Toolbox of self-propelled nanomotors for bladder cancer therapy

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CRS 2025 ANNUAL MEETING & EXPOSITION
PHILADELPHIA, PA
JULY 13-18, 2025

NEXT-GENERATION DELIVERY INNOVATIONS

THE PROBLEM USING

NANOPARTICLES

0.7%

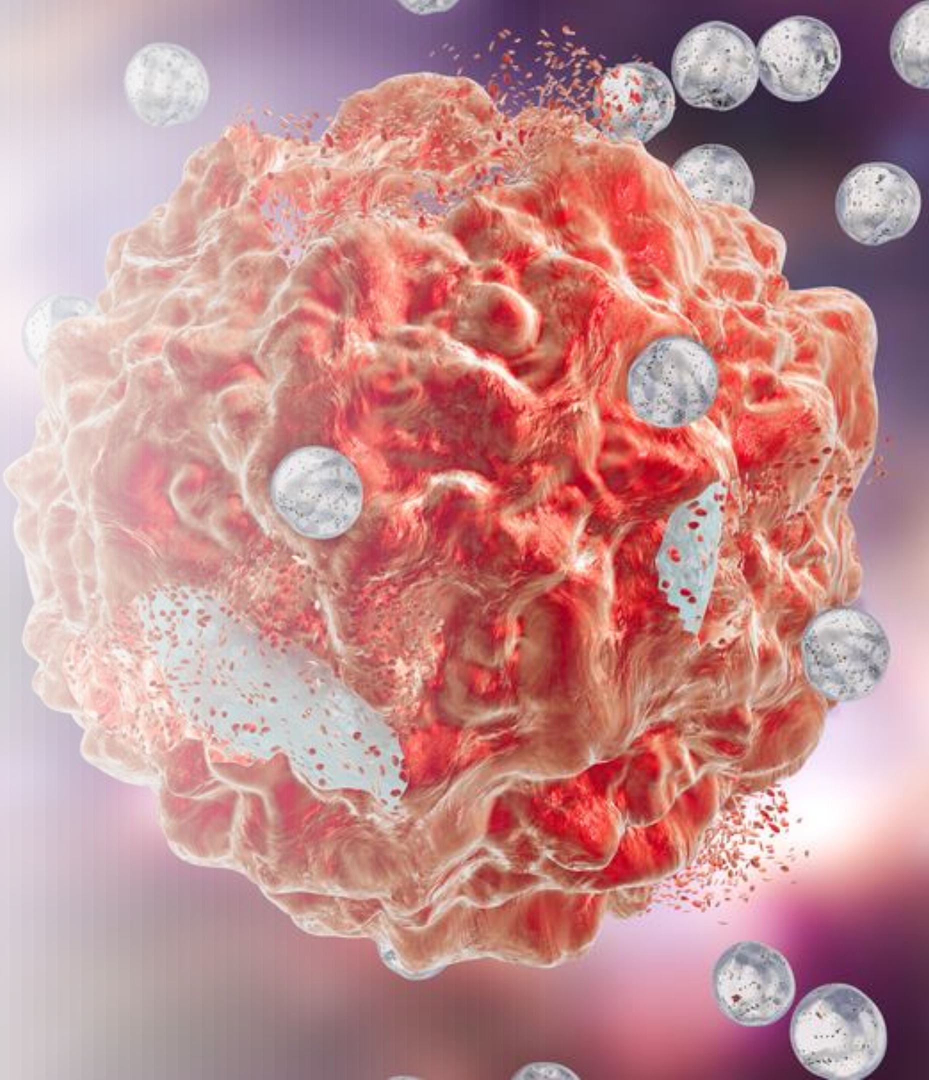
REACH TUMOR TARGET

Wilhem et al., *Nat Rev Mat*. **2016**

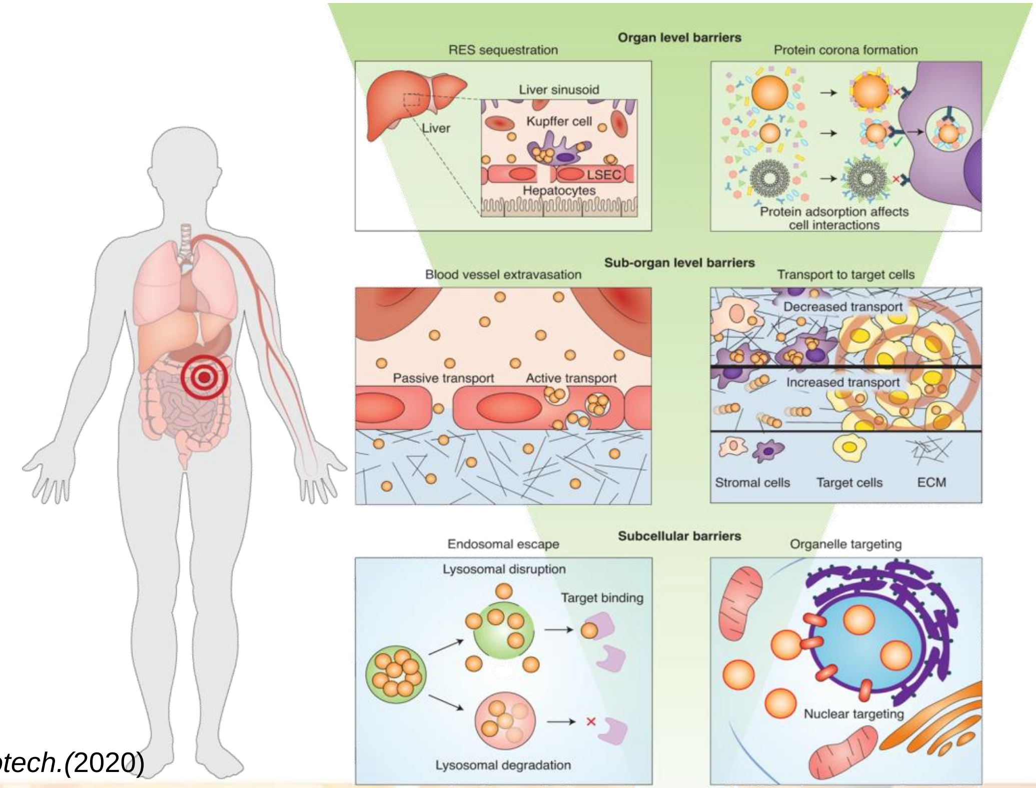
Nanoparticle Delivery Efficiency

100%	0.7%	0.0014%
I.V. Injection →	Tumor →	Cancer Cells

Dai et al. *ACS Nano* 2018, 12, 8423−8435



Why don’t they reach? Biological Barriers



W. Poon, et al. *Nature Nanotech.*(2020)

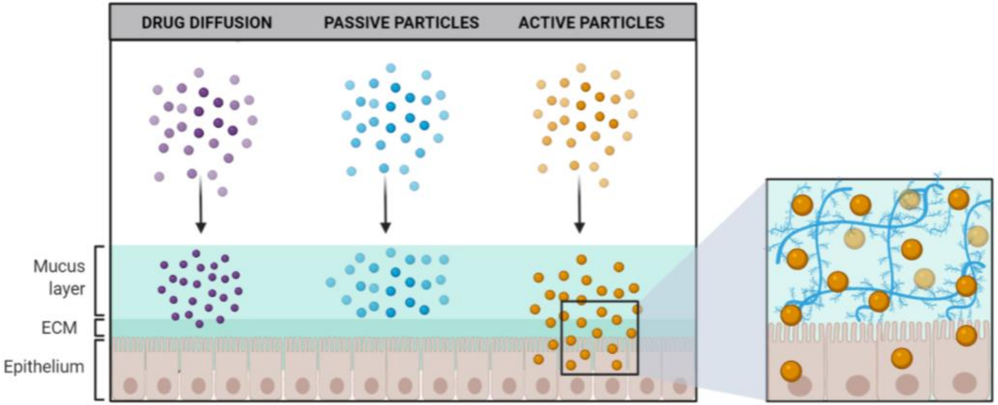
Patino et al. *Nanoscale* 2024
Dolci et al. *ACS Nano* 2023

Fraire et al. *ACS Nano* 2023
Ruiz-González et al. *Small* 2024
Serra et al. *ACS Nano* 2024
Ruiz-González et al. *ACS AMI* 2025

Fraire et al. *In preparation* 2025
Esporrín et al. *Adv. Funct.Mat.* 2025

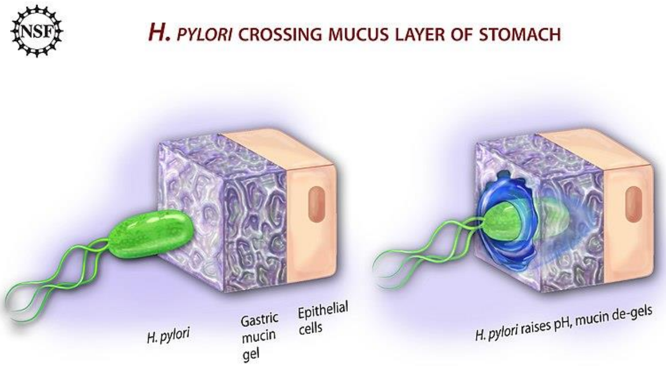
Crossing biological barriers: a challenge

Diffusion *vs* transport



Active self-propelled particles can interact with ECM and other BB liquifying them

Nature knows how to…



Wikipedia.org

Self-propelled nanomotors

Mimicking nature

G. Ariel *et al. Nature Commun*, 2015

Ma et al. *J.Am.Chem.Soc* 2016

1. Chemical Self-propelled Nanobots:

getting motion at the nanoscale

2. Collective behaviour of Nanobots

3D motion

3. Biomedical applications

The case of bladder cancer

1. Chemical Self-propelled Nanobots:
getting motion at the nanoscale

2. Collective behaviour of Nanobots
3D Motion

3. Biomedical applications
The case of bladder cancer

Nano-Microscale

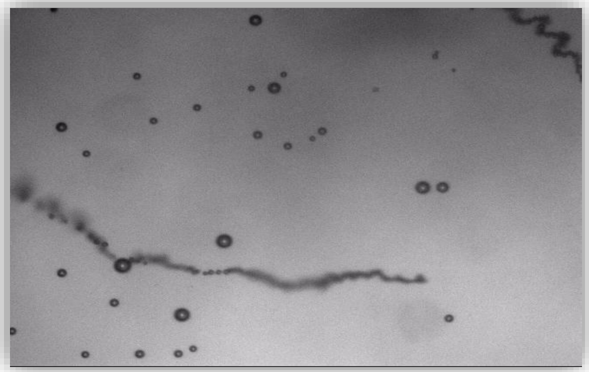
#1 Enzyme-powered Nanobots

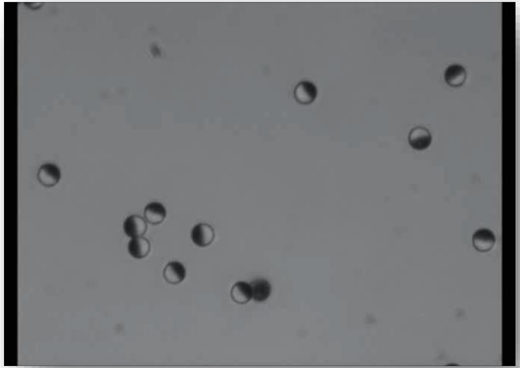
- From fundamental to biomedical applications
- From individual to collective motion
- Multiple enzymes and types of particles

NIMS IFW MAX PLANCK INSTITUTE FOR INTELLIGENT SYSTEMS IBEC Institute for Bioengineering of Catalonia

2010-2025

Origins: Catalytic Microswimers based on Pt-H_2O_2 reaction





Solovev et al. *ACS Nano* **2012**, 6, 1751
Solovev et al. *Angew.Chem.* **2011**, 50, 10875
Sanchez et al. *J.Am.Chem.Soc.* **2011**, 133, 14860
Sanchez et al. *J.Am.Chem.Soc.* **2011**, 133, 701
Sanchez et al. *Chem.Commun*. **2011**, 47, 698
Sanchez et al. *J.Am.Chem.Soc.* **2010**, 132, 13144
Solovev et al. *Adv. Funct. Mat.* **2010**, 20, 2430

Ma et al. *Small*, **2015**, 11, 5023
Choudhury et al. *Chem. Commun.* **2015,** 51, 8660
Ma et al. *J.Am.Chen.Soc.* **2015**, 137, 4976
Ma et al. *Chem. Commun*. **2015,** 51, 5467
Baraban et al. Angew. Chem.Int. Edit. **2013**, 52, 5552
Baraban et al. ACS Nano. **2012**, 6, 3383
Baraban et al. *Soft Matter,* **2012,** 8, 48

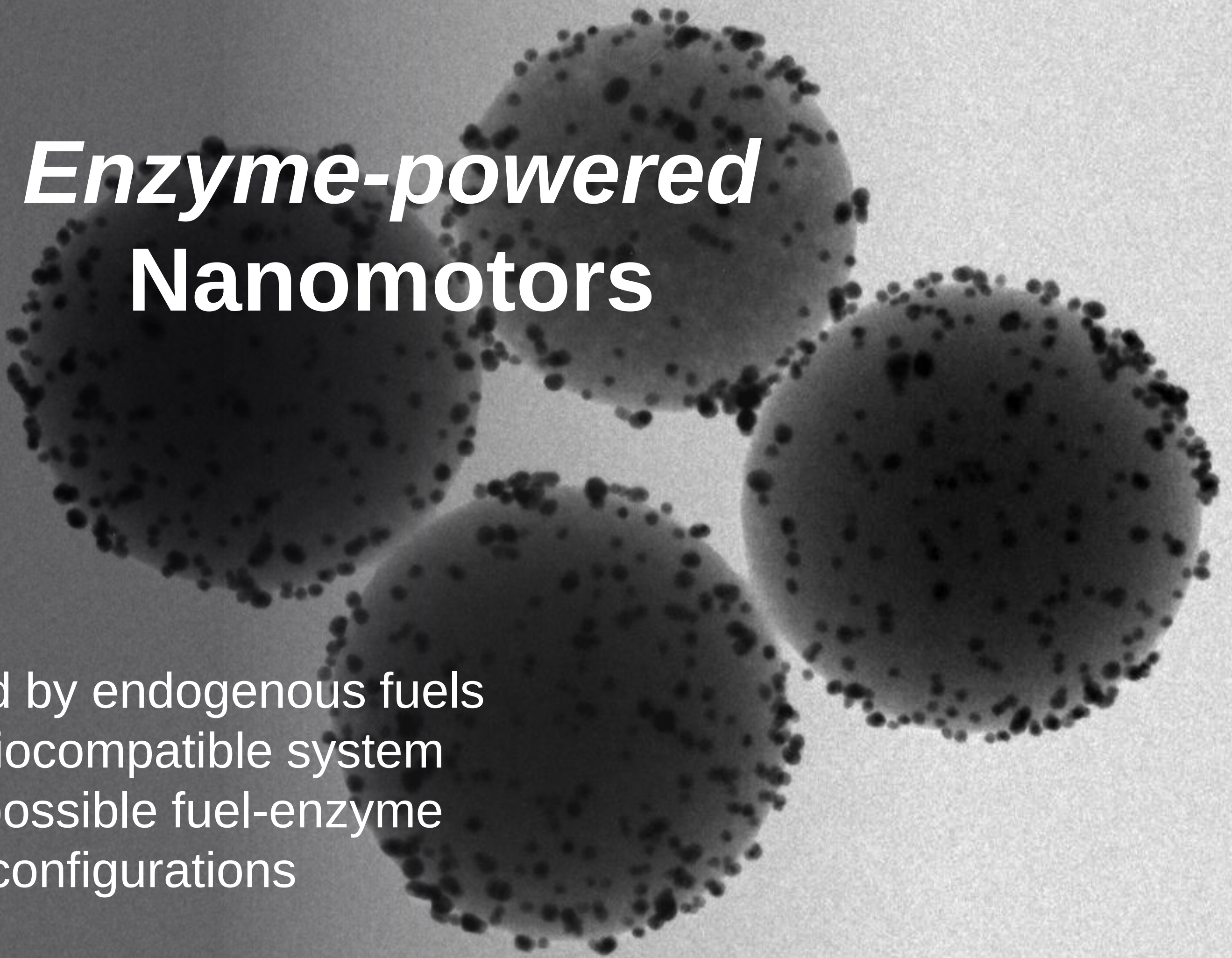
Drawbacks:

- Toxicity of peroxide fuel
- Metals in the motors
- Large size
- Expensive fabrication

Solution:

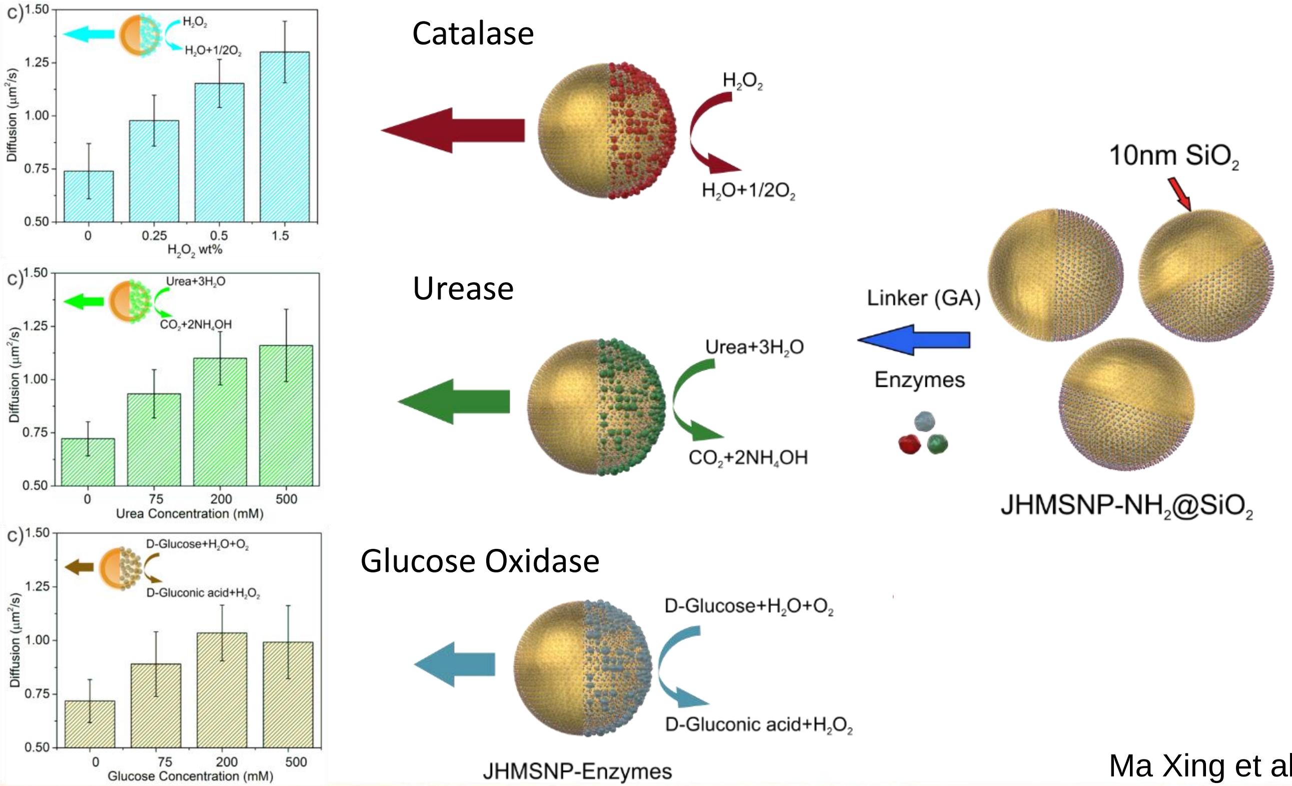
- Enzymes as biocatalysts
- Bioavailable fuels
- Biocompatible materials
- Simple/scalable synthesis

Enzyme-powered Nanomotors



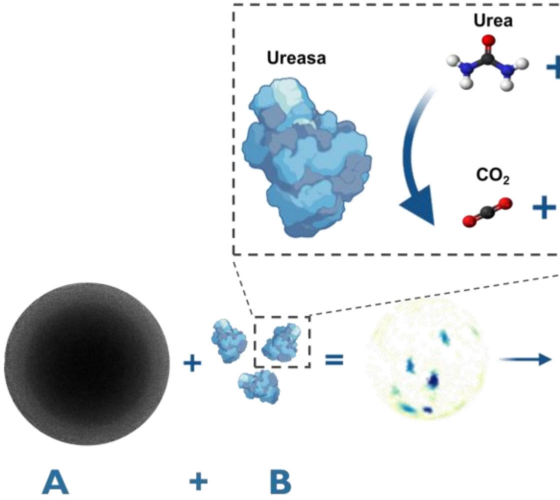
- Powered by endogenous fuels
- More biocompatible system
- Many possible fuel-enzyme configurations

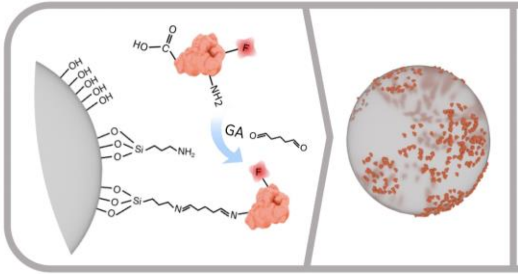
Enzyme-powered Spherical Nano-bots

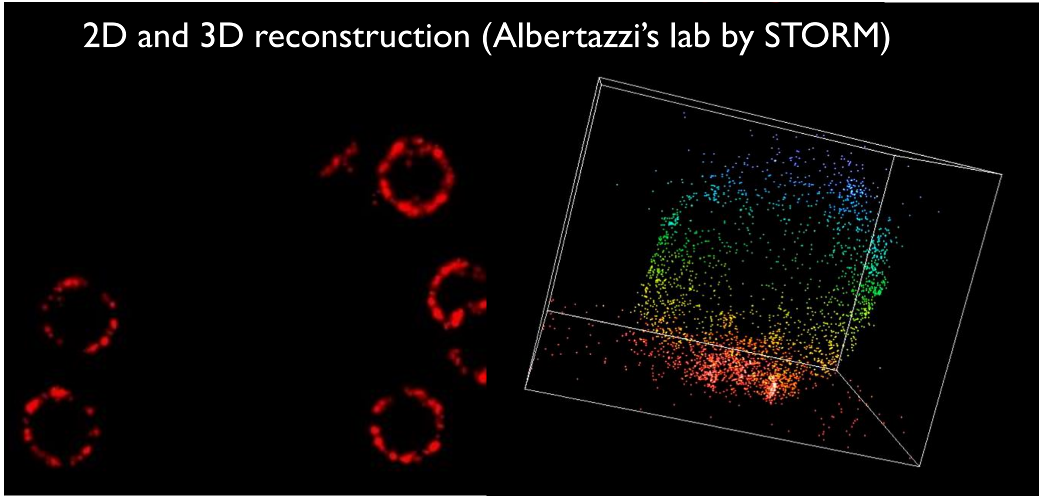


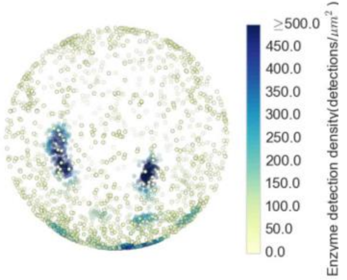
Ma Xing et al *Nano Lett.*, **2015**

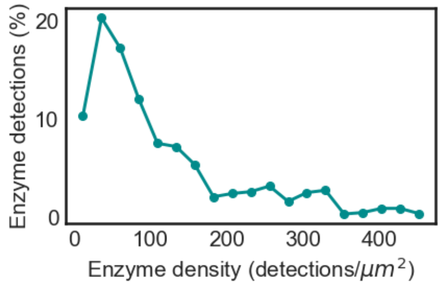
How to distribute enzymes on nanoparticles?







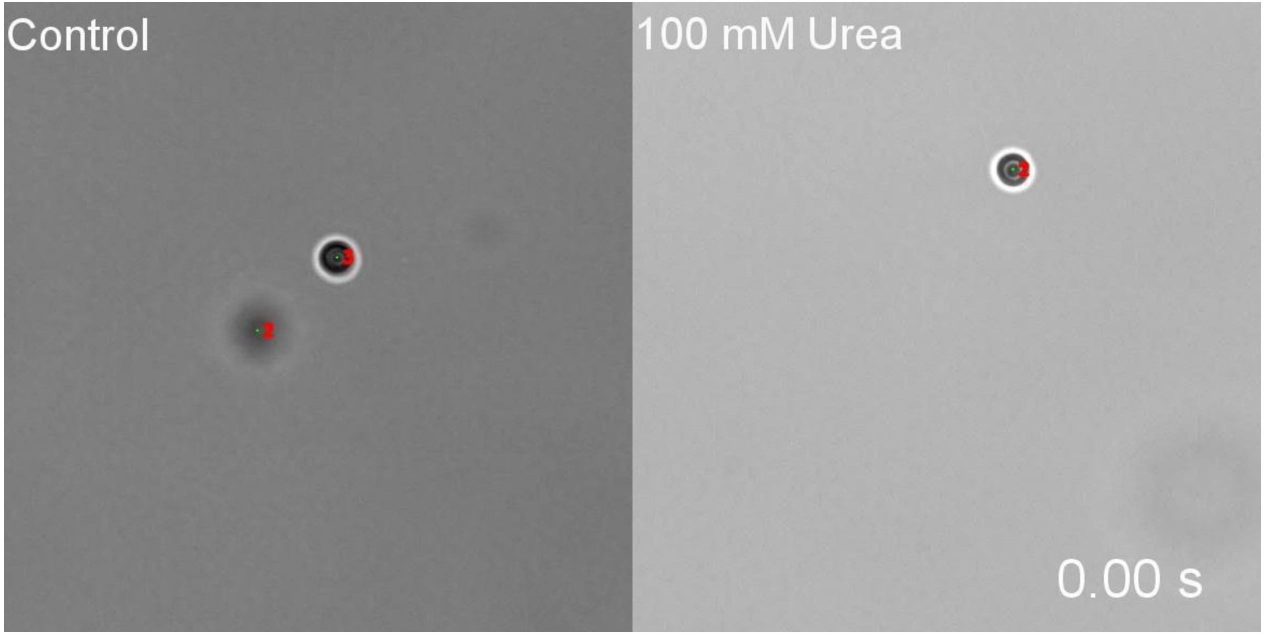




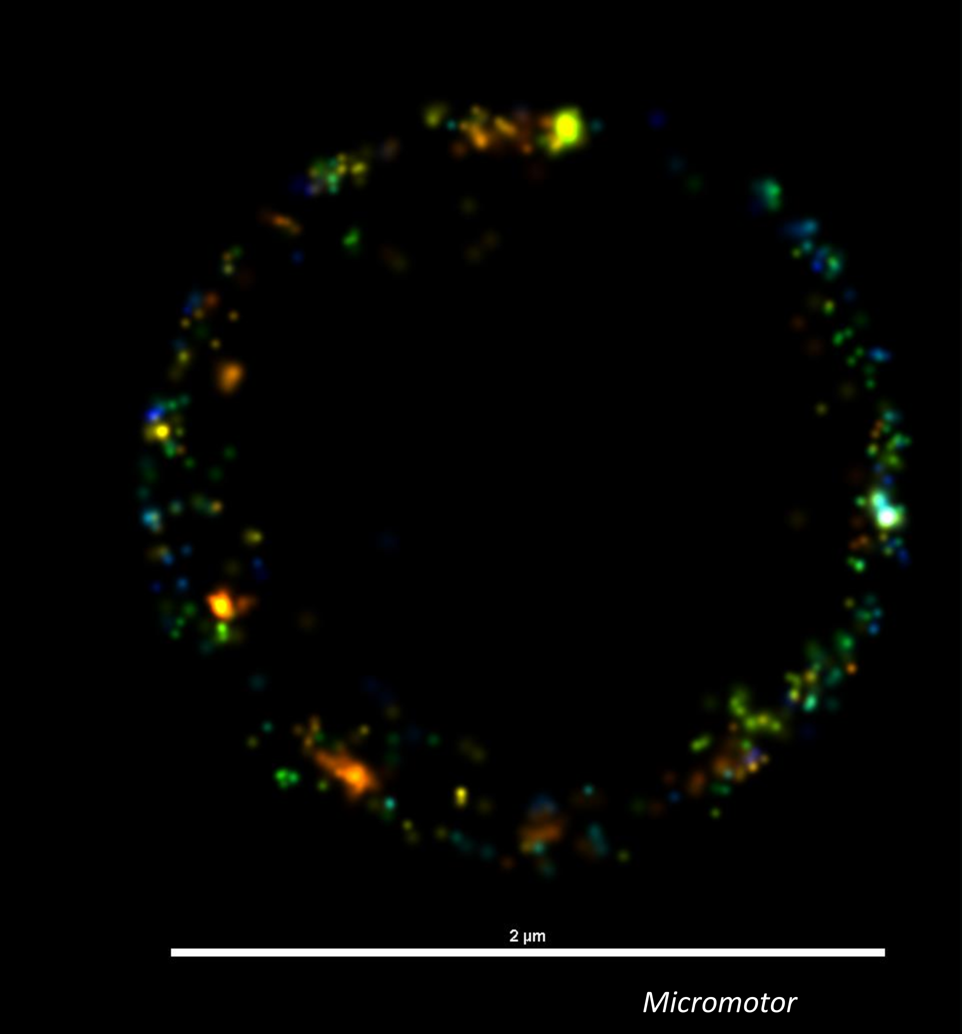
Patiño *et al*. *JACS* **2018**

Asymmetry is the key for motion

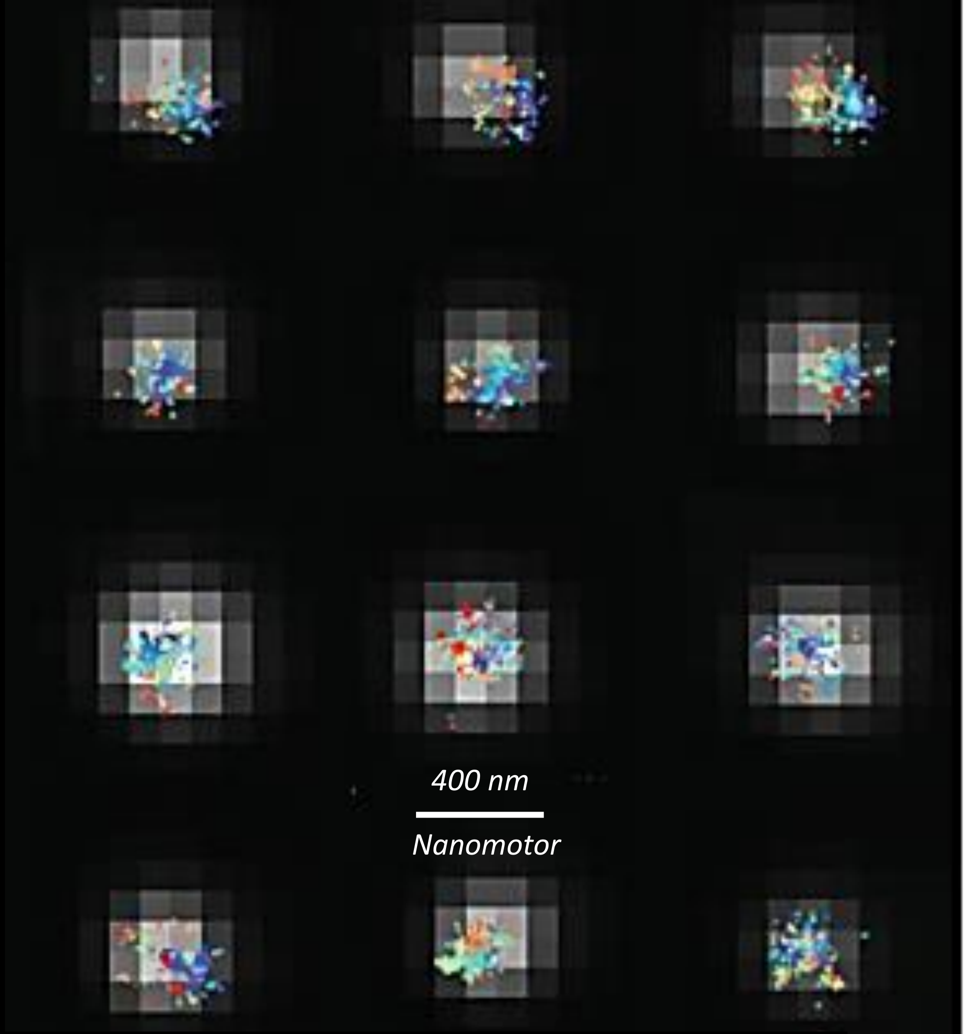
Generation of a chemical gradient around the particles



Patiño *et al*. *JACS* **2018** 140, 9317



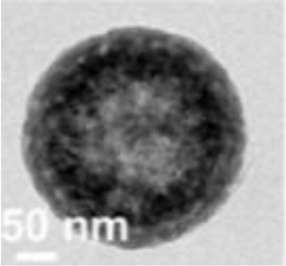
Quim Llàcer @IBEC w/Albertazzi @ICMS

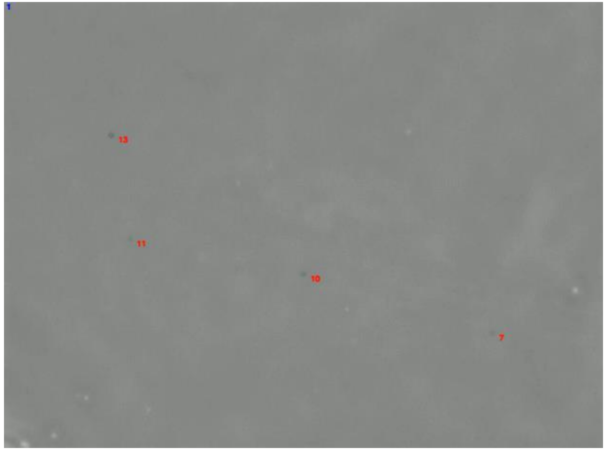


Patiño *et al.* In *JACS* 2018 and *Nanoscale* 2024

Particles + Urease= Biocompatible motors

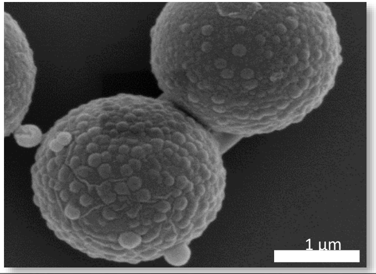
Nanoparticles

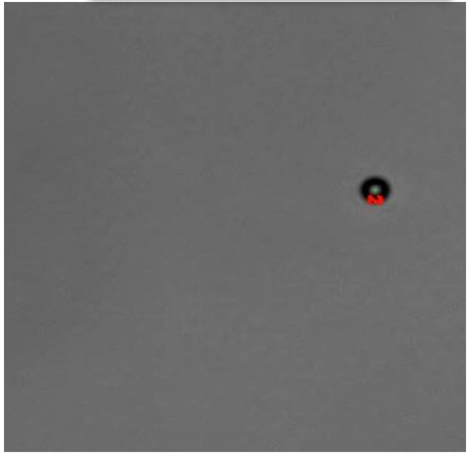




Ma Xing *Nano Lett.*, **2015**,15 7043

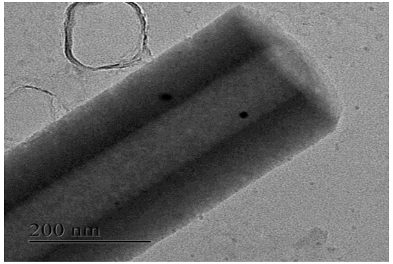
Microparticles





Patiño *JACS* **2018** 140, 9317

Nanotubes



X. Ma *JACS* **2016**, 138 (42), 13782

Multifunctional Nanobots: *Transport, sense, act and target*

FULL PAPER
Drug Delivery

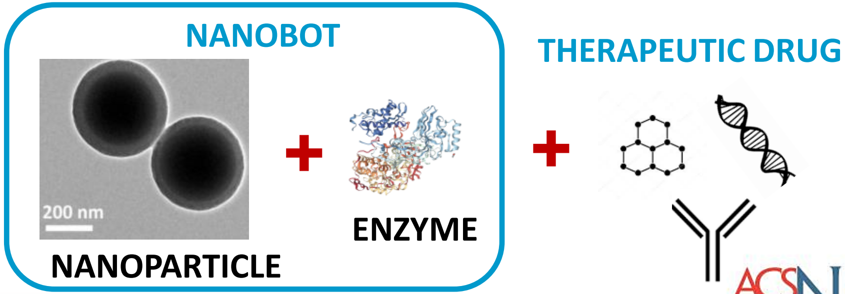
Enzyme-Powered Nanobots Enhance Anticancer Drug Delivery

Ana C. Hortelão, Tania Patiño, Ariadna Perez-Jiménez, Àngel Blanco, and Samuel Sánchez**

NANO LETTERS Letter
Cite This: *Nano Lett.* 2019, 19, 3440–3447 pubs.acs.org/NanoLett

Self-Sensing Enzyme-Powered Micromotors Equipped with pH-Responsive DNA Nanoswitches

Tania Patino,[§,&] Alessandro Porchetta,[∥,&] Anita Jannasch,[#] Anna Lladó,[‡] Tom Stumpp,[#] Erik Schäffer,[#] Francesco Ricci,[*,∥] and Samuel Sánchez[*,§,†]



IP : WO 2020/115124

ACS NANO
Cite This: *ACS Nano* 2019, 13, 12171–12183 www.acsnano.org

Enzyme-Powered Gated Mesoporous Silica Nanomotors for On-Command Intracellular Payload Delivery

Antoni Llopis-Lorente,[†,‡,§] Alba García-Fernández,[†,‡,§] Nerea Murillo-Cremaes,[∥] Ana C. Hortelão,[∥] Tania Patiño,[∥,∇] Reynaldo Villalonga,[⊥] Félix Sancenón,[†,‡,§] Ramón Martínez-Máñez,[*,†,‡,§] and Samuel Sánchez[*,∥,#]

ACS NANO
Cite This: *ACS Nano* 2019, 13, 429–439 www.acsnano.org
ARTICLE

Targeting 3D Bladder Cancer Spheroids with Urease-Powered Nanomotors

Ana C. Hortelão,[†] Rafael Carrascosa,[†] Nerea Murillo-Cremaes,[†] Tania Patiño,[*,†] and Samuel Sánchez[*,†,‡]

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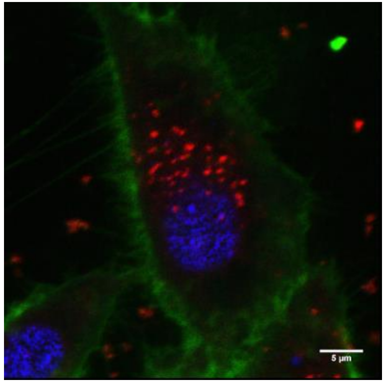
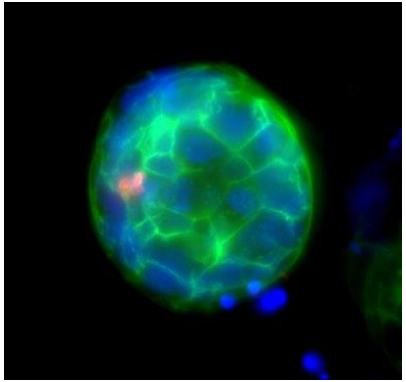
Urease Nanomotors: from *in vitro* to *in vivo*

In vitro





Enhanced delivery of drugs

2D cell cultures

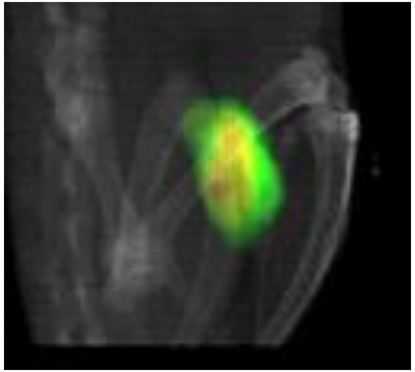
Penetrate and target using antibodies

3D Bladder Cancer Spheroids

Hortelao et al. *Adv. Funct.Mat.* 2018
Llopis et al *ACS Nano* 2019

Hortelao et al. *ACS Nano* 2019

In vivo



Medical Imaging of collective behavior

Intravenous and intravesical administration in mice

Hortelao et al. *Sci. Robot.* 2021

A single nanobot does little by itself

Billions of nanoparticles are needed to effectively treat tumors

1. Chemical Self-propelled Nanobots:

getting motion at the nanoscale

2. Collective behaviour of Nanobots

Mimicking bioconvection

3. Biomedical applications

The case of bladder cancer

Collective Intelligence in nature

National Geographic

Also for emerging behaviour see:

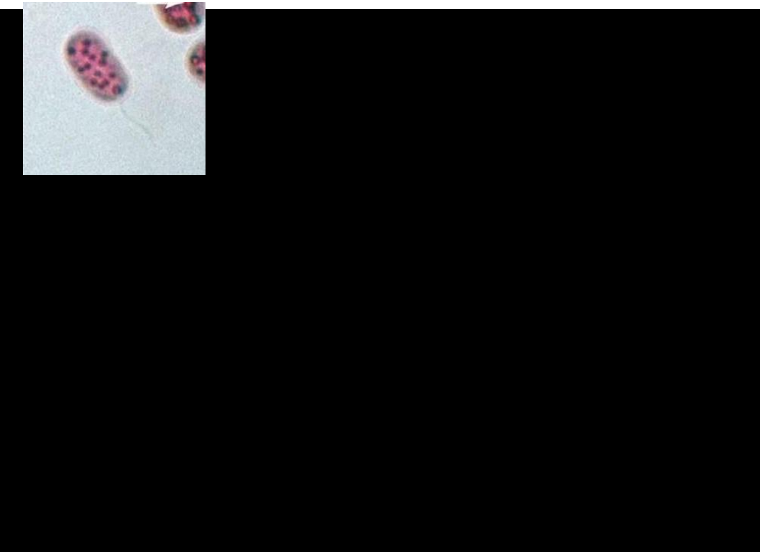
3D motion: Chen et al. *Nat. Commun*. 2024

Collective migration in gradients: Lin, Chen et al. *Small* 2025

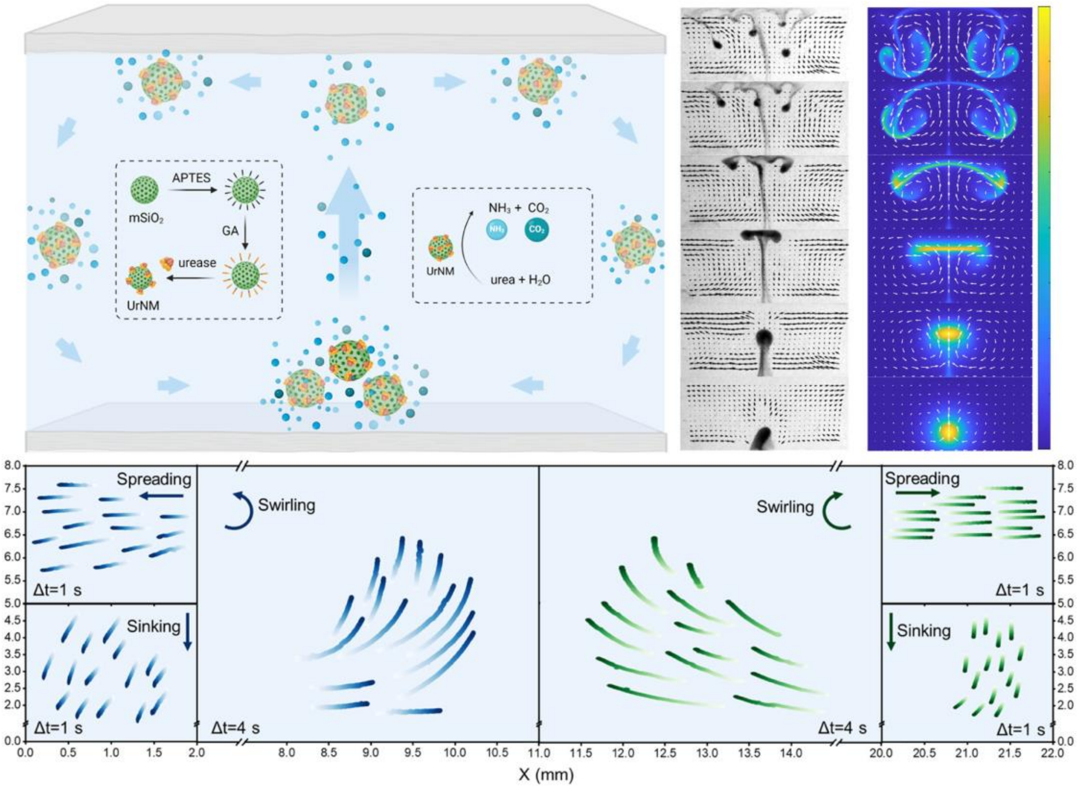
Hortelao et al. *Science Robot*. 2021

Collective motion mimicking microorganisms

Purple sulfur bacteria Chromatium okenii



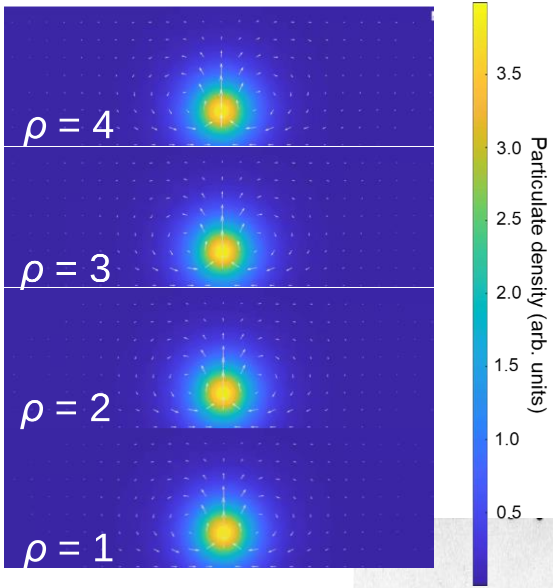
- Raise to the surface to respirate
- accumulate in the top layer
- Develop fingering instability

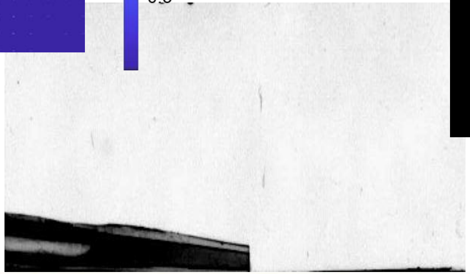


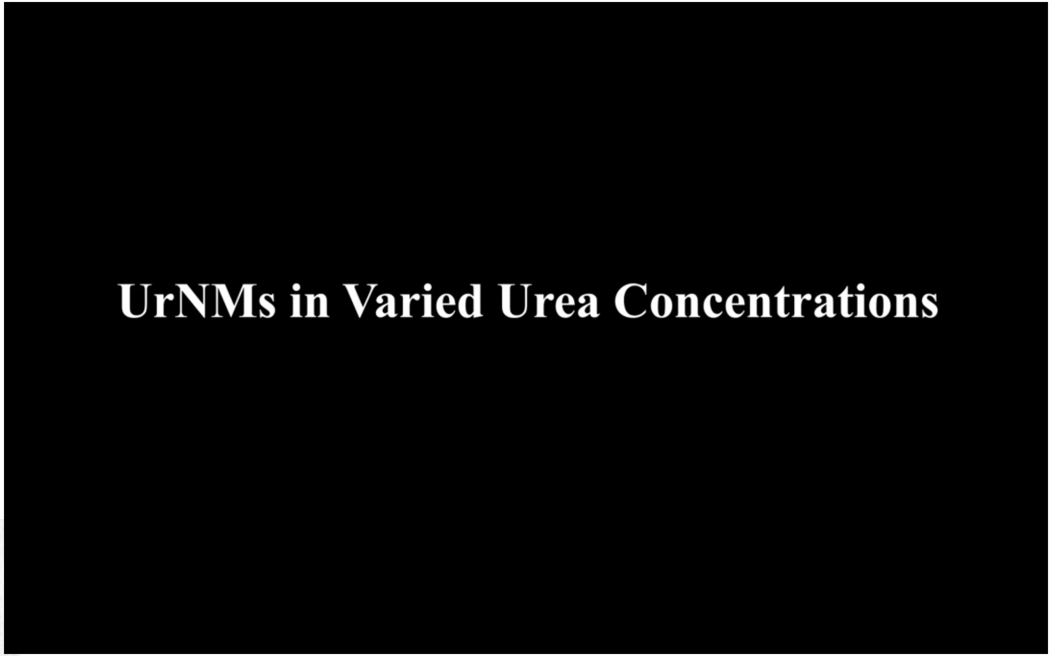
S.Chen et al. *Nat.Comm.* **2024**

Norbert Pfennig, Univ. Goettingen, 1966

Collective motion mimicking bioconvection







S.Chen et al. *Nat.Comm.* 2024

1. Chemical Self-propelled Nanobots:

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The case of bladder cancer

FACTS Bladder cancer

7th

MOST COMMON CANCER

550 K new patients/year

200 K deaths/year

HIGHEST

RECURRENCE RATE:

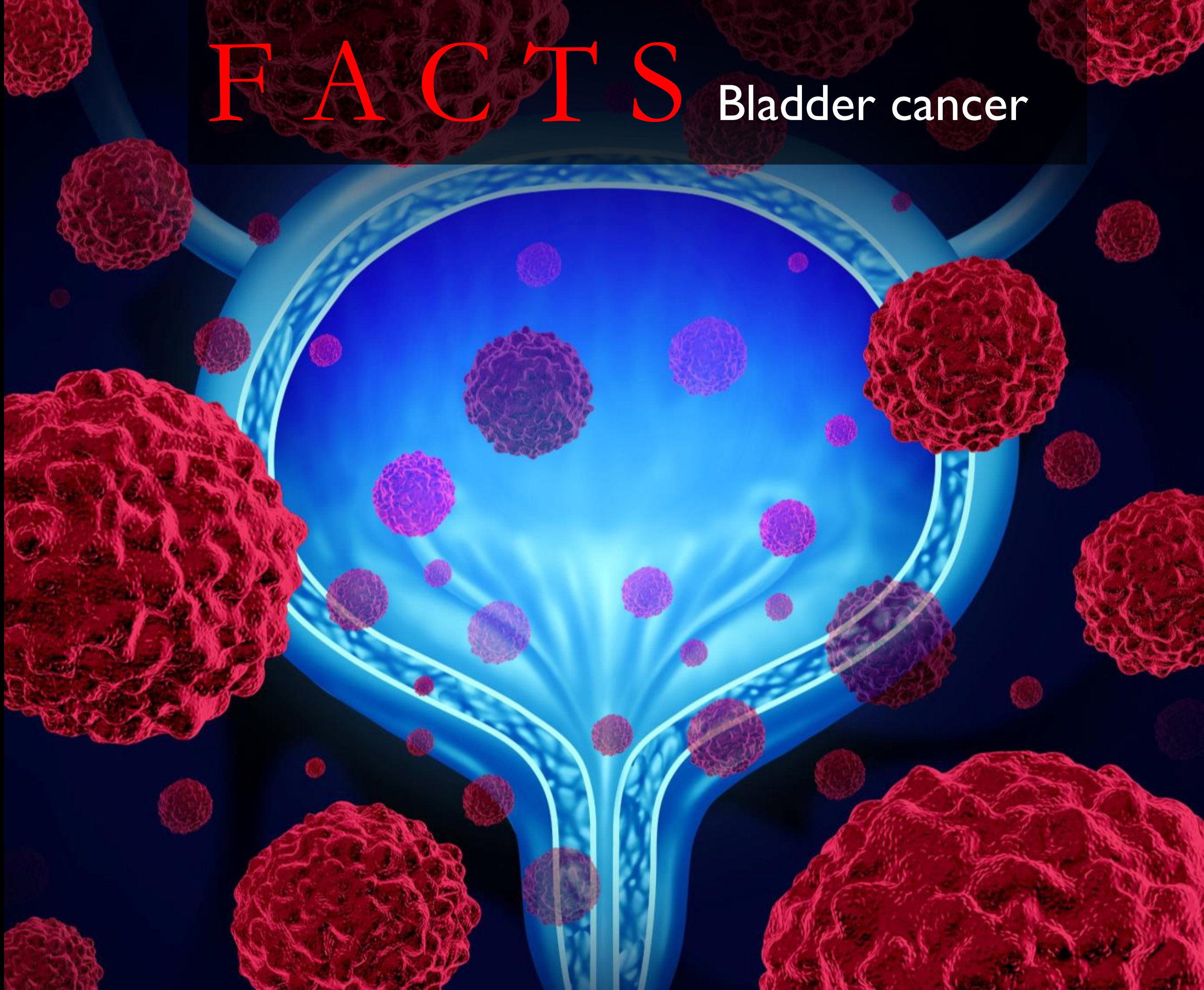
60%

MOST

EXPENSIVE

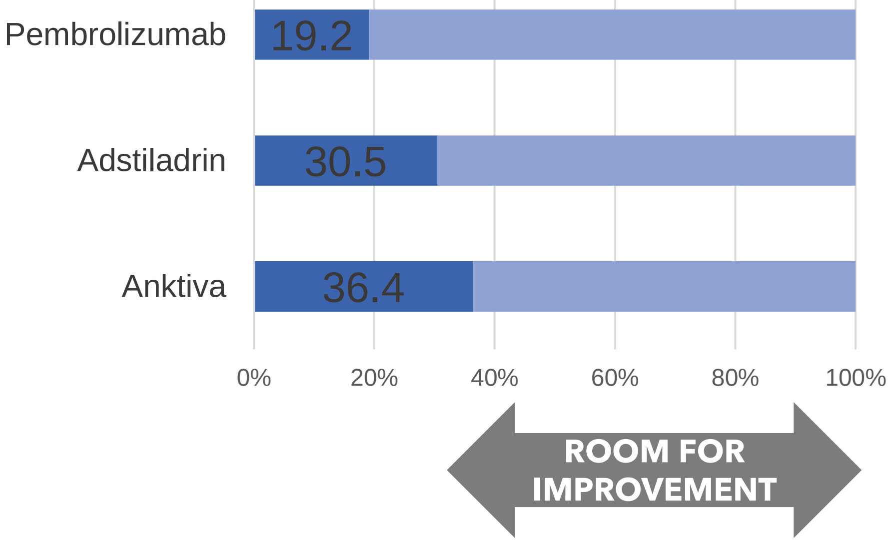
CANCER TO TREAT

187,000 $ per case



Bladder Cancer: Unmet medical need

Complete Response after 12 months of treatment:

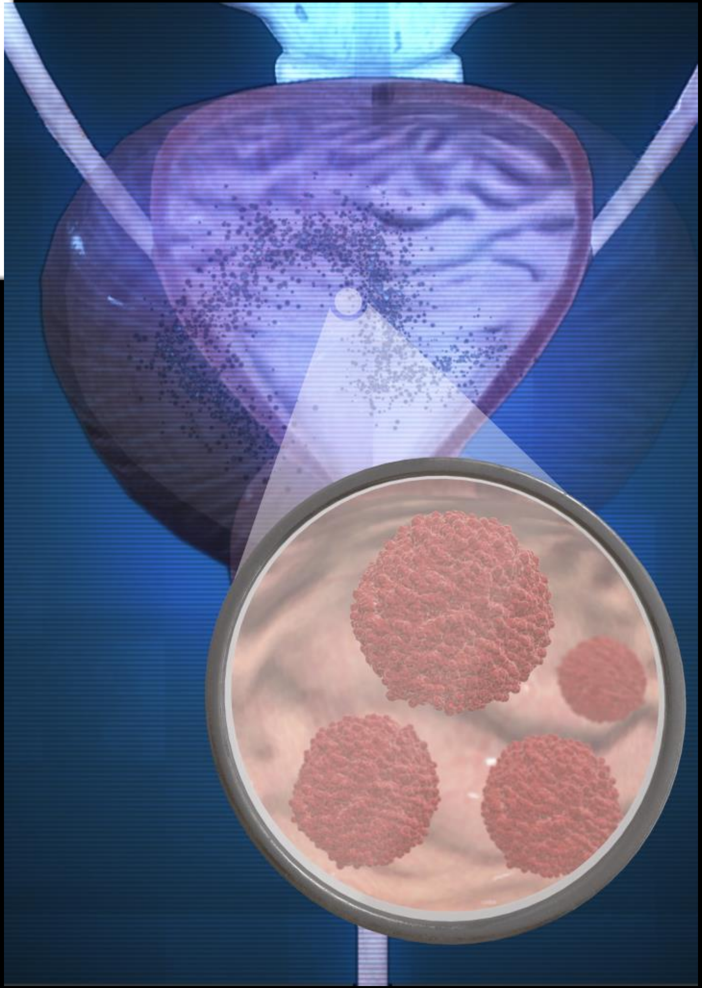


SCIENCE ROBOTICS | RESEARCH ARTICLE

NANOROBOTS

Swarming behavior and in vivo monitoring of enzymatic nanomotors within the bladder

Ana C. Hortelao[1]*, Cristina Simó[2]*, Maria Guix[1], Sandra Guallar-Garrido[3], Esther Julián[3], Diana Vilela[1], Luka Rejc[2†], Pedro Ramos-Cabrer[2,4], Unai Cossío[2], Vanessa Gómez-Vallejo[2], Tania Patiño[1,5‡], Jordi Llop[2‡], Samuel Sánchez[1,6‡]



- In vivo imaging of the collective motion of self-propelled nanomotors in living mice
- Nanomotors induce fluid mixing inside the bladder
- Nanomotors reach the whole volume of the bladder
- No toxicity was observed

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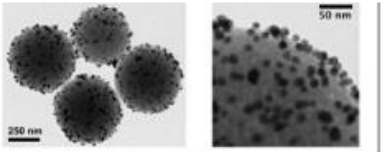
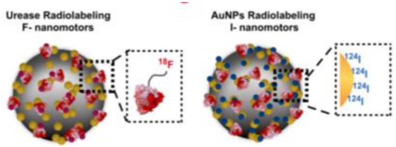
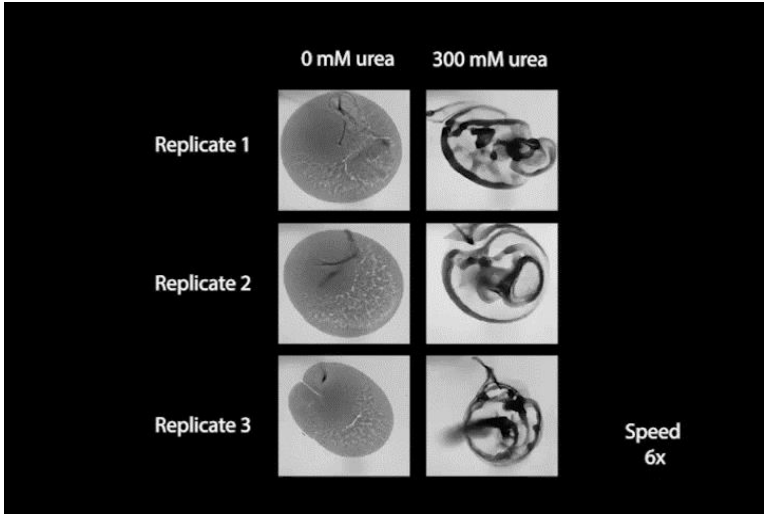
Imaging Swarms *in vitro*: optical and PET-CT

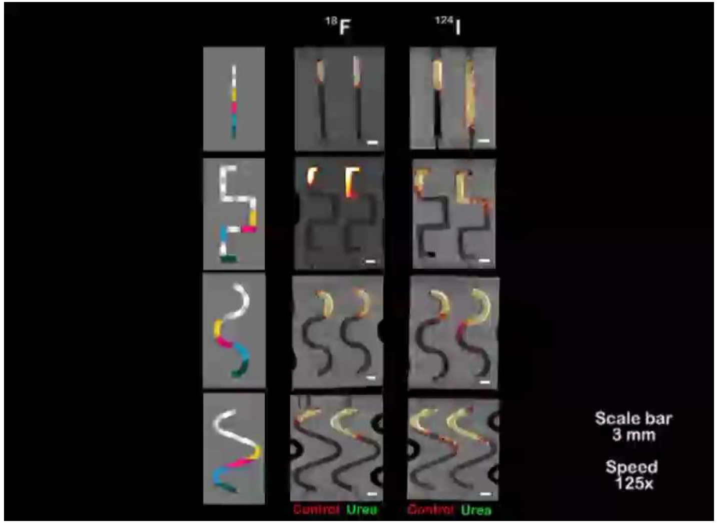




Optical Images of Millions of nanobots self-propelling collectively (Swarms)

PET-CT of Radiolabelled Nanobots swimming in microfluidic channels

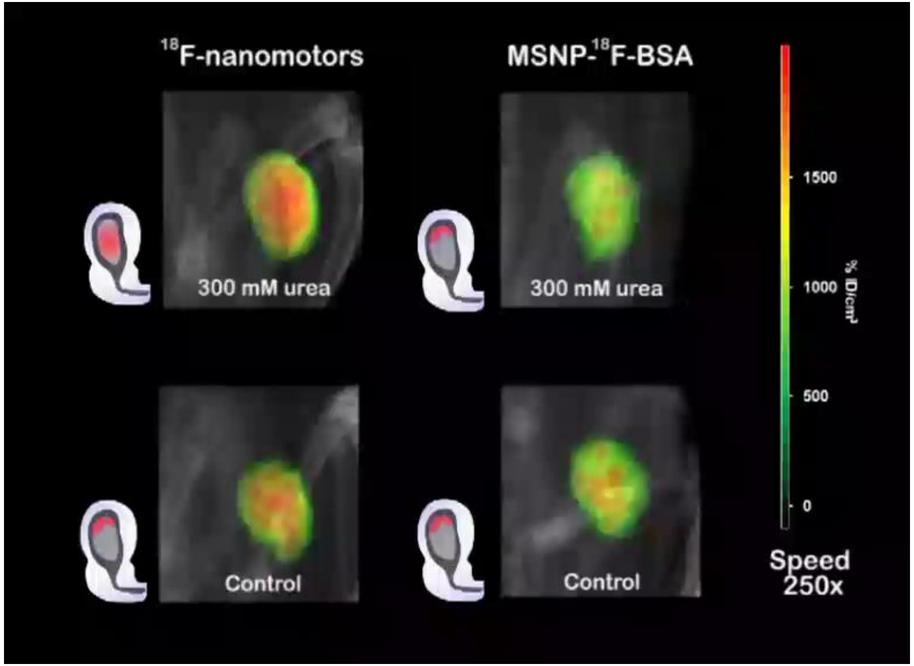


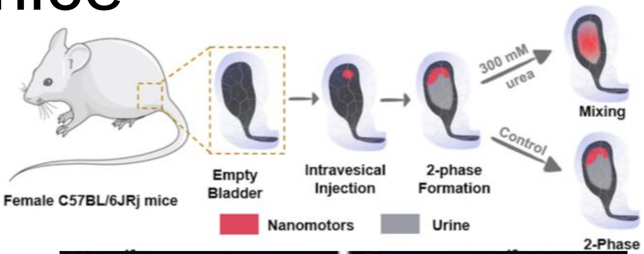


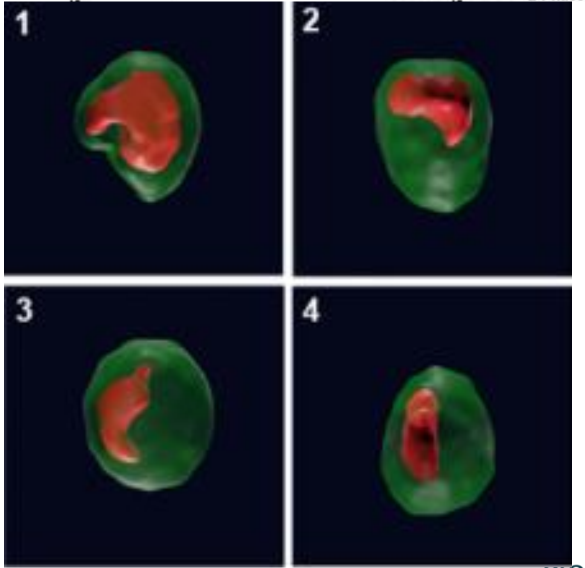
Hortelao et al. ***Sci. Robot*. 2021**

Imaging Nanobots in bladder of mice

Self-propulsion enables nanobots
to reach the whole volume of the bladder







Hortelao et al. ***Sci. Robot*. 2021**

PET-CT imaging of nanobots within the bladder *in vivo*

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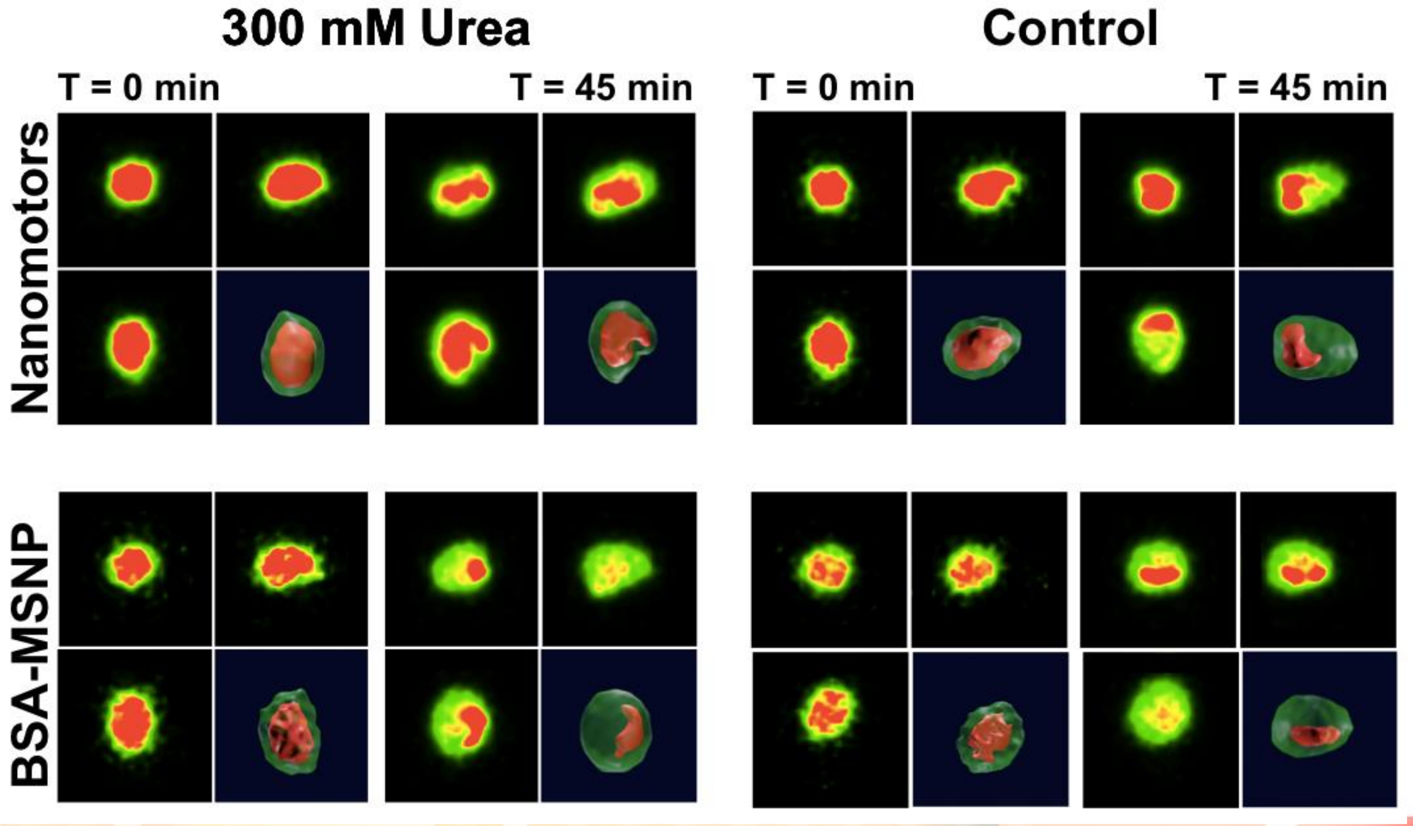
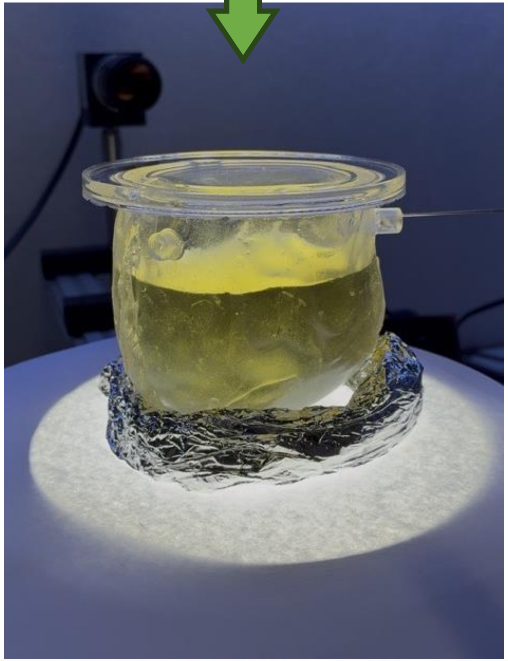


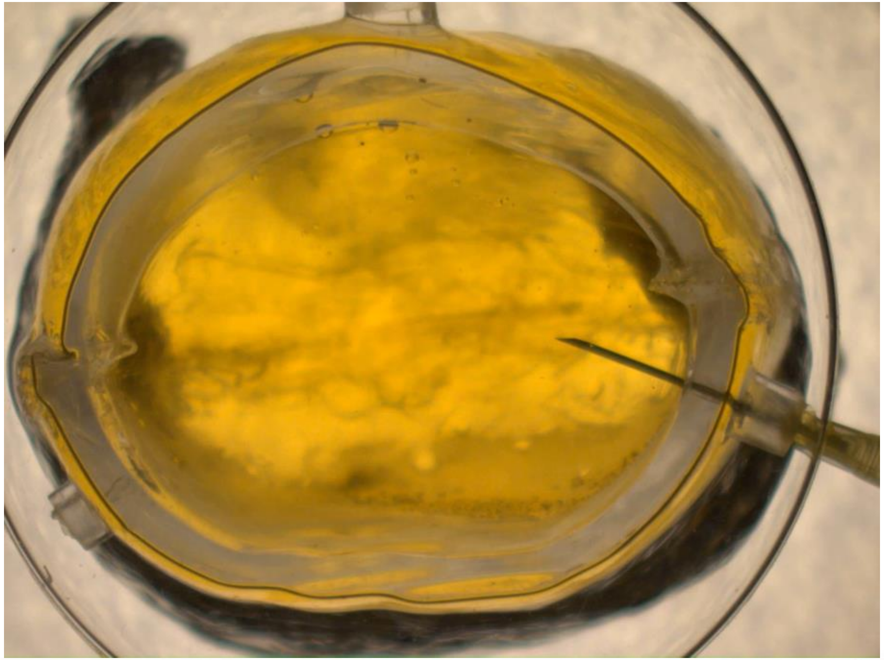
Hortelao, Simó et al. ***Sci. Robot*. 2021**

3D Printed Bladder Phantoms to test 3D motion

Camera



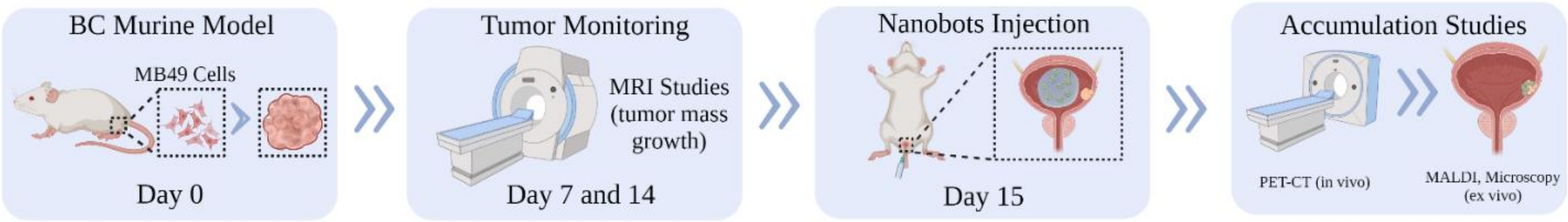
Color change indicates pH increase due to urea-urease reaction.
Pink: localization of urease-nanobots



S. Alvarez, unpublished

Nanobots treating Bladder Cancer tumors *in vivo*

Fundació "la Caixa"



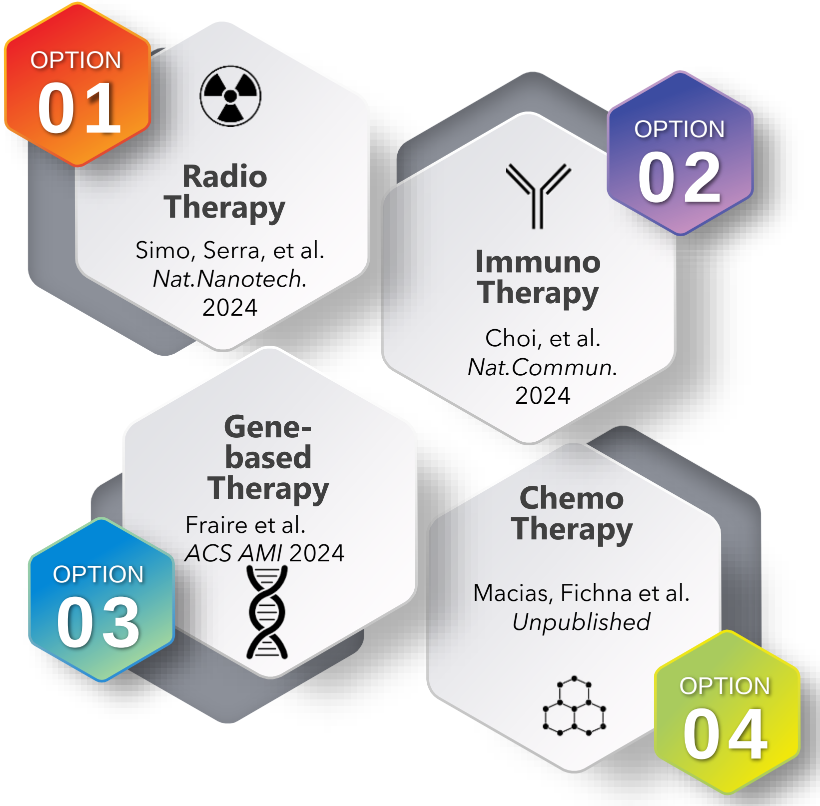
CLÍNIC BARCELONA Hospital Universitari

UAB Universitat Autònoma de Barcelona

CIC biomaGUNE CENTER FOR COOPERATIVE RESEARCH IN BIOMATERIALS

IRB BARCELONA INSTITUTE FOR RESEARCH IN BIOMEDICINE

Versatility of Nanobots for Bladder Cancer



nature nanotechnology

Article https://doi.org/10.1038/s41565-023-01577-y

Urease-powered nanobots for radionuclide bladder cancer therapy

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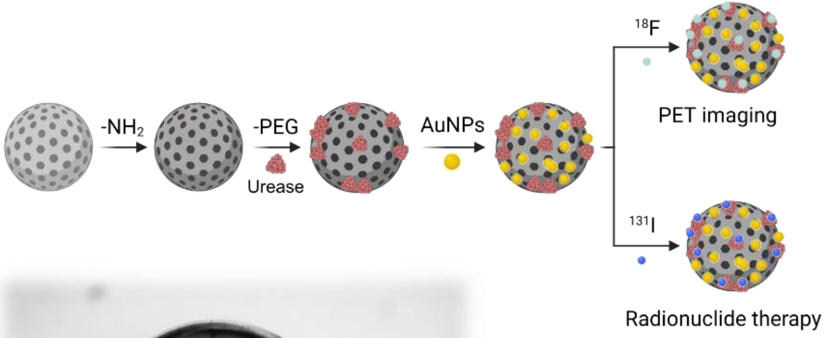
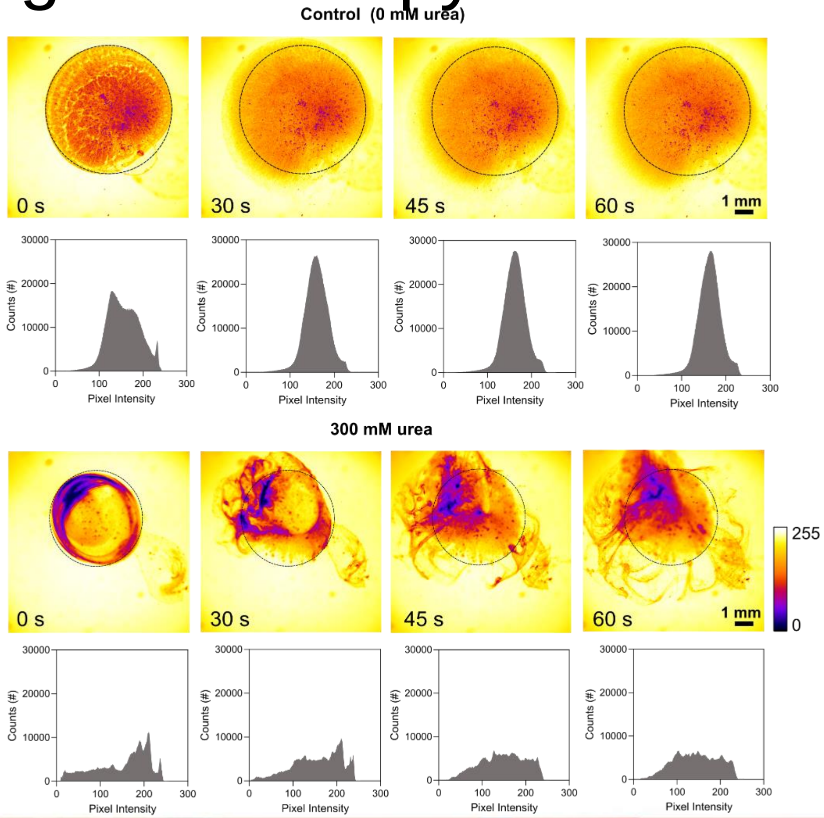
Check for updates

Cristina Simó[1,10,13], Meritxell Serra-Casablancas[2,13], Ana C. Hortelao[2], Valerio Di Carlo[2], Sandra Guallar-Garrido[3,11], Sandra Plaza-García[1], Rosa Maria Rabanal[4], Pedro Ramos-Cabrer[1,5], Balbino Yagüe[1], Laura Aguado[1,6], Lídia Bardia[7], Sébastien Tosi[7,12], Vanessa Gómez-Vallejo[1], Abraham Martín[5,6], Tania Patiño[2,8], Esther Julián[3], Julien Colombelli[7], Jordi Llop[1] & Samuel Sánchez[2,9]

Multifuncional nanobots: imaging and therapy





Simo, Serra et al. *Nature Nanotech.* 2024

Bladder Cancer model in mice

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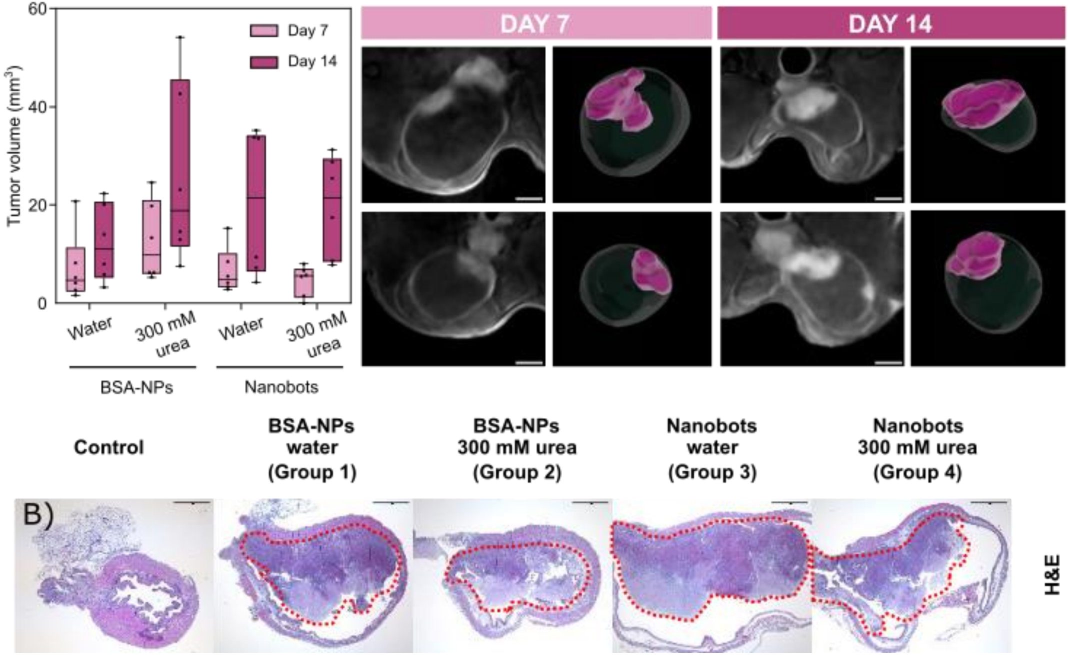

Simo, Serra et al. *Nature Nanotech.* 2024

Nanobots accumulate in bladder cancer tumours

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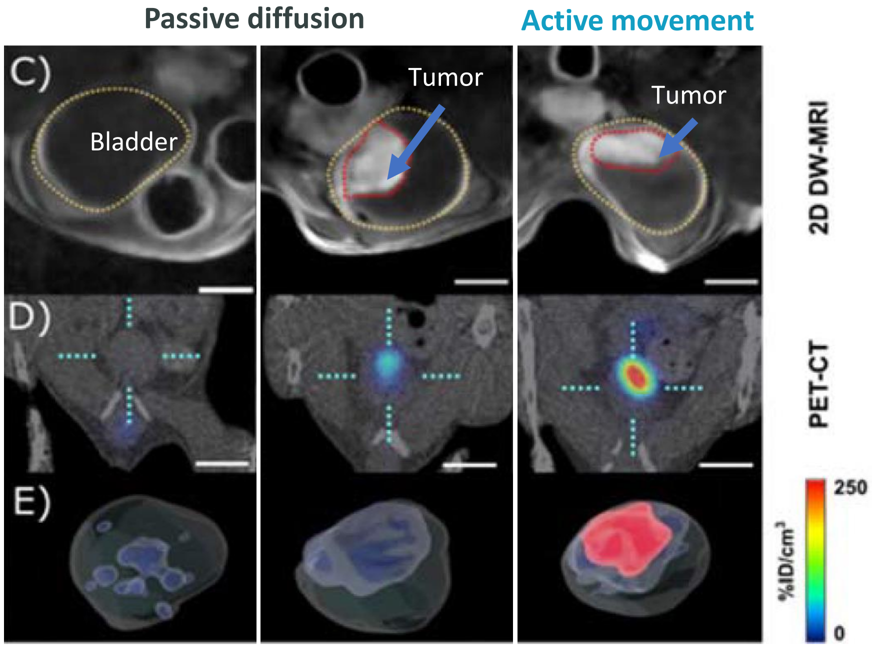
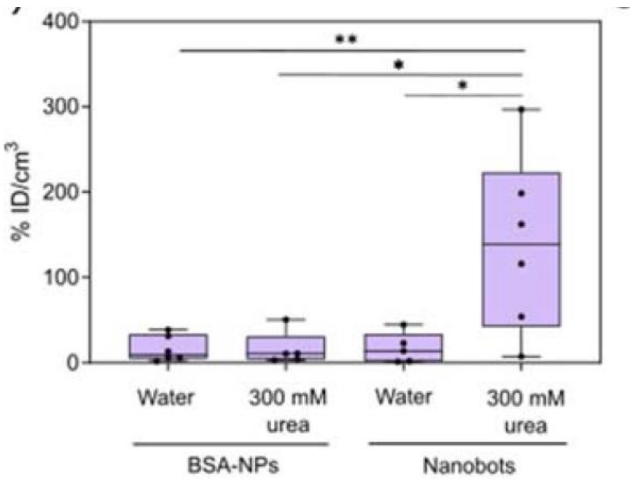
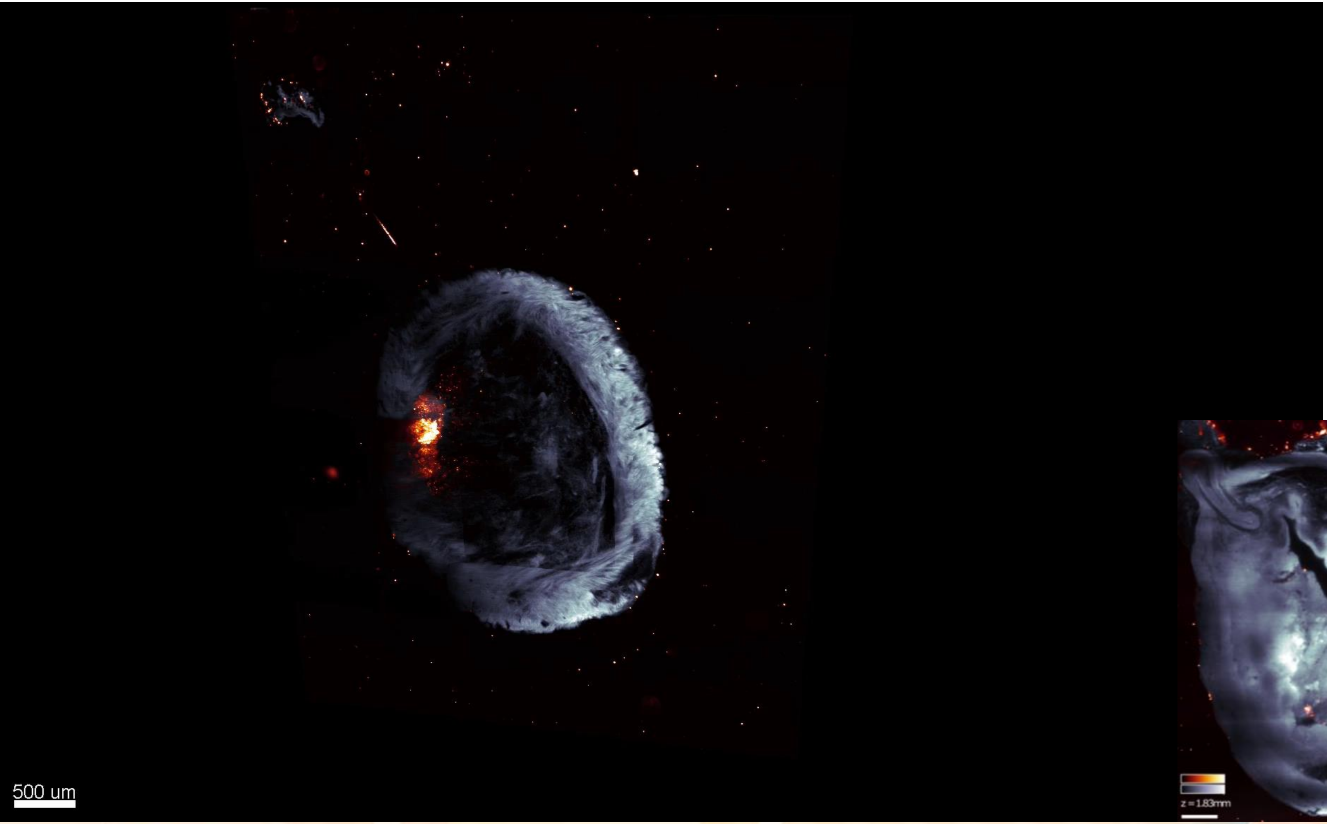
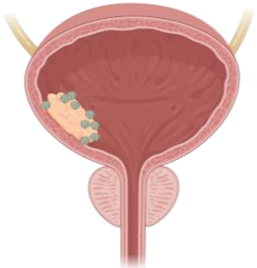




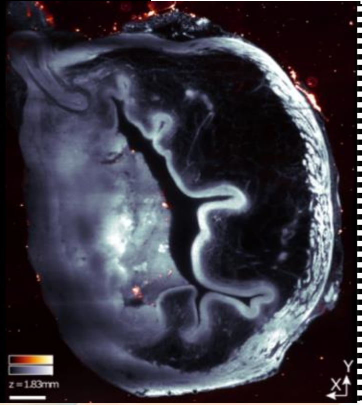
Simo, Serra et al. *Nature Nanotech.* 2024

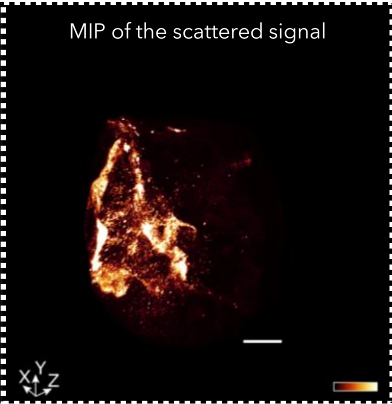
Nanobots reach and penetrate the tumor



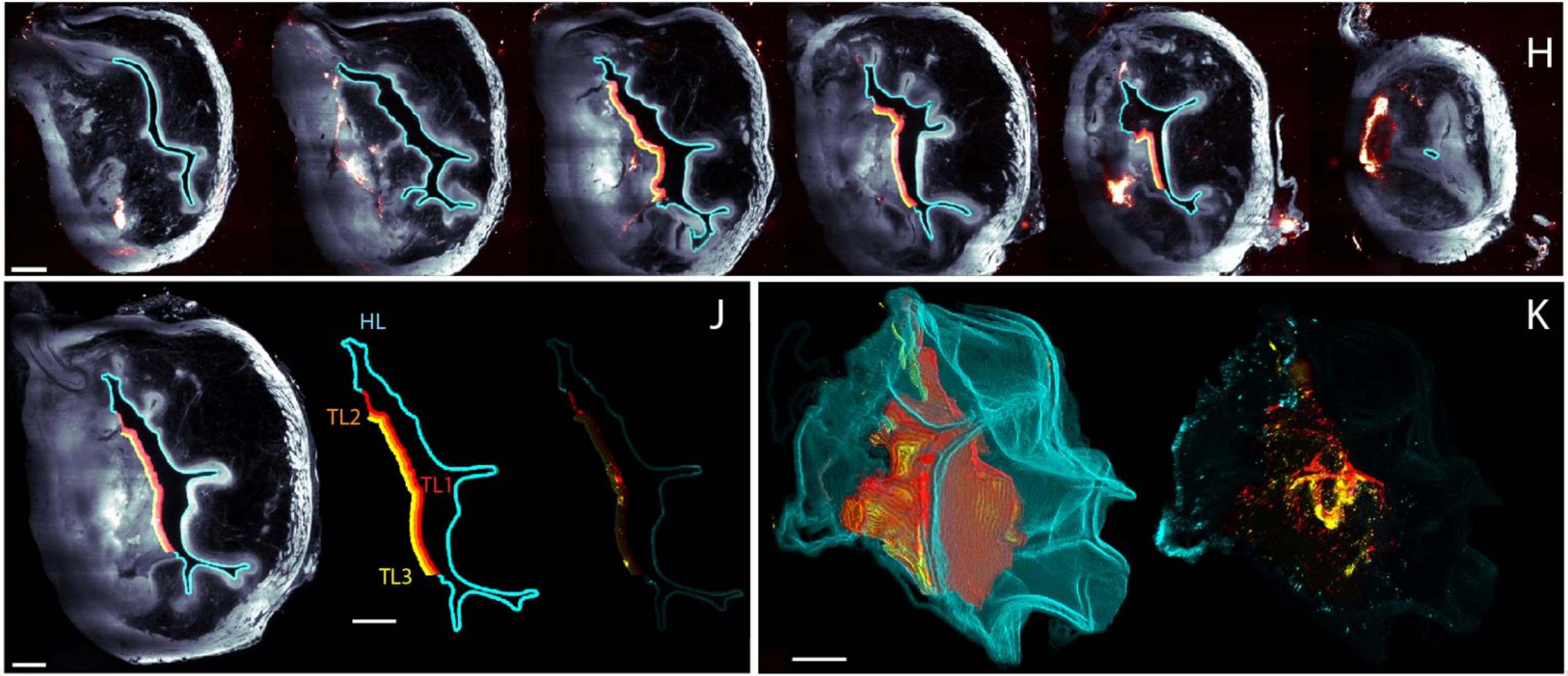


J. Colombelli. IRB Barcelona





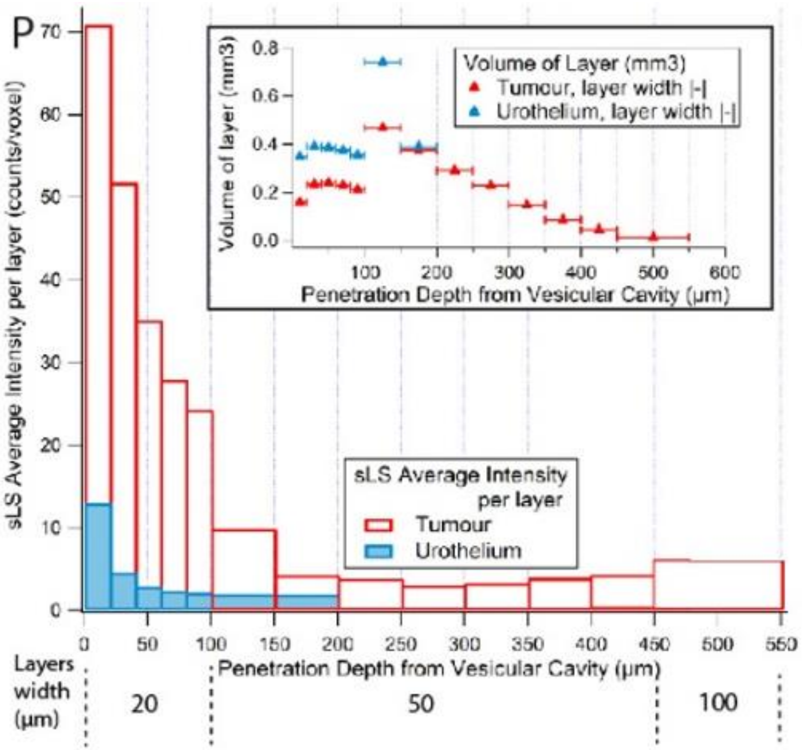
Ex-vivo Light-sheet microscopy of bladder

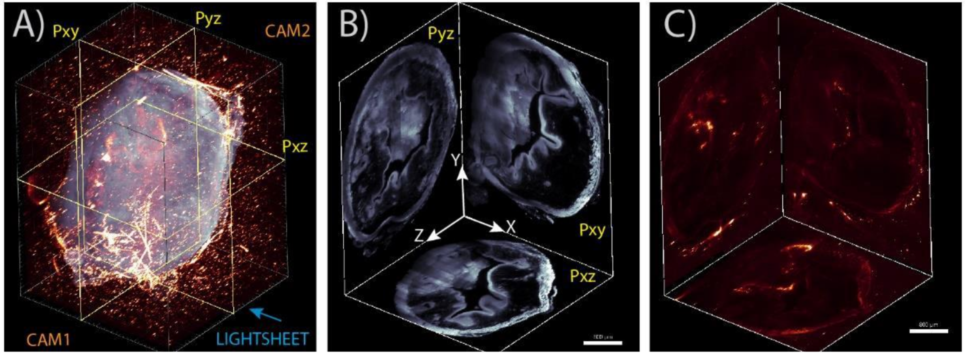


Simo, Serra et al. *Nature Nanotech.* 2024

J. Colombelli. IRB Barcelona

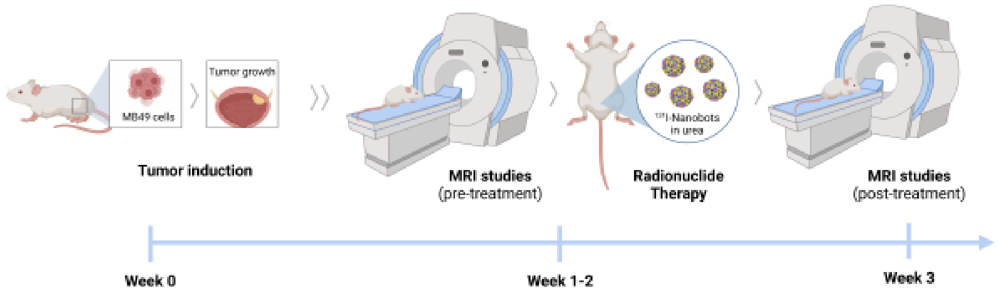
Penetration depth by Nanobots in bladder

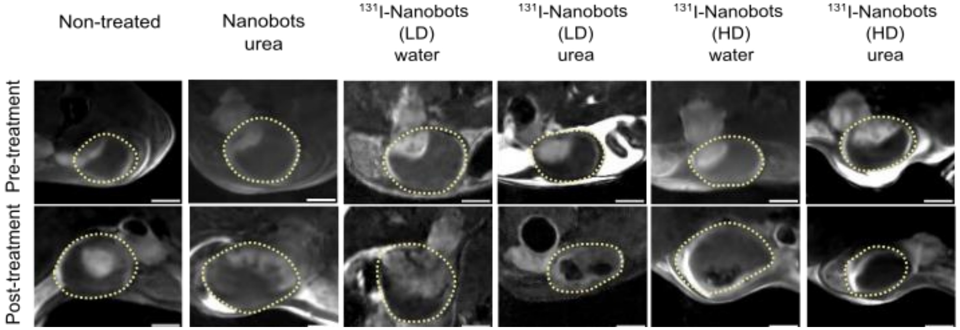


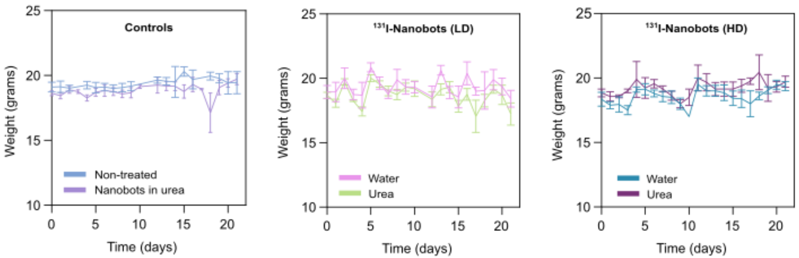


Orthogonal views with lightsheet imaging in fluorescence and scattered modes. A) Maximum Intensity Projection of a bladder volume with images in Autofluorescence (Grey) and Scattered sLS (Glow) modes.

Nanobot assisted Radionuclide-therapy



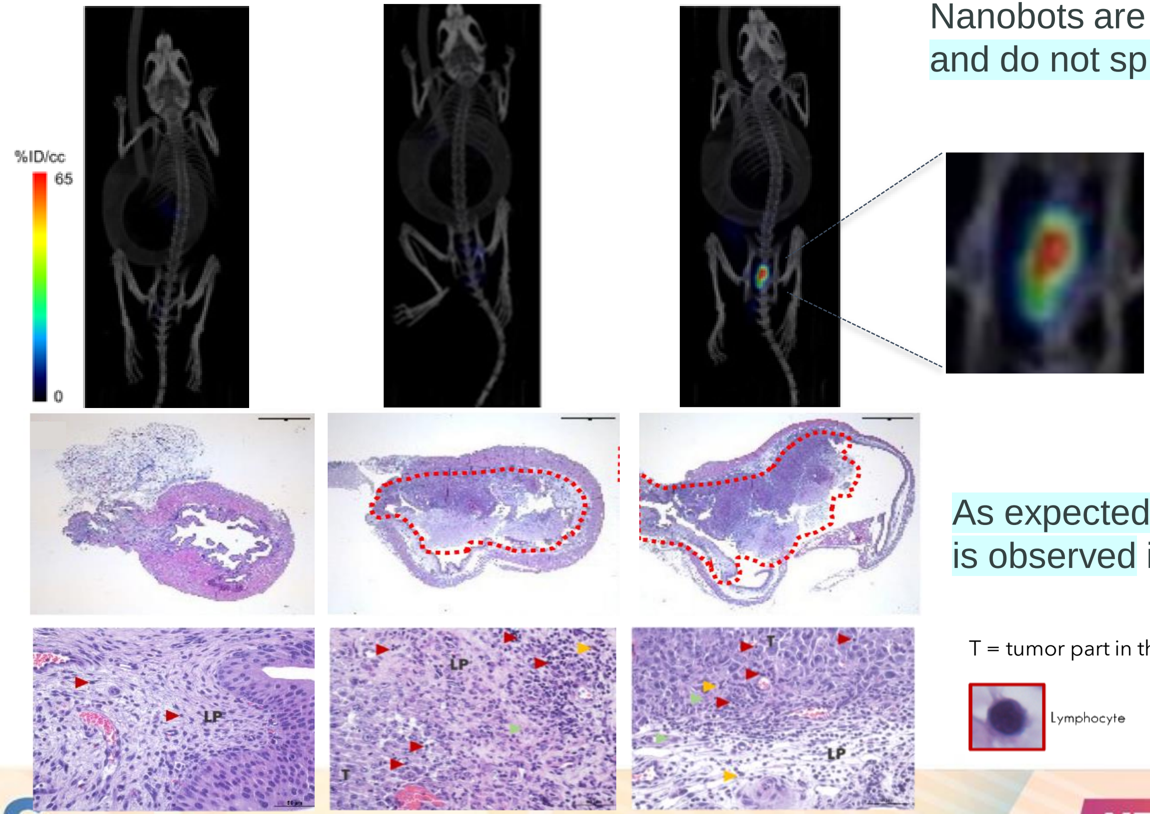




Simo, Serra et al. *Nature Nanotech.* 2024

Safety assessment of Nanobots in vivo

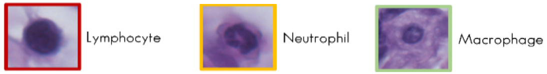
Control | Passive NMs | Active NMs



Nanobots are concentrated in the bladder and do not spread to other tissues

As expected, normal immune response is observed in Nanobots' treated mice

T = tumor part in the bladder; LP = Lamina Propria

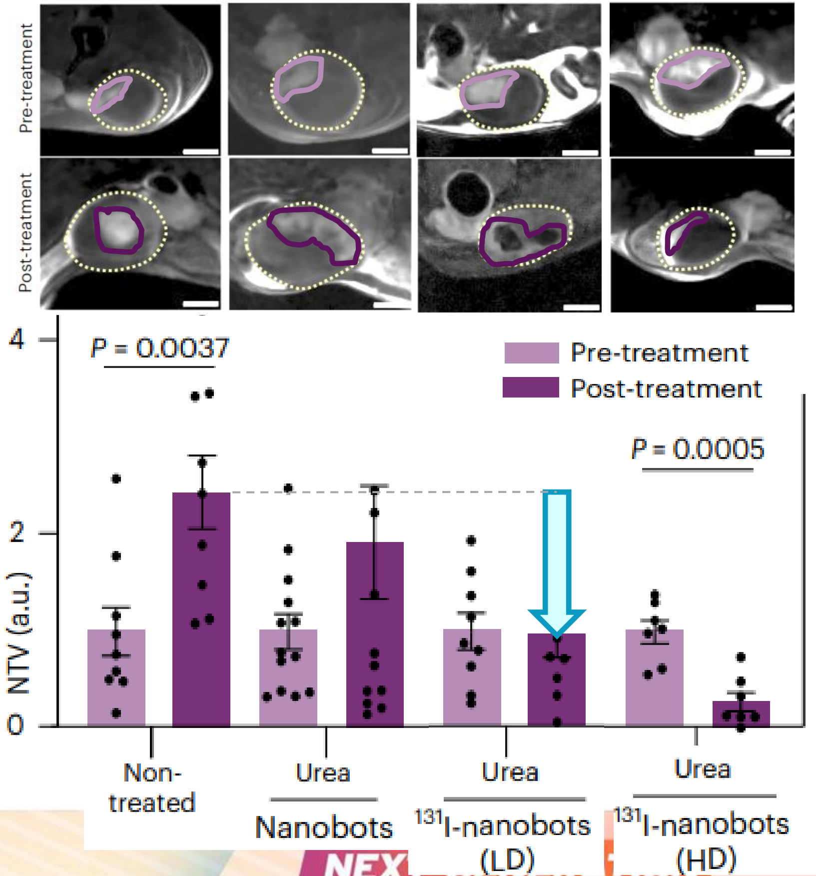


Simó, Serra et al. *Nature Nanotech.* 2024

Nanobot assisted Radionuclide-therapy

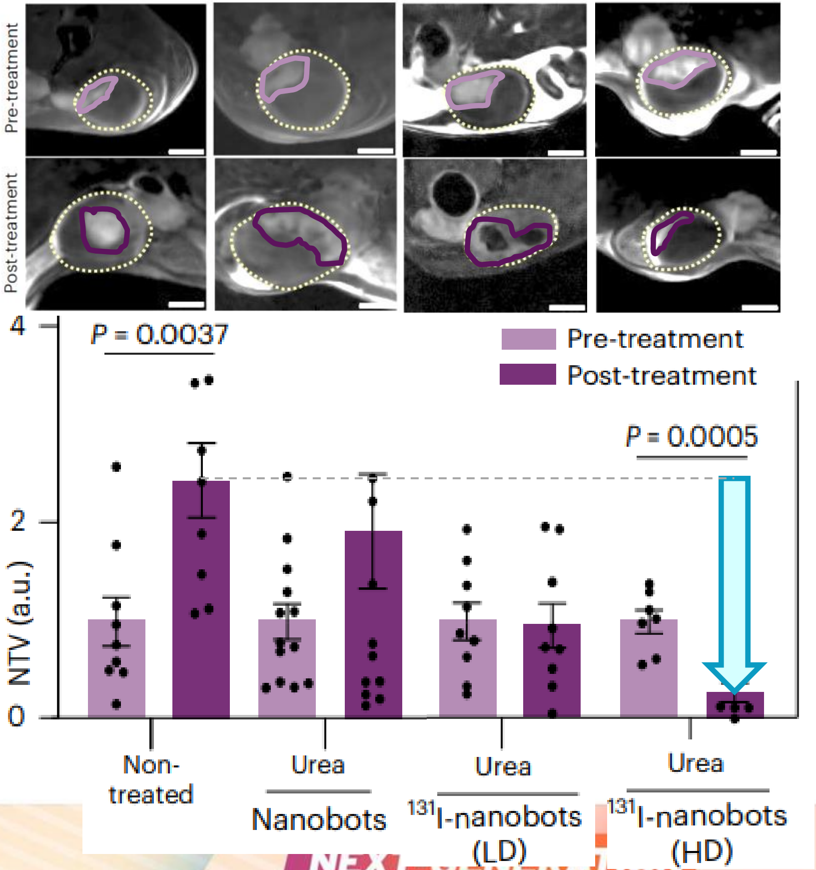
Extremely efficient nano-system:
Only with a SINGLE intravesical administration

At Low doses (LD) Nanobots **stop** tumor progression



Simo, Serra et al, *Nature Nanotech.* 2024

Nanobot assisted Radionuclide-therapy

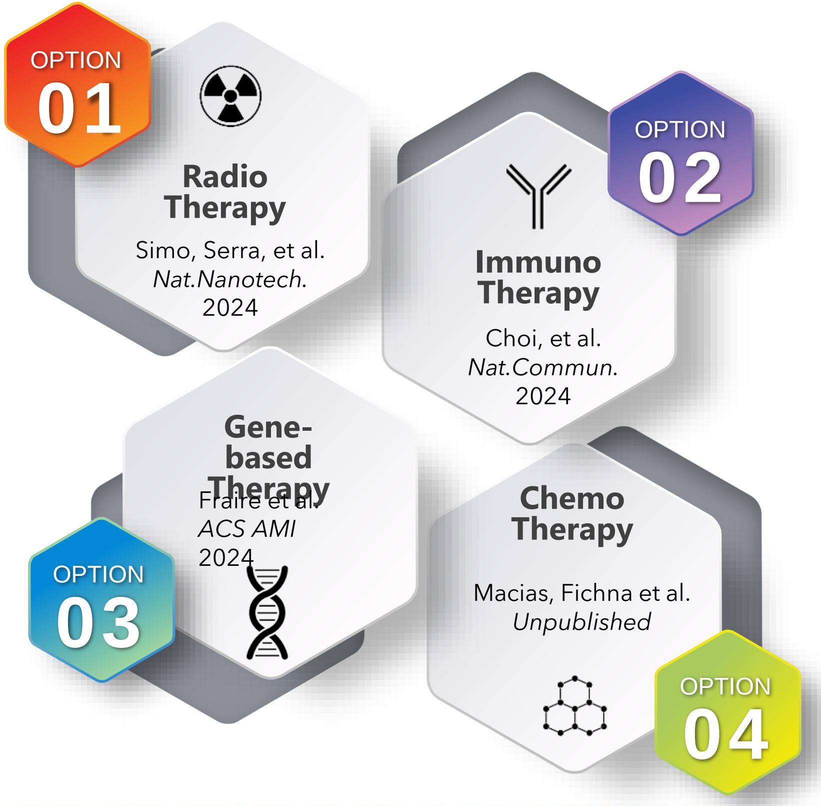


Extremely efficient nano-system:
Only with a SINGLE intravesical administration

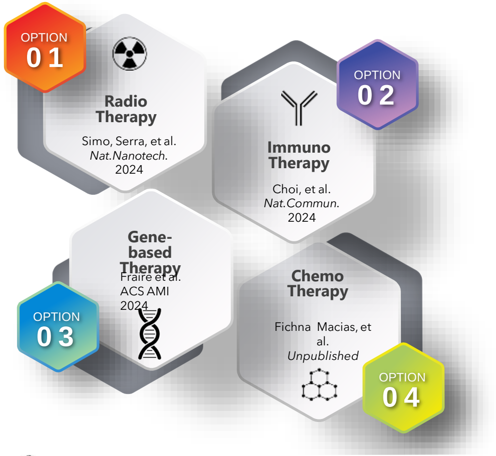
At Low high dosis (LD) Nanobots **radically reduce tumor volume**

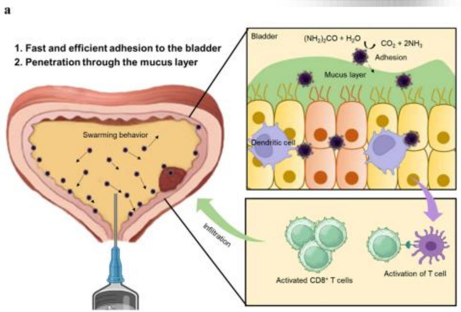
Simó, Serra et al., *Nature Nanotech.* 2024

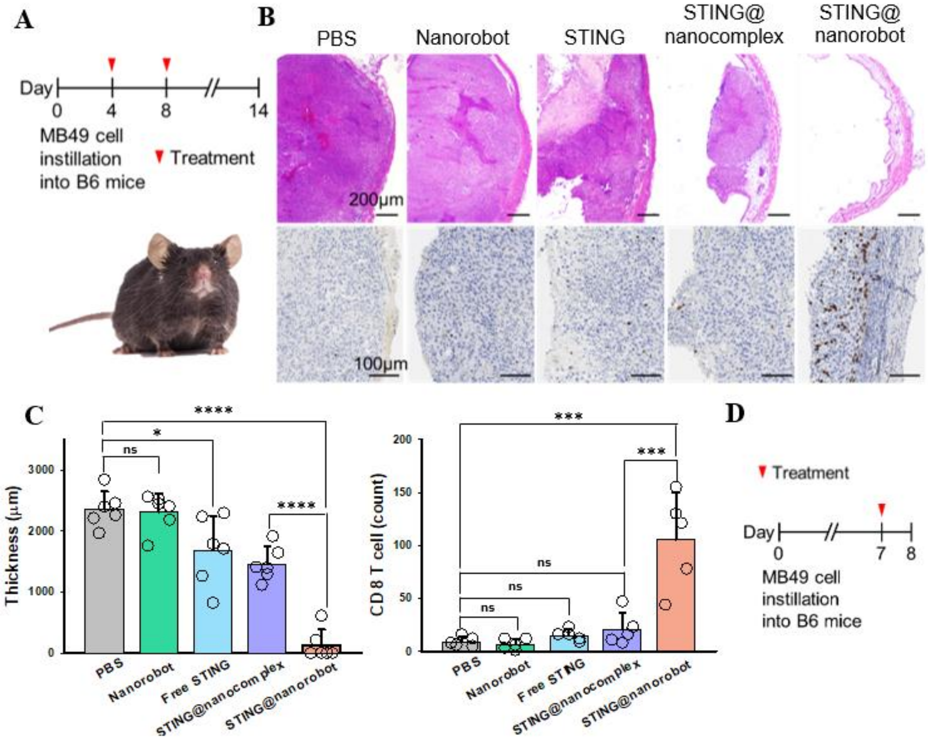
Versatility of Nanobots for Bladder Cancer



Nanobots with STING agonist for bladder cancer

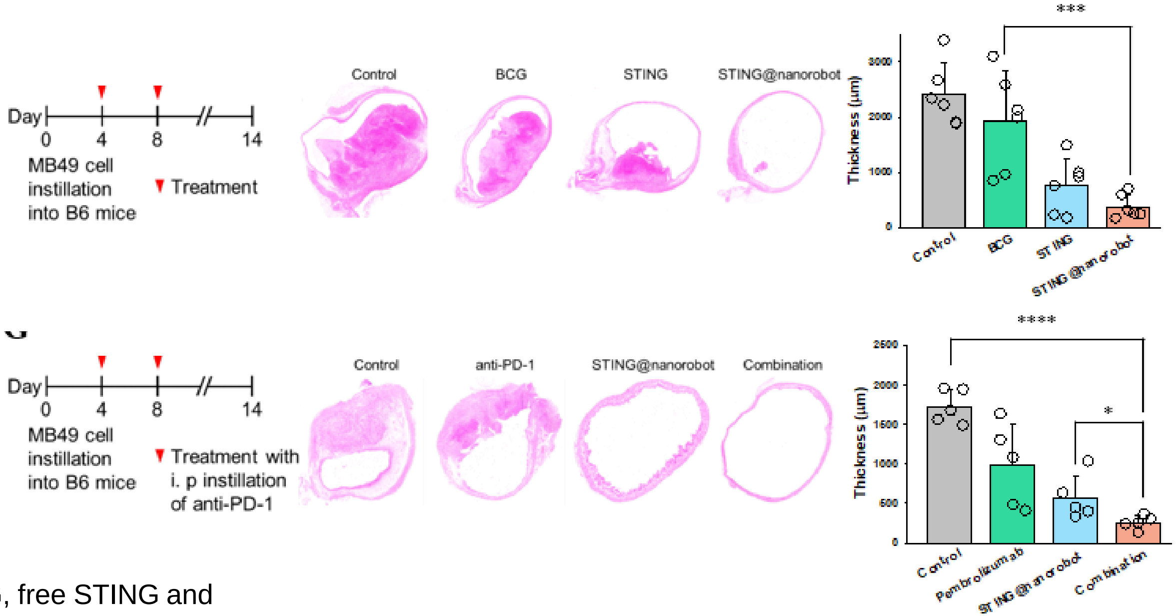






Choi et al. *Nat. Commun*. 2024

Immunotherapy with Nanobots

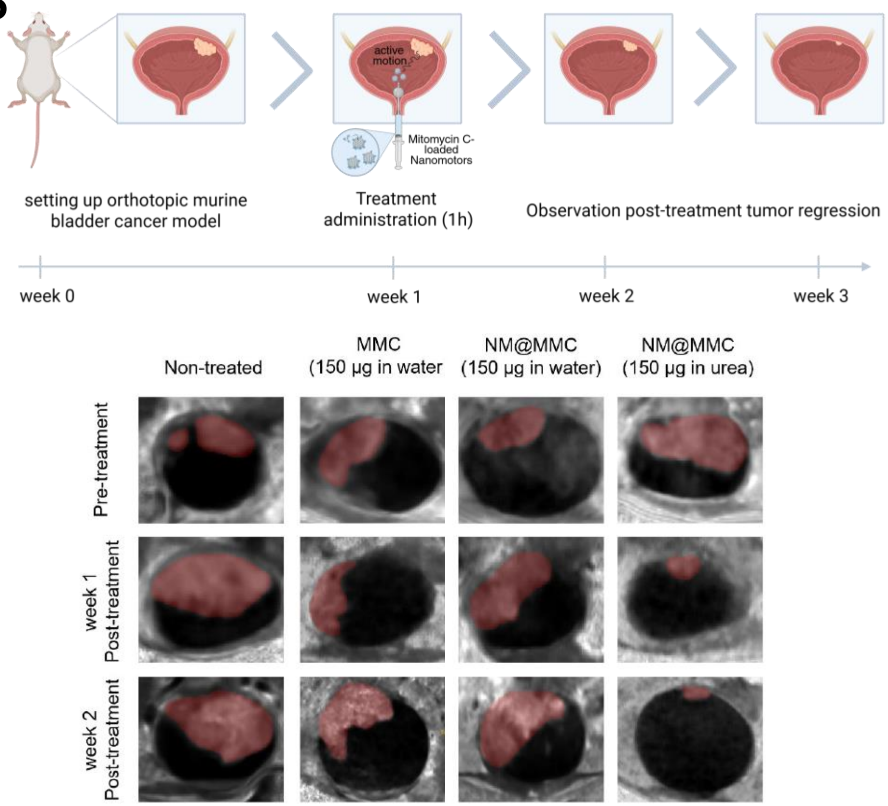


STING-nanobots **outperform standard of care** BCG, free STING and passive Nanoparticles

Very efficient in **combination** with *immune checkpoint inhibitors* (anti-PD-1)

Choi, et al. *Nat.Commun.* 2024

Chemotherapy with Nanobots



Nanobots with commercial drug Mitomycin-C **reduce 80%** tumor volume.
NEW!!!No recurrence after 2 weeks…and counting

Fichna et al. *Unpublished*. 2025

1. Chemical Self-propelled Nanobots:

getting motion at the nanoscale

2. Collective behaviour of Nanobots

Mimicking bioconvection

3. Biomedical applications

The case of bladder cancer…and beyond

	Passive Nanoparticles	Nanobots

#1 Nanobots penetrate Bladder tumors

In vivo results of tumor accumulation and penetration

UAB Universitat Autònoma de Barcelona

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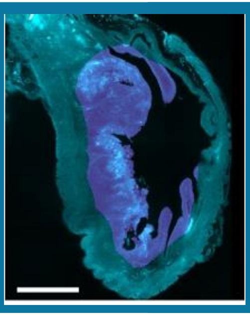
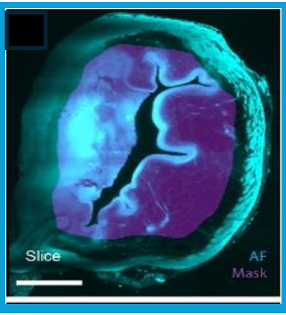
IRB BARCELONA

Serra et al. *Nat.Nanotech.* **2024**
Choi et al. *Nat. Commun.* **2024**



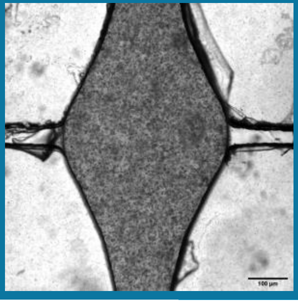


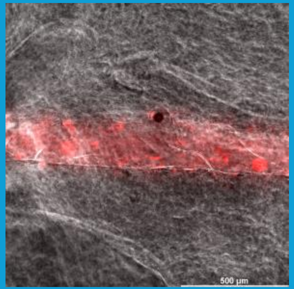
#2 Crossing ECM from tumors

IBEC ICMS TU/e

Bladder-on-chip devices (ICMS) will be used to test
Urease-nanobots penetration in different ECM

Inés Macías w/*Jaap den Toonder &*
Mohammad Jouy Bar (ICMS)



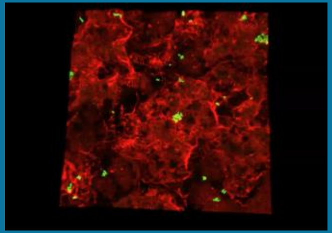


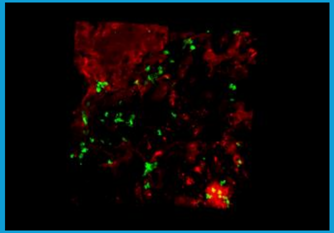
#3 Mucus crossing

VHIO VALL D'HEBRON Institute of Oncology

Catalase-nanobots penetrate mucus layers in:
Colorectal cancer
Pseudomyxoma Peritonei (PMP)

Serra et al. *ACS Nano* **2024**





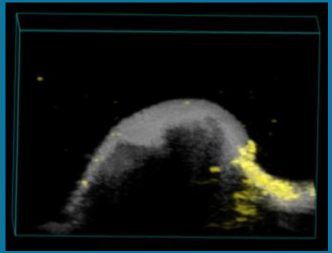
	Passive Nanoparticles	Nanobots

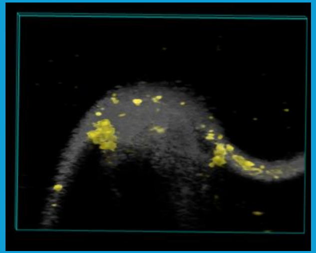
fundación García Cugat
para la investigación biomédica

#4 Spreading in joints

Urease-nanobots diffuse in synovial fluids in the joints and
Transport macromolecules and growth factors

Ruiz-González et al. *Small* **2024**



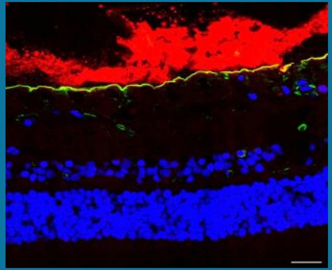


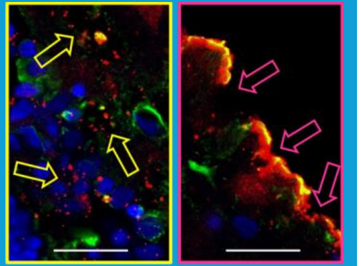
GHENT
UNIVERSITY

#5 Crossing ILM and vitreous

Urease-nanobots and collagenase-nanobots penetrate
Vitreous and the inner limiting membrane (ILM) to reach retinal
cells.

Fraire et al. *In preparation* **2025**

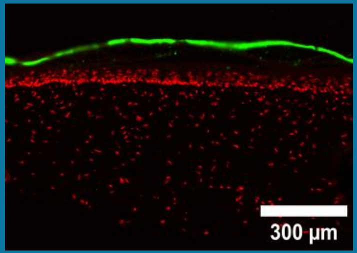


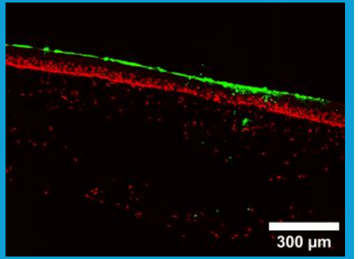


#6 Skin crossing with nanobots

Ex-vivo and in-vitro validation of nanobots crossing dermis

Prado et al. *in preparation* **2025**





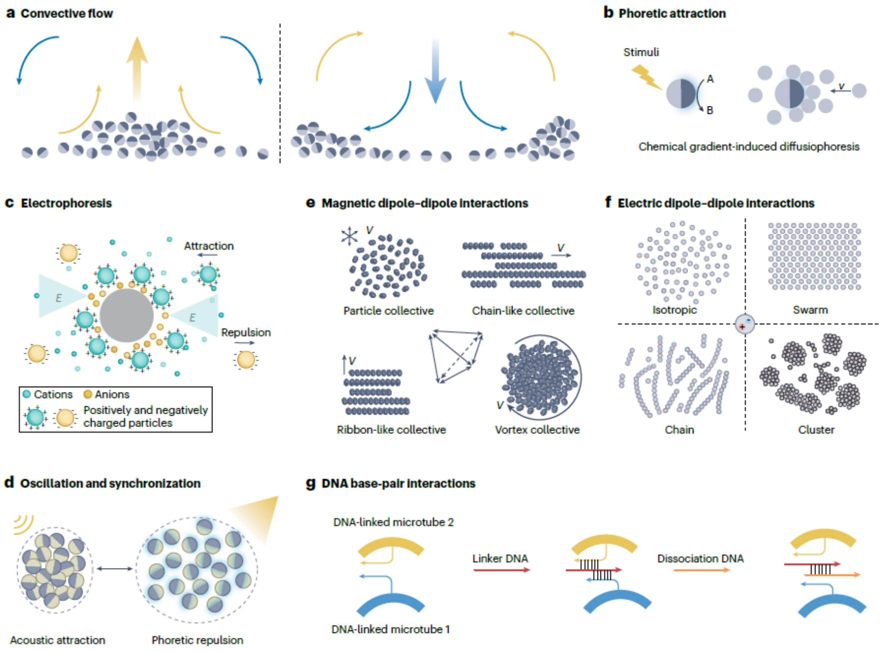
Some take-home messages

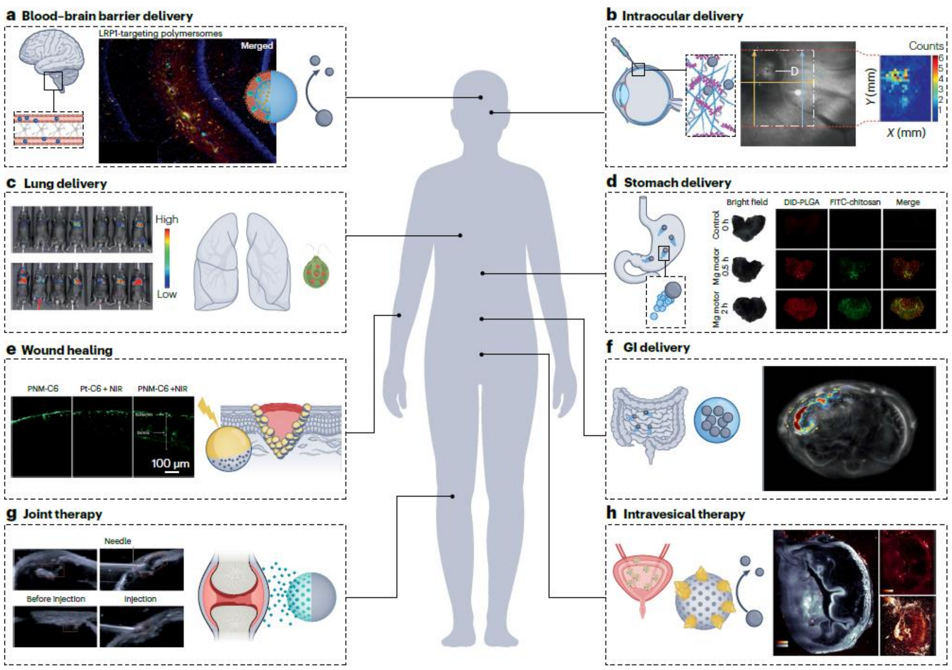
- ***Nanomtors:*** Chemically powered Nanoparticles that can move like biological microswimmers
- Self-propelled Nanomotors **can reach locations where passive nanoparticles cannot**
- Enzyme-powered Nanomotors can even more, chemically **interact with ECM and other biological barriers**
- Collective phenomena (**swarming**) help millions of Nanomotors to efficiently move, reach tumors, penetrate and transport drugs
- Nanobots have the potential to transport different payloads for **different diseases in oncology and beyond**

Perspective | Published: 13 June 2025

Swarming intelligence in self-propelled micromotors and nanomotors

Tania Patiño Padial, Shuqin Chen, Ana C. Hortelão, Ayusman Sen & Samuel Sánchez

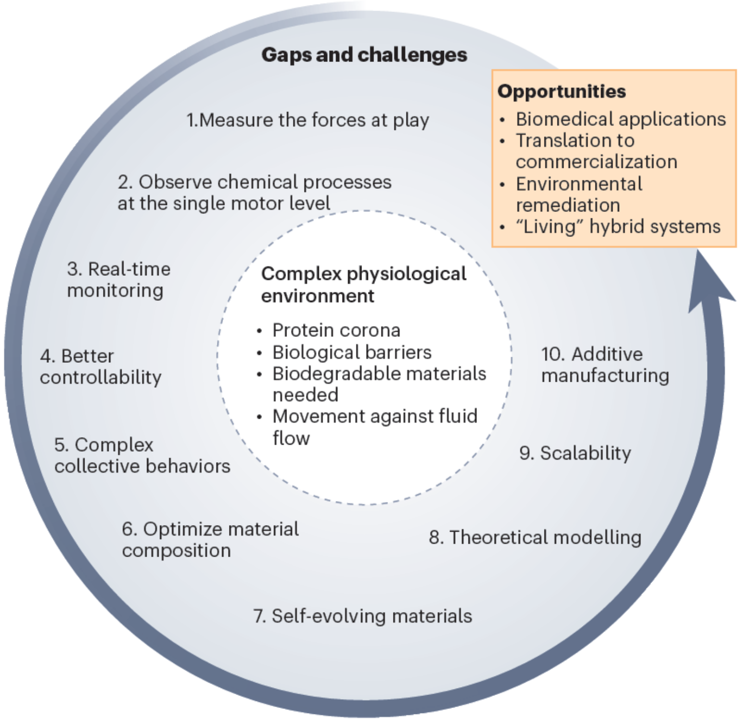




nature reviews materials

Patiño Padial, T., *et al.* Swarming intelligence in self-propelled micromotors and nanomotors (2025).
https://doi.org/10.1038/s41578-025-00818-x

Challenges, perspectives and future



Chen, et al. *Nat. Nanotech. (Invited Perspective)* *Accepted* **2025**

NANOBOTS
THERAPEUTICS

@SamuelNanobots

https://www.nanobotstx.com/

Co-Founder
Interim-CEO (2024)
and CSO
Spin Off 2023

Founding Institutions:

ICREA

IBEC
Institute for Bioengineering of Catalonia

EXCELENCIA SEVERO OCHOA

"la Caixa" Foundation

2016-2020
)

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2021-2022

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October 2024. The Medical Revolution