Dorsal skinfold chamber models in mice

Rücken hautkammermodelle bei Mäusen

Abstract

Background/purpose: The use of dorsal skinfold chamber models has substantially improved the understanding of micro-vascularisation in pathophysiology over the last eight decades. It allows in vivo physiological studies of vascularisation over a continuous period of time. The dorsal skinfold chamber is an attractive technique for monitoring the vascularisation of autologous or allogenic transplants, wound healing, tumorigenesis and compatibility of biomaterial implants. To further reduce the animals’ discomfort while carrying the dorsal skinfold chamber, we developed a smaller chamber (the Leipzig Dorsal Skinfold Chamber) and summarized the commercial available chamber models. In addition we compared our model to the common chamber.

Methods: The Leipzig Dorsal Skinfold Chamber was applied to 66 C57Bl/6 female mice with a mean weight of 22 g. Angiogenesis within the dorsal skinfold chamber was evaluated after injection of fluorescein isothiocyanate dextran with an Axio Scope microscope. The mean vessel density within the dorsal skinfold chamber was assessed over a period of 21 days at five different time points. The gained data were compared to previous results using a bigger and heavier dorsal skinfold model in mice. A PubMed and a patent search were performed and all papers related to “dorsal skinfold chamber” from 1st of January 2006 to 31st of December 2015 were evaluated regarding the dorsal skinfold chamber models and their technical improvements. The main models are described and compared to our titanium Leipzig Dorsal Skinfold Chamber model.

Results: The Leipzig Dorsal Skinfold Chamber fulfils all requirements of continuous in vivo models known from previous chamber models while reducing irritation to the mice. Five different chamber models have been identified showing substantial regional diversity. The newly elaborated titanium dorsal skinfold chamber may replace the pre-existing titanium chamber model used in Germany so far, as it is smaller and lighter than the former ones. However, the new chamber does not reach the advantages of already existing chamber models used in Asia and the US, which are smaller and lighter.

Conclusion: Elaborating a smaller and lighter dorsal skinfold chamber allows research studies on smaller animals and reduces the animals’ discomfort while carrying the chamber. Greater research exchange should be done to spread the use of smaller and lighter chamber models.

Keywords: angiogenesis, dorsal skinfold chamber, fat graft, intravital fluorescence microscopy

Zusammenfassung

Einleitung: Die Verwendung der Rückenhautkammer hat innerhalb der letzten 8 Jahrzehnten wesentlich zum Verständnis der Mikrozirkulation beigetragen. Diese Technik erlaubt in vivo Studien der Vaskularisation über einen kontinuierlichen Zeitraum. Die Rückenhautkammer bietet eine attraktive Möglichkeit, um die Vaskularisation von autolog oder allogen transplantiertem Gewebe, der Wundheilung, der Tumorgenese oder der Kompatibilität von Biomaterialien zu untersuchen. Um das...
Leid der Tiere, die im Rahmen dieser Rückenhautkammermodelle Verwendung finden, zu reduzieren, haben wir ein kleineres Kammermodell entwickelt (die Leipziger Rückenhautkammer). Zudem wurde eine Übersicht der herkömmlich angewandten Rückenhautkammermodelle zusammengestellt und diese mit unserem Leipziger Modell verglichen. **Methoden:** Die Leipziger Kammer wurde an 66 weiblichen C57Bl/6 Mäusen mit einem mittleren Gewicht von 22 g anwendet. Unter Injektion von fluoreszein Isothiozyanid Dextran wurde die Angiogenese mit einem Axio Scope evaluiert. Die mittlere Perfusionsrate wurde über 21 Tage an fünf definierten Zeitpunkten erhoben. Die Daten wurden mit denen, welche unter Anwendung der herkömmlichen Kammer generiert wurden, verglichen. Zudem führten wir eine PubMed Recherche sowie eine Patentsuche unter Verwendung der Schlagwörter „dorsal skinfold chamber“ für den Zeitraum 1. Januar 2006 bis 31. Dezember 2015 durch und untersuchten die entsprechenden Paper auf die erwähnten Rückenhautkammermodelle sowie auf deren technischer Angaben. Die meist genutzten Modelle wurden mit dem Leipziger Kammermodell verglichen. **Ergebnisse:** Das Leipziger Kammermodell erfüllt die Erfordernisse für Kammermodelle für kontinuierliche in vivo Untersuchungen, dabei erreichten wir jedoch eine deutliche Minderung des Leides der Versuchstiere. Es wurden fünf verschiedene Kammermodelle identifiziert, die deutliche Unterschiede in ihrer regionalen Anwendung finden. Die neu entwickelte Leipziger Rückenhautkammer könnte die in Deutschland überwiegend genutzte Titan-Rückenhautkammer ersetzen, die kleiner und leichter ist als die herkömmliche. Allerdings bestehen Kammermodelle, die im asiatischen und amerikanischen Raum genutzt werden, mit einem noch geringeren Gewicht und niedrigerer Größe. **Fazit:** Die Entwicklung einer kleineren und leichterer Rückenhautkammer erlaubt die Anwendung dieses Kammermodells an kleineren Tieren und mindert deren Leiden. Ein größerer Austausch über die Verwendung unterschiedlicher Kammermodelle kann dazu beitragen, die Anwendung kleinerer und leichterer Kammern zu propagieren. **Schlüsselwörter:** Angiogenese, Rückenhautkammern, Fettgewebstransplantation, intravitale Fluoreszenzmikroskopie

**Introduction**

Understanding the physiology and pathophysiology of microcirculation has always been intriguing as dysfunctional microcirculation can lead to diseases and plays an important role in inflammation. To assess microcirculation thoroughly, in vivo models were established. The first in vivo studies were done in 1882 by Kühne and co-workers using the mesenterium because of its dense vessel system [1]. Though, this tissue is not easily accessed and does not allow continuous analysis. Sandison was first to develop a transparent chamber to study microcirculation in the rabbits‘ ear in 1929 [2] and was followed by Clark and co-workers in 1930 and later by Algire and co-workers, who adapted the model to smaller animals establishing a dorsal skinfold chamber for the mouse in 1943 [3]. Along the time, observation chambers were equally established on rats and hamsters [4], [5], [6], [7], prepared as well on the animals‘ ear, cheek pouch or back [8], [9]. Since then the dorsal skinfold chamber became one of the main observation window models allowing continuous in vivo analysis of hemodynamic parameters such as functional vessel density and erythrocyte velocity over a period of time of about 3 weeks. In 1993 Lehr published on the use of the dorsal skinfold chamber in nude mice [10]. Thereafter dorsal skinfold chambers became increasingly popular. Visualizing tumours in animals and analysing various aspects of cancer physiology and vascularization, cell migration and metastasis is possible in the dorsal skinfold chamber [11], [12]. In addition, wound healing [13], thrombosis [14], [15] and volume therapy [16] studies are performed in dorsal skinfold chamber models. Currently the dorsal skinfold chamber model is broadly used in the field of biomaterial research, especially in the analysis of their biocompatibility [17], [18], [19], [20], [21], [22], [23].

**Potential analyses using dorsal skinfold chambers**

The dorsal skinfold chamber offers many possibilities for microvascular research: Repeated measurements in the
same animal over a period of time of 3 weeks can be performed [8]. The observations can be done through transillumination microscopy to analyse the microvascular diameter and functional vessel density. Epi-illumination fluorescence microscopy allows for studying distinct cellular and molecular aspects by using fluorescent agents. Rhodamin 6G (100 µl of rhodamine-6-G, 0.05%, intravenously; Sigma-Aldrich, Buchs, Switzerland) illustrates the leukocyte/endothelial cell interaction by staining leukocytes. This allows for identification of rolling leukocytes, which are defined as leukocytes with lower velocity than erythrocytes [24]. Fluorescein isothiocyanate (FITC)-labelled dextran, i.e. 0.4 mg 150 kDa FITC-dextran (Sigma Aldrich, St. Louis, MO) in 100 µl PBS intravenously, depicts the vascular permeability (extravasation) and allows for visualization of blood vessels (Figure 1). Equally, Texas Red (0.1 ml of 10 mg/ml intravenously; Invitrogen, Leek, The Netherlands) can be used to mark the blood vessels [25]. This permits blood flow analysis and vascular volume measurement, which can be done with the Velocity System Improvision (Perkin Elmer, Waltham, Massachusetts) [25].

**Figure 1: Vascularisation seen after intravenous injection of 0.5 ml FITC-labelled dextran 5% [150 kDa], 5x objective, Axio Vert Zeiss, AxioCam mR 5, Leipzig Dorsal Skinfold Chamber model**

The discovery of green fluorescent protein (GFP), and its derivatives such as blue, cyan, green, yellow, red, and far red fluorescent protein allows for creation of transgenic cell lines or animals that harbour GFP or its spectral variants under the control of the promoter of a gene of interest [26], [27]. By using these markers as a monitor system it is possible to monitor cells, tumour growth or metastasis development within the dorsal chamber. Moreover, fluorescence resonance energy transfer microscopy can be used in dorsal skinfold chambers, which permits the determination of the approach between two molecules within several nanometres. Hence, direct molecular interactions can be studied in vivo. Recently, Thunemann and colleagues gave an excellent description of this technique [27]. Furthermore, several add-ons are being developed to enlarge the portfolio of evaluation techniques with the dorsal skinfold chamber: Biel et al. introduced hyperspectral oxygen imaging within the dorsal skinfold chamber that allows for evaluation of tumour response to anti-angiogenic agents and simultaneously assesses the vascular density of the tumour and its oxygenation status [28]. Makale and his team developed a two-sided dorsal skinfold chamber with a planar oxygen sensor on one side of the skinfold to measure oxygen levels in the sandwiched subcutaneous tissue [29], [30]. Nishimura and co-workers combined the dorsal skinfold chamber technique and multiphoton laser scanning microscopy to analyse the revascularization process of pancreatic islet cells [25]. With the use of laser scanning confocal microscopy three-dimensional reconstruction of the microvascular architecture can be done [31].

In 2010 Erten and colleagues presented a new non-metallic Delrin® acetal polyoxymethylene chamber model, that permits MRI chamber studies [32].

**Refinement of dorsal skinfold chambers**

Given the huge increase of applications for dorsal skinfold chamber studies and the further development of inbred animal strains with low body weight [33], improving the dorsal skinfold chamber model itself in order to reduce the animals’ discomfort while carrying the chamber is a necessary goal. However, few studies are published discussing the development of smaller dorsal skinfold chambers. According to the three principles of refinement, reduction, and replacement of humane experimental techniques acclaimed by Russel and Burch in 1959 [34] we aimed to refine the dorsal skinfold chamber to reduce the animals’ discomfort by developing a smaller and lighter dorsal skinfold chamber model regarding manipulation, weight, proportion, biocompatibility to the regularly used model in Germany [10], [35]. Moreover, we performed a PubMed search of existing chamber models and compared them.

**Material and methods**

**General technical data of dorsal skinfold chamber models**

Dorsal skinfold chambers are generally made of two complementary plates sandwiching a laterally positioned fold of dorsal skin [29], [30], [35]. At the centre is an approximately 1 cm diameter circular observation area, where the skin is removed and covered by a round cover glass, that is fixed by a snap ring (Figure 2) [35], [36]. The frames of the dorsal skinfold chamber were originally made of stainless steel or aluminium with a Teflon coat-
Elaboration of the Leipzig Dorsal Skinfold Chamber

In cooperation with the Centre of Biotechnology and Biomedicine Leipzig, a new titanium dorsal skinfold chamber (Figure 2, Figure 3, and Figure 4b) has been developed and applied to a murine C57BL/6 dorsal skinfold chamber study of angiogenesis of autologous fat transplants (licence for animal testing approved by the local governmental animal care committee of Saxony (TVV 28/13) [37]. The study was conducted in accordance with the German legislation on protection of animals and the NIH (National Institute of Health) Guidelines for the Care and Use of Laboratory Animals.

Mounting a dorsal skinfold chamber

To achieve best operative results, mice should have a minimal weight of 20 g. They were anaesthetized through an intraperitoneal injection with ketamine (100 mg/kg bw; Ketamine™ 10%, Bela-Pharm, Vechta, Germany) and xylazine (25 mg/kg bw; Rompun® 2%; Bayer Health Care, Leverkusen, Germany). The preparation was done with sterile instruments. The titanium dorsal chamber can be autoclaved.

The mice’s backs were shaven and afterwards chemically depilated (Pilca Med; Olicia, Hamburg, Germany). To obtain medial position of the skinfold chamber, a midline was drawn with a sterile skin pen. The back plate of the dorsal skinfold chamber was fixed with six 4/0 polyfil resorbing sutures. Two incisions were made through the skin according to the two lower screws, so that the back plate had the right position and the dorsal skin was accurately stretched in order to correctly prepare the observation window. The animal’s side was transilluminated to define the excision site of the observation window. Preparation was done with a stereomicroscope.

The diameter of the preparation was slightly larger than the observation window diameter to prevent tissue compression and thereafter compromised blood supply [8]. Following this advice, the development of granulation tissue was diminished and the chamber lasted longer. Thereby the subcutaneous tissue, the panniculus carnosus and the retractor muscle were excised.
The preparation window was kept moist with sterile normal saline. Afterwards, the anterior chamber was fixed with titanium nuts. The space between the two retractors was about 2.4 mm. A coverslip is finally placed on the observation window and was fixed with a snap ring (Figure 3).

For recovery of the operation, the animal was placed on a 32°C warm plate until it awoke from anaesthesia. For the following three days after dorsal skinfold chamber implantation analgesics were added to the water. No changes of eating or sleeping habits were observed in the animals. The mice’s mobility was not constrained after mounting the chamber.

**Intravital microscopy**

Intravital florescence microscopy was performed using an Axio Vert microscope from Zeiss (Zeiss, Jena, Germany) with a 100 W, 12 V halogen lamp and a Zeiss filter set (BP 450–490, FT 510, LP 520) for blue and green and ultraviolet light measurements after fluorescein isothiocyanate (FITC) injection. Microscopy was performed using 5x and 20x long distance objectives from Zeiss (Zeiss, Axiotech Vario 100 HD, Acroplan 20X0.5 W, Zeiss, Jena, Germany) with a crop factor of 0.4 for the 20x magnification (Figure 1).

To obtain best results during intravital microscopy, the animal is sedated and placed on a Plexiglas holder, where the animal rests in a lateral position during the examination. To analyse the vascularisation 0.5 ml of FITC-labelled dextran (150,000 MG, Sigma-Aldrich) are injected into a lateral vein of the mouse-tail after disinfection. To facilitate the identification of the vein in a black 6 mouse, the tail can be incubated for 5 minutes in 30°C warm water to dilate the veins prior to injection. Immediately after successful injection the examination can be performed.

**MEDLINE research and patent research to dorsal skinfold chamber models**

We performed a PubMed search and a patent search to identify dorsal skinfold chamber models. The PubMed research with the terms “*dorsal* *skinfold* *chamber*” resulted in 368 hits. The paper examination was restricted to the years 2006 till 2016: A total of 231 papers were found and analysed.

Among the analysed papers we identified the animal model, material of the chamber and the originating country.

The patent search was done using the German patent website [38] with the terms “dorsal skin chamber”, “dorsal skinfold chamber”, “dorsal skinfold window”, “*dorsal* *window*”, and “Rückenhautkammer”, which is the German word for “dorsal skinfold chamber”.

**Results**

**The Leipzig Dorsal Skinfold Chamber**

The average operation time with autologous fat transplantation takes 28 min, the dorsal skinfold preparation without fat transplant excision lasts for 25 min. The chamber in the mouse can be used immediately and does not require a recovery day. About 8% of the operated animals show inflammation signs within the observation window, as oedema formation or vasodilatation. In some rare cases, small air pockets occur below the cover glass. In these cases, the cover glass was removed and physiological saline solution was added below the cover glass.

Microscopic analysis of the blood vessels showed a physiologically stable vascular bed within the observation window. Moderate hyperaemia was seen within the first 24 hours after the implantation but subsides within a day or two.
Table 1: Data for different dorsal skinfold chamber models used in mice

| Model          | Material | Weight [g] | Height [mm] | Width [mm] | Flange angle [°] | Observation window diameter [mm] | Literature |
|----------------|----------|------------|-------------|------------|------------------|----------------------------------|------------|
| IROLA Chamber  | titanium | 3.8        | 30          | 35         | 30               | #                                | [47]       |
| Leipzig Chamber| titanium | 2.3        | 23.7        | 31.5       | 30               | 10.7                             | [37]       |
| APJ Chamber, small | titanium | #          | 24.63       | 27.18      | 45               | 12                               | [39, 48]  |
| Asia           | Duracon™ | 1.6        | 33.3        | 36.0       | 48               | 11                               | [43]       |
| Sweden         | acrylic glass | 0.6      | 23          | #          | #                | 12                               | [44]       |

# Data not available

The back chamber model usually cannot be used longer than 3 weeks because the elasticity of the skin reduces over time and the skin shrinks, leading to a deterioration of the observation window [8].

MEDLINE search: dorsal skinfold chamber models used in mice

Among all examined papers, 43 papers were excluded, as they did not involve mouse species. The remaining 189 papers were mouse dorsal chamber studies; 54 papers did not specify the chosen dorsal skinfold chamber model, 120 papers mentioned that the chamber model was made of titanium, 5 were made of aluminium. Only 10 papers reported using a non-metallic chamber in mice. These chambers were made of polyacetal resin, polyvinyl chloride plates, or Delrin®. Interestingly, studies from Germany, Austria and Switzerland, which made up 63% of all analysed studies, were all performed with titanium frames, mostly referring to the model presented by Lehr et al. or Laschke et al. [10], [35] as presented in Figure 4a. American research groups also use a titanium frame (mostly from APJ Trading) [39], that is smaller than the German one. Asian researchers published on the non-metallic dorsal skinfold chamber [25], [40], [41], [42], [43]. A specific PubMed search came up with one Swedish paper dating back to 1997 presenting a Plexiglas variation of the dorsal chamber [44]. Technical data, if available, are given in Table 1.

Patent research

Only 4 different patents were found (US20140121493A1, US20110173709A1 = WO002008108993A1, and DE 19814674 A1), but, though related to dorsal skinfold chambers, these patents do not describe a new chamber model. The German patent describes a technique to perform MRI scans using a skinfold chamber that has been used in several studies performed in Munich [45], [46].

Discussion

In comparison with the other presented models, the Leipzig Dorsal Skinfold Chamber fulfils the aim of refining and reducing the animals’ discomfort carrying the chamber when compared to the model that is widely used in Germany. However, the American titanium chamber outperforms the Leipzig Dorsal Skinfold Chamber in terms of frame (area 26% smaller than the commonly used German chamber and about 10% smaller than the Leipzig model) while having a similar sized observation window. When compared to the non-metallic models from Asia, the titanium frames are still inferior because of their higher weight and their disadvantage of not being compatible for MRI studies.

Surprisingly, no larger consent exists in the use of different dorsal skinfold chamber models. The mostly used chamber model comes along with the heaviest weight and largest frame.

In summary, the dorsal skinfold chamber is an ideal model to study angiogenesis while satisfying the need for intravital continuous measurements, and allowing analysis of diverse tissues and textures. The long history of application of this model underlines its high value in angiogenesis and in vitro assessment. Refinement of this exclusive model is repeatedly done melting novelty in biotechnology and medicine. The presented Leipzig Dorsal Skinfold Chamber allows similar studies as with its predecessor model but is smaller and lighter. Nonetheless, the currently used models in Germany do not completely satisfy the requirements of refinement for animal use as described by Russel and Burch [34]. Greater scientific exchange is necessary to spread the use of the already existing smaller and lighter dorsal skinfold chamber models.

Notes

Competing interests

We confirm that there are no known conflicts of interest associated with this publication and there has been no significant sponsorship or funding arrangements for this work that could have influenced its outcome.

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References

1. Kuhne W. Untersuchungen aus dem Physiologischen Institut der Universität Heidelberg. Vol. 2. Heidelberg: Nabu Press; 2010.

2. Sandison JC. A new method for the microscopic study of living growing tissues by the introduction of a transparent chamber in the rabbit’s ear. Anat Rec. 1924;26:4(2):281-7. DOI: 10.1002/ar.1090280403

3. Algire GH, Legallais FY. Recent developments in the transparent-chamber technique as adapted to the mouse. J Natl Cancer Inst. 1949 Oct;10(2):225-3.

4. Fulmer RI, Cramer AT, Liebelt RA, Liebelt AG. Transplantation of cardiac tissue into the mouse ear. Am J Anat. 1963 Sep;113:273-85. DOI: 10.1002/aja.101130206

5. Funk W, Endrich B, Messmer K. A novel method for follow-up studies of the microcirculation in non-malignant tissue implants. Exp Reg Med (Berl). 1986;186(4):259-70. DOI: 10.1007/BF01852303

6. Papenfuss HD, Gross JF, Intaglietta M, Treese FA. A transparent access chamber for the rat dorsal skin fold. Microvasc Res. 1979 Nov;18(3):311-8. DOI: 10.1016/0026-2862(79)90039-6

7. Greenblatt M. Hamster cheek pouch chamber: homograft studies of normal and neoplastic tissues. Prog Exp Tumor Res. 1972;16:380-95. DOI: 10.1159/000393383

8. Menger MD, Laschke MW, Vollmar B. Viewing the microcirculation through the window: some twenty years experience with the hamster dorsal skinfold chamber. Eur Surg Res. 2002 Jan-Feb;34(1-2):83-91. DOI: 10.1159/000048893

9. Endrich B, Asaišk K, Götz A, Messmer K. Technical report—a new chamber technique for microvascular studies in unanesthetized hamsters. Exp Reg Med (Berl). 1980;177(2):125-34. DOI: 10.1007/BF01851841

10. Lehr HA, Leunig M, Menger MD, Noite D, Messmer K. Dorsal skinfold chamber technique for intravital microscopy in nude mice. Am J Pathol. 1993 Oct;143(4):1055-62.

11. Baron VT, Welsh J, Abedinpour R, Borgan R. Intravital microscopy in the mouse dorsal skinfold chamber. Eur J Surg. 2002 Jan-Apr;34(1-2):83-91. DOI: 10.1159/000048893

12. Reeves KJ, Hurrell JE, Cecchini M, van der Pluijm G, Down JM, Eaton CL, Hamdy F, Clement-Lacroix P, Brown NJ. Prostate cancer cells home to bone using a novel in vivo model: modulation by the integrin antagonist GLPG0387. Int J Cancer. 2015 Apr 1;136(7):1731-40. DOI: 10.1002/ijc.29165

13. Machado MJ, Mitchell CA. Temporal changes in microvessel leakage during wound healing diagnosed by in vivo fluorescence recovery after photobleaching. J Physiol. 2011 Oct 1;589(Pt 19):4681-96. DOI: 10.1111/j.1469-7793.2011.08355

14. Boulaffail Y, Lamrani L, Rouzaud MC, Loyau S, Jandrot-Perrus M, Bouton MC, Ho-Tin-Noé B. The mouse dorsal skinfold chamber as a model for the study of thrombosis by intravital microscopy. Thromb Haemost. 2012 May;107(5):962-71. DOI: 10.1160/TH11-10-0705

15. Crescente M, Thomas GM, Demers M, Voorhees JR, Wong SL, Ho-Tin-Noé B, Wagner DD. ADAMTS13 exerts a thrombolytic effect in microcirculation. Thromb Haemost. 2012 Sep;108(3):527-32. DOI: 10.1160/TH12-01-0046

16. Schreier B, Börner S, Völker K, Gambaryan S, Schäfer SC, Kuhlenbrodt P, Gessner B. Kuhn M. The heart communicates with the endothelium through the guanylyl cyclase-A receptor: acute handling of intravascular volume in response to volume expansion. Endocrinology. 2008 Aug;149(8):4193-9. DOI: 10.1210/en.2008-0212

17. Aubin K, Vincent C, Proulx M, Mayrand D, Fradette J. Creating capillary networks within human engineered tissues: impact of adipocytes and their secretory products. Acta Biomater. 2015 Jan;11:333-45. DOI: 10.1016/j.actbio.2014.09.044

18. Doyle ME, Perley JP, Shalak TC. Bone marrow-derived progenitor cells augment venous remodeling in a mouse dorsal skinfold chamber model. PLoS ONE. 2012;7(2):e32815. DOI: 10.1371/journal.pone.0032815

19. Laschke MW, Augustin V, Kleer S, Tschernig T, Menger MD. Locally applied macrophage-activating lipopeptide-2 (MALP-2) promotes early vascularization of implanted porous polyethylene (Medpor®). Acta Biomater. 2014 Nov;11(1):4661-9. DOI: 10.1016/j.actbio.2014.07.004

20. Laschke MW, Schank TE, Scheuer C, Kleer S, Schuler S, Metzger W, Egiin D, Alini M, Menger MD. Three-dimensional spheroids of adipose-derived mesenchymal stem cells are potent initiators of blood vessel formation in porous polyurethane scaffolds. Acta Biomater. 2013 Jun;9(6):6878-84. DOI: 10.1016/j.actbio.2013.02.013

21. Meisinger JK, Song J, Price RJ. Arteriolar and venular remodeling are differentially regulated by bone marrow-derived cell-specific CX3CR1 and CCR2 expression. PLoS ONE. 2012;7(9):e46312. DOI: 10.1371/journal.pone.0046312

22. Ring A, Langer S, Tilkorn D, Goertz O, Henrich L, Steiner A, Steinau HU, Steinstraesser L, Hauser J. Induction of angiogenesis and neovascularization in adjacent tissue of plasma-collagen-coated silicone implants. Eplasty. 2010 Sep 28:10. pii: e61.

23. Upreti M, Jamshidi-Parsian A, Koonce NA, Webber JS, Sharma SK, Asea AA, Mader MJ, Griffin RJ. Tumor-Endothelial Cell Three-dimensional Spheroids: New Aspects to Enhance Radiation and Drug Therapeutics. Transl Oncol. 2011 Dec;4(6):365-76. DOI: 10.1593/tlo.110118

24. Wang Y, Perentes JY, Schäfer SC, Gonzalez M, Debeve E, Lehr HA, van der Bergh H, Krueger T. Photodynamic drug delivery enhancement in tumours does not depend on leukocyte-endothelial interaction. APMIS. 2014 Aug;122(8):638-46. DOI: 10.1111/apm.12257

25. Nishimura R, Goto M, Sekiguchi S, Fujimori K, Ushiyama A, Satomi S. Assessment for revascularization of transplanted pancreatic islets at subcutaneous site in mice with a highly sensitive imaging system. Transplant Proc. 2011 Nov;43(9):3239-40. DOI: 10.1016/j.transproceed.2011.09.095

26. Moreira JD, Jain RK. Imaging angiogenesis and the microenvironment. APMIS. 2008 Jul-Aug;116(7):695-715. DOI: 10.1111/j.1600-0463.2008.01148.x

27. Thunemann M, Schmidt K, de Wit C, Han X, Jain RK, Fukumura D, Feil R. Correlative intravital imaging of cGMP signals and endothelial interaction in a human mesothelioma xenograft model. Eur J Cardiothorac Surg. 2012 Aug;42(2):348-54. DOI: 10.1093/ejcts/ezr294

28. Nishimura R, Goto M, Sekiguchi S, Fujimori K, Ushiyama A, Satomi S. Assessment for revascularization of transplanted pancreatic islets at subcutaneous site in mice with a highly sensitive imaging system. Transplant Proc. 2011 Nov;43(9):3239-40. DOI: 10.1016/j.transproceed.2011.09.095

29. Fukumura D, Jain RK. Imaging angiogenesis and the microenvironment. APMIS. 2008 Jul-Aug;116(7):695-715. DOI: 10.1111/j.1600-0463.2008.01148.x

30. Thunemann M, Schmidt K, de Wit C, Han X, Jain RK, Fukumura D, Feil R. Correlative intravital imaging of cGMP signals and vasodilation in mice. Front Physiol. 2014;5:394. DOI: 10.3389/fphys.2014.00394

31. Biel NN, Lee JA, Sorg BS, Siemann DW. Limitations of the dorsal skinfold window chamber model in evaluating anti-angiogenic therapy during early phase of angiogenesis. Vasc Cell. 2014 Aug;6:8. DOI: 10.1186/2045-824X-6-17

32. Makale M, Chapter 8. Noninvasive imaging of blood vessels. Methods Enzymol. 2008;444:175-99. DOI: 10.1016/S0076-6879(08)02808-5

GMS Interdisciplinary Plastic and Reconstructive Surgery DGPW 2017. Vol. 6, ISSN 2193-8091
30. Makale MT, Lin JT, Calou RE, Tsai AG, Chen PC, Gough DA. Tissue window chamber system for validation of implanted oxygen sensors. Am J Physiol Heart Circ Physiol. 2003 Jun;284(6):H2288-94. DOI: 10.1152/ajpheart.00721.2002

31. Schweizer R, Merz K, Schlossier S, Spanholz T, Contaldo C, Stein JV, Enzmann V, Giovanoli P, Em D, Plock JA. Morphology and hemodynamics during vascular regeneration in critically ischemic murine skin studied by intravital microscopy techniques. Eur Surg Res. 2011;47(4):222-30. DOI: 10.1159/000335308

32. Erten A, Wrasidlo W, Scadeng M, Esener S, Hoffman RM, Bouvet M, Makale M. Magnetic resonance and fluorescence imaging of doxorubicin-loaded nanoparticles using a novel in vivo model. Nanomedicine. 2010 Dec;6(9):797-807. DOI: 10.1016/j.nano.2010.06.005

33. Janvier Labs. Research models: C57BL/6NRj Maus. [cited 2015 Feb 4]. Available from: http://www.janvier-labs.com/ti_files/_media/images/Fiches_DE/RESEARCH-MODEL-C57BL6NRj-DE.pdf

34. Russell W, Burch RL. The Principles of Humane Experimental Technique. London: Methuen; 1959.

35. Laschke MW, Vollmar B, Menger MD. The dorsalskinfold chamber: window into the dynamic interaction of biomaterials with their surrounding host tissue. Eur Cell Mater. 2011 Sep;22:147-64; discussion164-7. DOI: 10.22203/eCM.v022a12

36. Brown E, Munn LL, Fukumura D, Jain RK. In vivo imaging of tumors. Cold Spring Harb Protoc. 2010 Jul 1;2010(7):pdb.prot5452. DOI: 10.1101/pdb.prot5452

37. Sauber J, Meyer S, Langer S. Modulation der Adipozytenvitalität nach autologer Fettgewebstransplantation. In: Deutschsprachige Arbeitsgemeinschaft für Mikrochirurgie der peripheren Nerven und Gefässe; 2014; Zürich.

38. Deutsches Patent- und Markenamt. DPATISNet. [cited 2015 Feb 24]. Available from: https://depatisnet.dpma.de/DepatisNet/depatisnet?action=einsteiger

39. API Trading. Window Chambers. 2014 [cited 2015 Feb 4]. Available from: http://apitrading.com/chambers.html

40. Nishimura R, Ushiyama A, Sekiguchi S, Fujimori K, Ohuchi N, Satomi S, Goto M. Effects of glucagon-like peptide 1 analogue on early phase of revascularization of transplanted pancreatic islets in a subcutaneous site. Transplant Proc. 2013 Jun;45(5):1892-4. DOI: 10.1016/j.transproceed.2013.01.047

41. Nishimura M, Nii T, Trimova G, Miura S, Umzawa K, Ushiyama A, Kubota T. The NF-κB specific inhibitor DHMEQ prevents thrombus formation in a mouse model of antiphospholipid syndrome. J Nephropathol. 2013 Apr;2(2):114-21. DOI: 10.12860/jn.2013.19

42. Nishimura R, Nishioaka S, Fujisawa I, Shiku H, Shimada M, Sekiguchi S, Fujimori K, Ushiyama A, Matsue T, Ohuchi N, Satomi S, Goto M. Tacrolimus inhibits the revascularization of isolated pancreatic islets. PLoS ONE. 2013;8(4):e56799. DOI: 10.1371/journal.pone.0056799

43. Ushiyama A, Yamada S, Ohkubo C. Microcirculatory parameters measured in subcutaneous tissue of the mouse using a novel dorsal skinfold chamber. Microvasc Res. 2004 Sep;88(2):147-52. DOI: 10.1016/j.mvr.2004.05.004

44. Axelsson H, Bagge U, Lundholm K, Svanesberg E. A one-piece plexiglass access chamber for subcutaneous implantation in the dorsal skin fold of the mouse. Int J Microcirc Clin Exp. 1997 Nov-Dec;17(6):328-9. DOI: 10.1159/000179248

45. Eichhorn ME, Strieth S, Luedemann S, Kleespies A, Noth U, Passon A, Brix G, Jauch KW, Bruns CJ, Dellian M. Contrast enhanced MRI and intravitral fluorescence microscopy indicate improved tumor microcirculation in highly vascularized melanomas upon short-term anti-VEGF treatment. Cancer Biol Ther. 2008 Jul;7(7):1006-13. DOI: 10.4161/cbt.7.7.5997

46. Strieth S, Strelczyk D, Eichhorn ME, Dellian M, Luedemann S, Griebel J, Bellemann M, Berghaus A, Brix G. Static magnetic fields induce blood flow decrease and platelet adherence in tumor microvessels. Cancer Biol Ther. 2008 Jun;7(6):814-9. DOI: 10.4161/cbt.7.6.5837

47. IROLA Industriekomponenten. Rückenhautkammern und Zubehör. [cited 2015 Feb 5]. Available from: http://www.irona.de/sonstiges.htm

48. Wieghaus KA, Nickerson MM, Petrie Aronin CE, Sefcik LS, Price RJ, Paige MA, Brown ML, Botchwey EA. Expansion of microvascular networks in vivo by phthalimide neovascular factor 1 (PNF1). Biomaterials. 2008 Dec;29(35):4698-708. DOI: 10.1016/j.biomaterials.2008.08.029

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