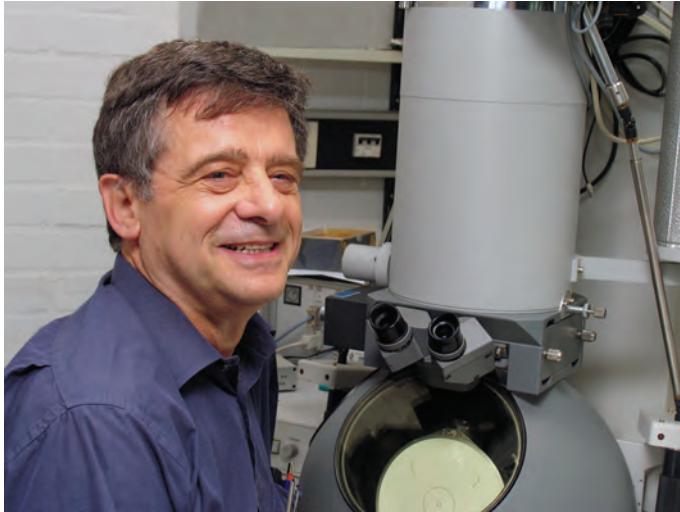




## Miscellaneous Research Groups

### Microscopy

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#### *Head*

Rudi Lurz (since 78)

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#### *Technician*

Beatrix Fauler

### Scientific overview

The lab is running two transmission electron microscopes: Philips CM100 and Tecnai Spirit. In addition, a high-resolution Tecnai Polara cryo-EM is available through the cooperation with the cryo-EM group in the institute (Thorsten Mielke, USN, Anwenderzentrum). All EMs are equipped with CCD cameras and optional cryo or tomography holder.

A broad range of preparation methods is established. Our main focus is on:

- ultra-thin sections of embedded samples;
- specific labelling of sections or isolated structures;
- visualization of nucleic acids and nucleic acid - protein interactions;
- cryo preparation and image acquisition of samples in vitreous ice.
- fine structural analysis of protein complexes or viruses after negative staining.

Within the institute we perform projects with all departments having wet labs.

#### *Research Group Development & Disease (Stefan Mundlos)*

- M. Kolanczyk: *Immuno-gold localization of a nitric oxide synthase.*
- U. Kornak: *Structural changes in mitochondria after expression of PYCR1.*

#### *Dept. of Human Molecular Genetics (H.-Hilger Ropers)*

- A. Kuss: *Structure of the nuclear membrane in Bod1 transfected MatCat cells*
- R. Ullmann: *Protein localization by immunolabelling of IMR-90 in fetal fibroblasts.*
- C. Scharff /S. Scotto: *Neurogenesis in bird brain.*

*Dept. of Vertebrate Genomics (Hans Lehrach)*

- G. Panopoulou: *Expression patterns in sections of in situ labelled sea urchin and amphioxus embryos.*
- J. Adjaye: *Morphological changes characterization of iPSC and ESC line during cultivation.*
- B. Lange: *The function of two cancer-related proteins for maintaining centriole integrity was confirmed in U2OS osteosarcoma cells after protein depletion by siRNA.*

*Dept. of Developmental Genetics (Bernhard Herrmann)*

- N. Véron: *Localization of the t-complex responder locus (Tcr).*
- M. Mayer: *Mice kidney podocytes in Slit12 knockouts.*

Collaborations outside the institute are often in continuation of projects started during the stay of the people in this institute.

- J.C. Alonso/S. Ayora, Centro Nacional de Biotecnología, Departamento de Biotecnología Microbiana, Madrid: *Replication and recombination in B. subtilis and phage SPP1.*
- M. Espinosa / A. Bravo, Centro de Investigaciones Biológicas (CSIC), Madrid: *Replication and mobilization of the promiscuous plasmid pMV158.*
- K. Geider, JKI Dossenheim, *Analysis of morphology and DNA of Erwinia phages.*
- S. Hertwig, Bundesinstitut für Risikobewertung (BfR), Berlin: *Phage PY54 from Yersinia enterocolitica replicates as a linear chromosome. EM analysis of the complexes of the C1 repressor with the operator region.*
- M. J. Loessner, Swiss Federal Institute of Technology (ETH), Zürich: *EM characterisation of phages (Listeria) and their DNA.*
- G. Multhaupt, FU Berlin, Institut für Chemie-Biochemie, *Assembly of  $\beta$ -amyloid fibrils monitored by EM.*
- E. Orlova, Birkbeck College, Dept. of Crystallography, University of London: *Image processing of data sets from components of phage SPP1.*
- A. Pingoud / V. Pingoud, Institut für Biochemie, Justus-Liebig-Universität Giessen: *Interaction of nucleases (CAD, EndoG, DNaseII) and regulatory proteins with DNA. Specific interaction of restriction enzymes and their recognition sequence on the DNA*
- C. Speck, DNA Replication Group MRC, Clinical Sciences Centre Faculty of Medicine, Imperial College, London Hammersmith, *Yeast replication: visualization of the MCM2-7 helicase loaded onto origin DNA.*
- P. Tavares, Laboratoire de Virology Moléculaire et Structurale, CNRS, Gif-sur-Yvette: *Life cycle of B. subtilis bacteriophage SPP1 (morphogenesis, DNA packaging, infection); fine structural analysis of the phage components.*
- J.N. Reeve, Ohio State University, Columbus: *Mapping of the archaeal transcription repressor (TrpY) from Methanothermobacter.*
- E. Wanker, Max-Delbrück-Centrum Berlin-Buch: *Effect of selected drugs on the formation of huntingtin,  $\alpha$ -synuclein or  $\beta$ -amyloid fibrils monitored by EM.*
- E. Weinhold, Institut für organische Chemie, RWTH Aachen: *Sequence specific labeling of DNA by covalent binding of modified cofactors of restriction enzymes.*
- J. Zakrzewska-Czerwinska, Institute of Immunology and Experimental Therapy, Polish Academy of Sciences, Wrocław: *Architecture of the partitioning complexes (segregosomes) in Streptomyces coelicolor.*

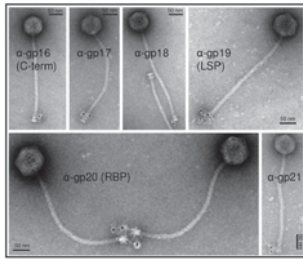


Figure 1: Immunolabelling of tail tip proteins of *Listeria* phage A118. LSP=lytic structural protein, RBP receptor binding protein. (collaboration with group Loessner, Zürich).

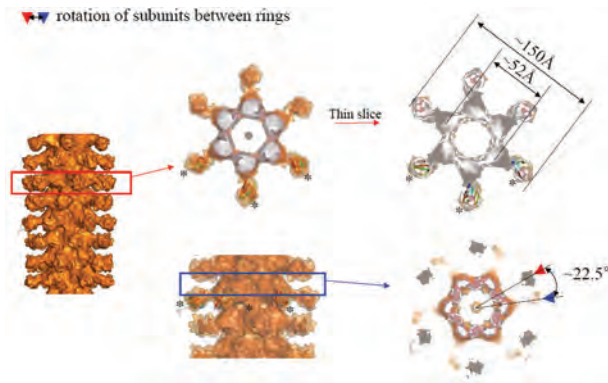


Figure 2: 3D Image reconstruction of the phage tail of the translational frameshift mutant pIA8 of phage SPP1 showing an additional IG like domain. (collaboration with the groups of P. Tavares and E. Orlova)

## General information

### Complete list of publications (2006-2009)

#### 2009

Evrin C, P Clarke, J Zech, R Lurz, J Sun, S Uhle, H Li, B Stillman, C Speck (2009) *A double-hexameric MCM2-7 complex is loaded onto origin DNA during licensing of eukaryotic DNA replication*. Proc Natl Acad Sci U S A 106(48): 20240-45.

Garcia P, B Martinez, J M Obeso, R Lavigne, R Lurz, A Rodriguez (2009) *Functional genomic analysis of two Staphylococcus aureus phages isolated from the dairy environment*. Appl Environ Microbiol 75 (24): 7663-73.

#### 2008

Aranda-Orgilles B, J Aigner, M Kunath, R Lurz, R Schneider, S Schweiger (2008) *Active transport of the ubiquitin ligase MID1 along the microtubules is regulated by protein phosphatase 2A*. PLoS One 3(10): 3507.

Auzat I., A Dröge, F Weise, R Lurz, P Tavares (2008) *Origin and function of the two major tail proteins of bacteriophage SPP1*. Mol Microbiol 70(3): 557-69.

Ehrnhoefer DE, J Bieschke, A Boeddrich, M Herbst, L Masino, R Lurz, S Engemann, A Pastore, EE Wanker (2008) *EGCG redirects amyloidogenic polypeptides into unstructured, off-pathway oligomers*. Nat Struct Mol Biol 15(6): 558-66.

Gasset-Rosa F, T Diaz-Lopez, R Lurz, A Prieto, M E Fernandez-Tresguerres, R Giraldo (2008) *Negative regulation of pPS10 plasmid replication: origin pairing by zipping-up DNA-bound RepA monomers*. Mol Microbiol 68(3): 560-72.

Graeber I, I Kaesler, M S Borchert, R Dieckmann, T Pape, R Lurz, P Nielsen, von Dohren, W Michaelis, U Szewzyk (2008) *Spongiibacter marinus gen. nov., sp. nov., a halophilic marine bacterium isolated from the boreal sponge Haliclona sp. 1*. Int J Syst Evol Microbiol 58 (Pt 3): 585-90.

Kaesler I, I Graeber, M S Borchert, T Pape, . Dieckmann, H von Dohren, P Nielsen, R Lurz, W Michaelis, U Szewzyk (2008) *Spongiispira norvegica gen. nov., sp. nov., a marine bacterium isolated from the boreal sponge Isops phlegraei*. Int J Syst Evol Microbiol 58 (Pt 8): 1815-20.

Karr EA, K Sandman, R Lurz, JN Reeve (2008) *TrpY regulation of trpB2 transcription in Methanothermobacter thermautotrophicus*. J Bacteriol 190 (7): 2637-41.

Klumpp J, J Dorscht, R Lurz, R Biemann, M Wieland, M Zimmer, R Calendar and M J Loessner (2008) *The terminally redundant, nonpermuted genome of Listeria bacteriophage A511: a model for the SPO1-like myoviruses of gram-positive bacteria*. J Bacteriol 190 (17): 5753-65.

Lange M, B Kaynak, U B Forster, M Tonjes, J J Fischer, C Grimm, J Schlesinger, S Just, I Dunkel, T Krueger, S Mebus, H Lehrach, R Lurz, J Gobom, W Rottbauer, S Abdelilah-Seyfried, S Sperling (2008) *Regulation of muscle development by DPF3, a novel histone acetylation and methylation reader of the BAF chromatin remodeling complex*. Genes Dev 22 (17): 2370-84.

Poh S L, F El Khadali, C Berrier, R Lurz, R Melki, P Tavares (2008) *Oligomerization of the SPP1 Scaffolding Protein*. J Mol Biol 378 (3): 551-64.

Pratto F, A Cicek, W A Weihofen, R Lurz, W Saenger, J C Alonso (2008) *Streptococcus pyogenes pSM19035 requires dynamic assembly of ATP-bound ParA and ParB on parS DNA during plasmid segregation*. Nucleic Acids Res 36(11): 3676-89.

### 2007

Pljevaljcic G, F Schmidt, A J Scheidig, R Lurz, E Weinhold (2007) *Quantitative labeling of long plasmid DNA with nanometer precision*. Chembiochem 8(13): 1516-9.

Ruiz-Maso J A, R Lurz, M Espinosa, G Del Solar (2007) *Interactions between the RepB initiator protein of plasmid pMV158 and two distant DNA regions within the origin of replication*. Nucleic Acids Res 35(4):1230-44.

Zawilak-Pawlik A, A.Kois, K.Stingl, I.G.Boneca, P Skrobuk, J Piotr, R Lurz, J Zakrzewska-Czerwinska, A Labigne (2007) *HobA—a novel protein involved in initiation of chromosomal replication in Helicobacter pylori*. Mol Microbiol 65(4): 979-94.

### 2006

Alonso J C, P Tavares, R Lurz, TA Trautner (2006) *Bacteriophage SPP1 in R Calendar* (ed) The Bacteriophages. Oxford University Press

Boeddrich A, S Gaumer, A Haacke, N Tzvetkov, M Albrecht, B O Evert, E C Muller, R Lurz, P Breuer, N Schugardt, S Plassmann, K Xu, J M Warrick, J Suopanki, U Wullner, R Frank, U F Hartl, N M Bonini, EE Wanker (2006) *An arginine/lysine-rich motif is crucial for VCP/p97-mediated modulation of ataxin-3 fibrillogenesis*. Embo J 25(7): 1547-58.

Sao-Jose C, S Lhuillier, R Lurz, R Melki, J Lepault., MA Santos, P Tavares (2006) *The ectodomain of the viral receptor YueB forms a fiber that triggers ejection of bacteriophage SPP1 DNA*. J Biol Chem. 281(17):11464-70.

Zemojtel T, M Kolanczyk, N Kossler, S Stricker, R Lurz, I Mikula, M Duchniewicz, M Schuelke, P Ghafourifar, P Martasek, M Vingron, S Mundlos (2006) *Mammalian mitochondrial nitric oxide synthase: characterization of a novel candidate*. FEBS Lett 580(2): 455-62.

Vinga I, A Dröge, A C Stiege, R Lurz, M A Santos, R Daugelavičius, P Tavares (2006) *The minor capsid protein gp7 of bacteriophage SPP1 is required for efficient infection of Bacillus subtilis*. Mol Microbiol. 61(6):1609-21.

Lioy V S, M T Martin, A G Camacho, R Lurz, H Antelmann, M Hecker, E Hitchin, Y Ridge, J M Wells, J C Alonso. (2006). *pSM19035-encoded {zeta} toxin induces stasis followed by death in a subpopulation of cells*. Microbiology 152(Pt 8): 2365-79.

### Guest scientists

*J. Klumpp*, Swiss Federal Institute of Technology (ETH), Zürich, 07.-13.05. 2006

*F. Pratto*, Centro Nacional de Biotecnología and C. Manfredi, Universidad Autónoma de Madrid, Madrid, 13.-26.05. 2006



*A. Bravo*, Centro de Investigaciones Biológicas (CSIC), Madrid, 28.05.-12.06. 2006

*Fátima Gaaset Rosa*, Centro de Investigaciones Biológicas (CSIC), Madrid, 25.06.-25.07. 2007

*R. Biemann*; Swiss Federal Institute of Technology (ETH), Zürich, 20.08.-14.09. 2007

*P. Tavares*, Unité de Virologie Moléculaire et Structurale, Gif-sur-Yvette, 17.-24.09. 2007

*Juan López Villarejo/ Ramon Diaz Orejas*, Centro de Investigaciones Biológicas (CSIC), 18.11.-07.12.2007

*Ambra Lo Piano/Sylvia*, Centro Nacional de Biotecnología, Madrid, 01.-28.09. 2008

*J. Klumpp*, Swiss Federal Institute of Technology (ETH), Zürich, 20.-30.04.2009

### **Public relations**

Demonstration of the EM facility to the public within *Die lange Nacht der Wissenschaften*. Practical demonstrations to classes schools in and outside Berlin. Several school apprentices (Schülerpraktikanten) for 2 to 3 weeks each.

## Miscellaneous Research Groups

### Cryo-electron Microscopy: Structure Determination of Macromolecular Complexes & Protein Modules

(Established: 2004)

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#### Head

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#### Scientist

Justus Loerke\* (04/05-11/08)

#### Technicians

Jörg Bürger\* (since 08/06)

Matthias Brünner\* (since 09/07)



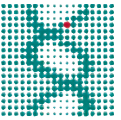
### Introduction

Sequencing the genomes of multiple organisms including *Drosophila*, zebra fish and human has revealed the total number of genes and the sequence of the encoded proteins. The next steps towards understanding biological processes including diseases require the characterization of the protein composition in a given cell, the protein function and protein protein-interactions. Consequently, understanding protein function at a molecular level requires profound knowledge of the structure of a protein and its different functional states.

However, key processes in biology involve large protein complexes such as multi-enzyme-complexes, the ribosome and RNA polymerases. Many of these complexes act as highly organized molecular machines, but often show a variable assembly and are subject to dynamical regulation. Furthermore, many signalling complexes or protein modules form only temporarily, making structure determination even more difficult.

Our group aims for structure determination of macromolecular protein complexes and protein modules using cryo-electron microscopy (cryo-EM) in combination with the single-particle approach. This technique has emerged as the key technology to gain structural information on macromolecular protein complexes without the need to crystallize these complex and dynamic systems. The molecules of interest are embedded in a thin layer of vitreous ice under near physiological conditions and imaged by transmission cryo-electron microscopy. Image processing then allows the reconstruction of the three-dimensional structure at sub-nanometer resolution.

\* externally funded



## Results

Starting in 2004, we have established a state-of-the-art cryo-EM facility within the Berlin-Brandenburg-wide research consortium UltraStructure Network (USN). The USN aims for a systematic analysis of macromolecular protein complexes combining methodology for complex isolation, analysis of the protein composition and function and, finally, cryo-EM structure determination. Our facility provides the latest techniques for cryo-EM structure determination including screening, semi-automated sample vitrification, data acquisition and intense computing resources for image processing. The Core instrument is a helium-cooled 300 kV Tecnai G2 Polara electron microscope (FEI) equipped with a 4k CCD camera (TVIPS). Additionally, a 100 kV Philips CM100 and a 120 kV Tecnai Spirit electron microscope are available through the close collaboration with the microscopy group of our institute (AG Rudi Lurz).

Within the framework of the USN, we support the isolation of protein complexes of various groups e.g. the “Protein Complexes and Cell Organelle Assembly Group” (AG Bodo Lange, MPIMG) and the “ribosome group” (Knud Nierhaus, MPIMG) with EM-screening techniques. We further solved several mainly ribosomal complexes at 1 nm resolution or below, which revealed important new insights into different functional states of the cellular protein biosynthesis machinery. One example is the structure of the active ribosome in complex with the signal recognition particle (SRP) and the SRP receptor at 8 Å resolution. This structure unveiled how the interaction of the SRP receptor with both, the ribosome and the SRP, displaces parts of the SRP molecule, leading to the exposition of ribosomal translocon binding sites (Halic et al. (2006) *Science* 312, 745-747). The cryo-EM structure of the yeast 80S ribosome in complex with the cricket paralysis virus IRES element at 7.3 Å resolution allowed for the very first time the de-novo modelling of the complete viral IRES RNA (Schüler et al. (2006) *Nature Structural & Molecular Biology* 13, 1092-1096).

The project “Anwenderzentrum” focused on new methods to further exploit the potential of cryo-EM structure determination in the sub-nanometer range, where conformational sub-states as well as different ligand binding states become increasingly crucial. New strategies for particle classification and sorting based on 3D variance analysis and multi-reference alignment allowed us in cooperation with Knud Nierhaus, Paola Fucini (MPIMG) and Christian Spahn (Charité) to identify a new tRNA intermediate of the 70S *E. coli* ribosome during EF4-mediated back-translocation (Connell et al. (2008) *Nature Structural & Molecular Biology* 15, 910-915). In cooperation with Roland Beckmann (LMU Munich) and Thomas A. Steitz (Yale University, USA) we could trace the ordered TnaC nascent chain within the exit tunnel of the ribosome (Seidelt et al. (2009) *Science*, in press). Visualizing eukaryotic ribosome-Sec61 complexes, we could further trace the nascent into the protein conducting channel. These structures provide a new structural basis for co-translational protein translocation, proving that the nascent chain interacts only with a single copy of the Sec61 complex (Becker et al. (2009) *Science*, in press). In Cooperation with Venkatraman Ramakrishnan (MRC-LMB, UK), we could for the very first visualize an antibiotic, kirromycin, in the ternary complex of the *T. thermophilus* 70S ribosome and elongation factor Tu (Schuette et al. (2009) *EMBO J.* 28, 755-765), proving the potential of cryo-EM to address pharmaceutical and medical relevant questions, which so far were out of reach of this technique.

## Current activities and future perspectives

Technical developments in the field of cryo-EM including modern electron microscopes such as the G2 Polara allow structure determination of macromolecular

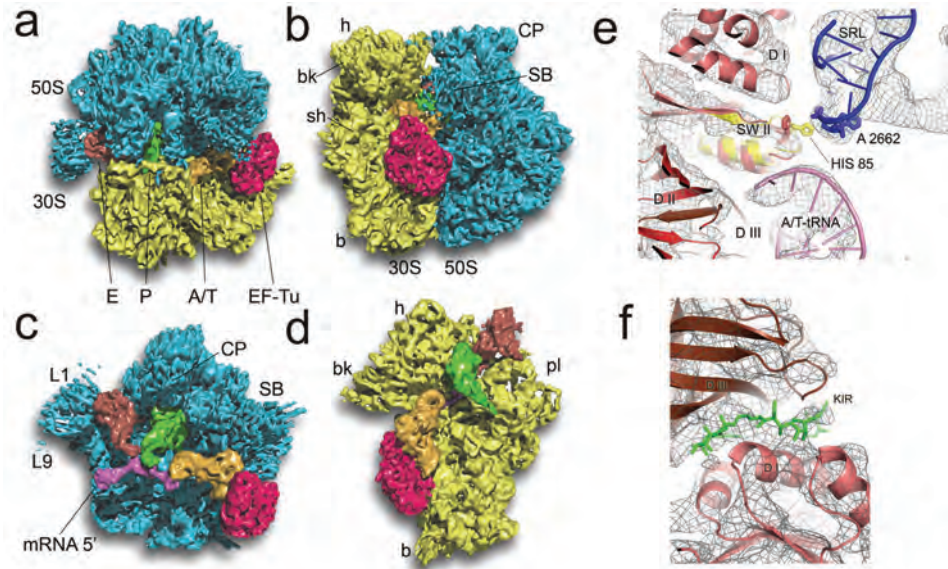


Figure 1: Cryo-EM structure of the 70S ribosome in complex with elongation factor EF-Tu, KPhe-tRNA, GDP and kirromycin shown from the top (a), from the L7/L12 side (b), from the 30S side, with the 30S subunit removed (c) and from the 50S side, with 50S subunit removed (d). The colors distinct the different components: 30S subunit, yellow; 50S subunit, blue; EF-Tu, red; A/T-tRNA, orange; P-tRNA, green; E-tRNA, brown; mRNA, pink. Details of the switch II region (e) and the kirromycin binding site (f) are highlighted (modified from Schuette et al. (2009) EMBO J. 28, 755-765).

complexes at sub-nanometer resolution. However, in the sub-nanometer range, intense image processing techniques such as particle classification and sorting are mandatory to overcome sample heterogeneity due to conformational flexibility. This requires not only more computing power, but also a high degree of automation for both, image acquisition and image processing, to process not only a few hundred thousands but also millions of particles. We currently focus on automated data acquisition using the Legion system (AMI group, The Scripps Research Institute, La Jolla, USA) or Etools (TVIPS) and aim to establish an automated image processing pipeline. Another focus lies on structural analysis of highly dynamic protein modules within the collaborative research centre 740 “From molecules to modules: Organisation and dynamics of functional units in cells”. Here we aim to implement molecular electron tomography as a new tool for initial structure determination and the analysis of macromolecular assemblies with varying stability and/or only temporary associated subunits.

### Internal cooperations

- Knud Nierhaus, Ribosome Group, *Structure determination of ribosomal complexes*;
- Bodo Lange, Department of Vertebrate Genomics, *Isolation and purification of protein complexes*;
- Rudi Lurz, Microscopy Group, *electron microscopy and electron tomography*.

### External cooperations

- Prof. C.M.T. Spahn, Prof. K.P. Hofmann, Charité – Universitätsmedizin Berlin
- Prof. P.-M. Kloetzel, Prof. E. Krüger, Dr. U. Seifert, Charité – Universitätsmedizin Berlin
- Prof. R. Beckmann, Prof. P. Cramer, Genzentrum München, Ludwig-Maximilians-Universität (LMU), München



- Prof. H. Oschkinat, Prof. Bernd Reif, Dr. Christian Freund, Leibniz-Institut für Molekulare Pharmakologie (FMP), Berlin
- Prof. E. Wanker, Max-Delbrück-Centrum für Molekulare Medizin, Berlin
- Prof. N. Grigorieff, Brandeis University, Waltham MA, USA
- Prof. P. Penczek, Dept. of Biochemistry and Molecular Biology, The University of Texas - Houston Medical School, Houston, TX, USA
- Dr. G.F.X. Schertler, MRC Laboratory of Molecular Biology, Cambridge, UK

## General information

### Selected publications

Becker, T., Mandon, E., Bhushan, S., Jarasch, A., Armache, J.-P., Funes, S., Jossinet, F., Gumbart, J. C., Mielke, T., Schulten, K., Westhof, E., Gilmore, R. and Beckmann, R. (2009) *Structure of monomeric yeast and mammalian Sec61 complexes interacting with the translating ribosome*, Science 326:1369-73

Seidelt, B., Innis, C.A., Wilson, D.N., Gartmann, M., Armache, J-P., Trabuco, L.G., Becker, T., Mielke, T., Schulten, K., Steitz, T.A. and Beckmann, R. (2009) *Structural insight into nascent chain-mediated translational stalling*, Science 326:1412-15

Schuette, J.-C., Murphy, F.V. 4th, Kelley, A.C., Giesebrecht, J., Connell, S.R., Loerke, J., Mielke, T., Zhang, W., Penczek, P.A., Ramakrishnan, V. and Spahn, C.M.T. (2009) *GTPase activation of elongation factor EF-Tu by the ribosome during decoding*. EMBO J. 28, 755–765

Connell, S.R., Topf, M., Qin, Y., Wilson, D.N., Mielke, T., Fucini, P., Nierhaus, K.H. and Spahn, C.M.T. (2008) *A novel tRNA-intermediate revealed on the ribosome during EF4 (LepA)-mediated back-translocation*. Nature Structural & Molecular Biology 15, 910-915

Connell, S.R., Takemoto, C., Wilson, D.N., Wang, H., Murayama, K., Terada, T., Shirouzu, M., Rost, M., Schüler, M., Giesebrecht, J., Dabrowski, M., Mielke, T., Fucini, P.M., Yokoyama, S. and Spahn, C.M.T. (2007) *Structural Basis for Interaction of the Ribosome with the Switch Regions of GTP-bound Elongation Factors*. Molecular Cell 25, 751-764

### External funding

DFG, Collaborative research centre 740 (SFB 740): *From molecules to modules: Organisation and dynamics of functional units in cells*, 01/07-12/10

EFRE: *Anwenderzentrum*, 05/ 06 – 11/ 08

EFRE: *Ultrastructure Network*, 06/03 – 06/06

### Teaching activities

Lecture as part of the program of study “Medizinische Physik”, Charité-Universitätsmedizin Berlin.

### Public relations

Practical demonstrations of the cryo-EM facility to the public within the “Long night of Science in Berlin”

Practical demonstrations to several visiting school classes from Germany and Austria

## Miscellaneous Research Groups

### High-throughput Technologies

(Established: 1992)



#### Head

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#### Secretary

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#### Scientists

Dr. Michael Kube\* (since 08/03)  
Dr. Heiner Kuhl\* (since 12/07)  
Dr. Mbaye Tine\* (since 11/08)  
Dr. Bernd Timmermann (02/06-06/08)

#### Tecnicians

Grzegorz Wozniak\* (since 04/02)  
Anett Kühn\* (since 05/07)  
Silvia Schmoger\* (again since 12/07)

Kathrin Huth\* (since 09/08)  
Aydah Sabah (since 11/08)  
Beatrice Baumann\* (again since 01/09)  
Steffen Scheer\* (since 04/09)  
Janina Thiel\* (again since 05/09)  
Dirk Wendland\* (since 09/09)  
Julia Cekanov (since 09/09)  
Sabine Gallert\* (01/09-06/09)  
Katja Heitmann\* (98-04, 08/08-04/09)  
Sabrina Ludwig\* (09/08-03/09)  
Beata Thalke\* (11/08-02/09)  
Thomas Przewieslik\* (07/08-12/08)  
Kristoff Stützner\* (09/06-12/08)  
Christian Warnt\* (07/06-12/08)  
Kathleen Barda\* (09/08-12/08)  
Franka Bläsing\* (08/08-12/08)  
Gabriele Bläss\* (03/02-12/08, part time)  
Christine Lübbert (08/08-12/08, part time)  
Beata Lukaszewska-McGreal\* (06/08-12/08, part time)  
Thilo Miersch\* (03/07-10/08)  
Petra Schupp\* (08/07-10/08)  
Nicole Greiner\* (11/07-08/08)  
Patricia Zysik\* (10/06-06/08)  
Anna Kosiura\* (04/04-06/08)  
Ina Krahnert\* (06/06-04/08)  
Monique Rönick\* (07/04-04/08)  
Steffen Wiechert\* (11/06-03/08)  
Tanja Koppe\* (05/07-03/08)  
Isabelle Kühndahl\* (08/05-08/07)  
Ilona Hauenschild\* (02/06-06/07)  
Patricia Klemmer\* (09/05-03/07)  
Mario Sonntag\* (03/02-01/07)  
Bettina Moser\* (10/01-12/06)

#### Lab Worker

Birol Köysüren\* (since 05/09)

### Scientific overview

The htpt-group is a co-operation partner of the international human genome sequencing project consortium, as described by H. Lehrach (Dept. Vertebrate Genomics), member of various European projects and several national project financed by BMBF, DFG and MPG. The group has established a good infrastructure for large-scale genomic analysis projects such as sequencing, mutation analysis and mass spectrometry, as has been partially described in the section of the service group.

\* externally funded

The recent publications of human chromosomes and of the completed human genome sequence were the ultimate successes of our major effort within the time period since 2000. Important steps on this successful way are the sequencing and final analysis of chromosome 21, the second finished human chromosome, still one of the most accurately analysed one, and our contribution to several regions of the human chromosomes 1, 3, 17, and X. Our next finalised projects along this line are the completed elucidation of chimpanzee chromosome 21, the ortholog to human chromosome 21 and major parts of the X-chromosome. The whole project was organised by a German-Asian consortium (X-chromosome only Germany), wherein MPIMG was responsible for the German part. These results, being summarised within the present report period, are not only important because chimpanzee is our closest relative, it is the first time that a large genomic arrangement, two complete chromosomes of man and chimpanzee, are comparatively analysed. Therefore, not only genes and variations within the coding elements are comparable, but also intronic regions and even more important, promoter elements are accessible for any comparative analysis and elucidation.

In addition, we have been involved in the analysis of model organisms such as mouse (chromosome 2 and 6), rhesus MHC and the complete analysis of the rat MHC (RT1) complex, which plays an important role in infectious diseases. The MHC region belongs to the most densely packed, gene rich regions and although it spans only over a 4 Mbases area, we have identified 220 genes, nearly as many as in the human chromosome 21 region, which is about 34 Mbases large.

Other launched projects concern contributions to the final sequence of chimpanzee chromosomes X and Y, with special interest to Xq28 and regions associated with mental retardation. We are also involved in national and international projects, from bacterial genomes to model organisms like the urochordate *Oikopleura* (M. Kube) and the European Sea bass (H. Kuhl), as listed below (project grants and MPG projects).

The early scientific interest related to *Oikopleura dioica* was focused on questions of systematics, the phenomenon of “marine snow” and of bioluminescence, research in *Oikopleura*'s nervous system, and ecological questions, like the influence on picoplankton. With a genome size of only around 75 Mbases (estimated number of 15.000 genes), smaller than *C. elegans*, and less than half that of *D. melanogaster*, the genome of *Oikopleura dioica* gives the chance for a closer look inside an early chordate genome. In addition, this organism has also other interesting features, making it a key system to understand the functions of human/ vertebrate genome. Within this line of interest is our scientific contribution to various established EU projects, especially our genome project on the European Sea bass, for the NoE **Marine Genomics Europe** (MGE).

*Dicentrarchus labrax* (European Sea bass) is a carnivorous teleost fish (genome size ~620 Mbases) with a natural distribution along the Atlantic and Mediterranean coasts of Europe, where it is a target for established fisheries and aquaculture industries. As a result of its economical importance *D. labrax* has



Figure 1: European Sea bass (*Dicentrarchus labrax*)

been the subject of considerable basic and applied research in the past decade. With the formation of the MGE and the AquaFirst project, European Sea bass research has advanced to the age of genomics. Several EST-sequencing and a BAC end-sequencing project have been started recently at MPIMG, complementing the

whole genome shotgun sequencing as a combined approach of Sanger- and next-generation sequencing-techniques (present status: three chromosome nearly finished and annotated).

In addition, we have managed several NGFN-2 and NGFNplus projects listed below. The project for disease gene identification and systematic re-sequencing of candidate genes of genomic regions of interest should be specifically mentioned as a pre-project, to develop necessary infrastructure for NGFNplus, where data exchange between the clinical partners, also non-NGFN partners, is organized by a Web interface (<http://www.resequencing.mpg.de/>). Finished genomic sequence data are submitted to public data bases or/and are presented on our project Web pages.

### Infrastructure of htpt-group

The htpt-group has established a good infrastructure for large-scale genomic analysis projects such as sequencing, medically related re-sequencing, mutation analysis and mass spectrometry, using most advanced methods and hardware systems. DNA samples are purified, using our patent related magn. beads methods and a novel PEG/org. solvent based precipitation method (Heiner Kuhl). Our angular gel electrophoresis system (patented) is able to visualise 384 sample on a MTP-sized gel and to be automatly processed exploring a capacity of more than 15.000 samples per day. Besides these 'high-throughput highlights', our lab equipment involves all necessary items to run large scale projects, e.g. thermocycler, centrifuges, incubators, protein purification systems and sophisticated computer equipment.

### Selected external cooperations

#### Academic

- MPI Bremen, *various bacterial genomic and metagenomic projects*
- MPI Marburg, *Metagenomics of rice and forest soil*
- J. W. Waagele, Uni. Bonn, *German-Deep Phylogeny-Consortium*
- H. Hofmann, EPFL, Lausanne, Switzerland, *Development of tailored magn. nanoparticles*
- NoE Marine Genomics consortium
- Centre National de Génotypage, France, *SNP-technology*
- B. Gerwick, University of California at San Diego, USA
- D. Gordon, University of Washington, USA
- A. Canario, Universidade do Algarve, Faro, Portugal
- J. Cerda, IRTA CSIC, Barcelona, Spain
- F. Bonhomme, University of Montpellier, France
- P. Prunet, INRA Rennes, France
- E. Lubzens IOLR Haifa, Israel
- A. Kaplan, Hebrew University, Jerusalem, Israel
- B. Wróbel, Polish Academy of Sciences, Warszawa, Poland
- P. Holland, University of Oxford, UK
- L. Bargelloni, University of Padova, Italy
- E. Sarropoulou, HCMR Crete, Greece
- D. Reinhard, University of Fribourg, Switzerland
- F. Nielson, Institute of Marine Research, University of Bergen, Norway
- K.S. Jakobsen, University of Oslo, Norway
- L. Contreras-Porcia, Santiago, Pontificia Universidad Católica de Chile
- M. Thorndyke, Kristineberg Marine Research Station, Fiskebackskil, Sweden
- M. Achtman, University of Cork, Ireland
- D. V. Cantonnel, Universidad de la República, Uruguay
- B. Kloareg, SB Roscoff, France
- L. Lauro, SZN Naples, Italy
- P. Schmid-Hempel ETH Zürich, Switzerland



### Industry

- Bruker Daltonik, Bremen and Leipzig
- micromod Partikeltechnologie GmbH, Rostock
- Scienion AG, Berlin
- Life Technology, Germany

## General information

### Complete list of publications (2006-2009)

#### 2009

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### Awards

Julia Cekanov

- Trainee award of the Max Planck Society 2008
- “Best trainee” award of the Chamber of Commerce and Industry, Berlin, 2008

### PhD thesis

Kuhl, Heiner (03/2008) *Ein Verfahren für BAC-DNA Aufreinigung im Hochdurchsatz zur Genomkartierung von *Dicentrarchus labrax**. PhD Thesis, Technical University of Berlin (supervisor: Richard Reinhardt)

### Student Theses

#### 2009

Alexander Migdoll (01/2009) *Vergleichende Genomanalyse der pflanzenassoziierten Bakterien *A. brassicae* und *A. palmae**. Master Thesis, University of Applied Sciences, Berlin

#### 2008

Katja Heitmann (10/2008) *Entwurf und Entwicklung eines kommerziellen Web-Portals mit Drupal*. University of Applied Sciences, Berlin

Anne Musahl (11/2008) *Vergleichende Analyse mitochondrialer Genome der Gastropoda unter besonderer Berücksichtigung der Pulmonata*. Bachelor Thesis, Humboldt University of Berlin

Steffen Andrew Scheer (12/2008) *SP3: Ein Workflow Management System für die parallele Sequenzdatenverarbeitung*. Diploma Thesis, Humboldt University of Berlin

#### 2006

Mazen Hassan (06/2006) *Einfluss von chemischen und physikalischen Parametern auf die größenfraktionierte DNA Fällung in PEG/Salz-Gemischen*. University of Applied Sciences, Berlin

### Patents

Kalkum M, Müller M, Nordhoff E, Reinhardt R, Eickhoff H, Rauth H.

- *Method and Device for processing extremely small substance quantities*, PCT/EP99/02964
- *Verfahren und Vorrichtung zum Prozessieren von Kleinstsubstanzen*, DE 198 23 719 A1

Rauth, H; Reinhardt, R; Nordhoff, E. *Verfahren zum Anbinden von Nucleinsäuren an eine Festphase*. PCT/EP00/08807, DE, EU, US

Rauth H; Reinhardt R; Nordhoff E: *Verfahren zur Umkehrphasenaufreinigung und -konzentrierung von Peptiden und Proteinen an magnetischen Partikeln*. PCT Nr. 60/175,958

Rauth H; Reinhardt R; Starke A: *Verfahren und Vorrichtung zur Gelelektrophorese*. DE 199 26 985.8

Sauer S; Kepper P; Reinhardt R; Lehrach H: *Method of analyzing nucleic acids with mass spectrometry*. EP1775 348 A1

### External funding

EU: *EURATools* (LSHG-CT-2005-019015), 03/06-08/10

EU: *AquaFirst* (FP6-513692)

EU: ASSEMBLE *Association of European Marine Biological Laboratories* (FP7-227799) 03/09-02/13

EU: LIFECYCLE *Building a biological knowledge-base on fish lifecycles for competitive, sustainable European aquaculture* (FP7-KBBE-2007-2A) 02/09-01/13

BMBF, NGFN Plus: *Verbund: Rnomics of Infectious Diseases* (BMBF 01GS 0805) 09/08-08/11

BMBF: *Infektionsnetz: Resistance and Susceptibility to intestinal infections, WP VI: Sequencing and annotation of selected cloned fragments or isolates relevant to intestinal homeostasis* (BMBF 01KI 0798) 07/09-11/10

DFG: Schwerpunkt: *Deep Phylogeny* SPP 1174

MPG/joint genome project with MPI Bremen: *Microbial Corrosion*

MPG/joint genome project with MPG/SARS Bergen: *Oikopleura, ca. 75 Mbases working draft, BAC-ends*

EU: NoE *Marine Genomics* (EU- FP6-2002-GLOBAL-1 Member of Scientific Steering Committee) 03/04-08/08

BMBF, NGFN-2: SMP-DNA: TP-02 *Chimpanzee-X sequencing* (BMBF 01 GR 0414) 07/05-12/08

BMBF, NGFN-2: SMP-DNA: TP-05 *Ratte*, 01/05-12/06

BMBF, NGFN-2: SMP-DNA: TP-16 *Re-Sequencing* (BMBF 01 GR 0414) 07/05-06/08

BMBF, NGFN-2: SMP-Epigenetic: *Methylom project* (BMBF 01 GR 0497) 05/05-04/08

EU: *STAR-rat A SNP and haplotype map for the rat* (EU LSHG-CT-2004-005235) 01/05-12/06

EU: NEST-Sleeping Beauty *Dormancy of cells and organisms- strategies for survival and preservation* (EU- NESTFP6-2003-NEST-B-1) 09/05-08/08

MPG: *Umweltgenomic* (Institutsübergreifende Projektförderung, MPIs in Berlin, Bremen, Marburg) 05/04-06/09

BMBF: *BioChancePlus* 12/06-05/09

## Teaching activities

### Courses

*Generation of cDNA libraries by Primer Extension*, within the SP1174 Deep Metazoan Phylogeny Project, 2006, 2007

*cDNA libraries by primer extension course*, PhD program at the MPIMG within the Marine Genomics Europe FP6 project, 2006, 2008

*Practical aspects of RNA extraction: "before and after" in cDNA Library construction*, PhD program at CCMAR Faro, Portugal within the Marine Genomics Europe FP6 project, 2007

## Organization of scientific events

Sleeping Beauty Workshop, Harnack House Berlin, 18.-20.05.2008

## Guest scientists

### 2009

Nadav Denekamp, Esther Lubzens, IOLR, Haifa, Israel, 25.01.-01.02.2009

Prof. Dr. Klaus Geider, BBA Dossenheim, Germany, 22.02.-24.02.2009

Caterina Pellizzari, University of Padova, Italy, 02.03.-14.04.2009

Isabel Gehring, JKI Dossenheim, Germany, 09. -28.03.2009

Lars Wöhlbrand, Uni Oldenburg, Germany, 04.-20.05.2009

Duduk, Bojan, Prof. Bertaccini, DiSTA Plant Pathology, Bologna, Italy, 02.-05.07.2009

David Goncalves, Eco-ethology research unit-ISPAL, Lisbon, Portugal, 13.-26.09.2009

### 2008

Tine Mbaye, Université de Montpellier 2, France, 23. -26.05. and 31.07.-31.10.2008 (Aquagenome short visit Research Program)

Sisco Monjo, Barcelona, Spain, 29.05.-18.07.2008

Nadav Denekamp, IOLR, Haifa, Israel, 04.-15.08.2008

Liliana Anjos, Center of Marine Science, University of Algarve, Faro, Portugal, 19.11.-16.12.2008

**2007**

Liliana Anjos, Center of Marine Science,  
University of Algarve, Faro, Portugal,  
14.01.-14.02.2007

Prof. Dr. Klaus Geider, BBA Dossenheim,  
Germany, 18.-23.08.2007

Sónia Massa, CCMAR, Universidade do  
Algarve, Portugal, 18.11.-06.12.2007

Dr. Serkan Uranbey, Ministry of Agriculture  
and Rural Affairs, Ankara, Turkey,  
24.11.-23.12.2007

Paola Gomez, MPI MB Bremen, Ger-  
many, 03.-05.12.2007

**2006**

Annika Busekow, Martina Ackermann,  
Steffi Arend, MPI Plön, Germany, 16.-  
20.01.2006

Prof. Dr. Klaus Geider, BBA Dossen-  
heim, Germany, 13.-15.03.2006

Vasso Terzoglou, HCMR Heraklion,  
Greece, 16.-26.03.2006