Engineered 3D-Vessels-on-Chip to study effects of dynamic fluid flow on human induced pluripotent stem cell derived endothelial cells

Graaf, M.N.S. de

Curriculum Vitae

Mees de Graaf was born on August 13th, 1985 in Weesp, the Netherlands. After graduating from secondary school, he pursued a career in yacht racing before obtaining his bachelor-degree in Life Science and Technology at Leiden University and Delft University of technology. During his bachelor he did an internship at Crucell BV (now Janssen Vaccines), engineering expression cassettes for Adenovirus based vaccines.

His bachelor research focused on protein engineering for solid-state nanopore sequencing under the supervision of Prof. Dr. Chirlmin Joo and Prof. Cees Dekker at the department of Bionanoscience at Delft University of Technology.

He obtained his master degree Life Science and Technology at Leiden University, focusing on chemical biology, immunology and biomaterials. His master research at Leiden University Medical Center under the supervision of Dr. Valeria Orlova, focused on the development of 3D-vascular models using human induced pluripotent stem cells.

He continued this work during his PhD-research under the supervision of Dr. Valeria Orlova and Prof. Dr. Christine Mummery, and further developed 3D-hiPSC derived vascular models. The results are presented in this thesis.

List of publications

Scalable microphysiological system to model three-dimensional blood vessels

Mees N. S. de Graaf, Amy Cochrane, Francijna E. van den Hil, Wesley Buijsman, Andries D. van der Meer, Albert van den Berg, Christine L. Mummery, and Valeria V. Orlova
APL Bioengineering 3, 026105, 2019;
https://doi.org/10.1063/1.5090986

Multiplexed blood–brain barrier organ-on-chip

M. Zakharova, M. A. Palma do Carmo, M. W. van der Helm, H. Le-The, **Mees N. S. de Graaf**, V. Orlova, A. van den Berg, A. D. van der Meer, K. Broersend and L. I. Segerink
Lab Chip, 20, 3132-3143, 2020;
https://doi.org/10.1039/D0LC00399A

Rapid Prototyping of Organ-on-a-Chip Devices Using Maskless Photolithography

Dhanesh G. Kasi, **Mees N. S. de Graaf**, Paul A. Motreuil-Ragot ,Jean-Phillipe M. S. Frimat ,Michel D. Ferrari, Pasqualina M. Sarro , Massimo Mastrangeli, Arn M. J. M. van den Maagdenberg , Christine L. Mummery and Valeria V. *Orlova*
Micromachines 13 (1), 49,2022;
https://doi.org/10.3390/mi13010049

Pressure-Driven Perfusion System to Control, Multiplex and Recirculate Cell Culture Medium for Organs-on-Chips

Mees N. S. de Graaf, Aisen Vivas, Andries D. van der Meer, Christine L. Mummery, Valeria V. Orlova
Micromachines, 13(8), 1359, 2022;
https://doi.org/10.3390/mi13081359

Three-Dimensional Vessels-on-a-Chip Based on hiPSC-derived Vascular Endothelial and Smooth Muscle Cells

Merve Bulut, Marc Vila Cuenca, **Mees N.S. de Graaf**, Francijna E. van den Hil, Christine L. Mummery, Valeria V. Orlova
Current Protocols, 2, e564;
https://doi.org/10.1002/cpz1.564

On-chip analysis of glycolysis and mitochondrial respiration using extra-cellular flux validated in human-induced pluripotent stem cell

Stefanie Fuchs, Ruben W.J. van Helden, Maury Wiendels, **Mees N.S. de Graaf**, Valeria V. Orlova, Christine L. Mummery, Berend J. van Meer, Torsten Mayr
Materials Today Bio,17, 100475
https://doi.org/10.1016/j.mtbio.2022.100475

Multiplexed fluidic circuit board for continues controlled perfusion of 3D blood vessels on a chip
Mees N. S. de Graaf, Aisen Vivas, Dhanesh G. Kasi, Francijna E. van den Hil, Robbert Passier, Albert van den Berg, Christine L. Mummery, Andries D. van der Meer, Valeria V. Orlova
Lab Chip, 2023, 23, 168-181
https://doi.org/10.1039/D2LC00686C

In preparation

Perfusable Engineered capillary using hydrogel guided self-assembly on-Chip and human iPSC-derived vascular cells
Mees N. S. de Graaf, Dhanesh G. Kasi, Francijna E. van den Hil, Arn van Maagdenberg, Christine L. Mummery, Valeria V. Orlova

Acknowledgement

This thesis is the result of the work and effort of many people who I would like to thank for their inspiration and support.

Valeria, thank you for the opportunity to be part of your research group.

Dear Christine, thank you for your guidance, patience and understanding during my research.

Lisa, I could not go without your support. I am so grateful you helped me out with everything possible, both in and out of the lab. Both Gia and I will miss you.

To the rest of Orlova group; Amy, Marc, Dennis, Dhanesh, Ulgu and Merve. I wish you all the best for the future.

All the people of the NOCI-consortium. Although I am going to miss you all, I will not miss the apenkoppen. I wish you all the very best on your own projects!

I would like to express my gratitude to the whole department of Anatomy and Embryology especially to Bert, for the help in scavage hunts through the depths of the LUMC.

Andries van der Meer, Wesley Buijsman and Aisen Vivas from the University of Twente, for their technical input and ingenuity.

Lennard Voortman and Annelies Boonzaier-van der Laan of the Light Microscopy Facility for their support over the years. You helped me to show to everybody what I was doing, probably the most important part of this work.

The late Mevrouw Esther Elkerbout, her interest in our research made this work possible. We are all very grateful for her contributions to our lab.

My dear parents, thank you for all the support during my whole academic career. My sister and brothers; Mare, Dirk and Olivier, thank you for being there for me when I was around.

Lieve Gia, het was zo'n feest om dit werk met jou te hebben mogen delen. Hier staan ook jouw eerste experimenten en jouw eerste poster presentatie in Graz. We gaan nog samen veel ontdekken.

Lieve Luc, dank voor je gezelschap in de nacht tijdens het laatste deel van dit verhaal. Samen schrijven is veel gezelliger, maar nu kunnen we weer vooral samen spelen.

Dear Banu, the greatest sacrifices come from the partner of the PhD-candidate. Thank you for being next to me with your wit and inspiration, your support and understanding and most of all: your patience.

It is finished now (really).

nunc est bibendum

Stellingen behorend bij het proefschrift:

Engineered 3D-Vessels-on-Chip to study effects of dynamic fluid flow on human induced pluripotent stem cell derived-endothelial cells

1. **3D-VoCs produced with VFP can be used to apply uniform shear stress to all cells.**
   This thesis
2. **τEQ resistors improve the throughput of 3D-VoC perfusion by allowing variation instead of eliminating it.**
   This thesis
3. **hiPSC-derived endothelial cells can swiftly adapt to changing haemodynamic conditions.**
   This thesis
4. **Confined hiPSC-derived endothelial cells prefer to adopt a tubular morphology; unconfined hiPSC-derived endothelial cells prefer to form monolayers.**
   This thesis
5. **Vascular models without correct haemodynamics should be considered a pathophysiological model.**
   This has implications for the translation to *in vivo.*
   Ming He et al.(2020) APL Bioengineering 4, 010904
6. **3D-models can be better disease models than 2D models.**
   However the clues are well hidden.
   Orlova et al. (2022) Stem Cell Reports 12;17(7):1536-1545
7. **Sticking feathers to something does not make it a chicken**
   By only looking at the parameters a model should have, one could overlook the features it shouldn't.
   Tyler M. Lu et al. (2021) PNAS vol 118(8) e2016950118
8. **"It is evident that the use of human organ chips instead of animal models for drug development and as living avatars for personalized medicine is ever closer to realization."**
   Donald E. Ingber (2022) Nature Reviews Genetics, 23, pages 467–491
   Now legislation is in, the field must now deliver.
9. **Anything worth doing, is worth doing right**. *Raoul Duke (1971)*
   Refine and validate a proof of concept before generating data.
10. **Assumptions are the mother of all failures.** *Eugene Fordsworthe*
    For interdisciplinary research assumptions are essential, however it is vital to understand how to extrapolate other people's assumptions.
11. **"All problems in microfluidics are small".** *Lisa van den Hil (2020)*
    Most problems encountered in microfluidic prototyping are not intrinsic to the design but fabrication and are easy to solve. However, the smallest imperfection still has detrimental effects on success and morale.
12. **"Mother Nature is a mad scientist".** Kramer (1997)
    Attempting to recapitulate it on a chip, makes you appreciate it even more.