



Self-organisation of human hepatocytes into hepatic cords on a radially perfused microfluidic device

A. Rajendran, Sakina Bensalem, Antonietta Messina, Nassima Benzoubir, Rasta Ghasemi, Jean-Charles Duclos-Vallée, Bruno Le Pioufle

► To cite this version:

A. Rajendran, Sakina Bensalem, Antonietta Messina, Nassima Benzoubir, Rasta Ghasemi, et al.. Self-organisation of human hepatocytes into hepatic cords on a radially perfused microfluidic device. Micro Physiological System World Summit, Jun 2023, Berlin, Germany. pp.343. hal-04466044

HAL Id: hal-04466044

<https://hal.science/hal-04466044>

Submitted on 20 Feb 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



sults confirmed that the peptides selected from the microfluidic BBB model display significantly higher brain targeting abilities *in vivo*. This study highlights the importance of using organ-on-a-chip technology for successful phage display screening and provides evidence for its potential benefits for the future application of human drug delivery system development.

Presentation: Oral

661

Peripheral inflammation microfluidic model to disclose polyphenol metabolites potential

Daniela Marques¹, Rafael Carecho^{1,2}, Inês P. Silva^{1,3}, Alexander S. Mosig⁴, Inês Figueira¹ and Cláudia Nunes dos Santos^{1,2,3}

¹NMS, NOVA Medical School, Faculdade de Ciências Médicas, Universidade NOVA de Lisboa, Lisboa, Portugal; ²ITQB, Instituto de Tecnologia Química e Biológica António Xavier, Universidade Nova de Lisboa, Oeiras, Portugal; ³iBET, Instituto de Biologia Experimental e Tecnológica, Oeiras, Portugal; ⁴Institute of Biochemistry II, Center for Sepsis Control and Care, Jena University Hospital, Jena, Germany

daniela.marques019@gmail.com

(Poly)phenols are found in a variety of plant-based foods and have been extensively studied considering their beneficial brain-health effects. Polyphenols consumption is linked with a reduction of inflammation markers and the neuroinflammation status of the brain [1], therefore contributing to the prevention of neurodegenerative diseases (NDs). Circulating microbiota-derived (poly)phenols metabolites (PM's) are found the most abundant in the bloodstream [2]; demonstrated protective effects in different neuronal systems by the reduction of neuroinflammatory markers, and brain microvascular endothelial cells (HBMEC) protection from an oxidative insult [3]. Despite that, the cross-communication between HBMEC cells and brain immune cells, microglia, in response to a peripheral inflammatory signal remains poorly explored.

Our goal is to unravel the potential of physiological relevant microbiota-derived dietary (poly)phenol metabolites, on the modulation of HBMEC and their communication with microglia cells (HMC3) upon peripheral inflammatory stimulation (IL-1 β , IFN γ , LPS, TNF α). The physiological feature to be considered is that the appearance in circulation is simultaneous for more than one PM's and accordingly a time course of increasing concentrations [4]. The use of a microphysiological system (MPS) model adapted from Raasch et al., will enable us to understand the mechanisms related (poly)phenols metabolites brain protective potential in a physiological environment, by the delivery of PM's according to their pharmacokinetic profile.

Within this physiological setup, the molecular mechanisms behind their neuroprotection will be studied, gathering more comprehensive modelling of events during neuroinflammation in the

presence of controlled delivery of physiologically relevant mixtures of PM's. Unravel the mode of action of physiological relevant protective polyphenolic molecules will be the fine tuning to the real physiological conditions that they act inside the human body, and we will establish the grounds for the development of dietary products enriched in specific polyphenols.

References

- [1] Carecho (2022). *Mol Nutr Food Res*.
- [2] Pimpão (2015). *Br J Nutr*.
- [3] Figueira (2017). *Sci Rep*.
- [4] Carregosa (2022). *CRFSFS*.
- [5] Raasch (2016). *Biomicrofluidics*.

Presentation: Poster

662

Self-organisation of human hepatocytes into hepatic cords on a radially perfused microfluidic device

Alan Raj Jeffrey Rajendran¹, Sakina Chantoiseau-Bensalem¹, Antonietta Messina², Nassima Benzoubir², Rasta Ghasemi³, Jean-Charles Duclos-Vallee⁴ and Bruno Le Pioufle¹

¹University Paris-Saclay, ENS Paris Saclay, CNRS LUMIN, Gif-sur-Yvette, France; ²UMR_S 1193, INSERM/Université Paris-Saclay, Villejuif France; ³University Paris-Saclay, ENS Paris Saclay, CNRS, Institut d'Alembert, Gif-sur-Yvette, France; ⁴Centre Hépatobiliaire, FHU Hépatinov, AP-HP, Hôpital Paul Brousse, Villejuif, France

alanrajjeffrey@gmail.com

Liver-on-a-chip devices in recent years have shown promising results as predictive human-based *in-vitro* models during preclinical studies. In this regard, this work presents an original microfluidic architecture permitting the culture and maintenance of human hepatocytes. In this designed micro-environment, the hepatoblasts self-organise and differentiate into a tissue that mimics the dimensions and hydrodynamic conditions of a hepatic cord. Reproducing the *in-vivo* hepatic micro-architecture, we have also included a space of Disse feature to increase interaction between the tissue and the medium flow. Biomarkers of hepatocyte functionality such as Albumin secretion, MRP2 staining, CFDA excretion were used to characterise the tissue during 14 days of cell culture.

Results show that in this microdevice, HepaRG-Hepatoblasts are able to successfully differentiate into the targeted hepatic cord structure and also have homogeneous albumin expression. This was not observed when loading the microsystem with pre-differentiated HepaRG-Hepatocyte or in conventional 2D cell cultures. For the first time homogeneous differentiation of bipotent HepaRG cells to hepatocytes is reported within a microfluidic device, thanks to our original architecture.



Such a microdevice shows to be a promising tool in studying differentiation of hepatocytes and the influence of drugs on hepatic cord morphology, viability and bile secretion functions.

References

- [1] Lee, P. J., Hung, P. J. and Lee, L. P. (2007). An artificial liver sinusoid with a microfluidic endothelial-like barrier for primary hepatocyte culture. *Biotechnol Bioeng* 97, 1340-1346. doi:10.1002/bit.21360
- [2] Nakao, Y., Kimura, H., Sakai, Y. et al. (2011). Bile canaliculi formation by aligning rat primary hepatocytes in a microfluidic device. *Biomicrofluidics* 5, 22212. doi:10.1063/1.3580753
- [3] Boul, Manon et al. (2021). A versatile microfluidic tool for the 3D culture of HepaRG cells seeded at various stages of differentiation. *Sci Rep* 11, 14075. doi:10.1038/s41598-021-92011-7

Presentation: Poster

663

A human bone-marrow-on-a-chip system for preclinical investigation of new therapeutic approaches for autosomal recessive osteopetrosis

Nina Stelzer^{1,2}, Ioanna Maria Dimitriou^{1,3}, Lea Heinemann¹, Melanie-Jasmin Ort^{1,3}, Martin Textor^{1,4}, Luis Lauterbach^{1,4}, Dario Gajewski⁵, Sina Bartfeld², Uwe Kornak⁵ and Sven Geißler^{1,4,6}

¹Center for Regenerative Therapies (BCRT), Berlin Institute of Health at Charité – Universitätsmedizin Berlin, Berlin, Germany; ²Department of Medical Biotechnology, Technische Universität Berlin, Berlin, Germany; ³Institute of Chemistry and Biochemistry, Department of Biology, Chemistry and Pharmacy, Freie Universität Berlin, Berlin, Germany; ⁴Julius Wolff Institute, Berlin Institute of Health at Charité – Universitätsmedizin Berlin, Berlin, Germany; ⁵Institute of Human Genetics, University Medical Center Göttingen, Berlin, Germany; ⁶Berlin Center for Advanced Therapies (BECAT), Charité Universitätsmedizin Berlin, Berlin, Germany

nina.stelzer@bih-charite.de

Sequential seeding and dynamic cultivation of human mesenchymal stromal cells (MSCs), osteoblasts (OBs) and bone marrow mononuclear cells (BMMNCs) on decellularized human cancellous bone allows to engineer clinically relevant Bone-on-a-Chip systems that enable analysis of pathomechanisms and therapies for genetic bone disorders like autosomal recessive osteopetrosis (ARO).

ARO is caused by a defect in the bone-resorbing osteoclasts and the course is lethal if the patients are not timely treated by hematopoietic stem cell (HSC) transplantation. However, this treatment harbors high risks since it relies on allografts. A solution would be the use of autologous HSCs, in which the genetic defect has been compensated or corrected by somatic gene therapy. Before somatic gene therapy becomes clinically relevant, potential adverse effects must be identified, which is the aim of this project. We plan

to evaluate two non-viral gene therapy strategies using a donor-independent iPSC-derived Bone-on-a-Chip system.

For dynamic 3D long-term cultivation, we use the HUMIMIC Chip2 from TissUse GmbH. First, monocytes are seeded onto the decellularized human cancellous bone scaffold and differentiated into osteoclasts, which represent the resorbing bone compartment. MSCs and osteoblasts are subsequently seeded to the osteoclasts and osteogenically stimulated representing the bone formation compartment. In the final step, mononuclear cells are added to the scaffold to monitor possible adverse effects of the gene therapy constructs on the immunological cell population. Bone remodeling is assessed by co-registering the scaffold with a micro-CT and additionally monitored by measuring bone formation and resorption products in the culture supernatant over the cultivation period.

The dynamic long-term cultivation allows the self-organisation of the bone cells and the interaction between different cell types, thus enabling extensive preclinical testing of novel gene therapy strategies for ARO and replacing the use of mouse models that only imperfectly reflect the human situation.

Presentation: Poster

664

Extracellular vesicles as a next-generation drug delivery platform in a more physiological MPS based microenvironment

Roberta Tasso^{1,2}, Maria Elisabetta Federica Palamà³, Maria Chiara Ciferri¹, Nicole Rosenwasser¹, Rodolfo Quarto^{1,2}, Maurizio Aiello^{3,4} and Silvia Scaglione^{3,4}

¹University of Genoa, Genoa, Italy; ²IRCSS Policlinico San Martino, Genoa, Italy; ³React4life, Genoa, Italy; ⁴CNR, Genoa, Italy

s.scaglione@react4life.com

Introduction: Tumor metastases represent the main cause of mortality in neoplastic patients. Current therapeutic protocols target cancer cells, but the damage of normal cells and tissues is the main unsolved hurdle. Therefore, the development of innovative targeted therapeutic strategies with minimal side effects and systemic toxicity represents the future clinical challenge. The role of the extracellular matrix (ECM) in tumor growth and progression is gaining growing interest. In particular, an oncofetal variant of fibronectin, termed extradomain B-FN (ED-B), is highly investigated (Vaida, 2020), since it is expressed by the newly synthesized perivascular areas of the stromal matrix in a wide range of tumor types. Among novel targeting strategies, extracellular vesicles (EVs) emerged as next-generation drug delivery platforms. EVs have an intrinsic tissue-homing capability, harnessing specific barcodes to find their target both locally and systemically.

Methods: Metastatic and non-metastatic breast cancer cell lines (MDA-MB-231 and MCF-10A, respectively) will be cultured in