I. Curriculum Vitae

Personal Details

Name:	Heiko Lickert
Date of birth:	December 12th, 1970
Place of birth:	Freiburg, Germany
Citizenship:	German
Work address:	HelmholtzZentrum münchen
	Institute of Stem Cell Research
	Ingolstädter Landstr. 1
	D-85764 Neuherberg
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Academic and Research Activities

Oct. 1992 – Dec. 1997 **Studies of Biology** at Albert-Ludwigs University Freiburg
Cell Biology, Molecular Biology, Biochemistry and Pharmacology
(Diploma overall mark: 1.1)

Jan. 1998 – Dec. 1998 Max-Planck Institute for Immunobiology Freiburg
Department of Molecular Embryology, Prof. Rolf Kemler
Diploma Thesis: "Influence of E-Cadherin Phosphorylation on Cell-Cell Adhesion" (**mark: 1.0**)

Jan. 1999 – Dec. 2001 Albert-Ludwigs University Freiburg
Max-Planck Institute for Immunobiology Freiburg
Department of Molecular Embryology, Prof. Rolf Kemler
PhD Thesis: "Wnt/β-Catenin Signalling in the Endoderm"
Overall mark: ***summa cum laude***

Jan. 2002 – July 2002 Max-Planck Institute for Immunobiology Freiburg
Department of Molecular Embryology, Prof. Rolf Kemler
Max-Planck **Post-Doctoral Fellowship**

Aug. 2002 – Dec. 2004 Samuel Lunenfeld Research Institute
Mount Sinai Hospital, Toronto, Canada
Department of Fetal Health and Development, Prof. Janet Rossant
Post-Doctoral Studies, Early Embryogenesis and Endoderm Development

Jan. 2005 – June 2009 HelmholtzZentrum münchen
Institute for Stem Cell Research
Junior Group Leader, Endoderm Development and Regeneration

Juli 2009 –Aug 2011 HelmholtzZentrum münchen
Institute for Stem Cell Research
Principal Investigator, Endoderm Development and Regeneration

August 2011 – now	HelmholtzZentrum münchen **Director** Institute of Diabetes and Regenerationsforschung

Scientific Awards

2002	Albert-Ludwigs University Freiburg **Hans-Spemann Award 2002** Recognition for academic excellence at the doctoral level. Awarded to a single individual by the Dr. Gerhard-Fritz foundation
2003	Max-Planck Society **Otto-Hahn Medal 2003** Recognition for outstanding scientific achievement during PhD studies. Awarded to a few PhDs across all disciplines of the Max-Planck Society.
2005	German Research Foundation (DFG) **Emmy-Noether Junior Group 2005-2009** 5-year funding for outstanding young scientists returning to Germany.
2010	European Research Council (ERC) **ERC Starting Grant 2010-2015** 5-year funding for pioneering frontier research.

II. Fellowships and Funding

Total amount acquired over the years: **5.1 Million €**

Listed below are all fellowships for which I wrote the proposal and raised funding on my own:

Jan. 2002 – July 2002 Max-Planck Society
Post-Doctoral Fellowship; Budget: 30.000 €
Department of Molecular Embryology, Prof. Rolf Kemler

Aug. 2002 – Dec. 2002 Canadian Institute of Health and Research (CIHR)
3-year Post-Doctoral Fellowship; Budget: 30.000 €
Samuel Lunenfeld Research Institute, Prof. Janet Rossant

Jan. 2003 – Dec. 2004 German Research Foundation (DFG)
Emmy-Noether Programm, Phase I
2-year Post-Doctoral Fellowship; Budget: 140.000 €
Samuel Lunenfeld Research Institute, Prof. Janet Rossant

Jan. 2005 – Dec. 2008 German Research Foundation (DFG)
Emmy-Noether Programm, Phase II
4-year Research Fellowship to establish an independent career
Junior group leader at the HelmholtzZentrum münchen
Subject: "Analysis of the signalling networks underlying
early endoderm development"
Budget: 1.2 Million €

Jan. 2009 – Dec. 2009 **Renewal for Emmy-Noether Programm, Phase II**
Budget: 300.000 €

Jan. 2008 – Dec. 2010 Ministry of Education and Research (BMBF)
Pilot Project in Cooperation with the European Screening Port GmbH
"Identification of drugs that influence ES cell differentiation
into pancreatic cells"; **Budget: 915.000 €**

Feb. 2010 – Jan. 2015 European Research Council (ERC)
ECR Starting Grant
"Deciphering mechanisms of ciliary disease with focus on the pancreas"
Funding period: 5 years
Budget: 1.5 Million €

These fundings were raised in joint effort together with my team colleagues or scientists at the Helmholtz Zentrum:

Jan. 2008 – Dec. 2009 Alexander von Humboldt Foundation
2-year Post-Doctoral Fellowship for Dr. Claude Van Campenhout
"Functional analysis of the Dlgh3 polarity protein during endoderm development"
Budget: 140.000 €

Jan. 2007 – Dec. 2011 Helmholtz Association of German Research Centers (HGF)
Systems Biology Alliance: Control of Regulatory Networks by microRNAs
As partner: "The systems biology of stem cell fate specification"
1 PhD Position, consumables; Budget: 50.000 €

One-time funding Helmholtz Association of German Research Centers (HGF)
Investment for Junior Group Leaders
As partner: "*In vivo* imaging of cell biological mechanisms in development"
5-channel high-speed resonance laser-scanning microscope; **Costs: 750.000 €**

Sept. 2009 – Aug. 2012 Chinese Scholarship Council
3-year PhD Fellowship for Dapeng Yang
"Functional analysis of miR-335 in mesendoderm differentiation"
Budget: 36.000 €

Listed bellow is a grant proposal currently under review:

German Research Foundation (DFG)
SFB Initiative – Gastrointestinal and Pancreatic Cancer
"Analysis of cilia and basal body function in tumor development of the pancreas" (Coordinator: Prof. Schmid, Klinikum Rechts der Isar)
Funding period: 4 + 4 years
Requested: 1 Postdoc, 1PhD, 30 T € / year consumables

III. Publications

In total I have published 23 peer-reviewed papers that have been cited over 900 times; Ø IF: 11.05 (3.2010)

Bauer A., **Lickert, H.**, Kemler, R. and Stappert, J. (1998). Modification of the E-cadherin-catenin complex in mitotic Madin-Darby Canine Kidney epithelial cells. J. Biol. Chem. 273: 28314-28321. **(Citations: 28, IF: 5.52)**

Lickert, H., Bauer, A., Kemler, R. and Stappert, J. (2000). CKII phosphorylation of E-cadherin increases E-cadherin/β-catenin interaction and strengthens cell-cell adhesion. J. Biol. Chem. 275: 5090-5095. **(Citations: 91; IF: 5.52)**

Serres, M., Filhol, O., **Lickert, H.**, Grangeasse, C., Chambaz, E.M., Stappert, J., Vincent, C. and Schmitt, D. (2000).The disruption of adherens junctions is associated with a decrease of E-cadherin phosphorylation by protein kinase CK2. Exp Cell Res. 257: 255-264. **(Citations: 30; IF: 3.95)**

Lickert, H., Domon, C., Huls, G., Wehrle, C., Duluc, I., Clevers, H., Meyer, B.I., Freund, J.N. and Kemler, R. (2000). Wnt/β-catenin signaling regulates the expression of the homeobox gene Cdx1 in embryonic intestine. Development 127: 3805-3813. **(Citations: 118; IF: 6.81)**

Lickert, H., Kispert, A., Kutsch, S. and Kemler, R. (2001). Expression patterns of Wnt genes in mouse gut development. Mech Dev. 105: 181-184. **(Citations: 38; IF: 2.53)**

Lickert, H., Kutsch, S., Kanzler, B., Tamai, Y., Taketo, M.M. and Kemler, R. (2002). Formation of multiple hearts in mice following deletion of β-catenin in the embryonic endoderm. Dev Cell 3: 171-181. **(Citations: 107; IF: 12.88)**

Lickert, H. and Kemler, R. (2002). Functional analysis of cis-regulatory elements controlling initiation and maintenance of early Cdx1 gene expression in the mouse. Dev Dyn. 225: 216-220. **(Citations: 27; IF: 3.02)**

Rottbauer, W., Saurin, A.J., **Lickert, H.**, Shen, X., Burns C.G., Wo, Z.G., Kemler, R., Kingston, R., Wu, C. and Fishman, M. (2002). Reptin and Pontin antagonistically regulate heart growth in Zebrafish embryos. Cell 111: 661-672. **(Citations: 52; IF: 31.25)**

Wehrle, C., **Lickert, H.** and Kemler, R. (2003). Wnt Signaling in Development. Handbook of Cell Signaling (Volume 1-3). Volume 2, Chapter 252, Academic Press. ISBN: 0-12-124546-2

Kunath, T., Gish, G., **Lickert, H.**, Jones, N., Pawson, T. and Rossant, J. (2003). Transgenic RNA interference in ES cell-derived embryos recapitulates a genetic null phenotype. Nat. Biotech. 21: 559-561. **(Citations: 150; IF: 22.3)**

von Both, I., Silvestri, C., Erdemir, T., **Lickert, H.**, Rossant, J., Harvey, R.P., Attisano, L., and Wrana, J.L. (2004). Foxh1 is essential for development of the anterior heart field. Dev Cell 7: 331-345. **(Citations: 64; IF: 12.88)**

Ben Abdelkhalek, H., Beckers, A., Schuster-Gossler, K., Pavlova, M.N., Burkhardt, H., **Lickert, H.**, Rossant, J., Reinhardt, R., Schalkwyk, L.C., Müller, I., Herrmann, B.H., Ceolin, M., Rivera-Pomar, R., and Gossler, A. (2004). The mouse homeobox gene Not is required for caudal notochord development and affected by the truncate mutation. Genes Dev 18: 1725-1736. **(Citations: 1; IF: 13.62)**

Lickert, H.*, Takeuchi, J.K.*, Walls, J., von Both, I., McAuliffe, F., Adamson, S.L., Wrana, J.L., Henkelman, R.M., Rossant, J. and Bruneau, B.G. (2004). Baf60c is essential for function of BAF chromatin remodelling complexes in heart development. Nature 432: 107-12. * = equal contribution**(Citations: 93; IF: 31.43)**

Lickert, H., Cox B., Taketo, M.M., Wehrle, C., Kemler, R. and Rossant, J. (2005). Dissecting Wnt/b-catenin signaling during gastrulation using RNA interference in mouse embryos. Development 132:2599-2609. **(Citations: 29; IF: 6.81)**

Tanaka, S.S., Yamaguchi, Y.L., Tsoi, B., **Lickert, H.**, and Tam, P.L. (2005). Activity of Interferon-induced transmembrane protein genes (Ifitm1 and Ifitm3) influences the localization of mouse primordial germ cells. Dev. Cell 9(6): 745-756. **(Citations: 38; IF: 12.88)**

Takeuchi, J.K.*, **Lickert, H.***, Bisgrove, B.W.*, Sun X., Yamamoto, M., Chawengsaksophak, K., Hamada, H., Yost,, J., Rossant, J., and Bruneau, B.G. (2007). Baf60c is a nuclear Notch signalling component required for the establishment of left-right asymmetry. PNAS 104(3): 846-851. * = equal contribution **(Citations: 15; IF: 9.38)**

David, R., Brenner C., Stieber J., Schwarz F., Brunner S., Vollmer M., Mentele E., Müller-Höcker J., Kitajima S., **Lickert, H.**, Rupp R., and Franz W.M. (2008). MesP1 drives vertebrate cardiovascular differentiation through Dkk-1-mediated blockade of Wnt-signalling. Nat Cell Biol 10(3): 338-345. **(Citations: 21; IF: 17.77)**

Uez, N., **Lickert H.**, Kohlhase, J., Hrabe de Angelis, M., Kuehn, R., Wurst, W., and Floss, T. (2008). Sall4 isoforms act during proximal-distal and anterior-posterior axis formation in the mouse embryo. Genesis 46(9): 463-77. **(Citations: 1; IF: 2.22)**

Tamplin, O., Kinzel, D., Cox, B., Bell, C.E., Rossant, J., and **Lickert, H.** (2008). Microarray analysis of Foxa2 mutant mouse embryos identifies novel genes in the gastrula organizer and its derivates. BMC Genomics 9(1):511. **(Citations: 3; IF: 3.93)**

Uetzmann L., Burtscher, I., and **Lickert, H.** (2008). A mouse line expressing Foxa2-driven Cre recombinase in node, notochord, floorplate, and endoderm. Genesis 46(10): 515-522. **(Citations: 2; IF: 2.22)**

Egea, J., Erlacher, C., Montanez, E., Burtscher, I., Yamagishi, S., Heb, M., Hampel, F., Sanchez, R., Rodriguez-Manzaneque, M.T., Bosl, M.R., Fassler, R., **Lickert, H.**, and Klein, R. (2008). Genetic ablation of FLRT3 reveals a novel morphogenetic function for the anterior visceral endoderm in suppressing mesoderm differentiation. Genes & Dev 22: 3349-3362. **(Citations: 5; IF: 13.62)**

Liao, W.Y., Uetzmann L., Burtscher, I., and **Lickert, H.** (2009). Generation of a mouse line expressing Sox17-driven Cre recombinase with specific activity in ateries. Genesis 47(7): 476-83 **(Citations: 1; IF: 2.22)**

Burtscher, I. and **Lickert, H.** (2009). Foxa2 regulates polarity and epithelialization in the endoderm germ layer of the mouse embryo. Development 136(6): 1029-1038. **(Citations: 4; IF: 6.81)**

Engert, S., Liao, W.Y., Burtscher, I., and **Lickert, H.** (2009). Sox17-2A-iCre: A knock-in mouse line expressing Cre recomibinase in endoderm and vascular endothelial cells. Genesis 47(9):603-10. **(Citations: 1; IF: 2.22)**

Cox, B., Vollmer, M., Tamplin, Lu, M., O., Biechele, S., Gertsenstein, M., Floss, T., Kuehn, R., Wurst, W., Rossant, J., **Lickert, H.** (2010). Phenotypic annotation of the mouse X chromosome. Genome Research in press **(IF: 11.224)**

Nikoletopoulou, V., **Lickert, H.,** Frade, J.M., Rencurel, C., Zhang, L., Bibel, M., and Barde, Y.A. (2010). Two tyrosin kinase receptors trigger the death of neurons in the developing nervous system. Nature under revision **(IF: 31.43)**

Kinzel, D., Boldt, K., Davis, E., Burtscher, I., Truembach, D., Diplas, B., Attie-Bitach, T., Wurst, W., Katsanis, N., Ueffing, M., and **Lickert, H.** (2010). Pitchfork regulates primary cilia disassembly and left-right asymmetry. Dev. Cell under revision. **(IF: 12.88)**

Van Campenhout, C., Giallonardo, P., Gloeckner, J.C., Eitelhuber, A., Gegg, M., Grant, S.G.N., Ueffing, M., and **Lickert, H.** (2010). Dlg3 establishes apical epithelial polarity through Nedd4 E3 ligases-mediated monoubiquitination and trafficking. Dev. Cell submitted. **(IF: 12.88)**

IV. Teaching, Seminars and Institutional Activities

1996 and 1997	**Biochemistry Course** Teaching Assistant in Biochemistry Practical Course at the University of Freiburg Organization of Lecture and Practical Course (6 weeks)
2003 and 2004	**International Exchange Course** Joint Course between University Toronto and Karolinska Institute Development and Perinatal Biology Organization of Lecture and Practical Course (2 weeks)
12/2002-12/2004	**Supervision of the Masters Thesis of Owen Tamplin** Prof. Janet Rossant lab Samuel Lunenfeld Research Institute, Toronto, Canada „Foxa2 target gene screen“
6/2003-9/2003	**Supervision of the Summer Student James Allen** Prof. Janet Rossant's lab Samuel Lunenfeld Research Institute, Toronto, Canada „*In situ* hybridization screen to identify novel endoderm genes“
6/2004-9/2004	**Supervision of the Summer Student Christine Witchell** Prof. Janet Rossant's lab Samuel Lunenfeld Research Institute, Toronto, Canada „Foxa2 target gene screen“
2005-2009	**Supervision of Several Students Assistants** Lickert lab, Institute for Stem Cell Research, HelmholtzZentrum münchen Florian Schwarz, Moritz Gegg, Daniel Meyer, Martina Simon, Nadine Brecht, Ralf Hiller, Johannes Sam
10/2007-5/2008	**Supervision of the Masters Thesis of Moritz Gegg** Lickert lab, Institute for Stem Cell Research, HelmholtzZentrum münchen Masters thesis: „Expression analysis of Dlgh family members during mouse development“
5/2008-04/2009	**Supervision of the Diploma Thesis of Silvia Engert** Lickert lab, Institute for Stem Cell Research, HelmholtzZentrum münchen Diploma thesis: „Sox17-2A-iCre activity and lineage analysis“
2/2005-10/2008	**Supervision of the PhD Thesis of Lena Uetzmann** Lickert lab, Institute for Stem Cell Research, HelmholtzZentrum münchen PhD thesis: „Cell-lineage tracing in the endoderm“
4/2005-3/2009	**Supervision of the PhD Thesis of Doris Kinzel** Lickert lab, Institute for Stem Cell Research, HelmholtzZentrum münchen PhD thesis: „Identification of Spemann-Mangold Organizer Genes“
5/2005-12/2008	**Supervision of the PhD Thesis of Sascha Imhof** Lickert lab, Institute for Stem Cell Research, HelmholtzZentrum münchen PhD thesis: „Lineage labelling in the endoderm“
1/2007-1/2010	**Supervision of the PhD Thesis of Marion Vollmer** Lickert lab, Institute for Stem Cell Research, HelmholtzZentrum münchen PhD thesis: „Phenotypic annotation of the mouse X chromosome“
4/2007-	**Supervision of the PhD Thesis of Perry Liao** Lickert lab, Institute for Stem Cell Research, HelmholtzZentrum münchen PhD thesis: „Analysis of Oct3/4 during endoderm differentiation“

5/2008-	**Supervision of the PhD Thesis of Moritz Gegg** Lickert lab, Institute for Stem Cell Research, HelmholtzZentrum münchen PhD thesis: „Analysis of a novel planar cell polarity molecule“
9/2009-	**Supervision of the PhD Thesis of Dapeng Yang** Lickert lab, Institute for Stem Cell Research, HelmholtzZentrum münchen PhD thesis: „Analysis of miRNA function during endoderm formation“
11/2009-	**Supervision of the PhD Thesis of Daniela Padula** Lickert lab, Institute for Stem Cell Research, HelmholtzZentrum münchen PhD thesis: „Pitchfork is a novel Shh siganling component“
2009/2010	German Society for Developmental Biology (GfE) **GfE Summer School 2010** A lecture course for Diploma/Master students, Ph.D. Students and young postdocs Organization of lecture and course together with Dr. Reinhard Köster

Oral Presentations at International Conferences

Numerous presentations, seminars or invited talks at national conferences and national and international institutes are not listed.

2001 **14th Scientific Meeting of the German Society of Developmental Biology**
(Ulm, Germany)
"Wnt/β-catenin signaling regulates the expression of the homeobox gene *Cdx1*"

2003 **5th EMBL Mouse Molecular Genetics Meeting**
(Heidelberg, Germany)
"A functional genomic approach to identify Wnt/β-catenin target genes regulating early embryonic decisions"

2004 **Great Lakes Mammalian Development Meeting**
(Toronto, Canada)
"A functional genomic approach to identify and characterize Wnt/β-catenin target genes regulating early embryonic decisions"

2004 **Experimental Biology 2004, American Association of Anatomists**
(Washington, DC, USA)
Regulatory RNAs: "A functional genomic approach to identify and characterize target genes using transgenic shRNAs"

2005 **16th Scientific Meeting of the German Society of Developmental Biology**
(Muenster, Germany)
"Dissecting Wnt/β-catenin signaling during gastrulation using RNA interference in mouse embryos"

2006 **International Symposium RNAi in vivo technologies (Munich, Germany)**
"BAF60c functions in heart development and specification of left-right axis"

2008 **67th Scientific Meeting of the Society for Developmental Biology (Philadelphia, USA)**
"Identification and functional analysis of Spemann/Mangold organizer genes"

2009 **7th German-Dutch Cardiology Meeting (Hamburg, Germany)**
"Pitchfork regulates cardiac left-right asymmetry"

2009 **18th Scientific Meeting of the German Society of Developmental Biology**
"Pitchfork regulates cilia disassembly and embryonic pattern formation"

Activities within the HelmholtzZentrum münchen

- Member of the writing committee for the POFII programme for the HelmholtzZentrum münchen "Systemic Analysis of Multifactorial Disease" (2009-2012)
- Coordination, organization and preparation of a presentation to demonstrate the activities of the young investigator groups at the HelmholtzZentrum münchen for the POFII evaluation. 1 hour presentation and defence in front of the scientific advisory board for the POF II programme, which was very well received.
- Writing, coordination and representation of the Institute of Stem Cell contribution to the Helmholtz Systembiology Initiative "Control of Regulatory Networks by non-coding RNAs"
- Representation of our HelmholtzZentrum münchen research activities at the young investigator meeting of the Helmholtz Society in Berlin
- Radioactive safety officer for the Institute of Stem Cell Research
- Rolling deputy director for the Institute of Stem Cell Research
- Representation of the Institute for Stem Cell Research to the outside world (e.g. media, visitors and guests)
- Organization of the bi-weekly seminar series in the Institute of Stem Cell Research
- Invitation of seminar speakers for the weekly POF seminar series (e.g. Patrick Tam, Elizabeth Robertson, Philippe Soriano, Rolf Kemler, Anne Grapin-Botton, James Wells etc.)
- Participation in workshops for senior staff: Leadership and communication, conflict management and negotiation, annual appraisals
- Our group provides knowledge and technical support in trangenesis, knock-in and knock-out strategies using embryonic stem cells and mouse lines to several groups at the HelmholtzZentrum münchen.
- Our group generates diploid and tetraploid mouse chimeras for derivation of mouse lines and for experimental purposes.
- We have generated many commonly used transgenic mouse lines (e.g. Cre expressing and fluorescent protein expressing mouse lines).
- We perform embryo transfer to generate SPF mice.
- Our group offers help and support for the BAC recombineering technology to many groups at the HelmholtzZentrum münchen
- We offer help with the production of recombinant leukaemia inhibitor factor (LIF) for ES cell culture to reduce the amount of cost associated with buying LIF (yearly cost for our group > 10.000 Euros).

V. Research Achievements

After high school I **studied biology** at the Albert-Ludwigs University in Freiburg, Germany and finished my **diploma with distinction**. During undergraduate studies I became very interested in developmental biology. For this reason I joined **Prof. Rolf Kemler's group** at the Max-Planck Institute in Freiburg. I did my **diploma work** in the field of **embryonic morphogenesis, where Rolf Kemler is one of the leading scientists** (Lickert et al., 2000). I went on to study β-catenin signalling during my **PhD thesis** in the same lab and I was able to identify one of the first **Wnt/β-catenin target genes**, the *caudal*-related homeobox gene1 (*Cdx1*) (Lickert et al., 2000; Lickert and Kemler, 2002). Moreover, I **provided functional proof that Wnt/β-catenin signaling pathway is essential for the formation of the endodermal germ-layer** (Lickert et al. 2002). For my PhD thesis (**overall grade: *summa cum laude***) I received the **Hans-Spemann Prize 2002** from the University of Freiburg (awarded to a single student per year) and the **prestigious Otto-Hahn Medal 2003** from the Max-Planck Society. A decade ago during my PhD it became clear to me that **endoderm development was and still is understudied.** I saw the great opportunity to **combine the knowledge from mouse embryology and stem cell technologies to allow cell-replacement therapy** as an attractive approach to treating crippling endodermal disease, such as diabetes.

For my **post-doc I joined Prof. Janet Rossant's lab** at the Samuel Lunenfeld Research Institute in Toronto, Canada. Janet Rossant is one of the **leading scientists in the field of developmental biology and stem cell research**. I joined her lab to complete my knowledge in stem cell biology, manipulating the mouse embryo and to learn techniques such as **tetraploid aggregations, which speeds up the intrinsically slow mouse genetics** by enabling the generation of embryos directly from embryonic stem cells. For my studies I received a **Canadian Institute of Health (CIHR) post-doc fellowship**, which I relinquished after the first 6 months when I was awarded **a 2 year Emmy-Noether fellowship**. I focused my research efforts on trying to define the pathways that establish **definitive endoderm in the mouse embryo** and developed assays to explore the inductive roles of definitive endoderm (Lickert et al., 2005; Tamplin et al., 2008). However, it is essential to **determine the function of genes *in vivo***. With that in mind, I collaborated with Tony Pawsons's laboratory to find a way to use **siRNA to rapidly assess gene function in mice** (Kunath et al., 2003). Using this approach, we functionally analyzed ***BAF60c*** and revealed that it **conferred specificity to Swi/Snf chromatin remodelling in the heart and left-right axis development** (Lickert et al., 2004; Takeuchi et al., 2007). In addition, we **analyzed the function of two novel Wnt/β-catenin target genes during mouse embryogenesis** (Lickert et al., 2005).

After my post-doc I applied for **group leader positions** internationally and I received job offers from Oxford University, New York University and the Institute for Stem Cell Research at the **HelmholtzZentrum münchen**. Due to the award of the **prestigious 5 year Emmy-Noether fellowship** and the excellent research environment at the Institute for Stem Cell Research (headed by the **Leibniz laureate**, Magdalena Goetz), I decided to return to Germany. I started my **own lab on the development of the endoderm-derived organs, pancreas, liver and lung**. To understand the formation of these organs, the **endodermal progenitor cells** have to be identified and characterized. Moreover, the **signals and factors** that trigger specification, differentiation and morphogenesis of the organ primordia from the primitive gut tube have to be understood. **Elucidating the developmental mechanisms** that lead to embryonic pattern formation and the development of the endoderm-derived organs will be beneficial in **triggering endogenous mechanisms of repair** as well as **directing embryonic stem cell differentiation** and is of **significant interest for regenerative medicine**.

Since the establishment of the Emmy-Noether (German Research Foundation) and Helmholtz Society funded endoderm development group in January 2005, we have generated many **transgenic mouse lines expressing fluorescent marker** proteins to directly **image mouse embryogenesis and pancreas organogenesis** using static culture systems. This allowed us for the first time to visualize a clear sequence of events occurring during endoderm germ layer formation in wild type and mutant mouse embryos (Burtscher an Lickert, 2009). Expression profiling of endoderm and Spemann/Mangold organizer deficient embryos revealed a **molecular program underlying the specification and differentiation** of these tissues (Tamplin et al., 2008). To identify novel genes involved in endoderm and organizer development, we carried out a large-scale whole-mount *in situ* expression screen (314 genes) and identified **5 novel endoderm genes** and **10 novel Spemann/Mangold organizer genes**. We have **generated knock-out and conditional knock-out alleles for two of these organizer genes** and have functionally analyzed both of these genes in great detail on all levels of complexity. We named one gene ***Pitchfork*** and demonstrated that it is **involved in ciliogenesis and Shh signalling** (Kinzel et al. under revision). ***Pitchfork*** **haploinsufficiency** leads to **left-right patterning defects**, **heart failure**, **polydactyly** and **male infertility**, precluding functional analysis in the endoderm-derived organs. Therefore, we have generated a **conditional allele to analyze Pitchfork function during pancreas development**. *Pitchfork* mutations in human cause Meckle-

Gruber syndrome, a severe ciliary dysfunction disease. **Ciliopathies** are >30 pleiotropic diseases with a wide spectrum of human phenotypes. These include **cyst formation in the kidney, liver and pancreas**, **obesity** and a **predisposition to diabetes and cancer**. We named the other gene ***Cep20*** and demonstrated that it is involved in **basal body docking**, **ciliogenesis** and is a **novel component of the Wnt/planar cell polarity pathway** (Gegg et al in preparation). To **identify the endodermal progenitor cells** and **analyze the signals and factors regulating endoderm development**, we established several **endoderm-specific Cre recombinase expressing mouse lines** (Uetzmann et al., 2008; Liao et al., 2009; Engert et al., 2009; Gegg et al., in preparation). Using these mouse lines we can show that the Forkhead transcription factor a2 (**Foxa2**) and the SRY-related HMG box transcription factor, **Sox17**, **mark the endodermal stem cells *in vivo***, which contribute to all differentiated endodermal cells in the endoderm-derived organs. Using the Foxa2-Cre line, we demonstrate that **Wnt/β-catenin signalling and the pluripotency factor Oct4 are essential for endoderm development and maintenance of endodermal stem cells** (Liao et al in preparation). Finally, we have carried out a **phenotype-driven screen to identify X-linked genes involved in endoderm development and disease** (Cox et al., 2010 in press). Thereby, we have identified among others the cell polarity gene **Disc-large homolog 3 (Dlg3) to be important for endoderm and Spemann/Mangold organizer development** (Van Campenhout et al., submitted). In a screen for **protein-protein interaction partners for Dlg3**, we identified the **E3-ubiquitin ligase family member Nedd4** as interaction partner for Dlg3, which links to Rho GTPases-mediated cell polarity. Human **Dlg3 is involved in X-linked mental retardation**. The failure of anterior neural induction and forebrain deletions in our mouse mutants, might provide mechanistic details for this disease. Additionally, the Dlg3 mutants will provide **valuable information on the process of asymmetric progenitor cell division in cell-fate specification**.

During the last five years **as a team leader** I have **acquired and managed** my own budget. I have hired, trained and guided my own personnel and I have built up a laboratory from scratch. I execute the administration and I have developed and improved the scientific ideas and concepts for experimental research. I have attended several management courses to **improve** my scientific **leadership potential** and have given seminars both at the university and outside the university. I have supervised many students and post-docs and have received very positive feed-back on my **very good didactic and teaching skills**. I have **successfully applied for research grants**, including the prestigious German **Emmy-Noether fellowship** and the **ERC starting grant** (see funding ID) and have **published several papers** from my own lab.

Throughout my research career I have shown **independent thinking** and I have always embraced collaborations to generate synergisms. I have **successfully collaborated with both national and international researchers, resulting in a number of high impact publications**, e.g. with Tony Pawson's laboratory to establish **RNAi knockdown in mouse embryogenesis** (Kunath et al., 2003), with Jeff Wrana's, Benoit Bruneau's and Hiroshi Hamada's and Joe Yost's laboratories on **heart and left-right axis development** (von Both et al., 2004; Lickert et al., 2004; Takeuchi et al., 2007), with Hans Clevers and Makoto Taketo on **Wnt/β-catenin signalling in the endoderm and in gastrointestinal cancer** (Lickert et al., 2000; Lickert et al., 2002; Lickert et al., 2005), with Palle Serup and Jan Nygaard Jensen from the Hagedorn Research Institute, **β Cell Biology Consortium** on **Notch target gene function in β cells and imaging pancreas development**. Importantly, these collaborations have given me the opportunity to work with world-class scientists, become established and connected in several research fields (Stem Cell Research, Developmental Biology, Diabetes Research) and to learn **new methodologies and approaches** to expand my horizons to **new scientific concepts and ideas**. Together with the talks I have given at national and international conferences, as well as the many visits to partner institutes, this has **generated visibility and acceptance** within the scientific community.

As a researcher, I am very **enthusiastic** and I have always discussed **new ideas** to establish and improve projects. I have proven to be **able to follow new research directions** and to acquire the knowledge and expertise required to establish novel methodologies to investigate new research avenues. The summary of my research career achievements and scientific contributions demonstrates that I have been, and will continue to be, a **very successful** independent researcher. In total I have **published 23 peer-reviewed papers (Ø IF: 11.05)** that have been cited over 900 times, which have **established new mechanisms and principals** in embryonic development and stem cell research. This demonstrates that **I am able to generate ideas** and perform hypothesis-driven and exploratory experiments, which result in **new scientific concepts and paradigms**. **This was recognized early in my career** with the award of the **Hans Spemann Prize** 2002, **Otto-Hahn Medal** 2003 and many fellowships, most importantly the **Emmy-Noether award and ERC starting grant**. In summary, I believe that I have the right **mixture of enthusiasm, dedication and skill to be able to lead my own research institute and to make interesting discoveries in the future**.

VI. Research Concept

Our long-term goal is to better **understand pancreas development** in the mouse model, to **identify the progenitor cells** *in vivo* and the **signals and factors that govern differentiation and proliferation** of β cells. This knowledge can be used to trigger **endogenous mechanisms of repair** after chronic tissue injury and to direct **stem cell differentiation into β cell in culture**. Moreover, we are interested in the **cell biology of the pancreatic β cell** to identify the cellular and molecular mechanism leading to β-cell replication, insulin secretion and glucose sensing. Therefore, we are studying **the role of the primary cilium** in sensing the environment, regulating insulin secretion and intimately linking the β cell to the cell cycle. Taken together, our studies are of significant interest for **cell-replacement therapies** and provide insights into the **pathogenesis of Diabetes** as well as contribute to the **development of novel treatments**. Specifically our research will focus on the following key topics:

1. **Identification and analysis of the signals and factors that regulate pancreas development**
2. **Translation of developmental concepts to differentiate β cells in culture and trigger endogenous mechanisms of repair *in vivo***
3. **Analysis of the role of primary cilia for β cell function**

Tackling β cell biology from these different angles (mouse genetics, pancreas development, stem cell biology and cell biology) has the great advantage to go back and forth from the *in vitro* and culture system to the mouse model and translate knowledge into both directions. Over the last years we have **successfully established ES endoderm differentiation**, **pancreas organ and embryo culture system** and **many ES cell lines and mouse lines**, specifically labelling progenitor cells and differentiated cells in the embryonic and adult pancreas. This has and will allow us to directly investigate the effect of small molecules, signals, factors or miRNAs by **life imaging on single-cell level** in ES cell culture, in *ex vivo* pancreas organ culture and during pancreas development *in vivo*. We are actively **cooperating with world leading scientists** in the reseach fields of Diabetes and endoderm research as well as developmental, stem cell and systems biology on a national and international scale. Key findings will be **translated to the human ES cell and induced pluripotent stem cell system (iPS)** in cooperation with the newly hired iPS junior group/core facility at the HelmholtzZentrum münchen. Moreover, we will **closely cooperate with the clinical investigation groups** to extend our investigations to human islets of non-diabetic and diabetic subjects and to generate iPS cells to investigate the aetiology of β cell dysfunction. I am very confident that we will **quickly establish a national and international competitive Institute of β Cell Biology** and will offer great cooperations, expertise and technology to the β Cell and Diabetes Community in Munich.

1. Identification and analysis of the signals and factors that regulate pancreas development

There are **two major initiatives under way to correct the β cell deficit** of diabetes: one would generate β-cells *ex vivo* that are suitable for transplantation and the second would stimulate regeneration of β-cells in the pancreas. Both initiatives rely on the **identification of the endodermal progenitor cells** *in vivo* and the analysis of the **signals and factors triggering pancreas development** in the mouse model. To address these key questions I have received **Emmy-Noether funding** over the last five years. I have outlined our activities and ongoing projects on the last pages. We are now well equipped and set up to specifically identify progenitor cells by genetic lineage tracing, novel factors and signalling molecules by conditional gene targeting and to understand the influence on endoderm development and the formation of the pancreas *in vivo*. We have **ongoing cooperations and students exchange with the Hagedorn Institute** (β Cell Biology Consortium, J. N. Jensen and P. Serup) to investigate the function of Notch target genes in β-cell differentiation and in imaging pancreas development in the mouse embryo and organ culture system. We also focus on the function of the pluripotency gene Oct4, the Wnt/β-catenin and Shh signalling and the function of cilia in **pancreas development by functional analysis in the mouse model**. We have received **1.5 Million € for "Deciphering mechanisms of ciliary disease" with particular emphasize on the endoderm-derived organ, pancreas** (see below). Overall, our **studies of endoderm development** in the mouse model system **over the last decade** generated not only a huge amount of sustainable resources (Cre-expressing and fluorescent protein tagged mouse lines and ES cell lines, antibodies, identification of novel genes), but also a profound knowledge in developmental biology, stem cell biology and cell biology, which is all important for cell-replacement and regenerative therapies.

2. Translation of developmental concepts to differentiate β cells in culture and trigger endogenous mechanisms of repair *in vivo*

The major forms of Diabetes are characterized by decreased β-cell number raising hope for **regenerative medicine**. We currently **translate the knowledge from the animal model** to improve stem cell differentiation protocols to **generate endoderm progenitor cells for transplantation**. It has recently been shown that pancreatic progenitor cells when transplanted into diabetic mice differentiate into glucose-sensitive and insulin-secreting cells to normalize blood sugar levels. In this respect we have started an **academic-industrial cooperation with the European Screening Port Hamburg** (see funding ID) to identify **drugs that improve β-cell differentiation**. Therefore, we generated knock-in lineage tagged ES cells for the pluripotency marker ($Oct4^+$) and the endodermal stem cell marker ($Foxa2^+$). The **expression of Foxa2** in the pancreatic primordium precedes pancreas morphogenesis and persists in all endoderm-derived epithelial cell types of the organ through development and adulthood. In addition to controlling fetal pancreas development, **Foxa2 controls multiple aspects of insulin secretion** in mature β cells. Thus identifying drugs that induce/regulate Foxa2 during ES cell differentiation can serve 1. to **improve *in vitro* β-cell differentiation protocols** and 2. to **modulate mature β cell function**. The selectivity and specificity of the identified drugs can be tested further using our life imaging systems in ES cell differentiation culture, pancreatic organ culture and islet cell cultures, before turning to the more laborious *in vivo* models. This project serves as proof-of-principal and we will closely **work together with the planned "Wirkstoffzentrum"** at the HelmholtzZentrum munich. We plan to generate knock-in ES cells to monitor $Foxa2^+$ endoderm progenitors and $Pdx1^+$ pancreatic progenitors in ES cell differentiation culture to identify **drugs that can improve the efficiency to obtain transplantable progenitor cells**. Additionally, we are planning to extend the screening initiative to **whole-genome RNAi screens** to identify **molecules that regulate pancreatic differentiation**. We have already a fruitful cooperation in the Helmholtz Systems Biology Initiative to identify **miRNAs that regulate endoderm differentiation**. The identification of signals, factors, drugs and miRNAs are not only essential to identify molecules that can direct β-cell differentiation in culture, but might **also trigger mechanisms of repair** *in vivo*. Islet neogenesis, the budding of new islets from pancreatic progenitor cells located in or near ducts, has long assumed to be an active process in the postnatal pancreas. However, a recent genetic lineage tracing, using the insulin promoter from the Melton lab, has challenged this view and concluded that new β-cells could only be generated by replication of existing β-cells. This remains highly controversial because the insulin promoter might not be active in the pancreatic stem/progenitor cells, thus we have generated an inducible Foxa2-iCre line to **test if new islet can be formed by pancreatic progenitors**. If we find formal proof that Foxa2 marks progenitor cells in the pancreas, the identified **Foxa2-inducing drugs could be used to trigger endogenous mechanisms of repair**.

3. Analysis of the role of primary cilia for β cell function

Recently, I have received **an ERC starting grant to focus on the function of primary cilia in endoderm development** (see funding ID). Cilia perform diverse cellular functions; affecting cell motility, fluid transport as well as developmental signaling. Cilia defects lead to a wide range of **human ciliary dysfunction syndromes** (ciliopathies) and increasing evidence implicates an **intriguing involvement of cilia in modern human epidemics, such as obesity and Diabetes**. Central features of Bardet-Biedl and Alström syndrome include obesity, insulin resistance, and type 2 Diabetes. Moreover, the **ciliogenic transcription factor RFX3** is expressed in endocrine cells during embryogenesis and in the adult and is essential for cilia formation. Just before birth, **$Rfx3^{-/-}$ islets contain considerably less insulin-, glucagon-, and ghrelin-producing cells, whereas pancreatic polypeptide-positive cells are markedly increased in number**. **In adult mice, the defect leads to small and disorganized islets, reduced insulin production, and impaired glucose tolerance**. We identified **two novel genes, *Cep20* and *Pitchfork***, and as outlined above, could show that both genes are **essential for ciliogenesis and embryonic development** and are potentially involved in human ciliopathies. In the projects proposed for the ERC starting grant **we specifically focus on cilia function in pancreas development and homeostasis** using conditional gene deletion in the mouse, imaging cilia biology in culture and by identifying protein-protein interaction partners for our novel proteins. **Strikingly, insulin secretion and ciliogenesis both crucially depend on similar cellular and molecular mechanisms** such as targeted vesicular trafficking to the apical membrane. Moreover, β cells posses cilia which sense the outside environment and are absolutely essential for Ca^{2+}, cAMP, Shh and Wnt/PCP signaling all cascades that are essential for β cell formation, maintenance and function. Finally, **cilia are an intimate connection to the cell cycle** as all G0 cells posses cilia, whereas proliferating cells do not. **Loss of cilia might cause pancreatic cancer** and we have **applied for SFP funding** to investigate a potential role of *Pitchfork* in the development of pancreatic cancer. Altogether, we think **that cilia are an exciting new entry point to understand β cell biology** and we have the funding and all methodologies, plus mouse lines in place to investigate immediately this novel and exciting research opportunity.

VII. Teaching Concept

As a Professor at the TUM I would take part in the training of the Faculty of Medicine, especially in the "Medical Life Science and Technology" PhD course of students. The main areas of the program are currently neurosciences, molecular medicine and medical imaging. Our research, technology and expertise would perfectly complement and add to the program in several ways. I could offer lectures and seminars in β-cell biology, stem cell biology and developmental biology, all highly relevant topics in the area of regenerative medicine and identification of disease mechanisms. Moreover, I could offer lectures and courses on cutting edge technologies in life science for which the Nobel prize was awarded in Physiology or Medicine 2007, such as manipulating embryonic stem cells, generating mouse knock-out models for human disease and homologous recombination in bacteria and ES cells. As medical imaging is already a part of the program, I could further strengthen this topic by offering lectures, seminars and courses in life cell imaging technologies in mouse embryos, organ cultures and embryonic stem cells. Finally, as these cell-based assays allow for drug screening I would offer lectures and seminars on small compound and RNA interference screens to identify pharmacological intervention sites. These are all ideas that will be discussed with the faculty members to offer integration of the most interesting parts for the PhD training program. Obviously, we would actively participate in educating and training PhD students in our own lab. Altogether, I think that our research and expertise would be a valuable addition to the already existing program. If necessary, I would also lecture in the bio-scientific training courses of the TU Munich.

From section IV. Teaching, Seminar and Institutional Activities and from section V. Research and Achievements it should be obvious that I will be able to lecture at the University. I have trained, guided and supervised many post-docs, technicians and PhD students, some of which received *summa cum laude* for their thesis. I have given hundred of seminars and talks nationally and internationally and have been invited to many Universities and Institutes including Oxford, Cambridge, Harvard, etc., which clearly shows that my talks are well received. Many of my P.I. colleagues and also team members have mentioned and attested my excellent didactic and teaching skills. Thus I will dedicate time for basic lectures, student seminars, journal clubs, retreats, PhD research schools, international students exchange and practical courses as a future TUM Professor, teaching and preparing the next generation of graduates for a successful career in biomedical research.