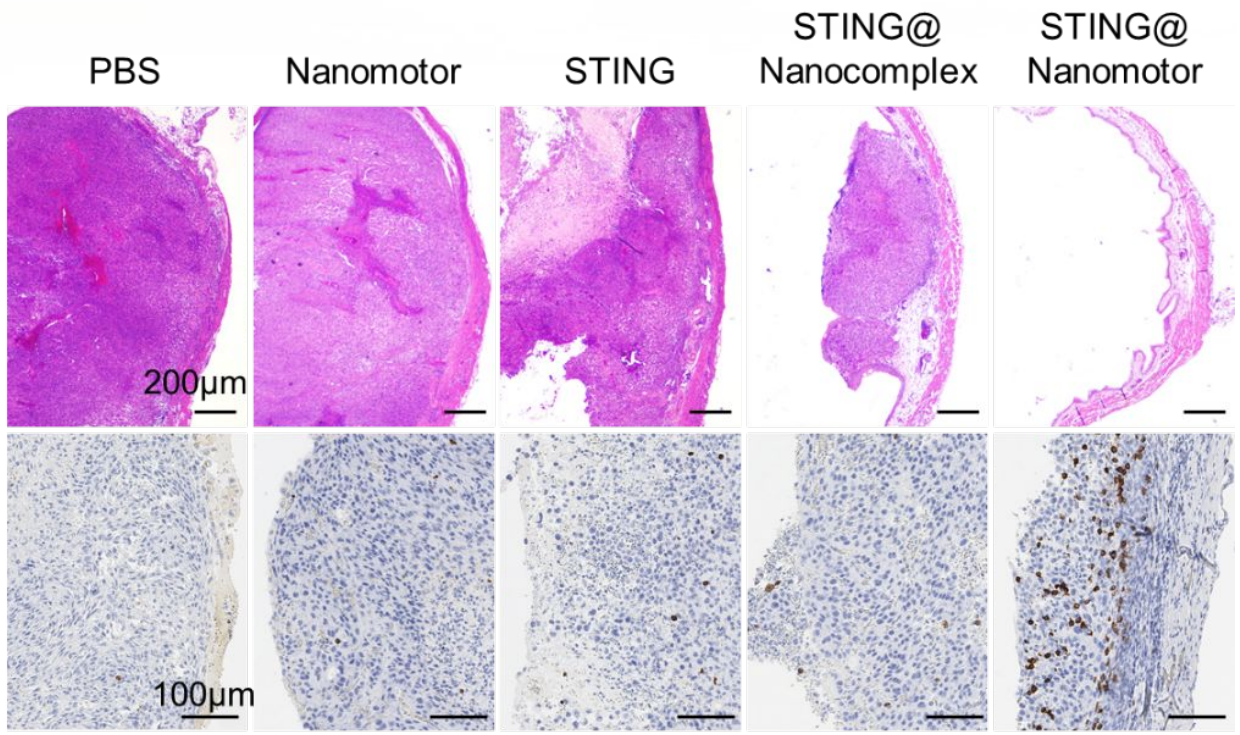
Hahn et al. Nature Communications, In Revision (2024)

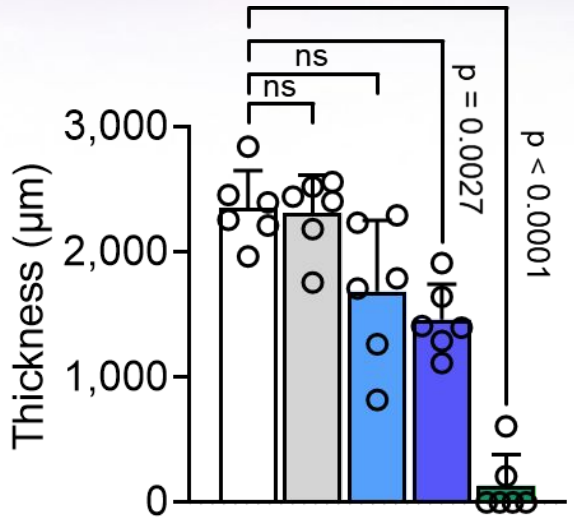
In Vivo Antitumor Effect of Nanomotors

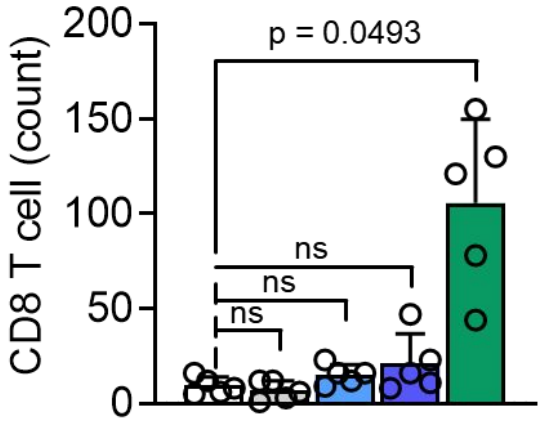
❖ Orthotopic bladder cancer treatment

- Significant anti tumor effect of STING@nanomotor (94.2% of inhibition after 14 d)
- Recruitment of activated T cells (11.2-fold compared with PBS)









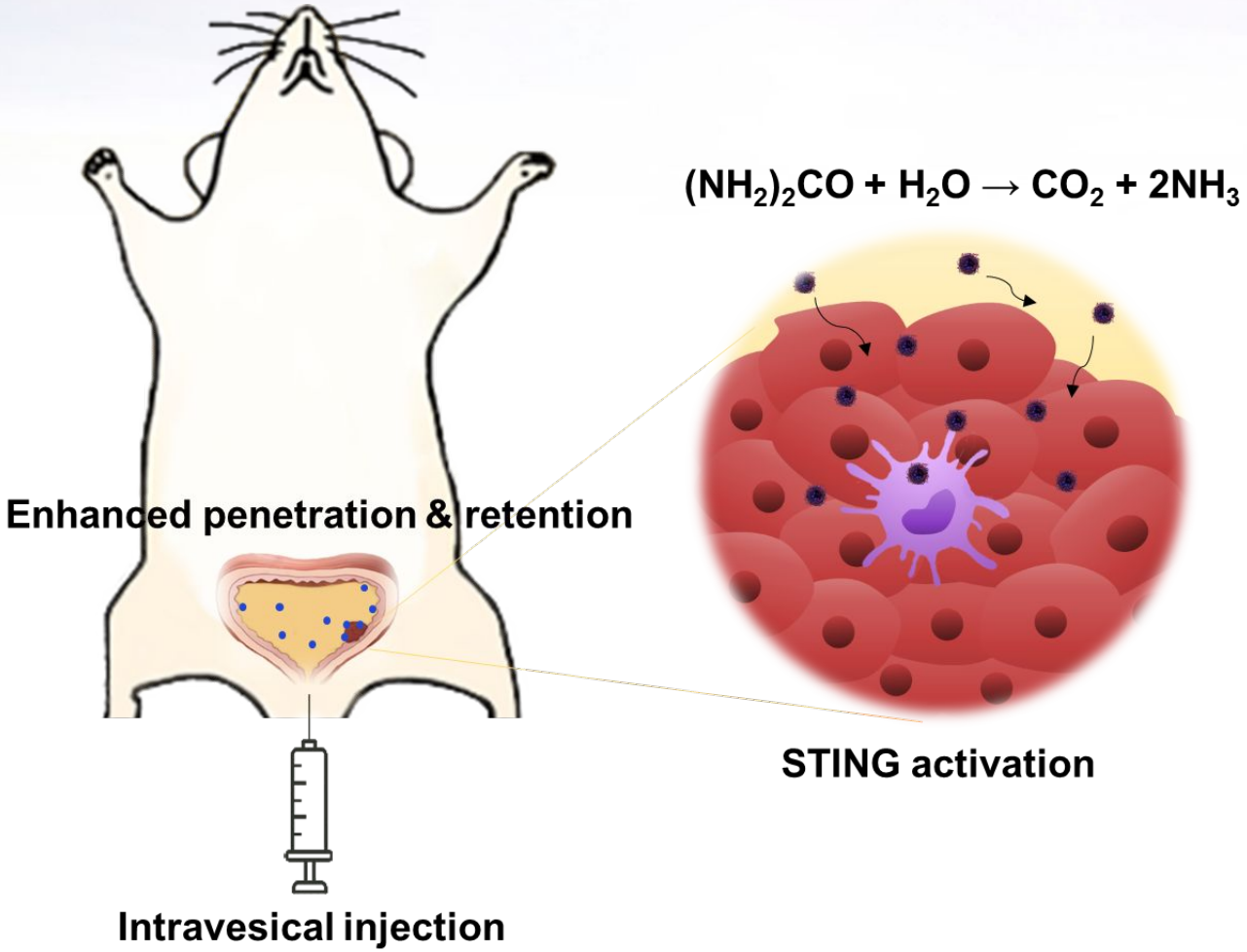
Hahn et al. Nature Communications, In Revision (2024)

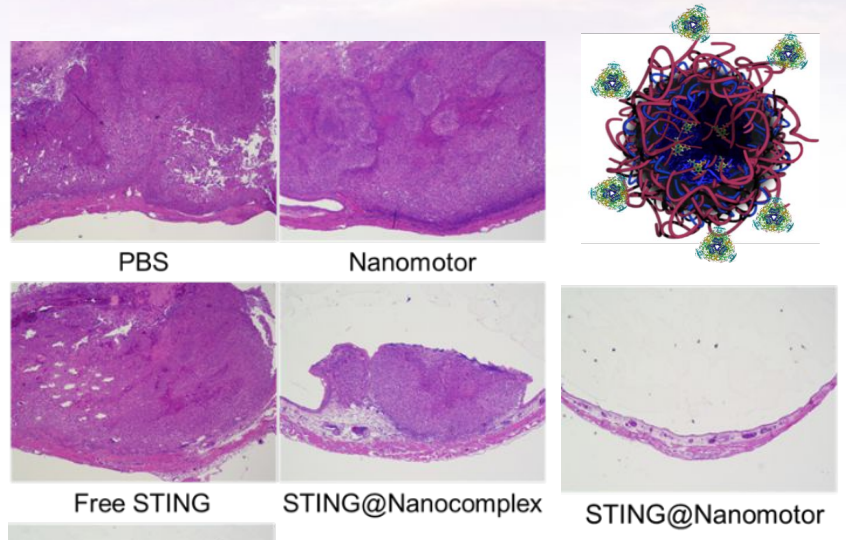
III. Summary and Future Works

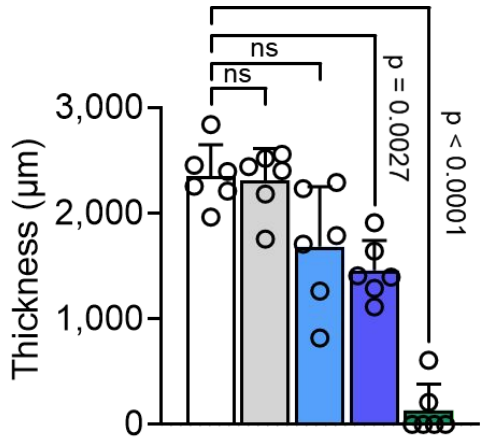
- For Further Applications of Smart Micro/Nanomotors

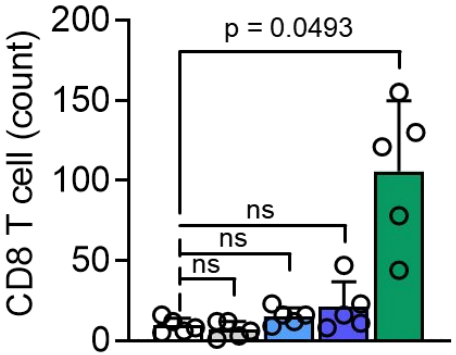
Summary

❖ Successful orthotopic bladder cancer immunotherapy



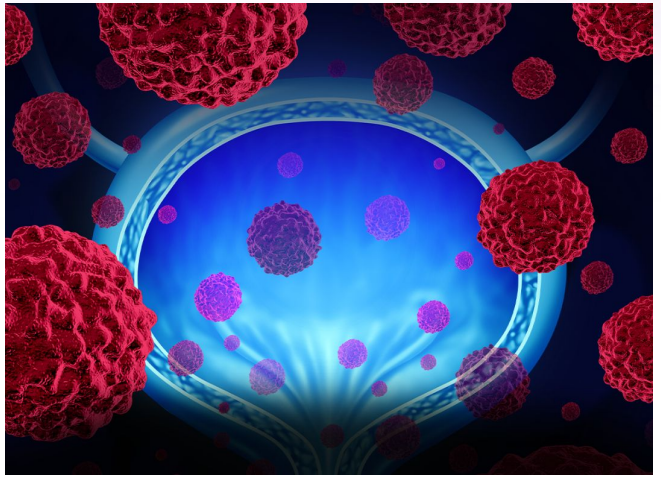






Future Works

❖ Collaboration for clinical bladder cancer immunotherapy



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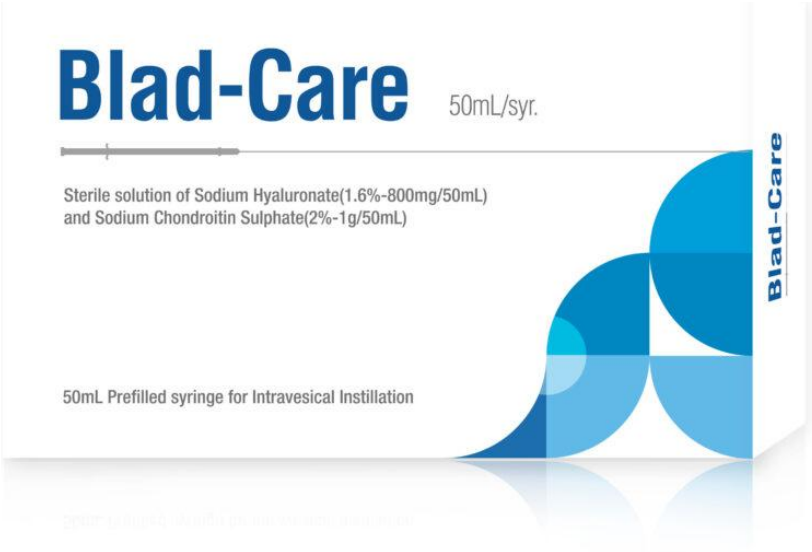

Acknowledgement

❖ Financial support

- NRF, MHW, MSMV, MSMEs&S, World Class 300, TIPS, Interojo, LG Innotek,

❖ Collaboration

- POSTECH: Prof. YC Sung, KM Kim, UY Jung, SJ Jung, JY Sim
- Stanford University: Prof. Zhenan Bao, David Myung
- Harvard Medical School, MGH: Prof. Andy Yun, Mei Wu
- Univ. of Washington: Prof. AS Hoffman, PS Stayton, DH Kim
- Karolinska Institute: Prof. Berggren
- Allergan Co. (Dr. Chee-yub Won)
- Roche group (Dr. Christian Reiser)

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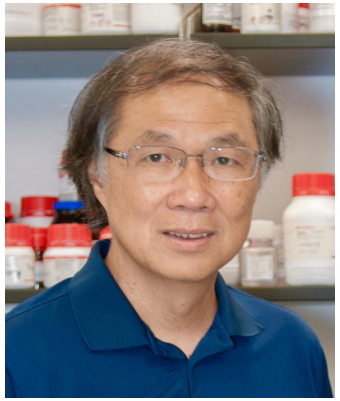


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Thank You for Your Kind Attention !!!

Seok Cheon Endowed Chair Prof. Sei Kwang Hahn

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