

## BIOCOMPATIBILITY OF MICROSTRUCTURED POLYMER MATERIALS WITH POTENTIAL USE IN RECONSTRUCTIVE SURGERY

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Reconstruction of peripheral nerves remains an urgent surgical problem. Autologous nerve grafting is the gold standard for bridging nerve defects, but it is limited by the shortage of donor material, which drives interest in biocompatible polymers for artificial conduits. The aim of this study was to evaluate biocompatibility *in vitro* and tissue response to subcutaneous *in vivo* implantation of perspective microstructured materials. The cytotoxicity of porous polycaprolactone (PCL), PCL–collagen composite, fibrous PCL, and nanofibrous polyamide was assessed on L929 fibroblasts. For *in vivo* testing, material samples were implanted into C57BL/6 mice, and histological analysis was performed after 14 days. *In vitro* porous PCL exhibited the highest viability and adhesion, while fibrous PCL showed the lowest. *In vivo* porous PCL and nanofibrous polyamide caused minimal inflammation, whereas PCL–collagen composite and fibrous PCL induced granulomatous inflammation, macrophage infiltration, and formation of fibrous capsule. The most biocompatible materials — porous PCL and nanofibrous polyamide — show promise for a biomimetic conduit with an outer barrier shell of porous PCL and an inner aligned scaffold of polyamide nanofibers.

**Keywords:** artificial conduits, targeted regeneration, scanning electron microscopy, polycaprolactone, polyamide, foreign body reaction, macrophage infiltration, cytotoxicity

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## АНАЛИЗ БИОСОВМЕСТИМОСТИ МИКРОСТРУКТУРИРОВАННЫХ ПОЛИМЕРНЫХ МАТЕРИАЛОВ, ПЕРСПЕКТИВНЫХ ДЛЯ ПРИМЕНЕНИЯ В РЕКОНСТРУКТИВНОЙ ХИРУРГИИ

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Реконструкция периферических нервов остается актуальной задачей хирургии. «Золотым стандартом» восстановления дефектов служит аутологичная нейрорепликация, ограниченная дефицитом материала, что обуславливает интерес к биосовместимым полимерам для искусственных кондуитов. Цель данной работы — оценить биосовместимость *in vitro* и тканевую реакцию на подкожную имплантацию *in vivo* перспективных микроструктурированных материалов. Цитотоксичность пористого поликапролактона (ПКЛ), композита ПКЛ с коллагеном, волокнистого ПКЛ и нановолокнистого полиамида оценивали на фибробластах L929. Для проведения *in vivo* испытаний образцы материалов имплантировали мышам C57BL/6 с, через 14 суток выполняли гистологический анализ. *In vitro* максимальную жизнеспособность и адгезию показал пористый ПКЛ, минимальную — волокнистый ПКЛ. *In vivo* пористый ПКЛ и нановолокнистый полиамид вызвали минимальное воспаление, а композит ПКЛ с коллагеном и волокнистый ПКЛ — гранулематозное воспаление, макрофагальную инфильтрацию и формирование фиброзной капсулы. Наиболее биосовместимые материалы — пористый ПКЛ и нановолокнистый полиамид — перспективны для создания биомиметического кондуита с барьерной оболочкой из пористого ПКЛ и ориентированным каркасом из полиамидных нановолокон.

**Ключевые слова:** искусственные кондуиты, направленная регенерация, сканирующая электронная микроскопия, поликапролактон, полиамид, реакция на инородное тело, макрофагальная инфильтрация, цитотоксичность

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Development of biocompatible polymer materials is one of the most important areas for modern reconstructive surgery and tissue engineering. Such materials can be used in barrier membranes, framework structures, cellular scaffolds, and implantable structures designed to repair damaged tissues. Regardless of the specific application, they are subject to a number of general requirements: absence of noticeable cytotoxicity, controlled tissue integration, minimal display of chronic inflammatory reaction, preservation of structural stability in the implantation zone, and prevention of excessive fibrosis [1–3].

Peripheral nerve repair is one of the fields where such materials are highly significant and sought-after. Traumatic peripheral nerve damage remains an urgent problem in reconstructive surgery and neurology, as it can lead to persistent motor, sensory and trophic disorders, considerably worsening the quality of life of patients [4, 5]. Despite the continuous introduction of new microsurgical techniques, autotransplantation remains the gold standard for the repair of extended defects in nerve trunks. However, this approach has a number of significant limitations, including a shortage of donor material, risk of neuroma formation, mismatching nerve diameters, longer surgery times, and inevitable loss of sensitivity in the donor area [6, 7].

In this regard, techniques involving artificial nerve conduits — implantable tubular structures connecting the ends of the damaged nerve and creating a controlled microenvironment for fiber regeneration — have been actively developed in recent years. Such conduits have several functions: they mechanically isolate the regeneration zone from surrounding tissues, prevent ingrowth of scar tissue, and support directed growth of axons and migration of Schwann cells [8, 9]. The effectiveness of a conduit depends not only on its geometry, but also on the properties of the materials used: their biocompatibility, porosity, hydrophilicity, mechanical stability, degradation rate, and the nature of the local immune response [1, 2, 10].

Synthetic polymers are particularly interesting as materials for implantable structures used in reconstructive surgery; they allow control of the mechanical properties, thickness, microrelief, porosity, and spatial architecture of the material. One of these materials is polycaprolactone, which is widely used in experimental tissue engineering because of its good mechanical characteristics, high degree of biocompatibility, and the ability to form both film and fibrous structures [11–13]. However, even materials demonstrating acceptable cytocompatibility *in vitro* can cause a foreign body reaction of varying severity *in vivo*. Excessive macrophage infiltration, formation of giant foreign body cells, and emergence of a dense fibrous capsule can limit implant integration and worsen tissue regeneration conditions [3, 14, 15].

This is a particularly important problem for nerve conduits. On the one hand, the implant's outer wall must act as a barrier to prevent connective tissue from penetrating into the conduit lumen. On the other hand, it should not trigger a pronounced chronic inflammatory response or uncontrolled scarring, because fibrosis in the defect area can mechanically compress regenerating axons and impair microcirculation, thereby hindering functional recovery [10, 14, 16]. Thus, before conducting experiments on the damaged peripheral nerve models, it is necessary to measure the local tissue response to the material.

Modern treatment strategies increasingly rely on complex biomimetic structures rather than simple hollow tubes. The internal architecture of such implants may incorporate porous, spongy, or fibrous elements that mimic the bundled structure of native nerves and enable contact guidance for growing axons

[17–19]. Oriented fibers introduced to the inner cavity of the conduit increase the surface area for cell adhesion, support the migration of Schwann cells, and guide the direction of neurite growth [20–22]. However, such components of the conduit should be tested for biocompatibility before their use; the severity of the tissue reaction to them may depend not only on the chemical composition of the material, but also on its microstructure, sponginess, pore size, and resistance to deformation.

Thus, investigating the biocompatibility of microstructured polymer materials is important not only for the development of artificial nerve conduits, but also for a wider range of reconstructive surgeries that require implantable barriers and guiding structures. Peripheral nerve repair represents one of the most challenging and representative contexts for such materials, as even a moderate inflammatory response or excessive fibrosis can significantly impair regeneration.

The aim of this work was to study the structural characteristics and *in vitro* biocompatibility of experimental polymer materials, and to assess the severity of local tissue responses following *in vivo* subcutaneous implantation, in order to determine their suitability for use in reconstructive surgery. Additionally, the materials were assessed as potential structural elements of artificial nerve conduits.

## METHODS

### The polymers

The tested materials included the following components: polycaprolactone (PCL), molecular weight 80,000 g/mol (Sigma-Aldrich, USA); polyvinylpyrrolidone (PVP), molecular weight 10,000 g/mol (Sigma-Aldrich, USA); bovine type I collagen (CLG) (VUP Medical, Czech Republic); polyamide-46 (PA) (Foshan Xutian, China).

### Production of polymer films

The PCL and CLG polymer films were made by layering polymer solutions on a Teflon scaffold [23]. We used two-component solutions, PCL+PVP and PCL+CLG, with hexafluoroisopropanol (Sigma-Aldrich, USA). The number of layer application and drying cycles was selected separately for each solution in order to achieve the required film thickness. The films were dried at room temperature for 24 hours until the solvent evaporated completely. The PCL+PVP samples were then washed in 96% ethanol (Sigma-Aldrich, USA) for 48 hours to create a porous structure, followed by drying for 24 hours at room temperature.

### Production of fibrous materials

Porous PCL was produced by electrospinning from a 14% PCL solution in glacial acetic acid (HIMMED, Russia); the electrospinning unit used was HZ-11 (Ame-energy, China). The polymer solution was electrospun onto a foil on a grounded rotating collector until the desired film thickness was reached. The material was dried on the collector at room temperature for 24 hours until complete solvent evaporation.

The oriented PA46 nano- and microfiber material was produced by layered electrospinning following the procedure described above [20]. We sequentially sprayed PA46 formic acid solutions (Component Reagent, Russia) onto a rotating grounded wire collector to produce a composite multilayer material consisting of freely hanging parallel polymer fibers of

**Table 1.** Composition and structural characteristics of the investigated polymer materials

| Name of the material, <i>in vivo</i> testing | Composition        | Thickness, $\mu\text{m}$ | Characteristics of structural elements             |
|----------------------------------------------|--------------------|--------------------------|----------------------------------------------------|
| Type 1                                       | Porous PCL         | 65                       | Pore diameter $0.44 \pm 0.17 \mu\text{m}$          |
| Type 2                                       | PCL+CLG 1 : 1 mass | 35                       | Pore diameter $0.10 \pm 0.03 \mu\text{m}$          |
| Type 3                                       | Fibrous PCL        | 500                      | Fiber diameter $0.69 \pm 0.32 \mu\text{m}$         |
| Filler                                       | Fibrous PA         | 10                       | Layers of oriented fibers, diameters 60 and 200 nm |

**Note:** PCL — polycaprolactone; CLG — collagen; PA — polyamide.

different diameters. The material was dried on the collector at room temperature for 24 hours until complete solvent evaporation.

### Structure characteristics

SEM images of the materials were acquired using a TESCAN AMBER GMH scanning electron microscope (TESCAN, Czech Republic) operated at an accelerating voltage of 1 kV with an Everhart–Thornley secondary electron detector. To analyze the size of the pores left by leached out collagen in the PCL+CLG sample, we pre-incubated it for 7 days in sterile water at 37 °C. To analyze the sizes of fibers in the fibrous PCL sample, we applied a monolayer of the polymer on a glass base. The images and the dimensional characteristics were analyzed using ImageJ software (NIH, USA).

### Plasma activation of the surface of polymer materials

Before biological tests, all samples except PCL+CLG were treated in plasma to increase their hydrophilicity and biocompatibility as well as to sterilize them. We used a PT-5CM 5L 300W unit (Jiangsu Danyang, China). The processing lasted 20 seconds, the power output was 60% of its maximum limit. Preliminary tests have confirmed that these settings largely preserve the mean fiber diameter and fiber orientation in fibrous materials.

### *In vitro* biocompatibility analysis

The cytotoxicity of the materials was analyzed using direct contact testing with differential fluorescent staining. Samples measuring  $5 \times 5 \text{ mm}$  were sterilized by plasma and UV irradiation for 20 minutes. The L929 fibroblast cell line was provided from the Collection of Cell Cultures of the Core Shared Research Facility of Institute of Developmental Biology of the Russian Academy of Sciences. The cells were plated at a density of  $5 \times 10^4$  cells/well into four-well plates in DMEM/F12 medium (1 : 1) with the addition of 10% fetal bovine serum and 1% penicillin-streptomycin solution, and cultured for 72 hours. The medium was stained with 1  $\mu\text{M}$  of propidium iodide and 2  $\mu\text{M}$  of calcein-AM, and incubated for 20 minutes. The samples were washed in phosphate-buffered saline and visualized using a fluorescence microscope (Axiovert 200M, Zeiss, Germany). The cells were counted in two independent samples of each material type, across six randomly selected fields of view.

### Preparation of samples for implantation

For animal testing, manufactured materials were cut into squares with a side of 5 mm. The samples were stored dry in an airtight container at room temperature. Two hours before implantation, they were immersed in an antimycotic antibiotic solution (Capricorn Scientific, Germany).

### *In vivo* study design

The *in vivo* evaluation of the response to the investigated materials involved their implantation in immunocompetent male C57BL/6 mice ( $n = 25$ ) aged 6–12 weeks and weighing  $25 \pm 5 \text{ g}$ . Group sizes for subcutaneous implantation biocompatibility testing were determined to provide a sufficient number of sections for microanalysis, enabling a descriptive assessment of the tissue response. According to GOST ISO 10993-6-2021, the interstate standard for assessing the biological effect of medical products, such testing requires at least three animals for each material. The mice were kept in isolated cages in the vivarium of Sechenov University. The 24-hour day/night cycle was standard, access to food and water *ad libitum*. The animals were randomly divided into five experimental groups ( $n = 5$  per group). Groups 1–3 received porous PCL, PCL–CLG composite, fibrous PCL, respectively; group 4 received fibrous PA, and group 5 served as a sham-operated control (surgical access without implantation).

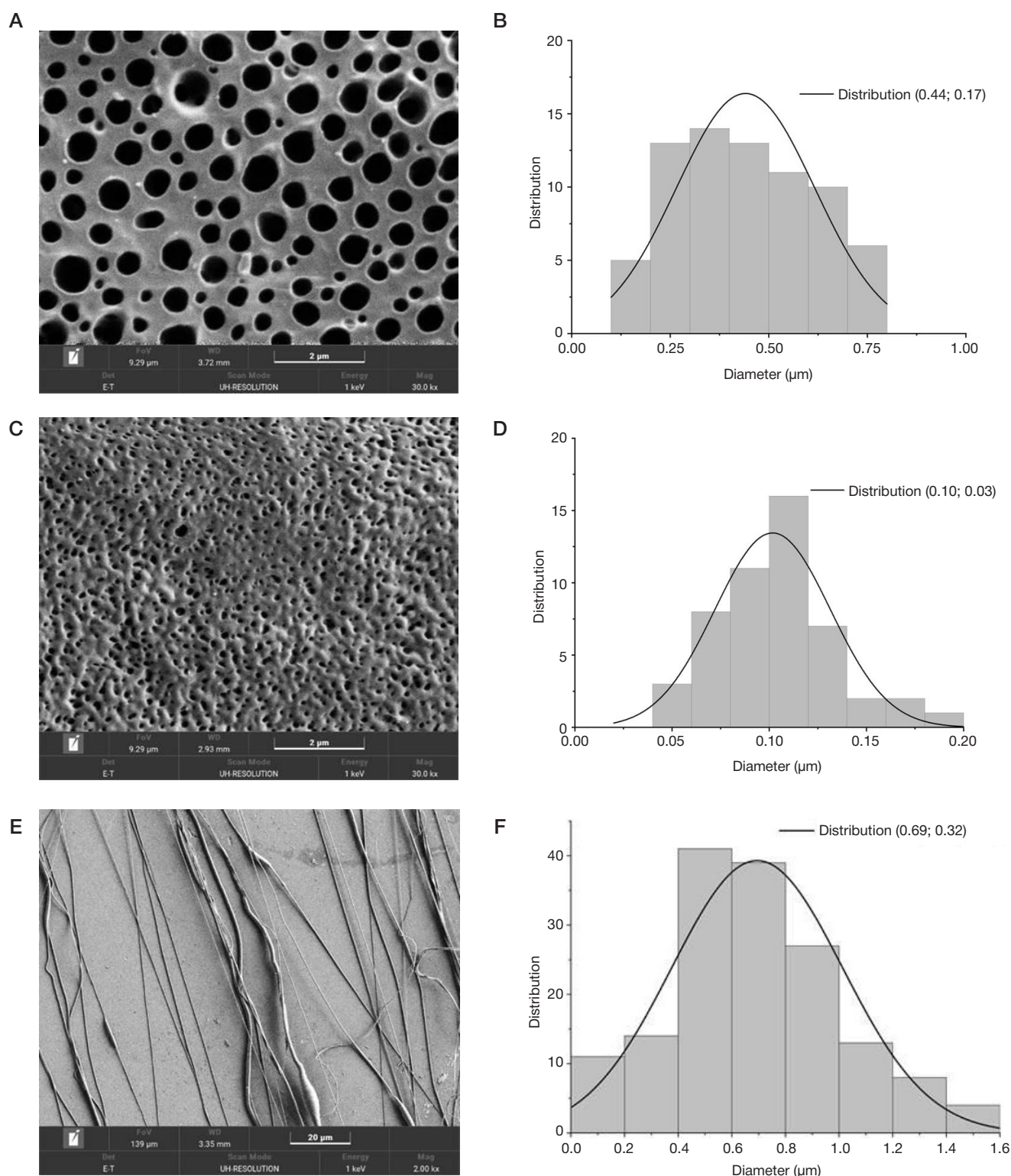
### Surgery

Surgical interventions were performed under sterile conditions, complying with asepsis and antisepsis rules. We used an intraperitoneally administered combination of tiletamine/zolazepam (Zoletil 100, VIRBAC, France) and xylazine (Xyla, Interchemie, the Netherlands) for general anesthesia; the doses were 20 mg/kg and 5 mg/kg, respectively. Dexpanthenol was applied to the conjunctiva to prevent corneal drying (Korneregel, Bausch & Lomb, Germany).

The hair was shaved in the interscapular area, and the surgical field was treated with a solution of povidone-iodine (Yuzhpharm, Russia). A 1–1.5 cm longitudinal skin incision was made. The studied material was implanted into a subcutaneous pocket made in the adipose tissue (blunt dissection) in the projection of the right shoulder blade. The wound was closed with a simple interrupted suture of 4–0 polyglactin (Vicryl, Ethicon, USA) and treated with antiseptic. Post-surgery, the animals received ketoprofen (Ketonal, Sandoz, Slovenia) at a dose of 5 mg/kg, and enrofloxacin (Bairil 5%, Bayer Animal Health, Germany) at a dose of 20 mg/kg, subcutaneously once a day for 3 days.

### Histological examination

On day 14 post-surgery, the animals were euthanized in a CO<sub>2</sub> chamber (Euthanizer-2M, Russia). The 14-day follow-up period is prescribed by Part 6 of GOST ISO 10993-6-2021 (Study of Local Action After Implantation), which recommends a minimum observation period of 13 days after implantation. Skin fragments with subcutaneous tissue, underlying muscle, and the implanted conduit were excised *en bloc* and fixed in 10% neutral buffered formalin. After standard histological

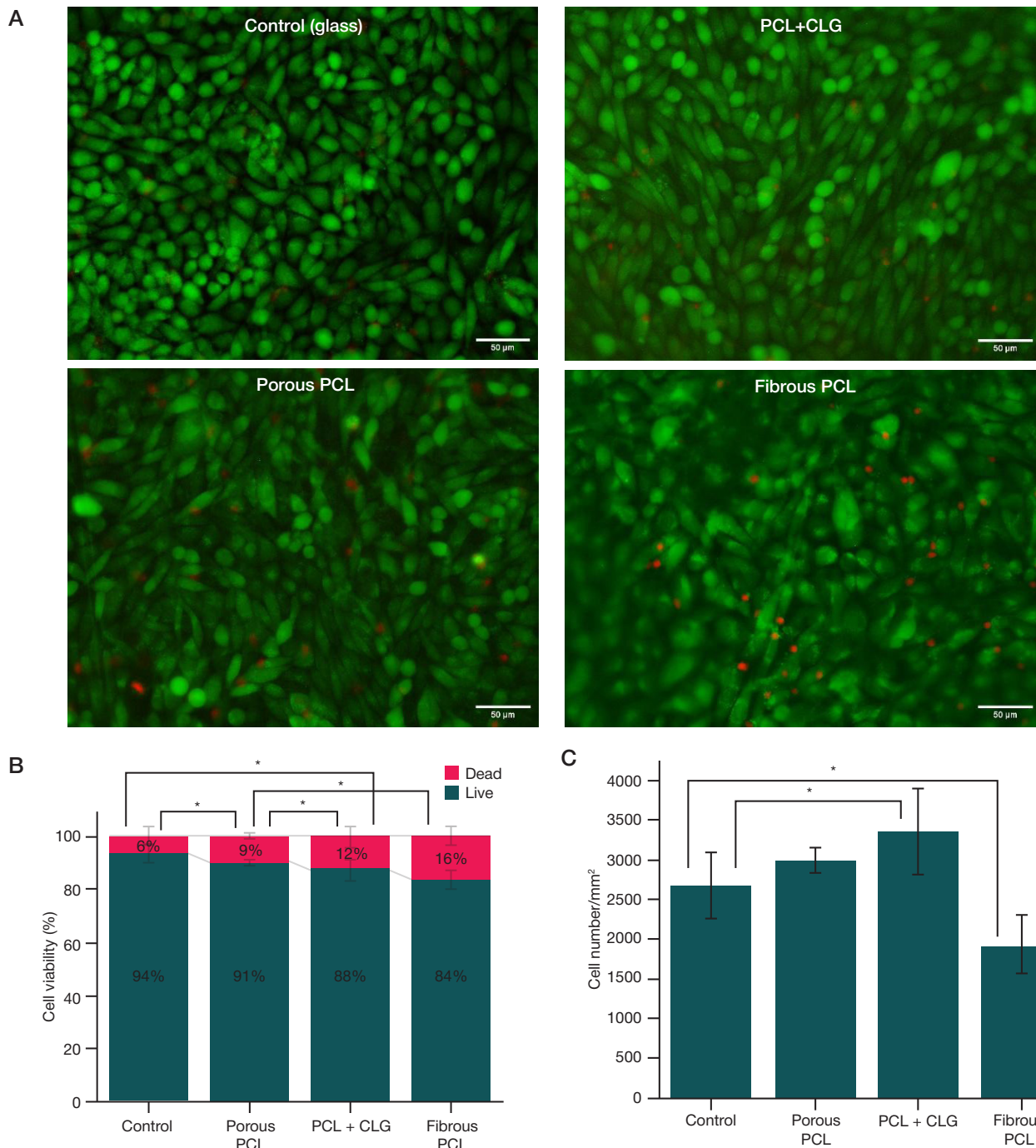


**Fig. 1.** Micrographs and SEM data. The numerical values are given as mean and standard deviation (M; SD). **A, B.** Porous PCL. **C, D.** PCL+CLG (after washing in water). **E, F.** Fibrous PCL

processing, the samples were embedded in paraffin wax. Sections 3–4  $\mu\text{m}$  thick were stained with hematoxylin and eosin according to the standard protocol. The resulting slide mounts were digitized with a NanoZoomer S20 scanner (Hamamatsu, Japan) at 40 $\times$  magnification. The tissue reaction — the extent of inflammatory infiltrate, the presence of foreign body giant cells, the thickness of the connective tissue capsule, and the degree of neoangiogenesis — was measured using NDP.view 2 (Hamamatsu, Japan).

### Statistical analysis

Statistical processing was performed in the Origin 2022 program (OriginLab, USA). The histogram of the measured dimensions of the structural elements was bell-shaped and nearly symmetric, thus a normal approximation was used to estimate the mean and describe the distribution. The normality of the distribution was checked using the Kolmogorov–Smirnov test. The data are presented as mean and standard deviation



**Fig. 2. A.** Micrographs of mouse fibroblast cells L929 cultured on different materials. Fluorescence analysis of live/dead cell ratio (staining: calcein-AM / propidium iodide). Scale bar — 50  $\mu$ m. **B.** Viability of L929 cells when cultured on different materials ( $n = 6$ ). **C.** Cell density on different materials. **B, C.** Data are presented as mean  $\pm$  standard deviation (Mean  $\pm$  SD). Statistical differences were analyzed using an unpaired two-tailed Student's  $t$ -test for data between two groups ( $n = 6$ ,  $*p < 0.05$ )

( $M \pm SD$ ). Statistical differences between the two groups were assessed using an unpaired Student's  $t$ -test ( $*p < 0.05$ ).

## RESULTS

The structure of materials

For *in vitro* and *in vivo* biocompatibility tests, four types of materials with different compositions and structures were produced, two of which are polymer films, and two more are 3D materials made of micro- and nanofibers. Table 1 gives composition and characteristics of these materials.

The structures of materials (Types 1–3) were examined using scanning electron microscopy. Fig. 1 presents micrographs of the sample surfaces along with the size distribution of structural elements (pore and fiber diameters).

### *In vitro* biocompatibility assessment

*In vitro* biocompatibility tests were performed on L929 mouse fibroblast cell cultures. The cell line and incubation time for cytotoxicity testing of the material in direct contact were selected in accordance with ISO 10993-5, the international standard for "Biological evaluation of medical devices." After 72 hours of cultivation, we used fluorescence microscopy to

**Table 2.** Quantitative results of *in vitro* material biocompatibility (Mean  $\pm$  SD)

| Type of material   | Proportion of living cells, % | Total number of cells/mm <sup>2</sup> |
|--------------------|-------------------------------|---------------------------------------|
| Control (glass)    | 94.4 $\pm$ 3.7                | 2695 $\pm$ 422                        |
| Porous PCL         | 90.5 $\pm$ 1.3                | 2987 $\pm$ 161                        |
| PCL+CLG 1 : 1 mass | 87.7 $\pm$ 4.3                | 3366 $\pm$ 536                        |
| Fibrous PCL        | 83.8 $\pm$ 3.6                | 1920 $\pm$ 372                        |

determine the ratio of live and dead cells as well as the average number of cells per 1 mm<sup>2</sup> of polymer surface area (Fig. 2, Table 2).

### ***In vivo* biocompatibility assessment (subcutaneous implantation model)**

Postoperative clinical observation confirmed the animals' satisfactory condition after implantation. The wounds healed by primary intention: they were completely closed by day 7, and by day 13, the surgical site was fully covered with hair. The sutures remained intact throughout. There were no macroscopic signs of hyperemia or other skin changes above the implantation area.

The histological slides from the control group had normal morphological structure of the skin of the back: stratified keratinizing epithelium with appendages, subcutaneous fat and underlying muscle tissue without signs of inflammatory infiltration (Fig. 3).

### **Histology of polymer film implants**

In the porous PCL implantation group, the material remained directly under the skin as a dense structure 5–6 mm long and 20–40  $\mu$ m thick. There was no cellular infiltration into the body of the polymer. A thin connective tissue capsule formed around the implant, consisting of 3–4 collagen fiber bundles with fibroblasts and lined by macrophages and scattered multinucleated foreign body giant cells. There were no signs of active capsule vascularization or dystrophic changes in the surrounding tissues. In four of the five samples, the inflammatory response was minimal. In one sample, we observed moderate neutrophil infiltration, presumably resulting from local mechanical injury caused by implant migration (Fig. 4).

The PCL+CLG composite material did not differ visibly in size or density from porous PCL. However, in all samples, it induced a foreign body reaction that resulted in pronounced granulomatous inflammation. Along the entire length of the implant, we registered several layers of macrophages and foreign body giant cells (quantitatively — 4–5 times more than in the porous PCL group). The connective tissue capsule

was noticeably thick (up to 100  $\mu$ m) and consisted of 10–20 parallel collagen fiber bundles. It was richly vascularized and accompanied by a pronounced perivascular infiltrate of lymphocytes and macrophages. The surrounding tissues exhibited significant vascular congestion.

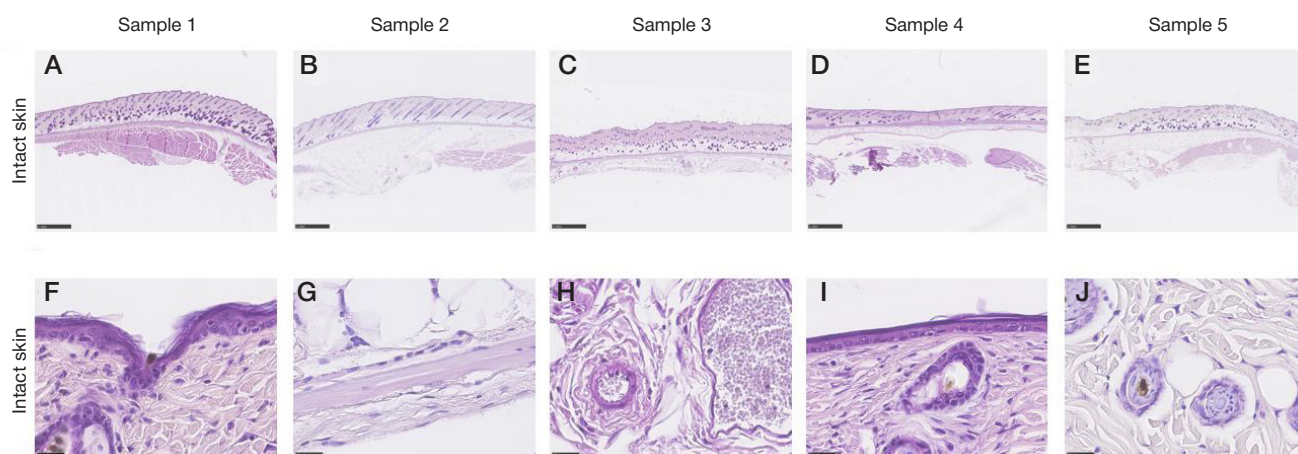
Fibrous PCL (mean thickness 300–350  $\mu$ m, range from 200 to 400  $\mu$ m) had a looser structure with oval gaps (diameter 10–30  $\mu$ m) formed by leaching of the polymer material during histological processing. In three of the five samples, the material was abundantly infiltrated by lymphocytes and macrophages, forming multiple foreign body giant cells mainly around voids. There was a dense network of congested vessels in the body of the material. A dense capsule of 3–5 collagen fiber bundles formed around the polymer. In one of the samples, the surrounding tissues grew into the material unevenly, which may indicate that this sample had a heterogeneous structure.

### **Histology of PA implant**

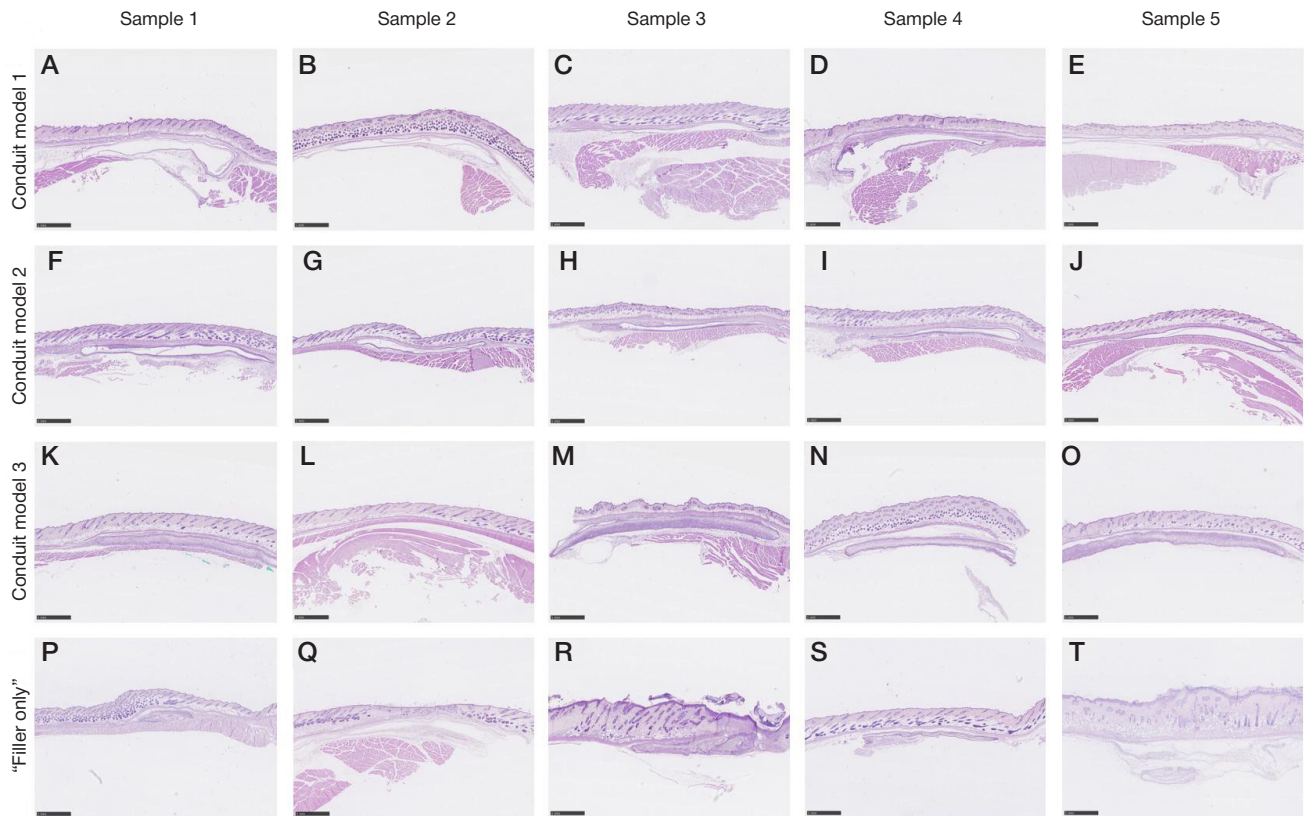
In the fibrous PA group, the material appeared as a tangle of loose fibers in all but one sample, where it formed a horizontally oriented film. Among all the studied materials, the filler elicited the weakest immune response, with minimal macrophage infiltration and only a few isolated foreign body giant cells. There was no fibrous connective tissue capsule around the sample, nor were there any signs of neoangiogenesis (Fig. 5). In two animals, we observed inflammatory and destructive skin changes at the implantation site, and in one of them, the epithelial layer integrity was compromised.

### **DISCUSSION**

The results of this study should be considered as part of the primary preclinical screening of micro- and nanostructured polymer materials potentially applicable in the fields of reconstructive surgery and tissue engineering. The subcutaneous implantation model does not reproduce the specific microenvironment of a particular organ or tissue. However, it allows evaluation of the universal parameters of biocompatibility of implanted



**Fig. 3.** Morphological structure of the mouse back skin in the control group. Hematoxylin-eosin staining, magnifications  $\times 25$  (A–E) and  $\times 800$  (F–J)



**Fig. 4.** Morphological assessment of implantation sites of materials and filler models. Designations of material and filler models: Model 1 — porous PCL; Model 2 — PCL + CLG; Model 3 — fibrous PCL; Filler — fibrous PA. Hematoxylin-eosin staining, magnifications  $\times 25$

materials: the severity of the foreign body reaction, the degree of inflammatory infiltration, the formation of a connective tissue capsule, signs of neoangiogenesis, and local damage to surrounding tissues [1–3, 15]. These characteristics are important for various implantable structures, including barrier membranes, support matrices, intraluminal fillers, and guide frames.

Artificial nerve conduits (ANCs) that enable reconnection of damaged nerves and provide a controlled regeneration environment are one of the most demanding applications of such materials. The conduit wall material should make the structure mechanically stable and fixable in the damage zone; it should also act as a barrier that prevents the surrounding connective tissue from growing into the lumen of the implant. Among the options registered for medical use, there are conduits based on natural polymers, in particular collagen, and products made of synthetic materials, including polyvinyl alcohol and polyglycolic acid [24].

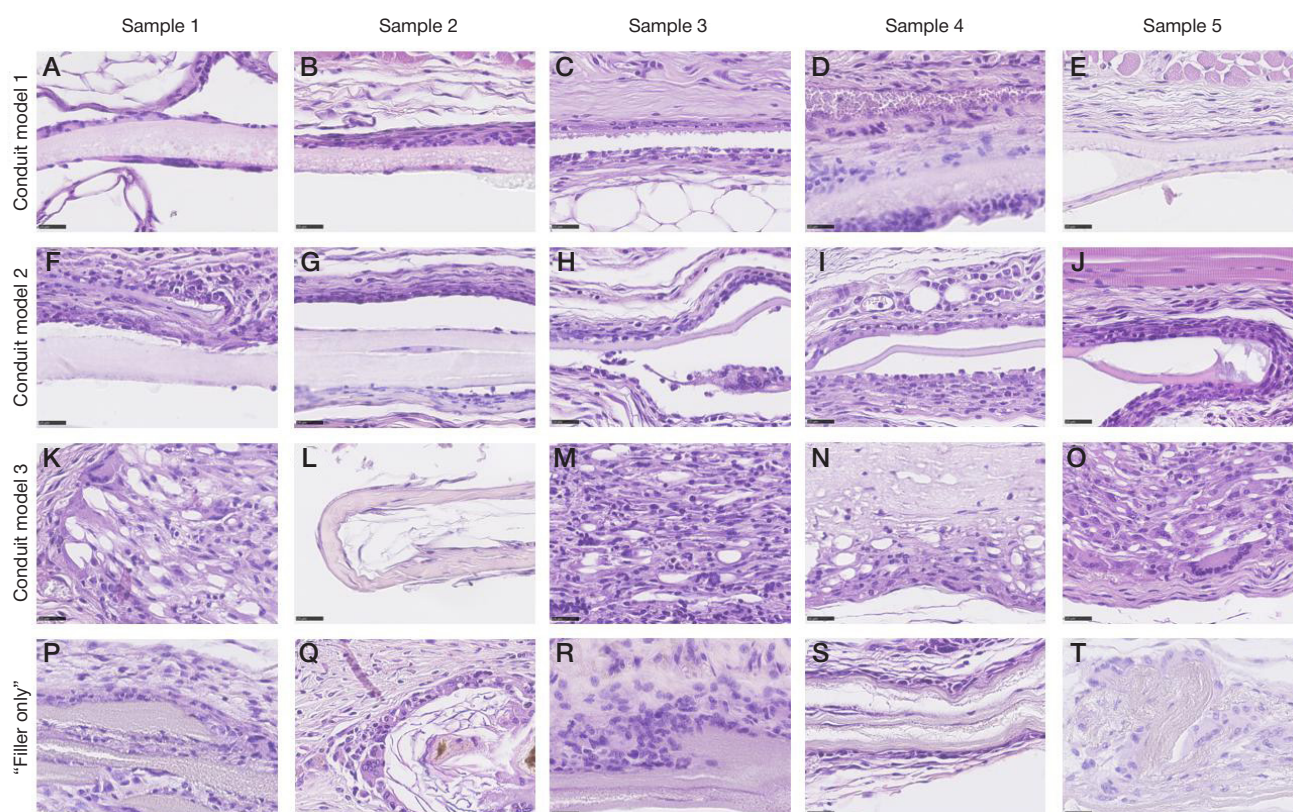
For this study, we chose PCL as one of the main materials of the implantable structure's outer wall. It is FDA-approved, exhibits the required mechanical properties and adaptability, can be fabricated into thin implantable films, and demonstrates good biocompatibility [11]. Earlier experiments investigated the fit-for-purpose of ANC prototypes based on fibrous structures [12] and extruded spirals [13] made from PCL.

For *in vitro* and *in vivo* tests, we made films of porous PCL, films of the PCL+collagen composite, and fibrous PCL consisting of electrospun micron fibers. Porous and fibrous materials are potentially fit for reconstructive implants because they can combine a barrier function with the ability to diffuse gases, nutrients, and biologically active molecules [10, 16]. In the context of nerve conduits, this is especially important in the reconstruction of extended defects, where it is necessary to maintain cell viability in the inner cavity of the implant and at the same time limit the ingrowth of scar tissue. Analysis of

the structure of the obtained materials showed that the porous PCL had a large pore size compared to the PCL+CLG film, however, both options had the pore size significantly smaller than connective tissue cells, which means they are potentially capable of preventing their penetration into the interior of the structure.

Before testing, PCL-based materials were treated with low-temperature plasma to enhance the hydrophilicity, biocompatibility, and surface adhesiveness. *In vitro* experiments with L929 fibroblast cultures confirmed the absence of pronounced cytotoxicity of the tested materials, as cell viability exceeded 80% after 72 hours of cultivation. Fibrous PCL exhibited cell population density about a third lower than that registered in film materials. These data are consistent with the findings of the previously published papers that demonstrated how polymer material's surface microstructure modifies cellular adhesion and cell distribution [23].

Modern implantable structures for peripheral nerve repair can include not just the outer wall, but also internal elements that function as a guiding framework. Such elements can be grooves and channels in the body of the material, hydrogels, spongy structures, multichannel constructs, and bundles of oriented fibers in the inner cavity of the conduit [19, 25]. Previously, the authors of the above-mentioned articles showed that a material composed of nylon nanofibers (50–100 nm in diameter) can direct neurite growth by mimicking the ultrastructure of the extracellular matrix, and that the direction of nerve process growth coincides with the orientation of the fibers [21]. It has also been shown that a composite material containing fiber layers with diameters of 60 and 200 nm stimulates the proliferation and polarization of Schwann cells, and in *ex vivo* conditions promotes directed growth of axons of dorsal root ganglia [20]. Therefore, a material composed of oriented polyamide nanofibers can be considered a promising component of the conduit's internal architecture, designed to



**Fig. 5.** Morphological assessment of implantation sites of materials and filler models. Designations of material and filler models: Model 1 — porous PCL; Model 2 — PCL + CLG; Model 3 — fibrous PCL; Filler — fibrous PA. Hematoxylin-eosin staining, magnifications  $\times 800$

provide contact guidance and proper spatial organization for regenerating axons [22].

The *in vivo* part of the study has confirmed that not only the chemical composition, but also the physical structure, porosity, and surface topography of polymer materials significantly influence the nature of the local immune response. Porous PCL and fibrous polyamide were the materials that elicited the most favorable tissue response: there was minimal inflammatory reaction, no pronounced granulomatous inflammation, and no massive fibrous capsule formation. This type of response can be considered the most desirable for implantable structures, where a combination of bioinertness, structural stability, and the absence of uncontrolled fibrosis is required.

These results are of particular importance for the development of artificial nerve conduits. An extensive foreign body reaction and dense scar tissue around the implant can mechanically block regeneration, disrupt the trophism of growing axons, and limit the physiological mobility of the reconstructed nerve trunk [14, 15]. In our study, only a thin connective tissue capsule formed around the porous PCL, with no signs of active neoangiogenesis or pronounced inflammatory infiltration, which indicates the high biocompatibility of the material and makes it a promising candidate for external barrier layers in implantable structures. Such layers are especially beneficial for nerve regeneration: they maintain the lumen of the conduit and limit extraneural fibrosis without triggering a chronic macrophage response [3, 26].

The results of fibrous polyamide implantation deserve special attention. This material caused the least prominent tissue reaction of all samples: no pronounced connective tissue capsule formed around it, and the macrophage reaction was minimal. This means it might be tolerated well by the surrounding tissues when used in reconstructive surgery. The results of this experiment are especially important for the function of nerve conduits, since the intraluminal filler should

not only guide the direction of cell and axon growth but also avoid provoking inflammation inside the regeneration zone. The data obtained are consistent with the previously shown ability of oriented polyamide nanofibers to support the growth of neurites and the directed migration of cells of the peripheral nervous system [20, 21].

Unlike porous PCL and fibrous polyamide, PCL+CLG composite and fibrous PCL triggered a more pronounced inflammation. The formation of a dense fibrous capsule (thickness up to 100  $\mu\text{m}$ ) around the PCL+CLG implant indicates an intense foreign body reaction. Collagen is widely used in biomedical materials, but in this case, its inclusion in the composite film did not improve the tissue response profile: the tissues exhibited reinforced macrophage infiltration, formation of foreign body giant cells, and pronounced vascularization of the capsule. This means that the results of *in vitro* cytocompatibility studies should be interpreted carefully: the absence of pronounced cytotoxicity does not always predict a favorable tissue response after *in vivo* implantation.

The response of the tissues to fibrous PCL also was less benign. This material has a loose structure with gaps measuring 10–30  $\mu\text{m}$  in diameter, around which macrophages and foreign body giant cells concentrated. On the one hand, an interconnected porous network can assist the diffusion of oxygen and nutrients as well as stimulate angiogenesis [10]. On the other hand, excessive laxity and insufficient mechanical stability of the fibrous structure can promote inflammatory infiltration and facilitate granuloma formation. The heterogeneous tissue penetration into the sample and the formation of large voids probably stem from the low strain resistance of loose fibers and from stretching during implantation. The vascular network that formed within the material confirms its capability to support angiogenesis, but the severity of the macrophage response limits its use in its initial form.

The data obtained should be taken into account in the further design of fibrous implantable materials. Reducing the severity of the inflammatory reaction may require additional structural stabilization; options include local fusion, gluing, or formation of nodal fiber fixation sites. Previous experiments have shown that the rigidity, regularity, and spatial organization of porous PCL structures can affect macrophage adhesion and polarization, including a shift towards the M2 phenotype associated with anti-inflammatory and reparative responses [27]. Therefore, optimizing both the chemical composition and the material architecture is essential for creating safe, functional implantable structures.

Thus, our study shows that micro- and nanostructured polymer materials with similar *in vitro* biocompatibility can trigger significantly different tissue reactions *in vivo* when implanted in an animal model. Among the materials investigated, the most promising were porous PCL and fibrous polyamide. In the broad context of reconstructive surgery, they can be considered for use in barrier and guiding implantable structures. In the specific context of peripheral nerve repair, our study supports the need for further development of a hybrid biomimetic conduit combining an outer wall of porous PCL and an inner oriented framework of polyamide nanofibers.

#### Study limitations and directions for further research

The *in vivo* subcutaneous implantation in mice is a classic step in the primary screening of biosafety and local tissue response to new polymeric materials. However, it does not allow evaluating the reaction in a specific reconstructive case, since the subcutaneous microenvironment in that case may differ significantly from the tissues for which these materials are intended to be used. In particular, the key processes in peripheral nerve repair operations are Wallerian degeneration, myelin degradation, endoneural microenvironment remodeling, and directed migration of Schwann cells [28].

The used animal model also disallows assessing how the materials will function when molded into the structure ready for implantation, including their mechanical stability in the defect area, capability to maintain the conduit lumen, direct axonal growth, and assist restoration of nerve conduction. Additionally, we did not perform immunohistochemical verification of the cellular composition of the inflammatory infiltrate, including the macrophage response and macrophage polarization; this limits interpretation of the mechanisms underlying the local immune response. In this regard, the next stage of the study may be the design and testing of a biomimetic structure combining an external insulating shell of porous PCL and an internal guide matrix based on fibrous PA. Confirmation of the applicability of such a design in peripheral nerve repair surgery requires its testing on traumatic nerve defect models with assessment of morphological, electrophysiological, and functional outcomes. Another promising area is functionalizing the developed structures with adhesive peptide motifs (e.g., RGD or IKVAV) [29] and neurotrophic factors (including NGF and BDNF) [30]

to specifically stimulate cell adhesion, promote axonal growth, and enhance the implant's regenerative potential.

#### CONCLUSIONS

We designed and described four types of micro- and nanostructured polymer materials potentially applicable in reconstructive surgery and tissue engineering: porous PCL, a composite of PCL and type I collagen, fibrous PCL, and a material made of highly oriented polyamide nanofibers. Porous PCL (thickness 65  $\mu\text{m}$ ; pore diameter  $0.44 \pm 0.17 \mu\text{m}$ ) demonstrated the most favorable biocompatibility profile: in *in vitro* tests on fibroblast culture L929, the proportion of living cells was  $90.5 \pm 1.3\%$ , and the cell population density was  $2987 \pm 161 \text{ cells/mm}^2$ . These results did not differ significantly ( $p > 0.05$ ) from glass controls ( $94.4 \pm 3.7\%$ ;  $2695 \pm 422 \text{ cells/mm}^2$ ), which indicates the material does not have a pronounced cytotoxic effect. A thin connective tissue capsule of 3–4 bundles of collagen fibers formed around the samples implanted subcutaneously. There were no signs of active neoangiogenesis, and a minimal inflammatory response was registered in 4 out of 5 samples. The PCL+CLG composite (thickness 35  $\mu\text{m}$ ; pore diameter  $0.10 \pm 0.03 \mu\text{m}$ ) exhibited comparable *in vitro* cytocompatibility (proportion of living cells  $87.7 \pm 4.3\%$ ; density  $3366 \pm 536 \text{ cells/mm}^2$ ), but *in vivo*, it triggered the most pronounced foreign body reaction: formation of a thick fibrous capsule (up to 100  $\mu\text{m}$ ; 10–20 parallel bundles of collagen fibers), macrophage infiltration with 4–5 times more giant foreign body cells than in the porous PCL group, and a pronounced perivascular lymphocyte-macrophage reaction. Fibrous PCL (thickness ~300–350  $\mu\text{m}$ ; fiber diameter  $0.69 \pm 0.32 \mu\text{m}$ ) demonstrated the lowest *in vitro* cell viability and population density ( $83.8 \pm 3.6\%$ ;  $1920 \pm 372 \text{ cells/mm}^2$ ). For both indicators, the differences with porous PCL and PCL+CLG composite were significant ( $p < 0.05$ ). Three out of five implanted samples triggered granulomatous inflammation with the formation of multiple giant foreign body cells around voids inside the material. Fibrous polyamide (thickness 10  $\mu\text{m}$ ; oriented fibers diameters 60 and 200 nm) caused the least pronounced tissue reaction among all the materials investigated: there formed no pronounced connective tissue capsule and there were no signs of neoangiogenesis. We registered a macrophage response only in one sample. This is consistent with the previously described ability of oriented polyamide nanofibers to support directed neurite growth and migration of Schwann cells.

Thus, among the studied materials, porous PCL and fibrous PA can be considered as the most promising candidates for base materials of barrier and guiding implantable structures used in reconstructive surgery. In the context of peripheral nerve reconstruction, these results justify developing a hybrid biomimetic conduit that combines an external tubular wall of porous PCL with an internal oriented framework of polyamide nanofibers, followed by evaluation of its effectiveness in functional models of peripheral nerve injury.

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