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Visions for the field by a pioneer

Vladimir Mironov

3D Bioprinting Solutions, Russia

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Visions for the field by a pioneer

Vladimir Mironov MD, PhD
Chief Scientific Officer
3D Bioprinting Solution
Moscow, Russia

Classification of bioprintists

First generation of bioprintists:

Boland, Forgacs, Hutmacher, Mironov, Wei Sun...

Second generation of bioprintist:

Jos Malda, Jurgen Groll, Michael Gelinsky...

Third generation of bioprintists:

Our main achievements

- **International Society for Biofabrication**
- **Annual Conference on Biofabrication**
- **Journal Biofabrication**
- **Textbooks and PhD courses on biofabrication and bioprinting**
- **Bioprinting of first functional animal organ**
- **Emerging bioprinting industry**

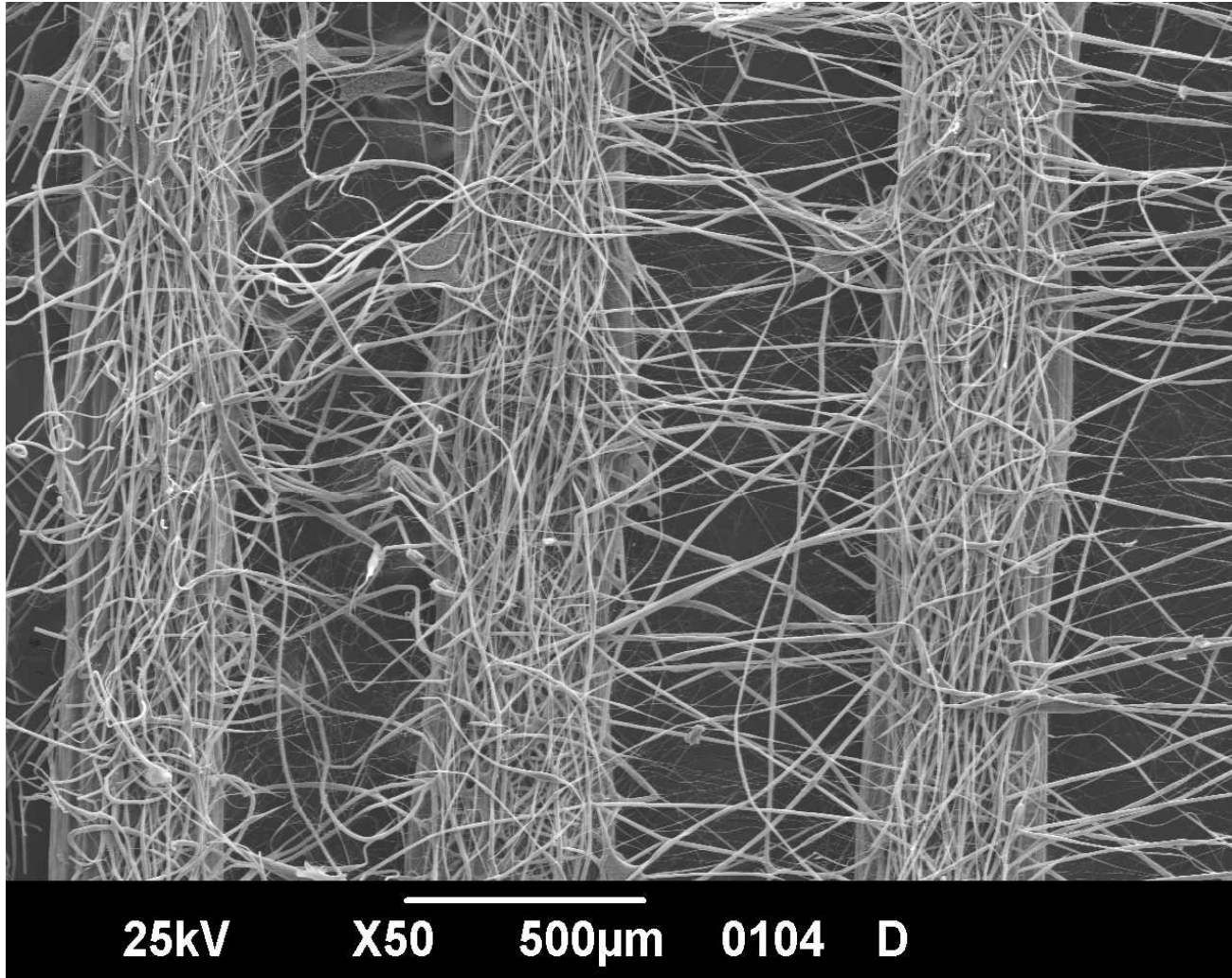
Our main goals for the next 5 years

- **European Society for Biofabrication - 2019**
- **First European Conference on Biofabrication (Pisa, Italy, 2019)**
- **1 billion euro European Future Emerging Technology (FET) Flagship Project 2020**
- **World Biofabrication Congress (Hawaii, USA, 2022)**
- **Bioprinting of first human organ ???**

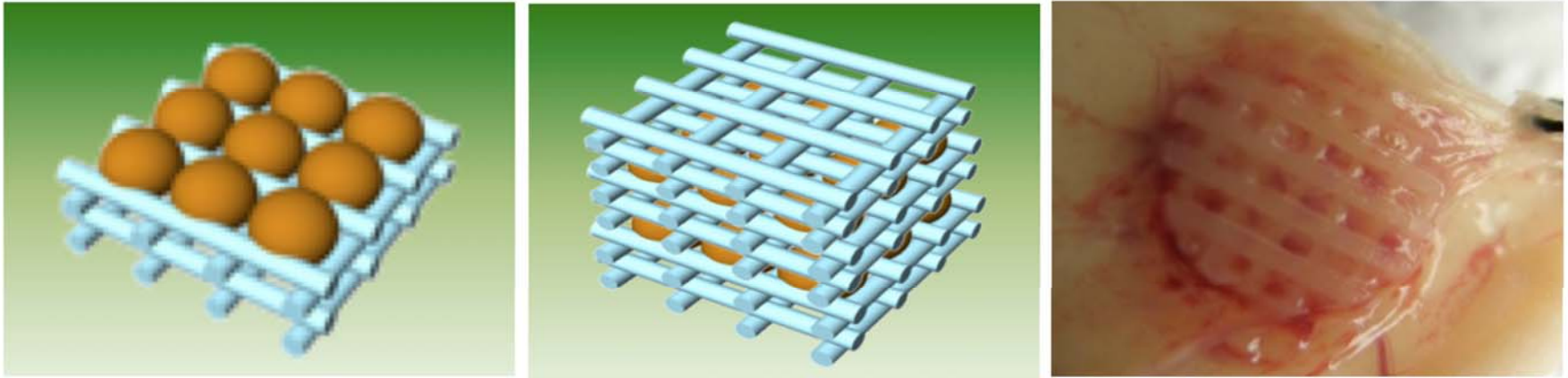
New Trends in 3D Bioprinting

- **Hybrid Bioprinting**
- **In vivo Bioprinting**
- **Magnetic Bioprinting**
- **Acoustic Bioprinting**
- **4D Bioprinting**

Trend 1. Hybrid 3D Bioprinting



Bioreactor-free Hybrid Bioprinting



Hierarchically Assembled Mesenchymal Stem Cell Spheroids Using Biomimicking Nanofilaments and Microstructured Scaffolds for Vascularized Adipose Tissue Engineering

Taek Gyoung Kim¹, Suk-Hee Park², Hyun Jung Chung¹, Dong-Yol Yang², Tae Gwan Park^{1,*}

Advanced Functional Materials

[Volume 20, Issue 14, pages 2303–2309, July 23, 2010](#)

Tissue engineering approach for treatment microtia



Famous Vacanti's mouse



Microtia

Modern Treatment of Microtia



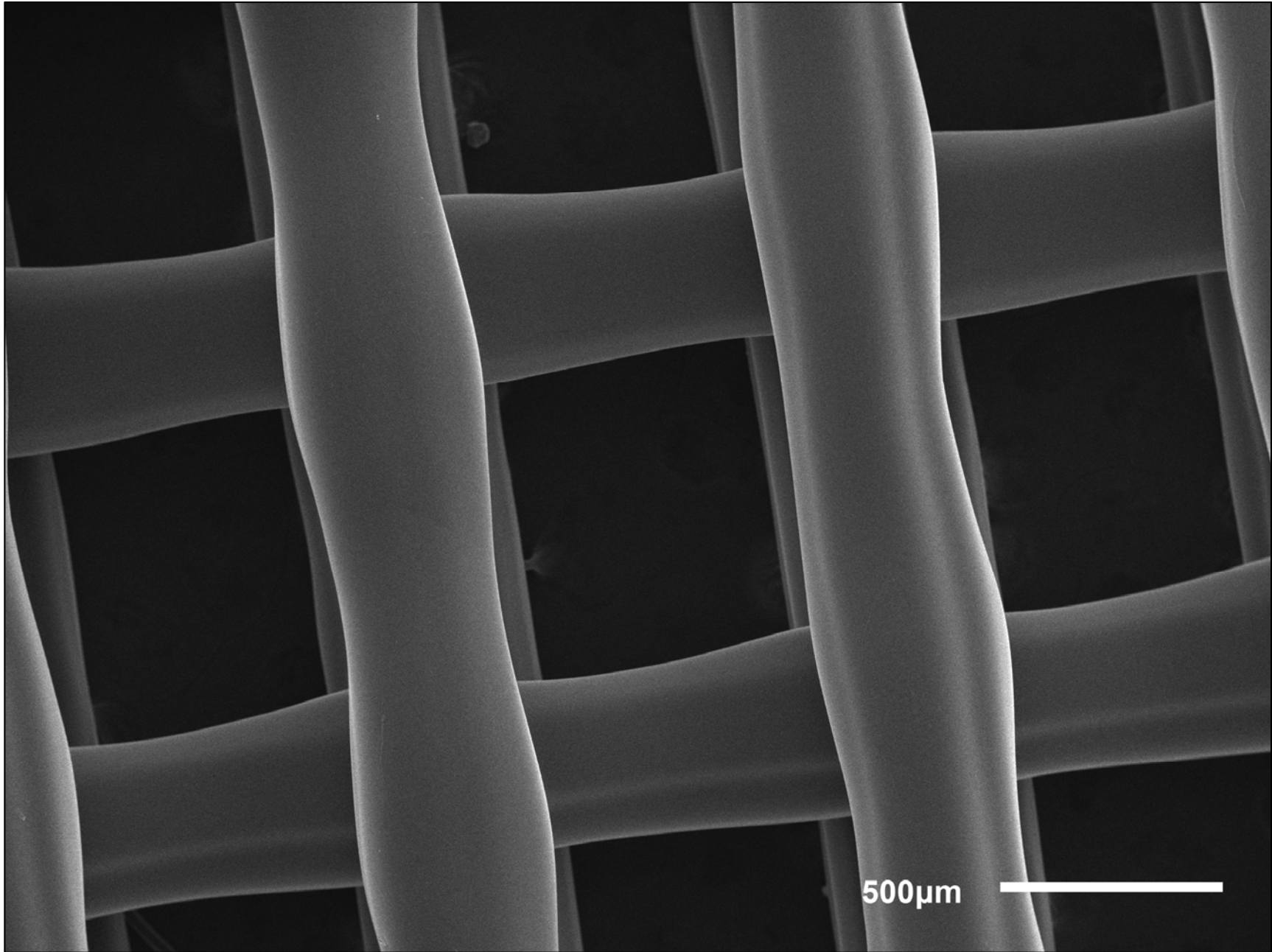
**Painted
silicone**



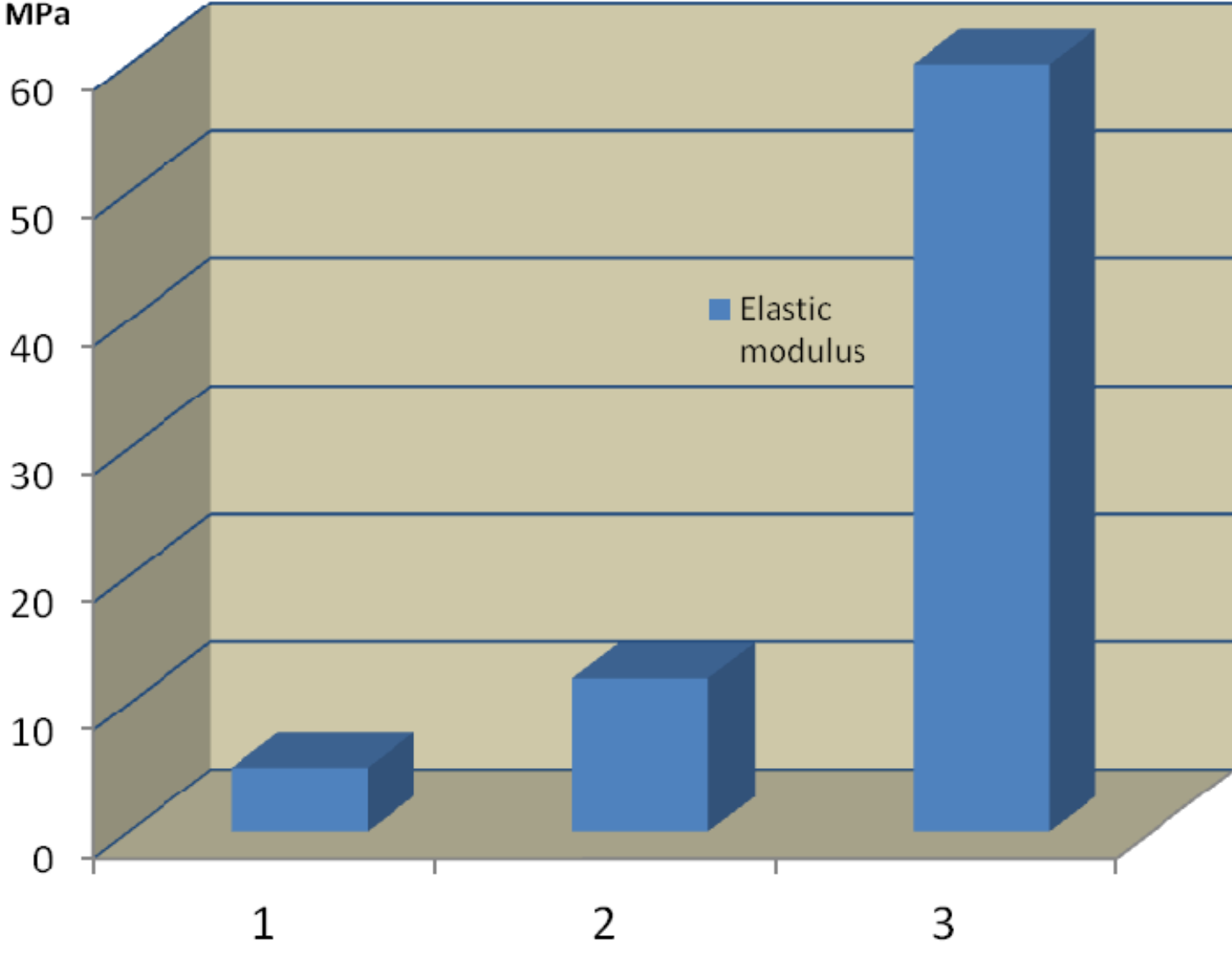
**“Porex”- porous
polyethylene**



**Autologous
rib cartilage**



Material Properties of Auricular Implant



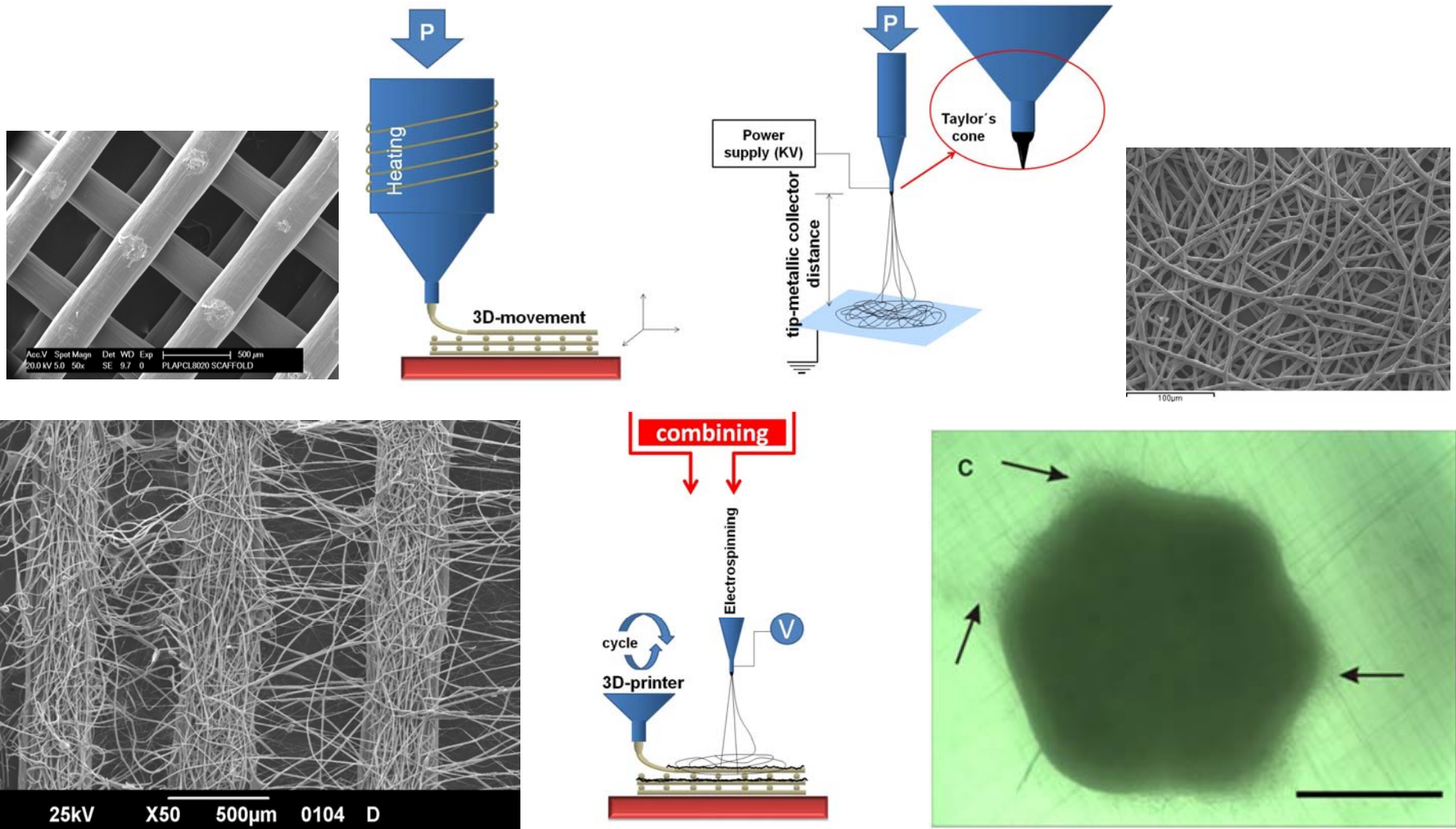
Fabrication & Testing of Auricular Implant

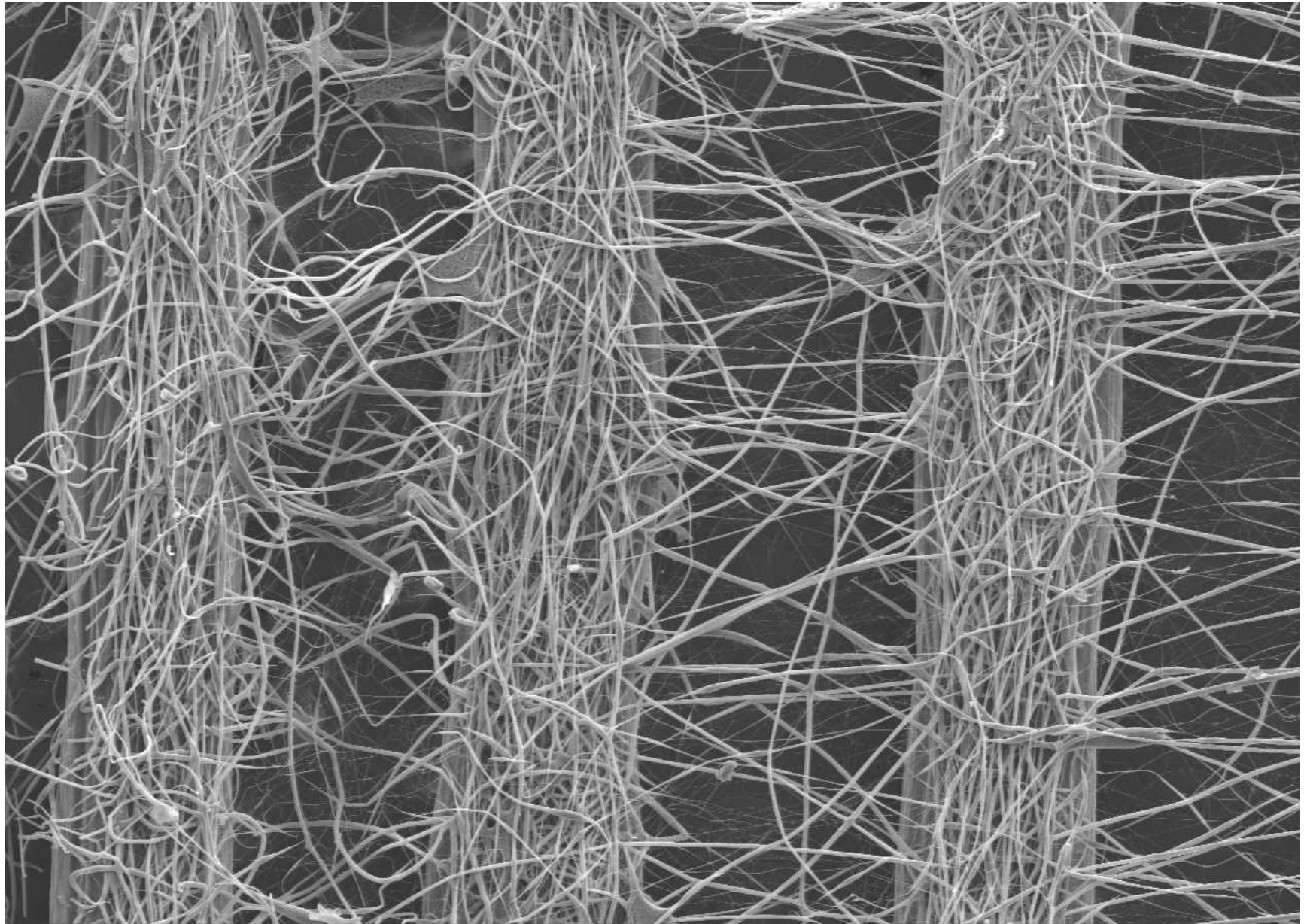


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Hybrid Electrospinning & Fused Deposition Modeling Technology





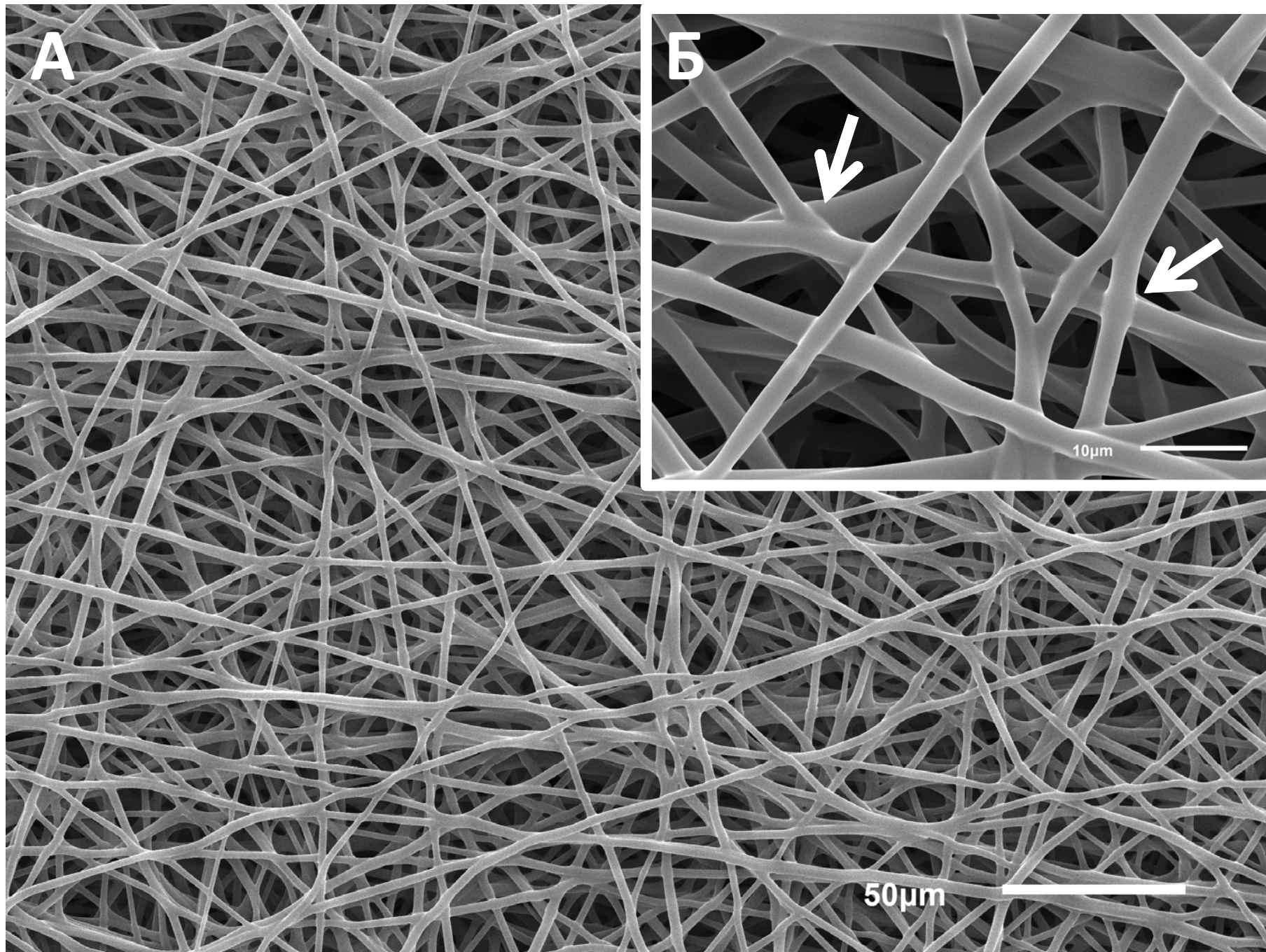
25kV

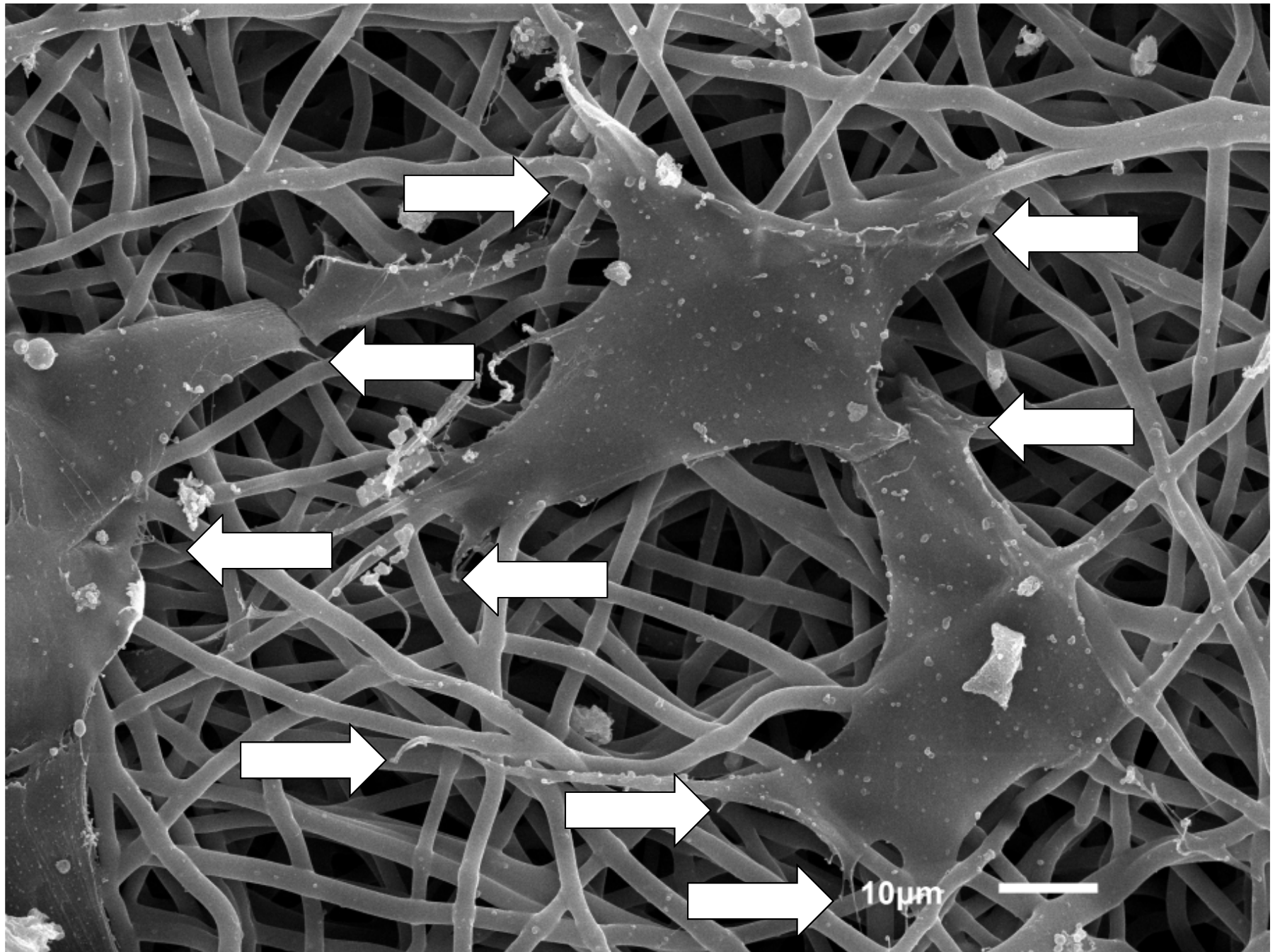
X50

500μm

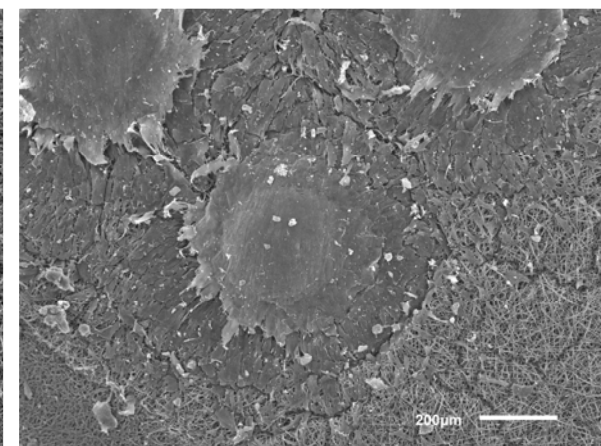
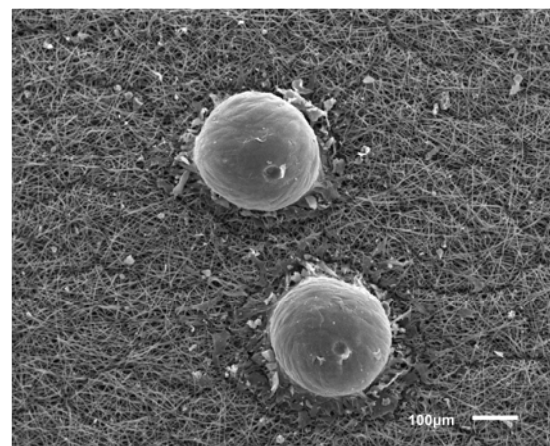
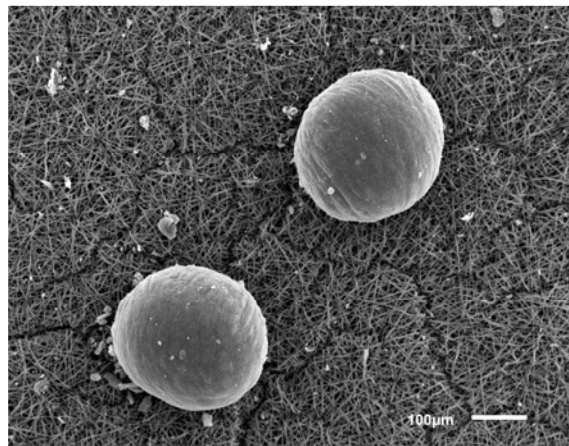
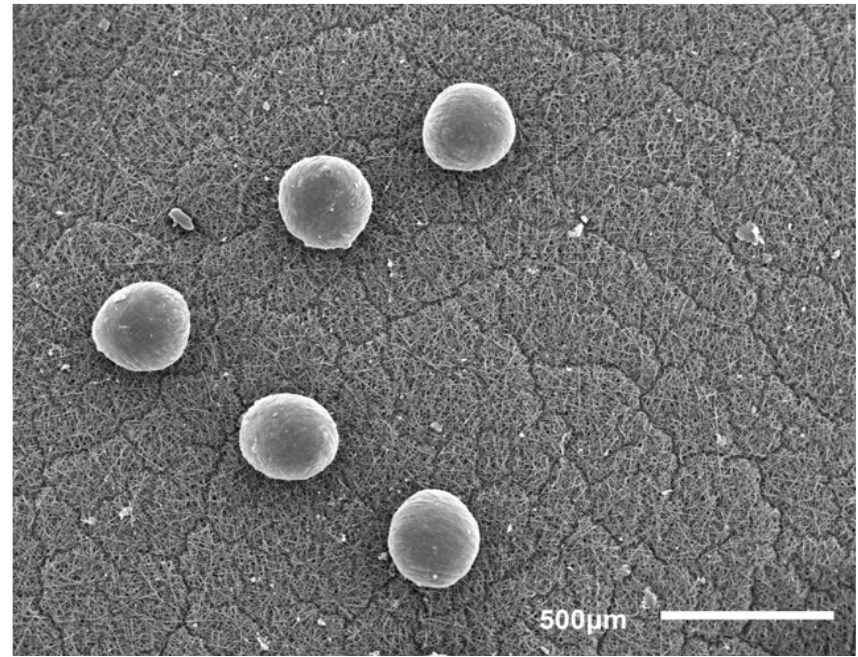
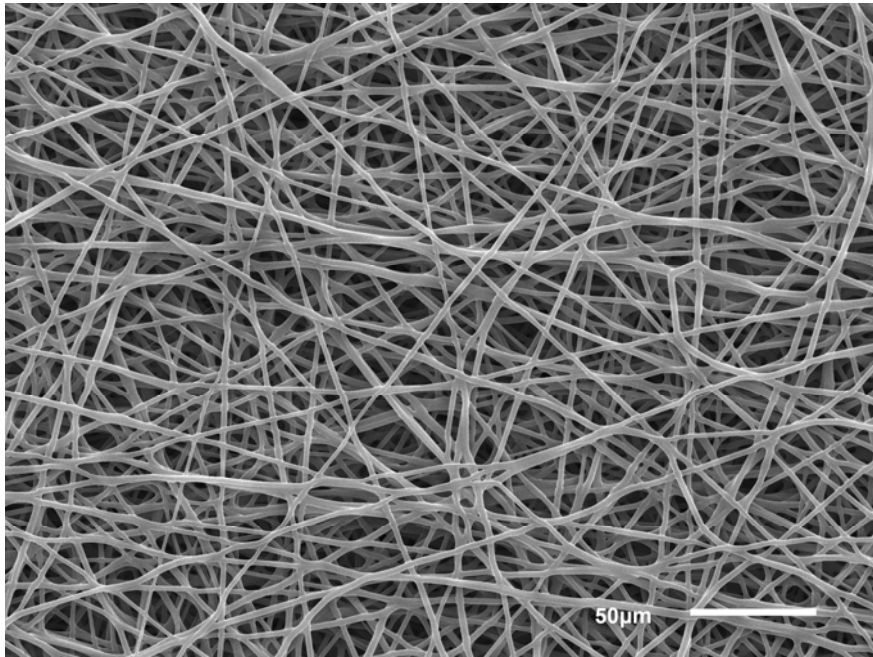
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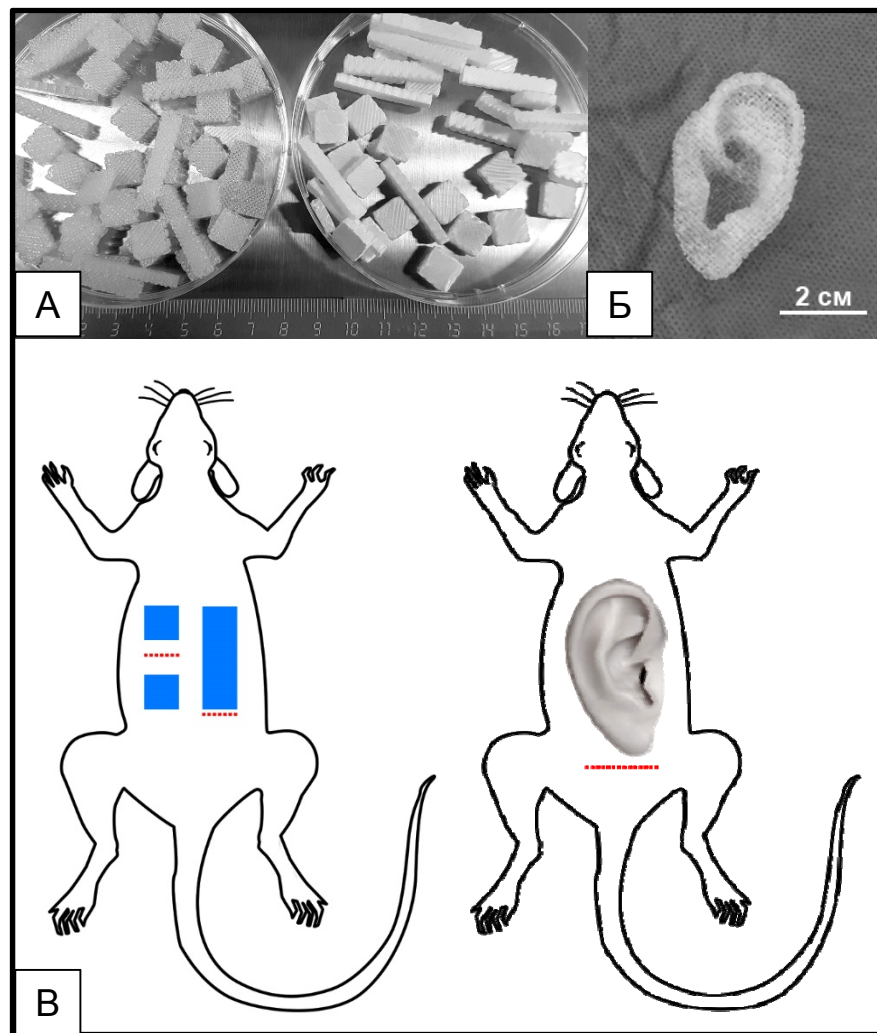
D





Tissue spheroids on electrospun matrices

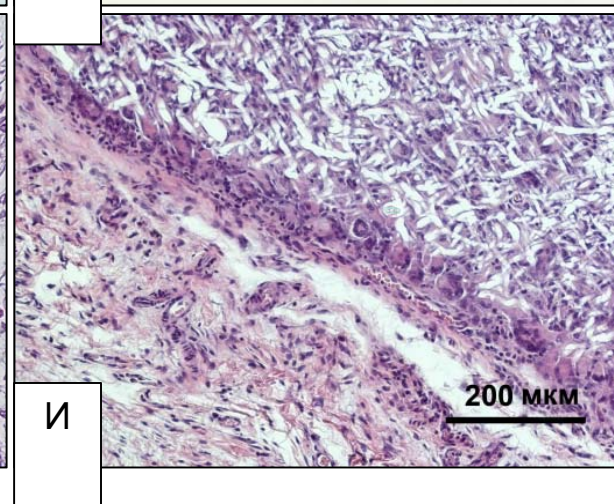
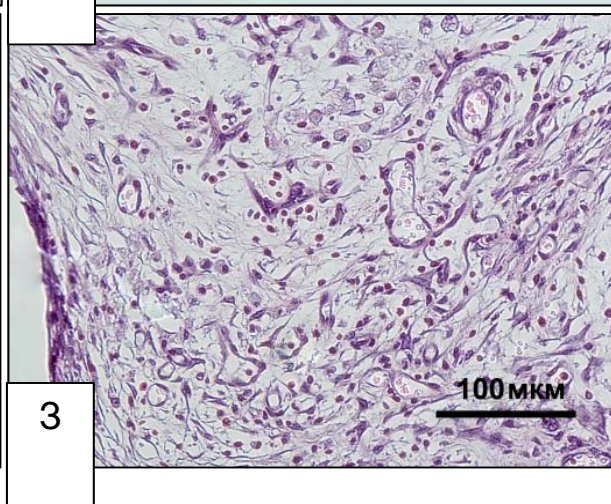
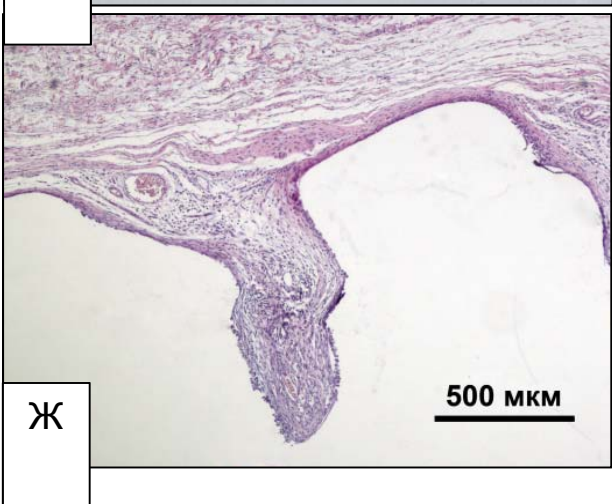
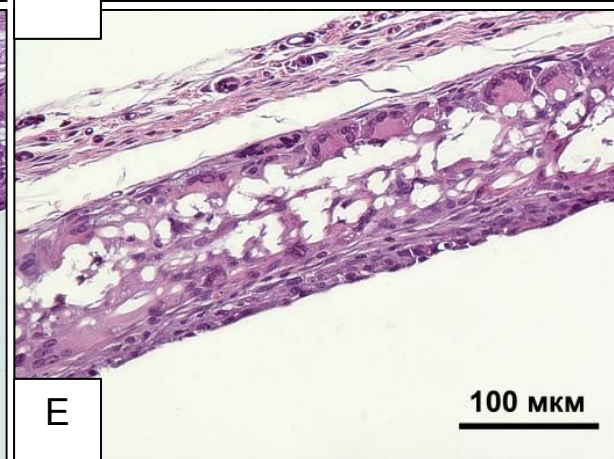
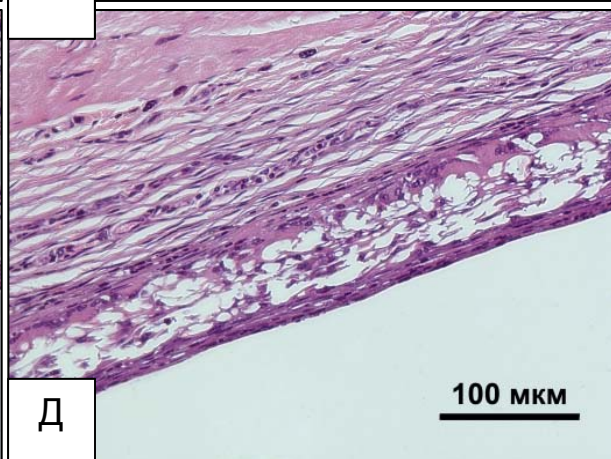
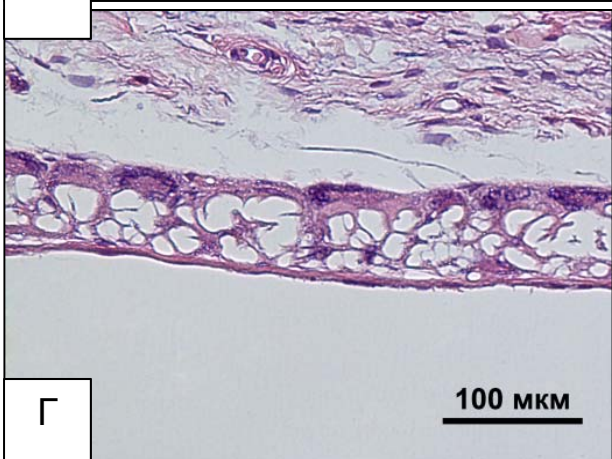
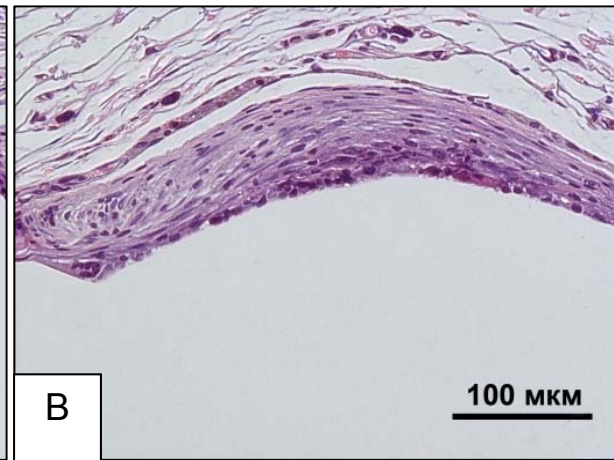
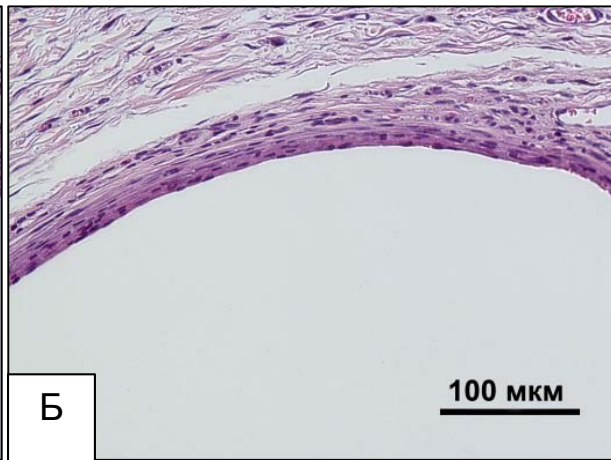
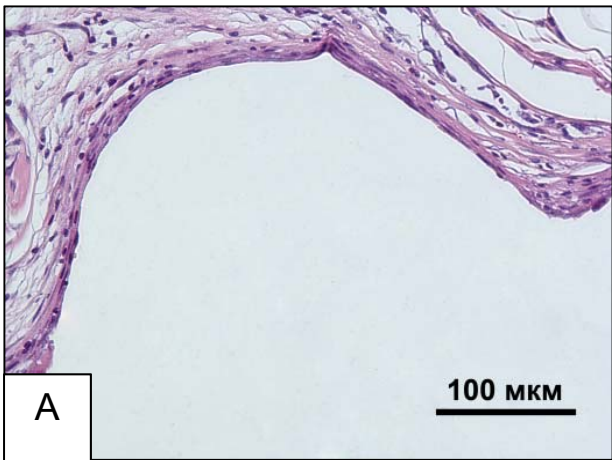


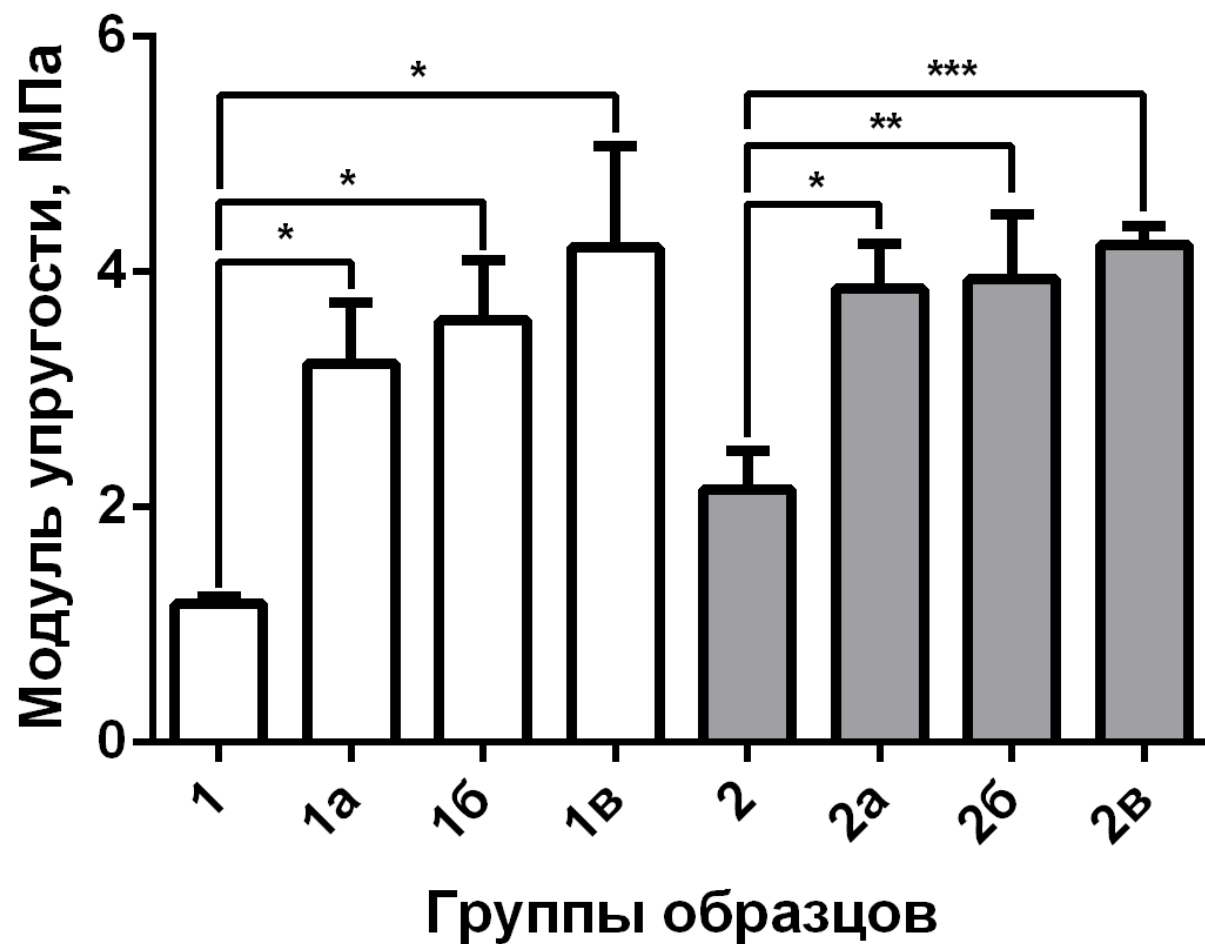


Scheme of implantational experiments

Polyurethane auricular prostheses one month after implantation



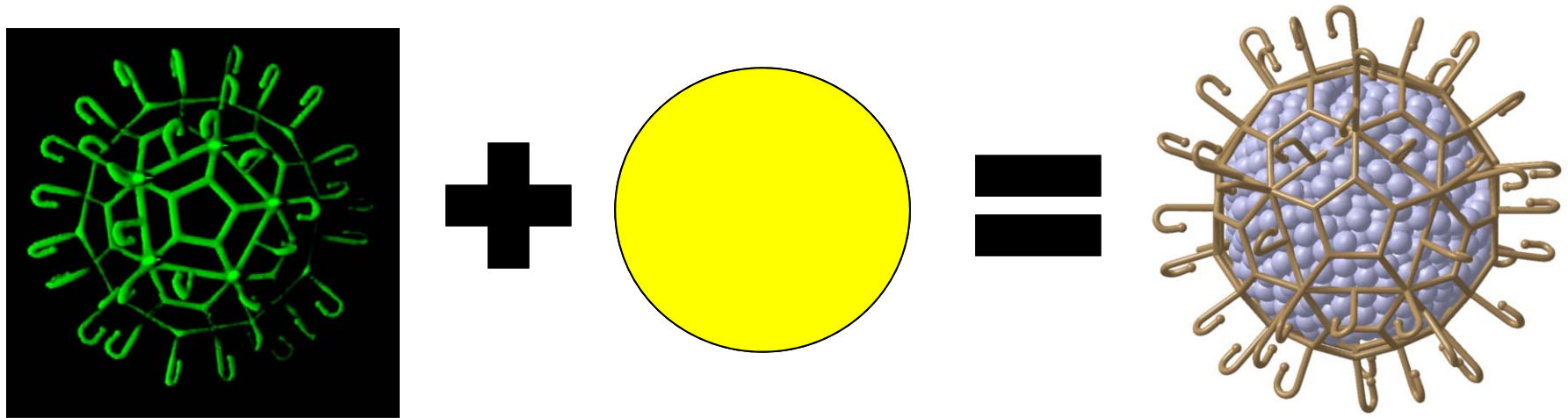




Modulus of elasticity of polyurethane auricular prostheses before and after subcutaneous implantation

*** – $p < 0,005$, ** – $p < 0,01$, *** – $p < 0,001$.**

Biofabrication of Tissue Spheroids Encaged in Interlockable Microscaffolds or simply - **LOCKYBALLS**



INITIAL GOAL:

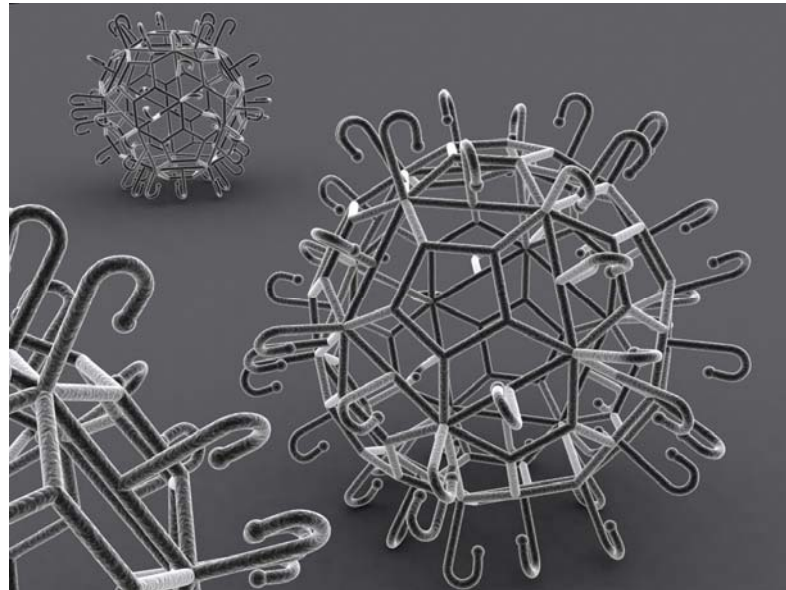
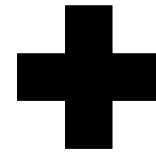
to make tissue spheroids rapidly interlockable

It is more than just scaffold cellularization

LOCKYBALLS IS A BRAZILIAN INVENTION



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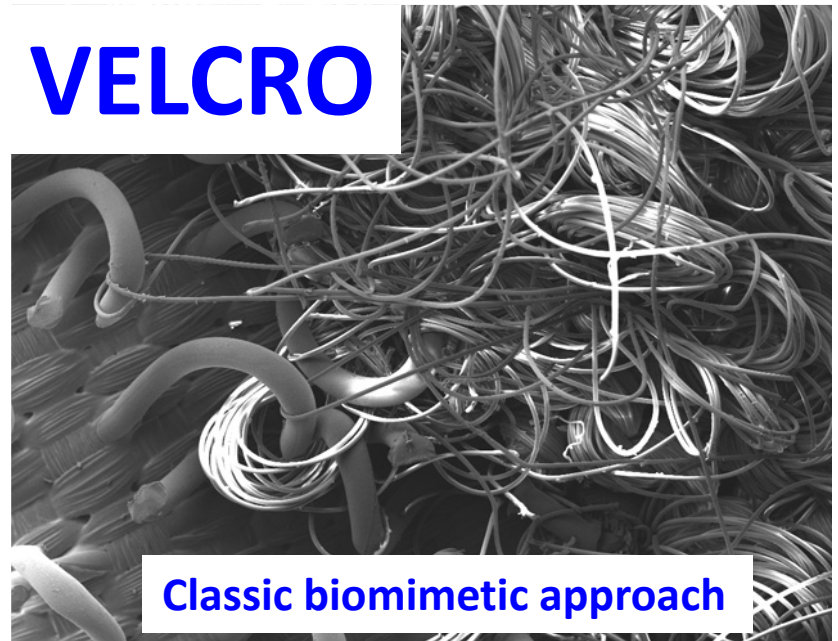


VELCRO

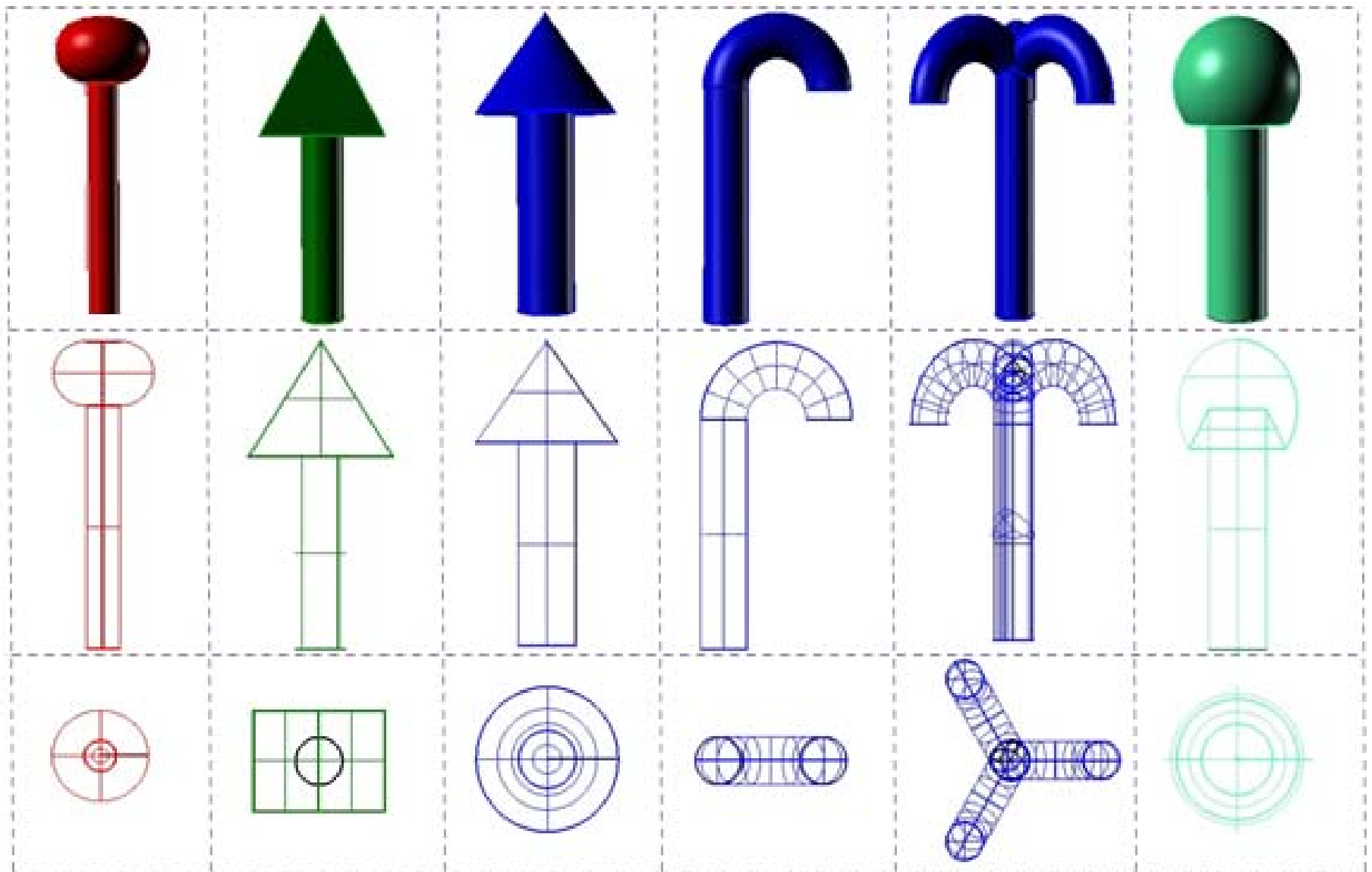


George de Mestral (Switzerland, 1948)

VELCRO

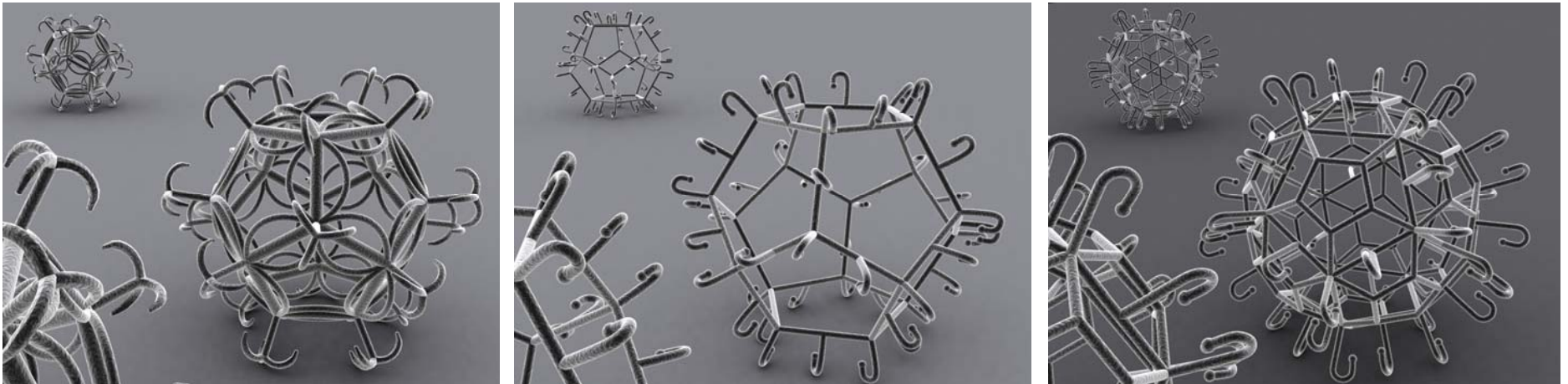


Classic biomimetic approach

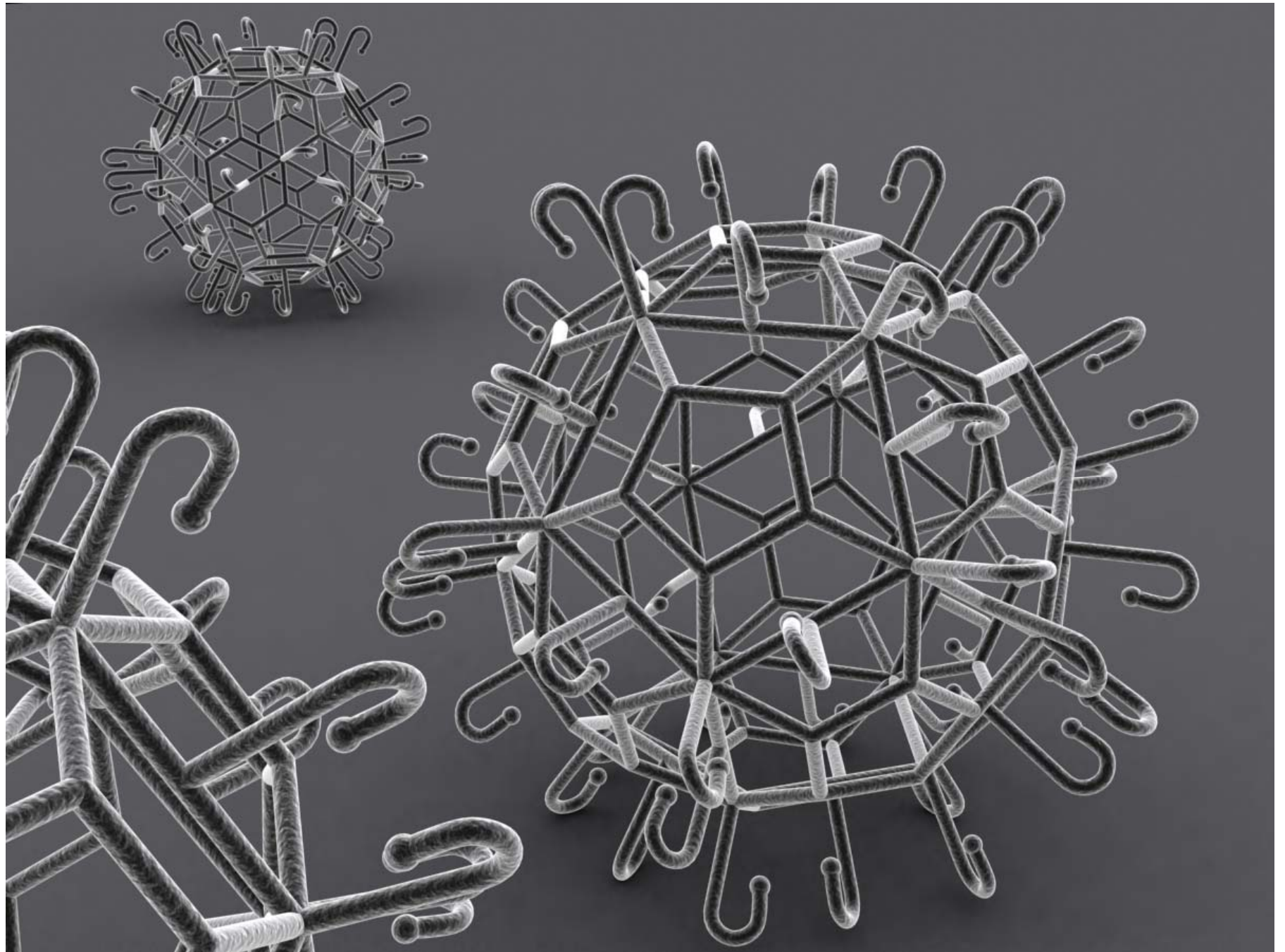


Journal of Nanotechnology, 2012

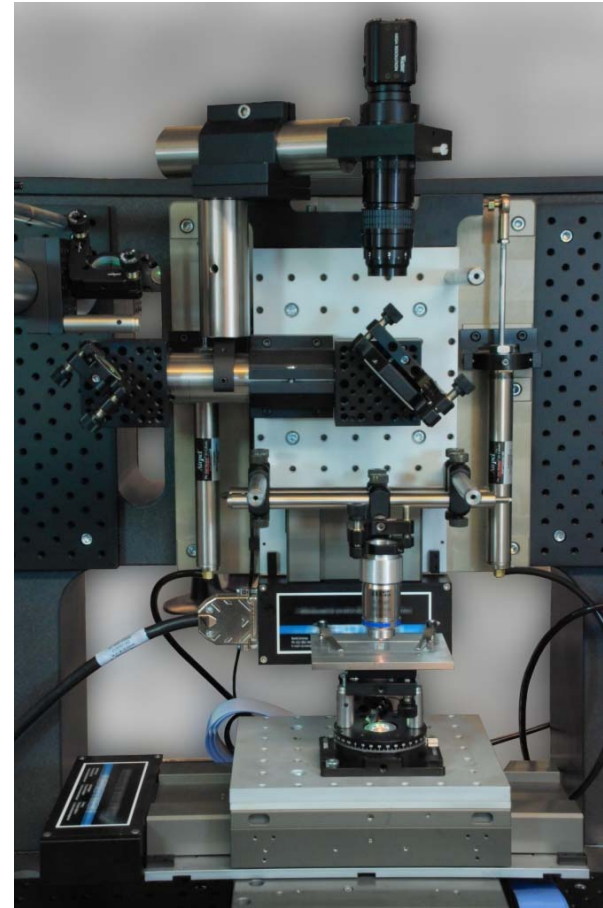
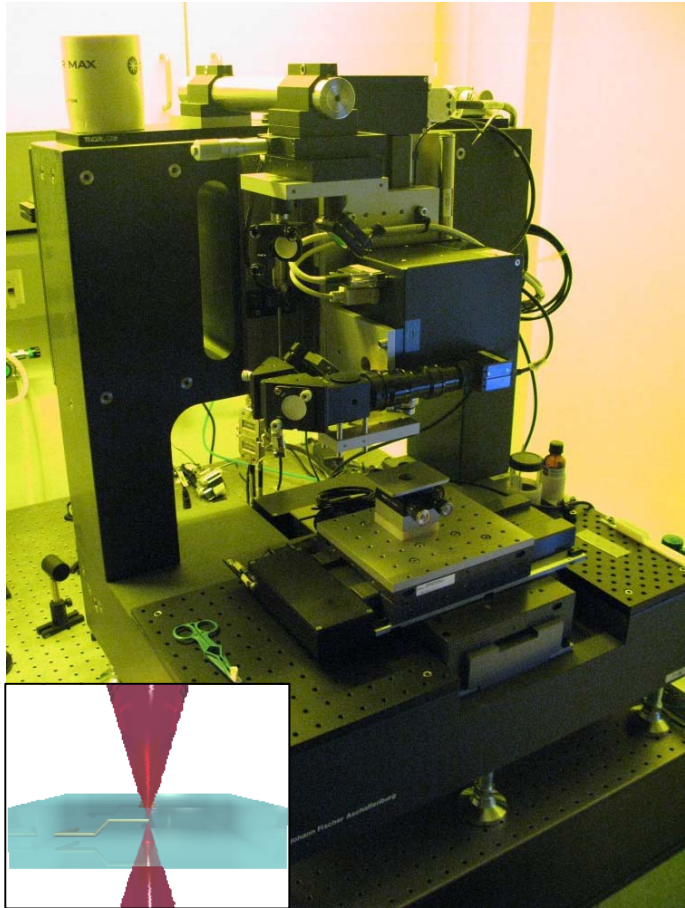
Computer-Aided Design of Interlockable Microscaffolds or Lockyballs



Journal of Nanotechnology, 2012

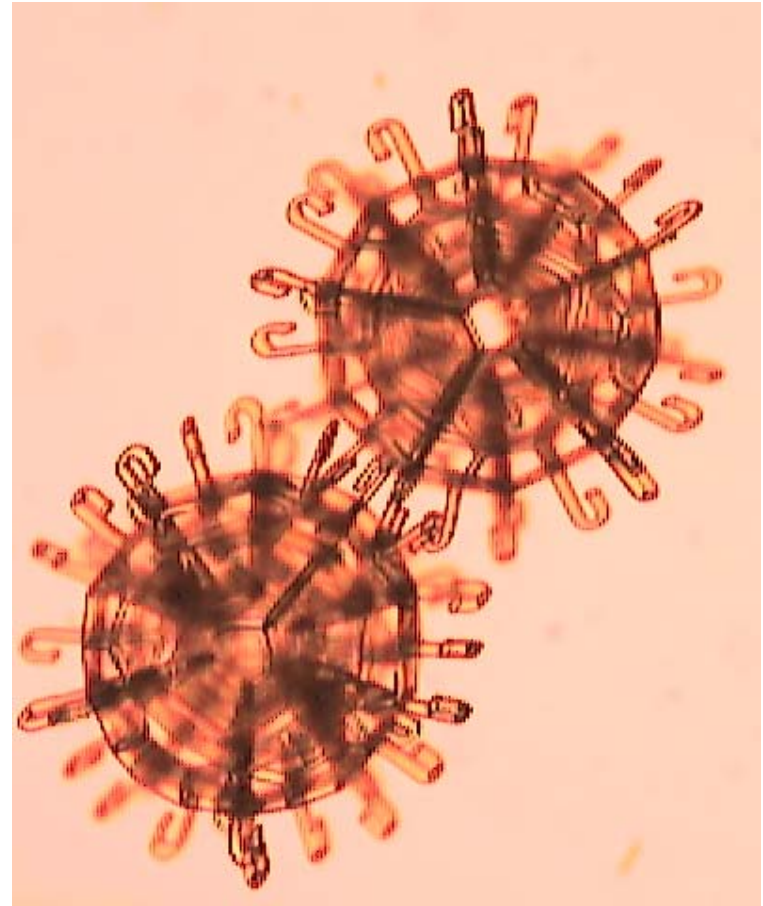
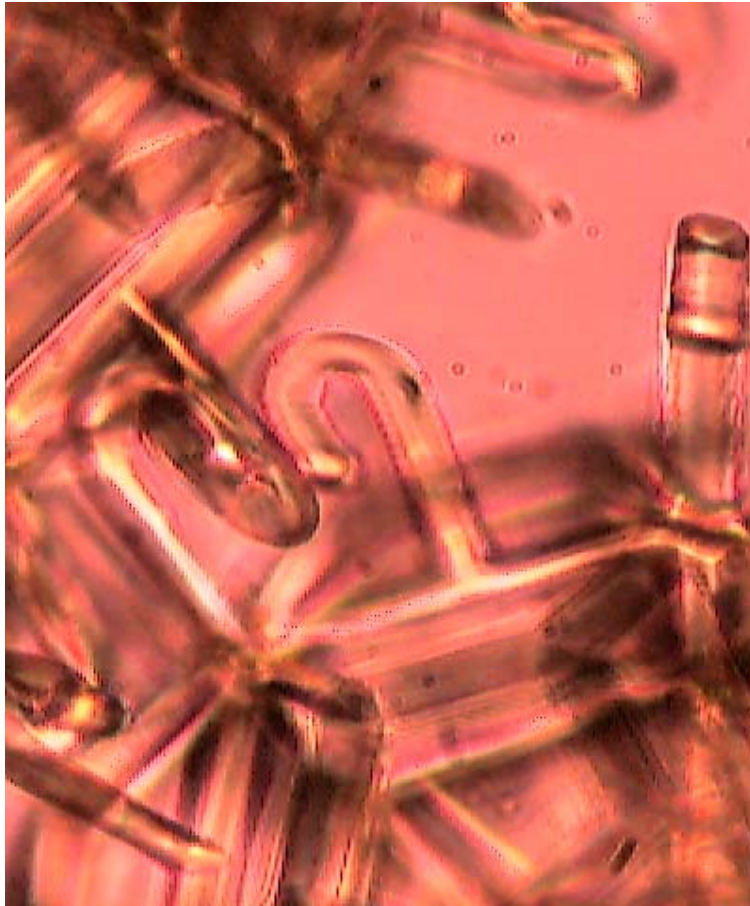


Technology: Two Photon Polymerization (2PP)

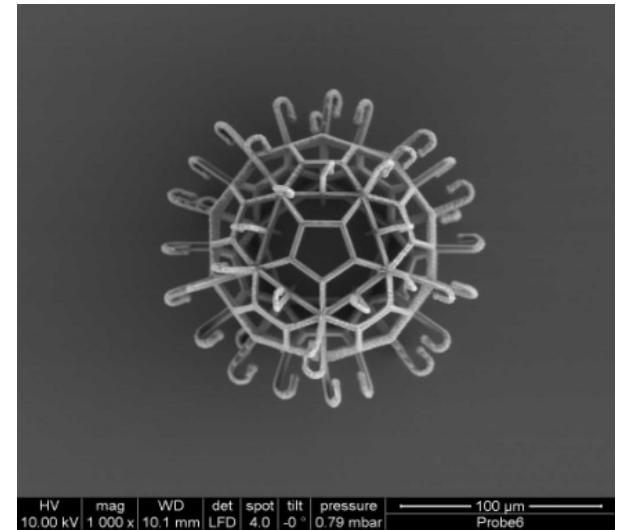
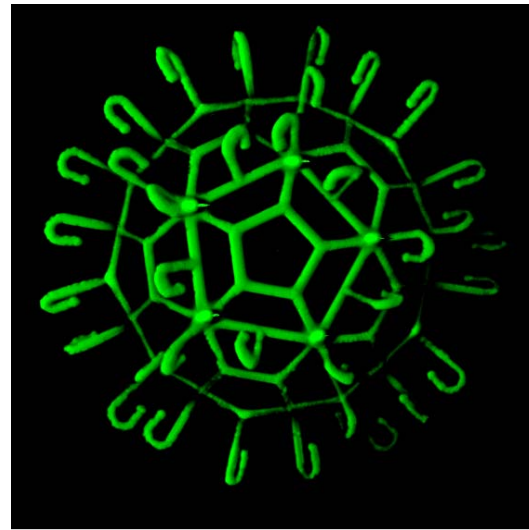
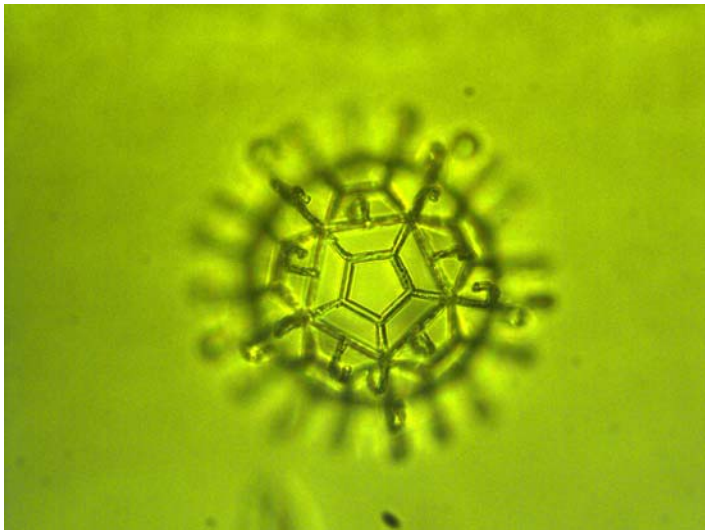


According to Prof. Boris Chichkov, Hannover Laser Center, Germany

Concentric Lockyballs

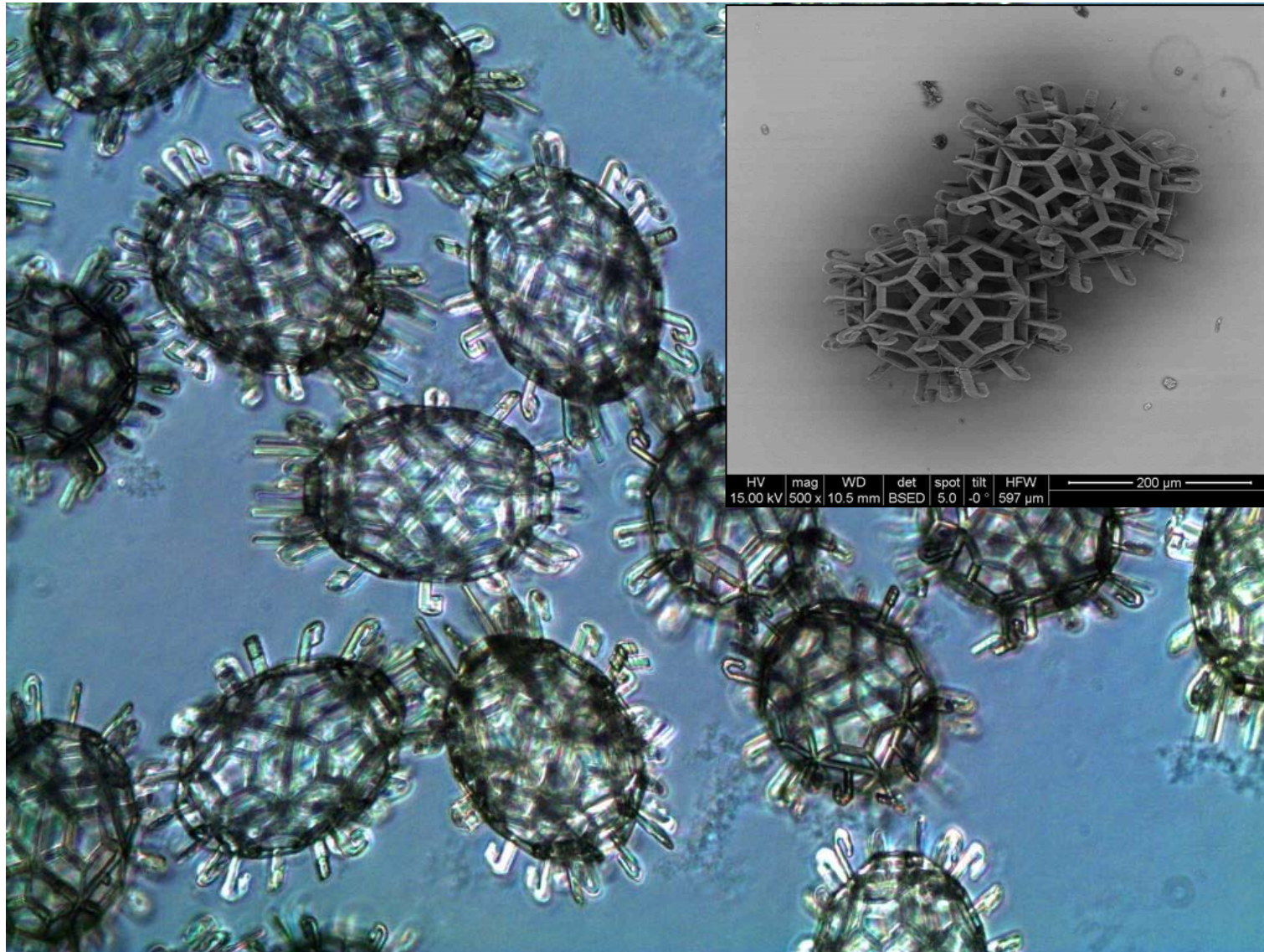


Interlockable Microscaffold or Simply 'Lockyballs' Fabricated by Two Photon Polymerization Technology

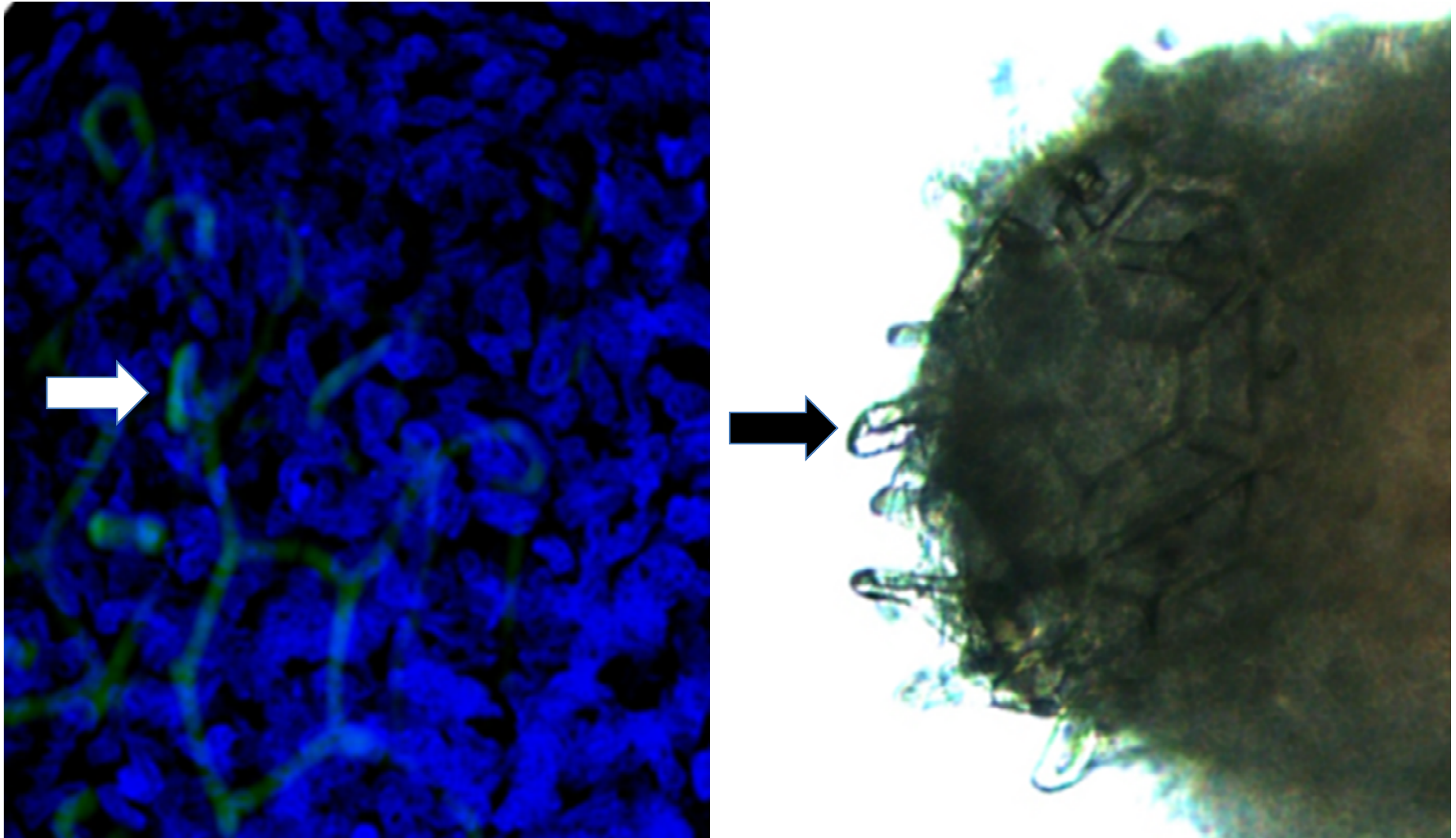


Journal of Nanotechnology, 2012

Lockyballs = Interlockable Microscaffolds

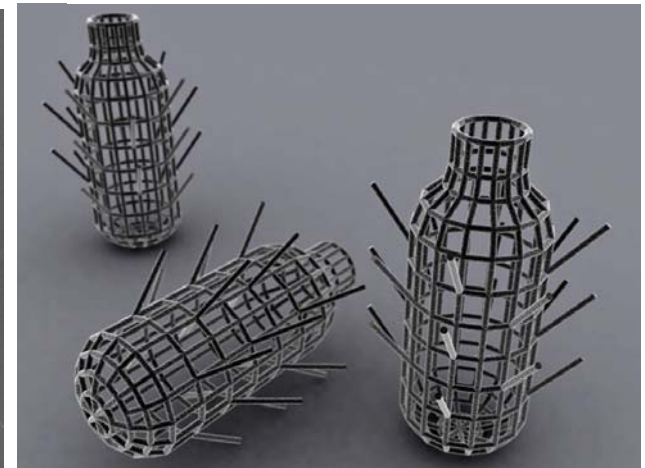
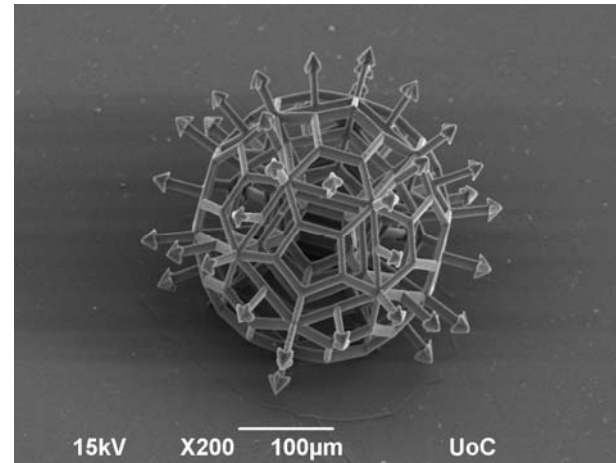
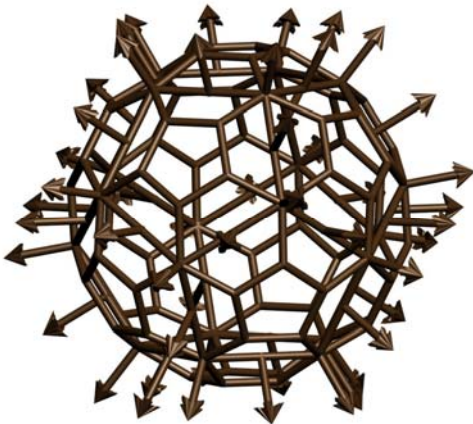
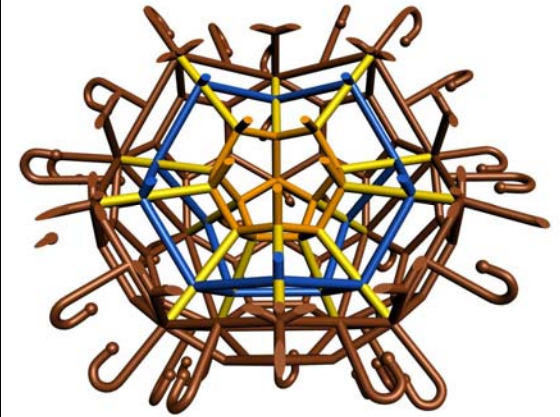
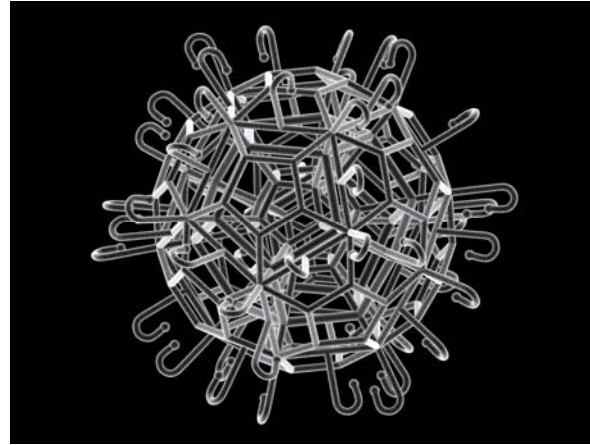
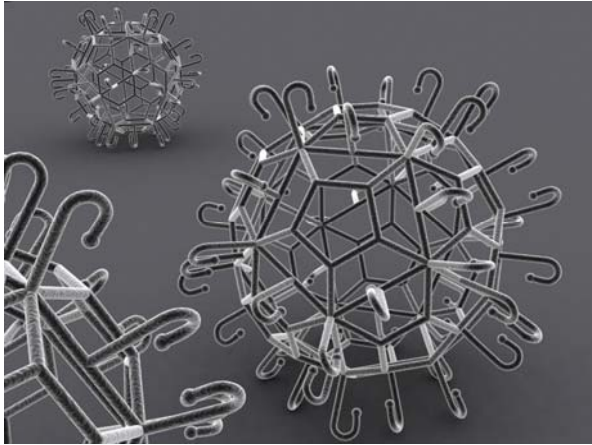


Cell Seeded Lockyballs

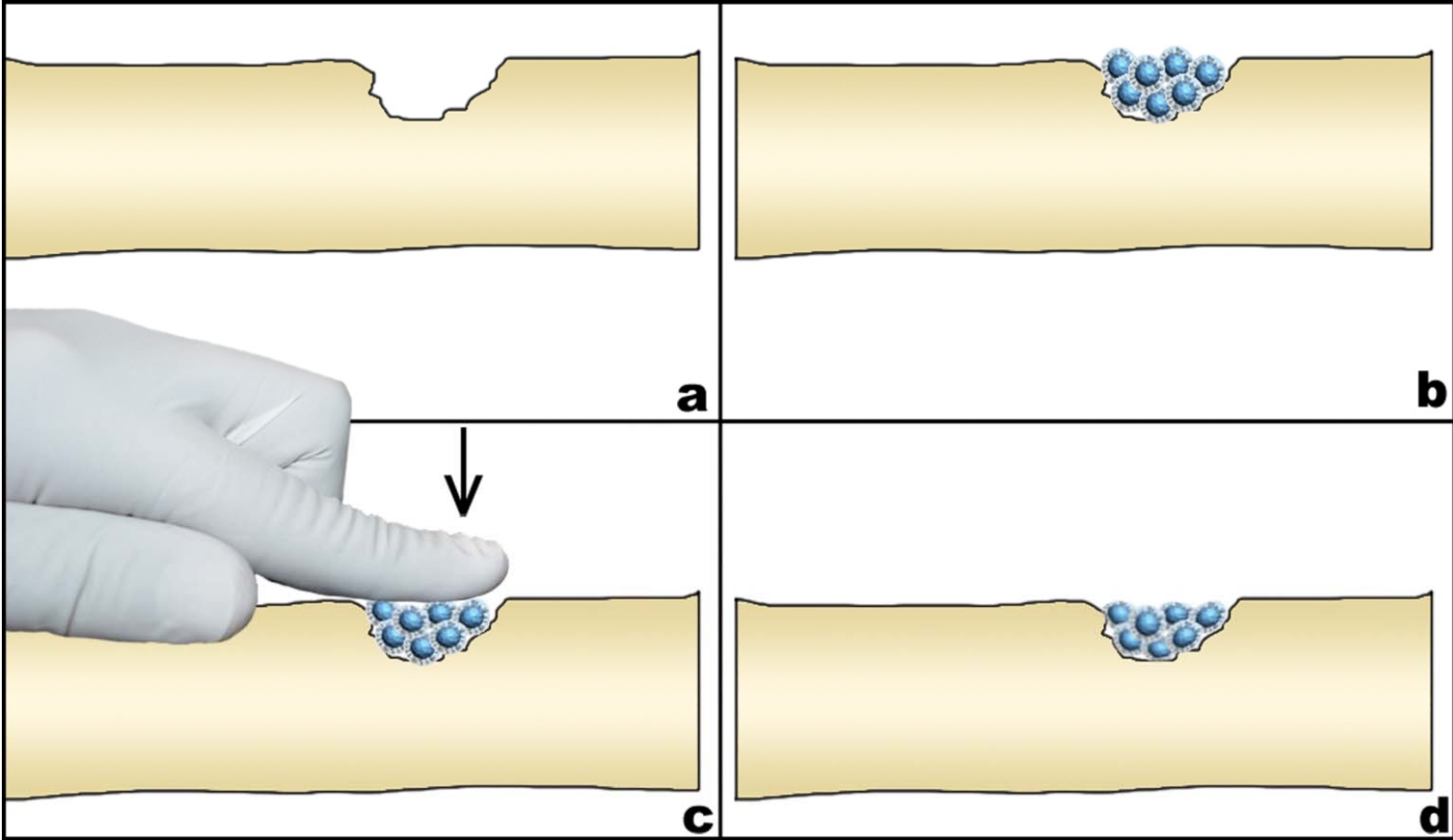


(LEANDRA BAPTISTA, INMETRO, XEREM, RJ, BRAZIL)

LOCKYBALLS FAMILY



IN SITU RAPID TISSUE BIOFABRICATION USING LOCKYBALLS

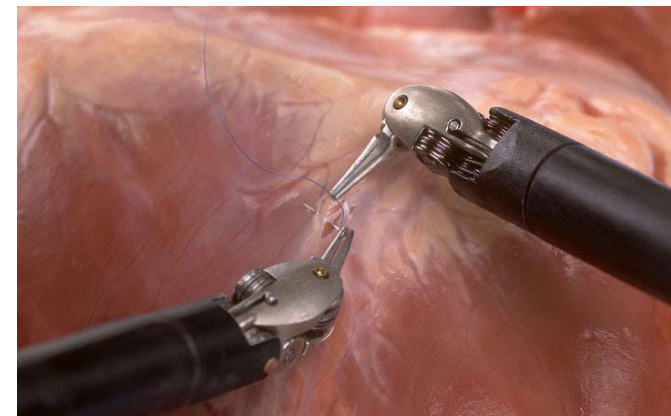


Scheme demonstrating in vivo rapid 3D tissue biofabrication using lockable tissue spheroids

Trend 2: In vivo 3D Bioprinting



“Da Vinci” - First Generation of Robotic Surgery Tool (Intuitive Surgery Inc, CA)



What commercially available robotic arm is the best ?

**Da Vinci,
Intuitive Surgery,
USA**

A white and blue surgical robot with two articulated arms, each holding a surgical instrument. It stands on a base with a control console.

**Zeus,
USA**

A blue surgical robot with two articulated arms, positioned over a patient on a table. The robot is used for minimally invasive surgery.

**MIROsurge or KUKA/DLR,
Germany**

A photograph of a surgical robot in an operating room. The text "ENDOSCOPIC TELESURGERY" is at the top. Below the image, it says "One Miro guiding an endoscopic stereo camera two Miro's guiding endoscopic forceps".


**Surgenius,
Italy**

A surgical robot with two articulated arms, positioned over a patient on a table. A surgeon in blue scrubs is visible on the left side of the frame.

**Baxter, Rethinks
Robotics, USA**

A small, red and white humanoid robot with a friendly face, two arms, and a torso. It is designed for collaborative work.

**Frida-ABB,
Sweden**

A small, white and grey humanoid robot with a friendly face, two arms, and a torso. It is designed for collaborative work.

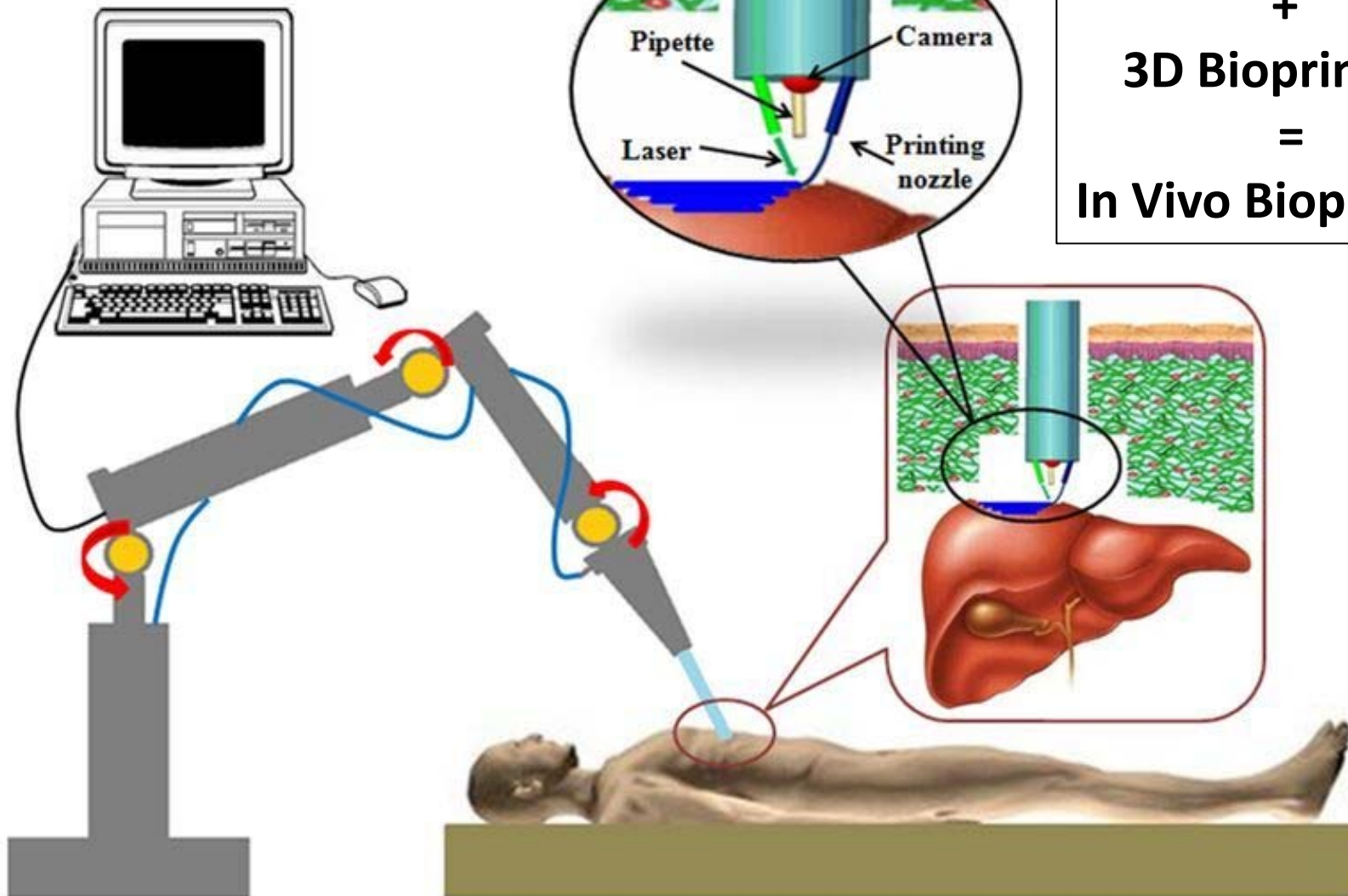
**Motoman,
Japan**

A white and blue industrial robot arm with a gripper, mounted on a base. It is designed for manufacturing tasks.

**DLR/KUKA,
Germany**

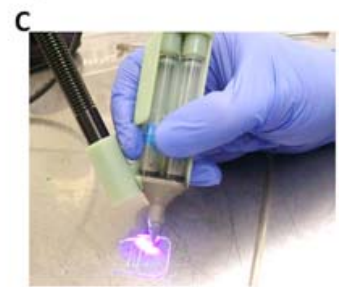
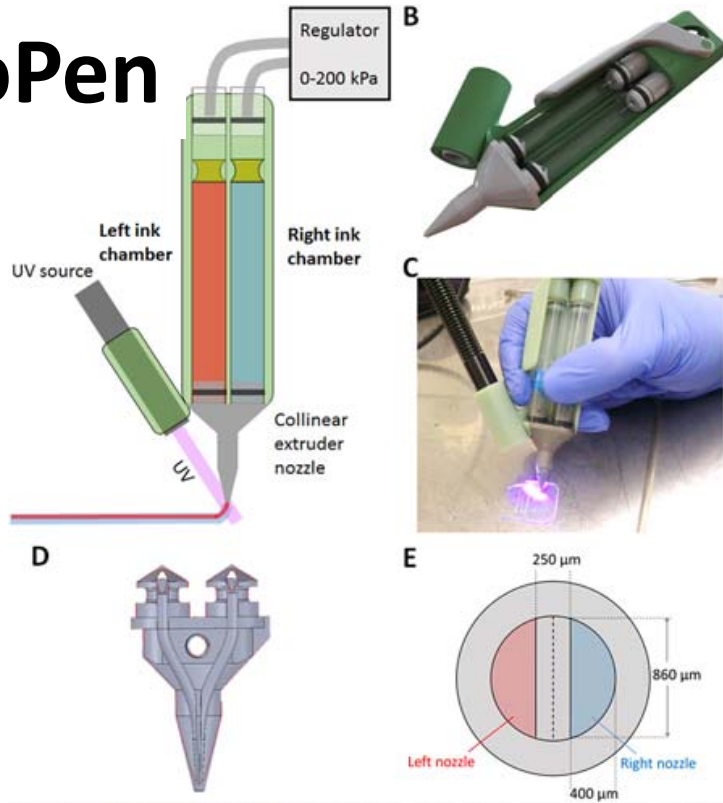
An orange industrial robot arm with a gripper, mounted on a base. It is designed for manufacturing tasks.

In Vivo Bioprinter



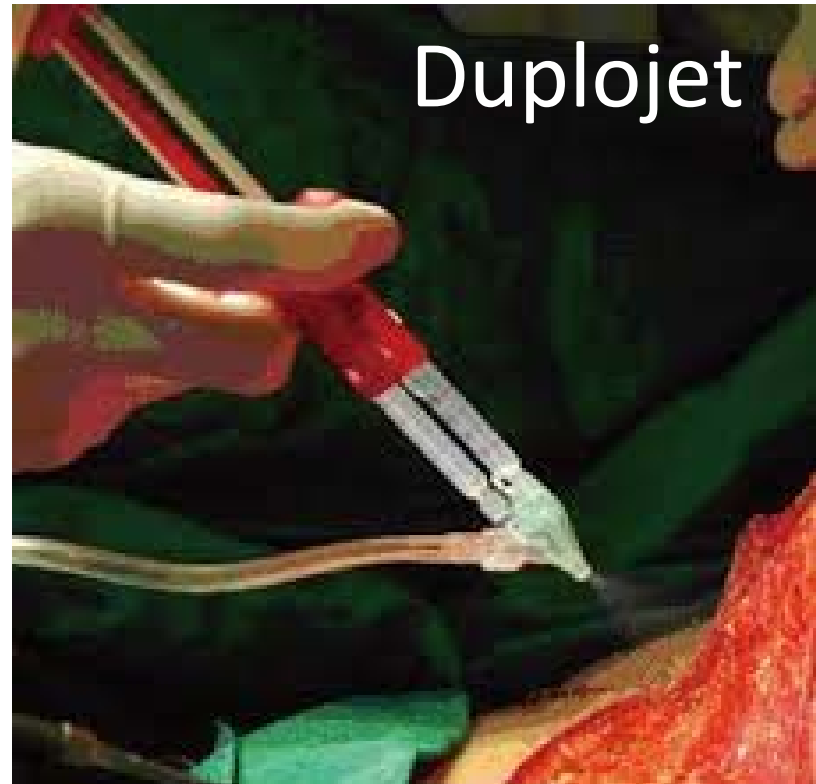
**Robotic Surgery
+
3D Bioprinting
=
In Vivo Bioprinting**

BioPen



Cell Gun

Duplojet



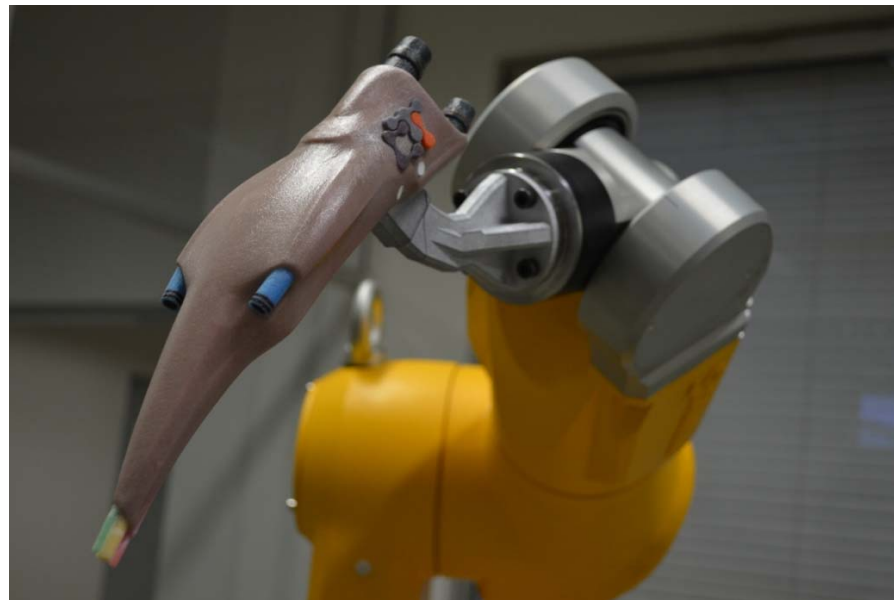
Vivostat



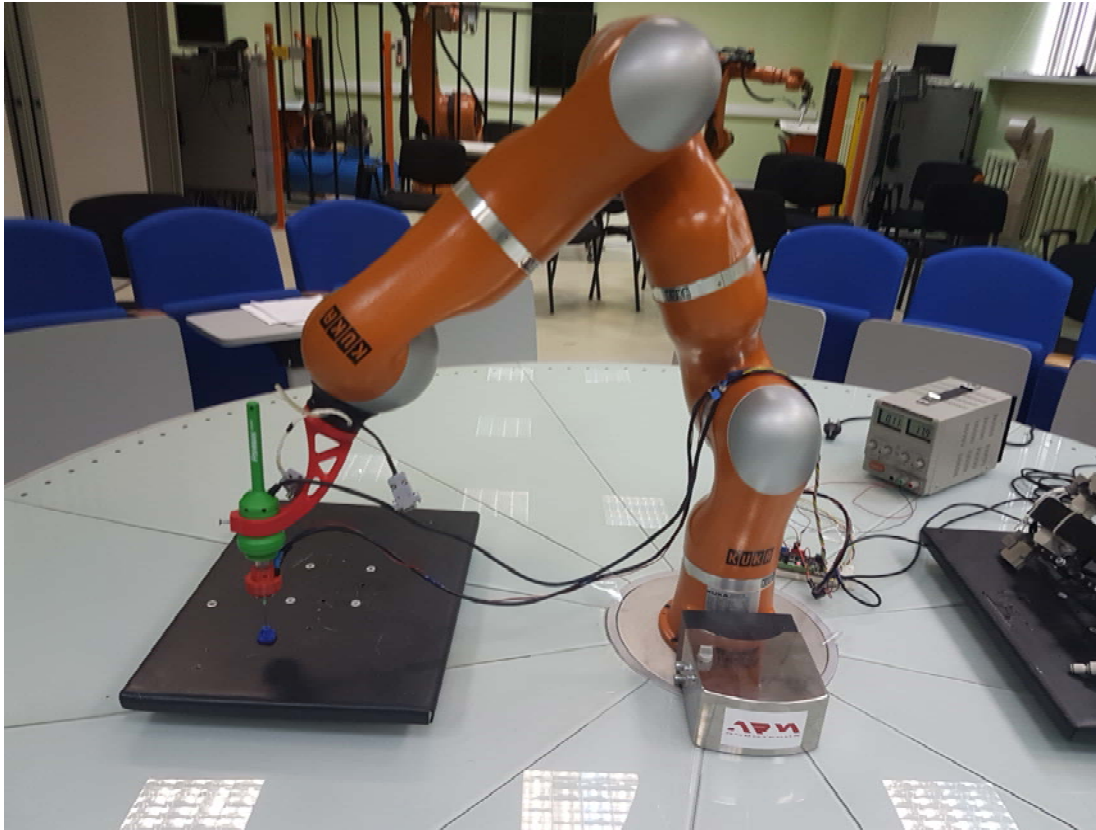
Skington (RenovaCare)



In Vivo Bioprinter



First Russian In Vivo 3D Bioprinter

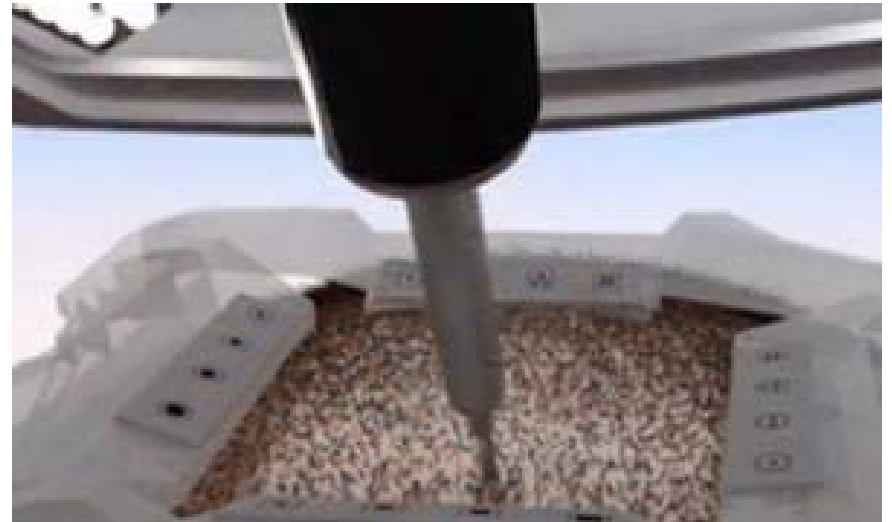
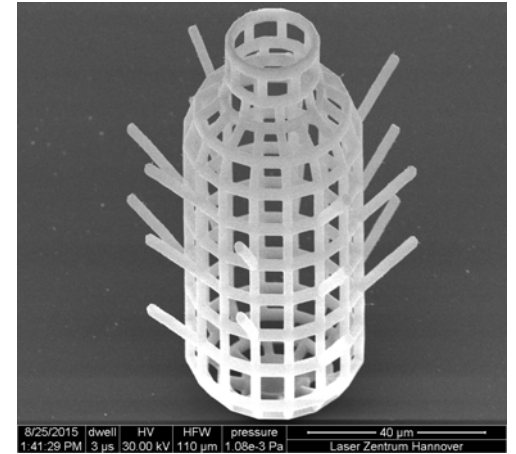
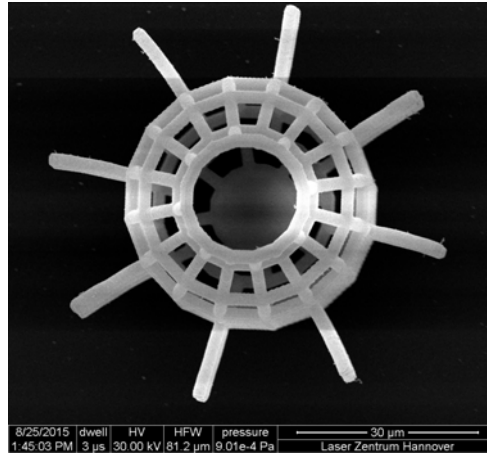
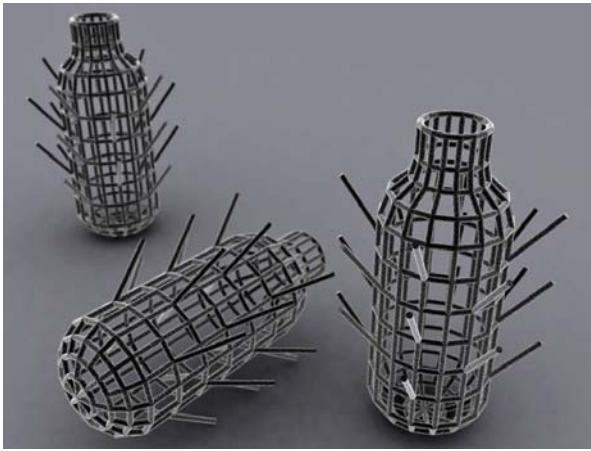
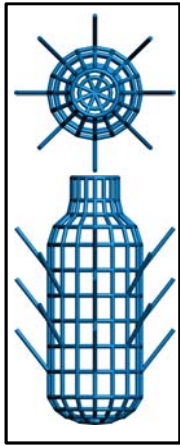


**Articulated robot (Kuka, Germany) + automated syringe (Fishman, USA)
+ software (Russia) = in vivo 3D Bioprinter (Russia)**

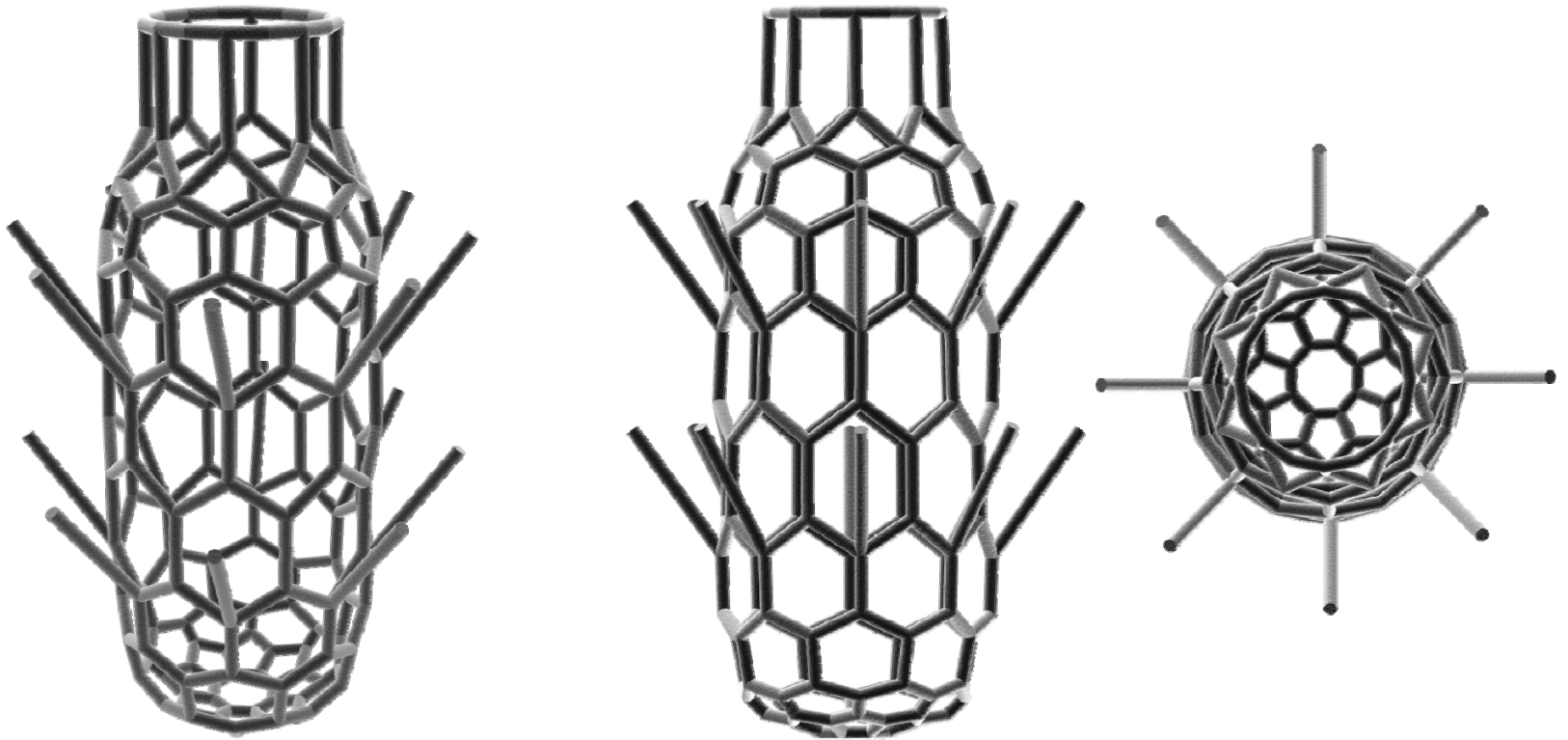
Problem: Baldness or Alopecia



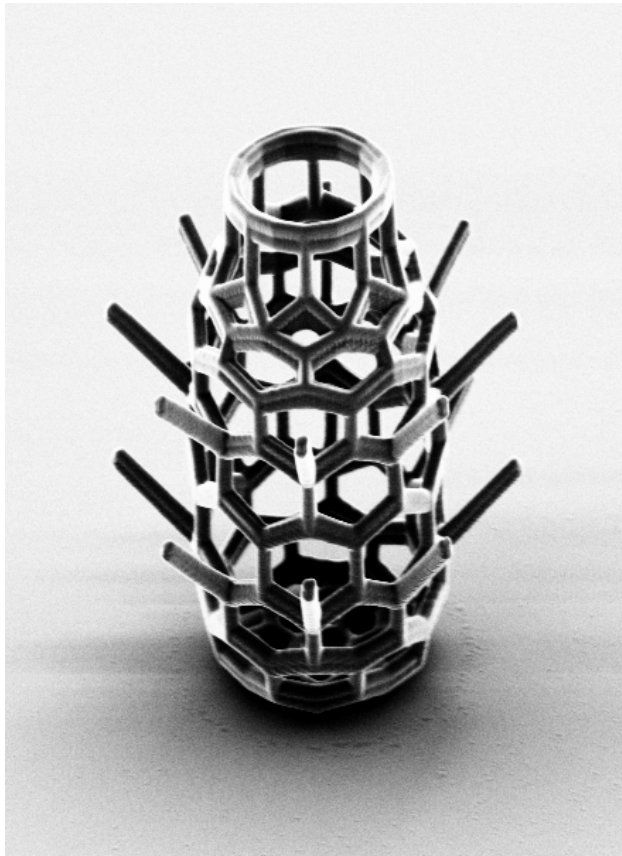
Project Capillinser



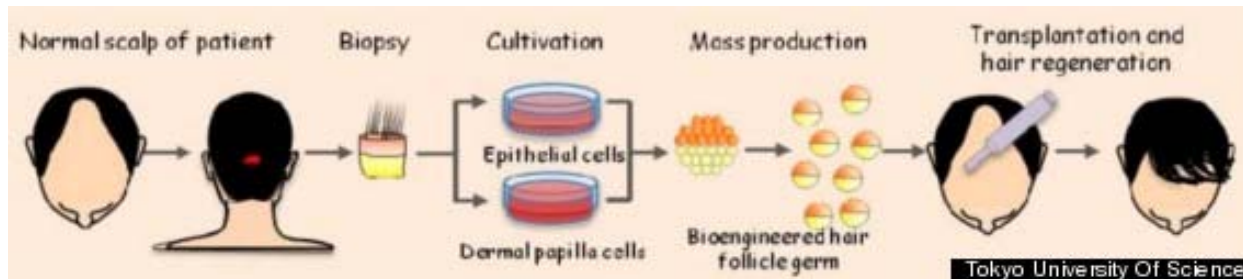
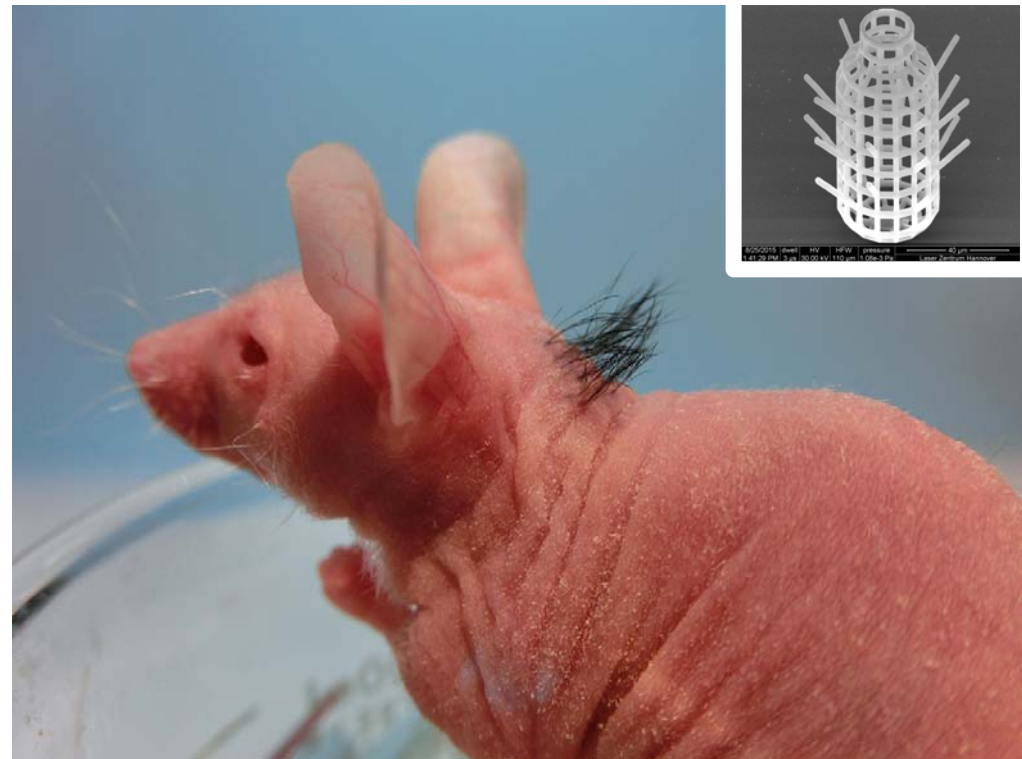
Design of Capillinsler



Capillinsler from ORMOCER[®] material



Project Capillinser: Bioprinting of Human Hair



Takashi Tsuji
RIKEN,
Kobe, Japan

Laser-Assisted Hair Transplantation

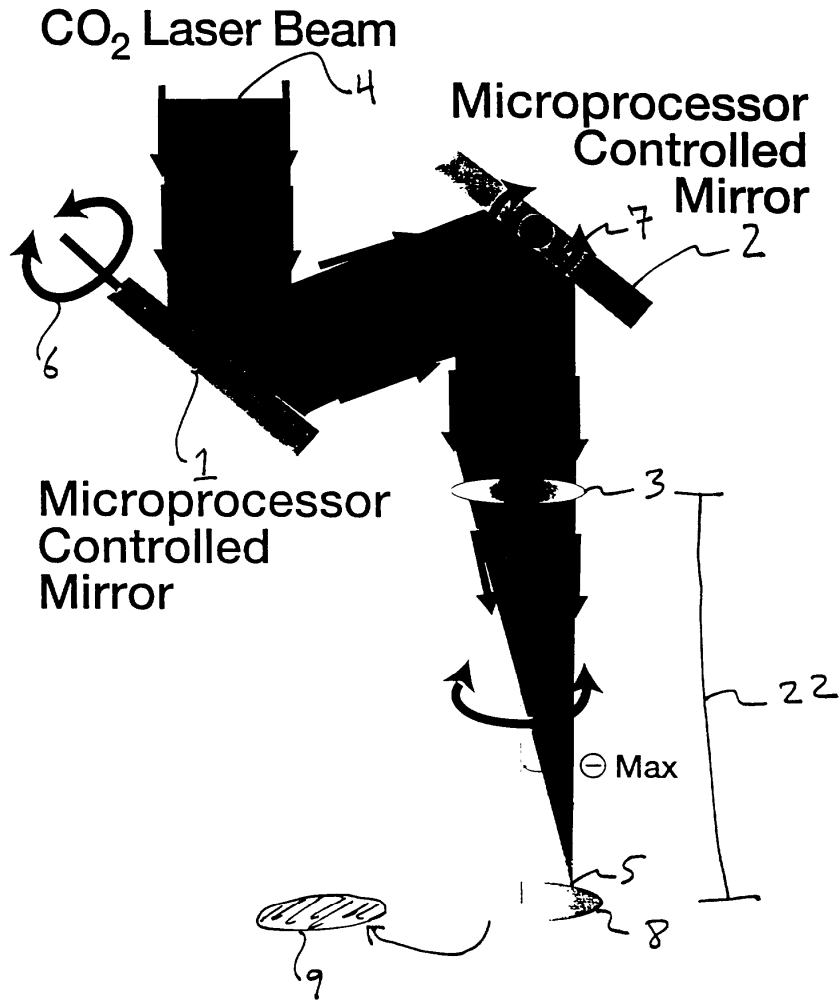


figure 1

U.S. Patent

Nov. 1, 1994

5,360,447

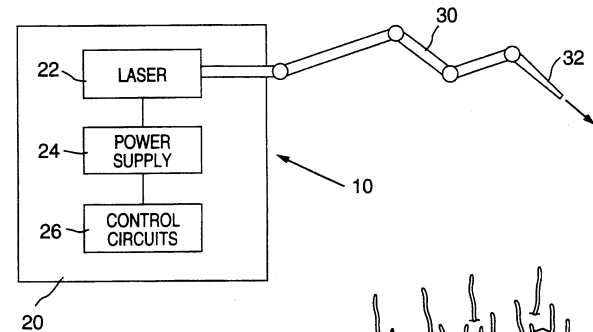


FIG. 1

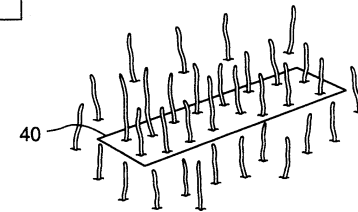


FIG. 2

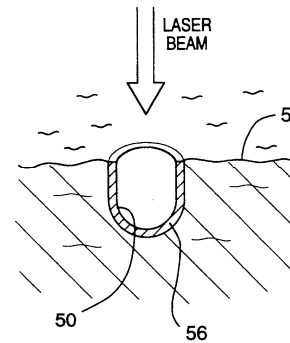


FIG. 3

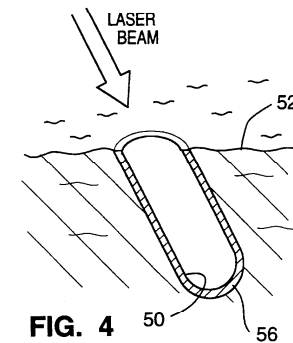
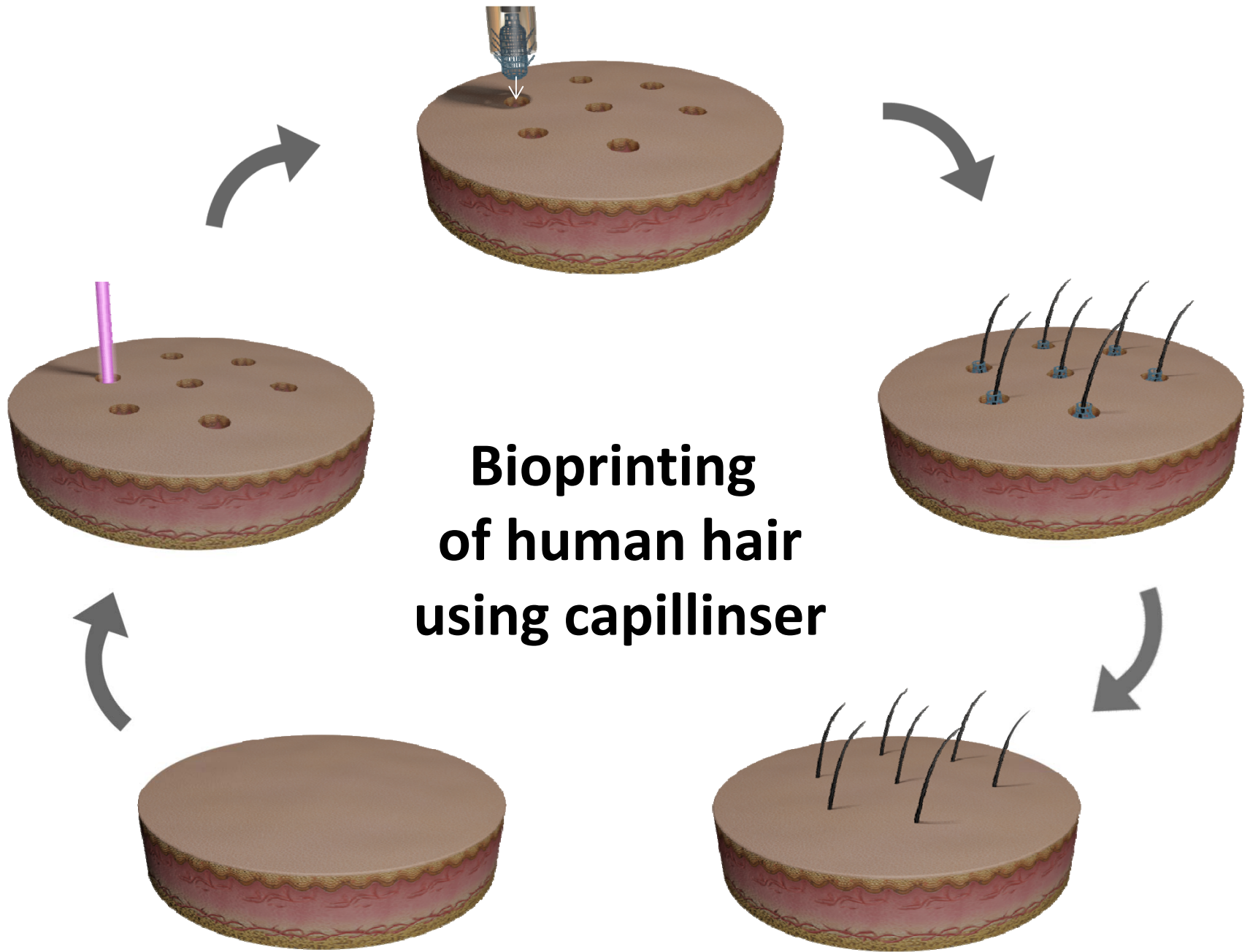
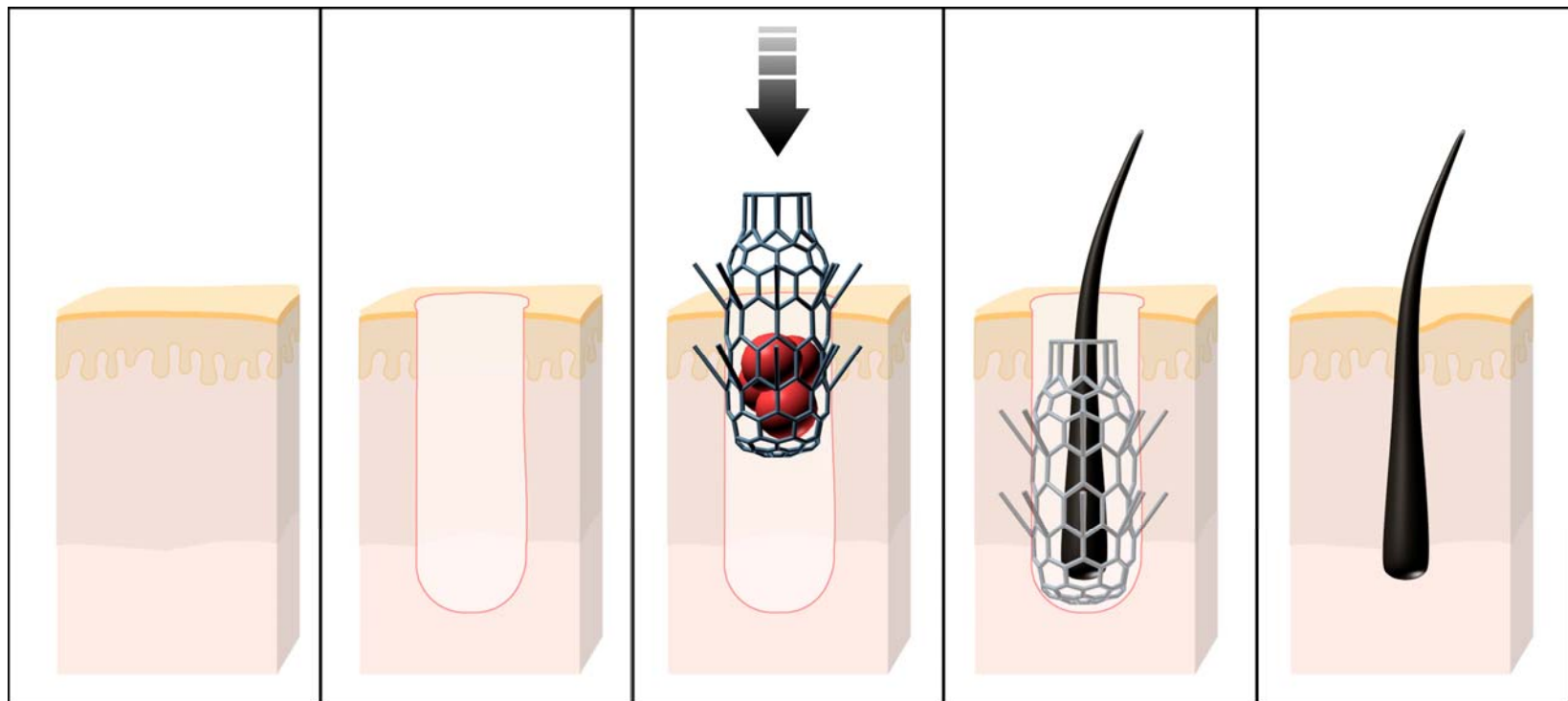


FIG. 4

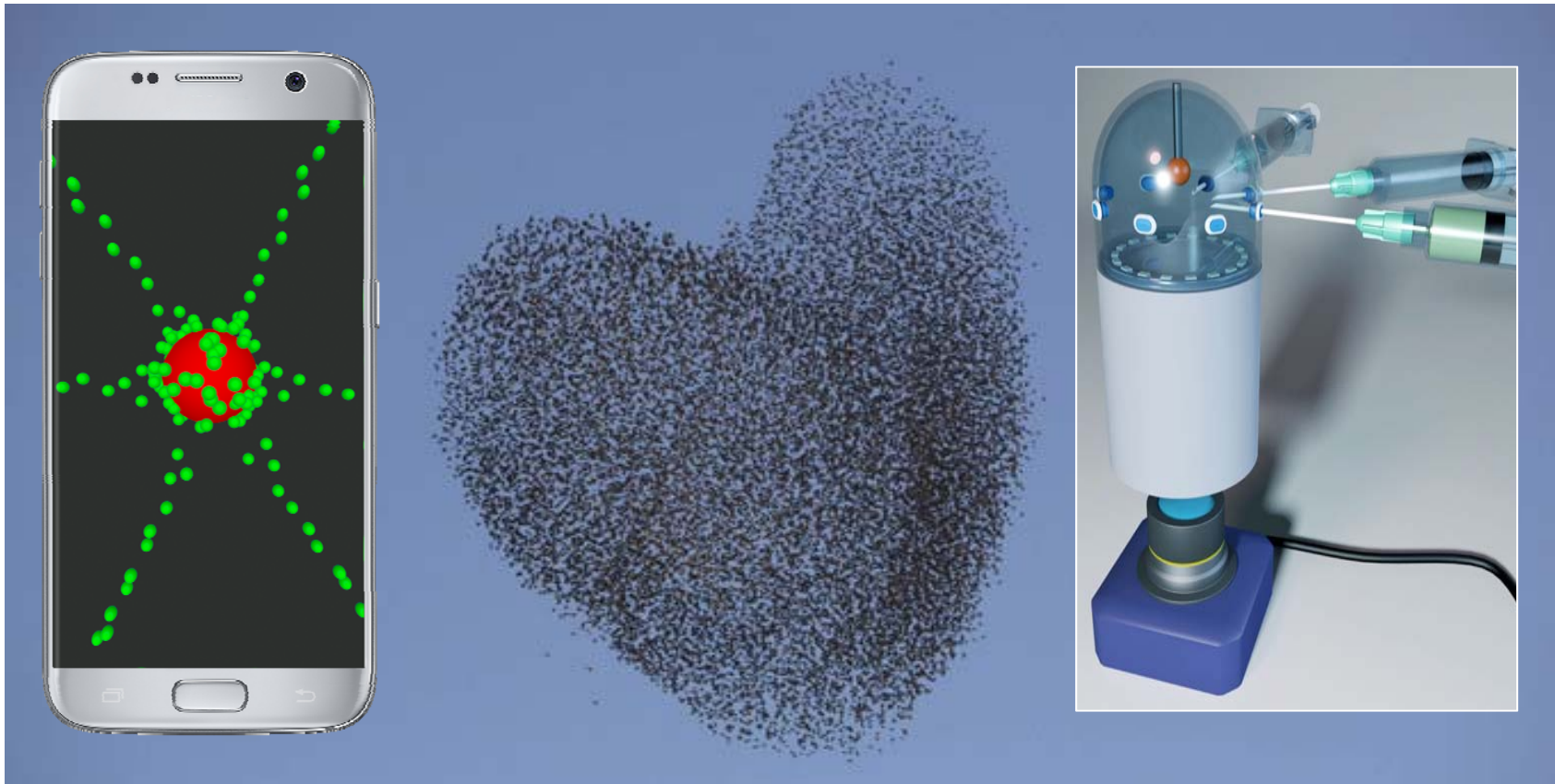


**Bioprinting
of human hair
using capilliner**

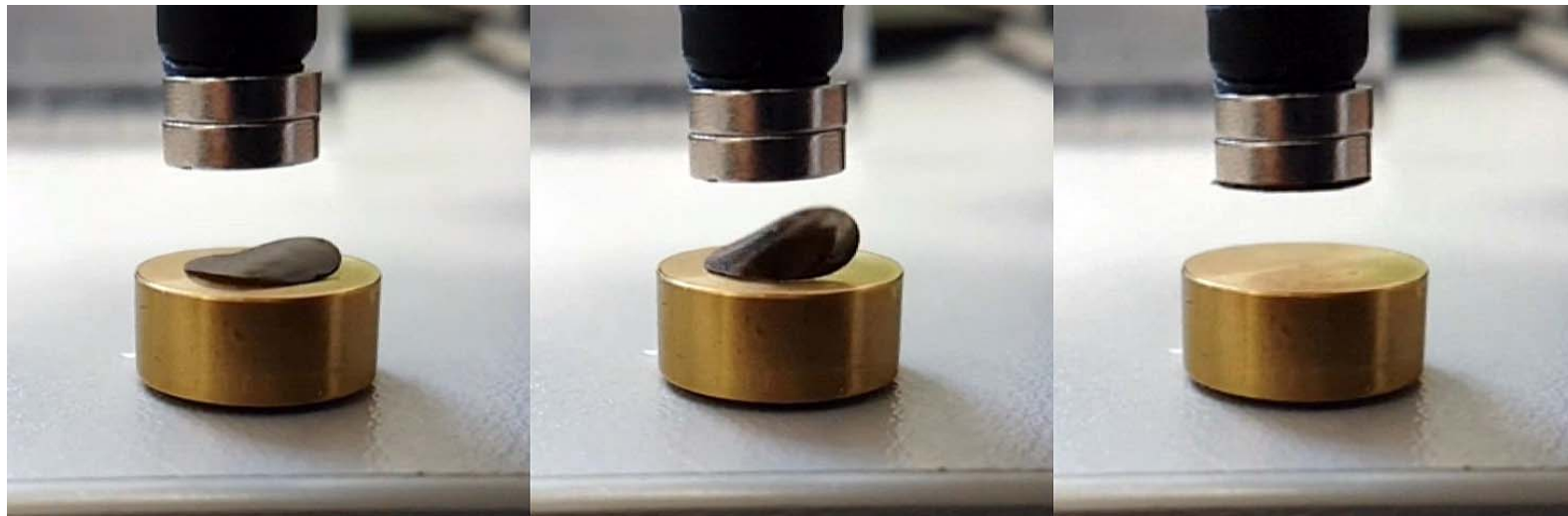
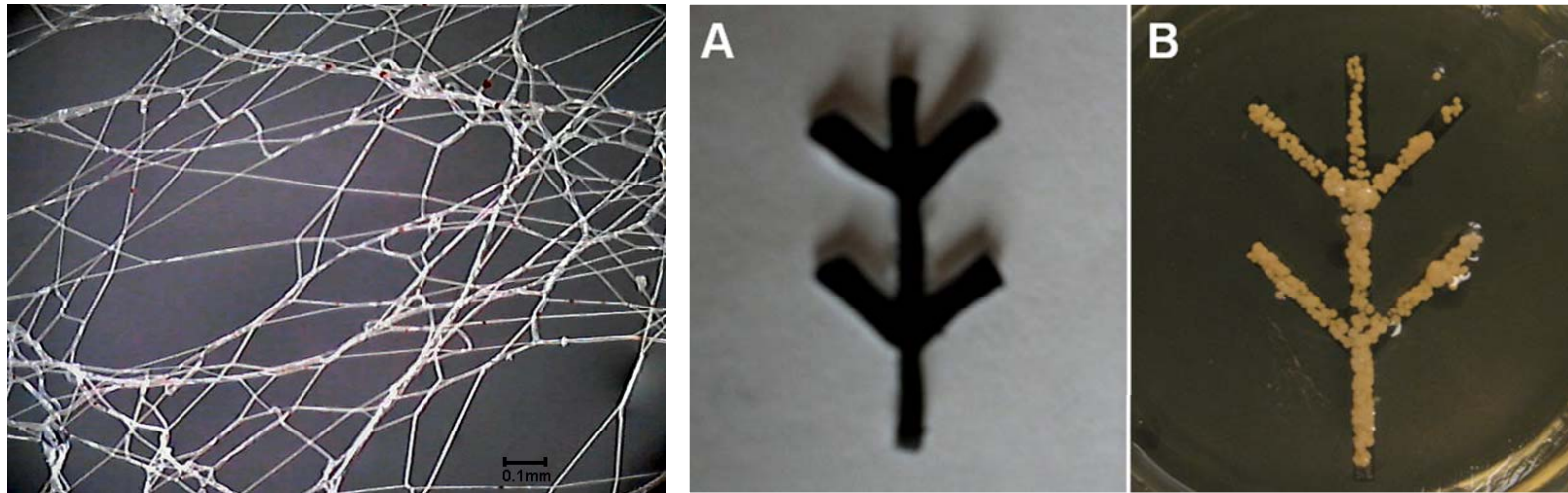
Capillinser

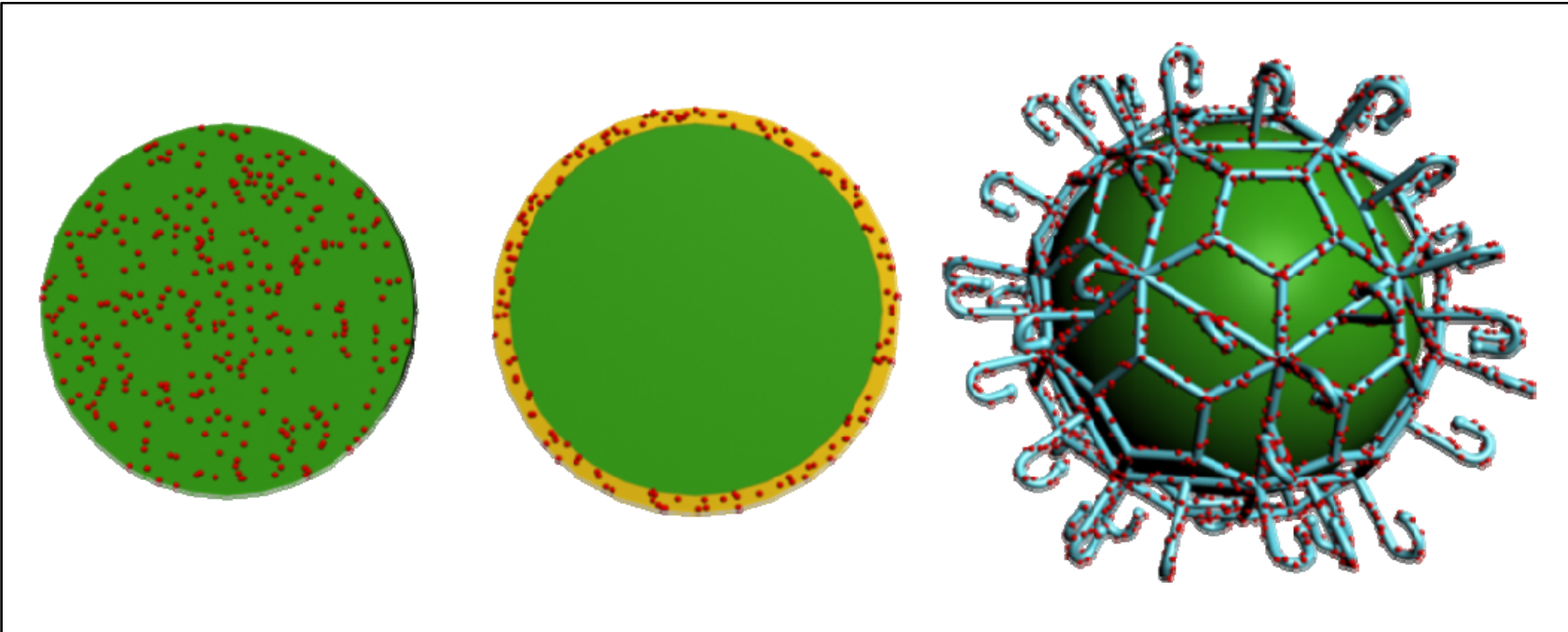
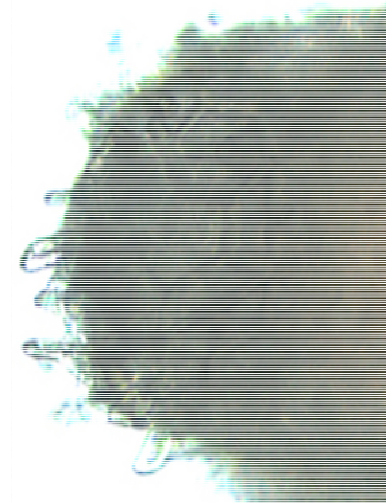
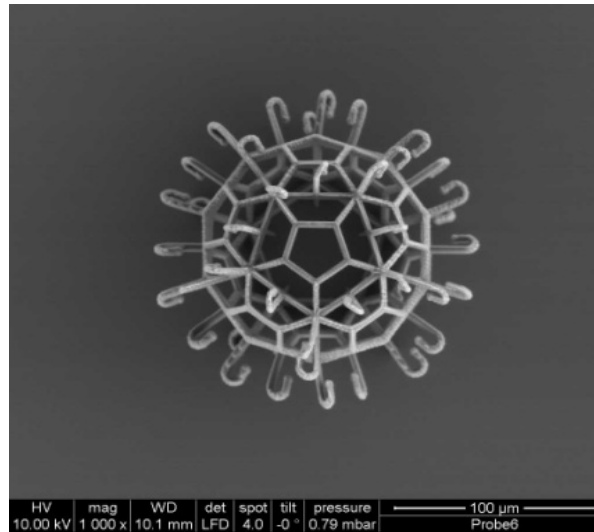
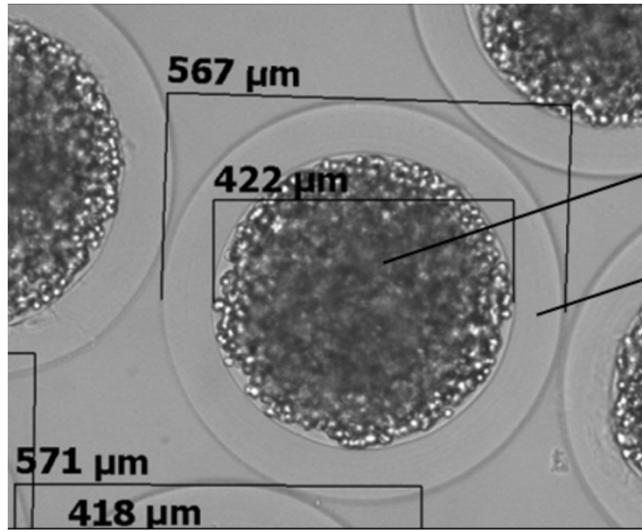


Trend 3. Magnetic 3D Bioprinting

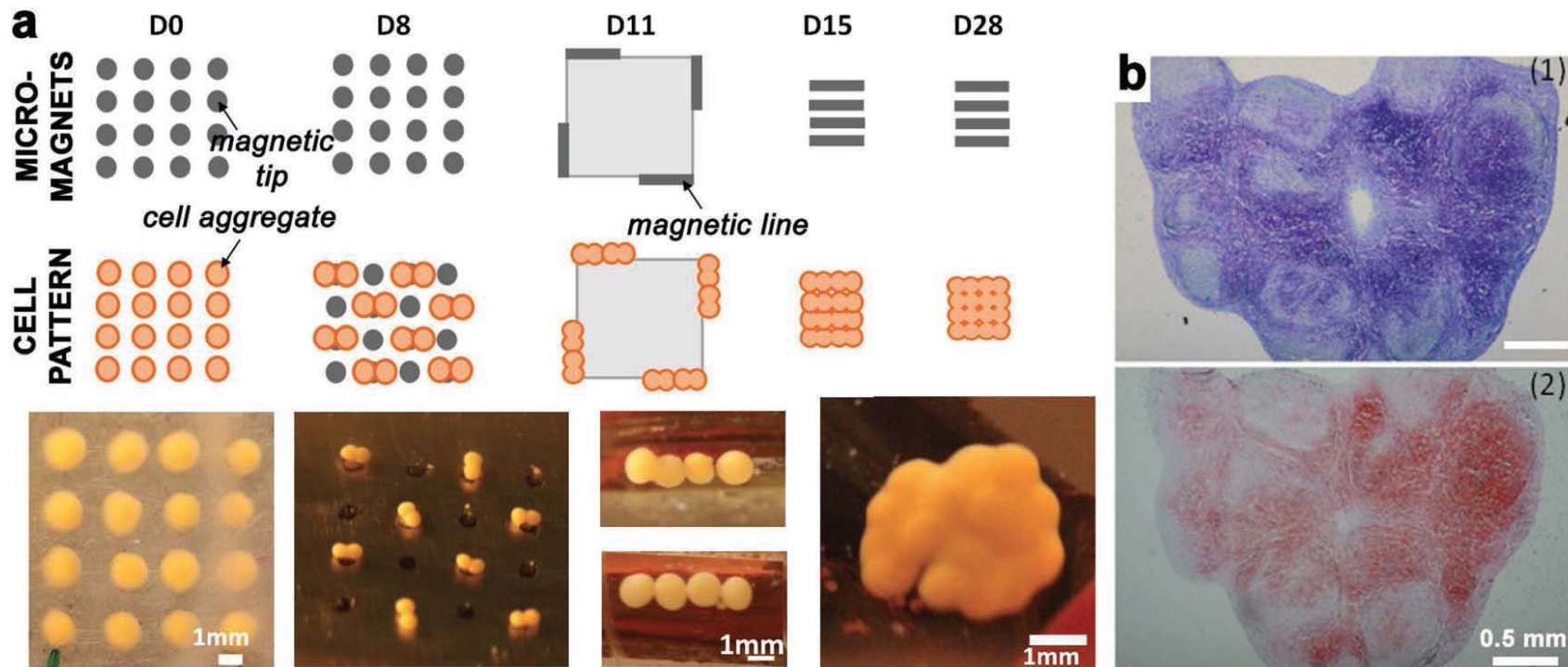


Magnetic forces based patterning



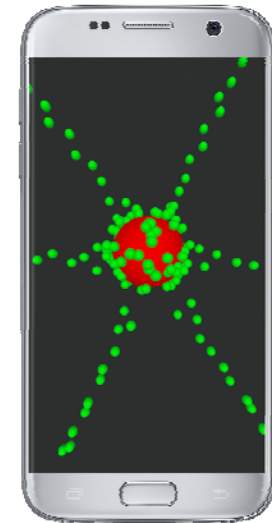
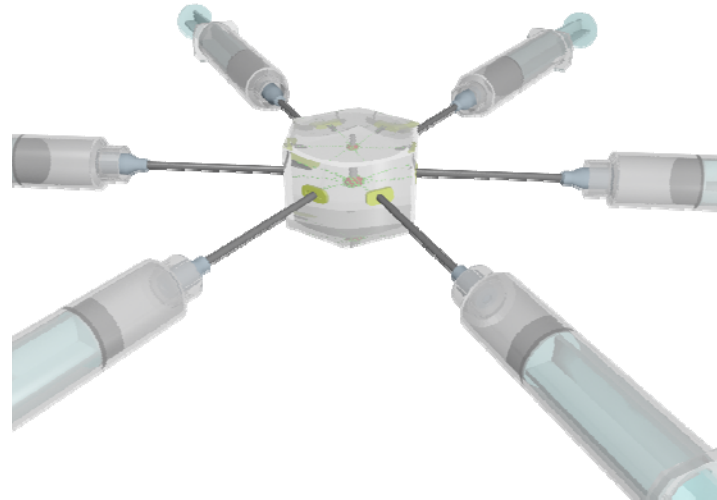
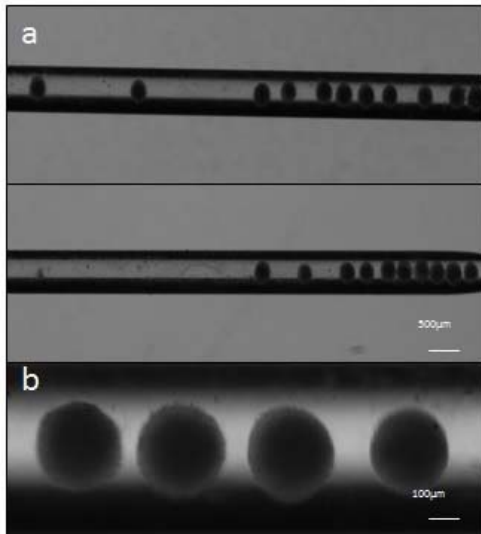


Label-based magnetic assembly of tissue constructs from tissue spheroids



According to Prof. Claire Wilhelm, Paris, France

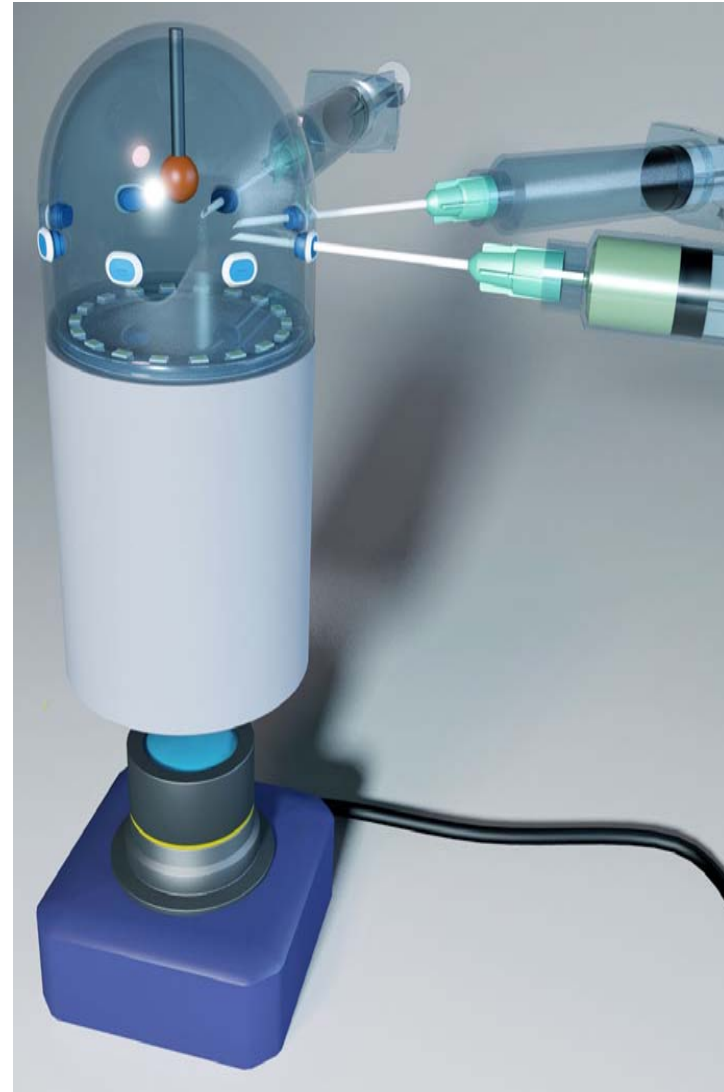
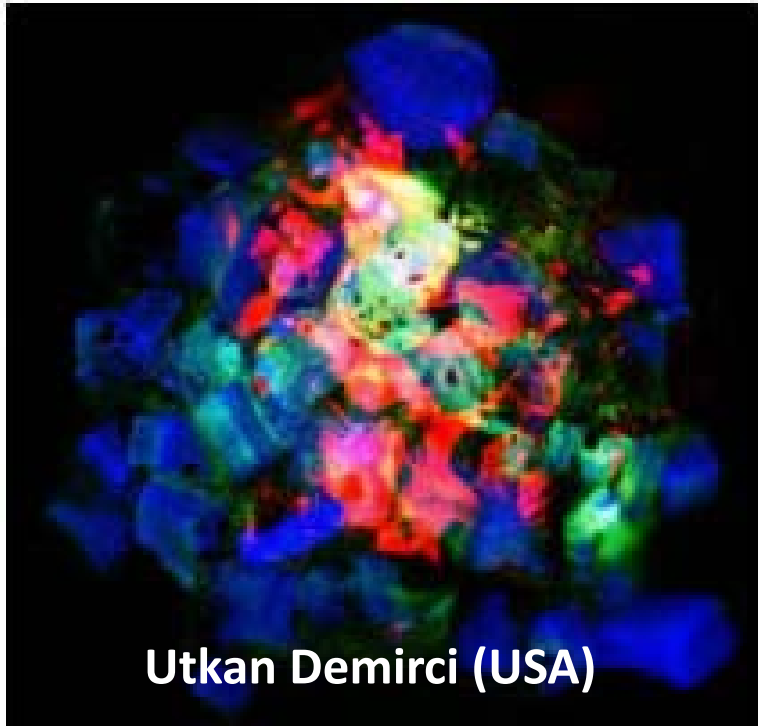
Label-Based Magnetic Patterning of Tissue Spheroids in Microgravity in Space



Magnetic levitation: frog and mice can fly

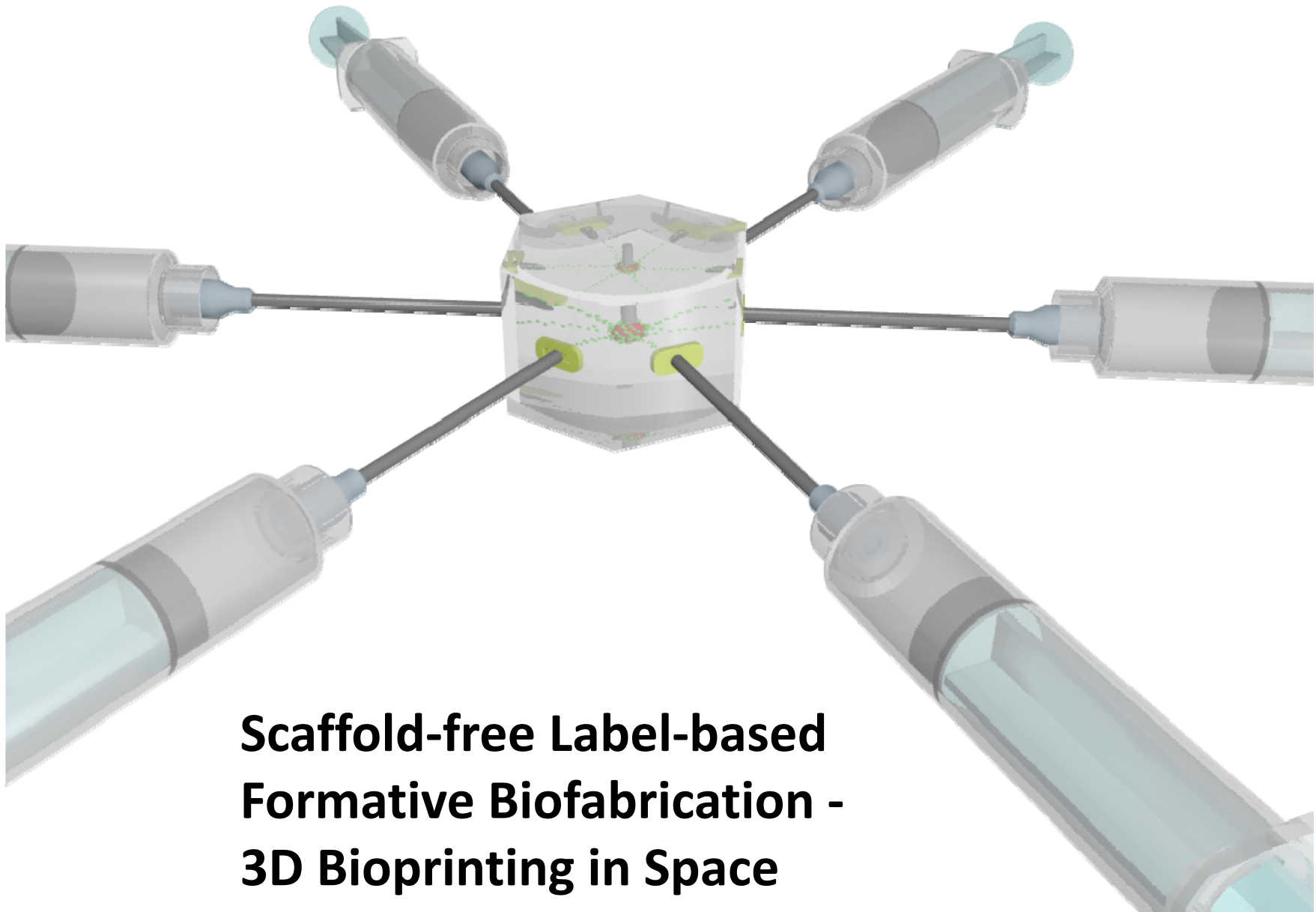


Magnetic space bioprinter

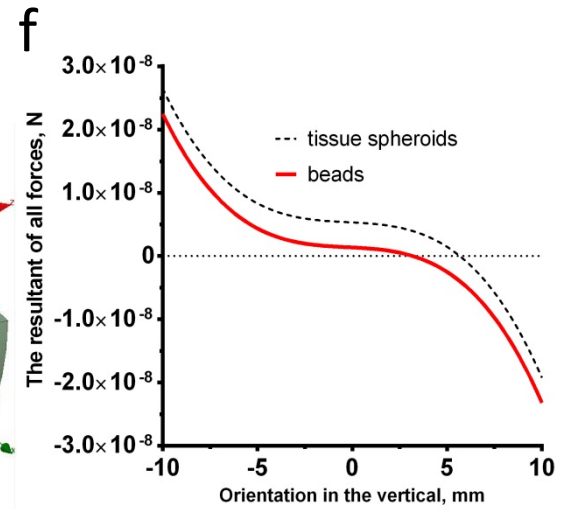
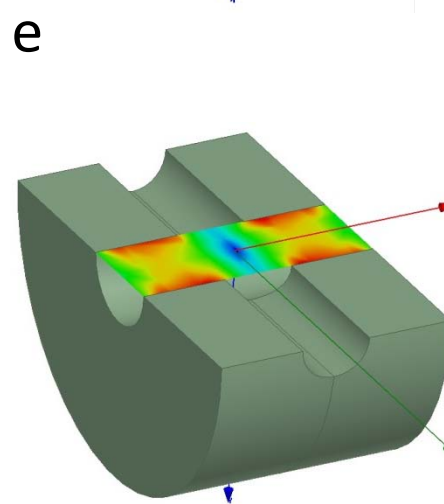
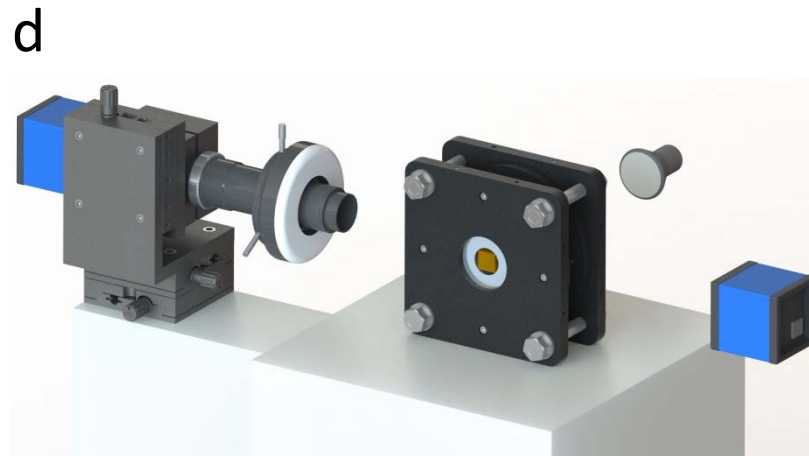
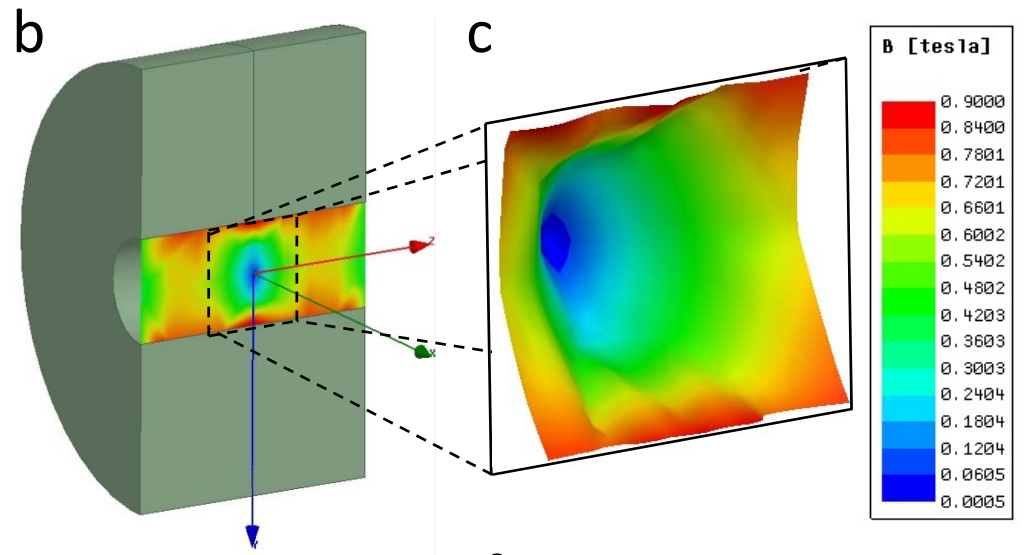
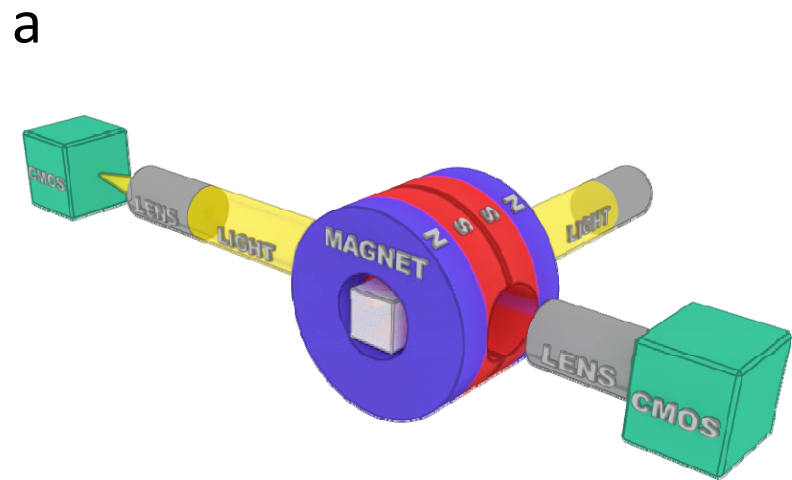


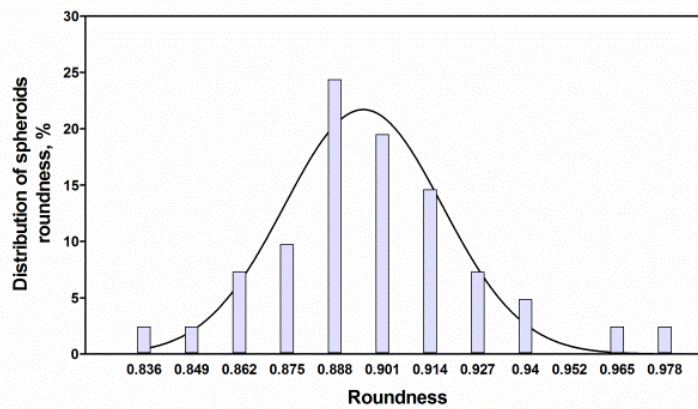
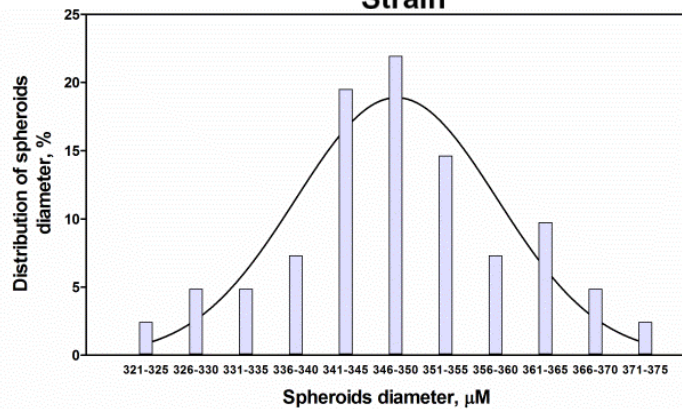
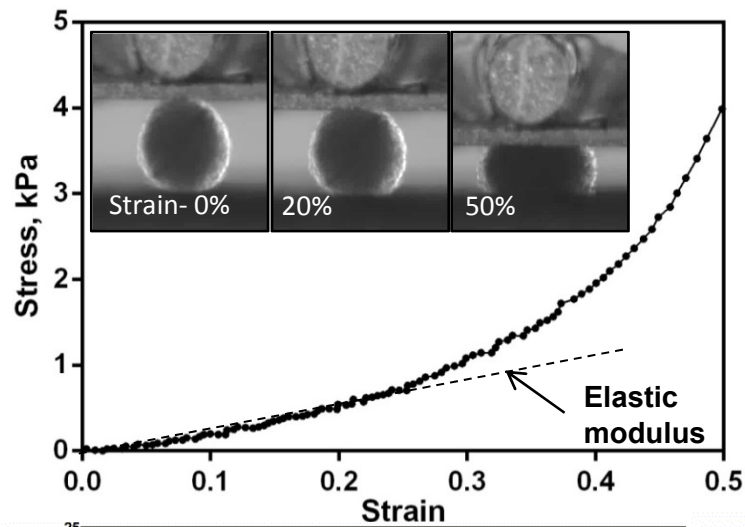


Space tissue spheroids transportation container



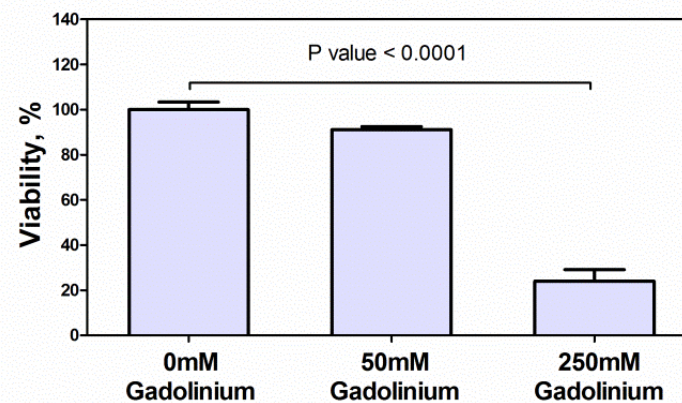
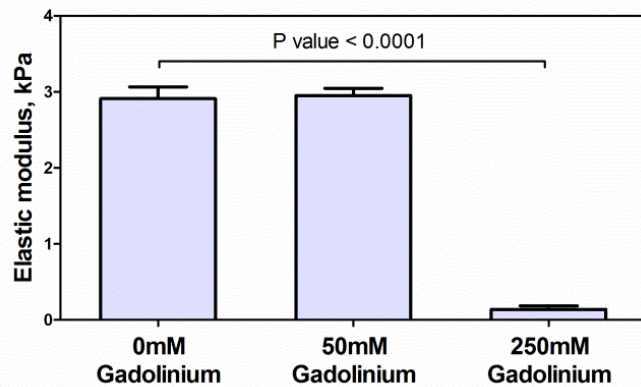
**Scaffold-free Label-based
Formative Biofabrication -
3D Bioprinting in Space**

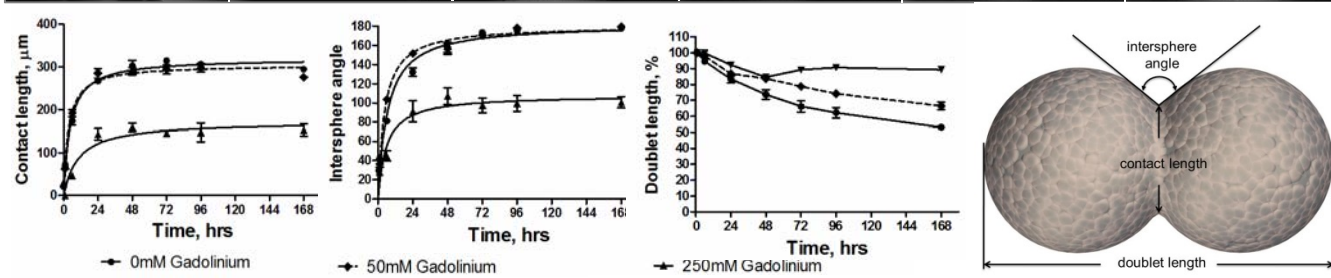
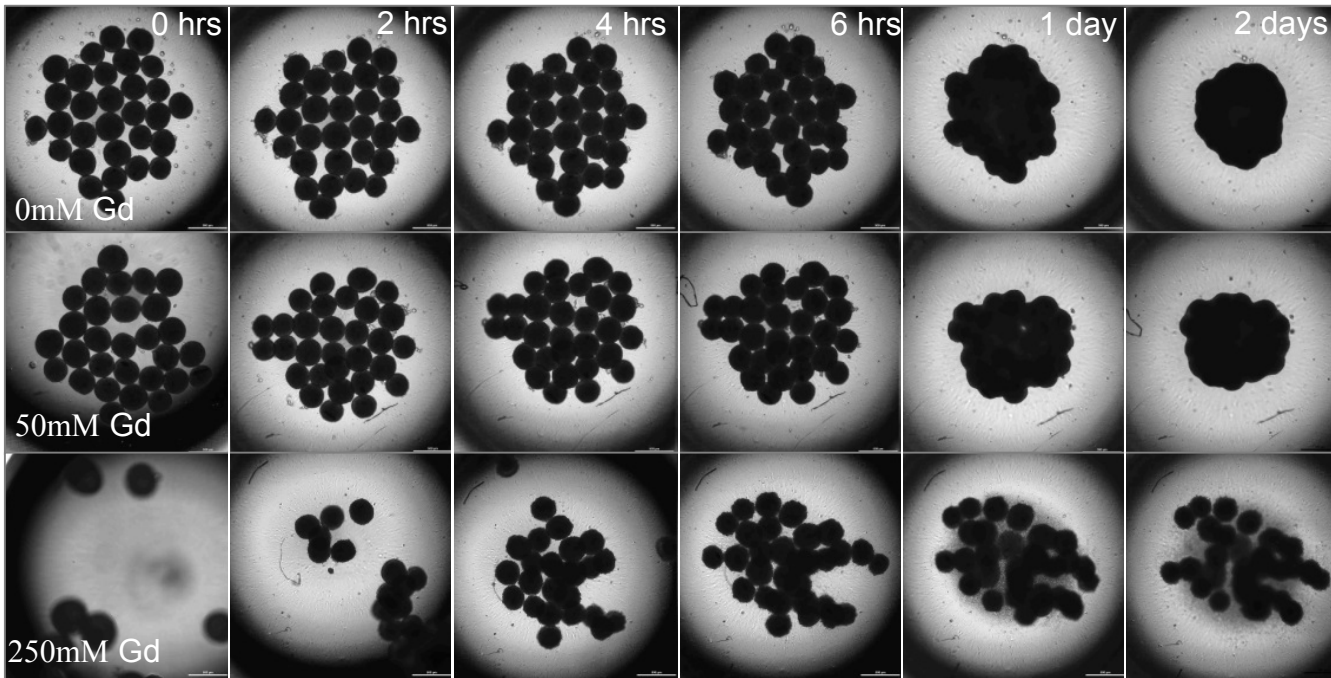
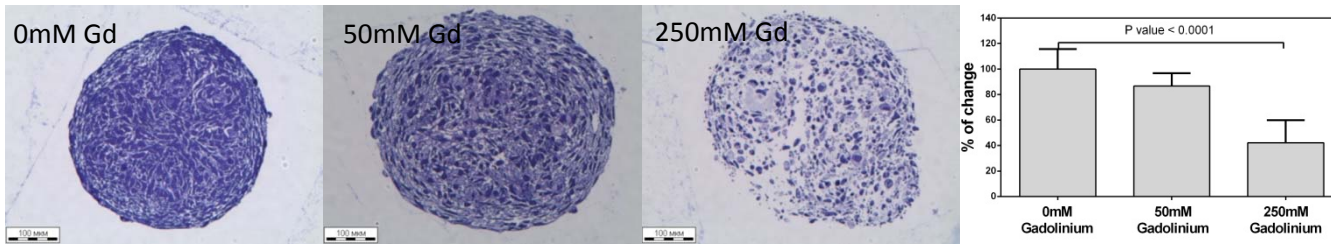


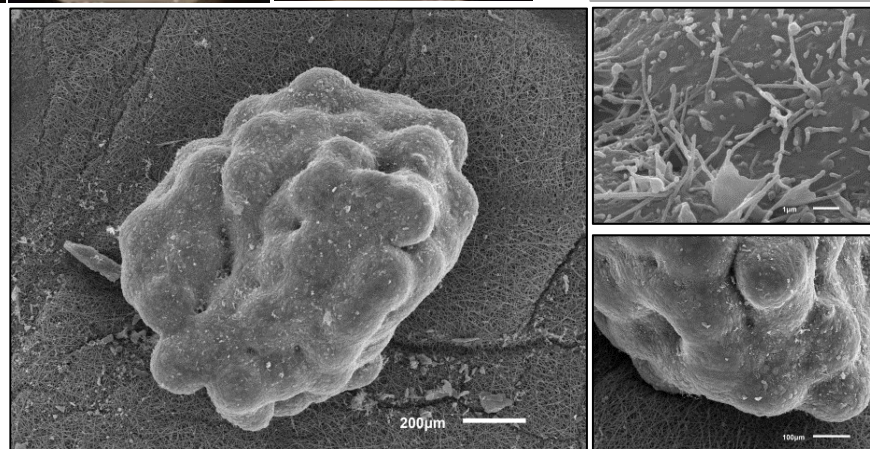
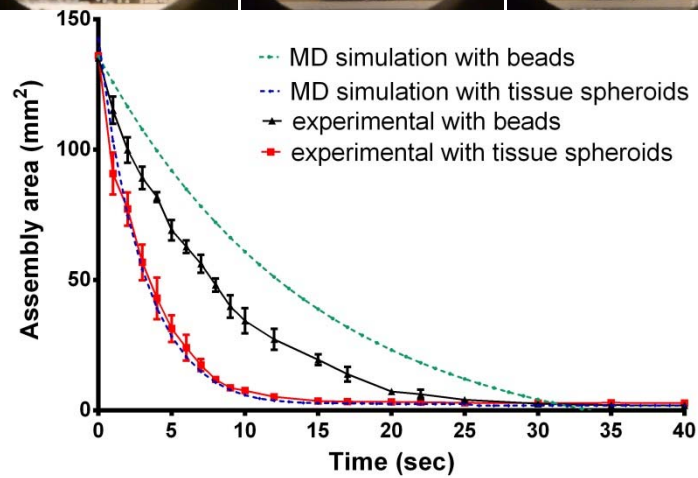
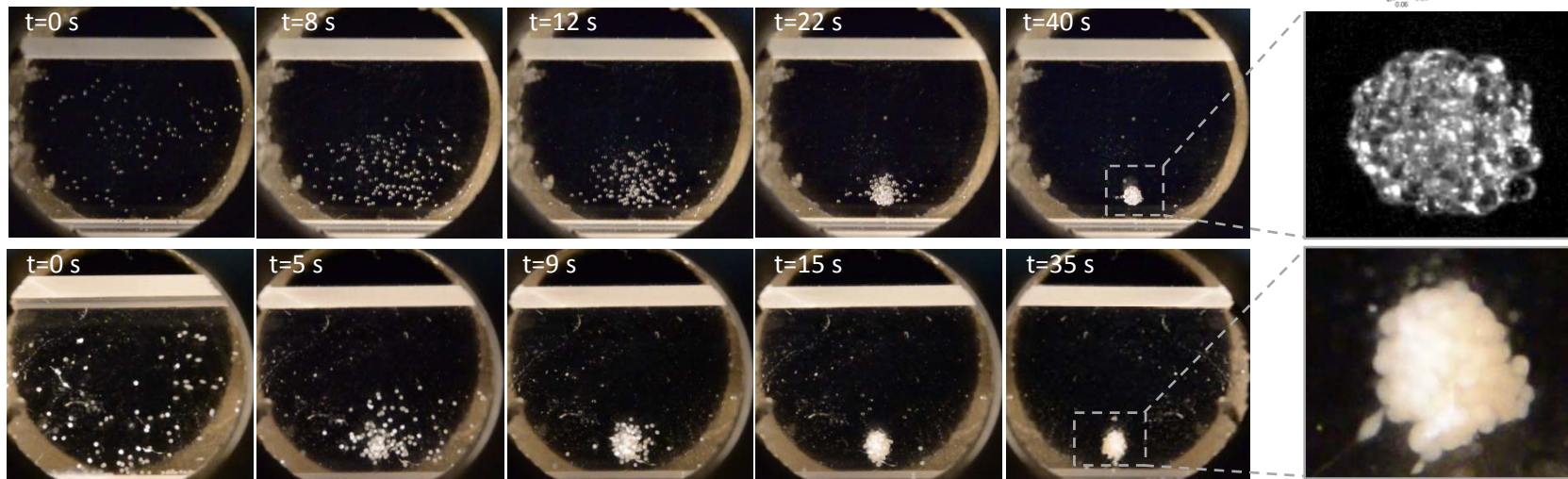
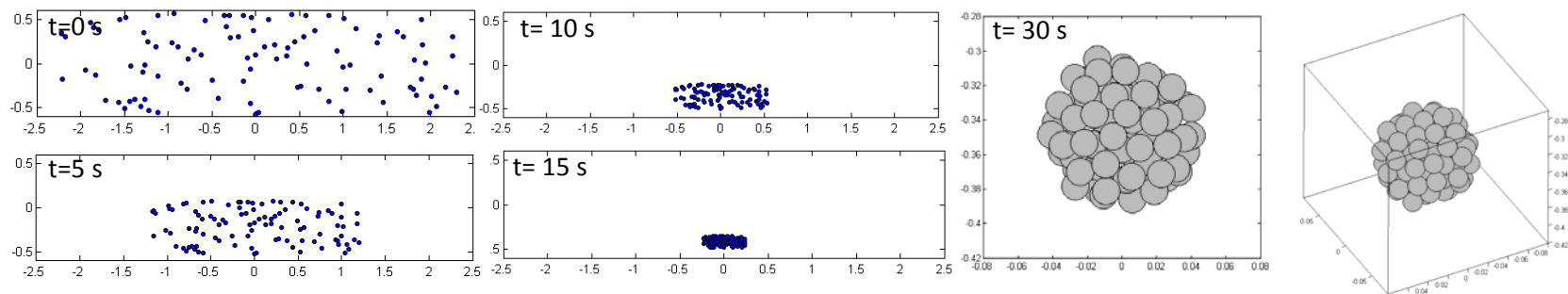


Effect of gadolinium on mechanical properties of tissue spheroids

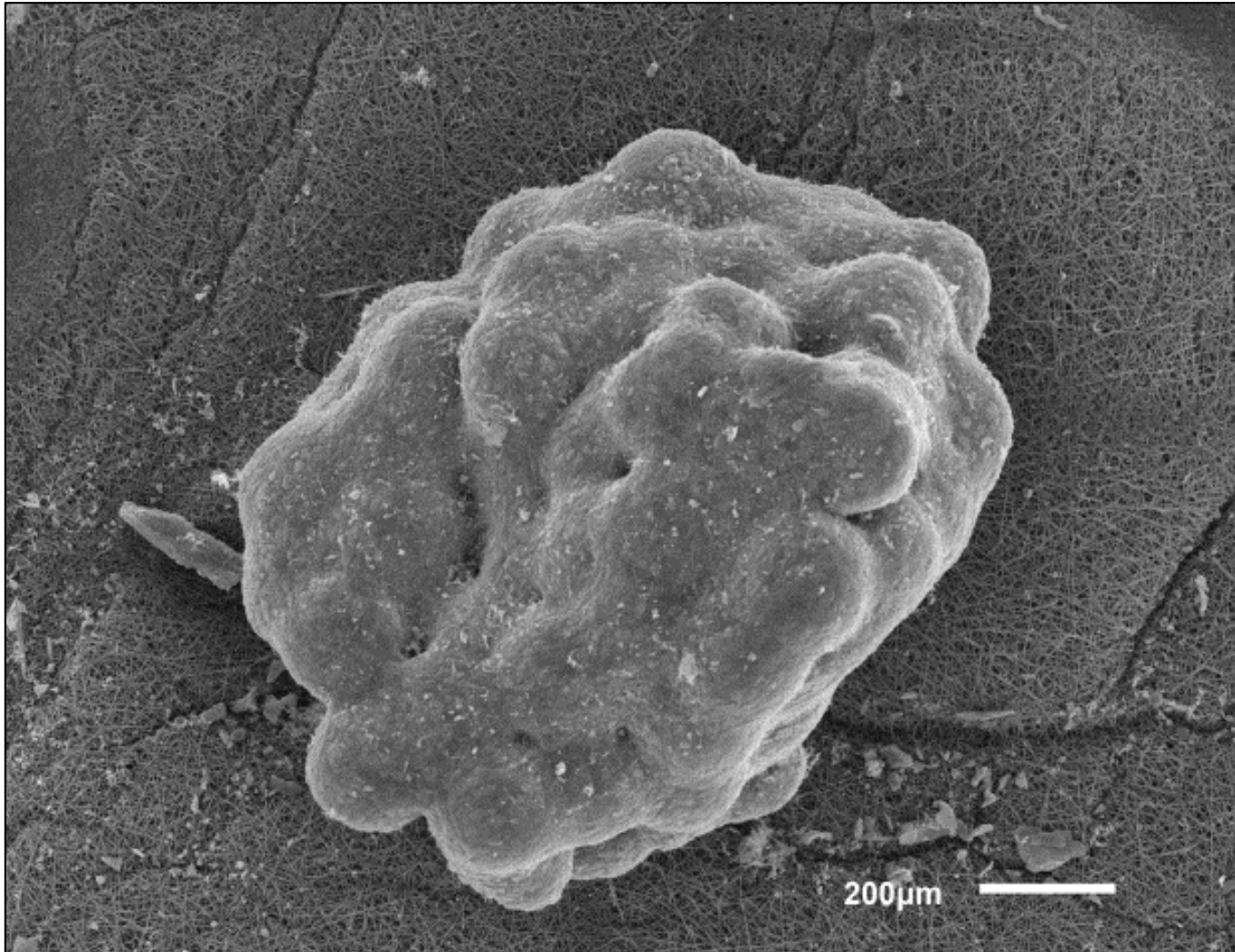
Effect of gadolinium on viability of tissue spheroids



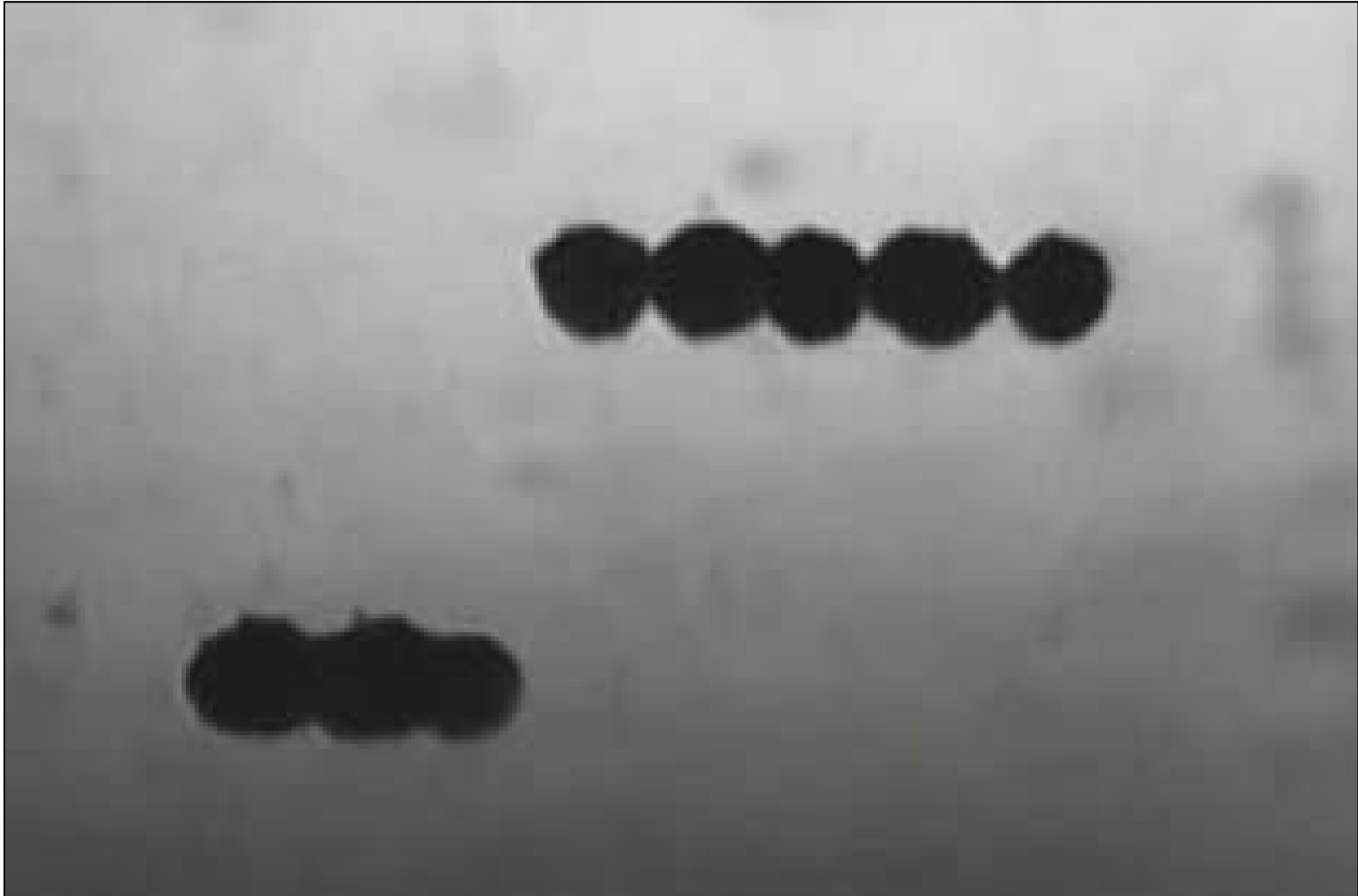




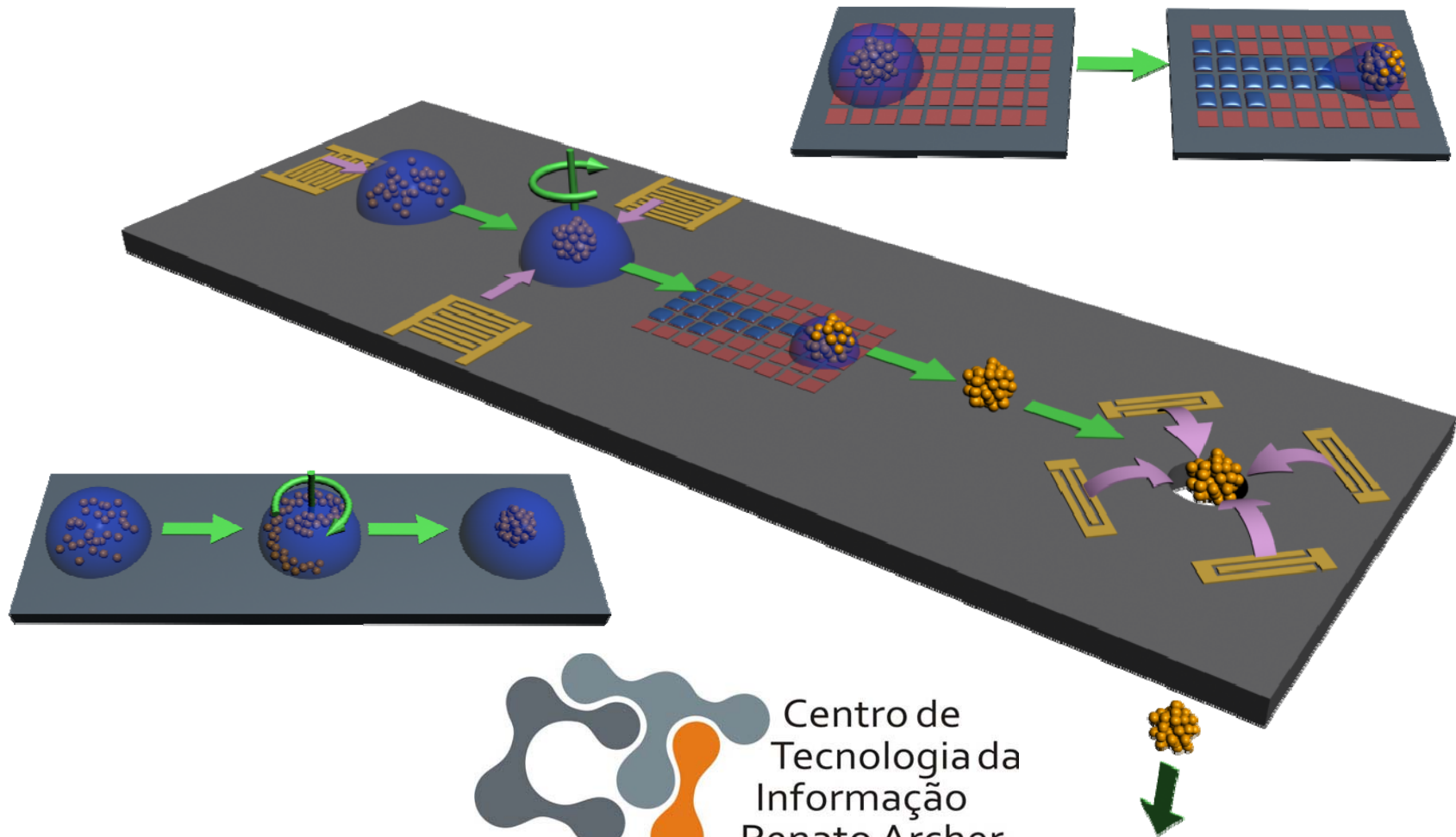
Implementation First Time of Scaffold-free, Label-free and Nozzle-free Magnetic Levitational Assembly of Tissue Spheroids



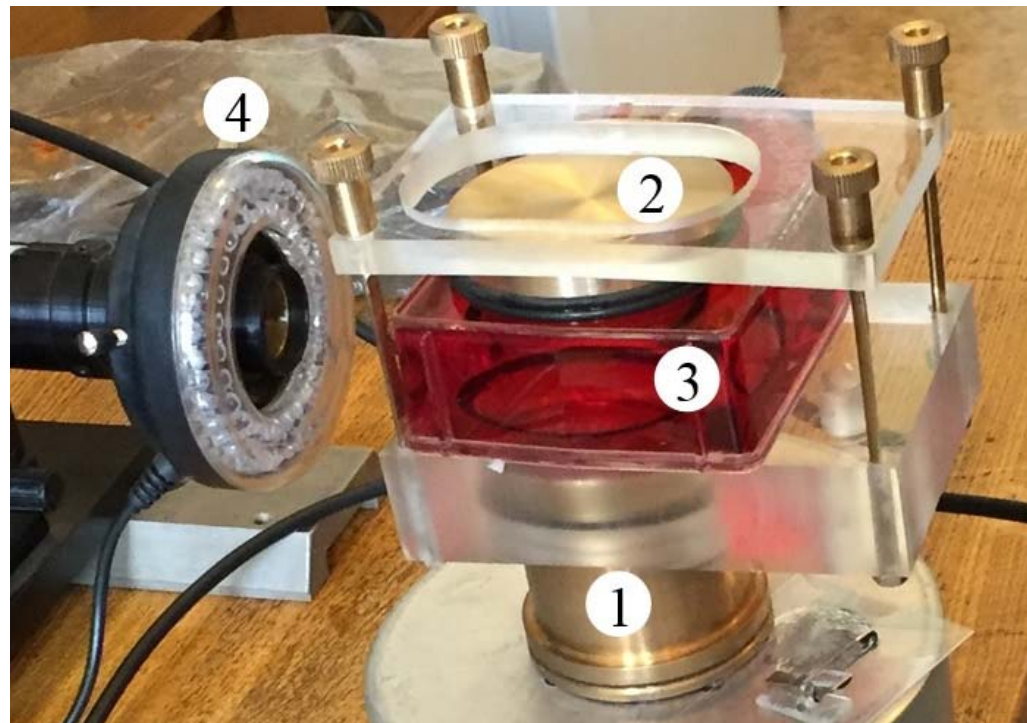
Trend 4: Acoustic Bioprinting



Surface Acoustic Waves Bioprinter

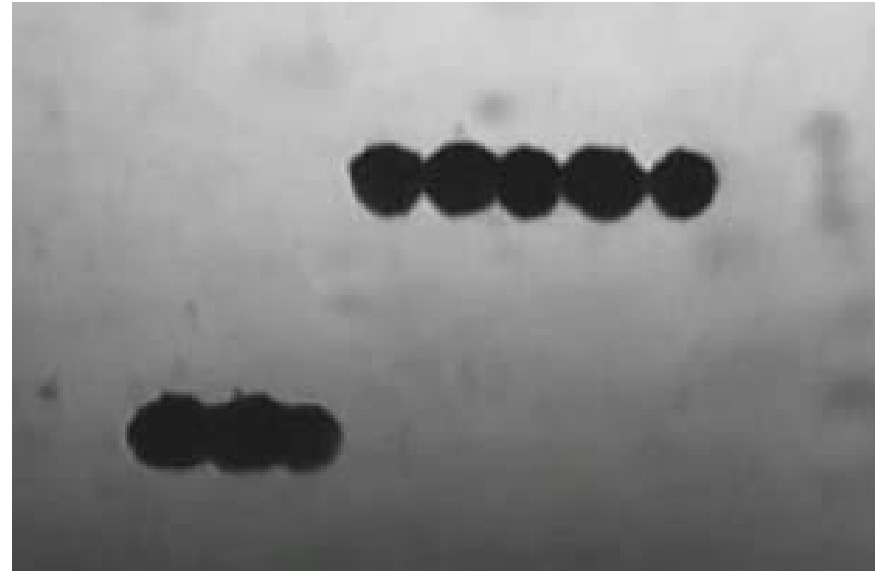
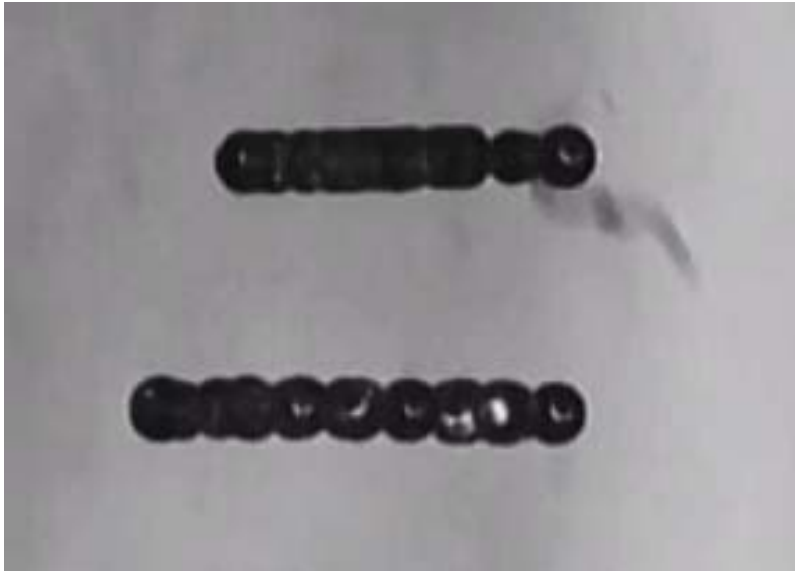


Scaffold-free Label-free Acoustic Levitational Assembly of Tissue Spheroids

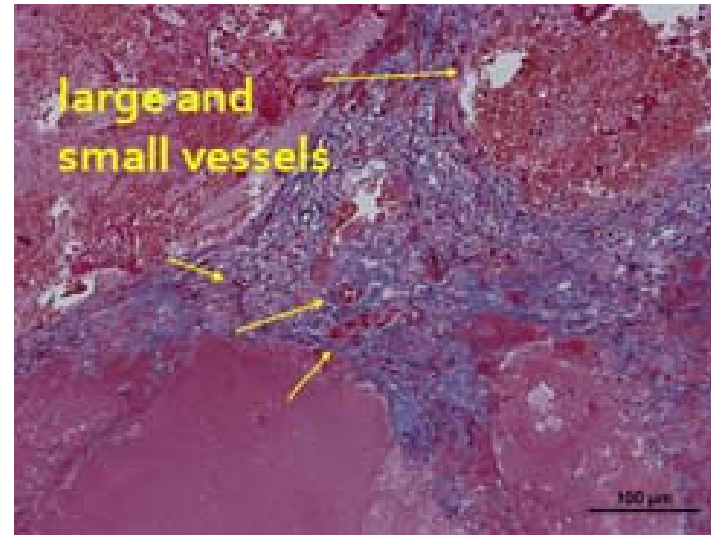
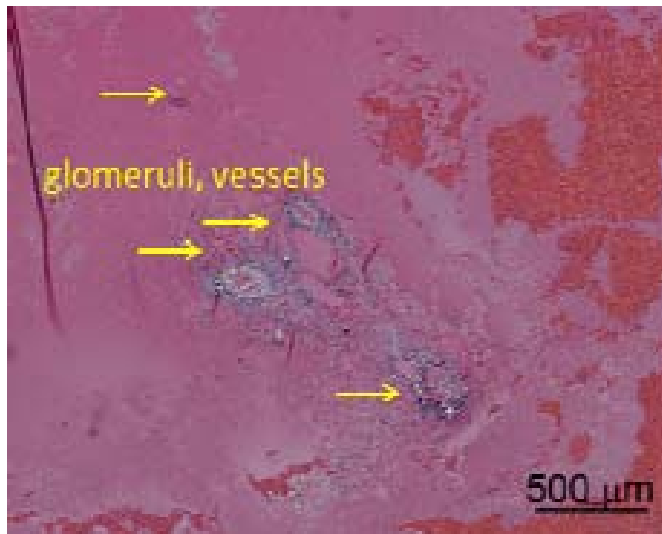
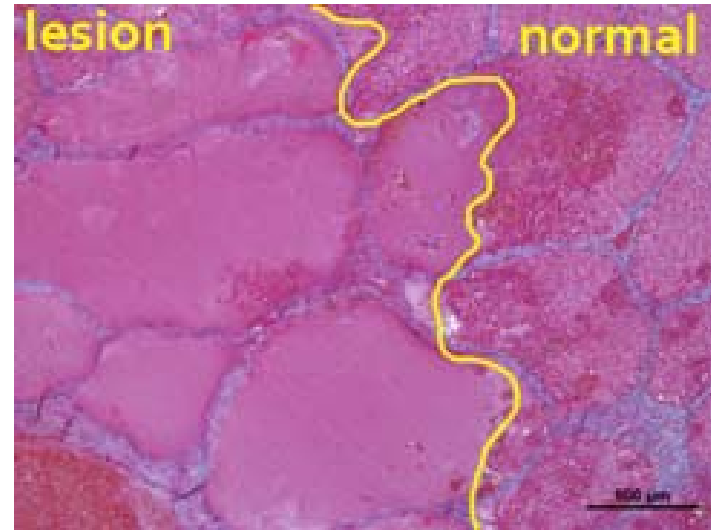


Experimental set-up for ultrasonic levitation of tissue spheroids.
1 – ultrasound source, 2 – reflector, 3 – culture medium, 4 – video camera.

Scaffold-free Label-free Acoustic Levitational Assembly of Tissue Spheroids



In vivo kidney acoustic decellularization

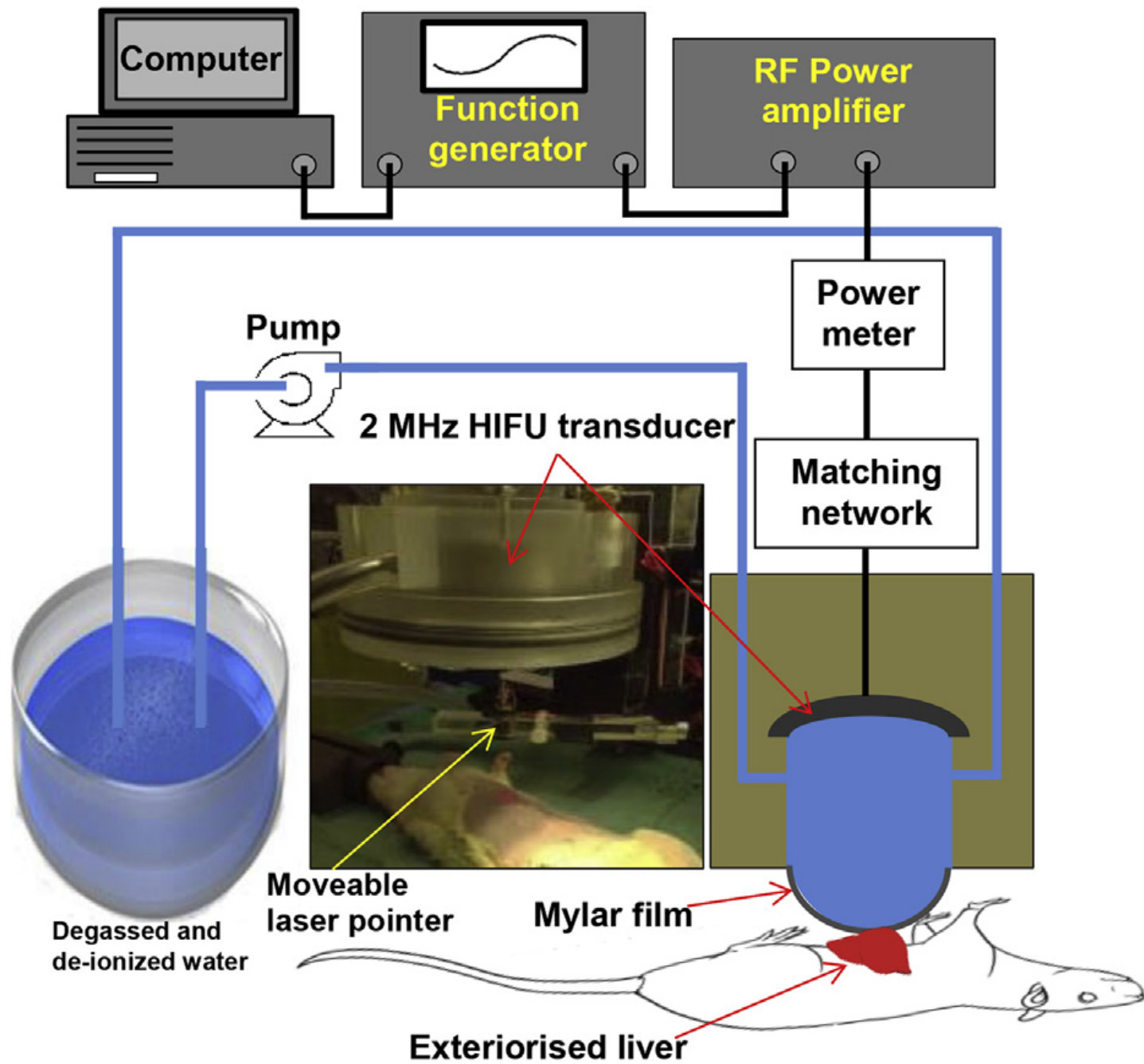


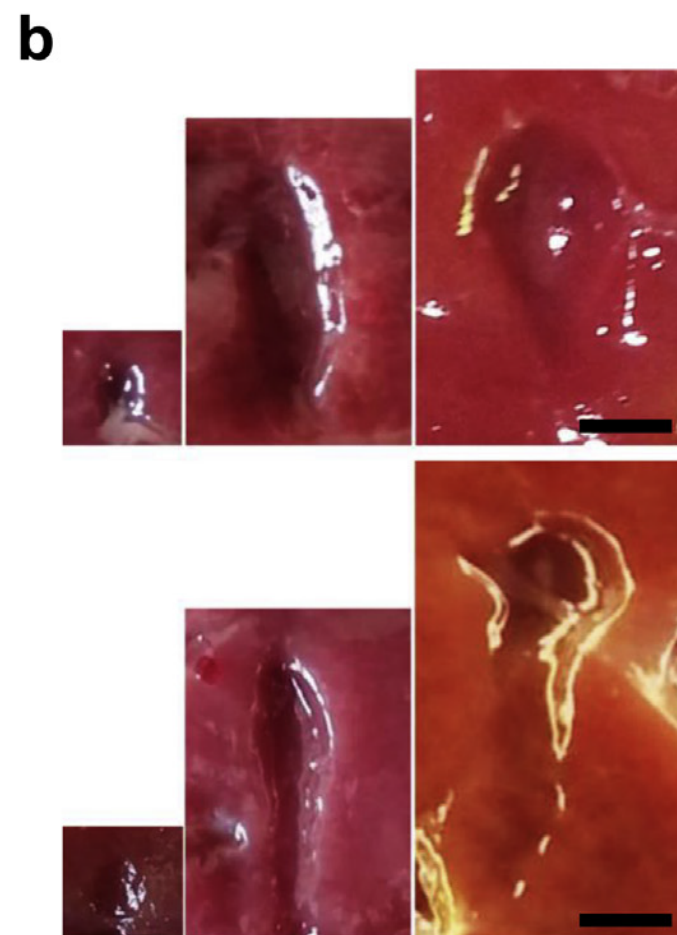
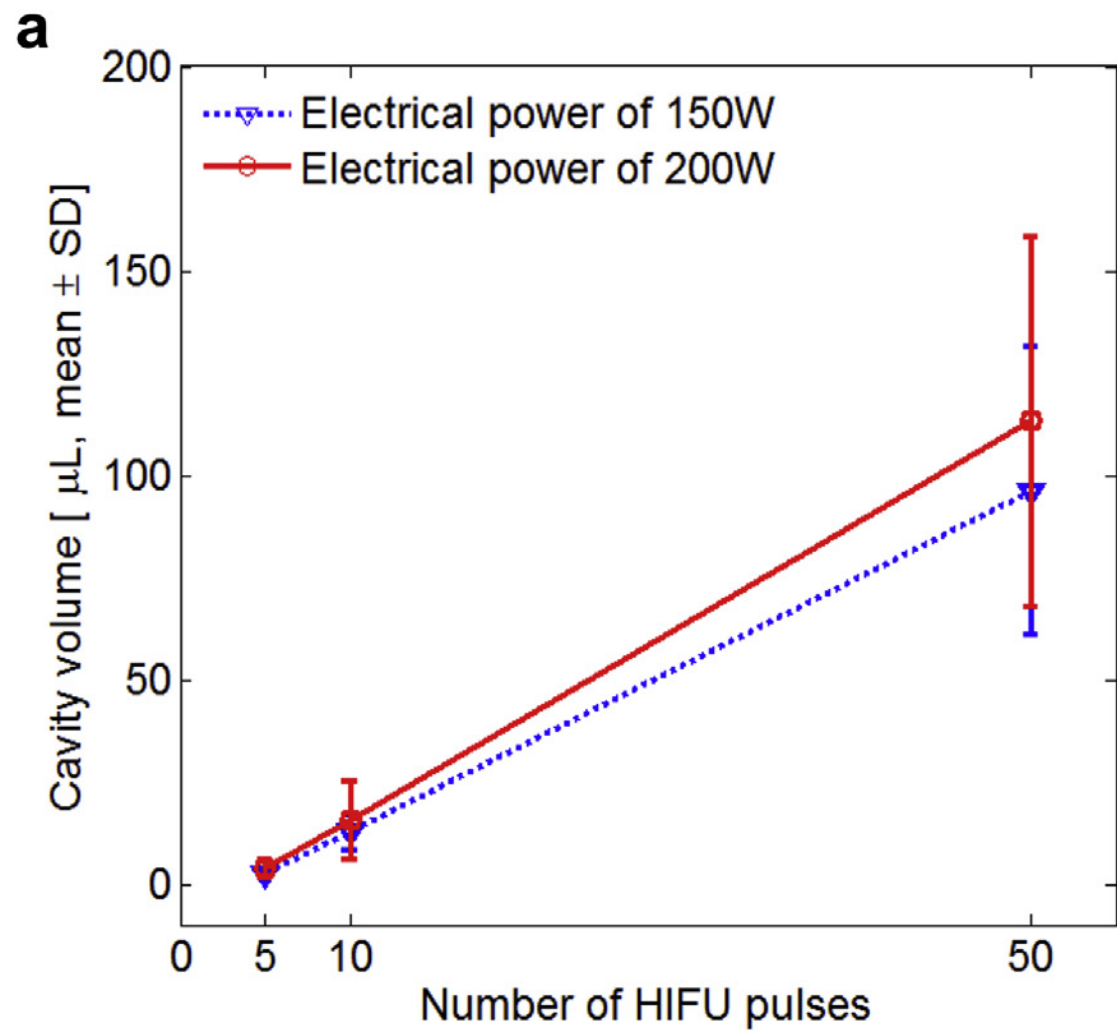
Ki Joo Pahk et al.

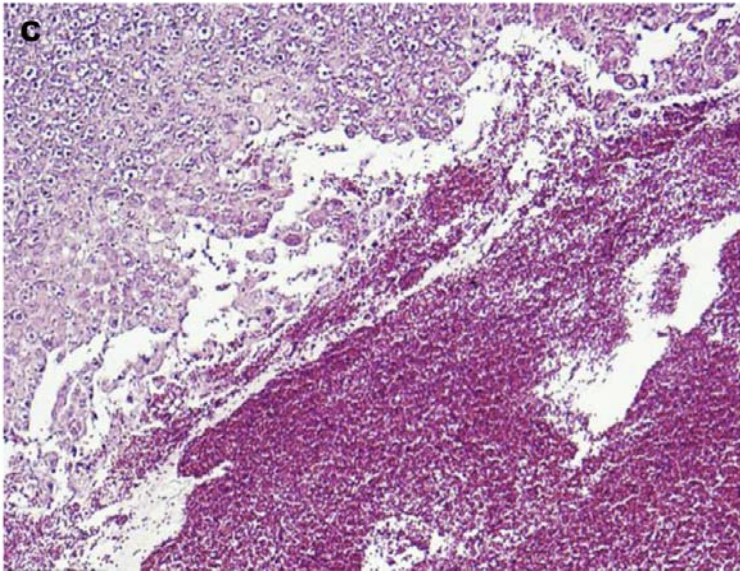
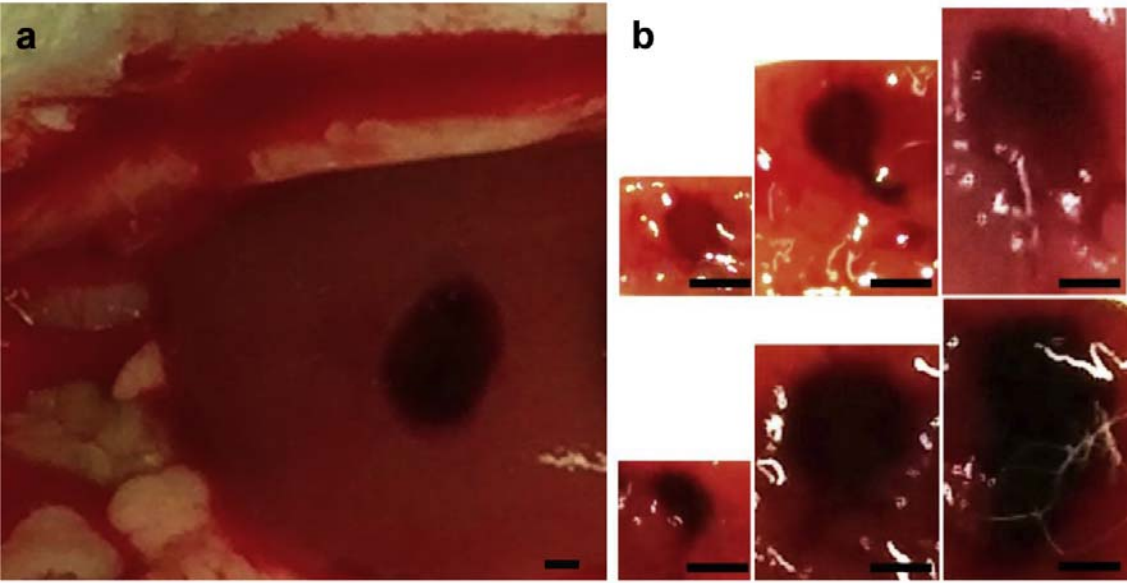
**A novel approach to ultrasound-mediated
tissue decellularization
and intra-hepatic cell delivery in rats**

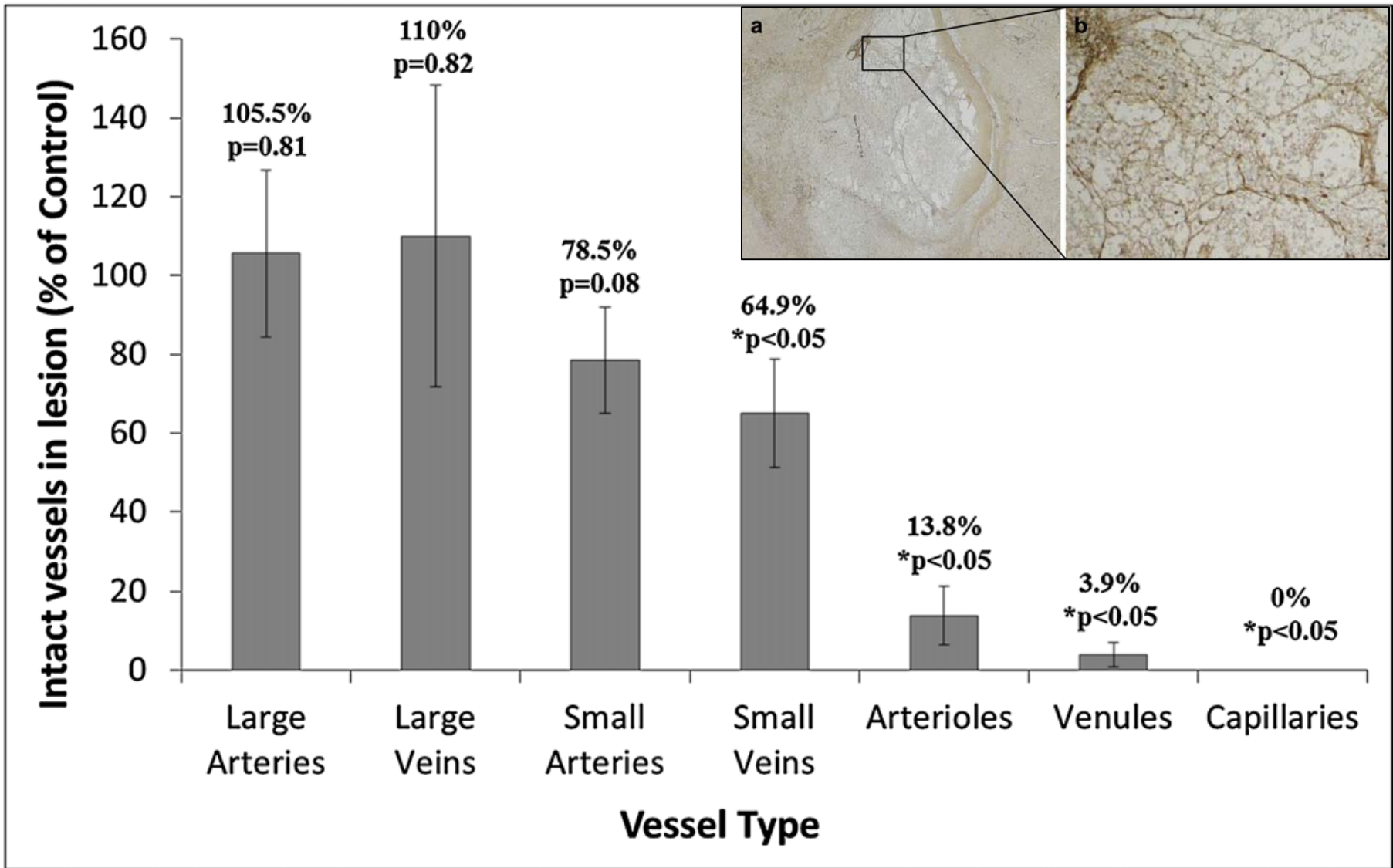
**Ultrasound
in Medicine and Biology**

May 2016









Vessel Type	Large Arteries	Large Veins	Small Arteries	Small Veins	Arterioles	Venules	Capillaries
Inner Diameter	>1 mm	>1 mm	0.3-1 mm	0.1-1 mm	20-300 μ m	20-100 μ m	<10 μ m
Total Wall Thickness	500-1000 μ m	100-500 μ m	50-500 μ m	10-200 μ m	5-50 μ m	1-20 μ m	0.5 μ m
Approximate Layer Thickness	Intima	0.5 μ m	0.5 μ m	0.5 μ m	0.5 μ m	0.5 μ m	0.5 μ m
	Media	300-600 μ m	40-200 μ m	30-300 μ m	4-80 μ m	3-30 μ m	0 μ m
	Adventitia	200-400 μ m	60-300 μ m	20-200 μ m	6-120 μ m	2-20 μ m	0 μ m

It has not escaped our notice...

"It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material."

A Structure for Deoxyribose Nucleic Acid

Watson J.D. and Crick F.H.C.

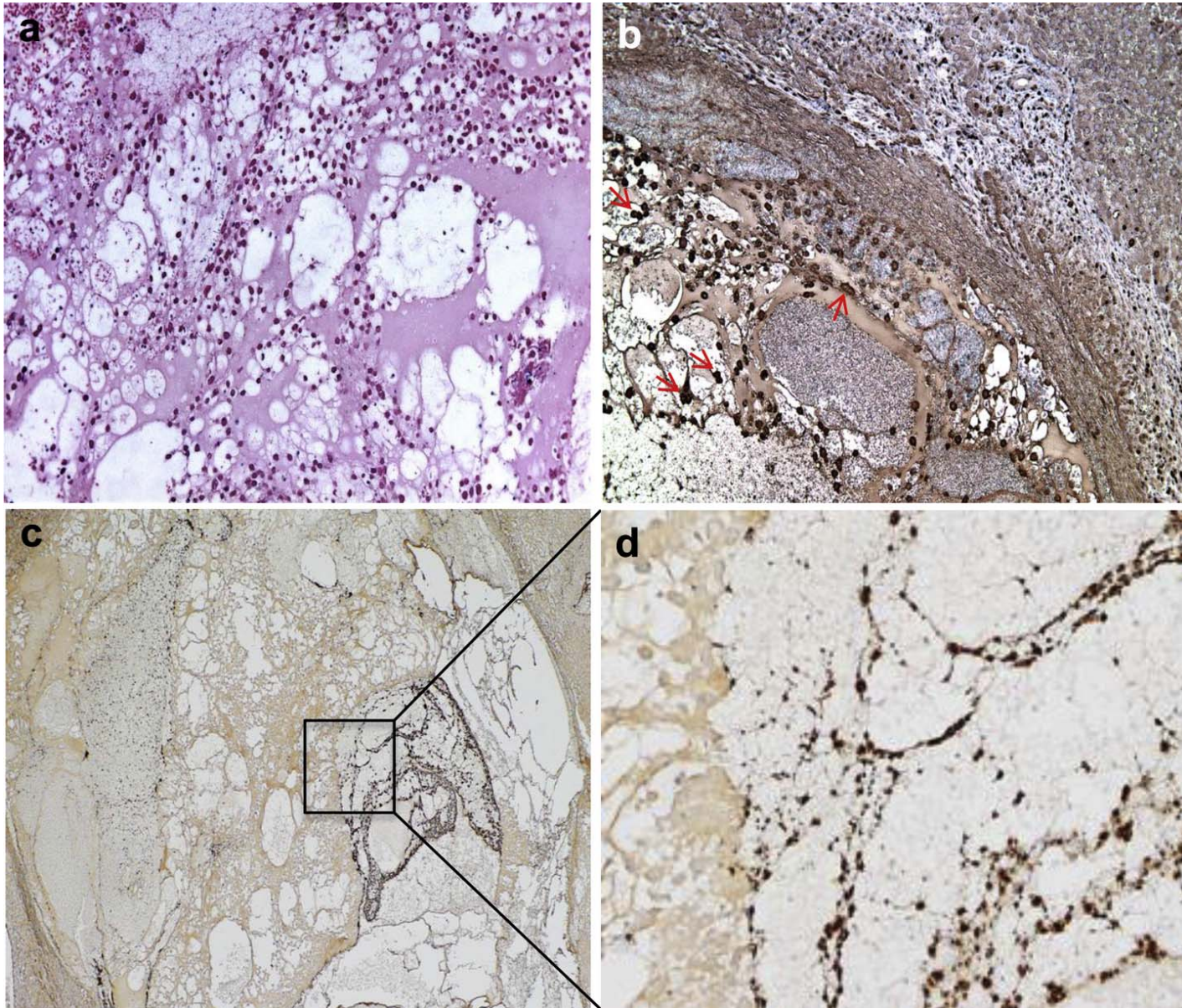
Nature 171, 737-738 (1953)

"It has not escaped our notice that the in vivo decellularization immediately suggests a possible technology for in vivo organ biofabrication."

New Trends in 3D Bioprinting

Mironov V.

Hannover, Germany, (2017)



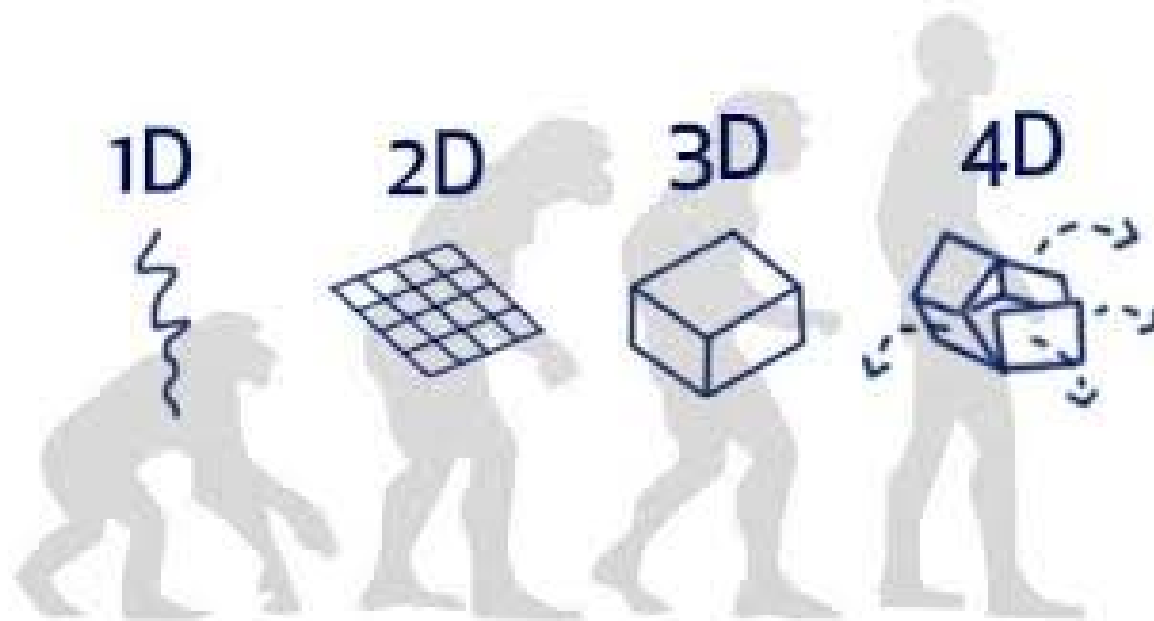
According to Ki Joo Pahk et al., 2016

Speculations

Moreover, liver organoids created ex vivo from allogenic or xenogenic scaffolds and appropriate cells could be grafted inside the cavity for integration into the recipient liver. (Ki Joo Pahk et al. 2016)

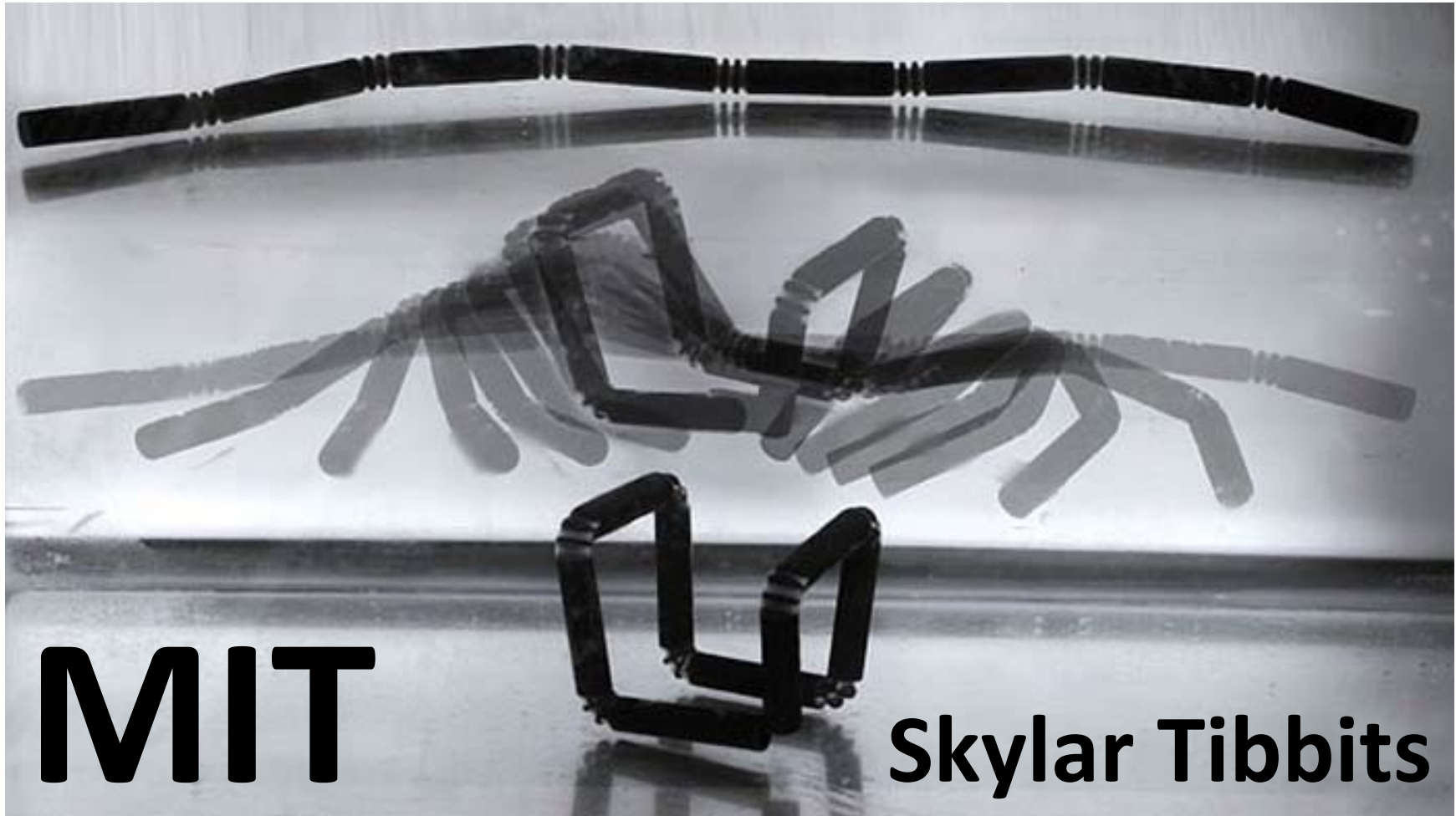
Moreover, kidney organoids created ex vivo from autologous induced pluripotent stem cells could be grafted inside the cavity for integration into the recipient kidney (Vladimir Mironov, Mainz, 2017)

Trend 5. 4D Bioprinting

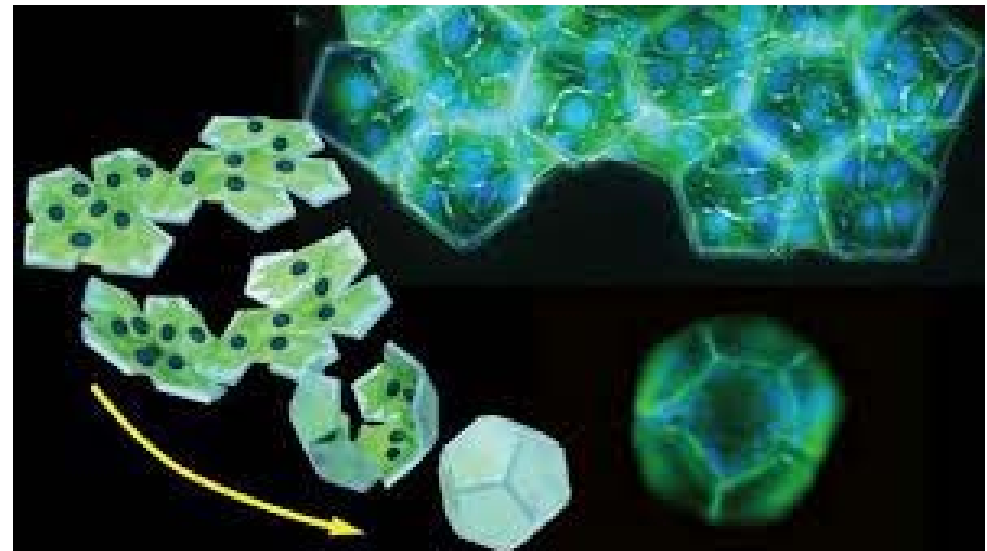
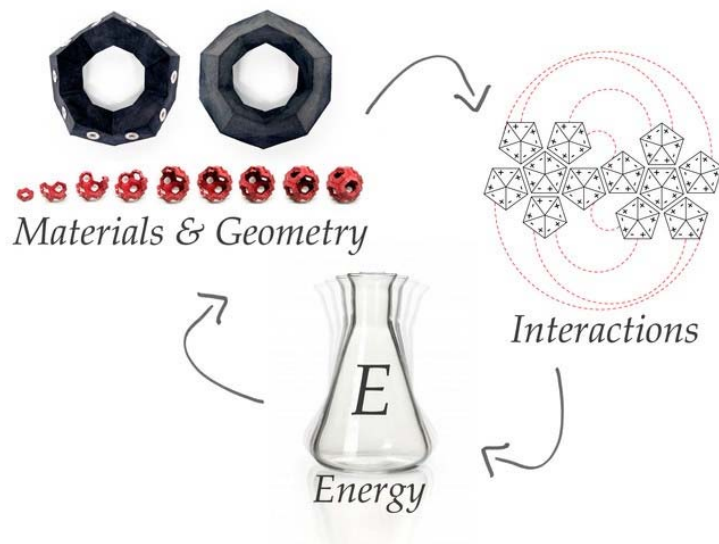
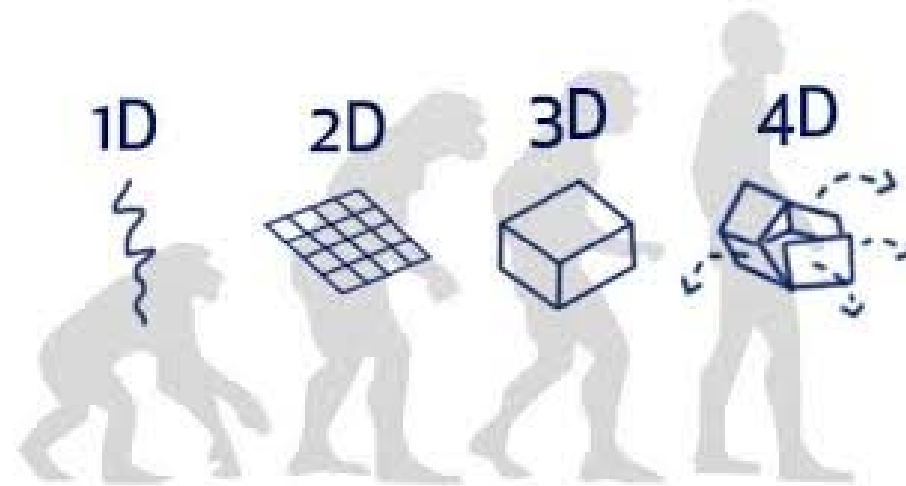


4D Bioprinting is a post-printed programmable self-assembly

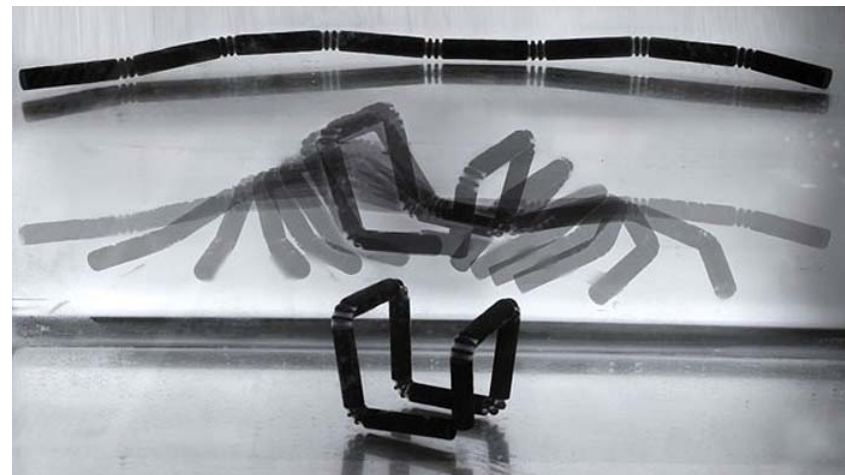
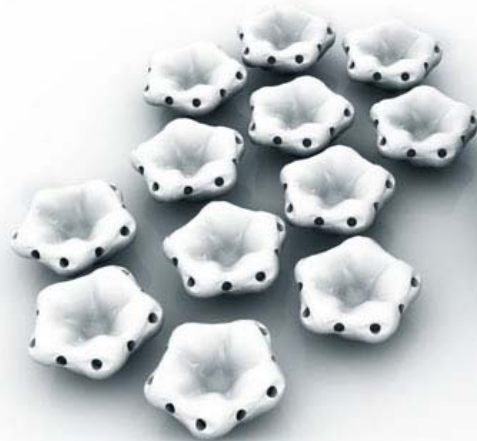
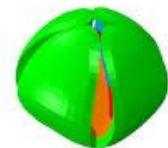
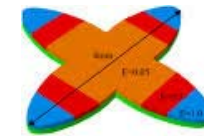
4D printing: printing of programmable self-assembled and self-folded materials



4D printing: printing of programmable self-assembled and self-folded materials



4D bioprinting

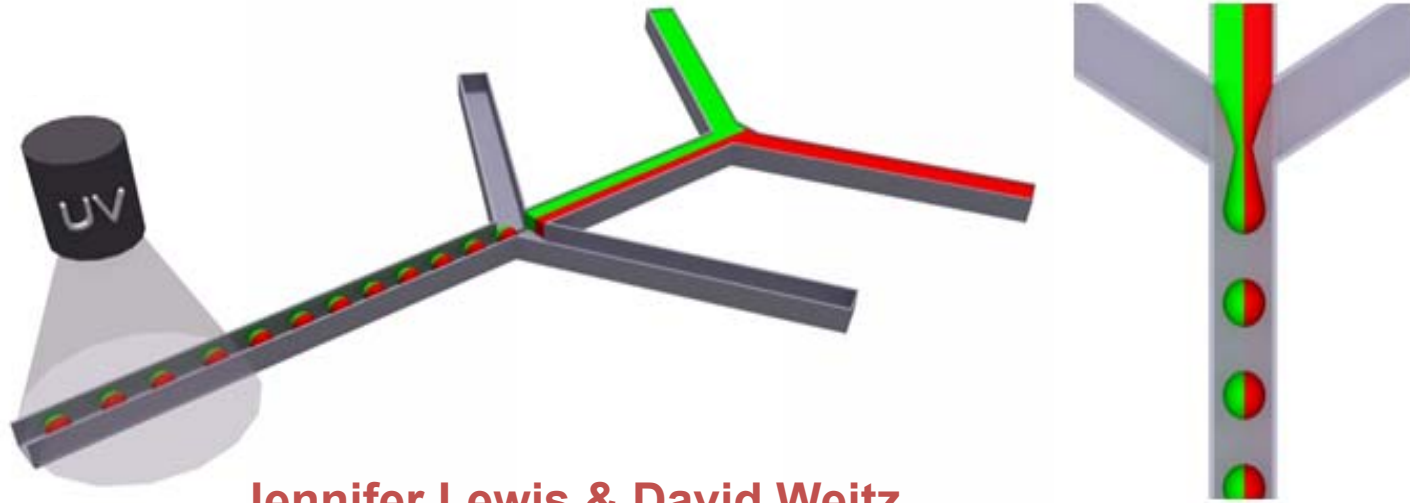


Jia An, Chua Chee Kai and Vladimir Mironov

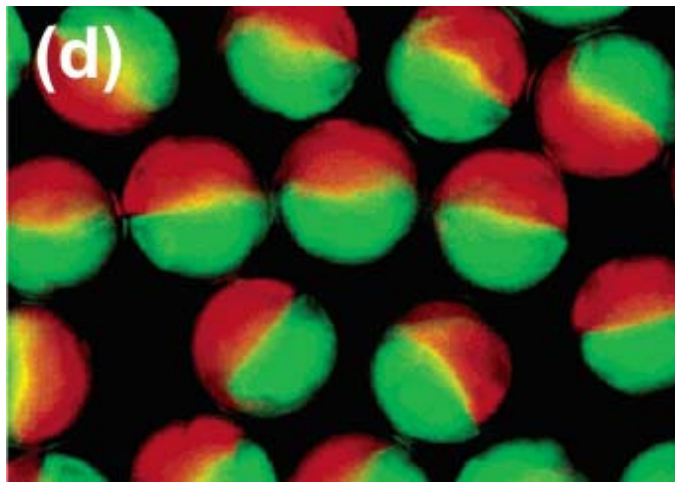
[A Perspective on 4D Bioprinting](#)

International Journal of Bioprinting, 2015

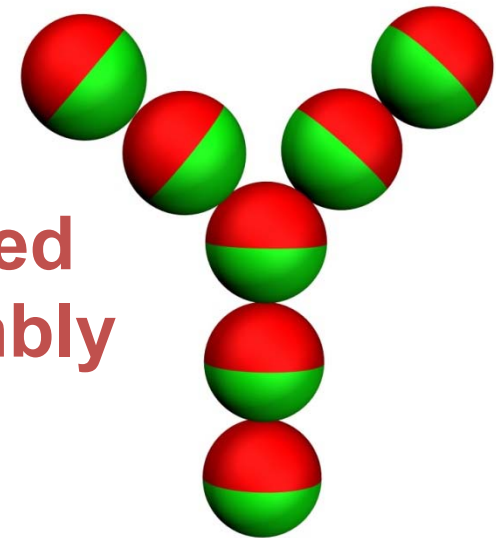
Digital Microfluidics: Droplet Generator

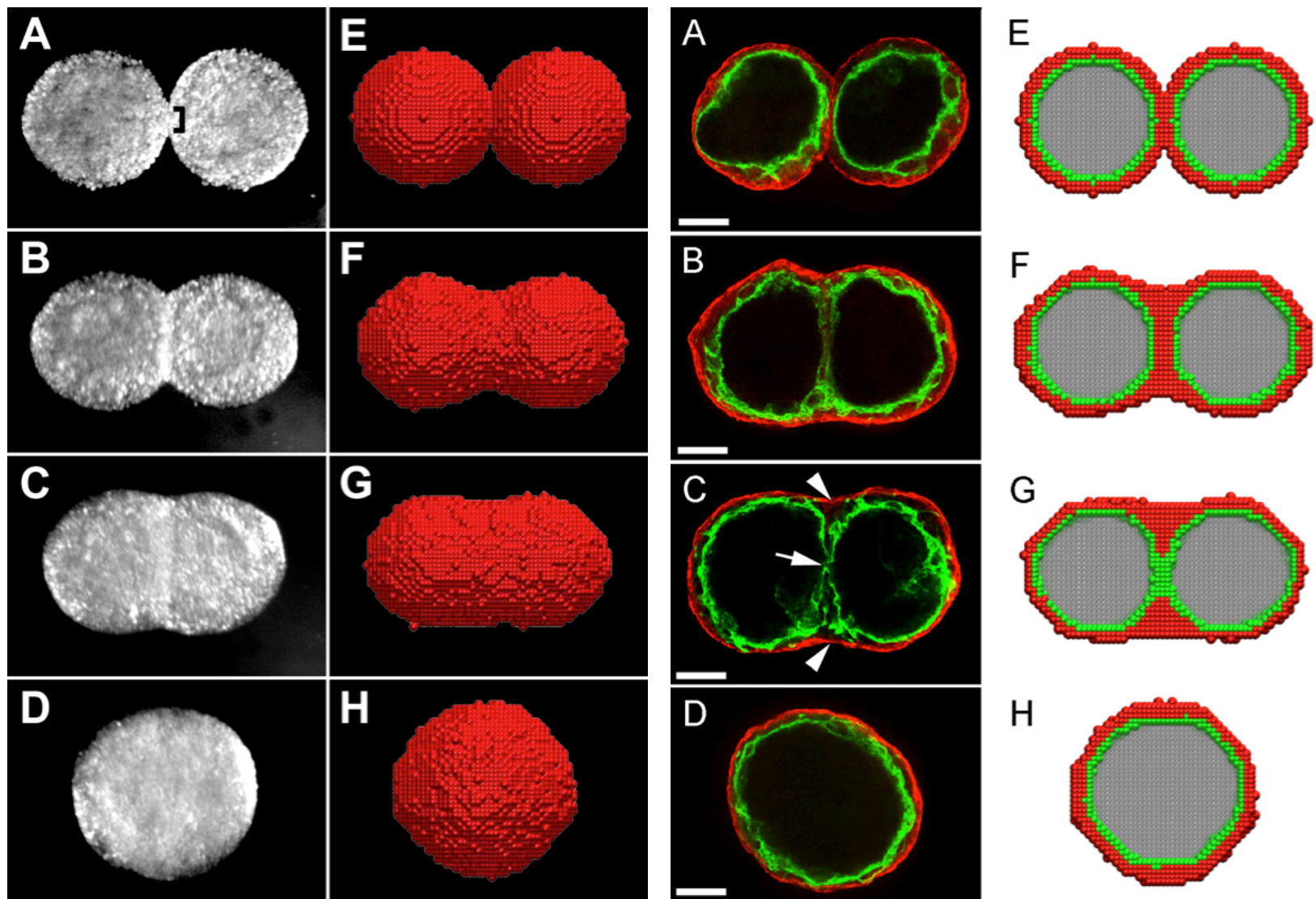


Jennifer Lewis & David Weitz



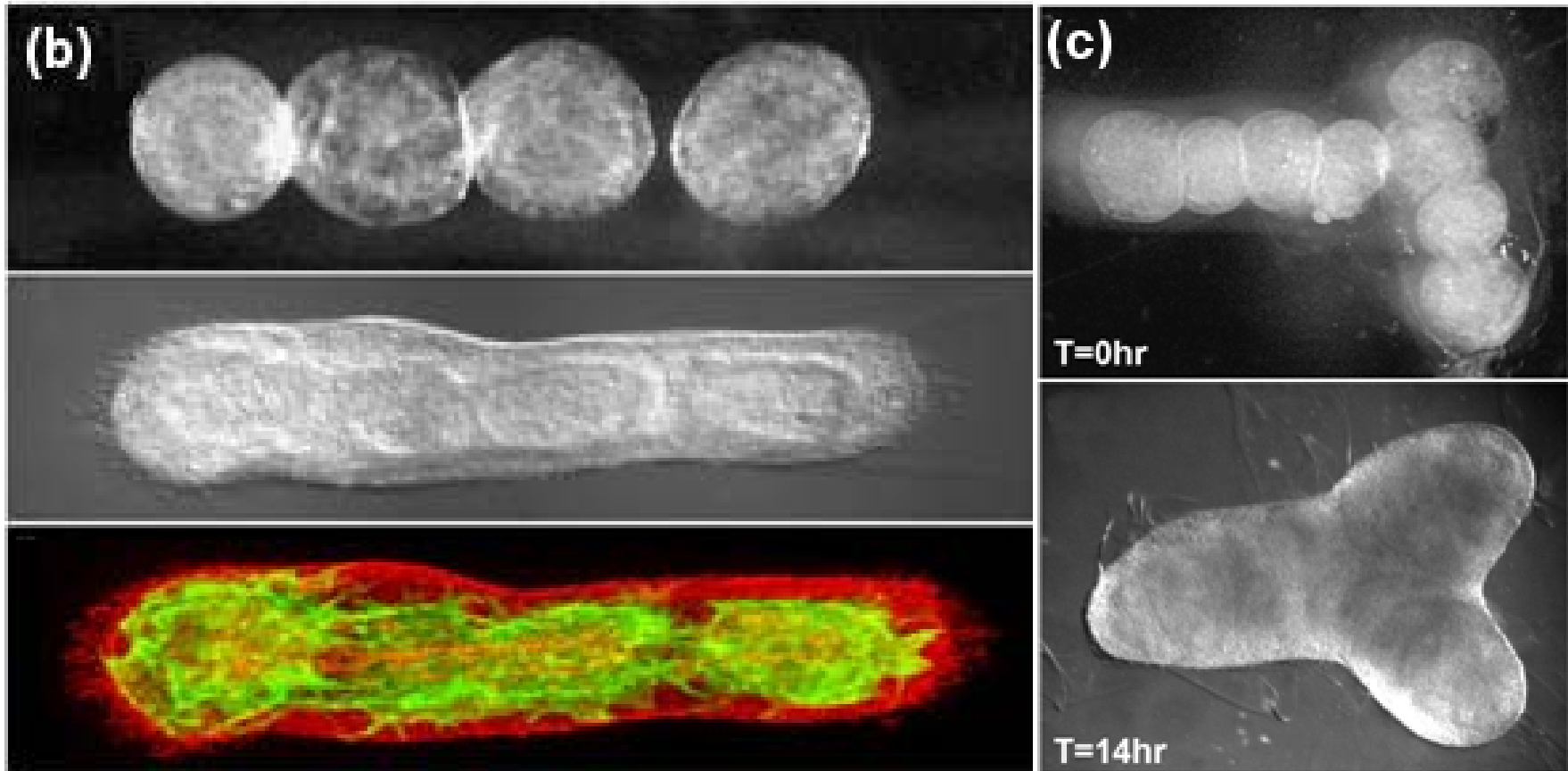
Self-directed
self-assembly





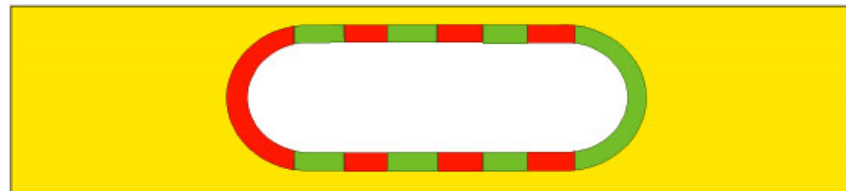
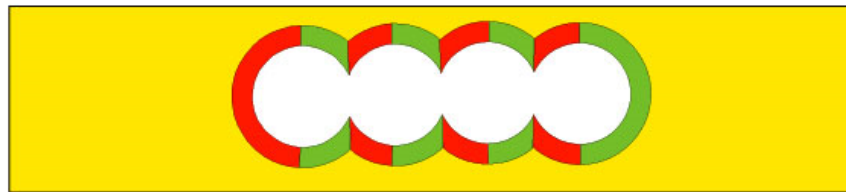
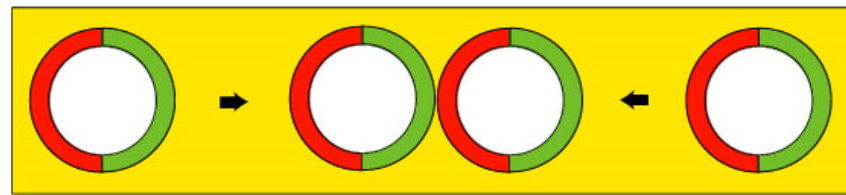
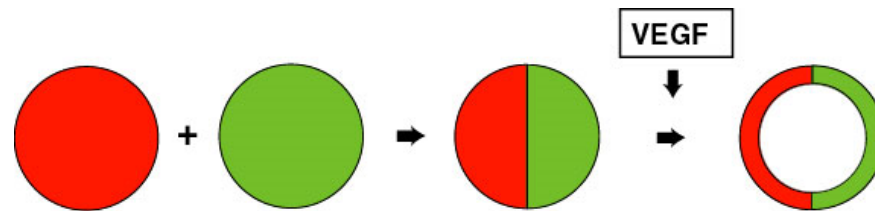
Biomaterials, 2009

Digital Bioprinting: Tissue Spheroids Fusion (Linear and Branched Segments of Vascular Tree)



Regenerative Medicine, 2008; Biomaterials, 2009

4D Bioprinting – Programmable Self-Assembly



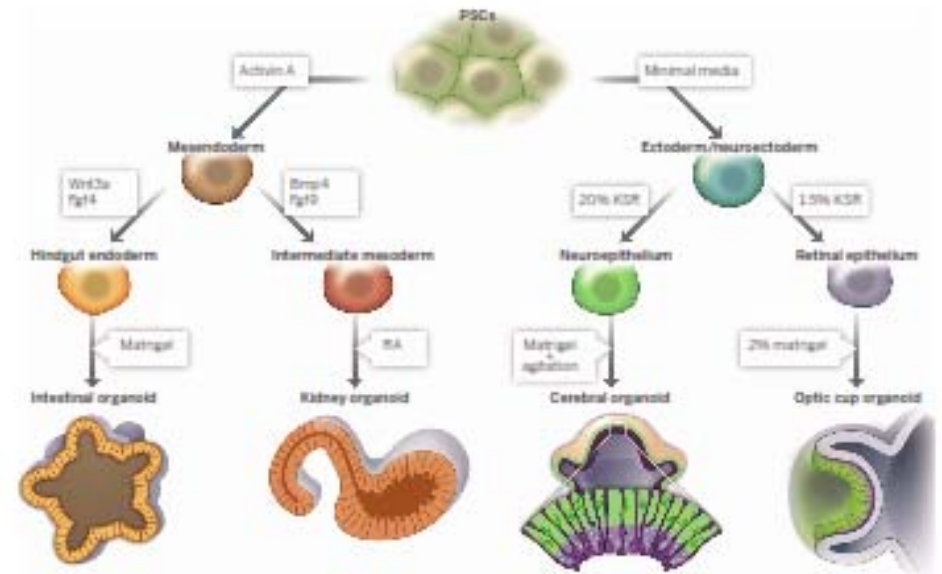
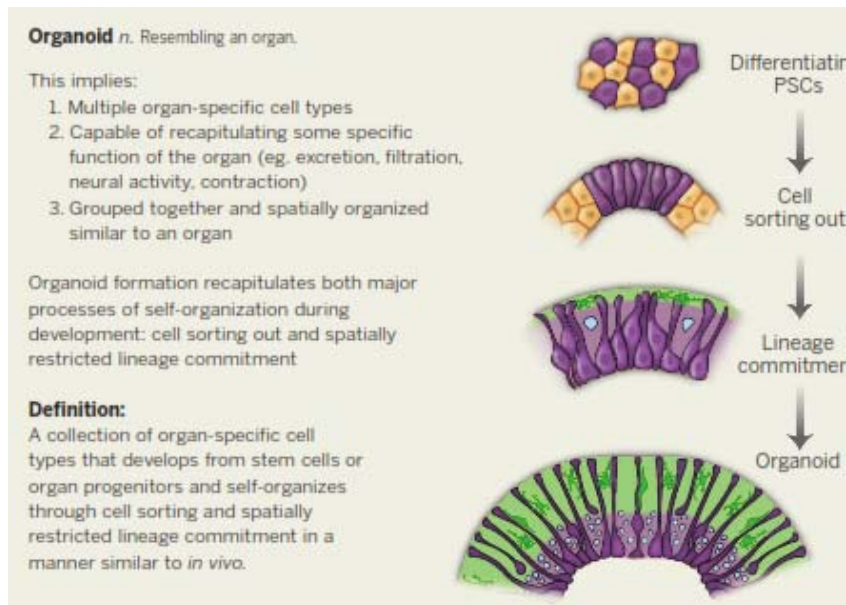
Established Trends in 3D Bioprinting

- **Hybrid Bioprinting**
- **In vivo Bioprinting**
- **Magnetic Bioprinting**
- **Acoustic Bioprinting**
- **4D Bioprinting**
- **Bioprinting organ-on-a-chip**

New emerging trends

- **Organoids**
- **Bioprinting of living machines**
- **Tissue elimineering**
- **Synthetic cells and synthetic morphogenesis**
- **Bioprinting in Space**

Definition of **organoids** (organ-like)



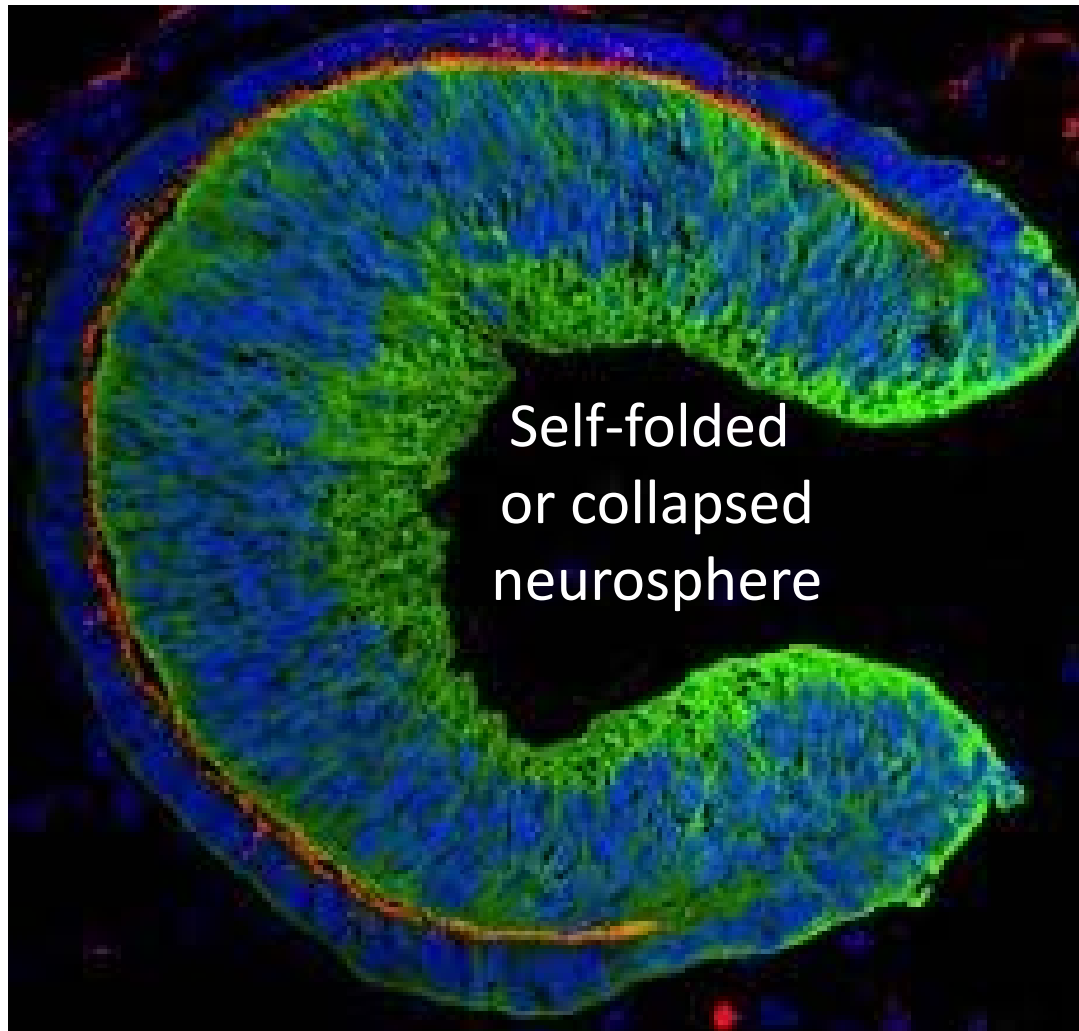
Lancaster & Knoblich,

Organogenesis in a dish:

Modeling development and disease using organoid technologies

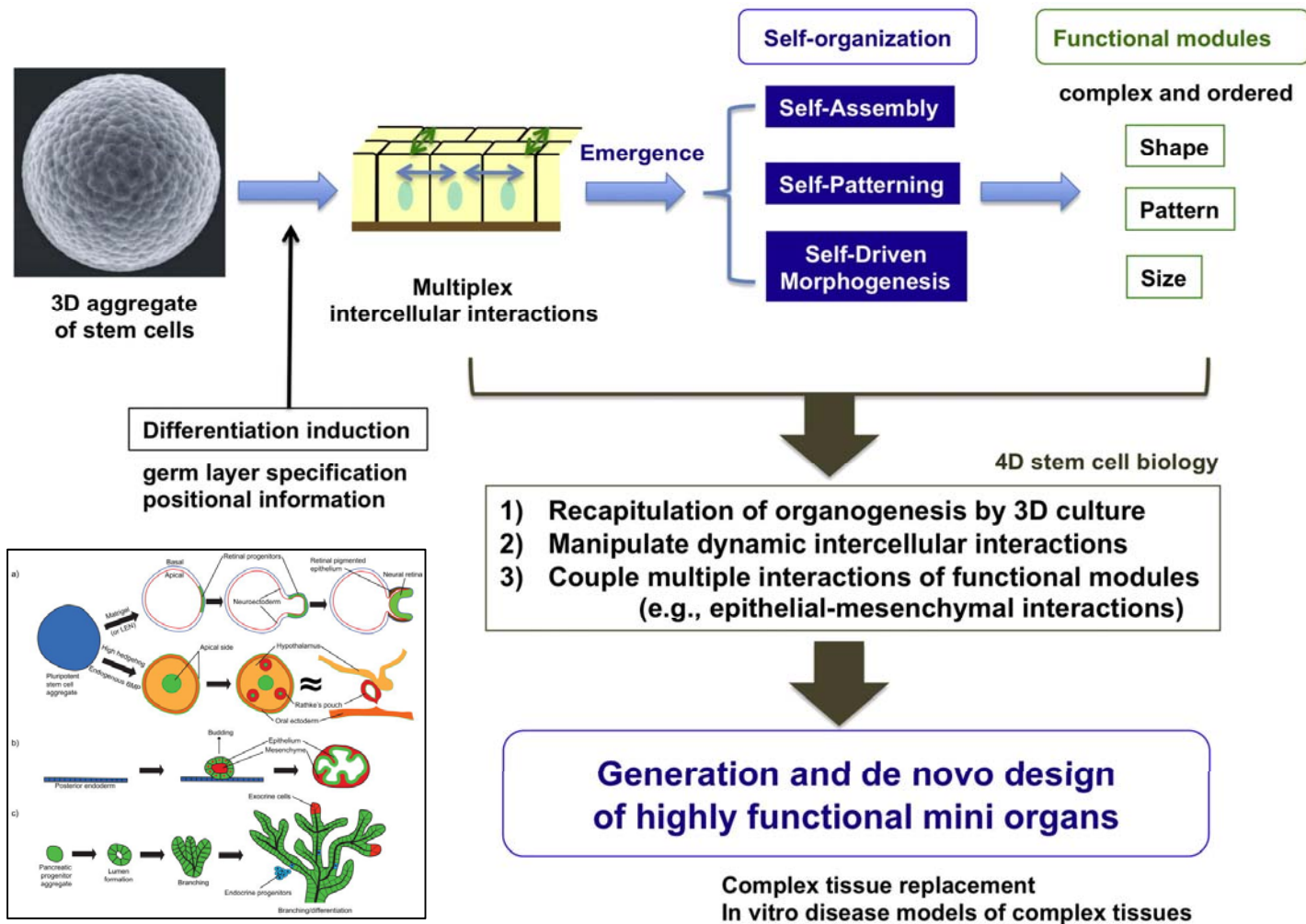
Science 2014

Stem cell-based organogenesis

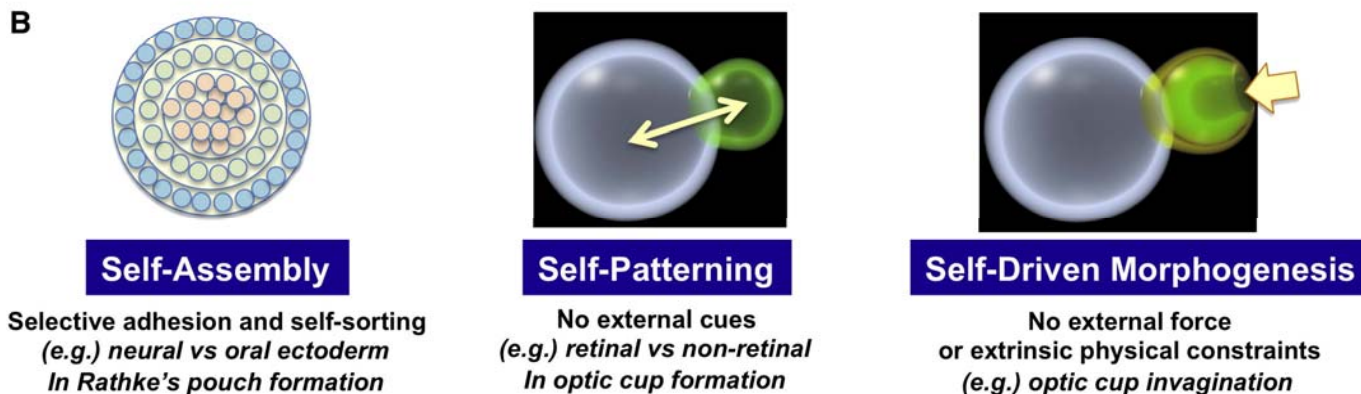
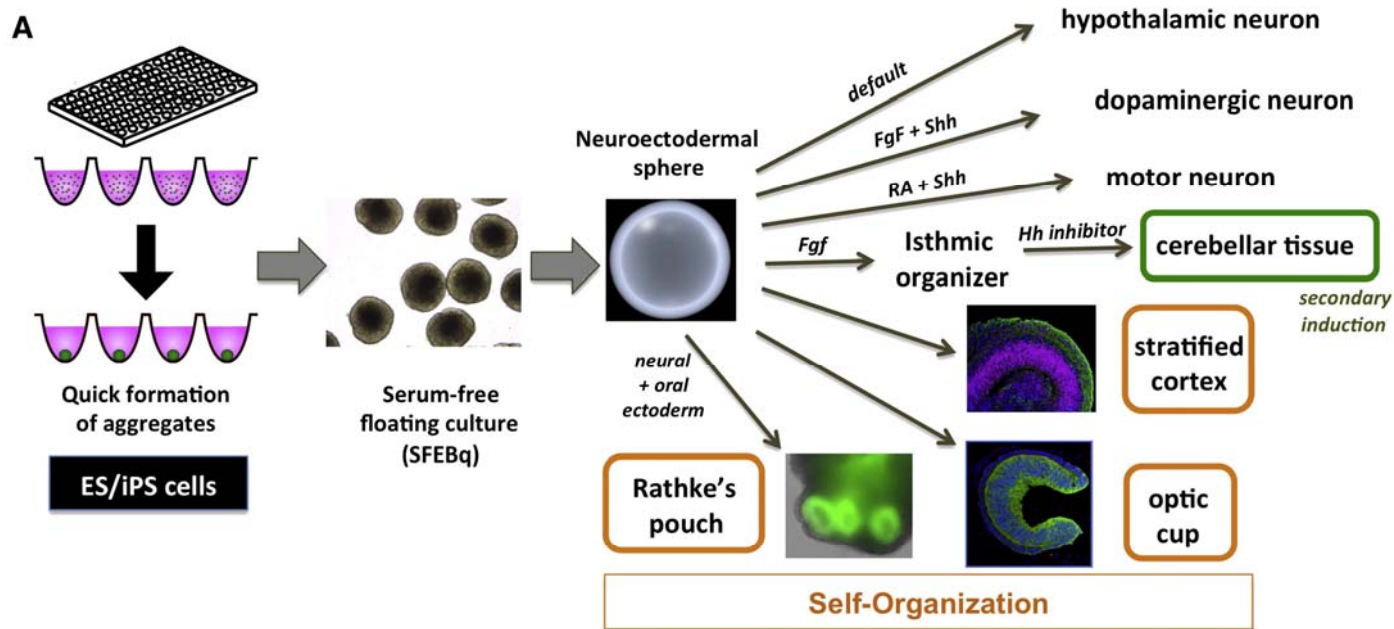


Dr. Yoshiki Sasai
RIKEN, Japan

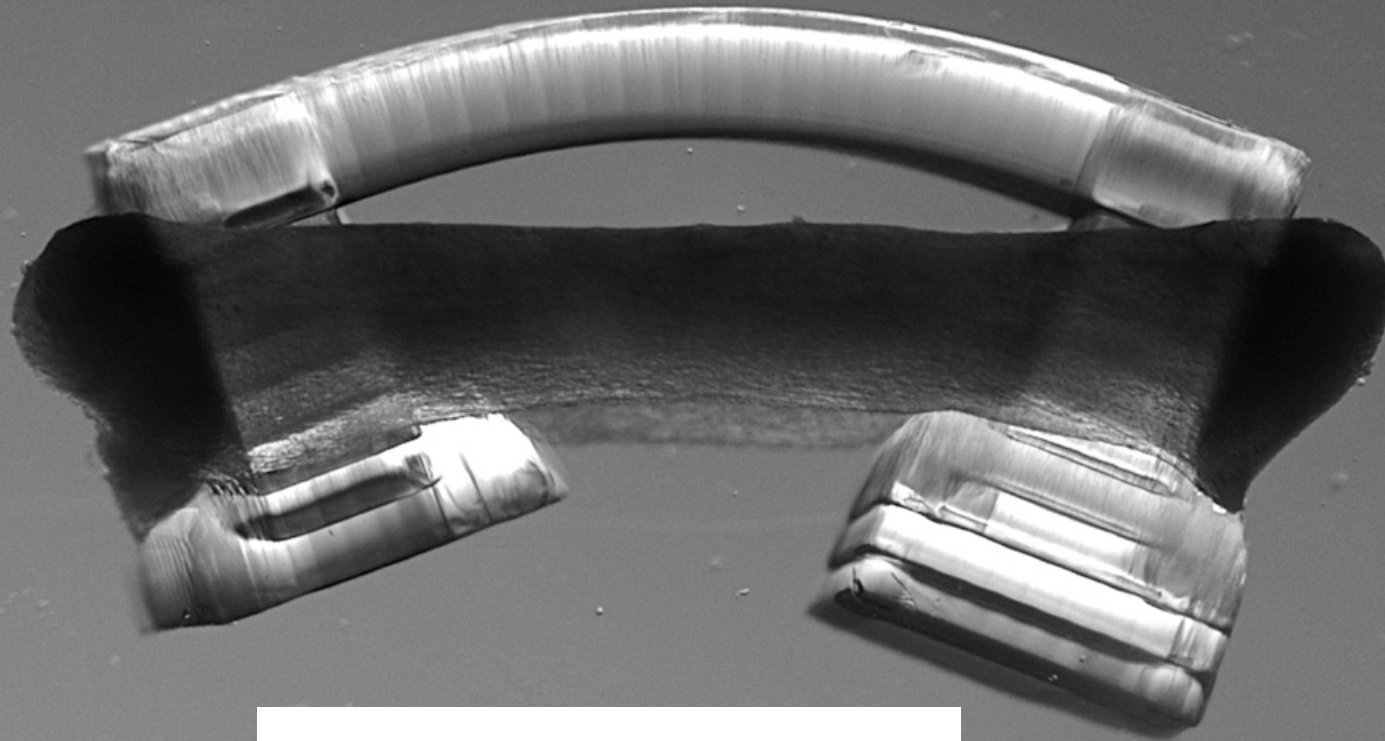
Stem Cell-Based *in vitro* Organogenesis



4D Stem Cell Biology: Stem Cell-Based Organogenesis



A new class of miniature biological robots, or bio-bots




Living machine

Ritu Raman, Caroline Cvetkovic, Sebastien G. M. Uzel, Randall J. Platt,
Parijat Sengupta, Roger D. Kamm, and Rashid Bashir.

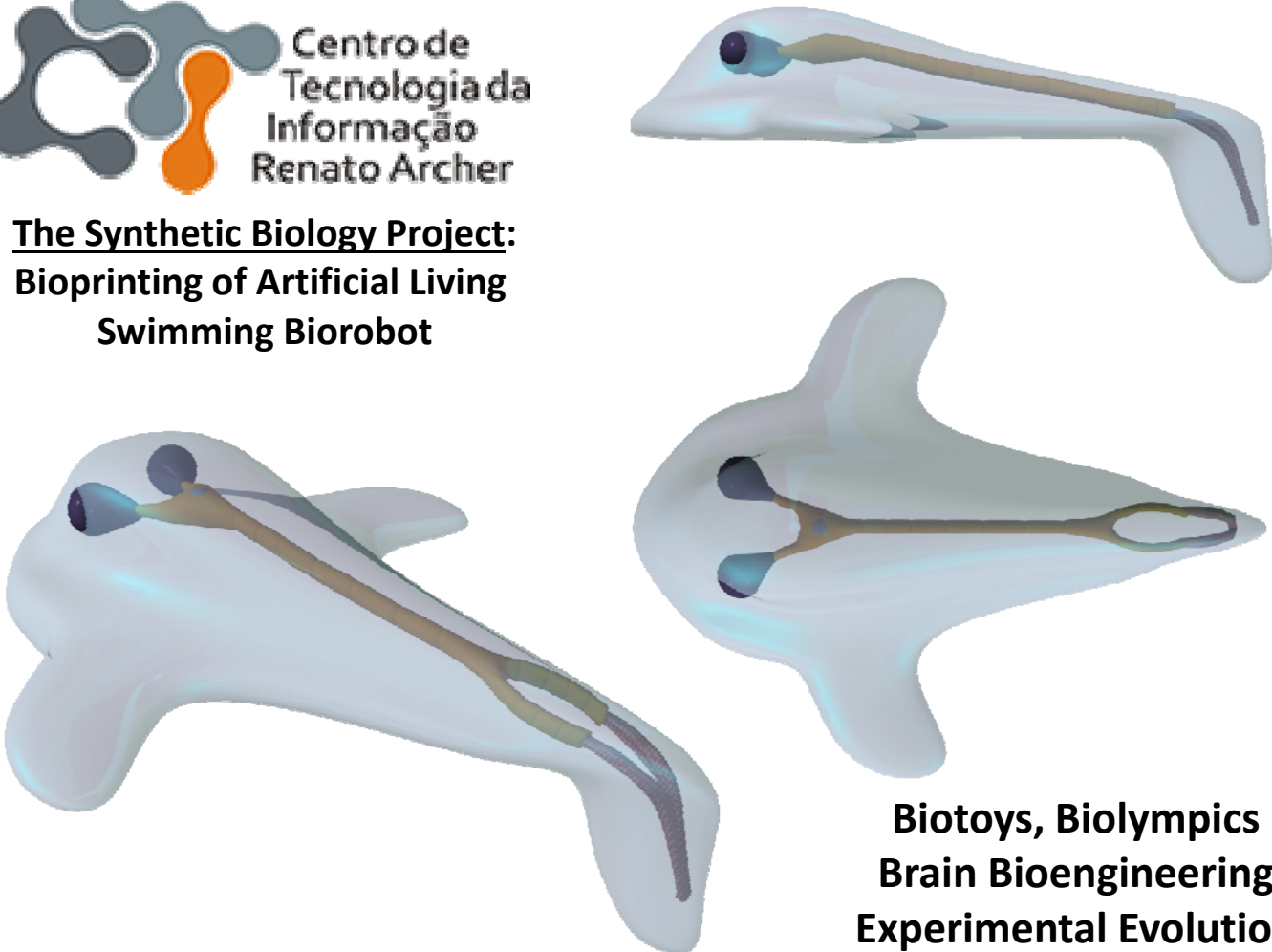
Optogenetic skeletal muscle-powered adaptive biological machines.

PNAS, March 14, 2016

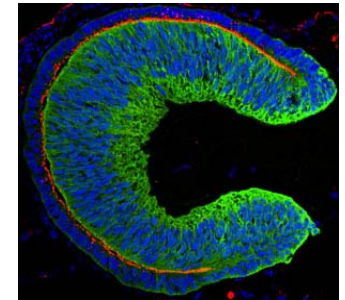
3D Bioprinting as a Synthetic Biology

 Centro de
Tecnologia da
Informação
Renato Archer

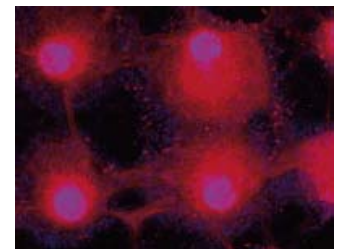
**The Synthetic Biology Project:
Bioprinting of Artificial Living
Swimming Biorobot**



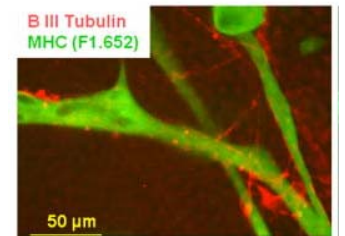
**Biotoys, Biolympics
Brain Bioengineering
Experimental Evolution**



Retina



Neural networks



**Neural-muscular
junction**

(according to Y. Sasai, Japan; S. Takeuchi, Japan; J. Hickman, USA)

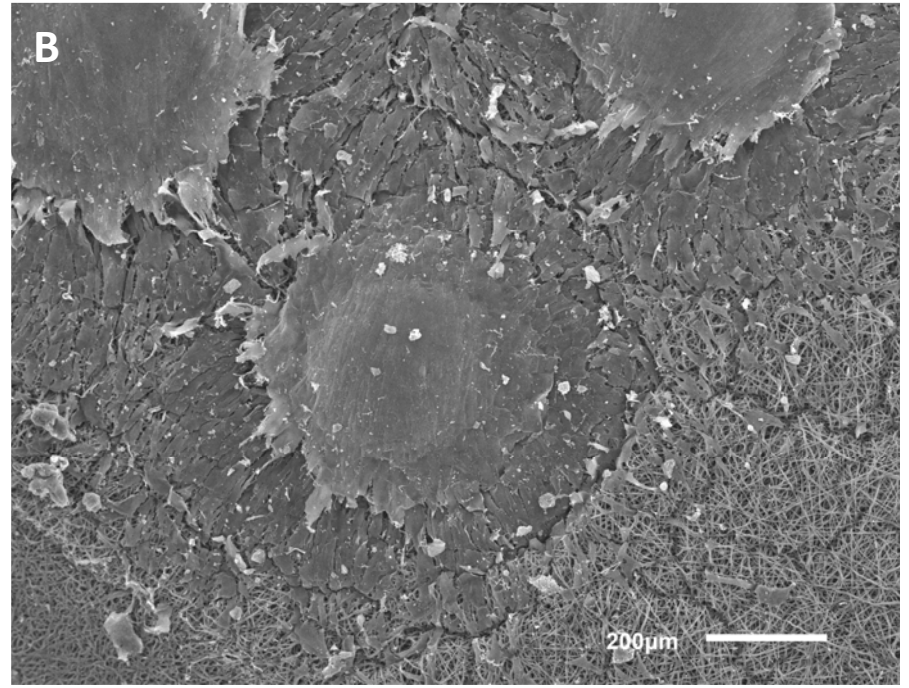


Foreign body reaction on implants leads to fibrotic capsular contracture

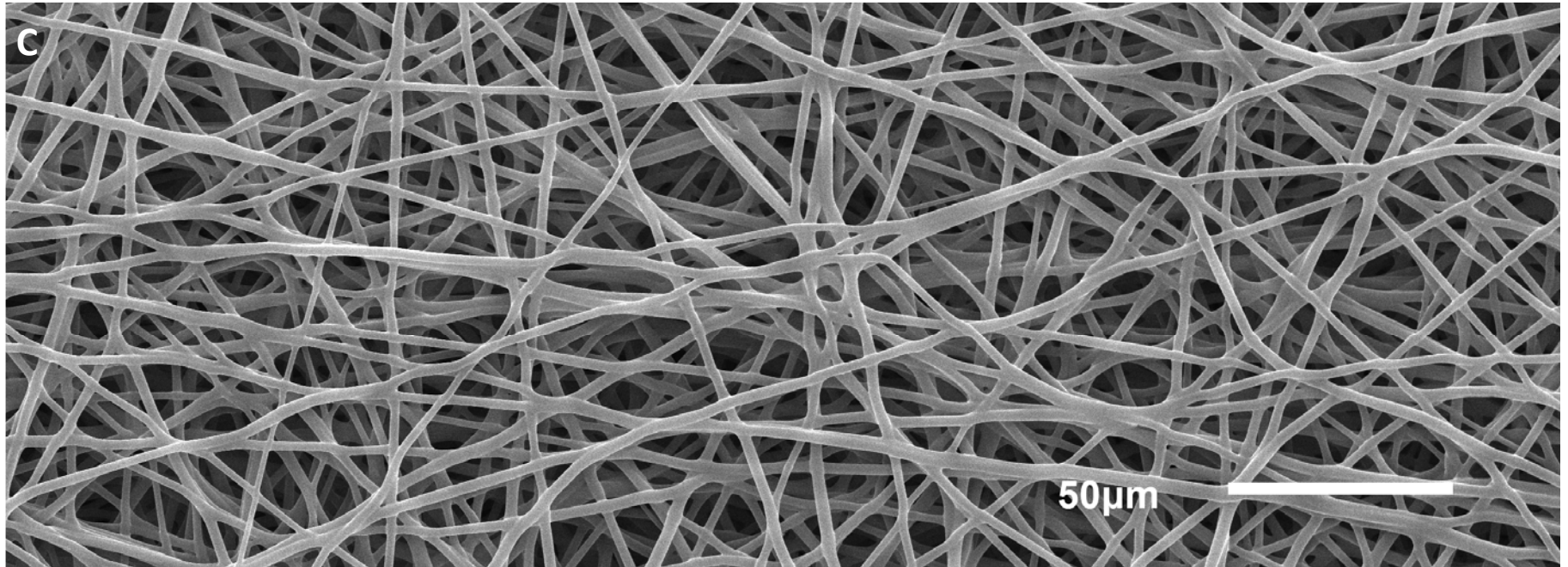
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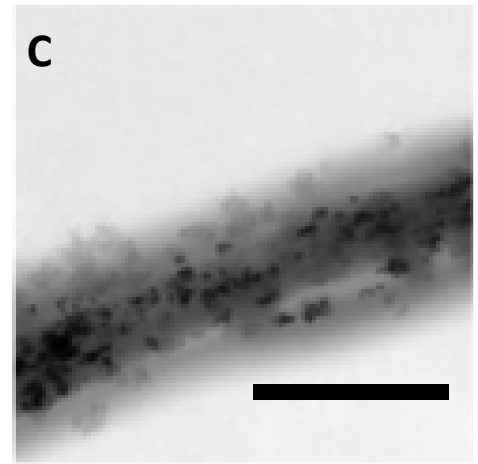
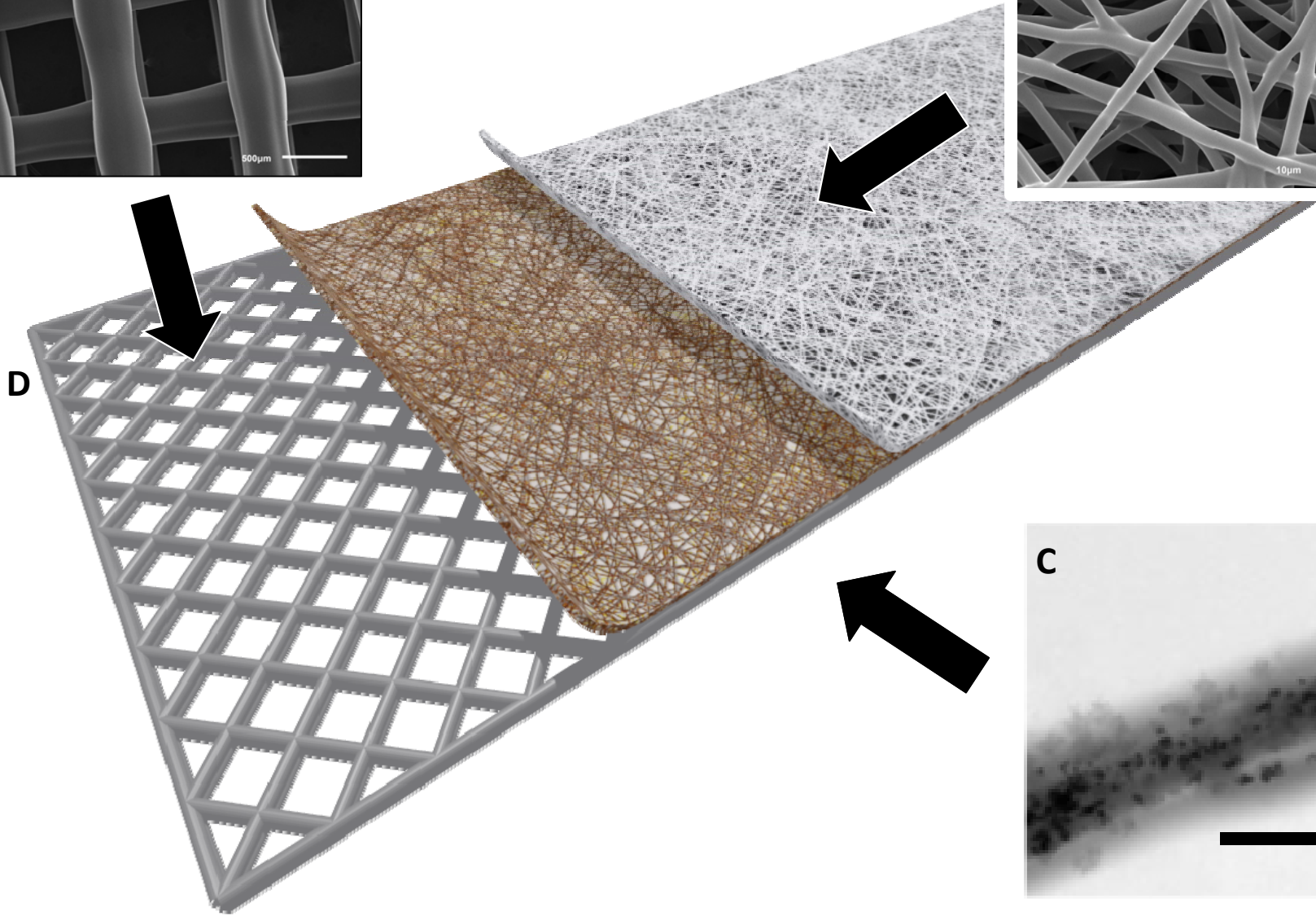
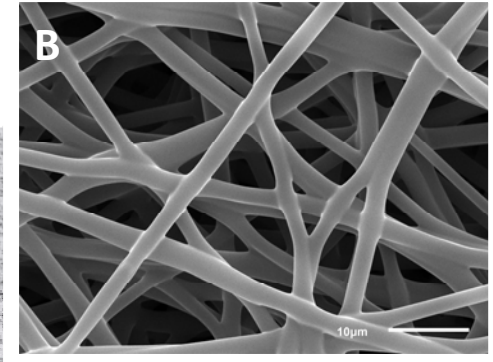
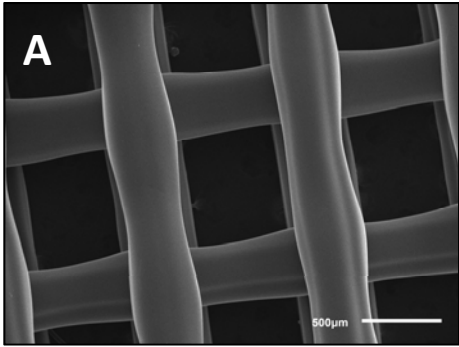


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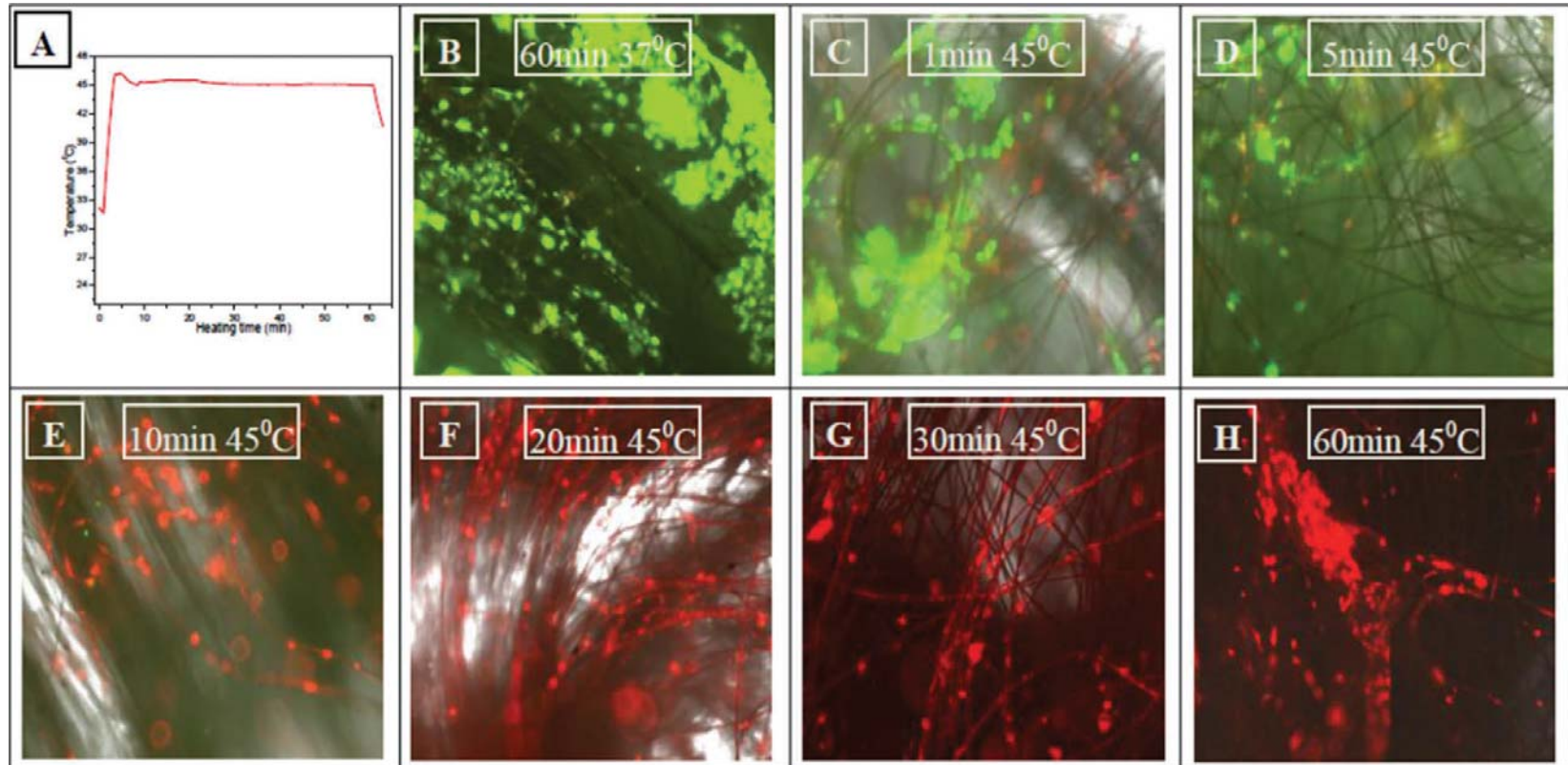


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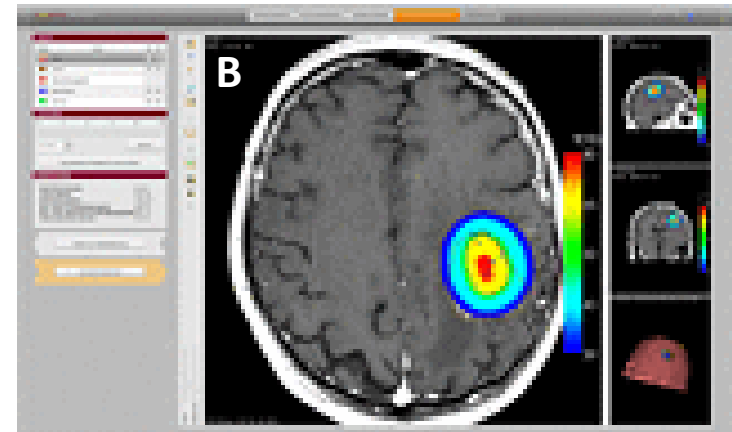




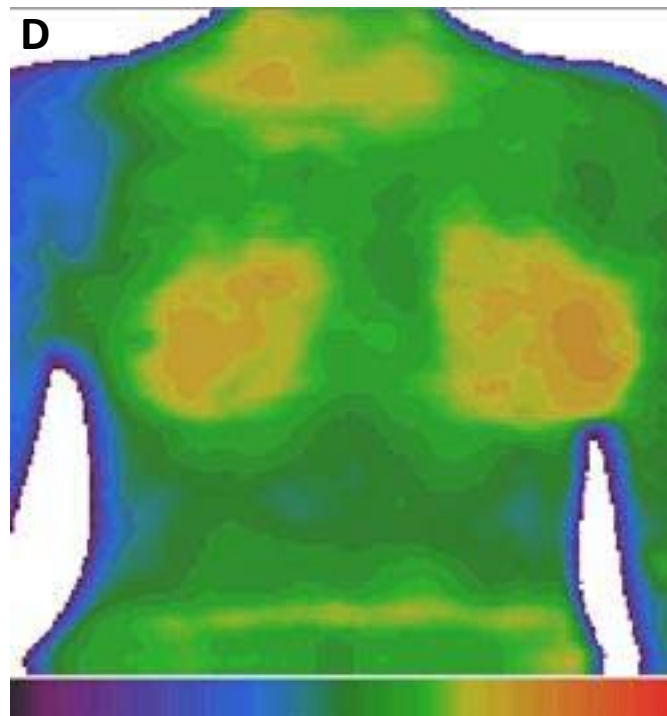
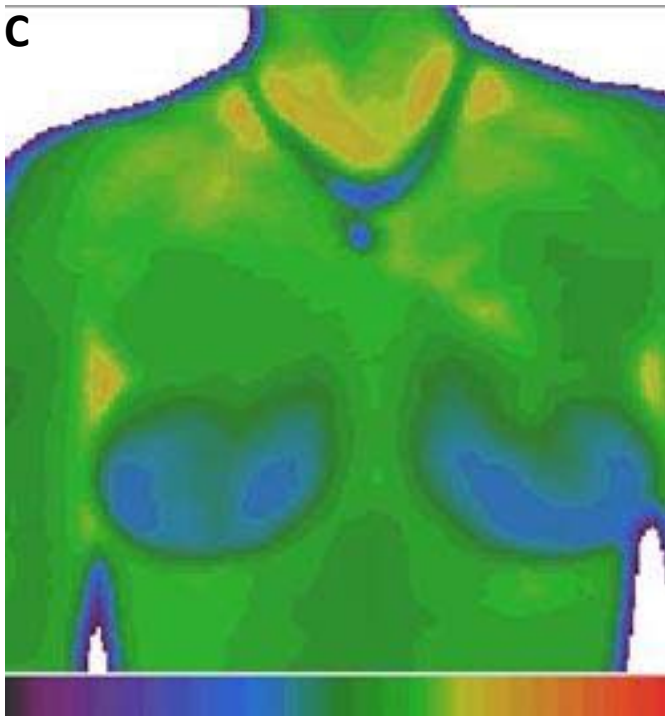
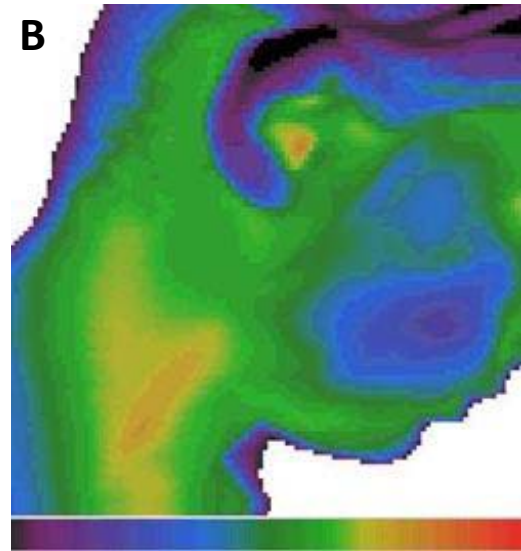
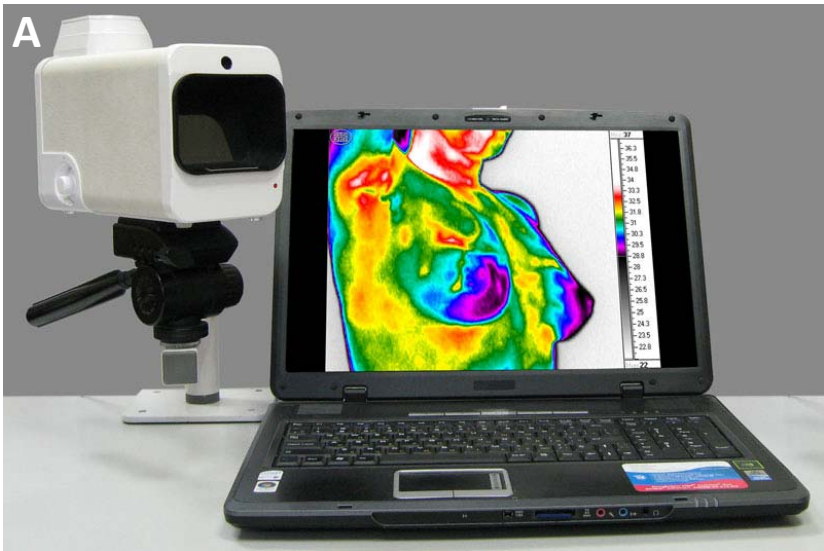
Iron oxide magnetic nanoparticles



**Alternated magnetic field generator-
induced hyperthermia-mediated cell death
(According to Prof. Claire Wilhelm – Paris, France)**



**Alternated magnetic force generator
in clinic in treatment of glioblastoma
(According to MagForce, Germany)**



3D Bioprinting Solutions Team

