UCL-HMGU-UWA (UHU) Research Collaboration on

“Bioengineering, Regeneration and Repair”

17th July – 18th July 2017
In Schloss Hohenkammer
Schloss Hohenkammer GmbH
Schlossstraße 18–25
85411 Hohenkammer
CONTENTS

- Welcome Notes 3
- Program 4
- Location map 8
- Abstracts & Delegates list 9
- Abstract and biography 10
**Welcome Note**

We are very pleased to welcome you to this year’s UCL-UWA-HMGU Collaborative Research Network Meeting 2017, on “Bioengineering, Regeneration and Repair” from 17th – 18th July, in the beautiful venue of “Hotel Schloss Hohenkammer”, which is an old castle to the north of Munich.

The aim of the meeting is to promote collaborative research in the area of regenerative medicine and to showcase research arising from collaborations that have evolved since our previous meetings. The meeting aims to strengthen the international network and to identify and facilitate collaborative projects for seed funding.

The two day scientific programme will provide opportunities for some selected presentations, collaborative project discussions and “one to one” discussions. The relaxed atmosphere of this meeting should encourage an open exchange of the latest concepts and data, with free discussions amongst expert faculty and young investigators.

We would like to thank you for participating in this year’s meeting and hope that it will be an engaging, exciting, and prosperous meeting for all participants.

With best regards from the local organizing committee

Heiko Lickert, Silke Meiners, and Donna Thomson

---

**Acknowledgement**

The organizing committee would like to express our special thanks to Donna Thomson (HMGU) and Kaori Sumikawa (HMGU) who worked hard to organize and realize this meeting. Donna will be available during the meeting if you have a question or need any help.
# Meeting Programme

**Monday 17th July 2017**

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>9:45 – 10:15</td>
<td>Welcome Coffee and Registration</td>
</tr>
<tr>
<td>10:15 – 10:30</td>
<td><strong>Official Opening of the UWA – Helmholtz Zentrum München Collaboration</strong>&lt;br&gt;Heiko Lickert / Silke Meiners&lt;br&gt;Geoff Laurent / Cecilia Prêle</td>
</tr>
</tbody>
</table>
| 10:30 – 11:50 | **Session #1: Regenerative approaches**<br>
|               | **Yuval Rinkevich:** Successions between fibroblast lineages underlies dermal development, and its phenotypic transition from regeneration to scarring |
|               | **George Yeoh:** The role of liver progenitor cells in development of hepatocellular carcinoma |
|               | **Heiko Lickert:** Beta cell heterogeneity and regeneration |
|               | **Nina Tirnitz-Parker:** Liver progenitor cells as a therapeutic target - the role of key signalling pathways in regeneration versus carcinogenesis |
| 11:50 – 13:00 | Lunch                                                                 |
| 13:00 – 14:20 | **Session #2: Bioengineering and epithelial stem cells**              |
|               | **Michael Edel:** Advancing iPS cell technology to treat human disease |
|               | **Micha Drukker:** Post transcriptional regulation of end of pluripotency |

**Talk**<br>10min
<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
</tr>
</thead>
<tbody>
<tr>
<td>14:20 – 14:40</td>
<td><strong>Coffee break</strong></td>
</tr>
<tr>
<td>14:40 – 16:00</td>
<td><strong>Chair: George Yeoh</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Robert Hynds:</strong> Redefining airway basal cell culture conditions for cell therapies</td>
</tr>
<tr>
<td></td>
<td><strong>Anika Böttcher:</strong> Dissecting the gut stem cell lineage hierarchy</td>
</tr>
<tr>
<td></td>
<td><strong>Alecia-Jane Twigger:</strong> Human mammary gland organogenesis and function</td>
</tr>
<tr>
<td></td>
<td><strong>Rodney Dilley:</strong> Tympanic membrane organ culture</td>
</tr>
<tr>
<td>16:00 – 16:20</td>
<td><strong>Afternoon Tea</strong></td>
</tr>
<tr>
<td>16:20 – 17:40</td>
<td><strong>Session #3: Enabling technologies</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Stefan Stricker:</strong> Editing fate changes</td>
</tr>
<tr>
<td></td>
<td><strong>Herbert Schiller:</strong> Molecular and cellular composition of the lung – from mass spectrometry driven proteomics to single cell transcriptomics</td>
</tr>
<tr>
<td></td>
<td><strong>Silke Meiners:</strong> Regulation of proteasomal protein turnover in lung cell differentiation and disease</td>
</tr>
<tr>
<td></td>
<td><strong>Deirdre Coombe:</strong> Dermal fibroblast extracellular matrix regulates keratinocyte self-renewal and gene expression</td>
</tr>
<tr>
<td>19:30 – 23:00</td>
<td><strong>Dinner</strong></td>
</tr>
</tbody>
</table>

**Kiryu Yap:** Bio-engineering vascularised liver organoids

**Richard M. Day:** Biomaterials for hollow organ tissue engineering.
<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Speaker(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9:00 – 9:20</td>
<td><strong>Session #3: Enabling technologies</strong></td>
<td><strong>Fabian Theis:</strong> Reconstructing branching lineages in single cell genomics</td>
</tr>
</tbody>
</table>
| 09:20 – 10:00| **Session #4: Clinical application and cell-based therapies** | **Yuben Moodley:** Mesenchymal stromal cell infusion induces acute systemic immunological responses in patients with chronic obstructive pulmonary disease  
**Andrew Lucas:** Differential effects of exogenous IGF-1 administration on young adult and geriatric mice following pneumonectomy  
**Carsten Schmidt-Weber:** Differential response of E1 versus E2 primed airway epithelial cells to TGF-beta and IL-6 |
| 10:00 – 10:20| **Coffee Break**                             | Foyer                                                                                                                   |
| 10:20 – 12:20| **Speed networking**                         |                                                                                                                         |
| 12:30 – 13:30| **Lunch**                                    |                                                                                                                         |
| 13:30 – 15:00| **Session #4: Clinical application and cell-based therapies** | **Ali Önder Yildirim:** Cigarette smoke drives B cell positioning and immune pathogenesis of COPD  
**Irmgard Irminger:** Regulation of telomere length                                                                 |
in cancer and lung fibrosis

**Georgios Stathopoulos:** Pulmonary repair and mutagenesis in response to tobacco carcinogens

**Wissam Chiha:** AAV-mediated expression of BDNF and CRMP2 promotes neuroprotection of adult rat retinal ganglion cells and axons following optic nerve injury

**Cecilia Prêle:** STAT3-mediated Immune regulation in Idiopathic pulmonary fibrosis

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>15:00 – 15:10</td>
<td><strong>Closing Remarks</strong></td>
</tr>
<tr>
<td>15:10 – 15:30</td>
<td><strong>Light Refreshments</strong></td>
</tr>
<tr>
<td>16:00</td>
<td><strong>Depart – Shuttle to airport / Munich</strong></td>
</tr>
</tbody>
</table>
## Delegates list

<table>
<thead>
<tr>
<th>Name</th>
<th>Affiliation</th>
<th>Talk</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anika Böttcher</td>
<td>HMGU</td>
<td>17.07.2017</td>
<td>11</td>
</tr>
<tr>
<td>Antje Brand</td>
<td>HMGU</td>
<td>no talk</td>
<td>12</td>
</tr>
<tr>
<td>Ingo Burtscher</td>
<td>HMGU</td>
<td>no talk</td>
<td>12</td>
</tr>
<tr>
<td>Wissam Chiha</td>
<td>UWA</td>
<td>18.07.2017</td>
<td>13</td>
</tr>
<tr>
<td>Deirdre Coombe</td>
<td>UWA</td>
<td>17.07.2017</td>
<td>14</td>
</tr>
<tr>
<td>Richard Day</td>
<td>UCL</td>
<td>17.07.2017</td>
<td>15</td>
</tr>
<tr>
<td>Rodney Dilley</td>
<td>UWA</td>
<td>17.07.2017</td>
<td>15</td>
</tr>
<tr>
<td>Li Deng</td>
<td>HMGU</td>
<td>no talk</td>
<td>16</td>
</tr>
<tr>
<td>Micha Drukker</td>
<td>HMGU</td>
<td>no talk</td>
<td>16</td>
</tr>
<tr>
<td>Michael Edel</td>
<td>UWA</td>
<td>17.07.2017</td>
<td>17</td>
</tr>
<tr>
<td>Isis Fernandez</td>
<td>HMGU</td>
<td>no talk</td>
<td>18</td>
</tr>
<tr>
<td>Rob Hynds</td>
<td>UCL</td>
<td>17.07.2017</td>
<td>18</td>
</tr>
<tr>
<td>Irmgard Irminger-Finger</td>
<td>UWA</td>
<td>18.07.2017</td>
<td>19</td>
</tr>
<tr>
<td>Geoff Laurent</td>
<td>UWA</td>
<td>no talk</td>
<td>20</td>
</tr>
<tr>
<td>Heiko Lickert</td>
<td>HMGU</td>
<td>17.07.2017</td>
<td>21</td>
</tr>
<tr>
<td>Andrew Lucas</td>
<td>UWA</td>
<td>18.07.2017</td>
<td>22</td>
</tr>
<tr>
<td>Silke Meiners</td>
<td>HMGU</td>
<td>17.07.2017</td>
<td>23</td>
</tr>
<tr>
<td>Hiromi Miyoshi</td>
<td>Guest (Riken, Tokyo Metropolitan University)</td>
<td>no talk</td>
<td></td>
</tr>
<tr>
<td>Yuben Moodley</td>
<td>UWA</td>
<td>18.07.2017</td>
<td>24</td>
</tr>
<tr>
<td>Cecilia Prele</td>
<td>UWA</td>
<td>18.07.2017</td>
<td>25</td>
</tr>
<tr>
<td>Yuval Rinkevich</td>
<td>HMGU</td>
<td>17.07.2017</td>
<td>26</td>
</tr>
<tr>
<td>Herbert Schiller</td>
<td>HMGU</td>
<td>17.07.2017</td>
<td>27</td>
</tr>
<tr>
<td>Elke Schlüssel</td>
<td>HMGU</td>
<td>Organization</td>
<td></td>
</tr>
<tr>
<td>Otmar Schmid</td>
<td>HMGU</td>
<td>no talk</td>
<td>28</td>
</tr>
<tr>
<td>Carsten Schmidt-Weber</td>
<td>HMGU</td>
<td>18.07.2017</td>
<td>28</td>
</tr>
<tr>
<td>Georgios Stathopoulos</td>
<td>HMGU</td>
<td>18.07.2017</td>
<td>29</td>
</tr>
<tr>
<td>Stefan Stricker</td>
<td>HMGU</td>
<td>17.07.2017</td>
<td>30</td>
</tr>
<tr>
<td>Fabian Theis</td>
<td>HMGU</td>
<td>18.07.2017</td>
<td>30</td>
</tr>
<tr>
<td>Donna Thomson</td>
<td>HMGU</td>
<td>Organization</td>
<td></td>
</tr>
<tr>
<td>Nina Tirnitz-Parker</td>
<td>UWA</td>
<td>17.07.2017</td>
<td>31</td>
</tr>
<tr>
<td>Alecia - Jane Twigger</td>
<td>HMGU</td>
<td>17.07.2017</td>
<td>32</td>
</tr>
<tr>
<td>Joanne van Vuurren</td>
<td>UWA</td>
<td>no talk</td>
<td>32</td>
</tr>
<tr>
<td>Kiryu Yap</td>
<td>UWA</td>
<td>17.07.2017</td>
<td>32</td>
</tr>
<tr>
<td>George Yeoh</td>
<td>UWA</td>
<td>17.07.2017</td>
<td>33</td>
</tr>
<tr>
<td>Ali Önder Yıldırım</td>
<td>HMGU</td>
<td>18.07.2017</td>
<td>34</td>
</tr>
</tbody>
</table>
Abstracts and Delegates index

(in alphabetical order of Surname)
Dissecting intestinal stem cell lineage decisions

Tissue polarity is fundamental for organ formation and function and mutations in polarity genes are the underlying cause of many diseases including cancer. Intestinal tissue polarity is evident in its organization into crypt-villus units. Growth factor gradients along the crypt-villus axis are thought to define precise positioning of cells and thus assure stem cell proliferation and maintenance as well as differentiation of specific cell types in a distinct spatial order. However, the signals regulating ISC proliferation versus differential lineage allocation are still little understood.

We identified Lgr5+ ISCs that express Flattop (Fltp, also known as Cfap126), a Wnt/planar cell polarity (PCP) effector and reporter gene. Short-term genetic lineage tracing and functional analysis showed that Wnt/PCP activated Fltp+ ISCs are lineage committed to secretory Paneth and enteroendocrine cells, while retaining multi-lineage capacity in vitro. Surprisingly, Wnt/β-catenin and Wnt/PCP activated Lgr5+ ISCs were not distinguishable by the expression of stem cell signature genes or lineage-specifying genes, suggesting that lineage commitment and cell-cycle exit is triggered at the post-transcriptional level by polarity cues. Furthermore, computational determination of a pseudotime from single-cell gene expression data allowed us to reconstruct the ISC differentiation path into Paneth and enteroendocrine cells. Pseudotime cell-ordering reinforced that both lineages directly allocate from ISCs, excluding the existence of formerly predicted bi- or multipotent secretory progenitors.

Taken together, we identified the Wnt/PCP pathway as a new niche signal regulating stem cell fate. Our results indicate that active Wnt/PCP signaling represents the earliest step in lineage commitment of ISCs towards the Paneth and enteroendocrine cell fate and precedes lateral inhibition.

Biography

10/2010 – present Postdoctoral Fellow, Helmholtz Centre Munich, Institute of Diabetes and Regeneration Research, Munich, Germany
Advisor: Prof. Dr. Heiko Lickert

09/2005 – 09/2010 Ph.D. (Dr rer nat) in Molecular Medicine
Max Planck Institute of Biochemistry, Munich, Germany
Advisor: Prof. Dr. Reinhard Fässler

10/1999 – 06/2005 Diploma studies in Biology, University of Jena, Germany and University of Lund, Sweden
Antje Brand

Biography
Antje is Acting Director of the Institute for Lung Biology (ILBD) and Disease at Helmholtz Zentrum München. She is also Manager of the German Center for Lung Research (DZL) site Munich, the Comprehensive Pneumology Center (CPC-M). The DZL is a government founded center that unites leading universities and non-university-based lung research organizations into one coherent organization. Antje has a background in biomedical sciences and was head and coordinator in various projects on raising public awareness, public outreach and scientific management the Max-Planck Society and the Helmholtz Association. She is affiliated to the ILBD/CPC since its official start in April 2010. She also acted as a coordinator for the establishment of the UHU agreement.

Ingo Burtscher

Biography
Studied Molecular Biology at University of Vienna, finishing his Masters at the Institute of Pathology in Cancer Research in 1999. For his PhD he went to Queen Mary and Westfield College in London working on Down Syndrome and related Dementia where he graduated in 2004. In 2005 he joined the Lab of Heiko Lickert where he focused on time lapse imaging in the mouse embryo studying molecular events of endoderm formation during gastrulation. Furthermore, he established numerous knock in mouse models also using recently CrisprCas technology. He is Head of the Stem Cell Group, working with both mouse ESCs and human iPS and ESCs.
Neurotrauma leads to immediate degeneration of affected tissue and secondary degeneration of intact proximate tissue. Partial transection (PT) of the dorsal rat optic nerve (ON) models secondary degeneration as it leaves ventral RGC axons and somata intact and vulnerable to secondary degeneration. RGCs in central and dorsal retina are affected by primary and secondary degeneration. We investigated the neuroprotection of intravitreally administered bi-cistronic adeno-associated viral-vectors (AAV-2) encoding BDNF and/or non-phosphorylatable collapsing response mediator protein-2 (CRMP2) with green fluorescent protein (GFP) on RGC survival and axonal integrity following partial ON transection. Three months after PT of ON, the number of RGCs declined by over 60% in AAV-GFP controls in dorsal and central retina and 56% in ventral retina relative to uninjured controls. The number of RGCs in dorsal retina was not enhanced by AAV treatment, while in central retina, all AAV treatments significantly restored the number of RGCs to uninjured levels. In ventral retina, RGCs were significantly protected after treatment with AAV-BDNF-GFP and AAV-BDNF. Similarly we observed a significant decrease in βIII-tubulin immunoreactivity in dorsal and ventral ONs following partial ON transection. AAV mediated expression of CRMP2 or when combined with BDNF, significantly upregulated βIII-tubulin immunoreactivity compared AAV-GFP following injury. This is further supported by preliminary electron microscopy data of ventral ON following injury. AAV mediated expression of CRMP2 or when combined with BDNF was significantly neuroprotective to the number of axons (p≤ 0.05) compared to AAV GFP. Results indicate BDNF and CRMP2 mediated RGCs survival in central retina, while in RGCs vulnerable to secondary degeneration, only BDNF was efficacious, suggesting axonal integrity and cell viability are dissociable. Differential neuroprotection may be evoked by a disparity between primary and secondary degeneration and growth factor signalling mechanisms.

Biography

Wissam is a PhD candidate at The University of Western Australia in the field of Neuroscience. My research interests are in understanding the genetic differences between primary and secondary degenerative events in neurotrauma and exploiting current advances in gene therapy as a potential therapeutic approach. Her ultimate aim is to provide successful therapies and improve the quality of life for individuals with trauma to the brain and spinal cord.
Deirdre Coombe

Dermal fibroblast extracellular matrix regulates keratinocyte self-renewal and gene expression.

Large-scale expansion of keratinocytes under serum and feeder free conditions for clinical use is challenging, as keratinocytes show diminished self-renewal and increased commitment to terminal differentiation. Identification of xenogeneic-free culture conditions for primary human keratinocytes that retain the self-renewal capacity of these cells will dramatically enhance their clinical use. As the tissue microenvironment largely determines a cell’s fate and a key component of the microenvironment is the extracellular matrix (ECM), an acellular ECM derived from human dermal fibroblasts was used as a basis for a xenogeneic-free keratinocyte expansion protocol. Comparing the effect of ECM from adult or foetal dermal fibroblasts with a type I collagen substrate on keratinocyte growth and gene expression revealed the dramatic contribution of ECM to these processes. Although adult ECM was a superior substrate for the growth of primary human keratinocytes in serum free medium compared to the traditional substrate of bovine type-I collagen, this effect was extremely pronounced with foetal ECM. The keratinocytes proliferated more rapidly and retained their small size, a characteristic of undifferentiated cells, and gene array analyses revealed that keratinocytes expanded on the foetal matrix markedly up-regulated genes associated with cell cycle, mitotic division and DNA repair, whereas genes associated with differentiation were down regulated. In contrast, keratinocytes expanded on type I collagen exhibited exactly the opposite gene expression pattern, and keratinocytes expanded on adult ECM displayed an intermediate pattern. The compositional differences between the adult and foetal matrices revealed by proteomic analysis and immunofluorescence may provide clues as to the ECM proteins that regulate the self-renewal of keratinocytes.

Biography

Deirdre Coombe, PhD, BSc Hons (University of Adelaide) is a Professor of Biomedical Sciences, at Curtin University, Western Australia. She has an international reputation for her work with carbohydrates in the extracellular matrix and in particular with carbohydrate-protein interactions and the therapeutic applications of carbohydrate-based drugs. She also has a keen interest in the extracellular matrix and its contribution to cell and tissue differentiation as well as to cancer cell migration and invasion. She obtained her PhD degree from the University of Adelaide in 1983. She has worked at the Australian National University; Imperial Cancer Research Fund, London; National Institute for Medical Research, London; Glycobiology Institute and Sir William Dunn School of Pathology both of Oxford University. In 1994 she returned to Australia and setup her own research lab at the Institute for Child Health Research (now Telethon Kids Institute) in Perth, Western Australia before joining Curtin University in 2000. She has had continuous research funding for 23 years and during that period has raised in excess of AU$8 million in research grants and research contracts. She has published in excess of 50 research articles and numerous conference abstracts, 4 book chapters and has edited an eBook. She is an inventor on 6 patent families, four of these patent families are either in the national phase or granted. In 2006 she co-founded Glycan Biosciences Pty Ltd to commercialise one of her research projects. This company now has its headquarters in Philadelphia USA and is called Glycan Biosciences LLC. She continues to work closely with Glycan Biosciences LLC. Her experience straddles academia and business and she has a keen interest in the translation of academic, biomedical research into the clinic.
Richard Day

Manufacture & Delivery of Adherent Cells

Biodegradable microcarriers could offer a novel approach for localized delivery of adherent cells. The talk will provide a summary of recent studies investigating the attachment of human skeletal muscle myoblasts (HSMM) to the surface of highly porous TIPS microcarriers and assessment of their targeted delivery and retention in vivo. HSMM attached readily to the surface of TIPS microcarriers. Once attached to the surface of TIPS microcarriers, myoblasts proliferated when maintained in suspension culture. Attachment of HSMM to TIPS microcarriers did not impair their ability to migrate, proliferate and form skeletal muscle myosin heavy chain-positive myotubes. Bioluminescence indicated myoblasts transplanted in vivo on the surface of TIPS microcarriers were retained at the delivery site and remained viable as the microcarriers biodegrade. The results indicate it is technically feasible to use TIPS microcarriers for culture and targeted in vivo delivery of human myoblasts.

Biography

Richard Day leads the Applied Biomedical Engineering Group, part of the Centre for Cardiovascular Biology and Medicine, Division of Medicine at UCL. The group is focussed on the development and translation of innovative biomedical engineering technology for unmet clinical needs. Current research activity relates to regenerative medicine, focussing on cell therapy and drug delivery for clinical conditions associated with gastroenterology, cardiovascular biology, and ophthalmology. The group is actively exploring clinical translation of biomaterials for tissue repair and cell delivery. This includes pre-clinical mechanistic studies investigating progenitor cell delivery and engraftment and a phase I clinical safety study of a synthetic microparticle device for tissue repair.

Rodney Dilley

Using silk fibroin for surgical reconstruction of the eardrum

Reconstruction of ear tissues after surgical treatment or trauma is limited by highly specialised surgical staff and costly facilities and also has a measurable failure rate. In order to improve access and optimise outcomes we have been developing a silk-based tissue engineering system to generate devices which can be easily implanted and rapidly restore function. A device for eardrum perforation has been developed and tested in the laboratory and is nearing clinical testing. In this presentation the novel areas of materials engineering, soft tissue imaging, stem cell biology and tissue engineering used for developing these 3D silk devices will be presented and opportunities for collaborative studies in these areas discussed. Applications of tissue engineering and 3D bio-printing in otological surgery will also be discussed.
Biography

Rod Dilley is Head of Molecular and Cellular Otolaryngology Laboratory at Ear Science Institute Australia and Associate Professor at University of Western Australia’s Ear Sciences Centre and Centre for Cell Therapy and Regenerative Medicine. Since gaining PhD at UWA on pathological mechanisms in microvascular grafts, and postdoctoral study in Seattle USA on cardiovascular hypertrophy, he moved to Melbourne and established research programs on cardiac tissue engineering and vascular tissue remodelling in hypertension and atherogenesis. Returning to Perth in 2011 his work at Ear Sciences Centre has focused on wound repair in ear and hearing disorders. The work of his multidisciplinary team includes development of novel materials and devices for tissue engineering and reconstructive ear surgery.

Li Deng

Biography

Li Deng conducts research in the area of molecular virology. She takes an integrated approach to investigate microbes-viruses interactions by combining microcosm experiments employing model microbes and viruses, and culture-independent, high-throughput metagenomics. She is currently focusing on viruses from both environment (e.g. water) and human (e.g. gut and lung). In addition, an applied research direction of her is to synthesize viruses as "phage therapy" for curing diseases caused by pathogenic bacteria which have already gained resistance to antibiotics.

Li Deng studied Environmental Engineering at the Tsinghua University in China (BEng), Environmental Science at the University of Nottingham in the UK (MSc), and Microbiology at the University of Bristol in the UK (PhD). After her post-doctoral training at the University of Arizona, US, she joined the Groundwater Ecology Institute, later moved to the Institute of Virology at the Helmholtz Centre Munich in Germany, as the head of DFG Emmy Noether group, as well as Helmholtz Young Investigator group.

Micha Drukker

Post transcriptional regulation of end of pluripotency

Cell fate transitions can be promoted by networks with bimodal equilibrium. Here, we show that cross-regulation between the RBP TDP-43 (TARDBP) and paraspeckles, nuclear granules formed by the IncRNA NEAT1, regulates the choice between pluripotency and differentiation. TDP-43 promotes self-renewal by regulating an evolutionary conserved global switch in alternative polyadenylation, including the transcript encoding the pluripotency factor SOX2, which exposes it for miR-21-induced degradation. In embryonic stem cells, TDP-43 also prevents the formation of paraspeckles by repressing the long isoform of NEAT1. Conversely, reduction of TDP-43 during differentiation triggers the short-to-long isoform switch of NEAT1, which polymerizes paraspeckles that recruit TDP-43 and relocalise it away from other RNA targets. While TDP-43 inhibits differentiation and improves somatic cell reprogramming, paraspeckles promote early differentiation in a manner that is functionally independent of lineage choice. Thus, a bimodal equilibrium of TDP-43 and paraspeckles govern cell fates, a mechanism relevant to cancer and neurodegeneration.

Biography

Micha Drukker is a principle investigator and the head of the human induced pluripotent stem cell core at the Helmholtz Institute in Munich. Micha is involved in basic and translational research in the stem cell field, and his
achievements include the first analysis of the immunological properties of differentiated human embryonic stem (ES) cells, which has promoted the development of strategies to overcome the immunogenicity of human ES cells including by derivation of patient-matched pluripotent stem cells through therapeutic cloning and induction of pluripotency in somatic cells by reprogramming. More recently, Micha discovered cell surface markers enabling purification and monitoring of some of the earliest developmental progenitors from human ES cells mutually exclusively sorted from teratoma-initiating cells, and his most recent work focuses on the regulation of early pluripotent stem cell differentiation. Micha also leads projects aiming to produce and genetically engineered induced pluripotent stem cells for tissue restoration under clinical standards.

Michael Edel

To successfully treat or accurately model human disease with cells derived from induced pluripotent stem cells (iPSC), it is dependent on the quality of the starting iPSC.

The level of genetic instability and engraftment of cells in a hostile damaged tissue environment with no pathology are thought to be the potential barriers to clinical application and accurate disease modeling. Key to these issues is the removal of c-Myc from the reprogramming cocktail. Here, we develop an improved method that adopts a feeder free synthetic mRNA transfection methods replacing c-Myc producing high quality iPSC from clinically easy to access cells with reduced cell stress, reduced genetic instability and reduced threat of pathology in a spinal cord injured rat model. With improved genetically stable iPSC, we used clinical grade cell culture conditions (Thermo Fischer), to establish a protocol that could be adopted as a SOP for generating GMP clinical grade human iPSC.

Biography

Dr. Michael Edel completed his Science degree in Anatomy and Human Biology and Physiology with a Masters describing the pathology associated with human spine degeneration at the University of Western Australia. His PhD thesis focused on mechanisms of neoplastic growth in the field of Pathology at the same University. His high level of scholarship has been recognised with awards including the French/Australia Government fellowship (1998), Anges Watt PhD student Scholarship (1996), the John Nott traveling Fellowship to spend 3 months at Harvard Medical School Boston (2000) and the DURSI fellowship with Dr. Miguel Beato at the CRG (2004). He has specialised during his post-doctoral fellowships on basic cell biology and molecular genetic mechanisms of spinal cord injury, neural stem cells and cancer resulting in a number of high impact publications the past ten years (Cell 2005, Nature Biotechnology 2008, Genes and Development 2010 and Stem Cells and Development 2012). In 2007 he was the principle investigator on a Carlos III grant entitled: “understanding the role of the cell cycle in self-renewal and pluripotency”, with Dr. Juan Carlos Izpisua Belmonte at the CMRB. In 2010 he was awarded a Ramon y Cajal tenure track position scoring 93/100 and ranked top 10 researcher in Spain that year in his field. In 2011 he was the principle Investigator of a MINECO grant (BFU2011-26596) specialising on new methods to treat spinal cord injury entitled: “Investigation into the role of the cell cycle and apoptosis in human clinical-grade induced pluripotent stem cells and adult stem cells for future application to treat spinal cord injury”. In 2014 he received continued funding from MINECO (BFU2014 54467-P) to derive a clinical grade protocol to safely generate neural cell types to treat spinal cord injury and spinal muscular atrophy. He is currently a group leader at the University of Barcelona Institute of Neurosciences, AQU accredited Associate Professor at the University of Barcelona, Faculty of Medicine where he leads a group of six staff/students on multiple projects to investigate new cell based applications to study and treat spinal cord injury as well as other eye and lung diseases. His work is supported by Caxia Impulse and has collaborations in Industry to search for
new cell based therapy applications. The overall mission of his research is to understand the role of cell cycle genes in attaining ground state pluripotency and reducing the threat of cancer for application of stem cells as a cell replacement therapy for neurological and ocular disease.

Isis Fernandez

**Biography**

Isis obtained her medical degree in Cartagena, Colombia where she was trained as a clinician with a personal slant towards critical care. Afterwards, she pursued a physician scientist career in the department of Pulmonary and Critical Care of Brigham and Women’s Hospital, Harvard Medical School in Prof. Rosas’ Lab where she worked on syndecans in lung fibrosis and cancer, as well as detection of Interstitial Lung Abnormalities by HRCT in smokers. Then, she joined the Lab of Prof. Eickelberg at the Comprehensive Pneumology center, where she has been working compartmental biomarker screening in IPF and animal models, and the innate immunity role in lung fibrotic disorders.

Robert Hynds

**Redefining airway basal cell culture conditions for cell therapies**

Cell therapy could potentially improve patient outcomes in a range of conditions through replacement of malfunctioning cells, stimulation of endogenous epithelial regeneration or by immunomodulation. Transplantation of tissue stem cells has proven life-saving in multiple epithelial organs. KRT5+/TP63+ basal cells are progenitor cells in the human airway epithelium and these cells can be expanded in culture and differentiated to form epithelia containing multiciliated and mucosecretory cells in air-liquid interface and 3D organoid models. Despite this, early pre-clinical and clinical data concerning the transplantation of airway basal cells indicates that expanding sufficient numbers of cells suitable for transplantation remains a challenge for the field. Our data demonstrate that airway epithelial cell isolation and expansion is improved by culture on 3T3-J2 fibroblast feeder cells and by the use of a ROCK inhibitor, Y-27632. In these conditions, cells retain the capacity to differentiate appropriately, *in vitro* and *in vivo*, over long culture periods. Future experiments must focus on the mechanistic nature of 3T3-J2 feeder cell support of epithelial stem cells, which remains poorly understood, and investigate the long-term regenerative potential of these cells *in vivo*.

**Biography**

Rob Hynds is a postdoctoral research associate in Prof. Charles Swanton’s Translational Cancer Therapeutics Laboratory at University College London and The Francis Crick Institute (London, U.K.). He completed his PhD at University College London in Prof. Sam Janes’s Lungs for Living Research Centre (University College London, U.K.), publishing primarily on novel methodologies for human airway epithelial cell expansion. Rob’s interests also include the generation of *in vitro* and *in vivo* models that faithfully recapitulate the heterogeneity of patient non-small cell lung cancers. Email: rob.hynds@ucl.ac.uk.
Regulation of telomere length in cancer and lung fibrosis


Short telomeres are a feature of pulmonary fibrosis (PF). Idiopathic PF (IPF) and familial PF are strongly associated with mutations in two key regulators of telomere length in 1) hTERT, the enzyme required for telomere elongation and a regulator of telomere length, cell division, and senescence and 2) in TERC, the RNA subunit of TERT. Mutations in either of these genes increase susceptibility to IPF. Indeed, TGFβ, the driver of lung fibrosis, down-regulates telomerase activity. Short telomeres are normally observed in highly proliferating tissues. Critically short telomeres activate signalling towards p53, leading to cell senescence or apoptosis. However, alteration of the telomere structure could also lead to chromosomal instability, cell cycle arrest, and apoptosis. Whether short telomeres are a consequence or cause in lung fibrosis remains unclear. Thus, cellular senescence, short telomeres, and hTERT or TERC mutations are predisposing factors for IPF, however, the mechanism(s) by which these factors contribute to pro-fibrotic proliferation remains unexplained. Our group explores the hypothesis that the tumor suppressor BRCA1-associated RING domain 1 (BARD1) and oncogenic isoforms of BARD1 are involved in the regulation of telomere length and structure in lung fibrosis. We have shown that BARD1 acts downstream of TGFβ causing epithelial cell apoptosis and fibroblast proliferation. We investigate the role of BARD1 in telomere maintenance in fibroblasts and epithelial cells in healthy lung and tissues from IPF patients and from mice with experimentally induced lung fibrosis.

Biography

Irmgard is group leader at the University and University Hospitals of Geneva, Professor at the University of Western Australia, and Scientific Director of BARD1 Life Sciences Limited in Perth. She studied biology and biochemistry at the University of Zurich, where she obtained a master in molecular biology and biochemistry and a PhD in molecular genetics. After several years as postdoctoral researcher at the Molecular Cell Biology Department at the Harvard University, she returned to Switzerland and first had a position as independent researcher at the Biochemistry Department of the University of Geneva and then at the Medical Faculty of the University of Geneva, having obtained a Swiss federal career development award. She focused her research on the molecular pathways at the aging and cancer interface as part of the Biology of Aging Institute. Since 2006 she heads the Molecular Gynecology and Obstetrics Laboratory at the Geneva University Hospitals. The main interest of this laboratory has been the function of tumor suppressor genes in normal and cancer cells and their implication in carcinogenesis and cancer progression, in particular the breast cancer genes BRCA1 and BARD1. Over the years, Dr. Irmgard Irminger-Finger built up her reputation as expert in the Cancer and Aging field and as expert on the BRCA1 and BARD1 genes, as author of more than 90 scientific articles, speaker at more than 200 conferences and meetings, editor of scientific journals, and member of specific study groups and Task Forces on Cancer. The work of her group has led to several patents that paved the way to applications in cancer diagnostics and therapy. Dr. Irmgard Irminger-Finger has received numerous awards and grants both for academic research and for her entrepreneurial work as founder of a successful biotech startup.
Geoff Laurent

Biography

Professor Geoff Laurent is an Emeritus Professor at the University of Western Australia. From 2012 to June 2017 he was the Director of the Institute for Respiratory Health and Director of the Centre for Cell Therapy and Regenerative Medicine at The University of Western Australia. Prior to his appointment at the University of Western Australia he was Director of the Centre for Respiratory Research, Vice-Dean of Enterprise and Head of the Research Department of Internal Medicine at University College London. Professor Laurent has published over 250 articles in international journals of medicine and biomedical research. He received the European Respiratory Societies Presidential Award for his contribution to lung science and is a Past President of the British Association for Lung Research.

He is the Editor-in-Chief of the International Journal of Biochemistry and Cell Biology and has edited several books including a four volume Encyclopedia of Respiratory Medicine. Professor Laurent has led the development of research programs investigating key mediators regulating inflammation and tissue remodeling in fibrotic diseases. He has made fundamental discoveries relating to the key cytokines, lipid mediators and proteases regulating fibroblast function in fibrosis. These discoveries have led to partnerships with industry to develop new drugs to treat chronic lung diseases. These achievements were recognized when he was elected a Fellow of the Academy of Medical Sciences in 2006. He continues to conduct research based at UWA and is a Director of a Life Science company listed on the Australian stock exchange. Professor Laurent is a Scientific Advisor and Consultant for Helmholtz Zentrum München – Deutsches Forschungszentrum für Gesundheit und Umwelt (HMGU). Helmholtz Zentrum München is the foremost German Research Center for Environmental Health. As part of this role he helps coordinate The UCL, UWA, Helmholtz (UHU) collaboration currently funded through to 2019.
Although β-cell heterogeneity was discovered more than 50 years ago, the underlying principles have been explored only during the past decade. Islet-cell heterogeneity arises during pancreatic development and might reflect the existence of distinct populations of progenitor cells and the developmental pathways of endocrine cells. Heterogeneity can also be acquired in the postnatal period owing to β-cell plasticity or changes in islet architecture. Furthermore, β-cell neogenesis, replication and dedifferentiation represent alternative sources of β-cell heterogeneity. In addition to a physiological role, β-cell heterogeneity influences the development of diabetes mellitus and its response to treatment. Identifying phenotypic and functional markers to discriminate distinct β-cell subpopulations and the mechanisms underpinning their regulation is warranted to advance current knowledge of β-cell function and to design novel regenerative strategies that target subpopulations of β cells. In this context, the Wnt/planar cell polarity (PCP) effector molecule Flattop can distinguish two unique β-cell subpopulations with specific transcriptional signatures, functional properties and differential responses to environmental stimuli. In vivo targeting of these β-cell subpopulations might, therefore, represent an alternative strategy for the future treatment of diabetes mellitus.

Biography

Scientific Career and Research Area

Heiko Lickert obtained his PhD in Biology from the University of Freiburg and his PhD and Postdoctoral studies were carried out in the laboratory of Prof. Rolf Kemler at the Max Planck Institute in Freiburg and in the laboratory of Prof. Janet Rossant at the Mount Sinai Hospital, Toronto, Canada. Currently he is a W3 Professor and Chair of Beta Cell Biology in the Medical Faculty of the Technical University Munich, the Director of the Institute of Diabetes and Regeneration Research and Principal Investigator in the Institute of Stem Cell Research at the Helmholtz Center Munich. He is also in the Steering Committee of the Helmholtz Diabetes Center and in the Research Coordination Board of the German Center for Diabetes Research. His work has been funded by the European Research Council and an Emmy-Noether fellowship from the German Research Foundation.

The primary objective of the Institute of Diabetes and Regeneration Research is to develop regenerative therapeutic approaches to treat diabetes mellitus. The lack or dysfunction of insulin-producing β-cells is the cause of type I or type II diabetes, respectively. In vitro generation of β-cells from pluripotent stem cells for cell-replacement therapy or triggering endogenous mechanisms of β-cell repair have great potential in the field of regenerative medicine. Both approaches rely on a thorough understanding of β-cell development and homeostasis in vitro and in vivo.
Andrew Lucas

Differential effects of exogenous IGF-1 administration on young adult and geriatric mice following pneumonectomy.

Differential effects of exogenous IGF-1 administration on young adult and geriatric mice following pneumonectomy.
Joe Yasa1,2,3*, Diana Engineer4, Cecilia M. Prêle1,2, Michaela Lucas5,6, Liu Lui5, Wenhua Huang5, Geoff J. Laurent1,2 & Andrew D. Lucas1,2#1 Centre for Cell Therapy and Regenerative Medicine, School of Medicine and Pharmacology, The University of Western Australia (UWA), Perth WA 6009, Australia. 2 Institute for Respiratory Health, School of Medicine and Pharmacology, UWA, Perth WA 6009, Australia. 3 School of Veterinary and Life Sciences, Murdoch University (MU), Perth WA 6150, Australia. 4 Centre for Microscopy, Characterization and Analysis, Harry Perkins Institute of Medical Research, The University of Western Australia 6 Verdon Street, Perth WA 6009 Australia. 5 School of Medicine and Pharmacology, UWA, Perth WA 6009 Australia. 6 Institute for Immunology and Infectious Diseases, MU, Perth WA 6150, Australia. Authors for correspondence: *joe.yasa@yahoo.com; # andrew.d.lucas@resphealth.uwa.edu.au

In young adult mouse (aged 8-12 weeks) unilateral pneumonectomy results in growth of new alveolar tissue in the remaining lung, restoring lung mass, volume, protein and DNA content within 14 days after surgery. This phenomenon has been termed compensatory lung growth and is much less prevalent in older mammals, including mice and humans. The aim of the present study was to find out whether sustained exogenous infusion of insulin-like Growth Factor (IGF)-1 could enhance regenerative lung growth in young adult mice and very old mice (aged 22-24 months) following left lung pneumonectomy (PNX). IGF-1 is a multifactorial growth factor that is indispensable for lung development, growth and repair and which has been implicated in driving regenerative lung growth following pneumonectomy. Following PNX in 12 week old mice there is a rapid increase in lung volume which already at day 4 approaches pre-operative volumes. IGF-1 supplementation following PNX in these mice significantly increased Ki67+ lung cell frequencies at day 21, a time when the pneumonectomy-associated mechanical stimuli has largely dissipated. However, there was no significant difference in lung volume increases between PBS and IGF-1 treated groups, by day 21 post surgery. In contrast in old mice, the was a much less pronounced increase in lung volume of the right lung following surgery at day 4. IGF-1 supplementation following PNX surgery significantly increased the volume of air in the lungs compared to PBS treated old mice, however this increase did not approach the volume of preoperative lung volumes and there was no significant impact on tissue content or cell proliferation.

Biography

Andrew Lucas, PhD is a biologist working in the Tissue Regeneration Group at the Centre for Cell Therapy and Regenerative Medicine, University of Western Australia. Currently his main research interests are the regulation of lung growth following lung resection. He obtained his doctorate in Skin Immunology at the University of Sydney, and then he spent 5 years as a Postdoc working at the Sir William Dunn School of Pathology, at the University of Oxford, working with Professors Siamon Gordon and Gordon McPherson on human chemokines and modelling murine leukocyte trafficking through mucosal epithelia, respectively. Andrew returned to Perth in 2004 and worked with Professors Mallal and Phillips at the Institute for Immunology and Infectious Diseases, Murdoch University, characterising drug hypersensitivity responses in humans.

Since 2015, he has led a cell biology project at the Institute for Respiratory Health and the Centre for Cell Therapy and Regenerative Medicine, studying lung regeneration using a murine left sided pneumonectomy model that he established in collaboration with Dr Cecilia Prele and Assoc. Professor Michaela Lucas, mentored by Professor Geoff Laurent.
Silke Meiners

Regulation of proteasomal protein turnover in lung cell differentiation and disease

The ubiquitin-proteasome system is central for controlled protein degradation within the cell. The proteasome is composed of a 20S catalytic core and associated proteasome activators that form proteasome super complexes. Binding of proteasome activators controls substrate entry and turnover. We have recently proposed that these activators function as building blocks that rapidly bind to the 20S catalytic core to form super complexes that adjust substrate specificity and turnover according to cellular needs. Proteasome function has been shown to be essential for cellular differentiation by regulating specific substrate degradation to adjust for the altered needs and function of the differentiated cell. We have recently shown an essential role for the 26S proteasome in myodifferentiation of lung fibroblasts (Semren et al., ARJCCM 2015). Little consideration, however, has been given to the regulation of proteasome function in airway stem cell differentiation. Dysfunctional stem cell differentiation is a major component of several chronic lung diseases including non-small cell lung cancer (NSCLC), chronic obstructive pulmonary disease (COPD), and asthma. We have started to decipher the role of proteasome function for ASC differentiation using a model of in vitro differentiation of human bronchial airway epithelial cells (Schamberger et al., Sci Rep 2015) revealing an unexpected regulation of the proteasome regulator PA200.

Biography

Silke Meiners was trained as a biochemist and molecular biologist at the universities of Bonn (Germany), Norwich (GB), and Berlin, where she obtained her PhD degree. After her postdoc training at the Charité in Berlin, she set up her own working group to validate the proteasome – the main protein degradation machinery of the cell – as a new therapeutic target for therapy of cardiovascular diseases. Since 2010, Dr. Meiners is an independent group leader in the Comprehensive Pneumology Center in Munich (Germany) and dedicated to translational lung research. Her lab works on proteasome function in lung disease which is emerging as a novel pathomechanistic target for chronic lung diseases.
Yuben Moodley

Mesenchymal stromal cell infusion induces acute systemic immunological responses in patients with chronic obstructive pulmonary disease

Rationale: Chronic Obstructive Pulmonary Disease is inflammatory airways disease with limited therapeutic options. Mesenchymal stromal cells have anti-inflammatory properties that may provide novel therapeutic options.

Objectives: To determine safety, bio-distribution and acute immunological changes following intravenous administration of MSCs in COPD patients.

Methods: Allogeneic bone marrow-derived MSCs were systemically administered on two occasions 7 days apart into patients with stable COPD (n=9). The first infusion utilised indium-111-labelled MSCs which were tracked radiologically over 7 days. Blood was obtained across the first 7 days to assess inflammatory mediators and immune cells. A second infusion of MSCs (unlabelled) was performed 7 days after the first infusion where lung function was assessed after 3 weeks and safety assessments were performed across 1 year.

Measurements and Main Results: Indium-111 accumulated in the lungs within minutes after infusion, followed by progressive uptake in the liver, spleen and bone marrow across 7 days post-infusion. There were no infusional or attributable short-term adverse effects. Plasma levels of pro-inflammatory cytokines, markers of oxidative stress and macrophage activation fell 7 days post-first infusion. Immunosuppressive myeloid subsets and T-regulatory cells increased 2 and 7 days post-infusion respectively. Long-term assessments showed minimal improvements in lung function however some patients showed a reduction in hospital admissions.

Conclusions: Systemically administered MSCs accumulated in the lungs within minutes without obvious infusional or short term adverse effects and induced early acute anti-inflammatory responses. Although no clinical improvement was observed, we provide mechanistic data that supports further study of MSCs as a potential treatment in COPD.

Biography

Dr Yuben Moodley is a Respiratory Physician at Fiona Stanley Hospital, Perth and Associate Professor of Respiratory Medicine at the University of Western Australia. He has a strong track record in clinical and basic science lung research. Dr Moodley has obtained an MD describing novel findings in non-invasive markers of lung inflammation. He then completed his PhD under the supervision of Dr Darryl Knight and Prof Phillip Thompson examining the differences in IL-6 signal transduction between healthy fibroblasts and fibroblasts obtained from the lung of patients with Idiopathic Pulmonary Fibrosis. Dr Moodley worked under the supervision of Prof Alan Trounson, a pioneer in stem cell science. Their innovative studies have led to the potential development of cellular therapies in lung injury. He is serves on the steering committee of the Australian IPF registry. Research interests include lung regenerative medicine and stem cell therapy, mechanisms and biomarkers for IPF and COPD. Reviewer for the following journals: American Journal of Respiratory and Critical Care Medicine, American Journal of Respiratory Cell and Molecular Biology, Respirology, Journal of Clinical Pathology, Thorax, Clinical Allergy and Immunology, Stem Cell and Development Reviews, Cell Therapy, Respiratory Research. Associate Editor of Respiratory since 01/03/07.
The STAT3 signalling pathway has recently been implicated in the pathogenesis of Idiopathic Pulmonary Fibrosis (IPF). Hypothesis: We hypothesise that the pro-fibrotic effects of STAT3 involve B cell-mediated immune regulation. Methods: We have analysed immune cell composition in human lung biopsy tissue and examined the effect of B cell depletion on bleomycin-induced lung fibrosis in vivo. Results: A trend towards increased B-cell activating factor, APRIL and CXCL13 are observed in IPF patient serum versus age match controls. In addition we observed an increase in the number of mature B cells in the lungs of IPF patients. Genetic depletion of B cells in gp130757F;μT−/− attenuated bleomycin-induced fibrosis. The therapeutic potential of depleting follicular B cells using anti-CD20 treatment was assessed. Mice were given two 100 μg doses of anti-CD20 antibody (provided by Genentech Inc USA), or IgG2a isotype control i.p. 7 days prior to and 7 days after bleomycin, and the extent of fibrosis measured 21 days after the last dose. FACS analysis of blood taken on days 0, 7 and 28 days post-bleomycin-treatment revealed an almost complete depletion of CD19+ and B220+ B cells. However, the extent of fibrosis, assessed using micro-CT imaging and HPLC analysis of hydroxyproline levels, was not significantly different between treatment groups. Conclusion: Although antibody depletion of follicular B cells had no effect on bleomycin-induced fibrosis, residual B cells remained in the lung of these mice. Current studies are analysing B cell subsets in fibrotic lung tissue from mice and IPF patients.

Grant Support: This work is funded by NHMRC Project Grant GNT1067511 and a British Lung Foundation Priming Grant.

Biography

Dr Prêle is a Senior Research Fellow with the Institute for Respiratory Health and Centre for Cell Therapy and Regenerative Medicine, School of Biomedical Sciences, the University of Western Australia. She is also the Administrative Director for the Centre for Cell Therapy and Regenerative Medicine, University of Western Australia. Dr Prêle was awarded her PhD in Biochemistry from University College London, UK in 2001. After a brief postdoctoral position at Guy’s and St Thomas Hospital, Kings College London she relocate to Western Australia. Dr Prêle currently heads the Tissue Repair Group within CCTRM and IRH. Her research focus is on investigating the molecular mechanisms contributing to the development and progression of lung fibrosis and in particular, the analysis of the Jak/STAT signalling pathway. Dr Prêle receives research funding from the National Health and Medical Research Council and the British Lung Foundation.
Yuval Rinkevich

Successions between En1 + /- fibroblastic lineages drives dermal development, and its phenotypic transition from regeneration to scarring

All mammals and humans undergo metamorphosis in response to injury, from regeneration to scarring (RTS). Here we follow two functionally diverged fibroblastic lineages (ENFs & EPFs) and document their lineage successions during backskin development that coincides with RTS. We show that ENFs are dermal sculptures that develop and regenerate native architectures during fetal life, and that their lineage decline over time imposes a dermal tissue absent of such events. We show that EPFs are scar producers even at fetal stages, wherein their numbers are bellow a threshold needed to generate macroscopic scars, but that their dynamics predicts scar emergence. We show that clonal advantages to EPFs rather than programed cell-lineage death, most likely are primary succession mechanisms, and that RTS can be partly circumvented by transplantations of fetal ENFs or decellularised fetal dermis. Our findings provide a mechanism for regenerative decline in mammals, carry clinical implications by suggesting that human dermal regeneration could be reached by coxing or transplanting ENFs alone, and provide a model for comparative regeneration studies between taxon groups.

Biography

Since 2015, Young Principle Investigator with supervising and mentoring position at the Institute for Lung Biology and Disease, Comprehensive Pneumology Center (CPC), Helmholtz Zentrum, Munich, Germany. He obtained a PhD degree in Biology from Technion Institute of Technology, Haifa in 2008. From 2008 until 2014, he was postdoctoral fellow of Prof. Irving L. Weissman, Stanford Institute for Stem Cell Biology and Regenerative Medicine at Stanford University, USA. In 2014 he became Basic Life Science Research Associate at Stanford University. He was on the Team of inventors of two Patents regarding ‘Isolation and Characterization of Progenitor Cells from Mesothelium and Methods’ and ‘Compositions for the Prevention and Treatment of Surgical adhesions’.

Yuval’s scientific focus lies in identifying principles of tissue/organ regeneration, and developing a knowledge basis for therapeutic strategies in clinical use. His lab is exploring the stem cells, embryonic lineages and mechanisms by which tissues/organse regenerate following injury, at multiple levels of biological organization. His research is currently funded by grants from the Else-Kröner-Fresenius Stiftung (EKFS), Human Frontier Science Program Organisation (HFSPO), German Research Foundation (DFG) and the Fritz Thyssen Stiftung (FTS).

Yuval is member of several Scientific Societies and publishes in peer-reviewed journals. He gives lectures at numerous, distinguished Conferences and Institutes, such as COST, GRC, ICB, TUM, EMBO, TERMIS, BMF, ATS, latest the Interstellar Initiative mentoring workshop, presented jointly by the Japan Agency for Medical Research and Development and the New York Academy of Sciences — intended to recognize promising Early Career Investigators in the fields of cancer, regenerative medicine, and neuroscience.
Herbert B. Schiller

Molecular and cellular composition of the lung – from mass spectrometry driven proteomics to single cell transcriptomics

Cellular activity and identity in health and disease is controlled by signals from the extracellular niche. So far, the heterogeneity of the extracellular matrix in the lung, its specific functions as part of the stem cell niche, and its plasticity after injury have not been fully characterized but promise to reveal key regulatory mechanisms in health and disease. We have applied proteomic workflows to these questions (Schiller et al, Molecular Systems Biology 2015; Schiller et al, AJRCCM 2017), and currently develop mass spectrometry-based methods to analyze the identity of protein complexes within the extracellular matrix. Furthermore, we use high throughput single cell RNA-seq to address how different cell types in the lung secrete and assemble their distinct niches. Single cell transcriptomics will reveal novel insights about the identities, transitions and lineage relationships of cells in healthy and diseased human lungs that may instruct new research hypothesis and therapeutic strategies of the future, as well as potentially uncover new diagnostic opportunities.

I will discuss how ‘imaging’ the cellular composition of both human and mouse lungs using high throughput single cell transcriptomics, as well as novel proteomics approaches to study the molecular identity and plasticity of the extracellular niche, can be combined with microscopy based imaging of the organ. This will ultimately deliver a cellular atlas of the lung with diverse maps of the many distinct niches that are likely associated with different cell types and their tissue localization.

Biography

Herbert Schiller obtained his Phd in Molecular Immunology from the Medical University of Vienna, followed by two postdocs with Reinhard Fässler and Matthias Mann at the Max Planck Institute of Biochemistry. He has expertise in mass spectrometry driven systems biology for more than 7 years. His postdoc mentor Matthias Mann is one of the pioneers of proteomics, which allowed him to work at the forefront of mass spectrometry driven systems biology. He developed and applied mass spectrometry based approaches to study integrin mediated mechanosensing (Schiller et al., EMBO Reports 2011; Schiller et al., Nature Cell Biology 2013), and lung tissue regeneration (Schiller et al., Molecular Systems Biology 2015). At HMGU he is an independent tenure track research group leader focusing on systems biology of chronic lung disease. His group uses mass spectrometry and high throughput scRNAseq methods to study mouse and human lungs in health and disease.
Otmar Schmid

Biography

Otmar is head of the Pulmonary Aerosol Delivery Group at the Comprehensive Pneumology Center, Helmholtz Zentrum München (Munich, Germany), and Adjunct Assistant Professor at the Missouri University of Science and Technology (Rolla, MO, USA). He received his Ph.D. in physics from the University of Missouri-Rolla (USA) and he held postdoctoral positions at Denver University (USA), the Max-Planck Institute for Chemistry (Mainz, Germany) and the Helmholtz Zentrum München. He has extensive experience in aerosol science and technology with a focus on the development of methods for dose-controlled delivery of aerosolized substances to cell and animal models of the lung. Most recently, he developed a bioreactor of the lung, which allows for aerosolized drug/nanoparticle delivery to mechano-activated alveolar lung tissue at the air-liquid interface, which allows for biomimetic in vitro studies of efficacy, toxicity and pharmacokinetics on inhalable substances. He has published more than 70 peer-reviewed papers and book chapters, he serves as consultant to pharma industry and he held positions on the boards of several aerosol associations including the International Society of Aerosols in Medicine (ISAM).

Carsten Schmidt-Weber

Differential effects of exogenous IGF-1 administration on young adult and geriatric mice following pneumonectomy

Biography

Prof. Carsten B. Schmidt-Weber main interest are the mechanisms of allergy, allergen tolerance and cist clinical translation. He is professor and holds the chair of Molecular Allergology at the Technical University Munich and is director of the Center of Allergy and Environment of the Technical University and Helmholtz Center Munich. He is managing the virtual network oft he Munich Allergy Research Center (MARC: http://www.marc-allergy.de/), which is a large Allergy research cluster covering more than 25 research groups in Munich. He is honorary member of the Allergy and Clinical Immunology at NHLI, Imperial College and has bonds with the Asthma MRC centre. Is member oft he Immunology board oft he EAACI.

Prof. Schmidt-Weber qualified at the Technical University in Darmstadt and the Friedrich-Alexander University in Erlangen-Nuremberg. He conducted his Biology-Diploma (1992) and PhD thesis (1996) at the Max-Planck Unit for Immunology and Rheumatology in Erlangen-Nuremberg. His postdoctoral work on IL-4 and IL-10 gene-regulation and immune tolerance was performed in the Pathology Department at the Brigham and Women’s Hospital of the Harvard Medical School. He was appointed by the Swiss Institute of Allergy and Asthma Research and founded the Department of Molecular Immunology (1998). His thesis on "Molecular mechanisms of T-lymphocyte regulation by transforming growth factor beta" was awarded with the venia legendi in Experimental Immunology by the Medical Faculty of the University of Zurich, Switzerland (2006) and joined the Imperial College 2007. On 1 of April 2010 he accepted the chair of Molecular Allergology at the Medical Faculty of the Technical University of Munich.
Georgios T. Stathopoulos

Pulmonary repair and mutagenesis in response to tobacco carcinogens

Lung adenocarcinoma is the number one cancer killer in the world and is mainly caused by environmental tobacco and radon exposures. Despite significant efforts, the respiratory epithelial cells that suffer mutations and provide the cellular source of lung adenocarcinoma remain unknown. In addition, the mode of mutation acquisition of these cells over time has not been explored prospectively. We have developed mouse models to mark respiratory epithelial lineages and to follow their fate and genomic lesions after single carcinogen exposure. We have also developed unique cell lines derived from carcinogen-induced lung adenocarcinomas that feature an amazing mutation spectrum. These models have allowed us to longitudinally study how the airway and alveolar epithelia are repaired upon carcinogenic insults, how transcription factors and tumor suppressors determine the survival or death of mutated epithelial cells of the lungs, and how point mutations and copy number alterations accumulate over time in developing lung tumors. The lessons learnt from mice, we translate to our human cohort of 377 loco-regional lung adenocarcinomas, which is carefully phenotyped, and is currently being genomically analyzed. The ultimate aim of these ongoing studies is to identify addiction partners of driver oncogenes and to target them for lung adenocarcinoma prevention and therapy.

Biography

Georgios is a Research Group Leader at the Comprehensive Pneumology Center of the Helmholtz Zentrum Munich and an Associate Professor of Physiology at the Faculty of Medicine of the University of Patras, Greece. He obtained his MD in Patras (1989-1995), and his Pneumology board certification (1997-2002) and PhD (2003-2007) Athens. He worked as clinical consultant to the Greek National Health System (2006-2009) and as Research Fellow (2003-2004) and Assistant Professor (2009-2010) at Vanderbilt University, Nashville, TN. In 2011 he was appointed to his Patras position where he founded the Laboratory for Molecular Respiratory Carcinogenesis and in 2015 to Munich where he initiated the group of Lung Carcinogenesis.

Georgios’ collaborators are looking into the pathobiology of lung and pleural malignancies, including early carcinogenesis and late dissemination. They are using fate models to dig into chest tumor origins and modular cell-animal systems to investigate oncogene-immunity interactions. They top this by teaching respiratory physiology and research to medical and graduate students.

Stefan Stricker

Editing fate changes

Myriads of epigenomic features have been comprehensively profiled in health and disease across cell types, tissues and individuals. Although current epigenomic approaches can infer function for chromatin marks through correlation, it remains challenging to establish which marks actually have causative roles in gene regulation and disease processes. The new field of epigenome editing allows to induce and remove individual chromatin marks and potentially facilitates strategies for high-throughput progression from profiles to function. To enable epigenome engineering and epigenomic screens we generated a multitude of molecular tools and will show on the example of the SRY (sex determining region Y)-box transcription factor Sox1 the application of CRISPR and epigenome editing tools to induce endogenous gene expression and phenotypic changes. Moreover, Sox1 induction restores neuronal differentiation potential of largely glial progenitors. However, since only a small fraction of progenitors are able to respond to the incentive stimulus in a meaningful way and a majority of cells remained Sox1 negative, we investigated which barriers interfere with targeted Sox1 induction. To our surprise we find that among a series of euchromatic processes, targeting DNA de-methylases has the highest influence on releasing Sox1 activity.

Biography
Stefan H. Stricker is the head of the MCN Junior Research Group, Munich Center for Neurosciences, Ludwig-Maximilian-Universität and the German Research Center for Environmental Health and the Biomedical Center Munich, Germany. He obtained a diploma in biology at the Ludwig-Maximilian-Universität in Munich, Germany, in 2003. He then received a Böhringer Ingelheim Foundation scholarship, joined the Barlow laboratory at the Research Center for Molecular Medicine and received his Ph.D. in 2008 from the Universität Wien, Austria. A European Molecular Biology Organization (EMBO) long-term fellowship allowed him to conduct his postdoctoral projects in the Smith, Pollard and Beck laboratories at the Cambridge Stem Cell Institute, UK, and the University College London (UCL) Cancer Institute in London, UK. His research focuses on the mechanisms of epigenetic features that determine cellular properties.

Fabian Theis

Reconstructing branching lineages in single cell genomics

Single-cell technologies have gained popularity in developmental biology because they allow resolving potential heterogeneities due to asynchronicity of differentiating cells. Common data analysis encompasses normalization, followed by dimension reduction and clustering to identify subgroups. However, in the case of cellular differentiation, we may not expect clear clusters to be present - instead cells tend to follow continuous branching lineages.

We show that modeling the high-dimensional state space as a diffusion process, where cells move to close-by cells with a distance-dependent probability well reflects the differentiating characteristics. Based on the underlying diffusion map transition kernel, we then order cells according to a diffusion pseudotime (DPT), which allows for a robust identification of branching decisions and corresponding trajectories of single cells. We demonstrate the method on scRNA-seq data of myeloid differentiation. DPT identifies a dominant branching into different myeloid lineages and a minor subpopulation of lymphoid outliers. Moreover, a graded transition reflecting erythroid differentiation is identified that dissent from previously stated cluster sequences. We identify driver genes and propose how to include additional data sets for integrative analysis across multiple downstream lineages.
Fabian Theis received PhD degrees in Physics and Computer Science in 2002 and 2003, respectively. After working as postdoc at Regensburg, Tokyo and Tallahassee, he took up a position as Bernstein fellow at the Max-Planck Institute for Dynamics and Self-Organisation at Göttingen. He later joined the Helmholtz Zentrum Munich, first as group leader and since 2013 as director of the Institute of Computational Biology; he is also full professor for Biomathematics at the Department of Mathematics of the Technical University of Munich. His research interests include machine learning applied to biological questions, in particular for modeling single cell heterogeneities, and multi-omics data integration in the context of systems medicine.

Nina Tirnitz-Parker

Liver progenitor cells as a therapeutic target - the role of key signalling pathways in regeneration versus carcinogenesis.

Chronic liver diseases are major causes of global morbidity and mortality. Most forms of chronic liver injury are characterised by continuous inflammation and reparative scarring or fibrosis, which can progress to cirrhosis and eventually liver cancer formation - complications of end-stage liver disease that are increasingly prevalent worldwide. Stem cell-like liver progenitor cells (LPCs) are activated and proliferate when hepatocytes undergo replicative arrest. While it was originally thought that the predominant role of LPCs was to reconstitute liver tissue under stress conditions, highly versatile functions in the regulation of wound healing, fibrogenesis and carcinogenesis have been emerging. Dr Tirnitz-Parker’s laboratory investigates how liver progenitor cells communicate with other hepatic cell types to regulate these processes. By gaining a greater understanding of the underlying pathways and cellular mechanisms, the group aims to find new potential treatment targets for the promotion of regenerative responses and the prevention of liver disease progression and cancer. This talk will focus on the role of the tumour necrosis factor-like weak inducer of apoptosis (TWEAK)/Fn14 pathway in the liver progenitor cell response, fibrogenesis, hepatocellular carcinoma and cholangiocarcinoma.

Nina Tirnitz-Parker is a Senior Research Fellow at Curtin University and Adjunct Senior Research Fellow at the University of Western Australia. She is Laboratory Head of the Liver Disease and Regeneration Group in the School of Biomedical Sciences, Curtin Health Innovation Research Institute at Curtin University in Perth. Dr. Tirnitz-Parker is currently the national scientific representative on the Australian Liver Association Executive Committee.
Human mammary gland organogenesis and function

Alecia-Jane Twigger, Lisa K. Meixner, Christina H. Scheel

Human mammary epithelial cells undergo major changes within the breast during key stages of development including embryogenesis, puberty, pregnancy, lactation and subsequent involution. Understanding the cellular identity and signalling pathways driving these important modifications directs our knowledge of the glands plasticity under normal conditions. Recent development of a mammary organoid model has allowed researchers to study plasticity and differentiation of single cells from the resting breast in an easy to manipulate model. One final hurdle for the in vitro study of human mammary cells remains, and that is to render them able to functionally lactate. A unique source of mammary epithelial cells isolated during lactation from human milk has been identified and may provide an ideal cell candidate for creating a functional human mammary organoid. Detailed characterisation and comparison of these cells to resting mammary tissue will provide insight into the differences in cellular composition of the mammary gland during these different mammary gland states and their potential to create a functional organoid model. We hypothesise that once further characterised, these cells will be able to form complex structures in culture and functionally produce milk. Development of such a model would allow us to understand the finer points of normal adult mammary gland plasticity leading to its reconstruction for milk production. In addition, the model would provide an ideal comparison for further studies in abnormal development such as in cases of lactation difficulties and breast cancer.

Biography

Dr. Alecia-Jane Twigger has worked in the field of lactation and mammary gland biology over the past five years. She started her research career at the University of Western Australia in the prestigious Hartmann Human Lactation Research Group, where she completed her Honours and PhD in human milk cell characterisation. After being awarded the inaugural International Society for Research into Human Milk and Lactation Postdoctoral Fellowship, she has joined the Scheel laboratory at the Helmholtz Zentrum München and hopes to adapt their patented mammary organoid model to investigate human milk cell regenerative capacity and function.

Joanne van Vuuren

Functional significance of TRIM35 in haematopoietic and hepatic homeostasis

Utilizing the choline-deficient, ethionine supplemented (CDE) diet as a model for chronic liver injury, I further investigated the link between TRIM35 and hepatocellular carcinoma. By scanning the mice with MRI at regular intervals, I established that the CDE diet, when used at 67% of its potency, induces fat nodules throughout the liver, and the onset and volume of these nodules are significantly enhanced by the loss of TRIM35. In addition, several markers of inflammation were found to be significantly increased in TRIM35−/− mice fed a high-fat or CDE diet, indicating TRIM35 as a modulator of inflammatory responses associated with chronic liver injury.
Biography
After completing Bachelor and Master’s degree in life science at the University of Utrecht in the Netherlands, Joanne continued as a PhD student at the Perkins Institute for Medical Research in Perth, Western Australia, where she investigated the role of a novel E3 ubiquitin ligase, TRIM35, in haematopoiesis and hepatic homeostasis. Using a TRIM35 knockout model, she identified TRIM35 as a regulator of the haematopoietic stem cell and progenitor populations in the haematopoietic compartments of mice.

Kiryu Yap

Bioengineering vascularised liver organoids

Bio-engineered liver organoids offer the potential of personalised tissue that can be used in transplantation surgery to treat liver disease, or for in vitro disease modelling and drug testing/development studies. Our group has developed an organoid system that comprises of parenchymal cells derived from human liver progenitor cells either isolated from adult liver or differentiated from induced pluripotent stem cells. These cells are supported by endothelial cells that develop intrinsic microvasculature within the organoids, and stromal cells that support cell differentiation and tissue assembly. Organoid development is facilitated by the use of an extracellular matrix hydrogel derived from human liver, and a porous biodegradable scaffold that provides structural support. Progress is being made in animal studies using mice with liver disease, with the aim to demonstrate therapeutic efficacy of organoid transplantations.

Biography

Dr Kiryu Yap is a clinician currently undertaking a PhD at St Vincent’s Institute and The University of Melbourne in Australia. He holds clinical and academic appointments at the Department of Surgery, St Vincent’s Hospital Melbourne, and the Department of Gastroenterology, at Monash Medical Centre. His research interests involve tissue engineering, stem cell biology, and surgical oncology.

George Yeoh

The role of liver progenitor cells in development of hepatocellular carcinoma

Lifestyle practices underlie a significant increase in liver disease. Chronically, this leads to end-stage disease and death, often due to cancer. Understanding the carcinogenic process that leads to hepatocellular carcinoma (HCC) is hampered by our inability to detect liver cancers early in its development so disease progression can be followed. There is also a paucity of animal models that are clinically relevant. Models such as those that subject rodents to liver damage or partial hepatectomy followed by administration of mutagenic chemicals such as acetylaminofluorene or diethylnitrosamine are totally irrelevant. In human liver pathologies associated with chronic liver
damage and diet induced mouse models of fatty liver disease that progress to HCC, liver progenitor cells (LPCs) are observed. We will present data that strongly suggest a link between the LPCs and HCC in both humans and rodents and proffer the view that understanding the molecular and cellular changes that occur in LPCs will lead to a better understanding of hepatocarcinogenesis.

Biography

Senior Honorary Research Fellow, Discipline of Biochemistry & Molecular Biology, School of Molecular Sciences. Emeritus Professor, School of Biomedical Sciences. Laboratory Head, Liver Development & Cancer Laboratory, Centre for Medical Research, Harry Perkins Institute of Medical Research. Director, Centre for Cell Therapy & Regenerative Medicine. Board Member; Cancer Council of Western Australia, Institute for Respiratory Health, Cancer Council of Australia. Advisory Board Member, Cancer Australia. Research Interests: Regulation of liver gene expression. Genetic changes responsible for liver cancer. Liver stem cells and their applications in treating liver disease.

Ali Önder Yildirim

Cigarette smoke drives B cell positioning and immune pathogenesis of COPD

The development of chronic obstructive pulmonary disease (COPD) pathogenesis remains unclear, but emerging evidence supports a crucial role of B cells induced tertiary follicle formation (TLO) in the progression of COPD. The mechanism underlying TLO generation, particularly during chronic CS exposure, however, remains to be defined. Here, we demonstrate that oxysterols are also critically involved in TLO generation and the immune pathogenesis of COPD. Mice deficient in oxysterol pathways, exhibited decreased TLO formation and subsequent CS-induced emphysema. Collectively, our studies are interrogate oxysterol-dependent TLO formation in the pathogenesis of COPD, and identify a novel therapeutic target for the treatment of COPD and other chronic diseases driven by the generation of tertiary lymphoid organs.

Biography

Ali Önder Yildirim is one of the members of the scientific leadership board at the Translational Research Center Comprehensive Pneumology Center (CPC), PI and member of the German Center for Lung Research (DZL) in Disease Area COPD and Platform Imaging in Munich, Germany. He studied Veterinary Medicine at the Firat University, Turkey and obtained Doc. Vet. Med. in Veterinary Medicine at the Justus-Liebig-University, Giessen, Germany in 2002. He worked as a Postdoctoral Fellow at the Department of Internal Medicine Clinical Research and the Department of Clinical Chemistry & Molecular Diagnostics at the Philipps-University of Marburg, before he started his career as a Group Leader of the research group “Immunopathology of COPD” at the Comprehensive Pneumology Center (CPC), Helmholtz Zentrum Muenchen, Institute of Lung Biology and Disease.

His main scientific focus is translational research in Chronic Obstructive Pulmonary Disease (COPD). Ali Önder and his group aim to identify the involvement of B and T-cells to parenchymal lung tissue damage and small airway remodeling in response to cigarette smoke induced COPD and to decipher the role of protein arginine methyltransferases (PRMTs) in the immunopathogenesis of COPD.