International Symposium
in honor of Prof. Dr. Elaine Fuchs

25. Friedrich Merz Stiftungsgastprofessur 2015

Natural Barriers:
From Skin Stem Cells to Cancer

Location: Goethe University, Campus Westend, Foyer PA building
Theodor-W.-Adorno-Platz 1, D-60323 Frankfurt am Main, 9.00 am to 4.00 pm

Dear Colleagues!

The Johann Wolfgang Goethe Universität in Frankfurt am Main and the Friedrich-Merz-Foundation award the Friedrich-Merz-Stiftungsprofessur in 2015 to Professor Elaine Fuchs (Rockefeller University, NY).

The Stiftungsprofessur is awarded for the 25th time.

Professor Fuchs will be in Frankfurt for about five days. Tuesday 10 November 2015 is reserved for a scientific symposium that concentrates on stem cells, skin and cancer, i.e. on topics that relate to the scientific work of Professor Fuchs.

Elaine Fuchs, originally trained as a chemist and a biochemist, investigated the skin as the most extended interphase (i.e. barrier) in biology for over thirty years. Therefore, it is not surprising that the epidermis is her inexhaustible source of new questions and the inspiration to advance cell biology, developmental biology and cancer biology. Elaine Fuchs' contributions to science are very broad and she always distinguished herself with her ability to tackle a scientific question by addressing it with unconventional methodology. This is apparent in the discovery of the genetic origin of the blistering dermatitis in the nineties, as recalled in numerous interviews, up to the newest developments in her laboratory at Rockefeller, the *in utero* investigation of the embryo surface. This allows observations in a strictly physiological microenvironment.

On behalf of the Goethe Universität and Merz Pharmaceuticals, we invite you to an exciting symposium.

Prof. Dr. Ernst H.K. Stelzer

Dr. Stefan Albrecht

Schramek D, Sendoel A, Segal JP, Beronja S, Heller E, Oristian D, Reva B, **Fuchs E** (2014) Direct in vivo RNAi screen unveils myosin IIa as a tumor suppressor of squamous cell carcinomas. *Science* 17;343(6168):309-13. doi: 10.1126/science.1248627.

Heller E, Kumar KV, Grill SW, **Fuchs E** (2014) Forces generated by cell intercalation tow epidermal sheets in mammalian tissue morphogenesis. *Dev Cell* 31;28(6):617-32. doi: 10.1016/j.devcel.2014.02.011.

Hsu YC, Li L, **Fuchs E** (2014) Transit-amplifying cells orchestrate stem cell activity and tissue regeneration. *Cell* 8;157(4):935-49. doi: 10.1016/j.cell.2014.02.057.

Oshimori N, Oristian D, **Fuchs E** (2015) TGF-β promotes heterogeneity and drug resistance in squamous cell carcinoma. *Cell* 26;160(5):963-76. doi: 10.1016/j.cell.2015.01.043.

Adam RC, Yang H, Rockowitz S, Larsen SB, Nikolova M, Oristian DS, Polak L, Kadaja M, Asare A, Zheng D, **Fuchs E** (2015) Pioneer factors govern super-enhancer dynamics in stem cell plasticity and lineage choice. *Nature* 21;521(7552):366-70. doi: 10.1038/nature14289. Epub 2015 Mar 18.

Elaine Fuchs

Epithelial Stem Cells in Silence, Action and Cancer

Howard Hughes Medical Institute, The Rockefeller University, NewYork, NY, USA

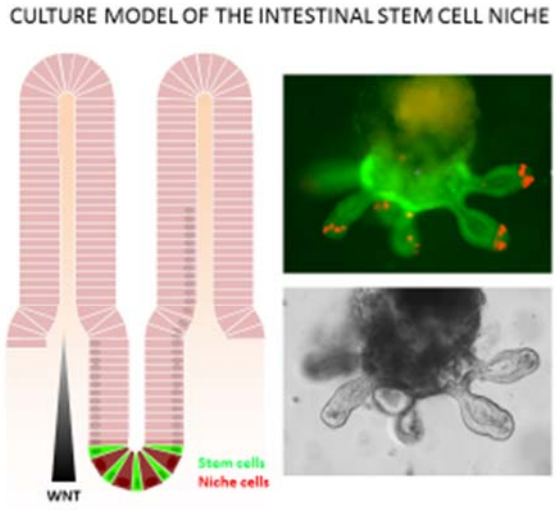
Program

09:00 - 09:15	Introduction Dr. Stefan Albrecht, Chief Scientific Officer of Merz Pharmaceuticals GmbH Prof. Dr. Ernst H.K. Stelzer, Goethe University
09:15 - 10:00	**Epithelial Stem Cells in Silence, Action and Cancer** Elaine Fuchs (Howard Hughes Medical Institute, The Rockefeller University) http://www.rockefeller.edu/research/faculty/labheads/ElaineFuchs/
10:00 - 10:15	Coffee break
	Chair: Dr. Francesco Pampaloni
10:15 - 11:00	**Cellular and molecular determinants of the intestinal stem cell niche** Henner Farin (Inst. for Tumour Biology and Experiment. Therapy, Georg-Speyer-Haus) http://www.georg-speyer-haus.de/forschung/forschungsgruppen/farin/forschung.html
11:00 - 11:45	**Modelling human brain development in cerebral organoids** Madeline Lancaster (MRC Laboratory of Molecular Biology, University of Cambridge) http://www2.mrc-lmb.cam.ac.uk/group-leaders/h-to-m/madeline-lancaster/
11:45 - 13:00	Lunch break
	Chair: Prof. Dr. Anna Starzinski-Powitz
13:00 - 13:45	**Cell Biology of the tumour microenvironment** Erik Sahai (The Francis Crick Institute, London) http://www.crick.ac.uk/research/a-z-researchers/researchers-p-s/erik-sahai/
13:45 - 14:30	**Cancer cell of origin and tumour heterogeneity** Cédric Blanpain (Interdisciplinary Research Institute, Université Libre de Bruxelles) http://blanpainlab.ulb.ac.be/index.htm
14:30 - 15:00	Coffee break
15:00 - 15:45	**Long-term single cell quantification: New tools for old questions** Timm Schroeder (Cell Systems Dynamics, ETH Zurich) https://www.bsse.ethz.ch/department/people/detail-person.html?persid=193443
15:45 - 16:00	Closing Remarks Ernst H.K. Stelzer (Goethe University, Buchmann Institute for Molecular Life Sciences) http://www.physikalischebiologie.de/people/ernst-hk-stelzer

Dr. Farin Henner
Georg-Speyer-Haus, Institute for Tumor Biology and Experimental Therapy, D-60596 Frankfurt, Germany

Cellular and molecular determinants of the intestinal stem cell niche

Mammalian Wnt proteins are believed to act as short-range signals, yet have not been previously visualized in vivo. Self-renewal, proliferation and differentiation are coordinated along a putative Wnt gradient in the intestinal crypt. Wnt3 is produced specifically by Paneth cells. We have now generated an epitope-tagged, functional Wnt3 knock-in allele. Wnt3 covers basolateral membranes of neighboring stem cells. In intestinal organoids, Wnt3-transfer involves direct contact between Paneth cells and stem cells. Plasma membrane localization requires surface expression of Frizzled receptors, which in turn is regulated by the transmembrane E3 ligases Rnf43/Znrf3 and their antagonists Lgr4-5/R-spondin. By manipulating Wnt3 secretion and by arresting stem cell proliferation, we demonstrate that Wnt3 is propagated away from its source in a cell-bound manner though cell division, and not through diffusion. We conclude that stem cell membranes constitute a reservoir for Wnt proteins, while Frizzled receptor turnover and plasma membrane dilution through cell division shape the epithelial Wnt3 gradient.



Wnt signaling specifies the stem cell niche that resides at the bottom of the intestinal crypt. 3D intestinal organoids as a model for epithelial signaling processes.

Dr. Madeline A. Lancaster
MRC Laboratory of Molecular Biology,
Cambridge Biomedical Campus, Cambridge, CB2 0QH, U.K.

Modeling human brain development in cerebral organoids

Human brain development exhibits a number of unique characteristics, such as dramatic size expansion and the formation of unique neuron populations. Until very recently, model organisms were the only experimental tools available to functionally examine brain developmental mechanisms on the whole organ scale. This has obvious limitations when it comes to human-specific features. In an effort to better understand human brain development, we developed a new model system, called cerebral organoids. Cerebral organoids, or "mini-brains", are 3D tissues generated from human pluripotent stem cells that allow modelling of brain development in vitro (Figure 1). Through a process of directed differentiation and a supportive 3D microenvironment, neural precursor tissue can spontaneously self-organize to form the stereotypic organization of the early human embryonic brain. We were able to show that cerebral organoids can also model a neurodevelopmental disorder, microcephaly, characterised by a significantly reduced brain size. This makes brain organoids particularly powerful for not only examining human specific mechanisms, but also pathogenesis of neurological disease. We have now performed extensive characterization of brain organoids and their potential uses. Current findings reveal the timed generation of excitatory neurons as well as inhibitory interneurons and the presence of important non-neural cell types, namely astrocytes and oligodendrocytes. Thus brain organoids provide a relevant model system to study a variety of neurological diseases such as autism, schizophrenia, and neurodegeneration.

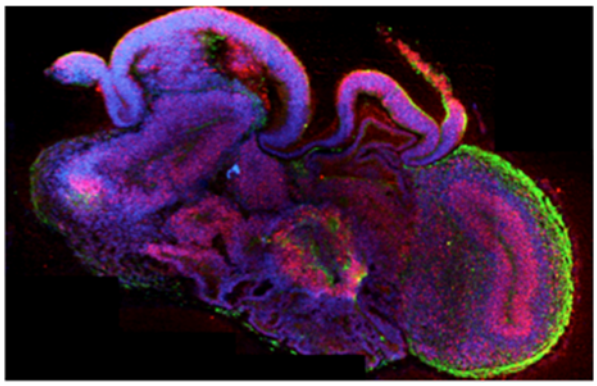


Figure 1 Example of a cerebral organoid. Immunofluorescent staining of a cryosectioned organoid. Sox2+ neural stem cells (red) and Tuj1+ neurons (green) exhibit typical organization. DAPI stains all cells (blue).

Dr. Erik Sahai
The Francis Crick Institute London, London NW1 2BE, U.K.

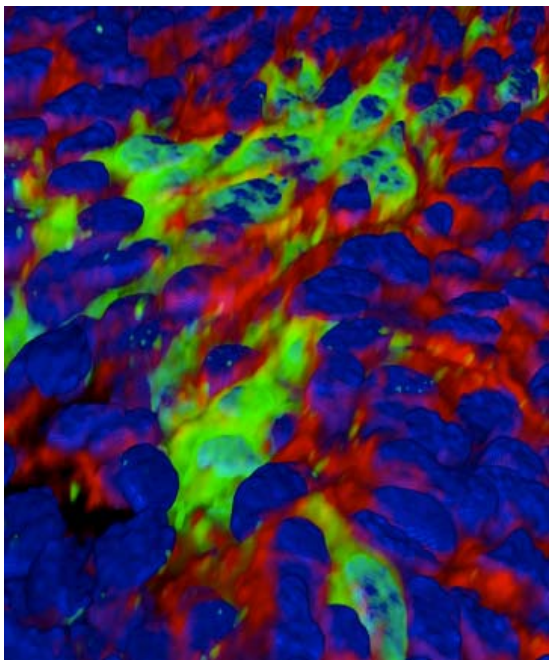
Heterotypic squamous cell carcinoma – fibroblasts cell-cell contacts

The invasion of tumours into surrounding tissue is associated with significant morbidity and mortality. This process is influenced by stromal cells within the tumour environment, in particular Cancer-Associated Fibroblasts (CAFs) can promote tumour invasion. In this study, we describe heterotypic cell-cell contacts between squamous cell carcinoma cells and CAFs. Cancer cells making these contacts move significantly faster than isolated cancer cells. We develop quantitative tools for analysing the extent and duration of heterotypic cancer cell-CAF contacts. Using this methodology, we demonstrate that long-lived contacts are mediated by protocadherins. These junctions are stabilised by Rho-ROCK signalling and antagonised by RTK and Src signalling. Loss of specific proto-cadherin function leads to altered patterns of invasion and prevents cancer cells from using CAFs to traverse areas lacking favourable matrix for cell migration. Finally, we demonstrate the existence of heterotypic cell-cell contacts in primary explants of SCC and tissue sections. We propose that these contacts enable cancer cells to invade into environments for which they do not express appropriate matrix adhesion molecules.

Dr. Cédric Blanpain
WELBIO, IRIBHM, Université Libre de Bruxelles (ULB),
1070 Bruxelles, Belgium

Cancer cell of origin and tumor heterogeneity

Different theories have been proposed to explain tumour heterogeneity including the cancer cell of origin. Here, we developed genetically engineered mouse models allowing lineage tracing together with oncogenic activation in different cell lineages of the skin epidermis and the mammary gland and assessed whether the cancer cell of origin controls tumour heterogeneity. I will discuss evidence that the cancer cell of origin controls tumour heterogeneity and the underlying molecular mechanisms that promote multilineage differentiation, tumour propagation, EMT and metastasis in primary tumors. These results have important implications for our understanding of the mechanisms controlling tumor heterogeneity and the development of new strategies to block tumor initiation.



This work is supported by the ERC, WELBIO, the FNRS, the Fondation Bettencourt-Schuler and the Fondation Baillet-Latour.

Prof. Dr. Timm Schroeder
Department of Biosystems Science and Engineering,
ETH Zurich, Basel, Switzerland

Long-term single cell quantification: New tools for old questions

Stem cell systems are highly complex and dynamic, and consist of large numbers of different cells expressing many molecules. Despite intensive research, many long-standing questions in stem cell research remain disputed. One major reason is the fact that we usually only analyze populations of cells - rather than individual cells - at very few time points of an experiment. Tracking of individual cells would be an extremely powerful approach to improve our understanding of molecular cell fate control. We are therefore developing imaging systems to follow the fate of individual cells over many generations. We program new software to help recording and displaying the divisional history, position, properties, interaction, etc. of all individual cells over many generations. Our approaches also allow continuous long-term quantification of protein expression or activity in individual living cells. The resulting novel kind of continuous quantitative single cell data is used for the generation of improved models describing the molecular control of stem cell fates. I will discuss how we try to find answers for long standing questions in stem cell research.

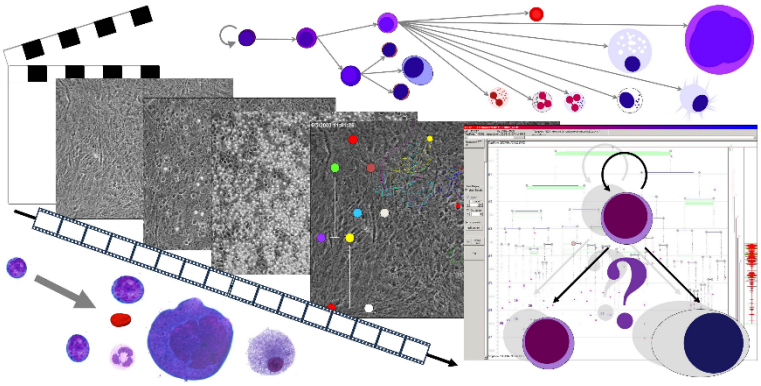


Figure 2 Analysis of molecular stem cell fate control by long-term bioimaging and continuous single cell quantification.

Chairs:

Prof. Dr. Anna Starzinski-Powitz
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Dr. Francesco Pampaloni
Physikalische Biologie (FB 15, IZN)
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Campus Westend

Friedrich Merz-Stiftungsgastprofessur 2015

Goethe-Universität Frankfurt am Main
Elaine Fuchs, Rockefeller University, New York

Scientific Talk on Monday, 9 November 2015

Skin: It's Biology and Promise for Medicine
Elaine Fuchs

Location: Goethe University, Campus Riedberg, Otto-Stern-Zentrum, Lecture Room 4 (H4)
Ruth-Moufang-Straße 2, 60438 Frankfurt am Main, 10.00 am to 11.00 am

International Scientific Symposium on Tuesday, 10 November 2015

Natural Barriers: From Skin Stem Cells to Cancer

Elaine Fuchs, New York
Epithelial Stem Cells in Silence, Action and Cancer

Henner Farin, Frankfurt am Main
Cellular and Molecular Determinants of the Intestinal Stem Cell Niche

Madeline Lancaster, Cambridge
Modelling Human Brain Development in Cerebral Organoids

Erik Sahai, London
Cell Biology of the Tumour Microenvironment

Cédric Blanpain, Bruxelles
Cancer Cell of Origin and Tumour Heterogeneity

Timm Schroeder, Zurich
Long-term Single Cell Quantification: New Tools for old Questions

Location: Goethe University, Campus Westend, Foyer PA building
Theodor-W.-Adorno-Platz 1, 60323 Frankfurt am Main, 9.00 am to 4.45 pm

Bürgerforum am Mittwoch, 11. November 2015

Perspektiven der Stammzellforschung
Boris Rhein, Manfred Schubert-Zsilavecz, Elaine Fuchs, Anna Starzinski-Powitz ,
Francesco Pampaloni, Manuel Grez

Ort: Goethe-Universität, Campus Westend, Foyer PA-Gebäude, Theodor-W.-Adorno-Platz 1, 60323 Frankfurt am Main, 17:30 Uhr

Seminar for Students, Predocs and Postdocs on Wednesday, 11 November 2015

Elaine Fuchs

Location: Goethe University, Campus Riedberg, BMLS, Seminar room 3rd floor
Max-von-Laue-Straße 15, 60438 Frankfurt am Main, 10.00 am to 12.00 am

Organisation:
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