hDMT FOUNDING PARTNERS

SCIENTIFIC EXPERTISE and FACILITIES

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December 2014

hDMT
HUMAN ORGAN AND DISEASE MODEL TECHNOLOGIES

TABLE OF CONTENTS

LEIDEN UNIVERSITY MEDICAL CENTER

LEIDEN UNIVERSITY MEDICAL CENTER

LUMC

Expertise and facilities:

Expertise

Group vascular diseases (Mummery)

- Biology of pluripotent stem cells and their differentiation to the cardiac and vascular lineages
- Use of human embryonic and induced pluripotent stem cells to create cardiac and vascular (genetic) disease models
- Generation of human iPS cell lines
- Biology of heart development and cardiac disease
- Vascular diseases and the biology of endothelial and vascular smooth muscle cells
- Genetic modification of human pluripotent stem cells
- Electrophysiology of cardiac myocytes by patch clamp, voltage sensitive dyes and micro-electrode arrays and their use in drug safety testing
- Calcium handling and contraction force measurements in cardiomyocytes
- Optical (optogenetic) and electrical pacing of heart cells
- Early development particularly of lateral plate, intermediate and paraxial mesoderm (heart)

Group microvascular disease (van Zonneveld, Rabelink)

- Biology of endothelial progenitor cells
- Biology and *in vitro* models of endothelial cell-cell and pericyte interaction
- Posttranscriptional regulation of EC and VSMC differentiation
- Access to microvascular disease-related clinical samples
- Access to patient-derived cell types suitable for iPS cell lines and the generation of *in vitro* models for microvascular destabilization

Group cardiac differentiation and disease (Passier)

- Heart development and disease
- Generation of human iPS cells
- Cardiac disease modeling using human iPS cells
- Human pluripotent stem cells and their differentiation to the cardiac lineage (including cardiac mesoderm, epicardial cells and cardiomyocyte subtypes such as atrial, ventricular and pace-maker cells)
- Transcriptional regulation of cardiac differentiation and disease
- Genetic modification of human pluripotent stem cells (including generation of fluorescent reporter lines)
- Electrophysiology of cardiomyocytes by patch clamp, voltage sensitive dyes and micro-electrode arrays and their use in drug safety testing
- High content imaging for drug toxicity screening and cardiac biology
- Microcontact printing of cardiomyocytes
- Calcium handling and contraction force measurements in cardiomyocytes

Facilities

Mummery/Passier

- State of the art cell culture rooms, FACS, live cell imaging, electrophysiology, imaging (including optogenetics)
- iPSC core facility for generation of disease lines, development of growth and differentiation protocols based on defined culture media and extracellular matrix proteins
- Availability of human fetal tissue for research

Van Zonneveld/Rabelink

- A pericyte stabilized microfluidic model for microvascular destabilization (with Hankemeijer/ Mimetas)
- Access to large collections of characterized clinical samples of patients relevant for the study of microvascular disease

Ongoing projects:

Mummery/Passier

1. Endothelial and smooth muscle cells in microfluidic chips (with Mimetas, UT): Muller Foundation; Plurimes FP7 EU)
2. Cardiomyocytes in microfluidic chips (with Mimetas)
3. Cytostretch (with TU Delft)
4. Pole technology (with Thomas Schmidt): FOM
5. Methods for cardiomyocyte maturation (cyclic stretch, hormones, pacing, optogenetics): Crack-It (phase 1, phase 2); ERC

Van Zonneveld/Rabelink

1. Microvascularity in OrganoPlates: A microvascular model is developed in different tissue contexts to study the influence of microvasculature on organ damage using metabolomics techniques (with LACDR & MIMETAS).
2. Impact of diabetes and renal failure on microvascular de-stabilization (NSN, NIRM)
3. Gender specific mechanisms in microvascular dysfunction in HFPEF (CVON, NHS)
4. Microvascular rarefaction in Atrial Fibrillation and Kidney transplantation (NHS, BMS)

Publications:

1. Davis, R.P. Casini, S., van den Berg, C., Hoekstra, M., Remme, C., Dambrot, C., Salvatori, D., Ward-van Oostwaard, D., Wilde, A.A., Bezzina, C.R., Verkerk, A., Freund, C., Mummery, C.L. Cardiomyocytes derived from pluripotent stem cells recapitulate electrophysiological characteristics of an overlap syndrome of cardiac sodium channel disease. **Circulation**, 2012 125(25):3079-91
2. Braam, S.R., Tertoolen, L., Casini, S., Matsa, E., Lu, H.R., Teisman, A., Passier, R., Denning, C., Gallacher, D.J., Towart, R., Mummery, C.L. Repolarization reserve determines drug responses in human pluripotent stem cell derived cardiomyocytes **Stem Cell Res.** 2013 10(1):48-56.
3. Bellin, M., Davis, R.P., Casini, S., *et al* Isogenic human pluripotent stem cell pairs reveal the role of a KCNH2 mutation in long-QT syndrome. **EMBO J** 2013 32, 3161–3175.
4. Orlova, V.V., Drabsch, Y., Freund, C., Petrus Reurer, S., van den Hil, F.E., Muenthaisong, S., ten Dijke, P., Mummery. C.L. Functionality of endothelial cells and pericytes from human pluripotent stem cells demonstrated in cultured vascular plexus and zebrafish xenografts, **Arterioscler. Thromb. Vasc. Biol.** 2014 34,177–186.

5. Orlova, V.V., van den Hil, F.E., Petrus-Reurer, S., Drabsch, Y., ten Dijke, P., Mummery, C.L. Endothelial Cells and Pericytes from human Pluripotent Stem Cells: methods for efficient generation, expansion and examination of functional competence. **Nature Protocols** 2014, 9:1514-1531.
6. Den Hartogh, S.C., Schreurs, C., Monshouwer-Kloots,,J.J., Davis, R.P., Elliott, D.A., Mummery, C., Passier, R. Dual reporter MESP1$^{mCherry/w}$-NKX2-5$^{eGFP/w}$ hESCs enable tracking of early human cardiac differentiation. **Stem Cells.** 2014 Sep 3. doi: 10.1002/stem.1842.
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8. van der Veer ,E.P., de Bruin, R.G., Kraaijeveld, A.O., de Vries, M.R., Bot, I., Pera, T., Segers, F.M., Trompet, S., van Gils, J.M., Roeten, M.K., Beckers, C.M., van Santbrink, P.J., Janssen, A., van Solingen, C., Swildens, J., de Boer, H.C., Peters, E.A., Bijkerk, R., Rousch, M., Doop, M., Kuiper, J., Schalij, M.J., van der Wal, A.C., Richard, S., van Berkel, T.J., Pickering, J.G., Hiemstra, P.S., Goumans, M.J., Rabelink, T.J., de Vries, A.A., Quax ,P.H., Jukema, J.W., Biessen, E.A., van Zonneveld, A.J. Quaking, an rna-binding protein, is a critical regulator of vascular smooth muscle cell phenotype. **Circulation research.** 2013;113:1065-1075.
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10. Rabelink, T.J., de Boer, H.C., van Zonneveld, A.J. Endothelial activation and circulating markers of endothelial activation in kidney disease. **Nature reviews. Nephrology.** 2010;6:404-414.

Relevant patents:

1. **Development of methods for efficient production of endothelial cells and smooth muscle cells from human Pluripotent Stem Cells (hPSC)** (ATVB 2013 en Nat. Protocols, 2014), **and a 2D culture system that mimics tumor blood vessels** (ATVB 2013). **Patent filed.**

Added value LUMC for hDMT:

- hiPSC derived vascular cells for microfluidic flow chips and high content screening
- hPSC derived cardiomyocytes for heart on chip formats
- mass production in bioreactors and cryopreserved supply of cardiac and vascular cells via spinout Pluriomics
- patient tissue for generating hiPSC with corresponding medical histories and informed consent for general use in screening
- hiPSC lines with various cardiac and vascular disease mutations showing disease phenotypes
- mesoderm lineage reporter hPSC lines
- technology to generate genetically engineered hPSC lines as reporters of disease phenotypes

Partner website http://www.lumc.nl

Added value hDMT for LUMC:

- opportunities for interaction and collaboration with pharma
- access to compound and drug libraries, shRNA libraries to identify disease targets
- feedback on disease models of interest to pharma
- opportunities to apply for co-funding
- access to advanced screening technology and state of the apparatus.

Leiden University

Leiden Amsterdam Center for Drug Research (LACDR)

Leiden University

Expertise and facilities:

Expertise

- Large-scale development of 3D cell culture models and advanced microfluidics systems
- Screening by RNAi and chemical libraries
- Metabolomics and high content imaging (Netherlands Metabolomics Center/NL Bioimaging node High Througput Microscopy (HTM) and EU Bioimaging node HTM).
- Central role within University of Leiden in drug research and development, in close collaboration with LUMC and CHDR.
- Automated medium-throughput screening on advanced 3D Organ on chip models

Facilities

- Leiden Cell Observatory: 3X automated confocal imaging systems with perfect focusing and automated stage (Nikon); multiphoton imaging (Nikon); BD Pathway 855 with robotics and automated cell culturing; automated liquid handling BIOMEK with robotic cell culturing;
- Cell culture laboratories; MLII facilities; automated FACS
- High throughput multiparameter image analysis pipeline (RHDF2, Cell Profiler and R)
- siRNA libraries for entire druggable human genome; compound libraries for all FDA approved drugs.
- Metabolomics and mass spectrometry facility for biochemical profiling of organ-on-a-chip systems
- Systems Pharmacology models and algorithms including PK/PD, reconstructed metabolic networks, biomarker discovery, and translational algorithms
- Rapid prototyping facility to produce custom-made microfluidic devices

Ongoing projects:

1. **Microvascular system in OrganoPlates:** A microvascular model is developed in different tissue contexts to study the influence of microvasculature on organ damage, and using metabolomics techniques to study disease mechanism and pharmacology (ABS/LACDR with MIMETAS & LUMC (Van Zonneveld/Mummery); PIs Hankemeier/Vulto).
2. **Chemotherapeutic combination therapy screening on cancer stem cell spheroids:** Aim of the project is the development of an organotypical model consisting of intestinal tumor stem cell spheroids that are grown in 3D in an ECM (vasculature added). The models are screened for effectivity of different chemotherapeutics in combination with pump inhibitors (ABS/LACDR in collaboration with MIMETAS & UMCU; PIs Hankemeier/Vulto).
3. **LgR5⁺ gut epithelial organoid culture in low volumes:** Aim of the project is to screen intestinal gut organoids in minimal volumes and study boundary formation (ABS/LACDR with MIMETAS & Hubrecht Lab; PIs Hankemeier/Vulto).
4. **Neuronal co-cultures in microfluidic plates, and metabolomics for functional studies**

of disease genes for Alzheimer (LACDR with Mimetas and Erasmus MC (Kushner/Van Duijn); PIs Hankemeier/Vulto; funding EU, pharma)

5. **Metabolomics of organ-on-chip system of pancreatic cancer** (ABS/LACDR with Mimetas; PIs Hankemeier/Vulto, funding: EU)
6. **Arrayed 3D ECM-embedded spheroids for multiple cancer types for drug screens** (PI EHJ Danen; funding KWF & LU; collaboration NKI & LUMC).
7. **3D ECM-embedded tumor spheroids for studies on tumor angiogenesis and physical aspects of ECM organization in this process** (PI EHJ Danen; funding KWF & FOM; collaboration Physics Institute Leiden & AMOLF).
8. **Systems microscopy for high content RNAi screens** (PI B van de Water; funding EU FP7; collaboration Karolinska Institute and Weizmann Institute)
9. **A 3D liver model for *in vitro* toxicity studies** (PI B van de Water/L Price; funding NGI/NTC; collaboration OcellO)
10. **Fluorescent reporter cell models to study signalling and adaptive stress responses** (PI B van de Water; funding Pharma & EU FP7)

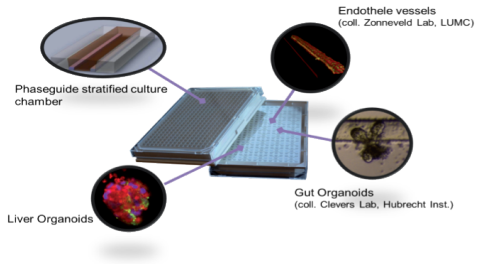

Figure 1. The OrganoPlate™ contains 96 3D cell culture rooms; the detailed picture shows a single room consisting of a lane for the gel with cells and a lane for perfusion of the medium. The two lanes keep separated by the phaseguide (see also the video on http://www.youtube.com/watch?v=BhFETKQqJY0).

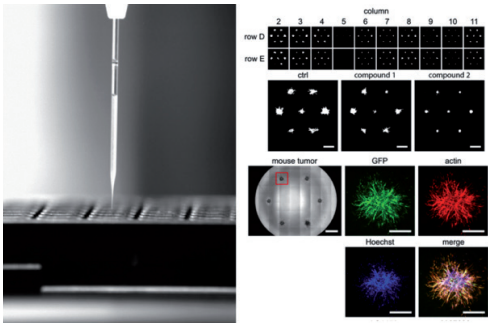

Figure 2. The onco-array contains a large amount of spheroids (mini-tumors) of different formats (6 per well/96 well plate; 1 per well/384 well plate; or 1 per well/1536 well plate (the last variant is in development). Upper right: a snap shot of a drug screen; lower right: an example of an array made from fresh biopsy material.

Publications:

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2. Truong, H.H, Xiong, J, Ghotra, .V.P, Nirmala, E., Haazen, L., Le Dévédec, S.E., Balcioğlu, H.E., He, S., Snaar-Jagalska, B.E., Vreugdenhil, E., Meerman, J.H., van de Water, B., Danen, E.H. β1 integrin inhibition elicits a prometastatic switch through the TGFβ-miR-200-ZEB network in E-cadherin-positive triple-negative breast cancer. **Science Signaling** 7(312):ra15 (2014).
3. Di, Z, Klop, M.J., Rogkoti, V.M., Le Dévédec, S.E., van de Water, B., Verbeek, F.J., Price, L.S., Meerman, J.H. Ultra High Content Image Analysis and Phenotype Profiling of 3D Cultured Micro-Tissues. **PLoS One** 9(10):e109688 (2014).
4. Yizhak, K., Le Dévédec, S.E., Rogkoti, V.M., Baenke, F., de Boer, V.C., Frezza, C., Schulze, A., van de Water, B., Ruppin, E. A computational study of the Warburg effect identifies metabolic

targets inhibiting cancer migration. **Mol Syst Biol** 10(20):744 (2014)
5. Truong, H.H.,. de Sonneville, J., Ghotra, V.P., Xiong, J.P., Price, L., Hogendoorn, P.C., Spaink, H.H., van de Water, B., Danen, E.H. Automated microinjection of cell-polymer suspensions in 3D ECM scaffolds for high-throughput quantitative cancer invasion screens. **Biomaterials** 33:181-188 (2012).
6. Trietsch, S.J., Israels, G.D., Joore, J., Hankemeier, T., Vulto, P., Microfluidic titer plate for stratified 3D cell culture. **Lab on a chip**, vol. 13, no. 18, pp. 3548-54
7. Vulto, P., Podszun, S., Meyer, P., Hermann, C., Manz, A., Urban, G.A. Phaseguides: a paradigm shift in microfluidic priming and emptying. **Lab Chip**, 2011, 11, 1596-1602.
8. Quist J., Vulto, P., Van der Linden, H. J., & Hankemeier, T. Tunable Ionic Mobility Filter for Depletion Zone Isotachophoresis. **Anal Chem** 2012; 84: 9065-9071.
9. Ellero-Simatos, S., Lewis, J.P., Georgiades, A., Yerges-Armstrong, L.M., Beitelshees, A.L., Horenstein, R.B., Dane, A., Harms, A.C., Ramaker, R., Vreeken, R.J., Perry, C.G., Zhu, H., Sànchez, C.L., Kuhn, C., Ortel, T.L., Shuldiner, A.R., Hankemeier, T., Kaddurah-Daouk, R. Pharmacometabolomics reveals that serotonin is implicated in aspirin response variability. **CPT Pharmacometrics Syst Pharmacol.** 2014 ;3: e125. doi: 10.1038/psp.2014.22.
10. Schoonen, J.W., van Duinen, V., Oedit, A., Vulto, P., Hankemeier, T., Lindenburg, P.W. Continuous-flow microelectroextraction for enrichment of low abundant compounds. **Anal Chem.** 2014: 86: 8048-8056.

Relevant patents:

1. Danen EHJ *et al*. (2011) WO2012131000: Method for obtaining a multicellular spheroid.
2. Leiden University and Mimetas hold a portfolio of patents related to the OrganoPlate™ and Phaseguide technology, which cannot be disclosed.
3. Leiden University holds several patents related to miniaturized analytical methods enabling coupling mass spectrometry with organ-on-a-chip systems.

Added value Leiden University for hDMT:

- Expertise in microfluidics and medium/high throughput organ-on-a-chip assays
- Expertise in 3D culture
- Expertise in cell-ECM interactions and implications for cell fate
- Fluorescence microscopy facility with automated high content high throughput confocal imaging and quantitative image analysis
- Expertise in drug/RNAi screening
- Expertise in metabolomics and systems pharmacology for translational research: from patients to organ-on-a-chip, and back

Added value hDMT for Leiden University:

- Dutch interaction network microfluidics
- Dutch interaction network 3D culture systems
- Innovative models for drug development
- Speed up development of new human-relevant *in vitro* models for drug (target) discovery
- Expertise on drug efficacy and safety assessment

Delft University of Technology

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The following groups at the Delft University of Technology actively participate in the hDMT:

- Electrical Components Technology and Materials (EWI)
- Bioelectronics (EWI)
- Department of Bionanoscience (AP)
- The Delft Bioinformatics Lab (EWI)

These groups use/share world class facilities such as:

- The Kavli Nanolab and Imaging Center
- The Else Kooij Lab for micro-fabrication (Former DIMES cleanroom)

Expertise and facilities:

Expertise

Group Electronic Components and materials (ECTM)

The incredible development of IC technologies for computers and mobile communication over the past thirty years has resulted in equipment and materials which can be used not only to fabricate computer chips, but also to fabricate, on a micron scale, whole systems which perform functions such as sensing, actuation for an almost endless variety of applications. The group ECTM is specialized in combining all these technologies into working devices with a growing emphasis on biomedical applications. Expertise relevant to the hDMT initiative includes:

- Vertical integration knowledge to combine basic technologies into functional devices;
- World renounced expertise in MEMS and sensor fabrication
- Expertise on bringing ideas to manufacturable devices and systems
- Extensive experience in the processing of polymers relevant for biomedical devices
- Excellent links with medium and high volume micro-fabrication foundries

Group Bioelectronics

Section Bioelectronics is specialized in integrated circuits and systems for electroceuticals, the electronic counterparts of pharmaceuticals. Expertise relevant to the hDMT initiative includes:

- Biosignal conditioning/detection
- Electrical stimulation and recording of cells and tissue
- Electroceuticals
- Bioelectronics and biomedical electronics

Group Bionanoscience

The department of Bionanocience is a young interdisciplinary department with currently 15 independent principles investigators (PIs) covering a broad range of expertise that is relevant to the hDMT initiative:

- Synthetic biology and biomimetics
- Nanoscience and –technology
- Quantitative cell biology
- Single molecule biophysics
- High resolution imaging
- Microfluidics and nano/microfabrication

Facilities

Else Kooij Lab (former DIMES cleanroom):

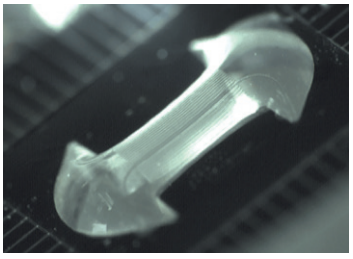
The Else Kooij Lab - a subsidiary of TUD – operates a 600 m^2 class 100 clean room fully equipped for the vertical integration of a large variety of micro-fabricated devices. In the lab students can realize their own design and concepts in silicon. Additionally the cleanroom acts as a small scale foundry for customers who want to prototype or pilot produce their devices. The Else Kooij lab has excellent working relations with the Philips Innovation Service Pilot line cleanroom so that concepts developed in the Else Kooij lab can be seamlessly transferred to production.

The capabilities of the Else Kooij Lab include:

- a full process line (0.5 µm CMOS/bipolar capability), class 100
- a class 10,000 laboratory for MEMS
- an electrical characterization laboratory
- process capabilities for the processing of active devices (epi, ion implantation, gate oxidation, stepper lithography)
- process capabilities for MEMS processing (LPCVD, PECVD, wafer bonding, DRIE etching, metal deposition)
- process capabilities for bio-devices (polymer deposition, processing, and etching)

The Else Kooij Lab for Micro-fabrication:

- Class 100, 0.5 um process line
- Active device and MEMS processing
- Polymer processing for hDTM devices
- Linked up with volume production



Cytostretch, a hDMT platform for:

- Electrophysiology under strain
- Porous stretchable membranes
- Integration of sensors
- Submicron PDMS features
- Integrated electronics

KAVLI Institute:

The Kavli institute of Nanoscience at the Department of Applied Sciences joins the efforts of the Department of Quantum Nanoscience and Bionanoscience. Facilities run by the institute that are relevant to the hDMT initiative consist of:

- Extensive biofacilities (ML1/2, general bio- and cell culture facilities)
- Kavli Nanolab (clean room facility for nanofabrication)
- Kavli Nanolab Imaging Center (collection of high end optical microscopes including spinning disk confocal, TIRF, SIM, scanning confocal, regular fluorescence etc.)

Ongoing projects:

Group Electronic Components and materials (ECTM)

ECTM in collaboration with Philips is developing the Cytostretch platform. The heart of the Cytostretch platform is a thin PDMS membrane suspended in a silicon chip. Cells are plated on the membrane, and can be stretched by applying a differential pressure across the membrane. Applications:

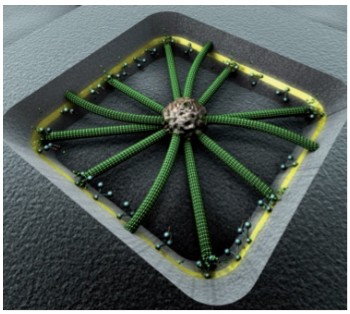
- Stretchable electrodes for electrophysiological characterization of the cells;
- Micro-fabricated groves to induce cell alignment;
- Through membrane holes to allow for cell interaction for cell bi-layers;
- Strain gauges for contractility measurements (under development);
- Integrated electronics for on-chip signal processing (under development).

Group Bioelectronics

Bio-Electronics is currently participating in the STW project (11693) "REASONS – Real-time Sensing of Neural Signals", in the Netherlands. This project targets the development of a completely new readout system for measuring the so called electrically evoked compound action potential (eCAP) coming from the auditory nerve. To develop this readout system, new electronic circuitry will be designed based on state of the art technologies integrated with the electrode itself. Existing systems will be tested extensively to develop novel measurement algorithms for the new readout system. Animal experiments will be performed on existing and new readout systems.

Group Bionanoscience

At the Department of Bionanoscience several projects are running related to the biophysics and nanotechnology of DNA, RNA and their associated proteins (ERC Advanced grant Cees Dekker; ERC Consolidator grant Nynke Dekker, ERC starting grant Chirlmin Joo). Furthermore there are several efforts to reconstitute essential cellular processes in artificial systems, with the eventual goal to build synthetic cells (e.g. NWO VIDI Christophe Danelon; NWO Top Cees Dekker). Specifically there is a large effort to reconstitute cytoskeletal processes relevant for cell division and migration in 3D matrices (ERC synergy grant Marileen Dogterom in collaboration with Anna Akhmanova, a cell biologist in Utrecht).



A microtubule aster is positioned by motor proteins in an "artificial cell", made with micro-fabrication and surface chemistry techniques. This process is relevant for the way mitotic spindles are positioned in dividing cells.

Publications

1. Hol, F.J.H. and C. Dekker. Zooming in to see the bigger picture: using nanofabrication to study bacteria, **Science**, in print (2014).
2. Preciado López, M., Huber,F., Grigoriev, I., Steinmetz, M.O., Akhmanova, A., Koenderink, G.H., Dogterom. M. Actin-microtubule coordination at growing microtubule ends, **Nature Communications 5**:4778 (2014).
3. Preciado López, M., Huber,F., Grigoriev, I., Steinmetz, M.O., Akhmanova, A., Koenderink, G.H., Dogterom. M. Actin-microtubule coordination at growing microtubule ends, **Nature**

Communications 5:4778 (2014).
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5. Lee, M., Lipfert, J., Sanchez, H., Wyman, C. and Dekker, N.H. Structural and Torsional Properties of the RAD51-dsDNA Nucleoprotein Filament, **Nucleic Acids Research** 41, 7023–7030 (2013).
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7. Khoshfetrat Pakazad, S., Savov, A., van de Stolpe, A. and R. Dekker. "A novel stretchable micro-electrode array (SMEA) design for directional stretching of cells," **J. Micromech. Microeng.**, vol. 24, 034003, (2014)
8. Yongjia Li, Andre L. Mansano, Yuan Yuan, Duan Zhao and Wouter A. Serdijn. An ECG Recording Front-End With Continuous-Time Level-Crossing Sampling, IEEE Transactions on Biomedical Circuits and Systems, Digital Object Identifier 10.1109/**TBCAS**.2014.2359183
9. van Dongen, M.N. and Serdijn, W.A. A Power-Efficient Multichannel Neural Stimulator using High-frequency Pulsed Excitation from an Unfiltered Dynamic Supply, **IEEE Transactions on Biomedical Circuits and Systems**, in print 2014.

Added value Delft University of Technology for hDMT

The added value of the TU Delft to the hDMT initiative is both on a fundamental as well as on a practical level. The fundamental research at molecular and cellular level (DNA-protein interactions, membranes, cytoskeleton, lipid vesicles) are crucial building blocks to understand the (mechanical properties of) cellular model systems, which in particular is relevant for cancer models. At the same time our engineering skills in micro- and nano-fabrication as well as in nano-fluidics will help in building disease models that are manufacturable and have economical relevance.

Added value hDMT for Delft University of Technology

One of the most exciting developments of our time is the spontaneous breaking up of barriers between disciplines which are as wide apart as (silicon) micro-fabrication, physics and life-sciences. Doctors and physicians are appreciating the potential of nano- and micro-technologies, while physicists and technologists are learning to understand the language of life-sciences, with the common goal to find technological solutions to one of the most urgent societal issues of the western world: "How can we continue to provide increasingly better healthcare at affordable cost for an aging society." The hDMT program offers the University of Delft the unique opportunity to work together with top-experts in academic and industrial life sciences to jointly develop societal relevant solutions.

University of Twente

UNIVERSITY OF TWENTE.

University of Twente

Expertise and facilities:

Expertise

- BioNanoTechnology
- Microfluidic devices design and testing including droplet microfluidics, microfluidics for cell culture, microfluidics for diagnostics
- Organic chemistry and polymer chemistry
- Membrane process technology
- Biofabrication technology and 3D manufacturing of scaffolds
- Technology inspired regenerative medicine

Facilities

- Mesa+ NanoLab (cleanroom) for nanofabrication
- Mesa+ BioNanoLab with high throughput robotics and high content imaging
- State of the art facilities for organic and polymer chemistry and process technology
- State of the art cell culture facilities
- State of the art facilities for molecular biology at ML1 and ML2 level

Ongoing projects:

Group van den Berg

1. **Human blood vessel model, e.g. for arterial (e.g. atherosclerosis) and venous thrombosis** (collaboration LUMC/Philips Research). Funding by ZonMW Cardiotox in hPSC (R. Passier, LUMC), ERC Advanced (C. Mummery, LUMC).
2. **Human Blood-Brain-Barrier model** (collaboration Mimetas, Wyss institute).

Group Karperien

1. **Microwell platforms for stem cell culture and cartilage engineering**
   Dutch Arthritis Association program grant, CSC grant Chinese Government (M. Karperien).
2. **Microwell platforms for culture and transplantation of Islets of Langerhans**
   (collaboration with Galapagos B.V. and E. de Koning, LUMC). Diabetes Cell Replacement Initiative (DCTI) (Karperien / van Apeldoorn).
3. **Microfluidic systems for preparation of microgels mimicking cellular micro-niches using in situ gelating hydrogels of ECM molecules.**
   Dutch Arthritis Association (Karperien).
4. **Microfluidic systems for the preparation of microgels for conformal encapsulation of**

Islets of Langerhans using in situ gelating hydrogels of ECM molecules.
(collaboration with Galapagos B.V. and E. de Koning, LUMC). Diabetes Cell Replacement Initiative (DCTI) (Karperien).

5. **Development of software tools for modelling of biological signaling routes.**
(collaboration with J van de Pol, UTwente) Dutch Arthritis Association program grant, MIRA voucher (Karperien, Post).

Group Stamatialis

1. **06C.12 High throughput screening of biologically active surface nano-topographies within the 06C.**
NANO-BIO INTERFACES & DEVICES (NBID). NanoNext project (together with Prof. Jan de Boer (TR group)).

Group Claessens

1. **Development of a platform to induce Lewy bodies (pathological characteristic of Parkinson's disease) in neuronal cell lines and primary neurons.**
Chris Raiss. Funded by the NWO VIDI grant of Mireille Claessens.
2. **Influence of the induction of different types of Lewy bodies on the activity of primary neurons using electrophysiological measuring.**
Collaboration with Joost le Feber. Proposal in preparation.
3. **Relationship between formation of different types of Lewy bodies and toxicity in a model system.**
Collaboration with Irene Konings and Kirsten Leijenhorst. Funding by Stichting Parkinson Fonds.
4. **Development of a platform to study signal transduction and protein aggregation in neuronal networks derived from iPS cells using super resolution microscopy.**
Project Amin Abolghassemi Fakhree. Collaboration with the group of Sjef Copray.
5. **Study on improvement of the quality of cartilage using protein-fibril-based scaffolds.**
Maurice van Dalen/DBE group. Funding by MESA+ graduate school.
6. **Lipid vesicles or supported lipid bilayers as model system for cell membranes.**

Group le Gac

1. **Lung on a chip.**

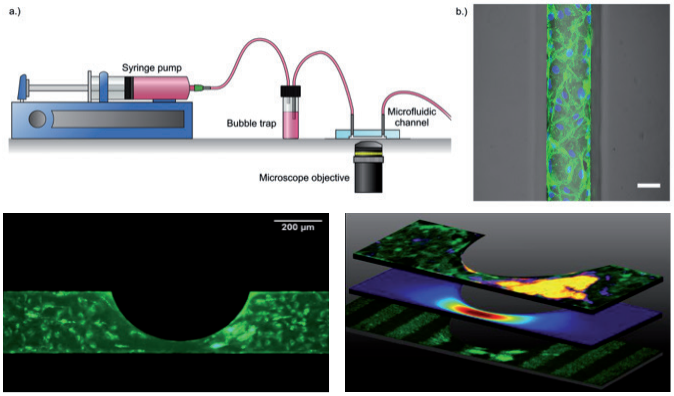

Figure 1: Blood vessels on a chip. A microfluidic endothelial cell model of atherosclerotic thrombus formation. Blood flown through the channel causes increased shear rate in the stenotic area, leading to rapid aggregation of fluorescent platelets.

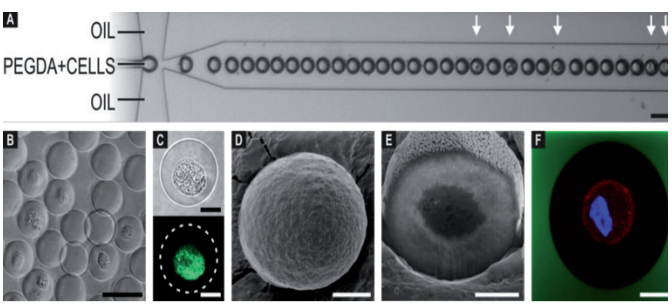

Figure 2: Engineering cellular microniches by single cell encapsulation in monodisperse microgels using droplet microfluidics. A) Details of the microfluidic chip. Single cell containing microgels (arrows). B) Single cells are nicely centered in the middle of the microgel and C) are alive (green stain). D) Scanning Electron Microscopic image of a microgel. E) Electron Photo Beam Milling of a microgel. F) Confocal microscopic image of a microgel. Cell nucleus (blue), cell membrane (red), hydrogel (black), background (green).

Publications:

1. Westein, E., van der Meer, A.D., Kuijpers, M.J., Frimat, J.P., van den Berg, A., Heemskerk, J.W..Atherosclerotic geometries exacerbate pathological thrombus formation poststenosis in a von Willebrand factor-dependent manner. **PNAS** 2013: 110(4) 1357-1362.
2. van der Meer, A.D., Orlova, V.V., ten Dijke, P., van den Berg, A., Mummery, C.L.. Three-dimensional co-cultures of human endothelial cells and embryonic stem cell-derived pericytes inside a microfluidic device. **Lab on a chip** 2013 DOI:10.1039/C3LC50435B.
3. Griep, L.M., Wolbers, F., de Wagenaar, B., *et al*. BBB ON CHIP: microfluidic platform to mechanically and biochemically modulate blood-brain barrier function. **Biomedical microdevices** 2013: 15(1) 145-150.
4. Stimberg, V.C., Bomer, J.G., van Uitert, I., van den Berg, A. and le Gac, S. High yield, reproducible and quasi-automated bilayer formation in a microfluidic format. **Small**, 2013, 9(7), 1076-1085.
5. Hofmeijer, J., Mulder, A.T.B., Farinha, A.C., van Putten, M.J.A.M., le Feber, J. Mild hypoxia affects synaptic connectivity in cultured neuronal networks. **Brain Research** 2014, 1557, 180-189.
6. Leijten, J, Georgi, N, Moreira Teixeira, L, van Blitterswijk, C.A., Post, J.N., Karperien, M. Metabolic programming of mesenchymal stromal cells by oxygen tension directs chondrogenic cell fate. **PNAS** 2014, 111(38):13954-9.
7. Buitinga, M., Truckenmüller, R., Engelse, M.A., Moroni, L., Ten Hoopen, H.W., van Blitterswijk, C.A., de Koning, E.J., van Apeldoorn, A.A., Karperien, M. Microwell scaffolds for the extrahepatic transplantation of islets of Langerhans. **PLoS One.** 2013 May 30;8(5):e64772. doi: 10.1371/journal.pone.0064772.
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9. Schivo, S., Scholma, J., Urquidi Camacho, R.A., van de Pol, J., Karperien, M., Post, J.N., Biological networks 101: computational modeling for molecular biologists, **Gene.** 2014 Jan 1;533(1):379-84. doi: 10.1016/j.gene.2013.10.010. Epub 2013 Oct 12.
10. Truckenmüller, R., Giselbrecht, S., Escalante-Marun, M, Groenendijk, M., Papenburg, B., Rivron, N., Unadkat, H., Saile, V, Subramaniam, V., van den Berg, A., van Blitterswijk, C., Wessling, M., de Boer, J., Stamatialis, D.. Fabrication of cell container arrays with overlaid topographies, **Biomed. Microdev.**, 14 (2012) 95-107.

Relevant patents:

Group Karperien

1. P96086EP00: **A dextran-based tissuelette containing platelet-rich plasma lysate for cartilage repair.** 2011. L. Moreira Teixeira, P. J. Dijkstra, M. Karperien.
2. P88580EP00: **Functionalized VHH for application in tissue repair, organ regeneration, organ replacement and tissue engineering.** 2009. M. Karperien, E. Rodrigues, M. El Khatabi, C.A. van Blitterswijk, J. de Boer, C.T Verrips.
3. P89756EP00: **Heparin Tyramine Based Hydrogels.** 2009. M. Karperien, R. Jin, L. Moreira-Teixeira, P. Dijkstra, J. Feijen.
4. P89757EP00: **Dextran-Hyaluronic Acid Based Hydrogels.** 2009. M. Karperien, R. Jin, L. Moreira-Teixeira, P. Dijkstra, J. Feijen.
5. P89239EP00: **Scaffold for diabetes treatment.** 2009 A.A. van Apeldoorn, C.A. van Blitterswijk, M.A. Engelse, E.J.P. de Koning, M. Karperien.

Group Stamatialis

1. **High throughput screening method and apparatus for analyzing interactions between**

surfaces with different topography and environment, J. de Boer, C. van Blitterswijk, H. Unadkat, D.F. Stamatialis, B. Papenburg, M. Wessling WO 2009/058015 A1 (2009).

Group Claessens

1. **Provisional patent on platform to induce Lewy bodies (pathological characteristic of Parkinson's disease) in neuronal cell lines and primary neurons.**

Added value University of Twente for hDMT

- Expertise of the MESA+ institute for Nanotechnology and the MIRA institute for Biomedical Technology and Technical Medicine
- Leading Dutch center in BioNanoTechnology
- Leading Dutch center for applied microfluidics
- Leading Dutch center for technology inspired regenerative medicine
- Leading Dutch center in technology inspired applied cell biology

Added value hDMT for University of Twente

- Collaborations with University Medical Centers
- Access to patient material
- Translational research using technology developed at the University of Twente

EINDHOVEN UNIVERSITY OF TECHNOLOGY

TU/e Technische Universiteit **Eindhoven** University of Technology

Eindhoven University of Technology

Expertise and facilities:

Expertise

The expertise at TU/e contributed to hDMT enables development of the technical platforms needed to create a micro-environment in which complex tissue structures can be grown, manipulated and studied, mimicking *in vivo* processes. This expertise can be divided into 3 classes: materials, device integration, and modelling.

MATERIALS (Groups Meijer, Broer/Schenning, den Toonder)

- Artificial extracellular matrices, with controlled stiffness and biological functionality.
- Responsive materials, controllable by light, temperature, electrical field, magnetic fields, or other stimuli.
- Membrane materials – PDMS, SU-8, collagen, LC networks, and other materials
- Conductive soft (polymer based) materials.
- Tuneable (nano)porous materials.
- Hydrogels, elastomers, thermoplastic polymers, liquid crystal networks, with tunable elastic, morphological, biochemical, and electronic properties.

DEVICE INTEGRATION (Groups den Toonder, Broer/Schenning, Coehoorn)

- Devices with integrated microactuators that can apply deformation, forces, or fluid flow.
- Devices with surface topography that can steer fluidic or biological processes.
- Organic electronics for applying electrical stimuli or reading out electrical signals.
- Devices allowing for magnetic actuation of particles for diagnostics.
- Out-of-cleanroom device manufacturing approaches: soft lithography, laser micromachining, 3D-printing, polymer technology.
- Methods for cell patterning in devices: microfluidics, printing.

MODELING (Groups Storm, Coehoorn)

- Modeling, understanding, and predicting the relationship between material properties (both mechanical and electronic) at larger length scales and structure at smaller scales.
- Modeling of biological gels and tissues, functional polymer surfaces for biosensing, self-organization in charged lipid systems, electronic processes in organic LEDs, viral and synthetic self-assembly, and dendrimers and hyperbranched polymers for drug delivery.

Facilities

- Microfab lab @ TU/e: a state-of-the-art microfabrication facility (640 m^2) for efficient and flexible manufacturing of fully functional microsystems research prototypes on the basis of non-cleanroom processing: soft lithography, laser micromachining, 3D-printing, polymer processing.
- Cell and tissue lab: fully equipped cell culture room, containing >6 safety cabinets and >15 cell incubators; fully equipped biochemical room; several fluorescence, confocal and 2-photon microscopes, with mechanical analysis equipment.
- Cleanroom: Nanolab@TU/e, with advanced cleanroom equipment for thin film deposition, lithography, and analysis.
- Extensive in-house computing cluster facilities and supercomputer access.

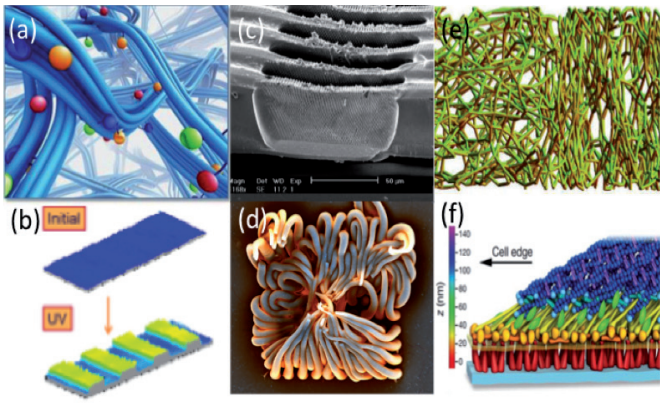

Figure 1: Illustration of the TU/e expertise.
(a) Artificial extracellular membrane;
(b) switchable surface topographies;
(c) porous membranes integrated in a microchannel;
(d) magnetic microactuators integrated in a microfluidic device;
(e) multiscale modeling of collagen mechanics;
(f) modeling of cell-matrix interactions.

Ongoing projects:

1. **Cancer metastasis on a Chip;** PI Jaap den Toonder, funded by TU/e and STW. With Erasmus MC + Philips
2. **Dynamic self-cleaning surfaces enabled by responsive materials.** PI Jaap den Toonder, funded by STW. With Broer/Schenning group + RUG.
3. **Bio-inspired Hairy Surfaces for Actuation or Sensing,** PI Jaap den Toonder, funded by DPI.
4. **Circulating cells,** PIs Jaap den Toonder and Carlijn Bouten, funded by CTMM.
5. **Development of a nano biosystem for the study of brain functions on chip,** PIs Jaap den Toonder and Regina Luttge, funded by TU/e.
6. **Polymers in Motion.** Pis Dick Broer, Bert Meijer, funded by NWO-CW.
7. **Next Generation Analytical Platforms for Environmental Sensing,** PI Albert Schenning, funded by EU.
8. **Membranes with Adjustable Interior in their Nanopores,** PIs D.J. Broer, A. Schenning, funded by DPI.
9. **Programme on Designer Biopolymer Materials,** PI Cornelis Storm, funded by FOM.
10. **Programme "Barriers in the Brain"**, PI Cornelis Storm, funded by FOM.
11. **Programme " Mechanosensing and Mechanotransduction by Cells",** PI Cornelis Storm, funded by FOM, with a consortium including prof. Mummery (Leiden).
12. **ICMS project "Order and Remodeling in Fibrous Biomaterials",** PI Cornelis Storm, funded by ICMS, with Carlijn Bouten,

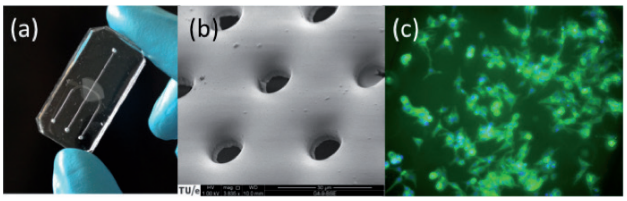

Figure 2. Example of the application of device integration, material processing in the cancer-on-a-chip project at TU/e. (a) Microfluidic chip made of polydimethylsiloxane (PDMS). (b) Within the chip, a thin PDMS membrane is integrated with well-defined pores of 10 µm diameter that separates two microchannels. (c) MCF-7 cancer cells (shown here) are cultured on the membrane.

Publications:

1. Jaap M.J. den Toonder and Patrick R. Onck. Microfluidic manipulation with artificial/bioinspired cilia. **Trends in Biotechnology,** February 2013, Vol. 31, No. 2, 85-91.
2. Liu, D; Bastiaansen, CWM; Toonder, den JMJ; Broer, DJ: Photo-switchable surface topologies in chiral nematic coatings (2012). **Angewandte Chemie - International Edition,** 51(4), 892.
3. Ravetto, A., Wyss, H.M., Anderson, P.D., Toonder, J.M.J. den & Bouten, C.V.C. (2014). Monocytic cells become less compressible but more deformable upon activation. **PLoS ONE,** 9(3), e92814-1/7.
4. van de Stolpe and J. den Toonder: Workshop meeting report Organs-on-Chips: human disease models, **Lab Chip 2013, published online,** DOI: 10.1039/c3lc50248a.
5. Schenning, APHJ (Albert); Gonzales-Lemus, Y; Shishmanova, IK; Broer, DJ (Dirk): Nanoporous membranes based on liquid crystalline polymers (2011). **Liquid Crystals,** 38, 1627.
6. W. P. J. Appel, E. W. Meijer, and P. Y. W. Dankers (2011). Enzymatic activity at the surface of biomaterials via supramolecular anchoring of peptides : the effect of material processing. **Macromolecular Bioscience,** 11, 1706-1712.
7. Dankers, P.Y.W., Boomker, J.M., Huizinga-van der Vlag, A., Wisse, E., Appel, W.P.J., Smedts, F.M.M., Harmsen, M.C., Bosman, A.W., Meijer, E.W. & Luyn, M.J.A. van (2011). Bioengineering of living renal membranes consisting of hierarchical, bioactive supramolecular meshes and human tubular cells. **Biomaterials,** 32(3), 723-733.
8. Novikova, E.A. and Storm, C.: Contractile fibers and catch-bond clusters: a biological force sensor?, **Biophys. J. 105,** 1336-1345 (Sep 17, 2013) .
9. Mesta, M., Carvelli, M., de Vries, R.J., van Eersel, H., van der Holst, J.J.M., Schober, M., Furno, M., Lüssem, B., Leo, K., Loebl, P., Coehoorn, R. and Bobbert, P.A. Molecular-scale simulation of electroluminescence in a multilayer white organic light-emitting diode, **Nature Materials** 12 (2013), 652.
10. C. Storm, J. Pastore, F.C. MacKintosh, T.C. Lubensky and P.A. Janmey: Nonlinear elasticity in biological gels, **Nature 435,** 191-194 (May 12, 2005)

Relevant patents: none

Added value Eindhoven University of Technology for hDMT

- The expertise at TU/e contributed to hDMT enables development of the technical platforms needed to create a micro-environment in which complex tissue structures can be grown, manipulated and studied, mimicking *in vivo* processes.
- Materials are essential in organ-on-a-chip devices, since they define the direct microenvironment of the biological tissue. The chemical, mechanical, and electronic properties of the material can drive biological processes such as cell differentiation and tissue formation. The materials expertise contribute the necessary material knowledge and expertise to synthesize, process, and integrate materials.

- Organ-on-chip are integrated devices – different components made of different materials must be combined to create a functioning device. We make integrated devices such as microfluidic devices with microactuators based on responsive materials that can apply deformation, forces, or fluid flow, surface topography that can steer fluidic or biological processes, organic electronics for applying electrical stimuli or reading out electrical signals, devices allowing for magnetic actuation of particles for diagnostics, etc.
- Theoretical and numerical models can be essential for an efficient and effective design of organ on chip applications, and may help to guide and understand cell and tissue behavior in the chip environment.

Added value hDMT for Eindhoven University of Technology

- Collaboration with hDMT partmers, with complementary expertise (medical / clinical expertise, cell-biology, and complementary technology), all needed to develop organ-on-a-chip, provides opportunities for TU/e to contribute to exciting and highly relevant applications in this area.
- hDMT provides the opportunity to leverage our developed materials and technologies.
- hDMT provides TU/e with novel research questions, which will certainly drive new developments in materials, technologies, manufacturing approaches, devices, and models.
- Availability of infrastructure at hDMT partners provides TU/e new opportunities (for characterization and processing).

HUBRECHT INSTITUTE

Hubrecht Institute

Developmental Biology
and Stem Cell Research

Hubrecht Institute

Expertise and facilities:

Expertise

- Single-cell sequencing
- Organoid technology.
- Stem cells
- 4C, Hi-C technology

Facilities

- Hubrecht Imaging facility
- Mouse facility
- FACS facility
- Media Kitchen
- Single-cell sequencing facility

Ongoing projects:

Group Clevers

Lgr5 stem cells, Wnt signaling & cancer

Originally focused on T lymphocyte transcription factors, we cloned Tcf1 in 1991. With the discovery that Tcf factors are the final effectors of Wnt signaling, we changed our interests to the biology of Wnt signaling in intestinal self-renewal and cancer. We identified a series of adult tissue stem cells with the novel Lgr5 marker and technologies for long-term culture of these stem cells as epithelial organoids, currently our major focus of research.

Group van Oudenaarden

Quantitative biology of development & stem cells

The van Oudenaarden lab is using a combination of experimental, computational, and theoretical approaches to quantitatively understand decision-making in single cells with a focus on questions in developmental and stem cell biology. We are particularly interested in how cells use gene networks to make robust decisions even in the presence of significant fluctuations in gene expression.

Publications:

1. Barker, N., van Es, J.H., Kuipers, J., Kujala, P., van den Born, M., Cozijnsen, M., Haegebarth, A., Korving, J., Begthel, H., Peters, P.J., Clevers, H. Identification of stem cells in small intestine and colon by marker gene Lgr5. **Nature.** 2007 Oct 25;449(7165):1003-7. Epub 2007 Oct 14.
2. Sato, T., van Es, J.H., Snippert, H.J., Stange, D.E., Vries, R.G., van den Born, M., Barker, N., Shroyer, N.F., van de Wetering, M., Clevers, H. Paneth cells constitute the niche for Lgr5 stem cells in intestinal crypts. **Nature.** 2011 Jan 20;469(7330):415-8. doi: 10.1038/nature09637. Epub 2010 Nov 28.
3. Grün D, Kester L, van Oudenaarden A. Validation of noise models for single-cell transcriptomics. **Nat Methods.** 2014 Jun;11(6):637-40. doi: 10.1038/nmeth.2930. Epub 2014 Apr 20.
4. Junker, J.P., van Oudenaarden, A. Every cell is special: genome-wide studies add a new dimension to single-cell biology. **Cell.** 2014 Mar 27;157(1):8-11. doi: 10.1016/j.cell.2014.02.010.
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7. Junker, J.P., Noel, E.S., Guryev, V., Peterson, K.A., Shah, G., Huisken, J., McMahon, A.P., Berezikov, E., Bakkers, J. and van Oudenaarden,A. Genome-wide RNA tomography in the zebrafish embryo **Cell 159,** 662 – 675 (2014).
8. Ritsma, L., Ellenbroek, S.I.J., Zomer, A., Snippert, H.J., de Sauvage, F.J., Simons, B.D., Clevers, H., van Rheenen, J. Intestinal crypt homeostasis revealed at single-stem-cell level by *in vivo* live imaging. **Nature.** 2014 Mar 20;507(7492):362-5.
9. Stange, D.E., Koo, B.K., Huch, M., Sibbel, G., Basak, O., Lyubimova, A., Kujala, P., Bartfeld, S., Koster, J., Geahlen, J.H., Peters, P.J., van Es, J.H., van de Wetering, M., Mills, J.C., Clevers, H. Differentiated Troy+ chief cells act as reserve stem cells to generate all lineages of the stomach epithelium. **Cell.** 2013 Oct 10;155(2):357-68.
10. Huch, M., Dorrell, C., Boj, S.F., van Es, J.H., Li, V.S., van de Wetering, M., Sato, T., Hamer, K., Sasaki, N., Finegold, M.J., Haft, A., Vries, R.G., Grompe, M., Clevers, H. *In vitro* expansion of single Lgr5+ liver stem cells induced by Wnt-driven regeneration. **Nature.** 2013 Feb 14;494(7436):247-50.

Relevant Patents: None

Added value Hubrecht Institute for hDMT

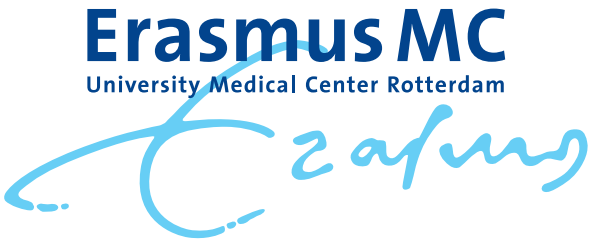
The Hubrecht Institute performs basic research in the field of developmental biology, with an emphasis on the biology of stem cells. The institute aspires to be a world leader in this field. The institute currently ranks as one of top institutes worldwide in the field of developmental biology and stem cell research. This is reflected by the citation impact score of 2.86, which puts the Hubrecht at the top of the list of all institutes and universities in the Netherlands. Internationally, this score is also impressive and is comparable to the EMBL Heidelberg (2.98), Harvard (2.40), and MIT (2.45).

To maintain and improve this position we implement the following strategy:

1. We use an international recruitment strategy focusing strictly on excellence.
2. We have a tenure-track system for junior group leaders with a flat organizational structure; group leaders have full scientific freedom and receive all the positive and negative consequences of such responsibility. Currently approximately half of the junior group leaders receives tenure after 6 years. The evaluation procedure is transparant and is based on external referees.
3. The institute is equipped with the most advanced equipment (microscopes, cell sorters, DNA sequencers) managed from a well-embedded facility support.
4. We aim at increasing the critical mass of the institute by active national and international grant recruitment (including donations from foundations and wealthy individuals) and by closely collaborating with UMC Utrecht.
5. We collaborate with the best national and international groups in the field of stem cell biology and developmental biology.

Researchers at the Hubrecht Institute study a variety of biological processes, mainly concerning the developmental biology of animals. Developmental biologists are interested in the mechanism by which an organism grows from a single fertilized egg into a fully formed adult. This encompasses many areas, from basic (pre-)embryonic processes, such as the establishment of a body plan, to the specifics of organ growth in adult animals. Closely linked to developmental biology is stem cell research. Embryonic, fetal, adult and cancer stem cells are all studied. Deregulation of developmental processes can lead to cancer, which is also a key theme of research within the institute. Knowledge and expertise gained within the Hubrecht will be beneficial for prevention and treatment of diseases and therefore for the quality of life.

ERASMUS MC



Erasmus MC

Content will follow soon

GALAPAGOS

Galápagos

Galapagos

Galapagos has discovered drug targets (starting points for the development of novel drugs) using cells from patients for more than fifteen diseases. These targets form the basis of drug discovery programs aimed at identifying small molecules or antibodies that alter the activity of these proteins, thereby potentially changing the course of the disease. By studying the disease process and key points of intervention, it is our goal to develop new drugs that stop the disease rather than just treat the symptoms.
Galapagos is progressing one of the largest pipelines in biotech, with three Phase 2 programs, two Phase 1 programs, five pre-clinical, and more than 20 discovery programs.

Expertise and facilities:

Expertise

- Over 100 *in vitro* human primary cell-based disease models (lung and skin fibrosis, cystic fibrosis, bone and joint diseases, inflammation, cancer, metabolic disease, infectious disease).
- Drug target identification and validation
- Drug discovery and medicinal chemistry
- Toxicology
- Animal models for fibrosis, bone and joint diseases, cystic fibrosis, inflammation, cancer, metabolic disease, infectious disease
- Strong expertise in collaborative research with patient foundations, academic research institutions, biotech and big pharma
- Strong connections with decision makers and budget holders in big pharma, biotech, and patient foundations
- Good understanding of patient and market needs

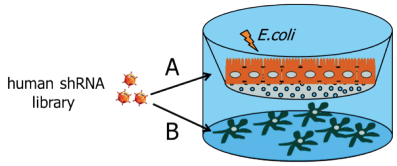
Facilities

- State-of-the-art and ISO-certified ML2 laboratories
- Robotics for automated liquid handling
- High throughput plate reader technology
- High throughput screening
- High content imaging
- High throughput flow cytometry
- Complex (co)-cultures of primary cells
- Adenoviral shRNA libraries
- Compound libraries

Ongoing projects:

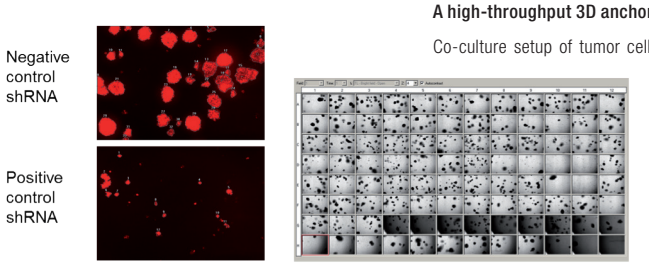
1. **Development of various organ-on-a-chip assays** with Mimetas. Performed with company research budget. Principal investigator: Richard Janssen
2. **Setting up co-cultures and 3D cultures in the field of metabolic disease, inflammatory bowel disease, fibrosis, cystic fibrosis, immune-oncology.** Performed with company research budget. Principal investigator: Richard Janssen
3. **Development of a liver-on-chip. Performed with company research budget.** Principal investigator: Richard Janssen

Examples of established complex cell culture systems:



An IBD-relevant co-culture setup

Co-culture setup of dendritic cells (DC) with polarized colon epithelium established at Galapagos in 96-well format to study inflammatory bowel disease. Human polarized colon epithelial cells are grown on a trans-well insert. Human DC are grown at the bottom of the well. Effects of E.coli on immune cells and epithelium are determined by assessing barrier function of epithelium and by inflammatory responses of DC and epithelium. Role of individual genes in these processes can be identified through adenoviral shRNA-based knockdown of genes of interest in either colon epithelial cells (A) or DC (B).



A high-throughput 3D anchorage independence assay to study cancer growth.

Co-culture setup of tumor cells and mesenchymal cells in soft agar established at Galapagos in 96-well format. Role of individual genes in tumor growth can be determined through individual knockdown using adenoviral shRNA. As shown, knockdown of a positive control gene results in very strong reduction in number and size of colonies in soft agar. Using high content imaging, tumor growth in 3D can be quantified rapidly and thousands of experiments can be performed.

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2. Lekkerkerker, A.N., Aarbiou, J., van Es, T., Janssen, R.A.. Cellular players in lung fibrosis. **Curr Pharm Des.** 2012;18(27): 4093-102. Review.
3. Ley, S., Weigert, A., Hériché, J.K., Mille-Baker, B., Janssen, R.A., Brüne, B. RNAi screen in apoptotic cancer cell-stimulated human macrophages reveals co-regulation of IL-6/IL-10 expression. **Immunobiology.** 2013 Jan; 218(1):40-51.
4. Ley, S., Weigert, A., Weichand, B., Henke, N., Mille-Baker, B., Janssen, R.A., Brüne, B. The role of TRKA signaling in IL-10 production by apoptotic tumor cell-activated macrophages **Oncogene.** 2013 Jan 31;32(5):631-40.
5. Moulin, V., Morgan, M.E, Eleveld-Trancikova, D., Haanen, J.B., Wielders, E., Looman, M.W., Janssen, R.A., Figdor, C.G., Jansen, B.J., Adema, G.J. Targeting dendritic cells with antigen via dendritic cell-associated promoters. **Cancer Gene Ther.** 2012. 19:303-11.
6. Camus, S., Quevedo, C., Menéndez, S., Paramonov I, Stouten PF, Janssen RA, Rueb S, He S, Snaar-Jagalska BE, Laricchia-Robbio L, Izpisua Belmonte, J.C. Identification of phosphorylase kinase as a novel therapeutic target through high-throughput screening for anti-angiogenesis compounds in zebrafish. **Oncogene.** 2012 Sep 27;31(39):4333-42.
7. Van Maanen, M.A., Stoof, S.P., van der Zanden, E.P., de Jonge, W.J., Janssen, R.A.,

Fischer, D.F., Vandeghinste, N., Brys, R., Vervoordeldonk, M.J., Tak, P.P. The alpha7 nicotinic acetylcholine receptor on fibroblast-like synoviocytes and in synovial tissue from rheumatoid arthritis patients: a possible role for a key neurotransmitter in synovial inflammation. **Arthritis Rheum.** 2009 May;60(5):1272-81.

Relevant patents:

Patent number	Title	Scope
EP1022335	High-throughput screening of gene function using libraries for functional genomics applications	Adenoviral libraries and methods for producing adenoviral libraries
EP1444346	siRNA knockout assay method and constructs	shRNA
US6340595	High throughput screening of gene function using adenoviral libraries for functional genomics applications	A library of a multitude of unique expressible nucleic acids in adenoviral vectors and a process for producing a library of adenoviral vectors
US6413776	High throughput screening of gene function using adenoviral libraries for functional genomics applications	A method of producing a recombinant adenoviral vector library
US7029848	High throughput screening of gene function using libraries for functional genomics applications	A method for determining the function of a nucleic acid sequence (method of screening using adenoviral vectors)

Added value Galapagos for hDMT:

- Input in format of assays
- Validation of assays
- High throughput screening of assays for internal research programs
- Connections with pharma
- Focused approach
- Access to expensive and state-of-the-art equipment (robots, readout equipment)
- Business development expertise

Added value hDMT for Galapagos:

- Access to unique cellular assays
- Access to patient material
- Access to (latest) biology/disease know how
- Access to ONE institute with complementary disciplines

GENMAB

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Expertise/facilities:

Expertise

- Full spectrum pre-clinical and clinical development expertise for antibody based drugs
- Proven track record to bring antibody based drug to the market (Arzerra)
- Antibody biology
- Oncology and hematology as therapeutic areas
- Immunology and immune effector mechanisms (ADCC, CDC, T-cell activation etc.)
- Identification of new disease targets for antibody-based therapeutics
- Translational knowledge related to cancer pathophysiology
- Drug discovery
- Antibody screening knowledge & capabilities
- Novel antibody formats with enhanced effector functions and biological characteristics
- Broad assay technology base (functional and biophysical)

Facilities/capabilities

- 4000m^2 lab and office facility in Utrecht
- State-of-the-art laboratories for Cell and Molecular Biology, Protein Biochemistry
- Cell line development and cell banking
- Protein production and purification
- Immunohistochemistry capabilities (High Throughput)
- High throughput screening facility with automated liquid handling (robots), analysis, and data handling. Microplate and FACS based
- Various high-end readers and imaging instruments
- Mass spectrometry and other analytical platforms
- Access to cancer and immune system specific *in vivo* models (mouse)

Ongoing projects:

1. **Clinical programs including Daratumumab (HuMax®-CD38)** by Janssen Biotech, Ofatumumab (Arzerra®) by GlaxoSmithKline, and HuMax®-TF-ADC.
2. **An array of pre-clinical programs** including HuMax®-AXL-ADC.
3. **Collaborations on DuoBody and HexaBody technology** with companies including Janssen Biotech, Novartis, Eli Lilly, Kirin Kyowa Hakko, and a number of academic institutions including the Leiden University Medical Center, University Utrecht, University of Virginia Medical School, The Scripps Research Institute, University of Southern Denmark, University of Patras, University of Kiel.
4. **Technology innovation projects** including antibody discovery platforms, cell based assay technologies (incl. 3D models) amongst others.
5. **Open innovation projects:** Genmab is actively stimulating pre-competitive use of its format technologies to advance science and catalyze the translation from scientific concept to a product development opportunity.

Publications:

1. Labrijn, A.F., Meesters, J.I., Priem, P., de Jong, R.N., van den Bremer, E.T., van Kampen, M.D., Gerritsen, A.F., Schuurman, J., Parren, P.W. Controlled Fab-arm exchange for the generation of stable bispecific IgG1. **Nat Protoc.** 2014;9:2450-63.
2. Schuurman, J., Graus, Y.F., Labrijn, A.F., Ruuls, S., Parren, P.W. Opening the door to innovation. **MAbs.** 2014;6:812-9.
3. Diebolder, C.A., Beurskens, F.J., de Jong, R.N., Koning, R.I., Strumane, K., Lindorfer, M.A., Voorhorst, M., Ugurlar, D., Rosati, S., Heck, A.J., van de Winkel, J.G., Wilson, I.A., Koster, A.J., Taylor, R.P., Saphire, E.O., Burton, D.R., Schuurman, J., Gros, P., Parren, P.W.. Complement is activated by IgG hexamers assembled at the cell surface. **Science.** 2014;343:1260-3.
4. de Goeij, B.E., Peipp, M., de Haij, S., van den Brink, E.N., Kellner, C., Riedl, T., de Jong, R., Vink, T., Strumane, K., Bleeker, W.K., Parren, P.W. HER2 monoclonal antibodies that do not interfere with receptor heterodimerization-mediated signaling induce effective internalization and represent valuable components for rational antibody-drug conjugate design. **MAbs.** 2014;6:392-402.
5. Brei,j E.C., de Goeij, B.E., Verploegen, S., Schuurhuis, D.H., Amirkhosravi, A., Francis, J., Miller, V.B., Houtkamp, M., Bleeker, W.K., Satijn, D., Parren, P.W. An antibody-drug conjugate that targets tissue factor exhibits potent therapeutic activity against broad range of solid tumors. **Cancer Res.** 2014;74:1214-26.
6. Labrijn, A.F., Meesters, J.I., de Goeij, B.E., van den Bremer, E.T,, Neijssen, J., van Kampen, M.D., Strumane, K., Verploegen S, Kundu A, Gramer MJ, van Berkel PH, van de Winkel JG, Schuurman J, Parren, P.W. Efficient generation of stable bispecific IgG1 by controlled Fab-arm exchange. **Proc Natl Acad Sci U S A.** 2013;110:5145-50.
7. Overdijk, M.B., Verploegen, S., van den Brakel, J.H., Lammerts van Bueren, J.J., Vink, T., van de Winkel, J.G., Parren, P.W., Bleeker, W.K. Epidermal growth factor receptor (EGFR) antibody-induced antibody-dependent cellular cytotoxicity plays a prominent role in inhibiting tumorigenesis, even of tumor cells insensitive to EGFR signaling inhibition. **J Immunol.** 2011;187:3383-90.
8. de Weers, M., Tai, Y.T., van der Veer, M.S., Bakker, J.M., Vink, T., Jacobs, D.C., Oomen, L.A., Peipp, M., Valerius, T., Slootstra, J.W., Mutis, T., Bleeker, W.K., Anderson, K.C., Lokhorst, H.M., van de Winkel, J.G., Parren, P.W. Daratumumab, a novel therapeutic human CD38 monoclonal antibody, induces killing of multiple myeloma and other hematological tumors. **J Immunol.** 2011;186:1840-8.
9. van der Neut Kolfschoten, M., Schuurman, J., Losen, M., Bleeker, W.K., Martínez-Martínez, P., Vermeulen, E., den Bleker, T.H., Wiegman, L., Vink, T., Aarden, L.A., De Baets, M.H., van de Winkel, J.G., Aalberse, R.C., Parren, P.W.. Anti-inflammatory activity of human IgG4 antibodies by dynamic Fab arm exchange. **Science.** 2007;317:1554-7.

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1. 7,282,568. **Human monoclonal antibodies against interleukin 8 (IL8).** Inventors: Teeling, J., P. Parren, O. Baadsgaard., D. Hudson, J. Peterson. Issued: Oct. 16, 2007.
2. 7,438,907. **Human monoclonal antibodies against CD25.** Inventors: Schuurman, J., C.E.G. Havenith, P. Parren, J.G.J. van de Winkel, D.L. Williams, J. Petersen, O. Baadsgaard. Issued: Oct. 21, 2008.
3. 7,622,559. **Human monoclonal antibodies against interleukin 8 (IL8).** Inventors: Teeling, J., P. Parren, O. Baadsgaard., D. Hudson, J. Peterson. Issued: Nov. 24, 2009.
4. 7,829,673. **Antibodies against CD38 for treatment of multiple myeloma.** Inventors: De Weers, M., Y. Graus, J. Oprins, P. Parren, J. van de Winkel, M. van Vugt. Issued: Nov. 9, 2010.
5. 7,850,962. **Human monoclonal antibodies against CD20.** Inventors: Teeling, J., M. Glennie,

P. Parren, A.F. Gerritsen, S. Ruuls, Y. Graus, J. van de Winkel. Issued: Dec. 14, 2010.

6. 8,105,588. **Human monoclonal antibodies against interleukin 8 (IL8).** Inventors: Teeling, J., P. Parren, O. Baadsgaard., D. Hudson, J. Peterson. Issued: Jan. 31, 2012.
7. 8,182,812. **Human monoclonal antibodies against CD25.** Inventors: Schuurman, J., C.E.G. Havenith, P. Parren, J.G.J. van de Winkel, D.L. Williams, J. Petersen, O. Baadsgaard. Issued: May 22, 2012.
8. 8,529,902. **Human monoclonal antibodies against CD20.** Inventors: Teeling, J., S. Ruuls, M. Glennie, J. van de Winkel, P. Parren, J. Petersen, O. Baadsgaard, H. Huang. Issued: Sep. 10, 2013.
9. EP 1 951 303 B1. **Therapy with anti-CD4 antibodies and radiation.** Inventors: Parren, P., O. Baadsgaard, D. Alexander. Issued: Feb. 2, 2011.
10. EP 1 590 364 B1. **Human monoclonal antibodies against interleukin 8 (IL8).** Inventors: Teeling, J., P. Parren, O. Baadsgaard., D. Hudson, J. Peterson. Issued: Oct. 5, 2011.
11. EP 1 572 746 B1. **Human monoclonal antibodies to epidermal growth factor receptor (EGFR).** Inventors: Van de Winkel, J.G.J., M.A. van Dijk, E. Halk, A.F. Gerritsen, J. Petersen, O. Baadsgaard, W.K. Bleeker, P. Parren. Issued Nov. 2, 2011.
12. EP 1 558 648 B1. **Human monoclonal antibodies against CD20.** Inventors: Teeling, J., S. Ruuls, M. Glennie, J. van de Winkel, P. Parren, J. Petersen, O. Baadsgaard, H. Huang. Issued Jan. 11, 2012.
13. EP 1 578 397 B1. **Human monoclonal antibodies against CD25.** Inventors: Schuurman, J., C.E.G. Havenith, P. Parren, J.G.J. van de Winkel, D.L. Williams, J. Petersen, O. Baadsgaard. Issued: Dec. 26, 2012.
14. EP 1 740 946 B1. **Human monoclonal antibodies against CD20.** Inventors: Teeling, J., M. Glennie, P. Parren, A. Gerritsen, S. Ruuls, Y. Graus, J. van de Winkel. Issued: Nov. 6, 2013.
15. EP 1 898 698 B1. **Non-human mammalian arthritis model featuring human antibodies against citrullinated peptides.** Inventors: Toes, R., T. Huizinga, M. Molenaar, P. Parren, J. van de Winkel. Issued: May 21, 2014.
16. EP 2 330 130 B1. **Human monoclonal antibodies against CD20.** Inventors: Teeling, J., S. Ruuls, M. Glennie, J. van de Winkel, P. Parren, J. Petersen, O. Baadsgaard, H. Huang. Issued: August 27, 2014.
17. EP 1 960 431 B1. **Use of effector-function-defective antibodies for treatment of auto-immune diseases.** Inventors: Losen, M., P. Martinez-Martinez, M.H. De Baets, Y. Graus, J. Schuurman, P. Parren. Issued: October 1, 2014.

Added value Genmab for hDMT:

- Extensive Drug development and valuation expertise
- Provide user requirement for device and cell model design from target intervention screening purpose perspective
- In depth knowledge and expertise in oncogenic drivers, solid tumor and hematology therapeutic areas and immunology/ immune effector mechanisms
- Complementary expertise in the field of therapeutic antibodies/ biologics
- Proprietary antibody platforms
- Clinically validated antibody based drug compounds and compound libraries
- Expertise in experimental system validation
- Head-to-head model validation (2D/3D cell based assays and (mouse) xenograft *in vivo* models)
- High throughput capacities (for testing and validation)
- Alliances and networks with relevant Academia, Biotech, and Pharma
- Experience establishing industry-academia collaborations and alliances

Added value hDMT for Genmab:

- Access to cellular test systems with a potential predictive power for drug discovery
- Potential to further reduce animal testing in drug development
- Novel avenues for performing mechanism of action studies
- Access to patient derived cells and associated model systems
- Expand existing networks and open innovation program
- Extended knowledge (biology and technology)

Affiliation	Scientific representative	Business representative	Technical expertise group leaders	Organ/disease model expertise	(Stem) cell and molecular technology	"Chip" technology	Readout technology	Implementation
Leiden University Medical Centre	Christine Mummery*		Christine Mummery*	*Heart and vessels, smooth muscle, endothelium* Cardiac arrythmias, Cardiac hypertrophy, vascular disease and tumor blood vessels	PLURIPOTENT STEM CELLS iPS cells Genetic modification (lineage reporters and mutation repair)		REPORTER GENE READOUT Differentiation tracking Reporter genes Electrophysiology Image analysis	STEM CELL PRODUCTION
			Thomas Schmidt				Single molecule, super resolution microscopy	
University of Leiden W&N			Thomas Hankemeijer (LACDR)	Microvasculature & vascular disease, gut epithelium, cancer, liver, neurons		Phaseguide based microfluidics	Metabolomics, imaging	Non-commercial drug development, understanding disease mechanisms
			Bob van de Water; Erik Danen (LACDR)	Cancer, breast, liver, kidney	siRNA, shRNA, reporters toxicity	3D *in vitro* (cancer, liver, kidney); cancer spheroid assays	High throughput/high content automated (confocal) imaging; BAC reporters cellular stress response; multi-parameter automated image analysis	RNAi screening; compound screening; disease mechanism; drug safety; non commercial drug development
			Thomas Schmidt (Physics)				Single molecule, super resolution microscopy	Cell biology and biophysics
Galapagos, Leiden	Richard Janssen	Nathalie ter Wengel	Richard Janssen	Complex *in vitro* disease models of almost every human primary cell type available *In vitro* and *in vivo* models for fibrosis, bone and joint diseases, metabolic disease, cancer, infectious disease, cystic fibrosis	DRUG TARGET DISCOVERY adenoviral shRNA and cDNA libraries		CELL ASSAYS Lung, liver, and skin fibrosis, cystic fibrosis, bone and joint diseases, inflammation, cancer, metabolic disease, infectious disease HIGH CONTENT IMAGING MULTIPLEX READOUTS HIGH THROUGHPUT FLOW CYTOMETRY	Target discovery Drug discovery and development High throughput screening
Genmab (Utrecht)	Paul Parren	Yvo Graus	Thilo Riedl	CANCER Mouse xenograft solid and leukemic tumor models, metastasis models, PDX models. *In vitro* immune effector functions.	IMMUNOLOGY ANTIBODY TECHNOLOGIES Human antibody libraries		IHC tissue microarrays Cell based assays (2D, 3D)	ANTIBODY DISCOVERY DRUG DEVELOPMENT
TUDelft	Lina Sarro* Ronald Dekker		Lina Sarro* Ronald Dekker	*Bacteriae* Cardiac diseases Neurological diseases		ELECTRICAL CELLS integrated electrodes (Cytostretch)	ELECTRICAL READOUT Electrical readout Electrolute/pH Sensor technology	
			Cees Dekker* Marileen Dogterom, Nynke Dekker Greg Bokinsky Liedewij Laan	*Cancer:* Cell division and movement; cytoskeleton *Bacteriae:* Engineered networks	Single molecule Technology/cell Biology for DNA-protein interactions and gene regulation	Specialized Microfluidics; Nano-engineered Devices; artificial cells	Force probes, microscopy	
			Mark Van Loosdrecht*				Modeling	
			Jeroen Kalkman				3D optical imaging	
						DIMES		MICROFABRICATION

UTwente	Albert van den Berg* *Roman Truckenmuller*		Albert van den Berg*	*Blood brain barrier* Thrombosis / atherosclerosis	CELL DIFFERENTIATION PLATFORM Droplet (single cell) technology	MICROFLUIDICS Microfluidics Integrated electrodes Optical detection	Electrical sensing Mass spectrometry analysis	Microfabrication
			Roman Truckenmuller			Functionalized micro- and nano polymer film technology		
			Clemens van Blitterswijk*		TopoChip platform Cell printing			
			Marcel Karperien	Cartilage Langerhans	3D cell printing			
			Han J.G.E. Gardeniers				Microfluidics-coupled HPCL	
			Severine le Gac	Lung on a Chip				
			Dimitri Stamatialis	Kidney on a Chip				
			Leon Terstappen	Circulating tumor cells, cancer cell invasion		Cell sorting		
			Richard van Wezel	Brain on a Chip		Multielectrode array (MEA)		
TUEindhoven	Jaap den Toonder		Jaap den Toonder		Microfluidics approaches to cell patterning	MATERIALS AND INTEGRATION Actuators, membranes, integrated systems		
			Bert Meijer* Dick Broer* Albert Schenning			Artificial extracellular matrix, nanoporous polymers, responsive materials and surfaces.		
			Cees Storm Reinder Coehoorn*			Computational multiscale modeling		
Hubrecht Institute, Utrecht	Alexander van Oudenaarden*				QUANTITATIVE BIOLOGY of development & stem cells		Single cell genomics Transcriptomics	
	Hans Clevers*		Rob Vries	*Digestive tract, Liver, Pancreas, Kidney* Colon cancer, IBD	ADULT STEM CELLS Adult stem cells Organoid culture Genetic modification		REPORTER GENE READOUT Lineage tracing Pathway activation	
			Wouter de Laat				Biomedical genomics, 4C technology	
Philips Research, Eindhoven	Anja van de Stolpe	Jos Brunner	Ronald Dekker Anja van de Stolpe (MD) Reinder Coehoorn*	*Cancer (breast, prostate)* *Skin/Hair* *Brain*		INTEGRATION Integrated microfluidics Rapid prototyping	CELL BIOLOGY MODELING AND PATHOLOGY STAINING Computational Signal transduction pathway models, advanced stainings	Medical/cosmetics device development Cancer diagnostics and treatment, radiotherapy planning
Philips Innovation Services Eindhoven	Niels Kramer							PRODUCTION MODEL TESTING FACILITIES

*KNAW member