11th Student Symposium on Molecular Medicine

Novel Pharmaceutical Approaches – From Bench to Bedside

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Morning Session

09:00	**Introduction**	
09:05 - 09:50	**Hartmut Geiger** *Institute of Molecular Medicine and Stem Cell Aging, Ulm University*	Aging and Rejuvenation of Somatic Stem Cells
	Amanda Amoah *Institute of Molecular Medicine and Stem Cell Aging, Ulm University*	Age-related changes occurring in human HSCs
09:50 - 10:35	**Jennifer Altomonte** *Clinic for internal Medicine II, Klinikum rechts der Isar, TU Munich*	Oncolytic viruses as innovative, multimodal cancer therapeutics
	Teresa Krabbe *Clinic for internal Medicine II, Klinikum rechts der Isar, TU Munich*	Adoptive T cell therapy as a complimentary immunotherapeutic and delivery system for an improved oncolytic virus platform
10:35 - 11:00	**Coffee Break**	
11:00 - 11:45	**Franz Theuring** *Institute for Pharmacology and Toxicology, Charité Berlin*	Treatment of Alzheimer's Disease by employing Tau-Aggregation-Inhibitors – Being a Tauist in the Land of Amyloid
	Nora Lemke *Institute for Pharmacology and Toxicology, Charité Berlin*	Characterization of Tau-protein as a biomarker of Alzheimer's disease
11:45 - 12:15	**Student Representatives** *Ulm University*	Master Programmes & International Graduate School in Molecular Medicine
12:15 - 13:30	**Lunch Break incl. Poster Session**	

Afternoon Session

12:45 - 13:30	**Poster Session**	
13:30 -14:15	**Matthias Peipp** *Section for Stem Cell and Immunotherapy, University Hospital Schleswig-Holstein, Kiel*	Antibody Engineering - Tailor-made next generation antibodies in cancer immunotherapy
	Sebastian Lutz *Section for Stem Cell and Immunotherapy, University Hospital Schleswig-Holstein, Kiel*	Activating NK Cell Receptors as Novel Trigger Molecules for Bispecific Antibody-Derivatives to Enhance Anti-Tumor NK cell Responses
14:15 - 14:25	**Poster Prize Award Ceremony**	
14:25 - 15:00	**Coffee Break**	
15:00 - 15:45	**Johann Schredelseker** *Walter-Straub-Institute for Pharmacology and Toxicology, LMU Munich*	Activation of mitochondrial VDAC2 for the treatment of cardiac arrhythmia
	Fabiola Wilting *Walter-Straub-Institute for Pharmacology and Toxicology, LMU Munich*	Pharmacological mode of action of efsevin on VDAC2
15:45 - 16:30	**Ralph Neumüller** *Boehringer Ingelheim, Vienna*	Targeting oncogenic gene transcription
16:30 - 16:35	**Closing Remarks**	

Abstracts

Aging and Rejuvenation of Somatic Stem Cells

Prof. Dr. Hartmut Geiger
Institute of Molecular Medicine and Stem Cell Aging, Ulm University

Stem cell function declines upon aging. Aging of for example hematopoietic stem cells (HSCs) is associated with impaired blood cell formation in the elderly. The process of blood cell formation is called hematopoiesis. The cellular molecular mechanisms of stem cell aging are still poorly understood, precluding rational approaches to ameliorate stem cell aging and thus tissue attrition with age. Hematopoietic stem cell (HSC) function declines upon aging.
We demonstrate a critical mechanistic role of the activity of the small RhoGTPase Cdc42 in HSC aging and identify it as a target to pharmacologically rejuvenate age-associated phenotypes of LT-HSCs via inhibition of Cdc42 activity.Cytoplasmatic as well as nuclear polarity in young and aged LT-HSCs with respect to the proteins Cdc42, tubulin and AcH4K16 is regulated by Cdc42 activity (aged LT-HSCs are apolar).
We also demonstrate an unexpected shift from canonical to non-canonical Wnt signalling due to elevated expression of Wnt5a in aged HSCs that causes activation of Cdc42 upon aging.
Additional novel data indicate that apolarity correlates with the mode of stem cell division, so that upon aging HSCs generate more frequently daughter cells similar to each other through a symmeric mode of division.

Age-related Changes occuring in Human HSCs

Amanda Amoah, M.Sc.
Institute of Molecular Medicine and Stem Cell Aging, Ulm University

Hematopoietic stem cells (HSC) are crucial for maintaining blood homeostasis throughout life. They are described as multipotent because they have the ability to self-renew, thereby sustaining the stem cell pool, and to differentiate into any mature cell type of the blood. Recent findings using mouse models, however, show distinct functional and phenotypic changes that occur in HSCs upon aging, which are reversible.
To explore the prospects of rejuvenation, we sought to characterize aging-induced changes in human HSCs. Our results show that although the number of CD34+ cells in low density bone marrow remain unchanged, the number of multipotent hematopoietic stem and progenitor cells (CD34 + CD38 -) and the number of HSCs (CD34 + CD38 - CD90 +) increase upon aging.
Furthermore, we observed a delay in aged HSCs in their response to cytokine stimulation ex vivo irrespective of cytokine cocktail and oxygen conditions. Similar to murine HSCs, we observe an increase in the amount of active Cdc42 relative to the total Cdc42 protein upon aging and a significant decrease in the frequency of cells that present with a polar distribution of tubulin and Cdc42 in the cytoplasm and Ac-H 4 K 16 in the nucleus. Collectively, these findings identify functional and phenotypic changes occurring in human HSCs upon aging.

Oncolytic viruses as innovative, multimodal cancer therapeutics

PD Dr. Jennifer Altomonte
Clinic for internal Medicine II, Klinikum rechts der Isar, TU Munich

In recent years, great progress has been made in the development of immune-based cancer therapies, in which the patient's own immune system is harnessed to fight against the invading cancer. Although immunotherapies have the potential to offer safe, systemic, and long-lasting tumor responses, the tolerogenic microenvironment of most tumors is a challenge that must be addressed in order to fully exploit the therapeutic capacity of this approach.
Oncolytic viruses offer a novel treatment option, due to their elegant multimodal mechanism of action. Their inherent ability to specifically target and lyse tumor cells provides an efficient tumor debulking function. In addition, oncolytic viruses offer the potential to mediate changes in the tumor microenvironment to break immune tolerance and stimulate potent immune responses directed against uninfected tumor cells and distant metastases.
Oncolytic viruses therefore represent a newly evolving aspect of cancer immunotherapy, and are under intense development as rationally designed combination therapies. Viral engineering technology allows us to customize oncolytic vectors for improved safety, enhanced efficacy and immune stimulation, or noninvasive imaging of viral biodistribution through the expression of reporter genes. An overview of the field of oncolytic virus therapy will be presented, with an emphasis on viro-immunotherapeutic stages.

Adoptive T-cell therapy as a complimentary immunotherapeutic and delivery system for an improved oncolytic virus platform

Teresa Krabbe, M.Sc.
Clinic for internal Medicine II, Klinikum rechts der Isar, TU Munich

Vesicular stomatitis virus (VSV) is an attractive oncolytic virotherapy platform due to its potent tumor cell killing and its potential to induce antitumor immune responses; however, the clinical translation of oncolytic VSV faces numerous challenges. As for most oncolytic viruses, inefficient systemic delivery remains a major hurdle. Wild type VSV is also known to cause neurotoxicity, a severe side effect. To address systemic delivery we combined VSV with adoptively transferred T cell receptor transgenic T cells (TCR T cells) as carrier cells.
We demonstrate that CD8+ T central memory cells (CD8+ T cm) are efficient virus carriers that support intracellular virus production, with minimal decrease in cell viability after infection. Loading of VSV onto CD8+ T cm not only improves the safety of the virus compared to systemic administration of naked virus, but tumor-bearing NSG mice also benefit from the combination therapy in terms of fast and effective tumor cell killing.
To further improve safety, we have engineered the VSV vector such that its targeting glycoprotein was deleted and replaced by the surface proteins from Newcastle disease virus (NDV), which has a substantially enhanced safety profile in rodents and humans. This vector also has the potential to provide an improved immunotherapeutic platform via the induction of cell fusion-mediated immunogenic cell death. We hypothesize that the combination of the enhanced rVSV-NDV vector with adoptive T cell therapy will result in enhanced safety and immunotherapeutic responses as a translational approach for treating solid tumors.

Treatment of Alzheimer's Disease by employing Tau-Aggregation-Inhibitors – Being a Tauist in the Land of Amyloid

Prof. Dr. Franz Theuring
Institute for Pharmacology and Toxicology, Charité Berlin

Alzheimer's disease (AD) is an irreversible, neurodegenerative disorder characterized by the progressive loss of memory and thinking skills. There are currently two main hypotheses regarding the cause of dementia in AD: the amyloid cascade hypothesis based on aggregation of extracellular Aβ, and the tau aggregation hypothesis based on intracellular tau aggregates. For the last 20 years disease modifying treatments for AD have focussed mainly on reducing levels for amyloid with absolutely no success.
However, tau aggregation pathology correlates well with clinical dementia in AD, therefore we believe that a tau-aggregation- inhibitor (TAI) based on Methylthioninium (MT) could have therapeutic utility. TAIs work by dissolving existing tau aggregates and preventing the further aggregation of tau protein from forming new tangles. MTC (Methylthioninium chloride), the first identified TAI, offers an alternative and passed a positive Phase 2 clinical trial. This provided prominent support to the rationale for treating AD using TAI therapy, and two Phase 3 clinical trials for treating AD with a novel stabilized reduced form of MT (LMTX) that has improved efficacy, tolerability and absorption had been undertaken.
Results on the preclinical development of TAIs and the various clinical studies will be presented.
Most interestingly, the very same compounds exhibit synuclein-aggregation-inhibitor activity when tested in our a-synuclein-transgenic mice, an animal model for Parkinson's Disease.

Characterization of Tau-protein as a biomarker of Alzheimer's disease

Nora Lemke, M.Sc.
Institute for Pharmacology and Toxicology, Charité Berlin

Neurodegenerative diseases, such as Alzheimer's and Parkinson's disease, are one of the major challenges for health care systems in the ageing societies of the western world, with currently over 6 million people with dementia in the European Union and 44.4 million people worldwide.
The most common form of dementia is Alzheimer's disease (AD), which represents about 70 % of all cases.
However, identification of AD is quite challenging and often AD patients are only diagnosed in advanced stages. One of the main reasons for this might be the lack of accuracy in the results of assays used for identification and quantification of biomarkers for the disease.
We aim to further our understanding of the tau protein, a known AD biomarker, by applying imm nochemical methods in combination with analytical methods. In our studies, we want to identify, characterize and finally quantify the tau protein obtained from a transgenic, diseased state mouse model by means of mass spectrometry after enrichment of the protein. This study is part of the EU project "ReMiND", which is aiming to overcome the limitations caused by a lack of reference measurement procedures for established AD biomarkers by establishing new, accurate and traceable measurement methods.

Antibody Engineering – Tailor-made next generation antibodies in cancer immunotherapy

Prof. Dr. Matthias Peipp
Section for Stem Cell and Immunotherapy, University Hospital Schleswig-Holstein, Kiel

The implementation of therapeutic antibodies has revolutionized the therapy of cancer patients. Based on the clinical success of prototypic tumor targeting antibodies such as rituximab and trastuzumab the way for a variety of next generation antibodies with improved characteristics was opened. Innovations in techniques to generate humanized or even human molecules were key for the clinical success of first generation antibodies. Despite the proven clinical activity in different cancer entities, not all patients respond to antibody therapy. Consequently, novel approaches to improve this generally well tolerated therapy are major areas of research. Novel insights into the mechanisms of action mediated by therapeutic antibodies have fueled innovations in antibody engineering. Especially effector functions triggered by the Fc part of therapeutic antibodies have been suggested to play important roles in the elimination of tumor cells.
Here, engineering strategies aiming at improving the IgG intrinsic Fc effector mechanisms such as antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP) or complement dependent cytotoxicity (CDC) are presented and discussed. Besides engineering conventional IgG antibodies innovative antibody derivatives such as bispecific antibodies and antibody fusion proteins will be presented. Together, a brief overview in currently established and emerging antibody engineering strategies to improve immunotherapy of cancer is given.

Activating NK Cell Receptors as Novel Trigger Molecules for Bispecific Antibody-Derivatives to Enhance Anti-Tumor NK cell Responses

Sebastian Lutz, M.Sc.
Section for Stem Cell and Immunotherapy, University Hospital Schleswig-Holstein, Kiel

Natural killer (NK) cells play an important role in cancer immunosurveillance. Their cytotoxic abilities are governed by integrating signals mediated through stimulatory and inhibitory receptors.
Activating NK cell receptors such as NKp46 and NKG2D scan host cells for the expression of self-molecules which become upregulated upon malignant transformation. For potent NK cell activation the cell surface expression levels of such self-molecules are critical, and tumor cells escape NK cellrecognition by downmodulating these danger ligands.
To mimick the induced-self phenotype required for efficient tumor recognition, recombinant bispecific antibodies engaging activating NK Cell receptors and binding to tumor associated antigens will be generated. Phage display as a strategy to isolate NKG2D-specific antibodies will be presented.
In addition the generation and functional characterization of NKp46-directed bispecific antibodies will be described. With their abilities to trigger NK cell cytotoxicity, bispecific antibodies directed against tumor-associated antigens and activating NK cell receptors may represent attractive molecules in antibody-based cancer immunotherapy.

Activation of mitochondrial VDAC2 for the treatment of cardiac arrhythmia

Johann Schredelseker, Ph.D.
Walter-Straub-Institute for Pharmacology and Toxicology, LMU Munich

Current antiarrhythmic drugs display major side effects and are thus difficult to apply making the search for safer drug targets a major endeavor of cardiovascular research. We recently demonstrated that the newly synthesized compound efsevin restores rhythmic cardiac contractions in a zebrafish cardiac fibrillation model.
We identified a direct interaction of efsevin with the voltage-dependent anion channel 2 (VDAC2) in the outer mitochondrial membrane and confirmed that efsevin effects are mediated through VDAC2 by transient VDAC2 knockdown and overexpression. To assess the efficacy of efsevin in a mammalian cardiac disease model we used isolated cardiomyocytes from a murine model for catecholaminergic polymorphic ventricular tachycardia (CPVT), an inherited form of arrhythmia. Treatment with efsevin completely eliminated arrhythmogenic events such as diastolic Ca^{2+} waves and spontaneous action potentials in CPVT cardiomyocytes. Furthermore, treatment with efsevin reduced episodes of ventricular tachcardia in vivo. In a translational approach we used iPSC-derived cardiomyocytes from a CPVT patient to test efficacy of efsevin in a human model. Comparable to the results from murine cardiomyocytes we found a significant reduction of diastolic Ca^{2+} waves in these cells under efsevin treatment. Taken together our data indicate that VDAC2 is a potent target for the treatment of cardiac arrhythmia.

Pharmacological mode of action of efsevin on VDAC2

Fabiola Wilting, M.Sc.
Walter-Straub-Institute for Pharmacology and Toxicology, LMU Munich

The synthetic compound efsevin binds to the voltage-dependent anion channel 2 (VDAC2) in the outer mitochondrial membrane and thereby suppresses cardiac arrhythmia. To investigate the pharmacological mode of action of efsevin, we recombinantly expressed and purified VDAC2 and reconstituted single channels in lipid bilayers. Addition of efsevin reduced the conductance of VDAC2 by inducing a shift from the anion-selective open state of the channel towards a cation-selective low conductance state.
To investigate the influence of this shift on mitochondrial Ca^{2+} handling we measured mitochondrial Ca^{2+} uptake in cultured cardiomyocytes. Indeed, efsevin dose-dependently enhanced the uptake of Ca^{2+} from the sarcoplasmic reticulum (SR) into mitochondria. In order to establish a causative link between the enhanced mitochondrial Ca^{2+} uptake and the antiarrhythmic effect of efsevin we performed two lines of experiments on isolated CPVT cardiomyocytes.
In a gain-of-function approach kaempferol, an agonist of the mitochondrial Ca^{2+} uniporter in the inner mitochondrial membrane, suppressed arrhythmogenic Ca^{2+} waves comparable to efsevin, while in a loss-of-function approach blockade of mitochondrial Ca^{2+} uptake with Ru360 suppressed the antiarrhythmic effect of efsevin. We therefore conclude that efsevin suppresses arrhythmia by enhancing mitochondrial Ca^{2+} uptake.

Targeting oncogenic gene transcription

Dr. Ralph Neumüller
Boehringer Ingelheim, Vienna

Aberrant transcriptional regulation can drive neoplastic transformation and sustain oncogenic growth. In the course of neoplastic transformation cancer cells can become addicted to transcription from large regulators elements (called super-enhancers) that maintain cancer cell identity. Interference with oncogenic gene transcription has thus been proposed as a promising therapeutic strategy.

I will discuss approaches undertaken at Boehringer Ingelheim Oncology to inhibit oncogenic gene transcription by targeting super-enhancers, transcriptional elongation and chromatin remodeling complexes.

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