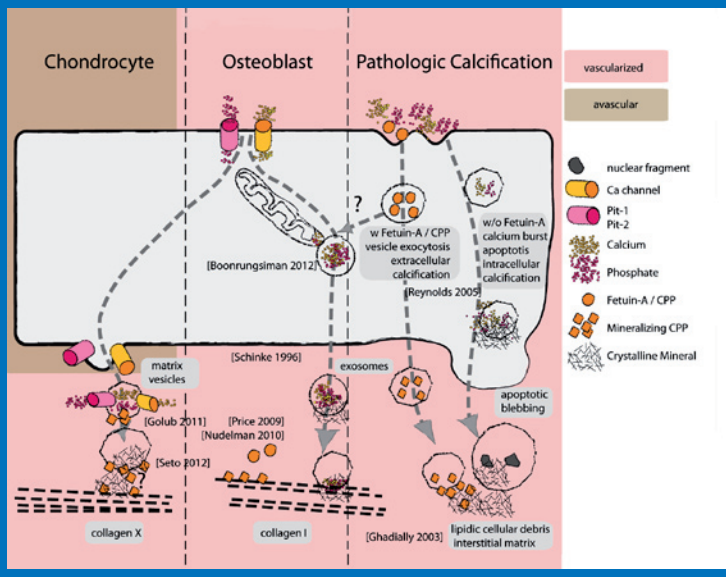
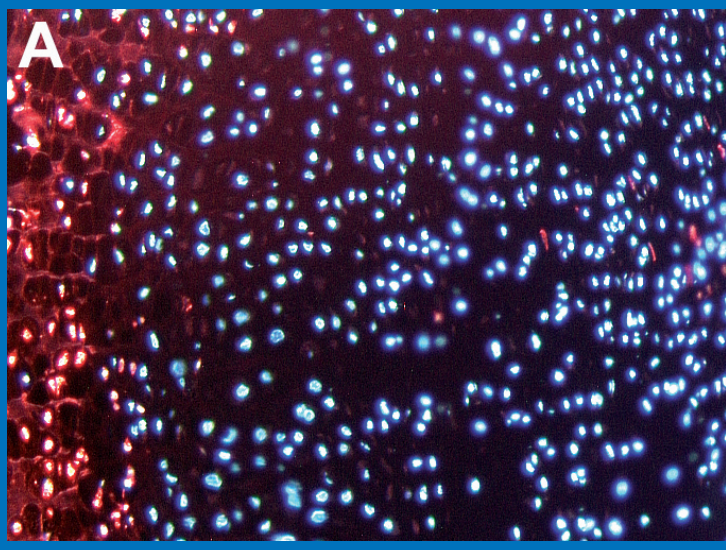
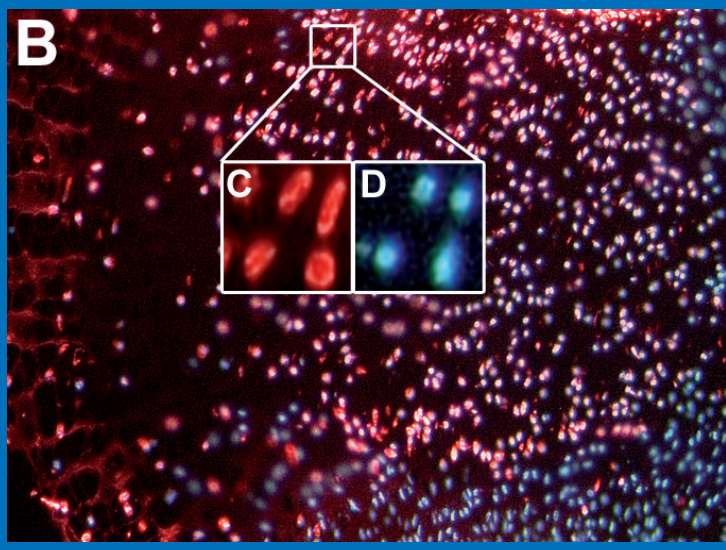
Biointerface

Faculty of Medicine

Cell-Material Interactions: Translating Basic Science Into Clinical Applications







Director

Univ.-Prof. Dr. rer. nat.
Wilhelm Jahnen-Dechent

RWTH Aachen University Hospital
Pauwelsstrasse 30, 52074 Aachen

Helmholtz-Institute for Biomedical Engineering
Pauwelsstrasse 20, 52074 Aachen

Phone: +49 (0)241 80-80157 (Secretary)
+49 (0)241 80-80163 (Office)
Fax: +49 (0)241 80-82573
Email: rsous@ukaachen.de
Web: http://www.biointerface.rwth-aachen.de

Staff

Sous, Renate, Administrative Assistant
Adamzyk, Carina MSc
Bienert, Michaela MSc
Blaeser, Andreas MSc
Brylka, Laura MSc
Büscher, Andrea MTA
Dietzel, Eileen MSc
Eickhoff, Jonas
Elsas, Johannes cand med
Falkenstein, Julia BSc
Floehr, Julia MSc
Gräber, Steffen CTA
Graf, Michael BSc
Herrmann, Marietta PhD
Hoß, Mareike PhD
Kandt, Pierre cand med
Kinkeldey, Anne Dipl Biol
Kruppa, Daniel BSc
Laaf, Dominic
Labude, Norina MTA
Leisten, Isabelle Dipl Biol
Markulin, Dora MSc
Neuß-Stein, Sabine PD PhD
Pan-Bartneck, Yu PhD
Petersen, Svenja cand med
Pottbacker, Kirsten BSc
Schaub, Linda BTA
Schutters, Kristof MSc
Thönes, Stephan Dipl Biol
van de Kamp, Julia MSc
Ventura Ferreira, Monica PhD
Weßling, Jennifer PhD

Fig Title. Top: Hypothetical role of fetuin-A in cell and matrix mineralization. *Cartilage mineralization (mainly collagen X) is driven by matrix vesicles. A role of fetuin-A in the formation and stabilization of matrix vesicles has never been demonstrated. However, fetuin-A deficient mice have premature growth plate mineralization, suggesting a role of fetuin-A in hypertrophic chondrocyte mineralization. Mitochondria have been shown to provide at least some mineral for osteoblast mineralization of collagen I. Fetuin-A was shown to regulate mineralization in cultured osteoblasts. Pathological calcification in VSMCs was equally inhibited by fetuin-A. In the absence of fetuin-A, calcification started in intracellular vesicles. These vesicles burst and released their content into the cytoplasm causing cell death and dystrophic calcification. Fetuin-A also prevented the formation of calcifying apoptotic blebs that formed following an intracellular calcium burst and apoptosis. Chondrocytes mineralize mainly collagen X, osteoblasts mineralize predominantly collagen I; however the calcified matrix in pathological calcification is extremely variable ranging from elastin to cell debris, collectively described as "calcified lipidic debris".* ***Bottom:*** *Fetuin-A distribution in the growth plate. Bones were cultured in the presence of fluorescence-labeled fetuin-A. Note the accumulation of fetuin-A (red color) in the mineralized part of the growing bone. Bones were cultured without (A) and with (B) retinoic acid in the presence of fluorescence-labeled fetuin-A. Bones cultured with retinoic acid show increased fetuin-A accumulation inside proliferative zone chondrocytes (C,D). Cell nuclei are stained blue.*

Introduction

The year 2012 was both busy and successful for the Biointerface group - 28 peer-reviewed papers,[1-28] two PhD theses, one MD thesis and four Master/Diploma theses.[29-36] PhD students Marietta Herrmann[5,8,9] and Monica Ventura Ferreira[16,24-27] finished their thesis work and remained in the „writing mode", until they left the group for their next assignments. Marietta has joined the prestigious bone research program at AO foundation in Davos, Switzerland. We wish Marietta all the best and keep in touch. Monica went back to her home country Portugal for a stint, but luckily decided to come back to RWTH to take a post-doctoral position in the group. Welcome back! After one year in the lab Andreas Pasch returned to Berne, Switzerland, to pursue a career as a University clinical doctor/researcher. Our long-term colleague, Yu Pan-Bartneck moved on to an exciting job in an international business development firm, which involves a lot of travel. Yu is very fondly remembered for being energetic, cheerful and generally a good sport. We finally published some „very long-term" projects. One particular project that has been going for years is the description of the bone phenotype of fetuin-A/α_2-Heremans-Schmid glycoprotein (Ahsg) deficient mice.

Role of Fetuin-A in Longitudinal Bone Growth

Figure 1 shows an overview of the hypothetical roles of fetuin-A in cell and matrix mineralization. In the healthy state, calciprotein particles (CPP) are readily cleared by liver Kupffer cells and by spleen marginal zone macrophages, whereas fetuin-A deficiency or very high calcium and

(Laura Brylka)

phosphate concentrations might lead to pathological calcification, like calcification of atherosclerotic plaques or soft tissue calcification. We hypothesize that CPP might also be produced in bone remodeling processes, as fetuin-A is one of the most abundant non-collagenous proteins in bone and would form CPP with amorphous calcium phosphate,

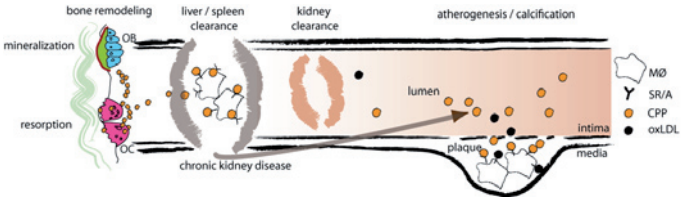


Fig. 1: Calciprotein particle (CPP) metabolism. In bone remodelling CPP are formed by fetuin-A and mineral ions released by resorbing osteoclasts. These CPP will be re-deposited in newly formed bone. CPP spill over into circulation is rapidly cleared by macrophages in liver and spleen.[9] Cleared CPP are degraded and excess mineral can be excreted by the kidney. In chronic kidney disease, this clearing mechanism is missing, causing elevated blood calcium and phosphate levels, and leading to more CPP formation. This might also occur in other disease states, which lead to an increased Ca and Pi blood product. In atherogenesis for instance, CPP may be internalized by plaque forming calcified atherosclerotic plaque. Taken from ref[2].

Fetuin-A Knockouts Have Short Legs

Fetuin-A is a mineral binding protein, which is made in the liver and accumulates in mineralized bone matrix. When we made the fetuin-A knockout mice a decade and a half ago, we immediately looked at the bone. A previous paper, which we co-authored, reported on subtle changes in bone structure, which were interpreted as growth and differentiation perturbance of osteoblasts in the absence of fetuin-A, a decoy receptor of TGF-β. The predominant physiological role of fetuin-A is the prevention of pathological calcification - seasoned readers of the HIA report series will remember this from previous issues. Fetuin-A is a carrier protein that solubilizes and helps the clearance of mineralized matrix and especially of lipidic mineralized debris.[2,8,9] Against this background we revisited the bone phenotype and detected a striking detail that was so blatantly obvious - we keep asking ourselves, how we could miss it for years. Have a look at figure 2 and take a guess: compare the leg length in wildtype and Ahsg knockout mice. Notice something?

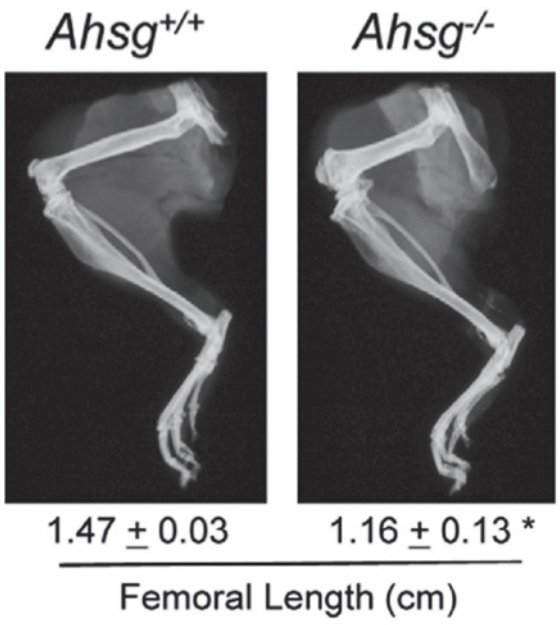


Fig. 2: Radiographs of the hindlegs from 4 months old Ahsg+/+ and Ahsg-/- mice. The femoral length is given below.

The femora in Ahsg-/- mice are much shorter than in wildtype mice. A similar phenotype is observed in animals suffering from retinoic acid intoxication. Hypervitaminosis A leads to premature growth plate closure, which causes shortened growth oft the femoral bones. Because of these similarities, we hypothesized that fetuin-A might play a role in retinoid signaling in the bone. We established a bone organ culture system to investigate the role of retinoic acid together with fetuin-A in endochondral ossification. Preliminary results show that retinoic acid decreased bone growth similar to what happens in hypervitaminosis A. Further studies on this true „tissue culture" will reveal if there is any interdependency of retinoic acid and fetuin-A.

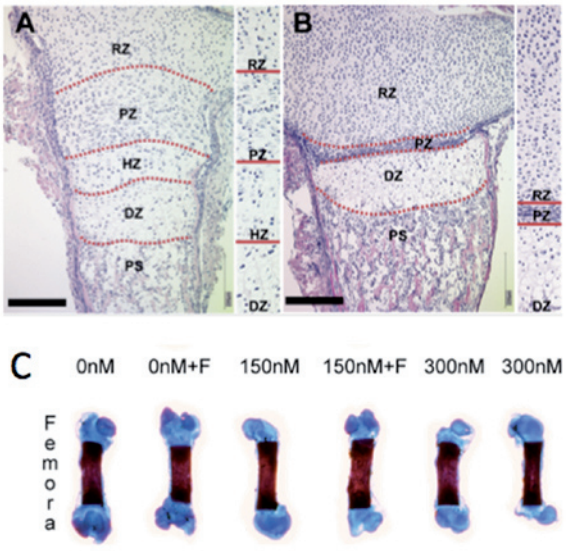


Fig. 3: Bone organ culture in the presence of retinoic acid. Bones isolated from newborn mice were cultured for four days in minimal medium with (B) or without (A) retinoic acid. (C) Retinoic acid causes a concentration dependent decrease in bone growth.

In summary, the observed shorter bone length in fetuin-A deficient mice was most likely due to increased or premature growth-plate cartilage mineralization. This also corresponds to an overall shorter bone length, increased cortical thickness and slightly increased bone diameter at the midshaft position. Collectively, these changes resulted in macroscopically stronger femora and tibia in fetuin-A deficient mice compared to wildtype adult mice, despite similar bone material properties.
Our findings reconcile the role of fetuin-A as an inhibitor of mineralization with this odd bone phenotype. We posit that fetuin-A stabilizes and helps the clearance of surplus mineral from soft tissues and from circulation. Mineral is transported in the form of calciprotein particles (CPP), rapidly forming in the presence of fetuin-A in supersaturated mineral solutions. In the absence of fetuin-A, supersaturated mineral solutions precipitate more quickly. CPP formation and clearance help maintaining mineral homeostasis and prevent ectopic mineralization. We developed a serum test based on the detection of CPP nanoparticles by light scattering to measure the imminent risk of calcification in dialysis patients.[19] This test made it to the front page of „Kidney News", a newspaper for 11,000 participants of the 2012 ASN Kidney Week, the annual meeting of the American Society of Nephrology, showing that fetuin-A function and the concept of CPP metabolism have gained recognition by clinicians worldwide.

Stem Cells and Tissue Engineering

(Sabine Neuss-Stein)

This work aims at stem cell-based tissue engineering. Mesenchymal stem cells (MSC), hematopoietic stem cells (HSC), germline-derived pluripotent stem cells (gPS cells) and other stem cell types are applied and combined with biomaterials. Stem cell/biomaterial interactions are analyzed in detail using cell-based assays, molecular biology, protein chemistry and electron microscopy.

gPS cells have a broad differentiation potential and thus are an appealing source for tissue engineering. Biomaterials can inhibit, support or induce proliferation and differentiation of stem cells. We identified (i) polymers, which maintain self-renewal and differentiation potential of gPS cells for feeder-free expansion, and (ii) polymers supporting the cardiomyogenic differentiation of gPS cells. To identify cytocompatible gPS cell/biomaterial combinations, cell morphology, viability, cytotoxicity, apoptosis, proliferation and differentiation potential were all analyzed. Pluripotency of gPS cells was visualized by the endogenous Oct4-promoter-driven GFP. Viability and proliferation assays demonstrated that gPS cells adhere to various synthetic polymers and on gelatine-coated tissue culture polystyrene. Figure 4 shows that Resomer® LR704 is an alternative substrate for feeder-free gPS cell maintenance

and in addition was found to be suitable for cardiomyogenic differentiation of gPS cells. Spontaneous beating in embryoid bodies cultured on Resomer® LR704 occurred already on day 8 of differentiation, much earlier compared to other biomaterials (Fig. 4). This indicates that Resomer® LR704 supports spontaneous cardiomyogenic differentiation of gPS cells, which was also confirmed on the molecular, protein and functional level.[11]

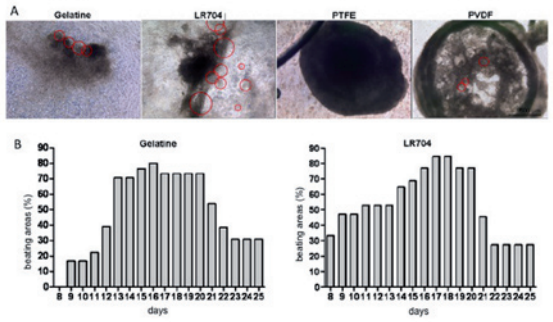


Fig. 4: Beating cells developed in gPS cell-derived embryoid bodies. (A) Red circles highlight beating areas on day 11 of differentiation on gelatine, Resomer® LR704, PTFE and PVDF. (B) Quantification of beating areas on gelatine and on Resomer® LR704 between day 8 and 25 of differentiation.

Compared to gPS cells, MSC have a more restricted plasticity. Under physiological conditions, they are involved in tissue regeneration and repair, particularly in wound healing. Due to their high self-renewal capacity and excellent differentiation potential *in vitro*, MSC are ideally suited for their use in regenerative medicine. The complex interactions of MSC with their surrounding and their influence on the molecular and functional levels are widely described but not completely understood. MSC secrete e.g. hepatocyte growth factor (HGF), whose concentration is enhanced in wounded areas and which is shown to act as a chemoattractant for MSC. In a current study we produce HGF-loaded biomaterials based on collagen and fibrin gels to develop a recruitment system for endogenous MSC to improve wound healing. Here, we report that HGF incorporated into collagen or fibrin gels leads to enhanced and directed MSC migration *in vitro*. HGF-loaded biomaterials might be potentially used as *in vivo* wound dressings to recruit endogenous MSC out of their tissue-specific niche towards the wounded area. (Fig. 5).

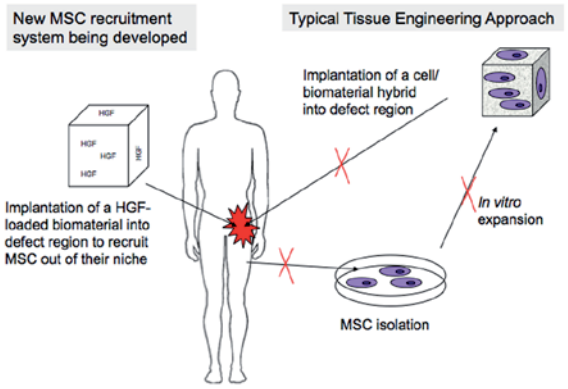


Fig. 5: Schematic representation of MSC recruitment via HGF-loaded biomaterials. HGF-loaded biomaterials will be transplanted to guide endogenous MSC out of their tissue-specific niche towards a wounded area.

As demonstrated for gPS cells, biomaterials can support the differentiation fate of stem cells (Fig. 4). Besides, biomaterials are required to allow for a spatial distribution of applied stem cells within a defined area in the body. In a recent study, we analyzed the interaction of a large panel of stem cell types with an array of biomaterials and demonstrated that a prediction of stem cell behaviour on a specific biomaterial is not yet possible. Interestingly, even ontogenetically related stem cell types, such as MSC, preadipocytes and dental pulp stem cells (DPSC), exhibit distinct adhesion properties on the very same biomaterial surface. Therefore, we investigated integrin and extracellular matrix (ECM) protein expression of stem cells to relate gene expression to adhesion behaviour. MSC, preadipocytes and DPSC were cultured on synthetic polymers (Fig. 6). Analysis of adhesion molecules yielded that only one molecule, integrin α_4, might play a significant role in differential adhesion on polymers for preadipocytes compared to DPSC and MSC.[10] Thus, our studies on the molecular interactions of stem cells and polymers are expected to lead to a more profound understanding of stem cell/biomaterial interactions to eventually allow for a rational biomaterial design.

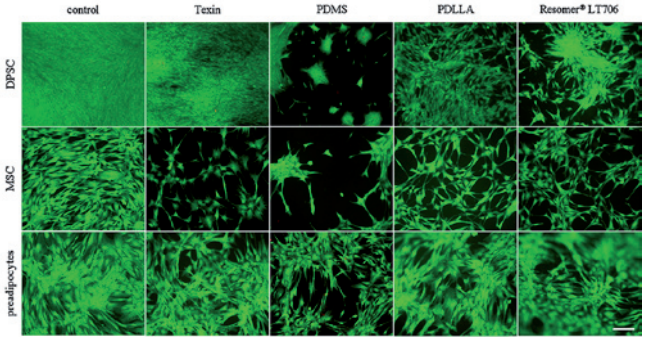


Fig. 6: Live/dead staining of DPSC, MSC and preadipocytes. Cells were cultured on Texin, PDMS, PDLLA and Resomer® LT706 for 7 days; scale bar=200µm.

Expansion of Human Cord Blood-Derived Hematopoietic Stem Cells

(Mónica Sofia Ventura Ferreira)

Cord blood-derived hematopoietic stem cells (CB-HSC) are appealing for transplantation in hematopoietic disorders. However, the low yield of CB-HSC per graft is often insufficient for treatment of adults. Traditional approaches for HSC *ex vivo* expansion include the use of cytokines and/or stromal cell support, but are still unsatisfactory. Biomaterial-based strategies might provide new perspectives. Our work combines cytokines, stromal

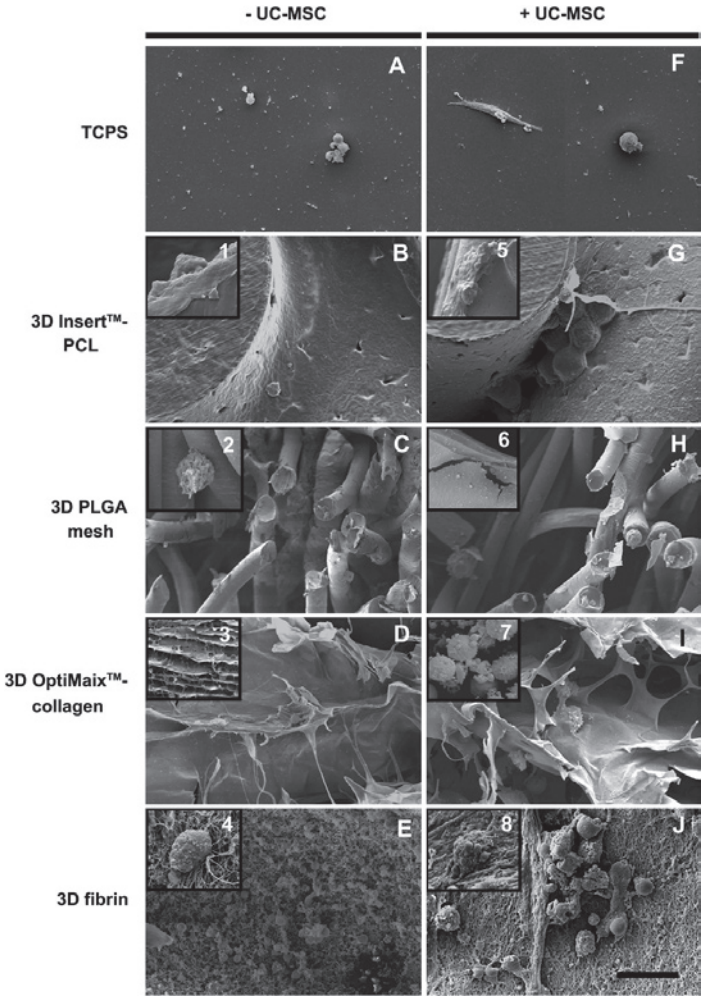


Fig. 7: Mesenchymal stem cells (MSC) expand hematopoietic stem cells in 3D scaffold-based cultures. Representative scanning electron microscopy of CD34+ cells expanded for 10 days on different 3D biomaterial-scaffolds in presence of strong cytokine supplementation and MSC support. TCPS served as control. Scale bar = 50 µm.

support and biomaterial scaffolds to better recapitulate the native bone marrow (BM) microenvironment and promote HSC expansion. While the rationale for choosing some biomaterials rather than others for HSC expansion is not clear, we proposed biomaterial identification to start with the assessment of a series of basic compatibility parameters. In my PhD work, I conducted a systematic evaluation of HSC viability, cytotoxicity, and apoptosis after exposure to sixteen two-dimensional (2D) bio- and synthetic polymers from our biomaterial bank. Long-term polymer-based cultures in presence of standard cytokines showed no cytotoxic or apoptotic effects for HSC for six of the 2D polymers tested.[6] In a subsequent study,[26] we further analyzed the efficiency of those 2D polymers to expand HSC compared to tissue culture polystyrene (TCPS) in the presence of SCF, TPO, FGF-1, Angptl-5 and IGFBP2, a novel combination of cytokines for HSC culture simultaneously analyzed in our hands.[25] HSC were analysed systematically in terms of morphology and functionality both *ex vivo* and *in vivo*.[26] Our studies identified fibrin as the most efficient 2D polymer for CB-HSC expansion in cultures including strong cytokine supplementation, followed by Resomer® RG503 and PCL. The Presence of filopodia in fibrin-expanded cells was main indicator for superior cell adhesion capacities (Fig. 7). In a subsequent study[24] three polymers were used as 3D scaffolds, in combination with strong cytokine supplementation and MSC support for HSC expansion. Results showed that cell expansion was greatly stimulated by adding MSC support to cultures. HSC cultured on 3D fibrin scaffolds with MSC support reached the highest overall growth and showed the best engraftment in mice.

Selected References

[1] Bartneck M, Keul HA, Wambach M, Bornemann J, Gbureck U, Chatain N, Neuss S, Tacke F, Groll J and Zwadlo-Klarwasser G, in Nanomedicine, Elsevier, 2012, pp. 1282-1292.
[2] Brylka L and Jahnen-Dechent W, The Role of Fetuin-A in Physiological and Pathological Mineralization. Calc Tiss Int, 2013.
[3] Dreymueller D, Denecke B, Ludwig A and Jahnen-Dechent W, Embryonic Stem Cell-Derived M2-Like Macrophages Delay Cutaneous Wound Healing. Wound Repair Regen, 2013, 21, 44-54.
[4] Duarte Campos DF, Blaeser A, Weber M, Jäkel J, Neuss S, Jahnen-Dechent W and Fischer H, Three-Dimensional Printing of Stem Cell-Laden Hydrogels Submerged in a Hydrophobic High-Density Fluid. Biofabrication, 2012, 5, 015003.
[5] Elsas J, Sellhaus B, Herrmann M, Kinkeldey A, Weis J, Jahnen-Dechent W and Häusler M, Fetuin-A in the Developing Brain. Dev Neurobiol, 2012, n/a-n/a.
[6] Ventura Ferreira MS, Labude N, Piroth D, Jahnen-Dechent W, Knüchel R, Hieronymus T, Zenke M and Neuss S, Compatibility of Different Polymers for Cord Blood-Derived Hematopoietic Progenitor Cells. J Mat Sci Mat Med, 2012, 23, 109-116.
[7] Hale JS, Li M, Sinyuk M, Jahnen-Dechent W, Lathia JD and Silverstein RL, Context Dependent Role of the Cd36 - Thrombospondin - Histidine-Rich Glycoprotein Axis in Tumor Angiogenesis and Growth. PLoS ONE, 2012, 7, e40033.
[8] Herrmann M, Kinkeldey A and Jahnen-Dechent W, Fetuin-A Function in Systemic Mineral Metabolism. Trends Cardiovasc Med, 2012, 22, 197-201.
[9] Herrmann M, Schäfer C, Heiss A, Gräber S, Kinkeldey A, Büscher A, Schmitt MMN, Bornemann J, Nimmerjahn F, Herrmann M, Helming L, Gordon S and Jahnen-Dechent W, Clearance of Fetuin-A-Containing Calciprotein Particles Is Mediated by Scavenger Receptor-A. Circ Res, 2012, 111, 575-584.
[10] Hoss M, Apel C, Dhanasingh A, Suschek CV, Hemmrich K, Salber J, Zenke M and Neuss S, Integrin α_4 Impacts on Differential Adhesion of Preadipocytes and Stem Cells on Synthetic Polymers. J Tissue Eng Regen Med, 2012.
[11] Hoss M, Sarić T, Denecke B, Peinkofer G, Bovi M, Groll J, Ko K, Salber J, Halbach M, Schöler HR, Zenke M and Neuss S, Expansion and Differentiation of Germline-Derived Pluripotent Stem Cells on Biomaterials. Tiss Eng Part A, 2012.
[12] Jahnen-Dechent W and Ketteler M, Magnesium Basics. Clinical Kidney Journal, 2012, 5, i3-i14.
[13] Kaesler N, Schettgen T, Mutucumarana VP, Brandenburg V, Jahnen-Dechent W, Schurgers LJ and Krüger T, A Fluorescent Method to Determine Vitamin K-Dependent Gamma-Glutamyl Carboxylase Activity. Anal Biochem, 2012, 421, 411-416.
[14] Kramann R, Brandenburg VM, Schurgers LJ, Ketteler M, Westphal S, Leisten I, Bovi M, Jahnen-Dechent W, Knüchel R, Floege J and Schneider RK, Novel Insights into Osteogenesis and Matrix Remodelling Associated with Calcific Uraemic Arteriolopathy. NDT, 2012.
[15] Kramann R, Couson SK, Neuss S, Floege J, Knüchel R and Schneider RK, Uraemia Disrupts the Vascular Niche in a 3D Co-Culture System of Human Mesenchymal Stem Cells and Endothelial Cells. NDT, 2012, 27, 2693-2702.
[16] Leisten I, Kramann R, Ventura Ferreira MS, Bovi M, Neuss S, Ziegler P, Wagner W, Knüchel R and Schneider RK, 3D Co-Culture of Hematopoietic Stem and Progenitor Cells and Mesenchymal Stem Cells in Collagen Scaffolds as a Model of the Hematopoietic Niche. Biomaterials, 2012, 33, 1736-1747.
[17] Pan Y, Bartneck M and Jahnen-Dechent W, Cytotoxicity of Gold Nanoparticles. Methods Enzymol, 2012, 509, 225-242.
[18] Pan Y, Leifert A, Graf M, Schiefer F, Thoröe-Boveleth S, Broda J, Halloran MC, Hollert H, Laaf D, Simon U and Jahnen-Dechent W, High-Sensitivity Real-Time Analysis of Nanoparticle Toxicity in Green Fluorescent Protein-Expressing Zebrafish. Small, 2012.

[19] Pasch A, Farese S, Gräber S, Wald J, Richtering W, Floege J and Jahnen-Dechent W, Nanoparticle-Based Test Measures Overall Propensity for Calcification in Serum. JASN, 2012, 23, 1744-1752.
[20] Schurgers LJ, Joosen IA, Laufer EM, Chatrou MLL, Herfs M, Winkens MHM, Westenfeld R, Veulemans V, Krueger T, Shanahan CM, Jahnen-Dechent W, Biessen E, Narula J, Vermeer C, Hofstra L and Reutelingsperger CP, Vitamin K-Antagonists Accelerate Atherosclerotic Calcification and Induce a Vulnerable Plaque Phenotype. PLoS ONE, 2012, 7, e43229.
[21] Seto J, Busse B, Gupta HS, Schäfer C, Krauss S, Dunlop JWC, Masic A, Kerschnitzki M, Zaslansky P, Boesecke P, Catala-Lehnen P, Schinke T, Fratzl P and Jahnen-Dechent W, Accelerated Growth Plate Mineralization and Foreshortened Proximal Limb Bones in Fetuin-a Knockout Mice. PLoS ONE, 2012, 7, e47338.
[22] Tugues S, Honjo S, König C, Noguer O, Hedlund M, Botling J, Deschoemaeker S, Wenes M, Rolny C, Jahnen-Dechent W, Mazzone M and Claesson-Welsh L, Genetic Deficiency in Plasma Protein Hrg Enhances Tumor Growth and Metastasis by Exacerbating Immune Escape and Vessel Abnormalization. Cancer Res, 2012.
[23] Van De Kamp J, Kramann R, Anraths J, Schöler HR, Ko K, Knüchel R, Zenke M, Neuss S and Schneider RK, Epithelial Morphogenesis of Germline-Derived Pluripotent Stem Cells on Organotypic Skin Equivalents in Vitro. Differentiation, 2012, 83, 138-147.
[24] Ventura Ferreira MS, Jahnen-Dechent W, Labude N, Bovi M, Hieronymus T, Zenke M, Schneider RK and Neuss S, Cord Blood-Hematopoietic Stem Cell Expansion in 3D Fibrin Scaffolds with Stromal Support. Biomaterials, 2012, 33, 6987-6997.
[25] Ventura Ferreira MS, Labude N, Walenda G, Adamzyk C, Wagner W, Piroth D, Müller AM, Knüchel R, Hieronymus T, Zenke M, Jahnen-Dechent W and Neuss S, Ex Vivo Expansion of Cord Blood-Cd34(+) Cells Using Igfbp(2) and Angptl-5 Impairs Short-Term Lymphoid Repopulation in Vivo. J Tissue Eng Regen Med, 2012.
[26] Ventura Ferreira MS, Schneider RK, Wagner W, Jahnen-Dechent W, Labude N, Bovi M, Piroth DM, Knüchel R, Hieronymus T, Müller AM, Zenke M and Neuss S, 2D Polymer-Based Cultures Expand Cord Blood-Derived Hematopoietic Stem Cells and Support Engraftment of Nsg Mice. Tiss Eng Part C, 2012.
[27] Wessels I, Rosenkranz E, Ventura Ferreira M, Neuss S, Zenke M, Rink L and Uciechowski P, Activation of Il-1β and Tnfα Genes Is Mediated by the Establishment of Permissive Chromatin Structures During Monopoiesis. Immunobiology, 2012.
[28] Westenfeld R, Krueger T, Schlieper G, Cranenburg ECM, Magdeleyns EJ, Heidenreich S, Holzmann S, Vermeer C, Jahnen-Dechent W, Ketteler M, Floege J and Schurgers LJ, Effect of Vitamin K2 Supplementation on Functional Vitamin K Deficiency in Hemodialysis Patients: A Randomized Trial. AJKD, 2012, 59, 186-195.

Theses

[29] Bienert M, Osteogenic Differentiation of Human Mesenchymal Stem Cells on Silk Matrices: Continuous Vs. Static Culture. Master Thesis, RWTH Aachen University 2012.
[30] Blaeser A, Development and Design of a Computer-Controlled 3D Printing System for Submerged Deposition of Cell Loaded Hydrogels. Master Thesis, RWTH Aachen University 2012.
[31] Brylka L, The Role of Fetuin-A in Longitudinal Bone Growth. Master Thesis, RWTH Aachen University 2012.
[32] Herrmann M, Pathology of Ectopic Calcification in Fetuin-A Deficient Mice: Compensatory Gene Regulation and Mineralized Matrix Metabolism. PhD Thesis, RWTH Aachen University 2012.
[33] Hoffmann V, Expression of the Pluripotency Gene Nanog and Transcription Factor Analysis in Human Mesenchymal Stem Cells of the Umbilical Cord and Its 3D Aggregates. MD Thesis, RWTH Aachen University 2012.
[34] Kruppa D, Osteogenic Differentiation of Human Mesenchymal Stem Cells on Silk Matrices: Continuous Vs. Static Culture. Bachelor Thesis, RWTH Aachen University 2012.
[35] Thönes S, Establishment of a Technique for the Encapsulation of Human Mesenchymal Stem Cells. Diploma Thesis, RWTH Aachen University 2012.
[36] Ventura Ferreira MS, A Multifactorial Strategy for Expansion of Human Cord Blood-Derived Hematopoietic Stem Cells. PhD Thesis, RWTH Aachen University 2012.

Team

Lab out to the Museum of Natural Sciences, Brussels