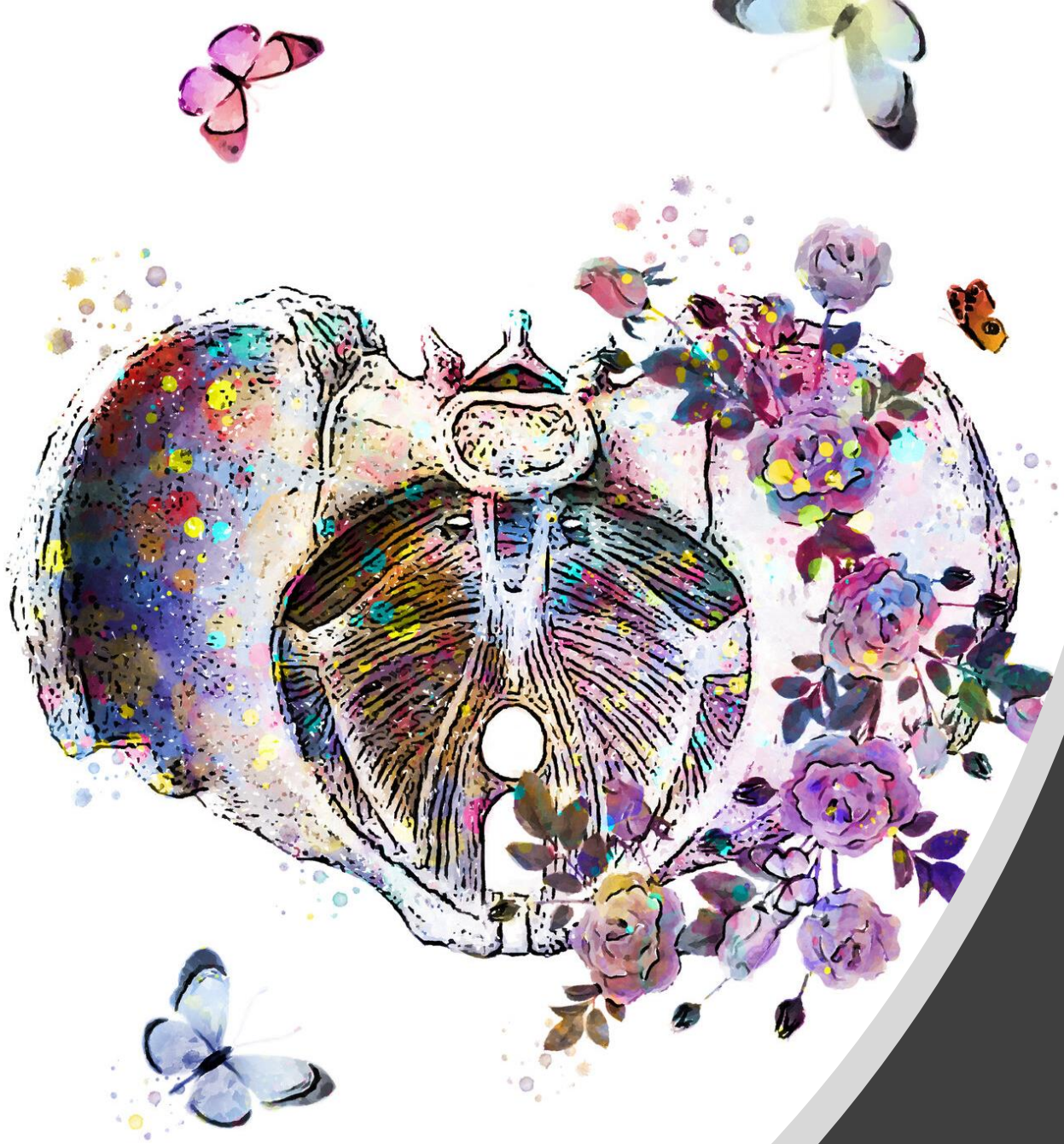
What is new in Urogynecology Basic Science ?

סוזנה מוסטפא מיח'איל

המרכז הרפואי לגליל

Basic Research

- Basic research is not the same as development
- A crash program for the latter may be successful; but for the former it is like trying to make nine women pregnant at once in the hope of getting a baby in a month’s time



Pelvic Organ Prolapse

המרכז הרפואי לגליל
רפואה מקצועית ואקדמית


PATHOGENESIS
PATHOGENESIS
INFECTION
CHRONIC
RECURRENT
DISEASE
TRANSPLANT
ACUTE
BREAKDOWN
POTENTIAL
PROCESSES
INFLAMMATION
IMMUNE
RENAL
ACUTE
MECHANISM
DEVELOPMENT
MICROBIAL
SKIN
CANCER
ETHOLOGY
MECHANISM
MALIGNANCY
DESCRIBE
IMMUNOSUPPRESSION
INFECTION
MICROBIAL
IMMUNOSUPPRESSION

Original Article | Published: 06 February 2021

Upregulation of PTK7 and β-catenin after vaginal mechanical dilatation: an examination of fibulin-5 knockout mice

Ryo Uemura, Daisuke Tachibana ✉, Masayuki Shiota, Kayo Yoshida, Kohei Kitada, Akihiro Hamuro, Takuya Misugi & Masayasu Koyama

International Urogynecology Journal **32**, 2993–2999 (2021) | Cite this article

Introduction and hypothesis

Pelvic organ prolapse (POP) in women is associated with deficiency of elastic fibers, and fibulin-5 is known to be a critical protein in the synthesis of elastin. The purpose of this study is to investigate the related pathway for the synthesis of elastin via fibulin-5 using fibulin-5 knockout mice.

Methods

Fibulin-5 knockout mice were generated using the CRISPR/Cas9 system, and vaginal dilatation was used to mimic vaginal delivery. We divided the mice into three groups: $Fbln5^{+/+}$ mice immediately after dilatation ($Fbln5^{+/+}$ day0), $Fbln5^{+/+}$ mice 3 days after dilatation ($Fbln5^{+/+}$ day3) and $Fbln5^{-/-}$ mice 3 days after dilatation ($Fbln5^{-/-}$ day3). Proteins related to elastogenesis in the vaginal wall were measured by liquid chromatography mass spectrometry (LC-MS/MS) analysis, and differences in the expression of these proteins between the $Fbln5^{-/-}$ mice and the $Fbln5^{+/+}$ mice were analyzed using western blotting.

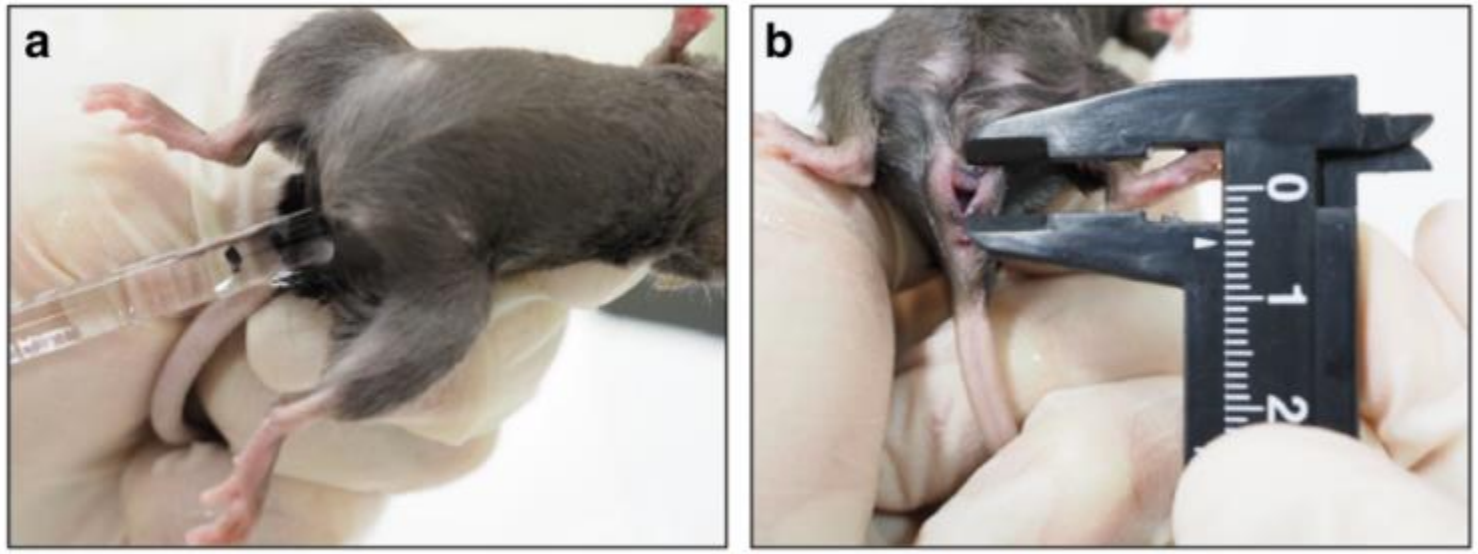
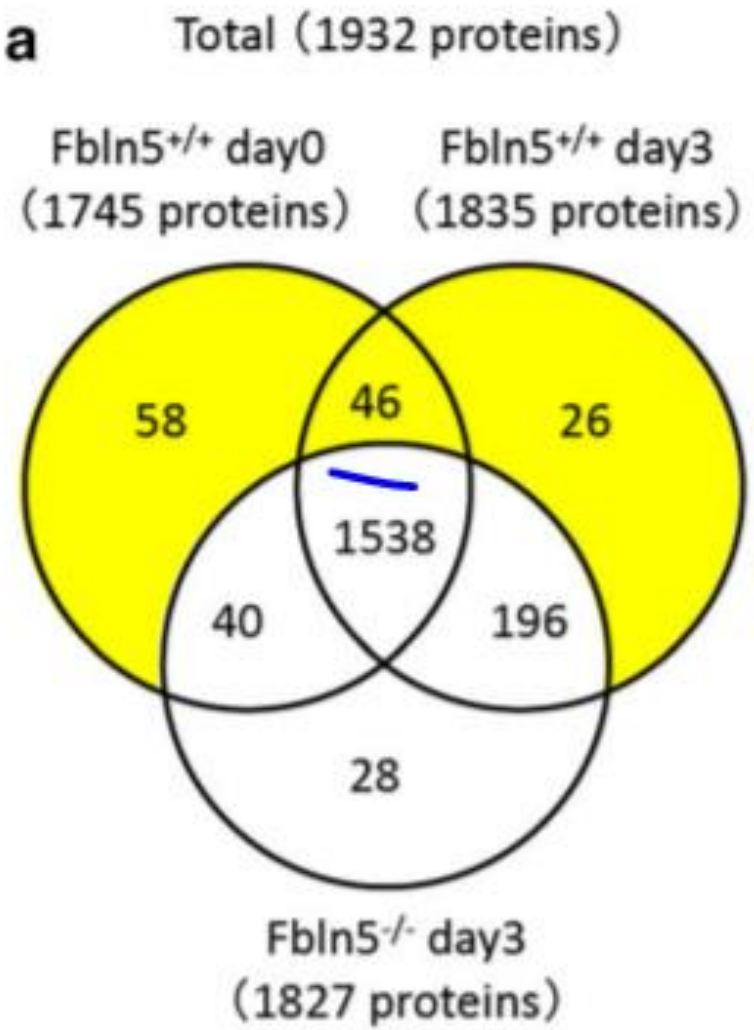


Fig. 1 Images of vaginal stimulation: **A** The vagina of a 14-week-old mouse was dilatated under anesthesia. A 6-mm glass rod was inserted into the vagina and held for 10 s. **B** The ostium of the mouse vagina after vaginal stimulation

a

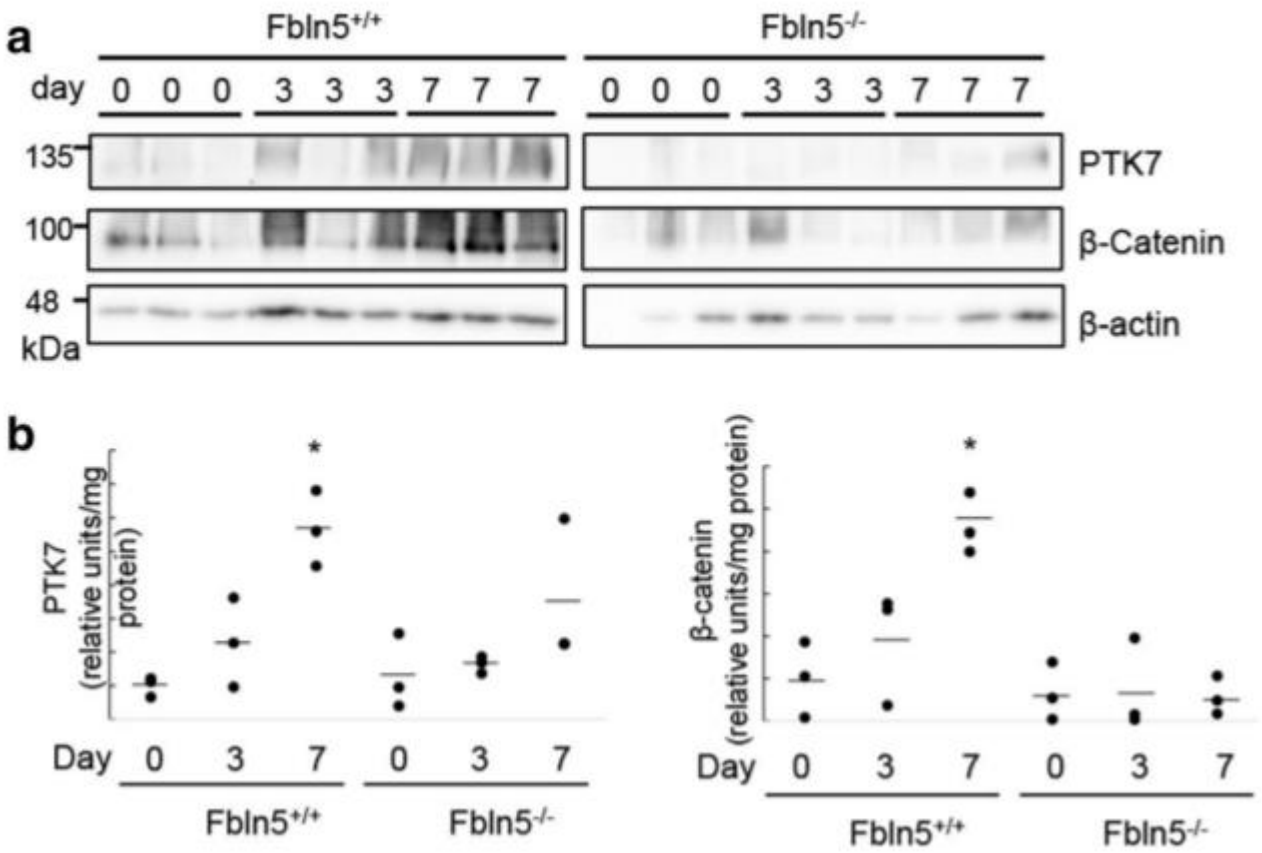


b

Fold change (day3/day0)	Number of proteins
day3 only	26
Fold change ≧ 1.5	17
1.5 > Fold change ≧ 0.75	10
0.75 > Fold change	19
day0 only	58
Total	130

Table 1 List of proteins that were not identified in the posterior vaginal wall of $Fbln5^{-/-}$ mice but identified in $Fbln5^{+/+}$ mice. They also increased by > 1.5 times in $Fbln5^{+/+}$ between day0 and day3 groups: Proteins were identified at a 95% confidence level using the Mascot algorithm. Accession numbers are from the UniProt database. The unit of quantitative value is in fmol/μg protein

Identified proteins	Gene symbol	Accession number	Quantitative value		Fold change (day3/day0)
			Day0	Day3	
Carnitine O-palmitoyltransferase 1, liver isoform	CPT1A	CPT1A_MOUSE	0.96	4.70	4.90
Fibulin-5	FBLN5	FBLN5_MOUSE	0.96	4.17	4.34
Inactive tyrosine-protein kinase 7	PTK7	PTK7_MOUSE	0.87	3.15	3.63
Carbonic anhydrase 12	CA12	CAH12_MOUSE	1.11	3.23	2.89
Mitochondrial import receptor subunit TOM34	TOMM34	TOM34_MOUSE	1.01	2.29	2.28
D-beta-hydroxybutyrate dehydrogenase, mitochondrial	BDH1	BDH_MOUSE	1.01	2.29	2.28
60S acidic ribosomal protein P1	RPLP1	RLA1_MOUSE	1.01	2.29	2.28
Visinin-like protein 1	VSNL1	VISL1_MOUSE	1.01	2.29	2.28
Nuclear pore complex protein Nup214	NUP214	NU214_MOUSE	0.96	1.88	1.96
Probable ATP-dependent RNA helicase DDX46	DDX46	DDX46_MOUSE	0.96	1.88	1.96
Monocarboxylate transporter 4	SLC16A3	MOT4_MOUSE	0.96	1.88	1.96
Carboxypeptidase D	CPD	CBPD_MOUSE	0.96	1.88	1.96
Rho guanine nucleotide exchange factor 12	ARHGEF12	ARHGC_MOUSE	0.96	1.88	1.96
RAC-alpha serine/threonine-protein kinase	AKT1	AKT1_MOUSE	1.42	2.78	1.95
Rho guanine nucleotide exchange factor 7	ARHGEF7	ARHG7_MOUSE	1.42	2.78	1.95
Apoptosis-inducing factor 1, mitochondrial	AIFM1	AIFM1_MOUSE	1.42	2.78	1.95
Retinol-binding protein 4	RBP4	RET4_MOUSE	2.01	3.44	1.71



Results

In the LC-MS/MS analysis, protein tyrosine kinase 7 (PTK7) was not detected in the $Fbln5^{-/-}$ day3 group, although the expression increased by > 1.5 times between the $Fbln5^{+/+}$ day0 and day3 groups. PTK7 and β-catenin are known to act in the Wnt/β-catenin pathway, and both were upregulated after dilatation in the $Fbln5^{+/+}$ mice, though not in the $Fbln5^{-/-}$ mice.

Conclusion

Our findings suggest that these proteins are involved in elastogenesis via fibulin-5, and the impairment of these proteins might be the underlying cause of POP manifestation.

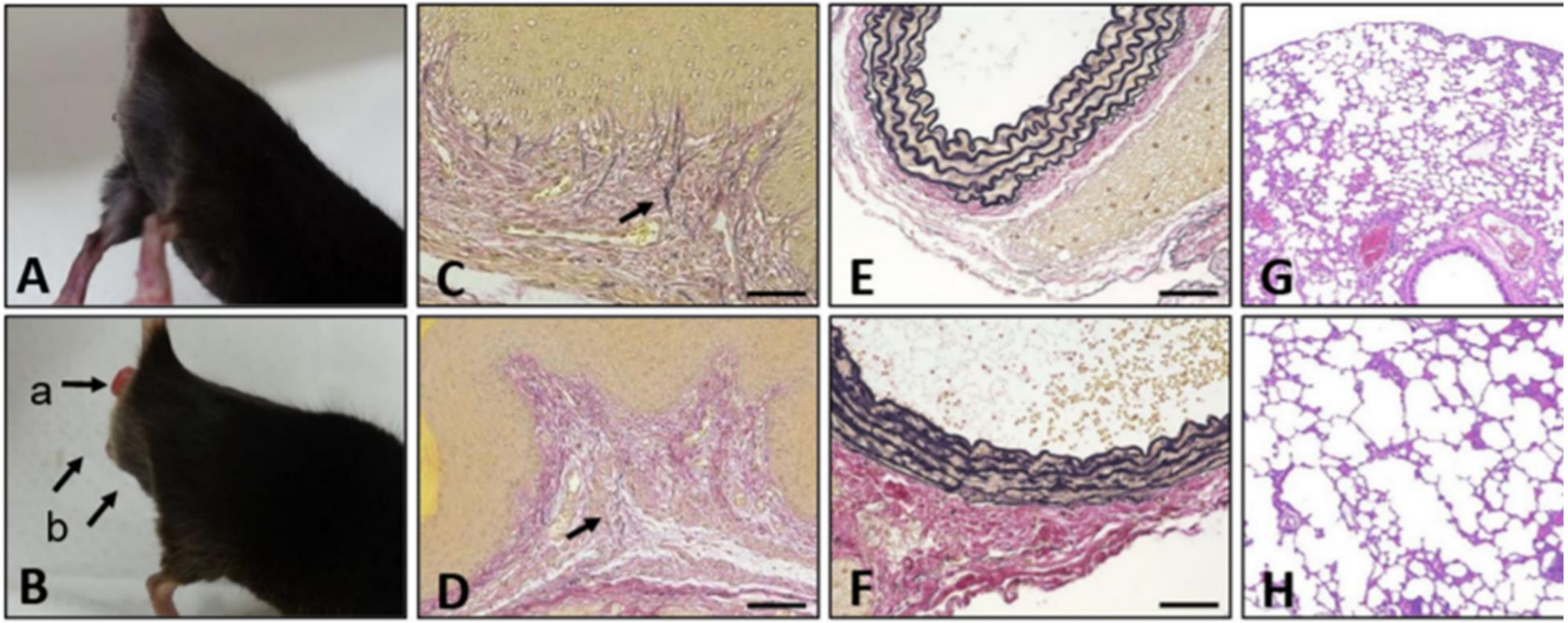


Fig. 2 Histological analysis of Fbln5$^{+/+}$ mice or Fbln5$^{-/-}$ mice at 20 weeks: **A** Fbln5$^{+/+}$ mice did not show any pelvic organ prolapse. **B** Rectal prolapse (arrow a) and perineal body prolapse (arrow b) were observed in Fbln5$^{-/-}$ mice. **C**, **D** Elastica van Gieson (EVG) staining from the posterior vaginal wall from Fbln5$^{+/+}$ or Fbln5$^{-/-}$ mice. In Fblin5$^{+/+}$ mice, long and thick elastic fibers were observed. In Fbln5$^{-/-}$ mice, the elastic fibers were fragmented and thin. Elastic fibers are indicated with arrows. Bar = 50 μm. **E**, **F** Elastica van Gieson staining of cross sections of the descending aorta. The elastic fi Fbln5$^{-/-}$ mice were fragmented and thickened. Bar = 50 μm. **G**, sections stained with hematoxylin and eosin staining from Fbl Fbln5$^{-/-}$ mice. Expanded alveoli were seen in Fblin5$^{-/-}$ mice. 200 μm

- Treatment

Current Medical Science
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Application of Artificial Intelligence in Medicine: An Overview

Peng-ran LIU†, Lin LU†, Jia-yao ZHANG, Tong-tong HUO, Song-xiang LIU, Zhe-wei YE#
Department of Orthopedics, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China

2.2 AI in the Perioperative Period

The perioperative period is the period around the whole operation, from the patient receiving surgical treatment to a basic recovery; it includes three parts: preoperative preparation, surgical period, and postoperative recovery period. During the whole process of the perioperative period, there are also lots of achievements with the application of AI technologies.

2.2.1 Three-dimensional Printing (3DP) 3DP is a technology that partly employs AI technology during its processes. It is one type of rapid prototyping technology that uses powdered metal or other adhesive biomaterials to construct objects by layer-by-layer printing based on digital model files (created from CT or MRI data with

polymers

MDPI

Article

Fabrication of Drug-Eluting Polycaprolactone/poly(lactic-*co*-glycolic Acid) Prolapse Mats Using Solution-Extrusion 3D Printing and Coaxial Electrospinning Techniques

Yi-Pin Chen [1,†], Tsia-Shu Lo [2,†], Yu-Ting Lin [3], Yu-Han Chien [3], Chia-Jung Lu [3] and Shih-Jung Liu [3,4,*]

- In this study, we developed hybrid degradable mesh/drug-eluting nanofibrous membranes for the repair of POP

- PCL is a semi-crystalline polymer possessing a melting temperature of 59~64 ◦C and a glass transition temperature of −60 ◦C

- Due to its non-toxicity and biocompatibility, PCL is widely employed as resorbable sutures, scaffolds in regenerative therapy, and carriers in drug delivery systems

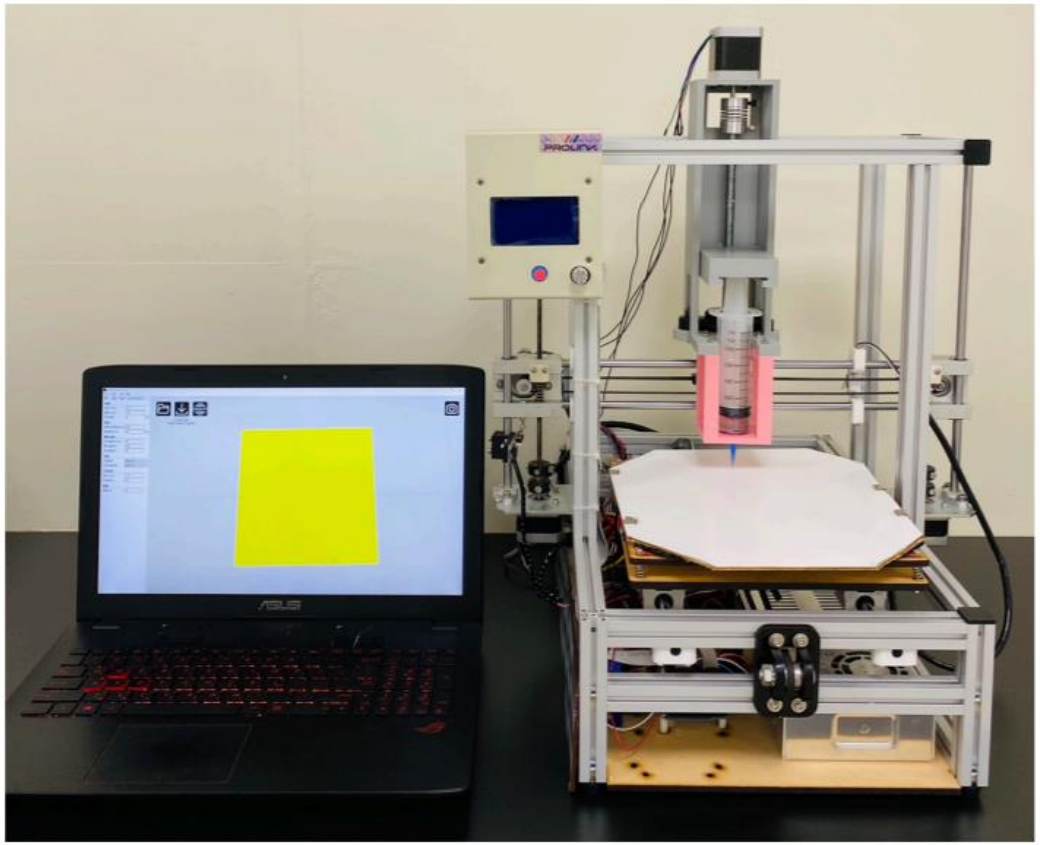


Figure 1. Photo of the lab-made solution-extrusion 3D printer.

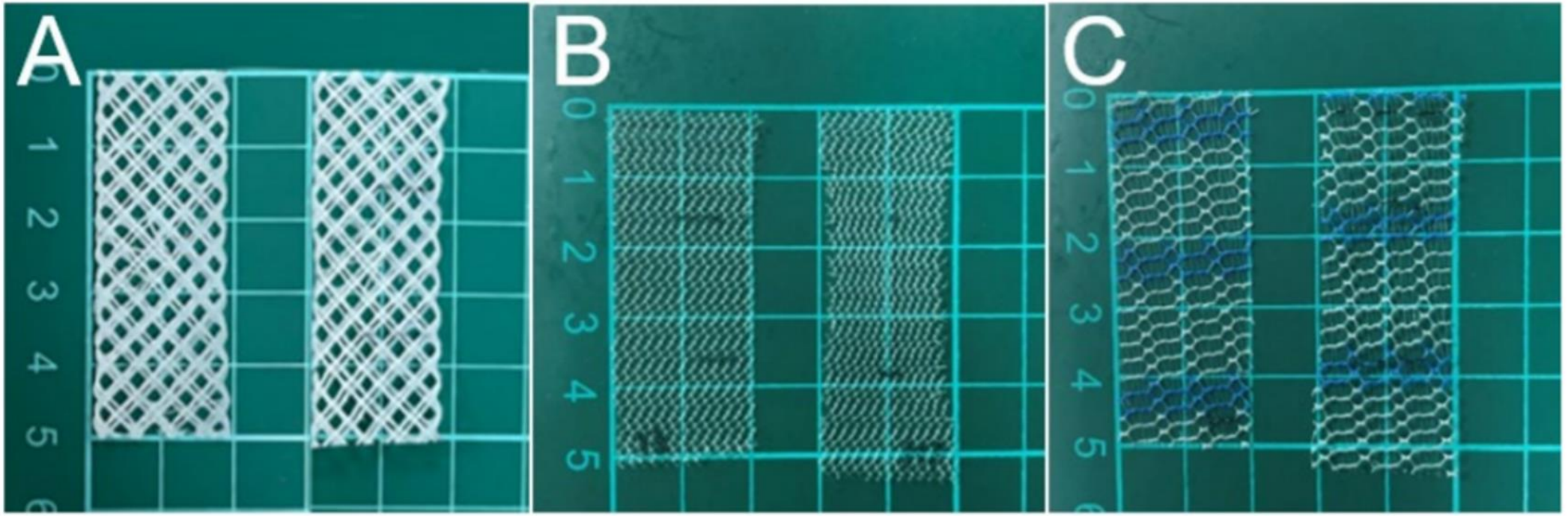


Figure 4. (**A**) 3D-printed polycaprolactone (PCL), (**B**) Surelift and (**C**) HalbaMesH prolapse meshes after 10,000 cycles of fatigue tests.

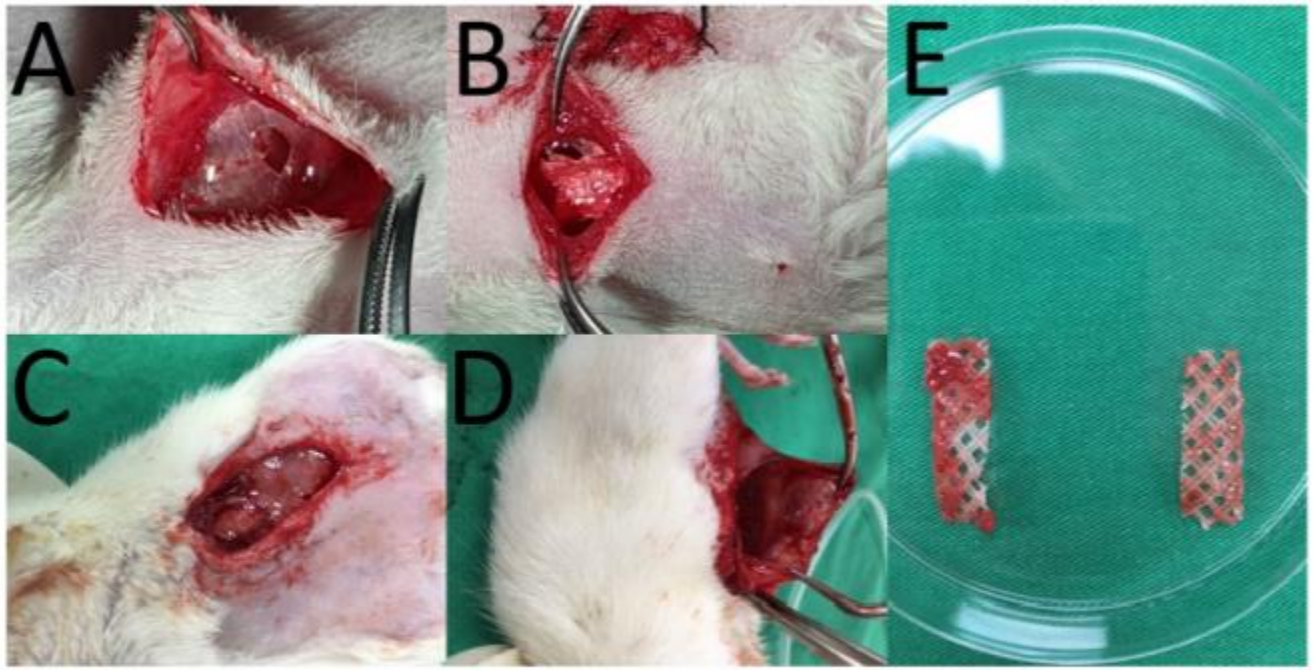


Figure 2. Polycaprolactone (PCL) meshes implantation. (**A**) expose the peritoneum (**B**) put the PCL mesh on peritoneum Retrieve the PCL meshes at 28 days post-implantation. (**C**) Expose the mesh, (**D**) cut mesh from peritoneum, (**E**) retrieved meshes.

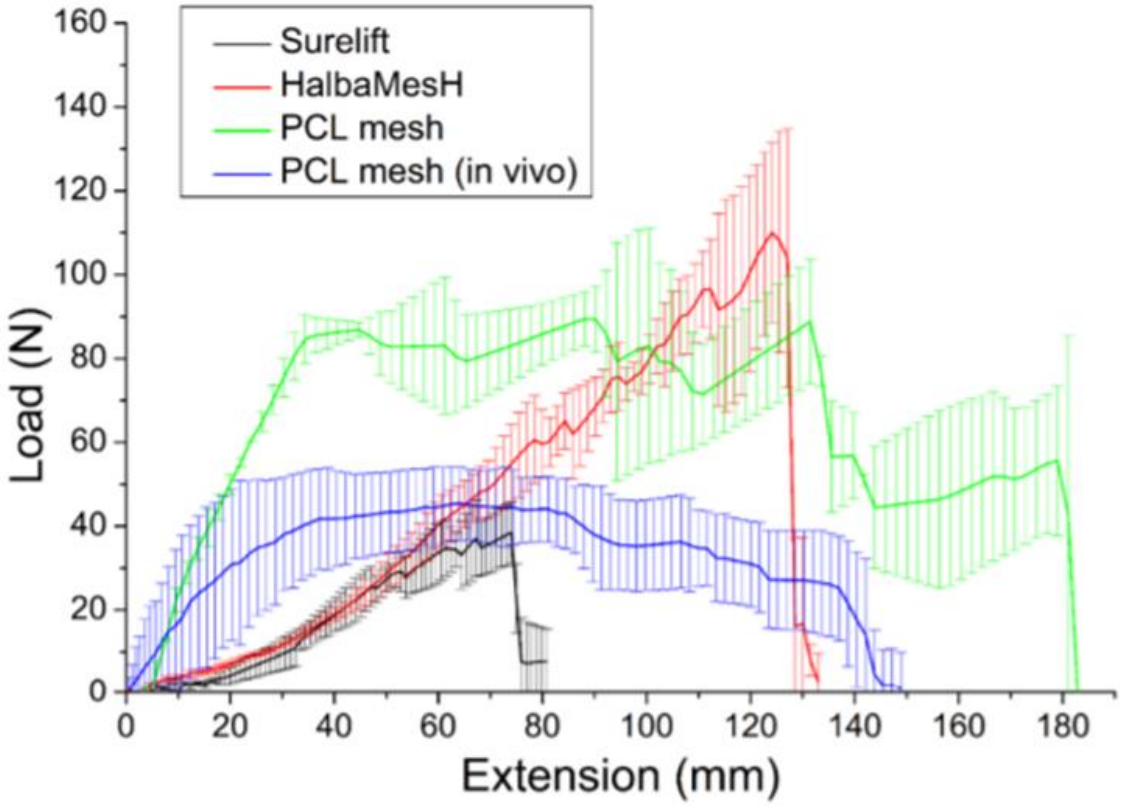


Figure 3. Tensile properties of 3D-printed polycaprolactone (PCL) meshes, retrieved PCL meshes in the in vivo experiments, and commercially available Surelift and HalbaMesH prolapse meshes.

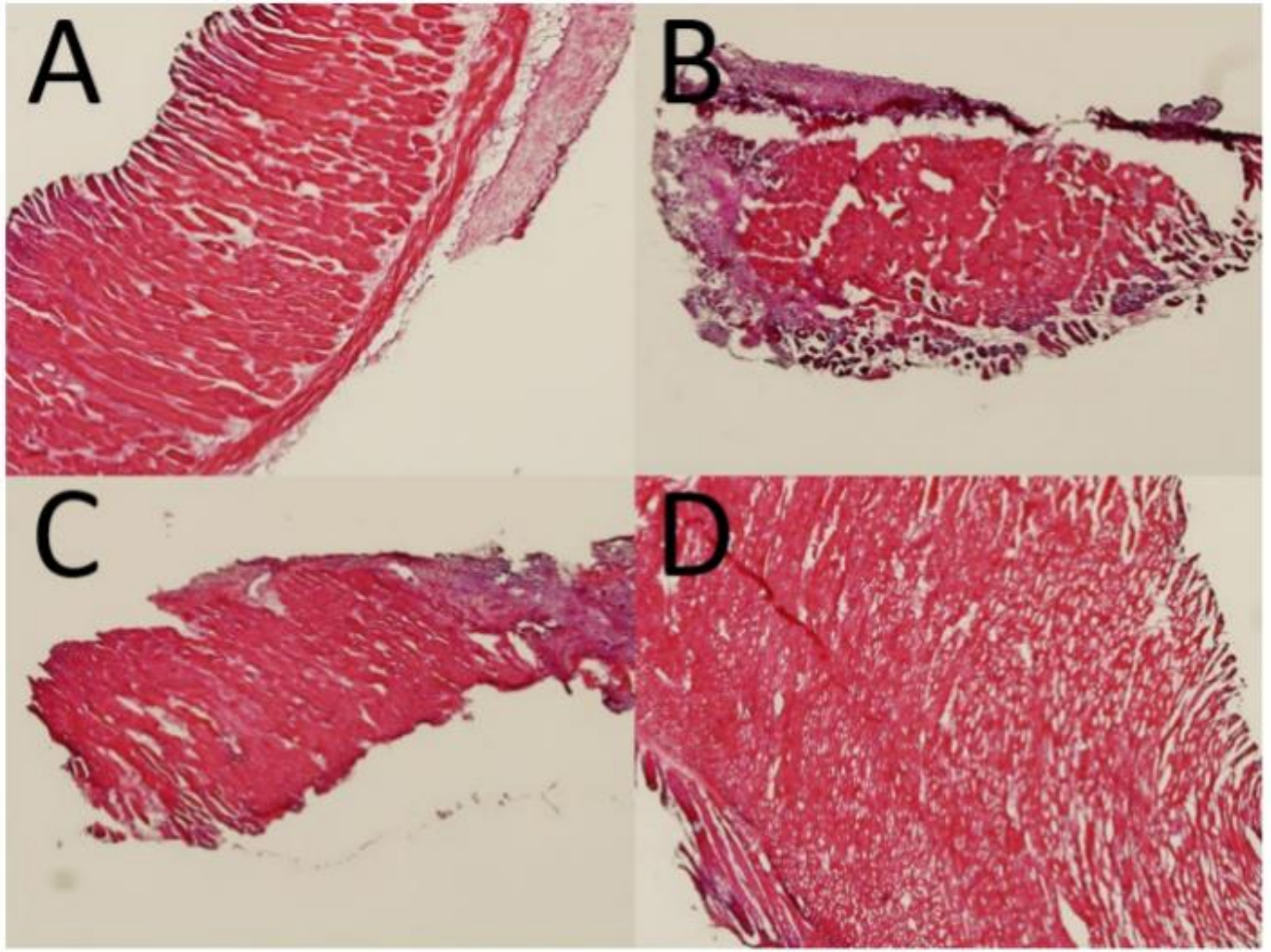


Figure 11. Histological images at (**A**) 1, (**B**) 4, (**C**) 7, and (**D**) 28 days post implantation.

DOI: 10.1111/1471-0528.17040

BJOG An International Journal of Obstetrics and Gynaecology

RESEARCH ARTICLE

Evaluation of the short-term host response and biomechanics of an absorbable poly-4-hydroxybutyrate scaffold in a sheep model following vaginal implantation

Chantal M. Diedrich[1] | Zeliha Guler[1] | Lucie Hympanova[2,3] | Eva Vodegel[1] | Manuel Zündel[4,5] | Edoardo Mazza[4,5] | Jan Deprest[2] | Jan Paul Roovers[1]

Objective: To evaluate the host- and biomechanical response to a fully absorbable poly-4-hydroxybutyrate (P4HB) scaffold in comparison with the response to poly-propylene (PP) mesh.

Methods: P4HB scaffolds were surgically implanted in the posterior vaginal wall of sheep. The comparative PP mesh data were obtained from an identical study protocol performed previously.

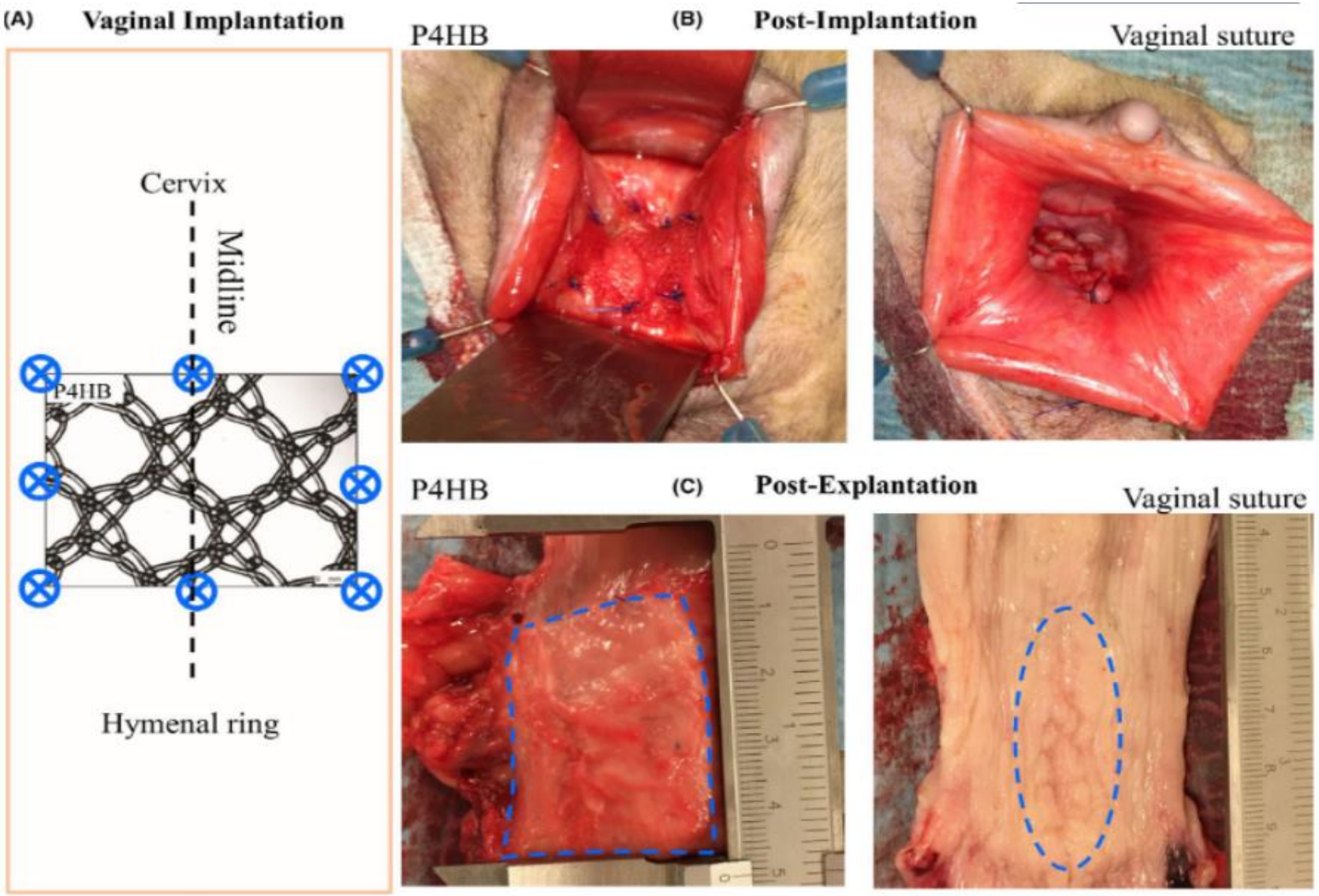


FIGURE 1 (A) Schematic and (B) photographic representation of poly-4-hydroxybutyrate (P4HB) vaginal implantation in the posterior compartment. Fixation points using non-resorbable polypropylene (PP) 3/0 sutures and vaginal closure using a running closure with 3/0 polyglactin 910 (Vicryl). (C) After en bloc excision of the vagina: the left panel illustrates the subcutaneous view with the remaining P4HB material; the right panel shows the mucosal side of the vagina with the healed vaginal closure

Main outcome measures: Gross necropsy, host response and biomechanical evaluation of explants, and the in vivo P4HB scaffold degradation were evaluated at 60- and 180-days post-implantation. Data are reported as mean ± standard deviation (SD) or standard error of the mean (SEM).

Results: Gross necropsy revealed no implant-related adverse events using P4HB scaffolds. The tensile stiffness of the P4HB explants increased at 180-days (12.498 ± 2.66 N/mm SEM [p =0.019]) as compared to 60-days (4.585 ± 1.57 N/mm) post-implantation, while P4HB degraded gradually. P4HB scaffolds exhibited excellent tissue integration with dense connective tissue and a moderate initial host response. P4HB scaffolds induced a significantly higher M2/M1 ratio (1.70 ± 0.67 SD, score 0–4), as compared to PP mesh(0.99 ± 0.78 SD, score 0–4) at 180-days.

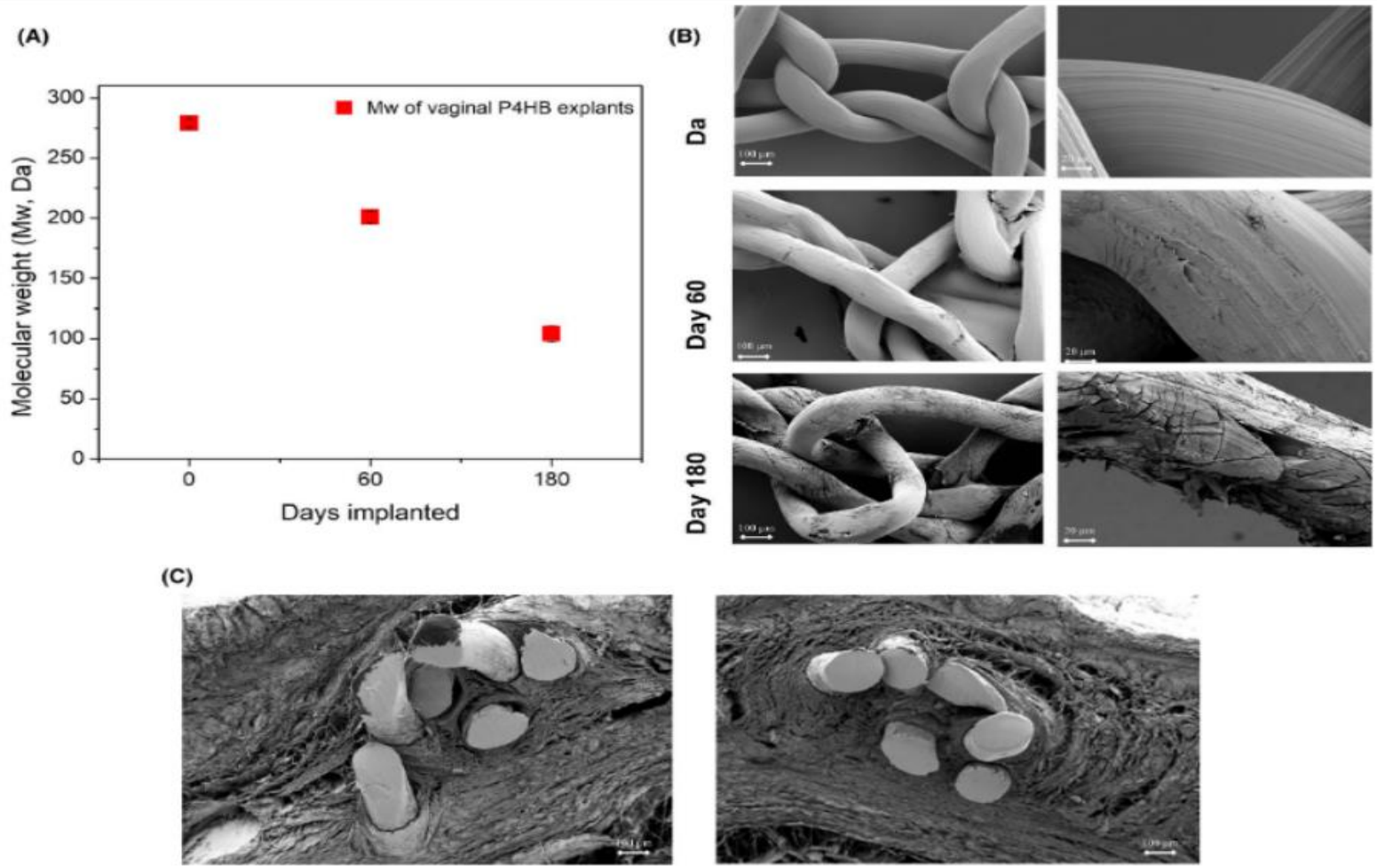


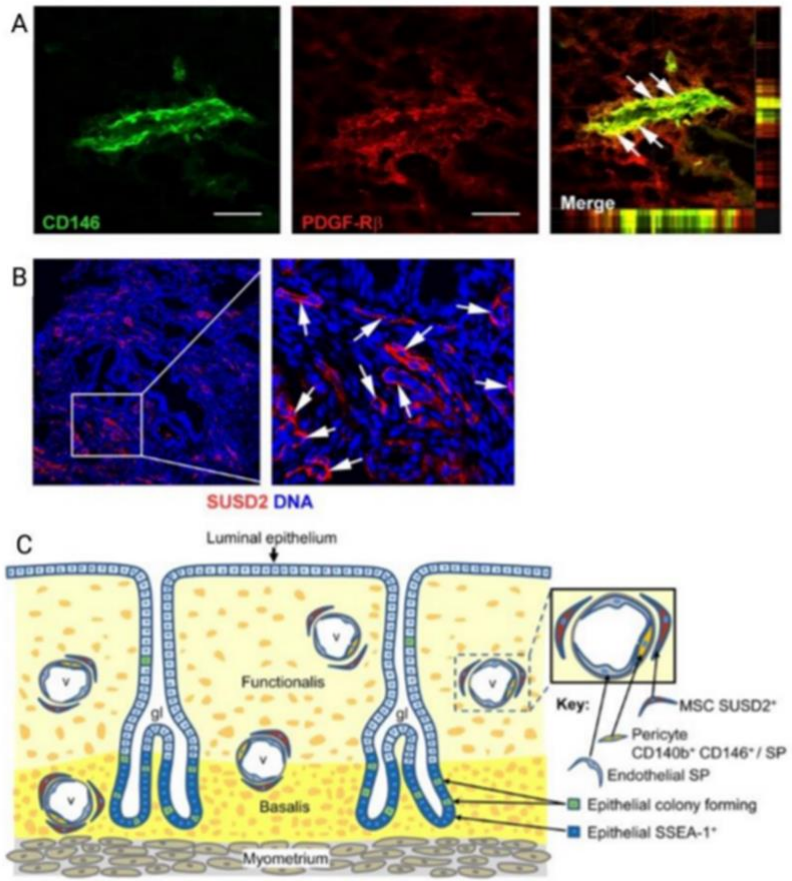
FIGURE 5 In vivo degradation (A, B) and tissue integration (C) of vaginal poly-4-hydroxybutyrate (P4HB) explants at 0, 60 and 180 days post-implantation. (A) Change in molecular weight according to gel permeation chromatography ($n = 7$ for each time point); data points represent mean values per time point and error bars represent ±standard deviation (SD). (B) Scanning electron microscopy images illustrating microstructural change as a result of degradation over time. (C) Scanning electron microscopy images showing the integration of the P4HB implant in vaginal tissue at 60 and 180 days post-implantation

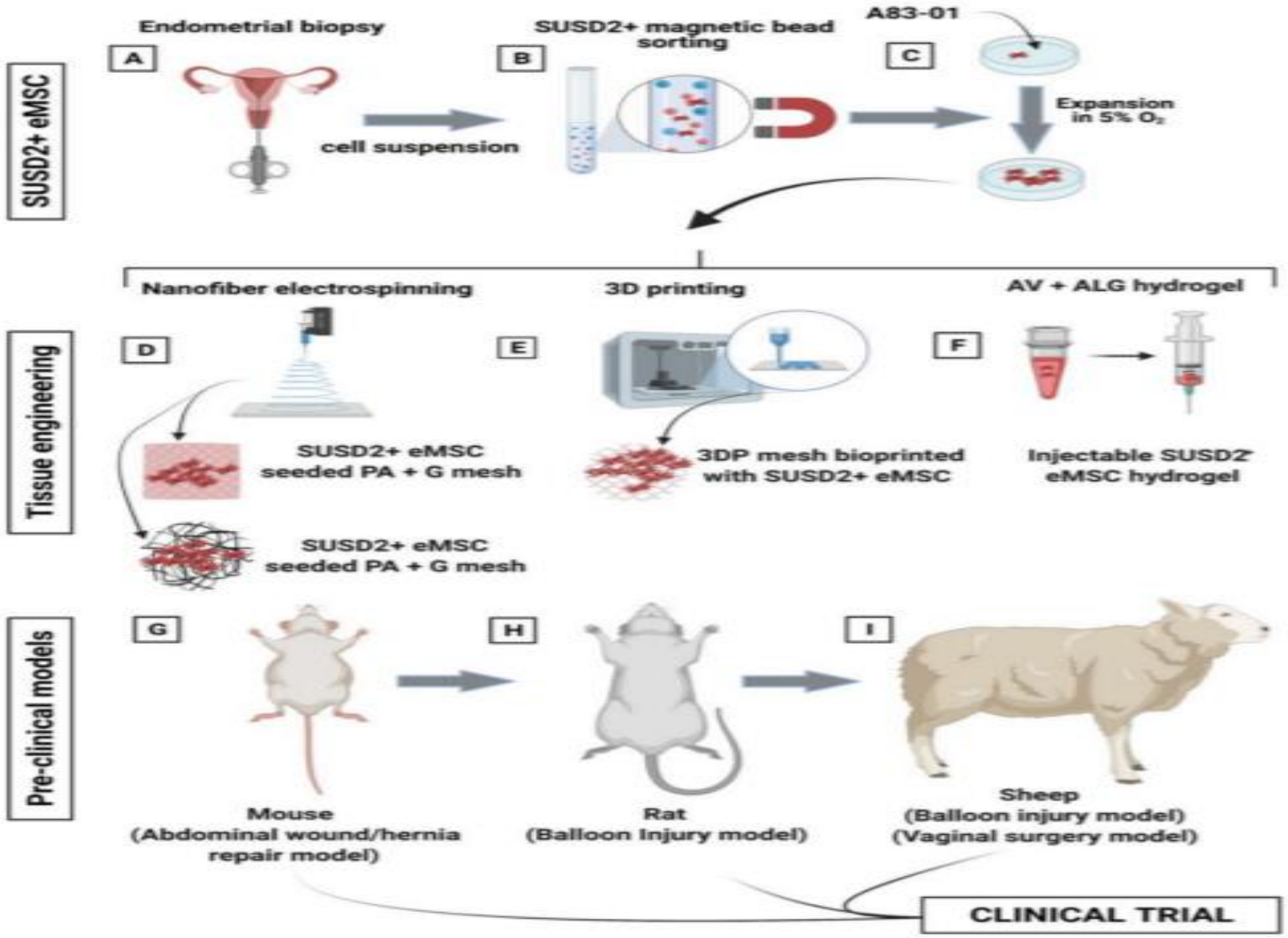
Conclusions: P4HB scaffold facilitated a gradual load transfer to vaginal tissue over time. The fully absorbable P4HB scaffold, in comparison to PP mesh, has a favorable host response with comparable load-bearing capacity. If these results are also observed at longer follow-up in-vivo, a clinical study using P4HB for vaginal POP surgery may be warranted to demonstrate efficacy.

Review > J Pers Med. 2021 Aug 26;11(9):840. doi: 10.3390/jpm11090840.

Endometrial SUSD2 + Mesenchymal Stem/Stromal Cells in Tissue Engineering: Advances in Novel Cellular Constructs for Pelvic Organ Prolapse

David M Z B Hennes [1 2 3], Anna Rosamilia [1 2 3], Jerome A Werkmeister [1 2], Caroline E Gargett [1 2], Shayanti Mukherjee [1 2]





International Journal of
Molecular Sciences

MDPI

Article

A Fibrin Coating Method of Polypropylene Meshes Enables the Adhesion of Menstrual Blood-Derived Mesenchymal Stromal Cells: A New Delivery Strategy for Stem Cell-Based Therapies

Federica Marinaro [1,*], Joana M. Silva [2,3], Alexandre A. Barros [2,3], Ivo M. Aroso [2,3], Juan C. Gómez-Blanco [1], Isaac Jardin [4,5], Jose J. Lopez [4,5], María Pulido [1], María Ángeles de Pedro [1], Rui L. Reis [2,3], Francisco Miguel Sánchez-Margallo [1,6,*], Javier G. Casado [5,6,7,†] and Esther López [1,†]

Abstract: Polypropylene (PP) mesh is well-known as a gold standard of all prosthetic materials of choice for the reinforcement of soft tissues in case of hernia, organ prolapse, and urinary incontinence. The adverse effects that follow surgical mesh implantation remain an unmet medical challenge. Herein, it is outlined a new approach to allow viability and adhesion of human menstrual blood-derived mesenchymal stromal cells (MenSCs) on PP surgical meshes. A multilayered fibrin coating, based on fibrinogen and thrombin from a commercial fibrin sealant, was optimized to guarantee a homogeneous and stratified film on PP mesh. MenSCs were seeded on the optimized fibrin-coated meshes and their adhesion, viability, phenotype, gene expression, and immunomodulatory capacity were fully evaluated. This coating guaranteed MenSC viability, adhesion and did not trigger any change in their stemness and inflammatory profile. Additionally, MenSCs seeded on fibrin-coated meshes significantly decreased CD4+ and CD8+ T cell proliferation, compared to in vitro stimulated lymphocytes ($p < 0.0001$). Hence, the proposed fibrin coating for PP surgical meshes may allow the local administration of stromal cells and the reduction of the exacerbated inflammatory response following mesh implantation surgery. Reproducible and easy to adapt to other cell types, this method undoubtedly requires a multidisciplinary and translational approach to be improved for future clinical uses.

SCAFFOLD GUIDED TISSUE ENGINEERING FOR THE TREATMENT OF ABDOMINAL WALL AND PELVIC ORGAN PROLAPSE - SHEEP MODEL

Flavia Medeiros Savi[1,2,3,4], Mairim Russo Serafini[3,5], Susana Mustafa Mikhail[6], Siamak Saifzadeh[3,7], Tara Shabab[1], Onur Bas[1,3,4], Nicholas O'Rourke[8,9], Dietmar W. Hutmacher[1,2,3,4], Alexandra Mowat[7,8]


Interstitial
Cystitis
Severe Pain
Diet
Normal
Outside
Pain and Suffering
Medication
Burning Pain in Bladder
No Cure
YET
Frequent Urination
Pelvic Pain
Painful
Bladder
Syndrome
Flares
Quality of
Life Degraded
Surgery
Life Changing

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Biomedicine & Pharmacotherapy

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Original article

Therapeutic effect of modulating the NLRP3-regulated transforming growth factor-β signaling pathway on interstitial cystitis/bladder pain syndrome

Hung-Jen Shih [a,b,c], Chao-Yuan Chang [d,e,f], Chung-Howe Lai [a,1], Chun-Jen Huang [d,e,f,*,1]

[a] Department of Urology, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan
[b] Department of Urology, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan
[c] Department of Urology, Changhua Christian Hospital, Changhua, Taiwan
[d] Integrative Research Centre for Critical Care, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan
[e] Department of Anesthesiology, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan
[f] Graduate Institute of Clinical Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan

- In conclusion, the NLRP3 inflammasome/IL-1β-related TGF-β/Smad pathway plays a crucial role in bladder injury in the LPS/PS model, and modulation of this pathway, such as by using curcumin, can effectively mitigate the sequelae of nchronic inflammation-induced IC/BPS.

- Imagine that … the world is something like a great chess game being played by the gods, and we are observers of the game. … If we watch long enough, we may eventually catch on to a few of the rules…. However, we might not be able to understand why a particular move is made in the game, merely because it is too complicated, and our minds are limited…. We must limit ourselves to the more basic question of the rules of the game.
- If we know the rules, we consider that we “understand” the world

THANK YOU