



PROFILE

Intrigued by drug development, innovative therapies and clinical studies

EDUCATION

Vrije Universiteit Brussel

PhD in Pharmaceutical Sciences

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PHD ABSTRACT

SHIFT FROM 2D TO 3D IN THE DEVELOPMENT OF A HUMAN SKIN CELL-DERIVED HEPATIC *IN VITRO* MODEL FOR TOXICOLOGICAL APPLICATIONS

Drug-induced liver injury (DILI) is a major threat to human health and is, together with the low efficacy of generated pharmaceuticals, at the basis of a 90% failure rate in drug development. As preclinical data, obtained using experimental animals, do not adequately represent the human situation, performing *in vitro* models based on human cells are highly needed.

In this doctoral thesis, the relevance for toxicological screening of using human skin-derived stem cells that have been differentiated towards hepatic cells (hSKP-HPC) has been highlighted. It could be shown that these cells, cultured as a simple monolayer, are suitable for investigating drug-induced phospholipidosis (DIPL). Upon exposure to amiodarone, known to induce phospholipidosis in humans, hSKP-HPC displayed typical hallmarks of DIPL, including phospholipids accumulation, lamellar body formation and typical changes in gene expression. As hSKP-HPC monolayers show an immature hepatic phenotype, the next objective was to try to enhance their maturation. Changes in intrinsic properties of undifferentiated stem cells in 3D spheroid cultures versus 2D monolayer culture conditions were explored. It was found that the 3D configuration of hSKP spheres plays a pivotal role in the preservation of the stemness signature. Consequently, 3D nano-scaffolds were generated by two-photon polymerization of biocompatible photopolymers to mimic the micro-architecture of hepatic cell plates in human liver. It could be demonstrated that these scaffolds supported homing and proliferation of hSKP.

Overall, these findings emphasize the biological importance of 'in vivo-like' conditions for culturing and differentiating human stem cells. Although further optimization is necessary, our results further pave the way to enhance hepatic maturation which is a prerequisite to reliably predict human-specific hepatotoxicity of new pharmaceuticals

PUBLISHED SCIENTIFIC ARTICLES

First -author

- **Natale, A.**; Vanmol, K.; Arslan, A.; Van Vlierberghe, S.; Dubruel, P.; Van Erps, J.; Thienpont, H.; Buzgo, M.; Boeckmans, J.; De Kock, J.; Vanhaecke, T.; Rogiers, V.; Rodrigues, RM. Technological advancements for the development of stem cell-based models for hepatotoxicity testing. *Archives of Toxicology* (2019) 3: 1789-1805. [Q1, IF₂₀₁₉ 5.059] (**7 citations**, August 2021)
- **Natale, A.**; Boeckmans, J.; Desmae, T.; De Boe, V.; De Kock, J.; Vanhaecke, T.; Rogiers, V.; Rodrigues, RM. Hepatic cells derived from human skin progenitors show a typical phospholipidotic response upon exposure to amiodarone. *Toxicology Letters* (2018) 284: 184-194. [Q1, IF₂₀₁₈ 3.499] (**8 citations**, August 2021)

Co-author

- Boeckmans, J.; **Natale, A.**; Rombaut, M.; Buyl, K.; Cami, B.; De Boe, V.; Rogiers, V.; De Kock, J.; Vanhaecke, T.; Rodrigues, R.M.; Human hepatic *in vitro* models reveal distinct anti-NASH potencies of PPAR agonists. *Cell Biology and Toxicology* (2020) 37:293-311. [Q1, IF₂₀₁₉ 6.284] (**3 citations**, August 2021)
- Boeckmans, J.; **Natale, A.**; Rombaut, M.; Buyl, K.; Rogiers, V.; Vanhaecke, T.; Rodrigues, R.M.; De Kock, J. Flow cytometric quantification of neutral lipids in a human skin stem cell-derived model of NASH. *MethodsX* (2020) 19:101068. [no ranking] (**3 citations**, August 2021)
- Boeckmans, J.; **Natale, A.**; Rombaut, M.; Buyl, K.; Rogiers, V.; De Kock, J.; Vanhaecke, T.; Rodrigues, R.M. Anti-NASH drug development Hitches a lift on PPAR-agonism. *Cells* (2020) 9;1: 1-20. ["Recent Advances in Liver Repair Strategies"] [Q1, IF₂₀₂₀ 6.600] (**34 citations**, August 2021)
- Boeckmans, J.; Buyl, K.; **Natale, A.**; Vandenbempt, V.; Branson, S.; De Boe, V.; Rogiers, V.; De Kock, J.; Rodrigues, R.M.; Vanhaecke, T. Elafibranor restricts lipogenic and inflammatory responses in a human skin stem cell-derived model of NASH. *Pharmacological Research* (2019) 144:377-389. [Q1, IF₂₀₁₉ 5.893] (**13 citations**, August 2021)
- Boeckmans, J.; Buyl, K.; **Natale, A.**; Vandenbempt, V.; Branson, S.; De Boe, V.; Rogiers, V.; De Kock, J.; Rodrigues, R.M.; Vanhaecke, T. Transcriptomics data of a human *in vitro* model of non-alcoholic steatohepatitis exposed to elafibranor. *Data in Brief* (2019) 3:25:104093. [no ranking] (**1 citation**, August 2021)
- Boeckmans, J.; **Natale, A.**; Buyl, K.; Rogiers, V.; De Kock, J.; Vanhaecke, T.; Rodrigues, R.M. Comment to 'Letter to the editor: Human-based systems: Mechanistic NASH modelling just around the corner?' *Pharmacological Research* (2018) 137:282-283. [Q1, IF₂₀₁₈ 5.574] (**1 citation**, August 2021)
- Boeckmans, J.; **Natale, A.**; Buyl, K.; Rogiers, V.; De Kock, J.; Vanhaecke, T.; Rodrigues, R.M. Human-based systems: Mechanistic NASH modelling just around the corner? *Pharmacological Research* (2018) 134: 257-267. [Q1, IF₂₀₁₈ 5.574] (**27 citations**, August 2021)

INTERNATIONAL LONG-TERM MOBILITY DURING PHD

- 15 October -15 November 2017: **Marie Sklodowska Curie Grant, Research and Innovation Staff Exchange (RISE).**
InoCure - Prague, Czech Republic

SUPERVISION OF MASTER/PHD THESES AND INTERNSHIPS

- MSc in Pharmaceutical Sciences: Eva Wulffaert (2020) [co-promotor]

POSTER PRESENTATIONS (FIRST AUTHOR ONLY)

- **Natale, A.**, Boeckmans, J., De Kock, J., Arslan, A., Vanmol, K., Van Vlierberghe, S., Dubruel, P., Van Erps, J., Rogiers, V., Rodrigues, R.M., Vanhaecke, T., (2018). *Influence of 3D scaffolds and fluidics on the hepatic differentiation of human skin derived precursors*. Poster session presented at ESTIV 2018, Berlin, **Germany**.
- **Natale, A.**, Vanhaecke, T., De Kock, J., Boeckmans, J., Arslan, A., Vanmol, K., Van Vlierberghe, S., Dubruel, P., Van Erps, J., Rogiers, V., Rodrigues, R.M. (2018). *Evaluation of innovative 3D culture methods for the differentiation of human skin derived stem cells towards hepatic cells*. Poster session presented at Invitrom 2018, Utrecht, **the Netherlands**.
- **Natale, A.**, Boeckmans, J., Rodrigues, R.M., De Kock, J., Vanhaecke, T., & Rogiers, V. (2019). Investigation of the stemness properties of human-skin derived precursors cultured in 3D spheroids and 2D monolayers. Poster session presented at IC-3r Symposium (VUB) Brussels, **Belgium**.
- **Natale, A.**, Vanhaecke, T., Boeckmans, J., De Kock, J., Van Vlierberghe, S., Dubruel, P., Van Erps, J., Arslan, A., Vanmol, K., Rogiers, V., Rodrigues, R.M. (2018). *Evaluation of innovative 3D culture methods for the differentiation of human skin derived stem cells towards hepatic cells*. Poster session presented at Eurotox 2018, Brussels, **Belgium**.
- **Natale, A.**, Boeckmans, J., De Kock, J., Arslan, A., Vanmol, K., Van Vlierberghe, S., Dubruel, P., Van Erps, Vanhaecke, T., Rogiers, V., Rodrigues, R.M. (2018). *Improvement of hepatic differentiation of human skin derived stem cells by 3D scaffolds and fluidics*. Poster session presented at BeSSCR 2018-annual meeting, Leuven, **Belgium**.
- **Natale, A.**, Boeckmans, J., De Kock, J., Arslan, A., Vanmol, K., Van Vlierberghe, S., Dubruel, P., Van Erps, Vanhaecke, T., J., Rogiers, V., Rodrigues, R.M. (2018). *Improvement of hepatic differentiation of human skin derived stem cells by 3D scaffolds and fluidics*. Poster session presented at Symposium BSTE: Next Generation Tissue Engineering 2018, Ghent, **Belgium**.
- **Natale, A.**, Boeckmans, J., De Kock, J., Vanhaecke, T., Rogiers, V., & Rodrigues, R.M. (2017). *Human skin stem cell derived hepatic cells to assess drug induced phospholipidosis in*. Poster session presented at PhD Day, Jette, **Belgium**.
- **Natale, A.**, Boeckmans, J., De Kock, J., Vanhaecke, T., Rogiers, V., & Rodrigues, R.M. (2017). *Skin stem cell derived hepatic cells as an in vitro model for the assesment of drug induced phospholipidosis'*. Poster session presented at HEPRO symposium: Liver Disease and Regeneration, Leuven, **Belgium**.

- **Natale, A.**, Boeckmans, J., Rodrigues, R.M., De Kock, J., Vanhaecke, T., & Rogiers, V. (2016). *Human skin precursor derived hepatic cells as in vitro model to study steatosis*'. Poster session presented at BSCDB & BeSSCT 1st Joint Spring Meeting Stem Cells as Disease Model and for Gene Therapy, Brussels, **Belgium**.
- **Natale, A.**, Boeckmans, J., De Kock, J., Vanhaecke, T., Rogiers, V., & Rodrigues, R.M. (2016). *Skin stem cell derived hepatic cells as an in vitro model for the assessment of drug induced phospholipidosis*'. Poster session presented at BELTOX Annual Scientific Meeting. Brussels, **Belgium**.