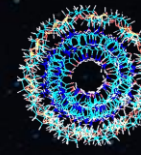




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In-Space Production of Janus Base Nanomaterials for Drug Delivery

Yupeng Chen, PhD

Associate Professor, University of Connecticut

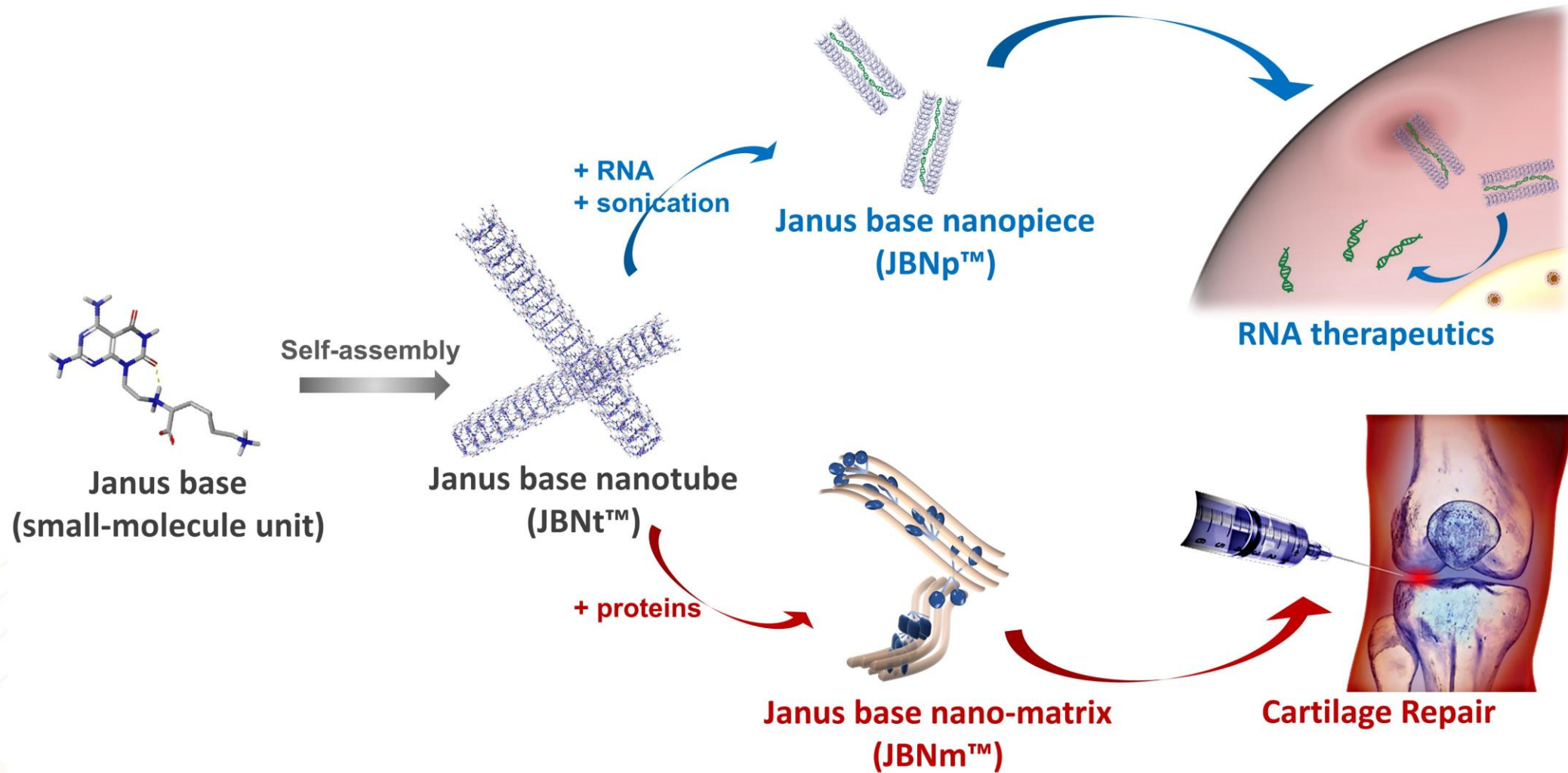
Scientific Advisor and co-Founder, Eascra Biotech

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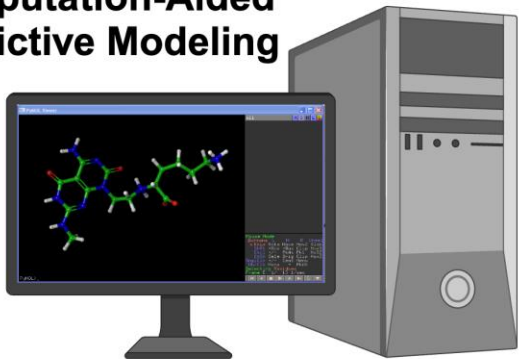


Two products: JBNp and JBNm

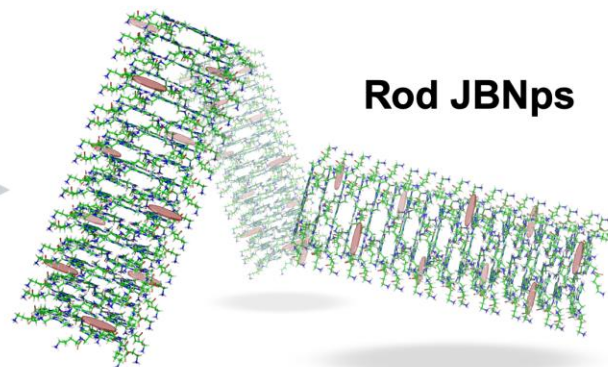


JBNs for improved targeting of solid tumors

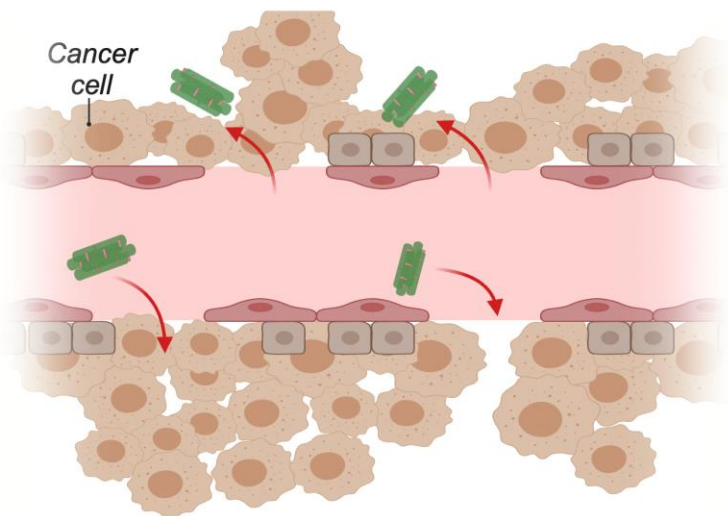
Computation-Aided
Predictive Modeling



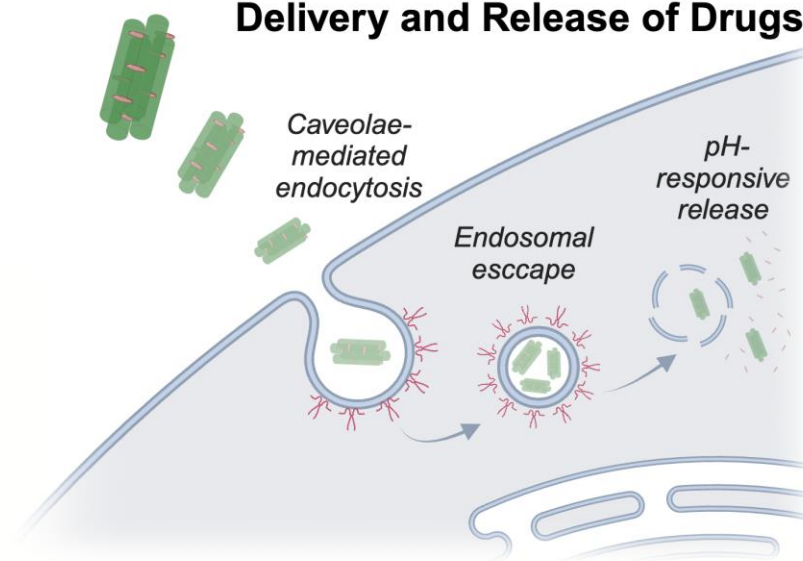
Rod JBNps



Penetration of Rod JBNp into
"hard-to-delivery" tissue



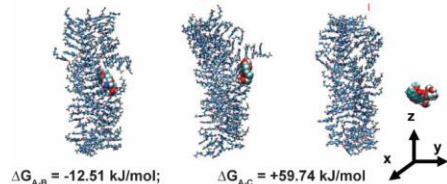
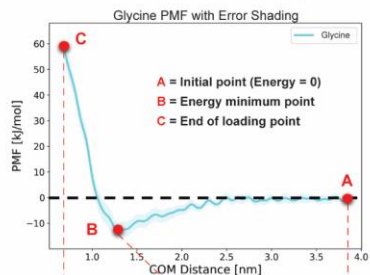
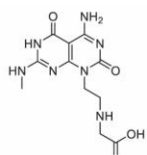
Delivery and Release of Drugs



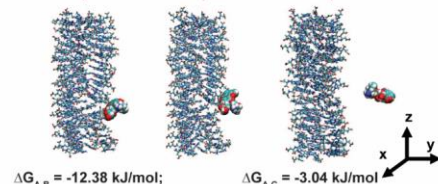
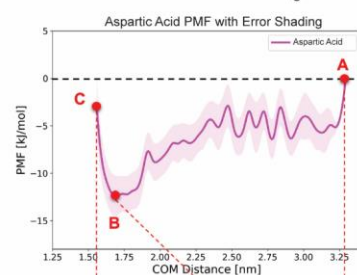
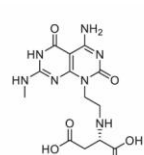
JBNps with a nano-rod shape tend to accumulate at the tumor site due to the **enhanced permeation and retention (EPR)** effect. Moreover, rod-shaped JBNps **penetrate the extracellular matrix (ECM)** of the tumor.

Computational Methodology for JBNp Optimization

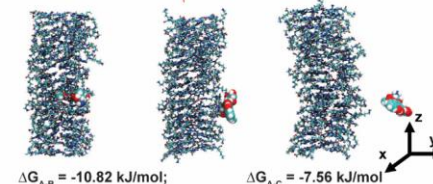
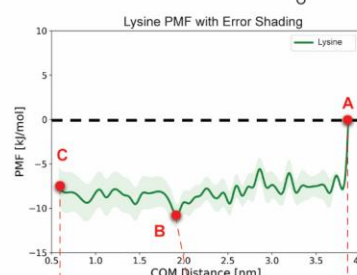
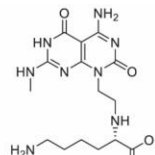
(i) **Gly-JBNt**



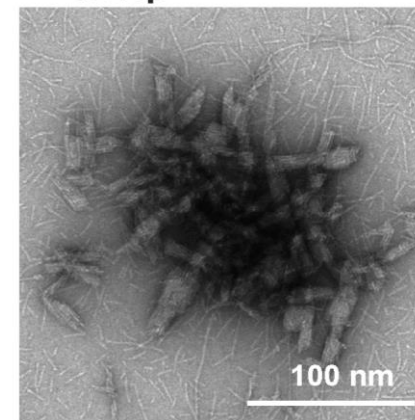
(ii) **AA-JBNt**



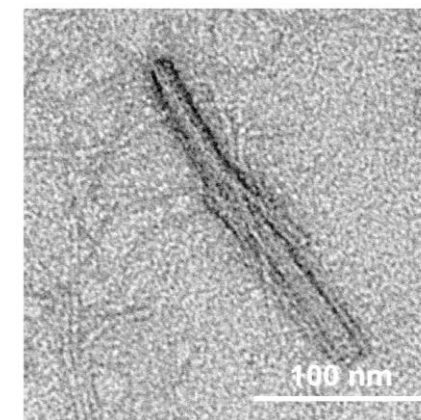
(iii) **Lys-JBNt**



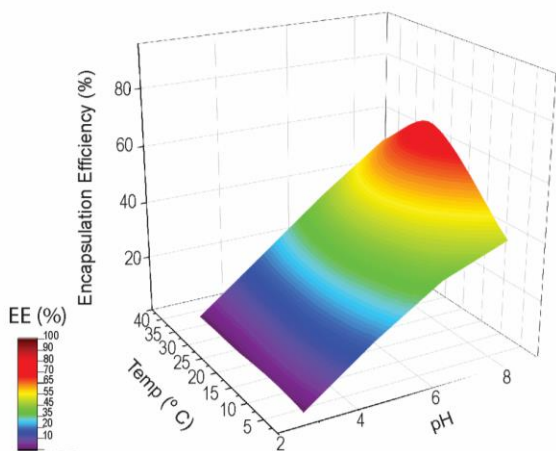
(ii) **Non-rod JBNp**



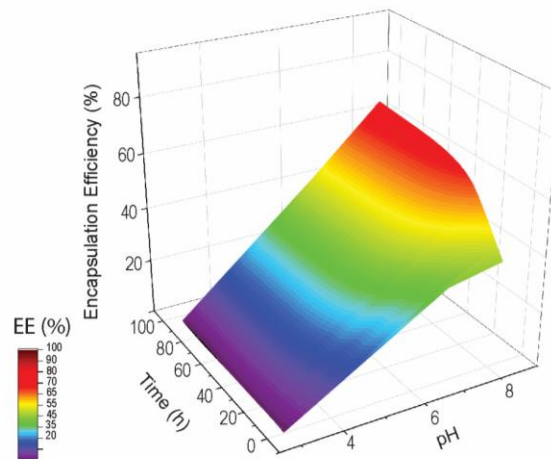
(iii) **Rod JBNp**



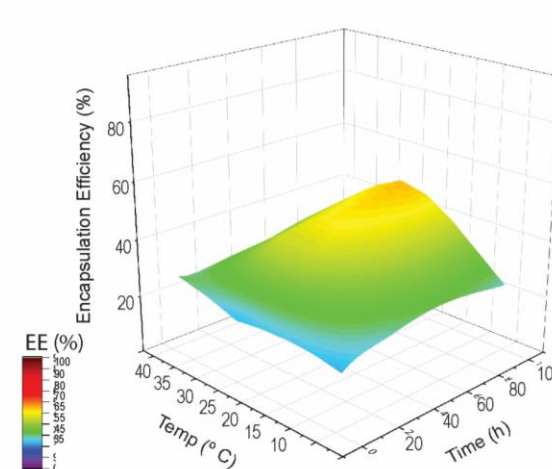
d Surface plot EE (%) vs Temp (°C), pH



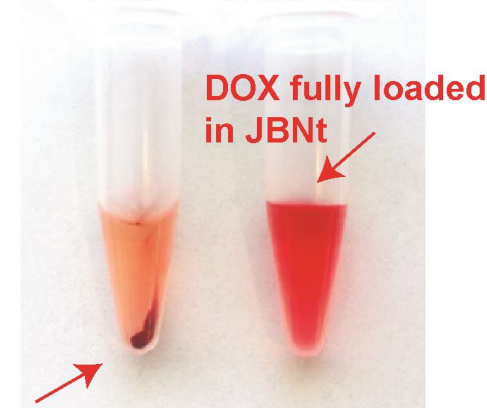
e Surface plot EE (%) vs Time (h), pH



f Surface plot EE (%) vs Time (h), Temp (°C)



PBS **JBNt-DOX**

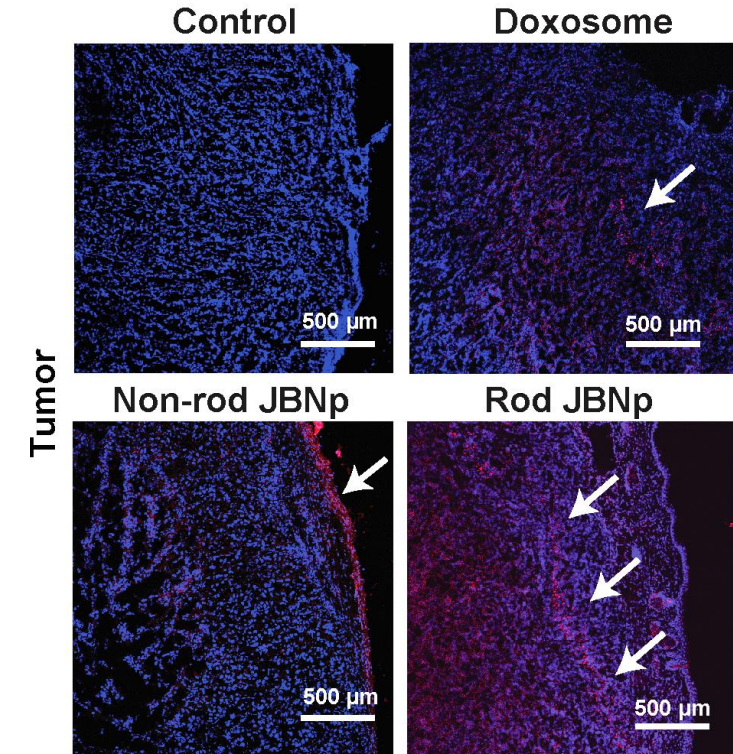
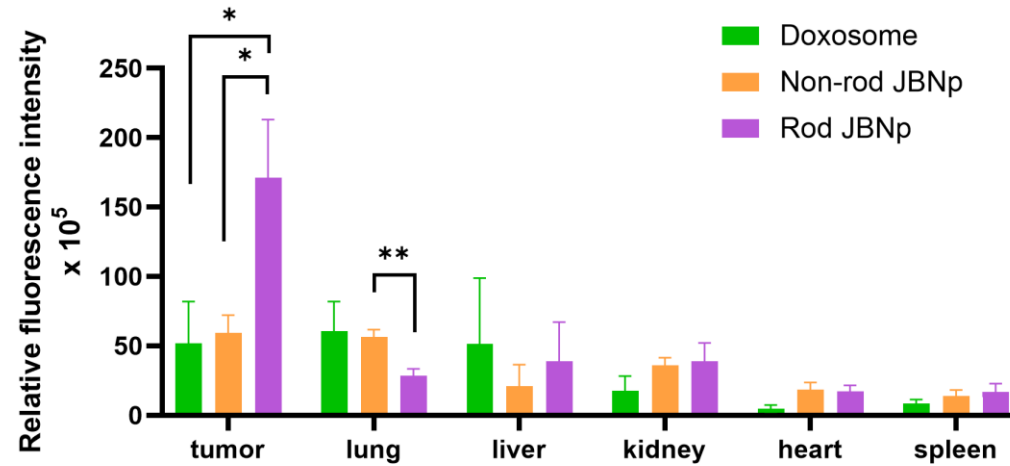
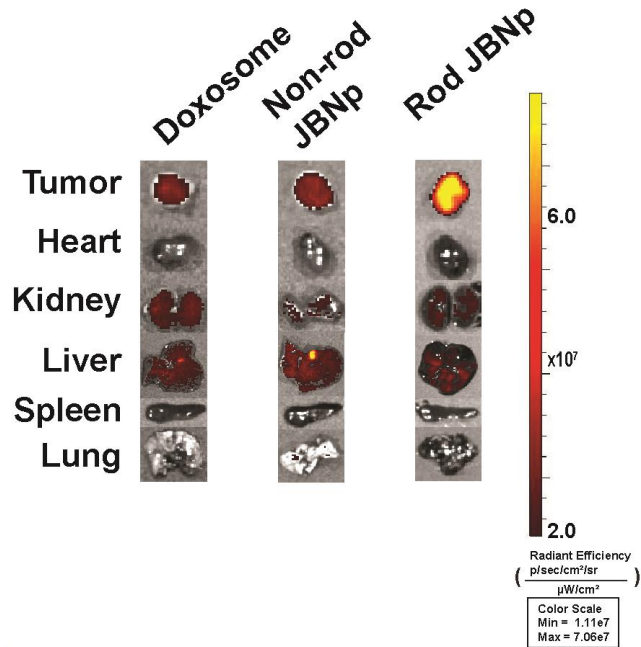


Unloaded DOX forms precipitation

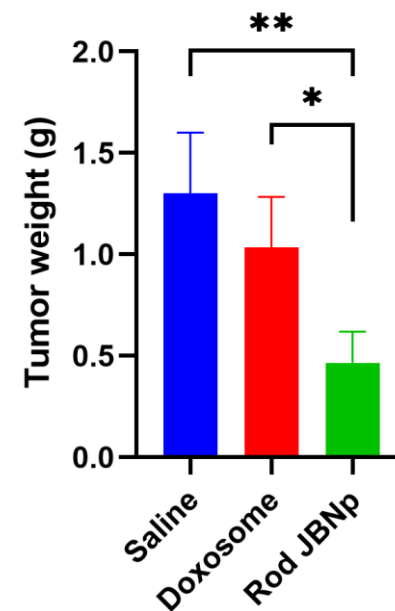
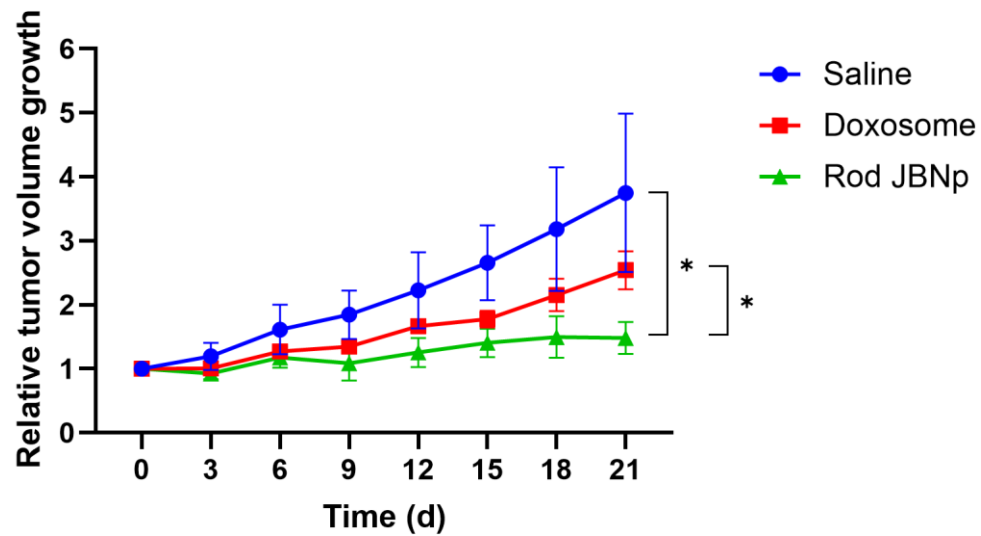
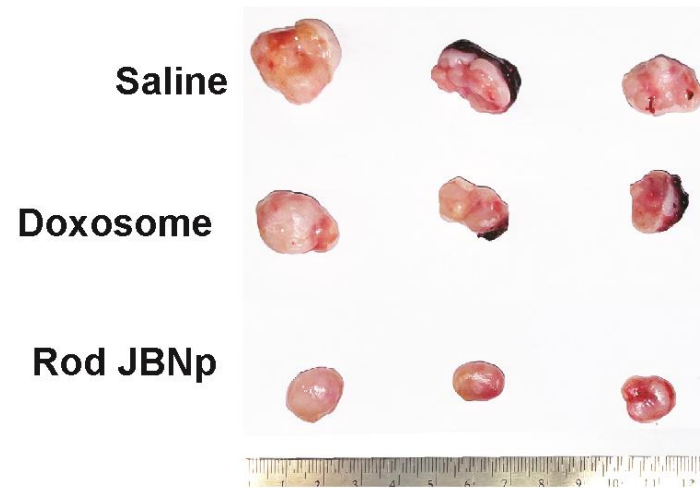
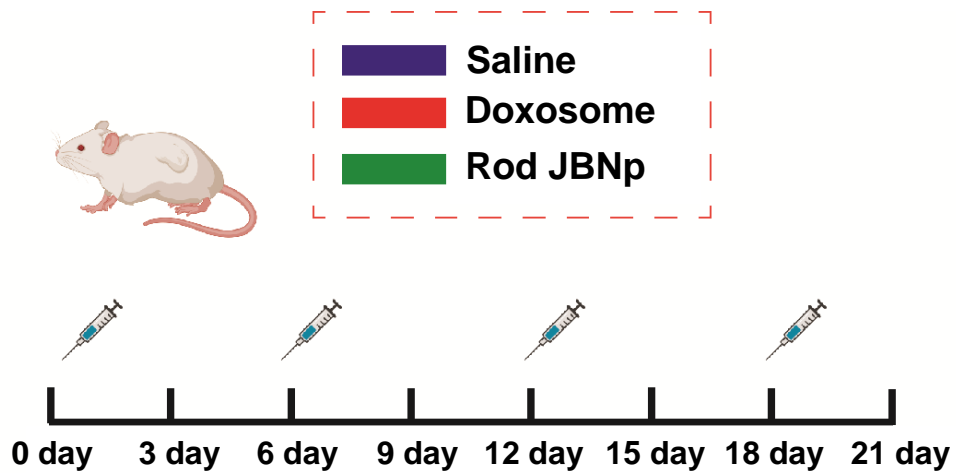
Rod-shaped JBNps showed tumor-specific biodistribution



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Rod-shaped JBNps showed high antitumor activity

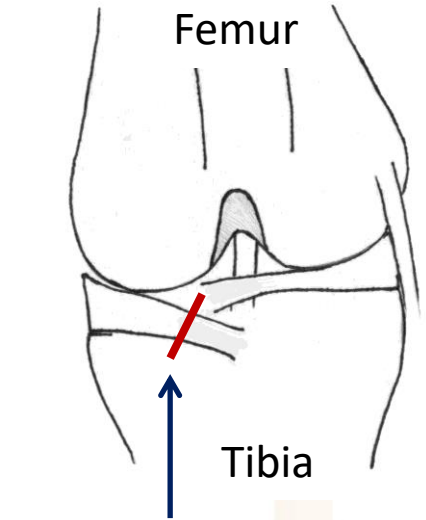


JBNs can deliver therapeutic RNA against osteoarthritis

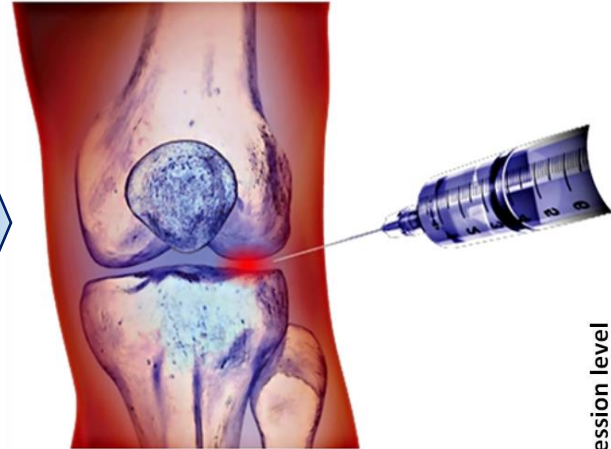
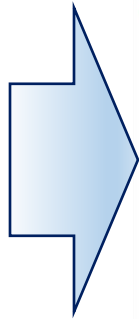


- Osteoarthritis (OA) is the leading cause of disability for aged patients. It affects 32.5 million US adults.
- Currently, **there is no approved disease-modification therapeutic for OA.**
(Corticosteroid and lubrication injections can only temporally relief symptoms.)
- **Cartilage is extremely challenging for drug delivery vehicle to infiltrate** due to its dense avascular and negatively charged tissue matrix.

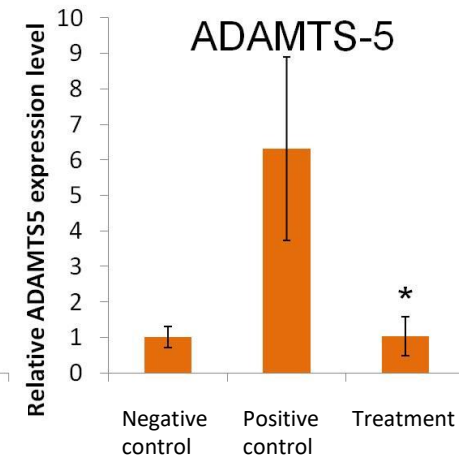
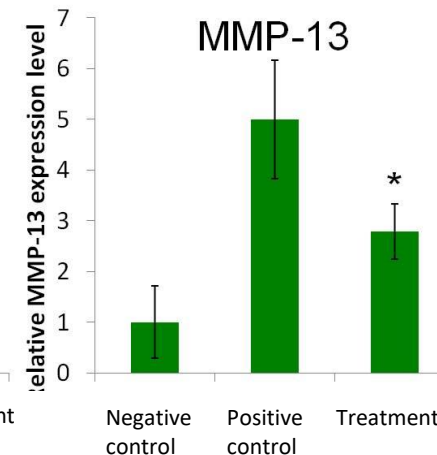
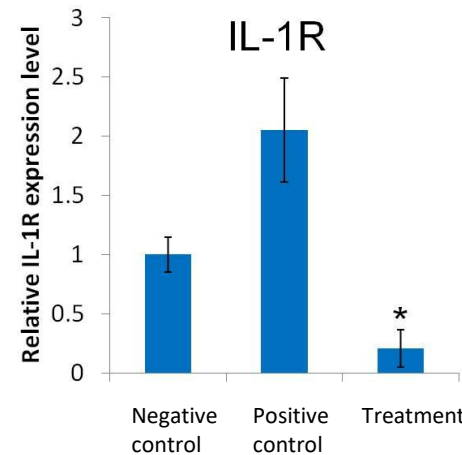
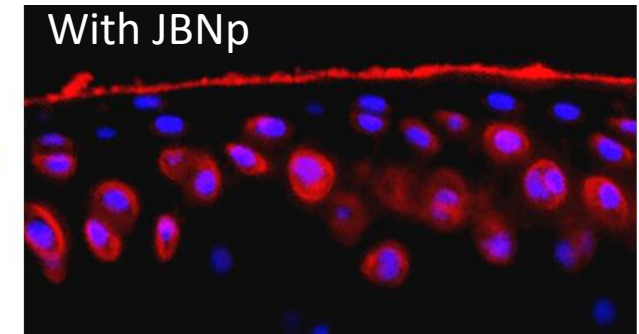
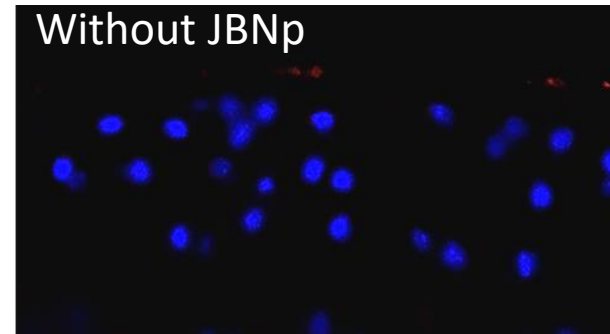
JBNs can deliver therapeutic RNA against osteoarthritis



Destabilization of medial meniscus (DMM) to induce OA

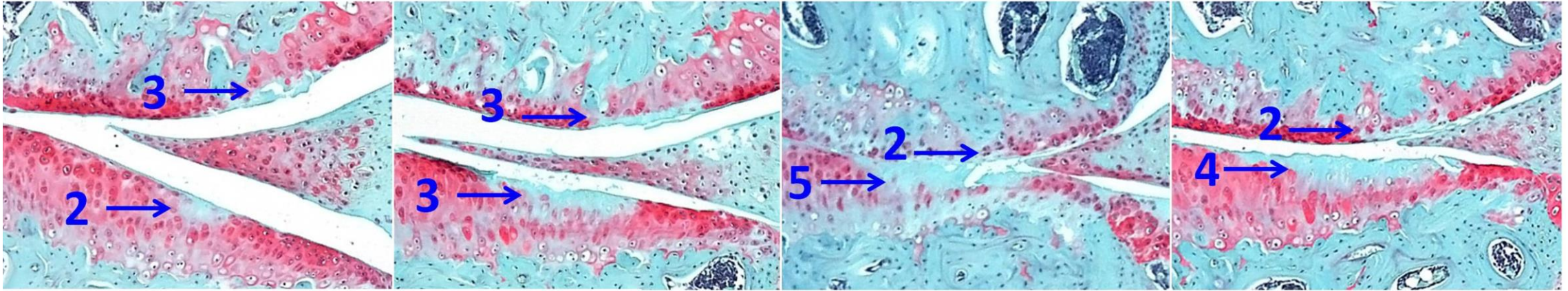


Injection of JBNps to inhibit an inflammation gene (IL-1R) as a treatment.

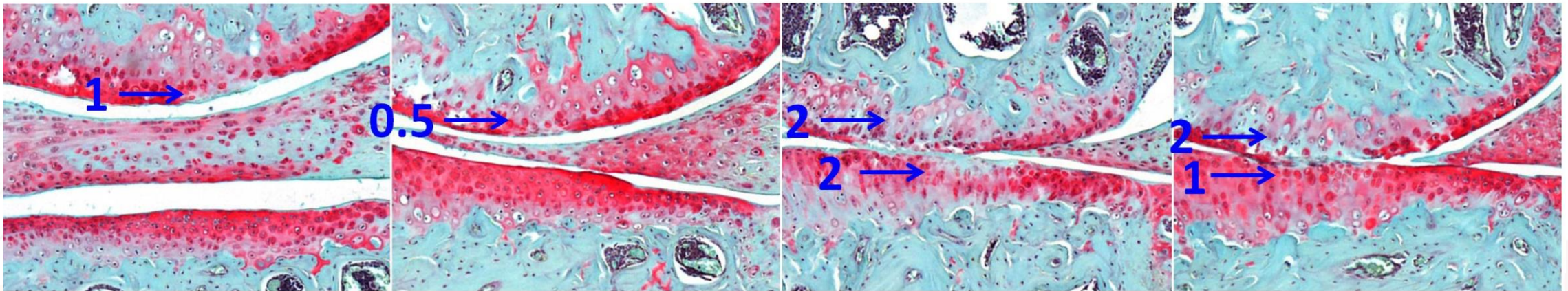


JBNs can deliver therapeutic RNA against osteoarthritis

Control (without treatment)

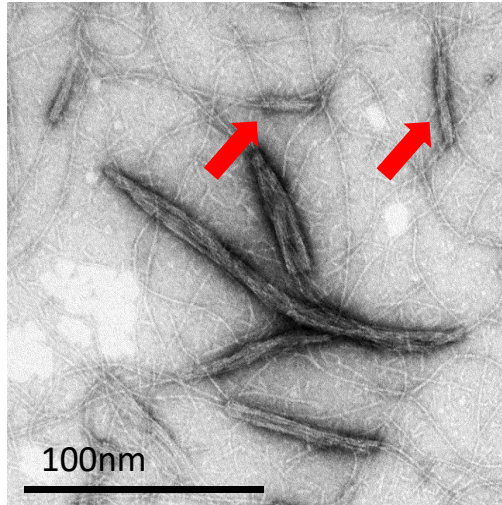


Treatment (with JBNp delivery)

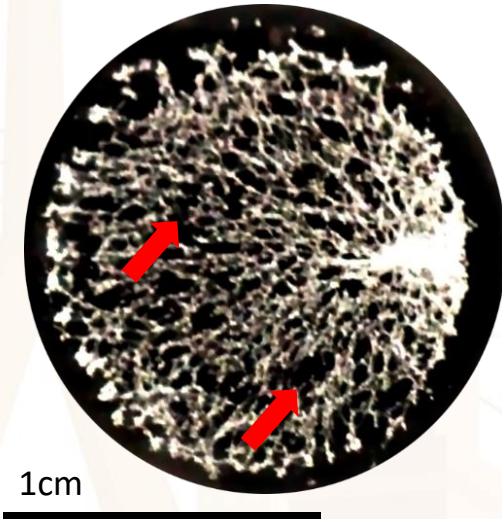


Why do we need in-space manufacturing of JBNs?

JBNp:



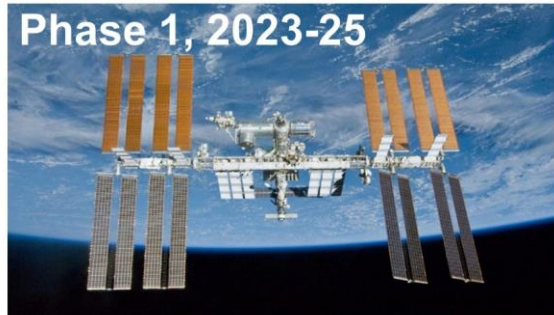
JBNm:



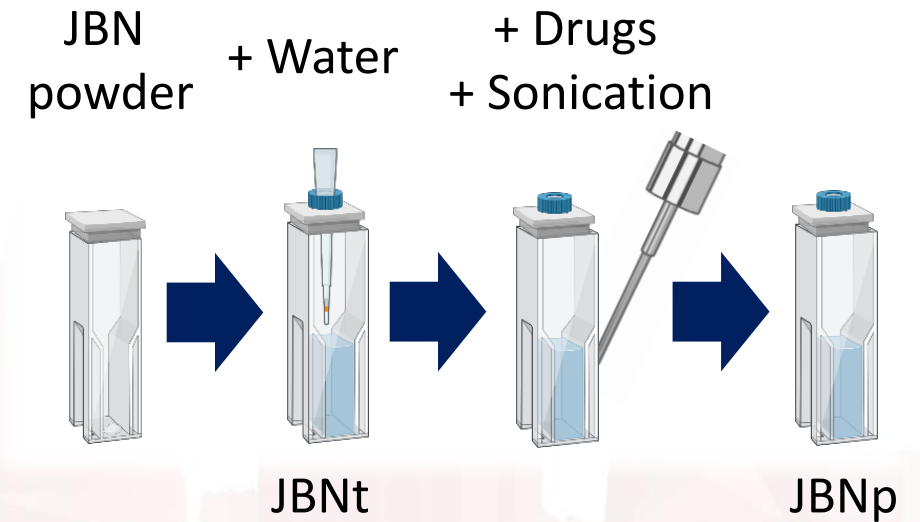
- JBNs assemble via a biomimetic process at **ambient temperature** with minimal equipment requirements, and it is eco-friendly, catalyst-free and crosslinker-free.
- It is known that crystallization can be improved by microgravity due to the **reduction of gravity-driven forces such as sedimentation and convection**. Similarly, JBNs can assemble in a more orderly fashion with better structural integrity.
- Therefore, in-space production can **increase JBN homogeneity and drug load efficiency** for improved bioactivity and reduced toxicity.

How do we accomplish in-space manufacturing of JBNs?

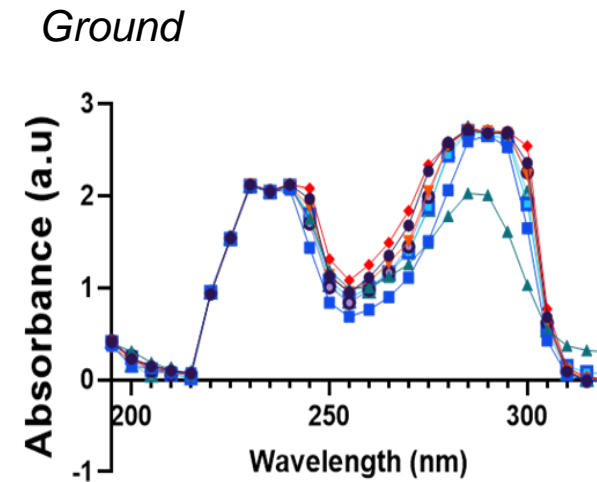
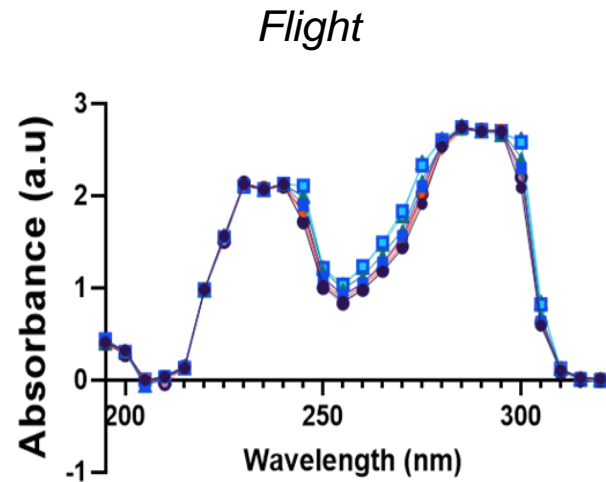
- Supported by NASA and CASIS, we partnered with Axiom Space to fabricate JBNs on the International Space Station (ISS).



- To translate the experiments on Earth into operations in space, we have developed “one-pot-reaction” strategy for producing JBNs.
- Most recently, we have successfully accomplished the Ax-2 mission to verify methodologies and produce JBNm. We have also accomplished the SpX-30 mission to test our flight tools and produce JBNp.



Improved homogeneity of in-space produced JBNs



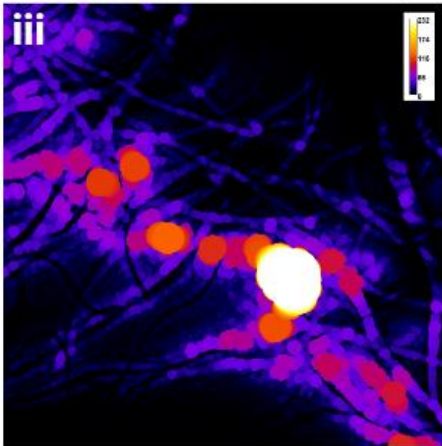
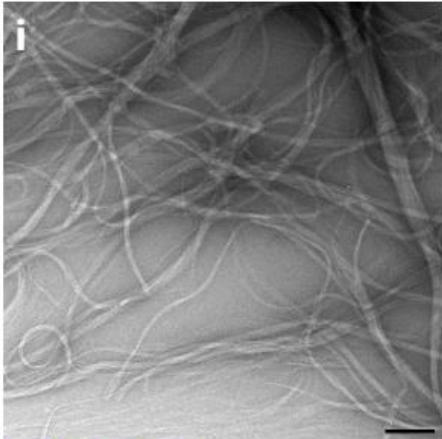
Legend for both graphs:

● JBN SN 9	▲ JBN SN 11	◆ JBN SN 13	■ JBN SN 15
■ JBN SN 10	▼ JBN SN 12	● JBN SN 14	▲ JBN SN 16

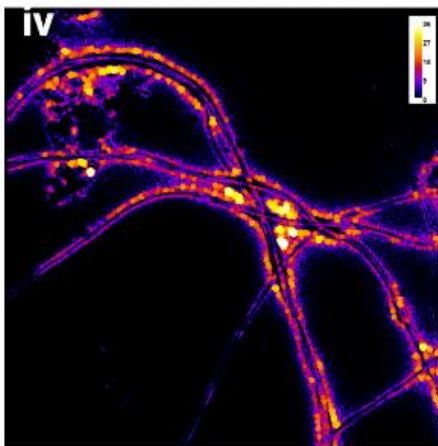
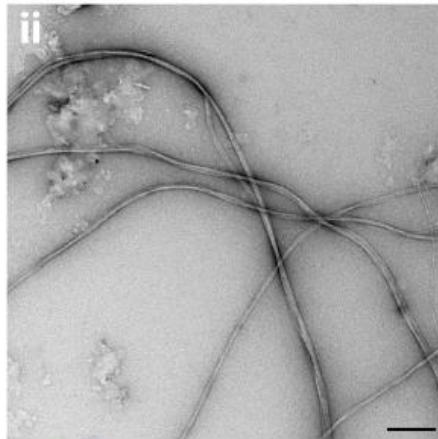
- JBN SN 9-14 are different JBN samples from the same group. Characterized by the UV-vis spectrometry, in-space produced JBN samples showed absorbance curves that were more similar, indicating better uniformity (in terms of protein cargo loading), compared to on-ground controls.

Improved assembly and cargo loading of JBNm

Flight

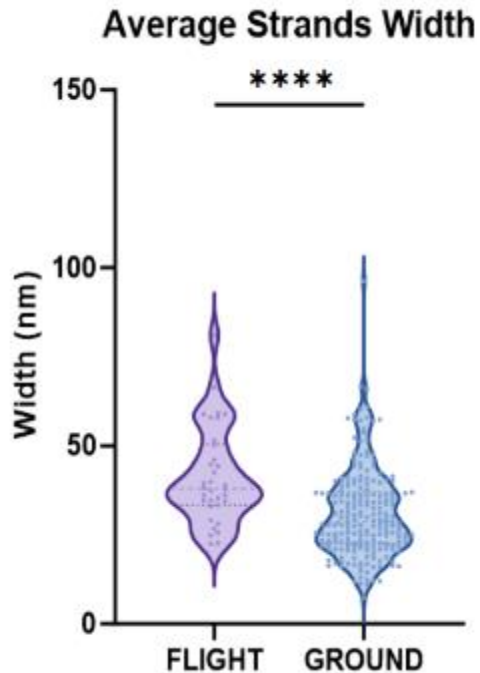


Ground

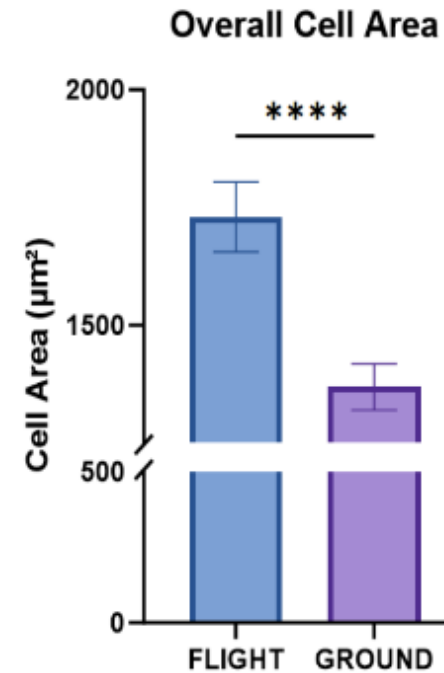


- In-space produced JBNm had dramatically increased formation of matrix bundles showing denser matrix.
- In-space produced JBNm presented improved protein cargo loading in its matrix bundles (demonstrated by brighter colors).

Improved bioactivities of in-space produced JBNm

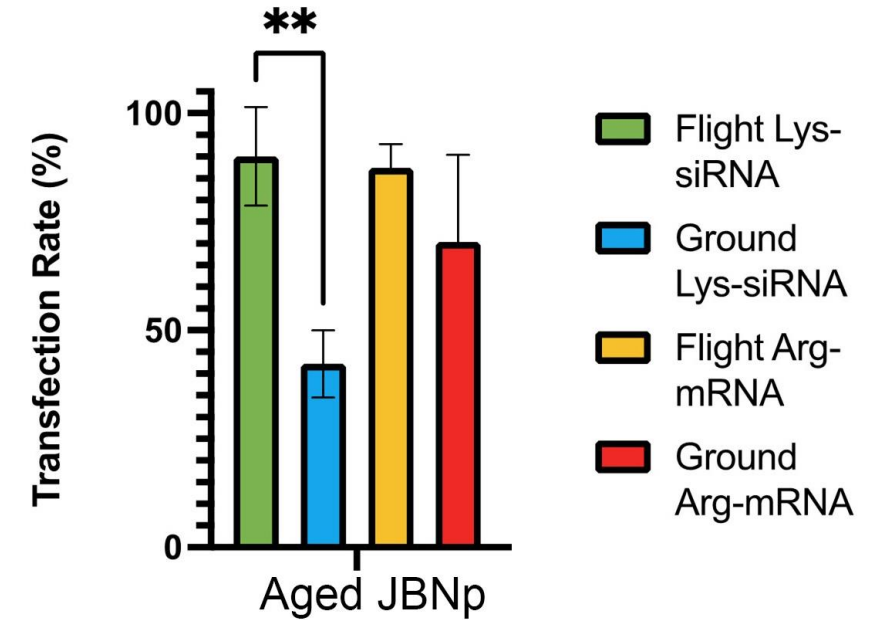
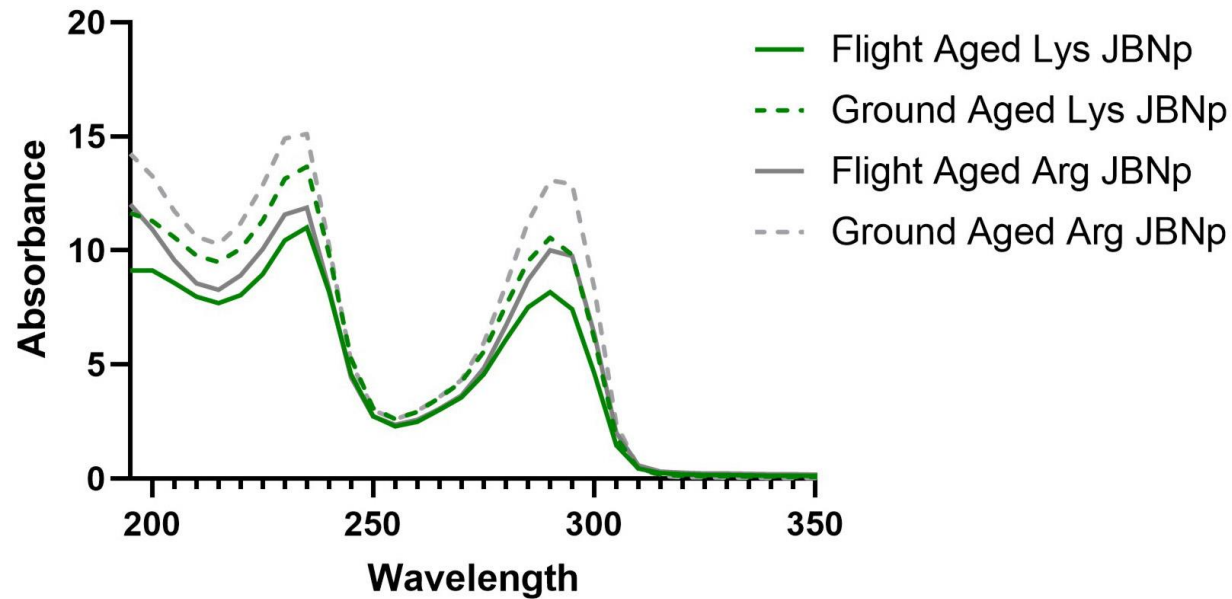


- In-space produced JBNm had significantly wider bundles (~40% increase than ground controls).
- Wider matrix bundles can provide more binding sites for cell adhesion.



- Chondrocytes adhered on in-space produced JBNm presented larger areas, which indicated the in-space produced JBNm had improved bioactivities for cell functions.

Improved assembly, loading and bioactivities of JBNp



Summary

- JBNs are versatile DNA-inspired nanomaterials for drug delivery.
- Computationally designed rod-shaped JBNs can be used to deliver chemotherapy drugs, dramatically **enhancing the targeting of solid tumors by more than 300%**.
- The JBNs can also be used for the delivery of therapeutic RNAs into articular cartilage as a **first-in-kind disease-modifying therapeutic against osteoarthritis**.
- In our recent Ax-2 and SpX-30 missions, we successfully demonstrated that in-space production can significantly **improve JBN homogeneity, assembly, cargo loading, and bioactivities**.

Acknowledgements



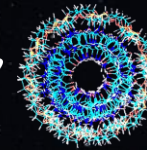
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We would like to thank the support from NASA, CASIS, NIH, NSF, Axiom Space, Eascra Biotech and the University of Connecticut.

We would like to thank Kevin Engelbert, Michael Roberts, Rose Hernandez, Kristin Kopperud, Davide Marotta, Kristin Kopperud, Derek Duflo, Gary Rodrigue, Lynn Harper, Lisa Carnell, Jana Stoudemire, Pinar Mesci, Jay Hoying, Brandon Williams, Honglu Wu, Matthew Wallace and all contributors.



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