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# Commercially available acellular matrices for adipose-derived stem cell-based tissue engineering: a comparative analysis of morphology and early cytocompatibility

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## Abstract

**Background** Acellular matrices are frequently used in regenerative medicine due to their structural and biochemical similarity to the native extracellular matrix. However, comparative data on their morphological characteristics and early interaction with human adipose-derived stem cells (ASCs), particularly in the context of cartilage tissue engineering, remain limited. This study aimed to compare the architectural characteristics of eight commercially available acellular matrices to assess their early interaction with adipose-derived stem cells under standardized in vitro conditions.

**Methods** Scanning electron microscopy was used to analyze apparent two-dimensional pore size, porosity, and surface morphology. Adipose-derived stem cells from the adipose tissue of four female donors were isolated, pooled and characterized for typical stem cell markers (CD13, CD29, CD44, CD73, CD90, CD105) by flow cytometry.  $1.25 \times 10^5$  cells were seeded onto biological triplicates of each matrix, and cell viability was assessed via Alamar Blue assay after 7 days of culture.

**Results** Several matrices with porosity values of 40–60% and pore sizes between 50 and 150  $\mu\text{m}$  showed comparatively high metabolic activity during the tested day-7 culture period. These findings highlight the importance of matrix composition and architecture in governing early ASC–matrix interactions.

**Conclusion** Despite structural and or biochemical similarities, considerable differences in early ASC metabolic activity were observed across matrices, indicating that additional parameters such as pore uniformity, interconnectivity, and surface properties act in concert with biochemical composition to influence cellular responses in a complex manner. This study represents a preliminary screening focused on morphological characteristics and early ASC–matrix interactions. These findings provide a foundation for further investigations into long-term survival, proliferation, differentiation, matrix remodeling, and biomechanical performance. By focusing on commercially available matrices, this work offers practical relevance and contributes to more informed early-stage scaffold selection for regenerative medicine applications.

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**Keywords** Acellular collagen matrices, Tissue engineering, Adipose-derived stem cells, Microstructure, Scanning electron microscopy

## Background

Acellular matrices (ACM) have gained rising attention in regenerative medicine due to their structural similarity to native extracellular matrix (ECM) and their high biocompatibility [1]. These matrices, derived from animal tissues or engineered biomaterials, serve as scaffolds in a wide range of tissue engineering approaches. ACM are most commonly used in skin regeneration, including the treatment of chronic wounds, burns, skin defects and ulcers [2–10], as well as in soft tissue repair and hernia reconstruction [11–15].

Commercially available and clinically approved collagen-based ACM offer several advantages, including excellent biocompatibility, low immunogenicity, biodegradability, and favorable mechanical properties [3, 16, 17]. In addition, their standardized production and validated sterilization ensure reproducibility, making them highly attractive for both experimental and translational applications [3, 18]. Functionally, ACM provide a structural and biochemical microenvironment that supports cell adhesion, migration, proliferation, and differentiation, and mediates cell–cell and cell–matrix interactions [19].

Despite similarities in their basic composition, commercially available ACM differ substantially in origin, structure, and biochemical properties. Many matrices are primarily based on collagen type I, the most abundant collagen in the human body, which plays a key role in maintaining the structural integrity of the ECM in most tissues, particularly in skin and bone. In contrast, collagen type II represents the principal ECM component in specialized tissues such as cartilage [20].

From a translational perspective, collagen type I-based matrices offer significant advantages: they are widely available, easier to process, and form the basis of most clinically approved scaffold products. In contrast, collagen type II—although biologically more representative of certain native tissues—is limited by more complex sourcing, processing, and scalability [21]. Moreover, collagen type II-based materials have been associated with reduced volume stability and increased arthritogenic potential, while their production remains technically more challenging due to their restricted tissue distribution [21, 22]. As a result, collagen type I-based ACM are currently the most widely used matrices in both research and clinical practice [1].

Beyond conventional collagen type I-based matrices, clinically applied acellular scaffolds also include

materials derived from decellularized human epidermis, as well as composite constructs incorporating synthetic polymers or bioactive components. Several commercially available matrices are used in clinical practice, including those investigated in the present study: *Novocart*<sup>®</sup>, *MatriDerm*<sup>®</sup>, *Integra*<sup>®</sup>, *OviTex*<sup>®</sup>, *SupraSDRM*<sup>®</sup>, *Resorba*<sup>®</sup> *Kollagen Resorb*, *Epiflex*<sup>®</sup>, and *Promogran*<sup>®</sup> *Protease Modulating Matrix*. These matrices differ substantially in architecture, porosity, and biochemical composition, factors that may influence cell adhesion, migration, and differentiation in a material-specific manner.

Among the cell types used in regenerative medicine, adipose-derived stem cells (ASCs) represent a particularly suitable and clinically accessible cell source. They can be obtained with minimal donor-site morbidity, provide high cell yields, and exhibit robust multilineage differentiation potential [23]. In combination with ACM, ASCs offer a promising strategy to generate cell-instructive microenvironments for tissue regeneration.

In this context, scaffold architecture and matrix composition are key determinants of cell behavior. Parameters such as pore size, porosity, and matrix organization influence cell infiltration, nutrient diffusion, and extracellular matrix deposition, while maintaining mechanical stability [24, 25]. However, optimal design parameters and the interaction between matrix composition and cellular response remain insufficiently understood [25, 26].

Therefore, the present study aims to systematically evaluate the structural and biochemical properties of eight commercially available ACM, with a particular focus on collagen composition and scaffold architecture. Using scanning electron microscopy (SEM) and cell-based assays, matrix morphology and early ASC compatibility are analyzed under standardized in vitro conditions. This approach enables the identification of material-specific properties that influence cell behavior and provides a rational basis for the selection and optimization of ACM in translational tissue engineering applications.

## Materials and methods

### Cell isolation (ASC)

This study was approved by the ethics committee of Ludwig-Maximilians-Universität (LMU) Munich, Germany, and conducted in accordance with the principles outlined in the Declaration of Helsinki (Project-ID 23–0584). Written informed consent was obtained from all donors

prior to their elective interventions. Adipose tissue was harvested from lipoaspirates of four Caucasian female donors (age range: 28–53, mean age 45.75 years), exclusively obtained from the upper thigh region. Preoperative screening confirmed that all donors tested negative for HIV, Hepatitis B, and Hepatitis C and were non-smokers.

The isolation of adipose-derived stem cells (ASCs) was performed using 0.2% collagenase type II (Worthington Biochemical Corp., Lakewood, USA) dissolved in Dulbecco's Phosphate Buffered Saline (DPBS) (Gibco, Thermo Fisher Scientific, Massachusetts, USA). The enzymatic digestion was conducted on the day of the intervention or, at the latest, within 24 h post-collection. ASCs were isolated following a standardized protocol as described in previous studies [27, 28].

The initial cell yield following the expansion of passage 0 (p0) cells ranged from  $7 \times 10^6$  to  $20 \times 10^6$  per donor. To minimize donor-specific fluctuations during this initial screening study, equal numbers of cells from each donor were pooled at passage 1 (p1) prior to experimental use. The pooled cell population was further expanded to p2, where characterization via flow cytometry (FACS) was performed prior to experimental application.

**Flow cytometry**

Flow cytometry was carried out to characterize the ASC surface markers ahead of conducting the main experiments. A standardized protocol previously established in our laboratory was used [27, 28]. Briefly,  $1 \times 10^6$  of pooled ASCs at passage 2 were stained with antibodies against CD13, CD29, CD44, CD73, CD90, CD105, CD31, CD45, and CD235, including corresponding isotype controls. Data were acquired and analyzed using FlowJo V10.6.1 (BD Biosciences, Heidelberg, Germany) (Table 1).

**Table 1** Antibodies and isotypes for flow cytometry analysis

| Antibody | Conjugate    | Isotype       | Manufacturer                                            |
|----------|--------------|---------------|---------------------------------------------------------|
| CD13     | BV711        | Mouse IgG, k  | BioLegend, California, USA                              |
| CD29     | FITC         | Mouse IgG, k  | EBioScience (Thermo Fisher Scientific, California, USA) |
| CD44     | Pacific blue | Mouse IgG1, k | BioLegend, California, USA                              |
| CD73     | AF700        | Rat IgG, k    | BioLegend, California, USA                              |
| CD90     | BV786        | Mouse IgG, k  | BioLegend, California, USA                              |
| CD105    | APC-A        | Mouse IgG, k  | BioLegend, California, USA                              |
| CD31     | PE-Cy7       | Mouse IgG, k  | BioLegend, California, USA                              |
| CD45     | PerCP        | Mouse IgG, k  | BioLegend, California, USA                              |
| CD235a   | COMP-PE      | Mouse IgG, k  | BioLegend, California, USA                              |

**Scanning electron microscopy**

All eight untreated matrices were prepared following a standardized protocol provided by the Department of Biology at LMU Munich. Samples were cut into small pieces and fixed with Tempfix (Plano GmbH, Wetzlar, Germany; Ref: G3305) for further processing. Subsequently, the matrices were mounted onto stubs (Plano GmbH, Wetzlar, Germany; Ref: 16170) before sputter-coating with platinum for 40 s using a BAL-TEC SCD 050 Sputter Coater (Oerlikon Balzers, Pfäffikon, Switzerland). Multiple SEM images of various regions of the ACM were then captured using the Zeiss Auriga Cross Beam FIB-SEM (Carl Zeiss Microscopy, Oberkochen, Germany).

**SEM image porosity and pore size analysis**

To evaluate SEM image-based surface porosity, images were imported into ImageJ (Version 1.54p, Open Source), and processed using the *Image > Adjust > Threshold* function, followed by *Analyze > Analyze Particles*. Prior to analysis, gray values were normalized across all images to ensure comparability. Thresholding was then applied using a consistent threshold range, with minor adjustments where necessary to account for differences in image contrast.

Porosity was calculated as the percentage of image area not occupied by matrix material (i.e., void space) based on pixel area (% area). This parameter represents an apparent two-dimensional (2D) surface porosity derived from SEM images and does not reflect true volumetric (3D) porosity. For each matrix type, six images from multiple randomly assigned regions were evaluated, and mean values were calculated ( $N=6$  images per matrix).

For pore size determination, images were calibrated in ImageJ using the provided scale bars (10  $\mu\text{m}$ , 20  $\mu\text{m}$ , or 100  $\mu\text{m}$ ). The scale was set using the *Analyze > Set Scale* function with a pixel aspect ratio of 1.0 standardized to each scale bar image.

Pore size was defined as the longest visible pore diameter measured in two-dimensional SEM projections. For each image, ten randomly selected pores were measured, resulting in a total of 60 measurements per matrix ( $N=6$  images; 10 pores per image). These measurements represent two-dimensional approximations of pore size and do not capture the full three-dimensional geometry or inter-connectivity of the pores.

Quantitative analysis was performed using SEM images acquired at comparable magnification levels across all matrices, ensuring that pore structures were resolved at a similar spatial scale. For each matrix, images were selected based on consistent magnification ranges that allowed clear identification of pore boundaries while maintaining comparability between matrices. For both

porosity and pore size analysis, identical image sets were used.

Nevertheless, slight variations in magnification were necessary due to differences in pore size and matrix architecture. This may limit direct quantitative comparability and is acknowledged as a methodological limitation.

#### Matrix preparation and seeding procedure

Sterile-packed matrices were put under a sterile hood and stored in a 15-cm petri dish (TPP; Ref: 93150). To prepare standardized samples, biopsy punches with diameters of 5 mm (PFM Medical; Ref: 48501) were used. For additional sterility, a sterile tissue was placed on the workspace of the sterile hood during the matrix preparation process.

The punched samples were washed in sterile DPBS and pre-incubated overnight in a 24-well plate (Corning Inc., USA; Ref: 353047) containing 1 ml of standard culture medium. Before cell seeding, the matrices were transferred to new wells and allowed to dry for at least 1 h inside the incubator.

Cells were trypsinized using TrypLE (Gibco; Ref: 12563-011) for 3–5 min, collected, centrifuged and counted before seeding.  $1.25 \times 10^5$  cells were suspended in 50  $\mu$ L standard medium, applied in 2–3 drops using a 100- $\mu$ L pipette. To ensure a homogeneous distribution, the cell suspension was regularly resuspended before application. After seeding, matrices were incubated for 3 h at 37 °C to allow cell attachment before adding 1 mL of standard culture medium. Media changes were performed 2 times per week.

#### Cell viability testing by Alamar Blue assay

To assess cell viability, a resazurin-based Alamar Blue assay was performed by detecting the mitochondrial metabolic activity. Alamar Blue measurements were performed on day 7 post-seeding using three independently seeded matrix samples per matrix type ( $N=3$ ). Samples were transferred to new wells in a 24-well plate containing 1 mL of standard phenol red-free DMEM-F12 medium (PAN Biotech; Aidenbach, Germany) supplemented with 10% Alamar Blue cell viability reagent (Invitrogen, Thermo Fisher Scientific, MA, USA). Following a 2-h incubation at 37 °C, three technical readouts of 100  $\mu$ L were transferred from each well into a black 96-well plate (Nunc™ MicroWell™ 96 wells; Thermo Fisher Scientific, MA, USA). The reduction of resazurin was quantified by fluorescent measurement at excitation/emission wavelengths of 560/590 nm, measured using an Infinite M Plex plate reader (Tecan Trading AG; Männedorf, Switzerland). A measured blind value (dye-only, without

cells) was subtracted from the original results. As a reference condition, ASCs cultured on standard tissue culture plastic (2D control) were included. Briefly,  $1.25 \times 10^5$  cells were seeded directly into each well of a 24-well plate and maintained under the same culture conditions as the experimental groups for 7 days ( $N=3$ ).

#### Statistical analysis

Statistical analysis was performed using GraphPad Prism version 10.4.1. for Mac (GraphPad Software, San Diego, USA). Data distribution was assessed using the Shapiro–Wilk test. For comparisons among matrix types, one-way ANOVA followed by Tukey's multiple comparisons test was used. Results are presented as mean  $\pm$  standard deviation, and a  $p$ -value of  $<0.05$  was considered statistically significant. The figures were designed with Adobe Illustrator 2023 (Adobe Creative Cloud, Adobe Inc., San Jose, CA, USA).

## Results

#### ASC characterization

To characterize the pooled ASCs from four donors prior to matrix seeding, flow cytometry was performed to assess the expression of typical surface markers. Cultured ASCs exhibited a spindle-shaped morphology and adherent growth behavior, consistent with mesenchymal stromal cell characteristics.

Based on established criteria from the International Federation for Adipose Therapeutics and Science (IFATS) and the International Society for Cellular Therapy (ISCT), cultured ASCs are defined by positive expression of CD44, CD73, CD90 and CD105, and negative expression of CD45 and CD31 [29].

In the present study, the pooled ASC population showed strong expression of CD13 (99.3%), CD29 (99.1%), CD44 (99.6%), CD73 (96.1%), CD90 (98.9%), and CD105 (97.4%), while expression of CD31 ( $<4\%$ ), CD45 ( $<1\%$ ), and CD235 ( $<2\%$ ) remained low, confirming the expected cultured ASC phenotype. Representative flow cytometry plots are shown in Fig. 1.

#### Matrix overview

Table 2 highlights the different matrices evaluated in this study, including their composition, key characteristics, and clinical applications as previously reported in the literature and manufacturer information. No publications matching our search were found for Kollagen® Resorb and SupraSDRM®; therefore, data for these matrices were exclusively derived from manufacturer-provided sources.

As shown in Table 2, the investigated matrices exhibit both notable commonalities and distinct differences. They vary considerably in biologic origin (bovine, ovine,

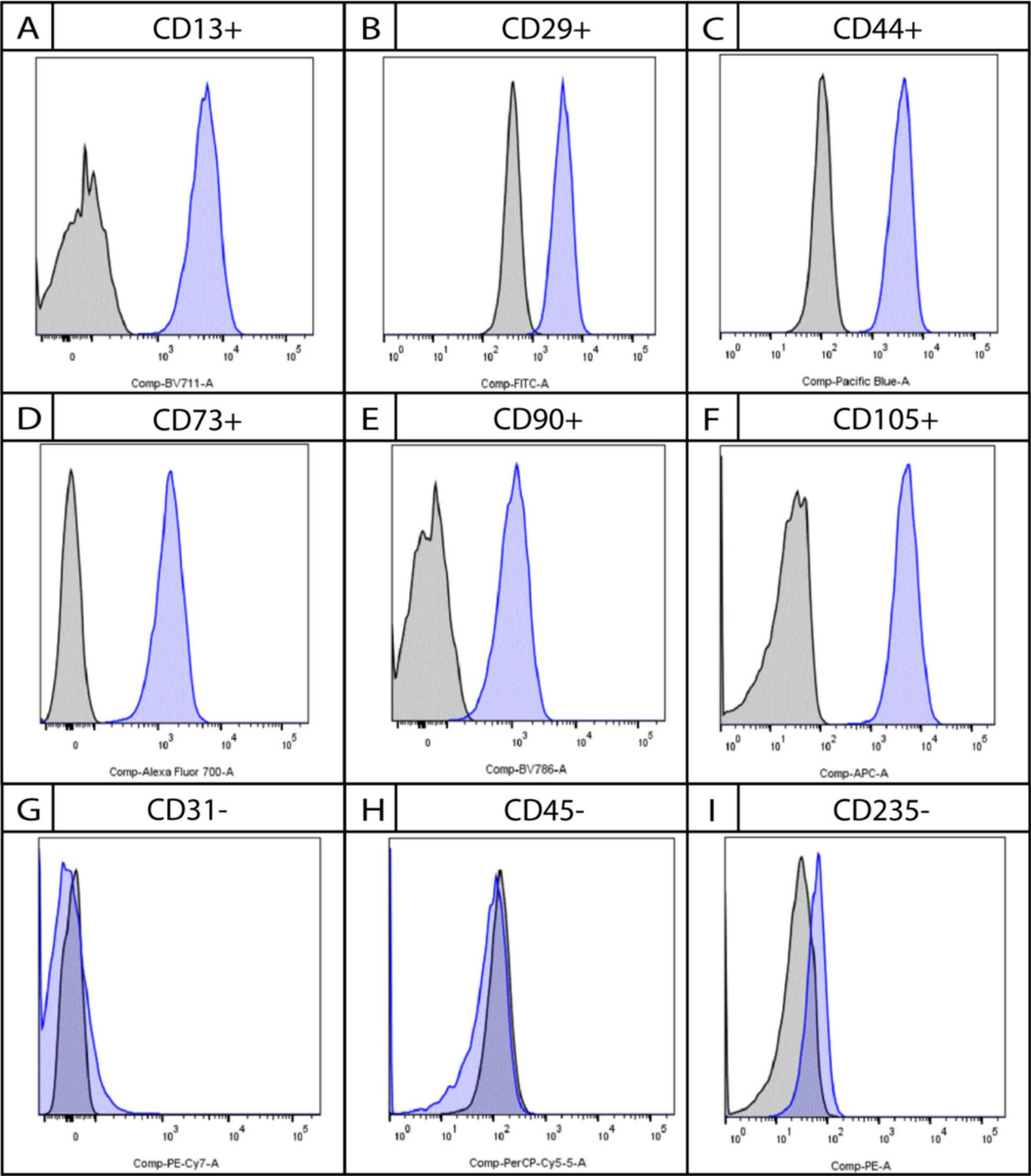


**Fig. 1** Representative flow cytometry plots of the pooled ASC population (passage 2) used for matrix seeding, showing expression of positive markers (CD13, CD29, CD44, CD73, CD90, CD105) and low expression of negative markers (CD31, CD45, CD235)

equine, porcine or human-derived), material composition (ranging from pure collagen type I to composite formulations incorporating additional components such as elastin, chondroitin sulfate or synthetic polymers), structural configuration (monolayer, bilayer, multilayer) and their intended clinical application.

Several products, such as MatriDerm®, Novocart®, and Integra®, are composed of bovine collagen, while

**Table 2** Matrices evaluated within this study

| Matrix                                                 | Material                                                                                                                    | Characteristics                                                                                                           | Clinical application                                                                                                                                         | Manufacturer                                            |
|--------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------|
| Matriderm® Flex 2 mm (Ref: 83462-200)                  | Native bovine collagen type I, III, V and elastin [30]                                                                      | Porous acellular matrix composed of bovine collagen and elastin [30]                                                      | Dermal replacement (Burns, chronic and acute wounds, ulcers) [6–8, 30]                                                                                       | Medskin Solutions, Dr. Suwelack AG, Billerbeck, Germany |
| OviTex™ Core Permanent 4 Layer (Ref: F10244-0408P)     | Ovine derived ECM and monofilament polypropylene [31]                                                                       | 4 layers, Textured and smooth side; generally, for reinforcement/repair of soft tissue, low inflammation response[14, 31] | Hernias [15, 32], abdominal wall defects [31, 33]                                                                                                            | TelaBio® Inc., Malvern, USA                             |
| Novocart® Basic (Ref: FR711)                           | Native Bovine collagen 1 [34]                                                                                               | Resorbable biphasic collagen type 1 matrix with collagen membrane and porous collagen sponge [34]                         | MACI [34–37], leading product for autologous chondrocyte implantation                                                                                        | Tetec AG, Reutlingen, Germany                           |
| KOLLAGEN resorb™ (Ref: 1 209)                          | Native Equine tendon collagen 1 fibrils [38]                                                                                | Biodegradable collagen matrix, low immunogenicity [38]                                                                    | Local hemostasis in several surgery fields [38]                                                                                                              | Resorba Medical GmbH, Nürnberg, Germany                 |
| EPIFLEX® (Ref: GT4026)                                 | Human epidermis [39]                                                                                                        | Freeze-dried acellular human skin [39]                                                                                    | Skin replacement for burns, scars, transplant seeded with autologous dermal fibroblasts [40], breast reconstruction [13], oral soft tissue augmentation [12] | DIZG, Berlin, Germany                                   |
| Promogran® Prisma Protease Modulating (Ref: M772028DE) | Freeze-dried composite of 55% collagen, 45% oxidized regenerated cellulose (ORC) [41]                                       | Binds on proteases and protects growth factors [9, 41]                                                                    | Diabetic foot ulcers [9, 42], chronic ulcers in general [43, 44]                                                                                             | Systagenix Wound Management Limited, Gargrave, UK       |
| Supra SDRM® (Ref: 410505)                              | Lactide-base copolymer [45]                                                                                                 | Bimodal combination of microporous structure and larger pores [45]                                                        | partial/full-thickness wounds, ulcers [10] (pressure, venous, diabetic), surgical, trauma, acute wounds (manufacturer information) [45]                      | Polymedics Innovations GmbH, Denkendorf, Germany        |
| Integra® SingleLayer (Ref: 3865299)                    | Native Bovine tendon collagen type 1 and chondroitin-6-sulfate (shark cartilage) [46], crosslinked with glutaraldehyde [47] | Porous resorbable collagen matrix with minimal inflammatory response [46]                                                 | dermal replacement for wounds [4, 5], chest wall deformities [48], scalp defects [49], deep facial defects [50], septorhinoplasty [51]                       | Integra Life Sciences, Princeton, USA                   |

The table highlights a comparison of material composition, characteristics, clinical application and manufacturer's description of each product. Sources are derived from manufacturer information and research papers. Manufacturer-provided information can be found under the following reference numbers in the table: [30, 31, 34, 38, 39, 41, 45, 46]

EPIFLEX® stands out as it is derived from human epidermis rather than animal or synthetic sources. KOLLAGEN resorb® consists of equine collagen I. OviTex® contains ovine-derived extracellular matrix. Promogran® Prisma is a freeze-dried collagen–cellulose composite. Some matrices consist of multiple materials, whereas Novocart® and KOLLAGEN resorb® are composed exclusively of type I collagen. SupraSDRM® is unique in that it is entirely polymer-based.

In terms of structure, most matrices consist of a single-layer sheet; however, OviTex® is an exception, comprising four matrix layers sutured together. The intended clinical applications also differ: while the majority of matrices are designed for general dermal regeneration, OviTex® is specifically used for hernia repair, and Novocart® is tailored for autologous chondrocyte implantation. Notably, Novocart® and SupraSDRM® are the only matrices that incorporate two distinct pore structures.

For in vitro handling, the matrices also differed in their behavior, especially concerning cell culture for several days. SupraSDRM® and Promogran® showed poor behavior in liquid, losing their shape rapidly after a few days of culture. All other matrices maintained their form during the 7-day culture period.

### Scanning electron microscopy (SEM) imaging and gross analysis

Scanning electron microscopy (SEM) was employed to examine the surface morphology and structure of the eight matrices. SEM images were acquired at different magnifications. For quantitative analysis, images with scale bars of 100 µm and either 20 or 10 µm were randomly selected from comparable magnification ranges to allow consistent evaluation of pore structure.

As shown in Fig. 2, the evaluated matrices exhibit distinct differences in surface architecture. MatriDerm®, Promogran®, Epiflex®, and Resorba® display comparable fibrous network structures, particularly at higher magnifications. In contrast, SupraSDRM® and OviTex® appear to have smaller pore dimensions, with OviTex® additionally showing a multilayered architecture with visible reinforcing sutures.

At lower magnifications, Resorba® and Novocart® demonstrate a comparable surface structure, although differences in pore size distributions are visible. At intermediate magnifications (20 µm scale bar), MatriDerm® and Novocart® present a more uniform structure compared to the other matrices. Integra® shows a comparable structural pattern, although direct visual assessment is partially limited by image darkening.

Overall, across matrices, variability in microstructural heterogeneity is evident, particularly when comparing

multilayered and monolayered matrices. It should be noted that SEM imaging of Integra® was affected by darkening artifacts due to its hydrated structure, which required modified sample preparation including dehydration. This may influence direct visual comparability of the corresponding images.

For each matrix, images are shown at low (100 µm), intermediate (20 µm), and high (10 µm) magnification to illustrate overall structure, pore distribution, and surface morphology. Images were selected from comparable magnification ranges across matrices to allow qualitative comparison of structural features. For quantitative analysis, images at 100 µm and either 20 µm or 10 µm scale were used as described in the Methods section.

### Porosity evaluation

SEM micrographs and ImageJ analysis were used to quantify SEM-derived surface porosity. The bar graph provides a clear visual representation of the obtained values across all eight matrices, highlighting both the mean values and the variability within each group. Resorba® exhibits the highest mean porosity ( $53.6 \pm 5.1\%$ ), followed by Integra® ( $50.8 \pm 4.4\%$ ), Novocart® ( $48.9 \pm 4.0\%$ ), MatriDerm® ( $47.6 \pm 2.2\%$ ), and Promogran® ( $45.0 \pm 3.3\%$ ), all of which fall within a comparable upper range. In contrast, OviTex® ( $11.6 \pm 2.2\%$ ) and SupraSDRM® ( $18.4 \pm 3.7\%$ ) display significantly lower porosity values compared to the other matrices. The relatively small error bars across most matrices indicate the consistency in matrix production.

Due to the high number of statistically significant differences among the eight matrices, we chose to present a graph displaying the mean porosity values for each matrix, including error bars highlighting the mean with standard deviation (SD). Additionally, a table summarizing all pairwise *p*-values is included in in Fig. 3, offering a clear overview of the statistical comparisons.

### Pore size evaluation

The data show considerable variation in pore sizes both within and between matrices. Among all, Resorba® (range: 192.5 µm, from 24.2 to 216.7 µm; mean pore size  $78.4 \pm 51.1$  µm) exhibited the widest range of values, while Novocart® (range: 100.4 µm, from 44.5 to 145 µm), showed the highest mean pore sizes ( $83.1 \pm 18.9$  µm). High pore size ranges indicate a highly heterogeneous structure. Integra® (range: 105 µm, from 19.2 to 124.3 µm) and Epiflex® (range: 99.74 µm, from 19.9 to 119.5 µm) also demonstrated broad distributions, but lower mean pore sizes (Integra®:  $53.2 \pm 23.3$  µm; Epiflex®:  $48.7 \pm 21.9$  µm). Intermediate ranges were observed in MatriDerm® (range: 78.42 µm, from 18.8 to 97.2 µm), Promogran® (range: 67.63 µm, from 35.5 to 103.2 µm)

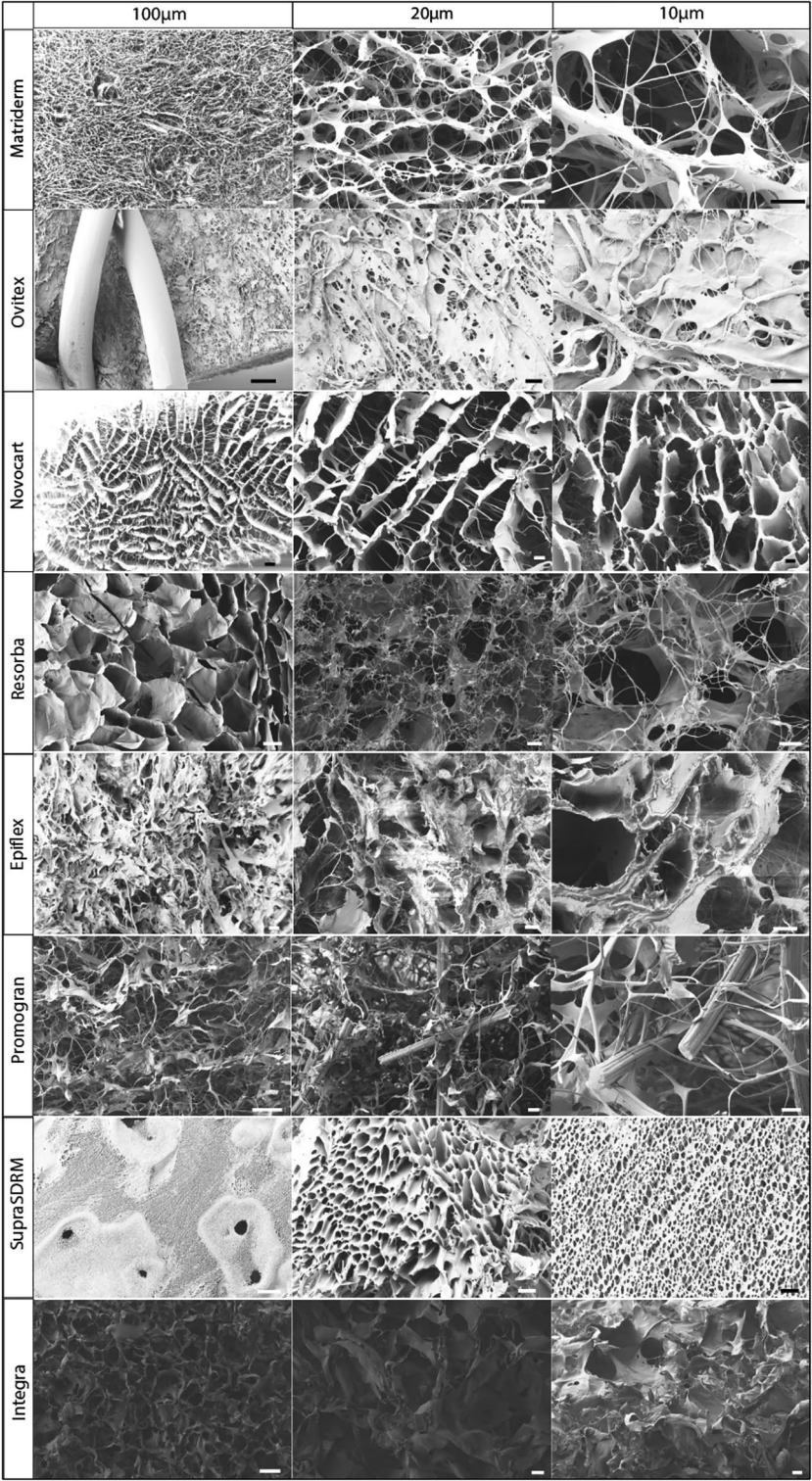


**Fig. 2** Representative SEM images of the eight evaluated matrices at three different magnifications

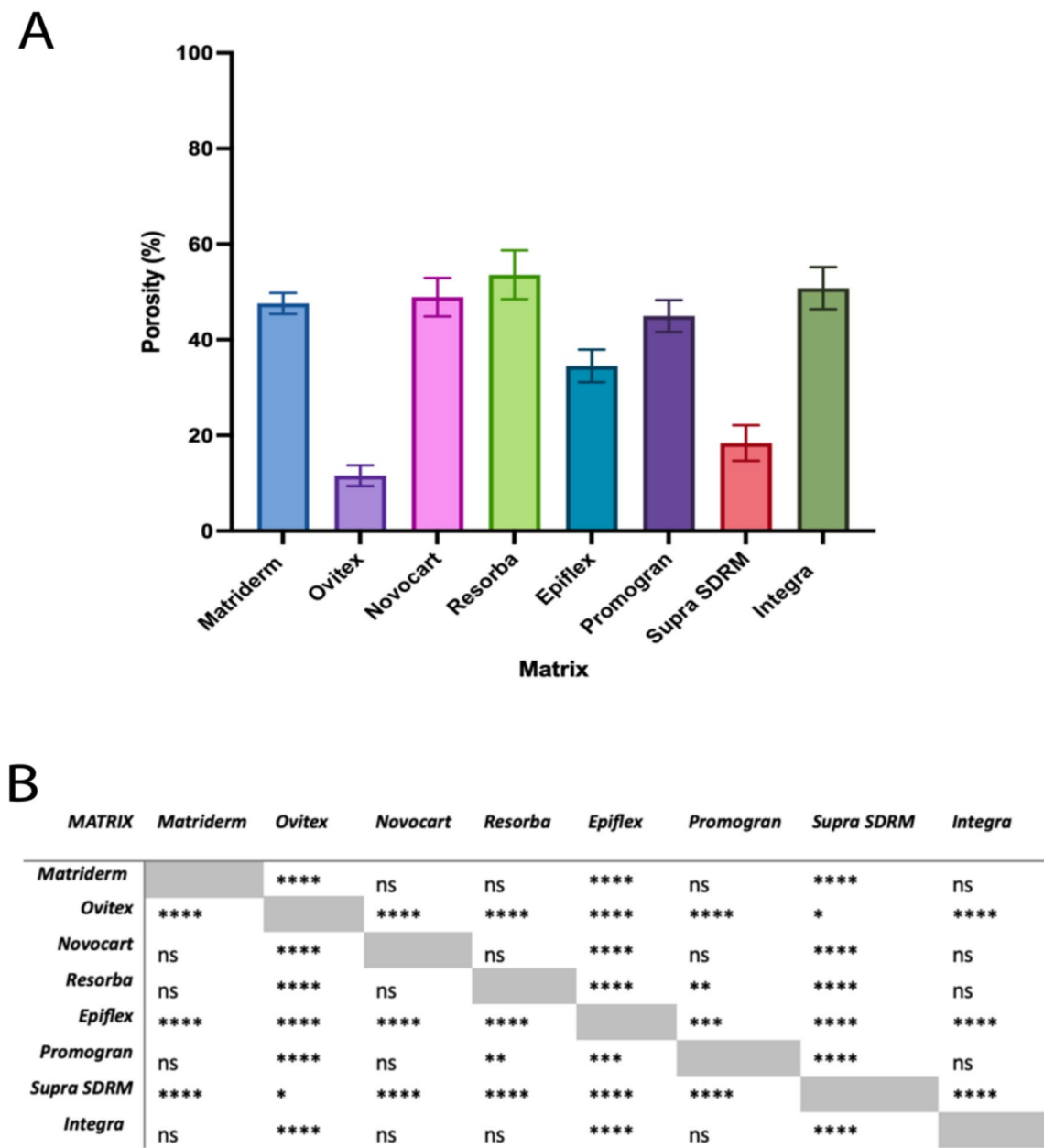


**Fig. 3** Apparent two-dimensional (2D) surface porosity of each matrix. **A** Bar graph representing surface porosity of the investigated matrices, calculated from SEM images as the percentage of image area not occupied by matrix material. Each bar represents the mean porosity value derived from six SEM images per matrix ( $n=6$  images per matrix). Bars represent mean  $\pm$  standard deviation (SD). **B** Overview of all pairwise p-value comparisons highlighting significant values evaluated by one-way ANOVA with Tukey's multiple comparisons test. Significance levels are indicated as non-significant (ns)= $p>0.05$ , \*= $p<0.05$ , \*\*= $p<0.01$ , \*\*\*= $p<0.001$ , \*\*\*\*= $p<0.0001$

and SupraSDRM® (range: 57.67  $\mu\text{m}$ , from 2.5 to 60.2  $\mu\text{m}$ ). In contrast, OviTex® presented the narrowest range (21.04  $\mu\text{m}$ , from 5.9 to 27.0  $\mu\text{m}$ ) and one of the lowest variances (15.1  $\pm$  4.2  $\mu\text{m}$ ), suggesting a more uniform pore structure. This uniformity is also observed in Promogran® (61.8  $\pm$  17.7  $\mu\text{m}$ ) and MatriDerm®

(42.0  $\pm$  15.6  $\mu\text{m}$ ), which show more consistent distributions across measured regions (Fig. 4). To facilitate a clearer understanding of the statistical comparisons, all pairwise p-values are summarized in the table adjacent to the graph. Matrices such as MatriDerm®, OviTex®,

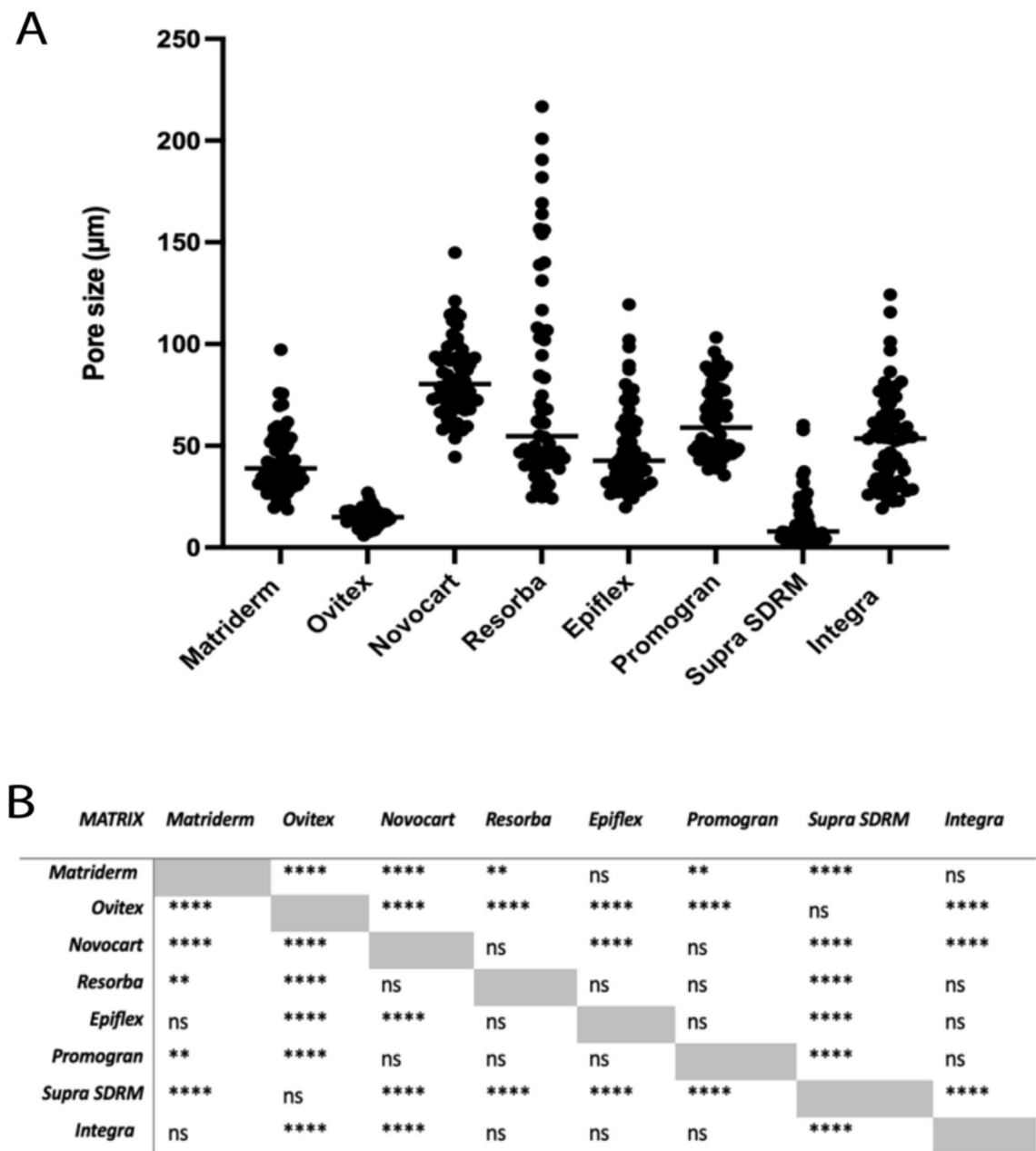


**Fig. 4** Surface 2D pore size distribution of each matrix. **A** Pore size distribution of the investigated matrices based on ten pore measurements per image across six SEM images per matrix (60 measurements per matrix in total). Pore size was defined as the longest visible pore diameter in two-dimensional SEM projections. **B** Quantitative comparison of pore size across matrices. Bars represent mean  $\pm$  SD. Statistical analysis was performed using one-way ANOVA with Tukey’s multiple comparisons test. Significance levels are indicated as (ns) =  $p > 0.05$ , \* =  $p < 0.05$ , \*\* =  $p < 0.01$ , \*\*\* =  $p < 0.001$ , \*\*\*\* =  $p < 0.0001$

and SupraSDRM<sup>®</sup> demonstrated the most frequent significant differences when compared to others.

**Alamar Blue cell vitality measurements**  
To evaluate ASC metabolic activity within the different matrices, an Alamar Blue assay was performed on day 7 post-seeding. The results are presented in Fig. 5 and indicate substantial variation in fluorescence intensity

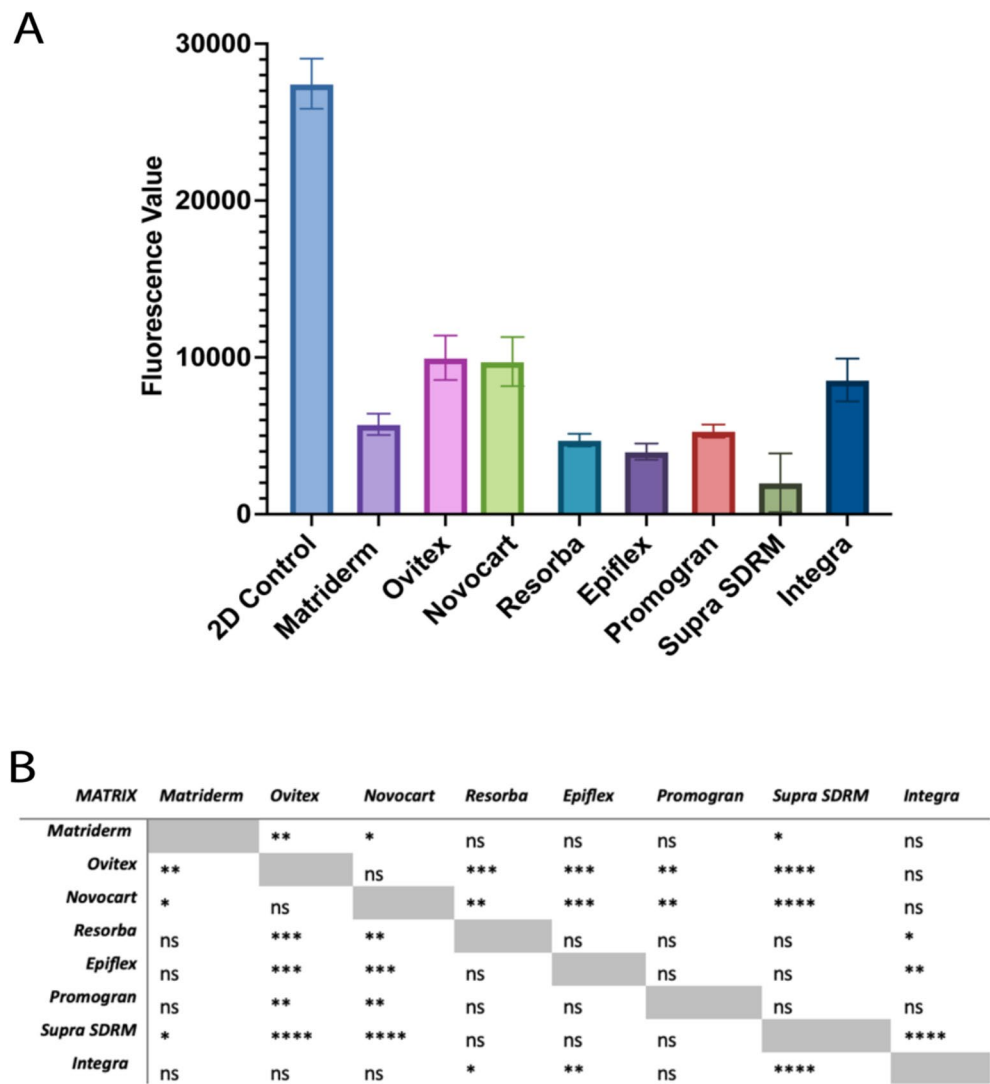


**Fig. 5** Alamar Blue assay results showing metabolic activity of ASCs 7 days post-seeding onto the investigated matrices and in 2D control conditions. **A** Bar graph representing background-corrected fluorescence intensity values, corresponding to cellular metabolic activity. Background correction was performed using matrix-only controls (matrices without cells). Bars represent mean  $\pm$  standard deviation (SD) of three independently seeded matrix samples per matrix type ( $N=3$ ). For each sample, technical fluorescence readouts were averaged prior to statistical analysis. **B** Statistical overview of comparisons of metabolic activity across matrices. Analysis was performed using one-way ANOVA with Tukey's multiple comparisons test. Significance levels are indicated as (ns) =  $p > 0.05$ , \* =  $p < 0.05$ , \*\* =  $p < 0.01$ , \*\*\* =  $p < 0.001$ , \*\*\*\* =  $p < 0.0001$

across the tested matrices. Statistically significant differences between groups are summarized in the according  $p$ -value table.

Among the investigated scaffolds, Integra<sup>®</sup>, OviTex<sup>®</sup> and Novocart<sup>®</sup> exhibited comparatively higher metabolic activity under the tested conditions. In contrast, SupraSDRM<sup>®</sup> and Epiflex<sup>®</sup> displayed markedly lower fluorescence signals, with SupraSDRM<sup>®</sup> only reaching approximately twice the fluorescence background levels.

MatriDerm<sup>®</sup>, Resorba<sup>®</sup> and Promogran<sup>®</sup> showed moderate and relatively consistent fluorescence values. Overall, the data indicate variability in ASC metabolic activity depending on the matrix type.

In addition to the matrix groups, a 2D control (ASCs cultured on tissue culture plastic) was included as a reference condition. Metabolic activity in the 2D control was markedly higher compared to all matrix groups.

## Discussion

In this study, eight commercially available acellular matrices were systematically compared regarding their microstructural characteristics and early ASC metabolic activity. The results demonstrate considerable variability between matrices, highlighting that scaffold architecture and composition influence early ASC–matrix interactions.

Macroscopically, differences in handling characteristics and apparent mechanical stability were observed between matrices during in vitro culture. Novocart®, OviTex®, and Epiflex® appeared comparatively more robust, whereas MatriDerm®, Integra®, and Resorba® showed more flexible behavior. SupraSDRM® and Promogran® exhibited structural changes under culture conditions, suggesting reduced stability in a hydrated environment. These observations align with prior reports emphasizing that matrix composition and cross-linking significantly affect mechanical integrity and degradation [52, 53]. However, our observations were not quantitatively assessed in the present study and should therefore be interpreted with caution.

SEM-based analysis revealed distinct differences in surface morphology and matrix architecture across all investigated materials. While several matrices, including MatriDerm®, Promogran®, Epiflex®, and Resorba®, exhibited comparable fibrous network structures, others showed clearly different structural characteristics. OviTex® demonstrated a multilayered architecture with reinforcing sutures, whereas SupraSDRM® appeared as a more homogeneous polymer-based structure with predominantly small pores.

Quantitative SEM image analysis further confirmed substantial variability in apparent surface porosity and pore size distribution. Resorba®, Integra®, Novocart®, MatriDerm®, and Promogran® exhibited higher apparent two-dimensional porosity values, whereas OviTex® and SupraSDRM® showed markedly lower porosity. In terms of pore size, Resorba® and Novocart® demonstrated the largest ranges, while OviTex® and SupraSDRM® exhibited smaller and more uniform pore structures.

When relating these structural characteristics to ASC metabolic activity, no single parameter alone fully explained the observed cellular response. While matrices such as Integra® and Novocart® combined relatively high porosity with relatively large pore sizes and showed high metabolic activity, other matrices did not follow this pattern. For instance, Resorba® exhibited high porosity and large pore sizes but only moderate metabolic activity. These findings are consistent with previous studies demonstrating that pore size and porosity alone are insufficient predictors of cellular response [22, 54]. In addition, parameters such as pore interconnectivity, heterogeneity,

and overall architectural organization play a critical role in regulating cell adhesion, migration and distribution, as well as nutrient diffusion and waste transport [25].

Furthermore, mechanical properties, including stiffness and viscoelasticity, as well as surface characteristics such as topography, wettability and biochemical composition, have been shown to influence cell behavior through mechanotransduction and cell–matrix signaling pathways [55–58]. These factors can affect not only early cell attachment and metabolic activity but also long-term processes such as differentiation and tissue remodeling [58].

In this context, the variability observed across matrices in the present study likely reflects the combined influence of multiple structural and compositional parameters rather than differences in pore size or porosity alone. These findings in the literature may help explain why matrices with similar pore size and porosity exhibited different metabolic activity in the present study.

A more detailed comparison of individual matrices further highlights differences between the eight analyzed ACMs. Integra® and Novocart® demonstrated consistently high metabolic activity, which aligns with their relatively favorable structural properties and their extensive characterization in previous studies [35, 36, 59]. In particular, Novocart® has been clinically established for matrix-assisted autologous chondrocyte transplantation (MACT), supporting its translational relevance in cartilage repair applications. Although previous investigations have primarily focused on chondrocyte-based use rather than stem cell-based approaches, the favorable ASC response observed in the present study suggests potential applicability beyond its current indication [35, 36, 60].

In addition to structural features, compositional features may contribute to these findings. Integra® contains collagen combined with chondroitin-6-sulfate, a sulfated glycosaminoglycan (GAG), which has been reported to influence scaffold hydration, elasticity, degradation kinetics, and growth factor retention [59, 61–63]. Such properties may support cell–matrix interactions by modulating biochemical signaling and local microenvironmental conditions [63].

Although MatriDerm® exhibited comparable structural characteristics, including relatively high apparent porosity and moderate pore size distributions, its metabolic activity remained lower than that of Integra®. Unlike Integra®, MatriDerm® consists of collagen and elastin, which may influence matrix elasticity, degradation behavior, and remodeling kinetics [63, 64]. Previous comparative studies between Integra® and MatriDerm® in regenerative applications have reported differences in resorption and tissue maturation despite similar overall architecture [65–67]. These compositional differences

may partly explain the distinct ASC response observed in the present study.

OviTex<sup>®</sup> exhibited high metabolic activity despite comparatively low apparent porosity and small pore sizes. Given its multilayered architecture, these findings cannot be directly compared with monolayer matrices. The observed metabolic activity may reflect altered cell distribution within the layered structure rather than uniform cell infiltration. Similar observations have been reported in other collagen-based and three-dimensional scaffold systems, where architecture, swelling behavior, and local pore organization contribute to heterogeneous cell distribution despite preserved overall viability [68]. However, in the absence of image-based validation, this interpretation remains speculative.

Promogran<sup>®</sup>, similar to MatriDerm<sup>®</sup>, demonstrated intermediate metabolic activity and was characterized by moderate porosity combined with relatively uniform pore distributions. Such balanced structural properties, comparable to those reported for collagen-based sponge-like scaffolds with interconnected and moderately sized pores, may support stable early ASC attachment and metabolic activity [69, 70]. However, these conditions did not reach the higher metabolic levels observed in Integra<sup>®</sup> and Novocart<sup>®</sup>, suggesting that additional compositional or architectural features may contribute to enhanced cellular response.

SupraSDRM<sup>®</sup> demonstrated low apparent porosity, small pore sizes, and the lowest metabolic activity among all matrices. According to manufacturer-reported specifications, the matrix is described as possessing a bimodal pore structure designed to support wound fluid management and skin cell migration. In the present study, however, SEM analysis predominantly revealed small and relatively uniform pores, with only limited evidence of a bimodal architecture. This discrepancy may reflect image-based sampling limitations or differences between manufacturer-defined applications and the present ASC-based culture setting.

The combination of low porosity, small pore size, and reduced metabolic activity suggests that the structural characteristics of SupraSDRM<sup>®</sup> may be less favorable for early ASC colonization under three-dimensional culture conditions [71]. Similar considerations may apply to Promogran<sup>®</sup>, which, like SupraSDRM<sup>®</sup>, is primarily intended for wound-healing applications rather than cartilage regeneration. The comparatively lower metabolic activity observed for both matrices may therefore reflect differences between scaffold design goals for skin repair and the structural requirements of ASC-based cartilage tissue engineering [72].

Resorba<sup>®</sup> exhibited comparatively high apparent porosity and large pore size variability, but only moderate

metabolic activity. This discrepancy may indicate that pore heterogeneity influences cell distribution within the scaffold, potentially affecting early metabolic read-out despite favorable pore dimensions [25, 73]. However, no direct mechanistic data are available to prove that heterogeneity really has impaired uniform seeding and distribution.

Epiflex<sup>®</sup> showed comparatively low metabolic activity despite maintaining structural integrity during culture. Previous studies have described favorable biocompatibility and clinical applicability of human-derived matrices such as Epiflex<sup>®</sup>, highlighting advantages including preserved extracellular matrix integrity, low immunogenicity, controlled biodegradability, lot-to-lot consistency, and validated sterilization processes [3, 40]. However, under the present in vitro conditions, Epiflex<sup>®</sup> demonstrated comparatively limited early ASC metabolic activity [74]. These findings suggest that, despite its established clinical performance, the ASC response to Epiflex<sup>®</sup> may depend strongly on the specific cellular and experimental context.

The inclusion of a two-dimensional control demonstrated markedly higher metabolic activity compared to all matrix groups. This finding highlights fundamental differences between monolayer and scaffold-based culture systems and emphasizes that reduced signal intensity in three-dimensional environments does not necessarily reflect reduced viability but rather altered assay behavior and cell distribution [75].

Reported optimal pore sizes for cartilage tissue engineering vary widely in the literature, typically ranging from approximately 50–300 µm, depending on the cell type and scaffold system [25, 76–79]. Experimental studies further suggest that optimal pore size may be cell-type dependent. For example, larger pores in the range of 200–400 µm have been associated with enhanced ASC chondrogenesis and improved nutrient transport, whereas smaller pore sizes may better preserve the phenotype of native chondrocytes [22, 80].

While several matrices in the present study fall within these ranges, the observed variability in metabolic activity indicates that such general thresholds cannot be directly translated to ASC-based systems. Furthermore, variations in measurement techniques and definitions of porosity limit direct comparison with previous studies.

Notably, only limited literature exists regarding the specific interaction of ASCs with clinically available acellular matrices. While several studies involve Novocart<sup>®</sup>, Integra<sup>®</sup>, and MatriDerm<sup>®</sup> with mesenchymal-derived stem cells (MSCs), bone marrow-derived stem cells (BMSCs) and ASCs [60, 81–83], relatively few have focused specifically on ASC metabolic activity using comparable experimental conditions. Among the

investigated matrices, Integra® appears to be the most extensively evaluated in ASC-based in vitro and in vivo studies [81, 82]. This highlights its relevance for stem cell-based regenerative applications. Many of the remaining matrices are primarily described in clinical contexts and application-specific reports, as summarized in Table 2.

According to our knowledge, no publication to date presents an evaluation of optimal pore sizes specifically for stem cells—particularly ASCs—on clinically available acellular matrices in relation to ASC response for cartilage regeneration. Existing recommendations regarding optimal pore dimensions are largely derived from bone or cartilage tissue engineering studies involving mixed cell populations and different scaffold systems. Consequently, the pore size ranges identified in the present study should be interpreted as comparative descriptors rather than definitive thresholds for ASC-based applications.

The observed variability in ASC metabolic activity among matrices with comparable pore sizes or porosity values further supports the concept that multiple scaffold parameters contribute to cellular response. Beyond pore architecture, factors such as interconnectivity, surface topography, stiffness, and biochemical composition likely influence matrix–cell interactions and may explain differences between structurally similar matrices, such as Integra® and MatriDerm®.

Several methodological limitations should be considered when interpreting these findings. Although SEM-based ImageJ analysis enabled quantitative comparison of matrix morphology, the derived porosity values represent apparent two-dimensional surface measurements rather than true volumetric porosity. Likewise, pore size measurements were obtained from two-dimensional projections and should therefore be regarded as relative descriptors of scaffold architecture. Image-based measurements also reflect morphometric sampling rather than fully independent biological replicates. In addition, SEM analysis required slight variation in magnification to adequately capture matrix-specific structures, limiting strict standardization across all materials. However, to fully visualize the internal architecture, techniques such as  $\mu$ CT—as mentioned before—would offer a more complete and accurate representation. This approach could reveal critical factors such as pore interconnectivity and overall scaffold architecture, which are essential for in vivo performance, where cell migration, nutrient diffusion, and vascular ingrowth depend on a continuous 3D network [1, 84].

The replicate structure of this study should also be interpreted cautiously. ASCs were pooled prior to experimental use, preventing assessment of donor-specific variability. Furthermore, only female donors from a single

anatomical harvest site were included, which may reduce biological heterogeneity.

In addition, direct comparison of OviTex® with the remaining matrices should be interpreted cautiously due to its multilayered architecture and reinforcing sutures. Unlike monolayer collagen matrices, the layered configuration may influence cell retention, distribution, and SEM-based surface analysis. Consequently, apparent porosity and pore size values derived from two-dimensional imaging may not fully reflect the internal structure of this scaffold.

The inclusion of a 2D control emphasized the marked differences between monolayer and scaffold-based culture systems. Higher metabolic activity in 2D likely reflects differences in cell spreading, nutrient accessibility, and assay response rather than superior biological compatibility [75].

Finally, metabolic activity was evaluated exclusively at day 7 post-seeding, providing only a limited snapshot of early cell–matrix interaction. This design does not distinguish between initial attachment, proliferation, and long-term cellular adaptation. Complementary assays, such as live/dead staining, DNA quantification, or differentiation analyses, would provide a more comprehensive assessment of ASC behavior on these matrices. In addition, mechanical properties under hydrated conditions were not quantified, despite qualitative differences in handling behavior observed during culture. These factors should be addressed in future studies to better define scaffold suitability for ASC-based cartilage tissue engineering.

## Conclusion

In conclusion, this study provides a comparative screening of eight commercially available acellular matrices with respect to microstructural characteristics and early ASC metabolic activity under standardized in vitro conditions. Considerable variability was observed between matrices, demonstrating that apparent porosity and pore size alone do not fully explain ASC response. Instead, the findings suggest that additional parameters, including scaffold composition, architectural organization, pore heterogeneity, and surface-related properties contribute to early cell–matrix interactions.

Among the investigated matrices, Novocart®, Integra®, and MatriDerm® demonstrated the most favorable balance between structural characteristics and early ASC metabolic activity. In contrast, matrices such as SupraSDRM® and Epiflex® showed lower metabolic activity under the tested conditions, while interpretation of OviTex® requires caution due to its multilayered architecture and limited structural comparability.

Importantly, this study represents a preliminary evaluation focused on early ASC–matrix compatibility rather

than definitive assessment of cartilage regeneration potential. The results emphasize the need for multiparametric scaffold characterization beyond SEM-derived morphology alone and highlight the importance of considering matrix-specific composition and architecture when selecting scaffolds for regenerative applications.

Given that most of the tested matrices have not previously been evaluated with ASCs, our ability to compare findings with existing literature remains limited—further emphasizing the novelty and relevance of this study's findings.

Future investigations should include long-term culture models, differentiation assays, histological validation, and three-dimensional imaging approaches to better understand scaffold colonization, remodeling, and functional integration.

Building on the use of clinically established matrices, this work provides a foundational comparison of their structural characteristics and early biological responses, providing insights for further optimization of scaffold selection in ASC-based cartilage tissue engineering.

#### Abbreviations

|         |                                                        |
|---------|--------------------------------------------------------|
| ACM     | Acellular matrix                                       |
| ASCs    | Adipose-derived stem cells                             |
| BMSCs   | Bone marrow-derived stem cells                         |
| DIZG    | Deutsches Institut für Zell-und Gewebeersatz           |
| DPBS    | Dulbecco's phosphate buffered saline                   |
| ECM     | Extracellular matrix                                   |
| FIB-SEM | Focused ion beam scanning electron microscopy          |
| IgG     | Immunoglobulin type G                                  |
| MACI    | Matrix-associated chondrocyte implantation             |
| MAT     | Matrix-assisted autologous chondrocyte transplantation |
| MSCs    | Mesenchymal stem cells                                 |
| Ref     | Reference number                                       |
| SD      | Standard deviation                                     |
| SEM     | Scanning electron microscopy                           |

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#### Author contributions

J.S. investigation, conceptualization, formal analysis, data curation, visualization, writing—original draft; P.A. and C.K. writing—review & editing, visualization, validation, supervision; A.K. visualization, data curation; P.S.W. and R.G. supervision; W.D. conceptualization, writing—review & editing, validation, supervision, funding acquisition.

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#### Data availability

All data are available upon reasonable request to the corresponding author.

#### Declarations

##### Ethics approval and consent to participate

This study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Ethics Committee ("Ethikkommission der medizinischen Fakultät") of Ludwig Maximilian University of Munich (Project-ID 23-0584).

#### Consent for publication

Patients were informed about the use of their cells and provided written informed consent for participation in the study.

#### Competing interests

The authors declare no competing interests.

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