Universität Heidelberg – Tokyo Institute of Technology

JOINT WORKSHOP

Life Science and Biological Technology

"Life Science for Better Life"

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International Training Program,
Japan Society for the Promotion of Science (JSPS)
&
Institut für Pharmazie und Molekulare Biotechnologie,
Universität Heidelberg

HEIDELBERG 2010

New Wave of Life Science and Biological Technology

Friday, July 16, 2010
(venue: INF 306, lecture hall 2)

13:00-13:10	**Gert Fricker** Opening remarks
13:10-13:25	**Yasunori Aizawa** Introduction of TITECH and International Training Program @ TITECH
	Chair: Yasunori Aizawa
13:25-13:50	**Makio Tokunaga (Dept. Biological Information, TITECH)** Single molecule imaging in living cells and stochastic feature of molecular interactions
13:50-14:15	**Karl Rohr** (**Dept. Bioinformatics, Uni HD)** Automated Analysis of Biomedical Image Data
14:15-14:40	**Stefan Wölfl (Dept. Pharm. Biology, Uni HD)** Cell based assays for detailed activity profiling of anti-cancer drugs and chemo protective agents
14:40-15:00	BREAK
	Chair: Stefan Wölfl
15:00-15:25	**Junji Hirota (Cent. Biol. Resources and Informatics, TITECH)** Regulation and Evolution of Odorant Receptor Genes
15:25-15:50	**Gert Fricker (Dept. Pharm. Technology and Biopharmacy, UH)** Drug Delivery to the Central Nervous System
15:50-16:15	**Yasunori Aizawa (Cent. Biol. Resources and Informatics, TITECH)** Exploring the Dark Matter of the Human Genome
16:15-16:35	BREAK
	Chair: Junji Hirota
16:35-17:00	**Christian Klein (Dept. Pharm. Chemistry, Uni HD)** Proteases from Dengue and other Flaviviruses as Targets for Drug Discovery
17:00-17:25	**Mitsuo Sekine (Dept. Life Science, TITECH)** New Triplex Forming Oligonucleotides Capable of Binding to DNA Duplexes under Neutral Conditions
17:25-17:50	**Andres Jäschke (Dept. Pharm. Chemistry, Uni HD)** Nucleic Acids as Catalysts and Regulators
17:50-18:00	**Andres Jäschke** Closing remarks
18:30	**BANQUET (venue: Kulturbrauerei)**

Single molecule imaging in living cells and stochastic feature of molecular interactions

Tokyo Institute of Technology
Research Center for Allergy & Immunology, RIKEN
Professor, Makio Tokunaga
(mtoku@bio.titech.ac.jp)

One popular technique is total internal reflection fluorescence (TIRF) microscopy, which is useful for single-molecule visualization, unfortunately, it can only observe targets located near the cell surface. In order to overcome this limitation, we developed a new variant of TIRF, a simple illumination method of fluorescence microscopy for molecular imaging, which is termed highly-inclined and laminated optical sheet (HILO) microscopy. The incident beam through an objective is highly inclined by a large refraction at the surface, and laminated as a thin sheet. Specimens are illuminated with the thin sheet of laser beam. The beam thickness dz of HILO illumination was determined from illumination intensity profiles through the z-direction at the different diameter R.

Illumination by the highly-inclined and thin beam increases image intensity and decreases background intensity, yielding a signal/background ratio about eightfold greater than that of epi-illumination. A high ratio yielded clear single-molecule images and three-dimensional images in cells, enabling one to visualize and quantify molecular dynamics, interactions and kinetics in cells for molecular systems biology.

Experimental probing of a protein-folding energy landscape can be challenging. To overcome the ensemble-averaging barrier, single-molecule experiments have been performed, but energy landscapes comprising multiple intermediates have not yet been defined. We performed mechanical unfolding of staphylococcal nuclease using intermolecular force microscopy, modified AFM with high resolution and feedback control of the positioning. The force dropped vertically just after its peak, and multiple transition states were detected as force peaks. The multiple and stochastic intermediates found in the present study provide new important information on protein folding.

Tokunaga M., Imamoto N., & Sakata-Sogawa K.: Highly inclined thin illumination enables clear single-molecule imaging in cells. *Nature Methods*, **5**, 159-161 (2008)

Yokosuka T., *et al.*: Newly generated T cell receptor microclusters initiate and sustain T cell activation by recruitment of Zap70 and SLP-76. *Nature Immunol.*, **6**, 1253-1262 (2005).

Makio TOKUNAGA, D.Sc.

Professor
Department of Biological Information
Graduate School of Bioscience and Bioengineering
Tokyo Institute of Technology
4259-B-35 Nagatsuta, Yokohama, Japan 226-8501
mtoku@bio.titech.ac.jp

Academic Experience:

INSTITUTION	DEGREES	DATES
University of Tokyo	Ph.D. in Physics	1982-1987
University of Tokyo	B.A. in Physics	1978-1982

RESEARCH APPOINTMENTS HELD:

1992-1997	Group leader, Yanagida Biomotron Project, ERATO, JST
1997-2000	Associate Professor, National Institute of Genetics
2000-2008	Professor, National Institute of Genetics
2008-	Professor, Tokyo Institute of Technology

Automated Analysis of Biomedical Image Data

Karl Rohr

University of Heidelberg, BIOQUANT Center, IPMB,
and German Cancer Research Center (DKFZ)
Dept. Bioinformatics and Functional Genomics, Biomedical Computer Vision Group (BMCV)
(k.rohr (at) **dkfz.de, k.rohr** (at) **uni-hd.de)**

Our research group „Biomedical Computer Vision (BMCV)" develops methods and algorithms for computer-based analysis of biological and medical images, in particular, multi-channel cell microscopy images. One main aim is to derive quantitative information about the position, shape, motion, and function of cellular as well as subcellular structures. The extracted information is important for the quantification of cellular processes and is a prerequisite for computational modelling in systems biology (e.g., reconstruction of molecular pathways). A focus of the group is on advanced image analysis methods for quantifying large scale high-throughput gene knockdown screens (RNAi screens) to study complex cellular processes such as cell division and virus-cell interactions. A challenge with these cell phenotype screens is to cope with the enormous amount of generated image data. Such a large amount of data cannot be analyzed manually but requires efficient and effective automatic computer-based techniques. Main research topics within our group are segmentation and quantification of high-throughput cellular screens, tracking and motion analysis of cells and virus particles, registration of live cell microscopy images, as well as segmentation of vessels and registration of medical tomographic images. The group closely collaborates with experimental groups and modeling groups.

Harder N, Mora-Bermúdez F, Godinez WJ, A. Wünsche, Eils R, Ellenberg J, and Rohr K. (2009) Automatic Analysis of Dividing Cells in Live Cell Movies to Detect Mitotic Delays and Correlate Phenotypes in Time, *Genome Research* 19:11, 2113-2124

Godinez WJ, Lampe M, Wörz S, Müller B, Eils R, Rohr K. (2009) Deterministic and Probabilistic Approaches for Tracking Virus Particles in Time-lapse Fluorescence Microscopy Image Sequences, *Medical Image Analysis* 13: 325-342

Ivanchenko S, Godinez WJ, Lampe M, Kräusslich HG, Eils R, Rohr K, Bräuchle C, Müller B, and Lamb DC. (2009) Dynamics of HIV-1 Assembly and Release, *PLoS Pathogens* 5:11, 2009

Matula P, Kumar A, Wörz I, Erfle H, Bartenschlager R, Eils R, Rohr K. (2009). Single-cell-based image analysis of high-throughput cell array screens for quantification of viral infection. *Cytometry A*, 75A:309-318

Yang S, Köhler D, Teller K, Cremer T, Baccon PL, Heard E, Eils R, Rohr K. (2008) Non-rigid registration of 3D multi-channel microscopy images of cell nuclei, *IEEE Transactions on Image Processing* 17:4, 493-499

KARL ROHR

Head of Biomedical Computer Vision Group
Associate Professor

University of Heidelberg, BIOQUANT Center, IPMB,
and German Cancer Research Center (DKFZ)
Dept. Bioinformatics and Functional Genomics
Biomedical Computer Vision Group
Im Neuenheimer Feld 267
69120 Heidelberg
Germany

Email: k.rohr (at) dkfz.de, k.rohr (at) uni-hd.de
Phone: +49 6221 54 51 298
http://www.bioquant.uni-heidelberg.de/bmcv

Short CV:

1994	PhD in Computer Science, University of Hamburg, Germany
1999	Habilitation in Computer Science, University of Hamburg, Germany
1999	Research stay, Harvard Medical School, Boston/MA, USA
2000-2004	Associate Professor, International University in Germany, Head of the Computer Vision & Graphics Group
Since 2004	Head of the Biomedical Computer Vision Group, Associate Professor, University of Heidelberg and German Cancer Research Center (DKFZ)
2007-2010	Guest Professor, International University in Germany
Since 2007	Member of the Excellence Cluster CellNetworks, University of Heidelberg

Cell based assays for detailed activity profiling of anti-cancer drugs and chemo protective agents

Stefan Wölfl, Igor Kitanovic, Hamed Alborzinia, Suzan Can, Pavlo Holenya, Ana Kitanovic, Elke Lederer

Institut für Pharmazie und Molekulare Biotechnologie, Universität Heidelberg

To understand the complex biological activity of potential new drug candiadates as well as the biological activity of dietary ingredients, that could be beneficial for health, we established a comprehensive cell based analytical work flow. We use our analytical systems for in detail analysis of the biological activity of single small molecules, as well as of complex mixtures which are only partially well defined, typically for functional active compounds found in the ever day diet. Starting from very basic cell proliferation and viability assays in a wide range of cell lines to establishing basic effects on cellular proliferation and general toxicity, we continue with assays of increased complexity that lead to high content analysis of biologically activities to describe the biological responses and long term effects of the studied compounds in more detail. To make our protocol routinely available we established a defined work flow of cell based assays that enables as to obtain good descriptions of basic biological activities, does dependence and time scale of the cellular response. Based on this data subsequent detailed analytical procedures are added to identify potential target molecules and target mechanisms. The latter include genome wide gene expression profiling, phospo-protein micro arrays as well as genetic and biochemical assays.

A central part of our approach is the online analysis of the metabolic response of cells to drug treatment using a cell chip biosensor system (BIONAS), which we optimized for the analysis with a wide range of cell lines. With this system we can monitor in real time the response of cells to drugs monitoring three important parameters very descriptive of cellular activity:

- respiration
- glycolytic activity
- cell morphology.

With this system we can establish the time scale of the biological responses, which is the basis to select time points for further (more expensive and time consuming) in detail analysis. In addition this system allows to clearly identify and differentiate between persistent and transient effects on cells.

PUBLICATIONS (Selected important publications since 2008):

Bonowski F, Kitanovic A, Ruoff P, Holzwarth J, Kitanovic I, Bui VN, Lederer E, Wölfl S. Computer controlled automated assay for comprehensive studies of enzyme kinetic parameters. **PLoS One.** 2010 May 19;5(5):e10727.

Kitanovic A, Walther T, Loret MO, Holzwarth J, Bonowski F, Kitanovic I, Bui VN, François JM, Wolfl S. Metabolic response to MMS-mediated DNA damage in S.cerevisiae is dependent on glucose concentration in the medium. **FEMS Yeast Research** 2009 9(4):535-51. PMID: 19341380

Willaredt MA, Hasenpusch-Theil K, Gardner HA, Kitanovic I, Hirschfeld-Warneken VC, Gojak CP, Gorgas K, Bradford CL, Spatz J, Wölfl S, Theil T, Tucker KL. A crucial role for primary cilia in cortical morphogenesis. **J Neurosci**. 2008 28(48):12887-900.

Schatzschneider U, Niesel J, Ott I, Gust R, Alborzinia H, Wölfl S. Cellular uptake, cytotoxicity, and metabolic profiling of human cancer cells treated with ruthenium(II) polypyridyl complexes [Ru(bpy)2(N--N)]Cl2 with N--N=bpy, phen, dpq, dppz, and dppn. **ChemMedChem.** 2008 3(7):1104-9.

Prof. Dr. Stefan Wölfl
Institute for Pharmacy and Molecular Biotechnology
Department of Biology, AG Bioanalytis and Molecular Biology
Ruprecht-Karls-Universität Heidelberg
69120 Heidelberg, Germany

Phone: +49-(0)6221-54 4878
Fax: +49-(0)6221-56 4884
E-mail: wolfl@uni-hd.de

Born: 6 May 1959 München

Academic Education and Degrees

INSTITUTION	DEGREES	DATES
Friedrich Schiller Universität Jena	Habilitation in Molecular Biology	1999
Freie Universität Berlin	PhD in Biochemistry	1990
Practical Year as Pharmacist (Public Pharmacy and Pharmaceutical Industry)		1984-1985
Freie Universität Berlin	Student of Pharmacy	1981-1984
Universität München	Student of Physics	1979-1980

RESEARCH APPOINTMENTS HELD

2003 - present	Professor Pharmaceutical Biology, Bioanalytics and Molecular Biology, IPMB, Ruprecht-Karls-Universität Heidelberg
2000-2003	Head Research Group Molecular Biology, Klinik für Innere Medizin, Friedrich-Schiller-Universität Jena
1994-2000	Junior Group Leader, Hans-Knöll-Institut für Naturstoffforschung Jena
1990-1994	PostDoc, Massachussets Institute of Technology, Cambridge, USA (Advisor: Alexander Rich)
1986-1990	Research Assistant, Freie Universitat Berlin (Advisor: Burghardt Wittig),

Other professional activities

1998/99	Thüringer-Forschungspreis 1998
1998	Cofounder: Clondiag Chip Technologies GmbH Jena
1990	“Fachapotheker für Offizin Pharamzie”
1985-2000	Pharmacist in Public Pharmacy (since 1986 part time)

Regulation and Evolution of Odorant Receptor Genes

Tokyo Institute of Technology
Associate Professor, Junji Hirota
(jhirota@bio.titech.ac.jp)

The olfactory system of mammals is capable of detecting millions of different types of chemicals in the environment. Olfactory sensory neurons (OSNs), the primary sensory neurons in the olfactory system, initiate the sense of smell by detecting odorants through odorant receptors (ORs). These ORs are G-protein coupled receptors with a putative seven-transmembrane domain structure and belong to the largest gene superfamily present in any genome analyzed so far. In mouse, ~1400 OR genes have been identified from the genomic sequence. According to the phylogenetic analysis, odorant receptor (OR) genes can be classified into two types: fish-like class I OR genes and terrestrial-specific class II OR genes. Class I ORs are phylogeneticaly more ancient and resemble the family of ORs first reported in fish. There are ~155 Class I OR genes in the mouse genome, all of which are located in a single cluster on Chromosome 7. By contrast, Class II OR genes, the terrestrial-specific OR genes, are distributed throughout the mouse genome. An OSN most likely expresses a single functional allele of a single OR gene from a large repertoire of receptor genes. This unique mode of gene expression is similar to the antigen receptor gene expression in the immune system, but the mechanisms underlying this feature of 'singular' OR gene expression are not understood. In this talk, recent progresses to understand OR gene regulation will be discussed.

[1] Hirota J, Omura M, Mombaerts P. Molecular and Cellular Neuroscience (2007), 34, 679-688
[2] Rothman A, Feinstein P, Hirota J, Mombaerts P. Molecular and Cellular Neuroscience (2005), 28, 535-548
[3] Hirota J, Mombaerts P. Proceeding of National Academy of Science, USA (2004), 101, 8751-8755
[4] Ishii T, Hirota J, Mombaerts P. Current Biology, (2003), 13, 394-400

JUNJI HIROTA

Associate Professor
Tokyo Institute of Technology
Center for Biological Resources and Informatics
jhirota@bio.titech.ac.jp
4259 Nagtsuda Rm. B1B2C-201 (Box# B63)
Midori Yokohama 226-8501, Japan
+81-45-924-5830 (TEL)
+81-45-924-5832 (FAX)

Academic Experience:

INSTITUTION	DEGREES	DATES
Tokyo Institute of Technology	Dr. Eng.	1992-1995
Tokyo Institute of Technology	M. Eng.	1990-1992
Tokyo Institute of Technology	B. Eng.	1986-1990

RESEARCH APPOINTMENTS HELD:

- Associate Professor: Center for Biological Resources and Informatics. Tokyo Institute of Technology (2008-present).
- Visiting Researcher: RIKEN Brain Science Intitiute (2008-present).
- Associate Professor, Osaka Prefecture University, Department of Biological Science, Graduate School of Science (2005-2008).
- Post-Doctoral fellow: The Rockefeller University, Professor Peter Mombaerts (2000-2005).
- Long-Term Fellow, Human Frontier Science Program (2000-2003).
- Research Associate of Mikoshiba Calcio Signal Net Project, ERATO, Japan Science and Technology Agency, Professor Katsuhiko Mikoshiba (1995-2000)

DRUG DELIVERY TO THE CENTRAL NERVOUS SYSTEM

Gert Fricker

University of Heidelberg, Institute of Pharmacy and Molecular Biotechnology,
Im Neuenheimer Feld 366, 69120 Heidelberg,
email: gert.fricker@uni-hd.de

The main research area of our group is the blood brain barrier. Most drugs or drug candidates do not reach the central nervous system, because they are not able to cross this barrier, which is formed by brain capillary endothelial cells. These cells are connected by extremely tight junctions and in addition they are equipped with a battery of potent export proteins recognizing a multitude of completely diverse substrates and thus making effective drug delivery to the CNS extremely difficult. An introduction into the anatomical and functional features of the blood-brain barrier will be given as well as into strategies to overcome it.

The blockade of export proteins has been proven to be a useful approach to delivery cytostatics like Taxol to the CNS for the treatment of glioblastoma. In vivo studies in a nude mice model with orthotopically implanted human brain tumors showed a dramatic decrease of tumor size after inhibition of p-glycoprotein in the blood-brain barrier [1].

In addition several technical strategies have been exploited to deliver drugs to the brain, e.g., the use of vector-coupled liposomes or surface modified and biologically degradable nanoparticles, which have been promising due to their potential in encapsulating drugs, their ability to escape p-glycoprotein in the blood brain barrier and to target the brain. Polysorbate-80 coated and drug loaded poly(n-butylcyano-acrylate) nanoparticles have been shown to exert a significant antitumoral efficacy in a rat glioma model suggesting that they are able to release their content beyond the blood brain barrier. It has been proposed that apolipoproteins get adsorbed on the surface of the nanoparticles in human plasma. Nanoparticles coated with such ligands thereby mimic lipoprotein particles and thus may be endocytosed via a lipoprotein receptor-mediated mechanism transporting the loaded drug preferentially into the brain. The permeation of such particles across the blood brain barrier was visualized by fluorescence labeling and subsequent confocal laser scanning microscopy [2]. These studies gave clear evidence of a localization of particle-associated fluorescence within microvessel endothelial cells as well as beyond the brain capillaries. Thus, it can be stated that brain capillary endothelial cells are able to internalize surface modified nanoparticles and to process their content across the barrier in vivo.

The present data indicate that colloidal polymeric systems represent a promising strategy to overcome the blood brain barrier. However, further efforts are required to clarify in more detail the fate of the polymer after drug release as well as clinical efficacy of the system.

1. Fellner et al., Transport of Paclitaxel (Taxol) across the blood brain barrier in vitro and in vivo. J. Clin. Invest., 110, 1309-1318 (2002)
2. Reimold et al., Delivery of nanoparticles to the brain detected by fluorescence microscopy, European Journal of Pharmaceutics and Biopharmaceutics 70, 627–632 (2008)

GERT FRICKER

Professor
Institute of Pharmacy and Molecular Biotechnology
INF 366, Heidelberg
gert.fricker@uni-hd.de

Academic Experience

INSTITUTION	DEGREES	DATES
Freiburg University	PhD in Chemistry	1981-1986
Freiburg University	Study of Chemistry and Medicine	1975-1986

RESEARCH APPOINTMENTS HELD

2002-today Director at the Institute of Pharmacy and Molecular Biotechnology

1995-today Professor for Pharmaceutical Technology and Biopharmacy, Heidelberg University

1993 Habilitation in Experimental Medicine, Freiburg Unviersity

1988-1995 Research Scientist, Sandoz Pharma AG, Basle Switzerland

1986-1988 Postdoctoral Fellow, University Hospital Zurich Switzerland

1981-1986 Research Assistant, University of Freiburg

Exploring the Dark Matter of the Human Genome

Tokyo Institute of Technology
Associate Professor, Yasunori Aizawa
(yaizawa@bio.titech.ac.jp)

Our group is currently trying to elucidate functional significance of two of the major aspects of the human genome that we are still far away from full understanding of; **long "noncoding" RNAs** and **retrotransposons**.

Recent mammalian transcriptome analyses uncovered thousands of novel transcripts of unknown function (TUFs). Low protein-coding potentials of TUFs encourage biologists to assume that TUFs underlie vital intracellular functions as noncoding RNAs, although the genuine biological significance mostly remains uncharacterized. To test this assumption, by using ex vivo differentiation protocol for human stem cells, we first screened for human TUFs whose expression levels were controlled in the differentiation process[1]. The subsequent structural and functional characterization led to serendipitous finding that two of the TUFs we identified are not noncoding but indeed encode novel and "peptide-like" small proteins. TUFs may contribute to a hidden layer of proteomics in mammalian biology.

In another research direction, we are studying biological and medical impacts of retrotransposon polymorphism (REP) in the human genome. Like single nucleotide polymorphism (SNP) and copy number polymorphism (CNP), REP is one of the major sources that induce structural variants in the human genome, although the biological and medical implication has not been assessed. One of the main reasons was lack of methodology for detecting REP locations in a genome-wide fashion. We thus set up an inverse PCR-based system to identify REP loci comprehensively in the human genome by using deep-sequencing technology. Some of the identified REP loci provide transcriptional regulatory elements originated from retrotransposons to neighboring genes, which modifies gene structures only in particular individuals. Our approach will open a new avenue to explore genomic causes of phenotypic variation among humans.

[1] *Nucleic Acids Res. 37*, 4987-5000 **2009**

YASUNORI AIZAWA

Associate Professor
Tokyo Institute of Technology
Center for Biological Resources and Informatics
yaizawa@bio.titech.ac.jp
4259 Nagatsuta Rm. B-714 (Post B64)
Midori Yokohama 226-8501, Japan
+81-45-924-5787 (TEL & FAX)

Academic Experience:

INSTITUTION	DEGREES	DATES
Kyoto University	Ph.D. in Phermaceutical Science	1994-1999
Kyoto University	B.A. in Phermaceutical Science	1990-1994

RESEARCH APPOINTMENTS HELD:
- Associate Professor: Center for Biological Resources and Informatics. Tokyo Institute of Technology (2005-present).
- Visiting Scholar: National Institute of Advanced Science and Technology (2005-present).
- Post-Doctoral fellowship with Professor Jef D. Boeke: Johns Hopkins University (2002-2005).
- Post-Doctoral fellowship with Professor Anna Marie Pyle: Columbia University (1999-2002).
- Graduate research with Professor Yukio Sugiura and Professor Takashi Morii.: Kyoto University (1990-1994).

Proteases from Dengue and other Flaviviruses as Targets for Drug Discovery

Prof. Dr. C. Klein
Medicinal Chemistry
Institute of Pharmacy and Molecular Biotechnology IPMB

The Dengue (DEN) virus and other Flaviviruses like West Nile virus (WNV) and Yellow fever are emerging infectious diseases that currently spread into the temperate zones. There are currently no antiviral therapies or vaccinations for Dengue virus available. The aim of the project is to design and discover small molecular drugs as novel therapeutical interventions for these diseases. Our efforts are targeted on the proteases of these viruses, since these are essential for viral replication and related infections such as HCV can effectively treated with protease inhibitors.

Our first steps were to establish a high-throughput assay for DEN protease, which included high-yield heterologous expression of the protein in a soluble and active form, establishment and fine-tuning of an assay procedure, and application of the assay for the screening of compound collections. In the meantime, the DEN protease and the assay procedure from our group are used by several groups around the world to screen for inhibitors.

We developed novel lead compounds for DEN protease inhibitors by a targeted screening of aldehydes as serine-reactive, electrophilic fragments. The "hit" compound from this screening was subsequently converted to a more drug-like ketoamide lead, for which we generated a comprehensive structure-activity (SAR) dataset. Various other functional groups are currently evaluated as serine-reactive fragments with "tuned" electrophilicity. The most promising compounds from this series are studied in a cell-culture-model of Dengue infection.

Simultaneously, work is under way to obtain various other flaviviral proteases, in particular from West Nile Virus and FSME virus, and to establish screening procedures for these enzymes. We also pursue a host factor that is linked to flaviviral infections as a novel target. Rational mutagenesis studies on the DEN protease have allowed us to identify critical residues for the intramolecular architecture of the DEN replication complex and to generate hyper-active protease mutants. These results are used to identify and target (allosteric) binding sites for small molecular inhibitors that are distinct from the catalytic center.

Literature: Steuer, C., Heinonen, K., Kattner, L., Klein, C.D.* Optimization of Assay Conditions for Dengue Virus Protease: Effect of Various Polyols and Non-Ionic Detergents. J. Biomol. Screening, 2009, 14, 1102-1108.

Prof. Dr. C. Klein
Medicinal Chemistry
Institute of Pharmacy and Molecular Biotechnology IPMB
University of Heidelberg, INF 364
D-69120 Heidelberg
Germany

c.klein@uni-heidelberg.de
Phone: ++49-6221-54-4875
FAX : ++49-6221-54-6430

Academic training and research appointments:

1990-1994	Undergraduate Studies in Pharmacy, Universität Bonn and ETH Zürich
1997-2000	Ph.D. Studies in Medicinal Chemistry, Universität Bonn, with Prof. Holzgrabe
1997-1998	Research Fellow at the Dept. of Medicinal Chemistry, University of Illinois, Chicago, USA, with Prof. Hopfinger
2000	Post-Doc with Prof. Hartmann, Universität Saarbrücken
2001-2003	Post-Doc with Prof. Folkers, ETH Zürich
2003-2007	Junior Group Leader at Universität Saarbrücken
2007	Offers of full professorships at Universität Leipzig and U. Heidelberg
since 2007	Professor of Medicinal Chemistry at Universität Heidelberg

New Triplex Forming Oligonucleotides Capable of Binding to DNA Duplexes under Neutral Conditions

Tokyo Institute of Technology
Professor, Mitsuo Sekine
(msekine@bio.titech.ac.jp)

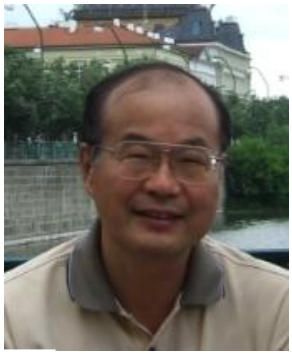
In our research group, we have recently studied a variety of methods for the synthesis of functionalized oligonucleotide derivatives directed toward development of nucleic acid drugs and probes for gene therapy and detection. In this paper, we report a new promising approach to the "anti-gene strategy" that has been long expected to be used as an effective tool for more straightforward gene silencing than the antisense and RNAi strategies.

The most serious problem facing this old but still unrealized approach is how to create oligonucleotide derivatives that can bind to DNA duplexes under neutral conditions. Formation of triplexes comprising of naturally occurring nucleobases is limited only under acidic conditions since it requires protonation of the cytosine base to bind the Hoogsteen hydrogen bonding site of G-C base pairs. A number of studies have been reported to produce new triplex forming oligonucleotides using modified nucleobases. However, the binding affinities of these precedents for DNA duplexes were insufficient and multi-step reactions were required for the synthesis of modified nucleoside 3'-phosphoramidite building blocks. In our method, two thiolated nucleobases, 2-thiothymine and 8-thioxoadenine were designed and used. Since the former base has been used as a modified base that could recognize the adenine base more precisely than the unmodified thymine base that tends to bind mistakenly to the guanine base. Particularly, the 2-thiothymine proved to exhibit significant stacking with nearby 5'-upstream nucleobases to stabilize the whole structure of triplexes.[1] 8-thioxoadenine was selected since it has a similar stacking effect and the conformation of the glycosyl bond is fixed to be in a *syn* form so that this base cannot bind to the complementary thymine. Interestingly, arrangement of these thiolated nucleobases in a consecutive base sequence resulted in significant stabilization of triplexes at pH 7.0.[2]

[1] *Nucleic Acids Res. 36*, 1952-1964, **2008**

[2] *Org. Lett. 11*, 605-608, **2009**

MITSUO SEKINE



Professor
Tokyo Institute of Technology
Department of Life Science, Graduate School of Bioscience and Biotechnology
msekine@bio.titech.ac.jp
Rm. J2-804 (Post J2-12)
4259 Nagatsuta Midori Yokohama 226-8501, Japan
+81-45-924-5706 (TEL)
+81-45-924-5772 (Fax)

Academic Experience:

INSTITUTION	DEGREES	DATES
Tokyo Institute of Technology	Ph.D. in Chemistry	1974-1977
Tokyo Institute of Technology	M.S. in Chemistry	1972-1974
Tokyo Institute of Technology	B.S. in Chemistry	1968-1972

RESEARCH APPOINTMENTS HELD:

- Professor: Department of Life Science, Faculty of Bioscience and Biotechnology, Tokyo Institute of Technology (1998-present)
- Associate Professor of Department of Life Science, Faculty of Bioscience and Biotechnology, Tokyo Institute of Technology (1990-1998)
- Associate Professor: Department of Life Science, Faculty of Science, Tokyo Institute of Technology (1989-1990)
- Lecturer: Department of Environmental and Chemical Engineering, Graduate School at Nagatsuta, Tokyo Institute of Technology (1988-1989)
- Research Associate: Department of Life Science, Graduate School at Nagatsuta (1977-1988)

Nucleic Acids as Catalysts and Regulators

Heidelberg University
Prof. Dr. Andres Jäschke
(jaeschke@uni-hd.de)

Our laboratory utilizes nucleic acids as tools in catalysis research, nanotechnology and pharmaceutical chemistry. Our work combines organic synthesis with molecular biology, combinatorial chemistry, enzymology and modern bioanalytical methods. Our research centers around the catalytic, templating and regulatory properties of RNA.

We have isolated from combinatorial libraries RNA molecules that catalyze C-C bond formation by Diels-Alder reaction. These catalysts show remarkable stereo-, regio- and chemoselectivities. We could demonstrate true catalysis of bimolecular reactions and enantioselective bond formation. Recently, we could solve in collaboration the structure of this ribozyme by X-ray crystallography. The mechanism and kinetics of the reaction are under investigation using various chemical, biochemical und physical techniques. Currently, this is the most-characterized artificial ribozyme known, and reveals fundamental insight into how RNA achieves catalysis. Furthermore, we are attempting to isolate RNA catalysts for other organic reactions.

To expand the catalytic repertoire of nucleic acids, we have developed hybrid catalysts that consist of an oligonucleotide and a transition metal complex. Iridium-catalyzed allylic substitutions were demonstrated to be accelerated by these catalysts, an the stereoselectivity of the reaction was modulated by the oligonucleotide.

In another research area we trigger molecular (e.g., catalytic) functions by external signals, preferably in a reversible manner. These signals may be effector molecules, light, or electric fields. We have developed ribozymes that are regulated by various effector molecules (theophylline, tobramycin, mRNA) and can be utilized for the sensitive detection of effectors from biological samples.

Finally, a team within our lab works on RNA regulation. During the last few years, many new functions of RNA have been discovered; including siRNA, miRNA, and riboswitches. Our laboratory develops strategies to directly isolate RNAs that bind small metabolites, and to elucidate their funtions.

Recent publications:

J. Am. Chem. Soc. **2010** (131), 2646-2654.
J. Am. Chem. Soc. **2010** (131), 8372–8377.
J. Am. Chem. Soc. **2010** (131), 8846-8847.
Angew. Chem. Int. Ed. **2009** (48) 4426-4429.
J. Am. Chem. Soc. **2009** (131) 6261-6270.
J. Am. Chem. Soc. **2008** (130) 8594-8595.

Andres Jäschke

Professor & Director
Heidelberg University
Institute of Pharmacy and Molecular Biotechnology
jaeschke@uni-hd.de
Im Neuenheimer Feld 364
69120 Heidelberg, Germany
+49-6221-54 48 53

Academic Experience:

INSTITUTION	DEGREES	DATES
Free University Berlin	Habilitation	1995-2000
Humboldt University Berlin	Ph.D. in Org. Chemistry	1989-1993
Humboldt University Berlin	Diplom in Chemistry	1984-1988

RESEARCH APPOINTMENTS HELD:
- Professor & Director: Institute of Pharmacy and Molecular Biotechnology. Heidelberg University (2002-present).
- Principal Investigator: Institute of Biochemistry, Free University Berlin (1995-2002).
- Post-Doctoral fellowship with Professor Alexander Rich: Massachussetts Institute of Technology (1993-1995).
- Graduate research with Professor Dieter Cech: Humboldt University Berlin (1989-1993).